Daratumumab (multiple myeloma)

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

EXTRACT

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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

No patients or families were involved in the present dossier assessment

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Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ASCT	autologous stem cell transplantation
CTCAE	Common Terminology Criteria for Adverse Events
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)
PFS	progression-free survival
PT	preferred term
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VGPR	very good partial response

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. 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 4 December 2023.

The company had already submitted a dossier for a previous benefit assessment of the drug to be assessed. The dossier was sent to IQWiG on 1 October 2018. In this procedure, by decision of 22 March 2019, the G-BA limited its decision until 01 March 2022. At the application of the company, the G-BA initially extended the deadline until 15 May 2023 with the decision of 2 December 2021 and once more until 1 December 2023 with the decision of 19 January 2023.

The limitation was set because the data available from the ALCYONE study at the time of the data cut-off of 12 June 2018, in particular on the outcome of overall survival, were classified as not yet conclusively assessable. The final data cut-off of the ALCYONE study was initially planned for late 2021. With an amendment to the study protocol, the final analysis for the outcome "overall survival" was increased from 330 events to 382 events and the originally planned end of the study 5 years after randomization of the last patient was no longer adhered to. For the reassessment after expiry of the decision, the conditions of the limitation required that the results of the final analysis of the ALCYONE study be presented in the dossier for all patient-relevant outcomes. In addition, a sensitivity analysis with censoring of all patients after the occurrence of 330 events in the outcome of overall survival should be presented and discussed in the dossier.

Research question

The aim of the present report was to assess the added benefit of daratumumab in combination with bortezomib, melphalan and prednisone (hereinafter referred to as "daratumumab + bortezomib, melphalan and prednisone") in comparison with the appropriate comparator therapy (ACT) in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation (ASCT).

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 + melphalan + prednisone

Therapeutic indication	**ACT**[a]
Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation	▪ Daratumumab in combination with lenalidomide and dexamethasone 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 ▪ bortezomib in combination with cyclophosphamide and dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy[b])
a. Presented is the ACT specified by the G-BA. b. See Appendix VI pertaining to Section K of the German Pharmaceutical Directive. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company named all treatment options according to the G-BA's specification of the ACT, but additionally lenalidomide in combination with dexamethasone. This has no consequences for the benefit assessment, as the company presented evidence versus the option bortezomib in combination with melphalan and prednisone (hereinafter referred to as “bortezomib + melphalan + prednisone”) named by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive added benefit.

Study pool and study design

The study pool for the benefit assessment consists of the studies ALCYONE and OCTANS. However, there are uncertainties regarding the unsuitability of ASCT for the included patients and the implementation of the ACT (see below).

ALCYONE study

The ALCYONE study is an ongoing, multicentre, open-label, randomized study comparing daratumumab + bortezomib + melphalan + prednisone with bortezomib + melphalan + prednisone in adults with newly diagnosed multiple myeloma for whom high-dose chemotherapy with subsequent ASCT is unsuitable.

In accordance with the inclusion criteria, patients were ineligible for ASCT if they were either younger than 65 years of age and had important comorbidities or if they were 65 years of age

and older. In addition, patients had to have an ECOG PS of 0 to 2 as a measure of general health.

A total of 706 patients were randomized to the study arms: 350 patients to the intervention arm and 356 patients to the comparator arm.

Treatment in both study arms was carried out in 6-week cycles. Treatment in the intervention arm was carried out in accordance with the Summary of Product Characteristics (SPC) for daratumumab. However, regarding the administration of bortezomib, the treatment in the control arm deviates from the regimen described in the SPC for bortezomib. Melphalan and prednisone were administered in compliance with the approval.

The study's primary outcome was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, health status, symptoms, health-related quality of life and adverse events (AEs).

Study OCTANS

The OCTANS study is an ongoing, open-label, randomized study comparing daratumumab + bortezomib + melphalan + prednisone with bortezomib + melphalan + prednisone in patients in the Asia-Pacific region with newly diagnosed multiple myeloma who are ineligible for ASCT. The definition of ASCT ineligibility in the OCTANS study corresponds to that in the ALCYONE study (see above). The inclusion and exclusion criteria of the OCTANS study as well as the other study and intervention characteristics largely correspond to those of the ALCYONE study.

A total of 220 patients were randomized in a 2:1 ratio to the study arms: 146 patients to the intervention arm and 74 patients to the comparator arm.

Primary outcome of the study is very good partial response or better. Patient-relevant secondary outcomes were overall survival, health status, symptoms, health-related quality of life and AEs.

Data cut-offs

In the dossier, the company presents results for both studies for the respective final data cut-off (ALCYONE study: 31 May 2023; OCTANS study: 23 December 2022).

Uncertainties of the studies ALCYONE and OCTANS

Uncertainties exist for the included studies ALCYONE and OCTANS. These and their effects on the benefit assessment are described below.

ASCT suitability and ASCT availability

According to the inclusion criteria of the studies ALCYONE and OCTANS, patients younger than 65 years with important comorbidities and patients who were 65 years of age and older were deemed ineligible for ASCT. However, the criteria for assessing the ASCT suitability in everyday health care have changed since the start of the two studies. It is difficult to define a maximum age for ASCT therapy. Instead, individual patient factors must be taken into account when making the decision, taking into account the patient's general condition, existing comorbidities and organ function. Consequently, taking into account current guidelines for the operationalization of ASCZT ineligibility, it is not appropriate to determine ineligibility of ASCT for patients solely on the basis of age (≥ 65 years), as was done in the ALCYONE and OCTANS studies.

In addition to the results for the total population, the company therefore also presented results for a post hoc defined subpopulation for both studies that represents an approximation to the population for whom ASCT is not suitable (ASCT ineligibility).

543 (77%) patients in the ALCYONE study and 122 (55%) patients in the OCTANS study fulfil these criteria. There is uncertainty that the proportion of patients for whom ASCT would actually not have been suitable is unclear for both the total population and for the subpopulations defined post hoc.

In addition to the uncertainty resulting from the inclusion criteria regarding the unsuitability of ASCT for the study populations of the ALCYONE and OCTANS studies, the company describes an additional uncertainty with regard to the transferability of the study results to the German health care context for the OCTANS study, which was conducted exclusively in the Asia-Pacific region: The company assumes that, particularly in the Chinese health care context, not all patients for whom ASCT would be suitable would actually receive it.

Approach of the company and consequences for the benefit assessment

The company described that consistently comparable effect estimations were obtained for the populations defined post hoc via the characteristic of ASCT ineligibility described above and for the total populations across all outcomes and that the consideration of the total population of the ALCYONE study for the benefit assessment was therefore justified. However, due to the additional uncertainty regarding the health care context described above, particularly in China, it only represents the OCTANS study as supplementary information.

According to the General Methods of the Institute, studies that do not completely fulfil an inclusion criterion of the research question of interest are included in the benefit assessment if the criterion is fulfilled in at least 80% of the (sub)population of interest of the study. Regardless of the degree of fulfilment (at least 80%, less than 80%), there may be situations in which suitable information on effect modification by the relevant inclusion criterion

(population or interventions) is available. In certain situations, the consideration of the study must be decided on the basis of the strength of the effect modification and the proportion of patients who do not fulfil the inclusion criterion or the degree of deviation of the interventions. In the present case, the subpopulation "ASCT ineligibility" of the study ALCYONE or OCTANS comprises 77% and 55% of the total population respectively (averaged over both studies approx. 72%), but the operationalization is subject to uncertainty. It is therefore also conceivable that ASCT was unsuitable for more than 80% of the total population of the ALCYONE study and the OCTANS study in accordance with the target population of the research question. In addition, the results for the decision-relevant outcomes are generally very similar between the total population and the "ASCT ineligibility" subpopulation. There was also no effect modification by the characteristic "ASCT ineligibility"/"ASCT eligibility" for any relevant outcome. For this reason, the results of the total population of the studies ALCYONE and OCTANS are used jointly for the present benefit assessment, despite the uncertainty regarding the operationalization of ASZT ineligibility.

Uncertainty regarding the implementation of the ACT

In the comparator arm of both studies, bortezomib was administered at a dosage that differed from that specified in the SPC. The benefit assessment is carried out within the existing approval. However, in the present benefit assessment, the bortezomib dosage regimen used in the studies ALCYONE and OCTANS is considered to be a sufficient approximation of the approval-compliant application.

Summarized assessment of the studies ALCYONE and OCTANS for the present benefit assessment

In the studies ALCYONE and OCTANS, there are uncertainties caused by the deviating definition of the suitability of ASCT at the start of the study compared with the current health care context and due to the deviating bortezomib dosage in the comparator arm. In addition, the OCTANS study was conducted exclusively in the Asia-Pacific region and for the most part in China, and there are potential differences in Chinese everyday health care with regard to the implementation of ASCT compared to the German health care context. The uncertainties do not fundamentally call into question the suitability of the studies ALCYONE and OCTANS or the consideration of the total populations in the benefit assessment, but they are taken into account for the certainty of conclusions.

Meta-analysis of the study results

Due to the similar designs and patient characteristics of the studies ALCYONE and OCTANS, a meta-analysis is generally possible and reasonable. In the pooled population of the total populations of both studies, the proportion of patients for whom ASCT was not suitable according to the above criteria was 72%. For the benefit assessment, the total populations of

the studies ALCYONE and OCTANS were summarized in a meta-analysis and used for the assessment of added benefit.

Deficiencies in follow-up therapies

According to the current S3 guideline, various active substances in different combinations are available for the treatment of patients with multiple myeloma in the 1st to 3rd recurrence. The choice of treatment must be individualized for each patient and depends on disease-, patient- and therapy-specific factors. Therefore, all drug classes are usually used and combined in an individual sequence. Nevertheless, the S3 guideline strongly recommends a triple combination therapy with 2 new substances (monoclonal antibody, immunomodulator, proteasome inhibitor) and a steroid for multiple myeloma in the 1st relapse, taking into account the increased toxicity.

In the ALCYONE and OCTANS studies, a relevant proportion of patients received a follow-up therapy as a first follow-up therapy that did not comply with the guideline recommendation. This applies in particular to the comparator arm, as a significantly larger proportion of patients there received follow-up therapy that was not in line with the guidelines due to earlier and more frequent progression. In addition, in the comparator arm of the studies ALCYONE and OCTANS, daratumumab was used in a very small proportion of patients compared to the current health care context and in some cases only in a later line of therapy, whereas in the intervention arm all patients received daratumumab-based therapy in the first line. All things considered, the described deficiencies in the follow-up therapies administered in the studies ALCYONE and OCTANS are considered to be serious. The important deficiencies with regard to the follow-up therapies used are taken into account for the outcome of overall survival when assessing the risk of bias and determining the extent.

Risk of bias

All results suitable for deriving the added benefit have a high risk of bias. The risk of bias of the results for the outcome of overall survival is rated as high mainly due to the low use of daratumumab in the administered follow-up therapies.

The observation periods of all other outcomes are shortened due to potentially informative reasons and the results are therefore potentially highly biased. All results on subjective outcomes or outcomes with subjective recording of outcomes, such as the outcomes recorded by questionnaire, the superordinate outcome of discontinuation due to AEs and the specific AE “respiratory, thoracic and mediastinal disorders” (System Organ Class [SOC], AEs) also have a high risk of bias due to the unblinded study design.

Summary assessment of the certainty of conclusions

Due to the high risk of bias of the results of all included outcomes, at most hints, for example of an added benefit, can be derived at the individual study level. For the outcome "overall survival", the serious deficiencies described in the follow-up therapies administered also mean that the observed effect cannot be quantified. As a rule, when the results of the studies ALCYONE and OCTANS studies are summarized in a meta-analysis, at most indications, for example of an added benefit, can be derived. However, due to the reasons described above, which limit the transferability of the results to the German healthcare context, the reliability of conclusions is reduced. Overall, based on a meta-analytical summary of the results of the studies ALCYONE and OCTANS, at most hints, for example of an added benefit, can be derived.

Results

Mortality

Overall survival

For the outcome of overall survival, both the meta-analysis of the originally planned final analysis on overall survival after 330 events (relevant for the benefit assessment) and the meta-analysis on the final analysis on overall survival showed a statistically significant difference in favour of daratumumab + bortezomib + melphalan + prednisone. For the outcome “overall survival”, there is a hint of added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone.

Morbidity

Symptoms (European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Core 30 [QLQ-C30])

Symptom outcomes were recorded using the EORTC QLQ-C30 symptom scales.

Fatigue

The meta-analysis shows a statistically significant difference in favour of daratumumab + bortezomib + melphalan + prednisone for the outcome of fatigue. However, the difference is no more than marginal for this outcome in the category of non-serious/non-severe symptoms/late complications. For the outcome “fatigue”, there is no hint of added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone; an added benefit is therefore not proven for this outcome.

Nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea

The meta-analysis showed no statistically significant difference between the treatment groups for each of the following outcomes: nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation and diarrhoea. For these outcomes, there is no hint of added benefit of

daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone; an added benefit is therefore not proven for these outcomes.

health status (EQ-5D VAS)

The meta-analysis showed no statistically significant difference between treatment groups for the outcome of health status, measured with the EQ-5D VAS. For the outcome "health status", there is no hint of added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone; an added benefit is therefore not proven for this outcome.

Health-related quality of life

EORTC QLQ-C30

Health-related quality of life was recorded with the EORTC QLQ-C30 functional scales.

Global health status

The meta-analysis showed a statistically significant difference in favour of daratumumab + bortezomib + melphalan + prednisone for the outcome "global health status". For the outcome "global health status", there is a hint of added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone.

Physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning

The meta-analysis showed no statistically significant difference between treatment groups for the outcomes of physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning. There is no hint of added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone; an added benefit is therefore not proven for these outcomes.

Side effects

Serious adverse events (SAEs), severe AEs and discontinuation due to AEs

The meta-analysis showed no statistically significant difference between treatment groups for the outcomes of SAEs, severe AEs and discontinuation due to AEs. Hence, there was no hint of greater or lesser harm from daratumumab + bortezomib + melphalan + prednisone im comparison with bortezomib + melphalan + prednisone for any of the outcomes "SAEs", "severe AEs" and "discontinuation due to AEs"; greater or lesser harm is therefore not proven for these outcomes.

Specific AEs

Infusion-related reaction

The analyses presented by the company for the outcome “infusion related reaction” are not suitable for the benefit assessment. However, the events underlying infusion-related reactions have been recorded through the specific AEs.

This resulted in no hint of greater or lesser harm from daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone; greater or lesser harm is therefore not proven.

Peripheral neuropathy (severe AEs)

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "peripheral neuropathy (severe AEs)". Hence, there was no hint of greater or lesser harm from daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone for the outcome “peripheral neuropathy” (severe AEs); greater or lesser harm is therefore not proven for this outcome.

Infections and infestations (SOC, severe AEs), vascular diseases (SOC, severe AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs)

The ALCYONE study showed a statistically significant difference to the disadvantage of daratumumab + bortezomib + melphalan + prednisone for the outcomes of infections and infestations (SOC, severe AEs), vascular diseases (SOC, severe AEs) and respiratory, thoracic and mediastinal disorders (SOC, AEs). For each of these outcomes, there is a hint of greater harm from daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

The overall assessment shows both positive and negative effects with different extents for daratumumab + bortezomib + melphalan + prednisone versus bortezomib + melphalan + prednisone.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

On the side of positive effects, there is a hint of a non-quantifiable added benefit for the outcome of overall survival, and a hint of a minor added benefit for “global health status”.

These positive effects are offset by negative effects exclusively for outcomes in the side effects category: For the specific AEs “infections and infestations” as well as “vascular diseases”, there are hints of greater harm with the extent “minor”. For the specific AE “respiratory, thoracic and mediastinal disorders”, however, there is a hint of greater arm with the extent “considerable”. The negative effects refer exclusively to the shortened period until the end of treatment (plus a maximum of 30 days). In addition, further specific AEs could only be selected on the basis of the results from the ALCYONE study. It can therefore not be ruled out that the extent of the selected specific AEs could deviate in a metanalytical summary.

The negative effects in the specific AEs do not completely challenge the positive effects in the outcomes of overall survival and global health status. The added benefit is rated as non-quantifiable.

In summary, there is a hint of non-quantifiable added benefit of daratumumab + bortezomib + melphalan + prednisone versus bortezomib + melphalan + prednisone for patients with newly diagnosed multiple myeloma who are ineligible for ASCT.

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

Table 3: Daratumumab + bortezomib + melphalan + prednisone – 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 ineligible for autologous stem cell transplantation	▪ Daratumumab in combination with lenalidomide and dexamethasone 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 ▪ bortezomib in combination with cyclophosphamide and dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy[b])	Hint of non-quantifiable added benefit
a. Presented is the ACT specified by the G-BA. b. See Appendix VI pertaining to Section K of the German Pharmaceutical Directive. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. 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, melphalan and prednisone (hereinafter referred to as "daratumumab + bortezomib, melphalan and prednisone") in comparison with the ACT in patients with newly diagnosed multiple myeloma who are ineligible for ASCT.

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 + melphalan + prednisone

Therapeutic indication	**ACT[a]**
Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation	▪ Daratumumab in combination with lenalidomide and dexamethasone 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 ▪ bortezomib in combination with cyclophosphamide and dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy[b])
a. Presented is the ACT specified by the G-BA. b. See Appendix VI pertaining to Section K of the German Pharmaceutical Directive. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company named all treatment options according to the G-BA's specification of the ACT, but additionally lenalidomide in combination with dexamethasone. This has no consequences for the benefit assessment, as the company presented evidence versus the option bortezomib in combination with melphalan and prednisone (hereinafter referred to as "bortezomib + melphalan + prednisone") named by the G-BA.

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 added benefit.

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: 26 September 2023)
- bibliographical literature search on daratumumab (last search on 4 September 2023)
- Search in trial registries/study results databases on daratumumab (last search on 29 September 2023)
- Search on the G-BA website on daratumumab (last search on 18 September 2023)

To check the completeness of the study pool:

- search in trial registries for studies on daratumumab (last search on 12 December 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
MMY3007 (ALCYONE[d])	Yes	Yes	No	Yes [3-7]	Yes [8,9]	Yes [10,11]
MMY3011 (OCTANS[d])	Yes[e]	Yes	No	Yes [12-15]	Yes [16]	[17]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.
e. During the approval process in China the OCTANS study was submitted to the National Medical Products Administration.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool for the benefit assessment consists of the studies ALCYONE and OCTANS. However, there are uncertainties regarding the unsuitability of ASCT for the included patients and the implementation of the ACT. These uncertainties and their effects on the benefit assessment are described in Section I 3.2 In addition to the ALCYONE study, the company initially also included the OCTANS study in its study pool. However, it does not use the OCTANS study to derive the added benefit (see Section I 3.2).

I 3.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the included studies – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ALCYONE	RCT, open-label, parallel-group	Adults (≥ 18 years of age) with newly diagnosed multiple myeloma ▪ for whom high-dose chemotherapy with autologous stem cell transplantation is unsuitable (≥ 65 years of age or < 65 years of age in the presence of important comorbidities) ▪ ECOG PS ≤ 2	Daratumumab + bortezomib + melphalan + prednisone (N = 350) bortezomib + melphalan + prednisone (N = 356)	Screening: ≤ 21 days before randomization treatment: bortezomib + melphalan + prednisone: max. 9 cycles of 6 weeks each daratumumab: until documented disease progression, unacceptable toxicity, withdrawal of consent or until the end of study[b] observation[c]: outcome-specific, at most until end of study[b]	162 centres in Argentina, Australia, Belgium, Brazil, Bulgaria, Croatia, Czech Republic, Georgia, Germany, Great Britain, Greece, Hungary, Italy, Japan, Korea, Macedonia, Poland, Portugal, Romania, Russia, Serbia, Spain, Turkey, Ukraine, USA 01/2015–ongoing first data cut-off: 12 June 2017 second data cut-off: 12 October 2017 third data cut-off: 12 June 2018 fourth data cut-off: 24 June 2019 fifth data cut-off: 31 May 2023	Primary: PFS secondary: overall survival, health status, symptoms, health-related quality of life, AEs

Table 6: Characteristics of the included studies – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
OCTANS	RCT, open-label, parallel-group	Adults (≥ 18 years of age) with newly diagnosed multiple myeloma ▪ for whom high-dose chemotherapy with autologous stem cell transplantation is unsuitable (≥ 65 years of age or < 65 years of age in the presence of important comorbidities), ▪ ECOG PS ≤ 2	Daratumumab + bortezomib + melphalan + prednisone (N = 146) bortezomib + melphalan + prednisone (N = 74)	Screening: ≤ 21 days before randomization treatment: bortezomib + melphalan + prednisone: max. 9 cycles of 6 weeks each daratumumab: until documented disease progression, unacceptable toxicity, withdrawal of consent or until the end of study[d] observation[c]: outcome-specific, at most until end of study[d]	39 centres in China, Hong Kong, Malaysia, South Korea and Taiwan 12/2017–ongoing first data cut-off: 02 July 2020 second data cut-off: 16 July 2021 third data cut-off: 23 December 2022	Primary: VGPR or better secondary: overall survival, health status, symptoms, health-related quality of life, AEs

a. Primary outcomes comprise information without regard to its relevance for this benefit assessment. Secondary outcomes include information only on relevant available outcomes for this benefit assessment.
b. The study ends when all patients who are still receiving daratumumab after the final analysis of overall survival can also receive it outside the study, or when all patients have completed treatment with daratumumab, or in July 2024 at the latest. The end of the study was adjusted with Amendment 8 of the study protocol dated 2 June 2021. Originally, the study was planned to end after 330 deaths or 5 years after the last patient was randomized.
c. Outcome-specific information is described in Table 8. After the final data cut-off and until the end of the study, there will only be limited monitoring of efficacy and SAEs of patients who continue to be treated with daratumumab. During this time, no further data are collected via the eCRF.
d. The study ends when all patients who are still receiving daratumumab after the final analysis of overall survival can also receive it outside the study, or when all patients have completed treatment with daratumumab.

AE: adverse event; eCRF: electronic case report form; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; SAE: serious adverse event; VGPR: very good partial response

Table 7: Characteristics of interventions – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Study	Intervention	Comparison
ALCYONE	Daratumumab 16 mg/kg BW IV[a] ▪ cycle 1 (duration 42 days): weekly (Days 1, 8, 15, 22, 29, and 36) ▪ cycles 2-9 (duration 42 days each): every 3 weeks (Days 1 and 22) ▪ from cycle 10: every 4 weeksb + ▪ bortezomib 1.3 mg/m2 BSA, SC ▪ cycle 1 (duration 42 days): Days 1, 4, 8, 11, 22, 25, 29 and 32) ▪ cycles 2-9 (duration 42 days each): Days 1, 8, 22 and 29 + ▪ melphalan 9 mg/m2 BSA, orally ▪ cycles 1-9 (duration 42 days each): Days 1, 2, 3 and 4 + ▪ prednisone 60 mg/m2 BSA, orally ▪ cycles 1-9 (duration 42 days each): Days 1, 2, 3 and 4	Bortezomib 1.3 mg/m^2 BSA, SC ▪ cycle 1 (duration 42 days): Days 1, 4, 8, 11, 22, 25, 29 and 32) ▪ cycles 2-9 (duration 42 days each): Days 1, 8, 22 and 29 + ▪ melphalan 9 mg/m2 BSA, orally ▪ cycles 1-9 (duration 42 days each): Days 1, 2, 3 and 4 + ▪ prednisone 60 mg/m2 BSA, orally ▪ cycles 1-9 (duration 42 days each): Days 1, 2, 3 and 4
	Treatment adjustments: daratumumab: dose modifications are not allowed[c] bortezomib, melphalan, prednisone: according to the specifications in the study protocol, dose reduction or drug discontinuation was allowed. patients who discontinue a single component of their treatment regimens are allowed to continue the treatment with the remaining components	
	Premedication before daratumumab ▪ paracetamol 650–1000 mg IV or orally ▪ antihistamine (diphenhydramine 25–50 mg IV or orally, or an equivalent of an H1 blocker) ▪ dexamethasone 20 mg IV or orallyd ▪ leukotriene inhibitors (optional) at Cycle 1, Day 1): montelukast 10 mg orally or equivalent **postmedication after daratumumab** for patients at increased risk of respiratory complications (e.g. mild asthma), the following drugs may be considered after the infusion: ▪ antihistamine (diphenhydramine or an equivalent) ▪ leukotriene inhibitor (montelukast or equivalent) ▪ short-acting beta 2-adrenergic receptor agonist (e.g. salbutamol) ▪ medication to control the respective respiratory disease (e.g. inhaled corticosteroids, long-acting bronchodilators)	

Table 7: Characteristics of interventions – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Study	Intervention	Comparison
	Allowed concomitant treatment ▪ during the study, all drugs and therapies deemed necessary for supportive therapy were allowed (except disallowed concomitant treatments as listed below) **recommended concomitant treatment** ▪ bisphosphonates ▪ therapy for tumour lysis syndrome ▪ infection prophylaxis (e. g. pneumocystis carinii/jorevicii prophylaxis, herpes zoster prophylaxis) ▪ measures to prevent haemorrhagic cystitis **disallowed concomitant treatment** ▪ other antineoplastic myeloma therapies ▪ systemic corticosteroids (> 10 mg prednisone/day or equivalent) – except in case of infusion-related side effects – and NSAIDS should be avoided ▪ strong CYP3A4 inhibitors and inducers should be avoided ▪ attenuated live vaccines and replicable vector vaccines	
OCTANS	See ALCYONE[e]	

a. Since Amendment 7 (ALCYONE) and Amendment 4 (OCTANS) of the study protocol (December 2019 and June 2020 respectively), patients have had the option of switching to subcutaneous daratumumab (1800 mg every 4 weeks) at the investigator's discretion.
b. Daratumumab was administered until documented disease progression, unacceptable toxicity or the end of the study.
c. In case of IRR, and depending on the severity, the infusion is interrupted until stabilization, the infusion speed is adjusted or treatment is stopped.
d. On days on which dexamethasone was administered, prednisone was not administered.
e. In addition to the concomitant treatments recommended in the ALCYONE study, proton pump inhibitors, sucralfate or H2 blockers were also permitted in the OCTANS study to prevent steroid-induced gastritis.

BSA: body surface area; BW: body weight; CYP: cytochrome P450; H1/2: type 1/2 histamine receptor; IRR: infusion-related reaction; IV: intravenous; NSAID: non-steroidal anti-inflammatory drug; SC: subcutaneous; RCT: randomized controlled trial

ALCYONE study

The ALCYONE study is already known from a previous benefit assessment procedure [18,19]. The ALCYONE study is a multicentre, open-label, randomized study comparing daratumumab + bortezomib + melphalan + prednisone with bortezomib + melphalan + prednisone. The study is ongoing.

The study included adults (≥ 18 years of age) with newly diagnosed multiple myeloma who were ineligible for high-dose chemotherapy with subsequent ASCT. In accordance with the inclusion criteria, patients were ineligible for ASCT if they were either younger than 65 years of age and had important comorbidities or if they were 65 years of age and older (see below

for an assessment of the suitability of the selected criteria). In addition, patients had to have a general condition according to a ECOG PS of 0 to 2.

Patient randomization was stratified by the factors of International Staging System (ISS) stage (I versus II versus III), region (Europe versus others), and age (< 75 years versus ≥ 75 years). A total of 706 patients were randomized to the study arms: 350 patients to the intervention arm and 356 patients to the comparator arm.

Treatment in both study arms was carried out in 6-week cycles. Treatment with daratumumab + bortezomib + melphalan + prednisone in the intervention arm was carried out in accordance with the SPC of daratumumab [20,21]. Regarding the bortezomib administration, treatment in the control arm deviates from the regimen described in the SPC of bortezomib [22] (for the consequences, see the following text section on the uncertainties regarding the ALCYONE and OCTANS studies). Administration of melphalan and prednisone in the control arm was in compliance with the approval [22].

In both arms, the patients were treated with the respective treatment regimen for 9 cycles. If any component of the treatment regimen was discontinued, continued treatment with the remaining components was allowed. As stipulated in the SPC, in the intervention arm, maintenance treatment with daratumumab monotherapy was administered after completion of the 9 cycles and was to be continued until disease progression, unacceptable toxicity or the end of the study. In accordance with Amendment 7 to the study protocol of 16 December 2019, after approval patients in the intervention arm could be administered daratumumab subcutaneously (SC) at the discretion of the treating physician starting on Day 1 of each cycle. 75 patients (21.7%) in the intervention arm were switched to SC administration. No maintenance therapy was planned in the control arm. The approach also corresponded to the specifications of the SPC [22]. In both study arms, starting subsequent anti-myeloma therapy was only allowed after confirmed disease progression. There were no restrictions regarding the type of follow-up therapy: the choice of subsequent anti-myeloma therapy was at the discretion of the treating physician.

The study's primary outcome was PFS. Patient-relevant secondary outcomes and outcome categories were overall survival, health status, symptoms, health-related quality of life and AEs.

Data cut-offs

A total of 5 data cut-offs are available for the ALCYONE study:

- First data cut-off of 12 June 2017: pre-specified interim analysis triggered by the achievement of 216 events in the primary outcome of PFS

- Second data cut-off of 12 October 2017: 120-day safety data cut-off requested by the US Food and Drug Administration (FDA)
- Third data cut-off of 12 June 2018: non-prespecified data cut-off
- Fourth data cut-off of 24 June 2019: pre-specified interim analysis triggered by the achievement of 200 events in the outcome of overall survival
- Fifth data cut-off of 31 May 2023: final analysis planned by protocol amendment 8 of 02 June 2021 after reaching approximately 382 events in the outcome of overall survival (originally the study was to be terminated after 330 deaths or 5 years after randomization of the last patient)

For the present benefit assessment, the fifth data cut-off of 31 May 2023 is used for the final analysis. See Section I 4.1 for the procedure for the outcome of overall survival.

Study OCTANS

The OCTANS study is an ongoing, open-label, randomized study comparing daratumumab + bortezomib + melphalan + prednisone with bortezomib + melphalan + prednisone in patients in the Asia-Pacific region (study centres in China, Malaysia, South Korea and Taiwan) with newly diagnosed multiple myeloma who are ineligible for ASCT. The definition of ASCT ineligibility in the OCTANS study corresponds to that in the ALCYONE study (see above). The inclusion and exclusion criteria of the OCTANS study as well as the other study and intervention characteristics largely correspond to those of the ALCYONE study.

Patient randomization was stratified by the factors of ISS stage (I versus II versus III) and age (< 75 years versus ≥ 75 years). A total of 220 patients were randomized in a 2:1 ratio to the study arms: 146 patients to the intervention arm and 74 patients to the comparator arm.

As in the ALCYONE study, treatment in the control arm deviated from the bortezomib administration regimen described in the SPC of bortezomib [22]. In accordance with Amendment 4 to the study protocol of 24 June 2020, patients in the intervention arm could be administered daratumumab subcutaneously (SC) at the discretion of the treating physician starting on Day 1 of each cycle. A total of 76 patients (52%) were enrolled in the study.

The primary outcome of the study is the response to treatment in the operationalization of VGPR or better. Patient-relevant secondary outcomes and outcome categories were overall survival, health status, symptoms, health-related quality of life and AEs.

Data cut-offs

A total of 3 data cut-offs are available for the OCTANS study:

- First data cut-off of 02 July 2020: pre-specified interim analysis, planned 6 months after the last patient received their 1st dose
- Second data cut-off of 16 July 2021: pre-specified safety data cut-off performed for the approval of the subcutaneous administration form of daratumumab in China
- Third data cut-off of 23 December 2022: pre-specified final analysis planned after a maximum of 3 years after the last patient had received their 1st dose

The third data cut-off was used for the present benefit assessment.

Uncertainties of the studies ALCYONE and OCTANS

Uncertainties exist for the included studies ALCYONE and OCTANS. Patients with newly diagnosed multiple myeloma for whom ASCT is not suitable should be included in the studies ALCYONE and OCTANS. However, based on current criteria, patients for whom ASCT may have been suitable were also included. In the OCTANS study, this uncertainty is further increased by the fact that access to ASCT is restricted in the Pacific-Asian health care context. In addition, bortezomib was administered in the comparator arm of the studies in a way that deviated from the specifications of the SPC. The uncertainties and their effects on the benefit assessment are described below.

ASCT suitability and ASCT availability

The therapeutic indication to be assessed of daratumumab + bortezomib + melphalan + prednisone comprises with newly diagnosed multiple myeloma who are ineligible for ASCT. According to the inclusion criteria of the studies ALCYONE and OCTANS, patients younger than 65 years with important comorbidities and patients who were 65 years of age and older were deemed ineligible for ASCT. As already described in dossier assessment A18-66 [18], these criteria were considered suitable for operationalizing the unsuitability of ASCT at the time of study planning. However, the criteria for assessing the ASCT suitability in everyday health care have changed since the start of the two studies. Biological age in good general health is currently considered to be more important than chronological age [23,24]. It is difficult to define a maximum age for ASCT therapy. Instead, individual patient factors must be taken into account when making the decision, taking into account the patient's general condition, existing comorbidities and organ function. Consequently, taking into account current guidelines for the operationalization of ASCZT ineligibility, it is not appropriate to determine ineligibility of ASCT for patients solely on the basis of age (≥ 65 years), as was done in the ALCYONE and OCTANS studies. The European Medicines Agency (EMA) also criticized this during the 2018 approval process for the ALCYONE study and requested data on a post hoc defined subpopulation (ASCT ineligibility), which should largely only include patients with ASCT ineligibility [10]. In addition to the results for the total population, the company therefore also presented results for a post hoc defined subpopulation for both studies, which

represents an approximation to the population for which ASCT is not suitable. This subpopulation comprised the following patients:

- age < 65 years with important comorbidities
- age 65 to 69 years with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) = 2
- ≥ 70 years

543 (77%) patients in the ALCYONE study and 122 (55%) patients in the OCTANS study fulfil these criteria. The chosen procedure for operationalizing the subpopulation (ASCT ineligibility) is comprehensible and is considered a sufficient approximation of the target population. However, both for the total population and for the subpopulations defined post hoc, there is an uncertainty that the proportion of patients for whom ASCT would actually not have been suitable is unclear. The assessment of an ineligibility for ASCT should be determined individually for each patient, without regard to chronological age. However, this assessment was not carried out for the studies ALCYONE and OCTANS and corresponding information can no longer be determined post hoc (e.g. due to missing information on existing comorbidities).

In addition to the uncertainty resulting from the inclusion criteria regarding the unsuitability of ASCT for the study populations of the studies ALCYONE and OCTANS, the company describes an additional uncertainty with regard to the transferability of the study results to the German health care context for the OCTANS study, which was conducted exclusively in the Asia-Pacific region (76% of patients came from China): ASCT is in principle also a treatment option for patients with multiple myeloma in the Asia-Pacific region. However, the company assumed that, particularly in the Chinese health care context, not all patients for whom ASCT would be suitable would actually receive it. This was also shown by estimates from the retrospective analysis of the database of the Worldwide Network of Blood and Marrow Transplantation (WBMT) presented by the company for the years 2006 to 2015 [25], a comparison of data from the Chinese Blood and Marrow Transplantation Registry (CBMTR) [26] with data from the European Society for Blood and Marrow Transplantation (EBMT) registry (both from 2019) [27,28] and the database of the German Centre for Cancer Registry Data [29]. According to these estimates, patients with newly diagnosed multiple myeloma receive ASCT significantly less frequently in China than in Europe or Germany (6% in China vs. 29% in Germany).

Approach of the company and consequences for the benefit assessment

The company states that for the populations defined post hoc via the characteristic of ASCT ineligibility described above and for the total populations in the studies ALCYONE and OCTANS, consistently comparable effect estimates were obtained across all outcomes and that the consideration of the total population of the ALCYONE study for the benefit

assessment was therefore justified. However, due to the additional uncertainty regarding the health care context described above, particularly in China, it only presents the OCTANS study as supplementary information and does not take it into account when deriving the added benefit.

According to the general methods of the Institute [1], studies that do not completely fulfil an inclusion criterion of the research question of interest are used for the benefit assessment if the criterion is fulfilled in at least 80% of the (sub)population of interest of the study. Regardless of the degree of fulfilment (at least 80%, less than 80%), there may be situations in which suitable information on effect modification by the relevant inclusion criterion (population or interventions) is available. In these situations, the inclusion of the study must be decided on the basis of the strength of the effect modification and the proportion of patients who do not fulfil the inclusion criterion, or the degree of deviation of the interventions. In the present case, the subpopulation "ASCT ineligibility" of the studies ALCYONE and OCTANS comprises 77% and 55% of the total population respectively (averaged over both studies 72%), but the operationalization is subject to uncertainty (see above). It is therefore also conceivable that ASCT was unsuitable for more than 80% of the total population of the ALCYONE study and the OCTANS study in accordance with the target population of the research question. In addition, the results for the decision-relevant outcomes are generally very similar between the total population and the "ASCT ineligibility" subpopulation. There was also no effect modification by the characteristic "ASCT ineligibility"/"ASCT eligibility" for any relevant outcome. For this reason, the results of the total population of the studies ALCYONE and OCTANS are used jointly for the present benefit assessment, despite the uncertainty regarding the operationalization of ASZT ineligibility. Although the potential difference in the health care context of the OCTANS study described by the company represents an additional uncertainty, it does not justify an exclusion of the study, taking into account the subgroup analyses presented by the company and the fact that patients from Asia were also included in the ALCYONE study.

Uncertainty regarding the implementation of the ACT

In the comparator arm of both studies, bortezomib was administered at a dosage that differed from that specified in the SPC. The company argues that several studies have shown that the bortezomib dosage regimen deviating from the approval is associated with better tolerability at comparable efficacy. The deviating dosage would also be recommended in international guidelines. Since the approval of daratumumab in the present therapeutic indication, there have been no adjustments to the dosage of bortezomib in either the approval of bortezomib [22] or in the German guideline recommendations [24]. The benefit assessment is carried out within the existing approval. However, in the present benefit assessment, the bortezomib dosage regimen used in the studies ALCYONE and OCTANS is considered to be a sufficient approximation of the approval-compliant application.

Summarized assessment of the studies ALCYONE and OCTANS for the present benefit assessment

The uncertainties of the ALCYONE study already addressed in benefit assessment A18-66 [18], which result from the deviating definition of the suitability of ASCT at baseline compared with the current health care context and from the deviating bortezomib dosage in the comparator arm, also apply to the OCTANS study. In addition, the OCTANS study was conducted exclusively in the Asia-Pacific region and for the most part in China, and there are potential differences in Chinese everyday health care with regard to the implementation of ASCT compared to the German health care context. The uncertainties do not fundamentally call into question the suitability of the studies ALCYONE and OCTANS or the consideration of the total populations in the benefit assessment, but they are taken into account in the certainty of conclusions (see Section I 4.2 and the following text section).

Meta-analysis of the study results

Due to the similar designs and patient characteristics (see below) of the studies ALCYONE and OCTANS, a meta-analytical summary is generally possible and useful. In addition, there was no heterogeneity in the studies in the outcomes relevant for the benefit assessment. In Module 4 A, the company also presents the study results in a meta-analysis due to similar study designs and patient characteristics, but only as supplementary information. In the pooled population of the total populations of both studies, the proportion of patients for whom ASCT was not suitable according to the above criteria was 72% (as described above). See above for the reason why the total population of both studies is nevertheless used.

For the benefit assessment, the total populations of the studies ALCYONE and OCTANS were summarized in a meta-analysis and used for the assessment of added benefit. The post hoc defined subpopulations "ASCT ineligibility" of both studies are not considered further below.

Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone

Study **outcome category** **outcome**	**Planned follow-up observation**
ALCYONE study	
Mortality	
Overall survival	Until death, withdrawal of consent, lost to follow-up or the final data cut-off (whichever occurred first)
Morbidity	
Symptoms (EORTC QLQ-C30)	Until 16 weeks after start of disease progression
Health status (EQ-5D VAS)	Until 16 weeks after start of disease progression
Health-related quality of life	
EORTC QLQ-C30	Until 16 weeks after start of disease progression
Side effects	
All outcomes in the side effects category	Until 30 days after the last administration of the study medication or until the start of subsequent anti-myeloma therapy (whichever occurred first)
Study OCTANS	
Mortality	
Overall survival	Until death, withdrawal of consent, lost to follow-up or the final data cut-off (whichever occurred first)
Morbidity	
Symptoms (EORTC QLQ-C30)	Until 16 weeks after start of disease progression
Health status (EQ-5D VAS)	Until 16 weeks after start of disease progression
Health-related quality of life	
EORTC QLQ-C30	Until 16 weeks after start of disease progression
Side effects	
All outcomes in the side effects category	Until 30 days after the last administration of the study medication or until the start of subsequent anti-myeloma therapy (whichever occurred first)

EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of life Questionnaire – Core 30; RCT: randomized controlled trial; VAS: visual analogue scale

The observation periods for the outcomes of the categories of morbidity, health-related quality of life and side effects were systematically shortened because they were surveyed only until 16 weeks after disease progression (morbidity and health related quality of life), or for the period of treatment with the study medication (plus 30 days or until the start of a subsequent anti-myeloma therapy [side effects]. Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

Characteristics of the study populations

Table 9 shows the characteristics of the patients in the studies included.

Table 9: Characteristics of the study populations as well as discontinuation of study/treatment – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Study characteristic category	ALCYONE		OCTANS	
	daratumumab + bortezomib + melphalan + prednisone	bortezomib + melphalan + prednisone	daratumumab + bortezomib + melphalan + prednisone	bortezomib + melphalan + prednisone
	N[a] = 350	N[a] = 356	N[a] = 146	N[a] = 74
Age [years], mean (SD)	71.3 (6.66)	71.5 (5.82)	69.8 (4.4)	69.7 (4.4)
< 65 years, n (%)	36 (10.3)	24 (6.7)	3 (2.1)	1 (1.4)
65 to < 75 years, n (%)	210 (60.0)	225 (63.2)	120 (82.2)	63 (85.1)
≥ 75 years, n (%)	104 (29.7)	107 (30.1)	23 (15.8)	10 (13.5)
Sex [F/M], %	54.3/45.7	53.1/46.9	41.8/58.2	37.8/62.2
Family origin, n (%)				
White	297 (84.9)	304 (85.4)	0 (0)	0 (0)
Asian	47 (13.5)	45 (12.6)	146 (100)	74 (100)
Other[b]	6 (1.7)[c]	7 (2.0)[c]	0 (0)	0 (0)
ECOG PS, n (%)				
0	78 (22.3)	99 (27.8)	50 (34.2)	21 (28.4)
1	182 (52.0)	173 (48.6)	71 (48.6)	40 (54.1)
2	90 (25.7)	84 (23.6)	25 (17.1)	13 (17.6)
ISS, n (%)				
I	69 (19.7)	67 (18.8)	37 (25.3)	19 (25.7)
II	139 (39.7)	160 (44.9)	68 (46.6)	32 (43.2)
III	142 (40.6)	129 (36.2)	41 (28.1)	23 (31.1)
Disease duration: time from first diagnosis to randomization [months], mean (SD)	1.09 (1.1)	1.27 (1.7)	0.9 (1.3)	0.7 (0.4)
Number of osteolytic lesions, n (%)				
None	71 (20.3)	83 (23.3)	25 (17.1)	12 (16.2)
1–10	145 (41.4)[c]	150 (42.1)[c]	50 (34.2)	28 (37.8)
> 10	134 (38.3)	123 (34.6)	71 (48.6)	34 (45.9)
Cytogenetic risk profile, n (%)	N = 314	N = 302		
Standard risk	261 (83.1)	257 (85.1)	117 (80.7)	54 (73.0)
High risk[d]	53 (16.9)	45 (14.9)	28 (19.3)	20 (27.0)
Treatment discontinuation, n (%)	270 (77.1[c, e])	118 (33.2[c, e])	144 (98.6[c, f])	30 (40.5[c, f])
Study discontinuation, n (%)	220 (62.9)[g])[c]	269 (75.6[g])[c]	43 (29.5[h])[c]	39 (52.7[h])[c]

Table 9: Characteristics of the study populations as well as discontinuation of study/treatment – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Study characteristic category	ALCYONE		OCTANS	
	daratumumab + bortezomib + melphalan + prednisone	bortezomib + melphalan + prednisone	daratumumab + bortezomib + melphalan + prednisone	bortezomib + melphalan + prednisone
	N[a] = 350	N[a] = 356	N[a] = 146	N[a] = 74

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Includes Black, African American and other.
c. Institute's calculation.
d. The assessment of the cytogenetic risk is based on FISH or karyotyping; related to the following high-risk markers: del(17p), t(4;14) and t(14;16).
e. Common reasons for treatment discontinuation in the daratumumab + bortezomib + melphalan + prednisone arm vs. the bortezomib + melphalan + prednisone arm were: disease progression (48% vs. 13%), adverse event (9% vs. 10%), death (8% vs. 2%). In addition, 4 (1.1%) vs. 2 (0.6%) of the randomized patients had not started treatment with the study medication.
f. Common reasons for treatment discontinuation in the daratumumab + bortezomib + melphalan + prednisone arm vs. bortezomib + melphalan + prednisone arm were: disease progression (43 % vs.22 %), adverse event (4 % vs. 5 %), non-compliance to intervention (3 % vs. 7 %). In addition, 2 (1.4%) vs. 3 (4.1%) of the randomized patients had not started treatment with the study medication.
g. Common reasons for study discontinuation in the intervention arm vs. the comparator arm were: death (49% vs. 61%), patient decision (9% vs. 8%) and lost to follow-up (4% vs. 5%).
h. Common reasons for study discontinuation in the intervention arm vs. the comparator arm were: death (23% vs. 31%), patient decision (6% vs. 18%) and lost to follow-up (1% vs. 4.1%).

ECOG PS: Eastern Cooperative Oncology Group Performance Status; f: female; FISH: fluorescence in situ hybridization; ISS: International Staging System; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

ALCYONE

The patient characteristics between the 2 treatment arms of the ALCYONE study are largely comparable. The mean age of the patients was about 71 years, and the majority were White (approximately 85% each). Overall, the proportion of women (approx. 54%) was slightly higher than the proportion of men (approx. 46%) in both study arms. The majority (approx. 75%) of the patients included had an ECOG PS of 0 or 1 and were to be assigned to ISS stage I or II (approx. 60%). The number of osteolytic lesions and the cytogenetic risk profile were largely comparable between the two study arms. At the time of the final data cut-off, there was a difference in treatment discontinuations between the treatment arms (77% vs. 33%). This difference in the final data cut-off is primarily attributable to the longer treatment duration in the intervention arm due to continuous treatment with daratumumab until disease progression or the occurrence of unacceptable toxicity (see Table 7 and Table 10).

OCTANS

Patient characteristics are balanced between the two treatment arms of the OCTANS study. The mean age of the patients was about 70 years, and they were exclusively of Asian family origin. With around 60%, the proportion of men was slightly higher than the proportion of women. The majority (83%) of the included patients had an ECOG PS of 0 or 1 and were assigned to ISS stage I or II (71%). The number of osteolytic lesions was largely comparable between the two study arms. In the cytogenetic risk profile, slightly fewer patients in the intervention arm had a high cytogenetic risk than in the comparator arm (19% vs. 27%). In the OCTANS study, too, more patients had discontinued treatment at the final data cut-off than in the control arm (99% vs. 41%). The higher proportion of treatment discontinuations in the daratumumab arm is plausible, as treatment with daratumumab was to be continued until progression, whereas treatment with bortezomib + melphalan + prednisone in the comparator arm ended after 9 cycles of 6 weeks each (see Table 7).

Study course

Table 10 shows patients' median treatment durations and the median observation period for individual outcomes or outcome categories.

Table 10: Information on the course of the study – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Study **duration of the study phase** **outcome category**	**daratumumab + bortezomib + melphalan + prednisone**	**bortezomib + melphalan + prednisone**
ALCYONE (data cut-off: 31 May 2023)	N = 350	N = 356
Treatment duration [months]	N = 346[a]	N = 354[a]
Median [min; max]	33.0 [0.03; 97.4]	12.0 [0.1; 15.7]
Mean (SD)	41.8 (31.5)	9.6 (4.1)
Observation period [months]	N = 350	N = 356
Overall survival[b]		
Median [min; max]	87.0 [0.0; 97.4]	85.9 [0.1; 97.9]
Mean (SD)	59.2 (30.2)	49.0 (30.0)
Morbidity, health-related quality of life		
EQ-5D VAS		
Median [min; max]	33.9 [ND]	18.9 [ND]
Mean (SD)	ND	ND
EORTC QLQ-C30		
Median [min; max]	33.9 [ND]	18.9 [ND]
Mean (SD)	ND	ND
Side effects	N = 346	N = 354
Median [min; max]	34.0 [ND]	12.9 [ND]
Mean (SD)	ND	ND
OCTANS (data cut-off 23 December 2022)	N = 146	N = 74
Treatment duration [months]	N = 144[a]	N = 71[a]
Median [min; max]	33.8 [0.3; 57.7]	12.0 [0.4; 17.3]
Mean (SD)	28.4 (15.9)	9.9 (4.2)
Observation period [months]	N = 146	N = 74
Overall survival[b]		
Median [min; max]	41.3 [0.1; 59.9]	40.7 [0.0; 58.7]
Mean (SD)	36.5 (15.1)	30.3 (16.7)
Morbidity, health-related quality of life		
EQ-5D VAS		
Median [min; max]	31.7 [ND]	13.8 [ND]
Mean (SD)	ND	ND
EORTC QLQ-C30		
Median [min; max]	31.7 [ND]	13.8 [ND]
Mean (SD)	ND	ND
Side effects	N = 144[a]	N = 71[a]
Median [min; max]	34.7 [ND]	12.9 [ND]

Table 10: Information on the course of the study – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Study **duration of the study phase** **outcome category**	**daratumumab + bortezomib + melphalan + prednisone**	**bortezomib + melphalan + prednisone**
Mean (SD)	ND	ND

a. For the treatment duration and the treatment duration of the side effects, only patients who received treatment were analysed.
b. The calculation was probably performed using the inverse Kaplan-Meier method.

EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of analysed patients; ND: no data; QLQ-C30: Quality of Life Questionnaire – Core 30; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

The median treatment durations in the ALCYONE and OCTANS studies are significantly longer (33.0 and 33.8 months respectively) in the intervention arm than in the comparator arm (12.0 months each). This is mainly due to the fact that in the intervention arm, treatment with daratumumab was continued until disease progression or the occurrence of unacceptable toxicity, whereas in the comparator arm, treatment was limited to a maximum of 9 cycles.

The median observation duration for the outcome of overall survival was comparable between the study arms in the studies ALCYONE and OCTANS. However, due to the shorter study duration in the OCTANS study with a median duration of around 41 months, it was significantly shorter than in the ALCYONE study (median 85.9 to 87.0 months).

For all other outcomes, the observation durations in the studies ALCYONE and OCTANS were both significantly shorter overall compared with the observation duration of the outcome of overall survival and also differed greatly between the treatment groups, with shorter observation durations in the comparator arms. For example, the fixed treatment duration in the comparator arm and the linking of the observation period for side effects to the treatment duration led to a notably longer observation period for the outcomes of the categories of side effects in the intervention arm (median 34.0 to 34.7 months) than in the comparator arm (median 12.9 months) of the two studies. These differences in observation times are taken into account when deriving the outcome-specific risk of bias for the outcomes in the side effects category (see Section I 4.2).

Subsequent therapies

In the dossier, the company presents information on follow-up therapies both at drug level aggregated across all lines of therapy and in the form of treatment regimens in the individual lines of therapy. In order to assess guideline-compliant use, information on the treatment regimens used in the individual lines of therapy is preferable to information on the drug level

aggregated across all lines of therapy in this therapeutic indication. In the ALCYONE study, up to 8 follow-up therapies were administered in the intervention arm and up to 7 in the comparator arm at the data cut-off of 23 May 2023. In the OCTANS study, a maximum of 4 follow-up therapies were administered in the intervention arm and a maximum of 7 in the comparator arm at the data cut-off of 23 December 2023. Overall, the number of patients with more than 2 follow-up therapies had decreased considerably compared to the previous lines of therapy. For this reason, only data on the 1st and 2nd follow-up therapy are shown in Table 11.

Table 11: : Information on the 1st and 2nd follow-up therapy directed against the multiple myeloma (≥ 2% of patients in ≥ 1 treatment arm) - RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Study **treatment regimen**[a]	**Patients with subsequent therapy, n (%)**	
	daratumumab + bortezomib + melphalan + prednisone	**bortezomib + melphalan + prednisone**
ALCYONE study[b] **(data cut-off 31 May 2023)**	**N = 346**	**N = 354**
First subsequent therapy		
Total	150 (43.4)	243 (68.6)
Dexamethasone + lenalidomide	39 (26.0[c]	63 (25.9[c]
Carfilzomib + dexamethasone + lenalidomide	13 (8.7[c]	15 (6.2[c]
Dexamethasone + ixazomib + lenalidomide	10 (6.7[c]	5 (2.1[c]
Cyclophosphamide + dexamethasone + thalidomide	6 (4.0[c]	16 (6.6[c]
Lenalidomide	5 (3.3[c]	8 (3.3[c]
Bortezomib + cyclophosphamide + dexamethasone	4 (2.7[c]	9 (3.7[c]
Daratumumab + dexamethasone + lenalidomide	1 (0.7[c]	18 (7.4[c]
Dexamethasone + lenalidomide + elotuzumab	1 (0.7[c]	8 (3.3[c]
Bortezomib + daratumumab + dexamethasone	0 (0[c])	11 (4.5[c]
Second subsequent therapy		
Total	70 (20.2)	117 (33.1)
Dexamethasone + lenalidomide	7 (10.0[c]	18 (15.4[c]
Daratumumab + dexamethasone + lenalidomide	0 (0[c])	11 (9.4[c]
Cyclophosphamide + dexamethasone + pomalidomide	7 (10.0[c]	3 (2.6[c]
Dexamethasone + pomalidomide	9 (12.9[c]	13 (11.1[c]

Table 11: : Information on the 1st and 2nd follow-up therapy directed against the multiple myeloma (≥ 2% of patients in ≥ 1 treatment arm) - RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Study **treatment regimen**[a]	**Patients with subsequent therapy, n (%)**	
	daratumumab + bortezomib + melphalan + prednisone	**bortezomib + melphalan + prednisone**
OCTANS study[b] **(data cut-off 23 December 2022)**	**N = 144**	**N = 71**
First subsequent therapy		
Total	54 (37.5)	45 (63.4)
Bortezomib + dexamethasone + lenalidomide	7 (13.0[c])	1 (2.2[c])
Carfilzomib + dexamethasone + lenalidomide	5 (9.3[c])	3 (6.7[c])
Bortezomib	4 (7.4[c])	1 (2.2[c])
Cyclophosphamide + dexamethasone + lenalidomide	3 (5.6[c])	0 (0[c])
Dexamethasone + ixazomib + lenalidomide	3 (5.6[c])	4 (8.9[c])
Dexamethasone + lenalidomide	3 (5.6[c])	4 (8.9[c])
Dexamethasone + ixazomib citrate + lenalidomide	2 (3.7[c])	2 (4.4[c])
Daratumumab	1 (1.9[c])	2 (4.4[c])
Lenalidomide	1 (1.9[c])	2 (4.4[c])
Daratumumab + dexamethasone + lenalidomide	0 (0[c])	3 (6.7[c])
Dexamethasone acetate + lenalidomide	0 (0[c])	3 (6.7[c])
Dexamethasone + investigational product + lenalidomide	0 (0[c])	2 (4.4[c])
Second subsequent therapy		
Total	13 (9.0)	15 (21.1)
Dexamethasone + lenalidomide	3 (23.1[c])	0 (0[c])
Daratumumab + dexamethasone + lenalidomide	0 (0[c])	2 (13.3[c])
Dexamethasone acetate + lenalidomide	1 (7.7[c])	2 (13.3[c])

a. The follow-up therapies are shown according to the entry in the eCRF.
b. Safety population: defined as the population of all study participants who have received the study medication at least once.
c. Institute's calculation based on the proportion of patients with follow-up therapy.

eCRF: electronic case report form; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

In the ALCYONE study, 43% of the patients in the intervention arm and 69% of the patients in the comparator arm had received at least one follow-up treatment of the multiple myeloma at the final data cut-off. Around half of these patients received a second follow-up treatment in each treatment arm.

In the OCTANS study, the proportion of patients with follow-up therapy was 38% in the intervention arm and 63% in the comparator arm. Just over a quarter of these patients had a second follow-up treatment.

According to the current S3 guideline, various active substances in different combinations are available for the treatment of patients with multiple myeloma in the 1st to 3rd recurrence. The choice of treatment must be made on a patient-specific basis and depends on disease-, patient- and therapy-specific factors [24]. Therefore, all drug classes are usually used and combined in an individual sequence. Nevertheless, the S3 guideline strongly recommends triple combination therapy with 2 of 3 new substances (monoclonal antibody, immunomodulator, proteasome inhibitor) and a steroid for multiple myeloma in the 1st relapse, taking into account the increased toxicity [24]. In addition, the importance of daratumumab was addressed in the oral hearing on daratumumab in combination with lenalidomide and dexamethasone in the present therapeutic indication from the 1st relapse in the German health care context [30]. A considerable added benefit was also declared for daratumumab in combination with lenalidomide and dexamethasone or with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have already received at least 1 therapy [31-34].

The company's information in the dossier shows that in the ALCYONE study, 159 (40%) of 393 patients with follow-up therapy received a double combination in the first follow-up therapy and 177 (45%) received a triple combination. In the OCTANS study, 21 (21%) of 99 patients with follow-up therapy received a double combination in the first follow-up therapy and 51 (52%) received a triple combination. Overall, the studies ALCYONE and OCTANS did not regularly use triple combinations, but a relevant proportion (21% to 40% of patients in the first follow-up therapy) used double combinations. It is unclear whether a triple combination in accordance with the recommendations of the S3 guideline would not have been suitable for a larger proportion of patients and whether they would have benefited from it.

In addition, the composition of the triple combinations administered did not comply with the recommendations of the S3 guideline to a relevant extent, particularly in the first follow-up therapy. In the ALCYONE study, 72 of 177 patients (41%) received a triple combination that did not correspond to the recommendation of the S3 guideline (e.g. cyclophosphamide + dexamethasone + thalidomide). In the OCTANS study, 13 out of 51 patients (25%) were administered triple combinations in the first follow-up therapy that were not recommended by the guidelines. Overall, a relevant proportion of patients received a follow-up therapy in the first follow-up therapy that did not comply with the guideline recommendation.

The company's information in the dossier also shows that the use of daratumumab as a follow-up therapy in the comparator arm was low across all lines of therapy in both the ALCYONE study and the OCTANS study. In the ALCYONE study, for example, only 93 (38%) of 243 patients

with follow-up therapy in the comparator arm received daratumumab as follow-up therapy. In the OCTANS study, this even applied to as few as 9 (20%) of 45 patients in the comparator arm. Overall, in the comparator arms of the studies ALCYONE and OCTANS, daratumumab was therefore used in a very small proportion of patients compared to the current health care context, and in some cases only in a later line of therapy, whereas in the intervention arm all patients received a daratumumab-based therapy in the first line.

All things considered, the described deficiencies in the follow-up therapies administered in the studies ALCYONE and OCTANS are considered to be serious. The serious deficiencies regarding the follow-up therapies used are taken into account for the outcome of overall survival in the assessment of the risk of bias and in the determination of the extent (see Section I 4.2).

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (at study level) – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
ALCYONE	Yes	Yes	No	No	Yes	Yes	Low
OCTANS	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for both studies.

Limitations resulting from the open-label study design are described in Section I 4.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company stated that the ALCYONE study was conducted in 25 countries. The vast majority of patients (83% of the total population) came from Europe. The OCTANS study is a bridging study to the ALCYONE study, which is being conducted in China, Hong Kong, Malaysia, South Korea and Taiwan to investigate the efficacy and safety of daratumumab in combination with bortezomib, melphalan and prednisone in a patient population from the Asia-Pacific region.

The demographic characteristics show that all participants included in the OCTANS study were of Asian family origin.

According to the company, there are no indications of biodynamic or kinetic differences between the individual population groups and Germany for either the ALCYONE study or the OCTANS study to the extent that they would have a significant impact on the study results. Therefore, the company assumes that under consideration of the uncertainty associated with the transferability of clinical data, the results are in principle transferable to the German health care context.

Due to the circumstances of the health care context with regard to ASCT ineligibility, there is greater uncertainty overall in the OCTANS study. It cannot be ruled out that, according to the standards of the German health care context in comparison with the Asia-Pacific health care context, some patients in the OCTANS study would have been assessed as eligible for ASCT. Due to the uncertainty regarding the unsuitability of ASCT in the study population of the OCTANS study and the associated questionable transferability to the German health care context, it did not use the OCTANS study to derive the added benefit.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also Section I 3.2.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - Overall survival
- Morbidity
  - Symptoms recorded using the EORTC QLQ-C30
  - Health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - Recorded with the EORTC QLQ-C30
- Side effects
  - SAEs
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Infusion related reaction
  - Peripheral neuropathy (HLT, severe AEs)
  - Other specific AEs, if any

The choice of patient-relevant outcomes deviates from that taken by the company, which used other outcomes in the dossier (Module 4 A).

Table 13 shows the outcomes for which data were available in the studies included.

Table 13: Matrix of outcomes – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone

Study	Outcomes									
	Overall survival	Symptoms (EORTC QLQ-C30)	health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs[a]	Severe AEs[a, b]	Discontinuation due to AEs[a]	Infusion related reaction	Peripheral neuropathy (HLT, severe AEs)	Further specific AEs[c]
ALCYONE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[d]	Yes	Yes
OCTANS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[d]	Yes	No

a. Although the SOC "neoplasms benign, malignant and unspecified (including cysts and polyps)" is included in the outcomes on side effects, the majority of these are secondary primary tumours (e.g. basal cell carcinoma).
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The following events are considered (MedDRA coding): infections and infestations (SOC, severe AEs), vascular diseases (SOC, severe AEs), respiratory tract, chest and mediastinum (SOC, AEs).
d. The analysis presented by the company is unsuitable for the benefit assessment, but the events underlying the outcome are recorded via the specific AEs. For justification, see the following text section
e. Further specific AEs are selected exclusively on the basis of the ALCYONE study; for justification, see the following text section.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HLT: high level term; MedDRA: Medical Dictionary for Regulatory Activities; QLQ-C30: Quality of life Questionnaire – Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

Analyses on the outcome of overall survival

With Amendment 8 of the study protocol of 02 June 2021, the number of events for the final analysis of overall survival was increased from 330 to 382 events and the originally planned end of the study 5 years after randomization of the last patient was not adhered to (see Section I 2). The company cites the achievement of median overall survival in both treatment arms as the reason for the increase in the planned number of events. Since the achievement of median overall survival is not considered mandatory for a final study analysis, the G-BA commissioned a sensitivity analysis on the outcome of overall survival with censoring of all patients after the occurrence of 330 events in order to be able to assess a potential bias due

to the subsequent increase in the necessary number of events in the outcome of overall survival for the final study analysis.

For the outcome "overall survival" of the ALCYONE study, the company therefore presented not only the analysis on the final data cut-off of 23 May 2023 (after 382 deaths) it used to derive the added benefit, but also the originally planned final analysis requested by the G-BA after the occurrence of the 330 events (see Section I 2). According to the justifications on the decision [35,36] of 02 December 2021, the 330 events were reached on 14 October 2021.

The decision to postpone the final analysis to the time point of approximately 382 death events under Amendment 8 to the study protocol was made with knowledge of the data and thus potentially event-driven. In the present benefit assessment, both the results of the sensitivity analysis requested by the G-BA and the final analysis on the data cut-off of 31 May 2023 are presented and each summarized in a meta-analysis with the results from the OCTANS study. For the derivation of the added benefit, the results on overall survival after reaching the originally planned 330 events are primarily used.

Analyses of patient-reported outcomes on morbidity and health-related quality of life

In its dossier, the company presents responder analyses for the patient-reported outcomes on morbidity and health-related quality of life, recorded with the EORTC QLQ-C30 instrument, for the proportion of patients with a first improvement or a first deterioration by ≥ 10 points (scale range 0 to 100) at the final data cut-off. Due to the expected progressive course of disease in the present therapeutic indication, an analysis on the deterioration of symptoms and health-related quality of life is primarily relevant for the present benefit assessment. Therefore, the time to first deterioration by ≥ 10 points is used for the present benefit assessment. The time to first deterioration by ≥ 15 points is used for the outcome “health status” recorded using the EQ-5D VAS

Outcomes in the side effects category

SAEs and discontinuation due to AEs

In the ALCYONE study, it was planned to observe outcomes in the side effects category up to 30 days beyond the end of treatment (see Table 8). With a planned treatment of 6 chemotherapy cycles of 42 days each (about 13.5 months), this corresponds to a maximum observation period of about 15 months in the comparator arm. A look at the respective Kaplan-Meier curve of the control arm of the ALCYONE study shows that 2 patients were considered in the outcome “SAEs” and 1 patient in the outcome “discontinuation due to AEs” (≥ 1 treatment component) as if they had been under observation for more than 42 months. This is not plausible. The Kaplan-Meier curve of the comparator arm for “discontinuation due to AEs” (all treatment components) also shows no person who was still at risk after 18 months. The estimate of the median time to event in the comparator arm resulting from these

individual patients is therefore not shown in Table 15 for the outcomes of SAEs, discontinuation due to AEs (at least 1 treatment component) and infections and infestations (SOC, severe AEs).

Infusion related reaction

The analyses presented by the company for the outcome "infusion-related reaction" are not suitable for the benefit assessment. An infusion-related reaction was documented as event related to the infusion of daratumumab in the electronic case report form (eCRF) of the included studies ALCYONE and OCTANS. However, since no placebo infusion was administered in the comparator arm, infusion-related reactions cannot occur in the comparator arm. A comparison between the study arms is therefore not possible on the basis of this outcome.

In the studies included, the events underlying the outcome "infusion-related reactions" are also included in the analyses on AEs (overall rates and specific AEs). Some specific AEs can be inferred to constitute infusion-related reactions since (1) they are plausible symptoms of cytokine release syndrome (e.g. preferred term [PT] dyspnoea, coughing, irritated throat and bronchospasm from SOC respiratory, thoracic and mediastinal disorders) and (2) they typically occur early at the time of the first infusion with daratumumab (see Kaplan-Meier curves in Appendix C of the full dossier assessment). Where a statistically significant difference between treatment groups is found for these specific AEs and the frequency thresholds shown in Appendix D of the full dossier assessment are exceeded, the events underlying the outcome of infusion-related reaction are therefore depicted by specific AEs in this benefit assessment (see Table 15).

Other specific AEs

In the dossier, the company presents event time analyses for AEs, SAEs and severe AEs at SOC and PT level separately for the studies ALCYONE and OCTANS. However, there are no meta-analyses on outcomes in the category of side effects at SOC and PT level. Meta-analyses cannot be calculated in full by the Institute, as no event time analysis is available for approx. 1 third of the potentially relevant further specific AEs for one of the two studies. In addition, neither data on the effect estimate nor on statistical significance are available for outcomes with 0 events in one treatment arm (e.g. the PTs bronchitis, chest discomfort or chills in the OCTANS study). The statistical significance of the event time analyses can be assessed using the log-rank test. The Firth correction for the Cox model [37-40] in combination with profile likelihood methods for the 95% CI offers one way of obtaining point and interval estimates.

Since a meta-analysis for the other specific AEs is not possible on the basis of the available data, the other specific AEs of the ALCYONE study are considered as an approximation and used for the benefit assessment. This appears justified in the present data situation, as it can be excluded with sufficient certainty that the addition of the results from the OCTANS study

would yield substantially different or further relevant specific AEs to the advantage or disadvantage of daratumumab + bortezomib + melphalan + prednisone compared to bortezomib + melphalan + prednisone (see I Appendix D.1 and I Appendix D.2).

The events in the PT COVID-19 are not suitable for deriving a conclusion, as these were only recorded in the intervention arm due to the late occurrence of the pandemic in the course of the study and the clearly longer observation period in this arm.

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias - RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone

Study	Study level	Outcomes									
		Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Infusion-related reaction	Peripheral neuropathy (HLT, severe AEs)	Further specific AEs[a, b]
ALCYONE	L	H[c]	H[d, e]	H[d, e]	H[d, e]	H[e]	H[e]	H[d, e]	–[f]	H[d, e]	H[d, e]
OCTANS	L	H[c]	H[d, e]	H[d, e]	H[d, e]	H[e]	H[e]	H[d, e]	–[f]	H[d, e]	–[g]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
f. The following events are considered (coded according to MedDRA): infections and infestations (SOC, severe AEs), vascular disorders (SOC, severe AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs).
c. Due to uncertainties in the use of adequate follow-up therapies.
d. Lack of blinding in subjective outcome or subjective recording of outcomes; applies to the other specific AEs for respiratory, thoracic and mediastinal disorders (SOC, AEs).
e. Shortened observation period for potentially informative reasons.
f. The analysis presented by the company is not suitable for the benefit assessment; however, the events underlying the outcome are recorded via the specific AEs. See Section I 4.1 of the present benefit assessment for the reasoning.
g. Further specific AEs are selected exclusively on the basis of the ALCYONE study. See Section I 4.1 of the present benefit assessment for the reasoning.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; HLT: High Level Term; L: low; MedDRA: Medical Dictionary for Regulatory Activities; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

All results suitable for deriving the added benefit have a high risk of bias. The risk of bias of the results on the outcome of overall survival is rated as high mainly due to the very low use of daratumumab in the administered follow-up therapies in the comparator arm (see follow-up therapies in Section I 3.2).

The observation periods of all other outcomes are shortened due to potentially informative reasons and the results are therefore potentially highly biased. The surveying of questionnaires was linked to disease progression, while the collection of side effects events was linked to the end of treatment (see Table 8). The effect estimates for side effects are therefore also based exclusively on data from approximately the first 14 months of the two studies, whereas, for example, the median observation periods for overall survival are around 85 months (ALCYONE) and around 40 months (OCTANS) (see Table 10). All results on subjective outcomes or outcomes with subjective recording of outcomes, such as the outcomes recorded by questionnaire, the outcome of discontinuation due to AEs and the specific AE "respiratory, thoracic and mediastinal disorders" (SOC, AEs) also have a high risk of bias due to the unblinded study design.

Summary assessment of the certainty of conclusions

Due to the high risk of bias of the results of all included outcomes, at most hints, for example of an added benefit, can be derived at the individual study level. For the outcome of overall survival, taking into account the described serious deficiencies in the administered follow-up therapies (see Section I 3.2), it also results that the observed effect is considered as non-quantifiable in the present data situation. As a rule, when the results of the studies ALCYONE and OCTANS studies are summarized in a meta-analysis, at most indications, for example of an added benefit, can be derived. However, due to the reasons described in Section I 3.2, which limit the transferability of the results to the German healthcare context, the reliability of conclusions is reduced. Overall, based on a meta-analytical summary of the results of the studies ALCYONE and OCTANS, at most hints, for example of an added benefit, can be derived.

I 4.3 Results

Table 15 summarizes the results of the comparison of daratumumab + bortezomib + melphalan + prednisone with bortezomib + melphalan + prednisone in patients with newly diagnosed multiple myeloma who are ineligible for ASCT. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier. The meta-analytical summary of the results of the studies ARC003 and ARC010 were used.

The figure on the meta-analysis calculated by the Institute for the outcome of overall survival can be found in I Appendix B of the full dossier assessment. The Kaplan-Meier curves for the time-to-event analyses of the outcomes in the included studies are shown in I Appendix C of the full dossier assessment. The results on common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in I Appendix D of the full dossier assessment.

Table 15: : Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Outcome category **outcome** **study**	**Daratumumab + bortezomib + melphalan + prednisone**		**Bortezomib + melphalan + prednisone**		**Daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone**
	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]**
Mortality					
Overall survival, originally planned final analysis on overall survival of the ALCYONE[b] study					
ALCYONE	350	NA 143 (40.9)	356	53.59 [46.32; 60.91] 187 (52.5)	0.66 [0.53; 0.82]; < 0.001[c]
OCTANS	146	NA [54.67; NC] 33 (22.6)	74	NA [41.49; NC] 23 (31.1)	0.60 [0.35; 1.03]; 0.060[c]
Total					0.65 [0.53; 0.80]; < 0.001[d]
Overall survival, final analysis on overall survival of the ALCYONE[e] study					
ALCYONE	350	82.96 [72.48; NC] 172 (49.1)	356	53.59 [46.32; 60.91] 217 (61.0)	0.65 [0.53; 0.80]; < 0.001[c]
OCTANS	146	NA [54.67; NC] 33 (22.6)	74	NA [41.49; NC] 23 (31.1)	0.60 [0.35; 1.03]; 0.060[c]
Total					0.64 [0.53; 0.78]; < 0.001[f]
Morbidity					
Symptoms (EORTC QLQ-C30 – time to first deterioration[g])					
Fatigue					
ALCYONE	350	45.93 [24.05; 68.83] 137 (39.1)	356	17.05 [11.60; 33.38] 135 (37.9)	0.78 [0.61; 1.00]; 0.049
OCTANS	146	17.97 [8.41; 34.86] 74 (50.7)	74	8.80 [5.55; NC] 34 (45.9)	0.71 [0.46; 1.09]; 0.117
Total					0.76 [0.61; 0.94]; 0.013[f]
Nausea and vomiting					
ALCYONE	350	77.31 [59.40; NC] 109 (31.1)	356	NA [33.74; NC] 95 (26.7)	0.87 [0.66; 1.16]; 0.344
OCTANS	146	51.19 [33.02; NC] 49 (33.6)	74	NC [21.78; NC] 16 (21.6)	1.18 [0.65; 2.14]; 0.588
Total					0.92 [0.71; 1.19]; 0.521[f]

Table 15: : Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Outcome category **outcome** **study**	**Daratumumab + bortezomib + melphalan + prednisone**		**Bortezomib + melphalan + prednisone**		**Daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone**
	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]**
Pain					
ALCYONE	350	79.47 [44.65; NC] 118 (33.7)	356	33.38 [18.14; 39.88] 116 (32.6)	0.75 [0.57; 0.98]; 0.033
OCTANS	146	44.09 [18.20; NC] 62 (42.5)	74	27.43 [11.14; NC] 25 (33.8)	1.01 [0.62; 1.64]; 0.966
Total					0.80 [0.64; 1.02]; 0.072[f]
Dyspnoea					
ALCYONE	350	58.32 [34.56; NC] 125 (35.7)	356	NA [33.64; NC] 91 (25.6)	1.07 [0.81; 1.41]; 0.623
OCTANS	146	NA [33.71; NC] 51 (34.9)	74	NC [21.55; NC] 18 (24.3)	1.21 [0.69; 2.10]; 0.502
Total					1.10 [0.86; 1.41]; 0.467[f]
Insomnia					
ALCYONE	350	44.16 [31.38; 63.05] 132 (37.7)	356	45.67 [25.10; NC] 111 (31.2)	0.90 [0.69; 1.16]; 0.410
OCTANS	146	NA [17.35; NC] 59 (40.4)	74	17.51 [11.11; NC] 29 (39.2)	0.82 [0.52; 1.30]; 0.409
Total					0.88 [0.70; 1.10]; 0.267[f]
Appetite loss					
ALCYONE	350	NA [36.01; NC] 116 (33.1)	356	55.13 [34.59; NC] 93 (26.1)	0.98 [0.74; 1.30]; 0.896
OCTANS	146	49.54 [33.02; NC] 51 (34.9)	74	NA [11.11; NC] 23 (31.1)	0.84 [0.51; 1.39]; 0.488
Total					0.94 [0.74; 1.21]; 0.648[f]
Constipation					
ALCYONE	350	NC [52.96; NC] 108 (30.9)	356	NA [39.88; NC] 92 (25.8)	0.88 [0.66; 1.18]; 0.394
OCTANS	146	NA [32.89; NC] 48 (32.9)	74	24.02 [22.05; NC] 21 (28.4)	0.85 [0.50; 1.45]; 0.548
Total					0.87 [0.68; 1.13]; 0.297[f]

Table 15: : Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Outcome category **outcome** **study**	**Daratumumab + bortezomib + melphalan + prednisone**		**Bortezomib + melphalan + prednisone**		**Daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone**
	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]**
Diarrhoea					
ALCYONE	350	NA [62.39; NC] 104 (29.7)	356	NA 81 (22.8)	0.96 [0.71; 1.30]; 0.806
OCTANS	146	NA [33.68; NC] 47 (32.2)	74	NA [22.05; NC] 15 (20.3)	1.07 [0.58; 1.97]; 0.827
Total					0.98 [0.75; 1.29]; 0.888[f]
Health status (EQ-5D VAS - time to first deterioration[h])					
ALCYONE	350	NA 72 (20.6)	356	NA [55.79; NC] 67 (18.8)	0.81 [0.57; 1.14]; 0.217[c]
OCTANS	146	NA 37 (25.3)	74	NA [32.85; NC] 13 (17.6)	1.00 [0.52; 1.91]; 0.995[c]
Total					0.85 [0.62; 1.15]; 0.293[f]
Health-related quality of life					
EORTC QLQ-C30 – time to first deterioration[i]					
Global health status					
ALCYONE	350	85.78 [68.83; NC] 105 (30.0)	356	44.45 [29.44; 66.89] 106 (29.8)	0.72 [0.55; 0.95]; 0.023
OCTANS	146	44.09 [32.72; NC] 51 (34.9)	74	27.43 [22.05; NC] 22 (29.7)	0.78 [0.47; 1.31]; 0.354
Total					0.73 [0.58; 0.93]; 0.012[f]
Physical functioning					
ALCYONE	350	NA [61.08; NC] 102 (29.1)	356	39.88 [32.66; NC] 98 (27.5)	0.76 [0.57; 1.01]; 0.063
OCTANS	146	44.09 [32.92; NC] 51 (34.9)	74	NA [18.37; NC] 19 (25.7)	1.08 [0.63; 1.85]; 0.791
Total					0.82 [0.64; 1.06]; 0.126[f]

Table 15: : Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Outcome category **outcome** **study**	**Daratumumab + bortezomib + melphalan + prednisone**		**Bortezomib + melphalan + prednisone**		**Daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone**
	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]**
Role functioning					
ALCYONE	350	45.90 [28.06; 62.23] 134 (38.3)	356	25.04 [16.85; 39.88] 126 (35.4)	0.83 [0.64; 1.06]; 0.138
OCTANS	146	NA [33.68; NC] 54 (37.0)	74	27.43 [8.80; NC] 27 (36.5)	0.71 [0.43; 1.15]; 0.162
Total					0.80 [0.64; 1.01]; 0.056[f]
Emotional functioning					
ALCYONE	350	NC [60.62; NC] 100 (28.6)	356	55.79 [45.67; NC] 79 (22.2)	0.89 [0.65; 1.21]; 0.451
OCTANS	146	NA [33.71; NC] 45 (30.8)	74	NA 15 (20.3)	1.01 [0.55; 1.85]; 0.972
Total					0.91 [0.69; 1.20]; 0.522[f]
Cognitive functioning					
ALCYONE	350	22.67 [11.50; 31.84] 166 (47.4)	356	23.36 [11.76; 25.10] 134 (37.6)	0.98 [0.77; 1.25]; 0.863
OCTANS	146	16.62 [8.77; 28.35] 76 (52.1)	74	20.37 [8.35; NC] 29 (39.2)	0.98 [0.63; 1.53]; 0.948
Total					0.98 [0.79; 1.21]; 0.852[f]
Social functioning					
ALCYONE	350	60.35 [28.02; NC] 131 (37.4)	356	34.30 [17.91; 61.01] 114 (32.0)	0.89 [0.69; 1.16]; 0.388
OCTANS	146	21.88 [11.24; 33.61] 71 (48.6)	74	21.52 [8.35; NC] 28 (37.8)	0.90 [0.57; 1.43]; 0.667
Total					0.89 [0.71; 1.12]; 0.324[f]

Table 15: : Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Outcome category **outcome** **study**	**Daratumumab + bortezomib + melphalan + prednisone**		**Bortezomib + melphalan + prednisone**		**Daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone**
	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]**
Side effects[j]					
AEs (supplementary information)					
ALCYONE	346	0.20 [0.13; 0.26] 338 (97.7)	354	0.26 [0.26; 0.33] 342 (96.6)	–
OCTANS	144	0.03 [0.03; 0.07] 144 (100.0)	71	0.16 [0.10; 0.20] 71 (100.0)	–
SAEs					
ALCYONE	346	35.91 [23.46; 52.27] 186 (53.8)	354	–[k] 117 (33,1)	1.17 [0.91; 1.50]; 0.216
OCTANS	144	20.96 [10.64; NC] 75 (52.1)	71	NC [NC; NC] 28 (39.4)	1.12 [0.72; 1.75]; 0.620
Total					1.16 [0.93; 1.44]; 0.187[f]
Severe AEs[l]					
ALCYONE	346	0.61 [0.49; 0.95] 291 (84.1)	354	0.95 [0.72; 1.08] 277 (78.2)	1.07 [0.90; 1.27]; 0.459
OCTANS	144	0.38 [0.26; 0.46] 133 (92.4)	71	0.66 [0.33; 0.82] 61 (85.9)	1.32 [0.96; 1.82]; 0.084
Total					1.12 [0.96; 1.31]; 0.138[f]
Discontinuation due to AEs (at least 1 therapy component)					
ALCYONE	346	NA 46 (13.3)	354	–[k] 40 (11,3)	0.81 [0.51; 1.29]; 0.382
OCTANS	144	NA 20 (13.9)	71	NC [NC; NC] 6 (8.5)	1.38 [0.55; 3.51]; 0.495
Total					0.90 [0.60; 1.36]; 0.623[f]
Specific AEs					
Infusion related reaction					
ALCYONE				No suitable data[m]	
OCTANS					

Table 15: : Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Outcome category **outcome** **study**	**Daratumumab + bortezomib + melphalan + prednisone**		**Bortezomib + melphalan + prednisone**		**Daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone**
	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]**
Peripheral neuropathy (HLT, severe AEs)					
ALCYONE	346	NA 10 (2.9)	354	NA 18 (5.1)	0.55 [0.25; 1.19]; 0.128
OCTANS	144	NA 5 (3.5)	71	NA 2 (2.8)	1.09 [0.21; 5.66]; 0.919
Total					0.62 [0.31; 1.26]; 0.189
Infections and infestations (SOC, severe AEs)					
ALCYONE	346	NA [76.52; NC] 108 (31.2)	354	–[k] 53 (15.0)	1.43 [1.002; 2.04]; 0.048
Vascular disorders (SOC, severe AEs)					
ALCYONE	346	NA 32 (9.2)	354	NA 8 (2.3)	2.38 [1.04; 5.44]; 0.040
Respiratory, thoracic, and mediastinal disorders (SOC, AEs)					
ALCYONE	346	47.77 [31.08; NC] 154 (44.5)	354	NA 74 (20.9)	1.94 [1.45; 2.60]; p < 0.001

Table 15: : Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Outcome category **outcome** **study**	**Daratumumab + bortezomib + melphalan + prednisone**		**Bortezomib + melphalan + prednisone**		**Daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone**
	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]**

a. HR, CI and p-value: Cox proportional hazard model stratified by ISS stage (I vs. II vs. III) and age (< 75 years vs. ≥ 75 years), in the ALCYONE study also by region (Europe vs. other).
b. Taking into account the originally planned analysis of 330 death events in the ALCYONE study. According to the justification on the decision [35,36] of 02 December 2021, the 330 events were reached on 14 October 2021.
c. p-value: log-rank test, stratified by ISS stage (I vs. II vs. III) and age (< 75 years vs. ≥ 75 years), in the ALCYONE study also by region (Europe vs. other).
d. Institute's calculation of an FEM meta-analysis.
e. Taking into account the final data cut-off of the ALCYONE study after approx. 382 death events (data cut-off of 31 May 2023).
f. FEM meta-analysis of the company based on the aggregate effect estimation of the studies ALCYONE and OCTANS.
g. A score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100).
h. A score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range of 0 to 100).
i. A score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range of 0 to 100).
j. When interpreting the results on side effects, it should be noted that the substantially shorter planned treatment duration and the associated discontinuation of follow-up in the comparator arm result in the HR reflecting only approximately the first 14 months after randomization.
k. No plausible information (see Section I 4.1).
l. Operationalized as CTCAE grade ≥ 3.
m. See Section I 4.1 for reasons.

CI: confidence interval; EORTC: European Organization for Research and Treatment of Cancer; FEM: Fixed effects model (fixed effect meta-analysis); HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section I 3.1, I 3.2 and I 4.2 for reasoning).

Mortality

Overall survival

For the outcome of overall survival, both the meta-analysis of the originally planned final analysis on overall survival after 330 events (relevant for the benefit assessment, see Section I 4.1) and the meta-analysis of the final analysis on overall survival showed a statistically significant difference in favour of daratumumab + bortezomib + melphalan + prednisone. For the outcome "overall survival", there is a hint of added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone.

Morbidity

Symptoms (EORTC QLQ-C30)

Fatigue

The meta-analysis shows a statistically significant difference in favour of daratumumab + bortezomib + melphalan + prednisone for the outcome of fatigue. However, the difference is no more than marginal for this outcome in the category of non-serious/non-severe symptoms/late complications. For the outcome "fatigue", there is no hint of an added benefit of daratumumab + bortezomib + melphalan + prednisone versus bortezomib + melphalan + prednisone; an added benefit is therefore not proven for this outcome.

Nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea

The meta-analysis showed no statistically significant difference between the treatment groups for each of the following outcomes: nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation and diarrhoea. For each of these outcomes, there is no hint of added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone; an added benefit is therefore not proven for these outcomes.

health status (EQ-5D VAS)

The meta-analysis showed no statistically significant difference between treatment groups for the outcome of health status, measured with the EQ-5D VAS. For the outcome "health status", there is no hint of added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone; an added benefit is therefore not proven for this outcome.

Health-related quality of life

EORTC QLQ-C30

Global health status

The meta-analysis showed a statistically significant difference in favour of daratumumab + bortezomib + melphalan + prednisone for the outcome "global health status". For the

outcome “global health status”, there is a hint of added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone.

Physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning

The meta-analysis showed no statistically significant difference between treatment groups for the outcomes of physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning. There is no hint of added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone; an added benefit is therefore not proven for these outcomes.

Side effects

SAEs, severe AEs and discontinuation due to AEs

The meta-analysis showed no statistically significant difference between treatment groups for the outcomes of SAEs, severe AEs and discontinuation due to AEs. Hence, there was no hint of greater or lesser harm from daratumumab + bortezomib + melphalan + prednisone im comparison with bortezomib + melphalan + prednisone for any of the outcomes “SAEs”, “severe AEs” and “discontinuation due to AEs”; greater or lesser harm is therefore not proven for these outcomes.

Specific AEs

Infusion related reaction

The analyses submitted by the company for the outcome of infusion-related reaction are unsuitable for the benefit assessment (see Section I 4.1). However, the events underlying infusion-related reactions have been recorded through the specific AEs.

This resulted in no hint of greater or lesser harm from daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone; greater or lesser harm is therefore not proven.

Peripheral neuropathy (severe AEs)

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "peripheral neuropathy (severe AEs)". Hence, there was no hint of greater or lesser harm from daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone for the outcome “peripheral neuropathy” (severe AEs); greater or lesser harm is therefore not proven for this outcome.

Infections and infestations (SOC, severe AEs), vascular diseases (SOC, severe AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs)

The ALCYONE study showed a statistically significant difference to the disadvantage of daratumumab + bortezomib + melphalan + prednisone for the outcomes of infections and infestations (SOC, severe AEs), vascular diseases (SOC, severe AEs) and respiratory, thoracic and mediastinal disorders (SOC, AEs). For each of these outcomes, there is a hint of greater harm from daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone.

I 4.4 Subgroups and other effect modifiers

For the studies ALCYONE and OCTANS, no subgroup analyses were used in the benefit assessment. The reasons for this are as follows:

The studies ALCYONE and OCTANS is relevant for the present research question. However, the results regarding the included population (patients for whom ASZT is not suitable) and regarding the implementation of the ACT are subject to uncertainty (see Section I 3.2). Any subsequent subgroup analyses would therefore be subject to additional uncertainty, in particular with regard to the included populations: It is unknown which potential subgroups patients still eligible for ASCT fall under and to what extent subgroup results would be biased as a result. The results from the subgroup analyses are therefore not considered interpretable and no subgroup analyses are used for the present benefit assessment.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 16).

Determination of the outcome category for symptom outcomes

It cannot be inferred from the dossier whether the following symptoms outcome is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Fatigue

For the outcome of fatigue (EORTC QLQ-C30), no sufficient information is available to classify the severity category as serious/severe. The outcome “fatigue” was therefore assigned to the outcome category "non-serious/non-severe symptoms/late complications".

Table 16: Extent of added benefit at outcome level: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Outcome category **outcome**	**Daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone** **median time to event (months)[a]** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival (taking into account the originally planned analysis of the ALCYONE study)	NA vs. NA -53.59 HR: 0.65 [0.53; 0.80] p < 0.001 probability: "hint"	Outcome category: mortality CI_u < 0.85 added benefit, extent: "non-quantifiable"[d]
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30, time to first deterioration by ≥ 10 points)		
Fatigue	17.97-45.93 vs. 8.80-17.05 HR: 0.76 [0.61; 0.94] p = 0.013 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications 0.90 ≤ CI_u < 1.00 lesser/added benefit not proven[e]
Nausea and vomiting	51.19–77.31 vs. NC–NA HR: 0.92 [0.71; 1.19] p = 0.521	Lesser/added benefit not proven
Pain	44.09-79.47 vs. 27.43-33.38 HR: 0.80 [0.64; 1.02] p = 0.072	Lesser/added benefit not proven
Dyspnoea	NA –58.32 vs. NC-NA HR: 1.10 [0.86; 1.41] p = 0.467	Lesser/added benefit not proven
Insomnia	NA–44.16 vs. 17.51–45.67 HR: 0.88 [0.70; 1.10] p = 0.267	Lesser/added benefit not proven
Appetite loss	49.54–NA vs. NA –55.13 HR: 0.94 [0.74; 1.21] p = 0.648	Lesser/added benefit not proven
Constipation	NC-NA vs. 24.02-NA HR: 0.87 [0.68; 1.13] p = 0.297	Lesser/added benefit not proven
Diarrhoea	NA vs. NA HR: 0.98 [0.75; 1.29] p = 0.888	Lesser/added benefit not proven

Table 16: Extent of added benefit at outcome level: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Outcome category **outcome**	**Daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone** **median time to event (months)[a]** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Health status (EQ-5D VAS; time to first deterioration by ≥ 15 points)		
EQ-5D VAS	NA vs. NA HR: 0.85 [0.62; 1.15] p = 0.293	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (time to first deterioration by ≥ 10 points)		
Global health status	44.09-85.78 vs. 27.43-44.45 HR: 0.73 [0.58; 0.93] p = 0.012 Probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit; extent: “minor”
Physical functioning	44.09–NA vs. NA –39.88 HR: 0.82 [0.64; 1.06] p = 0.126	Lesser/added benefit not proven
Role functioning	45.09-NA vs. 25.04-27.43 HR: 0.80 [0.64; 1.01] p = 0.056	Lesser/added benefit not proven
Emotional functioning	NC-NA vs. 55.79-NA HR: 0.91 [0.69; 1.20] p = 0.522	Lesser/added benefit not proven
Cognitive functioning	16.62-22.67 vs. 20.37-23.36 HR: 0.98 [0.79; 1.21] p = 0.852	Lesser/added benefit not proven
Social functioning	21.88-60.35 vs. 21.52-34.30 HR: 0.89 [0.71; 1.12] p = 0.324	Lesser/added benefit not proven
Side effects[f]		
SAEs	20.96–35.91 vs. NC HR: 1.16 [0.93; 1.44] p = 0.187	Greater/lesser harm not proven
Severe AEs	0.38-0.61 vs. 0.66-0.95 HR: 1.12 [0.96; 1.31] p = 0.138	Greater/lesser harm not proven

Table 16: Extent of added benefit at outcome level: daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone (multipage table)

Outcome category **outcome**	**Daratumumab + bortezomib + melphalan + prednisone vs. bortezomib + melphalan + prednisone** **median time to event (months)[a]** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Discontinuation due to AEs (at least 1 therapy component)	NA vs. NC HR: 0.90 [0.60; 1.36] p = 0.623	Greater/lesser harm not proven
Infusion-related reaction	No suitable data	Greater/lesser harm not proven
Peripheral neuropathy (HLT, severe AE)	NA vs. NA HR: 0.62 [0.31; 1.26] p = 0.189	Greater/lesser harm not proven
Infections and infestations (SOC, severe AE)[g]	NA vs. - HR: 1.43 [1.002; 2.04] HR: 0.70 [0.49; 0.998][h] p = 0.048 probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: “minor”
Vascular disorders (SOC, severe AEs)[g]	NA vs. NA HR: 2.38 [1.04; 5.44] HR: 0.42 [0.18; 0.96][h] p = 0.040 probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: “minor”
Respiratory, thoracic, and mediastinal disorders (SOC, AE)[g]	47.77 vs. NA HR: 1.94 [1.45; 2.60] HR: 0.52 [0.38; 0.69][h] p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm; extent: “considerable”

a. Minimum and maximum medians of time to event per treatment arm in the included studies.
b. Probability provided if statistically significant differences are present.
c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u).
c. See Section I 3.2 and Section I 4.2 for a rationale.
e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
f. When interpreting the results on side effects, it should be noted that the substantially shorter planned treatment duration and the associated discontinuation of follow-up in the comparator arm result in the HR reflecting only approximately the first 14 months after randomization.
g. The result is based on only one study (ALCYONE).
h. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organization for Research and Treatment of Cancer; HLT: High Level Term; QLQ-C30: Quality of Life Questionnaire Core 30; SAE: serious adverse; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of daratumumab + bortezomib + melphalan + prednisone versus bortezomib + melphalan + prednisone

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival hint of added benefit – extent: “non-quantifiable”	–
Outcomes with shortened observation period	
Health-related quality of life EORTC QLQ-C30: ▪ global health status: hint of an added benefit – extent: "minor"	–
–	Serious/severe side effects ▪ infections and infestations (severe AE): hint of greater harm – extent: “minor” ▪ vascular diseases (severe AE): hint of greater harm – extent: “minor”
–	Non-serious/non-severe side effects ▪ respiratory, thoracic, and mediastinal disorders (AE): hint of greater harm – extent: “considerable”
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire – Core 30	

The overall assessment shows both positive and negative effects with different extents for daratumumab + bortezomib + melphalan + prednisone versus bortezomib + melphalan + prednisone.

On the side of positive effects, there is a hint of a non-quantifiable added benefit for the outcome of overall survival, and a hint of a minor added benefit for “global health status”.

These positive effects are offset by negative effects exclusively for outcomes in the side effects category: For the specific AEs “infections and infestations” as well as “vascular diseases”, there are hints of greater harm with the extent “minor”. For the specific AE “respiratory, thoracic and mediastinal disorders”, however, there is a hint of greater arm with the extent “considerable”. The negative effects refer exclusively to the shortened period until the end of treatment (plus a maximum of 30 days). In addition, specific AEs could only be selected on the basis of the results from the ALCYONE study (see Section I 4.1). It can therefore not be ruled out that the extent of the selected specific AEs could deviate in a metanalytical summary.

The negative effects in the specific AEs do not completely challenge the positive effects in the outcomes of overall survival and global health status. The added benefit is rated as non-quantifiable.

In summary, there is a hint of non-quantifiable added benefit of daratumumab + bortezomib + melphalan + prednisone versus bortezomib + melphalan + prednisone for patients with newly diagnosed multiple myeloma who are ineligible for ASCT.

Table 18 summarizes the result of the assessment of the added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with the ACT.

Table 18: Daratumumab + bortezomib + melphalan + prednisone – 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 ineligible for autologous stem cell transplantation	▪ Daratumumab in combination with lenalidomide and dexamethasone 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 ▪ bortezomib in combination with cyclophosphamide and dexamethasone (only for patients with peripheral polyneuropathy or an increased risk of developing peripheral polyneuropathy[b])	Hint of non-quantifiable added benefit
a. Presented is the ACT specified by the G-BA. b. See Appendix VI pertaining to Section K of the German Pharmaceutical Directive. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived an indication of major added benefit based on the results of the ALCYONE study.

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.

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