

Proposal for the inclusion of daratumumab in the WHO Model List of Essential Medicines for the treatment of multiple myeloma

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**UNIKLINIK
KÖLN**

(2) Cochrane Cancer



**Cochrane
Cancer**

(3) Cochrane Haematology



**Cochrane
Haematology**

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LIST OF ABBREVIATIONS

<i>AE</i>	<i>Adverse events</i>
<i>ASCT</i>	<i>Autologous stem cell transplantation</i>
<i>ATC</i>	<i>Anatomical therapeutic chemical</i>
<i>CI</i>	<i>Confidence interval</i>
<i>CRAB</i>	<i>Calcemia, renal, anemia, bone lesions</i>
<i>CT</i>	<i>Computed tomography</i>
<i>CTCAE</i>	<i>Common Terminology Criteria for Adverse Events</i>
<i>DALY</i>	<i>Disability-adjusted life year</i>
<i>DaraRD</i>	<i>Daratumumab, Lenalidomide, Dexamethasone</i>
<i>DaraVD</i>	<i>Daratumumab, Bortezomib, Dexamethasone</i>
<i>ECOG</i>	<i>Eastern Cooperative Oncology Group</i>
<i>EMA</i>	<i>European Medicines Agency</i>
<i>EML</i>	<i>Essential Medicines List</i>
<i>EORTC</i>	<i>European Organisation for Research and Treatment of Cancer</i>
<i>ERD</i>	<i>Elotuzumab, Lenalidomide, Dexamethasone</i>
<i>ESMO - MCBS</i>	<i>European Society for Medical Oncology Magnitude of Clinical Benefit Scale</i>
<i>EU</i>	<i>European Union</i>
<i>FDA</i>	<i>Food and Drug Administration</i>
<i>FDF</i>	<i>finished dosage form</i>
<i>FDG</i>	<i>Fluorodeoxyglucose</i>
<i>G-BA</i>	<i>Gemeinsamer Bundesausschuss (Federal Joint Committee of Germany)</i>
<i>GB£</i>	<i>Great British Pound</i>
<i>GRADE</i>	<i>Grading of Recommendations Assessment, Development and Evaluation</i>
<i>HC</i>	<i>Health Canada</i>
<i>HIC</i>	<i>High-income country</i>
<i>HR</i>	<i>Hazard ratio</i>
<i>HTA</i>	<i>Health Technology Assessment</i>
<i>ICER</i>	<i>Incremental cost-effectiveness ratio</i>
<i>INHTA</i>	<i>International Network of Agencies for Health Technology Assessment</i>
<i>INN</i>	<i>International Nonproprietary Name</i>

<i>IRD</i>	<i>Ixazomib, Lenalidomide, Dexamethasone</i>
<i>KD</i>	<i>Carfilzomib, Dexamethasone</i>
<i>KRD</i>	<i>Carfilzomib, Lenalidomide, Dexamethasone</i>
<i>LMIC</i>	<i>Low- and middle-income country</i>
<i>MD</i>	<i>Mean Differences</i>
<i>MM</i>	<i>Multiple myeloma</i>
<i>MRI</i>	<i>Magnetic resonance imaging</i>
<i>NDMM</i>	<i>Newly diagnosed multiple myeloma</i>
<i>NICE</i>	<i>National Institute for Health and Care Excellence</i>
<i>OS</i>	<i>Overall survival</i>
<i>PaVD</i>	<i>Panobinostat, Bortezomib, Dexamethasone</i>
<i>PET</i>	<i>Positron emission tomography</i>
<i>PFS</i>	<i>Progression-free survival</i>
<i>PICO</i>	<i>Patient, Intervention, Control, Outcome</i>
<i>PMDA</i>	<i>(Japanese) Pharmaceuticals and Medical Devices Agency</i>
<i>PoVD</i>	<i>Pomalidomide, Bortezomib, Dexamethasone</i>
<i>QALY</i>	<i>Quality-adjusted life year</i>
<i>QLQ</i>	<i>Quality of Life Questionnaire</i>
<i>QoL</i>	<i>Quality of life</i>
<i>RCT</i>	<i>Randomised controlled trial</i>
<i>RD</i>	<i>Lenalidomide, Dexamethasone</i>
<i>RR</i>	<i>Risk ratio</i>
<i>RRMM</i>	<i>Relapsed or refractory multiple myeloma</i>
<i>SAE</i>	<i>Serious adverse events</i>
<i>SLiM</i>	<i>Sixty, light, magnetic</i>
<i>TEAE</i>	<i>Treatment emergent adverse events</i>
<i>TGA</i>	<i>Therapeutic Goods Administration</i>
<i>UI</i>	<i>uncertainty interval</i>
<i>UK</i>	<i>United Kingdom</i>
<i>US</i>	<i>United States</i>
<i>USA</i>	<i>United States of America</i>

<i>VCD</i>	<i>Bortezomib, Cyclophosphamide, Dexamethasone</i>
<i>VD</i>	<i>Bortezomib, Dexamethasone</i>
<i>VRD</i>	<i>Bortezomib, Lenalidomide, Dexamethasone</i>
<i>WHO</i>	<i>World Health Organization</i>

GENERAL ITEMS

1. Summary statement of the proposal for inclusion, change or deletion

This application advocates the inclusion of daratumumab in the core list of essential medicines for the treatment of newly diagnosed (NDMM) and relapsed or refractory multiple myeloma (RRMM) patients in transplant and non-transplant settings. Results of the evidence syntheses indicate that adding daratumumab to standard combination regimens probably leads to clinically important gain of overall survival, yet a higher number of people experiencing adverse events or serious adverse events. Evidence further suggests that more people receiving daratumumab may have a clinically important gain of quality of life, than people no receiving daratumumab.

Multiple myeloma (MM) is the second most common haematological malignancy with a global incidence of 138,509 (95% uncertainty interval [UI]: 121,000 to 155,480) and an age-standardized incidence rate of 2.1 per 100,000 population (95% UI: 1.8 to 2.3) in 2016. Since 1990, the incidence rate increased by 126% worldwide (1).

2. Relevant WHO technical department and focal point

Lorenzo Moja, Technical Officer, EML (Essential Medicines List) Secretariat

3. Name of organizations consulted and supporting the application

- Department I of Internal Medicine, University Hospital of Cologne
- Cochrane Cancer
- Cochrane Haematology

4. International Nonproprietary Name and Anatomical Therapeutic Chemical code of the medicine

International Nonproprietary Name (INN)

Daratumumab

Anatomical Therapeutic Chemical (ATC)

In the ATC classification system, daratumumab is classified as “other neoplastic agent” and can be identified by the ATC code: L01XC24 (2).

5. Dose forms and strengths proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths

Daratumumab is available as 100 mg/5 mL (20 mg/mL) and 400 mg/20 mL (20 mg/mL) solution in a single-dose vial (3, 4). Before intravenous infusion, the solution must be diluted with a 0.9% sodium chloride injection (3).

Table 1 shows the current market availability of daratumumab, including available finished dosage forms (FDFs), dosage strengths and packaging presentations, when available.

Table 1: Current international market availability (FDFs) of daratumumab (4)

Country of registration	Supplier	Dosage form	Dosage	Packaging presentation
United States of Amerika (USA)	Centocor Inc	Injection	100 mg / 5 ml	/

Country of registration	Supplier	Dosage form	Dosage	Packaging presentation
USA	Centocor Inc	Injection	400 mg / 20 ml	/
Canada	Centocor Inc	Solution	100 mg / 5 ml	5 ml
Canada	Centocor Inc	Solution	400 mg / 20 ml	20 ml

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class

This application covers one selected medicine out of the pharmacological class “antineoplastic and immunomodulating agents”(□). Specifically, it refers to the monoclonal antibody daratumumab.

This application is restricted to the listed medicine, due to the reason that other medicines out of the pharmacological class are still under evaluation for multiple myeloma treatment in on-going randomised controlled trials (e.g. NCT04240054, NCT04083898, NCT04119336, NCT02969837), and not yet approved for first-line treatment.

TREATMENT DETAILS, PUBLIC HEALTH RELEVANCE AND EVIDENCE APPRAISAL AND SYNTHESIS

7. Treatment details (requirements for diagnosis, treatment and monitoring)

Diagnosis

Early diagnosis of multiple myeloma is complicated because the condition presents with widely varying symptoms. Some patients with MM might be symptom-free, while others present common symptoms like bone pain (mostly in the back, hips or skull), fractures, symptoms of light chain amyloidosis, or high blood levels of calcium. Among other things, the latter might lead to kidney problems, abdominal pain, or extreme thirst (5). The International Myeloma Working Group has revised the criteria for myeloma diagnosis in 2014. They compose of clonal bone marrow plasma cells $\geq 10\%$ or biopsy-proven or extramedullary plasmacytoma and one (or more) myeloma defining events (see Table 2) (6).

Table 2: Myeloma defining events (6)

CRAB criteria	
HyperCalcemia	> 2.75 mmol/L (> 11 mg/dL)
Renal insufficiency	creatinine clearance < 40mL per min or serum creatine > 177 μ mol/L (> 2 mg/dL)
Anemia	haemoglobin value < 100 g/L
Bone lesions	One or more osteolytic lesions on skeletal radiography, computer tomography (CT), or positron emission tomography-computer tomography (PET-CT)
Biomarkers of malignancy (SLiM criteria)	
Clonal bone marrow plasma cell %-age	≥ 60 (S ixty) %
Involved to uninvolved serum free Light chain ratio	≥ 100
Focal lesions on Magnetic resonance imaging (MRI) studies	< 1

Daratumumab in transplant-ineligible newly diagnosed multiple myeloma patients

An exemplary medication plan for the treatment of **adult, transplant-ineligible NDMM patients** using daratumumab in combination with bortezomib, melphalan and prednisone is presented below (7):

- A dose of 16 mg/kg body weight of daratumumab is administered weekly in week 1 to 6, every 3 weeks in weeks 7 to 54, and every 4 weeks thereafter until disease progression.

- Bortezomib is given at a dose of 1,3 mg/m² two times a week in weeks 2, 4, and 5. Thereafter, it is given once per week in a 6-week cycle on weeks 1, 2, 4, and 5.
- 9 mg/m² of melphalan is administered on days 1 to 4 of the 6-week cycles.
- Prednisone is given at a dose of 60 mg/m² on days 2 to 4 of the 6-week cycles (7).

Furthermore, a triplet regimen of daratumumab, lenalidomide and dexamethasone is indicated for this patient population (8). The following recommended treatment schedule is based on 28-day cycles (9):

- Daratumumab is injected at a dose of 16 mg/kg body weight weekly in week 1 to 8, every two weeks in week 9 to 24, and every 28 days thereafter.
- 25mg of lenalidomide is given on days 1 to 21 of a 28-day cycle.
- Dexamethasone is administered at a dose of 40mg on days 1, 8, 15, and 22 of a 28-day cycle (9).

Daratumumab in transplant-eligible newly diagnosed multiple myeloma patients

For **NDMM patients who are eligible for stem cell transplantation**, a combined treatment of daratumumab, bortezomib, thalidomide and dexamethasone as induction therapy may be indicated (10). A possible treatment schedule, based on 28-day cycles, is listed below:

- Daratumumab is given at a dose of 16 mg/kg body weight weekly in week 1 to 8, and every two weeks in week 9 to 16.
- Bortezomib is given at a dose of 1,3 mg/m² on days 1, 4, 8, and 11 of a 28-day cycle.
- 40 mg of dexamethasone is given on days 1 and 2 in cycles 1 to 4. Additionally, 20 mg of dexamethasone is administered on days 8, 9, 15, and 16 in cycles 3-4 (11).

Daratumumab in relapsed or refractory multiple myeloma patients

A possible medication plan for MM patients in second-line treatment includes daratumumab plus bortezomib plus dexamethasone (12). Details on dosing recommendations can be found below:

- Daratumumab is given by intravenous infusion at a dose of 16 mg/kg body weight, once a week in weeks 1 to 9, every three weeks from weeks 10 to 24, and every 4 weeks from week 25 onwards.
- Bortezomib is subcutaneously injected at a dose of 1.3 mg/m² twice weekly on days 1, 4, 8 and 11 for 8×21-day cycles.
- Dexamethasone is administered orally at a dose of 80 mg per week (12).

Additionally, daratumumab monotherapy is recommended for **RRMM patients who had three previous therapies** (13). The corresponding dose and infusion schedule is described in the following:

- 16 mg/kg body weight of daratumumab is given by intravenous infusion once a week in weeks 1 to 8, every two weeks from weeks 9 to 24, and every 4 weeks from week 25 onwards. Treatment is continued until disease progression (13).

Monitoring

In accordance with the National Institute for Health and Care Excellence (NICE) guideline [NG35] “Myeloma: diagnosis and management” (14), patients who completed initial myeloma therapy should be monitored at least every three months, during which risk factors for disease progression

(high-risk fluorescence in-situ hybridization, impaired renal function, disease presentation) should be taken into account. Monitoring should comprise assessment of myeloma, and treatment-related symptoms, and multiple laboratory tests (full blood count, renal function, bone profile, serum immunoglobulins and serum electrophoresis, and, if appropriate, serum-free light-chain assay). Multiple myeloma patients should not be offered skeletal surveys routinely for disease monitoring. Taking into account previous imaging tests, one of the following can be considered: whole-body magnetic resonance imaging (MRI), whole-body low-dose CT, whole-body CT, spinal MRI, fluorodeoxyglucose (FDG) PET-CT.

8. Information supporting the public health relevance

Cancer is one of the most common non-communicable diseases worldwide with an estimated incidence of 18.1 million new cases in 2018 (15). Around the globe, cancer is the second leading cause of mortality and accounted for an estimate of 9.6 million deaths in 2018 (16). About 70% of the global deaths due to cancer occur in low- and middle-income countries (LMICs). Main reasons for a higher mortality, relative to incidence rates, in these regions are late-stage presentation and lack of access to diagnosis and treatment. Treatment services are available in less than 30% of LMICs, compared to over 90% in high-income countries (HIC).

Multiple myeloma is the second most common haematological malignancy and will account for 2.1% of all cancer deaths in the US in 2020 (17),(18). In 2018, there was an estimated amount of 159,985 (0.9%) new MM cases and 106,105 (1.1%) MM deaths, worldwide (15). Incidence rates are higher in HICs than in LMICs (cf. Figure 1). Globally, myeloma caused 2.1 million disability-adjusted life-years (DALYs) in 2016 (1). Globally, the incidence rate increased by 126% between 1990 and 2016 and is strongly related to age (19), (1). Based on the latest statistics in the US, the median age of myeloma diagnosis across all races and both genders is 69 years (18).

Estimated age-standardized incidence rates (World) in 2018, multiple myeloma, both sexes, all ages

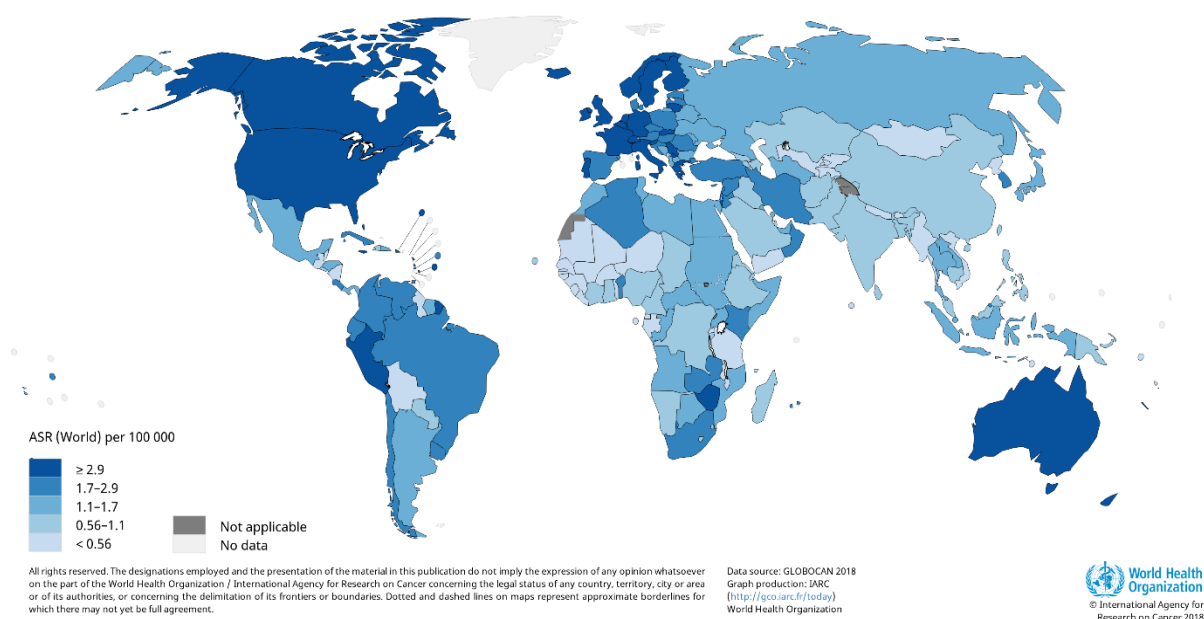


Figure 1: Estimated incidence rates of MM in 2018 (20)

In HICs, autologous stem cell transplantation (ASCT) is routinely used for younger patients with a good general state of health. However, ASCT is not available in many LMICs (1). Lack of access to general and specialized healthcare leads to wide disparities in survival rates between HICs and LMICs. In the UK, 52.3% of diagnosed MM patients are predicted to survive at least five years

(29.1% at least 10 years) (19). In comparison, a 5-year survival rate of only 7.6% was reported in Nigeria in a multi-centre retrospective study from 2003 to 2012 (21), and of 15.5% in Ghana in a single-centre retrospective study from 2002 to 2016 (22).

Daratumumab is a novel drug that targets CD-38, a human IgG1k monoclonal antibody. CD-38 is a 46-kDa type II transmembrane glycoprotein that is overexpressed by myeloma cells, making the myeloma cells a specific target for daratumumab (23). Daratumumab induces the death of myeloma cells in several ways, including direct induction of apoptosis (cell death), complement- and antibody-mediated cytotoxicity, and antibody-dependent cellular phagocytosis (24). Daratumumab also induces the clonal expansion of cytotoxic T-cells which could add to the anti-myeloma effects (25).

Daratumumab has been approved for the treatment of multiple myeloma patients with newly diagnosed and relapsed or refractory disease (26). Initial studies showed that in combination with proteasome-inhibitors, such as bortezomib, daratumumab increases progression-free survival rates at 12 months compared to standard treatment without daratumumab (60.7% vs. 26.9%). Combination therapies with proteasome-inhibitors also showed a higher overall response rate (82.9% vs. 63.2%), very good partial response rate (59.2% vs. 29.1%), and complete response rate (19.2% vs. 9.0%) (27).

9. Review of benefits, harms and toxicity: summary of evidence of comparative efficacy and safety

Methodological approach

The objective was to evaluate the efficacy and safety of daratumumab for transplant-ineligible newly diagnosed multiple myeloma (NDMM) patients (PICO 1), transplant eligible NDMM patients (PICO 2), and for relapsed or refractory multiple myeloma (RRMM) patients (PICO 3).

PICO 1 was answered on the basis of a Cochrane review in development (28). To answer the other two PICOs, rapid evidence syntheses were performed, according to the standard methodology as outlined in the Cochrane Handbook for Systematic Reviews of Interventions (29).

In a first step, we systematically searched for high-quality systematic reviews and health technology assessments in MEDLINE and the Cochrane Library until October 2020. The results of the search were screened in duplicate and eligible reviews and meta-analysis assessed with AMSTAR-2 after PICO-matching (30). Any disagreements were solved by discussion. Because methodological quality was low, another search for primary studies was conducted. We systematically searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, and clinicaltrials.gov until October 2020 for randomised controlled trials (RCTs). Full search strategies are included in Appendix I. We applied the same methodological approach as outlined in the Cochrane protocol for PICO 1 (28). Randomised controlled trials that studied combination therapies with the same regimen plus daratumumab for any line of therapy were included. Outcomes of interest were prioritised by a patient representative. Those were:

1. Overall survival (OS): from randomisation to death of any cause or last follow-up (Hazard-ratio (HR) at longest-follow up available).
2. Quality of Life if measured with a validated tool at longest follow-up
 - a. Number of participants with at least 10 points improvement of global health on a 0 to 100 Scale (higher score implies a higher quality of life)
 - b. Number of participants with at least 10 points worsening of global health on a 0 to 100 Scale (higher score implies a higher quality of life)

3. Adverse events (AEs): number of allocated participants that received at least one study drug with at least one event (event rates at longest follow-up available)
 - a. Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 : number of participants with at least one event
 - b. Infections
 - c. Pneumonia
4. Serious adverse events: number of allocated participants that received at least one study drug with at least one event (event rates at longest follow-up available)

Two authors independently screened the search results and extracted the data. If possible, outcome data were extracted from Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) dossiers, because of their access to study reports (31-33). Data synthesis was performed using Review Manager Software. Risk of bias in included studies was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (29). The certainty of evidence for outcomes was rated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (34).

Because overall survival was premature in all included trials and median survival was not reached in any group of any trial, we added the surrogate outcome progression-free survival. We had planned to compare overall survival estimates to observations in real life settings, but did not identify any mature data. To measure the clinical benefit of the treatments, the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) was applied (35). The clinical benefit was assessed according to the ESMO Magnitude of Clinical Benefit Scale v1.1, Form 2b: “for therapies that are not likely to be curative with primary endpoint of progression-free survival (PFS), if median PFS with standard treatment is >6 months” (36).

Description of studies

The results of the electronic search are illustrated in Figure 2 and Figure 3.

PICO 1: Transplant-ineligible newly diagnosed patients

The Cochrane review included two RCTs, reporting on 1443 patients (37). Both trials were multi-centric and participants were recruited from Europe, Asia, North- and South America, and the Pacific region, and had a mean age ranging across studies from 71.4 to 74.1 years. Patients with a diagnosis of MM according to the International Staging System were included (38). Follow-up is still ongoing. Latest results were reported after a median of 40 months follow-up in the ALCYONE trial and 36 months in the MAIA trial. The ALCYONE trial compared the effect of adding daratumumab to bortezomib and melphalan-prednisone. The MAIA trial compared the effect of adding daratumumab to lenalidomide and dexamethasone.

PICO 2: Transplant-eligible newly diagnosed patients

Two RCTs, reporting on 1744 patients were included (39, 40). Both trials were multi-centric and participants were recruited from Europe, Asia, North- and South America, and the Pacific region, and had a median age ranging across studies from 58 to 60 years. Patients with a diagnosis of MM according to the International Staging System with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 that were candidates for high-dose chemotherapy and autologous stem cell transplantation were included. Both trials applied an upper age limit of 65 (39) to 70 (40) years. Follow-up is still ongoing. Latest results were reported after a median of 18.8 months follow-up in the CASSIOPEIA trial and 22.1 months in the GRIFFIN trial. The CASSIOPEIA trial compared the effect of adding daratumumab to bortezomib, thalidomide and dexamethasone. The GRIFFIN trial compared the effect of adding daratumumab to bortezomib, lenalidomide and dexamethasone.

PICO 3: Relapsed or refractory patients

Four RCTs, reporting on 1308 patients were included (41-44). All trials were multi-centric and participants were recruited from Europe, Asia, North- and South America, and the Pacific region. Across studies, patients had a median age ranging from 61 to 65 years and had received a median of 1 to 2 prior lines of therapy. Patients with a diagnosis of MM according to the International Staging System who had relapsed or refractory disease that had received one or more lines of previous therapy were included. Follow-up is still ongoing. Latest results were reported after a median of 8.2 months in the LEPUS trial to 44.3 months in the POLLUX trial. The CANDOR trial compared the effect of adding daratumumab to carfilzomib and dexamethasone. CASTOR and LEPUS compared the effect of adding daratumumab to bortezomib and dexamethasone, and POLLUX the effect of adding daratumumab to lenalidomide and dexamethasone.

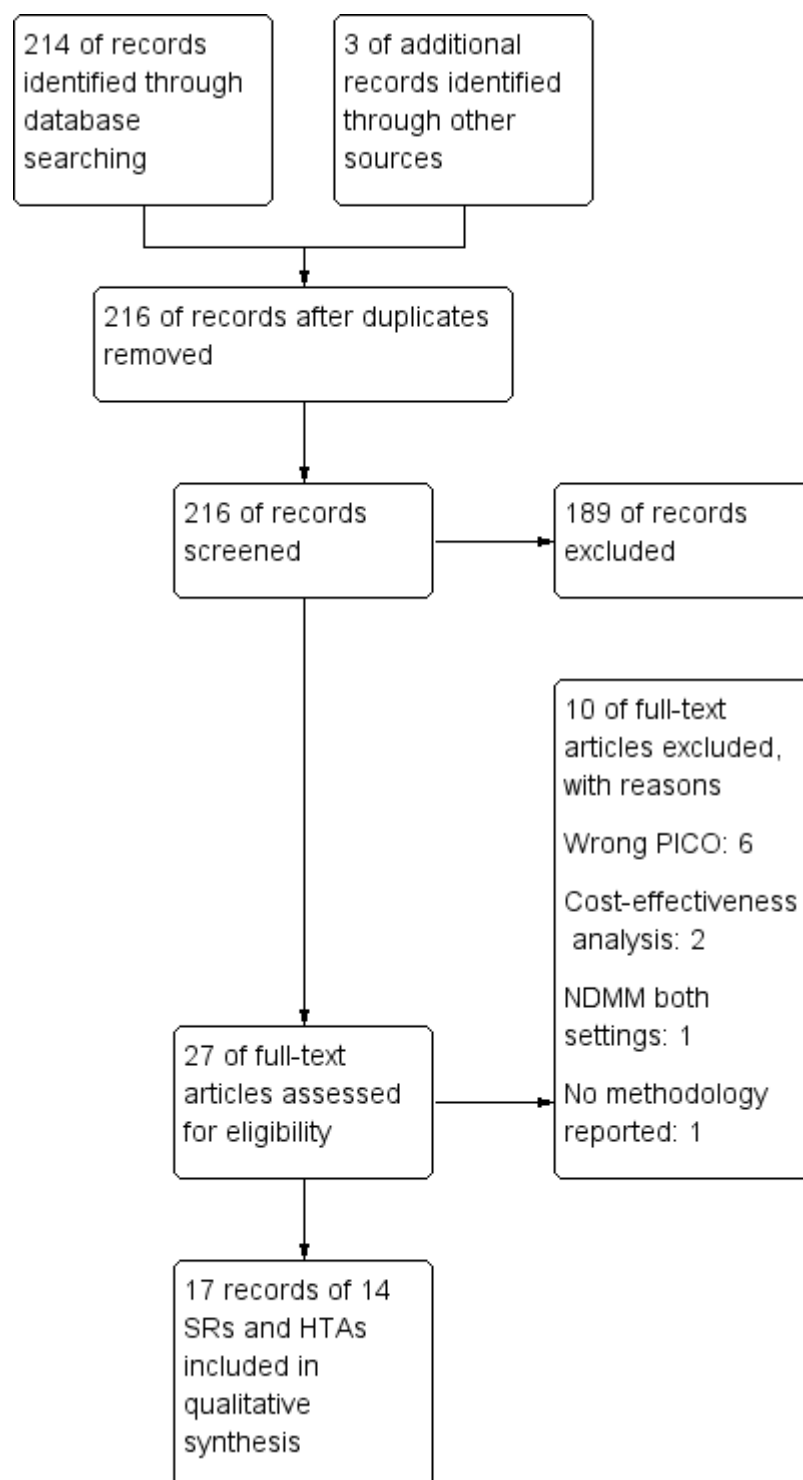


Figure 2: PRISMA Flow diagram of systematic search for high-quality systematic reviews and health technology assessments

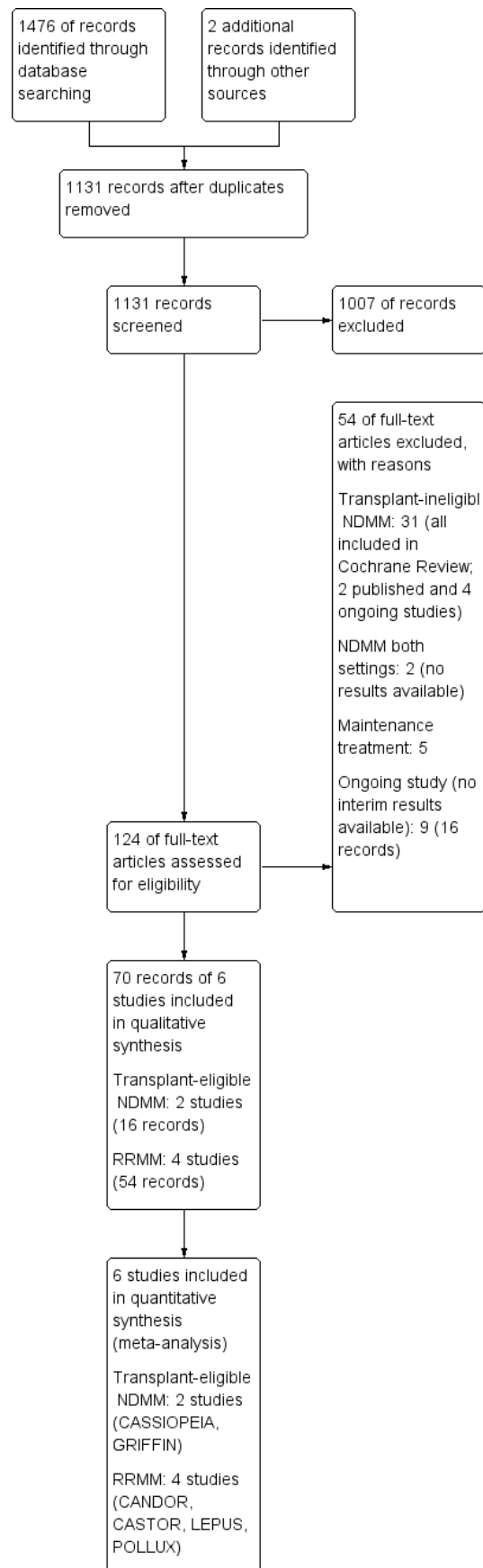


Figure 3: PRISMA Flow diagram of systematic search for primary studies

Risk of Bias

PICO 1: Transplant-ineligible newly diagnosed Multiple Myeloma

The summary of the risk of bias assessments of each of the included studies is presented in Figure 4 Risk of bias graph (PICO 1: Transplant-ineligible NDMM). The risk for selection bias was judged to be unclear for both trials, because study authors provided no information on concealment of allocation. Both trials were open-label studies, so there is a high risk of performance and detection bias for objectives outcomes, such as quality of life. Risk of attrition bias was high in one study, reasoned by an unclear status of participants in both groups after discontinuing the study (39% of participants in the intervention group and 64% of participants in the control group discontinued the study). No other sources of bias were identified. Overall risk of bias was high for survival outcomes and quality of life, and low for safety outcomes.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of overall survival assessment (detection bias)	Blinding of progression free survival assessment (detection bias)	Blinding of safety assessment (detection bias)	Blinding of quality of life assessment (detection bias)	Incomplete survival data (attrition bias)	Incomplete safety data (attrition bias)	Selective reporting (reporting bias)	Other bias
ALCYONE	+	+	-	+	-	-	-	+	+	+	+
MAIA	+	+	-	+	-	-	-	-	+	+	+

Figure 4 Risk of bias graph (PICO 1: Transplant-ineligible NDMM)

PICO 2: Transplant-eligible newly diagnosed Multiple myeloma

The summary of the risk of bias assessment of each of the included studies is presented in Figure 5. Both trials were open-label studies, so there is a high risk of performance and detection bias for objectives outcomes, such as quality of life. No other sources of bias were identified. Overall risk of bias was high for survival outcomes and quality of life, and low for safety outcomes.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of overall survival assessment (detection bias)	Blinding of progression free survival assessment (detection bias)	Blinding of safety assessment (detection bias)	Blinding of quality of life assessment (detection bias)	Incomplete survival data (attrition bias)	Incomplete safety data (attrition bias)	Selective reporting (reporting bias)	Other bias
CASSIOPEIA	+	+	-	+	-	+	-	+	+	+	+
GRIFFIN	+	+	-	+	-	-	-	+	+	+	+

Figure 5: Risk of bias graph (PICO 2: Transplant-eligible NDMM)

PICO 3: Relapsed or refractory Multiple Myeloma

The summary of the risk of bias assessments of each of the included studies is presented in Figure 6. Selection bias was unclear in the CASTOR and LEPUS trial, because the randomisation and masking were not reported in both trials, and for the LEPUS trial only a conference abstract was available. All four trials were open-label studies, so there is a high risk of performance and detection bias for subjective outcomes, such as quality of life. Blinding of quality of life assessment was not assessed in the LEPUS trial as the outcome was not yet reported and methods were scarcely reported in the abstract. Risk of attrition bias unclear in the LEPUS trial, because there was only an abstract available which did not contain a study flow diagram. Reporting bias is high in the LEPUS trial, because there was no study protocol available and only selected outcomes were reported in the abstract. No other sources of bias were identified. Overall risk of bias was high for survival outcomes and quality of life, and low for safety outcomes.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of overall survival assessment (detection bias)	Blinding of progression free survival assessment (detection bias)	Blinding of safety assessment (detection bias)	Blinding of quality of life assessment (detection bias)	Incomplete survival data (attrition bias)	Incomplete safety data (attrition bias)	Selective reporting (reporting bias)	Other bias
Candor	+	+	-	+	+	+	-	+	+	+	+
Castor	?	?	-	+	-	-	-	+	+	+	+
LEPUS	?	?	-	+	-	-		?	+	-	+
Pollux	+	+	-	+	-	-	-	+	+	+	+

Figure 6: Risk of bias graph (PICO 3: RRMM)

Comparative efficacy of treatments with daratumumab

PICO 1: Transplant-ineligible newly diagnosed Multiple Myeloma

Overall survival

Both studies reported overall survival for 1443 patients. Median survival was not reached in either group of both studies. In the ALCYONE trial, 83 patients (24%) in the daratumumab group and 126 patients (35%) in the control group had died at a median follow-up of 40.1 months (interquartile range (IQR) 37.4 to 43.1). At data cut-off in June 2019 (median observation of 36.7 months (range 0 to 49.0) in the daratumumab group and 35.9 months (range 0 to 49.9) in the control group), 85 patients (23.1%) in the daratumumab group and 103 patients (27.9%) in the control group had died in the MAIA trial.

Treatment with daratumumab probably increases overall survival when compared to treatment without daratumumab (HR 0.67, 95% confidence interval (CI) 0.5 to 0.85, I^2 39%, moderate-certainty evidence, see Figure 7) for participants receiving daratumumab. The clinical benefit of the treatments was planned to be assessed according to the ESMO-MCBS (35). However, the magnitude of clinical benefit could not be graded for survival, because median survival was not yet reached in either trial (36). We therefore added the outcome progression-free survival as a surrogate.

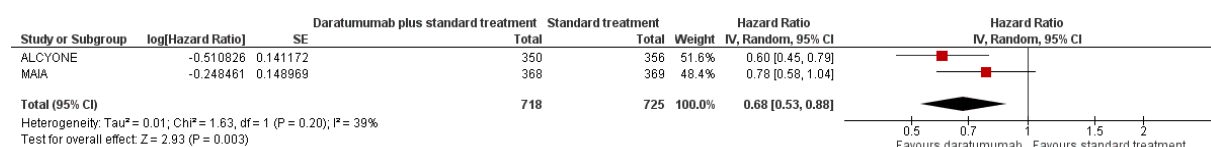


Figure 7: Forest plot for the outcome overall survival (PICO 1: Transplant-ineligible NDMM)

Progression-free survival

Both studies reported progression-free survival for 1443 patients. In the ALCYONE trial, median progression-free survival was 36.40 months (95% CI 32.13 to 45.90) in the daratumumab group and 19.29 months (95% CI 17.97 to 20.40) in the control group. In the MAIA trial, median progression-free survival was not reached in the daratumumab group, and was 33.84 months (95% CI 28.95 to 39.23) in the control group. At data cut-off in June 2019 (median observation of 36.7 months (range 0 to 49.0) in the daratumumab group and 35.9 months (range 0 to 49.9) in the control group), 120 patients (32.6%) in the daratumumab group and 171 patients (46.3 %) in the control group had progressed or died in the MAIA trial.

Treatment with daratumumab probably increases progression-free survival when compared to treatment without daratumumab (HR 0.48, 95% CI 0.36 to 0.63, I^2 65%, moderate-certainty evidence, see Figure 8Figure 7) for participants receiving daratumumab. The clinical benefit of the treatments was planned to be assessed according to the ESMO-MCBS (35). The magnitude of clinical benefit was graded as 4 out of 4 (progression-free survival benefit compared to comparator HR < 0.65 and estimated progression-free survival gain >3 months (36)).

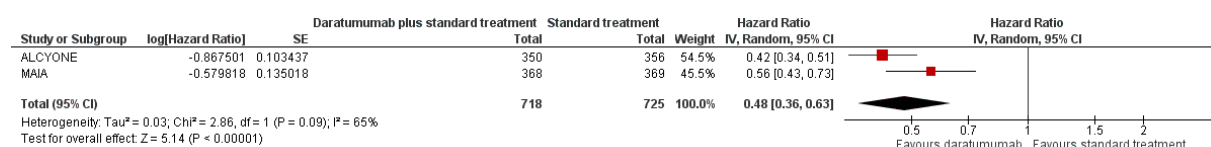


Figure 8: Forest plot for the outcome progression-free survival (PICO 1: Transplant-ineligible NDMM)

Quality of life

a) Global Health increase of ≥ 10 points

In both trials quality of life was assessed for 1443 patients with the global health status of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) on a scale from 0 to 100. A higher value implies a better global health status. Median observation ranged from 28.2 to 31.0 months in the daratumumab groups and from 17.3 to 22.0 months in the control groups. An increase of the global health status from baseline by at least 10 points was classified as clinically relevant (33) and reported for 429 patients (59.7%) in the daratumumab groups and 385 patients (53.1%) in the control groups.

More people receiving daratumumab probably gain at least 10 points of global health status after start of treatment when compared to people receiving no daratumumab (risk ratio (RR) 1.13, 95% CI 1.13 to 1.23, I^2 0%, moderate-certainty evidence, Figure 9).

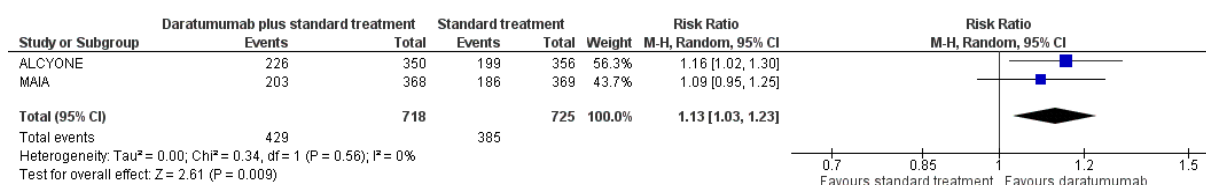


Figure 9: Forest plot for the outcome quality of life - global health increase of ≥ 10 points (PICO 1: Transplant-ineligible NDMM)

b) Global Health decrease of ≥ 10 points

In both trials quality of life after up to 12 months of treatment was assessed for 1443 patients with the global health status of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) on a scale from 0 to 100. A higher value implies a better global health status. Median observation ranged from 28.2 to 31.0 months in the daratumumab groups and from 17.3 to 22.0 months in the control groups. A decrease of the global health status from baseline by at least 10 points was classified as clinically relevant (33) and reported for 276 patients (38.4%) in the daratumumab groups and 275 patients (37.9%) in the control groups.

Evidence suggests that impairment of at least 10 points of global health status after start of treatment is probably similar for people receiving or not receiving daratumumab (RR 1.02, 95% CI 0.89 to 1.16, I^2 0%, moderate-certainty evidence, Figure 10).

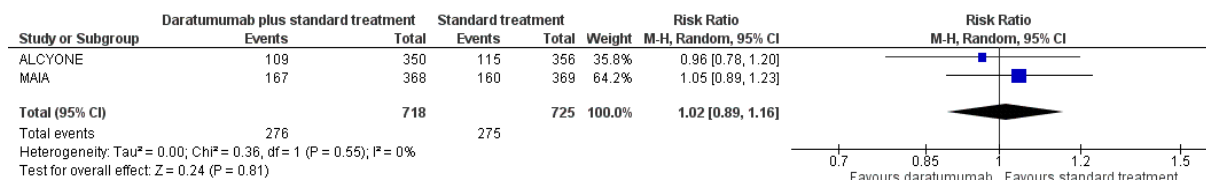


Figure 10: Forest plot for the outcome quality of life - global health decrease of ≥ 10 points (PICO 1: Transplant-ineligible NDMM)

PICO 2: Transplant-eligible newly diagnosed MM

Overall survival

One study (CASSIOPEIA) reported overall survival for 1085 patients. Median survival was not reached in either group. Overall survival was reported at a median follow-up of 18.8 months (range 0.0 – 32.2). Fourteen patients (2.6%) in the daratumumab group and 32 patients (5.9%) in the control group had died.

Treatment with daratumumab may increase overall survival when compared to treatment without daratumumab (hazard ratio (HR) 0.52, 95% CI 0.33 to 0.82, low-certainty evidence, see Figure 11) for participants receiving daratumumab. The clinical benefit of the treatments was planned to be assessed according to the ESMO-MCBS (32). However, the magnitude of clinical benefit could not be graded for survival, because median survival was not yet reached in either trial (33). We therefore added the outcome progression-free survival as a surrogate.

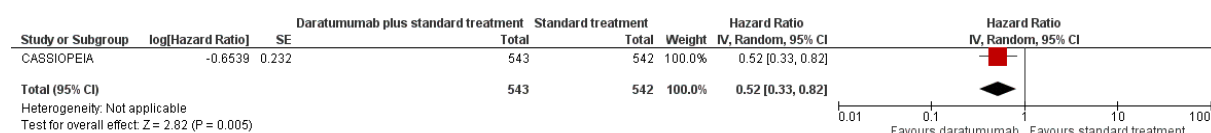


Figure 11: Forest plot for the outcome overall survival (PICO 2: Transplant-eligible NDMM)

Progression free survival

Both studies reported progression-free survival for 1292 patients. Median progression-free survival was not reached in either group of both studies. At data cut off in May 2019, in the CASSIOPEIA trial 79 events (14.5%) of disease progression occurred in the daratumumab group and 136 events (25.1%) in the control group. In the GRIFFIN trial, 4 events of disease progression (3.8%) occurred in the daratumumab group and 7 events in the control group (6.8%) at a median follow-up of 22.1 months.

Treatment with daratumumab may increase progression-free survival when compared to treatment without daratumumab (HR 0.49, 95% CI 0.36 to 0.68, I^2 0%, very low-certainty evidence, see Figure 12) for participants receiving daratumumab, but the evidence is very uncertain. The clinical benefit of the treatments was planned to be assessed according to the ESMO-MCBS (32). However, the magnitude of clinical benefit could not be graded for progression-free survival, because median progression-free survival was not yet reached in either trial (33).

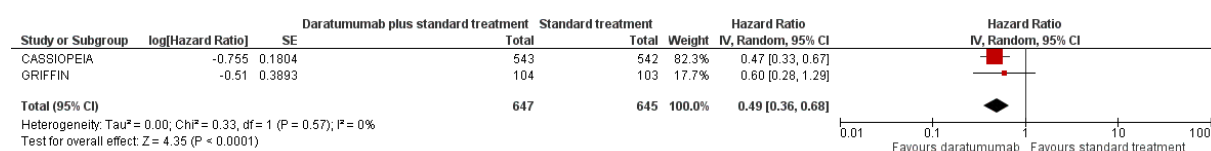


Figure 12: Forest plot for the outcome progression-free survival (PICO 2: Transplant-eligible NDMM)

Quality of life

a) Global Health increase of ≥ 10 points

In the CASSIOPEIA trial quality of life after up to 9 months of treatment was assessed for 1085 patients with the EORTC QLQ-C30 on a scale from 0 to 100. A higher value is to be regarded as an improvement of the global health status. The median observation was 9.0 months in the daratumumab group similar to the control group. An increase of the global health status from baseline by at least 10 points was classified as clinically relevant (33) and reported for 207 patients (38.1%) in the daratumumab group and 194 patients (35.8%) in the control group.

More people receiving daratumumab may gain at least 10 points of global health status after start of treatment when compared to people receiving no daratumumab (RR 1.07, 95% CI 0.91 to 1.24, low-certainty evidence, see Figure 13) at 9.0 months after start of treatment.

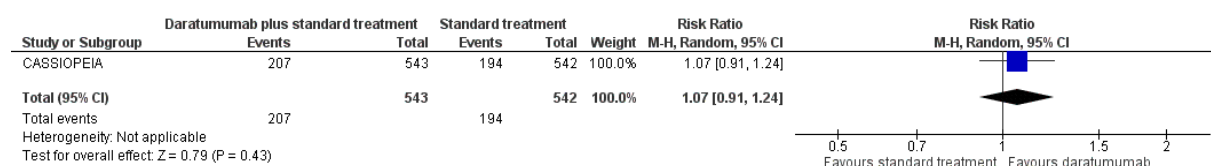


Figure 13: Forest plot for the outcome quality of life - global health increase of ≥ 10 points (PICO 2: Transplant-eligible NDMM)

b) Global Health decrease of ≥ 10 points

In the CASSIOPEIA trial quality of life after up to 9.0 months of treatment was assessed for 1085 patients with the EORTC QLQ-C30 on a scale from 0 to 100. A higher value is to be regarded as an improvement of the global health status. The median observation was 9.0 months in the

daratumumab group similar to the control group. Decrease of the global health status from baseline by at least 10 points was classified as clinically relevant (33) and reported for 120 patients (22.1%) in the daratumumab group and 139 patients (25.6%) in the control group.

Less people receiving daratumumab may have a decline of at least 10 points of global health status after start of treatment when compared to people receiving no daratumumab (RR 0.86, 95% CI 0.70 to 1.07, low-certainty evidence, see Figure 14) at 9.0 months after start of treatment.

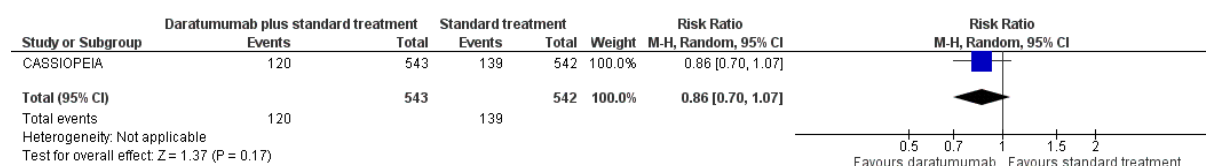


Figure 14: Forest plot for the outcome quality of life - global health decrease of ≥ 10 points (PICO 2: Transplant-eligible NDMM)

PICO 3: Relapsed or refractory Multiple myeloma

Overall survival

Four studies reported overall survival for 1717 patients. Median survival was not reached in either group of the four studies. In the CANDOR trial 59 patients (19%) died in the daratumumab group and 36 (23%) in the control group at data cut-off in July 2019. In CASTOR 102 deaths (42.5%) in the daratumumab group and 119 deaths (50.9%) in the control group occurred at the time of analysis in October 2018. LEPUS reported on 13 deaths (9%) in the daratumumab group and 18 deaths (26%) in the control group after a median follow-up of 8.2 months (range 0 to 20.5). In the POLLUX trial, 104 (37.0%) deaths had occurred in the daratumumab group and 121 (43.8%) deaths in the control group, at a median observation time of 17.3 months (95 % CI 17.0 to 17.8) in both groups.

Treatment with daratumumab probably increases overall survival when compared to treatment without daratumumab (HR 0.62, 95% CI 0.49 to 0.79, I^2 7%, moderate-certainty evidence, see Figure 15). The clinical benefit of the treatments was planned to be assessed according to the ESMO-MCBS (35). However, the magnitude of clinical benefit could not be graded for survival, because median survival was not yet reached in either trial (36).

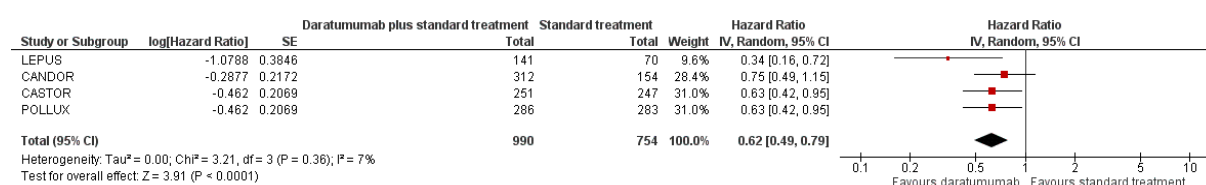


Figure 15: Forest plot for the outcome overall survival (PICO3: Relapsed or refractory MM)

Progression free survival

Four studies reported progression-free survival for 1744 patients. In the CANDOR trial, median progression-free survival was not reached in the daratumumab group and after 15.8 months (95% CI 12.10 to not estimable) in the control group. After a median follow-up time for progression-free survival of 16.9 months in the daratumumab group and 16.3 months in the control group, 110 patients (35%) had progressed or died in the daratumumab group and 68 patients (44%) in the control group. In the CASTOR trial median progression-free survival was 18.0 months in the daratumumab group and 7.3 months in the control group. The number of patients surviving without progression were not reported after a median follow-up of 42.0 months. In the LEPUS trial median progression-free survival was not reached in either group. The number of patients

surviving without progression were not reported after a median follow-up of 8.2 months in the daratumumab group and 6.3 months in the control group. In the POLLUX trial median progression-free survival was reached after 44.5 months in the daratumumab group and after 17.5 months in the control group. The number of patients surviving without progression were not reported at a median follow-up of 44.3 months (range 0 to 50.9).

Treatment with daratumumab may increase progression-free survival when compared to treatment without daratumumab (HR 0.40, 95% CI 0.29 to 0.56, I^2 81%, low-certainty evidence, see Figure 16) for patients receiving daratumumab. The clinical benefit of the treatments was assessed according to the ESMO-MCBS (35). The magnitude of clinical benefit was graded as 3 out of 4 (progression-free survival benefit compared to comparator HR < 0.65 and estimated progression-free survival gain >3 months (36)).

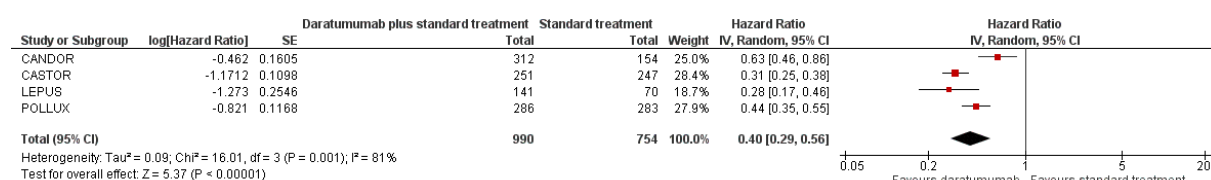


Figure 16: Forest plot for the outcome progression-free survival (PICO3: Relapsed or refractory MM)

Quality of life

a) Global Health increase of ≥ 10 points

In both trials quality of life was assessed for 1067 patients with the EORTC QLQ-C30 on a scale from 0 to 100. A higher value is to be regarded as an improvement of the global health status. Median observation ranged from 13.0 to 17.3 months in the daratumumab groups and from 13.3 to 17.3 months in the control groups. An increase of the global health status from baseline by at least 10 points was classified as clinically relevant (33) and reported for 256 patients (47.7%) in the daratumumab groups and 236 patients (44.5%) in the control groups.

More people receiving daratumumab may gain at least 10 points of global health status after start of treatment when compared to people receiving no daratumumab (RR 1.07, 95% CI 1.07 to 1.22, I^2 0%, low-certainty evidence, see Figure 17) at 9 months after start of treatment.

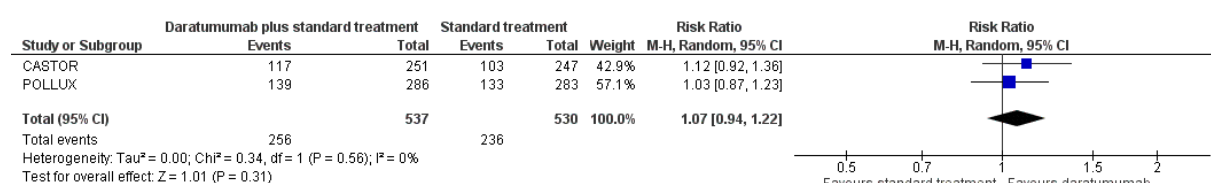


Figure 17: Forest plot for the outcome quality of life - global health increase of ≥ 10 points (PICO3: Relapsed or refractory MM)

b) Global Health decrease of ≥ 10 points

In the both trials quality of life was assessed for 1067 patients with the EORTC QLQ-C30 on a scale from 0 to 100. A higher value is to be regarded as an improvement of the global health status. Median observation ranged from 13.0 to 17.3 months in the daratumumab groups and from 13.3 to 17.3 months in the control groups. An increase of the global health status from baseline by at least 10 points was classified as clinically relevant (33) and reported for 276 patients (51.4%) in the daratumumab groups and 277 patients (52.3%) in the control groups.

Evidence suggests that impairment of at least 10 points of global health status after start of treatment is probably similar for people receiving or not receiving daratumumab (RR 0.98, 95% CI 0.88 to 1.10, I^2 0%, low-certainty evidence, see Figure 18) at 9 months after start of treatment.

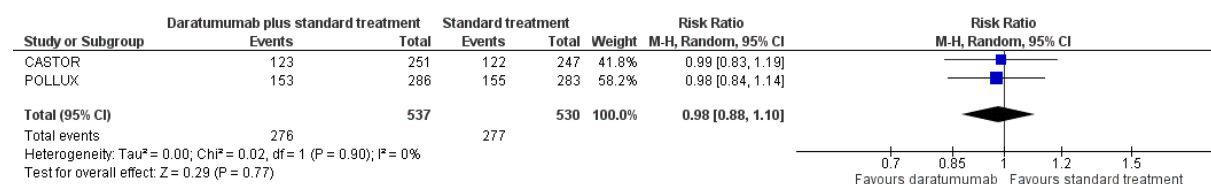


Figure 18: Forest plot for the outcome quality of life - global health decrease of ≥ 10 points (PICO3: Relapsed or refractory MM)

Comparative safety of treatments with daratumumab

PICO 1: Transplant-ineligible newly diagnosed Multiple myeloma

Adverse events (CTCAE grade ≥ 3)

Both studies reported adverse events (CTCAE grade ≥ 3) for 1429 patients. Median observation ranged from 32.7 to 34.0 months in the daratumumab groups and from 13.0 to 23.5 months in the control groups. Adverse events (CTCAE grade ≥ 3) were observed for 610 of 710 patients in the daratumumab groups and for 591 of 719 patients in the control groups. Treatment with daratumumab results in a slight increase of adverse events (CTCAE grade ≥ 3) when compared to treatment without daratumumab (RR 1.05, 95% CI 1.0 to 1.11, I^2 26%, high-certainty evidence, see Figure 19).

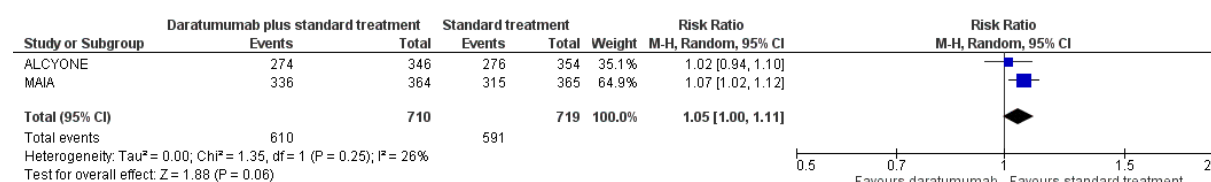


Figure 19: Forest plot for the outcome adverse events (CTCAE grade ≥ 3) (PICO 1: Transplant-ineligible NDMM)

Serious adverse events

Both studies reported serious adverse events for 1429 patients. Median observation ranged from 32.7 to 34.0 months in the daratumumab groups and from 13.0 to 23.5 months in the control groups. Serious adverse events were observed for 399 of 710 patients in the daratumumab groups and for 364 of 719 patients in the control groups. Treatment with daratumumab may increase serious adverse events when compared to treatment without daratumumab, but the evidence is very uncertain (RR 1.14, 95% CI 0.86 to 1.51, I^2 85%, very low-certainty evidence, see Figure 20).

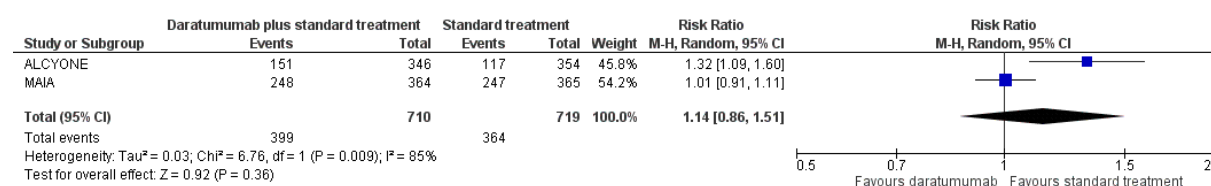


Figure 20: Forest plot for the outcome serious adverse events (PICO 1: Transplant-ineligible NDMM)

Infections and parasitic diseases

Both studies reported infections and parasitic diseases for 1429 patients. Median observation ranged from 32.7 to 34.0 months in the daratumumab groups and from 13.0 to 23.5 months in the control groups. Infections and parasitic diseases were observed for 213 of 710 patients in the

daratumumab groups and for 150 of 719 patients in the control groups. Treatment with daratumumab increases infections and parasitic diseases when compared to treatment without daratumumab (RR 1.42, 95% CI 1.19 to 1.70, I^2 0%, high-certainty evidence, see Figure 21).

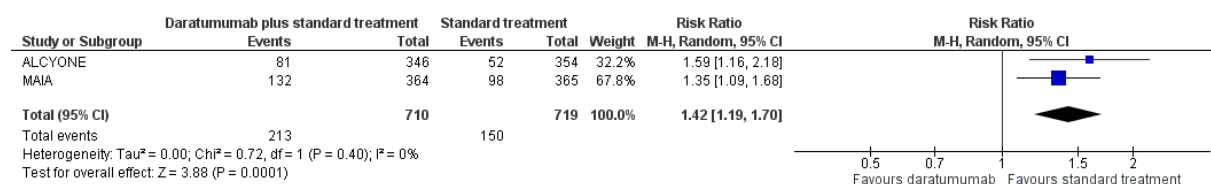


Figure 21: Forest plot for the outcome infections and parasitic diseases (PICO 1: Transplant-ineligible NDMM)

Pneumonia

Both studies pneumonia for 1429 patients. Median observation ranged from 32.7 to 34.0 months in the daratumumab groups and from 13.0 to 23.5 months in the control groups. Pneumonia was observed for 98 of 710 patients in the daratumumab groups and for 48 of 719 patients in the control groups. Treatment with daratumumab probably increases pneumonia when compared to treatment without daratumumab (RR 2.16, 95% CI 1.15 to 4.06, I^2 70%, moderate-certainty evidence, see Figure 22).

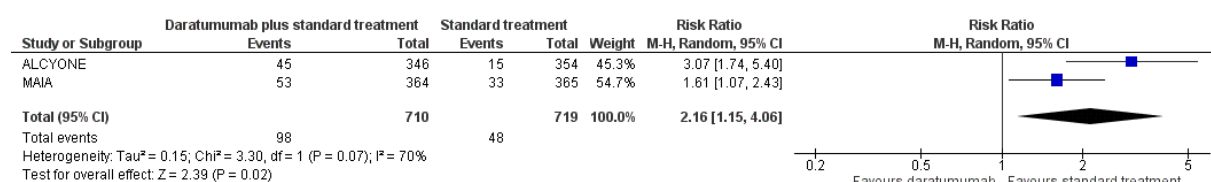


Figure 22: Forest plot for the outcome pneumonia (PICO 1: Transplant-ineligible NDMM)

PICO 2: Transplant-eligible newly diagnosed Multiple Myeloma

Adverse events (CTCAE grade ≥ 3)

The CASSIOPEIA trial reported adverse events (CTCAE grade ≥ 3) for 1074 patients. Median observation was 10.0 months in both groups. Adverse events (CTCAE grade ≥ 3) were observed for 432 of 536 patients in the daratumumab groups and for 409 of 538 patients in the control groups. Treatment with daratumumab results in a slight increase of adverse events (CTCAE grade ≥ 3) when compared to treatment without daratumumab (RR 1.06, 95% CI 1.00 to 1.13, high-certainty evidence, see Figure 23).

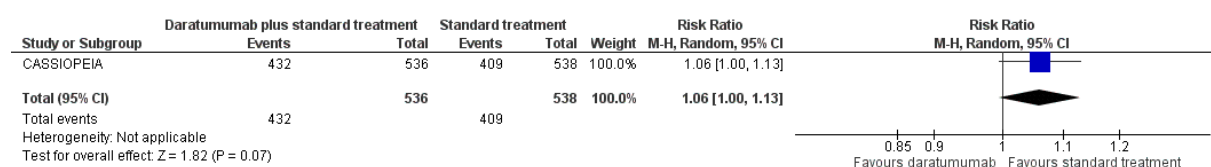


Figure 23: Forest plot for the outcome adverse events (CTCAE grade ≥ 3) (PICO 2: Transplant-eligible NDMM)

Serious adverse events

Both studies reported serious adverse events for 1275 patients. Median observation ranged from 10.0 to 22.1 months in the daratumumab groups and were similar in the control groups. Serious adverse events were observed for 290 of 635 patients in the daratumumab groups and for 307 of 640 patients in the control groups. Evidence suggests that people treated with daratumumab may experience less serious adverse events when compared to people treated without daratumumab (RR 0.91, 95% CI 0.73 to 1.14, I^2 52%, low-certainty evidence, see Figure 24).

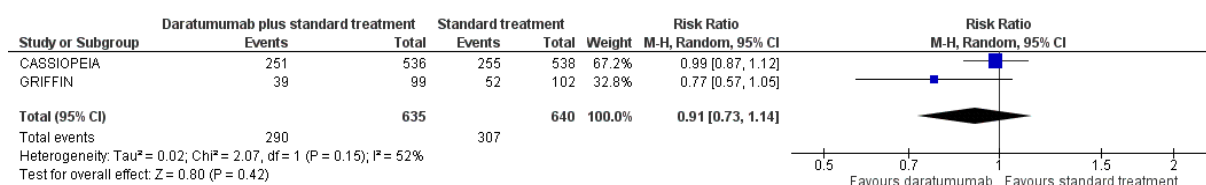


Figure 24: Forest plot for the outcome serious adverse events (PICO 2: Transplant-eligible NDMM)

Infections and parasitic diseases

Both studies reported infections and parasitic diseases for 1275 patients. Median observation ranged from 10.0 to 22.1 months in the daratumumab groups and were similar in the control groups. Infections and parasitic diseases were observed for 141 of 635 patients in the daratumumab groups and for 127 of 640 patients in the control groups. Treatment with daratumumab probably increases infections and parasitic diseases when compared to treatment without daratumumab (RR 1.12, 95% CI 0.90 to 1.39, I² 0%, moderate-certainty evidence, see Figure 25).

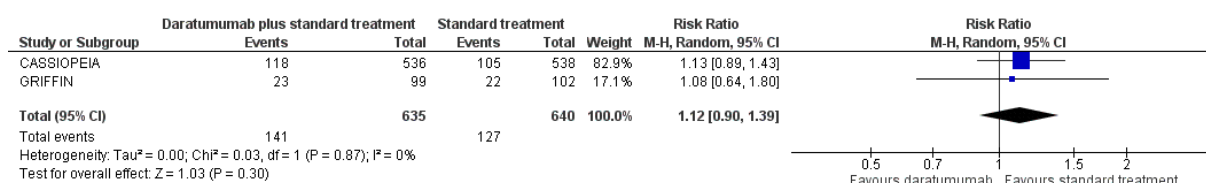


Figure 25: Forest plot for the outcome infections and parasitic diseases (PICO 2: Transplant-eligible NDMM)

Pneumonia

Both studies pneumonia for 1275 patients. Median observation ranged from 10.0 to 22.1 months in the daratumumab groups and were similar in the control groups. Pneumonia was observed for 24 of 635 patients in the daratumumab groups and for 23 of 640 patients in the control groups. Treatment with daratumumab may result in little to no difference in pneumonia when compared to treatment without daratumumab (RR 1.05, 95% CI 0.60 to 1.84, I² 0%, moderate-certainty evidence, see Figure 26).

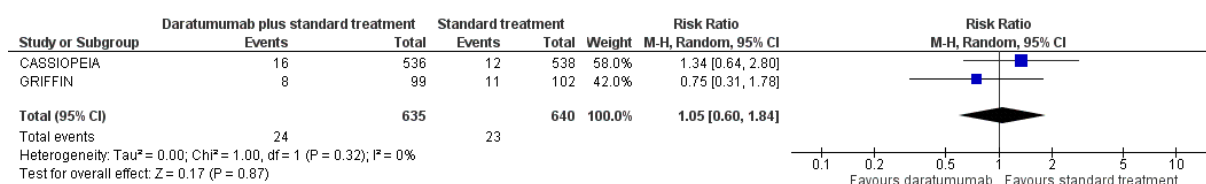


Figure 26: Forest plot for the outcome pneumonia (PICO 2: Transplant-eligible NDMM)

PICO 3: Relapsed or refractory Multiple myeloma

Adverse events (CTCAE grade ≥3)

Two studies reported adverse events (CTCAE grade ≥3) for 1044 patients. Median observation ranged from 13.0 to 17.3 months in the daratumumab groups and from 13.3 to 17.3 months in the control groups. In the CASTOR and POLLUX trial adverse events (CTCAE grade ≥3) were observed for 428 of 526 patients in the daratumumab groups and for 362 of 518 patients in the control groups. Treatment with daratumumab probably results in a slight increase of adverse events (CTCAE grade ≥3) when compared to treatment without daratumumab (RR 1.17, 95% CI 1.04 to 1.31, I² 64%, moderate-certainty evidence, see Figure 27).

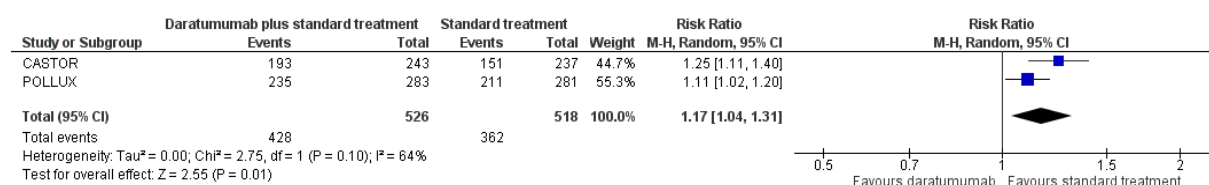


Figure 27: Forest plot for the outcome adverse events (CTCAE grade ≥ 3) (PICO3: Relapsed or refractory MM)

Serious adverse events

Four studies reported serious adverse events for 1713 patients. Median observation ranged from 13.0 to 17.3 months in the daratumumab groups and from 13.3 to 17.3 months in the control groups. Serious adverse events were observed for 482 of 974 patients in the daratumumab groups and for 294 of 739 patients in the control groups. Treatment with daratumumab may increase serious adverse events when compared to treatment without daratumumab (RR 1.21, 95% CI 1.09 to 1.35, I^2 0%, moderate-certainty evidence, see Figure 28).

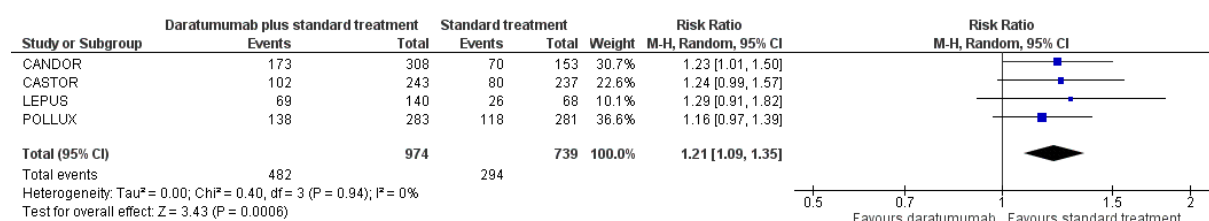


Figure 28: Forest plot for the outcome serious adverse events (PICO3: Relapsed or refractory MM)

Infections

The data on infections were not pooled, as they were reported heterogeneously across the trials. Median observation ranged from 8.2 to 34.3 months in the daratumumab groups and from 5.2 to 16.0 months in the control groups. The CANDOR and POLLUX trials reported on upper respiratory tract infections. In CANDOR events for grade 3 and grade 4 adverse events were reported separately. In the daratumumab group 7 grade 3 adverse events (2%) and 1 grade 4 (< 1%) upper respiratory tract infections occurred compared to 2 grade 3 (1%) and 0 grade 4 events in the control group. In the POLLUX trial 3 upper respiratory tract infections grade 3 or 4 (1%) occurred in the daratumumab and in the control group. Grade 3 or 4 treatment emergent events (TEAE) on upper respiratory tract infections were reported in the CASTOR trial (6 in the daratumumab group (3%) vs. 1 in the control group (0.4%)) and the LEPUS trial (20 in the daratumumab group (14%) vs. 3 in the control group (4%)).

Pneumonia

Both studies reported pneumonia for 1044 patients. Median observation time ranged from 13.4 to 34.3 months in the daratumumab groups and from 5.2 to 16.0 months in the control groups. Pneumonia was observed for 68 of 526 patients in the daratumumab groups and for 52 of 518 patients in the control groups. Treatment with daratumumab may increase pneumonia when compared to treatment without daratumumab (RR 1.28, 95% CI 0.86 to 1.90, I^2 24%, low-certainty evidence, see Figure 29).

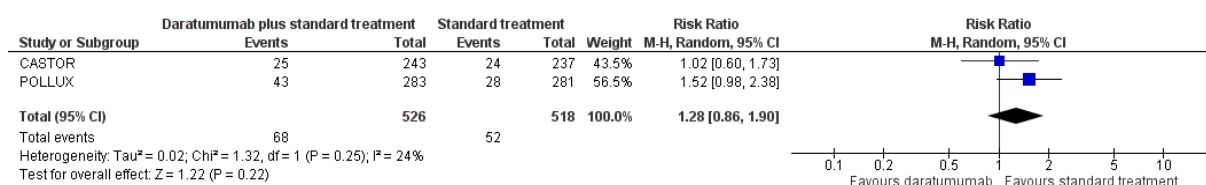


Figure 29: Forest plot for the outcome pneumonia (PICO3: Relapsed or refractory MM)

Summary of Findings

The summary of findings for the main comparisons are presented in Table 3 (PICO 1 Transplant-ineligible NDMM), Table 4 (PICO 2 Transplant-eligible NDMM), and (PICO 3 RRMM). The GRADE approach (34) was used to rate the certainty of evidence in seven prioritised outcomes. The outcomes overall survival, quality of life, on-study mortality, adverse events (CTCAE grade ≥ 3), serious adverse events, infections and parasitic diseases, and pneumonia, were prioritised by a patient representative because they were seen as the crucial outcomes to decide whether a treatment should be applied or not. Progression-free survival was added as a surrogate, because overall survival data were premature in all trials.

Table 3: Summary of Findings PICO 1, transplant-ineligible newly diagnosed multiple myeloma patients

Daratumumab plus standard treatment compared to standard treatment for transplant-ineligible newly diagnosed multiple myeloma patients

Patient or population: Transplant-ineligible newly diagnosed multiple myeloma patients

Setting: Outpatient

Intervention: Daratumumab plus standard treatment

Comparison: Standard treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard treatment	Risk with Daratumumab plus standard treatment				
Overall survival: at 36 months	690 per 1,000 alive	787 per 1,000 alive (724 to 851)	Hazard Ratio 0.69 (0.48 to 0.89)	1443 (2 RCTs)	⊕⊕⊕○ MODERATE ^a	Overall survival at 36 months was approximately 69% in the control groups (data read from graphs)
Progression-free survival: at 36 months	328 per 1,000 alive without progress	677 per 1,000 alive without progress (577 to 758)	Hazard Ratio 0.48 (0.36 to 0.63)	1443 (2 RCTs)	⊕⊕⊕○ MODERATE ^b	ESMO-Score: 4 out of 4 Progression-free survival at 36 months was approximately 33% in the control groups (data read from graphs)
Quality of life: Increase of global health status of ≥ 10 points from baseline to longest follow-up	531 per 1,000	600 per 1,000 (547 to 653)	Risk Ratio 1.13 (1.03 to 1.23)	1443 (2 RCTs)	⊕⊕⊕○ MODERATE ^c	Number of patients with at least 10 points increase on a scale from 0 to 100 (higher score indicates better quality of life) Median follow-up: 28.2 to 31.0 months in the daratumumab groups, and 17.3 to 22.0 months in the control groups
Quality of life: Decrease of global health status of ≥ 10 points from baseline to longest follow-up	379 per 1,000	387 per 1,000 (337 to 440)	Risk Ratio 1.02 (0.89 to 1.16)	1443 (2 RCTs)	⊕⊕⊕○ MODERATE ^c	Number of patients with at least 10 points decrease on a scale from 0 to 100 (higher score indicates better quality of life) Median follow-up: 28.2 to 31.0 months in the daratumumab groups, and 17.3 to 22.0 months in the control groups

Table 3: Summary of Findings PICO 1, transplant-ineligible newly diagnosed multiple myeloma patients

Daratumumab plus standard treatment compared to standard treatment for transplant-ineligible newly diagnosed multiple myeloma patients

Patient or population: Transplant-ineligible newly diagnosed multiple myeloma patients

Setting: Outpatient

Intervention: Daratumumab plus standard treatment

Comparison: Standard treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard treatment	Risk with Daratumumab plus standard treatment				
Adverse events (CTCAE grade ≥ 3)	822 per 1,000	863 per 1,000 (822 to 912)	Risk Ratio 1.05 (1.00 to 1.11)	1429 (2 RCTs)	⊕⊕⊕⊕ HIGH	Median follow-up: 32.7 to 34.0 months in the daratumumab groups, and 13.0 to 23.5 months in the control groups
Serious adverse events	506 per 1,000	577 per 1,000 (435 to 764)	Risk Ratio 1.14 (0.86 to 1.51)	1429 (2 RCTs)	⊕○○○ VERY LOW ^{d, e}	Median follow-up: 32.7 to 34.0 months in the daratumumab groups, and 13.0 to 23.5 months in the control groups
Adverse events: Infections and parasitic diseases	209 per 1,000	296 per 1,000 (248 to 355)	Risk Ratio 1.42 (1.19 to 1.70)	1429 (2 RCTs)	⊕⊕⊕⊕ HIGH	Median follow-up: 32.7 to 34.0 months in the daratumumab groups, and 13.0 to 23.5 months in the control groups
Adverse events: Pneumonia	67 per 1,000	144 per 1,000 (77 to 271)	Risk Ratio 2.16 (1.15 to 4.06)	1429 (2 RCTs)	⊕⊕⊕○ MODERATE ^f	Median follow-up: 32.7 to 34.0 months in the daratumumab groups, and 13.0 to 23.5 months in the control groups

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; MD: Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

- a. Downgraded one level due to serious study limitations (risk of bias), because of incomplete survival data in one trial
- b. Downgraded one level due to serious study limitations (risk of bias), because of incomplete survival data in one trial and no blinding of progression-free survival assessment.
- c. Downgraded one level due to serious study limitations (risk of bias), because of no blinding of quality of life assessment.
- d. Downgraded one level due imprecision because 95% CI overlaps no effect
- e. Downgraded two levels due to inconsistency, because of heterogeneous point estimates and no overlap of confidence intervals.
- f. Downgraded one level due to inconsistency, because of heterogeneous point estimates.

Table 4: Summary of Findings PICO 2, transplant-eligible newly diagnosed multiple myeloma patients

Daratumumab plus standard treatment compared to Standard treatment for transplant-eligible newly diagnosed multiple myeloma patients

Patient or population: Transplant-eligible newly diagnosed multiple myeloma patients

Setting: Outpatient

Intervention: Daratumumab plus standard treatment

Comparison: Standard treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard treatment	Risk with Daratumumab plus standard treatment				
Overall survival: at 18 months	952 per 1,000 alive	975 per 1,000 alive (961 to 984)	Hazard Ratio 0.52 (0.33 to 0.82)	1085 (1 RCT)	⊕⊕○○ LOW ^a	Overall survival at 18 months was approximately 95% in the control groups (data read from graphs)
Progression-free survival at 18 months	940 1,000 alive without progress	971 per 1,000 alive (959 to 978)	Hazard Ratio 0.49 (0.36 to 0.68)	1292 (2 RCTs)	⊕○○○ VERY LOW ^{a, b}	Progression-free survival at 18 months was approximately 94% in the control groups (data read from graphs)
Quality of life: Increase of global health status of ≥ 10 points from baseline to longest follow-up	358 per 1,000	383 per 1,000 (326 to 444)	Risk Ratio 1.07 (0.91 to 1.24)	1085 (1 RCT)	⊕⊕○○ LOW ^{c, d}	Number of patients with at least 10 points increase on a scale from 0 to 100 (higher score indicates better quality of life) Median follow-up: 9 months
Quality of life: Decrease of global health status of ≥ 10 points from baseline to longest follow-up	256 per 1,000	220 per 1,000 (179 to 435)	Risk Ratio 0.86 (0.70 to 1.70)	1085 (1 RCT)	⊕⊕○○ LOW ^{c, d}	Number of patients with at least 10 points decrease on a scale from 0 to 100 (higher score indicates better quality of life) Median follow-up: 9 months
Adverse events (CTCAE grade ≥3)	760 per 1,000	806 per 1,000 (760 to 859)	Risk Ratio 1.06 (1.00 to 1.13)	1074 (1 RCT)	⊕⊕⊕⊕ HIGH	Median follow-up: 10.0 months in both groups
Serious adverse events	480 per 1,000	437 per 1,000 (350 to 547)	Risk Ratio 0.91 (0.73 to 1.14)	1275 (2 RCTs)	⊕⊕○○ LOW ^{d, e}	Median follow-up: 10.0 to 22.1 months in the daratumumab groups, and similar in the control groups

Daratumumab plus standard treatment compared to Standard treatment for transplant-eligible newly diagnosed multiple myeloma patients

Patient or population: Transplant-eligible newly diagnosed multiple myeloma patients

Setting: Outpatient

Intervention: Daratumumab plus standard treatment

Comparison: Standard treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N _e of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard treatment	Risk with Daratumumab plus standard treatment				
Adverse events: Infections	198 per 1,000	222 per 1,000 (178 to 275)	Risk Ratio 1.12 (0.90 to 1.39)	1275 (2 RCTs)	⊕⊕⊕○ MODERATE ^d	Median follow-up: 10.0 to 22.1 months in the daratumumab groups, and similar in the control groups
Adverse events: Pneumonia	36 per 1,000	38 per 1,000 (22 to 66)	Risk Ratio 1.05 (0.60 to 1.84)	1275 (2 RCTs)	⊕⊕○○ LOW ^{d, e}	Median follow-up: 10.0 to 22.1 months in the daratumumab groups, and similar in the control groups

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; MD: Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

- Downgraded two levels due to indirectness, because control group did not receive standard of care maintenance.
- Downgraded one level due to serious study limitations (risk of bias), because of no blinding of progression-free survival assessment
- Downgraded one level due to serious study limitations (risk of bias), because of no blinding of quality of life assessment.
- Downgraded one level due to imprecision, because 95% CI overlaps no effect (Quality of life (QoL), serious adverse events (SAE), AE infections, AE pneumonia).
- Downgraded one level due to inconsistency, because of heterogeneous point estimates (SAE, Pneumonia).

Table 5: Summary of Findings PICO 3, relapsed or refractory multiple myeloma patients

Daratumumab plus standard treatment compared to Standard treatment for relapsed or refractory multiple myeloma patients

Patient or population: relapsed or refractory multiple myeloma patients

Setting: outpatient

Intervention: Daratumumab plus standard treatment

Comparison: Standard treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Ne of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard treatment	Risk with Daratumumab plus standard treatment				
Overall survival: at 18 months	740 per 1,000 alive	821 per 1,000 alive (769 to 875)	Hazard Ratio 0.69 (0.48 to 0.89)	1717 (4 RCTs)	⊕⊕⊕○ MODERATE a	Overall survival at 18 months was 74% in the control group of CANDOR (survival rates or Kaplan-Meier curves not available for other studies)
Progression-free survival at 18 months	328 per 1,000 alive without progression	731 per 1,000 alive without progression (624 to 805)	Hazard Ratio 0.40 (0.29 to 0.56)	1717 (4 RCTs)	⊕⊕○○ LOW a, b	ESMO-Score: 3 out of 4 Progression-free survival at 18 months was approximately 33% control groups (data read from graphs)
Quality of life: Increase of global health status of ≥ 10 points from baseline to longest follow-up	445 per 1,000	477 per 1,000 (418 to 543)	Risk Ratio 1.07 (0.94 to 1.22)	1067 (2 RCTs)	⊕⊕○○ LOW c, d	Number of patients with at least 10 points increase on a scale from 0 to 100 (higher score indicates better quality of life) Median follow-up: 13.0 to 17.3 months in the daratumumab groups, and 13.3 to 17.3 months in the control groups
Quality of life: Decrease of global health status of ≥ 10 points from baseline to longest follow-up	523 per 1,000	513 per 1,000 (460 to 575)	Risk Ratio 0.98 (0.88 to 1.10)	1067 (2 RCTs)	⊕⊕⊕○ MODERATE c	Number of patients with at least 10 points decrease on a scale from 0 to 100 (higher score indicates better quality of life) Median follow-up: 13.0 to 17.3 months in the daratumumab groups, and 13.3 to 17.3 months in the control groups

Daratumumab plus standard treatment compared to Standard treatment for relapsed or refractory multiple myeloma patients

Patient or population: relapsed or refractory multiple myeloma patients

Setting: outpatient

Intervention: Daratumumab plus standard treatment

Comparison: Standard treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N _e of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard treatment	Risk with Daratumumab plus standard treatment				
Adverse events (CTCAE grade ≥3)	814 per 1,000	952 per 1,000 (847 to 1,066)	Risk Ratio 1.17 (1.04 to 1.31)	1044 (2 RCT)	⊕⊕⊕○ MODERATE c	Median follow-up: 13.0 to 17.3 months in the daratumumab groups, and 13.3 to 17.3 in the control groups
Serious adverse events	398 per 1,000	482 per 1,000 (434 to 537)	Risk Ratio 1.21 (1.09 to 1.35)	1713 (4 RCTs)	⊕⊕⊕○ MODERATE a	Median follow-up: 13.0 to 17.3 months in the daratumumab groups, and 13.3 to 17.3 in the control groups
Adverse events: Infections	N/A	N/A	Risk Ratio N/A	1713 (4 RCTs)		Outcome not reported as defined at review protocol stage.
Adverse events: Pneumonia	97 per 1,000	124 per 1,000 (83 to 184)	Risk Ratio 1.28 (0.86 to 1.90)	1044 (2 RCTs)	⊕⊕○○ LOW a, d	Median follow-up: 13.0 to 17.3 months in the daratumumab groups, and 13.3 to 17.3 in the control groups

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; MD: Mean difference

GRADE Working Group grades of evidence

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Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded one level due to serious study limitations (risk of bias), because randomisation and masking were not described in one study, and preliminary results (abstract only) in another study

b. Downgraded one level due to inconsistency.

c. Downgraded one level due to serious study limitations (risk of bias), because randomisation and masking not described in one study, and both studies not blinded

d. Downgraded one level due to imprecision, because 95% CI overlaps no effect.

10. Summary of available data on comparative cost and cost-effectiveness of the medicine.

A scoping review was conducted to assess comparative costs and cost-effectiveness of daratumumab. We searched the electronic database MEDLINE (via PubMed) using the following keywords: myeloma, cost-effectiveness, cost-benefit, cost-utility, cost-analysis, ICER (incremental cost-effectiveness ratio), QALY (quality-adjusted life year), DALY (disability-adjusted life year), burden, daratumumab, and Darzalex. Furthermore, the International Network of Agencies for Health Technology Assessment (INHTA) database for health technology assessments (HTAs) was searched for HTAs on daratumumab regimens. We identified two eligible cost analyses and four cost-effectiveness analyses. Additionally, data from two HTAs, conducted by NICE, could be retrieved.

The main results are summarized in Table 6-Table 10. Further details on the studies' characteristics, results for different time horizons, and additional information can be found in the text below.

Cost analyses

In total, two studies (45, 46) analysed costs of the treatment regimen daratumumab, bortezomib, and dexamethasone (DaraVD). Additionally, one of these studies (46) evaluated costs of daratumumab, lenalidomide, and dexamethasone (DaraRD). Both analyses were performed from a USA payer perspective and regarded costs in the first year of treatment of RRMM patients.

Cost analyses on daratumumab, bortezomib, and dexamethasone (Table 6)

Ailawadhi et al. (45) analysed direct and indirect costs of thirteen different regimens for the treatment of RRMM patients, including DaraVD. Authors concluded that DaraVD was the most expensive treatment (US\$ 315,296 total costs per patient, per year) among all comparators. Costs were mainly driven by drug acquisition costs (US\$ 269,059 average costs per patient, per year). Since Ailawadhi et al. (45) assumed that patients would receive all treatments as planned, treatment costs in practice may differ from these results.

Hollmann et al. (46) performed their cost analysis in a comparable setting as Ailawadhi et al. (45), but based it on an intention-to-treat analysis and only included direct costs. They concluded that DaraVD, compared to elotuzumab, lenalidomide, and dexamethasone (ERD), carfilzomib, lenalidomide, and dexamethasone (KRD), ixazomib, lenalidomide, and dexamethasone (IRD), and DaraRD, may have the lowest costs (US\$ 13,890 average costs per patient, per month). Again, drug acquisition costs were the greatest cost driver (US\$ 12,515.87 average costs per patient, per month), followed by administration costs (US\$ 489.45 average costs per patient, per month).

Cost analysis on daratumumab, lenalidomide, and dexamethasone (Table 7)

Hollmann et al. (46) also analysed the direct costs of the regimen DaraRD. Costs of DaraRD were higher than most of the comparator regimens (US\$ 26,410 average costs per patient, per month). Only cost estimates for KRD were slightly higher (US\$ 27,432 average costs per patient, per month) than DaraRD. Main cost driver were drug acquisition costs (US\$ 25,453 average costs per patient, per month).

Cost-effectiveness analyses

Comparative cost-effectiveness data was found for daratumumab monotherapy (one HTA (47), two studies (48, 49)), DaraVD (one HTA (50), two studies (51, 52)) and DaraRD (two studies (51, 52)). Characteristics of the included studies and HTAs varied widely, especially regarding patient population (range of second-line treatment to a median of 5 prior lines of therapy) and time

horizon (3 years to lifetime horizon). Apart from the two HTAs conducted by NICE from a United Kingdom (UK) perspective, all studies were performed from a United States (US) payer perspective.

Cost-effectiveness analyses on daratumumab monotherapy (Table 8)

A single technology assessment by NICE (13) examined the cost-effectiveness of daratumumab monotherapy when compared to panobinostat, bortezomib, and dexamethasone (PaVD) and pomalidomide, bortezomib, and dexamethasone (PoVD) in second-line treatment of RRMM patients. Results of their base case analyses, regarding a time horizon of 15 years, indicate that patients receiving daratumumab monotherapy gain more QALYs but have higher costs than both comparators (c.f. Table X3). Scenario analyses of daratumumab monotherapy when compared to PoD for a time horizon of 10 and 5 years resulted in ICERs of GB£ 45,985, and GB£ 56,468, respectively. For daratumumab monotherapy when compared to PaVD, ICERs in these scenarios were GB£ 21,325 (10 years) and GB£ 17,517 (5 years).

Pelligra et al. (48) concluded that for heavily pretreated RRMM patients PoD marginally dominates daratumumab monotherapy due to similar effectiveness outcomes and lower costs. These results remained robust for all performed scenario analyses, including analyses for a 1-year, 10-year, 20-year, and a lifetime horizon. In comparison, the higher costs of daratumumab monotherapy were mainly driven by drug acquisition costs (US\$ 74,728 for daratumumab vs. US\$ 69,044 for PoD, per patient, 3-year time horizon), administration costs (US\$ 2,870 vs. US\$ 0, per patient, 3-year time horizon), and pre/post-medication costs (US\$ 1,186 vs. US\$ 0, per patient, 3-year time horizon).

Another study (49), which is not presented in Table X3 due to methodological uncertainties, indirectly compared the cost-effectiveness of daratumumab monotherapy to pomalidomide monotherapy for heavily pretreated RRMM patients over a lifetime horizon. This study (49) was only published as correspondence and did not provide references for important model input data (e.g. transition probabilities of health states, cost data, or utility values), nor did the authors specify which types of costs were included in the analysis. The analysis was performed from a US public payer perspective and concluded that daratumumab, compared to pomalidomide, is cost-effective at an ICER of US\$ 156,385.

Cost-effectiveness analyses on daratumumab, bortezomib, and dexamethasone (Table 9)

The committee paper by Kalita et al. (50), which is the basis for the current NICE technology appraisal guidance (TA573) (12), focused the treatment of second-line, bortezomib-naïve RRMM patients with DaraVD. As some information in the report were confidential, only ICERs could be extracted. Compared to bortezomib and dexamethasone (VD), DaraVD had an ICER of GB£ 93,061 in the base case analysis with a time horizon of 30 years. Scenario analyses for time horizons of 20, 10, and 5 years resulted in ICERs of GB£ 97,279, GB£ 134,555, and GB£ 238,026, respectively. In comparison to carfilzomib and dexamethasone (KD), DaraVD was dominant (higher QALYs and lower costs) for all analysed time horizons.

Combined cost-effectiveness analyses on daratumumab, bortezomib, and dexamethasone (Table 9) and daratumumab, lenalidomide, and dexamethasone (Table 10)

Two studies (51, 52) each examined the comparative cost-effectiveness of two daratumumab therapies, DaraVD and DaraRD:

Carlson et al. (51) compared the lifetime cost-effectiveness of eight drugs in eight different regimens and presented results separately for second and third-line patient populations. Results for DaraVD and DaraRD vs. the main comparator regimen lenalidomide and dexamethasone (RD) can be found in Table 9 and Table 10, respectively. Further analyses, comparing DaraVD and

DaraRD each to VD, IRD, ERD, and KRD, revealed that both, DaraVD and DaraRD, dominated all comparators in second- and third-line therapy populations (PaVD was not taken into account in third-line therapy, because Carlson et al. (51) considered the quality of data for this regimen as limited). Data input for these comparators was taken from the following trials: ASPIRE (53), ELOQUENT-2 (54), TOURMALINE-MM1 (55), and PANORAMA-1 (56). The ICER of DaraRD vs. DaraVD was US\$ 2,707,547 in second-line therapy, with marginally higher effectiveness (incremental QALYs 0.15), but significantly higher costs (incremental costs US\$ 398,345) for DaraRD. In third-line therapy, DaraVD dominated DaraRD with equal effectiveness outcomes and lower costs (incremental costs -US\$ 366,083).

Zhang et al. (52) calculated ICERs for DaraVD vs. VD and DaraRD vs. RD for a time horizon of 10 years. When interpreting the results, which are summarised in Table 9 and Table 10, it has to be considered that individual discontinuation adjustments were not taken into account in this model, as the necessary data was inaccessible to the study authors.

Table 6 Cost-analyses for DaraVD (daratumumab, bortezomib, dexamethasone)

Study	Study characteristics						Results	
	Country / Perspective	Patients	Time horizon, cycle length	Comparators	Type(s) of costs included	Underlying studies (Intervention)	Average costs per cycle	Average costs per patient, per year
Ailawadhi 2019 (45)	USA	Second-line treatment of RRMM patients	Time horizon of 1 year, 21-day cycle length	ERD, IRD, KD, PaVD, PoD, RD, VD, VCD (bortezomib, cyclophosphamide, dexamethasone), VRD (bortezomib, lenalidomide, dexamethasone)	Direct and indirect costs of: Initiation of second-line therapy (pre-screening), drug acquisition and administration, other medical costs (comorbidities and AE-related), subsequent therapy costs	GEN501 (57)	US\$ 18,894.61	US\$ 315,296 ^a
Hollmann 2019 (46)	USA	Second-line treatment of RRMM patients	Time horizon of 1 year, 21 days (cycles 1-8) and 28 days (cycles 9+) cycle length	ERD, KRD, IRD, DaraRD	Direct costs of: Drug acquisition and administration, monitoring, co-medications, AE-related costs, subsequent therapy costs	CASTOR	Cycles 1-2: US\$ 26,311 Cycles 3-6 ^b : US\$ 13,054 Cycles 9+: US\$ 6,628	US\$ 166,675.84

Explanations

a. Study authors assumed that patients would receive all treatments as planned, treatment costs in practice may differ from this results.

b. Potentially a typing error in the publication. We suppose that study authors probably intended to write "Cycles 3-8".

Table 7 Cost-analyses for DaraRD (daratumumab, lenalidomide, dexamethasone)

Study	Study characteristics						Results	
	Country / Perspective	Patients	Time horizon, cycle length	Comparators	Type(s) of costs included	Underlying studies (Intervention)	Average costs per cycle	Average costs per patient per year
Hollmann 2019 (46)	USA	Second-line treatment of RRMM patients	Time horizon of 1 year, 28-day cycle length	ERD, KRD, IRD, DaraVD	Direct costs of: Drug acquisition and administration, monitoring, co-medications, AE-related costs, subsequent therapy costs	POLLUX	Cycles 1-2: US\$ 40,437 Cycles 3-6: US\$ 27,179 Cycles 7+: US\$ 20,551	US\$ 316,918.87

Table 8 Cost-effectiveness analyses for daratumumab monotherapy

Study	Study characteristics						Results		
	Country / Perspective	Patients	Time horizon, cycle length	Comparator	Type(s) of costs included	Underlying studies	Total costs (DARA vs. control)	QALYs gained (DARA vs. control)	ICER
NICE 2018 (47)	UK	Second-line treatment of RRMM patients	Time horizon of 15 years	PoD	Direct costs of: Drug acquisition and administration, monitoring, co-medications, AE-related costs, subsequent therapy costs, terminal care costs	GEN501 (57)	GB£ 83,613 vs. GB£ 52,396	1.44 vs. 0.75	GB£ 44,988
				PaVD		SIRIUS (58)	GB£ 82,654 vs. GB£ 76,008	1.23 vs. 0.93	GB£ 21,910
Pelligra 2017 (48)	USA	Heavily pretreated (median of 5 prior lines of therapy) RRMM patients	Time horizon of 3 years, 28-day cycles	PoD	Direct medical costs of: Initial- and subsequent-line drug costs, AE prophylaxis costs, AE management in the initial line, healthcare resource utilization	SIRIUS (58) MM-002 (59)	US\$ 39,843 vs. US\$ 130,924	0.98 vs. 0.99	PoD marginally dominates daratumumab monotherapy

Table 9 Cost-effectiveness analyses for DaraVD (daratumumab, bortezomib, dexamethasone)

Study	Study characteristics						Results		
	Country / Perspective	Patients	Time horizon, cycle length)	Comparators	Type(s) of costs included	Underlying studies	Total costs (DARA vs. control)	QALYs gained (DARA vs. control)	ICER
NICE 2018 (50)	UK	Second line Bortezomib-naïve RRMM patients	Time horizon of 30 years	VD	Direct costs of: Drug acquisition and administration, co-medications, AE-related costs, subsequent therapy costs	CASTOR	Not reported	Not reported	GB£ 93,061
				KD		ENDEAVOR (60)	Not reported	Not reported	DAR/BORT/DEX dominates CAR/DEX
Carlson 2018 (51)	USA	Second line of therapy RRMM patients	Lifetime horizon, cycle length of 1 week	RD	Direct costs of: Drug acquisition and administration, supportive care, AE-related costs, postprogression treatment costs	CASTOR	US\$ 447,182 vs. US\$ 309,997	5.29 vs. 2.59	US\$ 50,704
		Third line of therapy RRMM patients					US\$ 423,119 vs. US\$ 281,754	4.38 vs. 2.04	US\$ 60,359
Zhang 2018 (52)	USA	RRMM patients	Time horizon of 10 years, 28-day cycles	VD	Direct costs of: Drug acquisition and administration, AE-related costs, subsequent-line drug costs, postprogression monitoring	CASTOR	US\$ 462,340 vs. US\$ 357,217	2.169 vs. 1.743	US\$ 284,180

Table 10 Cost-effectiveness analyses for DaraRD (daratumumab, lenalidomide, dexamethasone)

Study	Study characteristics						Results		
	Country / Perspective	Patients	Time horizon, cycle length	Comparators	Type(s) of costs included	Underlying studies	Total costs (DARA vs. control)	Total QALYs (DARA vs. control)	ICER
Carlson 2018 (51)	USA	Second line of therapy RRMM patients	Lifetime horizon, cycle length of 1 week	RD	Direct costs of: Drug acquisition and administration, supportive care, AE-related costs, postprogression treatment	POLLUX	US\$ 845,527 vs. US\$ 309,997	5.44 vs. 2.59	US\$ 187,728
		Third line of therapy RRMM patients					US\$ 789,202 vs. US\$ 281,754	4.38 vs. 2.04	US\$ 216,360
Zhang 2018 (52)	USA	RRMM patients	Time horizon of 10 years, 28-day cycles	RD	Direct costs of: Drug acquisition and administration, AE-related costs, subsequent-line drug costs, postprogression monitoring	POLLUX	US\$ 770,614 vs. US\$ 410,828	2.276 vs. 1.965	US\$ 1,369,062

REGULATORY INFORMATION

11. Summary of regulatory status and market availability of the medicine

Daratumumab is approved worldwide and in various jurisdictions such as:

Australian Government, Department of Health, Therapeutic Goods Administration (TGA)

- Daratumumab is licensed in Australia for the treatment of:
 - “DARZALEX is indicated for the treatment of patients:
 - with newly diagnosed multiple myeloma:
 - who are eligible for autologous stem cell transplant. For use in combination with: bortezomib, thalidomide, and dexamethasone.
 - who are ineligible for autologous stem cell transplant. For use in combination with: bortezomib, melphalan and prednisone, or lenalidomide and dexamethasone.
 - with multiple myeloma who have received:
 - at least one prior therapy. For use in combination with: bortezomib and dexamethasone, or lenalidomide and dexamethasone.
 - at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or
 - who are refractory” (61)

European Medicines Agency (EMA)

- Daratumumab is licensed in the European Union (EU):
 - “Darzalex is a cancer medicine used to treat adults with multiple myeloma (a cancer of the bone marrow). In patients with newly diagnosed multiple myeloma it is used:
 - in combination with the medicines lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone in patients who cannot have autologous stem cell transplant (a transplant of the patient's own blood-producing cells). Bortezomib, lenalidomide and melphalan are used for treating multiple myeloma and dexamethasone and prednisone suppress the immune system;
 - in combination with bortezomib, thalidomide (another medicine used to treat multiple myeloma), and dexamethasone, in patients who can have autologous stem cell transplant.”
 - „In patients with previously treated multiple myeloma it is used:
 - in combination with dexamethasone plus either lenalidomide or bortezomib;
 - on its own when the disease has come back after treatment with cancer medicines (including medicines known as proteasome inhibitors) and immunomodulatory medicines (that act on the immune system), or when the disease has not improved with these medicines.” (62)

US Food and Drug Administration (FDA)

- Daratumumab is licensed in the USA:

- “in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.”(63)

Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

- Daratumumab is licensed in Japan for the treatment of:
 - “Drugs with a new active ingredient indicated for the treatment of relapsed or refractory multiple myeloma.” (64)
 - “Drugs with a new indication and a new dosage for the treatment of multiple myeloma.” (65)

Health Canada (HC)

- Daratumumab is licensed in Canada for the treatment of:
 - “DARZALEX® (daratumumab) is indicated:
 - In combination with lenalidomide and dexamethasone, or with bortezomib, melphalan and prednisone, for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
 - in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.
 - for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are refractory to both a PI and an IMiD.” (66)

12. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopoeia)

Daratumumab is not mentioned in the British, International, European or United States Pharmacopoeia.

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10. Federal Joint Committee (G-BA). Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL):Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Daratumumab (neues Anwendungsgebiet: Multiples Myelom, neu diagnostiziert, Patienten für autologe Stammzelltransplantation geeignet, Kombination mit Bortezomib, Thalidomid und Dexamethason) 2020 [Available from: <https://www.g-ba.de/beschluesse/4426/>].
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APPENDIX

I. Search Strategies

Ia. Systematic Reviews

Medline (via Ovid) search strategy

Searches

- 1 exp MULTIPLE MYELOMA/
- 2 myelom*.tw,kf.
- 3 exp PLASMACYTOMA/
- 4 (plasm?cytom* or plasm?zytom* or plasma cytoma*).tw,kf.
- 5 (plasma* adj3 neoplas*).tw,kf.
- 6 (plasma cell adj1 (leukaem* or leukem* or tumor* or tumour*)).tw,kf.
- 7 ((plasmacytic* or plasmocytic* or plasmocyte*) adj1 (leukem* or leukaem*)).tw,kw.
- 8 kahler*.tw,kf.
- 9 or/1-8
- 10 (daratumumab* or dara-tumumab*).tw,kw,nm.
- 11 darzalex*.tw,kf,nm.
- 12 (human CD38 or human CD 38).tw,kf,nm.
- 13 (anti-CD38 monoclonal antibod* or antiCD38 monoclonal antibod*).tw,kf,nm.
- 14 (HuMax-CD38 or UNII-4Z63YK6E0E or 4Z63YK6E0E or JNJ 54767414 or JNJ-54767414 or 945721-28-8).tw,kf,nm.
- 15 or/10-14
- 16 meta analysis.mp,pt. or review.pt. or search*.tw. or systematic review.pt.
- 17 9 and 15 and 16

Ib. Primary studies

Cochrane Central Register of Controlled Trials (Central, 2020, Issue 01) in the Cochrane Library

ID Search

- #1 MeSH descriptor: [Multiple Myeloma] explode all trees
- #2 myelom*:ti,ab,kw
- #3 MeSH descriptor: [Plasmacytoma] explode all trees
- #4 (plasm*cytom* or plasm*zytom* or plasma cytoma*):ti,ab,kw
- #5 (plasma* NEAR/3 neoplas*):ti,ab,kw
- #6 (plasma cell NEAR/1 (leukaem* or leukem* or tumor* or tumour*)):ti,ab,kw

#7 ((plasmacytic* or plasmocytic* or plasmocyte*) NEAR/1 (leukem* or leukaem*)):ti,ab,kw

#8 kahler*:ti,ab,kw

#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

#10 (daratumumab* or dara-tumumab*):ti,ab,kw

#11 darzalex*:ti,ab,kw

#12 (human CD38 or human CD 38):ti,ab,kw

#13 HuMax-CD38 or UNII-4Z63YK6E0E or 4Z63YK6E0E or JNJ 54767414 or JNJ54767414 or "945721-28-8"

#14 #10 or #11 or #12 or #13

#15 #9 and #14 in Trials

Embase search strategy

Searches

1 MULTIPLE MYELOMA/

2 myelom*.tw,kw.

3 PLASMACYTOMA/

4 PLASMA CELL LEUKEMIA/

5 (plasma* adj3 neoplas*).tw,kw.

6 (plasma cell adj1 (leukaem* or leukem* or tumor* or tumour* or neoplasm*)).tw,kw.

7 (plasm?cytom* or plasm?zytom* or plasma cytoma*).tw,kw.

8 ((plasmacytic* or plasmocytic* or plasmocyte*) adj1 (leukem* or leukaem*)).tw,kw.

9 kahler*.tw,kw.

10 or/1-9

11 DARATUMUMAB/

12 (daratumumab* or dara-tumumab*).tw,kw.

13 darzalex*.tw,kw.

14 (human CD38 or human CD 38).tw,kw.

15 (anti-CD38 monoclonal antibod* or antiCD38 monoclonal antibod* or anti-CD 38 monoclonal antibod* or antiCD 38 monoclonal antibod*).tw,kw.

16 (HuMax-CD38 or UNII-4Z63YK6E0E or 4Z63YK6E0E or JNJ 54767414 or JNJ54767414 or 945721-28-8).tw,kw.

17 or/11-16
 18 10 and 17
 19 RANDOMIZED CONTROLLED TRIAL/
 20 CONTROLLED CLINICAL STUDY/
 21 random*.ti,ab.
 22 RANDOMIZATION/
 23 INTERMETHOD COMPARISON/
 24 placebo.ti,ab.
 25 (compare or compared or comparison).ti.
 26 (open adj label).ti,ab.
 27 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
 28 DOUBLE BLIND PROCEDURE/
 29 parallel groupUS\$ 1.ti,ab.
 30 (crossover or cross over).ti,ab.
 31 ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or
 intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti,ab.
 32 (controlled adj7 (study or design or trial)).ti,ab.
 33 (volunteer or volunteers).ti,ab.
 34 trial.ti.
 35 or/19-34
 36 (ANIMAL EXPERIMENT/ or ANIMAL EXPERIMENT/) not (HUMAN EXPERIMENT/ or
 HUMAN/)
 37 35 not 36
 38 PHASE 3 CLINICAL TRIAL/
 39 ("Phase 3" or "phase3" or "phase III" or P3 or "PIII").tw,kw.
 40 (38 or 39) not 36
 41 37 or 40
 42 10 and 17 and 41

MEDLINE (via Ovid) search strategy

Searches

- 1 exp MULTIPLE MYELOMA/
- 2 myelom*.tw,kf.
- 3 exp PLASMACYTOMA/
- 4 (plasm?cytom* or plasm?zytom* or plasma cytoma*).tw,kf.
- 5 (plasma* adj3 neoplas*).tw,kf.
- 6 (plasma cell adj1 (leukaem* or leukem* or tumor* or tumour*)).tw,kf.
- 7 ((plasmacytic* or plasmocytic* or plasmocyte*) adj1 (leukem* or leukaem*)).tw,kw.
- 8 kahler*.tw,kf.
- 9 or/1-8
- 10 (daratumumab* or dara-tumumab*).tw,kw,nm.
- 11 darzalex*.tw,kf,nm.
- 12 (human CD38 or human CD 38).tw,kf,nm.
- 13 (anti-CD38 monoclonal antibod* or antiCD38 monoclonal antibod*).tw,kf,nm.
- 14 (HuMax-CD38 or UNII-4Z63YK6E0E or 4Z63YK6E0E or JNJ 54767414 or JNJ54767414 or 945721-28-8).tw,kf,nm.
- 15 or/10-14
- 16 randomized controlled trial.pt.
- 17 controlled clinical trial.pt.
- 18 randomi?ed.ab.
- 19 placebo.ab.
- 20 drug therapy.fs.
- 21 randomly.ab.
- 22 trial.ab.
- 23 groups.ab.
- 24 or/16-23
- 25 exp ANIMALS/ not HUMANS/
- 26 24 not 25
- 27 CLINICAL TRIAL, PHASE III/
- 28 ("Phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw.
- 29 (27 or 28) not 25

30 26 or 29

31 9 and 15 and 30

II. References to included studies

MAIA

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