Daratumumab (Darzalex®) with bortezomib, lenalidomide and dexamethasone for the treatment of newly diagnosed multiple myeloma (MM)

General information

Drug description [1]

Daratumumab is a human monoclonal IgG1κ antibody against CD38 antigen.

Indication [2]

Darzalex® is indicated in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed MM who are eligible for autologous stem cell transplant.

Incidence [3]

In Austria, in 2022, a total of 556 persons were newly diagnosed with multiple myeloma. The age-standardised incidence rate[1] in Austria was in 2022 for males 7.2 per 100 000 and for females 4.9 per 100 000. As of 2022, the prevalence in absolute numbers was 3008.

Current treatment [4]

The Onkopedia treatment recommendation for the treatment of multiple myeloma is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [2]	FDA [5, 6]
Approval status for this indication: On September 19th, 2024, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending a change to the terms of the marketing authorisation for the medicinal product Darzalex®. The CHMP adopted a new indication as follows: Darzalex® is indicated: ❖ in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant. **Other indications**: Darzalex® is indicated: ❖ in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. ❖ in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant. ❖ in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.	**Approval status for this indication**: Not approved. On November 16th, 2015, the FDA approved Darzalex® for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy, including proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent. **Other indications**: Darzalex® is indicated for the treatment of adult patients with multiple myeloma: ❖ in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy ❖ in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant ❖ in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant ❖ in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy ❖ in combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy ❖ in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor ❖ as monotherapy in patients who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

[1] European Standard Population 2013.

❖ in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy. ❖ as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. ❖ Light chain (AL) amyloidosis Darzalex® is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic AL amyloidosis. ✓ **Orphan status** ✓ **Accelerated assessment[2]**	Of note, Darzalex Faspro® was approved on July 30th, 2024 in the following indication: "in combination with bortezomib, lenalidomide, and dexamethasone for induction and consolidation in patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant".

Marketing authorisation holder in EU [1]

Janssen-Cilag International N.V.

Costs [7]

5 ml Darzalex® concentrate for solution for infusion 100 mg (20mg/ml) = € 524.00 (ex-factory price).

Posology [1]

Dosing schedule in combination with lenalidomide and dexamethasone (4-week cycle regimen) and for monotherapy

The recommended dose is Darzalex® 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in table 1.

Table 1: DARZALEX dosing schedule in combination with lenalidomide and dexamethasone (Rd) (4-week cycle dosing regimen) and monotherapy

Weeks	Schedule
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24[a]	every two weeks (total of 8 doses)
Week 25 onwards until disease progression[b]	every four weeks

[a] First dose of the every-2-week dosing schedule is given at week 9.
[b] First dose of the every-4-week dosing schedule is given at week 25.

Dosing schedule in combination with bortezomib, melphalan and prednisone (6-week cycle regimens)

The recommended dose is Darzalex® 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in table 2.

Table 2: DARZALEX dosing schedule in combination with bortezomib, melphalan and prednisone ([VMP]; 6-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 6	weekly (total of 6 doses)
Weeks 7 to 54[a]	every three weeks (total of 16 doses)
Week 55 onwards until disease progression[b]	every four weeks

[a] First dose of the every-3-week dosing schedule is given at week 7.
[b] First dose of the every-4-week dosing schedule is given at week 55.

[2] This medicine had an accelerated assessment, meaning that it is a medicine of major interest for public health, so its timeframe for review was 150 evaluation days rather than 210.

Dosing schedule in combination with bortezomib, thalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed patients eligible for autologous stem cell transplant (ASCT)

The recommended dose is Darzalex® 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in table 3.

Table 3: DARZALEX dosing schedule in combination with bortezomib, thalidomide and dexamethasone ([VTd]; 4-week cycle dosing regimen)

Treatment phase	Weeks	Schedule
Induction	Weeks 1 to 8	weekly (total of 8 doses)
	Weeks 9 to 16[a]	every two weeks (total of 4 doses)
Stop for high dose chemotherapy and ASCT		
Consolidation	Weeks 1 to 8[b]	every two weeks (total of 4 doses)

[a] First dose of the every-2-week dosing schedule is given at week 9.

[b] First dose of the every-2-week dosing schedule is given at week 1 upon re-initiation of treatment following ASCT.

Dosing schedule in combination with bortezomib and dexamethasone (3-week cycle regimen)

The recommended dose is Darzalex® 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in table 4.

Table 4: DARZALEX dosing schedule in combination with bortezomib and dexamethasone (Vd) (3-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 9	weekly (total of 9 doses)
Weeks 10 to 24[a]	every three weeks (total of 5 doses)
Week 25 onwards until disease progression[b]	every four weeks

[a] First dose of the every-3-week dosing schedule is given at week 10.

[b] First dose of the every-4-week dosing schedule is given at week 25.

Warnings and precautions [1]

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infusion-related reactions

Darzalex® can cause serious IRRs, including anaphylactic reactions (see section 4.8). These reactions can be life-threatening, and fatal outcomes have been reported. All patients should be monitored throughout the infusion for IRRs. For patients that experience any grade IRRs, continue monitoring post-infusion until symptoms resolve. In clinical studies, IRRs were reported in approximately half of all patients treated with Darzalex®. The majority of IRRs occurred at the first infusion and were grade 1-2 Four percent of all patients had an IRR at more than one infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension, laryngeal oedema, pulmonary oedema and ocular adverse reactions (including choroidal effusion, acute myopia and acute angle closure glaucoma).

Symptoms predominantly included nasal congestion, cough, throat irritation, chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension and blurred vision). Patients should be pre-medicated with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs prior to treatment with Darzalex®. Darzalex® infusion should be interrupted for IRRs of any severity and medical management/supportive treatment for IRRs should be instituted as needed. For patients with grade 1, 2, or 3 IRRs, the infusion rate should be reduced when re-starting the infusion. If an anaphylactic reaction or life-threatening (grade 4) infusion reaction occurs, appropriate emergency resuscitation should be initiated immediately. Darzalex® therapy should be discontinued immediately and permanently (To reduce the risk of delayed IRRs, oral corticosteroids should be administered to all patients following Darzalex® infusions. Additionally, the use of post-infusion medicinal products (e.g. inhaled corticosteroids, short and long-acting bronchodilators) should be considered for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications should they occur. If ocular symptoms occur, interrupt Darzalex® infusion and seek immediate ophthalmologic evaluation prior to restarting Darzalex®.

Neutropenia/thrombocytopenia

Darzalex® may increase neutropenia and thrombocytopenia induced by background therapy (see section 4.8). Complete blood cell counts should be monitored periodically during treatment according to prescribing information for background therapies. Patients with neutropenia should be monitored for signs of infection. Darzalex® delay may be required to allow recovery of blood cell counts. No dose reduction of Darzalex® is recommended. Consider supportive care with transfusions or growth factors.

Interference with indirect antiglobulin test (indirect Coombs test)
Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab infusion. It should be recognised that daratumumab bound to RBCs may mask detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted. Patients should be typed and screened prior to starting daratumumab treatment. Phenotyping may be considered prior to starting daratumumab treatment as per local practice. Red blood cell genotyping is not impacted by daratumumab and may be performed at any time. In the event of a planned transfusion blood transfusion centres should be notified of this interference with indirect antiglobulin tests If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

Interference with determination of complete response
Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein.

Hepatitis B virus (HBV) reactivation
Hepatitis B virus reactivation, in some cases fatal, has been reported in patients treated with Darzalex®. HBV screening should be performed in all patients before initiation of treatment with Darzalex®. For patients with evidence of positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during, and for at least six months following the end of Darzalex® treatment. Manage patients according to current clinical guidelines. Consider consulting a hepatitis disease expert as clinically indicated. In patients who develop reactivation of HBV while on Darzalex®, suspend treatment with Darzalex® and institute appropriate treatment. Resumption of Darzalex® treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

Excipients
This medicinal product contains sorbitol (E420). Patients with hereditary fructose intolerance (HFI) must not be given this medicinal product unless strictly necessary. A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

Study characteristics [8]

Trial name/ NCT number	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
NCT03710603 Perseus	709 (1:1)	Subcutaneous daratumumab[3] combined with VRd[4] induction therapy before transplantation, with VRd consolidation therapy after transplantation, and with lenalidomide maintenance therapy (D-VRd group).	VRd induction and consolidation therapy and lenalidomide maintenance therapy alone (VRd group).	PFS	47.5 months	ongoing[5], open-label, multicentre, phase 3 trial	CD38	European Myeloma Network, Janssen Research and Development	Perseus [8]

Inclusion criteria[6]	**Exclusion criteria**	**Patient characteristics at baseline I (n=355) vs. C (n=354)**

[3] 1800 mg per week during cycles 1 and 2; 1800 mg every 2 weeks during cycles 3 through 6), which was coformulated with recombinant human hyaluronidase PH20 (2000 U per milliliter of solution).
[4] VRd consisted of subcutaneous bortezomib (1.3 mg per square meter of body-surface area on days 1, 4, 8, and 11 of each cycle), oral lenalidomide (25 mg on days 1 through 21 of each cycle), and oral or intravenous dexamethasone (40 mg on days 1 through 4 and days 9 through 12 of each cycle).
[5] The trial is currently ongoing; the estimated study completion date is 11/2029.
[6] For detailed in-and exclusion criteria, please see trial protocol.

❖ 18 to 70 years of age, inclusive. ❖ Monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma and documented multiple myeloma satisfying at least one of the calcium, renal, anemia, bone (CRAB) criteria or biomarkers of malignancy criteria: CRAB criteria: 1. Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than upper limit of normal (ULN) or >2.75 mmol/L (>11 mg/dL) 2. Renal insufficiency: creatinine clearance <40mL/min or serum creatinine >177 µmol/L (>2 mg/dL) 3. Anemia: hemoglobin >2 g/dL below the lower limit of normal or hemoglobin <10 g/dL 4. Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT Biomarkers of Malignancy: a. Clonal bone marrow plasma cell percentage ≥60% b. Involved: uninvolved serum FLC ratio ≥100 c. >1 focal lesion on magnetic resonance imaging (MRI) studies ❖ Measurable disease as defined by any of the following: a. Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or b. Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin FLC ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio ❖ Newly diagnosed subjects for whom high-dose therapy and autologous stem cell transplantation is part of the intended treatment plan. ❖ Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2. ❖ Clinical laboratory values meeting the following criteria during the Screening Phase: Adequate bone marrow function, Adequate liver function, Adequate renal function. ❖ Female subjects of reproductive childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously during the Treatment Period, during any dose interruptions, and for 3 months after the last dose of any component of the treatment regimen. ❖ A woman of childbearing potential must have 2 negative serum or urine pregnancy tests at Screening, first within 10 to 14 days prior to dosing and the second within 24 hours prior to dosing	❖ Prior or current systemic therapy or SCT for any plasma cell dyscrasia, with the exception of emergency use of a short course (equivalent of dexamethasone 40 mg/day for a maximum 4 days) of corticosteroids before treatment. ❖ Peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5. ❖ Prior or concurrent invasive malignancy (other than multiple myeloma) within 5 years of date of randomisation. ❖ Radiation therapy within 14 days of randomisation. ❖ Plasmapheresis within 28 days of randomisation. ❖ Clinical signs of meningeal involvement of multiple myeloma. ❖ Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) <50% of predicted normal. ❖ Moderate or severe persistent asthma within the past 2 years, or currently has uncontrolled asthma of any classification. ❖ Any of the following: a. Seropositive for human immunodeficiency virus (HIV) b. Seropositive for hepatitis B. c. Seropositive for hepatitis C. ❖ Concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with the study procedures or results. ❖ Any of the following: a. myocardial infarction within 6 months before randomisation, or an unstable or uncontrolled disease/condition related to or affecting cardiac function b. uncontrolled cardiac arrhythmia or clinically significant electrocardiogram (ECG) abnormalities c. screening 12-lead ECG showing a baseline QT interval >470 msec d. left ventricular ejection fraction (LVEF) <40% for subjects aged 65-70 years old ❖ Received a strong CYP3A4 inducer within 5 half-lives prior to randomisation. ❖ Allergy, hypersensitivity, or intolerance to boron or mannitol, corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to the Investigator's	❖ Median age (range) yr: 61.0 (32–70) vs 59.0 (31–70) ❖ Male sex — no. (%):211 (59.4) vs 205 (57.9) ❖ Race — no. (%) o Asian: 4 (1.1) vs 6 (1.7) o Black: 5 (1.4) vs 4 (1.1) o White: 330 (93.0) vs 323 (91.2) o Other: 4 (1.1) vs 3 (0.8) o Missing data: 12 (3.4) vs 18 (5.1) ❖ ECOG performance-status score — no. (%) o 0: 221 (62.3) vs 230 (65.0) o 1: 114 (32.1) vs 108 (30.5) o 2: 19 (5.4) vs 16 (4.5) o 3: 1 (0.3) vs 0 ❖ Type of measurable disease — no. (%) o IgG: 204 (57.5) vs 185 (52.3) o IgA: 65 (18.3) vs 85 (24.0) o Other: 13 (3.7) vs 11 (3.1) o Detected in urine only: 43 (12.1) vs 46 (13.0) o Detected in serum free light chains only: 29 (8.2) vs 27 (7.6) o Type could not be evaluated: 1 (0.3) vs 0 ❖ ISS disease stage — no./total no. (%) o I: 186/355 (52.4) vs 178/353 (50.4) o II: 114/355 (32.1) vs 125/353 (35.4) o III: 55/355 (15.5) vs 50/353 (14.2) ❖ Cytogenetic risk — no. (%) o Standard: 264 (74.4) vs 266 (75.1) o High: 76 (21.4) vs 78 (22.0) o Indeterminate: 15 (4.2) vs 10 (2.8) ❖ Median time since diagnosis of multiple myeloma (range) – mo: 1.2 (0.0–46.5) vs 1.1 (0.1–184.6)

❖ A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 3 months after receiving the last dose of any component of the treatment regimen. ❖ Male subjects of reproductive potential who are sexually active with females of reproductive potential must always use a latex or synthetic condom during the study and for 3 months after discontinuing study treatment. ❖ Male subjects of reproductive potential must not donate sperm during the study or for 3 months after the last dose of study treatment. ❖ Signed an informed consent form (ICF) (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study. ❖ Able to adhere to the prohibitions and restrictions specified in this protocol	Brochure), or sensitivity to mammalian-derived products or lenalidomide. ❖ Not able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder). Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. ❖ Pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of any component of the treatment regimen. Or, subject is a man who plans to father a child while enrolled in this study or within 3 months after the last dose of any component of the treatment regimen. ❖ Major surgery within 2 weeks before randomisation or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study. Kyphoplasty or Vertebroplasty is not considered major surgery. ❖ Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before randomisation or is currently enrolled in an interventional investigational study. ❖ Contraindications to the use of any components of the backbone treatment regimens, per local prescribing information. ❖ Gastrointestinal disease that may significantly alter the absorption of oral drugs ❖ Vaccination with live attenuated vaccines within 4 weeks of first study agent administration ❖ Unable or unwilling to undergo antithrombotic prophylactic treatment.	

Efficacy (I vs. C)	**Safety** (I vs. C, n=351 vs. n=347)
<u>Data cutoff date (August 1st, 2023), median follow-up of 47.5 months</u> **PFS:** 84.3% (95% CI, 79.5 to 88.1) vs. 67.7% (95% CI, 62.2 to 72.6). The hazard ratio for disease progression or death in the D-VRd group as compared with the VRd group was 0.42 (95% CI, 0.30 to 0.59; P<0.001); the P value crossed the prespecified stopping boundary for superiority for the first interim analysis (P = 0.0126). **Complete response**: 87.9% vs. 70.1%, P<0.001Complete response or better: 87.9% vs. 70.1%; P<0.001 Very good partial response or better: 95.2% vs. 89.3% Stable disease: 1.1% vs. 2.5%	**TRAEs of any grade:** 99.4% vs. 99.1% **Grade ≥3 AEs**: 91.5% vs. 85.6% **SAEs:** 57.0% vs 49.3% **Discontinuation[7]:** 8.8% vs 21.3% **Death due to Covid-19:** 1.1% vs 0.3% **Death due to AE:** 3.7% vs 4.6% **Death overall: n=34 vs n=44**

[7] discontinuation due to AE(s)

Progressive disease: 0.6% vs. 0.3%
Response could not be evaluated: 1.7% vs. 3.4%
MRD-negative status: sensitivity threshold of 10^{-5}: 75.2% vs. 47.5%, P<0.001; for at least 12 months 64.8% vs 29.7%; sensitivity threshold of 10^{-6}: 65.1% vs 32.2%

Patient-reported outcomes

Currently, no information on patient-reported outcomes is available. However, these results should be available when the study ends.

ESMO-MCBS version 1.1 [9]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2b	≥12 months	PFS: 16.6%	0.42 (0.30-0.59)	HR ≤0.65 AND interim PFS gain ≥10-<20%	2	-	NA	-	2

Risk of bias (RCT) [10]

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	unclear[8] unclear risk	yes[9] high risk	unclear

Ongoing trials [11]

NCT number/trial name	Description	Estimated study completion date
PERSEUS NCT03710603	Please see above.	11/2029
NCT05257083 (CARTITUDE-6)	A Study of Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (DVRd) Followed by Ciltacabtagene Autoleucel Versus Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (DVRd) Followed by Autologous Stem Cell Transplant (ASCT) in Participants With Newly Diagnosed Multiple Myeloma	08/2040
NCT03742297	Treatment for Elderly Fit Newly Diagnosed Multiple Myeloma Patients Aged Between 65 and 80 Years	01/2031
NCT04566328	Testing the Use of Combination Therapy in Adult Patients With Newly Diagnosed Multiple Myeloma, the EQUATE Trial	12/2027

Available assessments

NICE has published an assessment, "Daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable" on 2.2.2022 [12].

Other aspects and conclusions

- On **September 19th, 2024,** the CHMP adopted **a new indication for Darzalex®** "in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant."
- Perseus (NCT03710603) is an ongoing, phase 3, international, randomised, open-label trial assessing progression-free survival after treatment with daratumumab combined with bortezomib, lenalidomide, and dexamethasone (VRd) vs VRd alone.
- **The primary endpoint was PFS; PFS** was 84.3% (95% CI, 79.5 to 88.1) in the D-VRd group and 67.7% (95% CI, 62.2 to 72.6) in the VRd group.
- The **original ESMO-MCBS** was applied, resulting in a final adjusted magnitude of clinical benefit of 2.
- The **risk of bias was unclear** since the trial is ongoing. The risk is increased by the open-label design of the study and industry-funded background.
- Besides Perseus, for this specific indication, there is another study, NCT02252172, investigating the efficacy of "Daratumumab, Lenalidomide, and Dexamethasone with Lenalidomide and Dexamethasone in Participants With Previously Untreated Multiple Myeloma", as searched from ClinicalsTrials.gov.
- Based on the interim analysis, **efficacy has been shown in terms of improved PFS**. It has to be, however, noted that the majority of patients had an ECOG performance score of 0, and the median age was lower than the median age that is usually reported for the diagnosis [13]. PROs have yet to be collected as the study is ongoing.

[8] The study is ongoing.
[9] The study was sponsored by Janssen, the first author is funded by Janssen.

Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CADTH=Canada's Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, COPD= Chronic obstructive pulmonary disease, HBV=Hepatitis B virus, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FEV1= Forced Expiratory Volume in 1 second, FM=final magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, IRR=Infusion-related reaction, MM= multiple myeloma, MRD= Minimal residual disease, MG=median gain, n=number of patients, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, NICE=National Institute for Health Care Excellence, PE=primary endpoint, PFS=progression-free survival, PI=proteasome inhibitor, PRO= patient reported outcome, RBC= red blood cell, SAE=serious adverse event, ST=standard treatment, VRd=bortezomib, lenalidomide and dexamethasone

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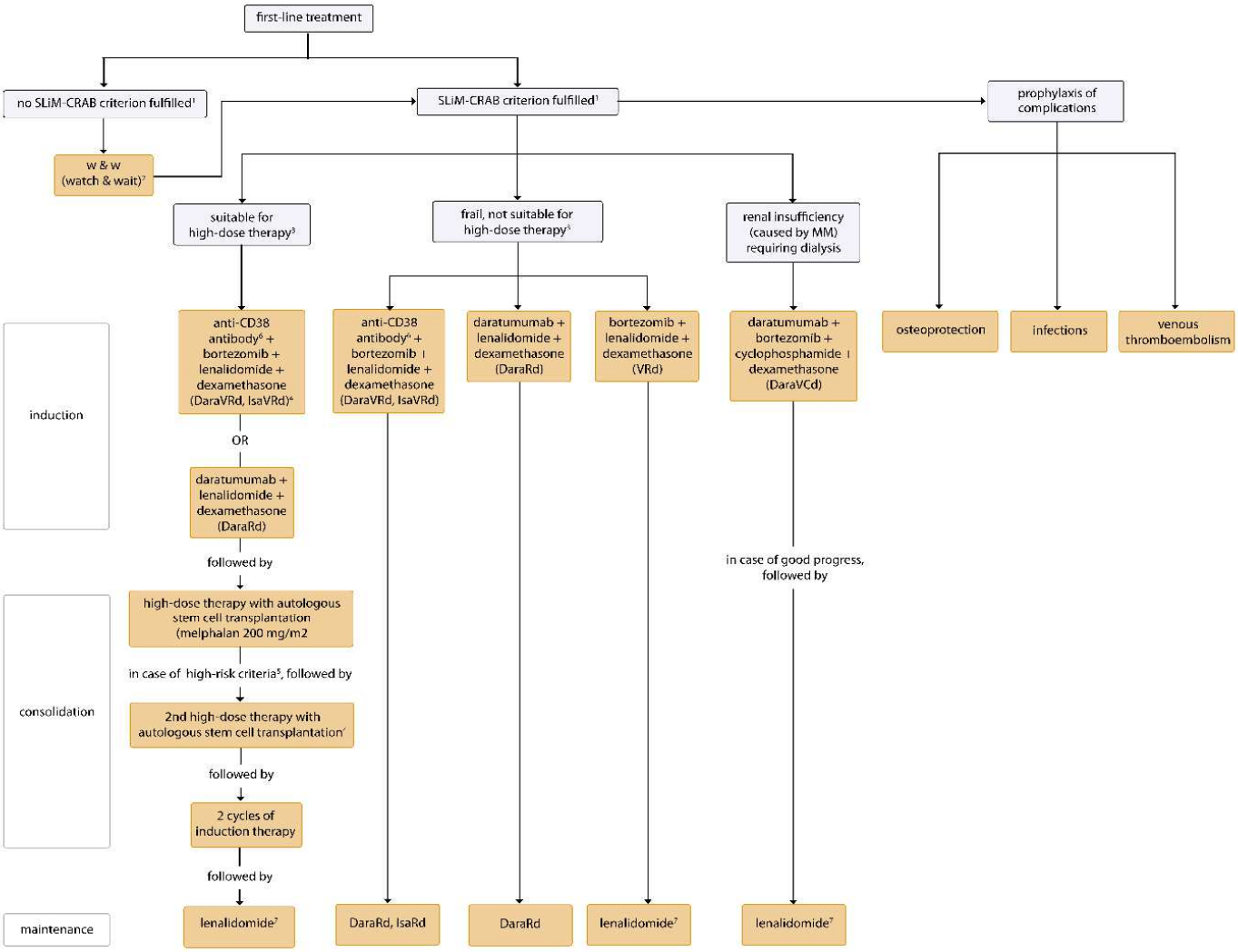
[13] NIH. Cancer Stat Facts: Myeloma. [cited 18.11.2024]. Available from: https://seer.cancer.gov/statfacts/html/mulmy.html.

Appendix – Figure 1:



Legend:

[1] *SLiM-CRAB criteria, please see https://www.onkopedia.com/de/onkopedia/guidelines/multiples-myelom/@@guideline/html/index.html#ID0E6AAG*

[2] *Watchful waiting with regular check-ups*

[3] *Suitability should be based more on comorbidities than on age; the essential parameter is the presence of contraindications for the high-dose therapy*

[4] *‚d' is for low-dosed dexamethasone*

[5] *High-risk criteria: high-risk genetics, R-ISS III, and/or complete remission not reached after 1st high-dose therapy*

[6] *Anti-CD38-antibody: daratumumab or isatiximab, both are not approved in this combination for this indicaton , off-label use*

[7] *Lenalidomide 10 mg*