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

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LAY SUMMARY

Multiple myeloma (MM) is a rare, incurable cancer of the plasma cells in the bone marrow. Bone marrow is the spongy tissue found at the centre of some bones, which produces blood cells for the body. Plasma cells are normally produced in a controlled way but in cases of MM, large amounts of abnormal plasma cells are produced. These fill the bone marrow and interfere with the production of other cells, including red and white blood cells and platelets. The cause of MM is unknown. Symptoms of MM varies but some may include bone pain, fractures, body weakness, malaise, bleeding, anaemia and infections. 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 in development as a treatment option for relapsed and refractory MM. It is intended to be added to pomalidomide and dexamethasone which are drugs already available to treat the condition. Isatuximab is administered intravenously as a solution concentrate and the unique way it acts may offer an additional treatment option for relapsed and refractory MM patients who have tried and failed to respond on current therapies.

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TARGET GROUP

Relapsed and/or refractory multiple myeloma (received at least 2 lines of prior therapies including lenalidomide and a proteasome inhibitor); in combination with pomalidomide and dexamethasone.

TECHNOLOGY

DESCRIPTION

Isatuximab (SAR650984) is a humanised Immunoglobulin G (IgG1) monoclonal antibody directed against the cell surface glycoprotein CD-38 with potential antineoplastic activity. Isatuximab specifically binds to CD38 on CD38-positive tumour cells. This may trigger antitumoral antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), inhibition of enzymatic activity and apoptosis eventually leading to cell lysis in CD38-expressing tumour cells. CD38, a type II transmembrane glycoprotein, is present on various immune cells and hematologic malignancies, and its expression has been correlated with poor prognosis.[1]

Isatuximab is being developed, in addition to pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior regimens, including lenalidomide and a proteasome inhibitor, and have demonstrated disease progression on the last therapy. Pomalidomide and dexamethasone alone is already indicated and marketed for this indication.[2]

In the phase III clinical trial (NCT02990338), isatuximab is administered intravenously as a solution for infusion at a dose of 10 mg/kg on day 1, 8, 15, and 22 of 1st 28-day cycle, then on day 1 and 15 of subsequent cycles in combination with pomalidomide and dexamethasone.[3]

Isatuximab is also under development for the treatment of:[4]

- Non-small cell lung cancer
- Metastatic castration resistant prostate cancer
- Plasma cell myeloma
- Acute lymphoblastic leukemia; and
- Acute lymphoblastic lymphoma.

Isatuximab does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

Isatuximab is a novel monoclonal antibody targeting a unique epitope on CD-38 resulting in a different mode of action compared to daratumumab. In addition to a differing mode of action, Isatuximab has a more preferable shorter intravenous administration time compared to daratumumab.

If licensed, Isatuximab will be the first monoclonal antibody to be combined with pomalidomide and dexamethasone. This will offer a new treatment combination for patients with relapsed and/or refractory multiple myeloma who have failed treatment with lenalidomide and a proteasome inhibitor.

DEVELOPER

Sanofi

REGULATORY INFORMATION and AVAILABILITY/MARKETING PLANS

Isatuximab was granted Orphan Drug Designation for replased and refractory multiple myeloma in the FDA and EMA in Dec 2016.[5]

PATIENT GROUP

BACKGROUND

Multiple myeloma (MM) is a rare, incurable disease characterised by uncontrolled proliferation of monoclonal plasma cells in the bone marrow, resulting in the over-production of monoclonal immunoglobulin and immunosuppression, and osteolysis and end-organ damage.[6] The disease is characterised by cycles of response and progression. With increasing lines of therapy, there is a decreasing duration of response and ultimately development of refractory disease.[7]

Relapsed and refractory MM is defined as a disease which becomes non-responsive or progressive while the patient is on salvage therapy or within 60 days of the last treatment in patients who had achieved a minimal response (MR) or better on prior therapy.[8] The genomic complexity and clonal evolution of MM over the course of treatment are thought to contribute to drug resistance and disease progression.[9]

The cause of MM is unknown, but 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] MGUS is characterised by an excess number of protein molecules (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. 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.[9]

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.[9] Other features and symptoms of MM can 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.[11]

MM patients experience a variety of disease-related events and subsequent disability, such as bone destruction leading to pain, height reduction and body shape changes, bone marrow failure, renal failure, immunodeficiency, and the psychosocial burden of a diagnosis of cancer. These aspects may have different importance for the patient in different periods of the disease. Therapeutic interventions may also produce troublesome side effects and functional impairments. A similar psychosocial burden may be present in caregivers of MM patients, with the role and level of care required evolving as the

disease progresses.[12] Health-related quality of life assessment tools that introduce the patient's perspective into the clinical process via standardised self-reports may add an additional dimension to traditional endpoints in both clinical trials and practice.[13]

CLINICAL NEED and BURDEN OF DISEASE

In 2015, MM was the 19th most common cancer in the UK with 4,920 new cases in England and Wales (2,835 male and 2,085 female). MM incidence is strongly linked to age, with almost half (45%) of new cases diagnosed in the UK between 2013-2015 presenting in persons aged 75 years and older. There were 3,079 MM deaths in 2016, accounting for 2% of all cancer mortality in the UK.[14] MM incidence rates are projected to rise by 11% in the UK between 2014 and 2035, to 12 cases per 100,000 people by 2035.[15] In 2016-17 NHS England reported 140,645 finished consultant episodes (FCEs) and 136,025 admissions under ICD code C90.0 (multiple myeloma) resulting in 90,685 FCE bed days.[16]

Almost half of patients with MM in England and Wales survive their disease for at least 5 years, with a third surviving for 10 years or more (2010-2011).[17] Increased life expectancy is mainly due to the availability of novel chemotherapeutic agents, IMiDs and PIs, and the adoption of haematopoietic stem cell transplantation.[18] The population likely to be eligible to receive isatuximab could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Multiple myeloma - lenalidomide (maintenance, post autologous stem cell transplantation) (ID475). 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. Daratumumab with bortezomib for treating relapsed or refractory multiple myeloma (ID974). Expected October 2018.
- NICE technology appraisal in development. Plitidepsin in combination with dexamethasone for treating relapsed or refractory multiple myeloma (ID1081). Expected October 2018.
- NICE technology appraisal in development. Multiple myeloma (newly diagnosed) - lenalidomide (ID474). Expected June 2018.
- NICE technology appraisal. Ixazomib with lenalidomide and dezamethasone for treating relapsed or refractory multiple myeloma (TA505). February 2018.
- NICE technology appraisal. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA510). March 2018.
- NICE technology appraisal. Daratumumab with lenalidomide and dexamethasone for treating relapsed and refractory multiple myeloma (TA454). July 2017.
- NICE technology appraisal. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (TA427). January 2017.
- NICE technology appraisal. Carfilzomib for previously treated multiple myeloma (TA457). July 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 for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (TA311). April 2014.
- NICE technology appraisal. Bortezomib and thalidomide for the first‑line treatment of multiple myeloma (TA228). July 2011.
- NICE technology appraisal. Bortezomib monotherapy for relapsed multiple myeloma (TA129). October 2007.
- NICE clinical guideline. Metastatic malignant disease of unknown primary origin in adults: diagnosis and management (CG104). July 2010.
- NICE diagnostic guidance in development. Multiple myeloma and related disorders - Freelite assays (and alternative technologies identified during scoping) for diagnosis in primary care (GID-DT28). Expected date of issue to be confirmed.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE guideline. Myeloma: diagnosis and management (NG35). February 2016.

NHS ENGLAND and POLICY 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.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/A. April 2013.

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]
- National Comprehensive Cancer Network. American NCCN Guidelines: Version 3 – NCCN Evidence Blocks: Myeloma Therapy. 2017[19]
- The International Myeloma Working Group. Revised International Staging System for Multiple Myeloma: A Report from IMWG. 2015[20]
- 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[21]
- The European Myeloma Network. European Myeloma Network Guidelines: European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. 2014[22]

CURRENT TREATMENT OPTIONS

Despite recent progress, MM remains incurable and the majority of patients will progress and require treatment. The health and treatment of MM patients is complex, reflecting the effects of the disease, other comorbidities, frailty and the ageing process. MM treatments also 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]

Treatment options for relapsed and refractory MM which include the novel agents thalidomide, bortezomib and lenalidomide as single-agents or in combination with dexamethasone have shown significant activity in patients with relapsed MM and are generally well tolerated. These agents have set the stage for the development of the next-generation immunomodulatory drugs (IMiDs) and the proteasome inhibitors (PIs) (i.e. pomalidomide and carfilzomib in relapsed and/or refractory disease). In general, doublet or triplet regimens are preferred above single agents for optimal effect.[23]

In instances of first relapse, current NICE guidelines recommend the use of:[24]

- Carfilzomib in combination with dexamethasone – only after one prior therapy, which did not include bortezomib
- Bortezomib – only after one prior therapy and 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 RISS system

Subsequent relapse treatment may include:

- Lenalidomide in combination with dexamethasone – two or more prior therapies
- Ixazomib in combination with lenalidomide and dexamethasone, through the CDF after two or more prior therapies.
- Panobinostat in combination with bortezomib and dexamethasone – relapsed and/or refractory, at least two prior therapies including bortezomib and an immunomodulatory agent
- Pomalidomide in combination with low-dose dexamethasone – third or subsequent relapse; three previous treatments including both bortezomib and an immunomodulatory agent
- Daratumumab monotherapy as 4th line therapy through the CDF
- Bendamustine for relapsed disease where all other treatments contraindicated or inappropriate is available through the CDF.

EFFICACY and SAFETY

Trial	**ICARIA-MM, NCT02990338; Isatuximab in combination with pomalidomide and dexamethasone vs pomalidomide and dexamethasone; phase III**
Sponsor	Sanofi
Status	Ongoing
Source of Information	Trial registry[2]
Location	EU (incl. UK), USA, Canada and other countries
Design	Randomised, active-controlled, open-label
Participants	n=300 (planned); aged ≥ 18 years; documented diagnosis of MM; must have received at least 2 prior MM treatment regimens; must have undergone at least 2 consecutive cycles of treatment for each regimen; patients whose

	prior therapy included a lenalidomide and a proteasome inhibitor alone or in combination; must be refractory to the last treatment regimen defined as progression on or within 60 days of last treatment
Schedule	Randomised to Isatuximab (intravenous) on Day 1, 8, 15, and 22 of 1st 28-day cycle, then on Day 1 and 15 of subsequent cycles in combination with pomalidomide per os on Day 1 to 21 + dexamethasone IV (intravenous) or per os on Day 1, 8, 15, 22 in 28-day cycles; or pomalidomide per os on Day 1 to 21 + dexamethasone IV (intravenous) or per os on Day 1, 8, 15, 22 in 28-day cycles
Follow-up	Not reported
Primary Outcomes	• Progression Free Survival (PFS) [Time frame: from the date of randomization to the date of first documentation of progression or the date of death from any cause, whichever comes first, assessed approximatively up to 18 months]
Secondary Outcomes	• Overall response rate (ORR) [Time Frame: From the date of randomization to the date of first documentation of progression, assessed approximately up to 18 months] • Overall Survival (OS) [Time Frame: up to 51 months] • Time to progression (TTP) [Time Frame: From the date of randomization to the date of first documentation of progression, assessed approximately up to 18 months] • Progression free survival (PFS) [Time Frame: From the date of randomization to the date of first documentation of progression or the date of death from any cause, whichever comes first, assessed approximately up to 18 months] • Duration of response (DOR) [Time Frame: From the date of randomization to the date of first documentation of progression or the date of death from any cause, whichever comes first, assessed approximately up to 18 months] • Number of patients with adverse events according to the National Cancer Institute - Common Toxicity Criteria (NCI-CTC) version 4.03 grade scaling [Time Frame: Up to 30 days after last study treatment administration] • Patient-reported outcome measured with Quality of Life questionnaire EORTC-QLQ-C30 [Time Frame: Approximately up to 18 months] • Patient-reported outcome measured with Quality of Life questionnaire MY20 [Time Frame: Approximately up to 18 months] • Patient-reported outcome measured with Quality of Life questionnaire EQ-5D-5L [Time Frame: Approximately up to 18 months] • Plasma concentrations of isatuximab (IPd Arm) [Time Frame: Up to 30 days after last study treatment administration] • Immune response (IPd Arm) : levels of human anti-drug antibodies (ADA) [Time Frame: Up to 60 days after last study treatment administration, or until test is negative whichever comes last]

Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date reported as November 2020

ESTIMATED COST and IMPACT

COST

The cost of Isatuximab is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☒ Other:Re-organisation of existing services

☐ Need for new services

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☒ None identified – unable to state if cost of single treatment with Isatuximab would be less expensive than current available treatments

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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