NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Daratumumab in combination for newly diagnosed systemic amyloid light-chain amyloidosis

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of daratumumab within its marketing authorisation in combination for newly diagnosed systemic amyloid light-chain amyloidosis.

Background

Amyloid light-chain (AL) amyloidosis is caused by plasma cells in the bone marrow producing abnormal forms of light-chain proteins. These can form amyloid deposits, which clump together into amyloid fibrils and build up as deposits in tissues and organs, gradually stopping them from functioning normally. AL amyloidosis usually affects multiple organs, but 1 organ is often more affected than others. Any organ except the brain can be involved. AL amyloidosis can cause general symptoms such as weight loss, fatigue, weakness, loss of appetite and bruising, and can also lead to kidney disease, heart disease, neuropathy, gastrointestinal problems, skin disease and joint disease.

About 500 to 600 cases of AL amyloidosis are diagnosed each year in the UK[1]. The 1-year mortality rate is estimated to be around 40%[2].

There is no standard treatment for AL amyloidosis. Current treatment options are based on anti-myeloma therapy, including immunomodulatory drugs (such as thalidomide) and proteasome inhibitors (such as bortezomib). A person's age, comorbidities, the extent of organ involvement and personal treatment preferences are taken into account when considering treatment options. Autologous stem cell transplant with high dose melphalan may be an option for some people aged up to 65 to 70 years. A palliative treatment approach may be appropriate for people with worse disease[3].

The technology

Daratumumab (Darzalex, Janssen) is a monoclonal antibody that binds to the cell-surface protein CD38, inhibiting the growth of these cells. CD38 is expressed on the plasma cells that produce the abnormal light-chain proteins, so inhibiting the growth of these cells may reduce the production of these proteins. It is available as an intravenous infusion, however the clinical trial referred to below used a subcutaneous formulation.

Daratumumab does not currently have a marketing authorisation in the UK for newly diagnosed systemic amyloid light-chain amyloidosis. If has been studied in a clinical trial with cyclophosphamide, bortezomib and dexamethasone (CyBorD), compared with CyBorD alone, in people with newly diagnosed systemic AL amyloidosis.

Intervention(s)	Daratumumab with cyclophosphamide, bortezomib and dexamethasone (CyBorD)
Population(s)	People with newly diagnosed systemic AL amyloidosis
Comparators	Established clinical management without daratumumab. This may include: • Melphalan and dexamethasone • Melphalan alone • Bortezomib with dexamethasone, an alkylating treatment and/or immunomodulatory drugs • Thalidomide, cyclophosphamide and dexamethasone • Autologous stem cell transplant with high dose melphalan • Best supportive care (None of the comparators listed currently have a marketing authorisation in the UK for this indication)
Outcomes	The outcome measures to be considered include: • complete haematologic response • response rates • progression-free survival • overall survival • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.

Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. The availability and cost of biosimilar and generic products should be taken into account.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (2019) NICE technology appraisal 573 Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (2018) NICE technology appraisal 510 **Terminated appraisals:** Daratumumab with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (terminated appraisal) (2017) NICE technology appraisal 454 **Appraisals in development (including suspended appraisals):** Daratumumab in combination for untreated multiple myeloma when stem cell transplant is suitable. NICE technology appraisal guidance ID1510. Publication date to be confirmed. Daratumumab in combination for untreated multiple myeloma when stem cell transplant is unsuitable. NICE technology appraisal guidance ID1492. Publication date to be confirmed. Carfilzomib with daratumumab and dexamethasone for treating relapsed or refractory multiple myeloma. NICE technology appraisal guidance ID2709. Expected publication date: 21 April 2021. Daratumumab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma. NICE technology appraisal guidance ID3775. Publication date to be confirmed. Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma. NICE technology appraisal guidance ID1352. Suspended.
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapter 46. Diagnostic service for amyloidosis (adults and children) Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domain 2. https://www.gov.uk/government/publications/nhs-outcomes-

	framework-2016-to-2017

Questions for consultation

Have all relevant comparators for daratumumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS newly diagnosed systemic amyloid light-chain amyloidosis? How should best supportive care be defined? Is stem cell transplant a relevant comparator – is the population likely to be eligible for treatment with daratumumab similar to the population eligible for a stem cell transplant?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom daratumumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which daratumumab will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

Do you consider daratumumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of daratumumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the appraisal committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1. Amyloidosis Patient Information Site. Understanding AL Amyloidosis. [online, accessed March 2020]

2. Gertz MA. (2018) Immunoglobulin light chain amyloidosis: 2018 update on diagnosis, prognosis, and treatment. American Journal of Hematology 93(9): 1169-1180

3. Wechalekar AD, Gillmore JD, Bird J et al. on behalf of the BCSH Committee (2014) Guidelines on the management of AL amyloidosis. British Journal of Haematology 168: 186-206