

Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma

Technology appraisal guidance

Published: 10 April 2019

[nice.org.uk/guidance/ta573](https://www.nice.org.uk/guidance/ta573)

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

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.

Contents

| | |
|--|----|
| 1 Recommendations | 4 |
| 2 Information about daratumumab | 5 |
| 3 Committee discussion | 6 |
| Treatment pathway | 6 |
| Clinical evidence..... | 7 |
| The company's economic model | 12 |
| Cost-effectiveness estimate..... | 15 |
| Cancer Drugs Fund..... | 17 |
| Conclusion | 18 |
| 4 Implementation..... | 19 |
| 5 Recommendations for data collection | 20 |
| 6 Appraisal committee members and NICE project team..... | 21 |
| Appraisal committee members..... | 21 |
| NICE project team | 21 |

1 Recommendations

- 1.1 Daratumumab plus bortezomib plus dexamethasone is recommended for use within the Cancer Drugs Fund as an option for treating relapsed multiple myeloma in people who have had 1 previous treatment. It is recommended only if the conditions in the [managed access agreement](#) for daratumumab plus bortezomib plus dexamethasone are followed.
- 1.2 This recommendation is not intended to affect treatment with daratumumab plus bortezomib plus dexamethasone 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.

Why the committee made these recommendations

Currently, treatment options for multiple myeloma include bortezomib or carfilzomib (both with dexamethasone) if a person has had thalidomide as the first treatment. For those who have had bortezomib first, carfilzomib is not a treatment option and retreatment with bortezomib is becoming routine.

Clinical trial results show that, as a second treatment, daratumumab plus bortezomib plus dexamethasone improves how long people live for before the disease gets worse when compared with bortezomib plus dexamethasone. The results also suggest that people who have daratumumab plus bortezomib plus dexamethasone live longer. However, how much longer they live in total is unclear because there are no long-term trial data. The benefits of daratumumab plus bortezomib plus dexamethasone compared with carfilzomib plus dexamethasone are unclear because they haven't been compared directly in a trial.

The estimates of cost effectiveness presented by the company and evidence review group differ greatly. These differences depend mostly on the estimates of how much longer people will live if they have daratumumab plus bortezomib plus dexamethasone rather than bortezomib plus dexamethasone. If the company's estimates are confirmed by extra trial data, there is potential for daratumumab plus bortezomib plus dexamethasone to be cost effective. Therefore it is recommended for use in the Cancer Drugs Fund while extra data on long-term survival are collected.

2 Information about daratumumab

| | |
|--|---|
| Marketing authorisation indication | Daratumumab (Darzalex, Janssen-Cilag) has a marketing authorisation 'in combination with...bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy'. |
| Dosage in the marketing authorisation | <p>Daratumumab 16 mg/kg body weight is administered by intravenous infusion every week for weeks 1 to 9, every 3 weeks for weeks 10 to 24 and every 4 weeks from week 25 onwards.</p> <p>Bortezomib is administered by subcutaneous injection at a dose of 1.3 mg/m² twice weekly on days 1, 4, 8 and 11 for 8×21-day cycles.</p> <p>Dexamethasone is administered orally at a dose of 80 mg weekly.</p> |
| Price | <p>The company has a managed access agreement, which includes a <u>commercial arrangement</u>, for daratumumab.</p> <p>There is also a <u>commercial arrangement</u> for bortezomib.</p> |

3 Committee discussion

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

Treatment pathway

This appraisal focuses on daratumumab plus bortezomib plus dexamethasone as a second-line treatment

- 3.1 The company presented evidence for daratumumab plus bortezomib plus dexamethasone as a second-line treatment only. It stated that offering this combination after only 1 previous treatment optimised its clinical and cost effectiveness. It also pointed out that there is a clinical need for treatment that combines 3 drugs at second line. The committee recognised that limiting this combination treatment to second line was narrower than its marketing authorisation and the population defined in the final NICE scope. However, the committee concluded that it would appraise daratumumab plus bortezomib plus dexamethasone after 1 previous treatment, having been presented only with evidence for its use as a second-line treatment.

The second-line treatment options for multiple myeloma include bortezomib and carfilzomib

- 3.2 The treatment pathway for multiple myeloma depends on whether or not a stem cell transplant is suitable. If it is, people have bortezomib as induction treatment before a transplant. If it is not, people have either thalidomide or bortezomib as first-line treatment. The clinical experts stated that, in England, most people with multiple myeloma will have bortezomib as their first treatment. The Cancer Drugs Fund clinical lead stated that a treatment algorithm currently being developed by NHS England will allow retreatment with bortezomib second line (despite disease progression), depending on a good response to the first course of bortezomib treatment. People who have thalidomide as their first treatment can then have bortezomib plus dexamethasone, or carfilzomib plus dexamethasone. The committee recognised that the treatment pathway for multiple myeloma is changing and that retreating with bortezomib will be routinely accessible in the near future to people who have previously had bortezomib. It therefore determined the relevant comparators based on the

evolving treatment pathway. The committee concluded that, after initial therapy, current second-line treatment options include:

- bortezomib retreatment, if bortezomib has been used first line
- bortezomib plus dexamethasone, or carfilzomib plus dexamethasone, if thalidomide has been used first line.

Clinical evidence

Clinical evidence for daratumumab plus bortezomib plus dexamethasone compared with bortezomib plus dexamethasone comes from CASTOR

3.3 The clinical evidence for daratumumab plus bortezomib plus dexamethasone compared with bortezomib plus dexamethasone came from the open-label trial CASTOR, an international trial with no UK centres. Because the company chose to focus on daratumumab plus bortezomib plus dexamethasone as a second-line treatment (see [section 3.1](#)), it presented data from the trial for patients who had only had 1 previous treatment (122/251 [49%] in the daratumumab plus bortezomib plus dexamethasone arm, and 113/247 [46%] in the bortezomib plus dexamethasone arm; from now the 'second-line subgroup'). The committee noted that CASTOR included only people whose disease had responded to at least 1 prior therapy, so none of the patients in the second-line subgroup would have had refractory disease. The trial population was stratified by number of previous treatments, meaning that randomisation was maintained in this second-line subgroup. The primary outcome of the trial was progression-free survival.

The second-line subgroup is appropriate for assessing clinical effectiveness

3.4 In the second-line subgroup in CASTOR, there were imbalances in the type of previous treatments between trial arms. Notably, more patients in the bortezomib plus dexamethasone arm (29%) had lenalidomide first line (a treatment not routinely offered in the NHS) than in the daratumumab plus bortezomib plus dexamethasone arm (12%). The Cancer Drugs Fund clinical lead suggested that this imbalance could have favoured daratumumab plus bortezomib plus dexamethasone because patients in this trial arm may have had a better prognosis. The clinical experts stated that there was no evidence to suggest that lenalidomide modifies the effect of subsequent treatments, but the

committee did not see any evidence of this. The company suggested that, between the arms of the second-line subgroup, other imbalances such as a cytogenetic abnormality (17p deletion) are also important and would have biased the results against daratumumab plus bortezomib plus dexamethasone. In response to the appraisal consultation document, the company tested for a statistical interaction between either previous lenalidomide use or 17p deletion and the overall survival benefit of daratumumab plus bortezomib and dexamethasone. It found none. The committee agreed that previous lenalidomide treatment and the presence of 17p deletion did not appear to modify the effect of daratumumab plus bortezomib plus dexamethasone on overall survival. However, the committee noted that the patient numbers may have been too small to detect such an interaction, and agreed that there was some uncertainty resulting from potential differences between treatment arms in the second-line subgroup. Overall, the committee concluded that the second-line subgroup was appropriate for assessing clinical effectiveness.

Daratumumab plus bortezomib plus dexamethasone improves progression-free survival compared with bortezomib plus dexamethasone

3.5 In the subgroup having treatment second line, there was an increase in progression-free survival with daratumumab plus bortezomib plus dexamethasone (median 26 months) compared with bortezomib plus dexamethasone (median 8 months) after a median follow-up of 27 months (pre-specified interim analysis; hazard ratio [HR] 0.23, 95% confidence interval [CI] 0.16 to 0.33; $p < 0.0001$). The committee understood from patient and clinical experts, and the clinical lead for the Cancer Drugs Fund, that an 18-month improvement in median progression-free survival was considered a 'game-changing' effect in the second-line treatment of multiple myeloma. It concluded that daratumumab plus bortezomib plus dexamethasone had a clinically important and statistically significant effect on progression-free survival compared with bortezomib plus dexamethasone.

Daratumumab plus bortezomib plus dexamethasone improves survival but by how long is undefined because there are no long-term data

3.6 Overall survival data from CASTOR were immature because more than half the patients in both arms were still alive at the interim analysis presented in the company's original submission, after a median of 27 months' follow-up. The available data showed that daratumumab plus bortezomib plus dexamethasone

reduced the risk of death by 50% compared with bortezomib plus dexamethasone (HR 0.50, 95% CI 0.30 to 0.84, $p=0.008$). In response to the appraisal consultation document, the company provided additional data from CASTOR representing an extra 4.3 months of follow-up (median follow-up 31.2 months). These data also showed daratumumab plus bortezomib plus dexamethasone improved overall survival, but they were still immature because a large proportion of people in both arms were still alive. The committee concluded that overall survival improved with daratumumab plus bortezomib plus dexamethasone, but that the long-term effect of treatment on survival was unknown because the data were immature.

Overall survival is still immature in the latest data cut

- 3.7 The company submitted further overall survival data from a later data cut. These provided an additional 9 months of follow-up compared with the data submitted in response to the appraisal consultation document. The new data were submitted only the day before the committee met, so were not reviewed by the ERG. Also, importantly, the new data were not adjusted for the effects of subsequent treatments and were not used to update the cost-effectiveness estimates. The committee agreed that the new data were still immature. Therefore it maintained its previous conclusion that the long-term effect of treatment on survival was unknown.

Results for minimal residual disease do not validate how much longer people who have daratumumab live for

- 3.8 The company presented data on minimal residual disease (a measure of the residual tumour cells in bone marrow in people with disease that completely responds to treatment). The clinical experts stated that, although minimal residual disease is not routinely measured in clinical practice, it is associated with better progression-free and overall survival. The committee noted that, in the whole trial population in CASTOR, 12% of patients in the daratumumab plus bortezomib plus dexamethasone arm had no residual disease, compared with 2% of patients in the bortezomib plus dexamethasone arm. At 31.2 months, the proportion of people with no residual disease having daratumumab plus bortezomib plus dexamethasone had increased. The clinical experts explained that observing no residual disease is unexpected at second line, and confirmed that daratumumab plus bortezomib plus dexamethasone would confer a long-term survival benefit. In response to the appraisal consultation document, the

company stated that there was an association between no minimal residual disease and longer overall survival established in studies of patients having treatment first line. It argued that there was no biologically plausible reason why this would be different at later lines of treatment. The committee agreed that there may be a documented association between minimal residual disease and short-term overall survival, and that it was not unreasonable to expect some people with no residual disease to live longer. However, it concluded that the relationship between these outcomes over the long term in people with relapsed disease had not been established and could not inform the economic model.

It is appropriate to adjust trial data for life-extending follow-on treatments not used in the NHS

3.9 The committee appreciated that treatments at third line and beyond that are not available in the NHS, and which are likely to prolong survival, would have biased the results of CASTOR. The company adjusted the overall survival results from CASTOR for these treatments, which the committee considered appropriate. The ERG considered that the company's method of adjustment (inverse probability of censoring weights) was appropriate. The committee was reassured that the company had done a number of sensitivity analyses and the adjusted hazard ratio for survival did not differ greatly. However, the committee noted that uncertainty would remain around the adjusted hazard ratio and adjusted survival estimates. This was because the optimal specification of the weighting model was uncertain, and because it was unclear whether there was any missing information for relevant confounders (variables that affect both the probability of switching treatment and survival). The committee concluded that adjusting for subsequent therapies was appropriate and that, although there may be uncertainty surrounding the estimates, the company had carried this out robustly.

How the clinical effectiveness of daratumumab plus bortezomib plus dexamethasone compares with carfilzomib plus dexamethasone is unclear

3.10 In the absence of a trial directly comparing daratumumab plus bortezomib plus dexamethasone with carfilzomib plus dexamethasone, the company carried out a network meta-analysis using data from the second-line subgroup of CASTOR and ENDEAVOR (which compared carfilzomib plus dexamethasone with bortezomib plus dexamethasone). The results of this meta-analysis favoured

daratumumab plus bortezomib plus dexamethasone for both progression-free survival and overall survival compared with carfilzomib plus dexamethasone. However, the duration of bortezomib treatment differed in CASTOR and ENDEAVOR. In CASTOR, it was capped at 24 weeks, which is consistent with the marketing authorisation for bortezomib, but in ENDEAVOR, patients could have bortezomib until disease progression. Because longer treatment with bortezomib would be expected to increase its clinical effectiveness, the ERG considered that not correcting for the duration of bortezomib treatment in ENDEAVOR may have underestimated the effectiveness of carfilzomib plus dexamethasone applied to current practice. This would overestimate the relative effectiveness of daratumumab plus bortezomib plus dexamethasone compared with carfilzomib plus dexamethasone in the network meta-analysis. The committee noted that, in the NICE technology appraisal of [carfilzomib for previously treated multiple myeloma](#), the committee for that appraisal had preferred adjusting for the length of bortezomib treatment. In response to the appraisal consultation document, the company carried out this adjustment in line with the method used in the carfilzomib appraisal and updated its estimates of the relative effectiveness of daratumumab plus bortezomib plus dexamethasone, which the committee concluded was appropriate.

The effect of previous bortezomib treatment on the effectiveness of daratumumab plus bortezomib plus dexamethasone needs exploring

3.11 Only people who have not had previous bortezomib can have carfilzomib plus dexamethasone. To compare the daratumumab combination with carfilzomib plus dexamethasone, the company's network meta-analysis used the second-line subgroups from CASTOR and ENDEAVOR in the base-case analysis, and a subset of these subgroups (which included only patients who had not had previous bortezomib) in a sensitivity analysis. The company stated that there was an interaction between treatment with daratumumab plus bortezomib plus dexamethasone and previous bortezomib on progression-free survival in patients who had had 1 or more previous treatments. However, it was unclear whether this was also true in patients who had only 1 previous treatment. The clinical experts advised that the available data suggested that the size of benefit may be greater for patients who have not had bortezomib. The company's sensitivity analysis using data from the second-line subgroup, but including only patients who had not had previous bortezomib, resulted in a smaller estimate of the clinical benefits of daratumumab plus bortezomib plus dexamethasone

relative to bortezomib plus dexamethasone and carfilzomib plus dexamethasone. The committee noted that the confidence intervals around the hazard ratio from this analysis and from the analysis including all patients at second line overlapped substantially. The committee noted the company's comment that the results from a subset of the second-line subgroup were uncertain because they represented a post-hoc analysis of a non-randomised group of patients. The committee concluded that the data for the second-line subgroup were more robust than the second-line bortezomib-naive subgroup. However, it still considered that it was appropriate to examine the cost-effectiveness estimates using the second-line bortezomib-naive data. This was because these data, although uncertain, more closely reflected people who have carfilzomib in clinical practice than the whole second-line subgroup.

The company's economic model

Long-term survival on daratumumab plus bortezomib plus dexamethasone is uncertain; the ERG's estimates are more plausible

3.12 The committee commented that, to model the average life expectancy of people having treatment in the model, it was necessary to extrapolate trial data from CASTOR (a short-term trial, with immature data) for more than 10-times the length of the actual trial follow-up. Because of this, the committee appreciated that any extrapolation would be associated with high uncertainty. In its original submission, the company extrapolated overall survival using a Gompertz curve for bortezomib plus dexamethasone and a log-logistic curve for daratumumab plus bortezomib plus dexamethasone. The ERG preferred the Weibull curve for both arms. The committee noted that, for these extrapolations:

- The company assumed that nobody in the bortezomib plus dexamethasone or carfilzomib plus dexamethasone arm would be alive at 10 years. By contrast, the clinical experts stated that around 5% to 10% of people currently having either second-line treatment for multiple myeloma would be expected to be alive 10 years on.
- The ERG estimated that 9% of people would be alive at 10 years if they had had bortezomib plus dexamethasone, which the committee considered more in line with the clinical experts' opinion.
- The clinical experts considered the company's prediction that 22% of people who had had daratumumab plus bortezomib plus dexamethasone would be alive at 20 years to

- be overoptimistic.

In response to the appraisal consultation document:

- The company's new estimate for 10-year survival on bortezomib plus dexamethasone using the new data cut was 6%, which the committee agreed was within a plausible range estimated by the clinical experts.
- The ERG's new estimate for 10-year survival on bortezomib plus dexamethasone increased to 12%, which was slightly above the plausible range estimated by the clinical experts.
- Both the company and ERG adjusted the estimates of survival on carfilzomib for the duration of bortezomib in ENDEAVOR using the same method as in NICE's technology appraisal guidance on [carfilzomib for previously treated multiple myeloma](#), which the committee considered appropriate (see [section 3.10](#)).
- The company's new estimate for 20-year survival on daratumumab plus bortezomib plus dexamethasone was 18% using the new data cut and an exponential rather than a log-logistic distribution to extrapolate the data.
- The ERG's new estimate for 20-year survival on daratumumab plus bortezomib plus dexamethasone increased to 11% using the new data cut and adjusting for follow-on life-prolonging treatments not used in the NHS.

The committee was aware of the substantial uncertainty in the extrapolation, which predicted survival up to 30 years based on a trial with a median follow-up of under 3 years, and in the relative treatment effect of daratumumab in the long term. The committee agreed that the clinical experts' estimate of 10-year survival on current treatments was useful in determining whether the company's or ERG's estimates of long-term survival on bortezomib plus dexamethasone and carfilzomib plus dexamethasone were plausible. However, given the immaturity of the data and without experience using the combination in clinical practice, it was harder to judge the plausibility of the long-term survival of daratumumab plus bortezomib plus dexamethasone compared with current treatments. The committee concluded that it was appropriate to consider that the company's and ERG's estimates could be within a plausible range. However, given the uncertainty, it preferred the ERG's more conservative survival estimate for the daratumumab combination at 20 years, which also reflected more closely the clinical expert advice at the first meeting that a survival of around 20% would be too high.

There is no current evidence to support that a person's prognosis on daratumumab plus bortezomib plus dexamethasone would improve over time

3.13 The choice of parametric curve for extrapolating trial data had a large effect on the overall survival estimates for daratumumab plus bortezomib plus dexamethasone. The company suggested that, in the absence of long-term data, trends in how the risk of death varied over time with each parametric curve may help determine which was likely to give the most plausible survival estimates. It noted that, over time, the log-logistic curve modelled a decreasing risk of death, the exponential curve modelled a constant risk of death, and the Weibull curve (preferred by the ERG) modelled an increasing risk of death. The company's own assumption was that risk of death would decrease over time. This was because people who remain alive longer would have a greater chance of having no minimal residual disease, and would have the highest chance of responding well to treatment, that is, may go into a long-term remission. The committee agreed that assumptions about the long-term effect of daratumumab were speculative because of a lack of evidence. It acknowledged that how the risk of dying changed over time for people having daratumumab plus bortezomib plus dexamethasone may have affected the extrapolation of the trial data. However, the committee concluded that it needed to see more data to be convinced by the decreasing risk of death over time suggested by the company. It also concluded that the ERG's assumptions about long-term survival were more reasonable than the company's on the basis of the available evidence and expert opinion (see [section 3.12](#)).

The effect of disease progression on quality of life is underestimated by the company

3.14 The company used utility values in the model based on EQ-5D data collected in CASTOR from the second-line population reflecting the period before and shortly after disease progression. The ERG stated that the difference between the modelled utility of people before and after disease progression was implausibly small because quality of life would be expected to decrease more after disease progression. The committee heard that a reason why quality of life might not have worsened after disease progression was that CASTOR measured disease progression with haematological markers (that is, symptoms might not have appeared so soon after progression). The committee agreed that quality of life would be expected to decrease the longer a person had progressed disease. As such, it considered that the ERG's estimate of post-progression utility was more plausible than the company's, even though it came from ENDEAVOR and

was not derived from EQ-5D data (the preferred quality-of-life measure in the [NICE methods guide](#)). In response to the appraisal consultation document, the company argued that the change in the utility value after disease progression may have appeared to be less than expected because the pre-progression utility value was underestimated, rather than post-progression utility overestimated. Either way, the committee agreed that the difference between the utility values before and after disease progression was underestimated, concluding that utility values from ENDEAVOR appeared more plausible.

Cost-effectiveness estimate

The most plausible cost-effectiveness estimate is above the range usually considered a cost-effective use of NHS resources

3.15 Because carfilzomib and some follow-on treatments in the model had confidential commercial access agreements, the exact incremental cost-effectiveness ratios (ICERs) for daratumumab plus bortezomib plus dexamethasone compared with bortezomib or carfilzomib (both plus dexamethasone) are confidential and cannot be reported here. Taking into account the committee's preferred assumptions:

- Using the company's assumption on the long-term survival with daratumumab plus bortezomib plus dexamethasone (using an exponential extrapolation; see [section 3.12](#)) and utility values based on CASTOR (see [section 3.14](#)), the ICERs were between £30,000 and £40,000 per quality-adjusted life year (QALY) gained for both the comparison with bortezomib plus dexamethasone and with carfilzomib plus dexamethasone.
- Using the ERG's assumption on the long-term survival with daratumumab plus bortezomib plus dexamethasone (using a Weibull extrapolation) and utility values based on ENDEAVOR, the ICER was between £40,000 and £50,000 per QALY gained for the comparison with bortezomib plus dexamethasone and was higher for the comparison with carfilzomib plus dexamethasone.

The committee recalled that it was appropriate to consider that the company's and ERG's estimates of overall survival could be within a plausible range (see [section 3.12](#)). However, taking both into account, it preferred the ERG's estimate of long-term survival with daratumumab plus bortezomib plus dexamethasone, given the level of evidence that it had seen to support survival modelling. The committee considered

- that the ICERs for the comparison with bortezomib plus dexamethasone were more relevant for decision making because:
- bortezomib plus dexamethasone is a comparator for all people with multiple myeloma who have had 1 previous treatment, whereas only people who have had previous thalidomide-based treatment can have carfilzomib plus dexamethasone
- the evidence for the comparison of daratumumab plus bortezomib plus dexamethasone with bortezomib plus dexamethasone came from a clinical trial directly comparing the 2 treatments and was more robust than the comparison with carfilzomib plus dexamethasone, which came from an indirect comparison of data from 2 trials.

The committee concluded that, based on the current evidence, the ICERs for daratumumab plus bortezomib plus dexamethasone were over £30,000 per QALY gained, and were more likely to be closer to the ERG's ICER estimates using the Weibull survival curve (between £40,000 and £50,000 per QALY gained). It concluded that daratumumab plus bortezomib plus dexamethasone did not represent a cost-effective use of NHS resources.

Daratumumab plus bortezomib plus dexamethasone is an innovative treatment

3.16 The company and patient experts stated that they considered daratumumab plus bortezomib plus dexamethasone to be innovative because it has a different mechanism of action from other available treatments for multiple myeloma. The committee agreed that the improvements in progression-free survival with daratumumab plus bortezomib plus dexamethasone were large and that this combination is a step-change in treating people with multiple myeloma. The patient experts stated that the psychological benefit of delaying a second relapse had not been captured in the quality-of-life measure in the trial. The committee agreed that this had not been captured in the model. It considered that daratumumab plus bortezomib plus dexamethasone is an innovative treatment and that this should be taken into account in its decision making. However, the committee concluded that, even taking into account the innovative nature of daratumumab plus bortezomib plus dexamethasone, it did not consider the treatment to be a cost-effective use of NHS resources, so could not recommend it for the routine treatment of multiple myeloma.

Cancer Drugs Fund

Daratumumab plus bortezomib plus dexamethasone meets the criteria to be considered in the Cancer Drugs Fund

3.17 Having concluded that daratumumab plus bortezomib plus dexamethasone could not be recommended for routine use, the committee then considered whether it could be recommended for treating multiple myeloma in people who have had 1 previous treatment within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's [Cancer Drugs Fund methods guide \(addendum\)](#). It considered that there was considerable unmet need at the point of second-line treatment. The key uncertainties in the evidence were about the long-term survival on daratumumab plus bortezomib plus dexamethasone and, in particular, whether the company's or ERG's extrapolation was more plausible. The committee noted that it could only consider daratumumab combination treatment for use in the Cancer Drugs Fund if the ICER had the plausible potential to be within the range considered a cost-effective use of NHS resources. It noted that the ICERs presented to committee for daratumumab plus bortezomib plus dexamethasone compared with bortezomib plus dexamethasone were between £30,000 and £50,000 per QALY gained. However, it agreed that the cost-effectiveness estimates would be lower if further data support the company's claim that a person's risk of dying decreases over time on daratumumab plus bortezomib plus dexamethasone. The committee considered it was reasonable to consider that daratumumab plus bortezomib plus dexamethasone had the plausible potential to be a cost-effective use of NHS resources. It heard that the ongoing CASTOR trial is anticipated to provide a further 3 to 4 years of data, which the committee considered could address the uncertainty around survival estimates. It concluded that daratumumab plus bortezomib plus dexamethasone met the criteria to be considered in the Cancer Drugs Fund, and recommended it as an option for people with multiple myeloma who have had 1 previous treatment. The committee recalled that the evidence related to people with relapsed disease (see [section 3.3](#)), and so its recommendations should apply only to relapsed disease.

Conclusion

Daratumumab plus bortezomib plus dexamethasone is recommended as an option within the Cancer Drugs Fund

- 3.18 The committee considered daratumumab plus bortezomib plus dexamethasone to be a clinically effective and innovative treatment for relapsed multiple myeloma in people who have had 1 previous treatment. It noted that this population had an unmet need for further treatment options. The long-term survival on this treatment was unclear, and the company's and ERG's estimates of survival past the point for which there were trial data varied widely. Because of this the cost-effectiveness estimates also varied. The committee concluded that, without further data on survival from the ongoing CASTOR trial, it was not possible to further determine survival on daratumumab plus bortezomib plus dexamethasone. However, it noted that there was potential for daratumumab plus bortezomib plus dexamethasone to be cost effective if extra data supported the company's expectation of long-term survival. The committee therefore recommended daratumumab plus bortezomib plus dexamethasone as an option within the Cancer Drugs Fund for people with relapsed multiple myeloma who have had 1 previous treatment.

4 Implementation

- 4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has multiple myeloma and have had only 1 previous treatment and the doctor responsible for their care thinks that daratumumab plus bortezomib plus dexamethasone 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](#).
- 4.2 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 document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 Recommendations for data collection

- 5.1 As a condition of the positive recommendation and the managed access agreement, the company is required to collect updated efficacy data on overall survival from the CASTOR clinical trial.

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.

Mary Hughes and Marcela Haasova

Technical leads

Ahmed Elsada

Technical adviser

Jeremy Powell

Project manager

ISBN: 978-1-4731-3284-9

Accreditation

