NICE National Institute for Health and Care Excellence

NICE guidance

Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma

Technology appraisal guidance
Published: 6 June 2023

www.nice.org.uk/guidance/ta897

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 is 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.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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

This guidance replaces TA573.

1 Recommendations

1.1 Daratumumab with bortezomib and dexamethasone is recommended as an option for treating multiple myeloma in adults, only if they have had just 1 previous line of treatment and:

- it included lenalidomide or
- lenalidomide is unsuitable as a second-line treatment and
- the company provides it according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with daratumumab with bortezomib and 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

This evaluation reviews the evidence for daratumumab with bortezomib and dexamethasone from NICE technology appraisal guidance 573. It also reviews new data collected as part of the managed access agreement.

The company proposed daratumumab with bortezomib and dexamethasone as a second-line treatment, which is narrower than its marketing authorisation. Second-line treatments for multiple myeloma include:

- bortezomib with dexamethasone
- carfilzomib with dexamethasone
- lenalidomide with dexamethasone

- carfilzomib with lenalidomide and dexamethasone.

Clinical trial evidence shows that daratumumab with bortezomib and dexamethasone decreases the risk of dying and the chance of myeloma returning or getting worse compared with bortezomib with dexamethasone. There is no direct evidence comparing it with carfilzomib with dexamethasone. An indirect comparison suggests that it decreases the risk of the myeloma returning or getting worse compared with carfilzomib with dexamethasone. No evidence was provided for a comparison with the lenalidomide treatments.

The most likely cost-effectiveness estimates for daratumumab with bortezomib and dexamethasone are below what NICE considers an acceptable use of NHS resources. Because no comparison was done with lenalidomide treatments, daratumumab with bortezomib and dexamethasone is only recommended for people who cannot have lenalidomide as a second treatment. This includes people who had lenalidomide as their first treatment, or when lenalidomide is unsuitable as a second-line treatment.

2 Information about daratumumab with bortezomib and dexamethasone

Marketing authorisation indication

2.1 Daratumumab (Darzalex, Janssen) is indicated '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

2.2 The dosage schedule is available in the summary of product characteristics for daratumumab.

Price

2.3 The list prices for daratumumab (excluding VAT; BNF online, accessed February 2023) are:

- £4,320 per 1,800 mg/15 ml solution for injection vial
- £360 per 100 mg/5 ml concentrate for solution for infusion vial
- £1,440 per 400 mg/20 ml concentrate for solution for infusion vial.

2.4 The company has a commercial arrangement. This makes daratumumab with bortezomib and dexamethasone available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by Janssen, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

Treatment pathway

Daratumumab plus bortezomib and dexamethasone

3.1 This evaluation reviews the evidence for daratumumab plus bortezomib and dexamethasone for relapsed multiple myeloma, which was approved for use in the Cancer Drugs Fund in NICE technology appraisal guidance 573. It also reviews new data collected as part of the managed access agreement. The company presented evidence for daratumumab plus bortezomib and dexamethasone as a second-line treatment only, in line with the original company submission and recommendation in technology appraisal guidance 573. The committee recognised that limiting this treatment to second line was narrower than its marketing authorisation. But concluded that it would appraise daratumumab plus bortezomib and dexamethasone after only 1 previous treatment, having been presented only with evidence for its use as a second-line treatment.

Evolving treatment pathway

3.2 Multiple myeloma is a chronic condition that affects how long people live and their quality of life. A clinical expert described it as a relapsing and remitting disease with a complex and evolving pathway. The Cancer Drugs Fund clinical lead explained that each appraisal is a snapshot in time. They explained that since daratumumab plus bortezomib and dexamethasone was available through the Cancer Drugs Fund several new multiple myeloma drugs have been recommended for routine commissioning in the NHS. This has changed what would be offered to people with a new diagnosis, and what subsequent treatment is offered

to those who could have daratumumab plus bortezomib and dexamethasone. The committee acknowledged that this makes interpreting clinical trial evidence for this appraisal challenging, because the trial (see section 3.5) started several years ago and may not reflect the current multiple myeloma pathway. The committee noted that the company submission also included new data collected as part of the managed access agreement. It was aware that this data may have limitations because the managed access period mostly took place during the COVID-19 pandemic. The pandemic may have affected the data collected in 2 ways. First, by affecting the care pathway, because some other treatment options were made available for an interim period. Second, because there may be excess mortality associated with COVID-19 in people who had daratumumab plus bortezomib and dexamethasone. The committee agreed that it would consider these limitations in its decision making.

New treatment option

3.3 Patient experts stated that in their experience, daratumumab plus bortezomib and dexamethasone had very few side effects. This was echoed in a patient survey done by Myeloma UK, which said that 95% of respondents would recommend the treatment, despite some people having side effects. One patient expert noted that having daratumumab plus bortezomib and dexamethasone had dramatically increased their quality of life. They said it helped with maintaining day to day routines, and meant that they were likely to be well enough for more options later in the treatment pathway. They explained that this was important because the condition becomes more resistant to treatment with each relapse. The committee recognised the need for effective, well-tolerated treatment options for people with multiple myeloma who have had a previous treatment.

Comparators

3.4 Treatment options for people with newly diagnosed multiple myeloma depend on if a stem cell transplant is a suitable treatment option. Once the disease progresses, treatment options depend on what treatments people have had before, response to these treatments, and patient

preference. The committee noted that progression through the pathway is slow, and each remission and progression may span several years. It noted that treatment choice at each line may differ in clinical practice depending on when a person entered the treatment pathway, and what treatments have been available to them before. For someone who has had 1 previous line of treatment, currently available options at second line are:

- bortezomib (see NICE's technology appraisal guidance on bortezomib monotherapy for relapsed multiple myeloma)
- carfilzomib plus dexamethasone (see NICE's technology appraisal guidance on carfilzomib for previously treated multiple myeloma)
- lenalidomide plus dexamethasone (see NICE's technology appraisal guidance on lenalidomide with dexamethasone for multiple myeloma after 1 treatment with bortezomib)
- carfilzomib plus lenalidomide and dexamethasone (see NICE's technology appraisal guidance on carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma).

The committee considered the available treatment options and if these were appropriately included in the evidence presented. The company submission focused on second-line treatment options, including bortezomib plus dexamethasone and carfilzomib plus dexamethasone, which aligned with the comparators included in the NICE scope. The clinical expert explained that most people for whom a transplant is suitable would now have lenalidomide at first line, so would have bortezomib or carfilzomib combination treatments at second line. But they explained that some people would not progress through the transplant pathway to lenalidomide maintenance at first line, so would be able to have lenalidomide at a later line. They also noted that for those who cannot have a transplant, lenalidomide plus dexamethasone is the most widely used first-line treatment option in clinical practice, and accounts for 70% to 80% of treatments used. Anyone whose disease relapsed following lenalidomide would have bortezomib or carfilzomib as a second-line treatment. But the clinical expert explained that lenalidomide combinations were also used as second-line treatment options. For 20% to 30% of people who cannot have a transplant, bortezomib combination treatments would be the preferred first-

choice treatment. They explained this would be used if a finite period of treatment is preferred or if a rapid response is needed. The Cancer Drugs Fund clinical lead confirmed that all these treatments are used in NHS practice. But they explained that second-line lenalidomide use may currently be higher than estimated by the clinical expert, but that this reflected the slow evolution of the multiple myeloma pathway. That is, in the past, people may have had thalidomide or bortezomib as first-line treatment if lenalidomide had not been available at first line, so these people would be able to have lenalidomide at second line, though this proportion was likely to reduce over time. The committee noted that it is complicated to determine the relevant comparators because of the evolving treatment pathway. It concluded that bortezomib plus dexamethasone and carfilzomib plus dexamethasone were the main comparators for this appraisal. The committee was aware the lenalidomide combination treatments had not been included in the scope, but understood that some people would have lenalidomide combination treatments at second line in the NHS. The committee agreed it could not make a recommendation for this population because it had seen no evidence for it.

Clinical evidence

Data sources

3.5 Clinical evidence for daratumumab plus bortezomib and dexamethasone compared with bortezomib plus dexamethasone came from the CASTOR trial. CASTOR is an ongoing, randomised, open-label, multicentre, phase 3 trial. The population included adults with relapsed or refractory multiple myeloma. Because the company chose to focus on daratumumab plus bortezomib and dexamethasone as a second-line treatment (see section 3.1), it presented data from the trial for people who had only had 1 previous treatment. In the original submission for technology appraisal guidance 573, the CASTOR trial had a median follow up of 26.9 months. After the period of managed access, this was 50.2 months for progression-free survival and 72.6 months for overall survival. The trial evidence showed that daratumumab plus bortezomib and dexamethasone reduced the risk of disease progression or death by 79% (hazard ratio [HR] 0.21, 95% confidence interval [CI] 0.15 to 0.31) compared with bortezomib plus dexamethasone. Daratumumab plus

bortezomib and dexamethasone also reduced the risk of death by 44% (HR 0.56, 95% CI 0.39 to 0.80) compared with bortezomib plus dexamethasone. The committee questioned if previous treatment with bortezomib or daratumumab (both available at first line) would affect the results in the NHS. The clinical expert and Cancer Drugs Fund clinical lead explained that having bortezomib or daratumumab before is not expected to affect the effectiveness of daratumumab plus bortezomib and dexamethasone, if these treatments are used for a finite time rather than until disease progression. They noted that there are often several years between remissions. The committee concluded that the CASTOR trial showed that daratumumab plus bortezomib and dexamethasone is clinically effective compared with bortezomib plus dexamethasone. It further concluded that CASTOR was the most suitable source for establishing the relative effect of these 2 treatments.

Adjusting for subsequent treatments

3.6 The CASTOR trial was a global trial, which meant not all subsequent treatments used in the trial (at third line and beyond) are available in the NHS. Because alternative treatments may affect survival results, the company presented an inverse probability of censoring weights (IPCW) analysis to adjust the survival estimates. The adjusted HR showed a small but important difference in the clinical trial results. In the CASTOR trial some people had daratumumab as a subsequent treatment, but not at fourth line (where it is recommended in the NHS, see NICE's technology appraisal guidance on daratumumab monotherapy). If a person has daratumumab at an earlier line, they would not have fourth-line daratumumab monotherapy. At the committee meeting the company explained that the adjusted analyses from the trial estimated that only a proportion of people who had second-line bortezomib plus dexamethasone would have had had fourth-line daratumumab monotherapy (the exact figure is academic in confidence). The clinical expert noted that in the NHS most people who have not had a CD38 targeted therapy previously (for example, daratumamab or isatuximab) would have fourth-line daratumumab monotherapy. The committee agreed it is appropriate to adjust the analyses for subsequent treatments not available in the NHS, but that the company's adjusted analyses did not reflect current practice. It agreed that most people progressing to

fourth-line treatment who had not had a CD38 targeted therapy before would have fourth-line daratumumab monotherapy. This is because no other CD38 targeted therapies were routinely commissioned at the time of the first committee meeting. The committee was aware that daratumumab monotherapy was expected to have a survival benefit at fourth line. The committee noted that the benefit appeared to have been underestimated in the adjusted analysis for people who had bortezomib plus dexamethasone. So, the hazard ratio estimated by the IPCW analysis is likely to be biased in favour of daratumumab plus bortezomib and dexamethasone. The committee concluded that the adjusted and unadjusted HRs were associated with uncertainty and reflected the higher and lower bounds of clinical effectiveness. The true effect of daratumumab plus bortezomib and dexamethasone compared with bortezomib plus dexamethasone was likely to lie between the adjusted and unadjusted HRs.

Indirect comparison

3.7 There was no trial directly comparing daratumumab plus bortezomib and dexamethasone with carfilzomib plus dexamethasone. So, the company did a network meta-analysis using data from the second-line subgroup of CASTOR and ENDEAVOR (which compared carfilzomib plus dexamethasone with bortezomib plus dexamethasone). Evidence from the network meta-analysis showed that daratumumab plus bortezomib and dexamethasone improves overall survival and progression-free survival compared with carfilzomib plus dexamethasone. The committee concluded that the network meta-analysis was appropriate for decision making.

SACT dataset

3.8 The CASTOR trial took place across 16 countries, with no study centres in England. Interpreting the available evidence is difficult because the clinical trial happened several years ago and the current multiple myeloma pathway in England is significantly different to when the trial started (see section 3.6). The systemic anti-cancer therapy (SACT) dataset provides real world evidence for people having daratumumab plus bortezomib and dexamethasone in the NHS in England, starting in

March 2019. During the managed access period data was collected on overall survival and median treatment duration. A naive comparison shows that overall survival reported in the SACT dataset is lower than that reported in the CASTOR trial. The population in the SACT dataset was on average older than in CASTOR, but limited data was available on comorbidities and any increased risk of mortality. To address the differences in patient population between CASTOR and the SACT data, the company did a matching-adjusted indirect comparison. This adjusted for differences in various baseline characteristics, including age. But the results showed that the prognostic factors explored did not explain the differences between the datasets. The committee agreed that the SACT dataset is more likely to reflect the true experience of people having daratumumab plus bortezomib and dexamethasone in England, but that it has several limitations. It mostly took place during the COVID-19 pandemic, had a shorter follow-up time than the CASTOR trial and data was missing for key prognostic variables (such as ECOG performance status and international staging system). The committee noted that SACT data might include excess mortality because of COVID-19. The committee would have liked to have seen the survival outcomes for people who entered the SACT dataset before March 2020 to see if this projected a different survival curve than the complete managed access period. The patient experts explained that many people with multiple myeloma shielded through the pandemic, which reduced the risk of being infected. But they noted that people who had daratumumab plus bortezomib and dexamethasone were still attending hospital appointments at least once a month. One patient expert explained that if people with multiple myeloma were infected with SARS-CoV-2 (the virus that causes COVID-19) they were likely to have poorer outcomes than the general population in England. The clinical expert explained that the pandemic is also likely to have changed treatment decisions, because oral ixazomib with lenalidomide and dexamethasone was made available at second line. This aimed to reduce frequent visits to hospital for treatment injections. The Cancer Drugs Fund clinical lead said that the use of ixazomib with lenalidomide and dexamethasone peaked at 15% of second-line treatments. Because of the availability of alternative treatment options at second-line, some people had daratumumab plus bortezomib and dexamethasone at third line. But it was clarified that this proportion was very small and would be unlikely to affect the results. The

committee was aware of the limitations of the SACT data but noted that it included a larger sample size than the CASTOR trial. The committee concluded that the SACT data appeared to be a better source to estimate absolute (baseline) event rates for overall survival. This is because it better represented the population in NHS clinical practice than the CASTOR trial. But it further concluded that the impact of COVID-19 on survival outcomes from the SACT data was uncertain. The committee considered this during decision making.

Real-world evidence for bortezomib plus dexamethasone

3.9 Although the SACT data provided evidence for people having daratumumab plus bortezomib and dexamethasone in the NHS, there was no data for comparator treatments. The company used data from 3 real-world cohorts of people who did not have daratumumab plus bortezomib and dexamethasone, to compare overall survival with SACT data in a naive comparison. The committee noted that the comparisons were likely to be at high risk of bias because the populations included in the studies differed. The company also presented a scenario analysis where it simulated a bortezomib plus dexamethasone survival curve using the absolute (baseline) event rates from the SACT data and applying the relative treatment effect observed in CASTOR. The real-world cohorts were then used to validate this comparison. The EAG noted that although the naive comparison has limitations, the cohorts show a similar survival trajectory to the simulated bortezomib plus dexamethasone curve. The committee concluded the scenarios were associated with uncertainty but suggest that the relative effects seen in CASTOR would hold in clinical practice.

Economic model

Company's model

3.10 The company chose a partitioned survival model to estimate the cost effectiveness of daratumumab plus bortezomib and dexamethasone. The model included 3 health states: progression-free, progressed disease and death. The probability of being in a given health state was calculated

using the overall survival and progression-free survival curves. The model time horizon was 30 years. The model had the same structure as the original appraisal but included data from CASTOR and the indirect comparison in the network meta-analysis. Also, baseline characteristics for age and gender were updated to reflect those seen in the SACT dataset. The company explained that this increased the age-related mortality in the model because the starting age was higher. The committee concluded that the model structure is acceptable.

Modelling survival

3.11 The company's base case used updated data from CASTOR to simulate time to stopping treatment, progression-free survival, and overall survival. The company fitted parametric curves to the trial data for daratumumab plus bortezomib and dexamethasone and bortezomib plus dexamethasone to extrapolate the observed data beyond the period of follow up. After technical engagement, the company changed the parametric function used to extrapolate the data for the bortezomib plus dexamethasone arm. It selected the Weibull curve based on it having good visual and statistical fit, and clinical plausibility, estimating a small proportion of people would be alive at 10 years. To simulate the survival path of people who have carfilzomib plus dexamethasone, the company applied the HRs from the network meta-analysis to the daratumumab plus bortezomib and dexamethasone arm. The committee recalled it was appropriate to use the SACT data for estimating survival for people who had daratumumab plus bortezomib and dexamethasone. NICE's technical support document 13 recommends using registry data to estimate absolute baseline event rates, and that randomised evidence should be used to quantify relative differences. The committee also agreed that the company's approach for the comparison of daratumumab plus bortezomib and dexamethasone with bortezomib plus dexamethasone allowed the 2 curves to diverge over time. This may overestimate the benefit of daratumumab plus bortezomib and dexamethasone.

SACT scenarios

3.12 The company presented 2 exploratory scenario analyses using the SACT data. In both cases, the model estimated overall survival with

daratumumab plus bortezomib and dexamethasone using a Weibull curve fitted to the SACT data to extrapolate to the time horizon of the model. The company then simulated a bortezomib plus dexamethasone arm by applying the either the adjusted or unadjusted HRs for overall survival from CASTOR (that is, the relative effect between treatments estimated from the randomised data) to the extrapolated daratumumab plus bortezomib and dexamethasone data from SACT. The company made several assumptions to estimate progression-free survival in this analysis. These included using time to treatment stopping data from the SACT dataset and applying an HR from CASTOR to account for people stopping treatment for reasons other than disease progression. The committee noted this was a reasonable approximation because progression-free survival data was not captured in the SACT dataset. The company then applied the progression-free survival relative treatment effect HR from CASTOR (either adjusted or unadjusted) to estimate progression-free survival with bortezomib plus dexamethasone. Analyses that used the additional follow-up data available in CASTOR could have been useful to reduce some of the uncertainty. The committee noted that this could be done in several ways. For example, by applying the appropriate shape and scale parameters (using a Weibull distribution) to the CASTOR data and adjusting them so that they match the survival in the SACT data. Or, the CASTOR data could be used to extrapolate beyond the SACT follow-up period but with appropriate survival constraints. The committee concluded that although these additional scenarios would be informative, they would need additional assumptions. So the simulations based on SACT data extrapolations using the relative treatment effect from the trial were preferred to model survival for daratumumab plus bortezomib and dexamethasone, and bortezomib plus dexamethasone. The committee noted that using the fixed HR from the trial and applying it to the SACT data reduced the risk of overestimating the benefit of daratumumab plus bortezomib and dexamethasone. It agreed that both the adjusted and unadjusted hazard ratio should be considered for decision making because the IPCW analysis did not accurately reflect subsequent treatment use in the NHS (see sections 3.4 and 3.5, and section 3.13). The committee agreed that the scenarios were associated with uncertainty because of the unknown impact of COVID-19 on the survival estimates, but that it would consider this in its decision making.

Subsequent treatment costs

3.13 The company modelled the costs of subsequent treatments using a basket approach, applying one-off costs based on the CASTOR trial. The committee recalled that the trial happened several years ago and subsequent treatments did not reflect current NHS practice. The model only included 1 subsequent line of treatment applied for the proportion of people still alive at the point of disease progression. But in practice people who have multiple myeloma are likely to have several subsequent treatments. The committee agreed this simplification prevented full exploration of subsequent treatments and their effects on the cost-effectiveness modelling. It noted that lenalidomide plus dexamethasone as a subsequent line of treatment is likely to have been overestimated and was inconsistent with the assumption that most people have lenalidomide at first line (see section 3.3). The committee agreed that it would have preferred to see estimates where the proportion was close to zero for those who have daratumumab plus bortezomib and dexamethasone at second line. This is because this would reflect the current treatment pathway. The committee also noted that the costs and clinical estimates for subsequent daratumumab treatment were not aligned in the modelling. It noted that a higher proportion of people who had bortezomib plus dexamethasone had costs for fourth-line daratumumab monotherapy than the company stated had been included in the clinical estimates using the adjusted effectiveness data. This would bias the company's cost-effectiveness estimates in favour of daratumumab plus bortezomib and dexamethasone. The committee agreed that the basket costs applied for subsequent treatments are not likely to reflect current practice. It noted that this was likely to reflect the evolving treatment pathway and the simplistic application in the model, but the impact of subsequent treatments on the cost-effectiveness results is uncertain.

Utilities

3.14 The company used utility values in the model based on EQ-5D data collected in the ENDEAVOR trial, which was preferred during the original evaluation of daratumumab plus bortezomib and dexamethasone. Disutilities were applied based on the rate of grade 3 and 4 adverse

events in CASTOR trial. The clinical and patient experts explained that grade 1 or 2 adverse events would not lead to people stopping treatment but would likely affect quality of life. One patient expert explained the positive experience they had had while having daratumumab, with limited side effects. The committee noted that grade 1 and 2 events were not included in the modelling but noted that these were more frequent in the bortezomib plus dexamethasone arm of the trial. It concluded that there is likely a small underestimate on how daratumumab plus bortezomib and dexamethasone affects quality of life.

Cost-effectiveness estimates

Acceptable ICER

3.15 NICE's manual on health technology evaluation notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, decisions about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the evidence presented but will also take into account other aspects including uncaptured health benefits. The committee agreed that CASTOR trial showed that daratumumab plus bortezomib and dexamethasone is a clinically effective treatment. It noted that the benefit was likely to remain long term and the relative effect is likely to hold when used outside the clinical trial setting. It also heard from patient and clinical experts about the relative ease and lack of side effects associated with taking this treatment, and the importance of having the most effective treatments possible available at second line. The committee recognised that there was uncaptured health benefit from not including low-level side effects of treatment, and the ease of administration (including using subcutaneous administration instead of intravenous). It agreed that it would accept an ICER at the upper end of the acceptable range if this was based on more conservative modelling assumptions. This is because it would allow the committee to have more confidence that residual uncertainties would not result in the cost effectiveness estimates being above what NICE considers an acceptable

use of NHS resources.

Company and EAG cost-effectiveness estimates

3.16 Because of confidential commercial arrangements for daratumumab, bortezomib and post-progression treatments, the cost-effectiveness results are confidential and cannot be reported here. After technical engagement the company and EAG had the same base case, which used updated data from CASTOR to simulate time to stopping treatment, progression-free survival, and overall survival (see section 3.11). The committee agreed that its preferred scenarios for the comparison with bortezomib plus dexamethasone used the extrapolated daratumumab plus bortezomib and dexamethasone data from SACT, and applied the relative treatment effect from CASTOR to estimate outcomes in the bortezomib plus dexamethasone arm (see section 3.11). The preferred scenarios for the comparison with carfilzomib plus dexamethasone applied the relative treatment effect from the network meta-analysis to the same analysis. The committee agreed that uncertainty remained in 3 areas of the cost-effectiveness estimates:

- The effect of COVID-19 on the outcomes in the SACT dataset (see section 3.8).
- Adjusting the relative treatment effect from CASTOR to account for use of subsequent treatments not available in the NHS. The adjusted and unadjusted HRs reflected the higher and lower bounds of clinical effectiveness (see section 3.5).
- Modelling the costs of subsequent treatments (see section 3.13).

The committee recalled that although bortezomib plus dexamethasone and carfilzomib plus dexamethasone were the main comparators for this appraisal, a small proportion of people would have second-line lenalidomide combination treatments. Lenalidomide combination treatments were not included as comparators in the scope of this appraisal. The committee was not able to evaluate the comparisons to lenalidomide because no evidence was submitted. So the committee was not able to make a recommendation for people for whom lenalidomide may be considered at second line.

Conclusion

3.17 The most likely cost-effectiveness estimates for daratumumab plus bortezomib and dexamethasone are within what NICE considers an acceptable use of NHS resources. The committee concluded that daratumumab plus bortezomib and dexamethasone is recommended for treating multiple myeloma in adults who have had just 1 previous line of treatment and:

- it included lenalidomide or
- lenalidomide is unsuitable as a second-line treatment.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has multiple myeloma and the doctor responsible for their care thinks that daratumumab with bortezomib and dexamethasone is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Charles Crawley
Chair, technology appraisal committee B

NICE project team

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

Tom Jarratt
Technical lead

Lorna Dunning
Technical adviser

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Project manager

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