

**NIHR Innovation Observatory
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bb2121 for relapsed and 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).

bb2121 is in development as a treatment option for relapsed and refractory MM. It is based on genetic therapies and targets the growth of specific proteins present in most MM cells. bb2121 is administered by injection 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.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Multiple myeloma (relapsed and refractory) – third line and subsequent in those who are refractory to their last treatment

TECHNOLOGY

DESCRIPTION

bb2121 is a genetically modified autologous T cell immunotherapy product consisting of a T lymphocyte-enriched population that contains cells transduced with an anti-BCMA02 CAR LVV encoding a CAR targeting BCMA. BCMA is a member of the tumour necrosis factor receptor superfamily, and is expressed nearly universally on multiple myeloma cells. bb2121, an autologous T cells transduced with anti-BCMA02 LVV produce an integral membrane protein, namely the anti-BCMA02 CAR, which is composed of: 1) an extracellular single-chain variable fragment (scFv) containing the light-chain variable region (VL) and heavy-chain variable region (VH) from a mouse anti-BCMA monoclonal antibody (C11D5.3); 2) the hinge and transmembrane domain from human CD8 α ; and 3) the T cell cytoplasmic signaling domains of bb2121 CD137 (4-1BB) and the CD3zeta chain, in tandem.^{1,2}

In contrast to newly diagnosed multiple myeloma (MM), relapsed and refractory MM responds poorly to immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs).³ T-cell therapies are a promising approach with a mechanism of action different than those of standard MM treatments, as T-cells genetically engineered to express CARs recognise specific antigens on malignant cells triggering T-cell activation and cytolysis.⁴

In the phase II clinical trial, bb2121 will be infused at a dose ranging from 150 - 300 x 10⁶ CAR+ T cells. A leukapheresis procedure will be performed to manufacture bb2121 CAR modified T-cells, with lymphodepleting therapy of fludarabine and cyclophosphamide administered over 3 days prior to infusion.⁵

bb2121 does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

Treatment advances in the past decade have significantly improved survival of MM patients. Nonetheless, there is still unmet medical need for more effective treatments, in particular, for relapsed and refractory patients who have been exposed to third line and subsequent treatment and are refractory to their last treatment. BCMA is a highly plasma cell-selective protein that is expressed on malignant plasma cells of essentially all MM patients, normal plasma cells, and a subset of mature B-cells, but no other non-hematopoietic tissues, and, therefore, is an ideal target for T-cell redirecting therapies.⁶

If licensed, bb2121 will offer an additional treatment option for relapsed and refractory MM patients who currently have few effective therapies available.

DEVELOPER

Celgene Ltd

REGULATORY INFORMATION and AVAILABILITY/MARKETING PLANS

bb2121 was awarded PRIME status for refractory and relapsed MM by the EMA in November 2017. bb2121 was also designated a Breakthrough Therapy for refractory and relapsed MM by the US FDA in November 2017, and granted Orphan Drug Designation for MM in 2016.⁷

PATIENT GROUP

BACKGROUND

MM is a rare, incurable disease characterised by uncontrolled proliferation of monoclonal plasma cells in the bone marrow, resulting in disruption of normal bone marrow function, 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.⁸

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.⁹ The genomic complexity and clonal evolution of MM over the course of treatment are thought to contribute to drug resistance and disease progression.³

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.¹⁰

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.¹⁰ 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 standardized 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 2,928 MM deaths in 2014, 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 now survive their disease for at least 5 years, with a third surviving for 10 years or more.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 bb2121 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. Multiple myeloma (relapsed, refractory) - ixazomib citrate (ID807). Expected February 2018.
- NICE technology appraisal in development. Daratumumab for multiple myeloma (ID933). Expected February 2018.
- NICE technology appraisal in development. Multiple myeloma (newly diagnosed) - lenalidomide (ID474). Expected June 2018.
- 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. 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. Myeloma: diagnosis and management (NG35). February 2016.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 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

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. 2017¹⁸

National Comprehensive Cancer Network. American NCCN Guidelines: Version 3 – NCCN Evidence Blocks: Myeloma Therapy. 2017¹⁹

Palumbo A, Avet-Loiseau H, Oliva S et al. on behalf of the International Myeloma Working Group. Revised International Staging System for Multiple Myeloma: A Report from IMWG. 2015²⁰

Bird JM, Owen RG, D'Sa S et al. on behalf of 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. 2014²¹

Engelhardt M, Terpos E, Klebe M et al. on behalf of the European Myeloma Network. European Myeloma Network Guidelines: European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. 2014²²

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.¹⁸

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 next-generation IMiDs and 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
- 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

EFFICACY and SAFETY

Trial	NCT03361748, EudraCT-2017-002245-29; bb2121 in addition to fludarabine and cyclophosphamide; phase II
Sponsor	Celgene Ltd
Status	Ongoing
Source of Information	Trial registry ⁵
Location	USA
Design	Single group assignment; open-label
Participants	n=94(planned); aged ≥ 18 years; documented diagnosis of MM; must have received at least 3 prior MM treatment regimens; must have undergone at least 2 consecutive cycles of treatment for each regimen, unless PD was the best response to the regimen; patients whose prior therapy included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody; must be refractory to the last treatment regimen defined as progression on or within 60 days of last treatment

Schedule	bb2121 autologous CAR T cells will be infused at a dose ranging from 150 - 300 x 10 ⁶ CAR+ T cells after receiving lymphodepleting chemotherapy with fludarabine and cyclophosphamide administered over 3 days
Follow-up	Minimum of 24 months post-bb2121 infusion (all primary and secondary outcomes)
Primary Outcomes	<ul style="list-style-type: none"> Overall Response Rate (ORR); percentage of subjects who achieved partial response (PR) or better according to International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma
Secondary Outcomes	<ul style="list-style-type: none"> Complete Response (CR) Rate; percentage of subjects who achieved CR or better according to IMWG Uniform Response Criteria for Multiple Myeloma Time to Response; time from first bb2121 infusion to first documentation of response Duration of Response; time from first response to disease progression or death from any cause Progression-free Survival (PFS); time from first bb2121 infusion to first documentation of progressive disease (PD), or death due to any cause, whichever occurs first Time to Progression (TTP); time from first bb2121 infusion to first documentation of PD Overall Survival (OS); time from first bb2121 infusion to time of death due to any cause Adverse Events (AEs); number of participants with adverse events (AEs), severity of adverse events, adverse events of special interest (AESI), and serious adverse events (SAEs) Pharmacokinetics – Cmax; maximum peak in BB2121 CAR T CD3+ cells Pharmacokinetics – Tmax; time to peak of BB2121 CAR T CD3+ cells Pharmacokinetics – AUC; area under the curve of CAR T CD3+ cells Biomarker – Cytokines; cytokine induction in the blood of subjects after infusion of bb2121 Biomarker – BCMA; percentage and level of expression of BCMA-expressing plasma cells in the bone marrow as well as the level of soluble BCMA in blood Immunogenicity; development of an anti-CAR antibody response Minimal Residual Disease (MRD); proportion of MRD evaluable subjects that are MRD negative Subject-reported outcomes as measured by European Organization for Research and Treatment of Cancer Quality-of-Life questionnaire (EORTC-QLQ-C30); questionnaire will be used as a measure of health-related quality of life Subject-reported outcomes as measured by EuroQoL Group EQ-5D-5L Health Questionnaire; questionnaire will be used as a measure of health-related quality of life Subject-reported outcomes as measured by EORTC-QLQ-MY20; 20-item myeloma module intended for use among patients varying in disease stage and treatment modality

Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date November 2023

ESTIMATED COST and IMPACT

COST

The cost of bb2121 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
- 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
- None identified – unable to state if cost of single treatment with bb2121 would be less expensive than current available treatments

OTHER ISSUES

☒ None identified

REFERENCES

- ¹ Berdeja JG, Lin Y, Raje N et al. Durable clinical responses in heavily pretreated patients with relapsed/refractory multiple myeloma: updated results from a multicentre study of bb2121 anti-bcma CAR T cell therapy. *Blood*. 2017;130(suppl1): 740. Available from: www.bloodjournal.org/content/130/Suppl_1/740.powerpoint [Accessed 26th February 2018]
- ² Lin Y, Berdeja JG, Raje N et al. First-in-human multicenter study of bb2121 anti-BCMA CAR T cell therapy for relapsed/refractory multiple myeloma: updated results. In: *Huntsman Cancer Institute Second Annual Multiple Myeloma Symposium*, University of Utah, 14 October 2017, Salt Lake City, USA. Available from: <http://www.huntsmancancer.org/education/conferences-seminars/multiple-myeloma-symposium/pdfs/yi-lin.pdf> [Accessed 30th January 2018]
- ³ 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>
- ⁴ Mikkilineni L, Kochenderfer JN. Chimeric antigen receptor t-cell therapies for multiple myeloma. *Blood*. 2017: blood-2017-06-793869. Available from: <https://doi.org/10.1182/blood-2017-06-793869>
- ⁵ ClinicalTrials.gov. *Efficacy and Safety Study of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma (KarMMa) (bb2121)*. Available from: <https://clinicaltrials.gov/ct2/show/NCT03361748> [Accessed 30th January 2018]
- ⁶ 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://dx.doi.org/10.1038/leu.2016.388>
- ⁷ Celgene. *Celgene Corporation and bluebird bio Announce bb2121 Anti-BCMA CAR-T Cell Therapy Has Been Granted Breakthrough Therapy Designation from FDA and Prime Eligibility from EMA for Relapsed and Refractory Multiple Myeloma*. Available from: <http://ir.celgene.com/releasedetail.cfm?releaseid=1049014> [Accessed 30th January 2018]. Last updated: 16th November 2017
- ⁸ Borrello I. Can we change the disease biology of multiple myeloma? *Leukemia Research*. 2012;36 Suppl 1:S3–12. Available from: [https://doi.org/10.1016/S0145-2126\(12\)70003-6](https://doi.org/10.1016/S0145-2126(12)70003-6)
- ⁹ Anderson KC, Kyle RA, Rajkumar SV, et al. Clinically relevant end points and new drug approvals for myeloma. *Leukemia*. 2008;22(2): 231-239. Available from: <http://dx.doi.org/10.1038/sj.leu.2405016>
- ¹⁰ NHS. *Multiple myeloma*. Available from: <https://www.nhs.uk/conditions/multiple-myeloma/causes/> [Accessed 31st January 2018]. Last updated: 16th February 2015
- ¹¹ The Mayo Clinic. *Multiple myeloma - symptoms*. Available from: <https://www.mayoclinic.org/diseases-conditions/multiple-myeloma/symptoms-causes/syc-20353378> [Accessed 31st January 2018]. Last updated: 15th December 2017
- ¹² Multiple Myeloma Research Foundation. *Caregiver self-care and financial support*. Available from: <https://www.themmr.org/caregiver-self-care-and-financial-support/> [Accessed 1st February 2018]. Last updated 17th March 2017
- ¹³ Kvam AK, Waage A. Health-related quality of life in patients with multiple myeloma – does it matter? *Journal of the European Hematology Association*. 2015;100: 704-705. Available from: <http://dx.doi.org/10.3324/haematol.2015.127860>
- ¹⁴ Cancer Research UK. *Myeloma incidence by sex and UK country*. Available from: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence#heading-Zero> [Accessed 1st February 2018] Last updated: 23rd January 2018
- ¹⁵ Smittenaar CR, Petersen KA, Stewart K, Moitt N. Cancer incidence and mortality projections in the UK until 2035. *British Journal of Cancer*; 115: 1147-1155. Available from: <http://dx.doi.org/10.1038/bjc.2016.304>
- ¹⁶ NHS England. *Hospital Admitted Patient Care Activity 2016-17: Diagnosis*. Available from: <https://digital.nhs.uk/catalogue/PUB30098> [Accessed 5th February 2018] Last updated: 3rd October 2017

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- ¹⁷ Cancer Research UK. *Myeloma survival*. Available from: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma#heading-Two> [Accessed 5th February 2018]
Last updated: 23rd January 2018
- ¹⁸ 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 5th February 2018]
- ¹⁹ American National Comprehensive Cancer Network. *American NCCN guidelines: Version 3 - NCCN Evidence Blocks: Myeloma Therapy*. Available from: https://www.nccn.org/professionals/physician_gls/pdf/myeloma_blocks.pdf [Login required]
- ²⁰ Palumbo A, Avet-Loiseau H, Oliva S et al. on behalf of the International Myeloma Working Group. Revised International Staging System for Multiple Myeloma: A Report from International Myeloma Working Group. *Journal of Clinical Oncology*. 2015;33(26): 2863-2869. Available from: <http://dx.doi.org/10.1200/JCO.2015.61.2267>
- ²¹ Bird JM, Owen RG, D'Sa S et al. on behalf of 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*. Available from: https://academy.myeloma.org.uk/wp-content/uploads/sites/2/2014/08/MYELOMA_GUIDELINE_Feb_2014_for_BCSH1.pdf [Accessed 5th February 2018]
- ²² Engelhardt M, Terpos E, Kleber M et al. European Myeloma Network Guidelines: European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. *Haematologica* 2014;99: 232–42. Available from: <https://doi.org/10.3324/haematol.2013.099358>
- ²³ Sonnevold 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>
- ²⁴ NICE. *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 5th February 2018]