NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Selinexor with low-dose dexamethasone for treating refractory multiple myeloma

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of selinexor with low-dose dexamethasone within its marketing authorisation for treating refractory 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 suppress the development of normal blood cells that are responsible for fighting infection, carrying oxygen around the body and blood clotting. 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, infections, hypercalcaemia (too much calcium in the blood) and kidney problems.

In 2015, 4,632 people were diagnosed with multiple myeloma in England.[1] It is most frequently diagnosed in older people, with 44% of new cases in England in people 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 family origin.[3] The 5-year survival rate for adults with multiple myeloma in England and Wales is about 47%.[4]

Multiple myeloma is an incurable disease. Treatment aims to prolong survival and maintain a good quality of life. There are a number of possible treatment sequences for multiple myeloma, based on the following NICE technology appraisal (TA) guidance:

First line	• Thalidomide or bortezomib, plus an alkylating agent and a corticosteroid (TA228).
Second line	• Bortezomib monotherapy (TA129). • Carfilzomib in combination with dexamethasone only if previous therapy did not include bortezomib (TA457).
Third line	• Lenalidomide (TA171). • Panobinostat in combination with bortezomib and dexamethasone for people who have had at least 2 prior therapies (TA380). • Ixazomib in combination with lenalidomide and dexamethasone, for use within the Cancer Drugs Fund

	(TA505).
Fourth line	• Panobinostat plus bortezomib and dexamethasone (TA380). • Pomalidomide plus dexamethasone (TA427). For use within the Cancer Drugs Fund: • Daratumumab monotherapy (TA510). • Ixazomib in combination with lenalidomide and dexamethasone for use within the Cancer Drugs Fund (TA505).
Fifth line	No standard of care. Bendamustine is available within the Cancer Drugs Fund where other treatments are not appropriate.

The technology

Selinexor (KPT-330, Karyopharm Therapeutics) is a selective inhibitor of nuclear export, which works by blocking the protein called exportin 1 (XPO1). Preventing the action of XPO1 proteins enhances anti-cancer proteins and induces death of cancerous cells. It is administered orally.

Selinexor does not currently have a marketing authorisation in the UK for treating multiple myeloma. It has been studied in combination with low-dose dexamethasone in a single-arm clinical trial in adults with multiple myeloma who:

- have had 3 or more prior therapeutic regimens including: an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab and a glucocorticoid, and

- are refractory to previous treatment with one or more glucocorticoid, a proteasome inhibitor (bortezomib and or carfilzomib), an immunomodulatory agent (lenalidomide and or pomalidomide) and an anti-CD38 monoclonal antibody (daratumumab).

A pre-specified subgroup of the study contained participants described as “penta-refractory”, who had previously received bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab, as well as alkylating agents, and whose disease was refractory to at least 3 of these. This group had had a median of 7 previous therapies.

Intervention(s)	Selinexor with low-dose dexamethasone
Population(s)	People with refractory multiple myeloma

Comparators	• Pomalidomide in combination with low-dose dexamethasone • Panobinostat in combination with bortezomib and dexamethasone • Ixazomib in combination with lenalidomide and dexamethasone • Daratumumab monotherapy • Bendamustine (not appraised by NICE but funded via the Cancer Drugs Fund; does not currently have a marketing authorisation in the UK for this indication) • Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • 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.
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.
Related NICE recommendations	**Related Technology Appraisals:** Bortezomib monotherapy for relapsed multiple myeloma

and NICE Pathways	(2007) NICE technology appraisal guidance 129. Static list. Carfilzomib for previously treated multiple myeloma (2017) NICE technology appraisal guidance 457. Review date July 2020. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (2018). NICE Technology Appraisal 510. Review date November 2020. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (2018). NICE Technology Appraisal 505. Review date December 2019. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (2009) NICE technology appraisal guidance 171. Static list. Panobinostat for treating multiple myeloma after at least 2 previous treatments (2016). NICE Technology Appraisal 380. Review date January 2019. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (2017). NICE Technology Appraisal 427. Review date January 2020. **Terminated appraisals** Bortezomib for treating multiple myeloma after second or subsequent relapse (terminated appraisal) (2017) NICE technology appraisal guidance 453. Daratumumab with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (terminated appraisal). NICE technology appraisal 454. Elotuzumab for previously treated multiple myeloma (terminated appraisal). NICE technology appraisal guidance 434. **Appraisals in development (including suspended appraisals)** Daratumumab with bortezomib for treating relapsed or refractory multiple myeloma [ID974] NICE technology appraisal guidance. Publication date to be confirmed. Elotuzumab with pomalidomide and dexamethasone for treating multiple myeloma after 2 therapies [ID1467] NICE technology appraisal guidance. Suspended. Ixazomib with lenalidomide and dexamethasone for untreated multiple myeloma [ID1170] NICE technology

	appraisal guidance. Publication date to be confirmed Pembrolizumab for previously treated multiple myeloma [ID1139] NICE technology appraisal guidance. Suspended. Plitidepsin with dexamethasone for treating relapsed or refractory multiple myeloma [ID1081] NICE technology appraisal guidance. Suspended. Pomalidomide in combination with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma [ID1358] NICE technology appraisal guidance. Suspended. Vorinostat in combination with bortezomib for the treatment of multiple myeloma in people who have received at least one prior therapy [ID501] NICE technology appraisal guidance. Suspended. **Related Guidelines:** Myeloma: diagnosis and management (2016). NICE guideline 35. Review date February 2019. **Related Guidelines:** Haematological cancers – improving outcomes (2016) NICE guideline 47 Review date to be confirmed. Myeloma: diagnosis and management of myeloma (2016). NICE guideline 35. Review date to be confirmed. **Related Quality Standards:** Haematological cancers (2017) NICE quality standard 150 **Related NICE Pathways:** Myeloma (2017) NICE pathway
Related National Policy	NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapter 29: blood and marrow transplantation services (adults and children) p98 NHS England (Jan 2015) National chemotherapy algorithms - multiple myeloma Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1 and 2.

Questions for consultation

Have all relevant comparators for selinexor with low-dose dexamethasone been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for refractory multiple myeloma after at least 3 prior therapies?

How should best supportive care be defined?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom selinexor with low-dose dexamethasone is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider selinexor with low-dose dexamethasone will fit into the existing NICE pathway, myeloma?

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 selinexor 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 selinexor 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 selinexor 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).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?

- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?

- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?

- Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

[1] Cancer Research UK 'Myeloma incidence by sex and UK region'. Accessed November 2018.
[2] Office of national statistics 'Cancer registration statistics, England'. Accessed November 2018.
[3] National cancer institute 'SEER Cancer Statistics Review, 1975-2008'. Accessed November 2018.
[4]Cancer Research UK 'Myeloma survival'. Accessed November 2018.