The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using daratumumab monotherapy in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Note that this document is not NICE’s final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE’s guidance on using daratumumab monotherapy in the NHS in England.

For further details, see NICE’s guide to the processes of technology appraisal.

**The key dates for this appraisal are:**

Closing date for comments: 7 April 2017

Second appraisal committee meeting: 20 April 2017

Details of membership of the appraisal committee are given in section 6.
1 Recommendations

1.1 Daratumumab monotherapy is not recommended, within its marketing authorisation, for treating relapsed and refractory multiple myeloma in adults, that is, after therapy including a proteasome inhibitor and an immunomodulatory agent and whose disease has progressed on the last therapy.

1.2 This guidance is not intended to affect the position of patients whose treatment with daratumumab monotherapy was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.
2 The technology

<table>
<thead>
<tr>
<th>Description of the technology</th>
<th>Daratumumab (Darzalex, Janssen) is a humanised monoclonal antibody that targets the CD38 protein, thereby killing multiple myeloma cells. It is given intravenously.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marketing authorisation</td>
<td>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’.</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>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.</td>
</tr>
<tr>
<td>Recommended dose and schedule</td>
<td>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.</td>
</tr>
<tr>
<td>Price</td>
<td>The list price for daratumumab monotherapy is £360.00 for 100 mg vial £1,440.00 for 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.</td>
</tr>
</tbody>
</table>

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 [Add link to website in-development page on ‘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 monotherapy, having considered evidence on the nature of multiple myeloma and the value placed on the
benefits of daratumumab monotherapy 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 quality of life. Patients value treatments that improve both survival and quality of life. The committee noted 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 understood that few options are available after NICE-recommended treatments (thalidomide, bortezomib and lenalidomide). The patient experts noted that this makes people anxious about their disease relapsing. 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, as the number of therapies a person receives increases. 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 noted that the company proposed that daratumumab be used after 3 previous treatments, that is, as a fourth-line treatment. The committee was aware that the marketing authorisation for daratumumab stipulates previous treatment with a proteasome inhibitor and an immunomodulatory agent, but does not specify the number of previous treatments. The committee heard from the clinical experts 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. It heard from the clinical experts that there are many possible sequences of treatments:

- The first treatment is either thalidomide (an immunomodulatory agent) 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 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 current clinical practice they would offer panobinostat plus bortezomib and dexamethasone, or pomalidomide plus dexamethasone, as recommended in NICE guidance.

- At fifth line, the committee understood that few people reach this stage, and that there is no standard of care at this point.

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

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, defined as the percentage of people who had a stringent complete response, complete response, very good partial response or partial response. Overall survival and progression-free survival were among the secondary outcomes.

- GEN501 (n=72) was a phase I/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 safety, defined as 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 40% of patients alive at the end of the trials.

4.5 The committee discussed whether the trial populations reflected the marketing authorisation for daratumumab. It noted that, based on the marketing authorisation, a person’s disease should not have responded to the last treatment for the person to be eligible to have daratumumab. This was seen in 97% of those in MMY2002 and 76% in GEN501. The committee agreed that MMY2002 matched the marketing authorisation more closely, and included more patients than GEN501, and therefore was a more appropriate source for decision-making.
Generalisability of the trial results to the NHS: previous treatments

4.6 The committee was aware that patients in MMY2002 and GEN501 had already had a median of 5 and 4 treatments, respectively, before having daratumumab. The clinical experts commented that this reflected clinical practice. However, the committee noted that some patients had as few as 2 previous treatments, and some had as many as 14 previous treatments. It 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), or the existing evidence on the benefit of successive treatments. The committee heard from the company that only a small number of patients had 2 or 14 previous treatments, which the company attributed to the heterogeneous nature of the condition, whereby a number of factors influence treatment (see section 4.1). The committee concluded that neither trial population fully reflected the place of daratumumab in clinical practice (after 3 previous treatments).

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

- Carfilzomib (MMY2002 50%, GEN501 19%): the committee was aware that carfilzomib was not available in the NHS at this stage of treatment, and so people in NHS clinical practice would not have had it.
- Pomalidomide plus dexamethasone (MMY2002 63%, GEN501 36%): the committee was aware that 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 clinical practice, people were unlikely to have had pomalidomide plus dexamethasone before daratumumab because both treatments were likely to be used after 3 previous treatments. It also heard from the evidence review group (ERG) that, because pomalidomide plus dexamethasone is an alternative treatment option 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 trial populations under-represented the proportion of patients in the NHS who would have had previous treatment with thalidomide.

The committee agreed that, because some of the treatments that patients had previously had in MMY2002 and GEN501 differed from those used in clinical practice, the underlying survival trend of patients could also differ. The committee heard from the clinical experts that, at this point in therapy, the prognosis of people was generally poor, and was not largely impacted by treatments received before daratumumab. The committee concluded that the use of previous treatments that were not available in the NHS was a limitation of the evidence, which introduced uncertainty about whether the effect of daratumumab from clinical trials could be generalised to clinical practice.

Generalisability of the trial results to the NHS: fitness of patients

The committee discussed the generalisability of the populations in MMY2002 and GEN501 to the NHS. The committee noted that 71% and 76% of patients in MMY2002 and GEN501 respectively switched to 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 immunomodulatory agent (MMY2002 95%, GEN501 64%) went on to have a proteasome inhibitor and an immunomodulatory agent after daratumumab. The comments from NHS England 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 committee heard from the clinical
experts that they could only speculate the proportion of people who have fifth-line treatment in the NHS. They considered that it was likely to be much lower (about 10%) than the clinical trials. The committee also noted the comment from NHS England that this was a higher rate than would be seen in the NHS after 4 or more lines of treatment. The committee concluded that patients in the clinical trials appeared fitter than people who would be seen in the NHS.

**Pooled data**

4.9 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 that pooling data from the 2 trials was appropriate, because the 2 trial populations differed, most importantly, in the median number of lines of previous therapy, and 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 agreed 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.

**Matching-adjusted indirect comparison (MAIC)**

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’ MAICs. Specifically, the company adjusted the individual patient-level baseline characteristics of the MMY2002 and GEN501 pooled population to match the 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).
The committee discussed the company’s approach to matching. It understood that the company adjusted only the characteristics it considered important in predicting progression and death based on best practice, published evidence, and expert opinion. The ERG did not agree with how the company selected the characteristics, noting a technical support document published by the Decision Support Unit, which recommends that, when only single-arm trial data are available, all the characteristics that could influence the outcomes of interest should be adjusted. The committee heard from the company that this report was not available when the submission was made to NICE, and that the company had adjusted only for selected characteristics to increase the number of patients being matched and produce stable estimates, but it agreed with the ERG’s approach to matching characteristics. The committee concluded that the maximum number of characteristics possible should be adjusted. Nevertheless, it recognised that the survival estimates would remain biased because of unobserved differences that will not be accounted for.

The committee noted that the ERG investigated the effect of adjusting all characteristics that could be adjusted on the effectiveness of daratumumab (see table 1).
Table 1 MAIC-adjusted hazard ratios, company base case, ERG exploratory analysis

<table>
<thead>
<tr>
<th></th>
<th>Pomalidomide plus dexamethasone compared with daratumumab</th>
<th>Panobinostat plus bortezomib plus dexamethasone compared with daratumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Company's base case: only important characteristics adjusted</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of characteristics adjusted</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Sample size before matching</td>
<td>148</td>
<td>125</td>
</tr>
<tr>
<td>Net effective sample size¹ after matching</td>
<td>84</td>
<td>80</td>
</tr>
<tr>
<td>PFS hazard ratio (95% CI)</td>
<td>1.24 (0.92 to 1.68)</td>
<td>0.92 (0.62 to 1.36)</td>
</tr>
<tr>
<td>OS hazard ratio (95% CI)</td>
<td>1.74 (1.24 to 2.46)</td>
<td>1.19 (0.73 to 1.92)</td>
</tr>
<tr>
<td><strong>ERG's preferred approach: all possible characteristics adjusted</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>MMY2002</td>
<td></td>
</tr>
<tr>
<td>Number of characteristics adjusted</td>
<td>28</td>
<td>16</td>
</tr>
<tr>
<td>Sample size before matching</td>
<td>93</td>
<td>84</td>
</tr>
<tr>
<td>Net effective sample size¹ after matching</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>PFS hazard ratio (95% CI)</td>
<td>0.88 (0.49 to 1.56)</td>
<td>1.18 (0.53 to 2.56)</td>
</tr>
<tr>
<td>OS hazard ratio (95% CI)</td>
<td>1.14 (0.57 to 2.27)</td>
<td>1.64 (0.69 to 4.00)</td>
</tr>
</tbody>
</table>

Abbreviations: PFS, progression-free survival; CI, confidence interval; OS, overall survival.

¹The number of matched patients. The smaller this number, the poorer the overlap between studies is, and the less stable the estimates are.

The committee noted that the ERG’s exploratory analysis highlighted the high degree of uncertainty in the results of the MAIC. Specifically, the effect of daratumumab sometimes reversed (that is, went from being more effective than the comparator to being less effective, or vice versa) when adjusting for more characteristics. Although the committee agreed that the ERG’s exploratory analysis reflected its preferred approach to matching characteristics, it recognised 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.
Subsequent therapies and overall survival

4.13 The committee noted that, in MMY2002 and GEN501, treatments received 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 heard from the clinical experts that almost half of the people who would have fifth-line treatment would have best supportive care including dexamethasone. 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 treatments that were not available in the NHS.

4.14 The committee considered the impact of the therapies received 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. 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 ERG looked at how long patients in the trials lived depending on which, if any, therapy they had after daratumumab. The committee interpreted this analysis as showing that treatment after daratumumab prolonged life, and that the impact of treatments on overall survival varied from one treatment to the other. It was unclear to the committee whether there were other important differences between the groups of patients who had the different therapies after daratumumab, which may have confounded the estimates of overall survival. The committee noted the company’s claim that daratumumab improves response to subsequent treatment, but it did not see any evidence in this regard. The committee concluded that the absolute life
expectancy seen in MMY2002 and GEN501 overestimated the overall survival benefit of daratumumab in patients who had treatment in the NHS.

4.15 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 were likely to be less confounded than that for daratumumab 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 therapies after pomalidomide plus dexamethasone, a smaller proportion had subsequent carfilzomib, lenalidomide and bortezomib than those who had therapies 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. The committee concluded that the effectiveness of pomalidomide plus dexamethasone was less biased than that of daratumumab.

Conclusion on clinical effectiveness

4.16 The committee noted the issues with the evidence on whether daratumumab was more effective than current options in the NHS. These included:

- 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 4.9)
poor generalisability of the trial results to people who would have
daratatumab in the NHS because of differences in:
  – treatments received before daratumumab (see sections 4.6 and 4.7)
  – the fitness of patients (see section 4.8)
potential confounding effect of subsequent treatments (see sections 4.13–4.15)
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 of the available
evidence, which meant that it could not fully interpret the clinical
effectiveness of daratumumab.

Cost effectiveness

4.17 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 noted that the
model reflected the limitations of the clinical-effectiveness data (see
section 4.16). 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

4.18 The committee recalled that the data on overall survival from MMY2002
and GEN501 were immature. It noted that the company extrapolated 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), which created considerable uncertainty about the effect of daratumumab beyond the follow-up period. Because of this, the committee considered that it was desirable to consider several alternative scenarios reflecting different assumptions about the long-term effects of daratumumab, including the assumption that daratumumab does not provide further benefit beyond the trial.

4.19 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, the committee applied hazard ratios from the MAIC to these curves to generate survival curves for pomalidomide plus dexamethasone, and panobinostat plus bortezomib plus dexamethasone. The committee recognised that the hazard ratios for pomalidomide plus dexamethasone, and those for 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 (MM-003 and PANORAMA-2). Because of this, the committee was concerned about the validity of the comparisons provided by the company.

4.20 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. 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 reinforced the uncertainty associated with the hazard ratios estimated from the MAIC.

4.21 The committee noted that the company’s modelling of survival (see section 4.19) assumed proportional hazards. 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 to avoid assuming proportional hazards. The committee commented that statistical testing for proportional hazards is normally done in randomised controlled trials in which the groups are the same except for treatment. In this case, the log-log plots that the committee saw 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 agreed that it would be useful to see results that did and did not assume proportional hazards when modelling overall and progression-free survival (that is, using both the company’s approach to fitting curves, and the ERG’s preference for independently fitted curves).

Utility values

4.22 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. The values chosen by the company to reflect the utility in the pre-progression and post-progression health states came from MM-003, which compared pomalidomide plus dexamethasone with dexamethasone only (Palumbo et al. 2013). The committee heard from the clinical experts that these utility values were lower than they would expect for people taking daratumumab because daratumumab is considered to be better tolerated. The patient experts highlighted the psychological benefit of daratumumab in reassuring people that an effective treatment is available at this stage, and that the favourable toxicity profile of this treatment might
mean even more options down the treatment pathway. The committee concluded that the current utility values did not reflect daratumumab’s additional benefits on quality of life perceived by the patient and clinical experts.

Cost of treatment in the model

4.23 The committee noted that the company estimated the cost of daratumumab and its comparators based on the time from starting to stopping each treatment. The ERG agreed that using time to stopping treatment was appropriate, but stated that the company estimated this post-hoc (that is, after the trial results had been compiled), and did not explain the methods it used. Because of this, the ERG explored estimating costs from progression-free survival (that is, assuming that people stop treatment at the point of disease progression). 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 agreed that it preferred using time to stopping treatment to estimate costs, but it would like the company to present detailed information on its calculations.

4.24 The committee discussed the cost of subsequent treatment in the model, noting that the company had not reflected the rate of subsequent treatments reported in the trials in its modelling. Instead, it modelled treatments available in the UK. This meant that the company included in its model 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 treatment after daratumumab in NHS clinical practice, but would likely receive best supportive care (see section 4.13). The committee preferred adjusting the treatment effect and costs to reflect therapies that would be used in NHS clinical practice. The
committee recognised that this would be difficult to do without introducing considerable uncertainty.

Cost-effectiveness results

4.25 The ERG found a number of errors in the company's model. The committee understood that some of these errors did not have a large impact on the results. Nevertheless, the ERG considered that the model may contain more errors, the effects of which were unknown. The committee concluded that the company’s quality assurance process had not provided it with enough assurance of the validity of the economic model.

4.26 In addition to the problems in the data informing the model (see section 4.16), the committee was concerned about some of the assumptions made by the company in the model, notably:

- extrapolating a large proportion of patients, over a lifetime time horizon, based on few patients at risk of dying (see section 4.18)
- comparing hazard ratios reflecting treatment effects in different trial populations (see section 4.19)
- excluding the benefit of daratumumab on quality of life highlighted by the patient and clinical experts (see section 4.22)
- including the effect of treatments received after disease progression, but not the cost associated with them (see section 4.24).

The committee considered the cost-effectiveness results presented by the company and the ERG, including confidential discounts for all comparator technologies. It noted that the ICERs for daratumumab compared with pomalidomide plus dexamethasone, and panobinostat plus bortezomib plus dexamethasone varied widely, reflecting the high degree of uncertainty in daratumumab’s clinical effectiveness compared with treatments currently offered in the NHS. Although the committee considered that some of these uncertainties could be reduced through
revised modelling, others such as those caused by uncontrolled trial data, would remain. The committee agreed that the current cost-effectiveness results were unreliable, and so it could not identify a most plausible ICER for daratumumab. The committee concluded that it could not recommend daratumumab as a cost-effective use of NHS resources.

4.27 The committee agreed that it would like to see analyses that:

- used the MMY2002 trial population (see section 4.5)
- adjusted for all potential confounders in the MAIC (see section 4.11)
- cross validated the MAIC analysis with data from other sources (see section 4.12)
- explained the definition and calculations to estimate time to stopping treatment (see section 4.23)
- presenting scenarios reflecting different assumptions about the long-term effects of daratumumab (see section 4.18)
- included scenario analyses using dependently and independently fitted curves (see section 4.21)
- explored alternative utility values to reflect daratumumab’s additional benefits on quality of life perceived by the patient and clinical experts (see section 4.22)
- carried out and documented further internal quality assurance (see section 4.25)
- present results as probabilistic ICERs within a fully incremental analysis.

**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 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. The committee recognised that people whose disease progressed after 3 previous lines of therapy have a poor prognosis, limited treatment options, and a high clinical unmet need. Given the issues related to comparative effectiveness and estimates of utility, the committee could not assess whether daratumumab was innovative.

**Further data collection**

4.29 The company made the committee aware of an ongoing study providing early access to daratumumab to patients with relapsed or refractory multiple myeloma who had already had at least 3 previous lines of therapy. The company noted that the study included 80–90 people recruited in the NHS. The committee understood that the study would collect data on health-related quality of life, but not clinical outcomes. The committee considered that these data could be useful in informing its decision because they would come from patients in the NHS. However, the committee lacked enough detail on this study, and recognised that the study was unlikely to reduce the clinical uncertainty in the current evidence.

4.30 The committee discussed further data collection within the Cancer Drugs Fund. It agreed that this could lessen the clinical uncertainty because the data collected would reflect the appropriate population, and management before and after daratumumab in the UK. However, the committee could not establish whether daratumumab had a ‘plausible potential to be cost effective’ given the current uncertainties.

**End-of-life considerations**

4.31 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](http://www.nice.org.uk).
4.32 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 of the many uncertainties in the relative effectiveness and survival modelling. The committee concluded that it could not make an informed decision as to whether daratumumab meets the end-of-life criteria.

**Pharmaceutical Price Regulation Scheme (PPRS) 2014**

4.33 The committee was aware of NICE’s position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion ‘that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines’. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

**Summary of appraisal committee’s key conclusions**

<table>
<thead>
<tr>
<th>TA10104</th>
<th>Appraisal title: Daratumumab for multiple myeloma</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key conclusion</td>
<td>Daratumumab monotherapy is not recommended, within its marketing authorisation, for treating relapsed and refractory multiple myeloma in adults, that is, after therapy including a proteasome inhibitor and an immunomodulatory agent and whose disease has progressed on the last therapy.</td>
<td>1.1</td>
</tr>
</tbody>
</table>
The committee agreed that the current cost-effectiveness results were unreliable, and so it could not identify a most plausible incremental cost-effectiveness ratio (ICER) for daratumumab.

### Current practice

<table>
<thead>
<tr>
<th>Clinical need of patients, including the availability of alternative treatments</th>
<th>The committee recognised the need for effective, well-tolerated treatment options for people with multiple myeloma who have had previous therapies.</th>
</tr>
</thead>
</table>

### The technology

<table>
<thead>
<tr>
<th>Proposed benefits of the technology</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</td>
<td>The committee noted that the company proposed that daratumumab be used after 3 previous treatments, that is, as a fourth-line treatment. It heard from the clinical experts that this is where they were likely to use daratumumab.</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>What is the position of the treatment in the pathway of care for the condition?</th>
<th>The committee noted that the company proposed that daratumumab be used after 3 previous treatments, that is, as a fourth-line treatment. It heard from the clinical experts that this is where they were likely to use daratumumab.</th>
</tr>
</thead>
</table>
### Adverse reactions
| The patient and clinical experts highlighted that daratumumab had a favourable toxicity profile. | 4.22, 4.28 |

### Evidence for clinical effectiveness

| Availability, nature and quality of evidence | 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 40% of patients alive at the end of the trials. | 4.4 |
| Relevance to general clinical practice in the NHS | 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.  

The committee agreed that some of the treatments that patients had previously had in MMY2002 and GEN501 differed from those used in clinical practice.  

The committee concluded that patients in the clinical trials appeared fitter than people who would be seen in the NHS. | 4.6, 4.7, 4.8 |
| Uncertainties generated by the evidence | The committee noted the issues with the evidence; data was 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. | 4.16 |
| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | No. | |
| Estimate of the size of the clinical effectiveness including strength of supporting evidence | 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 overestimated the overall survival benefit of daratumumab in patients who had treatment in the NHS. | 4.14 |

### Evidence for cost effectiveness
<p>| Availability and nature of evidence | 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. | 4.17 |
| Uncertainties around and plausibility of assumptions and inputs in the economic model | The committee was concerned about some of the assumptions made by the company in the model, notably extrapolating 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; excluding the benefit of daratumumab on quality of life highlighted by the patient and clinical experts; and including the effect of treatments received after disease progression, but not the cost associated with them. | 4.18, 4.19, 4.22, 4.24 |</p>
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorporation of health-related quality-of-life benefits and utility values</td>
<td>The committee concluded that the current utility values did not reflect daratumumab's additional benefits on quality of life perceived by the patient and clinical experts.</td>
<td>4.22</td>
</tr>
<tr>
<td>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?</td>
<td>No.</td>
<td></td>
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<tr>
<td>Are there specific groups of people for whom the technology is particularly cost effective?</td>
<td>No.</td>
<td></td>
</tr>
<tr>
<td>What are the key drivers of cost effectiveness?</td>
<td>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.</td>
<td>4.20</td>
</tr>
</tbody>
</table>
Most likely cost-effectiveness estimate (given as an ICER) | The ICERs varied widely, reflecting the high degree of uncertainty in daratumumab’s clinical effectiveness compared with treatments currently offered in the NHS. The committee agreed that the current cost-effectiveness results were unreliable, and so it could not identify a most plausible ICER for daratumumab. 4.26

<table>
<thead>
<tr>
<th>Additional factors taken into account</th>
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</thead>
<tbody>
<tr>
<td>Patient access schemes (PPRS)</td>
</tr>
<tr>
<td>End-of-life considerations</td>
</tr>
<tr>
<td>Equalities considerations and social value judgements</td>
</tr>
</tbody>
</table>

### 5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.
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.

Jessica Maloney
Technical Lead

Ahmed Elsada
Technical Adviser

Jeremy Powell
Project Manager

ISBN: [to be added at publication]