Daratumumab (Darzalex®) in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of newly diagnosed systemic light chain (AL) amyloidosis

General information

Drug description [1]	Indication [2]
Daratumumab is a human immunoglobulin Gk (IgGk) monoclonal antibody targeting CD38.	Daratumumab is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed AL amyloidosis.

Current treatment [3]

- First-line treatment is recommended with combination chemotherapy regimens similar to those used in myeloma but typically using dexamethasone.
- Proteasome inhibitor (PI)-based regimens are a preferred choice due to better response rates and outcomes in phase II studies and a bortezomib-alkylator-steroid combination is preferred where a rapid response is desirable (cardiac involvement, renal impairment, severe hypoalbuminaemia, fluid retention).
- Bortezomib is preferably given subcutaneously to reduce toxicity but may be given intravenously in patients with severe fluid overload where there is a concern about the adequacy of absorption.
- Thalidomide in combination with cyclophosphamide and dexamethasone is effective in the treatment of AL amyloidosis. Thalidomide should be used with caution in patients with cardiac stage III disease and those with grade III-IV neuropathy. In patients with grade III-IV neuropathy, strong consideration must be given to avoiding neurotoxic drugs (thalidomide and bortezomib).
- High dose melphalan (HDM) and autologous stem cell transplantation (ASCT) (HDM-ASCT) is the preferred first-line treatment for selected patients up to 65–70 years of age with estimated glomerular filtration rate >50 ml/min, low cardiac biomarkers, low-level plasma cell infiltration in the bone marrow at the time of transplant and lacking the contraindications mentioned in the next point.
- HDM-ASCT is not generally recommended as first-line therapy for patients with any of the following: Cardiac amyloidosis with N-terminal pro-brain natriuretic peptide >590 pmol/l and/or troponin-T > 0.06 ng/ml, severe autonomic neuropathy, significant gastrointestinal bleeding due to amyloid, advanced renal failure, age over 70 years, symptomatic recurrent amyloid-related pleural effusions or poor Eastern Cooperative Oncology Group performance status (>2).

Regulatory status

EMA [2]

Approval status for this indication: On 20 May 2021, the CHMP adopted a positive opinion recommending changes to the terms of the marketing authorisation for Darzalex®.

The CHMP extended the existing indication for Darzalex® 1,800 mg solution for injection (active substance: daratumumab; excipients: recombinant human hyaluronidase rHuPH20, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20, sorbitol, water for injections) as follows:

- Darzalex® is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed AL amyloidosis.

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 (MM) who are ineligible for autologous stem cell transplant.
- in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed MM 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 MM who have received at least one prior therapy.
- in combination with pomalidomide and dexamethasone for the treatment of adult patients with MM who have received one prior therapy containing a PI and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a PI and have demonstrated disease progression on or after the last therapy.
- as monotherapy for the treatment of adult patients with relapsed and refractory MM, whose prior therapy included a PI and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

FDA [4, 5]

Approval status for this indication: On 15 January 2021, the FDA granted accelerated approval to daratumumab plus hyaluronidase (Darzalex Faspro®) in combination with bortezomib, cyclophosphamide and dexamethasone for newly diagnosed AL amyloidosis.

- ✓ This indication is approved under **accelerated approval** based on the response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Other indications: Darzalex Faspro® is indicated for the treatment of adult patients with:

- MM combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant.
- MM 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 MM who have received at least one prior therapy.
- MM in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant.
- MM in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy.
- MM in combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor.
- MM as monotherapy, in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

✓ **Orphan status** ✓ **Medicine under additional monitoring** ✓ **Accelerated assessment**[1]	❖ Darzalex Faspro® is not indicated and is not recommended for the treatment of patients with AL amyloidosis who have NYHA Class IIIB or Class IV cardiac disease or Mayo Stage IIIB outside of controlled clinical trials.

Costs

1 vial Darzalex® solution for injection 1,800 mg/15ml**= € 6,288.00** (ex-factory price) [6]

Warnings and precautions (Darzalex Faspro®) [4]

- ❖ **Hypersensitivity and Other Administration Reactions:**
  - Permanently discontinue Darzalex Faspro® for life-threatening reactions.
- ❖ **Cardiac Toxicity in Patients with AL Amyloidosis:**
  - Monitor patients with cardiac involvement more frequently for cardiac adverse reactions and administer supportive care as appropriate.
- ❖ **Neutropenia:**
  - Monitor complete blood cell counts periodically during treatment. Monitor patients with neutropenia for signs of infection. Consider withholding Darzalex Faspro® to allow recovery of neutrophils.
- ❖ **Thrombocytopenia:**
  - Monitor complete blood cell counts periodically during treatment. Consider withholding Darzalex Faspro® to allow recovery of platelets.
- ❖ **Embryo-Foetal Toxicity:**
  - Can cause foetal harm. Advise pregnant women of the potential risk to a foetus and advise females of reproductive potential to use effective contraception.
- ❖ **Interference with cross-matching and red blood cell antibody screening:**
  - Type and screen patients prior to starting treatment. Inform blood banks that a patient has received Darzalex Faspro®.

Pre-/Post-medication [7]

- ❖ Darzalex® solution for subcutaneous injection can cause severe and/or serious IRRs, including anaphylactic reactions.
- ❖ Patients should be pre-medicated with antihistamines, antipyretics, and corticosteroids as well as monitored and counselled regarding IRRs, especially during and following the first and second injections.
- ❖ If an anaphylactic reaction or life-threatening (Grade 4) reactions occur, appropriate emergency care 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® injection.
- ❖ Patients with a history of the chronic obstructive pulmonary disease may require additional post-injection medicinal products to manage respiratory complications. The use of post-injection medicinal products (e.g. short- and long-acting bronchodilators and inhaled corticosteroids) should be considered for patients with chronic obstructive pulmonary disease.

Study characteristics [1, 4, 7, 8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ANDROMEDA, Study AMY3001 NCT03201965	388	dexamethasone + cyclophosphamide + bortezomib + Darzalex Faspro® 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from	dexamethasone + cyclophosphamide + bortezomib	Overall complete hematologic response rate (HemCR) based on International Amyloidosis Consensus Criteria guidelines	randomised, open-label, active-controlled, multicentre, phase 3 study with a safety run-in phase	-	Janssen Research & Development, LLC	[1] (safety run-in results)

[1] 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.

		weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity or a maximum of 2 years						

Efficacy (I vs. C)	Safety
HemCR: 53.3% vs. 18.1%, estimated Odds Ratio 5.13, p-value <0.0001 **Very good partial response (VGPR)**: -25.1% vs. 31.1% **Partial response (PR):** 13.3% vs. 27.5% **Hematologic VGPR or better (HemCR + VGPR):** 78.5% vs. 49.2% **Major organ deterioration PFS,** HR with 95% CI: 0.58 (0.37, 0.92), p=0.0211 **Median time to HemCR:** 59 days (range: 8 to 299) vs. 59 days (range: 16 to 340) **Median time to VGPR or better:** 17 days (range: 5 to 336) vs. 25 days (range: 8 to 171) **Median duration of HemCR** had not been reached in either arm. The median follow-up for the study is 11.4 months. OS data were not mature. A total of 56 deaths were observed: n=27 (13.8%) vs. n=29 (15%).	**I (n=188) vs. C (193)** Serious AEs: n=83/193 (43.01%) vs. n=68/188 (36.17%) Other (not including serious) AEs: n=182/193 (94.30%) vs. n=181/188 (96.28%) Dosage interruptions (defined as dose delays or skipped doses) due to an adverse reaction occurred in 36% in I. Cardiac Adverse Reactions: • Among patients in I, 72% of patients had baseline cardiac involvement with Mayo Cardiac Stage I (3%), Stage II (46%) and Stage III (51%). • Serious cardiac disorders occurred in 16% of patients (8% of patients with Mayo Cardiac Stage I and II and 28% of patients with Stage III). • Serious cardiac disorders in >2% of patients included cardiac failure (8%), cardiac arrest (4%) and arrhythmia (4%). • Fatal cardiac disorders occurred in 10% of patients (5% of patients with Mayo Cardiac Stage I and II and 19% of patients with Stage III) in I. • Fatal cardiac disorders that occurred in more than one patient in I included cardiac arrest (4%), sudden death (3%), and cardiac failure (3%). **Safety run-in results, n=28** Grade 3/4 TEAEs (>1 patient): n=20 (71.4%) TEAEs considered related to study treatment: n=26 (93%); TEAEs in 21 (75%) patients TEAEs considered related to daratumumab: n=21 (75%). IRR: n=1 (4%)

ESMO-MCBS version 1.1

The ESMO-MCBS is not applicable since no scorable endpoint had been reached at the time of analysis.

Risk of bias (study level) [9]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
unclear	unclear	No, open-label	unclear[2]	yes[3]	high

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[2] ANDROMEDA trial is ongoing until 08/2024;

[3] Industry-funded; the investigators and sponsor devised the study design and analysis. The sponsor conducted the final data analysis and verified data accuracy.

Abbreviations: AE=adverse event, AJ=adjustment, AL amyloidosis=systemic light chain amyloidosis, ASCT=autologous stem cell transplantation, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HDM=high dose melphalan, HemCR=Hematologic complete response, HR=hazard ratio, I=intervention, Int.=intention, IRR=infusion-related reaction, MG=median gain, MM=multiple myeloma, n=number of patients, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PI=proteasome inhibitor, PM=preliminary grade, PR=partial response, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse event, VGPR=very good partial response

References:

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