NICE guidance on daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma

On April 10, 2019, the National Institute for Health and Care Excellence (NICE) published guidance[1] that recommends daratumumab with bortezomib and dexamethasone within the Cancer Drugs Fund (CDF) as an option for treating relapsed multiple myeloma in people who have had one previous treatment, but only under the conditions in the managed access agreement.[2]

NICE appraised daratumumab with bortezomib and dexamethasone as a single technology appraisal. Janssen-Cilag (High Wycombe, UK) submitted evidence for clinical and cost-effectiveness,[3] which was critiqued by an evidence review group (ERG) at the Southampton Health Technology Assessments Centre.[3] An independent appraisal committee of health professionals, academics, lay members, and industry representatives met twice, considered the evidence, and developed the guidance. Clinical and patient experts attended the first meeting; company representatives attended both meetings.

In line with the then-anticipated marketing authorisation, the scope of the appraisal[4] covered adults with relapsed or refractory multiple myeloma who have had at least one previous treatment. The company chose to focus, however, on patients who have had only one previous treatment (for whom daratumumab with bortezomib and dexamethasone would be a second-line treatment), arguing that this would optimise clinical and cost-effectiveness.

In the UK National Health Service (NHS), patients with multiple myeloma not suitable for stem-cell transplantation receive either thalidomide or bortezomib as first-line treatment. Second-line treatment options include bortezomib retreatment, if bortezomib has been used as first-line treatment, and bortezomib with dexamethasone, or carfilzomib with dexamethasone, if thalidomide has been used as first-line treatment. The committee considered that, at second line, the principal comparator for daratumumab with bortezomib and dexamethasone is bortezomib with dexamethasone since this is available to everyone irrespective of previous therapy.

The key evidence came from CASTOR,[5] an open-label randomised controlled trial assessing daratumumab with bortezomib and dexamethasone against bortezomib with dexamethasone in previously treated patients with relapsed or refractory multiple myeloma. Focusing on second-line treatment, the company presented data from the subgroup of participants in CASTOR who had had only one previous therapy, noting that randomisation in CASTOR was stratified by the number of previous treatments. The primary outcome of the trial was progression-free survival. In its original submission, the company presented results from a prespecified analysis (the first interim analysis), after a median follow-up of 27 months. Over the course of the appraisal, the committee considered results provided in confidence from two later data cutoffs, reflecting median follow-ups of 31 months and 40 months.

In the subgroup of patients who had had only one previous therapy, median progression-free survival from the first interim analysis was 26 months for daratumumab with bortezomib and dexamethasone and 8 months for bortezomib with dexamethasone (hazard ratio [HR] 0·23 [95% CI 0·16–0·33]; p<0·0001). The committee understood that clinicians considered an 18-month improvement in median progression-free survival a substantial effect.

Data about overall survival from CASTOR were immature, with more than half of patients in both groups still alive at the first interim analysis. The available data showed that daratumumab with bortezomib and dexamethasone reduced the risk of death compared with bortezomib with dexamethasone (HR 0·50 [95% CI 0·30–0·84]; p=0·008). Results from later data cutoffs were consistent with the first interim analysis, but the data remained immature, making the committee unable to judge the long-term effect of daratumumab with bortezomib and dexamethasone on overall survival. The company presented data on minimal residual disease, which showed that, in the overall trial population, 12% of patients randomly assigned to daratumumab with bortezomib and dexamethasone had no residual disease, compared with 2% of those randomly assigned to bortezomib with dexamethasone. The company suggested that this difference in residual disease would translate into longer survival in people who have daratumumab with bortezomib and dexamethasone. The committee concluded that it was not unreasonable to expect some people with no residual disease to live longer than those with residual disease, but that this had not been established and could not inform the economic model.

To compare daratumumab with bortezomib and dexamethasone with carfilzomib plus dexamethasone, the company did a network meta-analysis with data from the second-line subgroups of CASTOR and ENDEAVOR.[6] The committee judged this comparison to be uncertain because of differences between the two studies and doubts about whether the results applied to people who have not had previous bortezomib (ie, those eligible for carfilzomib in the UK NHS).

Published Online
April 10, 2019
http://dx.doi.org/10.1016/S1470-2045(19)30222-0

For the analysis of cost-effectiveness, the company developed an economic model. In this model, it estimated the difference in average life expectancy between the two treatment groups by extrapolating CASTOR survival data adjusted for the effect of third-line and later-line treatments received in the trial but likely to prolong survival and not available in the NHS. The committee appreciated that the extrapolation spanned more than ten times the duration of the actual trial follow-up, which introduced substantial uncertainty. The company and the ERG preferred different statistical distributions to extrapolate the survival curves. The committee discussed the predictions for long-term survival, and agreed that, although they fell within a plausible range, it preferred the ERG's more conservative estimates because the uncertainty in the extrapolation was too high. The company suggested that survival on daratumumab with bortezomib and dexamethasone should be modelled with a decreasing risk of death over time to reflect a greater chance of having no minimal residual disease as people live longer. The committee agreed that the assumption of a decreasing risk of death over time was speculative, and that it needed to see more data to be convinced of such an effect.

To model quality of life before and after disease progression, the company used EQ-5D data collected from the subgroup of patients who had received only one previous therapy in CASTOR. The ERG considered the difference between the company's utility values before and after progression (0·03) to be implausibly small, so it preferred utility values from ENDEAVOR even though these were not from the main trial or derived from EQ-5D, the preferred quality-of-life measure in the NICE methods guide.[7]

Based on the company's exponential curve to predict long-term overall survival with daratumumab with bortezomib and dexamethasone and utility values from CASTOR, the incremental cost-effectiveness ratio (ICER) lay between £30 000 and £40 000 per quality-adjusted life-year (QALY) gained compared with bortezomib with dexamethasone. This amount increased to £40 000–50 000 per QALY in the ERG's analysis by use of a Weibull curve to predict long-term survival with daratumumab with bortezomib and dexamethasone and utility values from ENDEAVOR. The ICERs for the comparison with carfilzomib and dexamethasone were less robust than the comparison with bortezomib and dexamethasone. The committee's preferred ICER was closer to the ERG's estimate, which better reflected the level of evidence supporting survival modelling, and concluded that daratumumab with bortezomib and dexamethasone did not represent a cost-effective use of NHS resources.

The committee considered whether it could recommend daratumumab with bortezomib and dexamethasone within the CDF, noting the arrangements for the CDF agreed by NICE and NHS England in 2016, and NICE's CDF methods guide.[8] It considered that there was substantial unmet need at the point of second-line treatment, and that daratumumab with bortezomib and dexamethasone was an innovative treatment providing a step-change in treatment of multiple myeloma. The key uncertainties in the evidence were the long-term survival with daratumumab with bortezomib and dexamethasone (ie, whether the company's or ERG's estimates were more plausible). The committee heard that the ongoing CASTOR trial will provide up to 4 more years of data, which it considered could reduce the uncertainty around the survival estimates, and would lower the ICERs for daratumumab with bortezomib and dexamethasone compared with bortezomib with dexamethasone if further data support the company's claim that a person's risk of dying decreases over time on daratumumab with bortezomib and dexamethasone. The committee considered that daratumumab with bortezomib and dexamethasone had the plausible potential to be cost-effective, required for making a recommendation within the CDF. The committee therefore recommended daratumumab with bortezomib and dexamethasone within the CDF as an option for treating relapsed multiple myeloma in people who have had one previous treatment, under the conditions in the managed access agreement.

We declare no competing interests.

Ahmed Elsada, Amanda I Adler
ahmed.elsada@nice.org.uk

National Institute of Health and Care Excellence, London SW1A 2BU, UK (AE); Addenbrooke's Hospital, Cambridge, UK (AA)

1 NICE. NICE technology appraisal guidance 573. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma. April, 2019. http://www.nice.org.uk/guidance/TA573 (accessed April 10, 2019).
2 NICE. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma [ID974]. Cancer Drugs Fund—Data Collection Arrangement. March 12, 2019. https://www.nice.org.uk/guidance/gid-ta10174/documents/committee-papers-4 (accessed March 22, 2019).
3 NICE. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma [ID974]: committee papers. July 12, 2018. https://www.nice.org.uk/guidance/gid-ta10174/documents/committee-papers (accessed March 22, 2019).
4 NICE. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma [ID974]: final scope. Jan 3, 2018. https://www.nice.org.uk/guidance/gid-ta10174/documents/final-scope (accessed March 22, 2019).
5 Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; **375:** 754–66.
6 Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol* 2016; **17:** 27–38.
7 NICE. Guide to the methods of technology appraisal 2013. April, 2013. https://www.nice.org.uk/process/pmg9/chapter/foreword (accessed March 22, 2019).
8 NICE. NICE technology appraisal guidance: Cancer Drugs Fund. https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/cancer-drugs-fund (accessed March 22, 2019).