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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2020

Selinexor in addition to bortezomib and low-dose dexamethasone for relapsed or refractory multiple myeloma

NIHRIO ID	10759	**NICE ID**	10221
Developer/Company	Karyopharm Therapeutics Inc	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase III clinical trial

SUMMARY

Selinexor, in addition to bortezomib and low-dose dexamethasone, is in clinical development for the treatment of adults with relapsed or refractory multiple myeloma (RRMM) who have received 1 to 3 prior therapies. MM is a rare, incurable cancer of the plasma cells in the bone marrow where large amounts of abnormal plasma cells are produced and interfere with the production of red and white blood cells and platelets. People with MM will experience periods of time without symptoms followed by periods when the illness comes back ('relapsed' MM). Eventually, the periods without symptoms will shorten and the illness will become immune to the drugs given to treat it ('refractory' MM).

Selinexor is the first in a new family of drugs known as selective inhibition of nuclear export (SINE) compounds that blocks a protein called XPO1. By blocking XPO1, Selinexor blocks the nuclear export of tumour suppressor, growth regulatory, and anti-inflammatory proteins, leading to accumulation of these proteins in the nucleus and enhancing their anti-cancer activity in the cell. Bortezomib and low-dose dexamethasone are already currently used in progressive MM. If licensed, the addition of Selinexor to bortezomib and low-dose dexamethasone would increase the treatment options for RRMM, a patient group with clear unmet need.

PROPOSED INDICATION

Treatment of adults with relapsed or refractory multiple myeloma (RRMM) who have received 1 to 3 prior anti-multiple myeloma (MM) regimens.[1]

TECHNOLOGY

DESCRIPTION

Selinexor is a first-in-class orally bioavailable selective inhibitor of nuclear export (SINE) compound that specifically blocks the action of a protein called exportin 1 (XPO1) by forming a slowly reversible covalent bond at cysteine-528 in the cargo-binding groove of XPO1. XPO1 is found at high levels in many cancer cells, where it prevents the actions of proteins that help stop cancer growth. By inhibiting XPO1, selinexor forces the nuclear retention and functional activation of TSPs and prevents the translation of oncoprotein mRNAs. This leads to the selective induction of apoptosis in malignant cells, but largely sparing normal cells.[2-4]

Selinexor in addition to bortezomib and low-dose dexamethasone is currently in phase III clinical development for the treatment of adults with RRMM who have received 1 to 3 prior anti-MM regimens. In a phase III clinical trial (BOSTON; NCT03110562), participants will receive oral of selinexor 100 mg (once a week) plus subcutaneous injection of bortezomib 1.3 mg/m^2 and oral dose of dexamethasone 20 mg, or subcutaneous injection of bortezomib 1.3 mg/m^2 and oral dose of dexamethasone 20 mg in the comparator group. Each treatment cycle will have 35 days. Details of the dosing regimen and administration schedule assessed in each study are detailed in the clinical trial table section of this briefing.[1]

INNOVATION AND/OR ADVANTAGES

Despite significant improvements in the overall survival of patients with MM, the disease remains incurable and accounts for >80,000 annual deaths worldwide. Treatment options are limited for patients with MM whose disease has relapsed or is refractory to standard immunomodulatory drugs and proteasome inhibitors. XPO1 is one of eight known mammalian karyopherins responsible for the nuclear export of >200 cargo proteins, including nearly all tumour suppressor proteins (TSPs). In MM, XPO1 is overexpressed, leading to enhanced transport of TSPs out of the nucleus and allowing cancer cells to evade genome surveillance and cell-cycle regulation. Using genome-scale RNA interference, XPO1 was identified as a selective vulnerability in MM.[2]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Selinexor either monotherapy or in combination with bortezomib and dexamethasone does not currently have Marketing Authorization in the EU for any indication.

Selinexor is in phase III clinical development for dedifferentiated liposarcoma and endometrial cancer.[5] Selinexor is also in phase II clinical development for several indication such as diffuse large B-cell lymphoma, ovarian carcinoma, endometrial carcinoma, cervical carcinoma, breast cancer, glioblastoma, glioma, acute myeloid leukaemia, dedifferentiated liposarcoma, primary myelofibrosis, post-essential thrombocythemia myelofibrosis, post-polycythemia vera myelofibrosis, thymoma, advanced thymic epithelial tumor, non-small cell lung cancer, leukemia, and myelodysplastic syndromes.[6]

Selinexor was granted EU orphan drug designation in November 2014 for the treatment of plasma cell myeloma.[7]

PATIENT GROUP

DISEASE BACKGROUND

MM is a blood cancer arising from plasma cells (a type of white blood cell made in the bone marrow). Plasma cells form part of the immune system. Normal plasma cells produce antibodies, also called immunoglobulins, to help fight infection. MM develops when DNA is damaged during the development of a plasma cell. This abnormal cell then starts to multiply and spread within the bone marrow. The abnormal plasma cells release a large amount of a single type of antibody – known as paraprotein – which has no useful function.[8]

Unlike many cancers, MM does not exist as a lump or tumour. Most of the medical problems related to MM are caused by the build-up of abnormal plasma cells in the bone marrow and the presence of the paraprotein in the body. MM is called so because cancer often affects several areas of the body, such as the spine, skull, pelvis and ribs.[8,9] In the early stages, MM may not cause any symptoms. Eventually, MM causes a wide range of problems, including a persistent dull ache or areas of tenderness in the bones, weak bones that break easily, tiredness, weakness and shortness of breath caused by anaemia, repeated infections, and kidney problems. Less commonly, MM may cause bruising and unusual bleeding such as frequent nosebleeds, bleeding gums and heavy periods.[9]

Relapsed and refractory myeloma is defined as a disease that is nonresponsive while on salvage therapy or progresses within 60 days of last therapy in patients who have achieved minimal response or better at some point previously before then progressing in their disease course.[10]

The cause of MM is still unknown. There are some factors that are linked to a higher risk of MM such as having a condition called monoclonal gammopathy of unknown significance (MGUS), male gender, older age (60 years and over), black people, family history of MM or MGUS, and overweight/obesity.[9,11] MM disease-related events and subsequent disability may have different importance for the patient in different periods of the disease. Therapeutic interventions may also produce troublesome side effects and functional impairments.[12]

CLINICAL NEED AND BURDEN OF DISEASE

In 2016 myeloma was the 19th most common cancer in the UK accounting for 2% of all new cancer cases.[13] In England, in 2017, there were 5,034 newly diagnosed cases of MM and malignant plasma cell neoplasms (ICD-10: C90).[14] Incidence rates for MM in the UK are highest in people aged 85 to 89 years (2014-2016). Over the last decade, incidence rates have increased by a seventh (15%) represented by an increase in females of 12% and 15% for males. Incidence rates are projected to rise by 11% in the UK between 2014 and 2035 to 12 cases per 100,000 by 2035.[13]
In England in 2018-2019 there were 142,827 finished consultant episodes (FCE), 137,870 hospital admissions with a primary diagnosis of MM (ICD-10 code C90.0), resulting in 89,190 FCE bed days and 126,115 day cases.[15] In England in 2017, there were 2,756 registrations of death where MM was recorded as the underlying cause.[16]

Almost half (47%) of people diagnosed with myeloma in England and Wales survive their disease for 5 years or more, with a third surviving for 10 years or more (2010-11).[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The choice of therapy in the relapsed setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (i.e. clinical versus biochemical relapse; in the case of biochemical relapse, treatment can be delayed).[18]

A multidisciplinary team will discuss the best treatment option for the patient.[19] Treatment for MM can often help to control symptoms and improve quality of life. However, MM is incurable and relapsed MM needs additional treatment. The initial treatment for MM may be either non-intensive (for older or less fit patients) or intensive (for younger or fitter patients). Both non-intensive and intensive treatments involve taking a combination of anti-myeloma medicines. But intensive treatment involves higher doses and is followed by a stem cell transplant. The medicines usually include a chemotherapy medicine, a steroid medicine, and either thalidomide or bortezomib. High doses of chemotherapy medication affect healthy bone marrow, so a stem cell transplant will be needed to allow the bone marrow to recover.[9]

Further treatment is needed if MM returns. Treatment for relapses is similar to initial treatment, although non-intensive treatment is often preferred. A small group of people may benefit from a second course of high-dose treatment and a second stem cell transplant.[20] Treatment depends on the individual situation, such as how long they were in remission for, what treatment they had and their current level of health and fitness. If MM was in remission for longer than 18 months after initial treatment, the patient might have the same combination of drugs again. If the MM relapses in under 18 months the doctor may suggest a different type of treatment.[19]

CURRENT TREATMENT OPTIONS

NICE guidelines recommend the following treatments for relapsed MM:

- First relapse treatment include:[21]
    - Daratumumab plus bortezomib plus dexamethasone is recommended for use within the Cancer Drugs Fund as an option for treating relapsed multiple myeloma in people who have had one previous treatment. It is recommended only if the conditions in the managed access agreement for daratumumab plus bortezomib plus dexamethasone are followed.
    - Carfilzomib in combination with dexamethasone – only after one prior therapy, which did not include bortezomib
    - Bortezomib monotherapy – only after one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation
- Subsequent relapse treatment include:[21]
    - Lenalidomide in combination with dexamethasone for MM in people who have received at least two or more prior therapies

- Ixazomib in combination with lenalidomide and dexamethasone, through the Cancer Drugs Fund (CDF) after two or more prior therapies and the conditions in the managed access agreement for ixazomib are followed.

- Panobinostat in combination with bortezomib and dexamethasone for adult patients with relapsed and/or refractory MM, who have received at least at least two prior therapies including bortezomib and an immunomodulatory agent.

- Pomalidomide in combination with low-dose dexamethasone – for MM in adults at third or subsequent relapse; three previous treatments including both bortezomib and an immunomodulatory agent.

- Daratumumab monotherapy for adults whose previous therapy included a proteasome inhibitor and an immunomodulatory, and whose disease progressed on the last therapy, only if they have daratumumab after 3 previous therapies.

PLACE OF TECHNOLOGY

If licensed, selinexor in addition to bortezomib and low-dose dexamethasone will offer an additional therapy option for patients with RRMM who have received 1 to 3 prior anti-MM regimens.

CLINICAL TRIAL INFORMATION

Trial	**BOSTON,** NCT03110562, EudraCT2016-003957-14; KCP-330-023; A Phase 3 Randomized, Controlled, Open-label Study of Selinexor, Bortezomib, and Dexamethasone (SVd) Versus Bortezomib and Dexamethasone (Vd) in Patients With Relapsed or Refractory Multiple Myeloma (RRMM) **Phase III** **Location(s):** EU (including the UK), US, Canada, and other countries
Trial design	Randomised, active comparator-controlled, multicentre, crossover assignment, open-label
Population	n=402; aged 18 and older with a histological confirmed MM with measurable disease per IMWG guidelines; had at least 1 prior anti-MM regimen and no more than 3 prior anti-MM regimens.; documented evidence of progressive MM; prior treatment with bortezomib or other Proteasome Inhibitor (PI) is allowed; must have an ECOG Status score of 0, 1, or 2; and Resolution of any clinically significant non-hematological toxicities (if any) from previous treatments to ≤ Grade 1 by C1D1.
Intervention(s)	Selinexor 100 mg orally will be given on days 1, 8, 15, 22, and 29 of each 35-day cycle. Bortezomib 1.3 mg/m^2 subcutaneously will be given days 1, 8, 15, and 22 of each 35-day cycle. Dexamethasone 20 mg orally will be given days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle.
Comparator(s)	Bortezomib 1.3 mg/m^2 subcutaneously will be given days 1, 4, 8, and 11 of each 21-day cycle for the first 8 cycles. For cycles ≥ 9, bortezomib will be given on days 1, 8, 15, and 22 of each 35-day cycle. Dexamethasone 20 mg orally will be given on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle for the first 8 cycles. For cycles ≥ 9, dexamethasone will be given on days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle.
Outcome(s)	Compare progression-free survival (PFS) based on the Independent Review Committee's (IRC's) disease outcome assessments in patients randomized

	to the selinexor plus bortezomib plus dexamethasone arm versus the bortezomib plus dexamethasone arm [time frame: 15 months]
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of selinexor is not known yet.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Carfilzomib with daratumumab and dexamethasone for treating relapsed or refractory multiple myeloma (ID2709). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Isatuximab with carfilzomib and dexamethasone for treating relapsed or refractory multiple myeloma (ID1620). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Venetoclax with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma (ID1565). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (ID1477). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pomalidomide in combination with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma (ID1358). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Plitidepsin in combination with dexamethasone for treating relapsed or refractory multiple myeloma (ID1081). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Selinexor with low-dose dexamethasone for treating refractory multiple myeloma (ID1535). Expected publication date: January 2021.
- NICE technology appraisal in development. Elotuzumab with pomalidomide and dexamethasone for treating multiple myeloma after 2 therapies (ID1467). Expected publication date: August 2020.
- NICE technology appraisal. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (ID974). April 2019.
- NICE technology appraisal. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA510). March 2018.
- NICE technology appraisal. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA505). February 2018.
- NICE technology appraisal. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (TA427). January 2017.
- NICE technology appraisal. Panobinostat for treating multiple myeloma after at least 2 previous treatments (TA380). January 2016.
- NICE technology appraisal. Bortezomib monotherapy for relapsed multiple myeloma (TA129). October 2007.
- NICE guideline. Myeloma: diagnosis and management (NG35). May 2018.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- Mikhael J, et al., Treatment of Multiple Myeloma: ASCO and CCO joint Clinical Practice Guideline. 2019.[22]
- Moreau P, et al., Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2017.[18]

ADDITIONAL INFORMATION

Karyopharm Therapeutics Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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