Melphalan flufenamide (Pepaxti®) in combination with dexamethasone for the treatment of multiple myeloma (MM)

General information

Drug description [1]

Melphalan flufenamide (Pepaxti®, known as melflufen) is a first-in-class peptide-drug conjugate that targets aminopeptidases and thereby rapidly releases alkylating agents inside tumour cells. Due to its high lipophilicity and affinity for aminopeptidases, melflufen can passively enter tumour cells and release cytotoxic, hydrophilic alkylating agents that remain trapped within cells.

Indication [2]

Melphalan flufenamide (Pepaxti®) is indicated, in combination with dexamethasone, for the treatment of adult patients with MM who have received at least two prior lines of therapies, whose disease is refractory to lenalidomide and the last line of therapy.

Incidence [3]

In Austria, in 2020, a total of 521 persons were newly diagnosed with plasmacytoma/myeloma. The age-standardised incidence rate[1] was 7.3 per 100,000 men and 4.3 per 100,000 women.

Current treatment [4]

- For the treatment of MM (third-line and beyond), Onkopedia recommends the following:
  - The choice of therapy in patients with relapsed or refractory disease after second-line therapy depends on the patient´s aims and, essentially, on the patient´s experiences with prior therapies.
  - Recent data, regarding patients who received at least 2 lines of therapy, can be summarised as follows:
    - Repetition of second-line therapy in patients with long, deep remission and good tolerability.
    - New double- or triple combinations of second-line therapy agents.
    - Additional options:
      - Panobinostat, combined with bortezomib/dexamethasone (as compared to bortezomib/dexamethasone) leads to prolongation of PFS, but not of OS.
      - Pomalidomide combined with low-dosed dexamethasone (as compared with high-dosed dexamethasone) lead to a prolonged PFS and OS and increases the remission rate. The additional combination with cyclophosphamide increases the response rate, but also the haematological toxicity.
      - With daratumumab monotherapy, 30% of heavily pretreated patients achieve at least partial remission and a median PFS of 4 months.
      - Cytostatic agents: Efficient "classical" cytostatic agents are bendamustine, cyclophosphamide, doxorubicin and melphalan, each as monotherapy or as combination therapy. This also includes therapy regimens such as DCEP or DT-PACE that are partially administered by continuous infusion.

Regulatory status

EMA [2]	FDA [5]
Approval status for this indication: On 14 September 2023, the CHMP adopted a change to the existing indication for the treatment of adult patients with MM. The full indication for will be as follows: ❖ Melphalan flufenamide (Pepaxti®) is indicated, in combination with dexamethasone, for the treatment of adult patients with MM who have received at least two prior lines of therapies, whose disease is refractory to lenalidomide and the last line of therapy.	**Approval status for this indication**: FDA's Center for Drug Evaluation and Research has provided Oncopeptides AB (Oncopeptides) notice of its proposal to withdraw accelerated approval of Pepaxto® (melphalan flufenamide) because the post-approval confirmatory trial required as a condition of Pepaxto®'s approval failed to verify clinical benefit and available evidence demonstrates Pepaxto® is not shown to be safe or effective under its conditions of use (**Update** 24 August 2023). An Oncologic Drugs Advisory Committee (ODAC) was held on 22 September 2022, to discuss the results of the OCEAN confirmatory trial and the benefit-risk profile of Pepaxto® for the indicated population. The ODAC voted 14 to 2 that the benefit-risk profile of melphalan flufenamide was not favourable for the currently indicated patient population, given the results of the OCEAN confirmatory trial. **Other indications**: none

[1] European Standard Population 2013.

For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation. **Other indications**: none	

Manufacturer

Pepaxti® is manufactured by Oncopeptides AB.

Costs

Currently, there is no cost information available.

Warnings and precautions [6]

- **Thrombocytopenia**
  - Pepaxti® may cause thrombocytopenia. Thrombocytopenia (including platelet count decreased) was frequently reported in clinical studies. As thrombocytopenia may increase the risk for serious bleeding events, patients should be advised to contact a physician if signs or symptoms of bleeding and bruising occur.
  - Platelet counts should be monitored at baseline, during treatment, and as clinically indicated. Patients should be monitored more frequently during the first two months of treatment. Pepaxti® should not be administered if the platelet count is less than 50×10^9/L. Treatment should be withheld until platelet count is 50×10^9 /L or greater (without recent transfusions) and resume treatment at one dose level lower. The dose and/or dose schedule should be adjusted based on signs and symptoms of bleeding. Treating thrombocytopenia with transfusions and/or other treatments should be considered as clinically indicated.
- **Neutropenia**
  - Pepaxti® may cause neutropenia. Neutropenia (including neutrophil count decreased) was frequently reported in clinical studies. As neutropenia may increase the risk for infections, patients should be advised to contact a physician if signs or symptoms of infection occur. Neutrophil count should be monitored at baseline, during treatment, and as clinically indicated.
  - Patients should be monitored more frequently during the first two months of treatment. Pepaxti® should not be administered if absolute neutrophil count is less than 1×10^9/L. Treatment should be withheld until absolute neutrophil count is 1×10^9/L or greater and resume treatment at one dose level lower. The dose and/or dose schedule should be adjusted based on signs and symptoms of infection. Treating neutropenic patients with haematopoietic growth factors and/or prophylactic antimicrobials should be considered as clinically indicated.
- **Anaemia**
  - Anaemia was frequently reported in clinical studies. Red blood cell counts should be monitored at baseline, during treatment, and as clinically indicated. Patients should be monitored more frequently during the first two months of treatment. Treating anaemia with transfusions and/or erythropoietin should be considered as clinically indicated.
- **Infections**
  - Pepaxti® may cause infections, including Grade ≥ 3 infections such as pneumonia and upper respiratory tract infection. Patients should be closely monitored for signs of infection. Treating infections with antimicrobials should be considered as clinically indicated.
- **Gastrointestinal events**
  - Nausea and diarrhoea are very common, and vomiting is common during treatment with Pepaxti®. Prophylaxis with anti-emetic agents should be considered prior to and during infusion with melphalan flufenamide.
- **Thromboembolic events**
  - Venous thromboembolic events have been observed in patients receiving Pepaxti® in combination with dexamethasone. Patients with known risk factors for thromboembolism, including prior thrombosis, should be closely monitored. A decision to take prophylactic measures should be made after a careful assessment of the individual patient's underlying risk factors, including the occurrence of thrombocytopenia.
  - In high-risk patients, anti-thrombotic prophylaxis can be considered.
- **Mutagenicity**
  - Melphalan, a metabolite of melphalan flufenamide, is mutagenic in animals and chromosome aberrations have been observed in patients being treated with melphalan.

- **Carcinogenicity**
  - Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)
    - AML and MDS have occurred in patients with multiple myeloma who have received Pepaxti®. The leukaemogenic risk must be balanced against the potential therapeutic benefit when considering the use of melphalan flufenamide. Patients should be monitored closely before and during treatment for occurrence of AML and MDS.
  - Second primary malignancies (SPM)
    - The use of alkylating agents has been linked to the development of a SPM and SPMs have been reported also after use of Pepaxti®. When the melphalan flufenamide metabolite melphalan is used in combination with lenalidomide and prednisone, and to a lesser extent in combination with thalidomide and prednisone, it has been linked to an increased risk of solid SPMs for elderly patients with newly diagnosed MM. Melphalan flufenamide is not indicated in combination with lenalidomide or thalidomide. Patients should be monitored closely before and during treatment for occurrence of SPM.
  - Prior autologous stem cell transplant
    - Pepaxti is not recommended in patients who have progressed within 36 months after an ASCT (based on results from OCEAN trial).
- **Myeloablative conditioning treatment**
  - The efficacy and safety of Pepaxti® at doses required for myeloablation have not been studied in humans. Pepaxti® should not be used for conditioning treatment prior to stem cell transplantation.
- **Renal impairment**
  - Since patients with renal impairment may have marked bone marrow suppression, these patients should be closely monitored. There are insufficient data in patients with eGFR below 30 mL/min/1.73 m^2 to support a dose recommendation.
- **Attenuated live vaccines**
  - A risk of severe illness that may lead to fatal outcome has been described with the metabolite melphalan in patients receiving attenuated live vaccines. This risk is increased in patients who are already immunosuppressed by their underlying disease. An inactivated or mRNA-based vaccine should be used when such a vaccine exists.

Study characteristics [1, 7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up (I vs. C)	Characteristics	Biomarker	Funding	Publication(s)
OCEAN NCT03151811	495 (1:1)	melflufen 40 mg IV over 30 min on day 1 of each cycle + dexamethasone 40 mg orally on days 1, 8, 15, and 22 of each cycle	pomalidomide 4 mg orally daily on days 1 to 21 of each cycle + dexamethasone 40 mg orally on days 1, 8, 15, and 22 of each cycle	PFS assessed by IRC in the ITT population	15.5 vs. 16.3 months	randomised, controlled, open-label, head-to head, phase 3 study	-	Oncopeptides AB	OCEAN trial [1]

Inclusion criteria[2]	Exclusion criteria	Patient characteristics at baseline
❖ ≥18 years ❖ Previous diagnosis of MM with documented disease progression in need of treatment at time of screening. ❖ 2 to 4 previous lines of therapy, including lenalidomide and a proteasome inhibitor, either sequential or in the same line, and is refractory (relapsed and refractory or refractory) to both the last line of therapy and to lenalidomide (≥10 mg) administered within 18 months before randomisation.	❖ Primary refractory disease (ie, never responded with ≥ minimal response to any previous therapy). ❖ Evidence of mucosal or internal bleeding and/or platelet transfusion refractory. ❖ Any medical conditions that, in the investigator's opinion, would impose excessive risk to the patient or would adversely affect his/her participating in this study. ❖ Previous exposure to pomalidomide.	❖ Median age: 68 (60–72) vs. 68 (61–72) years ❖ Male sex: 57% vs. 56% ❖ Time since diagnosis: 4.0 (2.6–6.2) vs. 3.9 (2.5–6.2) years ❖ ECOG PS at baseline: • 0: 37% vs. 37% • 1: 53% vs. 55% • 2: 11% vs. 8%

[2] For detailed in- and exclusion criteria, please see Supplementary Appendix.

❖ Relapsed myeloma was defined as previously treated myeloma that progressed and required the initiation of salvage therapy but did not meet the criteria for either relapsed and refractory myeloma or primary refractory myeloma. Measurable disease defined as any of the following: • Serum monoclonal protein ≥0.5 g/dL by serum protein electrophoresis • ≥200 mg/24 hours of monoclonal protein in the urine on 24-hour urine electrophoresis • Serum free light chain ≥10 mg/dL AND abnormal serum kappa to lambda free light chain ratio. ❖ Life expectancy of ≥6 months. ❖ ECOG PS ≤2 ❖ Females of childbearing potential; men must agree to use a condom during sexual contact with a female of childbearing potential even if they have had a vasectomy from the time of starting study treatment through 3 months after the last dose of melflufen or 28 days after the last dose of pomalidomide. ❖ Ability to understand the purpose and risks of the study and provided signed and dated informed consent. ❖ 12-lead Electrocardiogram with QT interval calculated by Fridericia Formula interval of ≤470 msec. ❖ The following laboratory results must be met during screening and immediately before study drug administration on cycle 1 day 1: • Absolute neutrophil count ≥1,000 cells/mm^3 ($1.0x10^9$/L) (growth factors cannot be used within 10 days before the first drug administration) • Platelet count ≥75,000 cells/mm^3 ($75x10^9$/L) (without required transfusions during the 10 days before the first drug administration) • Haemoglobin ≥8.0 g/dl (red blood cell transfusions are permitted) • Total Bilirubin ≤1.5 x upper limit of normal, or patients diagnosed with Gilbert's syndrome, which have been reviewed and approved by the medical monitor	❖ Known intolerance to immunomodulatory drugs (grade ≥3 hypersensitivity reaction or at the investigators' discretion). ❖ Known active infection requiring parenteral or oral anti-infective treatment within 14 days of randomisation. ❖ Other malignancy diagnosed or requiring treatment within the past 3 years except for adequately treated basal cell carcinoma, squamous cell skin cancer, carcinoma in situ of the cervix or breast or very low and low risk prostate cancer in active surveillance. ❖ Pregnant or breast-feeding females. ❖ Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse compliance or follow-up evaluation. ❖ Known human immunodeficiency virus or active hepatitis B or C viral infection. ❖ Active hepatitis B viral infection. ❖ Patients with previous hepatitis B vaccine are permitted. ❖ Non-active hepatitis B may be enrolled at the discretion of the investigator after consideration of risk of reactivation. ❖ Concurrent symptomatic amyloidosis or plasma cell leukaemia. ❖ POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes). ❖ Previous cytotoxic therapies, including cytotoxic investigational agents, for MM within 3 weeks (6 weeks for nitrosoureas) before the initiation of therapy. The use of live vaccines within 30 days before initiation of therapy. Immunomodulatory agents, proteasome inhibitors, and/or corticosteroids within 2 weeks before the initiation of therapy. Other investigational therapies and monoclonal antibodies within 4 weeks of initiation of therapy prednisone up to but no more than 10 mg orally once daily or its equivalent for symptom management of comorbid conditions is permitted but dose should be stable for at least 7 days before randomisation. ❖ Residual side effects to previous therapy grade >1 before randomisation (alopecia any grade and/or neuropathy grade 2 without pain are permitted).	❖ International Staging System score at study entry: • I: 48% vs. 50% • II: 38% vs. 38% • III: 13% vs. 12% ❖ Cytogenetic risk group at diagnosis: • High risk: 34% vs. 35% • Standard: 52% vs. 52% ❖ Extramedullary disease at study entry: 13% vs. 12% ❖ Median number of previous lines of therapy: • 2: 46% vs. 45% • 3 or 4: 54% vs. 55% ❖ Previous ASCT: • Yes: 51% vs. 48% • No: 49% vs. 52% ❖ Refractory to previous therapy: • Alkylator: 32% vs. 30% ❖ Proteasome inhibitor: 66% vs. 65% ❖ Immunomodulatory agent: >99% vs. 100% ❖ Anti-CD38 monoclonal antibody: 20% vs. 16% ❖ Double refractory disease: 66% vs. 65% ❖ Triple-class refractory disease: 16% vs. 12% ❖ Last line[3]: >99% vs. 99%

[3] Did not have at least a minimal response or progression on therapy within 60 days of the last dose of treatment.

• Aspartate transaminase and alanine transaminase ≤3.0xupper limit of normal • Renal function: Estimated creatinine clearance by Cockcroft-Gault formula ≥45 mL/min ❖ Must be able to take antithrombotic prophylaxis. ❖ Must have had, or been willing to have, an acceptable central catheter.	❖ Previous peripheral stem cell transplant within 12 weeks of randomisation ❖ Previous allogeneic stem cell transplantation with active graft-versus-host-disease ❖ Previous major surgical procedure or radiation therapy within 4 weeks of the randomisation (this does not include limited course of radiation used for management of bone pain within 7 days of randomisation) ❖ Known intolerance to steroid therapy.	

Efficacy (I vs. C)	**Safety** (I vs. C)
Data cutoff 3 February 2021: **Median PFS:** 6.8 months (95% CI, 5.0–8.5) vs. 4.9 months (95% CI, 4.2–5.7); HR 0.79 (95% CI, 0.64–0.98); log-rank p=0.032 **ORR**: 33% (95% CI 27–39) vs. 27% (95% CI, 22–33); p=0.16 **CR**: 3%. vs. 1% **Very good PR**: 9% vs. 7% **PR:** 20% vs. 18% **Median OS**: 19.8 months (95% CI 15.1–25.6; at a median follow-up of 19.8 months) vs. 25.0 months (95% CI 18.1–31.9; at a median follow-up of 18.6 months); HR 1.10 (95% CI 0.85–1.44); log-rank p=0.47 **Time to first confirmed response**: 2.1 months (IQR 1.1–3.7) vs. 2.0 months (1.1–2.9) **Time to best confirmed response**: 3.2 months (IQR 1.9–5.9) vs. 2.8 months (1.2–5.6)	**Serious TEAEs**: n=95/228 (42%) vs. n=113/246 (46%) **Thrombocytopenia grade 3 or 4**: n=174/228 (76%) vs. n=31/246 (13%) **Grade 3 or 4 infections**: n=30/228 (13%) vs. n=53/246 (22%) **Development of second primary malignancies[4]:** n=3/228 (1%) vs. n=6/246 (2%) **Permanent treatment discontinuation due to a TEAE**: n=60/228 (26%) vs. n=54/246 (22%) **AEs leading to death[5]:** n=27/228 (12%) vs. n=32/246 (13%)

Patient-reported outcomes

- ❖ Baseline characteristics were generally well matched between patients reporting patient-reported outcomes (n=158) and the overall study population (n=495).
- ❖ Overall, mean baseline scores before treatment were similar between I and C: 63.8 vs. 64.3 in Global Health Status/QoL, 72.4 vs. 74.2 in physical functioning, 81.0 vs. 79.8 in emotional functioning, 35.1 vs. 32.6 in fatigue, 30.2 vs. 28.7 in pain, 24.7 vs. 22.6 in disease symptoms, 16.1 vs. 16.1 in side effects of treatment, and 64.0 vs. 66.9 for the EQ-5D-3L VAS, respectively.
- ❖ Mean scores remained generally constant between baseline and follow-up timepoints.
- ❖ Mean baseline scores before treatment with melflufen and dexamethasone were similar between the target population and the non–target population[6] groups: 65.3 vs. 61.9 in Global Health Status/QoL, 73.2 vs. 71.5 in physical functioning, 83.3 vs .78.0 in emotional functioning, 30.7 vs. 40.7 in fatigue, 26.2 vs. 35.4 in pain, 23.0 vs. 27.1 in disease symptoms, 15.9 vs. 16.3 in side effects of treatment, and 64.8 vs. 62.8 for the EQ-5D-3L VAS, respectively.
- ❖ Despite small patient numbers (n=44), the target population group showed a similar trend to that of the overall population.
- ❖ HRQoL was maintained throughout treatment with melflufen and dexamethasone, including in the target population, and was similar to that with pomalidomide and dexamethasone.

ESMO-MCBS for Haematological Malignancies Version 1.0 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM

[4] Including one (<1%) patient in the melflufen group who developed AML and one (<1%) in the pomalidomide group who developed myelodysplastic syndromes, both of which were fatal.
[5] Most commonly COVID-19 pneumonia (3% vs. 2%), pneumonia (1% vs. 2%), and multiorgan dysfunction syndrome (1% vs. 1%). TEAEs leading to death were considered possibly related to treatment with melflufen in 2 patients (one patient with AML and in one with pancytopenia and acute cardiac failure) and pomalidomide in 4 patients (2 patients with pneumonia, 1 with myelodysplastic syndromes, and 1 with COVID-19 pneumonia).
[6] Non-target population = patients with TTP <36 months after an ASCT.

Original	NC	2b	<6 months	PFS: +1.9 months	0.79 (0.64-0.98)	HR ≤0.65 AND gain ≥1.5 months	3	Serious AEs >20%	maintained	-1[7]; -1[8]	1
Adapted	-	-	-	-	-	-	-	-	-	-	-

Risk of bias (RCT) [11]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	-	no high risk	yes low risk	yes[9] high risk	**High risk**

Ongoing trials

No ongoing trials were identified.

Available assessments

- IQWIG assessed the efficacy of melphalan flufenamide combined with dexamethasone in adult patients with MM who received at least 3 prior lines of therapies whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody and who have demonstrated disease progression on or after the last line of therapy in December 2022 [12].
- The planned appraisal of the clinical and cost effectiveness of melphalan flufenamide with dexamethasone within its marketing authorisation for treating relapsed or refractory MM was suspended from NICE's work programme following on from information provided by the company in December 2021. As no further information has been received from the company the topic has been discontinued in December 2022 [13].
- NIHR carried out a Health Technology Briefing "Melphalan flufenamide in combination with dexamethasone for treating adult patients with relapsed or refractory multiple myeloma" in August 2020 [14].
- No further assessments were identified via CADTH and ICER.

Other aspects and conclusions

- In September 2023, the **CHMP adopted a change to the existing indication** for the treatment of adult patients with MM; Melphalan flufenamide (Pepaxti®) is now indicated, in combination with dexamethasone, for the treatment of adult patients with MM who have received at least two prior lines of therapies, whose disease is refractory to lenalidomide and the last line of therapy. In August 2023, FDA's Center for Drug Evaluation and Research has provided Oncopeptides AB (Oncopeptides) notice of its proposal to **withdraw accelerated approval** of Pepaxto® (melphalan flufenamide) because the post-approval confirmatory trial required as a condition of Pepaxto®'s approval **failed to verify clinical benefit** and available evidence demonstrates Pepaxto® is **not shown to be safe or effective** under its conditions of use.
- **OCEAN (NCT03151811)** is a randomised, open-label, phase 3 study to assess melflufen plus dexamethasone versus pomalidomide plus dexamethasone in patients with previously treated MM. Eligible patients had an ECOG performance status of 0–2; must have had relapsed or refractory MM, refractory to lenalidomide and to the last line of therapy; and have received 2 to 4 previous lines of therapy (including lenalidomide and a proteasome inhibitor). Patients with previous exposure to pomalidomide, known intolerance to immunomodulatory drugs or steroid therapy, primary refractory disease, or previous allogeneic HSCT with active graft-versus-host disease were excluded.
- **Primary endpoint** of the OCEAN trial was **PFS** assessed by an IRC in the ITT population. Median PFS was 6.8 months (95% CI 5.0–8.5) in the melflufen group and 4.9 months (95% CI, 4.2–5.7) in the pomalidomide group; HR was 0.79, (95% CI, 0.64–0.98); p=0.032).
- Analyses of patient-reported outcomes showed that **HRQoL was maintained** throughout treatment with melflufen and dexamethasone, including in the target population, and was similar to that with pomalidomide and dexamethasone.
- The **ESMO-MCBS of Haematological Malignancies** was applied, resulting in a final toxicity and QoL adjusted, magnitude clinical benefit grade of **1**; indicating **no substantial magnitude of clinical benefit**.

[7] Downgrading of 1 level due to incremental toxicity of treatment

[8] Downgrading of 1 level : treatment only leads to improved PFS (mature data shows no OS advantage) and QoL assessment does not demonstrate QoL improvement.

[9] The study was designed by the funder (Oncopeptides AB) together with key advisors in the MM community. Study data were collected by site staff and. The funders compiled and maintained the data collected by the investigators. Data were analysed by the study sponsor. All authors and the sponsor participated in the interpretation of the data and writing and reviewing of the manuscript.

- The **risk of bias** of the OCEAN trial was considered as **high**, due to the open-label design of the trial and the fact that the study was designed by the funder; furthermore, data was analysed and interpreted by the funder.
- **No ongoing trials**, evaluating melphalan flufenamide in patients with MM, were identified.
- The CHMP changed the existing indication of Pepaxti®, which is now correlating to the indication assessed by the OCEAN trial. Since the FDA proposes to withdraw the accelerated approval of Pepaxto® due to the results of the OCEAN trial (not showing Pepaxto® to be safe or effective for the assessed indication), further evaluation of melphalan flufenamide in pretreated patients with MM is urgently required. Of note, Pepaxti® is currently NOT under additional monitoring by the EMA.

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Abbreviations: AE=adverse event, AJ=adjustment, AML=acute myeloid leukaemia, ASCT=autologous stem cell transplant, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, DCEP=Dexamethasone, DT-PACE=dexamethasone, thalidomide cisplatin, doxorubicin, cyclophosphamide, etoposide, cyclophosphamide, etoposide, cisplatin, ECOG PS=Eastern Cooperative Oncology Group performance status, eGFR=estimated glomerular filtration rate, EMA=European Medicines Agency, EQ-5D-3L=EuroQol Group 5-Dimension 3-Level questionnaire, ESMO-MCBS=European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HR=hazard ratio, HRQoL=health-related quality of life, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, IQR=interquartile range, IQWIG=Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IRC= independent review committee, ITT=intention-to-treat, MDS=myelodysplastic syndrome, MG=median gain, MM=multiple myeloma, n=number of patients, NICE=National Institute for Health Care Excellence, ODAC=Oncologic Drugs Advisory Committee, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=Quality of Life, SAE=serious adverse event, SPM=second primary malignancies, ST=standard treatment, TEAE=treatment-emergent adverse events, TTP=time to progression, VAS=visual analogue scale

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