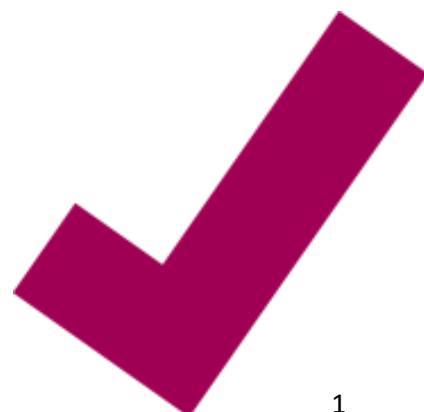


Clinical Commissioning Policy Proposition: Bendamustine with rituximab for relapsed mantle cell lymphoma



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Draft for Public Consultation

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1 Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About relapsed mantle cell lymphoma

Mantle cell lymphoma is a rare form of a type of cancer called non-Hodgkin's lymphoma. It happens when the body makes abnormal white blood cells – these are cells in the blood that fight infection. The abnormal white blood cells don't work properly, so they can't fight infection like normal white blood cells do. It is a condition that is characterised by episodes of treatment followed by periods of remission, and then commonly by subsequent relapse.

About current treatments

There is no current standard treatment for relapsed mantle cell lymphoma. Management of relapsed mantle cell lymphoma requires an individualised treatment approach, incorporating factors such as: functional status, prior treatments and response to them, and disease biology.

About the new treatment

Bendamustine is an anticancer drug belonging to a group of drugs called alkylating agents, which work by binding to DNA in cancer cells to prevent them from

multiplying. It is administered as an intravenous infusion on the first two days of a 4-week cycle of treatment.

Rituximab belongs to a group of drugs known as 'monoclonal anti-bodies'. It is a biological medicine that works by 'targeting' specific proteins (receptors) on the surface of cells relevant to the cause of the disease. It is administered as an intravenous infusion on the first day of each 4 week cycle.

What we have decided

NHS England has carefully reviewed the evidence to treat relapsed mantle cell lymphoma with bendamustine and rituximab in combination and have concluded that there is sufficient evidence to consider making the treatment available.

Draft for Public Consultation

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission bendamustine and rituximab in combination for relapsed mantle cell lymphoma.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether bendamustine and rituximab in combination for relapsed mantle cell lymphoma will be routinely commissioned is planned to be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

Mantle cell lymphoma is rare and is one of the most challenging haematological malignancies, owing to an aggressive disease course, a high rate of relapse, and lack of standard of care. Management of relapsed mantle cell lymphoma requires an individualised treatment approach, incorporating factors such as: functional status, prior treatments and response to them, and disease biology.

Most patients are initially diagnosed with advanced-stage disease. They are often symptomatic at presentation. Common features include widespread lymphadenopathy and splenomegaly, as well as bone marrow infiltration. Leukemic involvement is found in 20% to 30% of patients. The disease course can be highly variable. Some patients may have very aggressive disease, whereas others may have a much more indolent course. There is no consensus on relapsed or first line treatments.

First Line Treatment: Although mantle cell lymphoma often responds well to first-line chemo-immunotherapy with high overall response rates, the responses may not

be durable and sequential therapies may be necessary.

In the first line setting, up-front consolidation of chemo-immunotherapy with cytarabine, high-dose therapy and autologous stem cell transplant remains an attractive option for those young, fit patients with chemosensitive disease, regardless of the induction regimen chosen. Effective treatment options in the front-line setting for less fit and older patients have included the addition of rituximab to bendamustine, or rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). The latter followed with maintenance rituximab following induction therapy.

Treatments for patients with relapse:

For patients that relapse following chemotherapy there is no agreed standard therapy (Cheah, 2016). The European Society for Medical Oncology (ESMO) state that the selection of a salvage regime depends on the type and efficacy of prior regimens. In early relapses (<12-24 months), a non-cross-resistant scheme should be preferred (rituximab with bendamustine with high dose cytarabine (Ara-C) containing regimens e.g. rituximab with bendamustine and cytarabine (R-BAC) after CHOP or vice versa) and that rituximab should be added if the previous antibody-containing scheme achieved >6-12 months duration of remission. In cases of earlier relapse they state that the newer targeted approaches (ibrutinib, lenalidomide, bortezomib, temsirolimus) should be strongly considered (Dreyling M, 2014).

The British Committee for Standards in Haematology (BCSH) also state that the choice of therapy at relapse should be determined on an individualised basis by patient age, performance status, bone marrow reserve and initial therapy (McKay 2012). It is recommended that options for consideration at relapse should include rituximab, bortezomib and chemotherapy and that temsirolimus should be considered as a possible option.

It is also noted that although high dose chemotherapy with autologous stem cell transplant (ASCT) may be considered in patients that relapse after conventional first-line therapy, the benefit seems to be minor in this setting and that there is no

role for a second autograft at relapse. However the addition of rituximab and bendamustine with high dose cytarabine (Ara-C) should be strongly considered in younger and fitter patients.

Bendamustine is an alkylating antitumour agent. The antineoplastic and cytocidal effect of bendamustine hydrochloride is based on a cross-linking of DNA single and double strands by alkylation. As a result, DNA matrix functions and DNA synthesis and repair are impaired.

Bendamustine is not licensed for treatment of relapsed mantle cell lymphoma, and therefore will not be considered for NICE appraisal.

As stated above bendamustine-based regimens are considered to be an option for this patient group although it is not licensed for use in this population. When used in this indication it is administered by intravenous infusion at a dose of 90mg/m² on two days every 28 days for up to 6 cycles, concurrently with Rituximab 375 mg/ sq. m² on day 1.

4 Definitions

Mantle cell lymphoma (MCL) - a rare form of a type of cancer called non-Hodgkin's lymphoma. It happens when the body makes abnormal white blood cells

White blood cells – these are cells in the blood that fight infection. The abnormal white blood cells don't work properly, so they can't fight infection like normal white blood cells do.

Advanced disease – describes when there is disease in lymph nodes above and below the patients diaphragm, with or without disease in organs outside of the lymph nodes e.g. bone marrow.

Relapsed disease – describes when a condition has recurred following response to previous treatment, this may occur at any time following completion of treatment.

First line therapy- describes treatment regimen or regimens that are generally accepted for initial treatment of a given type and stage of cancer. It is also called primary treatment or therapy. It is often part of a standard set of treatments, e.g. surgery followed by chemotherapy and radiation. First-line therapy is the one accepted as the best treatment.

Overall survival (OS) – the length of time from either diagnosis or start of treatment that the patient is still alive.

Progression-free survival (PFS) – the length of time from either diagnosis or start of treatment to disease progression or patient death from any cause.

Overall response rate (ORR) – the ratio or percentage of patients who have achieved a complete or partial response at a designated time point.

5 Aims and Objectives

This policy proposition considered:

Bendamustine and rituximab in combination for treatment of relapsed mantle cell lymphoma (MCL).

The objectives were to establish via an evidence review the following:

- Efficacy, safety, toxicity profile, cost-effectiveness of bendamustine and rituximab in the relapsed MCL setting.
- Comparison of above with other treatment regimens e.g. Ibrutinib, Temsirolimus, Bortezomib and more conventional combination regimens and
- Whether Bendamustine achieved improved/equivalent outcomes in comparison with other current therapies/novel therapies

6 Epidemiology and Needs Assessment

Mantle cell lymphoma (MCL) is a distinct non-Hodgkin's lymphoma (NHL) sub-type that accounts for 6% of patients with non-Hodgkin's Lymphoma. In 2013 there were 13,400 cases of NHL in the UK (Cancer Research UK 2015). In England, there were 11,392 (6186 males, 5206 females) cases of NHL (Cancer Registration Statistics England 2013). The estimated number of UK cases of MCL was 510 (Haematological Malignancy Research Network data, 2004-2014). The European

age standardised incidence rate is 0.9/100k. 75% of these would present at an advanced and late stage and would be eligible for first line treatment. 50% of these would not be suitable for intensive treatment (Nazeef 2014).

7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

Rationale for policy proposition

Bendamustine and rituximab (BR) in combination should be commissioned by NHS England as a treatment option for relapsed mantle cell lymphoma (MCL) patients. This is on the basis of several factors – lack of cross resistance to first line agents, differences in side effect profile with other regimens used and comparative evidence of much higher response rates and the achievement of very significant progression-free and overall survival durations, and hence equivalence in clinical effectiveness to other rituximab based chemotherapies (R-CHOP, rituximab with cyclophosphamide, vincristine and prednisolone (R-CVP) and bendamustine) administered in the first line setting and inclusion on this basis in European Society for Medical Oncology (ESMO) Guidelines. In the relapsed setting, BR may also be less costly and less toxic than other drug alternatives.

This is an area of unmet need as mantle cell lymphoma is an aggressive tumour and survival in this setting is 1-2 years.

Summary of evidence from the evidence review

What evidence is available to assess how bendamustine-based regimens compare with other regimens used in the treatment of patients with relapsed mantle cell lymphoma in terms of efficacy, safety, quality of life and cost-effectiveness?

The single randomised controlled trial (RCT) identified provides good quality evidence that using BR instead of fludarabine plus rituximab results in significant improvements in median progression free survival (PFS) and this also results in improvements in overall survival (OS). In the RCT there was a subgroup of 47 patients with mantle cell lymphoma and it was shown that the median PFS was 17.6

months in the group that received BR compared with 4.7 months in the group that received fludarabine with rituximab, a difference of 13.3 months. Similarly an analysis of OS showed that patients that received BR lived for a median of 35.3 months compared with 20.9 months in the control arm. Overall response rates and complete response rates were also significantly higher in the experimental arm (70.8% and 37.5% vs. 26.1% and 13% respectively) (Rummel et al 2016). The trial methodology appears to be robust although it could be argued that as the results described are based on a subgroup analysis they may be viewed as hypothesis generating. This trial is also limited by the fact that the control regimen selected does not reflect current clinical practice. There may also be concerns that the results are not necessarily generalisable to current practice in that when the trial was started rituximab was not routinely accepted as a standard treatment and so only 42% of patients recruited had been exposed to rituximab prior to recruitment to this study. Similarly a protocol amendment was required during the study to allow the use of rituximab maintenance treatment in patients that responded to their allocated treatment. However this is the only RCT available and it only included a relatively small number of patients with mantle cell lymphoma and given the limitations outlined above there may be some concerns about basing any recommendations about it being the regimen of choice on such a limited set of evidence.

The Phase 2 trial data available support the results outlined above and indicate that this regimen is associated with high overall response rates and that if patients respond then they remain free from disease progression for a median period of 17+ months. These data are derived from uncontrolled studies and as such it is not possible to compare these outcomes with those that might be expected in similar patients treated with different chemotherapy regimens (Czuzman et al 2015, Friedberg et al 2011, Robinson et al 2008, Rummel et al 2005, Visco et al 2013, Weide et al 2007).

The safety data available indicate that this regimen is associated with high incidences of serious haematological toxicities and has the potential to cause a wide range of other debilitating adverse effects when used to treat patients with relapsed indolent non-Hodgkin's lymphoma or mantle cell lymphoma. However it is not possible to ascertain whether this regimen differs significantly from other regimens

that would be used in this indication.

No evidence was identified to support an assessment of the impact of using a bendamustine-based regimen on the quality of life of patients with relapsed mantle cell lymphoma and how this compares to treatment with other regimens. Similarly no evidence was identified to support an assessment of the relative cost effectiveness of this intervention compared to the use of other regimens.

Is there any evidence to guide the placement of bendamustine-based chemotherapy either in sequence or as an alternative to the approaches described above?

No evidence was identified to guide practice on how bendamustine-based regimens should be used in treatment pathways for patients with relapsed mantle cell lymphoma. Existing guidance from ESMO and BCSH does not offer much differentiation between regimens in terms of effectiveness and both state that choice of regimen is dependent on factors such as patient age, performance status, bone marrow reserve and initial therapy. The evidence identified in this review is not robust enough to impact on this approach.

Conclusion of Evidence Review

The data available to assess the safety and effectiveness of bendamustine and rituximab in combination in patients is limited to a subgroup analysis of an RCT in which it was compared with fludarabine and rituximab and seven Phase II studies. The data that are available support existing clinical professional guidelines which suggest that BR is one of a number of regimens which could be considered in this patient cohort. The results of the subgroup analysis of the RCT indicate BR is superior to fludarabine with rituximab in terms of both progression-free and overall survival (Rummel et al, 2016). The Phase II studies indicate that its use is associated with significant periods of progression-free survival and that the majority of patients achieve some level of response to treatment. The outcomes data available are limited by the fact that the studies were largely conducted before rituximab became established as a first-line treatment and before rituximab maintenance treatment became routinely available.

The safety data available indicate that BR is associated with significant adverse effects largely involving bone marrow suppression but there was no evidence identified to suggest that the overall tolerability of this regimen is significantly different from other regimens that may be used in this population. Unfortunately no data were identified which helped clarify the impact of BR on quality of life and no relevant health economic studies were identified.

8 Proposed Criteria for Commissioning

Bendamustine with rituximab should be considered in patients with relapsed mantle cell lymphoma when patients have been treated with one or more previous chemotherapies or autologous stem cell transplantation, which have a performance status of 0-1.

It should only be given in patients who have not previously been treated with bendamustine.

The decision to treat with bendamustine with rituximab must be made by either the haematology multi-disciplinary team or lymphoma multi-disciplinary team, and the patient, and the first cycle must be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy.

Decision to continue or stop treatment should be made by either the haematology multi-disciplinary team or lymphoma multi-disciplinary team, and the patient.

9 Proposed Patient Pathway

Bendamustine with rituximab should be considered for all patients with confirmed mantle cell lymphoma who have already undergone one or more prior chemotherapy treatments (excluding bendamustine) or autologous stem cell transplantation.

10 Proposed Governance Arrangements

Any provider organisation treating patients with this intervention will be required to provide assurance that the internal governance arrangements have been completed

before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

11 Proposed Mechanism for Funding

Routine Commissioning.

12 Proposed Audit Requirements

Systemic Anti-Cancer Treatment (SACT) dataset.

13 Documents That Have Informed This Policy Proposition

- National CDF: <https://www.england.nhs.uk/cancer/cdf/>
- CDF Drugs Fund List: <https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/>
- ESMO Guidelines: Dreyling M, Geisler C et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 (Suppl 3): iii83-iii92
- BSCH Guidelines: McKay P, Leach M, Jackson R, Cook G, Rule S. Guidelines for the investigation and management of mantle cell lymphoma. Br J Haematol, 159, 405-26. 2012
- PICO 1604, NHS England, Bendamustine for Relapsed/refractory Mantle Cell Lymphoma
- Evidence Review 1604, UKMI/NHS England, Bendamustine-based chemotherapy for treatment of relapsed or refractory Mantle Cell Lymphoma (MCL)
- Preliminary Policy Proposal, NHS England, Bendamustine for relapsed/refractory Mantle Cell Lymphoma (MCL)

14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

15 References

BSCH Guidelines: McKay P, Leach M, Jackson R, Cook G, Rule S. Guidelines for the investigation and management of mantle cell lymphoma. *Br J Haematol*, 159, 405-26. 2012

Cancer Research UK Non-Hodgkin lymphoma incidence statistics. February 2016. <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma/incidence#heading-Zero>. Accessed 14/09/16.

Cheah YC, Seymour JF, Wang ML. Mantle Cell Lymphoma. *J. Clin Oncol* 2016; 34:1256-69

Czuczman MS, Goy A et al. Phase II study of bendamustine combined with rituximab in relapsed/refractory mantle cell lymphoma: efficacy, tolerability, and safety findings. *Ann Hematol*. 2015; 94: 2025-32

ESMO Guidelines: Dreyling M, Geisler C et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014,25 (Suppl 3): iii83-iii92

Friedberg JW, Vose JM et al. The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/ refractory indolent and mantle cell non-Hodgkin lymphoma. *Blood* 2011; 117: 2807-12

Haematology Malignancy Research Network Mantle Cell Lymphoma statistics. <https://www.hmrn.org/statistics/incidence>

Nazeef M, Kahl BS. 2015. Mantle Cell Lymphoma: First-line therapy in patients not eligible for stem cell transplantation. *Curr. Treat. Options in Oncol* (2015) 16:29

Robinson KS, Williams ME et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2008; 26: 4473-9

Rummel MJ, Al-Batran SE et al. Bendamustine plus rituximab is effective and has a favourable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's Lymphoma. *J Clin Oncol* 2005; 23: 3383-9

Rummel M, Kaiser U et al. Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicentre, randomised, open-label, non-inferiority phase 3 trial. *Lancet Oncol* 2016; 17: 57-66

Visco C, Finotto S et al. Combination of rituximab, bendamustine, and cytarabine for patients with mantle cell non-Hodgkin Lymphoma ineligible for intensive regimens or autologous transplantation. *J Clin Oncol* 2013; 31: 1442-9

Vose JM. Mantle Cell Lymphoma: Update on Diagnosis, Risk-Stratification and Clinical Management. *Am J Hematol* 2015.

Weide R, Hess G et al. High anti-lymphoma activity of bendamustine/mitoxantrone/rituximab in rituximab pretreated relapsed or refractory indolent lymphomas and mantle cell lymphomas. A multicenter phase II study of the German Low grade Lymphoma Study Group (GLSG). *Leukaemia & Lymphoma* 2007; 48: 1299-1306

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