Horizon Scanning in Oncology

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Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology No.79
ISSN online 2076-5940

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Ludwig Boltzmann Institut
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Vienna, February 2018

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

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Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

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DSD: Horizon Scanning in Oncology No. 79
ISSN-online: 2076-5940

http://eprints.hta.lbg.ac.at/view/types/

Abstract

Introduction

Mantle cell lymphoma (MCL) is an uncommon subtype of lymphoid malignancy with usually aggressive clinical behaviour. Rituximab (MabThera®) is a monoclonal antibody approved for the treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL), rheumatoid arthritis and granulomatosis with polyangiitis and microscopic polyangiitis. To date, neither the European Medicines Agency (EMA) nor the US Food and Drug Administration (FDA) have granted marketing authorisation for rituximab as maintenance therapy in patients with MCL after autologous stem-cell transplantation (ASCT).

Methodology

Published and grey literature were identified by searching the Cochrane Library, CRD Database, Embase, Ovid Medline, PubMed, Internet sites and contacting the manufacturer, resulting in 197 references overall. A quality assessment was conducted to assess the risk of bias at the study level based on the EUnetHTA internal validity for randomised controlled trials. The magnitude of clinically meaningful benefit that can be expected from a new anti-cancer treatment based on the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) has not been applied since it can only be used for solid tumours.

Results from the LyMa trial

The LyMa trial was conducted to assess the efficacy and safety of rituximab maintenance therapy in MCL patients after ASCT. To this end, a total of 299 patients who were younger than 66 years of age were enrolled, 240 of whom were randomly assigned to receive either rituximab maintenance therapy or to undergo observation. At the LyMa study stopping date (July 1, 2015), the rate of event-free survival (EFS) at four years was 79% in patients of the rituximab maintenance group compared to 61% in patients of the observation group. At four years, patients of the rituximab maintenance group had a progression-free survival (PFS) rate of 83% versus 64% in observation group patients. The rate of overall survival (OS) at four years was higher in the rituximab group (89%) than in the observation group (80%). Median OS, PFS and EFS had not been reached. The most frequent adverse event (AE) of grade ≥3 in both groups within the first six months of treatment was neutropenia, occurring more often in the rituximab maintenance group (41.1%) than in the observation group (26.3%). Other frequent AEs of grade 3–4 within the first six months were infections (6.3%) and thrombocytopenia (5.4%) in the rituximab maintenance group and thrombocytopenia (4.2%) and infections (3.4%) among patients in the observation group.

Conclusion

Although rituximab maintenance therapy provides essential benefits for patients with MCL after ASCT, relevant issues, including schedules of rituximab administration, the applicability of study results in older patients or patients with worse performance status, types of previously administered chemotherapeutical regimens, the role of MRD and, not least, the impact of rituximab maintenance therapy on QoL need to be clarified. Due to the small number of MCL-affected patients, gathering significant evidence might prove difficult. Anyhow, more data is warranted to confirm the results of the LyMa trial.

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1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to predefined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

EUnetHTA HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is rituximab?
A0022	Who manufactures rituximab?
A0007	What is the target population in this assessment?
A0020	For which indications has rituximab received marketing authorisation?
Health problem and current use	
A0002	What is mantle cell lymphoma?
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A0006	What are the consequences of mantle cell lymphoma for the society?
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D0005	How does rituximab affect symptoms and findings (severity, frequency) of mantle cell lymphoma?
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D0012	What is the effect of rituximab on generic health-related quality of life?
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Safety	
C0008	How safe is rituximab in relation to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying rituximab?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of rituximab?
A0021	What is the reimbursement status of rituximab?

2 Drug description

Generic/Brand name/ATC code:

Rituximab/MabThera®/L01XC02

B0001: What is rituximab?

monoclonal antibody

Rituximab (MabThera®) is a monoclonal antibody targeting the CD20 antigen which is located on normal pre-B and mature B lymphocytes. CD20 is found on both normal and malignant B cells and is expressed on >95% of all B-cell non-Hodgkin's lymphomas (NHL). The binding of rituximab to the CD20 antigen triggers a host cytotoxic immune response against CD20-positive cells. In detail, the antigen-binding fragment (Fab) domain of rituximab binds to the CD20 antigen on B lymphocytes and the fragment crystallisable (Fc) domain mediates B-cell lysis by recruiting immune effector functions. Possible mechanisms are complement-depending cytotoxicity and antibody-dependent cellular cytotoxicity. On B lymphocytes, the binding of rituximab to CD20 antigen induces cell death due to apoptosis [2, 3].

targeting the CD20 antigen

administered intravenously

Rituximab is available as a concentrate for solution for infusion in vials containing 100 mg of rituximab each; each mL contains 10 mg of rituximab. It is administered as an intravenous infusion (IV) through a dedicated line; it should not be given as an IV push or bolus. For the first infusion, the recommended initial rate is 50 mg/h which can be escalated after the first 30 minutes in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h. For all indications, subsequent infusions can be given at an initial rate of 100 mg/h and increased by 100 mg/h increments every 30 minutes to a maximum of 400 mg/h [2].

In the phase III LyMa trial, the schedule for maintenance therapy was the administration of 375 mg of rituximab IV per square metre of body surface area every two months for three years [4].

premedication: antipyretic, antihistaminic

Prior to the administration of rituximab, patients should receive premedication including an antipyretic and an antihistaminic. An administration of glucocorticoids should be considered in patients with NHL and chronic lymphocytic leukaemia (CLL) who do not receive rituximab in combination with glucocorticoid-containing therapy [2].

monitoring is required

Patients who receive rituximab should be closely monitored for the onset of cytokine release syndrome [2], a large rapid release of cytokines into the blood causing fever, nausea, headache, rash, rapid heartbeat, low blood pressure and breathing problems. Most patients experience a mild reaction, but severe or life-threatening reactions are possible [5]. In patients with a severe cytokine release syndrome, the infusion of rituximab should be interrupted immediately and aggressive symptomatic treatment should be administered [2].

A0022: Who manufactures rituximab?

Roche Pharma AG (product licence holder)

3 Indication

A0007: What is the target population in this assessment?

Rituximab is indicated in patients with mantle cell lymphoma (MCL) after autologous stem-cell transplantation (ASCT).

patients with MCL after ASCT

4 Current regulatory status

A0020: For which indications has rituximab received marketing authorisation?

To date, neither the European Medicines Agency (EMA) nor the US Food and Drug Administration (FDA) have granted marketing authorisation for rituximab as maintenance therapy in patients with MCL after ASCT.

currently not approved for maintenance therapy in patients with MCL after ASCT, but for several other indications

The EMA approved rituximab (MabThera®) for the following indications [6]:

- The treatment of previously untreated patients with stage III–IV follicular lymphoma (FL) in combination with chemotherapy
- As maintenance therapy in patients with FL who respond to induction therapy
- As monotherapy for the treatment of patients with stage III–IV FL who are chemo-resistant or are in their second or subsequent relapse after chemotherapy
- In combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy in patients with CD20-positive diffuse large B-cell NHL
- In combination with chemotherapy for the treatment of patients with previously untreated and relapsed/refractory CLL
- In combination with methotrexate for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying antirheumatic drugs including one or more tumour-necrosis-factor (TNF) inhibitor therapies
- In combination with glucocorticoids for the induction of remission in patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

In April 2017, the EMA granted orphan designation for rituximab for treatment in solid organ transplantation [6].

In the US, the FDA approved rituximab (trade name: Rituxan®) for the treatment of [7]:

approved indications of rituximab in the US

- Relapsed or refractory, low-grade or follicular, CD20-positive B-cell NHL (as a single-agent)
- Patients with previously untreated follicular, CD20-positive B-cell NHL in combination with first-line chemotherapy and, in patients

achieving a complete or partial response (PR) to rituximab in combination with chemotherapy, as single-agent maintenance therapy
- Non-progressing (including stable disease), low-grade, CD20-positve B-cell NHL as a single agent after first-line cyclophosphamide, vincristine and prednisolone (CVP) chemotherapy
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens
- In combination with fludarabine and cyclophosphamide for the treatment of patients with previously untreated and previously treated CD20-positive CLL
- in combination with methotrexate for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies
- Patients with GPA and MPA.

5 Burden of disease

A0002: What is mantle cell lymphoma?

MCL: uncommon NHL subtype

MCL is a subtype of NHL and is thought to have two different cellular origins leading to different forms of the disease [8]:

"classical" and "leukaemic" variant

The "classical" MCL arises from naïve B cells (about 80% of MCL cases) that express SOX11 (a transcription factor) and involves lymph nodes and extranodal sites, e.g. the gastrointestinal tract. Due to acquisition of additional genetic abnormalities, a progression to more aggressive forms of MCL with blastoid or pleomorphic morphologies is possible. The other variant of MCL (termed "leukaemic" variant), developing from antigen-experienced SOX11-negative B cells, often spares lymph nodes and mainly affects the peripheral blood, bone marrow and spleen. Although this type of MCL often appears clinically indolent, secondary abnormalities (particularly TP53 mutations) can cause a very aggressive course [8]. Cytologically, four types of MCL are defined, including the small-cell variant, the mantle-zone variant, the diffuse variant and the blastic variant [9].

A0004: What is the natural course of mantle cell lymphoma?

variable course, usually aggressive

The course of MCL is variable [8] and the clinical behaviour is usually aggressive [10]. At the time of diagnosis, most patients have advanced disease [8], only a few patients present with localised disease [11]. The overall 5-year survival rate for advanced-stage MCL is about 50%, in patients with limited-stage MCL about 70% [12].

blastoid MCL type is considered more aggressive

The blastoid type of MCL is deemed to be more aggressive. Although, patients without anaemia or splenomegaly, patients with a normal serum-free light-chain ratio or patients with tumour cells not overexpressing cyclin D, may show longer survival. As reported in several studies, patients aged >60

with an increased mitotic index or patients with an increased Ki-67 staining were associated with significantly worse overall survival [8].

prognostic indices: MIPI, IPI, FLIPI

The most commonly used prognostic indices for MCL are the International Prognostic Index (IPI), the Follicular Lymphoma International Prognostic Index (FLIPI) and the Mantle Cell Lymphoma International Prognostic Index (MIPI). All of these indices comprise information about the age of the patient, the lactate dehydrogenase (LDH) level and the stage of the disease, varying in the way of incorporation of information about nodal involvement, performance status and blood counts [8]. The MIPI is the prognostic index most commonly used, incorporating ECOG performance status, age, leukocyte count and LDH [9]. MIPI is particularly suited for patients with MCL and allows a classification of patients into low-risk, intermediate-risk and high-risk groups, helping to facilitate risk-adapted treatment decisions in patients affected by advanced stage MCL [13].

A0006: What are the consequences of mantle cell lymphoma for the society?

A0023: How many people belong to the target population?

MCL:
5–7% of malignant lymphoma

median age at diagnosis: 68 years

MCL is an uncommon subtype of lymphoid malignancy, representing 5% to 7% of malignant lymphoma in Western Europe with an annual incidence of 1–2/100,000. MCL is more common in men than in women (3:1 ratio) [14]; the median age at MCL diagnosis is 68 years [8]. In 2015, a total of 1,318 persons were newly diagnosed with NHL in Austria. The age-standardised incidence rate for the European Standard Population (2015, newly diagnosed NHL cases) is 18.8 per 100,000 per year in men and 12.7 per 100,000 per year in women [15].

A0005: What are the symptoms and the burden of disease of mantle cell lymphoma?

75% of MCL patients present lymphadenopathy

The majority of patients with MCL (approximately 75%) typically present with lymphadenopathy, the remaining 25% of patients present with extranodal disease. Commonly affected sites include the lymph nodes, spleen, Waldeyer's ring, bone marrow, blood and extranodal sites such as the gastrointestinal tract (where the manifestations occasionally present as lymphomatous intestinal polyposis), breast, pleura and orbit [8].

approximately 1/3 of patients have B symptoms

Systemic B symptoms are shown by up to one third of patients and include fever (temperature >38 °C), night sweats (drenching) and unintentional weight loss (>10% of body weight over the past six months). In patients with the "leukaemic" variant of MCL, lymph nodes are often spared and leukaemic presentations predominate; a common symptom is splenomegaly in the absence of lymphadenopathy. Affection of the central nervous system occurs in <5% of MCL cases, but is more common in the SOX11-negative variant of MCL [8, 16].

A0003: What are the known risk factors for mantle cell lymphoma?

multiple risk factors but limited clinical use

According to Wang et al. [12], the development and progression of MCL is a complex process that includes the joint effects of multiple families of risk factors and their interactions. Only a few potential risk factors have been validated; however, their clinical use has been limited.

A0024: How is mantle cell lymphoma currently diagnosed according to published guidelines and in practice?

diagnosis based on tissue biopsy

In patients with suspected MCL, the diagnosis should be based on a tissue biopsy [8], preferably obtained from a lymph node [14]. In patients with leukaemic manifestations only, a bone marrow biopsy could be sufficient if additional diagnostic measures are used [14]. Immunohistochemistry should be applied to evaluate the involvement of cyclin D1. Karyotyping or fluorescence in situ hybridisation can be useful to detect the t(11;14) (q13;32) translocation [8] which is the molecular hallmark of MCL that can be shown in most MCL cases and identifies the disease [9].

t(11;14) (q13;32) is a hallmark of MCL

diagnostic measures for staging

For the staging of MCL, the following diagnostic measures should be applied: a complete blood count, chemistry profile, LDH level, a bone marrow evaluation (with immunophenotyping flow cytometry of the bone marrow and blood) and computed tomography (CT) of the chest, abdomen and pelvis or fluorodeoxyglucose-positron emission tomography (FDG-PET/CT). Depending on the presence of clinical symptoms, an endoscopy of the gastrointestinal tract (which is also applied if a dose-intense regimen will be used) or evaluation of the cerebral spin fluid (in case of neurologic symptoms, or if the patient has the blastoid variant or a high Ki-67) can be applied [9].

The Ann Arbor staging system, first published in 1971 and extended by the "Cotswold modifications" in 1989 has been originally developed for the staging of Hodgkin lymphoma but is also used for the staging of NHL. A more recent classification system is the Lugano classification, published in 2014 [17].

According to the Lugano classification, 4 stages of MCL are defined [14]:

4 stages of MCL are defined by the Lugano classification

- Stage I (I_E): 1 lymph node or extranodal site (I_E) is involved
- Stage II (II_E): 2 or more lymph node regions or localised extranodal sites (II_E) on the same side of the diaphragm are involved
- Stage III: lymph node regions or lymphoid structures (e.g. thymus, Waldeyer's ring) on both sides of the diaphragm are involved
- Stage IV: diffuse or disseminated extralymphatic organ involvement.

differential diagnosis

In situ mantle cell neoplasia, CLL, follicular lymphoma, marginal zone lymphoma (nodal or extranodal), lymphoblastic lymphoma [8] and diffuse large B-cell lymphoma (DLBCL) should be considered for differential diagnosis.

6 Current treatment

A0025: How is mantle cell lymphoma currently managed according to published guidelines and in practice?

NCCN treatment recommendations

The National Comprehensive Cancer Network (NCCN) [11] recommends the following treatment options for MCL, based on the clinical stage of the disease:

1st-line and follow-up treatment (stages I–II)

For the first-line therapy and follow-up of stage I-II MCL, the NCCN recommends – outside of a clinical trial – radiotherapy (RT) with 30–36 Gy alone or a combination of immunochemotherapy with or without RT.

aggressive treatment options (stage II and stages III–IV)

For the initial induction therapy of stage II (bulky) and stage III–IV disease, the panel included the following regimens for aggressive therapy:

- Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) + rituximab
- Dose-intensified CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) (maxi-CHOP) alternating with rituximab + high-dose cytarabine (NORDIC regimen)
- Rituximab and methotrexate with augmented CHOP (CALGB regimen)
- Sequential R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and R-ICE (rituximab, ifosfamide, carboplatin, etoposide)
- Alternating R-CHOP and R-DHAP (rituximab, dexamethasone, cisplatin, cytarabine).

All of those regimens (except for hyper-CVAD + rituximab) include first-line consolidation with high-dose therapy followed by autologous stem-cell rescue (HDT/ASCR). For patients who are in remission after first-line therapy with R-CHOP and are not eligible for HDT/ASCR, maintenance treatment with rituximab, administered every eight weeks until disease progression, is recommended [11]. However, rituximab is not yet approved for this indication either in Europe or in the US.

less aggressive treatment options (stage II and stages III–IV)

For less aggressive therapy in patients with stage II (bulky) and stage III–IV disease, recommended regimens include:

- Bendamustine + rituximab
- Bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP)
- Cladribine + rituximab
- R-CHOP
- Modified Hyper-CVAD with rituximab maintenance in patients older than 65 years.

optimal therapy for relapsed or refractory MCL not defined

The optimal treatment for patients with relapsed or refractory disease still needs to be defined. Patients who experience relapse following complete remission (CR) to induction therapy, patients who obtain only partial remission to induction therapy or patients with progressive disease are appropriate candidates to participate in clinical trials. If no appropriate clinical trial is available, those patients can receive second-line chemotherapy regimens (with or without rituximab) recommended for patients with diffuse large B-cell lymphoma. Alternatively, the following regimens are recommended for these patients as second-line chemotherapy:

- Bendamustine ± rituximab
- Bortezomib ± rituximab
- Cladribine ±rituximab
- FC (Fludarabine, cyclophosphamide) ± rituximab
- FCMR (Fludarabine, cyclophosphamide, mitoxantrone, rituximab)

- FMR (Fludarabine, mitoxantrone, rituximab)
- Lenalidomide ± rituximab
- PCR (pentostatin, cyclophosphamide, rituximab)
- PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab.

In patients with relapsed or refractory disease that is in remission after second-line therapy, an allogeneic transplantation is an appropriate therapeutical option.

7 Evidence

systematic literature search in 5 databases: 165 hits

manual search: 32 additional references

A literature search was conducted on 11 January 2018 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were "rituximab", "MabThera", "mantle cell lymphoma", and "maintenance therapy". Also, the manufacturer was contacted, who submitted 14 references (5 of them had already been identified by systematic literature search) and results from a literature search and a list of completed/ongoing clinical trials. A manual search identified 31 additional references (web documents and journal articles).

overall: 197 references included: 5 studies, 1 analysis

Overall, 197 references were identified. Included in this report are:

- LyMa, a phase III study assessing rituximab maintenance therapy in mantle cell lymphoma patients after ASCT [4]
- A double-randomised intergroup trial assessing the efficacy and safety of a fludarabine-containing induction regimen and rituximab maintenance therapy [18]
- A phase III study of the German Low Grade Lymphoma Study Group investigating rituximab maintenance therapy after rituximab-containing chemotherapy for relapsed MCL and FL [19]
- 2 retrospective studies [20, 21] and one analysis [22].

study level risk of bias assessed based on EUnetHTA internal validity for RCTs

To assess the risk of bias at the study level, the assessment of the methodological quality of the evidence was conducted based on the EUnetHTA internal validity for randomised controlled trials (RCTs) [23]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patients and treating physicians, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 5 (see appendix).

external validity

The external validity of the included trials was assessed using the EUnetHTA guideline on applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals, considering the following elements: population, intervention, comparator(s), outcomes and setting [24].

The evaluation of the magnitude of "clinically meaningful benefit" that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS), was been applied, since it can only be used for solid tumours [25].

magnitude of clinically meaningful benefit based on ESMO-MCBS couldn't be assessed

7.1 Quality assurance

This report has been reviewed by an internal reviewer and an external reviewer. The latter was asked for the assessment of the following quality criteria:

internal and external review

- How do you rate the overall quality of the report?
- Are the therapy options in the current treatment section used in clinical practice and are the presented standard therapies correct?
- Is the data regarding prevalence, incidence and amount of eligible patients correct?
- Are the investigated studies correctly analysed and presented (data extraction was double-checked by a second scientist)?
- Was the existing evidence from the present studies correctly interpreted?
- Does the current evidence support the final conclusion?
- Were all important points mentioned in the report?

The LBI-HTA considers the external assessment by scientific experts from different disciplines a method of quality assurance of scientific work. The final version and the policy recommendations are under full responsibility of the LBI-HTA.

quality assurance method

7.2 Clinical efficacy and safety – phase III study

The LyMa trial, a randomised, prospective phase III trial, was conducted to assess the role of rituximab maintenance therapy in patients with MCL who had undergone ASCT [4, 26, 27]. From September 2008 to August 2012, a total of 299 patients younger than 66 years of age were enrolled, 240 of whom were randomised to either the rituximab maintenance group (n = 120) or the observation group (n = 120). Included patients had a median age of 58 (rituximab maintenance group) and 56 (observation group) years and were predominantly male. All patients had untreated MCL, Ann Arbor stage II–IV disease, were eligible for ASCT and had an Eastern Cooperative Oncology Group (ECOG) performance status score of less than 3.58% (rituximab maintenance), and 52% (observation group) of patients had a low risk MIPI score. In both groups, 35% of patients had more than 30% of Ki-67-positive cells. Detailed patient characteristics including inclusion and exclusion criteria can be found in Table 4.

LyMa trial: randomised, prospective phase III trial

Patients were included in the trial at the time of diagnosis and received four courses of R-DHAP, repeated every 21 days as an induction chemotherapy

R-DHAP as induction chemotherapy

(investigators were also allowed to use carboplatin or oxaliplatin instead of cisplatin). Only patients having a CR and those with a PR whose tumour mass was reduced by ≥75% after the induction therapy, were eligible to undergo transplantation. After four courses of R-DHAP, the overall response rate (ORR) was 89% and the complete response rate (CRR) was 77%. Patients having a PR and patients whose tumour mass had been reduced by <75% received a rescue induction therapy with four courses of R-CHOP every two weeks.

R-BEAM as conditioning regimen prior to ASCT

Prior to transplantation, patients received R-BEAM as conditioning regimen, consisting of rituximab, carmustine, etoposide, cytarabine and melphalan. A total-body radiation was not applied to reduce the risk of long-term effects. Of 299 enrolled patients, 257 patients underwent transplantation; 65% of those patients had a CR and 24% had an unconfirmed CR. The median time from ASCT to randomisation was 2.1 months in either group. Patients assigned to the rituximab maintenance group received 375 mg of rituximab per square metre of body surface area, given IV every two months for three years. In the rituximab maintenance group, a total of 83 patients completed the scheduled 3-year course of treatment.

primary endpoint: EFS after 4 years

The primary endpoint of the LyMa study was event-free survival (EFS) after four years from randomisation with events defined as disease progression, relapse, death, severe infection (grade 4 with life-threatening severity) or allergy to rituximab leading to treatment discontinuation after randomisation. Secondary endpoints were progression-free survival (PFS) including freedom from disease progression, relapse and death from any cause, overall survival (OS) defined as the period from the date of randomisation to the date of death from any cause. Further secondary endpoints were CRR, PR and ORR, measured after induction and after ASCT. Hospitalisations, all toxicities, all adverse events (AEs), all serious AEs (SAEs) and all deaths (listed and summarised by cause of death) were defined as safety endpoints.

median follow-up from inclusion: 54.4 months

The LyMa study stopping date was July 1, 2015; median follow-up from inclusion was 54.4 months, median follow-up from randomisation was 50.2 months. Clinical efficacy data of the LyMa trial are presented in Table 1 and AEs are listed in Table 2.

7.2.1 Clinical efficacy

D0001: What is the expected beneficial effect of rituximab on mortality?

statistically, OS was significantly prolonged in the rituximab maintenance group: 89% vs. 80%

OS was a secondary endpoint of the LyMa trial. With 89% (95% CI 81–94), the 4-year rate of OS was statistically significantly higher in patients of the rituximab maintenance group compared with 80% (95% CI 72–88) in patients of the observation group with a hazard ratio (HR) for death of 0.50 (95% CI 0.26–0.99; p = 0.04).

median OS was only reached in the high-risk patient population

Median OS was reached neither in the overall patient population nor in any subgroup except for high-risk patients (56.2 months, p < 0.001, as compared with the low-risk group). The 4-year rate of OS among patients of the included patient population was 78% (95% CI, 73–82).

D0006: How does rituximab affect progression (or recurrence) of mantle cell lymphoma?

The primary endpoint of the LyMa trial was EFS after four years; median EFS from randomisation was not reached in either group. The 4-year rate of EFS calculated from randomisation was 79% (95% CI 70–86) in patients of the rituximab group compared to 61% (95% CI 51–70) in patients of the observation group (p = 0.001), with a HR for disease progression, relapse, death, rituximab allergy or severe infection of 0.46 (95% CI 0.28–0.74; p = 0.002). 21% of rituximab maintenance group patients had an event (according to protocol definition) compared to 39% of observation group patients.

higher 4-year EFS rate in patients receiving rituximab: 79% vs. 61%

PFS was a secondary endpoint of the present phase III study and was not reached in the included patient population as calculated from inclusion; the 4-year rate of PFS among these patients was 68% (95% CI 62–73). Median PFS was not reached among low-risk and intermediate-risk patients, whereas median PFS in high-risk patients was 47.4 months. With 83% (95% CI 73–88), the 4-year rate of PFS was significantly higher in patients receiving rituximab maintenance therapy compared to 64% (95% CI 55–73) in the observation group (HR for disease progression, relapse or death, 0.40; 95% CI 0.23–0.68; p < 0.001).

PFS after 4 years significantly higher in rituximab maintenance group: 83% vs. 64%

D0005: How does rituximab affect symptoms and findings (severity, frequency) of mantle cell lymphoma?

No evidence was found to answer this research question.

D0011: What is the effect of rituximab on patients' body functions?

No evidence was found to answer this research question.

D0012: What is the effect of rituximab on generic health-related quality of life?

D0013: What is the effect of rituximab on disease-specific quality of life?

No evidence was found to answer these research questions as neither health-related quality of life (HRQoL) nor quality of life (QoL) were endpoints of the present study.

no evidence re HRQoL or QoL

Table 1: Efficacy results of the LyMa trial [4]

Descriptive statistics and estimate variability	Treatment group	Rituximab	Observation
	Number of patients	120	120
	EFS median EFS, months 4-year EFS rate, % (95% CI)	 NR 79 (70–86)	 NR 61 (51–70)
	PFS median PFS, months 4-year PFS rate, % (95% CI)	 NR 83 (73–88)	 NR 64 (55–73)
	OS median OS, months 4-year OS rate, % (95% CI)	 NR 89 (81–94)	 NR 80 (72–88)
	QoL	NA	NA
Effect estimate per comparison	*Comparison groups*		Rituximab maintenance vs. observation
	4-year EFS rate	HR[1]	0.46
		95% CI	0.28—0.74
		Log-rank test p value	0.002
	4-year PFS rate	HR[2]	0.40
		95% CI	0.23—0.68
		Log-rank test p value	< 0.001
	4-year OS rate	HR[3]	0.50
		95% CI	0.26—0.99
		Log-rank test p value	0.04

Abbreviations: CI = confidence interval, EFS = event-free survival, HR = hazard ratio, NA = not available, NR = not reached, OS = overall survival, PFS = progression-free survival, QoL = quality of life, [1] = HR for disease progression, relapse, death, rituximab allergy or severe infection, [2] = HR for disease progression, relapse or death, [3] = HR for death

7.2.2 Safety

C0008: How safe is rituximab in relation to the comparator(s)?

neutropenia: most frequent AE of grade >3

The most common grade 3 and 4 AE was neutropenia. Within the first six months, 41.1% of patients of the rituximab maintenance group and 26.3% of observation group patients experienced neutropenia. Other frequent AEs of grades 3–4 within the first six months were infections (6.3%) and thrombocytopenia (5.4%) in the rituximab maintenance group and thrombocytopenia (4.2%) and infections (3.4%) among patients in the observation group. Death due to second cancer occurred in three patients of the rituximab maintenance group and in one patient in the observation group.

Grade 1–2 toxicities that occurred after transplantation were infections (126 events in 80 patients in the rituximab maintenance group, 67 events in 54 patients in the observation group) and neutropenia (92 events in 35 patients in the rituximab maintenance group, 45 events in 29 patients in the observation group). No late effects of rituximab maintenance therapy were reported.

The most frequent reasons for discontinuation of rituximab maintenance treatment were disease progression and neutropenia. In four patients of each group, a serious infection after transplantation occurred, including spondylitis, pyelonephritis, septicaemia and varicella pneumonia in rituximab maintenance group patients; septicaemia, cellulitis, meningitis and severe pneumonia in observation group patients.

disease progression and neutropenia most common reasons for treatment discontinuation

No calculation of statistical significance was applied for safety parameters.

C0002: Are the harms related to dosage or frequency of applying rituximab?

No evidence was found to answer this research question.

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of rituximab?

During pregnancy, rituximab should only be used if the mother's potential benefit justifies the potential risk of the foetus, as postmarketing data indicates that B-cell lymphocytopenia (generally lasting <6 months) can occur in infants who were exposed to rituximab in utero. Rituximab was detected postpartum in the serum of infants who were exposed in utero. There is no data available as to whether rituximab is secreted into human milk [7].

rituximab can cause B-cell lymphocytopenia after exposure during pregnancy

Table 2: LyMa trial: Grade 3 and 4 toxicities [27]

Adverse Event (Intensity of AEs rated by using NCI-CTC criteria)	Intervention			Control		
	<6 months n = 112 n (%)	6–12 months n = 102 n (%)	12–36 months n = 99 n (%)	<6 months n = 118 n (%)	6–12 months n = 110 n (%)	13–36 months n = 104 n (%)
Haematology (all)	51 (45.5)	25 (24.5)	22 (22.2)	44 (37.3)	14 (12.7)	26 (25.0)
Neutropenia	46 (41.1)	16 (15.7)	12 (12.1)	31 (26.3)	1 (0.9)	3 (2.9)
Thrombocytopenia	6 (5.4)	4 (3.9)	5 (5.1)	5 (4.2)	2 (1.8)	4 (3.8)
Infections classified as an event	1 (0.9)	1 (1.0)	2 (2.0)	1 (0.8)	1 (0.9)	2 (1.9)
Infections	7 (6.3)	2 (2.0)	3 (3.0)	4 (3.4)	2 (1.8)	3 (2.9)
Cutaneous	0 (0.0)	0 (0.0)	2 (2.0)	1 (0.8)	0 (0.0)	1 (1.0)
GI function	1 (0.9)	1 (1.0)	1 (1.0)	1 (0.8)	0 (0.0)	0 (0.0)
Pulmonary function	1 (0.9)	1 (1.0)	2 (2.0)	3 (2.5)	1 (0.9)	4 (3.8)
Cardiac function	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.0)
Neurology	4 (3.6)	2 (2.0)	4 (4.0)	0 (0.0)	2 (1.8)	1 (1.0)
Transaminases	5 (4.5)	4 (4.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bilirubin	1 (0.9)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine	2 (1.8)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AE = adverse event, GI = gastrointestinal, n = number, NCI = National Cancer Institute, CTC = common toxicity criteria

7.3 Clinical effectiveness and safety – further studies

There is no further study available that has investigated rituximab maintenance therapy in patients with MCL after ASCT.

phase III study investigating rituximab maintenance after rituximab chemotherapy

Kluin-Nelemans et al. [18] conducted a double-randomised trial assessing two objectives, comparing the response rates of R-FC (rituximab, fludarabine and cyclophosphamide) induction regimen to the application of R-CHOP in patients not eligible for high-dose therapy. Patients who had a response were randomised again to maintenance therapy with rituximab or interferon alfa. A total of 485 patients at a median age of 70 years and predominantly male were included in the primary analysis of response; 274 patients were randomised to receive either rituximab at 375 mg/m^2 every two months or standard interferon alfa at a dose of three million units three times per week, given until disease progression. Analysis showed that CR rates were similar in both R-FC (40%) and R-CHOP (34%), p = 0.10. In patients receiving R-FC, progressive disease occurred more often (14% vs. 5% with R-CHOP), OS was statistically significantly shorter (47% vs. 62% after four years) and more patients died during the first remission. The frequency of grade 3 or 4 infections was balanced between the two groups; haematological toxic effects occurred more often in patients receiving R-FC. The primary analysis of maintenance therapy showed a risk reduction of progression or death by 45% in patients receiving rituximab compared to the patients receiving interferon alfa (HR 0.55; 95% CI, 0.36–0.87; p = 0.01). After four years, 58% of patients who received rituximab were in remission versus 29% of patients who received interferon alfa. In patients showing a response to R-CHOP who received rituximab maintenance therapy, the OS after four years was statistically significantly improved: the 4-year survival rate was 87% compared to 63% with interferon alfa, p = 0.005.

pretreated patients, no ASCT

response duration statistically significantly longer in rituximab maintenance group

However, a prospective, randomised, open-label multicentre phase III study of the German Low Grade Lymphoma Study Group (GLSG) [19] investigated rituximab maintenance therapy after rituximab-containing chemotherapy in patients with recurring and refractory FL and MCL. 195 patients with a median age of 62 years, all having advanced stage III or IV disease were included. 58% of patients had FL, 34% had MCL and 8% of patients had other lymphoma subtypes; all patients had received at least one type of chemotherapy before. The patients were randomly assigned to receive four courses of fludarabine, cyclophosphamide and mitoxantrone (FCM) alone or in combination with rituximab (R-FCM). Patients responding to the treatment were randomised again for rituximab maintenance therapy; they received two courses (each course consisting of four doses of 375 mg/m^2/day given for four consecutive weeks) of rituximab given three and nine months after completion of salvage therapy. Patients assigned to the observation group received no further treatment. After 147 patients, randomisation was stopped due to the fact that R-FCM revealed a statistically significantly better outcome; hence, all subsequent patients received R-FCM. Analyses showed that the duration of response was significantly prolonged in patients receiving rituximab maintenance therapy after R-FCM compared to the observation group. Median survival was not reached in either study arm; the estimated proportion of patients alive at three years was 77% after rituximab maintenance therapy versus 57% in the observation group.

retrospective study in 157 MCL patients, approx. 1/3 received rituximab maintenance

Graf et al. [20] conducted a retrospective study in 157 MCL patients who underwent ASCT to investigate the benefit of rituximab maintenance therapy. The median age of the patients was 57 years, 85% of patients were male. 32% of patients received different maintenance rituximab regimens (a median of 8 doses of rituximab was administered at a dose of 375 mg/m^2); 68% of patients did not receive rituximab maintenance therapy. 92% of patients received rituximab before ASCT; transplant conditioning was radiation based in 78% of patients. Rituximab maintenance treatment started at a median of 77 days after ASCT. After a median follow-up of five years after ASCT, analyses showed that the administration of rituximab was associated with a statistically significantly improved PFS (HR 0.44; 95% CI 0.24-0.80, p = 0.007) and an improved OS (HR 0.46; 95% CI 0.23–0.93, p = 0.03) compared to patients not receiving rituximab maintenance therapy. 34% of rituximab maintenance therapy patients had grade 4 neutropenia, compared to 18% in patients not receiving rituximab (p = 0.04). 32% of patients received granulocyte colony stimulating factor for neutropenia in the rituximab maintenance group versus 12% in patients without rituximab maintenance therapy (p = 0.005).

PFS statistically significantly improved, benefit in OS

retrospective study in 191 patients, 39% received rituximab maintenance

191 MCL patients treated with ASCT were included in a singlecentre retrospective study [21] to assess the effectiveness of maintenance rituximab therapy. At the time of diagnosis, the median age of patients was 59 years, 74% of patients were male and nearly all of the patients had stage III–IV disease. 67% of patients had received one frontline therapy prior to ASCT; 56% received a high-dose cytarabine containing frontline treatment. For conditioning therapy prior to ASCT, 53% of patients received chemotherapy only, 47% underwent radiation-based conditioning regimens. The majority of patients received rituximab prior to ASCT, 39% of patients received rituximab maintenance after ASCT. Rituximab maintenance therapy was administered in 3 different dosing schedules. 5-year PFS was 53% (95% CI: 45%–60%) and OS was 71% (95% CI: 63%–77%) for patients receiving ASCT. The 5-year cumulative incidence of relapse was 41% (95% CI: 34%–48%) with a total of 83 relapses occurring at a median of 2.1 years (ranging from 0.2 to 13.4). Rituximab maintenance therapy after ASCT was significantly associated with superior PFS and OS; the benefit of rituximab maintenance therapy was assessed in all age groups. The most common cause of non-relapse mortality in study patients was secondary cancer in 7%.

rituximab maintenance statistically significantly associated with superior PFS and OS

double-randomised trial with 2 objectives

R-CHOP induction + rituximab maintenance is effective for older patients with MCL

analysis of 72 patients, 22 received rituximab maintenance for 2 years

An analysis in 72 patients to evaluate the outcome for MCL patients after ASCT conducted by Dietrich et al. [22] is only available in form of an abstract. MCL patients receiving rituximab maintenance therapy after ASCT in a phase II trial were compared with patients who had undergone ASCT but did not receive rituximab maintenance. A total of 72 patients with a median age of 60 years were included; 22 patients participated in the phase II trial and were randomised to receive rituximab maintenance therapy after ASCT. All patients received rituximab prior to the ASCT; high-dose cytarabine (HD-ARA-C) was administered in 45 patients. ASCT was performed in 51 patients after administering first-line treatment; 27 patients achieved CR before ASCT. The median observation time after ASCT was 56 months. PFS after two years was 90% in the rituximab maintenance group compared to 65% in the control group. Two-year OS was 88% in the rituximab maintenance group versus 80% in the control group. Univariate analysis showed a significantly better PFS in the patients receiving rituximab maintenance (HR 0.21; p = 0.014). The beneficial effect of rituximab maintenance therapy (HR 0.23; p = 0.02) was also shown by multivariate adjustment for age (HR per year 0.98; p = 0.79), year of transplant (HR per calendar year 1.0; p

PFS prolonged in patients receiving rituximab maintenance

= 0.96), achievement of CR prior to ASCT (HR 1.59; p = 0.26), upfront ASCT (HR 0.81; p = 0.80) and HD-ARA-C treatment (HR 0.69; p = 0.63).

8 Estimated costs

A0021: What is the reimbursement status of rituximab?

Rituximab (MabThera®) is available as a concentrate for solution for infusion in vials of 100 mg (one package contains two vials) at € 613.45 (ex-factory price) and 500 mg at € 1,516.43 [28].

costs for 1 dose of rituximab: approx. € 2,129.90

In the LyMa trial, patients received 375 mg of rituximab per square metre of body surface area, given intravenously every two months for three years. The total number of planned rituximab doses was 23, comprising 18 doses administered every other month for three years as trial medication, four doses as induction therapy and one dose given with the preparative regimen for transplantation [4]. Assuming a body surface area of 1.73 m^2, costs for one dose (649 mg) of rituximab are approximately € 2,129.90 (using two vials of 100 mg and one vial of 500 mg). According to the LyMa trial schedule with a total of 23 doses of rituximab (induction therapy + preparative regimen for ASCT + three years of maintenance therapy) a total course of rituximab maintenance therapy costs approximately € 48,987.70.

total course of rituximab maintenance therapy € 48,987.70

9 Ongoing research

In February, a search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted. The following phase III studies, evaluating the use of rituximab maintenance therapy in MCL, were identified:

6 ongoing phase III trials

- **NCT01933711:** An open-label, prospective, randomised phase III trial to evaluate rituximab maintenance therapy versus observation in patients with aggressive CD20-positive B-cell lymphoma and MCL. The estimated study completion date is December 2018.
- **NCT01996865:** A multicentre, open-label phase III trial (MAGNIFY) of lenalidomide plus rituximab followed by lenalidomide versus rituximab maintenance in patients with relapsed/refractory follicular lymphoma, marginal zone lymphoma or MCL. Estimated study completion date is March 2023.
- **NCT00209209** (EudraCT Number: 2005-005375-15): A phase III, open-label randomised study (MCLelderly) investigating two independent questions in the MCL treatment of elderly patients. One aim of the trial is to investigate whether rituximab plus a combination of fludarabine with cyclophosphamide results in a higher reduction of lymphoma mass than rituximab combined with the

standard chemotherapy scheme; the second aim is to evaluate if maintenance with rituximab can substitute the interferon maintenance and even improve PFS in patients after successful initial cytoreductive therapy. Estimated study completion date is December 2018.

- **NCT01865110** (EudraCT Number: 2012-002542-20): A randomised, open-label phase III trial evaluating the efficacy of alternating immunochemotherapy (consisting of R-CHOP + R-HAD versus R-CHOP alone, followed by maintenance therapy consisting of additional lenalidomide + rituximab versus rituximab alone) in patients ≥60 years with MCL. Estimated study completion date is March 2024.
- **NCT03267433:** A randomised, open-label phase III study evaluating rituximab with or without stem-cell transplant in patients with minimal residual disease-negative MCL in first complete remission. Estimated study completion date is January 2032.
- **NCT00877214:** A randomised, open-label phase III trial investigating the significance of extended rituximab maintenance therapy in follicular lymphomas and the significance of rituximab maintenance therapy in other indolent and mantle cell lymphomas compared to observation. Estimated study completion date is April 2022.

several ongoing phase II trials

There are several phase II trials investigating the role of rituximab maintenance therapy in MCL in different settings and combinations with other drugs:

- **NCT02633137:** A phase II study evaluating sequential chemotherapy and lenalidomide followed by rituximab and lenalidomide maintenance in MCL patients. Estimated study completion date is December 2018.
- **NCT00878254:** A phase II trial investigating rituximab in combination with methotrexate, doxorubicin, cyclophosphamide, leucovorin, vincristine, ifosfamide, etoposide, cytarabine and mesna in previously untreated MCL patients. Estimated study completion date is December 2019.
- **NCT01267812:** A phase II study of bortezomib and rituximab maintenance therapy (weekly administration) in patients with MCL who have previously undergone hematopoietic stem-cell transplantation. Estimated study completion date is July 2018.
- **NCT01472562:** A phase II multicentre trial evaluating the efficacy and safety of first-line lenalidomide + rituximab in patients with previously untreated MCL. Estimated study completion date is October 2020.
- **NCT01665768:** A phase II study investigating rituximab maintenance therapy with mTor inhibition (by everolimus) after high-dose consolidative therapy in CD20+, B-cell lymphomas, gray zone lymphoma and Hodgkin's lymphoma. Estimated study completion date is July 2020.

10 Discussion

rituximab: currently not approved for the assessed indication

Rituximab (MabThera®) is a monoclonal antibody approved for the treatment of NHL, CLL, rheumatoid arthritis and granulomatosis with polyangiitis and microscopic polyangiitis. To date, rituximab has not received marketing authorisation either by the EMA or the FDA for the maintenance therapy in patients with MCL who have undergone ASCT.

LyMa trial: prolongation at 4 y:
+ 18% EFS
+ 19% PFS
+ 9% OS

The LyMa trial [4] was conducted to assess the efficacy and safety of rituximab maintenance therapy in MCL patients after ASCT. Analyses showed a prolonged EFS rate of 18 percentage points at four years: the EFS rate was 79% in patients of the rituximab maintenance group compared to 61% in patients of the observation group. The benefit of rituximab maintenance treatment has also been confirmed regarding PFS and OS results: at four years, patients of the rituximab maintenance group had a PFS rate of 83% versus 64% in observation group patients. The rate of OS at four years was higher in the rituximab group (89%) than in the observation group (80%). However, median OS, PFS and EFS were not reached.

most frequent AE of grade >3: neutropenia

The most frequent AE of grade >3 in both groups within the first six months of treatment was neutropenia, occurring more often in the rituximab maintenance group (41.1%) than in the observation group (26.3%). Neutropenia was the reason for discontinuation of the study treatment in nine patients among the rituximab maintenance group. However, the rate of neutropenia declined in the course of further treatment to 12.1% in rituximab maintenance group patients and 2.9% in the observation group patients after 12–36 months of treatment. At the time of final analysis, no late effects were reported in either group.

median values for EFS, PFS and OS not reached

no QoL data available

Although maintenance therapy with rituximab seems to be well tolerated by the majority of patients and rates of AEs declined in the course of treatment, the occurrence of late effects is not determined. Although no late effects of rituximab maintenance therapy were reported at the time of final analysis of the LyMa trial, their subsequent occurrence cannot be ruled out. Furthermore, even though the LyMa trial showed beneficial effects of rituximab maintenance therapy for EFS, PFS and OS, median values for these study endpoints were not reached. Neither is any data available regarding patients' quality of life (QoL).

high risk of bias: open-label study, no info on the generation of randomisation sequence and the allocation concealment

wide CIs

The external and internal validity of the LyMa trial is compromised by methodological limitations. The LyMa trial is an open-label study; both the patients and the treating physicians were unmasked to treatment assignment. Furthermore, no information about the adequate generation of randomisation sequence or adequate allocation concealment was available. In addition, the effect estimates for the comparison of rituximab maintenance therapy versus observation show wide confidence intervals (CIs), indicating great variability. However, a high risk of bias could be detected due to the open-label, unblinded study design, the lack of information about the generation of randomisation sequence and allocation concealment, and other aspects increasing the risk of bias.

applicability of results in older and more diseased patients questionable

The patients included in the LyMa trial had a median age of 58 years in the rituximab maintenance group and 56 years in the observation group respectively. Study patients had a good performance status, more than 50% of them had a low-risk MIPI score and 35% of patients had more than 30% of Ki-67-positive cells. As the general median age of MCL patients at the time

of diagnosis is 68 years, the study population was substantially younger. Thus, the applicability of the study results for older patients, patients with worse performance status and the consideration of risk factors needs to be clarified, particularly considering their eligibility for ASCT. Nevertheless, maintenance therapy may also be a relevant issue for patients who did not receive ASCT for any reason.

questionable impact of prior treatment regimens

LyMa trial patients received both R-DHAP, a rituximab-containing induction chemotherapy, and R-BEAM, a rituximab-containing conditioning regimen before ASCT. It is unclear whether the beneficial effects of rituximab maintenance treatment are reproducible if other treatment regimens for induction chemotherapy and/or conditioning therapy are used. However, Kluin-Nelemans et al. [18] showed significantly improved OS in patients receiving rituximab maintenance therapy after R-CHOP induction therapy, even though study patients did not receive ASCT.

optimal rituximab schedule needs to be determined

A further issue warranting investigation is the schedule of rituximab administration. A study [29] comparing rituximab maintenance therapy administered every two months with rituximab maintenance every three months showed that patients in the every-2-months cohort were 3.4 times more likely to experience toxicities. In addition, patients receiving rituximab more frequently showed a trend for shorter PFS, resulting from more dose delays or omissions and early treatment discontinuation. Hence, the optimal frequency of rituximab application has yet to be determined. In addition, the ideal treatment length needs to be identified, since 83 of the 120 patients in the LyMa trial who received rituximab maintenance therapy, completed the 3-year-course of treatment. In light of this fact, the subsequent therapy for these patients beyond three years must be determined.

MRD for early prediction of recurrence

To select those patients who will benefit most from rituximab maintenance treatment, the minimal residual disease (MRD), which is defined as the minimal traceable persistence of lymphoma cells after successful treatment, can provide an early prediction of the recurrence of disease [30]. The clinical role of MRD analysis in MCL includes four major aspects: the prediction of disease recurrence, risk stratification, an early feedback on the efficacy of new treatment and personalised, pre-emptive medicine. There are several ongoing prospective clinical trials investigating the impact of MRD on the outcome of patients with MCL [31].

approx. € 48,987.70 for 3 years of rituximab maintenance

The costs for one dose of rituximab are approximately € 2,129.9 (ex-factory price) [28]. For a 3-year-course of rituximab maintenance therapy, as investigated in the LyMa trial, a total of 18 doses will be administered costing € 38,338.2. Additionally, costs for rituximab-containing induction chemotherapy and the preparative regimen for transplantation (comprising another five doses of rituximab) would incur, resulting in a total amount of € 48,987.7.

rituximab biosimilars approved in Europe

In 2017, the EMA granted marketing authorisation for two rituximab biosimilars, Truxima® (in February 2017) and Rixathon® (in June 2017). Both rituximab biosimilars were approved for the same therapeutic indications as MabThera® [32, 33]. In the U.S., the FDA accepted a biologics licence application for Rixathon® in September 2017 [34]. To date, no cost information is available for Austria for rituximab biosimilars. However, comparing the costs for MabThera® with Truxima® in Germany, the potential for cost saving is approximately 20% [35]. Price reductions for biosimilars are expected to range from 20% to 40% and potential cost savings of € 50–100 billion are forecasted by 2020 throughout Europe [36]. Since biosimilar medicines are approved according to the same standards regarding pharmaceutical quality,

cost-effective alternative

safety and efficacy applying to all biological medicines [37], they may provide a cost-effective alternative.

rituximab maintenance treatment provides a benefit in young and fit patients

lack of data on QoL

optimal schedule needs to be determined

Although rituximab maintenance therapy provides essential benefits for patients with MCL after ASCT, relevant issues, including schedules of rituximab administration, the applicability of study results in older patients or patients with worse performance status, types of previously administered chemotherapeutical regimens, the role of MRD and, not least, the impact of rituximab maintenance therapy on QoL need to be clarified. Due to the small number of MCL-affected patients, gathering significant evidence may prove to be difficult. However, more data is needed to confirm the results of the LyMa trial.

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12 Appendix

Table 3: Administration and dosing of rituximab [2]

	Technology	Comparator
Administration mode	Intravenous infusion (IV)	No active comparator is available
Description of packaging	Clear Type I glass vials with butyl rubber stopper containing 100 mg of rituximab in 10 mL. Packs of 2 vials.	
Total volume contained in packaging for sale	MabThera 100 mg concentrate for solution for infusion MabThera 500 mg concentrate for solution for infusion MabThera 1400 mg solution for subcutaneous injection MabThera 1600 mg solution for subcutaneous injection	
Dosing	LyMa trial: 375 mg of rituximab (IV) per square metre of body surface area, every 2 months for 3 years	
Median treatment duration	-	
Contraindications	For the use in NHL and CLL: ✲ Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients ✲ Active, severe infections ✲ Patients in a severely immunocompromised state For the use in rheumatoid arthritis: ✲ Granulomatosis with polyangiitis and microscopic polyangiitis ✲ Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients ✲ Active, severe infections ✲ Patients in a severely immunocompromised state ✲ Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease	
Drug interactions	To date, limited data on possible drug interactions are available ✲ Patients with HAMA or HACA titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies. ✲ In patients with rheumatoid arthritis, 283 patients received subsequent therapy with a biologic DMARD following rituximab. In these patients, the rate of clinically relevant infection while receiving rituximab was 6.01 per 100 patient years compared to 4.97 per 100 patient years following treatment with the biologic DMARD.	

Abbreviations: CLL = chronic lymphocytic leukaemia, DMARD = disease-modifying anti-rheumatic drug, HAMA = human anti-mouse antibody, HACA = human anti-chimeric antibody, IV = intravenous

Table 4: Characteristics of the LyMa trial [4, 26, 27]

Title: Rituximab after autologous stem-cell transplantation in mantle cell lymphoma [4, 26, 27]			
Study identifier	NCT00921414, EudraCT number 2007-004644-70, LyMa		
Design	Multicentre, open-label, randomised phase III study		
	Duration of main phase:		Enrolment: September 2008 to August 2012 Median length of follow-up from inclusion: 54.4 months Median length of follow-up from randomisation: 50.2 months Stopping date: July 1, 2015
Hypothesis	Superiority The study was designed to evaluate whether rituximab maintenance therapy after ASCT would prolong the duration of response in patients with mantle cell lymphoma. The total sample of 299 patients provided the trial with 80% power to detect a difference of 13 percentage points in the rate of event-free survival at 4 years at an alpha level of 0.05. O'Brien-Fleming boundaries were used to check for type I error. Time-to-event survival curves were estimated by using the Kaplan Meier method. Time-to-event endpoints in the different groups were compared with the use of log-rank tests and Cox proportional hazards regression. Response rates were expressed in percentage with 95% exact confidence intervals that were based on the Clopper-Pearson method. All statistical analyses were performed using SAS software, version 9.3.		
Funding	Roche and Amgen		
Treatment groups	Intervention (n = 120)		After ASCT, rituximab maintenance therapy was administered at a dose of 375 mg (IV) per square metre of body surface area every 2 months for 3 years. Prior to ASCT, patients received induction chemotherapy with four courses of R-DHAP, repeated every 21 days. The conditioning regimen before ASCT was R-BEAM.
	Control (n = 120)		After ASCT, patients underwent observation. Prior to ASCT, patients received induction chemotherapy with four courses of R-DHAP, repeated every 21 days. The conditioning regimen before ASCT was R-BEAM.
Endpoints and definitions	4-year event-free survival (primary endpoint)	EFS	EFS of patients who underwent ASCT and were randomised to one of the two arms of the protocol. Events were defined as disease progression, relapse, death, severe infection (grade 4 with life-threatening severity) or allergy to rituximab that led to discontinuation of treatment after randomisation). EFS was determined by using the Kaplan Meier method).
	4-year progression-free survival (secondary endpoint)	PFS	Period from the date of randomisation to the date of first documented disease progression, relapse, or death from any cause. Assessed by using the Kaplan Meier method.
	4-year overall survival (secondary endpoint)	OS	Period from the date of randomisation to the date of death from any cause.
	Complete response rate (secondary endpoint)	CRR	Assessed after induction and after ASCT on local assessment, based on the International Workshop to Standardise Response Criteria for NHL for evaluation of response in Non-Hodgkin's lymphoma (Cheson, 1999).
	Partial response rate (secondary endpoint)	PR	Assessed after induction and after ASCT. Patients without response assessment were considered as non-responders.
	Overall response rate (secondary endpoint	ORR	Assessed after induction and after ASCT. Patients without response assessment were considered as non-responders.
	Safety endpoints	-	Including hospitalisations, all toxicities (infections, haematological, general), AEs of special interest, all SAEs, all deaths.

Title: Rituximab after autologous stem-cell transplantation in mantle cell lymphoma [4, 26, 27]			
Study identifier	NCT00921414, EudraCT number 2007-004644-70, LyMa		
	Exploratory end-points	-	Including EFS, OS, EFS and PFS on 18 FDG-TEP/TDM, prognostic factors (IPI, MIPI, GOELAMS prognostic factors), MRD, detection of tumour makers, tumour bank (with tumour tissue, marrow and blood samples, serum).
Database lock	July 1, 2015		
Results and Analysis			
Analysis description	Interim analysis was performed when at least 82 patients had reached 3 years after ASCT. Included patients set (IPS), includes all patients who signed the consent regardless of the study drug being received or not; set used for secondary objectives. Intention to treat set (ITT), includes all patients randomised, used for primary and secondary objectives. Safety set (SS), includes all patients who received at least one dose of treatment.		
Analysis population	Inclusion	❁ MCL CD20-positive according to WHO 2008 classification ❁ Untreated MCL patients older than 18 and younger than 66 ❁ At least one measurable site ❁ ECOG performance status 0-1-2 ❁ Ejection cardiac function >50% ❁ Signed informed consent ❁ Measurable disease that requires treatment ❁ Absolute neutrophil count >1.0 x 10⁹/L ❁ Platelets >50 x 10⁹/L ❁ AST and/or ALT <3 x ULN ❁ Calculated creatinine clearance >50mL/min ❁ Bilirubin <2 x normal ❁ No other cancer (except in situ or baso-cellular)	
	Exclusion	❁ Other entity of lymphoma ❁ Active HBV, HCV ❁ HIV-positive ❁ Active systemic infection requiring treatment ❁ Uncontrolled diabetes ❁ Patient unable to receive one drug in the treatment plan	

Characteristics	Intervention (n = 120)	Control (n = 120)
Median age, years (range)	58 (27–65)	56 (29–65)
Male sex, n (%)	92 (77)	97 (81)
Ann Arbour stage, n/total n (%) II III IV	 7/119 (6) 15/119 (13) 97/119 (82)	 5/120 (4) 16/120 (13) 99/120 (82)
B-symptoms, n (%)	37 (31)	27 (22)
ECOG performance status score <3, n (%)	117 (98)	113 (94)
Bone marrow involvement, n (%)	76 (63)	73 (61)
Lactate dehydrogenase >ULN, n (%)	33/118 (28)	46/118 (39)
MIPI score, n (%) Low risk Intermediate risk High risk	 70 (58) 34 (28) 16 (13)	 63 (52) 31 (26) 26 (22)
Percent of Ki-67-positive cells >30%, n/total n (%)	32/92 (35)	29/83 (35)
Variant mantle cell lymphoma n/total n (%) On local review Blastoid Pleomorphic On central review Blastoid Pleomorphic	 12/120 (10) 1/120 (1) 2/95 (2) 10/95 (11)	 12/119 (10) 5/119 (4) 5/80 (6) 11/80 (14)

Title: Rituximab after autologous stem-cell transplantation in mantle cell lymphoma [4, 26, 27]			
Study identifier	NCT00921414, EudraCT number 2007-004644-70, LyMa		
	R-CHOP before ASCT, n (%)	4 (3)	7 (6)
	Disease status, n (%) After receipt of 4 courses of R-DHAP OR Complete remission or unconfirmed complete remission After ASCT OR Complete remission or unconfirmed complete remission	 119 (99) 102 (85) 120 (100) 113 (94)	 117 (98) 104 (87) 120 (100) 110 (92)
	Time from ASCT to randomisation, months Median Range	 2.1 0.4–4.2	 2.1 0.4–3.9
Applicability of evidence			
Population	The LyMa trial included patients (18–65 years) with untreated MCL, who had disease of Ann Arbor stage II–IV, ECOG performance status score <3 and eligibility for ASCT.		
Intervention	Rituximab is not yet approved for the maintenance therapy after ASCT, the indication assessed in the LyMa trial. The schedule for maintenance therapy in LyMa was the administration of 375 mg of rituximab (IV) per m^2 of body surface area every 2 months for 3 years, with a planned total number of 23 rituximab doses (4 doses induction therapy, 1 dose with preparative regimen for transplantation and 18 doses over 3 years).		
Comparators	Currently there is no data available comparing rituximab to another drug in this special setting (patients with untreated MCL after ASCT).		
Outcomes	There is evidence that rituximab maintenance therapy prolongs EFS, PFS and OS; however, there is neither long-term data nor data on QoL available. As the general median age of diagnosis of MCL is 68 years, the applicability of the results needs to be clarified given the young age of the study population (median age was 56 years in the rituximab maintenance group and 58 years in the observation group respectively).		
Setting	The LyMa trial is a multicentre study sponsored by the GOELAMS group and performed by the GOELAMS and GELA centres, now LYSA (The Lymphoma Study Association) for lymphoma studies. 66 French investigator centres participated.		

Abbreviations: AE = adverse event, ALT = alanine transaminase, ASCT = autologous stem-cell transplantation, AST = aspartate transaminase, CRR = complete response rate, ECOG = Eastern Cooperative Oncology Group, EFS = event-free survival, HBV = hepatitis B virus , HCV = hepatitis C virus, IPI = International Prognostic Index, IPS = included patients set, ITT = intention to treat, LYSA = Lymphoma Study Association, MCL = mantle cell lymphoma, MIPI = Mantle Cell Lymphoma International Prognostic Index, n = number, OS = overall survival, OR = overall response, ORR = overall response rate, PFS = progression-free survival, PR = partial response, QoL = Quality of life , R-DHAP= rituximab, dexamethasone, high-dose cytarabine, cisplatin, R-BEAM = rituximab, carmustine, etoposide, cytarabine, melphalan, SS = safety set, ULN = upper limit normal, WHO = World Health Organization

Table 5: Risk of bias assessment on study level is based on EUnetHTA (internal validity of randomised controlled trials) [23]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: no information available		Unclear
Adequate allocation concealment: no information available		Unclear
Blinding:	**Patient:** open-label	No
	Treating physician: open-label	No
Selective outcome reporting unlikely: efficacy outcomes reported as described in protocol; withdrawals and drop-outs were reported		Yes
No other aspects which increase the risk of bias: sponsor supplied rituximab for the R-BEAM regimen and for maintenance therapy and funded the trial		No
Risk of bias – study level		High

Abbreviations: R-BEAM = rituximab, carmustine, etoposide, cytarabine, melphalan