Daratumumab

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.3. Immunomodulators

ATC codes: L01FC01

Indication	Plasma cell myeloma ICD11 code: 2A83.1
INN	Daratumumab
Medicine type	Biological agent
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 100 mg per 5 mL ; 400 mg per 20 mL
EML status history	Application rejected in 2021 (TRS 1035)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Tags	Cancer
Wikipedia	Daratumumab
DrugBank	Daratumumab

Expert Committee recommendation

The Expert Committee acknowledged that daratumumab was associated with a clinically important survival benefit for patients with multiple myeloma, based on the results reported in the Cochrane systematic review presented in the application. Furthermore, the Committee noted that benefits of daratumumab are observed consistently across all patient subgroups – transplant-eligible newly diagnosed, transplant-ineligible newly diagnose, and relapsed/refractory multiple myeloma. The Committee also noted that the addition of daratumumab to conventional therapy was associated with a modest increase in toxicity. However, the Committee expressed reservations about the maturity of data on overall survival as the follow-up of the main studies is still ongoing. For most trials, follow-up was less than 3 years. The Committee considered that longer follow-up is required to determine the actual magnitude of benefit and its durability. The Committee considered that understanding the full magnitude of benefit (and harms) is required for new cancer medicines in order for recommendations to be made for inclusion of cancer medicines on the Model List, especially in situations where the price is extremely high, where cure is unlikely and where existing alternatives are listed, as is the case for daratumumab. The Committee noted that daratumumab is prohibitively expensive and has not been found to be cost-effective, even in high-income countries. The Committee expressed concern about the potential effect of this medicine on budgets, which would be used as part of regimens that include other expensive essential medicines

recommended in 2019, namely bortezomib and lenalidomide. The Committee considered that it would be helpful to collect information on access to and availability of bortezomib and lenalidomide for multiple myeloma to explore the effect of EML-listing on access to these cancer regimens in countries with different resources and health system capacity. While acknowledging the quality of the application in presenting evidence that demonstrates a major clinical benefit from daratumumab, the Committee nevertheless did not recommend inclusion of daratumumab on the EML at this time because of some uncertainty in the estimates of benefit due to immaturity of the trial data. The Committee requested that an application with updated survival data be submitted for consideration by the Expert Committee in 2023. Without committing a future Expert Committee to a favourable recommendation to include daratumumab on the EML, the Committee recommended that daratumumab be flagged to the Medicines Patent Pool as a candidate for consideration for negotiating public health-oriented licences, noting that negotiating such licences can take some time. The outcome of negotiations might provide important insight for future EML consideration on potential accessibility of this medicine in low- and middle-income countries. In addition, the Committee noted that WHO prequalification processes for monoclonal antibodies for cancer have resulted in prequalification of two molecules – rituximab and trastuzumab. The Committee considered that daratumumab would be a strong candidate for WHO prequalification to facilitate access to affordable and quality-assured products in the event it is listed as an essential medicine. The Committee considered that WHO prequalification and voluntary licence agreements are key actions that could facilitate the current regulatory pathways for approval of daratumumab, either originator or biosimilar, at the country level.

Background

Daratumumab had not previously been considered for inclusion in the EML. Other medicines for the treatment of multiple myeloma were reviewed by the Expert Committee in 2019. The Committee acknowledged the treatment of multiple myeloma to be complex and recognized the need to provide the best available care within the context of both non-transplant and transplant settings. The Committee recommended the addition of bortezomib, lenalidomide and thalidomide to the complementary list of the EML for treatment of multiple myeloma in both non-transplant and transplant eligible/available settings based on good evidence showing large improvements in survival outcomes with acceptable safety for patients with newly diagnosed multiple myeloma. Concerning treatment of multiple myeloma in transplant-eligible populations, the Committee noted the additional evidence presented supporting standard regimens used in the induction phase before autologous stem cell transplantation, which involved three-drug combinations: VTD (bortezomib, thalidomide, dexamethasone), VCD (bortezomib, cyclophosphamide, dexamethasone), PAD (bortezomib, doxorubicin, dexamethasone) and RVD (lenalidomide, bortezomib, dexamethasone). The Committee also noted the benefit of lenalidomide maintenance therapy following autologous stem cell transplantation. In the non-transplant setting, the Committee acknowledged that the proposed medicines are administered as part of treatment regimens including companion cytotoxic agents and/or steroids (melphalan, cyclophosphamide, prednisone and dexamethasone). Accordingly, the Committee recommended the addition of melphalan to the complementary list of the EML for treatment of multiple myeloma, and that the current listings for cyclophosphamide, doxorubicin, prednisone and dexamethasone be extended to include multiple myeloma as an indication (1).

Public health relevance

Multiple myeloma is the second most common haematological cancer with an estimated 176 404 cases and 117 077 deaths worldwide in 2020. In 2020, the age-standardized incidence and mortality rates were 1.9 per 100 000 population and 1.1 per 100 000 population, respectively (2). Between 1990 and 2016, the incidence increased by 126% worldwide, with the largest increase observed in low- and middle-income countries. Incidence is strongly associated with age (3,4). In high-income countries, autologous stem cell transplantation is routinely used for younger patients with a good general state of health. However, autologous stem cell transplantation is not available in many low- and middle-income countries (3). Lack of access to general and specialized health care has led to wide disparities in survival rates between high- and low/middle-income countries. In the United Kingdom of Great Britain and Northern Ireland, 52.3% of patients diagnosed with multiple myeloma are predicted to survive at least 5 years and 29.1% at least 10 years (4). In comparison, a 5-year survival rate of only 7.6% was reported in

Nigeria in a multicentre retrospective study from 2003 to 2012 (5), and of 15.5% in Ghana in a single-centre retrospective study from 2002 to 2016 (6).

Benefits

Transplant-ineligible newly diagnosed multiple myeloma A Cochrane systematic review (in development) evaluated the efficacy and safety of daratumumab in addition to antineoplastic therapy compared with antineoplastic therapy alone in adults with newly diagnosed multiple myeloma who were ineligible for transplant (7). The review included two randomized controlled trials (ALCYONE (8) and MAIA (9), 1443 participants). The overall risk of bias was judged to be high for survival outcomes and quality of life. Median survival was not reached in either group in both studies. The systematic review found moderate-certainty evidence that treatment with daratumumab probably increases overall survival compared with treatment without daratumumab (hazard ratio (HR) 0.67, 95% confidence interval (CI) 0.5 to 0.85). The magnitude of clinical benefit could not be graded for survival because median survival had not yet been reached in either trial. There was moderate-certainty evidence that treatment with daratumumab probably increases progression-free survival compared with treatment without daratumumab (HR 0.48, 95% CI 0.36 to 0.63). 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), using the European Society for Medical Oncology's magnitude of clinical benefit scale (ESMO-MCBS) v1.1. Quality of life was assessed in both trials using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) on a scale of 0 to 100. An increase or decrease from baseline of at least 10 points of global health status was classified as clinically relevant. An increase of at least 10 points was reported for 59.7% of patients in the daratumumab groups and 53.1% of patients in the control groups. Moderate-certainty evidence suggests that more people receiving daratumumab probably gain at least 10 points of global health status after start of treatment compared with people receiving no daratumumab (risk ratio (RR) 1.13, 95% CI 1.13 to 1.23). A decrease of at least 10 points was reported for 38.4% of patients in the daratumumab groups and 37.9% of patients in the control groups. Moderate-certainty evidence suggests that impairment of at least 10 points of global health status at 9 months after start of treatment is probably similar for patients in both groups (RR 1.02, 95% CI 0.89 to 1.16). Transplant-eligible newly diagnosed multiple myeloma Two randomized controlled trials (1744 participants) compared daratumumab with active controls in transplant-eligible participants with newly diagnosed multiple myeloma – CASSIOPEIA (10) and GRIFFIN (11). The CASSIOPEIA study reported overall survival after median follow-up of 18.8 months for 1085 participants. Fourteen participants (2.6%) in the daratumumab group and 32 participants (5.9%) in the control group had died. Median survival was not reached in either group. There is low-certainty evidence that treatment with daratumumab may increase overall survival compared with control (HR 0.52, 95% CI 0.33 to 0.82). The magnitude of clinical benefit could not be graded for overall survival because median survival had not yet been reached in either trial. Median progression-free survival was not reached in either group of both studies (1292 participants). In the CASSIOPEIA trial, at data cut off in May 2019, 79 events (14.5%) of disease progression occurred in the daratumumab group compared with 136 events (25.1%) in the control group. In the GRIFFIN trial, at median follow-up of 22.1 months, four (3.8%) and seven (6.8%) disease-progression events had occurred in the daratumumab and control groups, respectively. There was very-low-certainty evidence that daratumumab treatment may increase progression-free survival compared with control treatment (HR 0.49, 95% CI 0.36 to 0.68). 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. Quality of life was assessed in the CASSIOPEIA trial after up to 9 months of treatment using the EORTC QLQ-C30. An increase in the global health status from baseline by at least 10 points was reported for 38.1% of participants in the daratumumab group and 35.8% in the control group. There was low-certainty evidence that more people receiving daratumumab treatment may gain at least 10 points of global health status compared with those on control treatment (RR 1.07, 95% CI 0.91 to 1.24). A decrease of at least 10 points was reported for 22.1% of participants in the daratumumab group and 25.6% of participants in the control group. There was low-certainty evidence that fewer participants receiving daratumumab compared with control may have a decline of at least 10 points of global health status (RR 0.86, 95% CI 0.70 to 1.07). Relapsed or refractory multiple myeloma Results from four randomized controlled trials (CANDOR (12), CASTOR (13), LEPUS (14) and POLLUX (15); 1308

participants) comparing daratumumab with active controls in participants with relapsed or refractory multiple myeloma were included in a rapid evidence synthesis. The four studies reported overall survival for 1717 participants. Median survival was not reached in either group of the four studies. In the CANDOR trial, 59 participants (19%) died in the daratumumab group and 36 (23%) in the control group at data cut-off in July 2019. In the CASTOR trial, 102 (42.5%) deaths in the daratumumab group and 119 (50.9%) deaths in the control group occurred at the time of analysis in October 2018. The LEPUS trial reported 13 (9%) deaths in the daratumumab group and 18 (26%) deaths in the control group after a median follow-up of 8.2 months (range 0 to 20.5 months). 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. There was moderate-certainty evidence that daratumumab treatment probably increases overall survival compared with control treatment (HR 0.62, 95% CI 0.49 to 0.79). The magnitude of clinical benefit could not be graded for overall survival because median survival had not yet been reached in any of the trials. The four studies reported progression-free survival for 1744 participants. In the CANDOR trial, median progression-free survival was not reached in the daratumumab group and was 15.8 months (95% CI 12.10 months 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 (35%) participants had progressed or died in the daratumumab group versus 68 (44%) participants 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 participants surviving without progression was 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 participants surviving without progression was 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 participants surviving without progression was not reported at a median follow-up of 44.3 months. There was low-certainty evidence that treatment with daratumumab may increase progression-free survival compared with control (HR 0.40, 95% CI 0.29 to 0.56). The magnitude of clinical benefit was graded as 3 out of 4 (progression-free survival benefit compared with comparator HR < 0.65 and estimated progression-free survival gain > 3 months). Quality of life was assessed in two trials (CASTOR, POLLUX; 1067 participants) with the EORTC QLQ-C30. An increase in the global health status from baseline by at least 10 points was reported for 47.7% of participants in the daratumumab groups and 44.5% of participants in the control groups. There was low-certainty evidence that more participants receiving daratumumab may gain at least 10 points of global health status at 9 months after start of treatment compared with participants receiving control treatment (RR 1.07, 95% CI 1.07 to 1.22). A decrease of at least 10 points was reported for 51.4% of participants in the daratumumab groups and 52.3% of participants in the control groups. Low-certainty evidence suggests that impairment of at least 10 points of global health status at 9 months after start of treatment is probably similar for participants in both groups (RR 0.98, 95% CI 0.88 to 1.10).

Harms

Transplant-ineligible newly diagnosed multiple myeloma The ALCYONE and MAIA trials reported adverse events for 1429 participants (8,9). Common Terminology Criteria for Adverse Events grade ≥ 3 adverse events were seen in 86% of participants in the daratumumab groups and in 82% of participants in the control groups. There was high-certainty evidence that treatment with daratumumab results in a slight increase in adverse events of grade ≥ 3 compared with controls (RR 1.05, 95% CI 1.0 to 1.11). Serious adverse events were observed in 56% of participants in the daratumumab groups and in 51% of participants in the control groups. There was very-low-certainty evidence that treatment with daratumumab may increase serious adverse events compared with control treatment (RR 1.14, 95% CI 0.86 to 1.51). Both studies also reported on infections and parasitic diseases. These were observed in 30% of participants in the daratumumab groups and in 21% of participants in the control groups. There was high-certainty evidence that treatment with daratumumab increases infections and parasitic diseases compared with controls (RR 1.42, 95% CI 1.19 to 1.70). In addition, pneumonia was observed in 14% and 7% of participants in the daratumumab and control groups, respectively. There was moderate-certainty evidence that treatment with daratumumab probably increases pneumonia compared with control (RR 2.16, 95% CI 1.15 to

4.06). Transplant-eligible newly diagnosed multiple myeloma The CASSIOPEIA trial reported adverse events of grade ≥ 3 for 1429 participants (10). Grade ≥ 3 adverse events were observed in 81% of participants in the daratumumab group and in 76% of participants in the control group. There was high-certainty evidence that treatment with daratumumab results in a slight increase in adverse events of grade ≥ 3 compared with controls (RR 1.06, 95% CI 1.0 to 1.13). Both the CASSIOPEIA and GRIFFIN trials reported serious adverse events, infections and parasitic diseases and pneumonia for 1275 participants (10,11). Serious adverse events were observed in 46% of participants in the daratumumab groups and in 48% of participants in the control groups. There was low-certainty evidence that participants treated with daratumumab may experience fewer serious adverse events compared with participants on control treatment (RR 0.94, 95% CI 0.73 to 1.14). Infections and parasitic diseases were observed in 22% of participants in the daratumumab groups and in 20% of participants in the control groups. There was moderate-certainty evidence that treatment with daratumumab probably increases infections and parasitic diseases compared with controls (RR 1.12, 95% CI 0.90 to 1.39). In addition, pneumonia was observed in about 4% of participants in both treatment groups. There was moderate-certainty evidence that treatment with daratumumab may result in little to no difference in pneumonia compared with control treatment (RR 1.05, 95% CI 0.60 to 1.84). Relapsed or refractory multiple myeloma The CASTOR and POLLUX studies reported adverse events of grade ≥ 3 for 1429 participants (13,15). Grade ≥ 3 adverse events were observed in 81% of participants in the daratumumab groups and 70% of participants in the control groups. There was moderate-certainty evidence that treatment with daratumumab results in a slight increase in adverse events of grade ≥ 3 compared with control treatment (RR 1.17, 95% CI 1.04 to 1.31). The CANDOR, CASTOR, LEPUS and POLLUX studies reported serious adverse events for 1713 participants (12–15). Serious adverse events were observed in 49% of participants in the daratumumab groups and in 40% of participants in the control groups. There was moderate-certainty evidence that daratumumab may increase serious adverse events compared with control (RR 1.21, 95% CI 1.09 to 1.35). Data on infections were reported heterogeneously across the trials and were not pooled. The CANDOR and POLLUX trials reported on upper respiratory tract infections. In the CANDOR trial, events for grade 3 and 4 adverse events were reported separately. In the daratumumab group, seven (2%) grade 3 adverse events and one (< 1%) grade 4 upper respiratory tract infections occurred compared with two grade 3 (1%) and no grade 4 events in the control group. In the POLLUX trial, three grade 3 or 4 (1%) upper respiratory tract infections occurred in the daratumumab and in the control group. Grade 3 or 4 treatment emergent events of upper respiratory tract infections were reported in the CASTOR trial (six (3%) in the daratumumab group versus one (0.4%) in the control group) and in the LEPUS trial (20 (14%) in the daratumumab group versus three (4%) in the control group). The CASTOR and POLLUX studies reported data on pneumonia for 1044 participants. Pneumonia was observed in 13% of participants in the daratumumab groups and 10% of participants in the control groups. There was low-certainty evidence that treatment with daratumumab may increase pneumonia compared with controls (RR 1.28, 95% CI 0.86 to 1.90).

Cost / cost effectiveness

The application presented the findings of a scoping review that identified two cost analyses (16,17), two health technology assessments (18,19) and four cost–effectiveness studies (20–23) of daratumumab as monotherapy or in combination with bortezomib or lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma. Characteristics of the included studies and health technology assessments varied widely, especially regarding patient population (prior lines of therapy ranged from one to a median of five) and time horizon (3 years to life-time horizon). Cost analyses reported average costs per patient per year in excess of US$ 165 000, with drug acquisitions costs the main driver. Cost–effectiveness analyses reported incremental cost–effectiveness ratios versus different comparators ranging from US$ 30 000 to over US$ 1 million per quality adjusted life year.

WHO guidelines

WHO guidelines for the treatment of multiple myeloma are not available.

Availability

Daratumumab has regulatory approval in many countries including Australia, Canada, Europe, Japan and the

United States for use as monotherapy, or in combination with other medicines, for treatment of newly diagnosed or relapsed/refractory multiple myeloma. It has primary patent protection until 2036.

Other considerations

The EML Cancer Medicines Working Group advised that it did not support the inclusion of daratumumab on the EML for treatment of multiple myeloma at this time. The Working Group considered that use of daratumumab would be of greatest value for treatment of patients with newly diagnosed multiple myeloma who are not eligible for transplant. However, the Working Group noted that mature, long-term overall survival data for daratumumab are not yet available in any of the three treatment settings proposed. The Working Group also noted the increased toxicity and high costs associated with daratumumab treatment and toxicity management. The Committee noted the report of the Medicines Patent Pool that highlighted how the times from starting negotiations to close of agreement for voluntary licences and from licence to access can be long. Typically, it has taken generic manufacturers 3 to 4 years to develop a generic version of a new medicine and obtain approval from a regulatory authority or from WHO Prequalification. This time can be even longer for biological medicines, which require more lengthy and costly development and manufacturing processes. In addition, patents on the active ingredient, the formulations, the manufacturing processes and trade secrets are particularly important with biotherapeutic medicines. With few exceptions, the current regulatory pathways for approval of biosimilars by regulatory agencies are longer and considerably more costly than those for small molecule generics. Comments were received from the WHO Department Noncommunicable Diseases. The technical department advised that while there were some data to support daratumumab's clinical value, there are insufficient mature overall survival data available to fully justify its inclusion in the EML. Furthermore, the toxicity profile must also be considered.

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