

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 ($\pm$ 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 cytorreduction 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

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.

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.

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- α . 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 *Lyra* 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 (⁹⁰Y-IT) after R-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 pathway⁷⁰ 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

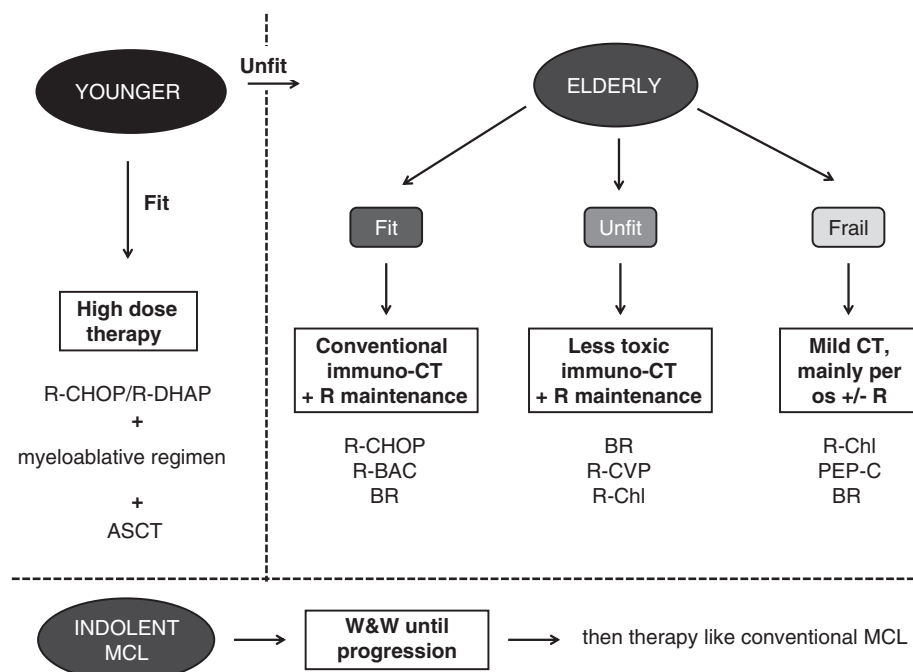


Figure 1. Therapeutic algorithm for first-line MCL patients. R, rituximab; CHOP, cyclophosphamide-doxorubicin-vincristine-prednisone; DHAP, dexamethasone-cytarabine-cisplatin; ASCT, autologous stem cell transplantation; CT, chemotherapy; BAC, bendamustine-cytarabine; B, bendamustine; CVP, cyclophosphamide-vincristine-prednisone; 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 after R-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
<i>Phase III</i> 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
<i>Phase II</i> 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 00963534	Phase II, single arm elderly Phase II, single arm elderly	57 60	01/2014 09/2014	R-BAC BR + lenalidomide	FIL NLG	Italy Denmark, Finland Norway, Sweden
01457144 00477412	Phase II, single arm elderly Phase II, single arm both	76 110	04/2015 04/2015	RiBVD R-HyperCVAD + bortezomib	GOELAMS M.D. Anderson Cancer Center	France USA
00114738 01472562	Phase II, single arm both Phase II, single arm both	80 31	06/2016 12/2014	R-EPOCH + bortezomib Rituximab + lenalidomide	NCI Weill Medical College of Cornell University	USA 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
<i>Phase III</i> 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 Tamsilolimus	Janssen Research and Development LLC	Worldwide
<i>Phase II</i> 01078142 01389427	Phase I/II, single arm relapse Phase I/II, single group assignment relapse	72 63	03/2014 06/2013	BERT R-CHOP or R-FC or R-HAD + Tamsilolimus	GLSG and EuMCLNet GOELAMS	Germany 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 01504776	Phase II, single arm both Phase II, single arm both	24 24	08/2015 04/2014	Alisertib + bortezomib + rituximab Panobinostat + bortezomib	NCI Anand Jillella	USA 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, etoposide-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 Oncology Group; TBI, total body irradiation. Details of the studies can be found at the internet site: <http://www.clinicaltrials.gov>.

Table 3. Published clinical studies investigating first-line dose-intensified therapy in MCL

Author	Study features	Evaluable patients	Therapeutic regimen	ORR% (CR%)	Median PFS (years)	Median OS (years)	Dropout rate	TRM	Secondary tumor rate
ASCT based regimens									
Dreyling et al. ³	Phase III, randomized	122	R-CHOP + TBI + ASCT versus R-CHOP + TBI + interferon- α	98 (81) versus 99 (37)	3.3 versus 1.4	NR (83% 3-y OS) versus NR (77% 3-y OS)	13% versus na	5% versus 0%	5%
Hermine et al. ⁷	Phase III, randomized	455	R-CHOP + TBI + ASCT versus R-CHOP/R-DHAP + HD-araC + ASCT	98 (63) versus 99 (61)	3.8 versus 7.3	6.8 versus NR	na	4%	na
Damon et al. ⁴⁵	Phase II	77	R-CHOP + methotrexate + HD-araC/etoposide + ASCT	88 (69)	NR (56% 5-y PFS)	NR (64% 5-y OS)	13%	3%	na
Van't Veer et al. ⁴⁶	Phase II	87	R-CHOP + HD-araC + ASCT	70 (64)	NR (36% 4-y PFS)	NR (66% 4-y OS)	30%	5%	na
Geisler et al. ⁵	Phase II	160	R-Maxi-CHOP + HD-araC + ASCT	96 (54)	7.4	NR (64% 10-y OS)	9%	5%	4%
Delarue et al. ⁶	Phase II	60	R-CHOP/R-DHAP + HD-araC + ASCT	100 (96)	6.9	NR (75% 5-y OS)	18%	1.5%	18%
Touzeau et al. ⁴⁷	Retrospective	396	Different ASCT-based schedules	83 (77)	NR (67% 3-y PFS)	NR (83% 3-y OS)	na	2.5%	6%
Non-ASCT based regimens									
Romaguera et al. ⁴	Phase II, monocentric	97	R-HyperCVAD	97 (87)	4.6	NR (64% 10-y OS)	29%	8%	5%
Merli et al. ⁴²	Phase II, multicentric	60	R-HyperCVAD	83 (72)	NR (73% 5-y PFS)	NR (61% 5-y OS)	63%	6.5%	1.5%
Bernstein et al. ⁴³	Phase II, multicentric	49	R-HyperCVAD	86 (55)	4.8	6.8	39%	2%	4%

Abbreviations: ASCT, autologous stem cell transplantation; CHOP, cyclophosphamide-doxorubicin-vincristine-prednisone; CR, complete response; DHAP, dexamethasone-cytarabine-cisplatin; HD-araC, high-dose cytarabine; HyperCVAD, hyperfractionated cyclophosphamide-vincristine-doxorubicin-dexamethasone + methotrexate-cytarabine; MCL, mantle cell lymphoma; na, not available; ne, not evaluable; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, rituximab; TBI, total body irradiation; y, years.

Promising data have been also achieved by RIT consolidation in elderly patients. Four cycles of R-CHOP followed by ^{90}Y -IT compared favorably with historical results of six cycles of R-CHOP in patients with previously untreated MCL. This regimen was well tolerated and may be applicable to most patients.⁷⁶

A rational algorithm for first-line treatment of elderly MCL patients is presented in Figure 1. Table 2A displays a list of the actively recruiting clinical trials, whereas Table 4 describes the most important published clinical studies investigating first-line conventional dose therapy in MCL.

WHAT ARE THE TREATMENT OPTIONS FOR FRAIL PATIENTS?

If treatment of elderly frail patients is considered, this should consist of mild immunochemotherapy usually very well tolerated, for example, chlorambucil combined with rituximab.^{77,78} Another effective and feasible oral metronomic combination is PEP-C (prednisone, etoposide, procarbazine and cyclophosphamide).⁷⁹ Such treatments should be applied with the perspective that cure will not be obtained, and that palliation should aim at improvement of quality of life.¹⁸ Bendamustine is also an active monotherapy that is well tolerated in older or frail patients and might be discussed in combination with rituximab in selected cases.^{53,80} On the other hand, single-agent therapy with rituximab (four gifts at weekly intervals) is not recommended, as only low ORR of 27% with 3% CR have been obtained.⁸¹

In selected cases of frail patients, it may be tempting to consider a monotherapy or combination with low-dose chemotherapy approach with targeted drugs, such as temsirolimus, bortezomib, lenalidomide, thalidomide, ibrutinib or new monoclonal antibodies, given their efficacy and acceptable toxicity profile. Unfortunately, no such study has been performed in this subset of patients so far and thus a clear recommendation cannot be given. A rational algorithm for first-line treatment of frail MCL patients is presented in Figure 1.

HOW TO TREAT REFRACTORY/RELAPSING PATIENTS?

Among younger patients, considering the modest efficacy and the increased toxicity of an autologous SCT approach in relapsed

MCL,⁵⁸ such treatment should be offered only to those who did not receive an appropriate first-line therapy. On the other hand, as allogeneic SCT, despite its still high treatment-related mortality and relapse rates, remains the only approach associated with long-term remissions in relapsed MCL,^{58,67,69} such a treatment should be discussed with all young and fit patients relapsing after an autologous SCT. Given the high treatment-related toxicity of the myeloablative conditioning especially among MCL patients, and the demonstration of a *graft-versus-lymphoma* effect based on responses to donor lymphocyte infusions, a non-myeloablative approach without T-depletion is advisable.^{18,65,67} Different reports described a significant proportion of patients cured with non-myeloablative allogeneic SCT^{58,67} and super imposable efficacy results from myeloablative conditioning and non-myeloablative in MCL are suggested by a retrospective register analysis of more than 200 refractory patients.⁶⁹ An early referral to allogeneic SCT is especially warranted for relapsed patients with high Ki67 levels refractory to conventional chemotherapy or autologous SCT because at least a quarter of these very high-risk patients may actually be cured by allogeneic SCT.⁶⁹ In younger patients without an human leukocyte antigen-matched donor, a haplo-identical transplantation has achieved promising results in recent studies.⁸² However, this approach is still experimental and should be performed in the context of clinical studies.

Elderly or unfit patients with refractory/relapsing MCL still represent a demanding challenge for the hemato-oncologist. The dismal prognosis and the absence of generally accepted therapeutic standards hamper the clinical management of such cases. As a general concept no curative treatment can be offered so far, aside from allogeneic SCT. Thus, the therapeutic goal should be the prolonged disease control, balancing the expected efficacy with the expected risk of toxicity and reduced quality of life. However numerous new, targeted options¹² in combination with rituximab-supplemented chemotherapy represent highly effective weaponry, able to achieve again a decent clinical response in the majority of relapsing patients.

Second-line therapy should be adapted to the age and performance status of the patient; therefore, a Comprehensive Geriatric Assessment re-evaluation may be performed before selecting a salvage treatment. Owing to the aggressiveness of the

Table 4. Published clinical studies investigating first-line conventional dose therapy in MCL

Author	Study features	Evaluable patients	Therapeutic regimen	ORR% (CR%)	Median PFS (months)	2-Years OS
<i>Conventional immunochemotherapy</i>						
Lenz <i>et al.</i> ⁴⁹	Phase III, randomized	112	CHOP versus R-CHOP	75 (7) versus 94 (34)	21 versus 14 (TTF)	76% versus 76%
Herold <i>et al.</i> ⁸⁰	Phase III, randomized	162 (43 MCL)	BOP versus COP	66 (22) versus 76 (20)	NR versus 28 (TTP) ^a	61% versus 46% (5-y OS) ^a
Herold <i>et al.</i> ¹²²	Phase III, randomized	90	MCP versus R-MCP	63 (15) versus 71 (32)	18 versus 20	52% versus 55% (4-y OS)
Gressin <i>et al.</i> ¹²³	Phase II	113	Rituximab-VADC	73 (46)	16 (no ASCT) 58 (ASCT) ^b	62% (3-y OS) ^b
Sachanas <i>et al.</i> ⁷⁸	Phase II	20	Rituximab-chlorambucil	95 (90)	89% (3-y PFS)	95% (3-y OS)
Kluin-Nelemans <i>et al.</i> ¹⁰	Phase III, randomized	485	Induction: R-CHOP versus R-FC Maintenance: rituximab versus interferon-alpha	86 (34) versus 78 (40) –	28 versus 28 (TTF) 58% versus 29% (4-y DOR)	62% versus 47% (4-y OS) 79% versus 67% (4-y OS)
Rummel <i>et al.</i> ⁵²	Phase III, randomized	514 (94 MCL)	R-CHOP versus rituximab-bendamustine	91 (30) versus 93 (40)	21 versus 35	'No differences'
<i>Combination with new drugs</i>						
Ruan <i>et al.</i> ⁷⁴	Phase II	36	R-CHOP + bortezomib	91 (72)	44% (2-y PFS)	86%
Houot <i>et al.</i> ⁷⁵	Phase II	39	Rituximab, doxorubicin, dexamethasone, chlorambucil, bortezomib	79 (59)	26	69%
Smith <i>et al.</i> ⁷⁶	Phase II	50	R-CHOP + 90Y-ibritumumab tiuxetan	64 (46)	31 (TTF)	73% (5-y OS)

Abbreviations: ASCT, autologous stem cell transplantation; BOP, bendamustine-vincristine-prednisone; CHOP, cyclophosphamide-doxorubicin-vincristine-prednisolone; COP, cyclophosphamide-vincristine-prednisone; CR, complete response; DOR, duration of response; FC, fludarabine-cyclophosphamide; MCL, mantle cell lymphoma; MCP, mitoxantrone-chlorambucil-prednisone; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, rituximab; TTF, time to treatment failure; TTP, time to progression; VADC, vincristine-doxorubicin-dexamethasone-chlorambucil; y, years. ^aData derived from the overall population of the study, not exclusively from patients with MCL. ^bForty-nine patients received ASCT consolidation.

disease, repetition of the first-line treatment is usually not advisable, unless a long-lasting remission was previously achieved, especially in elderly people. In fit patients, non-cross resistant drugs should be preferred as salvage treatment, for example, regimens containing rituximab, cytarabine and/or bendamustine, if possible in combination with a molecular approach such as bortezomib, lenalidomide or temsirolimus, an mammalian target of rapamycin inhibitor registered in Europe (BR, R-BAC, R-HADB, BERT, R-2B regimens).^{11,53,83–85} A tailored therapy concept, based on individual risk profile, for example, elevated Ki67 levels,^{5,22,23} might favor a cytarabine-based approach plus bortezomib (R-HADB) or combined with bendamustine (R-BAC) for fit patients, whereas a bendamustine-based regimen in combination with temsirolimus (BERT) or lenalidomide (R-2B) appears more suitable to elderly patients with a more indolent presentation. However, as these recommendations on tailored therapies are not evidence-based, an enrollment of these patients in clinical trials is highly recommended: a list of the actively recruiting clinical trials for relapsed MCL patients is presented in Table 2B. Especially during treatment of relapsed patients, an appropriate pre-emptive use of growth factors, according to the current guidelines (for example, <http://www.nccn.org/>), is recommended.

Nevertheless, although high response rates can now be obtained also in relapsing patients, survival curves do not display any plateau, and almost all patients will finally relapse. Limited data are available on rituximab maintenance in relapsed patients⁸⁶ and data of RIT consolidation come from a single, not homogeneous series.⁸⁷ Thus, it is crucial to enroll relapsed MCL patients into clinical trials implementing new molecules or consolidation concepts (for example, allogeneic SCT, RIT, maintenance with new drugs) to maintain long-lasting remissions.

On the other hand, in frail patients or subsequent relapse monotherapies with targeted drugs (in particular temsirolimus, bortezomib, lenalidomide, thalidomide or ibrutinib in the context of a clinical trial),^{70,88–94} as well as well tolerable combinations with rituximab, steroids or low-dose chemotherapy and palliative

radiotherapy should be considered. Oral palliative combinations, such as the metronomic PEP-C,^{79,95} could be also useful options in this setting. At the same time a multidisciplinary palliative support should be considered.

A rational algorithm for relapse treatment of MCL patients is presented in Figures 2 and 3. Table 2B displays a list of the actively recruiting relapse clinical trials, whereas Table 5 describes the most important published clinical studies investigating relapse therapy in MCL, comprising targeted drug monotherapies and associations.

FUTURE PERSPECTIVES

New maintenance strategies

Given the promising results obtained with rituximab maintenance after R-CHOP in elderly patients,¹⁰ considerable efforts are being made to further develop strategies to maintain clinical responses. In fact rituximab maintenance after first-line treatment is currently being investigated also in younger patients, after either autologous SCT regimens or conventional chemotherapy.^{96,97}

In addition to rituximab, other candidates might be suitable for maintenance therapy. The manageable toxicity and the oral formulation of lenalidomide, along with its efficacy, make this drug an attractive option in the context of maintenance regimens specifically in the elderly population, either alone or in combination with rituximab.^{93,94} Two phase II trials are presently investigating lenalidomide maintenance after a R-2B schema for elderly first-line or relapsed patients, respectively (NCT00963534⁸⁵) and NCT01737177), whereas the randomized phase III trial FIL-MCL0208 is addressing this issue in young patients after autologous SCT (EudraCT Number 2009-012807-25). Moreover, a combined lenalidomide-rituximab maintenance is being tested in two first-line trials after a BR ± bortezomib schema (phase II, Eastern Cooperative Oncology Group E1411—NCT01415752) or after an R-CHOP versus alternating R-CHOP/R-HAD induction regimen (phase III, European MCL Network MCL R2 Elderly—EudraCT Number 2012-002542-20).

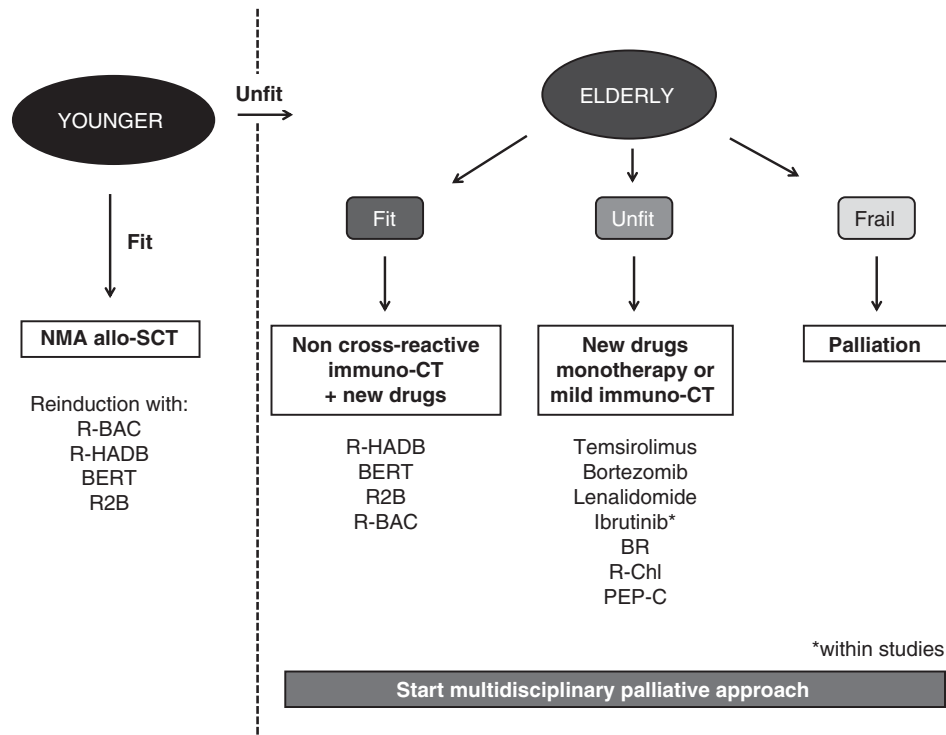


Figure 2. Therapeutic algorithm for second-line MCL patients. B, bendamustine; BAC, bendamustine-cytarabine; BERT, bendamustine-rituximab-temsirolimus; Chl, chlorambucil; CT, chemotherapy; HADB, cytarabine-dexamethasone-bortezomib; NMA allo-SCT, non-myeloablative allogeneic transplantation; PEP-C, metronomic prednisone-etoposide-procarbazine-cyclophosphamide; R, rituximab; R-2B, rituximab-lenalidomide-bendamustine.

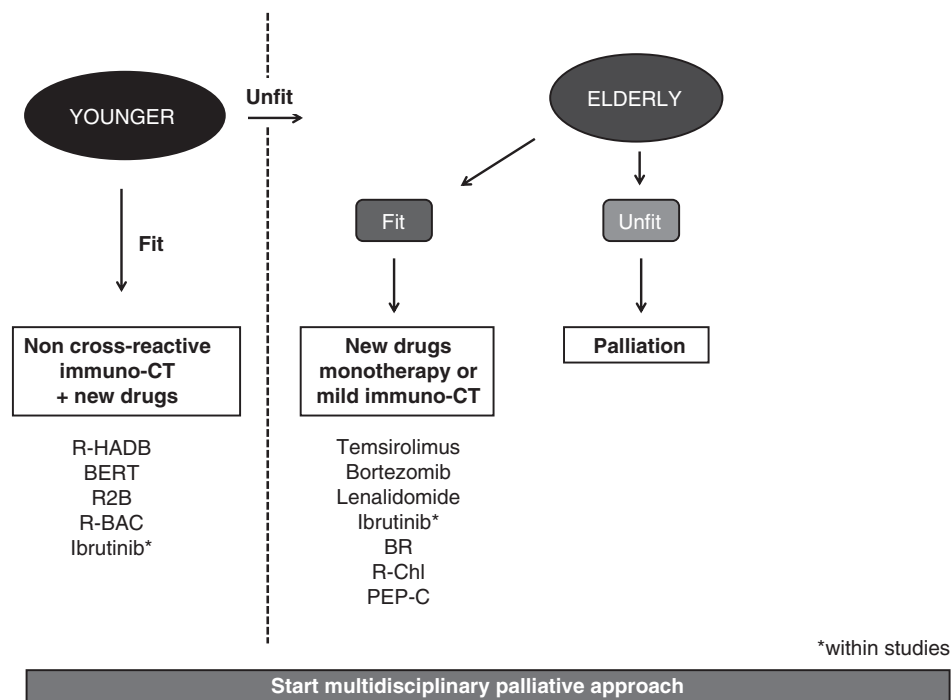


Figure 3. Therapeutic algorithm for further lines MCL patients. B, bendamustine; BAC, bendamustine-cytarabine; BERT, bendamustine-rituximab-temsirolimus; Chl, chlorambucil; CT, chemotherapy; HADB, cytarabine-dexamethasone-bortezomib; PEP-C, metronomic prednisone-etoposide-procarbazine-cyclophosphamide; R, rituximab; R-2B, rituximab-lenalidomide-bendamustine.

Table 5. Published clinical studies investigating relapse therapy in MCL

Author	Study features	Evaluable patients	Therapeutic regimen	ORR% (CR%)	Median PFS (months)	Median OS (months)
Conventional immunochemotherapy						
Forstpointner <i>et al.</i> ⁷²	Phase III, randomized	128 (48 MCL)	FCM versus R-FCM	46 (0) versus 58 (29)	8 versus 4	11 versus NR (65% 2-y OS)
Rummel <i>et al.</i> ¹²⁴	Phase III, randomized	208 (43 MCL)	Rituximab-bendamustine versus rituximab-fludarabine	84 (39) ^a versus 53 (16) ^a	30 ^a versus 11 ^a	'No differences' ^a
Morschhauser <i>et al.</i> ¹²⁵	Phase II	18 + 12	PDG	44 (22)	8.5	NR (76% 2-y OS)
Rodriguez <i>et al.</i> ¹²⁶	Phase II	14	DG	36 (18)	3	15.6
Wang <i>et al.</i> ³⁸	Phase II	29	Gemcitabine, oxaliplatin, rituximab	85 (64)	45% (1-y PFS)	58% (1-y OS)
Garbo <i>et al.</i> ¹²⁷	Phase II	16	R-HyperCVD	93 (45)	11	1900%
Visco <i>et al.</i> ¹¹	Phase II	20 ^b + 20	Gemcitabine, mitoxantrone, rituximab	47 (20)	54% (1-y PFS)	57% (1-y OS)
			Rituximab, bendamustine, cytarabine	100 (95)	first-line 95% (2-y PFS)	na
				80 (70)	relapse 70% (2-y PFS)	
Proteasome inhibitors						
Goy <i>et al.</i> ⁸⁸	Phase II	141	Bortezomib	33 (8)	6.7 (TTP)	23.5%
Baiocchi <i>et al.</i> ¹²⁸	Phase II	13	Bortezomib, rituximab	29 (29)	1.9	na
Lamm <i>et al.</i> ¹²⁹	Phase II	16	Bortezomib, rituximab, dexamethasone	81 (44)	12.1	38.6
Weigert <i>et al.</i> ⁸³	Retrospective	8	Rituximab, high-dose cytarabine, dexamethasone, bortezomib	50 (25)	5	15.5
Gerecitano <i>et al.</i> ¹³⁰	Phase I	10	Rituximab, cyclophosphamide, prednisone, bortezomib	60 (50)	na	na
Friedberg <i>et al.</i> ¹³¹	Phase II	7	Bendamustine, rituximab, bortezomib	71 (na)	na	na
Kouroukis <i>et al.</i> ¹³²	Phase II	25	Bortezomib, gemcitabine	60 (11)	11.4	na
mTOR inhibitors						
Witzig <i>et al.</i> ¹³³	Phase II	34	Temsirolimus	38 (3)	6.5 (TTP)	12
Ansell <i>et al.</i> ¹³⁴	Phase II	27	Temsirolimus	41 (4)	6 (TTP)	14
Hess <i>et al.</i> ⁵⁹	Phase III, randomized	54	Temsirolimus 175 mg per 75 mg	22 (2)	4.8	1280%
		54	Temsirolimus 175 mg per 25 mg	6 (0)	3.4	1000%
		53	Investigator's choice	2 (2)	1.9	970%
Ansell <i>et al.</i> ⁹¹	Phase II	69	Temsirolimus, rituximab	59 (19)	9.7	29.5
Renner <i>et al.</i> ¹³⁵	Phase II	35	Everolimus	20 (6)	5.5	na
Immunomodulatory rugs						
Zinzani <i>et al.</i> ⁹²	Phase II	57	Lenalidomide	35 (12)	8.8	NR
Goy <i>et al.</i> ⁹⁴	Phase II	134	Lenalidomide	28 (8)	4	19%
Wang <i>et al.</i> ⁹³	Phase II	44	Lenalidomide, rituximab	57 (36)	11.1	24.3
Zaja <i>et al.</i> ¹³⁶	Phase II	33	Lenalidomide, dexamethasone	52 (24)	12	20
Harel <i>et al.</i> ⁹⁰	Retrospective	58	Thalidomide ± bortezomib ± rituximab	50 (21)	NR (1-y TTF 29%)	NR (1-y OS 62%)
Ruan <i>et al.</i> ⁹⁵	Phase II	22	Metronomic prednisone, etoposide, procarbazine, cyclophosphamide, rituximab, thalidomide	73 (32)	10	NR (2-y OS 45%)
Antibody-based approaches						
Wang <i>et al.</i> ¹³⁷	Phase II	32	⁹⁰ Y-ibritumumab tiuxetan	31 (16)	6 (EFS)	21
Ferrero <i>et al.</i> ⁸⁷	Phase II	15 ^c + 30 ^c	⁹⁰ Y-ibritumumab tiuxetan	40 (20)	3.7	13.8
				72 (38)	8.9	32.2
Morschhauser <i>et al.</i> ¹¹³	Phase II	40 (15 MCL)	GA-101	27 (13)	2.7 ^a	na
Viardot <i>et al.</i> ¹¹⁵	Phase I	7	Blinatumomab	43 (14)	na	na
BCR signalling						
Wang <i>et al.</i> ⁷⁰	Phase II	111	Ibrutinib	68 (21)	13.9	NR (1.5-y OS 58%)
Kahl <i>et al.</i> ¹¹⁰	Phase I	16	Cal-101	62 (na)	3 (DOR)	na
Various						
Lin <i>et al.</i> ¹¹⁷	Phase I	10 ^d	Flavopiridol, fludarabine	80 (70)	21.9	na
Holkova <i>et al.</i> ¹¹⁸	Phase I	6	Flavopiridol, bortezomib	33 (17)	na	na
Davids <i>et al.</i> ¹²¹	Phase I	32 (8 MCL)	ABT-199	100 (0)	na	na
Evens <i>et al.</i> ¹²⁰	Phase II	11	Abexinostat	27 (na)	4	na

Abbreviations: CHOP, cyclophosphamide-doxorubicin-vincristine-prednisone; CR, complete response; DOR, duration of response; EFS, event-free survival; FCM, fludarabine-cyclophosphamide-mitoxantrone; HyperCVD, hyperfractionated cyclophosphamide-vincristine-doxorubicin-dexamethasone + + methotrexate-cytarabine; MCL, mantle cell lymphoma; na, not available; NR, not reached; ORR, overall response rate; OS, overall survival; (P)DG, (cisplatin)-dexamethasone-gemcitabine; PFS, progression-free survival; R, rituximab; TTF, time to treatment failure; TTP, time to progression; y, years. ^aData derived from the overall population of the study, not exclusively from patients with MCL. ^bTwenty patients received the schema as first-line therapy. ^cFifteen patients received the antibody as relapse monotherapy, 30 patients as consolidation after salvage treatment. ^dSix patients received the schema as first-line therapy.

In addition, despite some concerns about its cumulative neurotoxicity, bortezomib maintenance is currently tested in the HOVON 75 trial for young patients after high-dose induction therapy and autologous SCT (EudraCT Number 2006-000386-11).

Tailored treatment

As the clinical course of MCL can deeply vary among patients, there is an urgent need for reliable tools to assess the quality of

response after treatment and to estimate the subsequent relapse risk. Only such tools will allow a personalized therapy offered to individual patients, based on their actual risk of early relapse. PCR-based MRD analysis represents a standardized molecular approach,⁹⁸ which was largely superior to clinical remission criteria to predict relapse after a successful treatment.⁸ Thus, a MRD-driven pre-emptive rituximab strategy has been proposed in a small series of autotransplanted MCL patients^{99,100} and is currently under evaluation in another phase II trial after autologous SCT.¹⁰¹

Despite promising results, no randomized trials are available so far comparing this approach to conventional treatment. Thus, such a strategy cannot yet be recommended for clinical practice.¹⁸

Similar convincing results on large patient series have not been described for MRD analysis using multicolor flow cytometry.^{102,103} Although multicolor flow cytometry is a highly valuable method for accurate initial staging in MCL, this method was less sensitive for follow-up MRD analysis because of the immunophenotypical heterogeneity of MCL.¹⁰³ However, in the near future the situation might change through the standardized application of multicolor technique and novel antigen combinations, allowing a more precise detection of phenotypic aberrations even in low subpopulations.¹⁰⁴

Positron emission tomography imaging is a promising tool to precisely assess the quality of treatment response and has been proven to be predictive in small, mainly retrospective, series of MCL patients.^{26,27,105,106} Thus, a prospective study investigating positron emission tomography-based tailored therapy is advisable and is currently investigated in the *Lyma* trial (NCT00921414). Given the lack of available data, such a strategy currently cannot be recommended for clinical practice.

Finally, a treatment modulation on the basis of clinical or biological risk factors assessed at diagnosis (for example, MCL International Prognostic Index risk and Ki67 levels) deserves to be tested in prospective trials, as outlined by the Nordic Lymphoma Group MCL5 trial.¹⁰⁷

Innovative molecular targeted approaches

The growing insights into the molecular biology of MCL led to the systematic exploration of targeted approaches.^{12,108} Many new compounds have been tested and are currently being tested in MCL within clinical trials (Tables 2A, B and 5).

Bruton's tyrosine kinase is an essential component of the B-cell-receptor signaling pathway; its covalent oral inhibitor ibrutinib showed durable single-agent efficacy in relapsed or refractory MCL.⁷⁰ The impressive data from an international phase II trial on heavily pre-treated MCL patients described great efficacy and excellent tolerability: ORR was 68% (21% CR) with a median duration of response of 17.5 months, median PFS of 13.9 months and an estimated OS rate of 58% at 18 months. Prior treatment with bortezomib had no effect on the response rate. Moreover, ibrutinib monotherapy demonstrated to be feasible and safe: the most common adverse events were mild or moderate diarrhea, fatigue and nausea. Grade 3 or higher hematologic events were infrequent and included neutropenia (16%), thrombocytopenia (11%) and anemia (10%). Two phase III trials are currently ongoing, comparing ibrutinib versus temsirolimus monotherapies in relapsed patients (NCT01646021) and assessing a BR schedule $\pm$ ibrutinib in first-line (NCT01776840).

Another antagonist of the BCR signal cascade, CAL-101, a specific inhibitor of phosphatidylinositol 3-kinase delta isoform, showed profound activity in a large phase II trial of indolent non-Hodgkin's lymphomas¹⁰⁹ and is currently being tested in phase I/II trials in MCL patients: although a promising ORR of 62% was reported,¹¹⁰ mature results on remission duration are not yet available.

New monoclonal anti-CD20 antibodies (mAB), such as GA-101 (obinutuzumab) and ofatumumab, are currently being investigated in clinical trials; however, data on MCL are still limited to small patient series.^{111–113} Other intriguing approaches are the bispecific anti-CD19/anti-CD3 mAB, showing a high efficacy in a phase I/II trial particularly in MCL patients^{114,115} and the toxin-immunoconjugated mAB, such as the anti-CD79b DCDS4501A.¹¹⁶ Nevertheless, additional studies on larger patient cohorts are warranted.

Two cell cycle-targeted drugs (direct inhibitors of cyclin-dependent kinase 4 and 6, flavopiridol and PD0332991) showed

activity in relapsed MCL alone and in combination with fludarabine, rituximab or bortezomib.^{117–119} Finally, promising results come also from oral second-generation BCL-2 specific BH3 mimetic ABT-199 and a novel oral pan Histone Deacetylase Inhibitor Abexinostat.^{120,121}

CONFLICT OF INTEREST

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