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Ixazomib citrate for newly diagnosed multiple myeloma – maintenance therapy following autologous stem cell transplant

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LAY SUMMARY

Multiple myeloma (MM) is a rare, incurable cancer of the plasma cells in the bone marrow which is the spongy tissue found at the centre of some bones. MM is the second most common haematological cancer in the UK. Symptoms of MM vary but may include bone pain, fractures, body weakness, malaise, bleeding, anaemia and infections. MM is not usually considered a curable disease; treatment often involves a stem cell (or bone marrow) transplant that requires medications before and after to improve the success of treatment.

Ixazomib citrate is a novel oral medicinal product that is already licensed in the UK for the treatment of MM in patients who have received at least one prior therapy (in combination with lenalidomide and dexamethasone). Ixazomib citrate offers the potential advantage over similar medicines in its class of being more effective in its anticancer activity, less toxic (reduced side effects) and more convenient to administer (through its weekly oral dosing). If approved as maintenance therapy following stem cell transplant in newly diagnosed MM patients, ixazomib citrate has the potential to improve the success rates of treatment by improving progression free survival and overall survival as well as presenting a more convenient way of administration that allows long term administration and improvement of patients' quality of life.

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TARGET GROUP

Multiple myeloma (newly diagnosed) – maintenance therapy following autologous stem cell transplant; monotherapy

TECHNOLOGY

DESCRIPTION

Ixazomib citrate (Ninlaro; MLN 9708) is a prodrug that becomes quickly converted to its active metabolite, ixazomib, after administration.[1] Ixazomib citrate is an N-capped dipeptidyl leucine boronic acid which reversibly inhibits the chymotrypsin-like (CT-L) proteolytic (β5) site of the 20S proteasome to induce accumulation of ubiquitinated proteins, which ultimately leads to myeloma cell death.[1]

Ixazomib citrate is a second-generation boronate proteasome inhibitor (PI), and represents the first oral PI to be evaluated in multiple myeloma (MM) clinical trials.[2] Ixazomib citrate also exerts a time-dependent reversible proteasome inhibition but the proteasome dissociation half-life (t½) for ixazomib citrate was found to be approximately six times faster than that of bortezomib (t½ 18 minutes versus 110 minutes).[2]

Ixazomib citrate for maintenance therapy of adult patients with newly diagnosed MM following autologous stem cell transplant is the first oral proteasome inhibitor to be evaluated for this indication in the treatment of MM.[3]

In the currently ongoing randomised, placebo-controlled phase III trial (NCT02181413; TOURMALINE MM-3), ixazomib citrate 3 mg capsules or placebo are administered once a day, orally on days 1, 8 and 15 of a 28-day cycle for cycle 1 through 4 and ixazomib citrate 4mg capsules are administered once a day, orally on days 1, 8 and 15 of a 28-day cycle for cycles 5 through 26.[4]

Ixazomib citrate is indicated for the treatment of MM in patients who have received at least one prior therapy (in combination with lenalidomide and dexamethasone). In the UK, ixazomib citrate is funded for MM patients who have received two or three prior therapies. Common and very common side effects include: back pain; constipation; diarrhoea; nausea; neutropenia; peripheral neuropathy (monitor for symptoms); peripheral oedema; rash; thrombocytopenia; vomiting.[5, 6]

Ixazomib citrate is also at phase III stage of development for the following indications:[7]

- Maintenance therapy in newly diagnosed MM patients not treated with stem cell transplantation
- Newly diagnosed MM adult patients in combination with lenalidomide and dexamethasone not eligible for a stem cell transplant
- Relapsed or refractory systematic light chain amyloidosis in combination with dexamethasone or physicians choice of treatment

INNOVATION and/or ADVANTAGES

Compared with bortezomib, ixazomib citrate showed an improved pharmacokinetic, pharmacodynamic profile and antitumor activity in preclinical studies. Moreover, in clinical studies, its toxicity profile also appears to be better, particularly regarding peripheral neuropathy. Ixazomib

citrate also exerts antimyeloma activity as a single agent in patients refractory to bortezomib, and particularly in combination with alkylating agents and immunomodulatory drugs (IMiDs), leading to minimal residual disease (MRD) negativity in a significant proportion of patients with an easy management of adverse events. However, ixazomib's strength is its administration modality: oral at a flat dose. This characteristic allows long-term administration, preserving an optimal quality of life.[3]

If licensed for this indication, ixazomib citrate will offer a new treatment option as a maintenance therapy for patients newly diagnosed with MM that have undergone an autologous stem cell transplant. The use of ixazomib citrate as a maintenance therapy following autologous stem cell transplant has the potential of having better antitumour activity, improved progression free survival (PFS) and improved overall survival (OS), both end points of the TOURMALINE MM-3 trial, than current treatment options. Furthermore, ixazomib citrate offers patient convenience due to its weekly oral route of administration.

DEVELOPER

Takeda UK Ltd.

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, immunosuppression, osteolysis and end-organ damage.[8] 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, therefore the first remission has the longest duration potential, making it critical for long-term patient outcomes.[9]

The cause of MM is unknown, but is closely associated with a condition called monoclonal gammopathy of unknown significance (MGUS). Estimates suggest approximately 1 in every 100 people with MGUS go on to develop MM on an annual basis.[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.[10]

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.[11, 12] The early side effects from a stem cell transplant (SCT) are similar to those from chemotherapy and radiation, only more severe. One of the most serious side effects is low blood counts, which can lead to risks of serious infections and bleeding.[13]

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.[11] 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.[12]

CLINICAL NEED and BURDEN OF DISEASE

Multiple myeloma (MM), although a rare disease, is the second most common haematologic malignancy. It is found in the spectrum of plasma cell dyscrasias, which begins with monoclonal gammopathy of unknown significance (MGUS) to overt plasma cell leukaemia and extramedullary myeloma. MM is associated with significant morbidity due to its end-organ destruction. It is a disease of the older population and its incidence in the African American population is twice that of the European American population.[14]

In 2015, MM was the 19th most common cancer in the UK, accounting for 2% of all new cancer cases.[15]

Incidence rates for myeloma are projected to rise by 11% in the UK between 2014 and 2035, to 12 cases per 100,000 people by 2035.[15] The median age at presentation is approximately 70 years. Only 15% of patients are aged less than 60 years.[16]

In England and Wales in 2016 there were a total of 2,769 deaths due to multiple myelomas and malignant plasma cell neoplasms (ICD-10 C90.0).[17] In England, for adults diagnosed between 2011 and 2015 and followed up in 2016, the age-standardised five year survival was 51.4% (both genders).[18]

Between 2016 and 2017, in England the Hospital Episodes Statistics recorded a total of 139,638 hospital admissions due to multiple myeloma and malignant plasma cell neoplasms (ICD-10 code C90.0), of which 128,378 were day cases.[19] During the same time period, in England the NHS recorded a total of 1,852 finished consultant episodes (FCE) and 1,716 admissions, of which 60 were day cases, for autologous peripheral blood stem cell transplant (OPCS-4 code X33.4).[20]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (TA311). April 2014.
- 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. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/A. April 2013.

OTHER GUIDANCE

- National Comprehensive Cancer Network. Clinical Practice Guideline in Oncology: Multiple Myeloma. 2018.[21]
- Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2017.[22]
- International Myeloma Working group. Revised international staging system for multiple myeloma: a report from the International Myeloma Working Group. 2015.[23]
- British Committee for Standards in Haematology (BCSH) and the UK Myeloma Forum. Guidelines for the diagnosis and management of multiple myeloma 2014.[16]
- European Myeloma Network. European Myeloma network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. 2014.[24]

CURRENT TREATMENT OPTIONS

Myeloma is not considered a curable disease. The main aims of treatment are to reduce the myeloma, and to bring the patient into remission for as long as possible with the best quality of life. Usually, patients respond well to first line therapy, and this period tends to be where most patients experience the greatest length of remission.[25]

There are two stages involved in first-line therapy for patients intended to undergo an autologous Stem Cell Transplant (aSCT). The first stage is known as induction, which involves a combination of chemotherapy, steroids, immunomodulators and proteasome inhibitors. The second stage is to undergo an aSCT. The aim of the first line treatment is to remove as many of the myeloma cells as possible from the patient's bone marrow.[25]

Chemotherapy, proteasome inhibitor and Histone deacetylase inhibitors (HDACi) are directly toxic to cancer cells. Steroids can also increase the cancer-killing effects of other chemotherapies. Biological and immunomodulator therapies work to discourage the current/ future growth of other cancer cells. The exact drug, dose and combination will depend upon the patient's general health, age, and whether they will have a stem cell transplant at a later date.[25]

The most common combination used in first-line therapy, especially for younger or fitter patients prior to high-dose therapy and stem cell transplantation (HDTSCT), is bortezomib-thalidomide-dexamethasone (VTd),[26] CTD (cyclophosphamide-thalidomide -dexamethasone) is also commonly used.[25]

In the UK, for the first line treatment of newly diagnosed patients, NICE has provided the following recommendations:[27]

- Bortezomib in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high‑dose chemotherapy with haematopoietic stem cell transplantation.
- Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first‑line treatment of multiple myeloma in people for whom high‑dose chemotherapy with stem cell transplantation is considered inappropriate.
- Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first line treatment of multiple myeloma if:

- high dose chemotherapy with stem cell transplantation is considered inappropriate and
- the person is unable to tolerate or has contraindications to thalidomide.

Autologous stem cell transplantation and allogeneic stem cell transplantation may be contemplated as treatment options provided a number of suitability measures are taken into account.[27]

EFFICACY and SAFETY

Trial	NCT02181413, **TOURMALINE-MM3; adults 18 years and older; ixazomib citrate vs placebo; phase III**
Sponsor	Takeda Pharmaceuticlas (Millennium Pharmaceuticals, Inc)
Status	Ongoing
Source of Information	Abstract,[28] Trial registry[4]
Location	18 EU countries (including UK), Argentina, Australia, Brazil, Canada, Colombia, Israel, Japan, Korea, Republic of, Mexico, Singapore, South Africa, Taiwan, Thailand, United States
Design	Randomised, placebo-controlled
Participants	n=656; aged 18 and older; confirmed diagnosis of symptomatic multiple myeloma according to standard criteria, documented results of cytogenetics/ fluorescence in situ hybridization, underwent standard of care induction therapy (induction therapy must include proteasome inhibitor (PI) and/or immunomodulating drugs (IMiD)-based regimens as primary therapy for multiple myeloma), followed by a single autologous stem cell transplant (ASCT) with a high-dose melphalan (200 mg/m^2) conditioning regimen, within 12 months of diagnosis.
Schedule	Randomised to ixazomib citrate 3 mg, capsule, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 4. Ixazomib citrate 3 or 4 mg, capsules, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 5 through 26. Participants experiencing adverse events (AEs) attributed to study drug during any cycle may continue in the study but may have doses of study drug held or reduced by at least 1 dose level. Reduced doses are: 3 mg, 2.3 mg, 1.5 mg and discontinuation of study drug; or, ixazomib citrate placebo-matching capsule, orally, once on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 4. Ixazomib citrate placebo-matching capsules, orally, once on Days 1, 8 and 15 in a 28-day cycle for Cycles 5 through 26.
Follow-up	Active treatment period for 24 months thereafter followed up every 4 weeks until progression of disease or death (up to month 107)
Primary Outcomes	Progression Free Survival (PFS) from baseline to end of treatment (24 months)
Secondary Outcomes	• Overall Survival (OS) [Time frame: Baseline up to follow up period (107 months)] • Percentage of participants with any best response category before PD or subsequent therapy [Time frame: Baseline up to EOT (24 months) and thereafter every 4 week until initiation of the next line of therapy (up to 107 months)] • Time to Progression (TTP) [Time frame: Baseline until PD (Month 107)]

	• Second Progression-Free Survival (PFS2) [Time frame: Baseline up to end of treatment (24 months); thereafter followed up every 4 weeks until initiation of next-line therapy and then every 12 weeks until second progressive disease (PD2) or death (up to month 107)] • Time to start of the next line of therapy [Time frame: Baseline up to start of next line of therapy (after 24 months treatment period followed by every 4 weeks PFS and PD follow up period)] • Time to end of the next line of therapy [Time frame: Baseline up to end of next line of therapy (month 107)] • Duration of the next line of therapy [Time frame: From the start of next line therapy after PD to the last dose of next line therapy (up to month 107)] • Percentage of participants who develop a new primary malignancy [Time frame: Baseline until death or termination of the study (up to month 107)] • Percentage of participants with conversion from Minimal Residual Disease (MRD) Positive to MRD negative, and maintenance of MRD negativity [Time frame: Baseline up to EOT (24 months)] • Correlation between MRD status and Progression Free Survival (PFS) and Overall Survival (OS) [Time frame: Baseline up to month 107] • OS benefits in a high-risk population [Time frame: Randomization up to month 107] • PFS benefits in a high-risk population [Time frame: Randomization up to month 107] • Eastern Cooperative Oncology Group (ECOG) performance score [Time frame: Baseline up to EOT(24 months), thereafter every 4 weeks until initiation of next line therapy] • Percentage of participants who experience at least one Treatment Emergent Adverse Event (TEAE) or Serious Adverse Events (SAEs) [Time frame: First dose of study drug through 30 days after last dose of study drug (up to 24 months)] • Number of participants with markedly abnormal clinical laboratory values [Time frame: Baseline through 30 days after the last dose of study drug (up to 24 months)] • Health-related quality of life (HRQL) score based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Global Quality of Life Domain [Time frame: Baseline up to PD (up to month 107)] • Plasma concentration of ixazomib citrate[Time frame: Day 1 of Cycle 1 at multiple time points (up to 4 hours) post-dose; days 8 and 15 of cycle 1, days 1 and 8 of cycle 2, day 1 of cycles 3 through 10 (each cycle of 28 days): pre-dose] • Time to resolution of Peripheral Neuropathy (PN) events [Time frame: From randomization date through 30 days after the last dose of drug (up to 24 months)] • Time to improvement of PN events [Time frame: From randomization date through 30 days after the last dose of drug (up to 24 months)]
Key Results	-
Adverse effects (AEs)	-

Expected reporting date	Final study completion date reported as Jun 2025.

ESTIMATED COST and IMPACT

COST

Ixazomib, under the commercial name of Ninlaro, is already funded via the Cancer Drugs Fund (CDF) in England and Wales for the treatment of multiple myeloma in patients who have received two or three prior lines of therapies, in combination with lenalidomide and dexamethasone. The NHS list price for one cycle of ixazomib citrate (equivalent to 3 capsules) of 4mg is £6,336.00.[29] A confidential patient access scheme is currently in place.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: *improved patient convenience, improved progression free survival*

☐ 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: *Due to length of follow-up, overall survival data will not be available at the first interim analysis however PFS2 and MRD negativity have also been included as endpoints.*

☐ None identified

REFERENCES

1 Drugbank.ca. *Ixazomib*. 2018 Last update date: 27 June 2018. Available from: https://www.drugbank.ca/drugs/DB09570 [Accessed 27 June 2018]

2 Mofers A, Pellegrini P, Linder S, D'Arcy P. Proteasome-associated deubiquitinases and cancer. *Cancer and Metastasis Reviews*. 2017;36(4):635-53. Available from, https://link.springer.com/article/10.1007/s10555-017-9697-6 [Accessed 27 June 2018]

3 Offidani M, Corvatta L, Caraffa P, Gentili S, Maracci L, Leoni P. An evidence-based review of ixazomib citrate and its potential in the treatment of newly diagnosed multiple myeloma. *Onco Targets Ther*. 2014;7:1793-800. Available from: 10.2147/ott.S49187 [Accessed 27 June 2018]

4 ClinicalTrials.gov. *A Study of Oral Ixazomib Citrate (MLN9708) Maintenance Therapy in Participants With Multiple Myeloma Following Autologous Stem Cell Transplant*: *NCT02181413*. Jun 2014. Last Updated: May 2018. Available from: https://clinicaltrials.gov/ct2/show/study/NCT02181413 [Accessed 27 June 2018]

5 British National Formulary (BNF). *Ixazomib*. 2018 Last update date: 2018. Available from: https://bnf.nice.org.uk/drug/ixazomib.html#indicationsAndDoses [Accessed 27 June 2018]

6 Electronic Medicies Compendium (eMC). *NINLARO 3 mg hard capsules*. 2017 Last update date: 9 October 2017. Available from: https://www.medicines.org.uk/emc/product/7574/smpc [Accessed 27 June 2018]

7 ClinicalTrials.gov. *Search for ixazomib, phase III*. 2018 Last update date. Available from: https://clinicaltrials.gov/ct2/results?term=ixazomib&age_v=&gndr=&type=&rslt=&phase=2&Search=Apply [Accessed 28 June 2018]

8 Hipp S, Tai YT, Blanset D, Deegen P, Wahl J, Thomas O, et al. A novel BCMA/CD3 bispecific T-cell engager for the treatment of multiple myeloma induces selective lysis in vitro and in vivo. *Leukemia*. 2016 12/27/online;31:1743. Available from, http://dx.doi.org/10.1038/leu.2016.388 [Accessed 27 June 2018]

9 Borrello I. Can we change the disease biology of multiple myeloma? *Leukemia Research*. 2012 2012/11/01/;36:S3-S12. Available from: https://doi.org/10.1016/S0145-2126(12)70003-6 [Accessed 27 June 2018]

10 Mayo Clinic. *Multiple myeloma*. 2017 Last update date: December 2017. Available from: https://www.mayoclinic.org/diseases-conditions/multiple-myeloma/symptoms-causes/syc-20353378 [Accessed 28 June 2018]

11 Multiple Myeloma Research Foundation. *Caregiver self-care and financial support*. Available from: https://themmrf.org/2017/03/caregiver-self-care-and-financial-support/ [Accessed 29 June 2018]

12 Kvam AK, Waage A. Health-related quality of life in patients with multiple myeloma - does it matter? *Haematologica*. 2015;100(6):704-5. Available from: 10.3324/haematol.2015.127860 [Accessed 29 June 2018]

13 American Cancer Society (ACS). *Stem Cell Transplant for Multiple Myeloma*. 2018 Last update date. Available from: https://www.cancer.org/cancer/multiple-myeloma/treating/stem-cell-transplant.html [Accessed 30 July 2018]

14 Kazandjian D. Multiple myeloma epidemiology and survival: A unique malignancy. *Semin Oncol*. 2016 Dec;43(6):676-81. Available from: 10.1053/j.seminoncol.2016.11.004 [Accessed]

15 Cancer Research UK. *Myeloma Statistics*. 2018 Last update date: Not reported. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma#heading-Zero [Accessed 28 June 2018]

16 British Committee for Standards in Haematology (BCSH), UK Myeloma Forum. *Guidelines for the diagnosis and management of multiple myeloma 2014.* August 2014. Last Updated: Not reported. Available from: https://academy.myeloma.org.uk/wp-content/uploads/sites/2/2014/08/MYELOMA_GUIDELINE_Feb_2014_for_BCSH1.pdf [Accessed 29 June 2018]

17 Office for National Statistics (ONS). *Death Registrations Summary Statistics, England and Wales, 2016.* 2016. Date Published: Date Downloaded: Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables [Accessed 28/03/2018]

18 Office for National Statistics (ONS). *Cancer Survival in England: adults diagnosed between 2011 and 2015 and followed up to 2016.* 2016. Date Published: Date Downloaded: Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 28/03/2018]

19 NHS Digital. *Hospital Episode Statistics for England. Admitted Patient Care statistics, 2016-17. 2017*. Geographic coverage: England, Data collection period: 2016 to 2017; Dataset downloaded: 23 October 2017. Available from: https://digital.nhs.uk/catalogue/PUB30098 [Accessed 20 June 2018]

20 NHS Digital. *Hospital Episode Statistics for England: Main procedure and interventions by attendance type. 2017*. Geographic coverage: England, Data collection period: 2016-2017; Dataset downloaded: Dec 2017. Available from: https://digital.nhs.uk/catalogue/PUB30098 [Accessed 5 June 2018]

21 National Comprehensive Cancer Network. *NCCN Guidelines Version 4.2018: Multiple Myeloma.* February 2018. Last Updated: February 2018. Available from: https://www.nccn.org/professionals/physician_gls/pdf/myeloma_blocks.pdf, login required [Accessed 28 June 2018]

22 Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2017;28(suppl_4):iv52-iv61. Available from: 10.1093/annonc/mdx096 [Accessed 19 July 2018]

23 Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. *Journal of Clinical Oncology*. 2015;33(26):2863. Available from, doi/10.1200/JCO.2015.61.2267 [Accessed 29 June 2018]

24 Engelhardt M, Terpos E, Kleber M, Gay F, Wäsch R, Morgan G, et al. European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. *Haematologica*. 2014;99(2):232-42. Available from: 10.3324/haematol.2013.099358 [Accessed 29 June 2018]

25 Bloodwise. *Myeloma treatment and side effects*. 2017 Last update date: 30 January 2018. Available from: https://bloodwise.org.uk/info-support/myeloma/treatment [Accessed 29 June 2018]

26 Myeloma UK. *Velcade®, thalidomide and dexamethasone (VTD) and myeloma Infoguide*. 2018 Last update date: Not reported. Available from: https://www.myeloma.org.uk/documents/velcade-thalidomide-and-dexamethasone-vtd-and-myeloma-infoguide/ [Accessed 19 July 2018]

27 National Institute for Health and Care Excellence (NICE). *Myeloma: diagnosis and management (NG35).* February 2016. Last Updated: Not reported. Available from: https://www.nice.org.uk/guidance/ng35 [Accessed 29 June 2018]

28 Palumbo A, Morgan GJ, Rajkumar SV, Lonial S, Chng WJ, Iida S, et al. Two phase 3 studies of the oral proteasome inhibitor (PI) ixazomib for multiple myeloma (MM) in the maintenance setting: TOURMALINE-MM3, and -MM4. *Journal of Clinical Oncology*. 2016;34(15_suppl):TPS8068-TPS. Available from: 10.1200/JCO.2016.34.15_suppl.TPS8068 [Accessed 29 June 2018]

29 British National Formulary (BNF). *Ixazomib: capsule*. 2018 Last update date: 2018. Available from: https://bnf.nice.org.uk/medicinal-forms/ixazomib.html [Accessed 27 June 2018]