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HEALTH TECHNOLOGY BRIEFING AUGUST 2020

Melphalan flufenamide in combination with dexamethasone for treating adult patients with relapsed or refractory multiple myeloma

NIHRIO ID	9140	**NICE ID**	9670
Developer/Company	Oncopeptides AB	**UKPS ID**	650433

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Melphalan flufenamide in combination with dexamethasone is currently in clinical development for the treatment of adult patients with relapsed or refractory multiple myeloma (MM). 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 retreatment (refractory MM). Most patients will experience serial relapse to existing treatments at some point during their disease course, hence the need for newer treatment combination options.

Melphalan flufenamide is given by intravenous infusion and is designed to specifically target myeloma cells. Once inside the myeloma cells melphalan flufenamide causes damage to the DNA resulting in the death of these cancer cells. Dexamethasone works by stopping white blood cells from travelling to areas where cancerous myeloma cells are causing damage. When combined with melphalan flufenamide, dexamethasone

can also make melphalan flufenamide work more effectively. If licensed, melphalan flufenamide in combination with dexamethasone may provide an additional treatment option for patients with relapsed or refractory MM.

PROPOSED INDICATION

Treatment of adult patients with multiple myeloma (MM), whose disease is relapsed or refractory to at 2-4 lines of prior therapy.[1]

TECHNOLOGY

DESCRIPTION

Melphalan flufenamide (Melflufen) is a first-in-class anti-cancer peptide-drug conjugate that consists of melphalan conjugated to phenylalanine.[2,3] Melphalan flufenamide is a highly lipophilic alkylator and its lipophillicity characteristics allow for it to be rapidly taken up by myeloma cells. Melphalan flufenamide then undergoes intracellular hydrolysis via intracellular peptidases resulting in the release of the active metabolite melphalan.[4] Melphalan acts by causing DNA cross-links, which inhibits the replication function resulting in DNA double strand breaks.[5] Melphalan flufenamide has demonstrated inhibition of angiogenesis and induction of DNA damage with a lack of functional DNA repair leading to apoptosis of myeloma cells in preclinical studies.[3]

Dexamethasone is a corticosteroid used in myeloma treatment that works by stopping white blood cells from travelling to areas where cancerous myeloma cells are causing damage.[6] In high doses, dexamethasone can kill myeloma cells and when combined with other myeloma drugs, it can also make those drugs work more effectively.[7]

In the phase III clinical trial OCEAN (NCT03151811) participants are given 40 mg of melphalan flufenamide by intravenous infusion on day 1 of each 28 day cycle and 40 mg of dexamethasone through oral tablets on days 1, 8, 15 and 22 of each 28 day cycle.[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.[8] Patients with MM typically have recurrent relapses and current treatments available have limited efficacy leading to poor survival, highlighting the need for additional treatment options.[9] Melphalan is an alkylating agent that prolongs survival in MM. However, melphalan alone is associated with toxicities and development of drug resistance.[4] Melphalan flufenamide is being introduced with a mechanism of action that is designed to overcome melphalan's association with toxicities and drug resistance.[2]

The transport rate of melphalan flufenamide into cells is rapid whereas the transport rate of free melphalan out of cells is slower. This differential rate of transport results in a high intracellular concentration of melphalan. Tumour model studies have shown that melphalan flufenamide triggers at least a 10-fold higher loading of melphalan and is associated with a higher tumour cell cytotoxicity than melphalan alone. Melphalan flufenamide has been shown to induce synergistic anti-MM activity in combination with dexamethasone.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Melphalan flufenamide does not currently have Marketing Authorisation in the EU/UK for any indication.

In May 2015, melphalan flufenamide was granted an orphan designation by the EMA for the treatment of plasma cell myeloma (also called multiple myeloma).[10]

Melphalan flufenamide is also currently in phase II clinical development for the treatment of amyloidosis and renal impairment.[11,12]

PATIENT GROUP

DISEASE BACKGROUND

Multiple Myeloma (MM) is a type of bone marrow cancer that 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.[13,14] MM can affect multiple organs and systems including the bones, kidneys, blood and immune system.[15] Although the survival rates for MM have increased, it still remains a condition that is incurable and has a high relapse rate which is defined as the disease recurring after a prior response to treatment. Refractory myeloma is defined as disease that is non-responsive while on primary or salvage therapy, or progresses within 60 days of last therapy.[16]

The exact cause of MM is not known, however it is associated with a condition called monoclonal gammopathy of unknown significance (MGUS) where there is an excess of immunoglobulin proteins in the blood.[15] Risk factors for MM include age, gender and ethnicity. The risk of MM increases with age, with most people diagnosed in their mid-60s. Men are more likely to develop the disease than women. MM is twice as common in black populations compared with white.[17] Other risk factors include having a family history of the disease, having taken immunosuppressants and past exposure to radiation.[18]

In early stages, MM may not cause any symptoms or complications and can be diagnosed by routine blood or urine tests.[17] Most patients are diagnosed due to symptoms, which can include bone fracture or pain, low red and white blood counts, fatigue, calcium elevation, kidney problems or infections.[19] MM 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.[20]

CLINICAL NEED AND BURDEN OF DISEASE

In 2017, myeloma was the 19th most common cancer in the UK, accounting for 2% of all new cancer cases.[21] In England, in 2017, there were 5,034 newly diagnosed cases of multiple myeloma and malignant plasma cell neoplasms (ICD-10 code: C90). Incidence is strongly linked to age, with the highest ratio in people aged 70 to 89 years.[22] Over the last decade, incidence rates have increased by around 15% in the UK, represented by an increase in males by 17% and in females by 10%. Incidence rates are projected to rise by 11% in the UK between 2014 and 2035 to 12 cases per 100,000 by 2035.[21] A systematic review and economic evaluation carried out in Europe in 2015 found that almost 10% of patients treated were relapsed or

refractory to both proteasome inhibitors and immunomodulatory agent based treatment regimens.[23]

In England, in 2018-19, there were 142,827 finished consultant episodes (FCE) and 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.[24] In England, 2013-2017, the age-standardised net survival rate for myeloma was 82.7% for one year, 52.3% for five years and 29.1% for 10 years.[25] In England and Wales, in 2017, there were 2,756 registrations of death where MM was recorded as the underlying cause.[26]

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.[27] 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).[28] The length of the prior remission duration is a critical component in making a 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.[29]

A non-pharmacological treatment option for relapsed or refractory MM is a second autologous stem cell transplant, depending on the response to the first.[30] Patients may also receive medicines and procedures to prevent and treat problems caused by myeloma rather than the condition itself such as bone pain, fractures and anaemia.[14]

CURRENT TREATMENT OPTIONS

NICE guidelines recommend the use of a number of the following possible sequences of treatments for relapsed or refractory MM:[31]

- 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 three previous therapies

PLACE OF TECHNOLOGY

If licensed, melphalan flufenamide will offer an additional treatment option for adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and a proteasome inhibitor, and have demonstrated disease progression on or within 60 days of completion of the last therapy.

CLINICAL TRIAL INFORMATION

Trial	**OCEAN;** NCT03151811; A Randomized, Controlled, Open-label, Phase 3 Study of Melflufen/Dexamethasone Compared With Pomalidomide/Dexamethasone for Patients With Relapsed Refractory Multiple Myeloma Who Are Refractory to Lenalidomide **Phase III** – Ongoing **Locations:** 15 EU countries (incl UK), USA and other countries **Primary completion date:** 31 March 2021
Trial design	Randomised, controlled, open-label
Population	N=450; Adults aged 18 years or older; Diagnosis of MM with documented disease progression requiring further treatment; previously received 2-4 lines of therapy, including lenalidomide and a proteasome inhibitor
Intervention(s)	40mg melphalan flufenamide (intravenous infusion) 40mg dexamethasone (oral tablets)
Comparator(s)	4mg pomalidomide (oral capsules) 40mg dexamethasone (oral tablets)
Outcome(s)	Progression free survival [Time Frame: from randomisation to time of progression, or, if no progression, 24 months after end of treatment] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**HORIZON;** NCT02963493; A Single Arm, Open-Label, Phase 2 Study of Melflufen in Combination With Dexamethasone in Patients With Relapsed Refractory Multiple Myeloma Who Are Refractory to Pomalidomide and/or an Anti-CD38 Monoclonal Antibody **Phase II** - ongoing **Locations:** EU (not UK) and United States **Primary completion date**: September 2021
Trial design	Single group assignment, open-label
Population	N=157; Adults aged 18 years and older; prior diagnosis of MM with documented disease progression; a minimum of 2 prior lines of therapy including an immunomodulatory imide drug (IMiD) and a proteasome inhibitor
Intervention(s)	40mg melphalan flufenamide 40mg dexamethasone

Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Overall Response Rate (ORR) [Time Frame: From date of response until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 24 months] See trial record for full list of outcome measures
Results (efficacy)	Positive results were reported with an ORR of 29%, a median duration of response of 5.5 months and a median progression free survival of 8.5 months.[32]
Results (safety)	Adverse events (AEs) led to melphalan flufenamide dose reductions in 42 (27%) of patients and dose delays in 95 (61%) of patients. The most common AE leading to dose reduction was thrombocytopenia which occurred in 14% of patients. Serious AEs occurred in 49% of patients overall; most commonly reported were pneumonia (9%) and febrile neutropenia (5%).[33]

Trial	**ANCHOR;** NCT03481556; An Open-label, Phase 1/2a Study of the Safety and Efficacy of Melflufen and Dexamethasone in Combination With Either Bortezomib or Daratumumab in Patients With Relapsed or Relapsed-Refractory Multiple Myeloma **Phase II** - ongoing **Locations:** Czechia, France, Spain and United States **Primary completion date**: December 2020
Trial design	Single group assignment, open-label
Population	N=80; Adults aged 18 years and older; prior diagnosis of MM with documented disease progression following one to four prior lines of therapy
Intervention(s)	• Experimental Arm 1: Melphalan flufenamide (intravenous infusion) Dexamethasone (oral tablets) Bortezomib (subcutaneous administration) • Experimental Arm 2: Melphalan flufenamide (intravenous infusion) Dexamethasone (oral tablets) Daratumumab (intravenous infusion)
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Phase 1: Monitor and analyse the frequency and grade of adverse events occurring during Cycle 1 at each dose level to be tested. Each Regimen to be evaluated separately. [Time Frame: During the first cycle (28 days) of each cohort] • Phase 2: Overall Response Rate (ORR)

	[Time Frame: From the start of treatment until best response achieved before confirmed progression. For an average patient this is achieved within 6 months] See trial record for full list of outcome measures
Results (efficacy)	-
Results (safety)	-

Trial	NCT03639610; A Study of the Pharmacokinetics of Melphalan During Treatment With Melphalan and Dexamethasone in Patients With Relapsed Refractory Multiple Myeloma and Impaired Renal Function **Phase II** - ongoing **Locations:** Czechia, Greece and Poland **Primary completion date**:
Trial design	Single group assignment, open-label
Population	N=25; Adults aged 18 years and older; prior diagnosis of MM with documented disease progression following 2-4 prior lines of therapy
Intervention(s)	40mg melphalan flufenamide (intravenous infusion) 40mg dexamethasone (oral tablets)
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: [Time Frame: Cycle 1 and 2 – three measurements post infusion. At Day 1 of each cycle (28 days cycles)] • Pharmakokinetics tmax - Time of maximum observed concentration (tmax) • Pharmakokinetics Cmax - Maximum observed concentration (Cmax) • Pharmakokinetics AUCinf - Area under the concentration versus time curve between 0h and end of drug infusion (AUCinf) • Pharmakokinetics AUC0-t - Area under the concentration versus time curve between 0h and end of drug infusion (AUC0-t) • Pharmacokinetics t1/2 - Elimination phase half-life (t1/2) • Pharmacokinetics CL - Clearance (CL) parameters for melphalan during treatment with melflufen • Incidence of Treatment Emergent Adverse Events (Safety and Tolerability) [Time Frame: From screening to 30 days after last dose] See trial record for full list of outcome measures
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The estimated cost of melphalan flufenamide is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Carfilzomib with daratumumab and dexamethasone for treating relapsed or refractory multiple myeloma (ID2709). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Daratumumab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (ID3775). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Isatuximab with carfilzomib and dexamethasone for treating relapsed or refractory multiple myeloma (ID1620). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Venetoclax with bortezomib and dexamethasone for treating relapsed or refractory multiply myeloma (ID1565). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Selinexor with bortezomib and low-dose dexamethasone for treating relapsed or refractory multiple myeloma after 1-3 therapies (ID3793). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Carfilzomib with daratumumab and dexamethasone for treating relapsed or refractory multiple myeloma (ID2709). Expected publication date: to be confirmed.
- NICE technology appraisal guidance in development. Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 3 therapies (ID2701). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Idecabtagene vicleucel for treating relapsed and refractory multiple myeloma in people who have received at least 3 prior therapies (ID1442). August 2021.
- NICE technology appraisal guidance in development. Selinexor with low-dose dexamethasone for treating refractory multiple myeloma (ID1535). January 2021.
- NICE technology appraisal guidance. Lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies (TA171). June 2019
- NICE technology appraisal guidance. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (TA573). April 2019.
- NICE technology appraisal guidance. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA510). June 2018.
- NICE technology appraisal guidance. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA505). February 2018.
- NICE technology appraisal guidance. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (TA427). January 2017.
- NICE technology appraisal guidance in development. Panobinostat for treating multiple myeloma after at least 2 previous treatments (TA380). January 2016
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NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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OTHER GUIDANCE

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- European Society of Medical Oncology (ESMO). Clinical Practice Guidelines for diagnosis, treatment and follow-up: Multiple myeloma. 2017.[28]
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ADDITIONAL INFORMATION

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