

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma

Technology appraisal guidance

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Your responsibility

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

- 1.1 Daratumumab monotherapy is recommended for use within the Cancer Drugs Fund as an option for treating relapsed and refractory multiple myeloma in adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last therapy, only if:
- they have daratumumab after 3 previous therapies and
 - the conditions in the [managed access agreement](#) are followed.
- 1.2 This recommendation is not intended to affect treatment with daratumumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 Information about daratumumab

Description of the technology	Daratumumab (Darzalex, Janssen) is a humanised monoclonal antibody that targets the CD38 protein, thereby killing multiple myeloma cells. It is given intravenously.
Marketing authorisation indication	Daratumumab has a marketing authorisation in the UK for treating adults with 'relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy'.
Adverse reactions	The most common adverse reactions are infusion-related reactions including throat irritation, dyspnoea, nausea and cough. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Dosage in the marketing authorisation	The recommended dose of daratumumab is 16 mg/kg body weight given by intravenous infusion weekly from weeks 1 to 8, every 2 weeks from weeks 9 to 24, and every 4 weeks from week 25 onwards until disease progression.
Price	<p>The list price for daratumumab is £360.00 for the 100-mg vial and £1,440.00 for the 400-mg vial (excluding VAT). Assuming an average body weight of 73.91 kg, and an average treatment duration of 3.4 months, the cost of a course of treatment is £68,862 excluding administration costs, and £74,531 including administration costs.</p> <p>The company had agreed a patient access scheme with the Department of Health. However, the managed access agreement agreed between the company and NHS England has replaced this patient access scheme.</p>

3 Evidence

The appraisal committee (see [section 6](#)) considered evidence submitted by Janssen and a review of this submission by the evidence review group. See the [committee papers](#) for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of daratumumab, having considered evidence on the nature of multiple myeloma and the value placed on the benefits of daratumumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Nature of the condition

4.1 The committee was aware that multiple myeloma is a chronic condition that affects survival and quality of life. It understood that when deciding which treatments to use, response to previous treatments and toxicity are important, so having a range of treatment options is desirable. The committee recognised that few options are available after NICE-recommended treatments (thalidomide, bortezomib and lenalidomide), which makes people anxious about their disease relapsing. The patient experts highlighted the psychological benefits of a treatment that might be more effective than existing options. Also, its favourable toxicity profile might mean more options later in the treatment pathway. They also stressed the importance of quality of life after multiple lines of therapy because the adverse effects of treatment can build up over time. The committee recognised the need for effective, well-tolerated treatment options for people with multiple myeloma who have had previous therapies.

Clinical pathway

4.2 The committee discussed at which stage of therapy daratumumab would be used. It was aware that the marketing authorisation for daratumumab specifies previous treatment with a proteasome inhibitor and an immunomodulator, but does not specify the number of previous treatments. The company proposed that daratumumab is used after 3 previous treatments, that is, as a fourth-line treatment. The clinical experts also stated that they were likely to use daratumumab after 3 previous treatments. The committee concluded that it would appraise daratumumab at this point in the treatment pathway.

4.3 The committee considered the current treatment pathway for people with multiple myeloma, and what the comparators should be for daratumumab, that is, what treatments are currently offered fourth line in the NHS. It heard from the clinical experts that there are many possible sequences of treatments:

- The first treatment is either thalidomide (an immunomodulator) or bortezomib (a proteasome inhibitor), plus an alkylating agent (for example, melphalan or chlorambucil) and a corticosteroid (for example, dexamethasone), as recommended in NICE's technology appraisal guidance on [bortezomib and thalidomide for the first-line treatment of multiple myeloma](#).
- If treatment is not successful, people may have bortezomib as described in NICE's technology appraisal guidance on [bortezomib monotherapy for relapsed multiple myeloma](#).
- If these 2 lines of treatment are not successful, NICE's technology appraisal guidance recommends at third-line [lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy](#).
- As fourth-line treatment, the committee heard from the clinical experts that in clinical practice, they would offer [panobinostat plus bortezomib and dexamethasone](#), or [pomalidomide plus dexamethasone](#), as recommended in NICE guidance. Consultation comments suggested that bendamustine, listed as a comparator in the final scope, was also used as a fourth-line treatment. The committee heard from the clinical experts that bendamustine would be used as a last resort. Furthermore, it understood that bendamustine has a marketing authorisation for multiple myeloma only as a first-line treatment. Although available on the Cancer Drugs Fund for relapsed disease when all other treatments are contraindicated or inappropriate (off-label use), it was not routinely commissioned for this indication.
- At fifth line, the committee understood that few people reach this stage, and there is no standard of care.

The committee concluded that, because daratumumab would be used after 3 previous treatments (see [section 4.2](#)), the appropriate comparators were pomalidomide plus dexamethasone, and panobinostat plus bortezomib plus dexamethasone.

Clinical effectiveness

Clinical trials

4.4 The evidence on the clinical effectiveness of daratumumab came from 2 single-arm clinical trials, MMY2002 and GEN501:

- MMY2002 (n=124) was a phase II study investigating different doses of daratumumab;

- 106 patients had the licensed dose. The primary outcome was overall response rate. Overall survival and progression-free survival were among the secondary outcomes.
- GEN501 (n=72) was a phase I and II 2-part non-randomised study. During part 1, the dose was increased; during part 2, 42 of the 72 patients had the licensed dose of daratumumab. The primary outcome was the frequency and severity of adverse events. Overall survival and progression-free survival were among the secondary outcomes.

The committee noted that few patients in both trials had the licensed dose of daratumumab (16 mg/kg). It also noted that the data on overall survival were immature, with over 50% of patients alive at the end of the trials (median follow-up 20.7 months). In response to consultation, the company submitted more mature data providing an additional 10 months of follow-up (median follow-up 31.3 months). The committee welcomed the availability of new, more mature data, although it noted that these remained relatively immature, with 42% of patients alive at the end of the trials.

Treatments received before daratumumab

4.5 The committee was aware that patients in MMY2002 and GEN501 had a median of 5 and 4 treatments respectively, before having daratumumab. The clinical experts commented that this reflected clinical practice. Some patients had as few as 2 previous treatments, and some had as many as 14 previous treatments. The committee considered that patients who had so few or so many previous treatments did not reflect the place of daratumumab in clinical practice (after 3 previous treatments). The committee heard from the company that only a small number of patients had 2 or 14 previous treatments, and the number of previous treatments is just one of many factors influencing prognosis (see [section 4.1](#)). The company also noted that 73% of patients across the 2 trials had more than 3 previous treatments. Because of this, it argued that outcomes would improve in the less heavily pre-treated population seen in clinical practice who would have had only 3 previous treatments. The committee concluded that both trial populations did not fully reflect the place of daratumumab in NHS clinical practice (after 3 previous treatments), and that it was plausible that the number of previous therapies may affect survival, and therefore the effectiveness of daratumumab.

4.6 The committee discussed the treatments that patients had before daratumumab in the trials:

- Carfilzomib (MMY2002 50%, GEN501 19%): the committee was aware that carfilzomib was not available to patients in the NHS at this stage of treatment.
- Pomalidomide plus dexamethasone (MMY2002 63%, GEN501 36%): NICE recommends pomalidomide plus low-dose dexamethasone at third or subsequent relapse; that is, after at least 3 previous treatments including both lenalidomide and bortezomib. The committee agreed that, in NHS clinical practice, people were unlikely to have had pomalidomide plus dexamethasone before daratumumab because both treatments were likely to be used fourth line. It also heard from the evidence review group (ERG) that, because pomalidomide plus dexamethasone is an alternative treatment to daratumumab, it would be more appropriate to consider people who had not previously had pomalidomide plus dexamethasone as the relevant population.
- Thalidomide (MMY2002 47%, GEN501 45%): the committee heard from the clinical experts that the trials under-represented the proportion of patients in the NHS who would have had previous treatment with thalidomide.

The committee concluded that some of the previous treatments used in the trials were not available in the NHS, and therefore the generalisability of the effect of daratumumab to clinical practice was uncertain.

Proportion of people having treatment after daratumumab

- 4.7 The committee noted that 71% and 76% of patients in MMY2002 and GEN501 respectively had other treatments after daratumumab. It also noted that a high proportion of patients whose disease had not responded to both a proteasome inhibitor and an immunomodulator (MMY2002 95%, GEN501 64%) went on to have a proteasome inhibitor and an immunomodulator after daratumumab. Comments from the NHS England clinical lead suggested that this reflected a fit patient population. Conversely, the company suggested that it reflects daratumumab's favourable safety profile, which allows more people to have subsequent therapy than other less well-tolerated alternatives. The committee, however, did not see any evidence from the company to support this claim. The clinical experts speculated that the proportion of people who have fifth-line treatment in the NHS was likely to be much lower (about 10%) than in the clinical trials. The comments from the NHS England clinical lead also confirmed this difference. The committee concluded that patients in the clinical trials were more likely to have fifth- or subsequent-line treatment, and may have been fitter than people having treatment in the NHS.

Pooled data

- 4.8 The committee noted that the company pooled data from MMY2002 and GEN501 without adjusting for differences in the trial populations. The ERG did not consider this appropriate because the 2 trial populations differed, most importantly, in the median number of lines of previous therapy, and in the proportion of patients whose disease was refractory to the last treatment. Given the small sample size of the studies, and the limited data available, the committee considered that it would be useful to use all available data. However, it concluded that pooling data was not appropriate because the populations in MMY2002 and GEN501 differed.
- 4.9 The committee discussed whether MMY2002 or GEN501 was a more appropriate source of evidence on the clinical effectiveness of daratumumab. It noted that the marketing authorisation for daratumumab states that the disease should have progressed on the last therapy for the person to have daratumumab. This occurred in 99% of patients in MMY2002 and 83% in GEN501. The committee agreed that MMY2002 matched the marketing authorisation more closely, and so represented a more appropriate source of evidence for decision-making.

Matching-adjusted indirect comparisons

- 4.10 To compare daratumumab with pomalidomide plus dexamethasone and with panobinostat with bortezomib and dexamethasone in the absence of a common comparator (an 'anchor'), the company presented 'unanchored' matching-adjusted indirect comparisons (MAICs). Specifically, it adjusted individual patient-level characteristics in the MMY2002 and GEN501 pooled population to match the published study-level summary characteristics of patients in the comparator trials (1 of 2 arms of the MM-003 trial for pomalidomide plus dexamethasone, and the single-arm trial PANORAMA-2 for panobinostat plus bortezomib plus dexamethasone).
- 4.11 The committee discussed the company's approach to matching. It understood that the company adjusted for the characteristics it considered important in predicting progression and death based on best practice, published evidence, and expert opinion. For pomalidomide plus dexamethasone, 11 characteristics were adjusted. For panobinostat plus bortezomib plus dexamethasone, 5 characteristics were adjusted. The ERG did not agree with how the company

selected the characteristics because a technical support document published by the Decision Support Unit recommends that, when only single-arm trial data are available, all the characteristics that could influence the outcomes of interest should be adjusted. Because of this, the ERG preferred using MMY2002, which allows adjusting for more characteristics than the pooled dataset. In response to consultation, the company presented a sensitivity analysis in which it adjusted for all possible characteristics in the MMY2002 population only (26 characteristics adjusted), although it maintained that using the pooled dataset is preferable because this increases the size of the matched population, thus reducing uncertainty. However, the committee preferred adjusting for more characteristics, although it appreciated that there would be unobserved differences between trial populations that would not be accounted for, which, if also associated with progression or death, would bias the estimates of relative effectiveness.

- 4.12 The committee noted that the ERG investigated the effect of adjusting all characteristics with available data on the effectiveness of daratumumab. It agreed that the ERG's exploratory analysis highlighted the high degree of uncertainty in the results of the MAIC. Specifically, the effect of daratumumab on progression-free survival reversed (that is, went from being more effective than the comparator to being less effective, or the other way round) when adjusting for all characteristics in the MMY2002 population (ERG's analysis) compared with adjusting only for some characteristics in the pooled population (company's original base case). The committee agreed that all the estimates were unreliable. To characterise the uncertainty, the committee considered that the company could validate the results of the MAIC with data from the International Myeloma Foundation chart review. However, the company stated, in response to consultation, that there were no established methods to do so. Instead, it did a multivariate regression analysis of individual patient-level data from the pooled population for daratumumab, and of data from the International Myeloma Foundation chart review for pomalidomide plus dexamethasone to estimate hazard ratios comparing these 2 treatments. It then compared these hazard ratios with those estimated from the MAIC. The ERG considered that multivariate regression and MAIC were very different methods, and so it was inappropriate to use the multivariate regression to validate the results of the MAIC. The committee concluded that it could not establish whether the relative effectiveness of daratumumab against the comparator treatments reflected what would be seen in the NHS.

Treatments received after daratumumab and their impact on overall survival

- 4.13 The committee noted that, in MMY2002 and GEN501, treatments taken after daratumumab included dexamethasone, pomalidomide, cyclophosphamide, carfilzomib, bortezomib and lenalidomide, many of which were either not available in the NHS (for example, carfilzomib), or not available at this point in the treatment pathway (for example, lenalidomide and bortezomib). The committee agreed that the treatments that patients had after daratumumab in MMY2002 and GEN501 did not represent what would be offered in the NHS. It would have preferred to have seen estimates that adjusted for the effect of plausibly life-extending treatments that were not available in the NHS.
- 4.14 The committee considered the impact of the therapies taken after stopping daratumumab on the survival estimates reported in MMY2002 and GEN501. The committee was aware that many of these therapies prolonged life when used earlier in the treatment pathway, and were likely to prolong life when used after daratumumab. The committee understood that, based on the data cut of December 2015, daratumumab was associated with a relatively short median progression-free survival (MMY2002; 3.7 months, GEN501 part 2; 6.2 months), but a relatively longer median overall survival (MMY2002; 18.6 months, GEN501 part 2; not reached). In the more recent data cut (see [section 4.4](#)), median overall survival was 20.5 months in the pooled population. The ERG looked at how long patients in the trials lived depending on which, if any, therapy they had after daratumumab.
- The committee interpreted these data as showing that treatment after daratumumab prolonged life, and that the impact of treatments on overall survival varied from 1 treatment to the other. It was unclear to the committee whether there were other important differences between the groups of patients who had different therapies after daratumumab, which may have confounded the estimates of overall survival.
 - By contrast, the company considered these data to be biased because patients had to have lived long enough to have subsequent therapy, and because the company considered that daratumumab 'resets' the disease process to make subsequent treatments more effective than they would have been without daratumumab. The company considered that, to understand the effect of subsequent therapy, it would be more reasonable to look at the response to treatments taken directly after daratumumab that patients had already had before daratumumab and to which their disease was refractory. The response rate to these treatments, when taken after

- daratumumab, was 39%. The company took this as evidence to support the hypothesis that the treatment effect of daratumumab extends beyond direct tumour action to enhance the person's immune system and sensitise them to subsequent treatment, particularly immunomodulators (such as pomalidomide).
- The committee considered that it had not seen any empirical evidence to suggest that daratumumab improved response to subsequent therapy, and it heard from clinical experts that the synergistic, immune-mediated relationship between daratumumab and immunomodulators put forward by the company was unproven.

The committee concluded that the absolute life expectancy seen in clinical trials was likely to overestimate the overall survival benefit of daratumumab were it used in the NHS.

4.15 In response to consultation, the company disagreed that overall survival was confounded by subsequent treatment. It noted that there were 3 groups of patients who had daratumumab:

- patients whose disease did not respond to daratumumab and who died without having subsequent treatment
- patients whose disease responded to daratumumab and who continued to have it
- patients whose disease progressed while having daratumumab and who had treatment after daratumumab.

The company stated that the first 2 groups did not have subsequent treatment, so overall survival could not have been confounded in these groups. It reiterated that the third group was able to have subsequent treatment because of daratumumab's mechanism of action, but the committee recalled that it had not seen evidence about this (see [section 4.7](#)). The ERG agreed that these groups, although of potential interest, were of limited use without information from the same groups who had the comparator treatments. The committee concluded that it had not seen new evidence to change its previous conclusion about the effect of subsequent therapies (see [section 4.14](#)).

Treatments received after pomalidomide in MM-003

4.16 The committee discussed the possible confounding effect of subsequent therapies in the trial of the comparator treatment pomalidomide plus

dexamethasone (MM-003). The committee agreed that the estimate of overall survival for pomalidomide plus dexamethasone was less confounded than that for daratumumab. This is because a smaller proportion of patients had therapies after pomalidomide plus dexamethasone (44%) in MM-003 than after daratumumab (72%) in MMY2002 and GEN501. Of patients who had treatment after pomalidomide plus dexamethasone, a smaller proportion had subsequent carfilzomib, lenalidomide and bortezomib, which are not available in the NHS at that stage in therapy, than those who had treatment after daratumumab (MM-003; 2%, 5%, 18% compared with MMY2002 and GEN501 pooled data; 28%, 15%, 24% respectively). In addition, no one in MM-003 had subsequent pomalidomide plus dexamethasone, whereas 31% of the pooled daratumumab population did. In response to consultation, again the company disagreed that overall survival was less confounded for pomalidomide plus dexamethasone than for daratumumab. It stated that the 2 trial populations were similar, and so the increased proportion of patients on subsequent treatment in the daratumumab trial compared with MM-003 is because more people are able to have subsequent treatment after daratumumab than after pomalidomide plus dexamethasone. However, the committee had not seen proof of this hypothesis. The committee concluded that the evidence for the effectiveness of pomalidomide plus dexamethasone was less confounded by subsequent treatment than that for daratumumab.

Conclusion on clinical effectiveness

4.17 The committee noted these issues with the evidence on whether daratumumab was more effective than current options in the NHS:

- data limited to single-arm trials (see [section 4.4](#))
- small numbers of patients on the licensed dose of daratumumab (see [section 4.4](#))
- immature data on overall survival (see [section 4.4](#))
- mismatch between the populations in the 2 daratumumab trials, MMY2002 and GEN501 (see [section 4.8](#))
- poor generalisability of the trial results to people who would have daratumumab in the NHS because of differences in:
 - treatments taken before daratumumab (see [sections 4.5 and 4.6](#))

- – treatments taken after daratumumab, and their confounding effect (see [sections 4.13 to 4.16](#))
 - the fitness of patients (see [section 4.7](#))
- high degree of uncertainty in the relative effect estimates produced by the MAIC relating to:
 - the number of characteristics adjusted (see [sections 4.11 and 4.12](#))
 - the lack of cross validation of the MAIC estimates with other sources (see [section 4.12](#)).

Overall, the committee was concerned about the quality and validity of the available evidence, which meant that it could not fully interpret the clinical effectiveness of daratumumab. However, it acknowledged comments from clinical and patient experts on the possible benefits of daratumumab, and agreed that there was potential for daratumumab to be clinically effective compared with current treatment options.

Cost effectiveness

- 4.18 The company used a 4-state, partitioned-survival economic model, including states representing pre-progressed disease on treatment, pre-progressed disease off treatment, progressed disease and death. The committee noted that this model was similar to previous models used for multiple myeloma, and agreed that it was appropriate to capture the natural history of the disease. However, the committee agreed that the model reflected the limitations of the clinical effectiveness data (see [section 4.17](#)). As a result, the model output was of limited use in estimating the cost effectiveness of daratumumab.

Modelling of overall survival and progression-free survival

- 4.19 The committee was aware that the company did not use the updated data in the survival modelling (see [section 4.14](#)). The original data on overall survival from MMY2002 and GEN501 were immature (see [section 4.4](#)). This meant that the company extrapolated overall survival for a large proportion of patients (over 40%), based on few patients at risk of dying at the end of the trial (16 patients at 24 months, and 3 patients at 26 months), up to the end of the time horizon. This created considerable uncertainty about the long-term effect of daratumumab.

In response to consultation, the company modelled a scenario assuming that daratumumab does not provide further survival benefit relative to the comparator beyond the trial follow-up. The committee agreed that this scenario was useful to characterise the uncertainty in the long-term effect of daratumumab. However, it considered that because the trial data were immature, and the company based the extrapolation on a small proportion of patients who had died, the degree of uncertainty in the modelling was still high.

4.20 The committee considered how the company modelled the clinical effectiveness of daratumumab and its comparators. First, the company fitted parametric distributions to the Kaplan–Meier data on overall survival and progression-free survival pooled across MMY2002 and GEN501. This estimated overall survival and progression-free survival curves for daratumumab. Then, to generate survival curves for pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone, the company applied the hazard ratios for each of these treatments relative to daratumumab estimated from the MAIC to the survival curves for daratumumab. The committee recognised that the hazard ratios for pomalidomide plus dexamethasone, and panobinostat plus bortezomib plus dexamethasone were not comparable because they reflected the effect of each of these treatments relative to daratumumab in different trial populations (the relevant comparator trial populations; MM-003 for pomalidomide plus dexamethasone, and PANORAMA-2 for panobinostat plus bortezomib plus dexamethasone). The committee concluded that, because of the limitations in the evidence base (see [section 4.17](#)), the company's comparisons were unreliable.

4.21 The committee noted that the hazard ratios in the MAIC reflecting comparative effectiveness were highly sensitive to changes in the number of characteristics matched. For example, when the ERG estimated incremental cost-effectiveness ratios (ICERs) using a hazard ratio from a 'fully-adjusted' MAIC for overall survival, the ICER for daratumumab compared with panobinostat plus bortezomib plus dexamethasone increased relative to the base case, whereas the ICER for daratumumab compared with pomalidomide plus dexamethasone decreased. The committee agreed that this added to the uncertainty associated with the hazard ratios estimated from the MAIC.

4.22 The committee noted that the company's survival model (see [section 4.20](#)) depended on proportional hazards between treatments. The ERG did not agree

that the proportional hazards assumption held because its analysis of the log-log plots for overall survival showed crossing curves. Because of this, the ERG preferred fitting distributions independently for daratumumab and the comparators, rather than generating the survival curves for the comparators from the daratumumab curves, to avoid assuming proportional hazards. The committee commented that statistical testing for proportional hazards is normally relevant in randomised controlled trials in which the groups are the same except for treatment. In this appraisal, the log-log plots compared curves from 2 different trials (MMY2002/GEN501 and MM-003). So, the shape of these plots might change if the characteristics of patients in these populations were more balanced. The committee concluded that the evidence was insufficient to determine whether proportional hazards held or not.

Utility values

- 4.23 The committee was aware that the early phase trials presented by the company did not collect health-related quality-of-life data to estimate utility. In response to consultation, the company submitted utility data from an ongoing observational study providing early access to daratumumab for patients with relapsed or refractory multiple myeloma who had at least 3 previous lines of therapy. The company estimated utility values only from patients who were recruited in the NHS (n=90). Based on the average change in utility before and after daratumumab, the company included a utility increment of 0.04 in the model to reflect the additional benefit of daratumumab on quality of life. The ERG noted that the company had not investigated whether this utility increment was statistically significant or not, and it was not possible to tell whether the potential utility benefit would occur even without treatment with daratumumab because there was no comparator group in the study. The committee concluded that it could accept the company's utility increment reflecting the benefit of daratumumab on health-related quality of life.

Cost of treatment in the model

- 4.24 The committee noted that the company estimated the cost of daratumumab and its comparators based on the time from starting to stopping each treatment, as opposed to progression-free survival. The ERG agreed that using time to stopping treatment was appropriate, but stated that the company did not explain the 'calibration method' it used to estimate time to stopping treatment for pomalidomide plus dexamethasone. The committee understood from the

company that the calibration method involved adjusting the time to stopping treatment curve for daratumumab to match the mean and median time to stopping treatment for pomalidomide plus dexamethasone in MM-003. The committee heard from the clinical experts that in multiple myeloma, progression-free survival does not always reflect treatment duration, because people may continue treatment after disease progression, or stop treatment before disease progression, for example, because of adverse events. The committee concluded that it preferred using time to stopping treatment to estimate costs. But it agreed that the company, having modified an observed outcome for 1 treatment to estimate this outcome for another treatment and not having provided full details of its methods, produced results that were potentially unreliable.

- 4.25 The committee discussed the costs of subsequent treatments in the model, noting that the company had not reflected the subsequent treatments reported in the trials in its modelling. Instead, it modelled treatments available in the UK. This meant that the company's model reflected the benefits of the subsequent therapies in the trials, but not the costs associated with them. The committee did not agree with this. It recalled that most people would not have active treatment after daratumumab in NHS clinical practice (see [section 4.13](#)). In response to consultation, the company included the costs of all subsequent treatments available in the trials in a scenario analysis. The committee preferred adjusting the treatment effect and costs to reflect therapies that would be used in NHS clinical practice.

Cost-effectiveness results

- 4.26 The committee considered the company's revised analyses submitted during consultation. Although the committee agreed that these addressed some of its original concerns about the modelling, it remained concerned about some of the company's assumptions in the model; mainly, the extrapolation of overall survival (see [section 4.19](#)), and the use of hazard ratios reflecting treatment effects in different trial populations (see [section 4.20](#)). The committee concluded that it was primarily concerned about the underlying issues with the clinical data.
- 4.27 The committee considered the company's and the ERG's cost-effectiveness results, including confidential discounts for all comparator technologies. It

noted that the ICERs for daratumumab compared with pomalidomide plus dexamethasone, and with panobinostat plus bortezomib and dexamethasone, varied widely. This reflected the high degree of uncertainty in daratumumab's clinical effectiveness compared with current NHS treatments. The committee agreed that the degree of uncertainty in the current evidence was too high for it to be able to identify a most plausible ICER for decision-making. It considered that the scope of any further revisions to the modelling would be limited, and would not strengthen the evidence such that the committee would have enough confidence in the results to make decisions. The committee concluded that it could not recommend daratumumab as a cost-effective use of NHS resources.

Innovation

4.28 The committee understood that daratumumab was the first monoclonal antibody with a significant effect in people with multiple myeloma. The clinical experts considered it a major change in managing myeloma given its activity in a heavily pre-treated population, and favourable toxicity profile. They also noted that daratumumab is given as monotherapy without corticosteroids, which are associated with adverse effects. The committee also noted that most consultation comments regarded daratumumab as an important treatment offering a major change in management because of its perceived benefits on survival and quality of life at a relatively late stage of the disease, its new mechanism of action, and its favourable safety profile. The committee recognised that people whose disease has progressed after 3 previous lines of therapy have a poor prognosis, limited treatment options, and a high clinical unmet need, which daratumumab might help address. The committee was aware that daratumumab is administered by intravenous infusion, whereas pomalidomide plus dexamethasone is taken orally. It heard that intravenous administration is associated with time spent in hospital and discomfort, which may not be captured by the model. The committee concluded that it did not see evidence that daratumumab has demonstrable and distinctive benefits of a substantial nature other than those already captured in the quality-adjusted life year (QALY) measure.

End-of-life considerations

4.29 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [final Cancer Drugs Fund](#)

[technology appraisal process and methods](#).

- 4.30 The committee considered life expectancy for people with relapsed and refractory multiple myeloma and was satisfied that it was less than 24 months. The committee was unable to conclude whether the criterion of at least a 3-month life extension was met because the evidence on the relative effectiveness of daratumumab and the survival modelling did not permit this. The committee concluded that it could not make an informed decision as to whether daratumumab meets the criteria for life-extending treatments for people with a short life expectancy.

Cancer Drugs Fund considerations

- 4.31 Having concluded that it could not recommend daratumumab for routine use within its marketing authorisation for treating relapsed and refractory multiple myeloma in adults, the committee then considered if daratumumab could be recommended within the Cancer Drugs Fund. The committee discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England, noting the [addendum to the NICE process and methods guides](#). The committee was aware that, to recommend a drug for use within the Cancer Drugs Fund, there has to be significant remaining clinical uncertainty which needs more investigation (through data collection or clinical studies), and the drug has to have plausible potential to satisfy the criteria for routine commissioning.
- 4.32 The committee recalled the issues surrounding the clinical evidence (see [section 4.17](#)). It considered that collecting data through the Cancer Drugs Fund would provide evidence in a population reflecting NHS practice. This would reduce uncertainties about:
- the small number of patients who had the licensed dose of daratumumab in the clinical trials
 - treatments taken before daratumumab
 - treatments taken after daratumumab and their effect on overall survival
 - the fitness of people who have daratumumab and
 - possibly, the immaturity of the data on overall survival.

- As a result, the additional data, together with the data being collected within the Early Access programme (MMY3010; NCT02477891) would provide more robust evidence on the clinical effectiveness of daratumumab. This is because this evidence would include a larger number of patients whose underlying survival trend reflects that of NHS patients, and who had treatment long enough to detect meaningful effects, including those of treatments given in the NHS after daratumumab. The committee was aware that uncertainty would remain about comparative effectiveness because the Cancer Drugs Fund would provide only observational data for daratumumab and not the comparators. Nevertheless, the committee concluded that, on balance, the benefit of collecting further data would enhance the evidence for daratumumab while providing it to NHS patients until daratumumab's clinical and cost effectiveness could be reappraised based on new clinical evidence.

4.33 The committee discussed whether there was potential for daratumumab to be cost effective at its current price. It recalled its conclusion that the current cost-effectiveness results were unreliable, but given the range of ICERs presented to the committee, it considered that if daratumumab was shown to have a level of clinical benefit comparable with the upper end of the range of estimates presented, it has the potential to be cost effective compared with pomalidomide plus dexamethasone, and with panobinostat plus bortezomib and dexamethasone at its current price. The committee concluded that daratumumab met the criteria for inclusion in the Cancer Drugs Fund. It recommended daratumumab as an option for use within the Cancer Drugs Fund for adults with relapsed and refractory multiple myeloma, whose therapy included a proteasome inhibitor and an immunomodulator, and whose disease has progressed on the last therapy.

4.34 The committee recommended collecting data for adults with relapsed and refractory multiple myeloma who have had 3 prior therapies including a proteasome inhibitor and an immunomodulator, and whose disease has progressed on the last therapy. It recommended collecting data through the Cancer Drugs Fund on:

- overall survival
- progression-free survival and
- time to stopping treatment (duration of treatment).

- The committee considered that to inform future indirect comparisons, the Cancer Drugs Fund should also collect data on the following characteristics:
- age
- family origin (white, Asian, black)
- Eastern Cooperative Oncology Group (ECOG) score (0, 1, 2)
- creatinine clearance
- renal function
- time since diagnosis
- whether the person has had an autologous stem cell transplant
- number of previous regimens if other than 3
- nature of previous treatments
- whether the disease was refractory to bortezomib
- whether the disease was refractory to lenalidomide
- whether the disease was refractory to both lenalidomide and bortezomib
- type of disease (IgA, IgD, IgG, IgM, light chain kappa, light chain lambda)
- whether there were bone lesions
- treatments after daratumumab
- International Staging System
- cytogenetics.

The committee was aware that NICE, NHS England and the company will discuss data collection as part of the managed access agreement.

4.35 The committee was advised that the systemic anticancer therapy (SACT) dataset is limited in the number of outcomes it can collect. The SACT dataset can collect data on overall survival, time on treatment and simple patient characteristics, but would not be able to capture all of the characteristics the

committee highlighted. The committee noted that a pre-authorisation form could potentially capture some of the patient characteristics it had highlighted. However, the completeness and quality could not be guaranteed. On balance, the committee concluded that despite some of the potential limitations, additional data collection could still provide valuable information to address the clinical uncertainties.

Summary of appraisal committee's key conclusions

TA510	Appraisal title: Daratumumab monotherapy for treating relapsed and refractory multiple myeloma	Section
Key conclusion		
<p>Daratumumab monotherapy is recommended for use within the Cancer Drugs Fund as an option for treating relapsed and refractory multiple myeloma in adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last therapy, only if:</p> <ul style="list-style-type: none"> • they have daratumumab after 3 previous therapies and • the conditions in the managed access agreement are followed. <p>The committee concluded that the benefit of collecting further data through the Cancer Drugs Fund would enhance the evidence for daratumumab while providing it to NHS patients until daratumumab's clinical and cost effectiveness could be reappraised.</p>		1.1, 4.32
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee recognised the need for effective, well-tolerated treatment options for people with multiple myeloma who have had previous therapies.	4.1
The technology		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The committee understood that daratumumab was the first monoclonal antibody with a significant effect in people with multiple myeloma. The clinical experts considered it a major change in the management of the condition given its activity in a heavily pre-treated population, and favourable toxicity profile. They also noted that daratumumab is given as monotherapy without corticosteroids, which is a great benefit to people.</p>	<p>4.28</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The company proposed that daratumumab is used after 3 previous treatments, that is, as a fourth-line treatment. It heard from the clinical experts that this is when they are likely to use daratumumab.</p>	<p>4.2</p>
<p>Adverse reactions</p>	<p>The patient and clinical experts highlighted that daratumumab had a favourable toxicity profile.</p>	<p>4.1, 4.28</p>
<p>Evidence for clinical effectiveness</p>		
<p>Availability, nature and quality of evidence</p>	<p>The evidence on the clinical effectiveness of daratumumab came from 2 single-arm clinical trials, MMY2002 and GEN501. The committee noted that few patients in both trials had the licensed dose of daratumumab (16 mg/kg). It also noted that the data on overall survival were immature, with over 50% of patients alive at the end of the trials.</p>	<p>4.4</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>The committee noted that some patients in MMY2002 and GEN501 had so few or so many previous treatments, which did not reflect the place of daratumumab in clinical practice (after 3 previous treatments), or the existing evidence on the benefit of successive treatments.</p> <p>The committee agreed that some of the treatments that patients had previously had in MMY2002 and GEN501 differed from those used in clinical practice.</p> <p>The committee concluded that patients in the clinical trials appeared fitter than patients in the NHS.</p>	<p>4.5–4.7</p>

<p>Uncertainties generated by the evidence</p>	<p>The committee noted the issues with the evidence; data were limited to single-arm trials, and there was a high degree of uncertainty in the relative effect estimates produced by the matching-adjusted indirect comparison (MAIC). Overall, the committee was concerned about the quality of the available evidence, which meant that it could not fully interpret the clinical effectiveness of daratumumab.</p>	<p>4.17</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>No.</p>	<p>-</p>
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The committee understood that daratumumab was associated with a relatively short median progression-free survival (MMY2002; 3.7 months, GEN501 part 2; 6.2 months), but a relatively longer median overall survival (MMY2002; 18.6 months, GEN501 part 2; not reached). The committee concluded that the absolute life expectancy seen in MMY2002 and GEN501 was likely to overestimate the overall survival benefit of daratumumab in patients were it used in the NHS.</p>	<p>4.14</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The company used a 4-state, partitioned-survival economic model. The committee noted that the model reflected the limitations of the clinical-effectiveness data. As a result, the model output was of limited use in estimating the cost effectiveness of daratumumab.</p>	<p>4.18</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The committee was concerned about some of the company's assumptions in the model; extrapolating overall survival for a large proportion of patients over a lifetime time horizon based on few patients at risk of dying; comparing hazard ratios reflecting treatment effects in different trial populations; and including the effect of treatments taken after disease progression, but not the cost associated with them.</p>	<p>4.19, 4.20, 4.25</p>

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The committee concluded that it could accept the company's utility increment reflecting the benefit of daratumumab on health-related quality of life.</p>	<p>4.23</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>No.</p>	<p>-</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The committee noted that the results were highly sensitive to changes in the number of characteristics matched to derive the hazard ratio in the MAIC.</p>	<p>4.21</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The ICERs varied widely, reflecting the high degree of uncertainty in daratumumab's clinical effectiveness compared with current NHS treatments. The committee agreed that the degree of uncertainty in the current evidence was too high for it to be able to identify the most plausible ICER for decision-making.</p>	<p>4.27</p>
<p>Additional factors taken into account</p>		
<p>Patient access schemes (PPRS)</p>	<p>Not applicable.</p>	<p>-</p>
<p>End-of-life considerations</p>	<p>The committee concluded that it could not make an informed decision as to whether daratumumab meets the end-of-life criteria.</p>	<p>4.30</p>

Equalities considerations and social value judgements	Not applicable.	-
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5 Implementation

- 5.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available within the conditions of the [managed access agreement](#). This means that, if a person has relapsed and refractory multiple myeloma and the doctor responsible for their care thinks that daratumumab is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in [NHS England's Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – a new deal for patients, taxpayers and industry](#).
- 5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination or agreement of a managed access agreement by the NHS in Wales, whichever is the latter.
- 5.3 Daratumumab has been recommended according to the conditions in the managed access agreement. As part of this, NHS England and Janssen have agreed a commercial access agreement that makes daratumumab available to the NHS at a reduced cost. The financial terms of the agreement are commercial in confidence. Any enquiries from NHS organisations about the commercial access agreement should be directed to Janssen's customer services team on 01494 567400 or janssenukcustomerservices@its.jnj.com.

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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Accreditation

