Gemeinsamer Bundesausschuss

Daratumumab (New Therapeutic Indication: Multiple Myeloma, Newly Diagnosed, Patients Ineligible for Autologous Stem Cell Transplant, Combination with Lenalidomide and Dexamethasone)

Resolution of: 20 August 2020 Valid: unlimited
Entry into force on: 20 August 2020
Federal Gazette, BAnz AT 08 10 2020 B4

New therapeutic indication (according to the marketing authorisation of 19 November 2019):

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.

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

Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

Appropriate comparator therapy:

– Daratumumab in combination with bortezomib, melphalan, and prednisone

or

– Bortezomib in combination with melphalan and prednisone

or

– Bortezomib in combination with lenalidomide and dexamethasone

or

– Thalidomide in combination with melphalan and prednisone

or

– Lenalidomide in combination with dexamethasone

Extent and probability of the additional benefit of daratumumab in combination with lenalidomide and dexamethasone compared with lenalidomide in combination with dexamethasone:

Hint for a minor additional benefit

Study results according to endpoints:[1]

Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

MAIA study:

Daratumumab + lenalidomide + dexamethasone vs lenalidomide + dexamethasone

Total population

Mortality

Endpoint	**Daratumumab + lenalidomide + dexamethasone**		**Lenalidomide + dexamethasone**		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]
Overall survival					
	368	n.a. *85 (23.1)*	369	n.a. [47.3; n.a.] *103 (27.9)*	0.78 [0.58; 1.04] 0.089

Morbidity

Progression-free survival (PFS)[b]					
	368	NE [NE; NE] *120 (32.6)*	369	33.84 [28.95; 39.23] *171 (46.3)*	0.56 [0.44; 0.71] < 0.0001 AD = n.c.
EORTC QLQ-C30 – symptom scales (time until deterioration)[c]					
Fatigue	368	4.9 [4.7; 7.5] *226 (61.4)*	369	4.8 [4.6; 7.5] *218 (59.1)*	0.86 [0.71; 1.04] 0.127
Nausea and vomiting	368	38.0 [26.7; NE] *148 (40.2)*	369	30.1 [21.3; NE] *140 (37.9)*	0.92 [0.73; 1.16] 0.464
Pain	368	35.0 [27.2; NE] *147 (39.9)*	369	18.0 [10.8; 27.3] *162 (43.9)*	0.68 [0.54; 0.85] < 0.001 AD: + 17.0 months

[1] Data from the dossier assessment of the IQWiG (A20-14) and the addendum (A20-49) unless otherwise indicated.

Dyspnoea	368	27.2 [21.2; 36.2] *168 (45.7)*		369	15.7 [10.3; 22.0] *170 (46.1)*	0.79 [0.64; 0.99] 0.036
Insomnia	368	16.9 [10.2; 28.5] *184 (50.0)*		369	16.5 [10.2; 27.8] *166 (45.0)*	0.94 [0.76; 1.16] 0.550
Loss of appetite	368	34.4 [27.7; n.c.] *149 (40.5)*		369	26.0 [11.5; 32.2] *155 (42.0)*	0.80 [0.64; 1.01] 0.059
Constipation	368	21.7 [10.5; 32.5] *174 (47.3)*		369	16.1 [7.7; 26.0] *167 (45.3)*	0.86 [0.70; 1.07] 0.181
Diarrhoea	368	15.7 [10.3; 16.3] *227 (61.7)*		369	10.6 [10.0; 16.0] *196 (53.1)*	0.98 [0.81; 1.19] 0.845
Health status (EQ-5D VAS)						
Time until deterioration[d]						
7 points	368	17.4 [10.2; 26.9] *183 (49.7)*		369	10.3 [7.5; 17.0] *184 (49.9)*	0.83 [0.67; 1.02] 0.076
10 points	368	22.6 [15.7; 33.0] *173 (47.0)*		369	15.7 [9.3; 24.3] *171 (46.3)*	0.85 [0.68; 1.05] 0.126
		Values at start of study MV (SD)	Change at Cycle 12 MV [95% CI]		Values at start of study MV (SD)	Change at Cycle 12 MV [95% CI]	MD [95% CI] p value
Health status (EQ-5D VAS)						
Mean change at Cycle 12 compared with start of study[e]						
	349	62.6 (22.3)	10.1 [8.1; 12.1]	346	62.7 (21.5)	4.9 [2.8; 7]	5.2 [2.4; 8] < 0.001 Hedges' g: 0.28 [0.13; 0.43]

Health-related quality of life

	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 (time until deterioration)[c]					

Global health status	368	26.7 [17.5; n.c.] *167 (45.4)*	369	21.3 [11.4; 27.7] *160 (43.4)*	0.87 [0.70; 1.08] 0.201
Physical function	368	n.a. [27.8; n.c.] *147 (39.9)*	369	21.5 [12.7; 33.5] *158 (42.8)*	0.76 [0.61; 0.96] 0.018 AD = n.c.
Role function	368	10.2 [7.3; 18.2] *197 (53.5)*	369	10.2 [6.8; 15.7] *189 (51.2)*	0.90 [0.74; 1.10] 0.301
Emotional function	368	n.a. [32.5; n.c.] *140 (38.0)*	369	28.6 [16.5; 40.5] *138 (37.4)*	0.84 [0.66; 1.06] 0.140
Cognitive function	368	8.0 [7.4; 15.7] *221 (60.1)*	369	10.2 [7.5; 11.6] *193 (52.3)*	0.96 [0.79; 1.17] 0.689
Social function	368	10.7 [7.5; 21.2] *196 (53.3)*	369	7.5 [4.8; 10.4] *197 (53.4)*	0.81 [0.66; 0.99] 0.038 AD: + 3.2 months

Side effects

Endpoint	**Daratumumab + lenalidomide + dexamethasone**		**Lenalidomide + dexamethasone**		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]
Adverse events AE (presented additionally)					
	364	0.03 [n.c., n.c.] *364 (100)*	365	0.2 [0.1; 0.3] *362 (99.2)*	–
Serious adverse events (SAE)					
	364	12.9 [7.6; 16.9] *248 (68.1)*	365	9.8 [7.6; 12.7] *247 (67.7)*	0.92 [0.77; 1.10] 0.334
Severe adverse events (CTCAE grade ≥ 3)					
	364	0.7 [0.7; 1.1] *336 (92.3)*	365	1.9 [1.6; 2.9] *315 (86.3)*	1.35 [1.15; 1.58] < 0.001 AD: −1.2 months
Discontinuation because of AE[f]					

	364	n.a. [38.1; n.a.] *137 (37.6)*	365	n.a. *109 (29.9)*	1.15 [0.89; 1.48] 0.287
Specific adverse events					
Infusion-related reaction	No usable data				
Chills (PT, AE)		n.a. *47 (12.9)*		n.a. *6 (1.6)*	7.87 [3.36; 18.41] < 0.001
Respiratory, thoracic, and mediastinal disorders (SOC, AE)		4.7 [2.8; 7.4] *248 (68.1)*		19.4 [12.7; 31.3] *172 (47.1)*	1.78 [1.46; 2.17] < 0.001
Infections and infestations (SOC, SAE)		n.a. [45.0; n.c.] *130 (35.7)*		n.a. *90 (24.7)*	1.32 [1.01; 1.74] 0.042
Skin and subcutaneous tissue disorders (SOC, CTCAE grade ≥ 3)		n.a. *17 (4.7)*		n.a. *33 (9.0)*	0.47 [0.26; 0.85] 0.012
Neutropoenia (PT, CTCAE grade ≥ 3)		23.8 [12.9; n.c.] *186 (51.1)*		n.a. *129 (35.3)*	1.63 [1.30; 2.04] < 0.001
Anaemia (PT, CTCAE grade ≥ 3)		n.a. *49 (13.5)*		n.a. *75 (20.5)*	0.54 [0.38; 0.78] 0.001

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Information from the dossier of the pharmaceutical company (2nd data cut-off of 10 June 2019)
[c] Time to deterioration; defined as an increase in the score by ≥ 10 points (for the symptom scales) or decrease in the score by ≥ 10 points (for the functional scales) compared with the baseline
[d] Deterioration means reduction of the score by the respective number of points
[e] Higher (increasing) values indicate a better health status; positive effects (intervention minus control) indicate an advantage for the intervention.
[f] Discontinuation of at least one active ingredient component

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; 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; vs = versus; NE = cannot be estimated

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	no statistically significant difference
Morbidity	↑	Advantages in the symptom scales “pain” and “dyspnoea”
Health-related quality of life	↑	Advantages in the functional scales “physical function” and “social function”
Side effects	↓	Disadvantages in severe AE CTCAE grade ≥ 3, advantages and disadvantages in detail in individual specific AE

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

Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

approx. 3,470–3,670 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: 7 May 2020):

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

Treatment with daratumumab should be initiated and monitored only by specialists in internal medicine, haematology, and oncology who are experienced in the treatment of patients with multiple myeloma.

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide training material as well as a patient identification card. Training materials for healthcare professionals and blood banks include instructions on how to deal with the risks of interference with blood grouping caused by daratumumab (indirect anti-human globulin test or Coombs test). Daratumumab-induced interference with blood grouping may persist for up to six months after the last infusion of the medicinal product; healthcare professionals should therefore advise patients to carry their patient ID card for up to six months after the end of treatment.

4. Treatment costs

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

Annual treatment costs:

Adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Daratumumab	€ 133,101.46
Lenalidomide	€ 98,876.83
Dexamethasone	€ 105.13
Total:	€ 232,083.42
Additionally required SHI services:	€ 690.24 – 691.81
Appropriate comparator therapy:	
Daratumumab in combination with bortezomib, melphalan, and prednisone	
Daratumumab	€ 127,314.44
Bortezomib	€ 41,179.22
Melphalan	€ 528.87
Prednisone	€ 68.99
Total:	€ 169,091.52
Additionally required SHI services:	€ 384.57 – 386.04
Bortezomib in combination with melphalan and prednisone	
Bortezomib	€ 53,915.06
Melphalan	€ 528.87
Prednisone	€ 91.99
Total:	€ 54,535.92
Bortezomib in combination with lenalidomide and dexamethasone	
Induction	
Bortezomib	€ 33,962.24
Lenalidomide	€ 40,564.85

Designation of the therapy	Annual treatment costs/patient
Dexamethasone	€ 145.73
Follow-up treatment	
Lenalidomide	€ 53,241.37
Dexamethasone	€ 101.50
Total:	€ 128,015.69
Thalidomide in combination with melphalan and prednisone	
Thalidomide	€ 24,513.40
Melphalan	€ 587.63
Prednisone	€ 124.88
Total:	€ 25,225.91
Lenalidomide in combination with dexamethasone	
Lenalidomide	€ 98,876.83
Dexamethasone	€ 188.50
Total:	€ 99,065.33

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 2020

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/year	Costs/ patient/year
Bortezomib (in combination with daratumumab, melphalan and prednisone)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	4–8	38.8	€ 3,142.80
Bortezomib (in combination with melphalan and prednisone)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	4–8	50.8	€ 4,114.80
Bortezomib (in combination with lenalidomide and dexamethasone)	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	6	32	€ 2,592