

Daratumumab (smouldering multiple myeloma)

Addendum to Project A25-109
(dossier assessment)¹

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ASCT	autologous stem cell transplantation
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-MY20	Quality of Life Questionnaire-Multiple Myeloma 20
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
VRd	bortezomib-lenalidomide-dexamethasone

1 Background

On 13 January 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-109 (Daratumumab – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the analyses subsequently submitted by the pharmaceutical company (hereinafter referred to as ‘the company’) in the comments, taking into account the information provided in the dossier [2,3],

- on subsequent therapies
- on the selective recording of the symptom scale ‘disease symptoms’ and of the functional scale ‘future perspective’ of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Multiple Myeloma 20 (QLQ-MY20)

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

The randomized controlled trial (RCT) AQUILA was used for the benefit assessment of daratumumab in comparison with the appropriate comparator therapy (ACT). A detailed description of the study can be found in dossier assessment A25-109 [1].

2.1 Information on subsequent therapies subsequently submitted by the company

Benefit assessment A25-109 [1] described that the subsequent antineoplastic therapies administered in the comparator arm of the AQUILA study did not adequately represent the current standard of care following the development of multiple myeloma. Overall, in the comparator arm, only 33.3% of patients receiving first-line treatment for multiple myeloma were treated with a CD38 antibody in compliance with guideline recommendations in this line of treatment.

In its comments, the company stated that a large proportion of the subsequent therapies administered following the development of multiple myeloma in the AQUILA study were in line with the generally accepted state of scientific knowledge regarding first-line treatment of multiple myeloma. It described that 80% of the patients who were eligible for autologous stem cell transplantation (ASCT) received subsequent therapy that corresponded to the ACT in benefit assessment A25-105 (Isatuximab [multiple myeloma, first-line, eligible for ASCT]) [4] or that was in compliance with guidelines (see Table 1 and Table 2). For patients who were ineligible for ASCT, the company stated that over 60% of patients received subsequent therapy that corresponded to the ACT in benefit assessment A25-20 (isatuximab [multiple myeloma, first line, ineligible for ASCT]) [5] or that was in compliance with guidelines (see Table 1 and Table 2). The company concluded from this that there were no substantial deficiencies in the AQUILA study with regard to subsequent therapy.

The company's reasoning did not alter the assessment of subsequent therapies set out in the dossier assessment. When considering in isolation the proportion of patients in the comparator arm who received subsequent therapy in line with the ACTs specified in benefit assessments A25-105 and A25-20 respectively, the proportions were 43.9% (eligible for ASCT) and 53.1% (ineligible for ASCT). Overall, therefore, around half of all patients in the comparator arm were treated with subsequent therapies in line with the ACTs described in benefit assessments A25-105 and A25-20 (see Table 1).

In its comments, the company added patients who it considered to have received subsequent therapy in compliance with the guidelines to those patients who had received subsequent therapy in accordance with the ACTs. The proportion of patients in the comparator arm who, according to the company, received subsequent therapy in compliance with the guidelines was 36.6% (based on patients eligible for ASCT who received subsequent therapy) or 14.1% (based on patients ineligible ASCT who received subsequent therapy). The company did not

specify which guidelines this assessment was based on. The company cited bortezomib-lenalidomide-dexamethasone (VRd) as a guideline-compliant subsequent therapy for patients eligible for ASCT. However, current guidelines [6,7] do not recommend VRd as the first-line treatment of choice for multiple myeloma. In the comparator arm, 15 (36.6%) of the patients eligible for ASCT received VRd (based on patients eligible for ASCT who received subsequent therapy). These patients were therefore not treated in accordance with the guidelines, as claimed by the company.

For patients unsuitable for ASCT, the company specifically cited the combinations of daratumumab-VRd and isatuximab-VRd as guideline-compliant subsequent therapies. According to current guidelines, daratumumab-VRd and isatuximab-VRd are the first-line treatment of choice for multiple myeloma. However, only 9 (14.1%) patients in the comparator arm received these guideline-compliant combinations.

The information provided by the company regarding the use of subsequent therapies that corresponded to the ACTs in benefit assessments A25-105 and A25-20 respectively was appropriate; however, overall, only around half of the patients in the comparator arm received a subsequent therapy corresponding to the respective ACT. The company's data on guideline-compliant subsequent therapies included treatments that are not considered treatments of choice and were therefore overestimated (see VRd above). It cannot therefore be assumed that, as claimed by the company, a large proportion of patients in the AQUILA study received appropriate subsequent therapy. Even assuming that the information provided by the company was correct, it could not be ruled out with sufficient certainty that the observed effect in the overall survival outcome was not exclusively attributable to deficiencies in the subsequent therapies – in particular, the limited use of CD38 antibodies (see dossier assessment A25-109 [1]). The deficiencies regarding the subsequent therapies described in the dossier assessment therefore remained unchanged, even when taking into account the information provided in the commenting procedure.

Table 1: Information on first subsequent therapies – RCT, direct comparison: daratumumab vs. no intervention

Study First-line treatment	Patients with subsequent therapy, n (%)			
	daratumumab N = 64		No intervention N = 105	
AQUILA	ASCT-eligible	ASCT-ineligible	ASCT-eligible	ASCT-ineligible
Total	23 (35.9)	41 (64.1)	41 (39.0)	64 (61.0)
ACT-compliant ^a	9 (39.1 ^b)	19 (46.3 ^b)	18 (43.9 ^b)	34 (53.1 ^b)
Guideline-compliant according to the company ^c	8 (34.8 ^b)	3 (7.3 ^b)	15 (36.6 ^b)	9 (14.1 ^b)
Other therapies ^d	6 (26.1 ^b)	19 (46.3 ^b)	8 (19.5 ^b)	21 (32.8 ^b)
Combination of 3 or more components	6 (26.1 ^b)	9 (21.8 ^b)	8 (19.5 ^b)	11 (17.2 ^b)
Combination of 2 components	-	7 (17.1 ^b)	-	8 (12.5 ^b)
Monotherapy ^e	-	3 (14.3 ^b)	-	2 (3.1 ^b)

a. ACT in accordance with the benefit assessment procedures A25-20 [5] and A25-105 [4] (see Table 2).
b. Institute's calculation based on the proportion of patients with subsequent therapy, taking into account ASCT eligibility.
c. The company takes into account combinations that are not already included in the 'ACT-compliant' category. Guideline-compliant according to the company includes the VRd combination for patients in the 'ASCT-eligible' group. For patients in the 'ASCT-ineligible' group, guideline-compliant according to the company includes the quadruple combinations of daratumumab-VRd and isatuximab-VRd, as well as the combination of daratumumab, dexamethasone and iberdomide.
d. According to the company, the treatments listed here also include new combinations not covered by the guidelines; these may have been administered as part of clinical studies (e.g. bortezomib-daratumumab-dexamethasone-elranatamab-lenalidomide-melphalan) and would therefore also be in compliance with the guidelines. According to the company, these treatments were not included in the calculation of ACT- and guideline-compliant treatments.
e. Two patients in the daratumumab arm continued daratumumab monotherapy. In addition, one patient in the daratumumab arm received lenalidomide monotherapy without having developed multiple myeloma. In the comparator arm, one patient received lenalidomide monotherapy and one patient received isatuximab monotherapy without having developed multiple myeloma.

ACT: appropriate comparator therapy; ASCT: autologous stem cell transplantation; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial; VRd: bortezomib-lenalidomide-dexamethasone

Table 2: ACTs in previous procedures in the first-line treatment for multiple myeloma (analogous to the company's presentation)

ACT A25-105 isatuximab (multiple myeloma, first line, eligible for ASCT, in combination with bortezomib, lenalidomide and dexamethasone)	ACT A25-20 isatuximab (multiple myeloma, first line, ineligible for ASCT, in combination with bortezomib, lenalidomide and dexamethasone)
▪ An induction therapy consisting of ▫ Bortezomib + thalidomide + dexamethasone - or ▫ bortezomib + cyclophosphamide + dexamethasone^a - or ▫ daratumumab + bortezomib + thalidomide + dexamethasone - or ▫ daratumumab + bortezomib + lenalidomide + dexamethasone ▪ followed by high-dose therapy with melphalan and subsequent ASCT ▪ followed by consolidation therapy^b consisting of ▫ daratumumab + bortezomib + thalidomide + dexamethasone (only when using induction therapy with daratumumab + bortezomib + thalidomide + dexamethasone)^c - or ▫ daratumumab + bortezomib + lenalidomide + dexamethasone (only when using induction therapy with daratumumab + bortezomib + lenalidomide + dexamethasone)^d ▪ followed by maintenance treatment consisting of ▫ lenalidomide - or ▫ daratumumab + lenalidomide (only when using induction or consolidation therapy with daratumumab + bortezomib + lenalidomide + dexamethasone)	▪ daratumumab + lenalidomide + dexamethasone - or ▪ daratumumab + bortezomib + melphalan + prednisone - or ▪ bortezomib + melphalan + prednisone - or ▪ bortezomib + lenalidomide + dexamethasone - or ▪ thalidomide + melphalan + prednisone - or ▪ bortezomib + cyclophosphamide + dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy^e)
a. Only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy; see Appendix VI to Section K of the Pharmaceutical Directive. b. According to the G-BA, the concept of ‘consolidation’ therapy must be distinguished from that of ‘maintenance treatment’, which address different therapeutic goals. c. Only if D-VTd-based induction therapy is used does consolidation therapy with 2 cycles of D-VTd following high-dose therapy and ASCT correspond to the dosing regimen according to the SmPC for daratumumab and so is part of the ACT. d. Only if D-VRd-based induction therapy is used does consolidation therapy with 2 cycles of D-VRd with subsequent maintenance treatment with daratumumab + lenalidomide following high-dose therapy and ASCT correspond to the dosing regimen according to the SmPC for daratumumab and so is part of the ACT. e. See Appendix VI to Section K of the Pharmaceutical Directive.	
ACT: appropriate comparator therapy; ASCT: autologous stem cell transplantation; C: cyclophosphamide; D: daratumumab; d: dexamethasone; G-BA: Federal Joint Committee; R: lenalidomide; SmPC: summary of product characteristics; T: thalidomide; V: bortezomib	

2.2 Information subsequently provided by the company regarding the selective recording of the EORTC scales QLQ-MY20 ‘disease symptoms’ and ‘future perspective’

In Module 4 B, the company selectively presented results of the EORTC QLQ-MY20 scales ‘disease symptoms’ and ‘future perspective’. The scales ‘side effects of treatment’ and ‘body image’, which are also part of the EORTC QLQ-MY20, were not recorded in the AQUILA study. In Module 4 B, the company did not provide any justification for the selective recording of the EORTC QLQ-MY20 scales, nor did it provide any information on the validity of the individual scales. The selectively recorded results from the EORTC QLQ-MY20 scales ‘disease symptoms’ and ‘future perspective’ were therefore not used for benefit assessment A25-109.

In its comments, the company provided an explanation of the selection of these scales. It explained that, since 2025, it has been possible to use the EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30) without employing a disease-specific instrument, in combination with individual items and scales from the item library, and referred to the 2020 publication by Jean-Baptiste [8] for its selection of scales.

In the study cited by the company, 15 patients with smouldering multiple myeloma and 6 patients with multiple myeloma were asked to describe the symptoms they had experienced during the course of their smouldering multiple myeloma. In the next step, patients were asked to assess the instructions, items, response options, and recall periods on the EORTC QLQ-C30 and the 2 preselected EORTC QLQ-MY20 scales on disease symptoms and future perspective. Additionally, patients were asked how the scales on these instruments related to their disease and whether relevant content was missing. The selection of the 2 EORTC QLQ-MY20 scales – ‘disease symptoms’ and ‘future perspective’ – was based on a literature review, for which no more details were provided, and was not justified further.

One of the objectives of Jean-Baptiste’s 2020 study was to evaluate the content validity of the EORTC QLQ-C30 and the 2 EORTC QLQ-MY20 scales ‘disease symptoms’ and ‘future perspective’ in smouldering multiple myeloma. However, selecting individual scales from the EORTC QLQ-MY20 was not the objective of this study. Both scales of the EORTC QLQ-MY20 were specified by the authors of the study, and the selection was conducted without the involvement of the patients. In addition, the interviews specifically addressed patients who had not yet received treatment. This cannot be transferred to the AQUILA study, in which patients in the intervention arm were treated with daratumumab. It can be assumed that the scale ‘side effects of treatment’ is relevant to these patients. Against this background, it did not seem appropriate to omit the scale ‘side effects of treatment’. It cannot therefore be concluded from Jean-Baptiste’s 2020 publication [8] that an isolated recording of the ‘disease symptoms’ and ‘future perspective’ scales in the AQUILA study was appropriate.

The scales ‘disease symptoms’ and ‘future perspective’ from the EORTC QLQ-MY20 were not used for the benefit assessment.

The results of the ‘disease symptoms’ and ‘future perspective’ scales, together with the corresponding Kaplan-Meier curves, are presented in Appendix A as supplementary information.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure did not alter the conclusion on the added benefit of daratumumab drawn in dossier assessment A25-109.

The following Table 3 shows the result of the benefit assessment of daratumumab, taking into account dossier assessment A25-109 and this addendum.

Table 3: Daratumumab – probability and extent of added benefit

Therapeutic indication	ACT ^a	Probability and extent of added benefit
Adult patients with smouldering multiple myeloma who are at high risk of developing multiple myeloma	Watchful waiting	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

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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Appendix A Results of the EORTC QLQ-MY20 scales ‘disease symptoms’ and ‘future perspective’ presented as supplementary information

Table 4: Results (EORTC-QLQ-MY20 scales ‘disease symptoms’ and ‘future perspective’, time to event) – RCT, direct comparison: daratumumab vs. no intervention

Study Outcome category Outcome	daratumumab		No intervention		daratumumab vs. no intervention
	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]; p-value ^a
AQUILA					
EORTC QLQ-MY20 – time to first deterioration					
Disease symptoms ^b	194	35.94 [19.75; 52.47] 100 (51.5)	196	17.97 [13.70; 33.87] 106 (54.1)	0.72 [0.54; 0.94]; 0.018
Future perspective ^c	194	47.08 [25.63; 60.81] 96 (49.5)	196	29.34 [15.01; 48.16] 98 (50.0)	0.80 [0.60; 1.06]; 0.113
a. Cox proportional hazards model with treatment as the sole explanatory variable, and with the stratification factor of the number of risk factors associated with progression to multiple myeloma (< 3 risk factors vs. ≥ 3 risk factors). b. A score increase of ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100). c. A score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; MY20: Multiple Myeloma 20; N: number of analysed patients; RCT: randomized controlled trial					

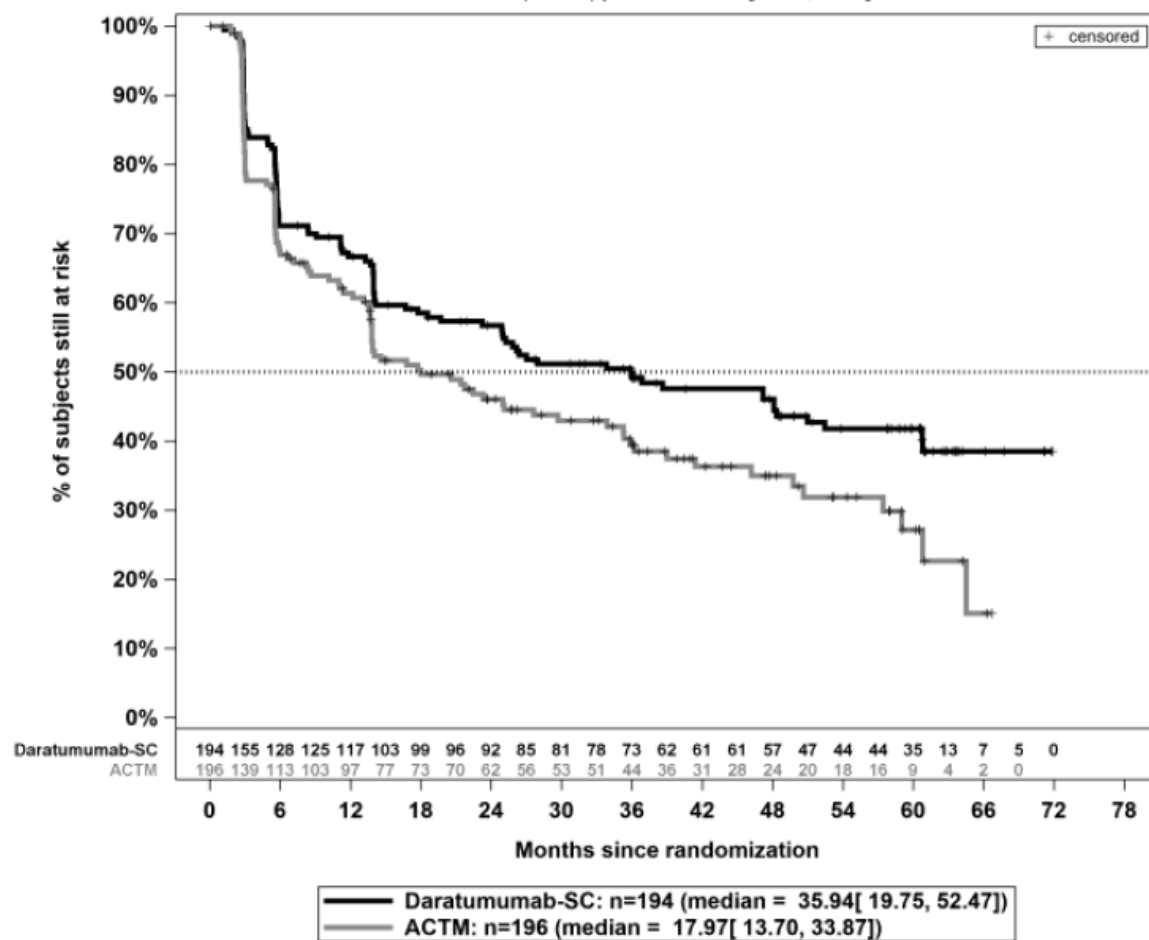


Figure 1: Kaplan-Meier curves for the outcome 'disease symptoms' (EORTC QLQ-MY20 – time to first deterioration) (AQUILA, data cut from 1 May 2024)

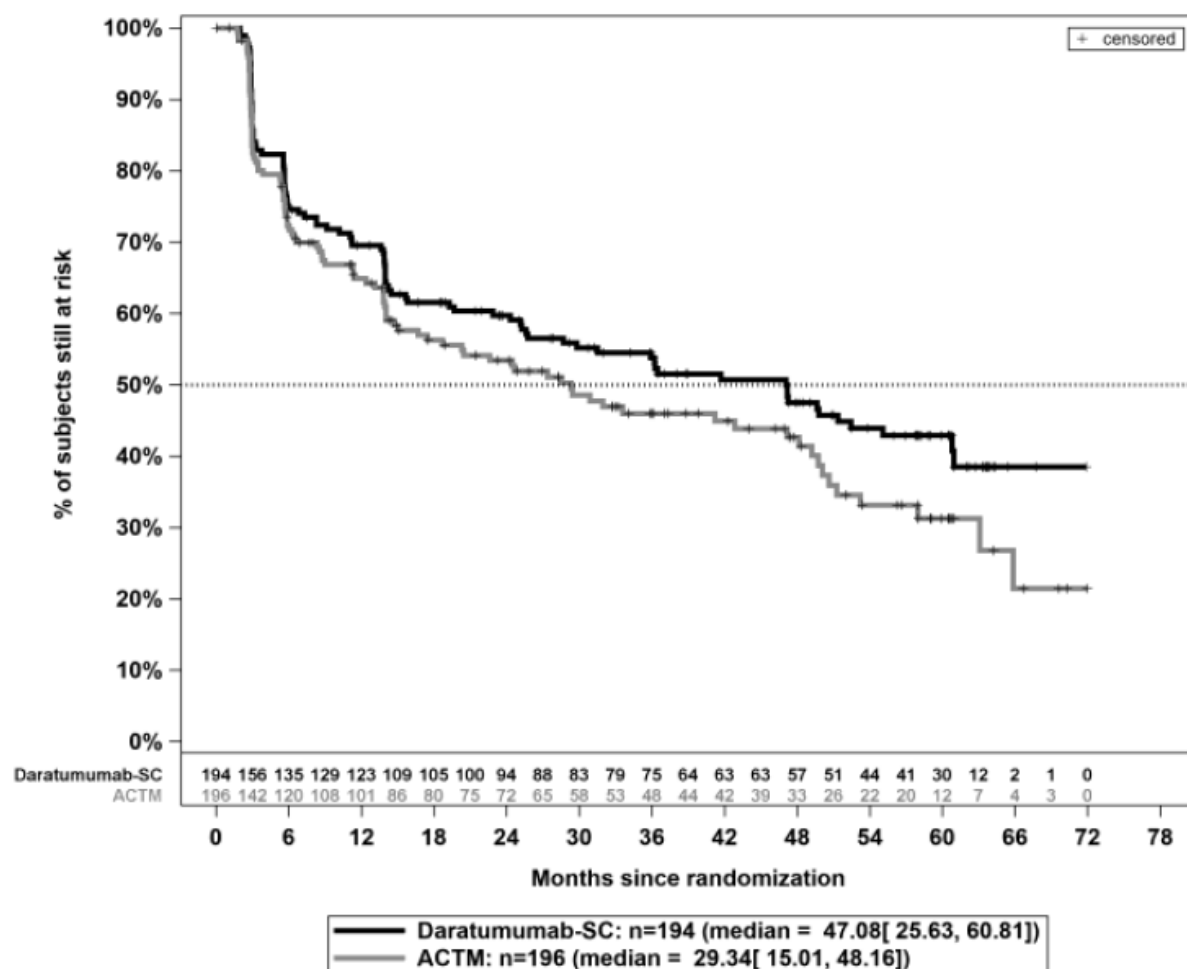


Figure 2: Kaplan-Meier curves for the outcome ‘future perspective’ (EORTC QLQ-MY20 – time to first deterioration) (AQUILA, data cut from 1 May 2024)