Horizon Scanning in Oncology

Daratumumab (Darzalex®) in combination with bortezomib, melphalan and prednisone for untreated myeloma

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology No. 81
ISSN online 2076-5940

Horizon Scanning in Oncology

Daratumumab (Darzalex®) in combination with bortezomib, melphalan and prednisone for untreated myeloma

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, May 2018

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

Author: Dr. med. Eleen Rothschedl
Internal review: Priv.-Doz. Dr. phil. Claudia Wild; Nicole Grössmann, MSc
External review: Dr. med. Raphael Teipel
Medizinische Klinik und Poliklinik I, Universitätsklinikum Dresden

DISCLAIMER

This technology summary is based on information available at the time of research and on a limited literature search. It is not a definitive statement on safety, effectiveness or efficacy and cannot replace professional medical advice nor should it be used for commercial purposes.

The HTA Core Model® for Rapid Relative Effectiveness for Pharmaceuticals, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. A working version (unpublished) of V3.0 of the Model was used. Use of the HTA Core Model® does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

CONTACT INFORMATION

Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

Responsible for Contents:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicise the research results of the Ludwig Boltzmann Institute of Health Technology Assessment.

Decision support documents of the LBI-HTA are only available to the public via the Internet at http://eprints.hta.lbg.ac.at.

DSD: Horizon Scanning in Oncology No. 81
ISSN-online: 2076-5940

http://eprints.hta.lbg.ac.at/view/types/

Abstract

Introduction

Multiple myeloma (MM) is a disease characterised by the neoplastic proliferation of plasma cells in the bone marrow. Daratumumab (Darzalex®) is a human monoclonal IgG1κ antibody directed against CD38, which is approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) as a monotherapy or in combination regimens for patients with MM who received prior lines of therapy. In May 2018, the FDA approved daratumumab in combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed MM who are ineligible for autologous stem-cell transplantation (ASCT).

Methodology

Published and grey literature were identified by searching the Cochrane Library, CRD Database, Embase, Ovid Medline, PubMed, Internet sites and contacting the manufacturer, resulting in 137 references overall. A quality assessment was conducted to assess the risk of bias at the study level based on the EUnetHTA internal validity for randomised controlled trials. The magnitude of clinically meaningful benefit that can be expected from a new anti-cancer treatment based on the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology has not been applied since it can only be used for solid tumours.

Results from ALCYONE trial

The ALCYONE trial assessed the efficacy and safety of the addition of daratumumab to bortezomib, melphalan and prednisone in patients with newly diagnosed MM who were ineligible for high-dose chemotherapy with stem-cell transplantation (SCT). A total of 706 patients were enrolled and received either nine cycles of bortezomib, melphalan and prednisone alone or in combination with daratumumab until disease progression. Analyses showed that patients of the daratumumab group had a lower risk of disease progression or death than patients of the control group: hazard ratio was 0.50 (95% CI, 0.38–0.65; $p < 0.001$). The 12-month rate and the 18-month rate of progression-free survival (PFS) were prolonged in patients receiving daratumumab (86.7% and 71.6% respectively) compared to control group patients (76.0% and 50.2% respectively). The overall response rate was higher in the daratumumab group (90.9%) than in the control group (73.9%). The median OS was not reached in either group. The most frequent adverse events (AEs) of grade 3 or 4 were neutropenia, thrombocytopenia and anaemia, occurring in 39.9%, 34.4% and 15.9% of daratumumab group patients and in 38.7%, 37.6% and 19.8% of control group patients respectively. The rate of serious AEs was higher in patients receiving daratumumab (41.6%) than in control group patients (32.5%).

Conclusion

The addition of daratumumab to the standard combination treatment of bortezomib, melphalan and prednisone in untreated MM patients resulted in a statistically significant benefit with a lower risk of disease progression or death, prolongation of PFS across all subgroups and a higher rate of negative status for MRD. These benefits need to be weighed against higher rates of infections and the occurrence of infusion-related reactions among patients receiving daratumumab. Furthermore, the costs for a four-drug regimen and the required concurrent medication have to be considered. Since no further valid OS data can be expected and quality of life (QoL) data is lacking, the clinical benefit of the assessed intervention remains to be proven.

Table of Contents

List of Tables

1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to predefined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

EUnetHTA
HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is daratumumab?
A0022	Who manufactures daratumumab?
A0007	What is the target population in this assessment?
A0020	For which indications has daratumumab received marketing authorisation?
Health problem and current use	
A0002	What is multiple myeloma?
A0004	What is the natural course of multiple myeloma?
A0006	What are the consequences of multiple myeloma for the society?
A0023	How many people belong to the target population?
A0005	What are the symptoms and the burden of multiple myeloma?
A0003	What are the known risk factors for multiple myeloma?
A0024	How is multiple myeloma currently diagnosed according to published guidelines and in practice?
A0025	How is multiple myeloma currently managed according to published guidelines and in practice?
Clinical effectiveness	
D0001	What is the expected beneficial effect of daratumumab on mortality?
D0006	How does daratumumab affect progression (or recurrence) of multiple myeloma?
D0005	How does daratumumab affect symptoms and findings (severity, frequency) of multiple myeloma?
D0011	What is the effect of daratumumab on patients' body functions?
D0012	What is the effect of daratumumab on generic health-related quality of life?
D0013	What is the effect of daratumumab on disease-specific quality of life?
Safety	
C0008	How safe is daratumumab in relation to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying daratumumab?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of daratumumab?
A0021	What is the reimbursement status of daratumumab?

2 Drug description

Generic/Brand name/ATC code:

Daratumumab/Darzalex®/L01XC24

B0001: What is daratumumab?

human monoclonal antibody directed against CD38

Daratumumab (Darzalex®) is a human monoclonal IgG1κ antibody directed against CD38. CD38 is a cell surface glycoprotein which is present on various immune cells and regulates the cytotoxic response of activated natural killer cells. Daratumumab is produced in a mammalian cell line (Chinese hamster ovary) using recombinant deoxyribonucleic acid (DNA) technology. The binding of daratumumab to natural killer cells simulates the normal CD38-CD31 interaction that proceeds on the surface of these cells. As CD38 is also present on multiple myeloma (MM) cells and plasma leukaemia cells, daratumumab may preferentially bind to these cells, thereby triggering anti-tumoural antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity [2, 3].

16 mg/kg of body weight administered IV, different dosing regimens for mono- and combination therapy

The recommended dose of daratumumab for monotherapy and in combination with lenalidomide (4-week-cycle regimen) is an intravenous (IV) administration of 16 mg/kg of body weight weekly (total of eight doses) on weeks 1 to 8, every two weeks (total of eight doses) on weeks 9 to 24 and every four weeks from week 25 onwards until disease progression. For combination therapy with bortezomib (3-week-cycle regimen), a modified dosing schedule is recommended: 16 mg/kg of body weight (IV) weekly on weeks 1 to 9 (total of nine doses), every three weeks (total of five doses) on weeks 10 to 24 and every four weeks from week 25 onwards until disease progression [2].

pre- and post-infusion medication to reduce the risk of IRR

To reduce the risk of infusion-related reactions (IRRs) with daratumumab, pre- and post-infusion medication should be administered. All patients should receive pre-infusion medication one to three hours prior to every daratumumab infusion, including [2]:

- A corticosteroid:
  - Monotherapy: methylprednisone 100 mg (IV) or equivalent, the dose may be reduced following the second infusion
  - Combination therapy: dexamethasone 20 mg (IV) prior to the first daratumumab infusion, oral administration may be considered prior to subsequent infusions
- Antipyretics: oral paracetamol, 650 to 1,000 mg
- Antihistamine: oral or IV diphenhydramine, 25 to 50 mg or equivalent.

To reduce the risk of delayed IRRs, post-infusion medication should be administered [2]:

- Monotherapy: oral corticosteroid (methylprednisolone) 20 mg or equivalent on each of the two days following all infusions
- Combination therapy: low-dose oral methylprednisolone (≤ 20 mg) or equivalent should be considered on the day after the daratumumab infusion.

In addition, for patients with a history of chronic obstructive pulmonary disease, the use of short- and long-acting bronchodilators and inhaled corticosteroids after daratumumab infusions should be considered. Also, prevention for a herpes zoster virus reactivation should be taken into consideration [2].

short- and long-acting bronchodilators for patients with a history of chronic obstructive pulmonary disease

A0022: Who manufactures daratumumab?

Janssen Biologics B.V.

3 Indication

A0007: What is the target population in this assessment?

Daratumumab is indicated in patients with newly diagnosed MM who are not eligible for high-dose chemotherapy with stem-cell transplantation (SCT).

patients with untreated MM, ineligible for SCT

4 Current regulatory status

A0020: For which indications has daratumumab received marketing authorisation?

To date, the use of daratumumab in combination with standard treatment in patients with newly diagnosed MM is not approved by the European Medicines Agency (EMA).

currently not approved for untreated MM

The EMA approved daratumumab (Darzalex®) for the following indications [4]:

approved indications in Europe

- Orphan designation was granted for the treatment of plasma-cell myeloma in July 2017
- As monotherapy for the treatment of adult patients with relapsed and refractory MM, whose prior therapy included a proteasome inhibitor (PI) and an immunomodulatory agent, and who have demonstrated disease progression on the last therapy (approved in May 2016)
- In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with MM who have received at least one prior therapy (approved in February 2017).

May 2018: FDA approval for daratumumab + bortezomib + melphalan + prednisone

In May 2018, the FDA granted marketing authorisation for daratumumab (Darzalex™) in combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed MM who are ineligible for autologous stem-cell transplantation (ASCT). The following further indications are approved in the US [5]:

- Patients with MM who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent (accelerated approval in November 2015)
- Patients with MM who have received at least one prior therapy, in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone (approved in November 2016)
- Patients with MM who have received at least two prior therapies (including lenalidomide and a PI), in combination with pomalidomide and dexamethasone (approved in June 2016).

5 Burden of disease

A0002: What is multiple myeloma?

MM: neoplastic proliferation of plasma cells in the bone marrow

MM is a disease characterised by the neoplastic proliferation of plasma cells in the bone marrow, often resulting in extensive skeletal destruction with osteolytic lesions, osteopenia and/or pathologic fractures. The disease is thought to develop from a pre-malignant stage of clonal plasma cell proliferation termed as "monoclonal gammopathy of undetermined significance" (MGUS). MGUS,

MGUS: pre-malignant stage

which is asymptomatic and present in over three percent of the population older than 50 years, appears to be the result of cytogenetic abnormalities. MGUS can progress to MM due to the following factors: additional genetic abnormalities, changes in the bone marrow microenvironment, an increased cell proliferation (because of cell-cycle dysregulation) or an evasion apoptosis. Some patients develop an intermediate asymptomatic but more advanced premalignant stage termed "smouldering multiple myeloma" (SMM) [6, 7]. The rate of progression of MGUS to MM is 1% per year; SMM progresses to MM at a rate of 10% per year over the first five years after diagnosis, then the rate declines to 3% per year over the following five years and to 1.5% per year thereafter [8].

A0004: What is the natural course of multiple myeloma?

highly variable course of disease

MM is a disease characterised by a highly variable course and a heterogeneous clinical behaviour [8]. Some patients progress rapidly despite treatment, whereas other patients do not require therapy for years. The prognosis of MM patients depends on staging, patient factors, disease biology, the availability of therapy and the response to therapy [9].

The 5-year relative survival rate[1] of MM is 50.7%. In general, 5% of MM cases are diagnosed at a local stage with a 5-year survival rate of 72%. 95% of cases are diagnosed at a distant stage when cancer has already metastasised resulting in a 5-year survival rate of 49.6% [10].

5-year relative survival rate: 50.7%

A0006: What are the consequences of multiple myeloma for the society?

A0023: How many people belong to the target population?

In Austria, 409 persons per year (2015) are newly diagnosed with myeloma; the disease is more common in men (219 newly diagnosed men in 2015) than in women (190 newly diagnosed women in 2015). The age-standardised incidence rate for the European Standard Population for myeloma (2015) is 5.8 per 100,000 per year in men and 4.1 per 100,000 per year in women [11].

MM incidence rate in Austria: 4.9/100,000 persons per year

In Europe, the median age at diagnosis is 72 years [8]. Based on 2013 to 2015 data from the US, approximately 0.8% of men and women will be diagnosed with myeloma at some point during their lifetime [10].

median age at diagnosis: 72 years

A0005: What are the symptoms and the burden of multiple myeloma?

Patients develop symptoms once the clonal plasma cell population is created and progresses to MM, owing to the infiltration of plasma cells into the bone marrow or other organs, or due to kidney damage caused by excess light chains [6]. The most common symptoms include anaemia, bone pain, renal disease (elevated creatinine), hypercalcaemia, or neurologic disease with radiculopathy, which represents the most common neurologic complication of MM. Due to a combination of immune dysfunction and physical factors, there is an increased risk of infections in patients with MM. Less common symptoms are paraesthesia, hepatomegaly, splenomegaly, lymphadenopathy; pleural effusion and diffuse pulmonary involvement are rare and usually occur in patients with advanced disease). Approximately seven percent of MM patients have extramedullary plasmacytomas (EP) at the time of diagnosis, which is associated with inferior survival. EP develops later in the course of MM in an additional six percent of patients [7].

most common symptoms: anaemia, bone pain, renal disease, hypercalcaemia, neurologic disease

approximately 7% of patients have EP at the time of diagnosis

A0003: What are the known risk factors for multiple myeloma?

MM is more common in men than women, with a higher incidence among persons of African American descent [7, 10]. In addition, the risk of developing MM increases with body mass index. Persons with a first-degree relative affected by MM have an approximately 3.7 times higher risk of developing the disease [7]. Furthermore, patients with a history of MGUS have a higher risk of developing MM [10]. Although the exact cause of MGUS is not entirely clarified yet, epidemiologic data suggests potential risk factors include genetic predisposition, older age, immunosuppression, hormonal factors and environmental exposures [6].

higher risk: men, African Americans, history of MGUS, family history of MM

[1] The relative survival rate compares the survival of patients diagnosed with cancer with the survival of people in the general population who are the same age, race and sex and who have not been diagnosed with cancer.

A0024: How is multiple myeloma currently diagnosed according to published guidelines and in practice?

initially: medical history and physical examination

According to the National Comprehensive Cancer Network (NCCN) [12], the initial MM diagnostic workup should include a medical history and physical examination. In addition, various assessments are recommended to differentiate symptomatic and asymptomatic MM: a complete blood count (with differential and platelet counts), examination of peripheral blood smear (to show abnormal distribution of red blood cells), blood urea nitrogen (BUN), serum creatinine (increased BUN and creatinine indicate decreased kidney function), creatinine clearance, serum electrolytes, serum calcium, albumin, lactate dehydrogenase (LDH) and beta-2 microglobulin.

various assessments are recommended

assessment of changes in protein levels to track disease progression and response to treatment

Serum and urine analyses should be conducted to evaluate the components of the monoclonal protein (M protein). To obtain more information about the type of M protein present, tests for serum quantitative immunoglobulins as well as serum protein electrophoresis (SPEP) and serum immunofixation electrophoresis (SIFE) should be conducted. The assessment of changes in protein levels, particularly of the M protein, could help to track disease progression and response to treatment. Urine analysis should include 24-hour urine for total protein analyses, urine protein electrophoresis (UPEP) and urine immunofixation electrophoresis (UIFE). Along with SPEP and SIFE, a serum-free light chain assay has a high sensitivity in screening for MM and related plasma cell disorders. In addition, it has a prognostic value in plasma cell disorders including MGUS, SMM, active myeloma, immunoglobulin light chain amyloidosis and solitary plasmacytoma.

A bone marrow evaluation (including bone marrow immunohistochemistry and/or bone marrow flow cytometry) is recommended to detect quantitative and/or qualitative abnormalities of bone marrow plasma cells. A skeletal survey or a whole-body low-dose computed tomography (CT) to evaluate lytic bone lesions is recommended, as well as metaphase cytogenetics on bone marrow and plasma cell fluorescence in situ hybridisation (FISH). Additional diagnostic tests (useful in certain circumstances) recommended by the NCCN include a whole-body or skeletal magnetic resonance imaging (MRI) or whole-body positron emission tomography (PET)/CT scan, a tissue biopsy to diagnose a solitary osseous or extraosseous plasmacytoma, a plasma cell proliferation, the evaluation of serum viscosity, human leucocyte antigen (HLA) typing, an echocardiogram and the evaluation of light chain amyloidosis [12].

criteria for diagnosis

Criteria for the diagnosis of MM are clonal bone marrow plasma cells ≥ 10% or plasmacytoma (extramedullary or of bone, proven by biopsy), and any one or more of the following events [8]:

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically hypercalcaemia with serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL), renal insufficiency with CrCl < 40 mL/min or serum creatinine > 177 µmol/L (> 2 mg/dL), anaemia with a haemoglobin value of > 20 g/L below the lower limit of normal or a haemoglobin value < 100 g/L, bone lesions with one or more osteolytic lesions on skeletal radiography, CT or PET/CT.
- Any one or more of the following biomarkers of malignancy, including ≥ 60% clonal bone marrow plasma cells, involved/uninvolved

serum-free light chain ratio ≥ 100, more than one focal lesion on MRI studies, where each focal lesion must be ≥ 5 mm.

ISS comprises 3 stages

According to the International Staging System (ISS), based on the combination of serum levels of beta-2 microglobulin and albumin, three stages of MM can be distinguished, whereby ISS stage III is associated with the poorest outcome [8]:

- ISS stage I: serum beta-2 microglobulin ≤ 3.5 mg/mL and serum albumin ≥ 3.5 g/dL
- ISS stage II: not stage I or III, 2 possibilities: serum beta-2 microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL or beta-2 microglobulin 3.5–5.5 mg/L, irrespective of the serum albumin
- ISS stage III: serum beta-2 microglobulin ≥ 5.5 mg/mL.

revised ISS

The revised International Staging System (R-ISS) includes data on the levels of serum beta-2 microglobulin, serum albumin and, additionally, serum LDH and a selected group of chromosomal abnormalities detected by FISH [8, 9].

differential diagnosis

Regarding the differential diagnosis of MM, the following conditions should be considered: MGUS, SMM, Waldenström's macroglobulinaemia, solitary plasmacytoma, primary amyloidosis, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes), and metastatic carcinoma [7].

6 Current treatment

A0025: How is multiple myeloma currently managed according to published guidelines and in practice?

ESMO recommends VMP or Rd for the front-line treatment of MM in non-transplant setting

The European Society for Medical Oncology (ESMO) recommends the two following treatment options for the front-line treatment of MM in elderly patients in the non-transplant setting (both approved in this setting by the EMA) [8]:

- Bortezomib (given subcutaneously) + melphalan + prednisone (VMP) or
- Lenalidomide + low-dose dexamethasone (Rd).

other treatment options

Rd + Bortezomib (VRd) is another option for MM front-line treatment; nevertheless, this combination regimen is not yet approved by the EMA. Additional options for the treatment of newly diagnosed MM are melphalan + prednisone + thalidomide (MPT, inferior to Rd in progression-free survival [PFS] and overall survival [OS]) or bortezomib + cyclophosphamide + dexamethasone (VCD), which is widely used (high response rates and prolonged PFS) although it is not approved by the EMA – due to a lack of control data. Other treatment options are cyclophosphamide + thalidomide + dexamethasone (CTD) and melphalan + prednisone (MP). A further treatment option is bendamustine + prednisone, which is approved by the EMA in patients with clinical neuropathy at the time of diagnosis.

NCCN recommendations

The NCCN recommends the following therapies for the initial treatment of MM patients who are non-transplant candidates [12]:

- Bortezomib + lenalidomide + dexamethasone or
- Lenalidomide + low-dose dexamethasone or
- Bortezomib + cyclophosphamide + dexamethasone.

Other recommended regimens are carfilzomib + lenalidomide + dexamethasone, carfilzomib + cyclophosphamide + dexamethasone, and ixazomib + lenalidomide + dexamethasone. The combination of bortezomib + dexamethasone is considered to be useful in certain circumstances [12].

NCCN: melphalan-containing regimens no longer standard of care

Since novel agents are available and accessible to patients in the US, the NCCN no longer considers melphalan-containing regimens as standard of care for the primary treatment of non-transplant candidates [12].

Of note, some of the regimens recommended by the NCCN are only approved in the US for the front-line treatment of MM. For example, carfilzomib + lenalidomide + dexamethasone, ixazomib + lenalidomide + dexamethasone are approved for the treatment of patients with MM, but only for those who have received at least one prior therapy. In Europe, the combination regimen of bortezomib + lenalidomide + dexamethasone is not approved for the treatment of MM at all.

7 Evidence

systematic literature search in 5 databases: 114 hits

A literature search was conducted on 4 April 2018 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were “daratumumab”, “L01XC24”, “Darzalex”, “multiple myeloma”, “untreated”, “initial”, and “first-line”. Also, the manufacturer was contacted, who submitted five references (three of them had already been identified by systematic literature search). A manual search identified 23 additional references (web documents and journal articles).

manual search: 23 additional references

overall: 137 references included: 1 study

Overall, 137 references were identified. Included in this report is one phase III study:

- ALCYONE, a multicentre, randomised open-label study evaluating the efficacy and safety of the addition of daratumumab to the standard treatment of bortezomib, melphalan and prednisone for patients with untreated myeloma who are ineligible for SCT [13].

study level risk of bias assessed based on EUnetHTA internal validity for RCTs

To assess the risk of bias at the study level, the assessment of the methodological quality of the evidence was conducted based on the EUnetHTA internal validity for randomised controlled trials (RCTs) [14]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patients and treating physicians, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 5 (see appendix).

applicability of study results

The external validity of the included trial was assessed using the EUnetHTA guideline on applicability of evidence in the context of a relative effective-

ness assessment of pharmaceuticals, considering the following elements: population, intervention, comparator(s), outcomes and setting [15].

The evaluation of the magnitude of "clinically meaningful benefit" that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was not applied, since it can only be used for the evaluation of solid tumours [16].

ESMO-MCBS could not be assessed

7.1 Quality assurance

This report has been reviewed by an internal reviewer and an external reviewer. The latter was asked for the assessment of the following quality criteria:

internal and external review

- How do you rate the overall quality of the report?
- Are the therapy options in the current treatment section used in clinical practice and are the presented standard therapies correct?
- Is the data regarding prevalence, incidence and amount of eligible patients correct?
- Are the investigated studies correctly analysed and presented (data extraction was double-checked by a second scientist)?
- Was the existing evidence from the present studies correctly interpreted?
- Does the current evidence support the final conclusion?
- Were all important points mentioned in the report?

The LBI-HTA considers the external assessment by scientific experts from different disciplines as a method of quality assurance of scientific work. The final version and the policy recommendations are under full responsibility of the LBI-HTA.

quality assurance method

7.2 Clinical efficacy and safety – phase III study

The ALCYONE trial [13, 17, 18] is a multicentre, randomised, open-label and active-controlled phase III trial evaluating the efficacy and safety of the addition of daratumumab to the standard combination treatment of bortezomib, melphalan and prednisone for MM. Between February 2015 and July 2016, a total of 706 patients with newly diagnosed, documented MM who were ineligible for high-dose chemotherapy with stem-cell transplantation (due to coexisting conditions or an age of 65 years or older) were enrolled and randomised to either the daratumumab group (n = 350) or the control group (n = 356). The patients had a median age of 71 years (both groups); approximately one third of the patients were older than 75 years (29.7% of patients in the daratumumab group and 30.1% of patients in the control group). 52% of patients in the daratumumab group and 48.6% of the patients in the control group had an ECOG performance status of 1. The median time since MM was initially diagnosed was 0.8 months in patients of both

ALCYONE trial: randomised, open-label, multicentre phase III trial

groups. According to the International Staging System (ISS), 40.6% of patients in the daratumumab group and 36.2% of patients in the control group had disease stage III. 16.9% of patients in the daratumumab group and 14.9% of patients in the control group had a high-risk cytogenetic profile. Detailed patient characteristics including inclusion and exclusion criteria can be found in Table 4.

1 cycle = 42 days, patients received up to 9 cycles of standard treatment

All patients received up to nine cycles (1 cycle = 42 days) of standard treatment, including bortezomib (subcutaneous, 1.3 mg/m^2 of body surface area, twice weekly on weeks 1, 2, 4 and 5 of cycle 1 and once weekly on weeks 1, 2, 4 and 5 of cycles 2 through 9), melphalan (oral, 9 mg/m^2, once daily on days 1 through 4 of each cycle) and prednisone (oral, 60 mg/m^2, once daily on days 1 through 4 of each cycle). Patients who were assigned to the daratumumab group received daratumumab at a dose of 16 mg/kg of body weight (IV) once weekly in cycle 1, every 3 weeks in cycles 2 through 9 and every four weeks thereafter until disease progression or unacceptable toxicity. In addition, dexamethasone was administered orally or IV at a dose of 20 mg simultaneously to daratumumab to manage infusion reactions. Dexamethasone (20 mg) was substituted for prednisone on day 1 of each cycle.

daratumumab dose: 16 mg/kg IV

PFS: primary endpoint

The primary endpoint of the ALCYONE trial was PFS, defined as the duration from the date of randomisation to either progressive disease or death, whichever came first. Key efficacy secondary endpoints were the overall response rate (ORR), the rates of very good partial response or better (including very good partial, complete and stringent complete responses), complete response (CR) or better (including complete and stringent complete responses), negative status for minimal residual disease (MRD, threshold of 1 tumour cell per 10^5 white cells) and OS. Other endpoints were safety, side-effect profile, time to response and duration of response.

median duration of treatment: 14.7 months in the daratumumab group

The median duration of treatment was 14.7 months in patients of the daratumumab group and 12 months in patients of the control group. At the clinical cut-off date in June 2017, 79.8% of patients in the daratumumab group and 62.1% of control group patients had completed all nine cycles of standard treatment. Thereafter, patients of the control group discontinued treatment and daratumumab group patients received further daratumumab monotherapy. The ALCYONE trial is ongoing, the estimated study completion date is 20 October 2021 [19]. Clinical efficacy data of the ALCYONE trial is presented in Table 1 and adverse events (AEs) are listed in Table 2.

7.2.1 Clinical efficacy

D0001: What is the expected beneficial effect of daratumumab on mortality?

median OS was not reached in either group

OS was a key efficacy secondary endpoint of the ALCYONE trial. At a median follow-up time of 16.5 months, 45 patients in the daratumumab group and 48 patients in the control group had died. In both groups, median OS was not reached.

follow-up for long-term survival is ongoing

For long-term survival, follow-up is ongoing. According to the study protocol, long-term follow-up will continue until 330 deaths have been observed or five years after the last patient has been randomised, whichever is first [18].

D0006: How does daratumumab affect progression (or recurrence) of multiple myeloma?

PFS was the primary endpoint of the ALCYONE trial; at the clinical cut-off date (12 June 2017) disease progression or death had occurred in 88 patients (25.1%) of the daratumumab group and in 143 (40.2%) patients of the control group. The hazard ratio (HR) for disease progression or death in the daratumumab group compared to the control group was 0.50 (95% confidence interval [CI] 0.38–0.65; $p < 0.001$). The 12-month rate of PFS was 86.7% (95% CI, 82.6–89.9) in patients of the daratumumab group versus 76% (95% CI, 71.0–80.2) in patients of the control group. After 18 months, the rate of PFS was 71.6% (95% CI, 65.5–76.8) in the daratumumab group compared to 50.2% (95% CI, 43.2–56.7) in the control group. In the daratumumab group, the median PFS was not reached (95% CI, could not be estimated [NE]); in the control group, the median PFS was 18.1 months (95% CI, 16.5–19.9; $p < 0.001$). The superiority of the addition of daratumumab to the standard treatment with bortezomib, melphalan and prednisone was consistent across all pre-specified subgroups, including patients aged 75 years or older and patients with a poor prognosis (ISS disease stage III, renal impairment or high-risk cytogenetic profile).

12-month PFS rate was 86.7% with daratumumab vs. 76% in control group

18-month PFS rate was 71.6% with daratumumab vs. 50.2% in control group

superiority of daratumumab in PFS was consistent across all subgroups

D0005: How does daratumumab affect symptoms and findings (severity, frequency) of multiple myeloma?

Patients of the daratumumab group showed an ORR of 90.9% compared to 73.9% in control group patients ($p < 0.001$). With 71.1% versus 49.7% ($p < 0.001$) the rate of very good partial response (PR) or better was statistically significantly higher in daratumumab group patients than in control group patients. Also, the rate of CR or better was statistically significantly higher in the daratumumab group (42.6%) than in the control group (24.4%, $p < 0.001$). In the daratumumab group, the rate of negative MRD status was more than three times as high as in the control group (22.3% vs. 6.2%, $p < 0.001$).

ORR higher in daratumumab group (90.9% vs. 73.9%)

statistically significant higher rate of very good PR or better and CR or better

The median time to response among daratumumab group patients was 0.79 months compared to 0.82 months in control group patients; the median time to best response was 4.9 months (daratumumab group) and 4.1 months (control group). In the daratumumab group, the median duration of response was not reached (95% CI, could not be estimated). In the control group, the median duration of response was 23.1 months (95% CI, 18.4–NE). 77.2% was the estimated percentage of patients who continued to have a response after 18 months in the daratumumab group versus 60.4% in the control group.

median time to response: daratumumab 0.79 months

control 0.82 months

D0011: What is the effect of daratumumab on patients' body functions?

Patients of the daratumumab group had a higher rate of grade 3 or 4 infections than patients of the control group (23.1% vs. 14.7%), the most common one was pneumonia (11.3% in the daratumumab group and 4% in the control group). 26.3% of daratumumab group patients had an upper respiratory tract infection (all grades) compared to 13.8% of control group patients.

higher rate of grade 3 and 4 infections in the daratumumab group

D0012: What is the effect of daratumumab on generic health-related quality of life?

D0013: What is the effect of daratumumab on disease-specific quality of life?

HRQoL and QoL: no evidence

No evidence was found to answer these research questions as neither health-related quality of life (HRQoL) nor quality of life (QoL) were endpoints of the present study.

Table 1: Efficacy results of ALCYONE trial

Descriptive statistics and estimate variability	**Treatment group**	**Daratumumab**	**Control**
	Number of patients	350	356
	PFS rate, % (95% CI) at 12 months at 18 months	 86.7 (82.6–89.9) 71.6 (65.5–76.8)	 76.0 (71.0–80.2 50.2 (43.2–56.7)
	Median PFS, months (95% CI)	NR (NE)	18.1 (16.5–19.9)
	ORR rate, %	90.9	73.9
	Best OR, % CR or better, % Stringent CR CR Very good PR or better Very good PR PR Stable disease Progressive disease Response could not be evaluated	 42.6 18.0 24.6 71.1 28.6 19.7 5.7 0 3.4	 24.4 7.0 17.4 49.7 25.3 24.2 21.3 0.6 4.2
	Negative status for MRD, %	22.3	6.2
	Median OS, months	NR	NR
	QoL	NA	NA
	Event of disease progression or death, %	21.5	40.2
	Median time to response, months Median time to best response, months Median duration of response, months (95% CI)	0.79 4.9 NR (NE)	0.82 4.1 21.3 (18.4–NE)
Effect estimate per comparison	Comparison groups		Daratumumab vs. control
	Disease progression or death	HR	0.50
		95% CI	0.38–0.65
		log-rank p-value	< 0.001
	ORR*	p-value	< 0.001
	CR or better*	p-value	< 0.001
	Very good PR or better*	p-value	< 0.001
	Negative status for MRD§	p-value	< 0.001

Abbreviations: CI = confidence interval, CR = complete response, CRR = complete response rate, HR = hazard ratio, MRD = minimal residual disease, NA = not available, NE = could not be estimated, NR = not reached, OR = overall response, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, PR = partial response, QoL = quality of life

** ORR, CR or better and very good PR or better: p value was calculated by the use of the Cochran-Mantel-Haenszel chi-square test*

§ MRD: p value was calculated by the use of Fisher's exact test

7.2.2 Safety

C0008: How safe is daratumumab in relation to the comparator(s)?

most frequent AEs of any grade: neutropenia and thrombocytopenia

The most frequent AEs of any grade occurring in ≥ 20% of patients in either group were neutropenia (49.7% of daratumumab group patients vs. 52.5% of control group patients), thrombocytopenia (48.8% vs. 53.7%), peripheral sensory neuropathy (28.3% vs. 34.2%) and anaemia (28.0% vs. 37.6%), upper respiratory tract infection (26.3% vs. 13.8%), diarrhoea (23.7% vs. 24.6%), pyrexia (23.1% vs. 20.9%) and nausea (20.8% vs. 21.5%).

most common AEs of grade 3 or 4: haematologic AEs

The most common AEs of grade 3 or 4, occurring in ≥ 10% of patients in either group, were haematologic AEs: neutropenia, thrombocytopenia and anaemia occurred in 39.9%, 34.4% and 15.9% of daratumumab group patients and in 38.7%, 37.6% and 19.8% of control group patients respectively.

infections were more frequent in patients receiving daratumumab, pneumonia was most common

Infections of grade 3 or 4 were more frequent in patients receiving daratumumab (23.1%) compared to control group patients (14.7%). The most common infection was pneumonia, occurring in 11.3% of daratumumab group patients and in 4% of control group patients. Owing to pneumonia of any grade, one patient in each group (0.3%) discontinued study treatment. Most infections resolved (in 87.9% of daratumumab group patients and 86.5% of control group patients) and the rates of study treatment discontinuation due to infections were similar between the groups (0.9% in the daratumumab group and 1.4% in the control group). Five patients (1.4%) of the daratumumab group died due to an infection: two patients died from pneumonia, one patient each died from peritonitis, septic shock and upper respiratory tract infection. In the control group, four patients (1.1%) died due to an infection, one patient each from septic shock, candida-related sepsis, bacterial pneumonia and sepsis. 14 patients (4%) of the daratumumab group and 16 patients (4.5%) of the control group died due to AEs that occurred within 30 days after the last trial treatment had been administered.

serious AEs in 41.6% (daratumumab group) and 32.5% (control group)

27.7% of patients had IRRs

second primary cancer in approx. 2.5% of patients

The rate of serious AEs was 41.6% in daratumumab group patients and 32.5% in control group patients; pneumonia was most common (10.1% of patients receiving daratumumab and 3.1% of control group patients). AEs led to discontinuation of study treatment in 4.9% of daratumumab group patients and 9% of control group patients. 27.7% of the patients receiving daratumumab experienced IRRs, mostly of grade 1 or 2 during the first infusion. Most common IRRs were dyspnoea, chills, hypertension, pyrexia and bronchospasm. 4.3% of the patients had grade 3 IRRs, grade 4 IRRs occurred in 0.6% of patients. Two patients (0.6%) in each group experienced a tumour lysis syndrome. A second primary cancer, which was pre-specified in the statistical analysis plan as an AE of clinical interest, has been diagnosed in 2.3% of daratumumab group patients and 2.5% of control group patients.

C0002: Are the harms related to dosage or frequency of applying daratumumab?

studies comparing different dosages of daratumumab

Concerning the tolerance of daratumumab in different dosing levels, data from a phase I/II, two-part trial, conducted in patients with relapsed myeloma or relapsed myeloma that was refractory to two or more prior lines of therapy is available [20]. In the dose- escalation part of the study, no maximum tolerated dose was found; at doses of 0.1 mg/kg and 1 mg/kg, dose-

limiting toxic effects were observed (grade 3 anaemia in 1 patient and grade 3 elevation of the aspartate aminotransferase level in 1 patient, respectively). After three additional patients received daratumumab at these dose levels without showing dose-limiting toxic events, the dose level of daratumumab was safely increased to 24 mg/kg. Lonial et al. [21] assessed daratumumab in different dosages (8 mg/kg vs. 16 mg/kg) in a two-part phase II trial in patients with refractory MM. Analyses showed that the safety profile in the 8 mg/kg group was similar to that in the 16 mg/kg group. Overall, daratumumab was well tolerated; there were no treatment discontinuations due to drug-related treatment-emergent AEs, IRRs, or death.

pharmacokinetic analyses

Xu et al. [22] conducted pharmacokinetic analyses using data from two trials [20, 21], showing that there was neither an apparent relationship between the peak concentration of daratumumab after the first dose ($C_{max, 1st}$) and the occurrence of IRRs nor between the peak concentration after multiple doses (C_{max}) and thrombocytopenia, anaemia, neutropenia, and lymphopenia. A numerically increase of the overall event rate with drug exposure was reported which was not observed for grade three infections.

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of daratumumab?

no evidence regarding the effect of daratumumab on newborns, infants or fertility

Daratumumab should not be administered during pregnancy unless the benefit of the treatment to the patients is considered to outweigh the potential risks to the foetus. There is no evidence of the effect of daratumumab on newborns or infants. No information about potential effects of daratumumab on the fertility of patients is available [2].

concomitant medication for patients with a history of COPD

For patients with a history of chronic obstructive pulmonary disease (COPD), the use of short- and long-acting bronchodilators and inhaled corticosteroids after daratumumab infusions should be considered [2] to prevent pulmonary complications (e.g. bronchospasm).

*Table 2: ALCYONE trial: Most common adverse events during treatment in the safety population**

AE (according to NCI CTCAE version 4.0)	**Intervention** (n = 346)		**Control** (n = 354)	
	Any grade n (%)	Grade 3 or 4 n (%)	Any grade n (%)	Grade 3 or 4 n (%)
Haematologic AEs				
Neutropenia	172 (49.7)	138 (39.9)	186 (52.5)	137 (38.7)
Thrombocytopenia	169 (48.8)	119 (34.4)	190 (53.7)	133 (37.6)
Anaemia	97 (28.0)	55 (15.9)	133 (37.6)	70 (19.8)
Non-haematologic AEs				
Peripheral sensory neuropathy	98 (28.3)	5 (1.4)	121 (34.2)	14 (4.0)
Diarrhoea	82 (23.7)	9 (2.6)	87 (24.6)	11 (3.1)
Pyrexia	80 (23.1)	2 (0.6)	74 (20.9)	2 (0.6)
Nausea	72 (20.8)	3 (0.9)	76 (21.5)	4 (1.1)
Infections	231 (66.8)	80 (23.1)	170 (48.0)	52 (14.7)
Upper respiratory tract infection	91 (26.3)	7 (2.0)	49 (13.8)	5 (1.4)
Pneumonia	53 (15.3)	39 (11.3)	17 (4.8)	14 (4.0)
Secondary primary cancer	8 (2.3)	NA	9 (2.5)	NA
Any infusion-related reaction	96 (27.7)	15 (4.3)	NA	NA

Abbreviations: AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, n = number, NA = not applicable, NCI = National Cancer Institute

** Safety population = all patients who received at least one dose of trial treatment*

7.3 Clinical effectiveness and safety – further studies

There are no further trials available assessing the addition of daratumumab to the standard combination regimen of bortezomib, melphalan and prednisone in patients with newly diagnosed MM who are not candidates for SCT.

no further trials are available

8 Estimated costs

A0021: What is the reimbursement status of daratumumab?

Daratumumab (Darzalex®) is available as a concentrate for solution for infusion in vials of 100 mg at € 524 and 400 mg at € 2,096 (ex-factory prices) [23].

100 mg = € 524
400 mg = € 2,096

In the ALCYONE trial, daratumumab was administered at a dose of 16 mg/kg of body weight once weekly in cycle one (1 cycle = 42 days), every three weeks in cycles 2 through 9 and every four weeks thereafter until disease progression or unacceptable toxicity [13].

costs for cycle 1: € 37,728
costs for 1 cycle of cycles 2–9: € 12,576
costs for 1 cycle beyond cycle 9: € 9,432

median treatment duration of the daratumumab group was 14.7 months

Based on the dosing regimen of the ALCYONE trial, the following costs for daratumumab treatment will incur: assuming an average body weight of 70 kg, 1,120 mg of daratumumab per week are needed. One vial of concentrate for solution for infusion containing 400 mg costs € 2,096, resulting in € 6,288 per week. Costs for the first cycle of daratumumab comprising six infusions are € 37,728. In cycles 2 to 9, when daratumumab is administered every three weeks, the costs for one cycle are € 12,576. In subsequent cycles, when daratumumab is administered every four weeks, one cycle costs € 9,432. The median treatment duration of ALCYONE trial patients was 14.7 months; assuming a cycle length of 42 days, 11 cycles of daratumumab treatment would be needed, costing approximately € 157,200.

additional costs for chemotherapy, pre- and post-infusion medication

In addition, costs for the combination treatment with bortezomib, melphalan and prednisone, as well as costs for concomitant pre- and post-infusion medication administered to reduce the risk of IRRs (including corticosteroids, antipyretics and antihistamines) incur.

9 Ongoing research

4 ongoing phase III trials

In April 2018, a search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted. The following phase III trials, assessing the use of daratumumab in patients with previously untreated MM, were identified:

- **NCT02541383:** CASSIOPEIA, a randomised, open-label, multicentre study to evaluate the use of daratumumab in combination with bortezomib, thalidomide and dexamethasone in transplant-eligible patients with previously untreated MM. Estimated study completion date is August 2024.
- **NCT03301220:** An open-label, multicentre study to assess whether daratumumab (administered subcutaneously) compared with active monitoring prolongs PFS in patients with high-risk SMM. Estimated study completion date is December 2025.
- **NCT02252172:** MAIA, a randomised, open-label trial comparing daratumumab, lenalidomide and dexamethasone versus lenalidomide and dexamethasone in patients with previously untreated MM who are not candidates for high-dose chemotherapy and autologous stem-cell transplantation. Estimated study completion date is November 2024.
- **NCT03217812:** A randomised, open-label, multicentre, controlled study comparing bortezomib, melphalan and prednisone to daratumumab, bortezomib, melphalan and prednisone in patients with previously untreated MM who are ineligible for high-dose chemotherapy. Estimated study completion date is October 2022.

numerous ongoing phase I and II trials

There are numerous phase I and phase II studies ongoing, evaluating the efficacy and safety of daratumumab-only or combination regimens including daratumumab in patients with previously untreated MM as well as in patients with relapsed and refractory MM.

10 Discussion

assessed indication: approved by the FDA, not approved by the EMA

Daratumumab (Darzalex®) is a human monoclonal IgG1κ antibody directed against CD38 [2]. It is approved by the EMA and the FDA as a monotherapy or in combination regimens for patients with MM who received prior lines of therapy [4, 5]. In May 2018, the FDA approved daratumumab in combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed MM who are ineligible for ASCT, whereas daratumumab is not approved by the EMA for the assessed indication.

ALCYONE trial, daratumumab group:

50% lower risk of disease progression or death

statistically significantly longer PFS, higher ORR rate

statistically significantly higher rates of very good PR or better and CR or better

higher rate of negative status for MRD

The ALCYONE trial [13] investigated the efficacy and safety of the addition of daratumumab to bortezomib, melphalan and prednisone in patients with newly diagnosed MM who were ineligible for high-dose chemotherapy with SCT. Analyses showed that patients of the daratumumab group had a lower risk of disease progression or death than patients of the control group: HR was 0.50 (95% CI, 0.38–0.65; $p < 0.001$). The 12-month rate and the 18-month rate of PFS were prolonged in patients receiving daratumumab (86.7% and 71.6% respectively) compared to control group patients (76.0% and 50.2% respectively). For PFS, the superiority of the addition of daratumumab to bortezomib, melphalan and prednisone was consistent across all pre-specified subgroups, including patients with a poor prognosis or patients of 75 years or older. The ORR was higher in the daratumumab group (90.9%) than in the control group (73.9%); the rates of very good PR or better and the rate of CR or better were statistically significantly higher in patients receiving daratumumab than in control group patients: 71.1% vs. 49.7% and 42.6% vs. 24.4% respectively. Also, the rate of negative status for MRD was more than three times as high in the patients of the daratumumab group (22.3%) as in the patients of the control group (6.2%).

median OS was not reached in either group

trial ongoing, QoL not assessed

no valid OS data expectable

The median duration of response was 21.3 months in the control group, whereas it was not reached in the daratumumab group. The median OS was not reached in either group. At a median follow-up of 16.5 months, death had occurred in 45 of 350 patients in the daratumumab group and in 48 of 356 patients in the control group. Although the ALYCONE trial is ongoing until October 2021, no valid follow-up data for long-term survival can be expected, owing to the fact that all patients in the control group discontinued treatment after nine cycles whereas all patients in the daratumumab group received further daratumumab as monotherapy. Neither is any data available regarding the QoL of the study patients.

most frequent AEs were haematologic

higher rates of serious AEs in the daratumumab group

The most frequent AEs of grade 3 or 4 were neutropenia, thrombocytopenia and anaemia, occurring in 39.9%, 34.4% and 15.9% of daratumumab group patients and in 38.7%, 37.6% and 19.8% of control group patients respectively. The rate of grade 3 or 4 infections (most commonly pneumonia) was higher in patients receiving daratumumab (23.1%) than in patients of the control group (14.7%); however, the rate of discontinuation of trial treatment due to infection was similar between the two groups (0.9% in the daratumumab group vs. 1.4% in the control group). The rate of serious AEs was higher in patients receiving daratumumab (41.6%) than in control group patients (32.5%). Of the patients receiving daratumumab, 27.7% experienced IRRs, mostly during the first infusion. 4.3% and 0.6% of daratumumab group patients had grade 3 and grade 4 IRRs respectively.

higher infection rates did not lead to discontinuation

In terms of safety, the higher rate of grade 3 or 4 infections among patients receiving daratumumab is worth mentioning, as is the higher rate of serious AEs. Interestingly, these facts did not lead to a higher rate of study treatment discontinuation. Despite the administration of pre-infusion medication, approximately one third of daratumumab group patients experienced IRRs.

high risk of bias

The external and internal validity of the ALCYONE trial is compromised by methodological limitations. ALCYONE was conducted as an open-label study; both the patients and the treating physicians were unmasked to treatment assignment, which may lead to a performance and/or detection bias. As the trial is currently ongoing, not all of the pre-specified endpoints from the protocol have been reported yet. However, a high risk of bias could be detected due to the open-label, unblinded study design and other aspects that may increase the risk of bias.

limited external applicability

Regarding the external validity it is noticeable that – with a cycle length of 42 days – the dosing schedule used in the ALCYONE trial differs from the approved dosing regimens [2] as well as from dosing regimens used in other trials [24, 25] with a usual cycle length of 21 or 28 days respectively.

more data in this special setting is needed

There are studies indicating the efficacy and safety of the addition of daratumumab to treatment regimens including lenalidomide plus dexamethasone (POLLUX trial [24]) or bortezomib plus dexamethasone (CASTOR trial [25]). However, these trials assessed three-drug regimens; included patients that had relapsed or relapsed and refractory MM and had received at least one prior treatment.

ALCYONE: first study with daratumumab in the front-line setting

ALCYONE was the first trial that investigated daratumumab for the front-line treatment of MM and there is no further study available to confirm the results of the ALCYONE trial with the administered four-drug regimen. Therefore, the results of an ongoing randomised, open-label, multicentre, controlled study comparing bortezomib, melphalan and prednisone to daratumumab, bortezomib, melphalan and prednisone in patients with previously untreated MM who are ineligible for high-dose chemotherapy (NCT03217812), conducted in the Asia Pacific region, will be of high interest.

more data required for daratumumab in front-line setting and with different backbone regimens

Likewise, the results from the MAIA trial (NCT02252172), comparing daratumumab, lenalidomide and dexamethasone with lenalidomide and dexamethasone in patients with previously untreated MM, may yield more evidence. Particularly in view of the fact that the NCCN no longer considers melphalan-containing regimens as standard of care for the primary treatment of transplant-ineligible MM patients in the US [12], the investigation of daratumumab in combination with a different backbone regimen might also be useful.

costs for 4 drugs and concurrent medication

According to the dosing regimen used in the ALCYONE trial, the costs of daratumumab are € 37,728 for the first cycle, € 12,576 in cycles 2 to 9 and € 9,432 in subsequent cycles [13, 23]. Patients of the ALCYONE trial had a median treatment duration of 14.7 months.

€ 157,200 for 11 cycles of daratumumab treatment

Assuming a cycle length of 42 days, 11 cycles of daratumumab treatment would be needed, costing approximately € 157,200. Additionally, costs for the standard treatment with bortezomib, melphalan and prednisone incur. Costs increase by the administration of required concurrent medication to reduce the risk of IRRs, including corticosteroids, antipyretics and antihistamines.

The addition of daratumumab to the standard combination treatment of bortezomib, melphalan and prednisone in untreated MM patients resulted in a statistically significant benefit with a lower risk of disease progression or death, prolongation of PFS across all subgroups and a higher rate of negative status for MRD. These benefits need to be weighed against higher rates of infections and the occurrence of IRRs among patients receiving daratumumab. Furthermore, the costs for a four-drug regimen and the required concurrent medication have to be considered. Since no further valid OS data can be expected and QoL data is lacking, the clinical benefit of the assessed intervention remains to be proven. Finally, more robust evidence, particularly for the use of daratumumab for the front-line treatment of MM is needed; as well as the investigation of appropriate and feasible combination regimens.

daratumumab provides a benefit

lack of QoL and OS data

robust evidence in different settings is required

11 References

[1] European Network for Health Technology Assessment (eunethta). HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals.Version 3.0. 2013 [cited 2015-10-30]. Available from: http://meka.thl.fi/htacore/model/HTA%20Core%20Model%20for%20Rapid%20REA%20of%20Pharmaceuticals%203.0.pdf.

[2] European Medicines Agency. Darzalex: EPAR - Product Information. [cited 2018-04-13]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004077/WC500207296.pdf.

[3] National Cancer Institute. NCI Drug Dictionary.Daratumumab. [cited 2018-04-14]; Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug/def/daratumumab.

[4] European Medicines Agency. Darzalex. [cited 2018-04-14]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004077/human_med_001979.jsp&mid=WC0b01ac058001d124.

[5] U.S. Food and Drug Administration. Drugs@FDA. Daratumumab. [cited 2018-04-14]; Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process.

[6] Rajkumar SV. Pathobiology of multiple myeloma. In: Kyle RA, editors. UpToDate. Waltham, MA. (cited 2018-04-20): UpToDate; 2018.

[7] Rajkumar SV. Clinical features, laboratory manifestations, and diagnosis of multiple myeloma. In: Kyle RA, editors. UpToDate. Waltham, MA. (cited 2018-04-20): UpToDate 2018.

[8] Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. [cited 2018-04-21]; Available from: http://www.esmo.org/Guidelines/Haematological-Malignancies/Multiple-Myeloma.

[9] Rajkumar SV. Staging and prognostic studies in multiple myeloma. In: Kyle A, editors. UpToDate. Waltham, MA. (cited 2018-04-20): UpToDate; 2018.

[10] National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Statistics. Myeloma. [cited 2018-04-20]; Available from: https://seer.cancer.gov/statfacts/html/mulmy.html.

[11] Statistik Austria. Krebserkrankungen - Myelom. [cited 2018-04-20]; Available from: https://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/plasmozytom_myelom/107469.html.

[12] National Comprehensive Cancer Network (NCCN). NCCN Guidelines Version 4.2018. Multiple Myeloma. [2018-04-20]; Available from: www.nccn.org.

[13] Mateos MV, Dimopoulos MA, Cavo M, Suzuki K, Jakubowiak A, Knop S, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. New England Journal of Medicine. 2018;378(6):518-28.

[14] EUnetHTA - European Network for Health Technology Assessment. Internal validity of randomized controlled trials 2013, adapted version (2015). Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/16_WP7-SG3-GL-int_val_RCTs_amend2015.pdf.

[15] EUnetHTA guidelines. Levels of evidence. Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals. February 2013 Available from: http://www.eunethta.eu/sites/default/files/sites/5026.fedimbo.belgium.be/files/Applicability.pdf.

[16] Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer

therapies: The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Annals of Oncology 2015; 26(8):1547-73.

[17] Mateos MV, Dimopoulos M, Cavo M, et al. Supplement to: Mateos M-V, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med 2018;378:518-28. .

[18] Mateos MV, Dimopoulos M, Cavo M, et al. Protocol for: Mateos M-V, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med 2018;378:518-28. .

[19] U.S. National Library of Medicine. ClinicalTrials.gov. A Study of Combination of Daratumumab and Velcade (Bortezomib) Melphalan-Prednisone (DVMP) Compared to Velcade Melphalan-Prednisone (VMP) in Participants With Previously Untreated Multiple Myeloma. [cited 2018-04-21]; Available from: https://clinicaltrials.gov/ct2/show/NCT02195479?term=NCT02195479&rank=1.

[20] Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. N Engl J Med 2015;373:1207-19.

[21] Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet (London, England). 2016;387(10027):1551-60. Epub 2016/01/19.

[22] Xu XS, Yan X, Puchalski T, Lonial S, Lokhorst HM, Voorhees PM, et al. Clinical Implications of Complex Pharmacokinetics for Daratumumab Dose Regimen in Patients With Relapsed/Refractory Multiple Myeloma. Clin Pharmacol Ther 2017 Jun; 101(6): 721–724.

[23] Warenverzeichnis Apothekerverlag Online. [cited 2018-04-13]; Available from: http://warenverzeichnis.apoverlag.at/.

[24] Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. [cited 2018-04-28]; Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1607751.

[25] Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. [cited 2018-04-28]; Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1606038.

12 Appendix

Table 3: Administration and dosing of daratumumab (Darzalex®) [2, 13, 23]

	Technology	Comparator
Administration mode	Intravenous infusion (IV)	No active comparator is available
Description of packaging	Darzalex® is a concentrate for solution for infusion and is a colourless to yellow liquid. It is supplied as a carton pack containing 1 glass vial. One mL of concentrate contains 20 mg daratumumab. Each vial of 5 mL concentrate contains 100 mg of daratumumab. Each vial of 20 mL concentrate contains 400 mg of daratumumab.	
Total volume contained in packaging for sale	Darzalex® concentrate for solution for infusion 100 mg Darzalex® concentrate for solution for infusion 400 mg	
Dosing	ALCYONE trial: 16mg/kg (IV) of body weight of daratumumab, once weekly in cycle 1, every 3 weeks in cycles 2 through 9 and every 4 weeks thereafter until disease progression or unacceptable toxic effects.	
Median treatment duration	Median duration of treatment with daratumumab in patients participating in the ALCYONE trial was 14.7 months.	
Contraindications	Hypersensitivity to the active substance or to any of the excipients (glacial acetic acid, mannitol (E421), polysorbate 20, sodium acetate trihydrate, sodium chloride, water for injections).	
Drug interactions	No interaction studies have been performed. As an IgG1κ monoclonal antibody, renal excretion and hepatic enzyme-mediated metabolism of intact daratumumab are unlikely to represent major elimination routes. As such, variations in drug-metabolising enzymes are not expected to affect the elimination of daratumumab. Due to the high affinity to a unique epitope on CD38, daratumumab is not anticipated to alter drug-metabolising enzymes. Clinical pharmacokinetic assessments of pomalidomide, thalidomide and bortezomib indicated no clinically relevant drug-drug interaction between daratumumab and these combination therapies. Interference with indirect antiglobulin test (indirect Coombs test): daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with DTT to disrupt daratumumab binding or other locally validated methods. Since the Kell blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. Alternatively, phenotyping or genotyping may also be considered. Interference with SPE and IFE tests: daratumumab may be detected on SPE and IFE assays used for monitoring disease monoclonal immunoglobulins (M proteins). This can lead to false-positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by IMWG criteria. In patients with persistent very good partial response other methods to evaluate the depth of response should be considered.	

Abbreviations: DTT = dithiothreitol, IMWG = International Myeloma Working Group, IFE = immunofixation electrophoresis, Ig = immunoglobulin, IV = intravenous, RBCs = red blood cells, SPE = serum protein electrophoresis

Table 4: Characteristics of the ALCYONE trial

Title: Daratumumab plus bortezomib, melphalan and prednisone for untreated myeloma [13, 17, 18]			
Study identifier	NCT02195479, EudraCT number: 2014-002272-88, ALCYONE trial		
Design	Multicentre, randomised, open-label, active-controlled phase III trial		
	Duration of main phase:	Enrolment: 9 February 2015 to 14 July 2016 Clinical cut-off date: 12 June 2017 Median follow-up: 16.5 months	
Hypothesis	Superiority A sample size of 350 patients per group (under the assumption of an annual dropout rate of 5%) was estimated to provide 80% power to detect a 27% lower risk of disease progression or death in the daratumumab group than in the control group, with the use of a log-rank test with a two-sided alpha level of 0.05. The primary efficacy end point was estimated with the Kaplan-Meier method, and the treatment effect (HR) and its two-sided 95% confidence interval were estimated with a stratified Cox regression model. Statistical significance was evaluated with a stratified log-rank test based on the predetermined alpha level at the clinical cut-off date.		
Funding	Janssen Research and Development		
Treatments groups	Intervention (n = 350)		Patients received up to nine (42-day) cycles of subcutaneous bortezomib (1.3 mg/m² of body surface area, twice weekly on weeks 1, 2, 4 and 5 of cycles 2 through 9), oral melphalan (9 mg/m², once daily on days 1 through 4 of each cycle) and oral prednisone (60 mg/m², once daily on days 1 through 4 of each cycle). Daratumumab (IV) at a dose of 16 mg/kg of body weight was administered with dexamethasone (oral or IV) at a dose of 20 mg once weekly in cycle 1, every 3 weeks in cycles 2 through 9 and every 4 weeks thereafter until disease progression or unacceptable toxic effects. Dexamethasone (20 mg) was substituted for prednisone on day 1 of each cycle.
	Control (n = 356)		Patients received up to nine (42-day) cycles of subcutaneous bortezomib (1.3 mg/m² of body surface area, twice weekly on weeks 1, 2, 4 and 5 of cycles 2 through 9), oral melphalan (9 mg/m², once daily on days 1 through 4 of each cycle) and oral prednisone (60 mg/m², once daily on days 1 through 4 of each cycle).
Endpoints and definitions	Progression-free survival (primary endpoint)	PFS	Time from randomisation to either disease progression or death.
	Overall response rate (key efficacy secondary endpoint)	ORR	The proportion of patients who achieved PR or better, according to the International Myeloma Working Group criteria, during or after the study treatment.
	Complete response rate (key efficacy secondary endpoint)	CRR	Defined as the percentage of patients achieving CR, as defined by a negative immunofixation of serum and urine, the disappearance of any soft-tissue plasmacytomas and < 5% plasma cells in the bone marrow. For those patients with a negative or low serum protein electrophoresis (≤ 0.2 g/L) and suspected daratumumab interference on immunofixation, a reflex assay with anti-idiotype antibody was used to confirm daratumumab interference and rule out a false-positive immunofixation. Patients who had confirmed daratumumab interference but met all other clinical criteria for stringent CR or CR were considered to have achieved stringent CR or CR.
	Minimal residual disease (MRD) negativity rate (key efficacy secondary endpoint)	-	The proportion of patients who were negative for MRD at any time point after randomisation (at a threshold of 1 tumour cell per 10^5 white cells).
	Overall survival (key efficacy secondary endpoint)	OS	The time from randomisation to the date of the patient's death.
	Time to response	-	The time between randomisation and the first efficacy evaluation in which the patients had met all criteria for PR or better.

<table>
<tr><td colspan="5">Title: Daratumumab plus bortezomib, melphalan and prednisone for untreated myeloma [13, 17, 18]</td></tr>
<tr><td>Study identifier</td><td colspan="4">NCT02195479, EudraCT number: 2014-002272-88, ALCYONE trial</td></tr>
<tr><td></td><td>Duration of response</td><td>-</td><td colspan="2">Calculated from the date of initial documentation of a response (PR or better) to the date of the first documented evidence of progressive disease, as defined by the International Myeloma Working Group criteria.</td></tr>
<tr><td>Database lock</td><td colspan="4">Clinical cut-off date: 12 June 2017</td></tr>
<tr><td colspan="5">Results and analysis</td></tr>
<tr><td>Analysis description</td><td colspan="4">Primary analysis
The primary analysis population was the intention-to-treat population of all the patients who underwent randomisation. The safety population comprised patients who received any dose of initial treatment.
Of two planned interim analyses, the first evaluated only safety after 100 patients had received at least two treatment cycles or had discontinued treatment. The second (reported here) assessed safety and efficacy when 231 events of disease progression or death had occurred. The final overall survival analysis will occur after 330 deaths.</td></tr>
<tr><td rowspan="4">Analysis population</td><td>Inclusion</td><td colspan="3">✲ Patients with newly diagnosed, documented MM
✲ Not eligible for high-dose chemotherapy with stem-cell transplantation owing to coexisting conditions or an age of ≥ 65 years
✲ Haemoglobin level of ≥ 7.5 g/dL
✲ Absolute neutrophil count of ≥ 1.0x10⁹/L
✲ Aspartate aminotransferase and alanine aminotransferase levels of 2.5 or fewer times the upper limit of the normal range
✲ Total bilirubin level of 1.5 or fewer times the upper limit of the normal range
✲ Creatinine clearance of ≥ 40 mL/min
✲ Corrected serum calcium level of ≤ 14 mg/dL (≤ 3.5 mmol per litre)
✲ Platelet count of ≥ 70x10⁹/L (if < 50% of bone marrow nucleated cells were plasma cells; otherwise, platelet count of > 50x10⁹/L)
✲ ECOG performance status of 0 to 2</td></tr>
<tr><td>Exclusion</td><td colspan="3">✲ Patients with primary amyloidosis, monoclonal gammopathy of undetermined significance, smouldering MM, Waldenström's macroglobulinaemia (or other conditions in which IgM paraprotein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions
✲ Previous systemic therapy or stem-cell transplantation
✲ Cancer within 3 years before randomisation (exceptions were squamous-cell and basal-cell carcinomas of the skin, carcinoma in situ of the cervix, and any cancer that was considered to be cured with minimal risk of recurrence within 3 years)
✲ Peripheral neuropathy, or grade 2 or higher neuropathic pain (as defined by the NCI CTCAE version 4.0)</td></tr>
<tr><td>Characteristics</td><td>Intervention
(n = 350)</td><td>Control
(n = 356)</td></tr>
<tr><td>Median age (range), years
Distribution, n (%)
< 65 years
65–74 years
≥ 75 years</td><td>71.0 (40–93)

36 (10.3)
210 (60.0)
104 (29.7)</td><td>71.0 (50–91)

24 (6.7)
225 (63.2)
107 (30.1)</td></tr>
<tr><td>Male, n
Female, n</td><td>160
190</td><td>167
189</td></tr>
<tr><td>Race, n (%)
White
Black
Asian
Other or unreported</td><td>
297 (84.9)
3 (0.9)
47 (13.4)
3 (0.9)</td><td>
304 (85.4)
3 (0.8)
45 (12.6)
4 (1.1)</td></tr>
<tr><td>ECOG performance status, n (%)
0
1
2</td><td>
78 (22.3)
182 (52.0)
90 (25.7)</td><td>
99 (27.8)
173 (48.6)
84 (23.6)</td></tr>
</table>

Title: Daratumumab plus bortezomib, melphalan and prednisone for untreated myeloma [13, 17, 18]			
Study identifier	NCT02195479, EudraCT number: 2014-002272-88, ALCYONE trial		
Analysis population *(continuation)*	Type of measurable disease, n (%)		
	IgG	143 (40.9)	140 (39.3)
	IgA	49 (14.0)	53 (14.9)
	Other (including IgD, IgM, IgE, and biclonal)	6 (1.7)	3 (0.8)
	Detected in serum and urine	91 (26.0)	105 (29.5)
	Detected in urine only	43 (12.3)	37 (10.4)
	Detected in serum-free light chains only	18 (5.1)	18 (5.1)
	ISS disease staging, n (%)		
	I	69 (19.7)	67 (18.8)
	II	139 (39.7)	160 (44.9)
	III	142 (40.6)	129 (36.2)
	Cytogenetic profile, n (%)		
	Standard-risk cytogenetic abnormality	261/314 (83.1)	257/302 (85.1)
	High-risk cytogenetic abnormality	53/314 (16.9)	45/302 (14.9)
	Median time since initial diagnosis of MM, months (range)	0.76 (0.1–11.4)	0.82 (0.1–25.3)
Applicability of evidence			
Population	The ALCYONE trial included patients (median age 71.0 years) with newly diagnosed MM who were not eligible for high-dose chemotherapy with stem-cell transplantation. Approximately one third of the patients were older than 75 years. The majority of patients had an ECOG performance status of 1, a standard-risk cytogenetic profile and ISS disease stage of II or III.		
Intervention	The administration of daratumumab in the ALCYONE trial differs from the approved dosing schedule, since one treatment cycle (usually comprising 21 or 28 days) comprises 42 days. The mode of administration and the dosing of daratumumab are consistent with the approved license. All patients of the control group discontinued treatment after nine cycles and all patients of the daratumumab group continued daratumumab as monotherapy.		
Comparators	There is currently no data available comparing daratumumab to another drug in this special setting. The results of NCT03217812, comparing bortezomib, melphalan and prednisone to daratumumab, bortezomib, melphalan and prednisone in patients with previously untreated MM who are ineligible for high-dose chemotherapy, and the results of the MAIA trial (NCT02252172), comparing daratumumab, lenalidomide and dexamethasone versus lenalidomide and dexamethasone in patients with previously untreated MM who are not candidates for high-dose chemotherapy and autologous stem-cell transplantation are awaited for October 2022 and November 2024 respectively.		
Outcomes	There is evidence that the addition of daratumumab to the standard treatment of bortezomib, melphalan and prednisone results in a lower risk of disease progression or death, prolongation of PFS and higher rates of negative status for MRD. Since the ALCYONE trial is ongoing, no data regarding long-term survival is available yet; QoL of patients has been not assessed in the ALCYONE trial. Patients receiving daratumumab have shown higher rates of grade 3 and 4 infections; approximately one third of daratumumab group patients have experienced IRRs.		
Setting	The ALCYONE trial is a multicentre study (162 sites in 25 countries across North and South America, Europe and the Asia-Pacific region) funded by Janssen Research and Development.		

Abbreviations: CR = complete response, CRR = complete response rate, CTCAE = Common Terminology Criteria for Adverse Events, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, Ig = immunoglobulin, ISS = International Staging System, IV = intravenous, MM = multiple myeloma, MRD = minimal residual disease, n = number, NCI = National Cancer Institute, ORR = overall response rate, PFS = progressive-free survival, PR = partial response

Table 5: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [14]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: Patients were randomly assigned by means of an interactive Web-response system in a 1:1 ratio		Yes
Adequate allocation concealment: Web-based randomisation system has been used		Yes
Blinding	**Patient:** open-label	No
	Treating physician: open-label	No
Selective outcome reporting unlikely: Not all of the pre-specified endpoints from the protocol have been reported yet; however, the trial is still ongoing. Reasons for discontinuations have been reported.		Unclear
No other aspects which increase the risk of bias: Janssen Research and Development are sponsoring the trial and designed it in collaboration with the academic authors; data has been compiled and maintained by the sponsor.		No
Risk of bias – study level		High-risk