Daratumumab (new therapeutic indication: systemic, light chain amyloidosis, first-line, combination with Cyclophosphamide, Bortezomib and Dexamethasone)

Resolution of: 20 January 2022 Valid until: patient group a1) 1 March 2025
Entry into force on: 20 January 2022
Federal Gazette, BAnz AT 14 03 2022 B4

New therapeutic indication (according to the marketing authorisation of 21 June 2021):

Darzalex is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis.

Therapeutic indication of the resolution (resolution of 20 January 2022):

- See new therapeutic indication according to marketing authorisation.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Adults with newly diagnosed systemic light chain (AL) amyloidosis

Appropriate comparator therapy:

- a patient-individual therapy, taking into account general condition, comorbidity and organ damage

Extent and probability of the additional benefit of Daratumumab in combination with Bortezomib, Cyclophosphamide and Dexamethasone compared with the appropriate comparator therapy:

a1) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom Bortezomib in combination with Cyclophosphamide and Dexamethasone is the patient-individual appropriate therapy

Hint for a minor additional benefit

a2) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom therapy other than Bortezomib in combination with Cyclophosphamide and Dexamethasone is the patient-individual appropriate therapy

An additional benefit is not proven.

Study results according to endpoints:[1]

Adults with newly diagnosed systemic light chain (AL) amyloidosis

a1) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom Bortezomib in combination with Cyclophosphamide and Dexamethasone is the patient-individual appropriate therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences for the benefit assessment.
Morbidity	↑	Advantage especially in the endpoint of severe organ damage, also advantage in the dyspnoea symptom scale.
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↔	Overall, no relevant differences for the benefit assessment; in detail, one advantage and one disadvantage in specific AEs.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

ANDROMEDA study: Daratumumab + cyclophosphamide + bortezomib + dexamethasone **vs** cyclophosphamide + bortezomib + dexamethasone (VCd)

Study design: randomised, open-label, two-armed

Mortality

Endpoint	Daratumumab + VCd		VCd		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Overall survival					

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-100) unless otherwise indicated.

	195	n.a. 27 (13.8)	193	n.a. 29 (15.0)	0.90 [0.53; 1.53] 0.706

Morbidity

Endpoint	Daratumumab + VCd		VCd		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Severe organ damage					
	195	n.a. 1 (0.5)	193	n.a. 7 (3.6)	0.12 [0.01; 1.01] 0.020
Endpoint component[2]: clinical manifestation of heart failure [b]	195	n.a. 0 (0)	193	n.a. 0 (0)	n.c.
Endpoint component[2]: clinical manifestation of kidney failure [c]	195	n.a. 1 (0.5)	193	n.a. 7 (3.6)	0.123 [0.015; 1.006] 0.0202
Symptomatology (EORTC QLQ-C30 symptom scales) [d]					
Fatigue	195	2.1 [1.9; 3.7] 116 (59.5)	193	1.9 [1.9; 2.8] 132 (68.4)	0.78 [0.60; 1.00] 0.054
Nausea and vomiting	195	n.a. [7.8; n.c.] 70 (35.9)	193	8.2 [4.7; n.c.] 80 (41.5)	0.75 [0.54; 1.03] 0.076
Pain	195	4.1 [2.8; 6.5] 107 (54.9)	193	3.8 [2.9; 4.8] 103 (53.4)	1.01 [0.77; 1.34] 0.926
Dyspnoea	195	21.3 [9.7; 21.3] 71 (36.4)	193	3.8 [2.8; 5.7] 99 (51.3)	0.62 [0.45; 0.84] 0.002 AD = 17.5 months
Insomnia	195	4.6 [2.9; 17.6] 94 (48.2)	193	3.8 [2.9; 6.5] 94 (48.7)	1.01 [0.76; 1.35]

[2] Data from the statement of the pharmaceutical company on process 2021-08-01-D-715 from 22.11.2021

Endpoint	Daratumumab + VCd		VCd		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
					0.934
Appetite loss	195	6.5 [4.1; n.c.] 86 (44.1)	193	5.0 [3.7; 6.5] 96 (49.7)	0.87 [0.65; 1.17] 0.348
Constipation	195	12.3 [3.9; n.c.] 85 (43.6)	193	4.9 [3.3; 14.9] 88 (45.6)	0.91 [0.67; 1.23] 0.527
Diarrhoea	195	7.5 [4.7; n.c.] 86 (44.1)	193	6.2 [3.8; 12.2] 88 (45.6)	0.89 [0.66; 1.21] 0.454
Health status (EQ-5D VAS) [e]					
MID: 15 points	195	13.0 [4.7; n.c.] 78 (40.0)	193	4.9 [3.7; 15.4] 87 (45.1)	0.88 [0.65; 1.20] 0.418
MID: 7 points	195	2.2 [1.9; 3.8] 108 (55.4)	193	2.8 [1.9; 2.9] 117 (60.6)	0.90 [0.69; 1.18] 0.458
MID: 10 points	195	3.2 [2.0; 5.5] 103 (52.8)	193	2.9 [2.1; 4.1] 106 (54.9)	0.96 [0.72; 1.26] 0.753

Health-related quality of life

Endpoint	Daratumumab + VCd		VCd		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
EORTC QLQ-C30 functional scales [f]					
Global health status	195	4.7 [2.8; 7.4] 102 (52.3)	193	2.9 [2.2; 3.8] 112 (58.0)	0.86 [0.66; 1.14] 0.295
Physical functioning	195	4.7 [2.8; 12.3] 94 (48.2)	193	3.8 [2.8; 4.7] 106 (54.9)	0.81 [0.61; 1.08] 0.153
Role functioning	195	2.3 [1.9; 4.6] 111 (56.9)	193	2.8 [2.0; 3.7] 121 (62.7)	0.90 [0.69; 1.17] 0.445
Emotional functioning	195	17.6 [17.6; n.c.] 64 (32.8)	193	5.0 [4.0; n.c.] 82 (42.5)	0.69 [0.50; 0.97] 0.032 AD = 12.6 months
Cognitive functioning	195	5.6 [3.9; 7.9] 99 (50.8)	193	3.8 [2.8; 4.7] 110 (57.0)	0.78 [0.59; 1.03] 0.085
Social functioning	195	2.8 [1.9; 3.1] 111 (56.9)	193	2.9 [2.0; 3.8] 115 (59.6)	1.01 [0.78; 1.32] 0.931
SF-36					
Physical component score (PCS) [e]					
MID: 10.05 points	195	19.3 [19.3; n.c.] 58 (29.7)	193	12.5 [8.5; n.c.] 71 (36.8)	0.76 [0.53; 1.07] 0.117
MID: 5 points	195	3.9 [2.8; 12.9] 94 (48.2)	193	2.8 [2.0; 3.7] 116 (60.1)	0.76 [0.58; 1.00] 0.051
Mental component score (MCS) [e]					
MID: 10.80 points	195	14.9 [9.3; n.c.] 68 (34.9)	193	n.a. [6.2; n.c.] 69 (35.8)	0.93 [0.67; 1.31] 0.688

Endpoint	Daratumumab + VCd		VCd		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
MID: 5 points	195	3.8 [2.9; 5.5] 101 (51.8)	193	3.8 [2.9; 5.0] 101 (52.3)	0.98 [0.74; 1.29] 0.874

Side effects [g]

Endpoint	Daratumumab + VCd		VCd		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	193	0.1 [0.1; 0.1] 189 (97.9)	188	0.2 [0.1; 0.3] 185 (98.4)	-
Serious adverse events (SAE)					
	193	n.a. [12.0; n.c.] 83 (43.0)	188	n.a. 68 (36.2)	1.01 [0.73; 1.41] 0.943
Severe adverse events (CTCAE grade ≥ 3)					
	193	3.6 [2.4; 4.9] 119 (61.7)	188	3.5 [2.5; 4.4] 114 (60.6)	1.01 [0.78; 1.32] 0.909
Therapy discontinuation due to adverse events [h]					
	193	n.a. 20 (10.4)	188	n.a. 17 (9.0)	1.04 [0.54; 2.01] 0.895
Specific adverse events [i]					
Peripheral neuropathies (HLT), AEs)[2, j]	193	n.a. 24 (12.4)	188	n.a. 19 (10.1)	1.036 [0.564; 1.900] 0.9103

Endpoint	Daratumumab + VCd		VCd		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Skin and subcutaneous tissue disorders (SOC, AEs)	193	14.9 [6.6; n.c.] 86 (44.6)	188	n.a. 42 (22.3)	1.99 [1.37; 2.91] < 0.001
Hypokalaemia (PT, severe AEs)	193	n.a. 3 (1.6)	188	n.a. 10 (5.3)	0.27 [0.07; 0.997] 0.0495

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[b] Defined as the need for a heart transplant, a left ventricular assist device or an intra-aortic balloon pump
[c] Defined as the development of end-stage kidney disease (need for haemodialysis or kidney transplantation)
[d] Time until the 1st deterioration, defined as an increase of ≥ 10 points compared to baseline on a scale of 0 to 100 points.
[e] Time until the 1st deterioration
[f] Time until the 1st deterioration, defined as a decrease of ≥ 10 points compared to baseline on a scale of 0 to 100 points.
[g] When interpreting the results on side effects, it should be noted that the significantly shorter planned treatment duration and the associated discontinuation of observation in the comparator arm mean that the hazard ratio only represents a comparison over approximately the first 7 months after randomisation.
[h] Discontinuation of at least one active ingredient component.
[i] Selection according to the methodology of the IQWiG; selection using events occurred in the study, based on frequency and differences between treatment arms, and taking into account patient relevance.
[j] Peripheral neuropathies with CTCAE grade ≥ 2.

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; HLT = high level term; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT = preferred term; SOC = system organ class; VAS = visual analogue scale; VCd = bortezomib in combination with cyclophosphamide and dexamethasone; vs = versus

a2) Adults with newly diagnosed systemic light chain (AL) amyloidosis for whom therapy other than Bortezomib in combination with Cyclophosphamide and Dexamethasone is the patient-individual appropriate therapy

No data are available to allow an assessment of the additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

2. Number of patients or demarcation of patient groups eligible for treatment

Adults with newly diagnosed systemic light chain (AL) amyloidosis

approx. 440 - 1030 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Darzalex (active ingredient: daratumumab) at the following publicly accessible link (last access: 8 December 2021):

https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf

Treatment with daratumumab should only be initiated and monitored by doctors experienced in treating adults with light chainlight chain (AL) amyloidosis.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and

a patient identification card. The training material for medical professionals and blood banks contains instructions on how to manage the risk of daratumumab interfering with blood typing (indirect antihuman globulin test or indirect Coombs test). Interference with blood typing induced by daratumumab may persist for up to 6 months after the last infusion of the medicinal product; therefore, medical professionals should advise patients to carry their patient identification card with them for up to 6 months after the end of the treatment.

4. Treatment costs

Annual treatment costs:

Adults with newly diagnosed systemic light chain (AL) amyloidosis

The annual treatment costs shown refer to the first year of treatment.

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone	
Daratumumab	€ 133,585.38
+ Bortezomib	€ 23,737.44
+ Cyclophosphamide	€ 285.88
+ Dexamethasone	€ 44.49
Total	€ 157,653.19
Additionally required SHI costs	€ 332.96 - € 333.63
Appropriate comparator therapy:	
Patient-individual therapy, taking into account general condition, comorbidity and organ damage	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®as last revised: 1 January 2022)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed:					
Daratumumab (in combination with bortezomib, cyclophosphamide	Bortezomib: Surcharge for production of a parenteral	€ 81	4	24	€ 1,944

and dexamethasone)	preparation containing cytostatic agents				
	Cyclophosphamide: Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	4	24	€ 1,944