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HEALTH TECHNOLOGY BRIEFING
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Carfilzomib in addition to daratumumab and dexamethasone for relapsed and/or refractory multiple myeloma

NIHRIO ID	19368	**NICE ID**	10015
Developer/Company	Amgen Ltd	**UKPS ID**	641986

Licensing and market availability plans	Currently in phase III trial

SUMMARY

Carfilzomib in addition to daratumumab and dexamethasone is in clinical development for patients with multiple myeloma (MM) who are refractory or have relapsed to prior treatments. 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 treatment ('refractory' MM).

Carfilzomib, is a proteasome inhibitor. Proteasome is a system within the cells that breaks down proteins that are no longer needed. Cancer cells have an increased need to produce and break down proteins as they multiply rapidly. When carfilzomib stops the proteasome from breaking down proteins in the cancer cells, the proteins build up and cause the cells to die, slowing down the growth of the cancer. The addition of daratumumab and dexamethansone to carfilzomib may potentially improve outcomes

and reduce side effects in patients with relapsed and/or refractory MM who have received prior therapies.

PROPOSED INDICATION

Previously treated relapsed and/or refractory multiple myeloma (MM).[a]

TECHNOLOGY

DESCRIPTION

Carfilzomib (Kyprolis) is a tetrapeptide epoxyketone proteasome inhibitor that selectively and irreversibly binds to the N terminal threonine containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome, and displays little to no activity against other protease classes. Carfilzomib had antiproliferative and proapoptotic activities in preclinical models in haematologic tumours. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumour growth in models of multiple myeloma. In vitro, carfilzomib was found to have minimal neurotoxicity and minimal reaction to non-proteasomal proteases.[1]

Carfilzomib in addition to daratumumab and dexamethasone is in clinical development for patients with relapsed and/or refractory MM after one to three prior therapies. In the phase III clinical trial (NCT03158688; CANDOR), carfilzomib is administered as intravenous (IV) infusion twice a week over 30 ± 5 minutes, on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. The administration may be within ± 2 days for each scheduled dose. The dose will be 20 mg/m^2 on cycle 1 days 1 and 2 and 56 mg/m^2 beginning on cycle 1 day 8 and thereafter. The dose will be calculated and capped based on body surface area of 2.2m^2. Dexamethasone 40 mg is administered orally or by IV infusion weekly and the IV administration of dexamethasone would be given on carfilzomib IV infusion days.[2]

Daratumumab will be administered as an IV infusion on days 1 and 2 of cycle 1, at a split-dose of 8 mg/kg in 500 mL normal saline. The dose of 16 mg/kg in 500 mL normal saline will be

[a] Information provided by Amgen Ltd on UK PharmaScan

given once weekly as a single infusion for the remaining doses of the first 2 cycles (days 8, 15, and 22 of cycle 1; and days 1, 8, 15, and 22 of cycle 2), then every 2 weeks for 4 cycles (cycles 3 to 6), and then every 4 weeks for the remaining cycles or until disease progression.[2]

INNOVATION AND/OR ADVANTAGES

The rationale for combining carfilzomib with daratumumab and dexamethasone is that they have demonstrated substantial activity in MM, with distinct and complementary mechanisms of action.[3] Additionally, due to the relapsing nature of MM, several options are needed to attack the disease differently and keep patients in remission as long as possible.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Carfilzomib in combination with daratumumab and dexamethasone does not currently have Marketing Authorisation in the EU/UK for any indication.

Carfilzomib in combination with either lenalidomide and dexamethasone or dexamethasone alone is licenced in the UK for the treatment of adult patients with MM who have received at least one prior therapy.[1]

The most common side effects with Carfilzomib (which may affect more than 1 in 5 people) are anaemia (low red blood cell counts), tiredness, nausea, diarrhoea, thrombocytopenia (low blood platelet counts), fever, dyspnoea (difficulty breathing), respiratory tract (airways) infection, cough and neutropenia (low levels of neutrophils, a type of white blood cell).The most serious side effects include toxic effects on the heart, lungs and liver, and hypertension (high blood pressure) that can be severe.[1]

Carfilzomib is also in phase II and III clinical development in variety of combinations for MM.[4]

Carfilzomib was granted an orphan designation in the EU in June 2008 for the treatment of MM with the sponsorship transferred to Amgen in June 2014.[5]

PATIENT GROUP

DISEASE BACKGROUND

Multiple Myeloma (MM) is characterised by uncontrolled proliferation of monoclonal plasma cells in the bone marrow, resulting in the over-production of monoclonal immunoglobulin, and immunosuppression, as well as osteolysis and end-organ damage.[6] MM can affect multiple organs and their respective systems, including blood, bones, kidney and immune system.[7] Although the survival rates for MM have increased, it still remains a condition that is incurable and features a high relapse rate.[8]

Refractory myeloma is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy. The origin of MM is thought to be unknown as malignant cells display various cytogenetic abnormalities.[9] MM is closely associated with a condition called monoclonal gammopathy of unknown significance (MGUS). In almost all cases, MM occurs in those who have previously had MGUS.[10]

Additional risk factors for MM include age, gender, and ethnicity. The risk of MM increases with age with most people diagnosed in their mid-60s and men more likely to develop the disease than women. MM is twice as common in black populations compared with white. In

early stages, MM may not cause any symptoms or complications and may be diagnosed by routine blood or urine tests.[11]

In many relapse trials, the occurrence of any grade treatment-related adverse events is approximately 50% and serious adverse events (SAE) 20%. Treatment-related adverse events are a frequent cause of premature discontinuation, which influence the outcome.[8] Patients often have pronounced symptoms and substantially reduced health-related quality of life (HRQoL). Around 80% of patients experience skeletal destruction, approximately 73% will have anaemia at diagnosis and about 30% of patients present with renal insufficiency. [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 multiple myeloma and malignant plasma cell neoplasms (ICD-10: C90). Incidence is strongly linked to age, with the highest rates in people aged 70 to 89 years.[14] Over the last decade, incidence rates have increased by a seventh (15%) represented by an increase in males of 15% and 12% for females. 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 2017-2018 there were 131,352 hospital admissions with a primary diagnosis of MM (ICD-10 code C90.0), resulting in 91,645 bed days and 120,702 day cases.[15] In England in 2016, there were 2,606 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).[13] Increased life expectancy is mainly due to the availability of novel therapeutic agents, and the adoption of haematopoietic stem cell transplantation.[17] A systematic review and economic evaluation carried in Europe in 2015 found that almost 10% of patients treated were relapsed or refractory to both proteasome inhibitor and immunomodulatory agent based treatment regimes.[18]

The UK patient population for relapse and/or refractory MM ranges between 25 to 50 per 100,000.[b] Applying this to the 2018 mid-year adult population estimates of England, the number of people with relapsed and/or refractory MM will be between 14,779 to 29,558.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Most patients experience serial relapse and will be treated with most available agents at some point during their disease course.[20] 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).[21] The length of the prior remission duration is a critical component in making a

[b] Information provided by Amgen Ltd on UK PharmaScan.

choice of salvage therapy. The depth of the first response, remission duration of the patient's prior therapies, and tumour burden at relapse can suggest the aggressiveness of the relapse.[22]

CURRENT TREATMENT OPTIONS

NICE guidelines recommend the use of a number of the following possible sequences of treatments for relapsed or refractory MM:[23]

In instances of first relapse, the guidelines recommend the use of:

- Carfilzomib in combination with dexamethasone – only after one prior therapy, which did not include bortezomib.
- Bortezomib – only after one prior therapy and for adults who have undergone, or are unsuitable for, bone marrow transplantation.
- Second autologous stem cell transplant – suitability determined by response to first transplant, number of prior treatments, overall health and fitness, and ranking on ISS system.

Subsequent relapse treatment may include:

- Lenalidomide in combination with dexamethasone for adults who have received two or more prior therapies.
- Ixazomib, with lenalidomide and dexamethasone, for adults who have already had two or three lines of therapy
- Panobinostat in combination with bortezomib and dexamethasone for adults who have received at least two prior regimens including bortezomib and an immunomodulatory agent
- Pomalidomide, in combination with low-dose dexamethasone for adults at third or subsequent relapse; that is, after three previous treatments including both lenalidomide and bortezomib
- Daratumumab monotherapy for adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last therapy, only if they have daratumumab after 3 previous therapies

PLACE OF TECHNOLOGY

If licensed carfilzomib in addition to daratumumab and dexamethasone will offer an additional treatment option for patients with relapsed and/or refractory multiple myeloma after 1 to 3 prior therapies.

CLINICAL TRIAL INFORMATION

Trial	**NCT03158688, CANDOR, EudraCT-2016-003554-33 ; adults aged 18 yrs and older; carfilzomib vs daratumumab both in combination with dexamethasone; phase III**
Sponsor	Amgen
Status	Ongoing
Source of Information	Trial registry[2]
Location	11 EU countries [incl UK], USA, Canada and other countries
Design	Randomised, open-label, parallel assignment, treatment group

Participants	N=466; aged 18 yrs and older; relapsed or progressive multiple myeloma after last treatment; measurable disease; received at least 1 but not more than 3 prior lines of therapy for multiple myeloma
Schedule	Randomised to one of two arms: • Carfilzomib and dexamethasone Carfilzomib is administered as intravenous (IV) infusion twice a wk over 30 ± 5 minutes, on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. The administration may be within ± 2 days for each scheduled dose. The dose will be 20 mg/m^2 on cycle 1 days 1 and 2 and 56 mg/m^2 beginning on cycle 1 day 8 and thereafter. The dose will be calculated based upon body surface area (BSA) and capped on 2.2m^2. Dexamethasone 40 mg is administered orally or by IV infusion weekly and the IV administration of dexamethasone would be given on carfilzomib IV infusion days. • Carfilzomib, dexamethasone and daratumumab Carfilzomib is administered as IV infusion twice a wk over 30 ± 5 min, on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. The administration may be within ± 2 days for each scheduled dose. The dose will be 20 mg/m^2 on cycle 1 days 1 and 2 and 56 mg/m^2 beginning on cycle 1 day 8 and thereafter. The dose will be calculated based on BSA and capped based on 2.2m^2. Dexamethasone 40 mg is administered orally or by IV infusion weekly and the IV administration of dexamethasone would be given on carfilzomib IV infusion days. Daratumumab will be administered as an IV infusion on days 1 and 2 of cycle 1, at a split-dose of 8 mg/kg in 500 mL normal saline. The dose of 16 mg/kg in 500 mL normal saline will be given once weekly as a single infusion for the remaining doses of the first 2 cycles (days 8, 15, and 22 of cycle 1; and days 1, 8, 15, and 22 of cycle 2), then every 2 wks for 4 cycles (cycles 3 to 6), and then every 4 wks for the remaining cycles or until disease progression. The IV administration of dexamethasone must be given on carfilzomib and/or daratumumab IV infusion days. On days when more than 1 investigational product is administered, the required order of administration is as follows: dexamethasone, pre-infusion medications for daratumumab, carfilzomib, daratumumab, and post-infusion medications for daratumumab.
Follow-up	Until disease progression
Primary Outcomes	Progression free survival (PFS) [Time frame: 28 mths]
Secondary Outcomes	• Overall Response Rate (ORR) [Time frame: 28 mths] • Rate of minimal residual disease negative-complete response [Time frame: 12 mths] • Duration of response (DOR) [Time frame: 28 mths] • Overall survival (OS) [Time frame: 28, 36, 48 and 58 mths] • Time to next treatment [Time frame: 28 mths] • Time to progression (TTP) [Time frame: 28 mths] • Time to response [Time Frame: 28 mths] • Persistence of minimal residual disease negative-complete response rate (MRD[-]CR) [Time frame: 28 mths] • Complete response rate (CRR) [Time Frame: 28 mths] • Minimal residual disease (MRD) negative-CRR [Time Frame: 12 mths] • Quality of life (QoL) questionnaire - core 30 items [Time frame: 28 mths] • QoL measured by European organisation [Time frame: 28 mths]

	• Subject incidence of treatment-emergent adverse events [Time frame: 28 mths]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as July 2022.

ESTIMATED COST

The NHS indicative price for carfilzomib is:[24]

- Kyprolis 10mg powder for solution for infusion vials (Amgen Ltd) costs £176 per vial
- Kyprolis 30mg powder for solution for infusion vials (Amgen Ltd) costs £528 per vial
- Kyprolis 60mg powder for solution for infusion vials (Amgen Ltd) costs £1056 per vial

RELEVANT GUIDANCE

NICE GUIDANCE

- 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. 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. Elotuzumab for multiple myeloma (ID966). Expected date of issue: To be confirmed.
- NICE technology appraisal in development. Selinexor with low-dose dexamethasone for treating refractory multiple myeloma (ID1535). Expected date of issue: January 2021.
- NICE technology appraisal. Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib (TA586). June 2019.
- NICE technology appraisal. Lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies (TA171). June 2019.
- NICE technology appraisal in development. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (TA573). 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. Carfilzomib for previously treated multiple myeloma (TA457). July 2017.
- 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). October 2018.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE quality standard. Haematological cancers (QS150). June 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. National chemotherapy algorithms - multiple myeloma. 2015.
- NHS England. NHS manual for prescribed specialist services). Chapter 29: blood and marrow transplantation services (adults and children). 2018/2019.

OTHER GUIDANCE

- The UK Myeloma Forum (UKMF) and the British Society for Haematology (BSH). Guidelines for screening and management of late and long-term consequences of myeloma and its treatment. 2017.[17]
- ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up: Multiple myeloma. 2017.[21]
- National Comprehensive Cancer Network. American NCCN Guidelines: Version 3 – NCCN Evidence Blocks: Myeloma Therapy. 2017.[25]
- The International Myeloma Working Group. Revised International Staging System for Multiple Myeloma: A Report from IMWG. 2015.[26]
- The Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH) and UK Myeloma Forum. Guidelines for the diagnosis and management of Multiple Myeloma. 2014.[27]

ADDITIONAL INFORMATION

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