IQWiG Reports – Commission No. A22-104

# Melphalan flufenamide (multiple myeloma) –

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

## Extract

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Melphalanflufenamid (multiples Myelom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 23 December 2022). 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**
Melphalan flufenamide (multiple myeloma) – Benefit assessment according to §35a Social Code Book V

**Commissioning agency**
Federal Joint Committee

**Commission awarded on**
4 October 2022

**Internal Commission No.**
A22-104

**Address of publisher**
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

**Medical and scientific advice**

- Jochem Potenberg, Waldkrankenhaus Protestant Hospital, Berlin, Germany

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

**Patient and family involvement**

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

IQWiG thanks the respondent for participating in the written exchange about how he experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

**IQWiG employees involved in the dossier assessment**

- Teresa Labahn
- Christiane Balg
- Reza Fathollah-Nejad
- Petra Kohlepp
- Ulrike Lampert
- Katrin Nink
- Mattea Patt
- Regine Potthast

**Keywords:** Melflufen, Melphalan-Flufenamide, Dexamethasone, Multiple Myeloma, Benefit Assessment, NCT03151811

# Part I: Benefit assessment

# I Table of contents

**Page**

# 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 |
| eGFR | estimated glomerular filtration rate |
| 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 |
| RCT | randomized controlled trial |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SPC | Summary of Product Characteristics |

## I 1 Executive summary of the benefit assessment

### Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug melphalan flufenamide (in combination with dexamethasone). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 4 October 2022.

### Research question

The aim of the present report is to assess the added benefit of melphalan flufenamide in combination with dexamethasone (hereinafter referred to as "melphalan flufenamide + dexamethasone") in comparison with the appropriate comparator therapy (ACT) in adults with multiple myeloma who have received at least 3 prior therapies, whose disease is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory agent, and 1 anti-CD38 monoclonal antibody, and who have demonstrated disease progression during or after the last therapy; for patients with prior autologous stem cell transplantation, the time to progression after transplantation should be at least 3 years.

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

Table 2: Research questions of the benefit assessment of melphalan flufenamide + dexamethasone

| **Therapeutic indication** | **ACT[a]** |
|---|---|
| Adults with multiple myeloma who have received at least 3 prior therapies, whose disease is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory agent and 1 anti-CD38 monoclonal antibody, and who have demonstrated disease progression during or after the last therapy; for patient with prior autologous stem cell transplantation, the time to progression after transplantation should be at least 3 years | Individualized treatment[b, c] selected from:<br>▪ bortezomib monotherapy<br>▪ bortezomib + pegylated liposomal doxorubicin<br>▪ bortezomib + dexamethasone<br>▪ carfilzomib + lenalidomide and dexamethasone<br>▪ carfilzomib + dexamethasone<br>▪ daratumumab + lenalidomide + dexamethasone<br>▪ daratumumab + bortezomib + dexamethasone<br>▪ daratumumab monotherapy (only for patients with disease progression on the last therapy)<br>▪ elotuzumab + lenalidomide + dexamethasone<br>▪ elotuzumab + pomalidomide + dexamethasone (only for patients with disease progression on the last therapy)<br>▪ isatuximab + pomalidomide + dexamethasone (only for patients with disease progression on the last therapy)<br>▪ ixazomib + lenalidomide + dexamethasone<br>▪ lenalidomide + dexamethasone<br>▪ panobinostat + bortezomib and dexamethasone<br>▪ pomalidomide + bortezomib and dexamethasone<br>▪ pomalidomide + dexamethasone (only for patients with disease progression on the last therapy)<br>▪ cyclophosphamide (in combination with other antineoplastic agents)<br>▪ melphalan<br>▪ doxorubicin<br>▪ carmustine (in combination with other cytostatic agents and an adrenal cortex hormone, particularly prednisone)<br>▪ vincristine<br>▪ dexamethasone<br>▪ prednisolone<br>▪ prednisone<br>▪ best supportive care[d]<br>Taking into account prior therapies as well as the extent and duration of response |

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the special situation of refractory patients is presumably taken into account when choosing the ACT.
c. For the implementation of individualized therapy in a direct comparative study, according to the G-BA, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified.
d. Best supportive care refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company explains that the G-BA was consulted regarding the ACT for the previously planned therapeutic indication of melphalan flufenamide + dexamethasone but not for the current therapeutic indication, which was later approved. For the current therapeutic indication, the company derived the ACT independently, defining it as individualized therapy of the physician's choice. In its derivation of the ACT, the company discusses various treatment options – but does not specifically list the drugs or drug combinations which it deems to be included in the ACT.

The present assessment is performed in comparison with the ACT specified by the G-BA of individualized therapy, selecting from various treatment options and taking into account prior therapies as well as the extent and duration of response.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

**Results**

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of melphalan flufenamide + dexamethasone in comparison with the ACT.

For its assessment, the company used the results of a subpopulation from the randomized controlled trial (RCT) OCEAN (QP-103). Under other investigations, the company additionally provided as supplementary information the single-arm approval study of melphalan flufenamide + dexamethasone, HORIZON (OP-106).

The company's approach is not appropriate. The data presented by the company are unsuitable for drawing any conclusions on the added benefit of melphalan flufenamide + dexamethasone in comparison with the ACT.

***OCEAN study presented by the company***

The OCEAN study is an ongoing, open-label RCT comparing melphalan flufenamide + dexamethasone versus pomalidomide + dexamethasone. The study included adults with recurrent, refractory multiple myeloma who received 2 to 4 prior treatment lines, including both lenalidomide and a proteasome inhibitor. These patients had to be either (a) refractory or (b) relapsed and refractory to both the last therapy line and lenalidomide within the past 18 months prior to randomization and have exhibited disease progression on or after the last therapy. The study excluded patients with primary refractory disease as well as those who had previously received pomalidomide.

A total of 495 patients were randomized to treatment with melphalan flufenamide + dexamethasone (n = 246) or pomalidomide + dexamethasone (n = 249).

In both study arms, treatment was administered until a reason for discontinuation arose (e.g. disease progression, unacceptable toxicity, or withdrawal of consent). Pomalidomide was applied in accordance with the Summary of Product Characteristics (SPC). The melphalan

flufenamide and dexamethasone dosage deviated in part from the specifications in the SPC. For melphalan, for instance, the SPC specifies a reduced initial dose of 30 mg (instead of 40 mg) for patients weighing up to 60 kg – with this reduced initial dose also being recommended for patients with renal impairment and an estimated glomerular filtration rate (eGFR) of 30 to 45 mL/min/1.72 $m^2$. OCEAN study participants, in contrast, received an initial dose of 40 mg, regardless of their weight or the presence or absence of renal impairment. According to the pomalidomide SPC, the dexamethasone dose can be reduced to a minimum of 10 mg in patients ≤ 75 years of age, e.g. in case of toxicity. In the OCEAN study, < 75-year-old patients were allowed to do the same only to a minimum dose of 12 mg.

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

*Subpopulation of the OCEAN study analysed by the company*

Regarding patients' prior therapies, some of the OCEAN study's inclusion criteria are stricter or more lenient than SPC specifications for melphalan flufenamide + dexamethasone or pomalidomide + dexamethasone. In the dossier's Module 4A, the company reports analysing the OCEAN study's subpopulation designed to match the target population of melphalan flufenamide + dexamethasone. The subpopulation analysed by the company comprises a total of 22 patients: 12 in melphalan flufenamide + dexamethasone arm and 10 in the pomalidomide + dexamethasone arm. The company's dossier presents analyses on these patients.

***Appropriate comparator therapy not implemented in the OCEAN study***

The OCEAN study data presented by the company are unsuitable for assessing the added benefit of melphalan flufenamide + dexamethasone in comparison with the ACT. This is due to a failure to implement the G-BA's specified ACT of individualized therapy taking into account prior therapies as well as the extent and duration of response; instead, all patients of the comparator arm received an undifferentiated treatment regimen consisting of pomalidomide + dexamethasone.

The company justifies the undifferentiated administration of pomalidomide + dexamethasone in the OCEAN study's comparator arm with the fact that in the context of individualized therapies, the majority of patients in the German healthcare context is treated with this drug combination from the 3rd line of therapy.

The company's reasoning is not substantive. For instance, the company concedes that both national and international guideline recommendations show that, alongside pomalidomide-based treatment regimens, daratumumab likewise represents the standard of therapy in recurrent, refractory, multiple myeloma from the 3rd line of therapy. In addition, the company explains that, from the 4th line of therapy, about 30% to 40% of patients in France, Germany, Italy, and the United Kingdom receive pomalidomide in combination with dexamethasone in a

double or triple combination; the MYRIAM registry cited by the company shows that, in the years 2017 to 2021, the percentage of pomalidomide-based treatment regimens was 35.1% in the 4th line of therapy and 44.4% in the 5th line of therapy. Accordingly, the majority of patients receives other, non-pomalidomide-based therapies after the 3rd line of therapy. For treatment of the 1st to 3rd recurrence, the current S3 guideline (2022) cited by the company describes that physically fit patients – such as those in the OCEAN study – reap greater added benefit from a triple combination than from a double combination.

Overall, the sources cited by the company show that pomalidomide-based treatment regimens represent one of several options for the treatment of patients in the present therapeutic indication. However, the company fails to adequately justify the extent to which the administration of pomalidomide + dexamethasone represents the most suitable treatment option for OCEAN participants taking into account prior therapy and the extent and duration of response. For the implementation of the ACT, investigators in the study should therefore have been offered several therapy options to choose from, where possible.

Irrespective of the OCEAN study being unsuitable for the benefit assessment, the presented results for the subpopulation show neither advantages nor disadvantages for melphalan flufenamide + dexamethasone.

***HORIZON study presented by the company as supportive evidence***

The HORIZON study is a single-arm, open-label study with melphalan flufenamide + dexamethasone. The study included adults with recurrent, refractory multiple myeloma who received at least 2 prior lines of therapy, including both an immunomodulator and a proteasome inhibitor. Patients had to have been refractory to pomalidomide and/or a monoclonal CD38 antibody. In the dossier, the company presents data for the subpopulation of patients who were triple refractory or intolerant to at least 1 immunomodulatory agent, 1 proteasome inhibitor, and 1 monoclonal CD38 antibody (referred to by the company as TCR [triple class refractory] population).

The HORIZON study is disregarded in the present benefit assessment because, due to the absence of a comparator arm, no conclusions on added benefit can be drawn for melphalan flufenamide + dexamethasone versus the ACT.

***Conclusion***

Overall, the data presented by the company do not allow comparing melphalan flufenamide + dexamethasone versus the ACT specified by the G-BA.

**Results on added benefit**

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of melphalan flufenamide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

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

Table 3 shows a summary of the probability and extent of added benefit of melphalan flufenamide + dexamethasone.

[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].

Table 3: Melphalan flufenamide + dexamethasone – probability and extent of added benefit

| **Therapeutic indication** | **ACT[a]** | **Probability and extent of added benefit** |
|---|---|---|
| Adults with multiple myeloma who have received at least 3 prior therapies, whose disease is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory agent and 1 anti-CD38 monoclonal antibody, and who have demonstrated disease progression during or after the last therapy; for patient with prior autologous stem cell transplantation, the time to progression after transplantation should be at least 3 years | Individualized treatment[b, c] selected from:<br>▪ bortezomib monotherapy<br>▪ bortezomib + pegylated liposomal doxorubicin<br>▪ bortezomib + dexamethasone<br>▪ carfilzomib + lenalidomide and dexamethasone<br>▪ carfilzomib + dexamethasone<br>▪ daratumumab + lenalidomide + dexamethasone<br>▪ daratumumab + bortezomib + dexamethasone<br>▪ daratumumab monotherapy (only for patients with disease progression on the last therapy)<br>▪ elotuzumab + lenalidomide + dexamethasone<br>▪ elotuzumab + pomalidomide + dexamethasone (only for patients with disease progression on the last therapy)<br>▪ isatuximab + pomalidomide + dexamethasone (only for patients with disease progression on the last therapy)<br>▪ ixazomib + lenalidomide + dexamethasone<br>▪ lenalidomide + dexamethasone<br>▪ panobinostat + bortezomib and dexamethasone<br>▪ pomalidomide + bortezomib and dexamethasone<br>▪ pomalidomide + dexamethasone (only for patients with disease progression on the last therapy)<br>▪ cyclophosphamide (in combination with other antineoplastic agents)<br>▪ melphalan<br>▪ doxorubicin<br>▪ carmustine (in combination with other cytostatic agents and an adrenal cortex hormone, particularly prednisone)<br>▪ vincristine<br>▪ dexamethasone<br>▪ prednisolone<br>▪ prednisone<br>▪ best supportive care[d]<br>taking into account prior therapies as well as the extent and duration of response | Added benefit not proven |

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the special situation of refractory patients is presumably taken into account when choosing the ACT.
c. For the implementation of individualized therapy in a direct comparative study, according to the G-BA, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified.
d. Best supportive care refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

## I 2 Research question

The aim of the present report is to assess the added benefit of melphalan flufenamide in combination with dexamethasone (hereinafter referred to as "melphalan flufenamide + dexamethasone") in comparison with the ACT in adults with multiple myeloma who have received at least 3 prior therapies, whose disease is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory agent, and 1 anti-CD38 monoclonal antibody, and who have demonstrated disease progression during or after the last therapy; for patients with prior autologous stem cell transplantation, the time to progression after transplantation should be at least 3 years.

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

Table 4: Research questions of the benefit assessment of melphalan flufenamide + dexamethasone

| **Therapeutic indication** | **ACT**[a] |
|---|---|
| Adults with multiple myeloma who have received at least 3 prior therapies, whose disease is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory agent and 1 anti-CD38 monoclonal antibody, and who have demonstrated disease progression during or after the last therapy; for patient with prior autologous stem cell transplantation, the time to progression after transplantation should be at least 3 years | Individualized treatment[b, c] selected from:<br>▪ bortezomib monotherapy<br>▪ bortezomib + pegylated liposomal doxorubicin<br>▪ bortezomib + dexamethasone<br>▪ carfilzomib + lenalidomide and dexamethasone<br>▪ carfilzomib + dexamethasone<br>▪ daratumumab + lenalidomide + dexamethasone<br>▪ daratumumab + bortezomib + dexamethasone<br>▪ daratumumab monotherapy (only for patients with disease progression on the last therapy)<br>▪ elotuzumab + lenalidomide + dexamethasone<br>▪ elotuzumab + pomalidomide + dexamethasone (only for patients with disease progression on the last therapy)<br>▪ isatuximab + pomalidomide + dexamethasone (only for patients with disease progression on the last therapy)<br>▪ ixazomib + lenalidomide + dexamethasone<br>▪ lenalidomide + dexamethasone<br>▪ panobinostat + bortezomib and dexamethasone<br>▪ pomalidomide + bortezomib and dexamethasone<br>▪ pomalidomide + dexamethasone (only for patients with disease progression on the last therapy)<br>▪ cyclophosphamide (in combination with other antineoplastic agents)<br>▪ melphalan<br>▪ doxorubicin<br>▪ carmustine (in combination with other cytostatic agents and an adrenal cortex hormone, particularly prednisone)<br>▪ vincristine<br>▪ dexamethasone<br>▪ prednisolone<br>▪ prednisone<br>▪ best supportive care[d]<br>taking into account prior therapies as well as the extent and duration of response |

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the special situation of refractory patients is presumably taken into account when choosing the ACT.
c. For the implementation of individualized therapy in a direct comparative study, according to the G-BA, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified.
d. Best supportive care refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company explains that the G-BA was consulted regarding the ACT for the previously planned therapeutic indication of melphalan flufenamide + dexamethasone but not for the current therapeutic indication, which was later approved. For the current therapeutic indication, the company derived the ACT independently, defining it as individualized therapy of the physician's choice. In its derivation of the ACT, the company discusses various treatment options – but does not specifically list the drugs or drug combinations which it deems to be included in the ACT.

The present assessment is performed in comparison with the ACT specified by the G-BA of individualized therapy, selecting from various treatment options and taking into account prior therapies as well as the extent and duration of response.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

## 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 melphalan flufenamide (status: 11 July 2022)
- bibliographical literature search on melphalan flufenamide (last search on 11 July 2022)
- search in trial registries / trial results databases for studies on melphalan flufenamide (last search on 11 July 2022)
- search on the G-BA website for melphalan flufenamide (last search on 11 July 2022)

To check the completeness of the study pool:

- search in trial registries for studies on melphalan flufenamide (last search on 17 October 2022); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any relevant studies for assessing the added benefit of melphalan flufenamide + dexamethasone in comparison with the ACT.

In contrast, the company's search for RCTs identified the OCEAN study (OP-103) [3-9] and used the results of a subpopulation for its assessment. The data presented by the company on the subpopulation are unsuitable for the present benefit assessment because the ACT of individualized therapy has not been implemented (see explanation in the below section titled "Appropriate comparator therapy not implemented in the OCEAN study").

To identify additional assessment-relevant evidence, the company searched for other investigations of any type other than RCTs. The company identified the single-arm approval study of melphalan flufenamide + dexamethasone, HORIZON (OP-106) [10,11] and presented this study's results as supplementary information. Due to the missing comparison with the ACT, the HORIZON study is unsuitable for the benefit assessment. Since no relevant other investigations were therefore available, the check for completeness was foregone.

Overall, the data presented by the company were unsuitable for drawing conclusions on the added benefit of melphalan flufenamide + dexamethasone in comparison with the ACT. Below, the evidence presented by the company is described, and the reasons for its unsuitability for the benefit assessment are provided.

**Evidence provided by the company**

***OCEAN study***

Table 5 and Table 6 describe the OCEAN RCT included by the company.

Table 5: Characteristics of the study included by the company – RCT, direct comparison: melphalan flufenamide + dexamethasone versus pomalidomide + dexamethasone (multipage table)

| Study | Study design | Population | Interventions (number of randomized patients) | Study duration | Location and period of study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|
| OCEAN | RCT, open-label, parallel-group | Adults with relapsed, refractory multiple myeloma[b]:<br>▪ 2 to 4 prior lines of therapy (including both lenalidomide and a PI)<br>▪ Refractory or recurrent and refractory to the most recent line of therapy[c] and lenalidomide (≥ 10 mg)[d] within the last 18 months prior to randomization<br>▪ Disease progression during or after the most recent therapy<br>▪ Life expectancy of ≥ 6 months<br>▪ ECOG-PS ≤ 2 | Melphalan flufenamide + dexamethasone (N = 246)<br>Pomalidomide + dexamethasone (N = 249)<br><br>Subpopulation thereof analysed by the company[b]:<br>▪ Melphalan flufenamide + dexamethasone (n = 12)<br>▪ Pomalidomide + dexamethasone (n = 10)<br><br>PRO population thereof [e]:<br>▪ Melphalan flufenamide + dexamethasone (n = 5)<br>▪ Pomalidomide + dexamethasone (n = 2) | ▪ Screening: up to 21 days<br>▪ Treatment: until disease progression[f], unacceptable toxicity, withdrawal of consent, death, or study discontinuation<br>▪ Observation: outcome-specific, at most for overall survival up to 24 months after disease progression or start of subsequent therapy, withdrawal of consent, loss to follow-up, or study discontinuation | 108 study centres in Austria, Belgium, Czech Republic, Denmark, Estonia, France, Greece, Hungary, Israel, Italy, Lithuania, Netherlands, Norway, Poland, Romania, Russia, South Korea, Spain, Taiwan, United Kingdom, United States<br><br>06/2017 – ongoing[g]<br><br>Data cut-offs<br>▪ 3 February 2021[h] | Primary: PFS<br>Secondary: overall survival, morbidity, health-related quality of life, AEs |

Table 5: Characteristics of the study included by the company – RCT, direct comparison: melphalan flufenamide + dexamethasone versus pomalidomide + dexamethasone (multipage table)

| Study | Study design | Population | Interventions (number of randomized patients) | Study duration | Location and period of study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes comprise exclusively data based on the information provided by the company's Module 4A.
b. Some OCEAN participants were not members of the approved population for melphalan flufenamide + dexamethasone. The company's dossier analyses the subpopulation of patients who, according to the company, are members of the target population for melphalan flufenamide + dexamethasone.
c. Refractory disease was defined as no response during therapy or progression within 60 days after the last dose.
d. Progression on treatment or within 60 days after completion of the lenalidomide-containing treatment regimen (after at least 2 cycles of lenalidomide with at least 14 doses per cycle).
e. Survey of PROs for patients who were included in the study from study protocol version 4.0 (4.1 for PROs of the health-related quality of life category). The PRO population comprises all patients of the subpopulation for which the PRO-based surveys for the outcomes of symptoms, health status, and health-related quality of life are available.
f. Disease progression was determined on the basis of the IMWG criteria [12].
g. The study has not yet been completed; according to Module 4A, the study is expected to end in 09/2024.
h. Therefore, the 3 February 2021 data cut-off presumably represents the pre-specified final PFS analysis, which was to occur after 339 PFS events. The analysis was in fact conducted after 355 events. In the dossier's Module 4A, the company states that the last data entry for this data cut-off was on 7 May 2020. In the study documents on the 3 February 2021 data cut-off, in contrast, the "database date" was reported as 7 May 2021 and described as the date until which protocol violations which occurred up to the 3 February 2021 data cut-off were subsequently entered. Further, the company's dossier provides inconsistent information on the time point (date) of data cut-offs or "database dates" (see section below on this topic).

AE: adverse event; CSR: clinical study report; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; IMWG: International Myeloma Working Group; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; PRO: patient-reported outcome; RCT: randomized controlled trial

Table 6: Characteristics of the intervention – RCT, direct comparison: melphalan flufenamide + dexamethasone versus pomalidomide + dexamethasone (multipage table)

| Study | Intervention | Comparison |
|---|---|---|
| OCEAN | Melphalan flufenamide:<br>40 mg, i.v., Day 1 of each cycle<br>(duration of a treatment cycle: 28 days)<br>+<br>Dexamethasone, orally:<br>Patients < 75 years of age: 40 mg<br>Patients ≥ 75 years: 20 mg<br>Days 1, 8, 15, 22 of each cycle<br>(Duration of 1 treatment cycle: 28 days) | Pomalidomide:<br>4 mg, orally, Days 1 to 21 of each cycle<br>(Duration of 1 treatment cycle: 28 days)<br>+<br>Dexamethasone, orally:<br>Patients < 75 years of age: 40 mg<br>Patients ≥ 75 years: 20 mg<br>Days 1, 8, 15, 22 of each cycle<br>(Duration of 1 treatment cycle: 28 days) |
| | Dose adjustments:<br>Dose adjustments, treatment interruptions and treatment discontinuation due to toxicity allowed[a]:<br>▪ Melphalan flufenamide dose reduction steps: (1) to 30 mg; (2) to 20 mg; discontinuation of treatment[b] in case of treatment interruptions lasting over 28 days or where no further reduction is possible<br>▪ Pomalidomide dose reduction steps: (1) to 3 mg; (2) to 2 mg; 3. to 1 mg; discontinuation of treatment[b] in case of treatment interruptions lasting over 28 days or where no further reduction is possible<br>▪ Dexamethasone dose reduction steps:<br>▫ At an in initial dose of 40 mg: (1) to 20 mg; (2) to 12 mg<br>▫ At an in initial dose of 20 mg: (1) to 12 mg; (2) to 8 mg | |
| | **Prior treatment[c]**<br>**Required:**<br>▪ 2–4 prior lines of therapy including lenalidomide and a PI and refractory (refractory or recurrent and refractory) to the most recent line of therapy and lenalidomide (≥ 10 mg) administered within 18 months prior to randomization<br>**Disallowed:**<br>▪ Prior treatment with pomalidomide<br>▪ Prior cytotoxic therapies within 3 weeks (6 weeks for nitrosoureas), IMiDs, PIs, and/or corticosteroids within 2 weeks prior to the start of randomization<br>▪ Other investigational products within 4 weeks prior to randomization<br>▪ Peripheral stem cell transplantation within 12 weeks prior to treatment start<br>▪ Prior allogeneic stem cell transplantation with active graft-versus-host disease<br>▪ Major surgery or radiotherapy within 4 weeks prior to treatment start | |
| | **Concomitant treatment**<br>**Allowed:**<br>▪ In patients of reproductive age: contraception required<br>▪ Antimicrobial prophylaxis in CMV infection and neutropenia<br>▪ Pneumocystitis prophylaxis<br>▪ Pomalidomide + dexamethasone arm: antithrombotic prophylaxis required<br>▪ Melphalan flufenamide + dexamethasone arm: antiemetic prophylaxis<br>▪ Bisphosphonate therapy, where indicated<br>**Disallowed:**<br>▪ Other antineoplastic therapies for treating multiple myeloma<br>▪ Corticosteroids > 10 mg prednisone per day (or prednisolone equivalent)[d] for non-malignant diseases (e.g. asthma, inflammatory bowel disease)<br>▪ Radiotherapy for bone pain allowed with limitations[e] | |

Table 6: Characteristics of the intervention – RCT, direct comparison: melphalan flufenamide + dexamethasone versus pomalidomide + dexamethasone (multipage table)

| Study | Intervention | Comparison |
|---|---|---|
| a. In case of treatment interruption of one drug, the other drug of the treatment arm can be continued.<br>b. After alleviation of the AE, continued treatment possible at the investigator's discretion and in coordination with the medical monitor if the patient substantially benefits from the therapy.<br>c. Information provided on the study's total population; for the subpopulation analysed by the company, the following criteria additionally apply: at least 3 prior lines of therapy, refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38-mAK and disease progression during or after the last therapy; in case of prior autologous stem cell transplantation, the time to progression after transplantation should be at least 3 years.<br>d. Prednisone up to 10 mg orally daily or its equivalent for comorbidity symptom treatment was allowed (at a stable dose ≥ 7 days prior to treatment start).<br>e. Radiotherapy of a limited area of an existing lesion was an option in consultation with the medical monitor and following the latter's approval.<br>AE: adverse event; anti-CD38-mAK: monoclonal CD38 antibody; CMV: cytomegalovirus; IMiD: immunomodulatory drug; i.v.: intravenous; PI: proteasome inhibitor; RCT: randomized controlled trial | | |

The OCEAN study is an ongoing, open-label RCT comparing melphalan flufenamide + dexamethasone versus pomalidomide + dexamethasone. The study included adults with recurrent, refractory multiple myeloma who received 2 to 4 prior treatment lines, including both lenalidomide and a proteasome inhibitor. These patients had to be either (a) refractory or (b) relapsed and refractory to both the last therapy line and lenalidomide within the past 18 months prior to randomization and have exhibited disease progression on or after the last therapy. The study excluded patients with primary refractory disease as well as those who had previously received pomalidomide.

A total of 495 patients were randomized to treatment with melphalan flufenamide + dexamethasone (n = 246) or pomalidomide + dexamethasone (n = 249). Stratification factors were age (≥ 75 years versus < 75 years), number of prior therapies (2 versus 3 to 4), and International Staging System (ISS) stage (I versus ≥ II).

In both study arms, treatment was administered until a reason for discontinuation arose (e.g. disease progression, unacceptable toxicity, or withdrawal of consent). Pomalidomide was administered in accordance with the specifications in the SPC [13]. The dosages of melphalan flufenamide [14] and dexamethasone [13] in part differed from the SPC. For instance, a reduced initial dose of 30 mg (instead of 40 mg) is specified for patients with a body weight of up to 60 kg – this reduced initial dose is also recommended for patients with renal impairment and an eGFR of 30 to 45 mL/min/1.73 $m^2$. Irrespective of weight or renal impairment, the OCEAN study, in contrast, administered an initial dose of 40 mg. In case of toxicity, the OCEAN study allowed reducing this initial dose of melphalan flufenamide in 2 steps to a minimum of 20 mg (see Table 6). The SPC specifies a 3rd dose reduction step down to 15 mg before melphalan flufenamide must be permanently discontinued [14]. According to the pomalidomide SPC [13], the dexamethasone dose can be reduced to a minimum of 10 mg in patients ≤ 75 years of age, e.g. in case of toxicity. In the OCEAN study, < 75-year-old patients were allowed to do the same only to a minimum dose of 12 mg.

After discontinuing dexamethasone, it was possible to continue treatment with the remaining drug component (melphalan flufenamide or pomalidomide) upon the investigator's discretion. No restrictions applied regarding subsequent therapies after the end of the study medication.

The primary outcome of the study was PFS. Patient-relevant secondary outcomes were overall survival, morbidity, health-related quality of life, and AEs.

*Subpopulation of the OCEAN study analysed by the company*

In the OCEAN study, some inclusion criteria regarding patients' prior therapies are stricter or more lenient than those specified in the SPCs for melphalan flufenamide+ dexamethasone or pomalidomide + dexamethasone [13,14]. Firstly, the OCEAN study allowed enrolling patients with 2 prior therapies (instead of at least 3 prior therapies) without any specifications regarding the interval between any prior stem cell transplantation and progression. Secondly, the OCEAN study's inclusion criteria specified that patients had to have received prior therapy with lenalidomide from the drug class of immunomodulatory agents, while the approval of melphalan flufenamide refers not to drugs, but to drug classes in terms of prior therapy.

In the dossier's Module 4A, the company reportedly analyses the OCEAN study's subpopulation designed to match the target population of melphalan flufenamide + dexamethasone. According to the company, the subpopulation hence comprises adult patients with multiple myeloma who received at least 3 prior lines, of therapy, whose disease is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory agent, and 1 monoclonal CD38 antibody and who have exhibited disease progression during or after the last therapy. In patients with prior autologous stem cell transplantation, the time to progression after transplantation was to be at least 3 years.

The subpopulation analysed by the company comprises a total of 22 patients: 12 in the melphalan flufenamide + dexamethasone arm and 10 in the pomalidomide + dexamethasone arm. The company's dossier presents analyses on these patients.

*Information on data cut-offs*

In the dossier's Module 4A, the company lists 3 February 2021 as the data cut-off when describing the OCEAN study. The company reports that 7 May 2020 is the date of the last data entry for this data cut-off and is therefore referred to as "database date" in the document with additional analyses [5] for the dossier (referred to by the company as recalculation document). However, in Module 4A, data cut-offs on 5 July 2020 and 7 May 2022 were additionally cited, depending on the outcome. For the outcome of overall survival, Section 4.4.2 of the company's dossier additionally presented, alongside analyses of a 3 February 2021 data cut-off, analyses on a follow-up conducted 1 year later dated 3 February 2022 – but the latter was not conducted separately for the OCEAN subpopulation analysed by the company.

For the 3 February 2021 data cut-off, this is presumably the final analysis of the PFS outcome, which was pre-specified to be conducted after the occurrence of 339 events (and was in fact

conducted after 355 events). Contrary to the information provided by the company in Module 4A and the supplementary analyses document, the study documents on the 3 February 2021 data cut-off cite 7 May 2021 as the "database date", describing it as the date until which protocol violations occurring up to the 3 February 2021 data cut-off were subsequently entered. It remains unclear what specifically prompted the more recent data cut-off (follow-up) of 3 February 2022 for the outcome of overall survival.

For the OCEAN study, the information on the data cut-off dates and the date of the last data entry ("database date") was overall inconsistent (1) within the dossier's Module 4A and (2) between Module 4A, the document containing additional analyses for the dossier, and the study report. Therefore, the data cut-off (and "database date") on which the data presented in the company's dossier rest remains unclear.

***Appropriate comparator therapy not implemented in the OCEAN study***

The OCEAN study data presented by the company are unsuitable for assessing the added benefit of melphalan flufenamide + dexamethasone in comparison with the ACT. This is due to a failure to implement the G-BA's specified ACT of individualized therapy taking into account prior therapies as well as the extent and duration of response; instead, all patients of the comparator arm received an undifferentiated treatment regimen consisting of pomalidomide + dexamethasone.

The company justifies the undifferentiated administration of pomalidomide + dexamethasone in the OCEAN study's comparator arm with the fact that, in the context of individualized therapies, the majority of patients in the German healthcare context is treated with this drug combination from the 3rd line of therapy.

The company's reasoning is not substantive. The company concedes that both national and international guideline recommendations [15-21] show that alongside pomalidomide-based treatment regimens, daratumumab likewise represents the standard of therapy in recurrent, refractory multiple myeloma from the 3rd line of therapy. In addition, the company explains that, from the 4th line of therapy, about 30% to 40% of patients in France, Germany, Italy, and the United Kingdom receive pomalidomide in combination with dexamethasone in a double or triple combination [22]; the MYRIAM registry [23] cited by the company shows that, in the years 2017 to 2021, the percentage of pomalidomide-based treatment regimens was 35.1% in the 4th line of therapy and 44.4% in the 5th line of therapy. Accordingly, the majority of patients receives other, non-pomalidomide-based therapies after the 3rd line of therapy. The current S3 guideline (2022) [24] cited by the company describes, for treatment of the 1st to 3rd recurrence, that physically fit patients – such as OCEAN participants – reap greater added benefit from a triple combination than from a double combination.

Furthermore, the company's dossier explains that no fixed treatment standard exists for the heterogeneous patient population with triple-class refractory multiple myeloma, and therapy must be individually optimized. The treatment decision would have to be assessed individually

in terms of refractoriness, general health, comorbidities, intolerance, and treatment goals. In the company's view, the various treatment options are therefore not equivalent for the individual patient. In this context, the company refers to the treatment options cited in various guidelines [15,16,21,25,26] according to which options include, among others, repeat therapy with previously used drugs and drug combinations or best supportive care.

Overall, the sources cited by the company show that pomalidomide-based treatment regimens represent one of several options for the treatment of patients in the present therapeutic indication. However, the company fails to adequately justify the extent to which the administration of pomalidomide + dexamethasone represents the most suitable treatment option for OCEAN participants taking into account prior therapy and the extent and duration of response. For the implementation of the ACT, investigators in the study should therefore have been offered several therapy options to choose from, where possible.

Irrespective of the OCEAN study being unsuitable for the benefit assessment, the presented results for the subpopulation show neither advantages nor disadvantages for melphalan flufenamide + dexamethasone.

***HORIZON study presented by the company as supportive evidence***

The HORIZON study is a single-arm, open-label study with melphalan flufenamide + dexamethasone. The study included adults with recurrent, refractory multiple myeloma who received at least 2 prior lines of therapy, including both an immunomodulator and a proteasome inhibitor. Patients had to have been refractory to pomalidomide and/or a monoclonal CD38 antibody. In the dossier, the company presents data for the subpopulation of patients who were triple refractory or intolerant to at least 1 immunomodulatory agent, 1 proteasome inhibitor, and 1 monoclonal CD38 antibody (referred to by the company as TCR [triple class refractory] population).

The HORIZON study is disregarded in the present benefit assessment because, due to the absence of a comparator arm, no conclusions on added benefit can be drawn for melphalan flufenamide + dexamethasone versus the ACT.

**Conclusion**

Overall, the data presented by the company do not allow comparing melphalan flufenamide + dexamethasone versus the ACT specified by the G-BA.

## I 4 Results on added benefit

No suitable data are available for assessing the added benefit of melphalan flufenamide + dexamethasone in comparison with the ACT in adult patients with multiple myeloma who have received at least 3 prior lines of therapy, whose disease is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory agent, and 1 anti-CD38 monoclonal antibody, and who have demonstrated disease progression during or after the last therapy (for patients with prior autologous stem cell transplantation, the time to progression after transplantation should be at least 3 years). This results in no hint of an added benefit of melphalan flufenamide + dexamethasone in comparison with the ACT; an added benefit is therefore not proven.

## I 5 Probability and extent of added benefit

Table 7 summarizes the result of the assessment of added benefit of melphalan flufenamide + dexamethasone in comparison with the ACT.

Table 7: Melphalan flufenamide + dexamethasone – probability and extent of added benefit (multipage table)

| **Therapeutic indication** | **ACT**[a] | **Probability and extent of added benefit** |
|---|---|---|
| Adults with multiple myeloma who have received at least 3 prior therapies, whose disease is refractory to at least<br>1 proteasome inhibitor,<br>1 immunomodulatory agent and<br>1 anti-CD38 monoclonal antibody, and who have demonstrated disease progression during or after the last therapy; for patient with prior autologous stem cell transplantation, the time to progression after transplantation should be at least 3 years | Individualized treatment[b, c] selected from:<br>▪ bortezomib monotherapy<br>▪ bortezomib + pegylated liposomal doxorubicin<br>▪ bortezomib + dexamethasone<br>▪ carfilzomib + lenalidomide and dexamethasone<br>▪ carfilzomib + dexamethasone<br>▪ daratumumab + lenalidomide + dexamethasone<br>▪ daratumumab + bortezomib + dexamethasone<br>▪ daratumumab monotherapy (only for patients with disease progression on the last therapy)<br>▪ elotuzumab + lenalidomide + dexamethasone<br>▪ elotuzumab + pomalidomide + dexamethasone (only for patients with disease progression on the last therapy)<br>▪ isatuximab + pomalidomide + dexamethasone (only for patients with disease progression on the last therapy)<br>▪ ixazomib + lenalidomide + dexamethasone<br>▪ lenalidomide + dexamethasone<br>▪ panobinostat + bortezomib and dexamethasone<br>▪ pomalidomide + bortezomib and dexamethasone<br>▪ pomalidomide + dexamethasone (only for patients with disease progression on the last therapy)<br>▪ cyclophosphamide (in combination with other antineoplastic agents)<br>▪ melphalan<br>▪ doxorubicin<br>▪ carmustine (in combination with other cytostatic agents and an adrenal cortex hormone, particularly prednisone)<br>▪ vincristine<br>▪ dexamethasone<br>▪ prednisolone<br>▪ prednisone<br>▪ best supportive care[d]<br>taking into account prior therapies as well as the extent and duration of response | Added benefit not proven |

Table 7: Melphalan flufenamide + dexamethasone – probability and extent of added benefit (multipage table)

| Therapeutic indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|
| a. Presented is the ACT specified by the G-BA.<br>b. According to the G-BA, the special situation of refractory patients is presumably taken into account when choosing the ACT.<br>c. For the implementation of individualized therapy in a direct comparative study, according to the G-BA, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). The choice and, if necessary, limitation of treatment options must be justified.<br>d. Best supportive care refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee | | |

The assessment described above deviates from the company's, which derived a hint of non-quantifiable added benefit on the basis of the results of the OCEAN study as well as the results of the HORIZON study which were provided as supplementary information.

The G-BA decides on the added benefit.

## I 6 References for English extract

Please see full dossier assessment for full reference list.

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Accessed: 27.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Oncopeptides AB. Clinical Study Report. OP-103 OCEAN TRIAL. A Randomized, Controlled, Open-Label, Phase 3 Study of Melflufen/Dexamethasone Compared with Pomalidomide for Patients with Relapsed Refractory Multiple Myeloma who are Refractory to Lenalidomide. 2021.

4. Oncopeptides AB. PRO Reporting for the OP-103 OCEAN TRIAL (Version 1.0). 2021.

5. Oncopeptides AB. Nachberechnungen zu Melflufen (Studie OCEAN). 2022.

6. Oncopeptides AB. A Study of Melphalan Flufenamide (Melflufen)-Dex or Pomalidomide-dex for RRMM Patients Refractory to Lenalidomide [online]. 2022 [Accessed: 26.10.2022]. URL: https://ClinicalTrials.gov/show/NCT03151811.

7. Oncopeptides AB. A Randomized, Controlled, Open-Label, Phase 3 Study of Melflufen/ Dexamethasone Compared with Pomalidomide/Dexamethasone for Patients with Relapsed Refractory Multiple Myeloma who are Refractory to Lenalidomide [online]. 2017 [Accessed: 26.10.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-003517-95.

8. Schjesvold FH, Dimopoulos M-A, Delimpasi S et al. Melflufen or pomalidomide plus dexamethasone for patients with multiple myeloma refractory to lenalidomide (OCEAN): a randomised, head-to-head, open-label, phase 3 study. The Lancet Haematology 2022; 9(2): e98-e110. https://dx.doi.org/https://doi.org/10.1016/S2352-3026(21)00381-1.

9. European Medicines Agency. Assessment report. Pepaxti; International non-proprietary name: melphalan flufenamide; Procedure No. EMEA/H/C/005681/0000 [online]. 2022 [Accessed: 18.11.2022]. URL: https://www.ema.europa.eu/documents/assessment-report/pepaxti-epar-public-assessment-report_en.pdf.

10. Richardson PG, Oriol A, Larocca A et al. Melflufen and Dexamethasone in Heavily Pretreated Relapsed and Refractory Multiple Myeloma. J Clin Oncol 2021; 39(7): 757-767. https://dx.doi.org/10.1200/jco.20.02259.

11. Oncopeptides AB. NCT 02963493 - A Study of Melphalan Flufenamide (Melflufen) Plus Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma (HORIZON) [online]. 2022 [Accessed: 09.08.2022].

12. Rajkumar SV, Harousseau J-L, Durie B et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011; 117(18): 4691-4695. https://dx.doi.org/10.1182/blood-2010-10-299487.

13. Bristol Myers Squibb. IMNOVID: Hartkapseln [online]. 2021 [Accessed: 12.10.2022]. URL: https://www.fachinfo.de.

14. Oncopeptides AB. Pepaxti 20 mg; Pulver für ein Konzentrat zur Herstellung einer Infusionslösung [online]. 2022 [Accessed: 10.10.2022]. URL: https://www.fachinfo.de.

15. Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie. Onkopedia Leitlinien Multiples Myelom [online]. 2018 [Accessed: 29.11.2022]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/multiples-myelom/@@guideline/html/index.html.

16. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. S3-Leitlinie Diagnostik, Therapie und Nachsorge für Patienten mit monoklonaler Gammopathie unklarer Signifikanz (MGUS) oder Multiplen Myelom. Leitlinie Kurzversion 1.0. 2022.

17. Chaplin F. Updated ESMO Clinical Practice Guidelines. 2017 [online]. 2017 [Accessed: 29.11.2022]. URL: https://multiplemyelomahub.com/medical-information/updated-esmo-clinical-practice-guidelines.

18. Dingli D, Ailawadhi S, Bergsagel PL et al. Therapy for Relapsed Multiple Myeloma: Guidelines From the Mayo Stratification for Myeloma and Risk-Adapted Therapy. Mayo Clin Proc 2017; 92(4): 578-598. https://dx.doi.org/10.1016/j.mayocp.2017.01.003.

19. Mayo Clinic. Treatment of Relapsed Myeloma – Mayo Consensus (v6) [online]. 2020 [Accessed: 29.11.2022]. URL: https://static1.squarespace.com/static/5b44f08ac258b493a25098a3/t/5ebc6d766a179e3b0e30c8d0/1589407097177/Treatment-of-Relapsed-Myeloma+rev7_May2020.pdf.

20. Moreau P, San Miguel J, Sonneveld P et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology 2017; 28(suppl_4): iv52-iv61. https://dx.doi.org/10.1093/annonc/mdx096.

21. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Multiple Myeloma, Version 1.2022, August 16, 2021. 2021.

22. Goldschmidt H, Gordon C, Moreau P et al. Use of Pomalidomide-based Regimens in Relapsed/Refractory Multiple Myeloma in Four European Countries - Findings From PREAMBLE [online]. 2019 [Accessed: 29.11.2022]. URL: https://library.ehaweb.org/eha/2019/24th/267022/philippe.moreau.use.of.pomalidomide-based.regimens.in.relapsed.refractory.html.

23. iOMedico. MYRIAM - Myeloma Registry Platform Quarterly Report Database cut: 31.12.2021. 2022.

24. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. S3-Leitlinie Diagnostik, Therapie und Nachsorge für Patienten mit monoklonaler Gammopathie unklarer Signifikanz (MGUS) oder Multiplen Myelom. Leitlinie Langversion 1.0 [online]. 2022 [Accessed: 29.11.2022].

25. Dimopoulos MA, Moreau P, Terpos E et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021; 32(3): 309-322. https://dx.doi.org/10.1016/j.annonc.2020.11.014.

26. Moreau P, Kumar SK, San Miguel J et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. Lancet Oncol 2021; 22(3): e105-e118. https://dx.doi.org/10.1016/s1470-2045(20)30756-7.

*The full report (German version) is published under https://www.iqwig.de/en/projects/a22-104.html.*