Daratumumab (newly diagnosed multiple myeloma, stem cell transplantation suitable)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Medical and scientific advice

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Hans Josef van Lier.

IQWiG thanks the respondent and the Plasmozytom/Multiples Myelom Selbsthilfegruppe NRW e. V. for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ECOG PS	Eastern Cooperative Oncology Group Performance Status
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)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug daratumumab (in combination with bortezomib, lenalidomide and dexamethasone). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 21 November 2024.

Research question

The aim of the present report was to assess the added benefit of daratumumab in combination with bortezomib, lenalidomide + dexamethasone (hereinafter referred to as "daratumumab + bortezomib, lenalidomide + dexamethasone") in comparison with the appropriate comparator therapy (ACT) in patients with newly diagnosed multiple myeloma for whom autologous stem cell transplantation is an option.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of daratumumab + bortezomib + lenalidomide + dexamethasone

Therapeutic indication	**ACT[a]**
Adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplantation	An induction therapy consisting of ▫ bortezomib + thalidomide + dexamethasone (VTd) or ▫ bortezomib + cyclophosphamide + dexamethasone (VCd)[b] or ▫ daratumumab + bortezomib + thalidomide + dexamethasone (D-VTd) ▪ followed by high-dose therapy with melphalan and subsequent autologous stem cell transplantation ▪ followed by consolidation therapy (only if induction therapy with D-VTd is used)[c] consisting of ▫ daratumumab + bortezomib + thalidomide + dexamethasone ▪ followed by maintenance therapy consisting of ▫ Lenalidomide

a. Presented is the ACT specified by the G-BA.
b. Only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy; see Appendix VI to Section K of the Pharmaceutical Directive.
c. Consolidation therapy with 2 cycles of D-VTd following high-dose therapy and autologous stem cell transplantation corresponds to the dosing regimen according to the SPC for daratumumab and is part of the ACT only if daratumumab + bortezomib + thalidomide + dexamethasone (D-VTd)-based induction therapy is used. The concept of "consolidating" therapy must be distinguished from that of "maintenance therapy" as the two types of therapy address different treatment goals.

ACT: appropriate comparator therapy; C: cyclophosphamide; D: daratumumab; d: dexamethasone; G-BA: Joint Federal Committee; T: thalidomide; V: bortezomib

On 26 November 2024, the G-BA adjusted the ACT after submission of the dossier by the company (19 November 2024). When determining the ACT in its dossier, the company mainly referred to a consultation with the G-BA from 2018. In doing so, the company considered induction therapy consisting of bortezomib-dexamethasone-based triple combination therapy as specified by the physician, followed by high-dose therapy with melphalan and subsequent autologous stem cell transplantation, followed by maintenance therapy consisting of lenalidomide, as ACT. Due to the adjustment of the ACT after submission of the dossier, this specification of the company does not correspond to the current ACT of the G-BA. The present assessment was conducted in comparison with the G-BA's ACT of 26 November 2024. The assessment is conducted using patient-relevant outcomes based on the data presented by the company in the dossier. Randomized controlled trials (RCTs) are used to derive the added benefit. This concurs with the company's inclusion criteria.

Results

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with the ACT for the present research questions. Based on its ACT, the company identified the RCT PERSEUS and used it for its assessment. However, the PERSEUS study is not suitable for the assessment of the added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone, because the G-BA's ACT was not implemented in the study. This is justified below.

Evidence presented by the company – PERSEUS study

The PERSEUS study is an ongoing, open-label RCT comparing daratumumab + bortezomib + lenalidomide + dexamethasone with a combination of bortezomib + lenalidomide + dexamethasone, each followed by autologous stem cell transplantation as well as consolidation and maintenance therapy. Adult patients with newly diagnosed multiple myeloma who were eligible for autologous stem cell transplantation were included. Patients had to have a general condition corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤ 2.

The PERSEUS study included a total of 709 patients who were randomly allocated in a 1:1 ratio to the intervention arm (N = 355) or the comparator arm (N = 354).

The study treatment was subdivided into the 3 phases of induction, consolidation and maintenance. Patients in both study arms received 4 cycles of treatment with bortezomib, lenalidomide and dexamethasone (28 days each) as an induction therapy. In the intervention arm, treatment is also administered in combination with daratumumab. This is followed by stem cell mobilization, high-dose chemotherapy with melphalan and an autologous stem cell transplantation. Autologous stem cell transplantation is followed by consolidation therapy

(drug combination identical to the induction phase) with 2 cycles (28 days each). In the maintenance therapy, a combination therapy of daratumumab + lenalidomide in the intervention arm or monotherapy with lenalidomide in the comparator arm is administered in 28-day cycles until disease progression or the occurrence of unacceptable toxicity.

Treatment with daratumumab + bortezomib + lenalidomide + dexamethasone in the intervention arm was largely in line with the Summary of Product Characteristics (SPC). The drug combination used in the comparator arm is not approved in this therapeutic indication.

Primary outcome of the PERSEUS study was PFS. Secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

ACT not implemented in the PERSEUS study

The G-BA has specified the following options for induction therapy within the framework of its ACT:

- bortezomib + thalidomide + dexamethasone or
- bortezomib + cyclophosphamide + dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy), or
- daratumumab + bortezomib + thalidomide + dexamethasone

Therefore, the induction therapy with bortezomib + lenalidomide + dexamethasone used in the comparator arm of the PERSEUS study does not correspond to the G-BA's specification.

For the consolidation therapy, the G-BA specified daratumumab + bortezomib + thalidomide + dexamethasone in its ACT, i.e. only if this combination has already been used in the induction therapy. In departure from this, consolidation therapy with bortezomib + lenalidomide + dexamethasone was administered in the comparator arm of the PERSEUS study. This therefore also does not correspond to the G-BA's ACT.

Overall, the induction and the consolidation therapy with bortezomib + lenalidomide + dexamethasone implemented in the study does not correspond to the ACT specified by the G-BA. Thus, the ACT was not implemented in the PERSEUS study. The PERSEUS study is thus unsuitable for assessing the added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone versus the ACT specified by the G-BA.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone versus the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit

Table 3 shows a summary of the probability and extent of the added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone.

Table 3: Daratumumab + bortezomib + lenalidomide + dexamethasone – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplantation	▪ An induction therapy consisting of: ▫ bortezomib + thalidomide + dexamethasone (VTd) or ▫ bortezomib + cyclophosphamide + dexamethasone (VCd)[b] or ▫ daratumumab + bortezomib + thalidomide + dexamethasone (D-VTd) ▪ followed by high-dose therapy with melphalan and subsequent autologous stem cell transplantation ▪ followed by consolidation therapy (only if induction therapy with D-VTd is used)[c] consisting of ▫ daratumumab + bortezomib + thalidomide + dexamethasone ▪ followed by maintenance therapy consisting of ▫ lenalidomide	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy; see Appendix VI to Section K of the Pharmaceutical Directive.
c. Consolidation therapy with 2 cycles of D-VTd following high-dose therapy and autologous stem cell transplantation corresponds to the dosing regimen according to the SPC for daratumumab and is part of the ACT only if daratumumab + bortezomib + thalidomide + dexamethasone (D-VTd)-based induction therapy is used. The concept of "consolidating" therapy must be distinguished from that of "maintenance therapy" as the two types of therapy address different treatment goals.

C: cyclophosphamide; D: daratumumab; d: dexamethasone; G-BA: Joint Federal Committee; T: thalidomide; V: bortezomib

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report was to assess the added benefit of daratumumab in combination with bortezomib, lenalidomide + dexamethasone (hereinafter referred to as "daratumumab + bortezomib, lenalidomide + dexamethasone") in comparison with the ACT in patients with newly diagnosed multiple myeloma for whom autologous stem cell transplantation is an option.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of daratumumab + bortezomib + lenalidomide + dexamethasone

Therapeutic indication	**ACT**[a]
Adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplantation	▪ An induction therapy consisting of ▫ bortezomib + thalidomide + dexamethasone (VTd) or ▫ bortezomib + cyclophosphamide + dexamethasone (VCd)[b] or ▫ daratumumab + bortezomib + thalidomide + dexamethasone (D-VTd) ▪ followed by high-dose therapy with melphalan and subsequent autologous stem cell transplantation ▪ followed by consolidation therapy (only if induction therapy with D-VTd is used)[c] consisting of ▫ daratumumab + bortezomib + thalidomide + dexamethasone ▪ followed by maintenance therapy consisting of ▫ lenalidomide

a. Presented is the ACT specified by the G-BA.
b. Only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy; see Appendix VI to Section K of the Pharmaceutical Directive.
c. Consolidation therapy with 2 cycles of D-VTd following high-dose therapy and autologous stem cell transplantation corresponds to the dosing regimen according to the SPC for daratumumab and is part of the ACT only if daratumumab + bortezomib + thalidomide + dexamethasone (D-VTd)-based induction therapy is used. The concept of "consolidating" therapy must be distinguished from that of "maintenance therapy" as the two types of therapy address different treatment goals.

C: cyclophosphamide; D: daratumumab; d: dexamethasone; G-BA: Joint Federal Committee; T: thalidomide; V: bortezomib

On 26 November 2024, the G-BA adjusted the ACT after submission of the dossier by the company (19 November 2024) as shown in Table 4. When determining the ACT in its dossier, the company mainly refers to a consultation with the G-BA from 2018 [1]. The company considers induction therapy consisting of bortezomib-dexamethasone-based triple combination therapy of physician's choice, followed by high-dose therapy with melphalan and

subsequent autologous stem cell transplantation, followed by maintenance therapy consisting of lenalidomide, as an ACT. Due to the adjustment of the ACT after submission of the dossier, this specification of the company does not correspond to the current ACT of the G-BA from 26 November 2024. The present assessment is conducted in comparison with the ACT specified by the G-BA (see Table 4). The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive the added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on daratumumab (status: 8 November 2024)
- bibliographical literature search on daratumumab (last search on 2 October 2024)
- Search in trial registries/study results databases on daratumumab (last search on 09 October 2024)
- Search on the G-BA website on daratumumab (last search on 9 October 2024)

To check the completeness of the study pool:

- search in trial registries for studies on daratumumab (last search on 18 December 2024); for search strategies, see I Appendix A of the full dossier assessment

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with the ACT for the present research questions.

Based on its ACT, the company identified the RCT PERSEUS [2] and used it for its assessment. However, the PERSEUS study is not suitable for the assessment of the added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone, because the G-BA's ACT was not implemented in the study. This is justified below.

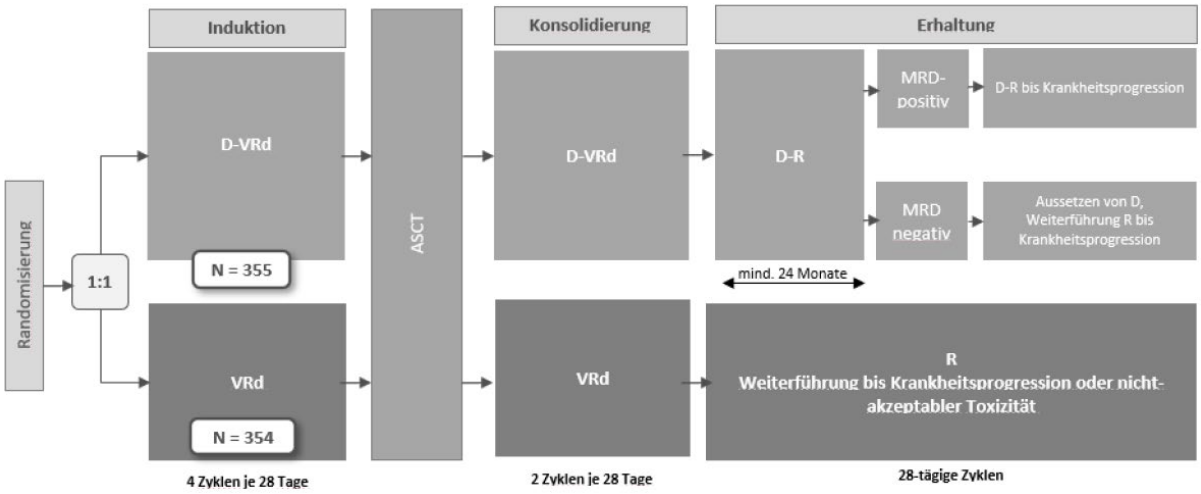
Evidence provided by the company

Design of the PERSEUS study

The PERSEUS study is an ongoing, open-label RCT comparing daratumumab + bortezomib + lenalidomide + dexamethasone with a combination of bortezomib + lenalidomide + dexamethasone, each followed by autologous stem cell transplantation as well as consolidation and maintenance therapy (see also below). Adult patients with newly diagnosed multiple myeloma who were eligible for autologous stem cell transplantation were included. On the one hand, the study included patients with ≥ 10% monoclonal plasma cells in the bone marrow. On the other hand, it included patients with a biopsy-proven plasmacytoma and documented multiple myeloma who had at least hypercalcaemia, renal insufficiency, anaemia or bone lesion (Calcium, Renal, Anaemia, and Bone [CRAB] criteria) or 1 biomarker for malignancy (60% clonal plasma cells in the bone marrow, free light chain ratio ≥ 100, 1 focal lesion on magnetic resonance imaging [MRI]). Moreover, patients had to be aged between 18 and 70 years and have a general condition corresponding to an ECOG PS of ≤ 2.

The PERSEUS study included a total of 709 patients who were randomly allocated in a 1:1 ratio to the intervention arm (N = 355) or the comparator arm (N = 354). Randomization was stratified by disease stage (stage I vs. stage II vs. stage III; based on the International Staging System) and cytogenetics (standard risk vs. high risk).

The study treatment was subdivided into the 3 phases of induction, consolidation and maintenance (see Figure 1). Patients in both study arms received 4 cycles of treatment with bortezomib, lenalidomide and dexamethasone (28 days each) as an induction therapy. In the intervention arm, treatment is also administered in combination with daratumumab. This is followed by stem cell mobilization, high-dose chemotherapy with melphalan and an autologous stem cell transplantation. In total, 309 (87%) patients in the intervention arm and 294 (83%) in the comparator arm underwent autologous stem cell transplantation. Autologous stem cell transplantation is followed by consolidation therapy (drug combination identical to the induction phase) with 2 cycles (28 days each). In the maintenance therapy, a combination therapy of daratumumab + lenalidomide in the intervention arm or monotherapy with lenalidomide in the comparator arm is administered in 28-day cycles until disease progression or the occurrence of unacceptable toxicity. In the intervention arm, the administration of daratumumab was discontinued if the minimal residual disease (MRD) status had been negative for at least 12 months and maintenance therapy had already lasted at least 24 months.



Induktion	Induction
Konsolidierung	Consolidation
Erhaltung	Maintenance
MRD positiv	MRD positive
MRD negativ	MRD negative
D-R bis Krankheitsprogression	Disease progression
Aussetzen von D, Weiterführung	Discontinuation of D, continuation
R bis Krankheitsprogression	R until disease progression
Randomisierung	Randomization
Weiterführung bis Krankheitsprogression oder nicht akzeptabler Toxizität	Continuation until disease progression or unacceptable toxicity
Zyklen	Cycles

ASCT: autologous stem cell transplantation; D: Daratumumab; d: dexamethasone; MRD: minimal residual disease; N: number of randomized patients; R: lenalidomide; V: bortezomib

Figure 1: PERSEUS study, schematic diagram of the study design

Treatment with daratumumab + bortezomib + lenalidomide + dexamethasone in the intervention arm was largely in line with the SPC [3]. The drug combination used in the comparator arm is not approved in this therapeutic indication.

Primary outcome of the PERSEUS study was PFS. Secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

ACT not implemented in the PERSEUS study

The G-BA has specified the following options for induction therapy within the framework of its ACT:

- bortezomib + thalidomide + dexamethasone or
- bortezomib + cyclophosphamide + dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy), or
- daratumumab + bortezomib + thalidomide + dexamethasone.

Therefore, the induction therapy with bortezomib + lenalidomide + dexamethasone used in the comparator arm of the PERSEUS study does not correspond to the G-BA's specification.

For the consolidation therapy, the G-BA specified daratumumab + bortezomib + thalidomide + dexamethasone in its appropriate therapy, i.e. only if this combination has already been used in the induction therapy. In departure from this, consolidation therapy with bortezomib + lenalidomide + dexamethasone was administered in the comparator arm of the PERSEUS study. This therefore also does not correspond to the G-BA's ACT.

Overall, the induction and the consolidation therapy with bortezomib + lenalidomide + dexamethasone implemented in the study does not correspond to the ACT specified by the G-BA. Thus, the ACT was not implemented in the PERSEUS study. The PERSEUS study is thus unsuitable for assessing the added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone versus the ACT specified by the G-BA.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with the ACT in patients with newly diagnosed multiple myeloma for whom autologous stem cell transplantation is an option. There is no hint of an added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of the added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone in comparison with the ACT.

Table 5: Daratumumab + bortezomib + lenalidomide + dexamethasone – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplantation	▪ An induction therapy consisting of ▫ bortezomib + thalidomide + dexamethasone (VTd) or ▫ bortezomib + cyclophosphamide + dexamethasone (VCd)[b] or ▫ daratumumab + bortezomib + thalidomide + dexamethasone (D-VTd) ▪ followed by high-dose therapy with melphalan and subsequent autologous stem cell transplantation ▪ followed by consolidation therapy (only if induction therapy with D- VTd is used)[c] consisting of ▫ daratumumab + bortezomib + thalidomide + dexamethasone ▪ followed by maintenance therapy consisting of ▫ lenalidomide	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy; see Appendix VI to Section K of the Pharmaceutical Directive.
c. Consolidation therapy with 2 cycles of D-VTd following high-dose therapy and autologous stem cell transplantation corresponds to the dosing regimen according to the SPC for daratumumab and is part of the ACT only if daratumumab + bortezomib + thalidomide + dexamethasone (D-VTd)-based induction therapy is used. The concept of "consolidating" therapy must be distinguished from that of "maintenance therapy" as the two types of therapy address different treatment goals.

C: cyclophosphamide; D: daratumumab; d: dexamethasone; G-BA: Joint Federal Committee; T: thalidomide; V: bortezomib

The assessment described above deviates from that of the company, which, based on the results of the PERSEUS study, derived a hint of a considerable added benefit of daratumumab + bortezomib + lenalidomide + dexamethasone compared with the ACT for patients with newly diagnosed multiple myeloma for whom autologous stem cell transplantation is an option.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

1. Gemeinsamer Bundesausschuss. Niederschrift (finale Fassung) zum Beratungsgespräch gemäß § 8 AM-NutzenV; Beratungsanforderung 2018-B-052; Daratumumab zur Behandlung des multiplen Myeloms [unpublished]. 2018.

2. Sonneveld P, Dimopoulos MA, Boccadoro M et al. Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med 2024; 390(4): 301-313. https://doi.org/10.1056/NEJMoa2312054.

3. Janssen-Cilag. DARZALEX 1800 mg Injektionslösung [online]. 10.2024 [Accessed: 27.11.2024]. URL: https://www.fachinfo.de/.

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