Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING
August 2018

Selinexor in combination with low-dose dexamethasone for penta-refractory multiple myeloma

NIHRIO ID	24079	**NICE ID**	9960
Developer/Company	Karyopharm Therapeutics	**UKPS ID**	N/A

Licencing and market availability plans	The company anticipate submitting a Marketing Authorisation Application to the EMA in early 2019.[1]

SUMMARY

Selinexor in combination with low-dose dexamethasone are in development for the treatment of patients with penta-refractory multiple myeloma who have received at least five prior therapies. 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. Symptoms of MM vary but some may include bone pain, fractures, body weakness, malaise, bleeding, and anaemia. The cause of MM is unknown.

Selinexor is the first treatment option that targets XPO1, a protein that is responsible for exporting tumour suppressor proteins from the cell nucleus. It belongs to a new family of therapies called selective inhibition of nuclear export (SINE) compounds that blocks XPO1 leading to controlled death of myeloma cells. Currently there is no standard of care for the fifth line treatment of MM. Selinexor and low-dose dexamethasone are being developed as an oral treatment. If licensed, this combination could be an effective treatment option for a patient group with clear unmet need.

PROPOSED INDICATION

Multiple myeloma – penta-refractory; in combination with low-dose dexamethasone[a]

TECHNOLOGY

DESCRIPTION

Selinexor (KPT-330) is a first-in-class, orally available, small molecule inhibitor of XPO1 protein (exportin 1, also called CRM1 or chromosome region maintenance 1 protein), with potential antineoplastic activity. XPO1, the major export carrier for proteins from the nucleus to the cytoplasm, is overexpressed in a variety of cancer cell types including MM. Selinexor modifies the essential XPO1-cargo binding residue cysteine-528, thereby irreversibly inactivating XPO1-mediated nuclear export of cargo proteins such as tumour suppressor proteins (TSPs), including p53, p21, BRCA1/2, pRB, FOXO, and other growth regulatory proteins (e.g. Iκ–B). As a result, via selective inhibition of nuclear export (SINE), selinexor restores endogenous tumour suppressing processes to selectively eliminate tumour cells while sparing normal cells.[2]

Selinexor in combination with low-dose dexamethasone is in development for the treatment of patients with relapsed and refractory multiple myeloma, i.e., refractory to immunomodulatory drugs (IMiDs), protease inhibitors (PIs) and anti-CD38 mAbs. In the phase II clinical trial in patients with penta-refractory MM (STORM; NCT02336815), selinexor is administered orally at a dose of 80 mg in combination with low-dose dexamethasone which is given orally at a dose of 20 mg. Both selinexor and dexamethasone are administered twice weekly each week.[3]

INNOVATION AND/OR ADVANTAGES

Selinexor is the first drug developed for MM with the novel mechanism of action specifically targeting the protein XPO1.[4] XPO1-mediated export of TSPs to the cytoplasm allows cancer cells to avoid genome surveillance and cell cycle regulation.[5] By inhibiting XPO1, selinexor prevents MM cells from moving TSPs out of the nucleus. TSPs retained in the nucleus carry out their normal functions of detecting cancerous cells, leading to apoptosis of the MM cells.[4] Normal cells exposed to selinexor undergo reversible cell cycle arrest and return to normal function when selinexor levels decline.

Three classes of novel drugs have greatly improved the treatment of MM over the past 15 years: PIs, IMiDs and anti-CD38 mAbs. Despite this, nearly all patients develop MM refractory to these agents, which is designated as triple class refractory MM.[a] Thus, triple class refractory MM represents a patient group with limited treatment options and a high unmet therapeutic need.[6]

The combination of selinexor and low-dose dexamethasone, has shown synergistic effects of inducing apoptotic cell death in a glucocorticoid receptor dependant manner.[5] Therefore, if licensed, selinexor in combination with low-dose dexamethasone, could be an effective treatment option for patients with triple class refractory MM.

[a] Company information

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Selinexor in combination with low-dose dexamethasone is not licensed in the EU for any indication.

Common treatment-related adverse events included: thrombocytopenia, anaemia, neutropenia, nausea, fatigue, anorexia, vomiting, asymptomatic hyponatremia, diarrhoea and weight loss.[7]

In 2014, selinexor was designated orphan drug status by the EMA for the treatment of plasma cell myeloma.[8]

PATIENT GROUP

DISEASE BACKGROUND

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 subclassifications 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]

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]

CLINICAL NEED AND BURDEN OF DISEASE

In 2015, MM was the 19th most common cancer in the UK[20] with 4920 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. 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.[21] A European systematic review and Markov model found that in 2015, between 5,384 – 12,062 MM patients were relapsed to both proteasome inhibitor and immunomodulatory agent based treatment regimes.[6]

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.[22] There were 3,079 MM deaths in 2016, accounting for 2% of all cancer mortality in the UK.[23]

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).[24] Increased life expectancy is mainly due to the availability of novel therapeutic agents described above including immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs), and the adoption of haematopoietic stem cell transplantation (which involves high doses of alkylating agents).[25]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Despite recent progress, MM remains incurable and the vast majority of patients will progress on available agents and require treatment with novel therapies. 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] The choice of treatment at relapse should consider the balance between efficacy and toxicity of the treatment schedule, disease related factors such as risk stratification of the disease, prior drug therapy and the patients' response to prior treatment. 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.[26]

CURRENT TREATMENT OPTIONS

NICE guidelines recommend the use of a number of possible sequences of treatments for relapsed or refractory MM:[27]

- Ixazomib, with lenalidomide and dexamethasone, is recommended for use within the Cancer Drugs Fund as an option for treating multiple myeloma in adults only if they have already had 2 or 3 lines of therapy and the conditions in the managed access agreement for ixazomib are followed.
- Lenalidomide in combination with dexamethasone is recommended, within its licensed indication, as an option for the treatment of multiple myeloma only in people who have

received two or more prior therapies. The drug cost of lenalidomide (excluding any related costs) for people who remain on treatment for more than 26 cycles (each of 28 days; normally a period of 2 years) will be met by the manufacturer.

- Panobinostat in combination with bortezomib and dexamethasone is recommended, within its marketing authorisation, 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' when the company provides panobinostat with the discount agreed in the patient access scheme.
- Daratumumab monotherapy is recommended for use within the Cancer Drugs Fund as an option for treating relapsed and refractory multiple myeloma in 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 and the conditions in the managed access agreement are followed.
- 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, only when the company provides pomalidomide with the discount agreed in the patient access scheme.

PLACE OF TECHNOLOGY

Most patients with MM will become quad-refractory to IMiDs and PIs and will ultimately become penta-refractory to anti-CD38 mAbs, therefore there is a high unmet need in this population.[7] Currently there is no standard of care at fifth line. [28]

If licensed, selinexor in combination with low dose dexamethasone could be an effective treatment option for patients who have penta-refractory MM.

CLINICAL TRIAL INFORMATION

Trial	STORM, NCT02336815, KCP-330-012; selinexor in combination with dexamethasone (single experimental arm); phase IIb
Sponsor	Karyopharm Therapeutics Inc
Status	Ongoing (according to trial registry) but published
Source of Information	Trial registry[3], publication[7]
Location	5 EU countries (not incl UK) and USA
Design	Single arm, open-label, non-randomised, uncontrolled study
Participants	n=202 (actual); aged ≥ 18 years; multiple myeloma; must have previously received ≥ 3 anti-MM regimens including: an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, and a glucocorticoid; MM refractory to previous treatment with one or more glucocorticoids, parenteral PI (i.e., bortezomib and/or carfilzomib), IMiD (i.e., lenalidomide and/or pomalidomide), and the anti-CD38 mAb, daratumumab. Refractory is defined as ≤ 25% response to therapy, or progression during therapy or progression within 60 days after completion of therapy
Schedule	Selinexor is administered orally at a dose of 80 mg (45 mg/m2 body surface area) in combination with low-dose dexamethasone which is given orally at a dose of 20 mg. These are both administered twice weekly in four week cycles.

Follow-up	-
Primary Outcomes	• Overall Response Rate (ORR) [Time Frame: 5-7 months]
Secondary Outcomes	• Duration of Response [Time Frame: 5-7 months] • Clinical Benefit Rate [Time Frame: 6 months]
Key Results	The Independent review committee-determined ORR (≥ partial response) for all patients was 21%, including 5% very good partial response. ORR was 21% for quad-refractory patients and 20% for penta-refractory patients. Clinical benefit rates were 32% (all), 29% (quad), and 37% (penta). Median overall survival was 9.3 months for all patients, >11 month (median not reached) for responders (≥ partial response), and 5.7 months for non-responders. Median duration of response in responding patients was 5 months, and median progression free survival in all patients was 2.1 months. Transcriptomic profiling revealed differentially expressed genes (DEGs) between responders and non-responders in both whole blood RNA and CD138+ bone marrow cells. Pathways enriched in responders included IL-6, IL-8 and IGF-1 pathways.
Adverse effects (AEs)	Common treatment-related adverse events included: thrombocytopenia, anaemia, neutropenia, nausea, fatigue, anorexia, vomiting, asymptomatic hyponatremia, diarrhoea and weight loss
Expected reporting date	Ongoing, but some of the patients' group data has been published.

ESTIMATED COST

The cost of selinexor and low-dose dexamethasone is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- 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. 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 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 guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE guideline. Myeloma: diagnosis and management (NG35). February 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[25]
- 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]

REFERENCES

[1] Karyopharm Therapeutics. *Karyopharm Reports Second Quarter 2018 Financial Results and Highlights Recent Progress.* Available from: http://investors.karyopharm.com/news-releases/news-release-details/karyopharm-reports-second-quarter-2018-financial-results-and [Accessed 20 August 2018]

[2] National Cancer Institute. *Selinexor.* Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug/def/selinexor [Accessed 03 July 2018]

[3] ClinicalTrials.gov. *Selinexor Treatment of Refractory Myeloma (STORM).* Available from: https://clinicaltrials.gov/ct2/show/NCT02336815 [Accessed 03 July 2018]

[4] Myeloma UK. *Selinexor (KPT-330).* Available from: https://www.myeloma.org.uk/wp-content/uploads/2018/03/Myeloma-UK-Selinexor-Horizons-Infosheet.pdf [Accessed 03 July 2018]

[5] Argueta C, Kashyap T, Klebanov B, Unger TJ, Guo C, Harrington S, Baloglu E, Lee M, Senapedis W, Shacham S, Landesman Y. Selinexor synergizes with dexamethasone to repress mTORC1 signaling and induce multiple myeloma cell death. *Oncotarget*. 2018 May 22;9(39):25529. Available from: http://doi.org/10.18632/oncotarget.25368

[6] Gatopoulou X, Bardenheuer K, Van Hoorenbeeck S, Kempel A. Treatment Patterns of Relapsed and Refractory Multiple Myeloma in Europe (EU-28). Value in Health. 2016 Nov 1;19(7):A715-6. Available from: https://www.valueinhealthjournal.com/article/S1098-3015(16)33480-5/pdf

[7] Vogl DT, Dingli D, Cornell RF, Huff CA, Jagannath S, Bhutani D, Baz R, Nooka AK, Richter J, Cole CE, Vij R. Selinexor and low dose dexamethasone (Sd) in patients with lenalidomide, pomalidomide, bortezomib, carfilzomib and anti-CD38 Ab refractory multiple myeloma (MM): STORM study. *Blood.* 2016 Dec 01;128(22):491. Available from: http://www.bloodjournal.org/content/128/22/491

[8] European Medicines Agency. *EU/3/14/1355.* Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2015/01/human_orphan_001451.jsp&mid=WC0b01ac058001d12b [Accessed 12 July 2018]

[9] Hipp S, Tai YT, Blanset D 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*. 2017;31: 1743-1751. Available from: https://doi.org/10.1038/leu.2016.388

[10] National Institute for Health and Care Excellence. *Clinical Knowledge Summaries - Multiple myeloma.* Available from: https://cks.nice.org.uk/multiple-myeloma [Accessed 04 July 2018]

[11] Sonnevald P, Broijl A. Treatment of relapsed and refractory multiple myeloma. *Journal of the European Hematology Association*. 2016;101: 396-406. Available from: http://dx.doi.org/10.3324/haematol.2015.129189

[12] Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, Blade J, Richardson P, Orlowski R, Siegel D, Jagannath S. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood*. 2011 Jan 1. Available from: https://doi.org/10.1182/blood-2010-10-299487

[13] Egan JB, Shi CX, Tembe W, Christoforides A, Kurdoglu A, Sinari S, Middha S, Asmann Y, Schmidt J, Braggio E, Keats JJ. Whole genome sequencing of multiple myeloma from diagnosis to plasma cell leukemia reveals genomic initiating events, evolution and clonal tides. *Blood*. 2012 Jan 1. Available from: http://doi.org/10.1182/blood-2012-01-405977

[14] Magrangeas F, Avet-Loiseau H, Gouraud W, Lodé L, Decaux O, Godmer P, Garderet L, Voillat L, Facon T, Stoppa AM, Marit G. Minor clone provides a reservoir for relapse in multiple myeloma. *Leukemia.* 2013 Feb;27(2):473. Available from: https://www.nature.com/articles/leu2012226

[15] National Institute for Health and Care Excellence. *Bortezomib and thalidomide for the first-line treatment of multiple myeloma.* Available from: https://www.nice.org.uk/guidance/ta228/chapter/1-Guidance [Accessed 05 July 2018]

[16] NHS Choices. *Multiple myeloma*. Available from: https://www.nhs.uk/conditions/multiple-myeloma/causes/ [Accessed 05 July 2018]

[17] Cornell RF, Kassim AA. Evolving paradigms in the treatment of relapsed/refractory multiple myeloma: increased options and increased complexity. *Bone Marrow Transplantation.* 2016:51; 479-491. Available from: https://dx.doi.org/10.1038/bmt.2015.307

[18] The Mayo Clinic. *Multiple myeloma - symptoms*. Available from: https://www.mayoclinic.org/diseases-conditions/multiple-myeloma/symptoms-causes/syc-20353378 [Accessed 05 July 2018]

[19] Anderson KC, Kyle RA, Rajkumar SV, Stewart AK, Weber D, Richardson PA. Clinically relevant end points and new drug approvals for myeloma. *Leukemia*. 2008 Feb;22(2):231. Available from: https://www.nature.com/articles/2405016

[20] Cancer Research UK. *Myeloma statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma [Accessed 03 July 2018]

[21] Cancer Research UK. *Myeloma incidence statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence [Accessed 03 July 2018]

[22] NHS England. *Hospital Admitted Patient Care Activity 2016-17: Diagnosis*. Available from: https://digital.nhs.uk/catalogue/PUB30098 [Accessed 05 July 2018]

[23] Cancer Research UK. *Myeloma mortality statistics*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/mortality [Accessed 05 July 2018]

[24] Cancer Research UK. Myeloma survival. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma#heading-Two [Accessed 05 June 2018]

[25] Snowden JA, Greenfield DM, Bird JM et al. on behalf of 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. *British Journal of Haematology*;2017(176): 888-907. Available from: http://www.b-s-h.org.uk/guidelines/guidelines/screening-and-management-of-late-and-long-term-consequences-of-myeloma-and-its-treatment/ [Accessed 05 July 2018]

[26] Nooka AK, Kastritis E, Dimopoulos MA, Lonial S. Treatment options for relapsed and refractory multiple myeloma. Blood. 2015 Jan 1;125(20):3085-3099. Available from: https://doi.org/10.1182/blood-2014-11-568923

[27] National Institute for Health and Care Excellence. *Managing relapse of myeloma.* Available from: https://pathways.nice.org.uk/pathways/myeloma#path=view%3A/pathways/myeloma/managing-relapse-of-myeloma.xml&content=view-node%3Anodes-subsequent-relapse [Accessed 12 July 2018]

[28] National Institute for Health and Care Excellence. *Daratumumab monotherapy for treating relapsed and refractory multiple myeloma.* Available from: https://www.nice.org.uk/guidance/ta510/ [Accessed 12 July 2018]

[29] Kumar SK, Callander NS, Alsina M, Atanackovic D, Biermann JS, Chandler JC, Costello C, Faiman M, Fung HC, Gasparetto C, Godby K. Multiple myeloma, version 3.2017, NCCN clinical practice guidelines in oncology. Journal

of the National Comprehensive Cancer Network. 2017 Feb 1;15(2):230-69. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28188192

[30] Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, Richardson P, Caltagirone S, Lahuerta JJ, Facon T, Bringhen S. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. Journal of clinical oncology. 2015 Sep 10;33(26):2863. Available from: https://dx.doi.org/10.1200%2FJCO.2015.61.2267

[31] Bird JM, Owen RG, D'Sa S et al. on behalf of the Haemato-oncology Task Force of the British Committee for Standards in Hameatology (BCSH) and UK Myeloma Forum. Guidelines for the diagnosis and management of Multiple Myeloma. Available from: https://academy.myeloma.org.uk/wp-content/uploads/sites/2/2014/08/MYELOMA_GUIDELINE_Feb_2014_for_BCSH1.pdf [Accessed 04 July 2018]

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.