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HOW TO MANAGE...

How to manage mantle cell lymphoma

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Mantle cell lymphoma (MCL) is no longer a hopeless disease. Considered to carry a uniformly dismal prognosis so far, during the last years it has been rediscovered as a heterogeneous clinical and biological entity. Such a complexity has been highlighted by molecular genetics, unraveling different pathways of cell survival and progression. Concurrently, the application of new therapeutic paradigms including rituximab, high-dose cytarabine and stem cell transplantation dramatically improved treatment activity and the introduction of innovative targeted molecules has already led to new patient perspectives. In this completely new and continually evolving landscape, the clinical hemato-oncologist might feel disoriented on what are the best current strategies to handle such a critical disease and the gold standard therapeutic options for MCL. Here we address some burning questions on how to manage MCL patients, spacing from prognostic issues to the dilemma of personalized treatment in different scenarios of the disease: how to diagnose an MCL? Which are the fundamental staging procedures? What are the most reliable prognosticators? Is there a place for watch and wait? Which are the best treatment options for younger, elderly and frail patients? Which patients are addressable to high-dose therapy? What is the role of allogeneic transplantation? What is the most appropriate approach for relapsing disease in different categories of patients? What novelties are going to be introduced in the near future? The practical algorithms here discussed represent an evidence-based approach derived from results of multicenter and randomized trials.

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INTRODUCTION

Mantle cell lymphoma (MCL) is a distinct histological subtype occurring in both elderly (>65 years) and young (<65 years) patients, with a pathognomonic chromosomal translocation t(11;14).[1] During the last three decades MCL was considered as a disease with a uniformly dismal prognosis; however, with the introduction of high-dose cytarabine chemotherapy (± autologous stem cell transplantation, SCT) and anti-CD20 antibody therapy with rituximab especially the outcome of younger patients has improved significantly, with some patients experiencing long-term disease-free survival.[2–7] At the same time, thanks to the promising results of combined induction conventional chemotherapy and rituximab, followed by rituximab maintenance, the therapeutic possibilities of elderly patients have also dramatically improved, with unprecedented levels of cytoreduction disclosed in minimal residual disease (MRD) studies.[8–11]

In addition, small molecules targeting specific signal pathways, including molecular alterations of the disease, are being incorporated into the therapeutic armamentarium and will further improve prognosis.[12] In the near future, more individualized approaches will take into account risk factors present at diagnosis, predictive biomarkers representing molecular alterations, as well as quality of the response assessed by molecular MRD analysis. In this article we will discuss our clinical approach to the management of MCL patients. First, we will present the criteria that allow a reliable diagnosis of MCL, and then we will discuss our personal algorithm and the rising questions that should help us to decide the best strategy of treatment in different clinical scenarios: first-line therapy for younger patients, for elderly (or unfit to receive high-dose chemotherapy) patients or for frail patients and the difficult challenge of salvage treatment of relapsed MCL in each of these different patient categories.

HOW TO DIAGNOSE A MCL?

The diagnosis of MCL is established according to the criteria of the WHO classification of hematological neoplasms. In general, histologic confirmation of diagnosis is mandatory and a lymph node biopsy is strongly recommended; in contrast, lymph node fine-needle biopsy is not appropriate. A bone marrow aspiration complemented using flow cytometry to identify the typical lymphoma immunophenotype and a bone marrow biopsy to quantify the percentage of infiltration are mandatory. Most tumors have a classic morphology of small–medium sized cells with irregular nuclei, dense chromatin and unapparent nucleoli. In addition to classic MCL, a blastoid variant of the disease has been described, characterized by high mitotic rate and particularly aggressive behavior with risk of central nervous system relapse, and is associated with INK4a/ARF deletions, TP53 mutations and complex karyotypes.[1,13–17] However, tumor cells may present with a spectrum of morphological variants, raising some difficulties in the differential diagnosis apart from chronic lymphocytic leukemia, marginal zone lymphomas, large B-cell lymphomas or blastic hematological proliferations. As an accurate histologic diagnosis is essential, second opinion by an experienced hematopathologist is advisable.[18]

Beside the classical immunophenotype (immunoglobulin M/D, CD19, CD20, CD22, CD43, CD79a, CD5 positive and CD23, CD10, CD200, BCL6 usually negative), the detection of cyclin D1

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overexpression or the chromosomal translocation t(11;14) is essential, as histomorphological phenotypes may differ significantly.[1] Nevertheless, rare cases of cyclin D1-negative variant of MCL have been recognized,[19] characterized by the same gene expression profile and secondary genomic alterations as classical MCL. In around 50% of these cases a cyclin D2 translocation may be detected.[20] SOX11, a transcription factor expressed in 90% of MCL, might also be applied to identify at least some of these cyclin D1-negative variants.[21] Moreover, Ki67 proliferative index staining is strongly recommended as a powerful prognostic indicator of long-term outcome.[5,18,22,23]

Finally, the classical laboratory evaluation comprises differential blood count, particularly leukocyte count, and standard serum chemistry analysis, including the determination of lactate dehydrogenase as one of the major risk parameters.[24]

HOW TO DEFINE THE STAGE AND PROGNOSIS OF MCL?

In order to define the stage of MCL, a computed tomography scan with iodine contrast of the neck, chest, abdomen and pelvis is mandatory. Positron emission tomography scan is not included in the consensus recommendations based on scarce data and especially limited therapeutic consequences, as the large majority of patients presents with an advanced-stage MCL (stages III–IV due to frequent bone marrow and/or gastrointestinal involvement).[25–27] Thus, only among the rare stage I–II patients positron emission tomography scan may be applied to confirm early-stage disease and guide localized treatment.[28]

Owing to the risk of central nervous system involvement in blastoid cases, cerebrospinal fluid evaluation might be considered at diagnosis for these patients. Cranial imaging with magnetic resonance is not usually required at first presentation, unless neurologic symptoms are present.[16,17] Additional diagnostics depends on the clinical presentation and includes an ear–nose–throat consultation and gastroscopy/colonoscopy, based on up to 60% asymptomatic infiltration of the bowel.[29] As the results from upper and lower endoscopy generally have only a modest impact on therapeutic decisions, they are mandatory only in limited stage or symptomatic patients and as confirmation of complete response within clinical trials.

After the diagnosis of an MCL, the classical International Prognostic Index is not suited to characterize its prognosis.[30] Instead, a new dedicated prognostic score, the MCL International Prognostic Index, allows to discriminate three prognostic subgroups: the low-risk group with a 5-year median overall survival (OS) of 60%, and the intermediate- and the high-risk group with a median OS of 51 and 29 months, respectively.[24] This score takes into account four parameters (age, performance status, lactate dehydrogenase and leukocyte count), could be easily calculated (see www.european-mcl.net/en/clinical_mipi.php) but proved to be effective also in a simplified categorized version (Table 1).[24,31] Although very effective in stratifying elderly patients, its usefulness is limited among youngest, as only a few patients under 65 years are classified in the high-risk group. Nevertheless, as MCL International Prognostic Index is highly applicable and has been validated in most independent series,[31–33] its use should be routinely applied in the clinical practice.[18]

IS THERE A PLACE FOR INITIAL WATCH AND WAIT?

Whereas most patients with MCL follow an aggressive clinical course associated with rapid progression, only temporary responses to chemotherapy and a high recurrence rate,[34] a minority of MCL cases (10–15%) will have an indolent behavior and may not need therapy for several years; in fact, a delayed treatment did not have an impact on the OS in this lower-risk group.[35] Most of these patients present with normal Eastern Cooperative Oncology Group performance status, normal serum lactate dehydrogenase level, splenomegaly, bone marrow and blood involvement, but without adenopathy. Nevertheless, a reliable diagnosis of such an indolent subtype is difficult to confirm, and most series are mainly based on a retrospective diagnosis.

Table 1. Simplified MIPI calculation

Points	*Age (years)*	*ECOG Performance Status*	*LDH/ULN*	*Leukocytes ($\times 10^9$/l)*
0	<50	0–1	<0.670	6700
1	50–59	—	0.670–0.999	6700–9999
2	60–69	2–4	1.000–1.499	10 000–14 999
3	>69	—	>1.499	>14 999
Risk stratification				
0–3 Points	Low risk			
4–5 Points	Intermediate risk			
6–11 Points	High risk			

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MIPI, Mantle Cell Lymphoma International Prognostic Index; ULN, upper limit of normal. For each prognostic factor, 0–3 points are given to each patient and points are summed up to define a category of risk.

Biomarker expression on tumor samples at diagnosis could give a more precise definition of these 'Watch and Wait' patients and are currently under evaluation: in fact, it would be worthwhile to recognize this patient subset upfront, especially in those frail elderly patients for whom a Watch and Wait approach is considered a serious option. Indolent MCLs predominantly show hypermutated immunoglobulin genes, noncomplex karyotypes and a peculiar gene expression profile (with a signature of 13 genes underexpressed in comparison with typical MCL).[36,37] In contrast, the role of transcription factor SOX11 expression is still controversial and not standardized as diagnostic tool, thus should not be applied alone to predict prognosis.[18,38,39]

In such selected patients, Watch and Wait is a valuable management approach and observation duration may vary from few months to more than a decade. These patients may undergo clinical evaluation every 3 months at least of the first 2 years, along with radiological evaluations in case of suspected progression or symptoms.[35] However, the clinical and biological studies on indolent MCL are still limited and further investigations are needed to clarify these issues.[18]

HOW TO DEFINE THE GROUP OF PATIENTS THAT MAY RECEIVE INTENSIFIED THERAPY?

Although no curative treatment is available for MCL so far, an intensive approach consisting of high-dose cytarabine and rituximab, followed by an autologous SCT, has been demonstrated to induce the highest response and survival rates in young and fit patients.[2,3,5–7,18] However, as MCL mostly affects elderly individuals, the toxic effects of treatment regimens are of particular concern, as underlying comorbidities or decreased organ function may compromise the eligibility for cytotoxic chemotherapy. Given that a good performance status and the absence of comorbidities are required for any intensified treatment aiming at complete remission (CR), a common approach consists of an upfront stratification of patients into younger (fit or unfit), elderly (fit or unfit) and frail categories. The Comprehensive Geriatric Assessment was demonstrated as a reliable tool for estimating life expectancy and tolerance of treatment to objectively identify patients eligible for a high-dose chemotherapy targeting at long-term control of the disease or patients for less intensive approaches only.[40,41] Thus, considering

the non-negligible toxicity of an autologous SCT program (even more severe if applied after intensive induction such as HyperCVAD[4,42,43]), we believe that high-dose therapy can be safely delivered only in younger and fit patients, usually <65 years but even up to 70 years for selected cases.[44] Therefore, a careful identification of patients eligible to autologous SCT is essential.

Moreover, as already stated, an early identification of the less common indolent variants of MCL would be valuable, as for this category of patients an intensive treatment may be spared.[35]

WHICH IS THE BEST TREATMENT OPTION IN THE GROUP OF YOUNGER FIT PATIENTS?

The major clinical trials of the last decade focused on improvement of the front-line treatment of MCL, leading to the definition of a 'gold standard' therapy for young and fit patients consisting of high-dose cytarabine and rituximab, followed by an autologous SCT.[2,3,5–7,18,45–47] First of all in CHOP-responding patients a consolidation with total body irradiation (TBI), high-dose cyclophosphamide and autologous SCT resulted in longer median progression-free survival (PFS 39 versus 17 months, $P = 0.011$) compared with a maintenance therapy with interferon-alpha. In a subsequent meta-analysis, OS was also superior in the autologous SCT arm after a longer follow-up.[48] Moreover, several phase II studies suggested that incorporation of high-dose cytarabine and rituximab to the induction regimen before autologous SCT leads to an increase in CR and PFS rates.[2,5,6,49] Finally, the recent European MCL Network younger phase III trial confirmed that an alternating induction of three courses of R-CHOP and R-DHAP followed by a high-dose cytarabine-containing myeloablative consolidation supported by autologous SCT achieved a significantly improved median time to treatment failure (TTF 88 versus 46 months, $P = 0.038$) and median OS (not reached versus 83 months, $P = 0.045$) in comparison with an R-CHOP induction followed by autologous SCT, with a comparable number of treatment-related deaths in both arms.[7] Impact of cytarabine on the TTF rate was closely linked to the quality of molecular remission, which was increased from 32 to 73% after induction.[50] Finally, for patients with compromised renal function or elderly, oxaliplatin could be a valuable alternative to cisplatin, considering its minor renal and also neural toxicity ('DHAOx' schedule instead of 'DHAP').[51]

Alternative effective immunochemotherapy induction regimens have been also explored outside of the context of an autologous SCT schedule. Rituximab-bendamustine (BR), either alone or in combination with cytarabine (R-BAC), showed excellent responses and survival rates, both in patients at diagnosis and relapsed MCL.[11,52,53] A randomized phase II trial is currently being performed by the Southwest Oncology Group, comparing BR versus R-HyperCVAD as upfront induction therapy before autologous SCT consolidation in younger patients (NCT01412879). However, the latter regimen seems to be more toxic and peripheral blood stem cell collection might be impaired.

The applied conditioning regimens before autologous SCT are similar to those used in other lymphoma subtypes, mainly BEAM or TBI-based.[3,5,6,47] Owing to the radiosensitivity of MCL cell lines, the role of TBI remains an important question. A small retrospective study suggested that TBI resulted in prolonged disease-free survival and OS compared with BEAM;[54] however, this observation has not been confirmed by a recent large survey.[55] A retrospective EBMT register study on more than 400 patients showed that TBI might benefit only for patients in partial response but not in CR after induction, with no significant improvement of OS.[56] Similarly in a comparative retrospective study including Nordic group, HOVON and European MCL Network protocols, TBI seems also to be beneficial only in the group of patients in partial response but not in CR.[57] Taken together, these studies suggest that TBI is not mandatory in patients in first CR but should be strongly considered in patients in partial response.[18] In contrast, the addition of rituximab during conditioning, as well as the benefit of the radioimmunotherapy (RIT), has not been demonstrated in interstudy comparisons.[2,5,58,59] Finally, integration of bendamustine into the BEAM regimen instead of carmustine (BeEAM) is currently explored in MCL.[60]

Besides autologous SCT-based regimens, another dose-intensified approach (R-HyperCVAD) with alternating R-CHOP-like and high-dose methotrexate/cytarabine cycles also achieved very high response and survival rates in a mono-center phase II study (overall response rate, ORR 97%, CR 87%, median TTF 4.6 years and 8-years OS 68%, among patients <65 years).[4] Unfortunately, these excellent results could not be replicated in multicenter approaches[42,43] and were never tested in a randomized, phase III trial. Moreover, this regimen is hampered by a significant therapy-associated toxicity, which led to a high dropout rate in the multicenter trial (63%). As yet no direct comparison has been performed between R-HyperCVAD and an autologous SCT-based approach: the only published report is a small retrospective analysis not powered to lead to reliable conclusions.[61] Finally, the recent combination of bortezomib to modified R-HyperCVAD has not yet demonstrated a clear superiority over the classical regimen.[62]

As no plateau in PFS curves has been observed even after such optimized treatments, and the achievement of molecular remission seems to be critical in MCL, the question of maintenance therapy has to be discussed in the setting of autologous SCT.[8,63] Although rituximab maintenance should be considered the new standard for elderly patients after R-CHOP induction,[10] these data still need to be confirmed for young patients in the context of intensive chemotherapy and autologous SCT. This question is currently addressed in the randomized *Lyma* trial (NCT00921414) and results are eagerly awaited. Thus, so far a maintenance therapy cannot be uniformly recommended after autologous SCT.[18] In this regards a recent phase II trial evaluating RIT consolidation with yttrium-90-ibritumomab tiuxetan (^{90}Y-IT) afterR-Hyper-CVAD resulted in unacceptable toxicity, advising against its use after high-dose chemotherapy.[64]

A rational algorithm for first-line treatment of young MCL patients is presented in Figure 1. Table 2A displays a list of the actively recruiting upfront clinical trials, whereas Table 3 describes the most important published clinical studies investigating first-line high-dose therapy in MCL.

IS ALLOGENEIC SCT A THERAPEUTIC OPTION IN FIRST LINE?

The approach of allogeneic SCT in MCL has emerged in the late 1990s, as highly toxic. Myeloablative allogeneic SCT could nevertheless achieve cure in some relapsed/refractory MCL patients.[65] Reduced-intensity conditioning regimens (RIC-allo), entailing lower toxicity and reduced transplant-related mortality, provided better results, making allogeneic SCT an option for a larger MCL population.[58] Although most authors agree that RIC-allo may be curative for some MCL patients, the paucity of literature does not allow any strong recommendations in favor of allogeneic SCT in first-line treatment of MCL. Most studies are mono-center reports or registry-based retrospective analysis and only one prospective trial is available.[58,65–69] In none of these studies, allogeneic SCT has been proved to be superior to autologous SCT. Moreover, the long-term disease control after rituximab and cytarabine-supplemented autologous SCT schemes along with the recent impressive efficacy and safety data coming from drugs targeting the B-cell-receptor pathway[70] are challenging the role of the more toxic allogeneic approaches. In conclusion, allogeneic SCT cannot be recommended upfront in MCL but may be considered for fit relapsed/refractory patients after an appropriate first-line treatment.[18] Whether an allogeneic

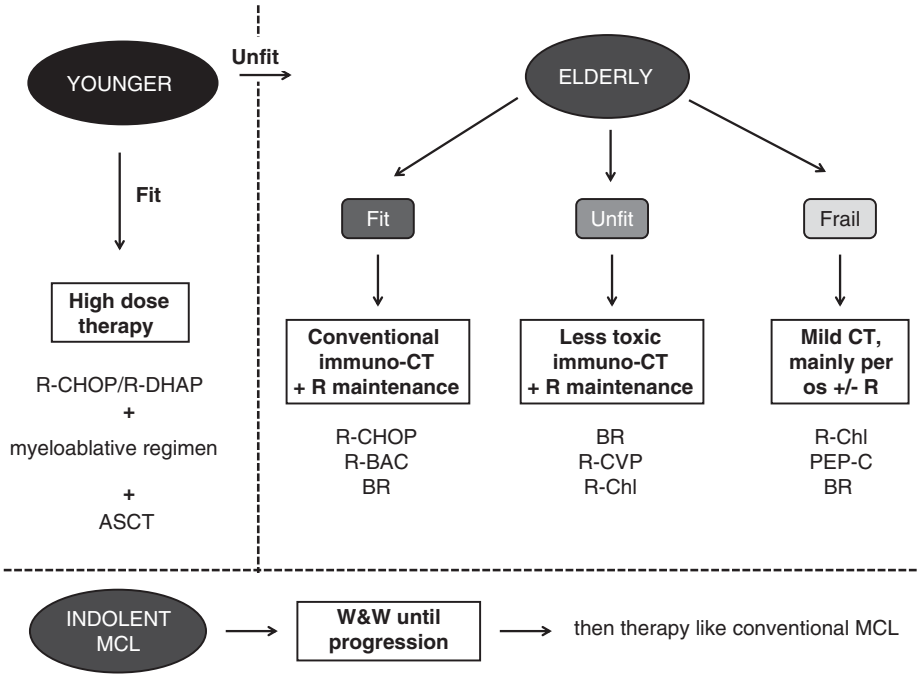

Figure 1. Therapeutic algorithm for first-line MCL patients. R, rituximab; CHOP, cyclophosphamide-doxorubicin-vincristine-prednisone; DHAP, dexamethasone-cytarabine-cisplatin; ASCT, autologous stem cell transplantation; CT, chemotherapy; BAC, bendamustine-cytarabine; B, bendamustine; CVP, cyclophosphamide-vincristine-prednisone; Chl, chlorambucil; PEP-C, metronomic prednisone-etoposide-procarbazine-cyclophosphamide; W&W, watch and wait.

SCT consolidation in first CR could confer a survival advantage for very high-risk MCL patients (for example, blastoid variant, elevated Ki67, TP53 mutations) is an intriguing hypothesis that still needs to be addressed in prospective trials and in the context of new targeted therapies.

WHICH ARE THE PREFERABLE TREATMENT OPTIONS IN ELDERLY PATIENTS OR UNFIT TO RECEIVE HIGH-DOSE CHEMOTHERAPY?

The standard first-line therapy for elderly MCL patients recently established consists of R-CHOP immunochemotherapy, followed by rituximab maintenance: such an approach resulted in a considerable improvement in response rates, MRD clearance and OS for patients not eligible to high-dose regimens.[10]

Both anthracycline (R-CHOP-like) and fludarabine-based (R-FC like) immunochemotherapy schedules already demonstrated efficacy for elderly fit patients with MCL.[49,71,72] On this basis, the European MCL Network conducted a large international phase III trial comparing R-CHOP with R-FC (followed by a second randomization between maintenance phase with interferon-alpha versus rituximab) for elderly patients.[10] Unexpectedly, the outcome of the fludarabine-containing regimen was disappointing: in fact, although CR rates after R-FC and R-CHOP were similar (40% versus 34%, $P = 0.10$), progressive disease was more frequent during R-FC (14% versus 5%). The median OS was also significantly inferior afterR-FC (4-year survival rate, 47% versus 62%, $P = 0.005$) and more patients in the fludarabine arm died due to relapsed lymphoma or infections. This inferior outcome is mostly due to a more frequent, long-lasting hematologic grade III–IV toxicity after R-FC. Thus, the use of upfront R-FC in elderly MCL patients is discouraged.[18] In contrast, rituximab maintenance reduced the risk of progression or death by 45% (58% patients in remission after 4 years versus 29% with interferon-alpha, $P = 0.01$), almost doubled duration of remission and significantly improved OS among patients responsive to R-CHOP.[10] In addition, promising data came also from two small series of elderly patients receiving maintenance rituximab after a reduced R-HyperCVAD ± bortezomib.[62,73] Thus, rituximab maintenance (one dose every 2 months until progression) should be offered to all patients responding to R-chemotherapy, especially R-CHOP induction.[18]

On the basis of the excellent performance of high-dose cytarabine containing induction arm of the European MCL Network Younger trial,[7] the current MCL R2 Elderly trial (EudraCT Number 2012-002542-20) randomizes patients to a standard induction with R-CHOP versus an alternating R-CHOP/R-HAD (rituximab, intermediate age-adjusted dose cytarabine and dexamethasone) arm.

Bendamustine combinations represent alternative attractive upfront regimens for elderly MCL patients. Notably, in a randomized first-line trial with 94 MCL patients, the BR schedule was at least as effective as R-CHOP (median PFS 35 versus 22 months, $P = 0.004$) and with fewer toxic effects (lower neutropenia, infections, polyneuropathy and alopecia), but OS was comparable in both study arms.[53] Furthermore, the promising activity of a new regimen combining rituximab, bendamustine and cytarabine (R-BAC) has been recently confirmed in primary and relapsed MCL (90% ORR with 83% CR on the total series of 40 patients), resulting in an excellent 2-year PFS of 70% for relapsed and 95% for first-line patients, respectively.[11] Currently, a phase II study of R-BAC accruing untreated elderly 'fit' (according to Comprehensive Geriatric Assessment) MCL patients is ongoing (EudraCT Number: 2011-005739-23).

Another candidate for combination with immunochemotherapy is bortezomib. Trials integrating the proteasome inhibitor with R-CHOP or into a doxorubicin, dexamethasone, chlorambucil and rituximab regimen (RiPAD + C) showed promising results, although safety issues should be still more extensively assessed.[74,75] Two clinical trials are currently ongoing, evaluating the combination of BR plus bortezomib or lenalidomide in first-line treatment of MCL patients (NCT01415752 and NCT00963534, respectively).

Table 2A. Actively recruiting clinical trials for MCL patients (first-line)

NCT code	*Study features*	*Estimated enrollment (patients)*	*Estimated primary completion date (month/years)*	*Therapeutic regimen*	*Sponsor*	*Location countries*
Phase III						
00209222	Phase III, randomized younger	360	12/2014	R-CHOP + TBI + ASCT versus R-CHOP/R-DHAP + HD-araC + ASCT	GLSG and EuMCLNeT	France, Germany, Poland
01865110	Phase III, randomized elderly	633	06/2021	R-CHOP versus R-CHOP/ R-HAD + maintenance rituximab versus rituximab/ lenalidomide	LYSARC and EuMCLNeT	France, Belgium, Germany, Italy, Netherlands, Portugal
EudraCT: 2009 01280725	Phase III, randomized younger	250	01/2015	R-CHOP + HD-araC + ASCT ± lenalidomide maintenance	FIL	Italy, Portugal
01776840	Phase III, randomized elderly	520	03/2018	BR versus BR + ibrutinib	Janssen Research and Development LLC	Worldwide
Phase II						
01412879	Phase II, randomized younger	180	12/2016	R-HyperCVAD + ASCT versus BR + ASCT	SWOG	USA
01415752	Phase II, randomized elderly	332	04/2015	BR ± bortezomib + rituximab maintenance ± lenalidomide	ECOG	USA
01662050	Phase II, single arm elderly	57	01/2014	R-BAC	FIL	Italy
00963534	Phase II, single arm elderly	60	09/2014	BR + lenalidomide	NLG	Denmark, Finland Norway, Sweden
01457144	Phase II, single arm elderly	76	04/2015	RiBVD	GOELAMS	France
00477412	Phase II, single arm both	110	04/2015	R-HyperCVAD + bortezomib	M.D. Anderson Cancer Center	USA
00114738	Phase II, single arm both	80	06/2016	R-EPOCH + bortezomib	NCI	USA
01472562	Phase II, single arm both	31	12/2014	Rituximab + lenalidomide	Weill Medical College of Cornell University	USA

Table 2B. Actively recruiting clinical trials for MCL patients (relapsed)

NCT code	*Study features*	*Estimated enrollment (patients)*	*Estimated primary completion date (month/years)*	*Therapeutic regimen*	*Sponsor*	*Location countries*
Phase III						
01449344	Phase III, randomized relapse	175	09/2016	R-HAD versus R-HADB	EuMCLNet	France, Germany
01646021	Phase III, randomized relapse	280	08/2014	Ibrutinib versus Temsirolimus	Janssen Research and Development LLC	Wordwide
Phase II						
01078142	Phase I/II, single arm relapse	72	03/2014	BERT	GLSG and EuMCLNet	Germany
01389427	Phase I/II, single group assignment relapse	63	06/2013	R.CHOP or R-FC or R-HAD + Temsilorimus	GOELAMS	France
01838434	Phase I/II, randomized both	99	08/2017	Rituximab and Lenalidomide ± idelalisib	Alliance for Clinical Trials in Oncology	USA
00513955	Phase II, randomized both	90	08/2014	CHOP ± bortezomib	Plymouth Hospitals NHS Trust	UK
01439750	Phase I/II, single arm elderly	50	10/2014	Rituximab + bortezomib + cladribine	Milton S. Hershey Medical Center	USA
01880567	Phase II, single arm both	50	12/2019	Rituximab + ibrutinib	M.D. Anderson Cancer Center	USA
01497275	Phase II, single arm both	35	03/2015	Rituximab + ^{90}Y-ibritumumab tiutexan + bortezomib	Duke University	USA
01652144	Phase II, single arm both	30	08/2014	AT7519M	NCIC Clinical Trials Group	Canada
01695941	Phase II, single arm both	24	08/2015	Alisertib + bortezomib + rituximab	NCI	USA
01504776	Phase II, single arm both	24	04/2014	Panobinostat + bortezomib	Anand Jillella	USA

Abbreviations: ASCT, autologous stem cell transplantation; B, bendamustine; BAC, bendamustine-cytarabine; BR, rituximab-bendamustine; CHOP, cyclophosphamide-doxorubicin-vincristine-prednisone; DHAP, dexamethasone-cytarabine-cisplatin; ECOG, Eastern Cooperative Oncology Group; EPOCH, ethoposide-prednisone-vincristine-cyclophosphamide-doxorubicin; EuMCLNet, European MCL Network; FIL, Fondazione Italiana Linfomi; GLSG,German Low-Grade Lymphoma Study Group; GOELAMS, Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang; HAD, cytarabine-dexamethasone; HD-araC, high-dose cytarabine; HyperCVAD, hyperfractionated cyclophosphamide-vincristine-doxorubicin-dexamethasone + methotrexate-cytarabine; LYSARC, The Lymphoma Academic Research Organization; MCL, mantle cell lymphoma; NCI, National Cancer Institute; NCIC, National Cancer Institute of Canada; NCT, national clinical trial; NLG, Nordic Lymphoma Group; R, rituximab; RiBVD, rituximab-bendamustine-bortezomib-dexamethasone; SWOG, South West Ongology Group; TBI, total body irradiation. Details of the studies can be found at the internet site: http://www.clinicaltrials.gov.

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