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REVIEW ARTICLE

Mantle cell lymphoma—Update on molecular biology, prognostication and treatment approaches

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Abstract

Mantle cell lymphoma (MCL) is clinically characterized by its heterogenous behavior with courses ranging from indolent cases that do not require therapy for years to highly aggressive MCL with very limited prognosis. The development and implementation of new targeted and immunotherapeutic approaches have already improved therapeutic options especially for refractory or relapsed disease. Nevertheless, to further optimize MCL treatment, early identification of individual risk profile and risk-adapted, patient-tailored choice of therapeutic strategy needs to be prospectively incorporated in clinical patient management. This review summarizes the current knowledge and standard of care regarding biology and clinical management of MCL, highlighting the implementation of new therapeutic approaches especially targeting the immune system.

KEYWORDS
MCL, pathogenesis, prognostication, therapy

1 | INTRODUCTION

Mantle cell lymphoma (MCL) is clinically characterized by its heterogenous behavior with courses ranging from indolent cases that do not require therapy for years to highly aggressive MCL with very limited prognosis.[1] Patients typically present with lymphadenopathy of several sites, most of the patients are diagnosed with advanced stage disease (Ann Arbor/Lugano stage III, IV). Extranodal manifestations occur in 90% of patients, including infiltration of bone marrow (53%–82%), blood (50%), liver (25%) and the gastrointestinal tract (20%–60%).[1,2] The spleen is enlarged in 40% of patients.[1] In some cases, leukemic manifestation in combination with massive splenomegaly is clinically prominent. These non-nodal, leukemic cases are often characterized by a more indolent clinical course. Accordingly, in the ICC/WHO 2022 update of lymphoid malignancies, MCL was subdivided in two distinct categories.[3,4] Nodal MCL (80%–90% of cases) is characterized by unmutated immunoglobulin heavy chain variable region genes (IGHV), Sex-Determining Region Y-Box 11 (SOX11) overexpression and a generally more aggressive clinical behavior. Non-nodal leukemic MCL (10%–20% of cases) typically displays mutated IGHV, SOX11 negativity and presents with indolent biological behavior. Histologically, besides "classical" MCL, pleomorphic and blastoid variants can be distinguished.[3,4] MCL with blastoid morphology often features high proliferation rates, displaying a more aggressive clinical course.[3–5]

Detection of the genetic hallmark of MCL, the chromosomal t(11; 14) (q13; q32) translocation, either by immunohistochemistry (cyclin D1 overexpression) or fluorescence in situ hybridization (chromosomal translocation) is crucial to confirm the diagnosis. In rare cases that are negative for cyclin D1, Cyclin D2 or Cyclin D3 may be overexpressed.[3] Staining for SOX11, a transcription factor specifically expressed in more than 90% of MCL cases, may help to establish the diagnosis in this specific samples.[6]

Traditionally, MCL was associated with a poor prognosis with a median overall survival (OS) of 3–5 years. However, major advances in the treatment of MCL patients have been achieved over the last years, especially by the development of an immunochemotherapy induction implementing cytarabine and anti-CD20 antibodies and addition of a consolidative high-dose therapy with autologous stem cell transplantation (ASCT).[7] Moreover, introduction of rituximab maintenance, especially for those patients not eligible for high-dose therapy, significantly improved survival rates in this group of patients.[8] The implementation of targeted therapies into the relapsed setting including the BTK-inhibitor ibrutinib has further improved outcomes for patients with relapsed or refractory disease.[9] Yet, long-term prognosis is still limited and patients with relapsed/refractory disease, especially those failing ibrutinib treatment, usually have a dismal outcome.[10] Therefore, improved understanding of cellular and molecular biology of MCL and identification of relevant factors determining prognosis to optimally use risk-adapted treatment approaches will be critical to further improve outcomes in this disease.

This review summarizes the current knowledge and standard of care regarding biology and clinical management of mantle cell lymphoma, highlighting the implementation of new therapeutic approaches especially targeting the immunosystem.

2 | PATHOGENESIS AND MOLECULAR BIOLOGY

The development of MCL is the result of a complex pathogenetic interplay between cellular and microenvironmental processes. Genetic hallmark of MCL and considered the primary oncogenic event in the pathogenesis is the chromosomal t(11; 14) (q13; q32) translocation, leading to overexpression of CyclinD1 and dysregulation of cell cycle at the G1–S phase transition.[11] CyclinD1 negative MCLs usually carry CCND2/CCND3 rearrangements with immunoglobulin genes instead. A subset of CyclinD1−/D2−/D3− MCL with aggressive features has cyclin E dysregulation.

The transcription factor SOX-11 is overexpressed in more than 90% of MCL cases, whereas a leukemic non-nodal variant, resembling chronic lymphocytic leukemia, lacks SOX-11 expression and is associated with a more indolent course.[12] In this subset of patients with leukemic, non-nodal presentation, SOX-11 expression proved to be prognostically relevant, identifying a favorable outcome in patients with negative SOX-11 with mutated IGHV.

The constitutive activation of the B-cell receptor (BCR) and its multiple downstream signaling pathways also play an important role in the development of the disease.[11]

Furthermore, genomic profiling revealed a high number of secondary genetic alterations and recurrent mutations affecting for example, regulation of cell cycle, DNA damage response and apoptosis pathways that contribute to the pathogenesis and aggressiveness of MCL.[11] The more aggressive behavior of classic MCL, compared with non-nodal MCL, was shown to be associated with a higher number of driver genetic alterations, particularly Copy Number Alterations.[13] In recent years, next generation sequencing approaches to unravel the genetic background of MCL led to the identification of numerous recurrent somatic mutations including genes involved in genotoxic stress pathways (*ATM*, *TP53*, *CDKN2A*), epigenetic regulators (*WHSC1*, *KMT2D*, *MEF2B*, *KMT2C*, *SMARCA4*, *SMARCB1*) and genes regulating DNA replication (*SAMHD1*), RNA processing (*HNRNPH1*) as well as cell homeostasis, cell growth and cell death (*CCND1*, *TP53*, *CDKN2A*, *CDKN1B*, *BIRC3*, *CARD11*, *TRAF2*, *RB1*, *POT1*, *NOTCH1/2*). Among these genes, the ataxia-telangiectasia mutant (ATM) gene is the most frequently mutated gene in newly diagnosed MCL. Remarkably, mutations in this gene did not correlate with any differences in clinical outcome compared to patients with unmutated ATM. Further recurrent somatic mutations with high mutation rates were detected in *TP53* (26.8%; 95% CI, 24.2%–29.6%), *RB1* (24.3%; 95% CI, 17.6%–32.1%), *CDKN2A* (23.9%; 95% CI, 20.1%–28.2%) and *CCND1* (20.2%; 95% CI, 16.8%–24.1%).[14] Yet, functional relevance remains unclear for most of the mutations and is currently under further investigation.

3 | PROGNOSTIC FACTORS

Important clinical and serological factors, associated with a worse clinical outcome include age, poor general condition, advanced stage of disease (Ann Arbor stage III or IV), splenomegaly and anemia, the serum level of β2-microglobulin and LDH, blastoid cytology, extranodal presentation and constitutional symptoms. A prognostic score that has been confirmed in numerous series, the MIPI (MCL International Prognostic Index), was established implementing four independent prognostic factors: age, performance status, LDH, and leukocyte count.[15] Yet, the most important prognostic markers independent of clinical features are the proliferation rate as measured by Ki-67 expression and the expression of p53. These two (p53 high and Ki67 > 30%), together with blastoid morphology, were recently reported to define a high-risk biology with significantly shorter failure-free and OS. Immunohistochemical determination of Ki-67 expression has been prospectively confirmed as a reliable prognostic marker and is, in combination with the MIPI (MIPI-c), a highly recommended tool to estimate individual risk profile and to identify high-risk patients (Ki-67 > 30%) who may qualify for more aggressive therapeutic approaches.[16] Furthermore, a cell proliferation gene signature (MCL35) that distinguishes patient subsets that differ by more than 5 years in median survival has been identified.

Some of the numerous recurrent genetic lesions observed in MCL were identified and validated to be associated with inferior outcomes. Deletions of 17p13 or mutations of *TP53* as well as deletions of *CDKN2A* were reported to be associated with worse clinical outcome in the majority of the studies published. Despite treated with high-dose cytarabine and ASCT, younger MCL patients with deletions of *CDKN2A* (p16) and *TP53* show an unfavorable prognosis. Furthermore, *TP53* mutations were significantly associated with high Ki67 (>30%), blastoid morphology, MIPI high-risk, and inferior responses to both induction- and high-dose chemotherapy.[17] Other genetic lesions with inferior outcomes include mutations in the *NOTCH* genes[18,19] and in *KMT2D* as well as MYC alterations and mutations in *WHSC1* and *CCND1*. Recently, whole-exome sequencing of 152 primary MCL samples lead to the definition of 4 robust MCL

biological clusters (C1-C4) with distinct outcomes (5-year OS rates for C1-C4 were 100%, 56.7%, 48.7%, and 14.2%, respectively). C1 featured mutated immunoglobulin heavy variable (IGHV), CCND1 mutation, amp(11q13), and active B cell receptor (BCR) signaling. C2 was enriched with del(11q)/ATM mutations and upregulation of NF-κB and DNA repair pathways. C3 was characterized by mutations in SP140, NOTCH1, and NSD2, with downregulation of BCR signaling and MYC targets. C4 harbored del(17p)/TP53 mutations, del(13q), and del(9p), and active MYC pathway and hyperproliferation signatures.[20] Accordingly, the new lymphoma classification systems now recommend to determine Ki67 proliferation index and *TP53* status mandatory at first diagnosis.[3,4]

However, despite several genetic lesions have been identified as promising candidates to predict high-risk disease behavior and inferior outcomes to available therapies, these prognostic markers did not enter diagnostic routine yet. Therefore, further biological studies investigating homogenously treated patient cohorts to validate and complement current findings, are of great importance to prospectively use biologic features to individually guide MCL therapy.

Concerning the prognostic impact of minimal residual disease (MRD) status, several studies have been published, providing evidence of the strong prognostic potential of MRD status predicting improved subsequent progression-free survival (PFS) for MRD-negative patients at the end of induction and before high-dose consolidation.[7] Furthermore, lack of molecular remission after end of currently recommended standard treatment was shown to be strongly predictive for early clinical relapse within 1–2 years.[7,21] However, use of MRD analysis in clinical routine is still limited. Furthermore, the impact of MRD monitoring in the context of the new targeted treatments, such as the BTK inhibitor ibrutinib, remains unclear. Current and potential future prognostic factors are listed in Table 1.

TABLE 1 Prognostic markers – current and future.

In clinical routine	Potential for future use
Age	"MCL35" RNA expression analysis
Performance status	SOX11 expression
Central nervous system involvement at diagnosis	*TP53* mutations/deletions by sequencing analysis
Stage of disease (I and II vs. III and IV)	*NOTCH1* mutations
Serum level of β2-microglobulin and LDH	*CDKN2A* mutations
Morphology (classic vs. blastoid)	*WHSC1* mutations
MIPI	*MYC* alterations
Ki67 (<30% vs. > 30%)	*CCND1* mutations
TP53 expression by immunohistochemistry	*BIRC3* mutations (concerning ibrutinib treatment)
	CARD11 mutations (concerning ibrutinib treatment)
	SMARCA4 mutations (concerning venetoclax treatment)
	MRD testing

4 | TREATMENT

The clinical course of MCL is characterized by generally high initial response rates; however, early relapses are frequent and most patients follow an aggressive clinical course. Nevertheless, 10%–15% of patients present with a more indolent subtype. These cases are commonly characterized by a leukemic, non-nodal lymphoma manifestation or a very low Ki67-Index (<10%). In these cases, watchful waiting under close monitoring is considered an appropriate strategy.[22] Yet, the majority of cases require an early treatment initiation even though advanced stage disease (stage III/IV) is still considered incurable. A recommended treatment algorithm is depicted in Figure 1.

4.1 | Therapy in patients ≤65 years

4.1.1 | Induction

In European countries, in young and fit patients (≤65 years), a dose-intensified concept containing an immunochemotherapy induction followed by a high-dose consolidation regimen and ASCT constitutes the current standard of care.[1,7,23] The administration of the R-CHOP/DHAP regimen compared to administration of R-CHOP alone prior to myelo-ablative consolidation with ASCT more than doubled Time to Treatment Failure (TTF) (109 vs. 47 months).[7] Yet, in the era of targeted therapies, the phase III TRIANGLE trial recently evaluated the remaining value of ASCT for first-line therapy: 870 patients <65 years were treated with either the current standard of care including ASCT (arm A), the additional application of ibrutinib (arm A + I) or an ibrutinib-combination without ASCT (arm I). As recently reported, 3-year-disease-free survival was higher in both ibrutinib-containing arms compared to intensive high-dose consolidation followed by ASCT (86% respectively 88% vs. 72%; p = 0,0008; HR 0,52).[24] Based on the more favourable toxicity profile in arm I, a high-dose concept including ASCT should be assessed critically.

On the other hand, for patients with indolent clinical forms of MCL, a frontline combination of ibrutinib and rituximab proved to be a promising chemotherapy-free regimen achieving a high rate of CRs and undetectable MRD.[25]

4.1.2 | Maintenance

Rituximab maintenance after ASCT is currently considered standard of care for younger patients with MCL based on the results of a large Phase III trial showing a significantly improved PFS (83% vs. 64% after 4 years) and OS (89% vs. 80% after 4 years) after 3 years of Rituximab maintenance compared to observation only.[26]

Recently, another Phase III trial revealed a benefit from a lenalidomide maintenance after autologous transplantation with improved

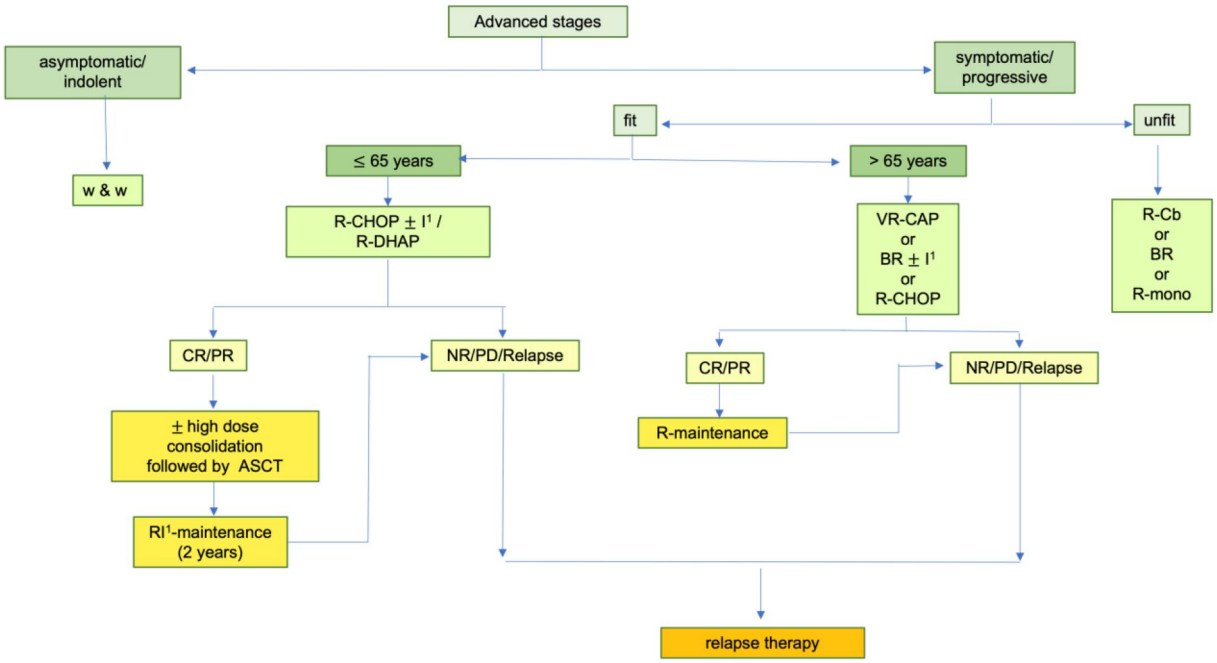

FIGURE 1 Treatment algorithm for first line therapy. Modified from: https://www.onkopedia.com/de/onkopedia/guidelines/mantelzell-lymphom/@@guideline/html/index.html. R-CHOP, Rituximab/Cyclophosphamide/Doxorubicin/Vincristin/Prednisone; R-DHAP, Dexamethasone/high-dose Cytarabine/Cisplatin; VR-CAP, Rituximab/Cyclophosphamid/Doxorubicin/Bortezomib/Prednisone; BR, Rituximab/Bendamustin; I, Ibrutinib; R-Cb, Rituximab/Chlorambucil; R, Rituximab; CR, Complete Remission; PR, Partial Remission; NR, Non Response; PD, Progressive Disease; ASCT, autologous stem cell transplantation, [1] off label.

PFS (80% vs. 64% after 3 years) compared to observation.[27] However, due to the elevated toxicitiy profile (especially hematotoxicity), lenalidomide maintenance should be only applied to patients not suitable to receive rituximab.

4.2 | Therapy in patients >65 years

4.2.1 | Induction

The group of the over 65 year-olds ineligible for transplantation presents very heterogenous regarding physical and cognitive performance. A suggested therapeutic algorithm is depicted in Figure 2. Fit patients >65 years should receive conventional immunochemotherapy followed by rituximab maintenance.[28] A combination of Bortezomib, Rituximab, Cyclophosphamide, Doxorubicine und Prednisone (VR-CAP) proved to be superior over R-CHOP in a large international Phase III trial with a doubled OS after 82 months (90,7 vs. 45,7 months). However, hematologic toxicity (especially > grade 3 thrombopenia) was significantly increased in the experimental arm (57% vs. 6%).[29] The combination of Rituximab, Bendamustine and Cytarabine (R-BAC) offers another useful option. Yet, this regimen was accompanied by severe hematotoxicities and should therefore be considered expecially in very fit older patients with high-risk features (e.g., blastoid variant, high LDH count).[30] Alternatively, for patients not qualifying for such intensive therapy regimens, R-Bendamustine (BR) offers an appropriate alternative. This combination resulted in similar response rates (93% vs. 91%) compared to R-CHOP and was even superior in progression-free survival (PFS) (35 vs. 21 months) with a more favorable toxicity profile observed.[31] The addition of ibrutinib to this combination was recently evaluated in the phase 3 SHINE trial, reporting a significant improvement of PFS from 52.9 to 80.6 months compared to BR alone. However, no effect on OS was observed.[32] Taken together, VR-CAP and BR-(I) represent the current standard approaches in older patients not eligible for high-dose therapy, who represent the majority of MCL patients. VR-CAP should be, in our opinion, preferably chosen for patients with a higher risk-profile such as high Ki67 expression or blastoid morphology. BR-(I) may be preferable especially in patients with a more indolent CLL-like presentation.

4.2.2 | Maintenance

A large, randomized, European phase III trial compared Rituximab maintenance to Interferon maintenance, confirming superiority of rituximab as maintenance therapy. In this study, after 4 years, 58% of the patients receiving rituximab after induction therapy with R-CHOP were in remission, compared to 29% in the Interferon arm ($p = 0.01$). PFS and OS were also significantly improved in the Rituximab arm (5-year PFS R vs. IFN 51% vs. 22%, 5-year-OS R vs. IFN 79% vs. 59%).[8] Based on these results, rituximab maintenance is generally recommended.

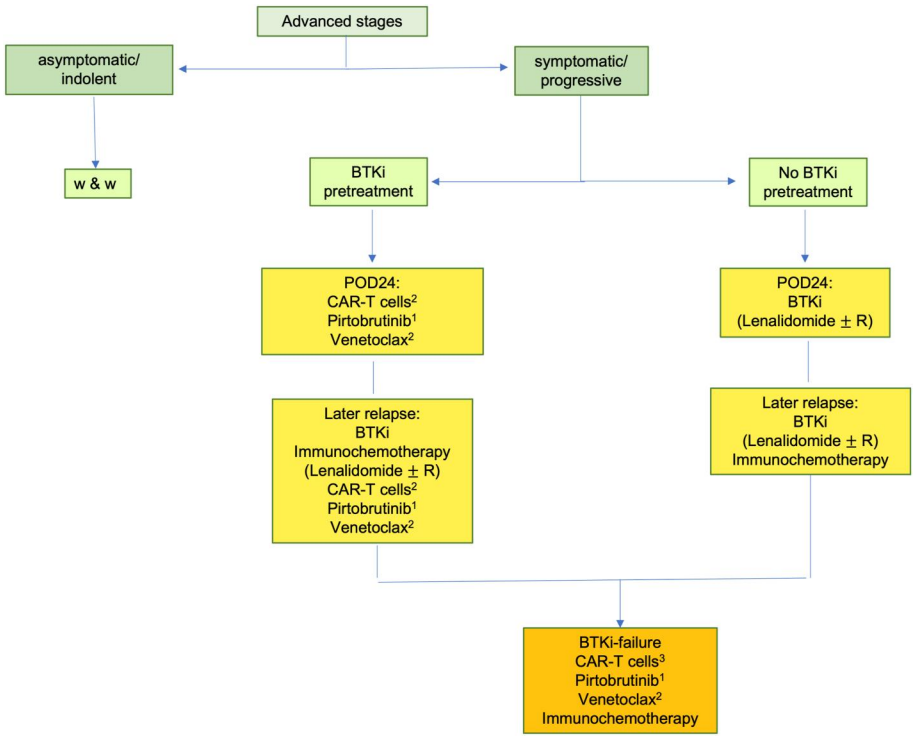

FIGURE 2 Treatment algorithm for relapse therapy. Modified from: https://www.onkopedia.com/de/onkopedia/guidelines/mantelzell-lymphom/@@guideline/html/index.html. POD24—Progression of Disease in between 2 years, BTKi- Bruton's Tyrosine Kinase Inhibitor. [1] compassionate use, [2] off label, [3] allogeneic transplantation for younger patients should only be discussed after CAR-T cells.

5 | RECURRENT AND REFRACTORY DISEASE

5.1 | Molecular targeted therapies

For relapsed MCL, several targeted treatment approaches are already available or under current investigation. A recommended treatment algorithm for relapse therapy is depicted in Figure 2.

Targeting the B-cell receptor pathway with the **Bruton's tyrosine kinase inhibitor** ibrutinib resulted in remarkable response rates leading to its approval in relapsed MCL. In a large international Phase II study, response rates of 68% were achieved with ibrutinib in patients with relapsed disease.[33] The combination with rituximab was effective in all cases with low Ki-67, whereas in highly proliferating disease, only half of the patients responded to this approach.[34] A pooled analysis of the results of three different trials testing ibrutinib as monotherapy revealed overall response rates of 66% with median PFS and OS of 12,8 resp. 25 months.[9] However, interindividual responsiveness is heterogenous and primary and secondary resistance has been reported with poor clinical outcome.[10] In patients with mutations in the *TP53* gene, median PFS was shown to be significantly worse. Patients suffering early relapses after ibrutinib therapy demonstrated very aggressive clinical courses.[10]

Second generation BTK inhibitor acalabrutinib was approved in October 2017 by the FDA for patients with relapsed/refractory MCL who had received at least one prior therapy as promising results, especially regarding tolerability, were observed in an open-label phase 2 study.[35] Acalabrutinib in combination with BR compared to BR alone in previously untreated MCL patients >65 years of age is currently evaluated in an ongoing phase-3 study (NCT02972840).

Zanubrutinib is a highly potent, selective, bioavailable, and irreversible BTK inhibitor with maximized BTK occupancy. It was approved in 2019 in the US and China for the treatment of patients with R/R MCL based on results from a phase II study in patients with R/R MCL. Long-term results of this study recently reported an ORR of 83%,7% (CR 77%,9%) after a median follow-up of 35,5 months. Median PFS and OS after 36 months was 47%,6% resp. 74%,8%.[36] The potential for use of zanubrutinib in the first-line setting is currently under evaluation in the randomized phase III MANGROVE study (NCT04002297) in which patients with treatment-naive MCL receive zanubrutinib + rituximab or bendamustine + rituximab.

Next-generation BTK-inhibitor pirtobrutinib is a highly potent and selective noncovalent BTK inhibitor that has nanomolar potency against wild-type and C481-mutant *BTK* and has just recently been FDA approved for the treatment of adult patients with relapsed or refractory MCL following at least 2 lines of systemic therapy including a BTK inhibitor, based on results of the phase 1/2 BRUIN trial reporting an ORR of 52%.[37] The BRUIN MCL-321 (NCT04662255) randomized, open-label, phase 3 study currently compares pirtobrutinib monotherapy versus investigator's choice of

covalent BTKi monotherapy (ibrutinib, acalabrutinib, or zanubrutinib) in patients with previously treated, BTKi naïve MCL.

For patients suffering early relapses after ibrutinib therapy, a monotherapy with the

BCL2-inhibitor venetoclax might be a promising alternative, as a phase I trial showed response rates of 75% in patients with relapsed MCL and 60% in patients having received prior ibrutinib therapy. Recently, the combination of ibrutinib and venetoclax proved to be highly effective in a small study cohort.[38] The potential advantage of ibrutinib combined with venetoclax over Ibrutinib alone is currently being examined in an ongoing phase-3 study (SYMPATICO) (NCT03112174).

Various studies confirmed a benefit of the orally available **immunemodulatory drug** lenalidomide in relapsed MCL, with response rates of 35 to 50%. In a randomized phase II trial, this approach was superior to monochemotherapy (response rate 46% vs. 23%). Based on an in vitro synergism, lenalidomide in combination with rituximab resulted in long lasting remissions in first-line therapy of a rather low risk patient cohort.[39]

5.2 | Immunotherapies

Regarding immunotherapy approaches, very promising results were recently reported for the already approved **autologous CD19 CAR T-cell** construct brexucabtagene autoleucel based on the results of the ZUMA-2 study. After a median follow-up of 35,6 months, treatment with brexucabtagene autoleucel was reported to induce durable overall response rates of 91% and a PFS of 25.8 months in patients refractory or intolerant towards BTK inhibitor treatment.[40] Another CD19-directed CAR T-cell product (lisocabtagene maraleucel) for relapsed/refractory MCL is currently being evaluated in the ongoing phase 1 study TRANSCEND NHL 001 (NCT02631044). Overall, results are very promising with long-lasting remissions even after BTKi-treatment failure. Therefore, CAR T-cell therapy should be offered to the group of high-risk patients refractory to BTK inhibitors.

The **CD20xCD3 bispecific antibody** glofitamab, evaluated as a monotherapy after pretreatment with obinutuzumab (1000mg or 2000mg) in a phase I/II trial in a cohort of 37 heavily pretreated patients with MCL, induced high and durable CR rates of 73%[41] and might also be a potential alternative for patients failing BTKi treatment.

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CONFLICT OF INTEREST

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