Gemeinsamer Bundesausschuss

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

Resolution of: 20 August 2020 Valid: unlimited
Entry into force on: 20 August 2020
Federal Gazette, BAnz AT 08 10 2020 B3

New therapeutic indication (according to the marketing authorisation of 20 January 2020):

Darzalex® is indicated 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.

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

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

Appropriate comparator therapy:

- An induction therapy consisting of:
  a bortezomib-dexamethasone-based triple combination therapy according to the doctor's instructions
- Followed by high-dose therapy with melphalan and subsequent autologous stem cell transplant

Extent and probability of the additional benefit of Daratumumab in combination with bortezomib, thalidomide, and dexamethasone compared with bortezomib, thalidomide, and dexamethasone:

Hint for a non-quantifiable additional benefit

Study results according to endpoints:[1]

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

CASSIOPEIA study (Part 1)

Daratumumab + bortezomib + thalidomide + dexamethasone (D-VTd) vs bortezomib + thalidomide + dexamethasone (VTd)

[1] Data from the dossier assessment of the IQWiG (A20-15) and the addendum (A20-50) unless otherwise indicated.

Mortality

Endpoint	Daratumumab + bortezomib + thalidomide + dexamethasone		Bortezomib + thalidomide + 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					
1st data cut-off	543	n.a. *14 (2.6)*	542	n.a. *32 (5.9)*	0.43 [0.23; 0.80] 0.007 AD = n.c.
2nd data cut-off	543	n.a. *26 (4.8)*	542	n.a. *48 (8.9)*	0.52 [0.33; 0.85] 0.007 AD = n.c.

Morbidity

Progression-free survival from the 1st randomisation (PFS)[b]					
1st data cut-off	543	NE [NE; NE] *45 (8.3%)*	542	NE [30.92; NE] *91 (16.8%)*	0.47 [0.33; 0.67] < 0.0001 AD = n.c.
2nd data cut-off	543	NE [NE; NE] *83 (15.3%)*	542	NE [30.92; NE] *151 (27.9%)*	0.49 [0.38; 0.65] < 0.0001 AD = n.c.
EORTC QLQ-C30 – symptom scales[c] 1st data cut-off					
Fatigue	543	9.23 [8.81; 9.56] *220 (40.5)*	542	8.87 [8.08; 9.59] *228 (42.1)*	0.86 [0.71; 1.04] 0.127
Nausea and vomiting	543	n.a. *80 (14.7)*	542	19.35 [10.71; n.c.] *81 (14.9)*	0.96 [0.70; 1.31] 0.782
Pain	543	12.03 [12.03; n.c.] *114 (21.0)*	542	n.a. [9.69; n.c.] *138 (25.5)*	0.74 [0.57; 0.95] 0.018 AD = n.c.
Dyspnoea	543	10.35 [9.40; 12.03] *181 (33.3)*	542	9.69 [9.07; 10.15] *194 (35.8)*	0.85 [0.69; 1.05] 0.126
Insomnia	543	13.18 [10.35; 13.18]	542	10.81 [10.09; n.c.]	0.86 [0.67; 1.11]

		120 (22.1)			*132 (24.4)*	0.250
Loss of appetite	543	n.a. *69 (12.7)*		542	n.a. [19.35; n.c.] *59 (10.9)*	1.16 [0.82; 1.66] 0.408
Constipation	543	9.53 [9.04; 10.28] *207 (38.1)*		542	9.23 [8.64; 9.59] *216 (39.9)*	0.88 [0.73; 1.08] 0.216
Diarrhoea	543	10.71 [10.45; n.c.] *82 (15.1)*		542	n.a. *66 (12.2)*	1.17 [0.84; 1.63] 0.345
Health status (EQ-5D VAS)						
Time until deterioration[d]						
7 points	543	10.35 [9.96; n.c.] *153 (28.2)*		542	10.42 [9.66; n.c.] *152 (28.0)*	0.92 [0.73; 1.16] 0.482
10 points	543	10.35 [10.35; n.c.] *150 (27.6)*		542	10.71 [9.66; n.c.] *148 (27.3)*	0.93 [0.74; 1.17] 0.545
	N[e]	Values at start of study MV (SD)	Change at end of study [f] MV [95% CI]	N[e]	Values at start of study[f] MV (SD)	Change at end of study [f] MV [95% CI]	MD [95% CI] p value
Health status (EQ-5D VAS)[g]							
Mean change at Cycle 12 compared with start of study							
	383	61.50 (23.13)	8.6 [6.5; 10.8]	358	61.04 (23.96)	7.7 [5.5; 9.9]	0.9 [−1.4; 3.2] 0.441

Health-related quality of life

	Daratumumab + bortezomib + thalidomide + dexamethasone		**Bortezomib + thalidomide + 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]
EORTC QLQ-C30 – functional scales 1st data cut-off					
Global health status	543	13.18 [11.07; 13.18] *120 (22.1)*	542	n.a. [10.05; n.c.] *139 (25.6)*	0.77 [0.60; 0.99] 0.043 AD = n.c.

Physical function	543	13.18 [10.35; 13.18] *143 (26.3)*	542	10.42 [10.05; 25.56] *142 (26.2)*	0.96 [0.75; 1.21] 0.707
Role function	543	13.18 [10.15; 13.18] *152 (28.0)*	542	10.28 [9.59; n.c.] *164 (30.3)*	0.84 [0.67; 1.05] 0.116
Emotional function	543	10.94 [10.65; 13.18] *92 (16.9)*	542	n.a. *97 (17.9)*	0.87 [0.65; 1.16] 0.348
Cognitive function	543	9.30 [9.04; 9.66] *210 (38.7)*	542	9.13 [8.87; 9.66] *220 (40.6)*	0.93 [0.76; 1.12] 0.436
Social function	543	10.12 [9.40; 13.18] *183 (33.7)*	542	9.43 [9.00; 9.76] *200 (36.9)*	0.84 [0.69; 1.03] 0.100

Side effects

Endpoint	**Daratumumab + bortezomib + thalidomide + dexamethasone**		**Bortezomib + thalidomide + dexamethasone**		Intervention vs control
	N	Patients with event n *(%)*	N	Patients with event n *(%)*	Relative risk [95% CI] p value
Adverse events AE (presented additionally)					
	536	535 *(99.8)*	538	536 *(99.6)*	-
Serious adverse events (SAE)					
	536	251 *(46.8)*	538	255 *(47.4)*	0.99 [0.87; 1.13] 0.892
Severe adverse events (CTCAE grade ≥ 3)					
	536	432 *(80.6)*	538	409 *(76.0)*	1.06 [1.00; 1.13] 0.069
Discontinuation because of AE					
	536	124 *(23.1)*	538	124 *(23.1)*	1.20 [0.95; 1.51] 0.135

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Data from the dossier of the pharmaceutical company
[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. The questionnaire was collected at only three time points: at the start of study, after the end of induction therapy (on day 28 in cycle 4), and on day 100 after ASCT.

[d] Time until deterioration (decrease) of the score by at least 7 or 10 points compared with baseline. The questionnaire was collected at only three time points: at the start of study, after the end of induction therapy (on day 28 in cycle 4), and on day 100 after ASCT.
[e] Number of patients with values at the end of the study
[f] Related to part 1 of the study (follow-up up to 100 days after implementation of the ASCT)
[g] Higher (increasing) values indicate a better health status; positive effects (intervention minus control) indicate an advantage for the intervention.

Abbreviations used:
AD = absolute difference; ASCT = autologous stem cell transplant; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D = European Quality of Life Questionnaire – 5 Dimensions; HR = hazard ratio; CI = confidence interval; MD = mean difference; MV = mean value; N = number of patients assessed; n = number of patients with (at least one) event; NE = cannot be estimated; n.c. = not calculable; n.a. = not achieved; SD = standard deviation; VAS = visual analogue scale; vs = versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑	Advantage in overall survival
Morbidity	↑	Advantages for pain
Health-related quality of life	↑	Advantages in global health status
Side effects	↔	No differences relevant for the benefit assessment

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 eligible for autologous stem cell transplant

approx. 1,800–1,900 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 eligible for autologous stem cell transplant

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Induction	
Daratumumab	€ 69,444.24
Bortezomib	€ 16,981.12
Thalidomide	€ 3,760.96
Dexamethasone	€ 58.30
Total induction:	€ 90,244.62
High-dose chemotherapy with melphalan and autologous stem cell transplant	
	€ 19,170.82
Consolidation	
Daratumumab	€ 23,148.08
Bortezomib	€ 8,490.56
Thalidomide	€ 1,880.48

Designation of the therapy	Annual treatment costs/patient
Dexamethasone	€ 35.48
Total consolidation:	€ 33,554.60
Total:	€ 142,970.04
Additionally required SHI costs:	€ 414.53 – 415.86
Appropriate comparator therapy:	
Induction therapy: Bortezomib-dexamethasone-based triple combination therapy according to the doctor's instructions[a]	
Bortezomib, thalidomide, dexamethasone	
Bortezomib	€ 16,981.12 – 25,471.68
Thalidomide	€ 6,581.86 – 10,342.64
Dexamethasone	€ 181.25
Total:	€ 23,744.23 – 35,995.57
High-dose chemotherapy with melphalan and autologous stem cell transplant	
	€ 19,170.82
[a] In addition to the combination therapy bortezomib + thalidomide + dexamethasone (VTD) listed, the triple combination bortezomib + cyclophosphamide + dexamethasone (VCD) also represents a suitable comparator for the present benefit assessment in the context of induction therapy according to the doctor's instructions. The costs are not shown because this triple combination is not approved in the present therapeutic indication.	

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	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	4	16–24	€ 1,296 – 1,944