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Pomalidomide (Imnovid) with bortezomib and dexamethasone for relapsed or refractory multiple myeloma- second line and beyond

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LAY SUMMARY

Multiple myeloma (MM) is a form of blood cancer that develops in the soft tissue inside the bone and causes pain and bone breakage. It is the 18th most common cancer in the UK and affects mostly people aged over 80 years. Approximately half of the people affected by myeloma in England and Wales survive their disease for five years or more with an increased chance of survival in younger people.
Patients with MM will experience periods of time without symptoms followed by periods when the illness comes back, eventually the periods without symptoms will shorten and the illness will become immune to the drugs given to treat it.

Pomalidomide with dexamethasone is currently approved for use in the UK to treat adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy. If approved, the combination of pomalidomide with bortezomib and dexamethasone will offer a treatment option for patients who have been previously exposed to lenalidomide (including refractory to lenalidomide) - a type of patients for which the outcomes with other novel regimens are uncertain.

TARGET GROUP

Relapsed or refractory multiple myeloma patients who have received at least one prior treatment regimen including lenalidomide.

TECHNOLOGY

DESCRIPTION

Pomalidomide (Imnovid) is an immunomodulatory agent with antineoplastic activity. It is shown to inhibit the proliferation and induce apoptosis of various tumour cells. Furthermore, pomalidomide enhances T-cell and natural killer (NK) cell-mediated immunity and inhibit the production of pro-inflammatory cytokines, like tumour necrosis factor alfa (TNF-alpha) or interlukin 6 (IL-6), by monocytes. The primary target of pomalidomide is thought to be the protein cereblon. It binds to this target and inhibits ubiquitin ligase activity. It is also a transcriptional inhibitor of cyclooxygenase-2 (COX2).[1]

Pomalidomide works in a number of ways in multiple myeloma: it blocks the development of tumour cells, prevents the growth of blood vessels within tumours and also stimulates some of the specialised cells of the immune system to attack the tumour cell.[2]

In the ongoing phase III clinical trial NCT01734928, 4 mg of pomalidomide will be taken orally on days 1-14 of a 21-day cycle along with 1.3 mg/m2 of bortezomib administered subcutaneously on days 1, 4, 8 and 11 of 21 days for cycles 1 -8 and on days 1, 8 of 21 days for cycle 9 and onward until disease progression, and dexamethasone 20 mg/day [≤ 75 years old] or 10 mg/day (> 75 years old) orally on days 1, 2, 4, 5, 8, 9, 11, 12 of 21 days for cycles 1-8 and on days 1, 2,8, 9 of 21 days for cycles 9 and onward until disease progression.[16]

A range of treatments have been approved by the EMA for use in multiple myeloma including bortezomib, lenalidomide, thalidomide, pomalidomide, carfilzomib, daratumumab, elotuzumab and ixazomib. This is in addition to conventional chemotherapy such as melphalan and prednisone. Pomalidomide with dexamethasone is currently approved for use in the UK to treat adult patients with relapsed and refractory who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.[3]

The most common side effects with Imnovid (which affect more than 1 in 10 patients), some of which were serious, include anaemia (low red-blood-cell counts), neutropenia (low white-blood-cell counts), fatigue (tiredness), thrombocytopenia (low platelet counts), pyrexia (fever), peripheral oedema (swelling, especially of the ankles and feet), peripheral neuropathy (nerve damage causing tingling, pain and numbness in the hands and feet) and pneumonia (infection of the lungs). [2]

Pomalidomide is also being investigated in several trials for the following indications:

- Isatuximab, Pomalidomide, and Dexamethasone vs. Pomalidomide and Dexamethasone in Refractory or Relapsed Multiple Myeloma Patients (NCT02990338)
- Daratumumab/Pomalidomide/Dexamethasone vs Pomalidomide/Dexamethasone in Refractory or Relapsed Multiple Myeloma (NCT03180736)

INNOVATION and/or ADVANTAGES

If licensed, pomalidomide with bortezomib and dexamethasone will offer a treatment option for patients who have received one or more prior therapies where their disease has progressed during or after their last anti-myeloma therapy including treatment with lenalidomide. Lenalidomide is approved for use by the EMA as combination therapy for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant and as monotherapy for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.[14] Currently there is limited clinical evidence on the effectiveness of myeloma treatments at second line in patients who have received and become refectory to lenalidomide in the newly diagnosed setting.

DEVELOPER

Celgene Corp.

AVAILABILITY, LAUNCH or MARKETING

Imnovid was designated orphan drug in the EU for multiple myeloma in 2009.[2]

PATIENT GROUP

BACKGROUND

Multiple myeloma (MM) is a form of blood cancer that develops in the bone marrow.[3] Myeloma is a malignancy of the plasma cells which normally produce immunoglobulin; abnormal immunoglobulin, produced by myeloma cells, interferes with normal blood cell production. It is the 18th most common cancer in the UK[4], affecting multiple organs and systems, such as bones, kidneys, blood and immune system.[8] It is often found in multiple places in the body, hence the name multiple myeloma.

Historically, myeloma has been considered an incurable disease and still today few, if any, patients are cured. Rarely, after stem cell transplantation, or following standard therapy, patients have been known to live without disease recurrence for decades, suggesting a possible cure in a small subset of patients.[5] The typical disease course for an individual patient includes periods of symptomatic myeloma followed by periods of remission. Over time, the periods of disease inactivity shorten following subsequent therapies and eventually the disease becomes refractory (nonresponsive).[4] Refractory myeloma (rrMM) may occur in patients who never see a response from their treatment therapies or it may occur in patients who do initially respond to treatment, but do not respond to treatment after relapse.[6] Despite the introduction of novel therapies, it is predicted that MM patients will still lose approximately 11 years of life on average compared with the general population.[7]

The cause or causes of myeloma are unknown, but there is some evidence to support a number of theories of its origin, including viral, genetic, and exposure to toxic chemicals, the most notable being Agent Orange.[4]

Myeloma causes a wide spectrum of complications, including significant bone destruction in the form of osteoporosis and lytic lesions. Often these lesions are in the spine, ribs, clavicles (collarbone), pelvis, or in a long bone such as the humerus (arm) or femur (leg). Small fractures or even major fractures may occur, causing pain, loss of height, more difficulty breathing, or difficulty walking.[4]

CLINICAL NEED and BURDEN OF DISEASE

In 2014 approximately 5,500 new cases of myeloma were diagnosed in the UK[8] representing a total of 2% of all cancers diagnosed in that same year. Myeloma is a condition more prevalent in old age with a peak rate of myeloma cases between 2012 and 2014 at the age range 85 to 89 years. Almost half (47%) of people diagnosed with myeloma in England and Wales survive their disease for five years or more. Around three quarters of people in England diagnosed with myeloma aged 15-49 survive their disease for five years or more, compared with a quarter of people diagnosed aged 80 and over.[9]

The latest Hospital Episode Statistics (2015/16) recorded approximately 133,500 finished consultant episodes (FCE), 129,217 admissions and 87,528 FCE bed days for multiple myeloma and malignant plasma cell neoplasms (ICD-10 code C.90.0).[10]

A 2014 observational chart review of 4,995 patients with MM in Belgium, France, Germany, Italy, Spain, Switzerland and the UK looked at the proportion of multiple myeloma patients receiving therapies across various treatment lines. The number of patients treated in rrMM reduced substantially with each subsequent line: 61% received second line treatment, 38% received third line treatment and only 15% were able to receive fourth line treatment.[11] The authors conclude that an unmet need remains for treatments that are better tolerated, along with efficacy in later treatment lines and improved quality of response.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal in development. Multiple myeloma - lenalidomide (post bortezomib) (part rev TA171) (GID-TAG452). Expected date of publication TBC
- NICE Technology appraisal in development. Pembrolizumab for previously treated multiple myeloma (GID-TA10193). Expected date of publication TBC
- NICE Technology appraisal in development. Multiple myeloma - carfilzomib (with lenalidomide and dexamethasone, after prior therapy) (GID-TAG511). Expected date of publication TBC
- NICE Technology appraisal in development. Multiple myeloma (one prior therapy) - vorinostat (with bortezomib) (GID-TAG435). Expected date of publication TBC
- NICE Technology appraisal in development. Multiple myeloma (relapsed, refractory) - daratumumab (with lenalidomide and dexamethasone) (GID-TA10104). Expected date of publication TBC
- NICE Technology appraisal. Multiple myeloma (relapsed, refractory) - ixazomib citrate (GID-TA10043). Expected publication date October 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 (TA 171) April 2014.

- NICE technology appraisal. Bortezomib monotherapy for relapsed multiple myeloma (TA129). October 2007.
- 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: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a
- NHS England. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult) B04/S/a
- NHS England. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Children) B04/S/b

OTHER GUIDANCE

International Myeloma Working Group (IMWG). *Criteria for the diagnosis of multiple myeloma.* Available from http://imwg.myeloma.org/international-myeloma-working-group-imwg-criteria-for-the-diagnosis-of-multiple-myeloma/ [Accessed 16 August 2017]

Moreau P, San Miguel J, Ludwig H, Schouten H, Mohty M, Dimopoulos M, Dreyling M. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2013 Aug 16;24(suppl_6):vi133-7. https://doi.org/10.1093/annonc/mdx096 [Accessed 16 August 2017]

Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H, Hajek R, Dimopoulos MA, Ludwig H, Einsele H, Zweegman S. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2017 Apr 27. https://doi:10.1093/annonc/mdx096 [Accessed 22 September 2017]

British Committee for Standards in Haematology, UK Myeloma Forum. *Guidelines for the diagnosis and management of multiple myeloma 2014.* Available from https://academy.myeloma.org.uk/wp-content/uploads/sites/2/2014/08/MYELOMA_GUIDELINE_Feb_2014_for_BCSH1.pdf [Accessed 16 August 2017]

CURRENT TREATMENT OPTIONS

A number of factors need to be considered when selecting treatment at relapse:

- Disease related factors (Type & risk status of disease, presence of refractory disease and aggressiveness of current relapse.[12,13]
- Treatment related factors (Type of prior treatment and prior response & toxicity).[12,13]
- Patient related factors (Age, frailty, performance status and co-morbidities).[12,13,14].

For first relapse, current NICE guidelines[15] recommend the use of:

- carfilzomib for the management of first relapse in MM in patients that have had only 1 previous therapy, which did not include bortezomib;
- bortezomib as a monotherapy option for the treatment of progressive MM in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for bone marrow transplantation.

A second autologous stem cell transplantation might also be offered to people with relapsed myeloma who are suitable. Their suitability will depend on a number of factors (good response to the first autologous stem cell transplant, not had many prior treatments, fitness level and low rank in the international staging system) that should be considered before offering this treatment option to patients.[15]

For subsequent relapses the following treatment might be offered:

- Lenalidomide in combination with dexamethasone is recommended as an option for the treatment of multiple myeloma only in people who have received two or more prior therapies;
- Panobinostat in combination with bortezomib and dexamethasone is recommended, as an option for treating multiple myeloma, that is, for adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent;
- Pomalidomide in combination with low-dose dexamethasone, is recommended as an option for treating multiple myeloma in adults at third or subsequent relapse; that is, after 3 previous treatments including both lenalidomide and bortezomib.

EFFICACY and SAFETY

Trial	NCT01734928; OPTIMISMM
Sponsor	Celgene
Status	Ongoing, not recruiting
Source of Information	Trial registry[16]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised; active/controlled; open label
Participants	N=559 (planned); adults > or =18 years; multiple myeloma diagnosis; had 1 but no more than 3 prior anti-myeloma regimens; disease progression after last regimen; prior treatment with lenalidomide
Schedule	Pomalidomide 4 mg will be taken orally on Days 1-14 of a 21-day cycle. Bortezomib 1.3 mg/m2 will be administered subcutaneously on Days 1, 4, 8 and 11 of 21 days for cycles 1 -8 and on Days 1, 8 of 21 days for cycle 9 and onward until disease progression. Dexamethasone 20 mg/day [≤ 75 years old] or 10 mg/day [>75 years old] will be taken orally on Days 1, 2, 4, 5, 8, 9, 11, 12 of 21 days for cycles 1-8 and on Days 1, 2, 8, 9 of 21 days for cycles 9 and onward until disease progression.
Follow-up	Subjects who permanently discontinued study treatment prior to progressive disease will continue to be followed up in the PFS follow-up phase until

	progressive disease. All subjects will be followed in the long-term follow-up phase until death or for at least 5 years after the last subject is randomised into the study, or longer if clinically indicated (unless the follow-up is shorter due to withdrawal of consent, loss to follow-up, or death).
Primary Outcomes	Progression Free Survival
Secondary Outcomes	Secondary Endpoints • Overall Survival (OS) • Safety (type, frequency, seriousness and severity of AEs, and relationship of AEs to study drug or comparator) • Overall response rate (ORR) (using the International Myeloma Working Group Uniform [IMWG] response criteria) • Duration of response
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

Pomalidomide is already marketed in the UK for the treatment of multiple myeloma previously treated with lenalidomide and bortezomib; a packet of 4 mg (21 capsules) has an NHS indicative price of £8,884.00.

Drug	Dose	Unit cost
Pomalidomide (Imnovid)	21 capsules of either: 1mg, 2mg, 3mg, 4mg	£8,884.00
Bortezomib (Velcade)	3.5mg powder in vial	£762.38
Dexamethasone	20/40mg, 50x2	£28.93

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ 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

OTHER ISSUES

☒ Clinical uncertainty or other research question identified: *safety and efficacy results not yet available (trial ongoing)*

☒ None identified

REFERENCES

[1] Drugbank. *Pomalidomide.* Available from https://www.drugbank.ca/drugs/DB08910 [Accessed 16 August 2017]

[2] European Medicines Agency. *Imnovid (previously Pomalidomide Celgene)*. Available from http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002682/human_med_001669.jsp&mid=WC0b01ac058001d124 [Accessed 16 August 2017]

[3] Myeloma UK. *What is myeloma?* Available from https://www.myeloma.org.uk/information/what-is-myeloma/ [Accessed 16 August 2017]

[4] Cancer Research UK. *Twenty most common cancers.* Available from http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Zero [Accessed 16 August 2017]

[5] Helen Diller Family Comprehensive Cancer Center. *About multiple myeloma.* University of California San Francisco. Available from http://cancer.ucsf.edu/research/multiple-myeloma/ [Accessed 17 August 2017]

[6] Multiple Myeloma Research Foundation. *Refractory myeloma*. Available from https://www.themmrf.org/multiple-myeloma/prognosis/refractory-multiple-myeloma/ [Accessed 17 August 2017]

[7] Drawid A, K.S., Kiely D, Hussein MA, Kaman M, et al., *Impact of novel therapies on multiple myeloma survival in the US: Current and future outcomes.* J Clin Oncol, 2015: p. (suppl; abstr e19536). Ludwig, H., et al., *Survival and years of life lost in different age cohorts of patients with multiple myeloma.* J Clin Oncol, 2010. **28**(9): p. 1599-605.

[8] Cancer Research UK. *Myeloma incidence statistics.* Available from http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence [Accessed 16 August 2017]

[9] Cancer Research UK. *Myeloma survival.* Available from http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma#heading-Two [Accessed 16 August 2017]
[10] Hospital Episodes Statistics 2015-2016. Primary diagnosis: 4 character. NHS Digital. Available from http://content.digital.nhs.uk/catalogue/PUB22378/hosp-epis-stat-admi-diag-2015-16-tab.xls x [Accessed 17 August 2017].
[11] Yong, K., et al., *Multiple myeloma: patient outcomes in real-world practice.* Br J Haematol, 2016. **175**(2): p. 252-264.
[12] Sonneveld P, Broijl A. Treatment of relapsed and refractory multiple myeloma. haematologica. 2016 Apr 1;101(4):396-406.
[13] Nooka AK, Kastritis E, Dimopoulos MA, Lonial S. Treatment options for relapsed and refractory multiple myeloma. Blood. 2015 Jan 1:blood-2014.
[14] Laubach J, Garderet L, Mahindra A, Gahrton G, Caers J, Sezer O, Voorhees P, Leleu X, Johnsen HE, Streetly M, Jurczyszyn A. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. Leukemia. 2016 May 1;30(5):1005-18.
[15] National Institute for Health and Care Excellence. *Myeloma: diagnosis and management* (NG35). 2016. Available from https://www.nice.org.uk/Guidance/NG35 [Accessed 17 August 2017]
[16] ClinicalTrials.gov. *Safety and Efficacy of Pomalidomide, Bortezomib and Low-dose Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma (OPTIMISMM)*. Available from https://clinicaltrials.gov/ct2/show/NCT01734928 [Accessed 16 August 2017]
[14] Electronic Medicines Compendium. *Revlimid SPC*. Available from Revlimid - Summary of Product Characteristics (SPC) - (eMC) [Accessed 21 September 2017]