IQWiG Reports – Commission No. A18-66

Daratumumab (multiple myeloma) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of the executive summary of the dossier assessment *Daratumumab (multiples Myelom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 20 December 2018). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Daratumumab (multiple myeloma) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

1 October 2018

Internal Commission No.:

A18-66

Address of publisher:

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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.

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Keywords: daratumumab, multiple myeloma, benefit assessment, NCT02195479

Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) 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 1 October 2018.

Research question

This report aims to assess the added benefit of daratumumab in combination with bortezomib, melphalan, and prednisone in comparison with the appropriate comparator therapy (ACT) in adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation (ASCT).

The G-BA's ACT is presented in Table 2.

Table 2[2]: Research questions of the benefit assessment of daratumumab

Indication	**ACT[a]**
Daratumumab in combination with bortezomib, melphalan, and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for stem cell transplantation	▪ **Bortezomib in combination with melphalan and prednisone** or ▪ Thalidomide in combination with melphalan and prednisone or ▪ Lenalidomide in combination with dexamethasone
a: Presentation of the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. From the options named by the G-BA, the company selected bortezomib in combination with melphalan and prednisone.

In the course of the dossier assessment, the G-BA changed the ACT for this assessment (discussion in the G-BA's Pharmaceuticals Subcommittee on 12 November 2018). The newly specified ACT is [1]:

- Combination therapy upon the physician's discretion

The dossier presented by the company includes the description of the added benefit of daratumumab in combination with bortezomib, melphalan, and prednisone in comparison with

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

one of the options of the original ACT (bortezomib in combination with melphalan and prednisone). These documents continue to be relevant for this assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. This corresponds to the company's inclusion criteria.

Results

Study pool and study characteristics

The study pool for the benefit assessment comprises the ALCYONE study. This is an open-label, randomized, actively controlled study for the direct comparison of daratumumab + bortezomib + melphalan + prednisone (D-VMP regimen) with bortezomib + melphalan + prednisone (VMP regimen).

The study included adults (≥ 18 years) with newly diagnosed multiple myeloma who were ineligible for high-dose chemotherapy with subsequent ASCT. Since the criteria for assessing a patient's eligibility for ASCT changed over the course of the study, it is possible for the study to have also included patients who would have been eligible for ASCT in accordance with current criteria. In addition to the results of the overall population, the company therefore presents the results of a subpopulation defined post hoc (ASCT ineligibility); this subpopulation represents an approximation of the population ineligible for ASCT. The subpopulation comprises 77% of the total study population. For both populations, this creates uncertainty in that the percentage of patients who actually would have been ineligible for ASCT is unclear. For the decision-relevant outcomes, the effect sizes in the total population and the subpopulation (ineligible for ASCT) are very similar.

In both study arms, the treatment was administered in 6-week cycles. The components of the D-VMP regimen were administered in accordance with the Summary of Product Characteristics (SPC) for daratumumab. However, the VMP regimen used in the comparator arm deviates from the regimen described in the SPC for bortezomib in terms of the dosing frequency for bortezomib. The company argues that several studies have shown the off-label bortezomib dosing regimen to be associated with better tolerability and comparable effectiveness. It further claims that the deviating dosage was also recommended in international guidelines. The benefit assessment is conducted for use as per the SPC. The bortezomib dosing regimen used in the ALCYONE study is, however, considered a sufficient approximation to the use as per the SPC. The uncertainty resulting from the deviating bortezomib dosing is taken into account in the results assessment.

The benefit assessment is done on the basis of the results for the total population, with supplementary consideration being given to the results of the subpopulation (ineligible for ASCT). However, the aforementioned uncertainties (percentage of patients who may be eligible for ASCT as well as deviating bortezomib dosing) mean that at most hints, for example of an added benefit, can be derived.

Risk of bias on the study and outcome levels

The risk of bias on the study level was rated as low in the ALCYONE study. On the outcome level, the results are rated as highly biased, with the exception of the outcomes of overall survival and severe AEs (CTCAE grade ≥ 3).

Results

Mortality: Overall survival

For the outcome of overall survival, a statistically significant difference in favour of daratumumab + bortezomib + melphalan + prednisone was found. This results in a hint of added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone.

Morbidity: Health status (EQ-5D VAS)

For the outcome of health status as measured by EQ-5D VAS, no statistically significant difference between treatment arms was found. This results in no hint of added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone; an added benefit is therefore not proven.

Morbidity: Symptoms (EORTC QLQ C30 – symptom scales)

For the outcome of fatigue, a statistically significant effect in favour of daratumumab + bortezomib + melphalan + prednisone was found. The difference, however, is no more than marginal for an outcome of the category of non-serious/non-severe symptoms/late complications. For the outcome of fatigue, this results in no hint of added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone; an added benefit is therefore not proven.

For each of the outcomes of nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea, no statistically significant difference between treatment arms was found. For each of these outcomes, this results in no hint of added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone; an added benefit is therefore not proven.

Health-related quality of life (EORTC QLQ C30 – functional scales)

For each of the outcomes of general health status, role functioning, emotional functioning, physical functioning, cognitive functioning, and social functioning, no statistically significant difference between treatment arms was found. For each of these outcomes, this results in no hint of added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone; an added benefit is therefore not proven.

Adverse events

For the outcomes of SAEs and severe AEs (CTCAE ≥ grade 3), the metaanalysis shows no statistically significant difference between treatment arms. For these outcomes, there was

therefore no hint of greater or lesser harm of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone; therefore, there is no proof of greater or lesser harm.

For the outcome of discontinuation (of all drug components) due to AEs, a statistically significant difference in favour of daratumumab + bortezomib + melphalan + prednisone was found. This results in a hint of lesser harm of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone.

For each of the outcomes of infections and parasitic diseases (SAEs), vascular disorders (severe AEs) as well as respiratory, thoracic, and mediastinal disorders (AEs), statistically significant differences to the disadvantage of daratumumab + bortezomib + melphalan + prednisone were found. This results in a hint of greater harm of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone.

For the outcome of peripheral neuropathy (AEs), a statistically significant effect in favour of daratumumab + bortezomib + melphalan + prednisone was found. The difference, however, is no more than marginal for an outcome of the category of non-serious/non-severe adverse events. For the outcome of peripheral neuropathy (AEs), there was therefore no hint of lesser harm of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone; therefore, there is no proof of greater or lesser harm.

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

On the basis of the results presented, the probability and extent of added benefit of the drug daratumumab in comparison with the ACT are assessed as follows:

All things considered, there are hints of both positive and negative effects of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone. Alongside the positive effect regarding overall survival, adverse events reveal 1 positive effect with the extent being considerable as well as 3 negative effects, 2 being considerable and 1 minor. The negative effects curb the positive effects, but do not negate them entirely, particularly in terms of overall survival.

[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 [2,3].

In summary, for patients with newly diagnosed multiple myeloma who are ineligible for ASCT, there is a hint of lesser added benefit of daratumumab + bortezomib + melphalan + prednisone in comparison with bortezomib + melphalan + prednisone.

Table 3 presents a summary of the probability and extent of added benefit of daratumumab.

Table 3: Daratumumab – probability and extent of added benefit

Indication	**ACT[a]**	**Probability and extent of added benefit**
Daratumumab in combination with bortezomib, melphalan, and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for stem cell transplantation	▪ **Bortezomib in combination with melphalan and prednisone** or ▪ Thalidomide in combination with melphalan and prednisone or ▪ Lenalidomide in combination with dexamethasone	Hint of minor added benefit
a: Presentation of the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

Note:

An addendum (A19-16) to dossier assessment A18-66 has been published.

References for English extract

Please see full dossier assessment for full reference list.

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

1. Federal Joint Committee Benefit assessment procedure on the drug of daratumumab (new therapeutic application: newly diagnosed multiple myeloma): appropriate comparator therapy. [Soon available under: https://www.g-ba.de/informationen/nutzenbewertung/402/#zweckmaessige-vergleichstherapie].

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3. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-66-daratumumab-multiple-myeloma-benefit-assessment-according-to-35a-social-code-book-v.10627.html.