Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Pembrolizumab in combination with pomalidomide and dexamethasone for treated multiple myeloma

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of pembrolizumab in combination with pomalidomide and dexamethasone within its marketing authorisation for treated multiple myeloma.

Background

Multiple myeloma is a form of cancer that arises from plasma cells (a type of white blood cell) in the bone marrow. Myeloma cells produce large quantities of an abnormal antibody, known as paraprotein. Unlike normal antibodies, paraprotein has no useful function and lacks the capacity to fight infection. Myeloma cells supress the development of normal blood cells that are responsible for fighting infection (white blood cells), carrying oxygen around the body (red blood cells) and blood clotting (platelets). The term multiple myeloma refers to the presence of more than one site of affected bone at the time of diagnosis. People with multiple myeloma can experience bone pain, bone fractures, tiredness (due to anaemia), infections, hypercalcaemia (too much calcium in the blood) and kidney problems.

In 2014, 4,652 people were diagnosed with multiple myeloma in England.[1] It is most frequently diagnosed in older people, with 45% of people diagnosed aged 75 years and over.[2] Multiple myeloma is more common in men than in women and the incidence is also reported to be higher in people of African and Caribbean family origin. The 5-year survival rate for adults with multiple myeloma in England and Wales is estimated to be 47%.[3]

Multiple myeloma is an incurable disease. The main aims of therapy are to prolong survival and maintain a good quality of life by controlling the disease and relieving symptoms. The choice of subsequent therapy is influenced by previous treatment and response to it, duration of remission, comorbidities and patient preference.

For people whose disease is relapsed or refractory after at least 1 prior therapy:

- NICE technology appraisal guidance 129 recommends bortezomib monotherapy as an option for people who are at first relapse having had 1

prior therapy and who have undergone, or are unsuitable for bone marrow transplantation.[1]

For people who have had at least 2 prior therapies:

- NICE technology appraisal guidance 171 recommends lenalidomide in combination with dexamethasone as a treatment option.

- NICE technology appraisal guidance 380 recommends panobinostat in combination with bortezomib and dexamethasone as a treatment option for people with relapsed and refractory multiple myeloma who have received at least 2 prior therapies including bortezomib and an immunomodulatory agent.

For people who have had at least 3 prior therapies:

- NICE technology appraisal guidance 427 recommends pomalidomide in combination with low –dose dexamethasone for treating multiple myeloma in adults at third or subsequent relapse

- Other treatment options include bendamustine (available through the Cancer Drugs Fund) or conventional chemotherapy regimens (for example, alkylating agents such as melphalan and cyclophosphamide).

Carfilzomib [ID934], daratumumab [ID933] and ixazomib citrate [ID807[are each subject to ongoing NICE appraisals for relapsed and refractory multiple myeloma.

The technology

Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised, antiprogrammed cell death 1 (PD-1) antibody involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells. It is administered intravenously.

Pembrolizumab does not have a marketing authorisation in the UK for treating multiple myeloma. It has been studied in combination with pomalidomide and dexamethasone compared with pomalidomide and dexamethasone alone in adults who have had 2 or more prior treatments of anti-myeloma therapy (immunomodulatory drug and proteasome inhibitor alone or in combination) and had been refractory to last therapy taken. People must have had no prior allogeneic haematopoietic stem cell transplantation within the last 5 years.

Intervention(s)	Pembrolizumab in combination with pomalidomide and dexamethasone

[1] TA129 did not cover bortezomib in combination with either pegylated liposomal doxorubicin or dexamethasone. TA129 did not make a recommendation for treating multiple myeloma after second or subsequent relapse.

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Population(s)	Adults with relapsed or refractory multiple myeloma who have been treated with a proteasome inhibitor and an immunomodulatory agent and whose disease has progressed on the last therapy
Comparators	For people who have had at least 2 therapies: • lenalidomide with dexamethasone • panobinostat with bortezomib and dexamethasone • Carfilzomib and dexamethasone with or without lenalidomide (subject to NICE guidance) • Daratumumab (subject to NICE guidance) • Ixazomib in combination with lenalidomide and dexamethasone (subject to NICE guidance) For people who have had at least 3 prior therapies: • Pomalidomide with dexamethasone (people must have had treatment with lenalidomide and bortezomib) • Panobinostat with bortezomib and dexamethasone • Carfilzomib and dexamethasone with or without lenalidomide (subject to NICE guidance) • Daratumumab (subject to NICE guidance) • Bendamustine (not appraised by NICE but funded through the Cancer Drugs Fund; does not currently have a marketing authorisation in the UK for this indication) • Conventional chemotherapy regimens (including but not limited to melphalan and cyclophosphamide)
Outcomes	The outcome measures to be considered include: • progression-free survival • overall survival • response rates • time to next treatment • adverse effects of treatment • health-related quality of life.

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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 patient access schemes for the intervention or comparator technologies 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. If the evidence allows, subgroup analyses based on number of lines of previous therapy will be considered
Related NICE recommendations and NICE Pathways	'Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib' (2017). NICE Technology Appraisal 427. Review date January 2020. 'Panobinostat for treating multiple myeloma after at least 2 previous treatments' (2016). NICE Technology Appraisal 380. Review date January 2019. 'Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy' (2009). NICE Technology Appraisal 171. Static list. 'Bortezomib monotherapy for relapsed multiple myeloma' (2007). NICE Technology Appraisal 129. Static list. **Appraisals in development (including suspended appraisals):** 'Lenalidomide for treating multiple myeloma after 1 prior treatment with bortezomib'. Part review of TA171. NICE technology appraisals guidance [ID667]. Publication date to be confirmed. 'Carflizomib for previously treated multiple myeloma' NICE technology appraisals guidance [ID934].

	Publication expected May 2017. 'Daratumumab for treating relapsed and refractory multiple myeloma' NICE technology appraisals guidance [ID933]. Publication date July 2017. 'Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma' NICE technology appraisals guidance [ID807]. Publication expected August 2017. 'Elotuzumab for treating relapsed or refractory multiple myeloma' Proposed NICE technology appraisal [ID855]. (suspended appraisal). **Related Guidelines:** NICE Guideline 35, Myeloma: diagnosis and management of myeloma. February 2016. **Related NICE Pathways:** Multiple myeloma: http://pathways.nice.org.uk/pathways/myeloma
Related National Policy	NHS England Manual for prescribed specialised services 2016/2017. Blood and marrow transplantation services (all ages). Chapter 29. https://www.england.nhs.uk/commissioning/specservices/npc-crg/blood-and-infection-group-f/f01/ Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1,2,4 and 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for pembrolizumab (in combination with pomalidomide and dexamethasone) been included in the scope? Which treatments are considered to be established clinical practice in the NHS for previously treated multiple myeloma?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom pembrolizumab (in combination with pomalidomide and dexamethasone) is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider pembrolizumab (in combination with pomalidomide and dexamethasone) will fit into the existing NICE pathway, 'Myeloma'?

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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 pembrolizumab (in combination with pomalidomide and dexamethasone) 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 pembrolizumab in combination with pomalidomide and dexamethasone 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 pembrolizumab in combination with pomalidomide and dexamethasone 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.

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] Cancer Research UK 'Myeloma incidence by sex and UK region'. Accessed February 2017.
[2] Cancer Research UK 'Myeloma incidence'. Accessed February 2017.
[3] Cancer Research UK 'Myeloma survival'. Accessed February 2017.