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HEALTH TECHNOLOGY BRIEFING MARCH 2019

Isatuximab in addition to carfilzomib and dexamethasone for relapsed and/or refractory multiple myeloma

NIHRIO ID	23794	**NICE ID**	10155
Developer/Company	Sanofi	**UKPS ID**	650338

Licensing and market availability plans	Currently in phase III trials

SUMMARY

Isatuximab in addition to carfilzomib 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 drugs given to treat it ('refractory' MM).

Isatuximab is a monoclonal antibody designed to recognise and attach to a specific target on the surface of cells involved in MM. This action activates certain components of the immune system so that they kill the cancerous plasma cells. Carilzomib combined with dexamethasone is already used for the treatment of MM. The addition of isatuximab to this combination may potentially improve outcomes in patients with relapsed and/or refractory MM who have received other prior therapies.

PROPOSED INDICATION

Relapsed and/or refractory multiple myeloma, second-line to fourth-line[a]

TECHNOLOGY

DESCRIPTION

Isatuximab (SAR650984) is a humanized IgG1 monoclonal antibody that binds to a specific epitope on the human CD38 receptor. CD38 is a type 2 transmembrane protein expressed on both hematopoietic and non-hematopoietic tissues, with the highest density being on plasma cells and germinal centre B cells. CD38 functions as a receptor involved in the transmission of activation and proliferation signals, as well as an ectoenzyme that has a role in calcium signalling and cell survival. CD38 receptor-mediated signalling produces a variety of downstream effects, and has variable signalling impact depending on several factors. It has a role in T-cell activation mediated by the downstream activation of nuclear factor kB.[1]

Isatuximab inhibits the suppressive function of regulatory T-cells by reducing their numbers, decreasing immune inhibitory cytokine production including IL-10, and blocking their trafficking. This results in improved NK- and T-cell-mediated anti-tumour immune responses. NK-cells release toxic proteins including granzymes and perforins, which will kill the target cells. Isatuximab multiple myeloma (MM) cell death is also mediated by the classical caspase-dependent apoptotic pathway, as well as the lysosomal cell death pathway, which is characterized by lysosomal enlargement, lysosomal membrane permeabilization, and cathepsin hydrolase release. Isatuximab induces reactive oxygen species production, which occurs downstream of lysosomal activation and contributes to MM cell death.[2]

Isatuximab in combination with carfilzomib and dexamethasone is in clinical development as second to fourth line therapy in the treatment of relapsed and/or refractory multiple myeloma. In the phase III trial (IKEMA; NCT03275285), isatuximab 20mg/ml is administered as an intravenous (IV) infusion on day 1, 8, 15 and 22 of the first cycle, then on day 1 and 15 of subsequent cycles, in combination with 2mg/ml carfilzomib (IV) on day 1, 2, 8, 9, 15 and 16 plus dexamethasone (IV or oral) on day 1, 2, 8, 9, 15, 16, 22 and 23 of a 28 day cycle.[3,4]

INNOVATION AND/OR ADVANTAGES

Approximately 80–100% of all myeloma cells express high levels of CD38 protein on their surface making isatuximab a good therapeutic target. While isatuximab is a humanized IgG1 monoclonal antibody like daratumumab, it binds to a specific epitope on the human CD38 receptor and may have more potent inhibition of its ectozyme function than daratumumab, thereby having the potential for some non-cross-reactivity. Further, whereas daratumumab induces crosslinking-dependent apoptosis, isatuximab may be able to promote apoptosis even without crosslinking.[1]

Isatuximab may also act through many different mechanisms including: antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, direct apoptosis, and inhibition of myeloid-derived suppressor cells resulting in the release of T-cell suppression. Isatuximab has shown significant clinical activity in patient populations who were heavily pre-treated with at least five lines of therapy, including pomalidomide, lenalidomide and/or carfilzomib.[1]

[a] Information provided by Sanofi on UK PharmaScan

Carfilzomib in combination with dexamethasone is already licensed for the treatment of adult patients with MM who have received at least one prior therapy.[5] The addition of isatuximab may potentially prolong progression free survival in patients with relapsed and/or refractory MM previously treated with 1 to 3 lines of therapy.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Isatuximab is in phase III clinical development for newly diagnosed multiple myeloma not eligible for transplant[6]. Isatuximab is also in phase II clinical development for advanced malignancies, selected CD38+ haematological malignancies, and lymphoma.[7]

Isatuximab was granted an orphan designation in the EU in April 2014 for the treatment of multiple myeloma.[8]

PATIENT GROUP

DISEASE BACKGROUND

Multiple Myeloma (MM) is an incurable orphan disease 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.[9] MM can affect multiple organs and their respective systems, including blood, bones, kidney and immune system.[10] Although the survival rates for MM have increased, it still remains a condition that is incurable and features a high relapse rate.[11]

Refractory myeloma is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy. Patients who never achieve at least a minimal response (i.e., at least a 25% reduction in M protein) to initial induction therapy and progress while on therapy are defined as primary refractory.[12] Additional mutations and genetic alterations that are present in relapsed or progressive MM make the disease more resistant to available agents, resulting in reduced remission or response to each line of salvage therapy, and ultimately leads to the development of relapsed/refractory MM.[13] The tumour behaviour at the second relapse and beyond, tends to be shorter due to this more aggressive tumour activity.[14]

The origin of MM is thought to be unknown as malignant cells display various cytogenetic abnormalities.[15] 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.[16] MGUS is characterised by an excess number of immunoglobulins present in the blood. MGUS does not cause any symptoms and treatment is not required. However, estimates suggest approximately 1 in every 100 people with MGUS go on to develop MM on an annual basis, and sub classifications of MGUS have allowed identification of patients with much higher rates of progression to frank MM. There is no known way to delay or prevent this development, and ongoing outpatient tests to check for cancer will usually be recommended in conjunction with a MGUS diagnosis.[17]

Additional risk factors for MM include age, gender, and ethnicity. Cases affecting those under 40 years of age are rare, with men more likely to develop the disease than women. MM is twice as common in black populations compared with white and Asian ethnicities. In early stages, MM may not cause any symptoms or complications and may be diagnosed by routine blood or urine tests.[18]

In the early stages of the condition, MM may not present any symptoms or complications and may be diagnosed by routine blood or urine tests such as an abnormal elevation in serum immunoglobulin levels.[9] Other features of MM are often denoted by the "CRAB" criteria, which include can include hyperCalcemia, Renal dysfunction, Anaemia and Bone disease. Symptoms associated with these CRAB criteria include bone pain (notably in the spine or chest), nausea, constipation, loss of appetite, physical and mental fatigue, frequent infections, reduced kidney function, anaemia, weight loss, loss of muscle control in the lower extremities, and excessive thirst.[18] MM can manifest into end-organ damage, which has major implications on patient quality of life. This represents an important point in the treatment pathway of MM as it indicates the requirement to begin aggressive treatment.[19]

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 influences outcome.[11] 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 2015 myeloma was the 19th most common cancer in the UK accounting for 2% of all new cancer cases. In England, in 2016, there were 4,731 newly diagnosed cases of multiple myeloma and malignant plasma cell neoplasms (ICD-10: C90).[21] Incidence is strongly linked to age, with the highest rates in people aged 85 to 89 (2013-2015). Over the last decade, incidence rates have increased by a sixth (17%) represented by an increase in males of 18% and 14% 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.[22]

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.[23] In England in 2016, there were 2,606 registrations of death where multiple myeloma was recorded as the underlying cause.[21]

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).[22] Increased life expectancy is mainly due to the availability of novel therapeutic agents, and the adoption of haematopoietic stem cell transplantation (which involves high doses of alkylating agents).[24] Nevertheless, a systematic review and Markov model carried in Europe in 2015 found that, despite the introduction of innovative medicines, relapsed and refractory MM remains a patient setting of poor outcomes with almost 10% of patients receiving treatment in any given year being relapsed or refractory to both proteasome inhibitor and immunomodulatory agent based treatment regimes.[25]

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).[26] 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.[27]

MM treatments have side effects, which may involve permanent organ damage. Periods of stability followed by relapse are typical, although the increasing use of consolidation and maintenance results in many patients on treatment for prolonged periods of time during disease stability.[17]

CURRENT TREATMENT OPTIONS

NICE guidelines recommend the use of a number of the following possible sequences of treatments for relapsed or refractory MM:[28]

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 bortezomibDaratumumab 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, isatuximab in addition to carfilzomib and dexamethasone will offer an additional second to fourth line treatment option for patients with relapsed and/or refractory multiple myeloma.

CLINICAL TRIAL INFORMATION

Trial	IKEMA, NCT03275285, EudraCT- 2017-001940-37; Isatuximab in combination with carfilzomib plus dexamethasone vs carfilzomib plus dexamethasone; phase III
Sponsor	Sanofi
Status	Ongoing
Source of Information	Trial registry[3,4]
Location	7 EU countries (incl UK), USA, Canada and other countries.
Design	Randomised, open label, parallel assignment, single blinded (outcomes assessor)
Participants	N=300 (planned); 18 yrs and older; MM previously treated with prior 1 to 3 lines and with measurable serum M-protein (≥ 0.5 g/dL) and/or urine M-protein (≥ 200 mg/24 hours).

Schedule	Pts are randomised to: • Experimental: Isatuximab (IV) on day 1, 8, 15 and 22 of 1st cycle, then on day 1 and 15 of subsequent cycles in combination with carfilzomib (IV) on day 1, 2, 8, 9, 15 and 16 + dexamethasone (IV or by mouth) on day 1, 2, 8, 9, 15, 16, 22 and 23 of a 28 day cycle. • Active comparator: Carfilzomib (IV) on day 1, 2, 8, 9, 15, 16 + dexamethasone (IV or by mouth) on day 1, 2, 8, 9, 15, 16, 22 and 23 of a 28 day cycle.
Follow-up	Active treatment until disease progression, unacceptable adverse reaction, pts' wish or other reason of discontinuation, follow-up 3 yrs
Primary Outcomes	Progression Free Survival (PFS) [Time Frame: Up to approx 36 mths]
Secondary Outcomes	Time Frame: up to approx 36 mths • Overall Response Rate (ORR) • Rate of very good partial response (VGPR) or better • Complete response (CR) rate • Rate of VGPR or better with minimal residual disease (MRD) negativity • Time to Progression (TTP) • Second Progression Free Survival (PFS2) • Duration of response (DOR) • Overall Survival (OS) [Time Frame: Up to approx 72 mths] • Number of pts with adverse events according to the National Cancer Institute - Common Toxicity Criteria (NCI- CTC) version 4.03 grading scaling [Time Frame: Up to 30 days after last study treatment administration] • Patient-reported outcome measured with Quality of Life questionnaire [Time Frame: Screening to 90 days after last study treatment administration] • Pharmacokinetics of isatuximab [Time Frame: Up to approx 10 mths] • Pharmacokinetics of carfilzomib [Time Frame: Up to 1 mth] • Immunogenicity (ADA) [Time Frame: Up to 13 mths]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as November 2023

ESTIMATED COST

The cost of isatuximab is not yet known.

Carfilzomib is already marketed in the UK. The NHS indicative price for carfilzomib is:

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

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Selinexor with low-dose dexamethasone for treating refractory multiple myeloma (ID1535). 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. Elotuzumab with pomalidomide and dexamethasone for treating multiple myeloma after 2 therapies (ID1467). 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. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (ID974). 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. Elotuzumab for multiple myeloma (ID966). Expected date of issue to be confirmed.
- 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. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (TA171). April 2014.
- NICE technology appraisal. Bortezomib monotherapy for relapsed multiple myeloma (TA129). October 2007.
- 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

- 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.[24]

- ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up: Multiple myeloma. 2017.[26]
- National Comprehensive Cancer Network. American NCCN Guidelines: Version 3 – NCCN Evidence Blocks: Myeloma Therapy. 2017.[29]
- The International Myeloma Working Group. Revised International Staging System for Multiple Myeloma: A Report from IMWG. 2015.[30]
- 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.[31]

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