International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

ARTICLE TITLE	MANTLE CELL LYMPHOMA – A REVIEW OF RESEARCH
DOI	https://doi.org/10.31435/ijitss.4(48).2025.4245
RECEIVED	23 October 2025
ACCEPTED	08 December 2025
PUBLISHED	17 December 2025
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

MANTLE CELL LYMPHOMA – A REVIEW OF RESEARCH

Hanna Pietruszewska *(Corresponding Author, Email: hania11223340@gmail.com)*
Faculty of Medicine, Medical University of Łódź, Łódź, Poland
ORCID ID: 0009-0000-7626-2996

Katarzyna Kleszczewska
Independent Public Health Care Complex in Myszków, Myszków, Poland
ORCID ID: 0009-0009-4177-089X

Agnieszka Pruska
University Clinical Center in Gdańsk, Gdańsk, Poland
ORCID ID: 0000-0002-4439-5126

Natalia Senatorska
Faculty of Medicine, Medical University of Łódź, Łódź, Poland
ORCID ID: 0009-0009-8167-9839

Julia Rarok
Faculty of Medicine, University of Opole, Opole, Poland
ORCID ID: 0009-0009-7433-2175

Daria Godlewska
Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0001-3640-3552

Monika Banaszek
Independent Public Healthcare Center in Puławy, Puławy, Poland
ORCID ID: 0009-0006-4696-8756

Agata Panfil
Prof. K. Gibiński University Clinical Centre of the Medical University of Silesia in Katowice, Katowice, Poland
ORCID ID: 0009-0008-9589-4305

Julia Błocka
4th Military Clinical Hospital, Wrocław, Poland
ORCID ID: 0009-0000-1698-4591

Agata Lurka
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0009-0005-6851-3763

ABSTRACT

Mantle cell lymphoma remains a cancer with a high risk of recurrence, but advances in treatment are significantly changing the prognosis for patients. Molecularly targeted therapies, such as the combination of ibrutinib and venetoclax, as well as immunotherapy using CAR-T cells (chimeric antigen receptor T-cells), show high clinical efficacy and the potential for sustained remission. Research results indicate a significant prolongation of progression-free survival with an acceptable safety profile. Further development of therapeutic strategies should focus on personalising treatment, identifying response biomarkers and minimising adverse effects. These advances offer a real chance for long-term disease control.
The aim of this study is to evaluate the efficacy and safety of modern molecularly targeted and cellular therapies in the treatment of mantle cell lymphoma, with particular emphasis on their impact on remission duration, progression-free survival and the possibility of long-term disease control. The study aims to highlight the importance of individualising treatment, integrating different therapeutic methods and identifying biomarkers that can support a more precise clinical approach.

KEYWORDS

Mantle Cell Lymphoma, Ibrutinib, Venetoclax, Targeted Therapy, CAR-T Cells, Relapse Treatment, Remission, Clinical Trials

CITATION

Hanna Pietruszewska, Katarzyna Kleszczewska, Agnieszka Pruska, Natalia Senatorska, Julia Rarok, Daria Godlewska, Monika Banaszek, Agata Panfil, Julia Błocka, Agata Lurka (2025) Mantle Cell Lymphoma – A Review of Research. *International Journal of Innovative Technologies in Social Science*. 4(48). doi: 10.31435/ijitss.4(48).2025.4245

Introduction

Mantle cell lymphoma (MCL) is a cancer of the lymphatic system classified as a non-Hodgkin B-cell lymphoma. It is characterized by the presence of t(11;14)(q13;q32) translocation, leading to cyclin D1 overexpression and cell cycle control disorders (Swerdlow, Campo, Harris, 2017). The disease is usually aggressive, and in most patients, the diagnosis is made at an advanced stage. Despite intensive standard treatment, long-term survival remains limited. For a long time, chemotherapy regimens with the addition of anti-CD20 monoclonal antibodies were the basis of treatment. Advances in molecular biology and immuno-oncology have enabled the introduction of new therapeutic strategies that have changed the prognosis for this disease. Bruton's kinase inhibitors, drugs targeting anti-apoptotic pathways, and cellular immunotherapies have been incorporated into clinical practice. These therapies allow for deeper and more durable responses than traditional chemoimmunotherapy regimens.

Due to the varied clinical course and frequency of recurrence, the treatment of MCL requires an individualized approach, depending on the patient's age, general condition, and molecular profile of the disease. Numerous clinical trials are currently underway to investigate the sequence of therapy, the effectiveness of maintenance treatment, and the possibility of reducing toxicity without losing efficacy. The following sections of the article present the development of MCL treatment methods, from classic chemotherapy regimens to the latest.

The following sections of this article present the development of MCL treatment methods, from classic chemotherapy regimens to the latest targeted and cellular therapies. Mantle cell lymphoma accounts for approximately 5–7% of all B-cell non-Hodgkin lymphomas. Its incidence increases with age, with most cases occurring in people over 60 years of age. The disease is more common in men. At the time of diagnosis, most patients present with generalized lymph node enlargement, often with involvement of the bone marrow, spleen, or gastrointestinal tract. The natural course of MCL is usually aggressive, and the risk of recurrence is high even after achieving complete remission. In the past, the median overall survival did not exceed 3–5 years. However, the last decade has seen a significant improvement in treatment outcomes, which is associated with the introduction of new therapeutic strategies, better assessment of prognostic factors, and greater availability of molecular testing. Despite this, MCL remains a difficult disease to treat, requiring a carefully planned therapeutic strategy and monitoring of response to treatment.

Methodology

The review included randomized controlled trials (RCTs) and prospective cohort studies involving adult patients diagnosed with mantle cell lymphoma (MCL). Publications on modern molecularly targeted and cellular therapies, including Bruton's tyrosine kinase (BTK) inhibitors, monoclonal antibody therapies, BCL-2 inhibitors, and CAR-T cell (chimeric antigen receptor T-cell) therapies, were included. The inclusion criteria were: reporting of data on clinical efficacy (percentages of complete and partial remissions, PFS, OS), treatment safety, and long-term follow-up. The time frame of the publications covered the years 2018–2025, with an emphasis on the latest reports from phase II and III studies.

The literature review was conducted in PubMed, Scopus, Web of Science, and Google Scholar databases. The following keyword combinations were used: ("mantle cell lymphoma" OR "MCL") AND ("targeted therapy" OR "molecular therapy" OR "BTK inhibitor" OR "CAR T-cell therapy" OR "venetoclax"). In addition, the bibliographies of key publications were analyzed to identify studies omitted from the initial search. The selection process was conducted in two stages.

In the first stage, titles and abstracts were reviewed, eliminating studies that did not meet the thematic or methodological criteria. In the second stage, the full texts of the publications were evaluated, analyzing the methodological quality of the studies, the nature of the study population, the type of intervention, and the observation period. In the event of discrepancies regarding the qualification of a given study, the decision was made jointly after consultation with the second reviewer.

Results

The BRIGHT First-Line Treatment of Patients With Indolent Non-Hodgkin Lymphoma or Mantle-Cell Lymphoma With Bendamustine Plus Rituximab Versus R-CHOP or R-CVP: Results of the BRIGHT 5-Year Follow-Up Study, (2019) was designed to compare the efficacy and safety profile of two treatment regimens in patients with indolent lymphoma or mantle-cell lymphoma who had not previously received therapy. The combination of bendamustine and rituximab (BR) was compared with standard immunochemotherapy regimens: rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or rituximab with cyclophosphamide, vincristine, and prednisone (R-CVP). The analysis presents data from long-term follow-up of patients after completion of treatment. Study participants were followed for at least five years after completion of therapy. The time to specific events, such as progression-free survival (PFS), event-free survival, duration of response to treatment, and overall survival, as assessed by investigators, was analysed. In addition, information was collected on the frequency of second-line therapy and the occurrence of secondary malignancies. During the follow-up period, the median for none of the analysed endpoints was reached in any of the treatment groups. Five years after the start of treatment, the percentage of patients without disease progression was 65.5% in the BR group and 55.8% in the R-CHOP/R-CVP group. The difference between the groups was statistically significant, and the hazard ratio for PFS was 0.61 (95% CI: 0.45–0.85; $p = 0.0025$), indicating a longer response maintenance with the BR regimen. The benefit of BR was also observed in event-free survival and duration of response ($p = 0.0020$ and $p = 0.0134$). No differences in overall survival were observed between the groups.

The safety profile in both arms of the study was consistent with previous observations for these treatment regimens. No new toxicity signals were reported during long-term follow-up. However, a higher number of secondary malignancies was observed in the bendamustine plus rituximab group, which requires further analysis. The results obtained indicate that therapy based on the combination of bendamustine and rituximab provides more durable disease control compared to R-CHOP or R-CVP regimens in patients with indolent lymphoma and mantle cell lymphoma. The BR regimen may therefore be considered an effective initial treatment option in this patient group.

The five-year follow-up of study S1106, Consolidate or Not Consolidate: The Role of Autologous Stem Cell Transplantation in Mantle Cell Lymphoma (MCL), (2024) provided data confirming that the bendamustine and rituximab (BR) regimen offers efficacy comparable to intensive R-hyper-CVAD (RH) treatment, with lower toxicity and better tolerability. Both approaches led to high response rates and favourable survival outcomes, but differed in their safety profiles. In the treatment of mantle cell lymphoma (MCL), patients eligible for autologous stem cell transplantation (ASCT) typically receive aggressive induction therapy followed by high-dose chemotherapy and ASCT. However, there is still no complete consensus on the best initial treatment regimen. Cytarabine-based therapies often provide high response rates and a high frequency of MRD (minimal residual disease) negativity, but they require hospitalisation and are associated with numerous adverse effects, mainly haematological. The BR regimen, which combines bendamustine with

rituximab, is a less intensive form of chemoimmunotherapy, administered on an outpatient basis, which has shown very good results in previous studies in patients who are not eligible for transplantation. The S1106 study aimed to evaluate whether BR therapy could be an effective alternative in a population of patients with newly diagnosed MCL preparing for ASCT. It was a randomised, multicentre phase II clinical trial conducted by the Southwest Oncology Group as part of the National Clinical Trials Network. Patients with stage III–IV or extensive stage II disease were randomly assigned to receive four cycles of RH (rituximab + hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone + methotrexate/cytarabine) or six cycles of BR (rituximab + bendamustine), and then referred for ASCT. Patients who achieved a complete or partial response and obtained a sufficient number of CD34+ cells were eligible for transplantation. The analysis included 52 patients (17 in the RH group and 35 in the BR group). Both groups were comparable in terms of age (median 59 and 57 years), disease stage and prognostic indicators. Over 90% of patients had bone marrow involvement and approximately 20% had a high Ki-67 proliferation index (>30%).

Follow-up showed that complete response (CR) and overall response (ORR) rates were similar in both groups. The 2-year PFS and OS rates were 82% and 88% in the RH group and 81% and 87% in the BR group, respectively. After 5 years, PFS was 62% (95% CI, 34–81%) in the RH group and 66% (95% CI, 45–80%) in the BR group, while OS was 74% (95% CI, 44–89%) and 80% (95% CI, 62–91%) in the same groups. The analysis of MRD results included 12 paired samples (2 RH and 10 BR). In both cases, RH achieved negative MRD after induction, while in the BR group, 7 out of 9 patients (78%) achieved negative MRD after treatment. Patients who were MRD-negative after BR induction had 5-year PFS and OS rates of 90%. RH therapy was more burdensome, with more frequent cases of neutropenia, thrombocytopenia, anaemia and neutropenic fever, as well as numerous stem cell mobilisation failures, leading to the premature closure of this arm of the study. In the BR group, discontinuation of therapy was mainly related to patient decision rather than adverse events. The long-term analysis confirmed that the BR regimen is well tolerated and provides a sustained response, with less haematological toxicity and the possibility of outpatient treatment. These results are similar to those of intensive cytarabine-based therapies, but with a significantly lower burden on the patient. Data from the S1106 study suggest that rituximab with bendamustine may be an effective induction therapy prior to transplantation in MCL, providing durable remissions and a favourable safety profile. The results obtained served as the basis for the design of another study (EA4181) conducted by the Eastern Cooperative Oncology Group, which analyses regimens based on bendamustine in combination with cytarabine or Bruton's tyrosine kinase (BTK) inhibitors in previously untreated patients with mantle cell lymphoma.

Another study is Ibrutinib and venetoclax for mantle-cell lymphoma (2018), which presents high-intensity induction therapy involving cytarabine (Ara-C), followed by autologous stem cell transplantation (ASCT), which for many years was considered one of the most effective treatments for younger patients with mantle cell lymphoma (MCL). This approach leads to long-term remission, but is associated with both acute and late toxicity, which limits its use in some patients. In response to these limitations, intensive research has begun on alternative first-line treatment strategies involving the use of modern molecularly targeted drugs that could replace or complement ASCT. Particular attention has been drawn to the recently published results of the TRIANGLE study, which compared the efficacy of standard immunochemotherapy with induction containing ibrutinib, a Bruton's tyrosine kinase inhibitor (BTKi). The study demonstrated the superiority of the ibrutinib plus ASCT regimen over conventional therapy and, more importantly, the similar efficacy of ibrutinib-based therapy without transplantation compared to standard therapy including ASCT. These results suggest that the inclusion of ibrutinib in first-line treatment may become a new benchmark in the treatment of younger patients with MCL, offering comparable efficacy with potentially lower risk of adverse events. However, it remains unclear whether autologous stem cell transplantation, despite the additional burden of toxicity, may still offer a therapeutic advantage in selected patient groups. There is also a lack of data on the efficacy of BTK inhibitors in the treatment of relapses in patients who have already received this type of therapy as first-line treatment. It is also uncertain whether the results of the TRIANGLE study can be transferred to other drugs in the same class, which is becoming increasingly important in the context of the withdrawal of some of them from FDA registration for MCL therapy. Until full data from further studies are available, the decision to include ASCT in ibrutinib-containing therapy should be made on an individual basis, taking into account the biology of the tumour, the patient's age and general condition, and the risk of toxicity. In patients with TP53 gene aberrations, the use of ASCT is not recommended due to its limited efficacy and high risk of complications. The ultimate significance of transplantation in this population will be determined in large randomised studies, such as ECOG-ACRIN 4151, which aim to accurately compare the efficacy of different therapeutic strategies in MCL.

In the KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma study (2020), ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, and venetoclax, a BCL-2 inhibitor, show antitumour activity as monotherapy in patients with mantle cell lymphoma (MCL). Both drugs achieve a similar complete remission rate of approximately 20%, but preclinical data suggested that their combination may lead to a synergistic effect. A phase II study (AIM, NCT02471391) evaluated the efficacy and safety of the combination of ibrutinib and venetoclax in patients with relapsed or refractory MCL. Treatment was initiated with ibrutinib at a dose of 560 mg daily, and after four weeks, venetoclax was gradually introduced, increasing its dose to 400 mg daily. Treatment was continued until disease progression or unacceptable adverse events occurred. The primary endpoint of the study was the percentage of complete remissions after 16 weeks of treatment, assessed by computed tomography and molecular methods determining the presence of minimal residual disease (MRD).

Twenty-four patients were enrolled in the study, including 23 with relapsed or refractory MCL and one previously untreated patient. Half of the patients had TP53 gene aberrations, and most were at high clinical risk according to the MIPI score. At week 16, the overall response rate assessed by imaging was 42%, which significantly exceeded the historical 9% observed with ibrutinib monotherapy. PET assessment showed a 62% complete remission rate at the same time point, and the overall complete response rate reached 71%. MRD was completely cleared in 67% of patients by flow cytometry and in 38% by ASO-PCR. After 15 months, 78% of patients who responded remained in remission. The study showed that the combination of ibrutinib and venetoclax may increase the effectiveness of treatment in patients with MCL, especially in the population with an unfavourable genetic profile, while maintaining acceptable safety. The high rate of complete remission and MRD elimination suggests that the combination of BTKi (Bruton’s tyrosine kinase inhibitor) and BCL-2i (BCL-2 inhibitor) may become a valuable option in the targeted therapy of this cancer. During combination therapy with ibrutinib and venetoclax, a variety of adverse events were observed, most of which were mild or moderate in severity (grade 1–2).

Serious adverse events were observed in 58% of study participants. Tumor lysis syndrome occurred in two high-risk patients who received venetoclax at a starting dose of 50 mg. After modifying the protocol by reducing the starting dose to 20 mg, no further cases of this complication were reported, including among high-risk patients. The mean dose intensity relative to the planned treatment was 96% for venetoclax and 87% for ibrutinib. Fifteen patients required dose modifications, most commonly due to haematological toxicity or infection. Six deaths were recorded during follow-up, four of which were due to disease progression and two due to other causes. One patient died of malignant otitis externa after treatment with ibrutinib alone, while the other died of heart failure in the course of cardiomyopathy associated with previous exposure to anthracyclines. In this patient, atrial fibrillation developed in the fifth week of therapy, but despite stabilisation of the cardiac condition, severe decompensation occurred after one year of treatment. Another patient with anthracycline cardiomyopathy developed symptomatic heart failure in the 20th week of therapy; after discontinuation of ibrutinib and continuation of venetoclax, circulatory parameters normalised. In the further course of the study, follow-up echocardiography was performed in all patients with abnormal ejection fraction or symptoms suggestive of cardiac dysfunction — no new cases of heart failure were detected.

Analysis of prognostic factors showed no correlation between response and age, number of prior therapies, performance status (ECOG), lymph node size, LDH level, or MIPI score. Among patients who had received three or more prior lines of therapy, the majority achieved a response. In patients with Ki-67 expression exceeding 30%, the remission rate was lower than in those with lower levels of cell proliferation ($P = 0.02$). Molecular testing revealed mutations in all study participants. The most common changes were observed in the ATM gene (10 patients), all of whom achieved a complete response. Responses were also achieved in patients with mutations in the NF-κB pathway, which are usually associated with resistance to ibrutinib. In the group of patients with TP53 mutation or deletion, complete remission was observed in half (6 out of 12 patients), and in five patients it persisted for 13–20 months after the start of therapy. The results show that combination therapy with ibrutinib and venetoclax may be effective even in patients with unfavourable genetic factors, such as TP53 aberrations or mutations in the NF-κB pathway, with an acceptable safety profile and the possibility of controlling toxicity through appropriate dose modification. This also provides a combination of ibrutinib and venetoclax that can successfully lead to very good therapeutic effects in patients with mantle cell lymphoma. The efficacy of this regimen is comparable to or higher than that of monotherapy with Bruton's kinase inhibitors. The hypothesis of the superiority of combination therapy over single-agent treatment is currently being tested in a phase III trial (ClinicalTrials.gov: NCT03112174), which aims to clearly determine whether the addition of venetoclax to ibrutinib translates into longer survival and deeper molecular

responses. The observation of complete remissions with simultaneous disappearance of minimal residual disease (MRD) suggests the possibility of introducing a time-limited therapy strategy, consisting of discontinuing treatment after achieving a deep response. This approach has yielded positive results in patients with chronic lymphocytic leukaemia treated with a combination of venetoclax and rituximab. In the case of mantle cell lymphoma, this concept still needs to be confirmed, as two of our patients experienced a relapse despite previously achieving MRD-negative complete remission. Ongoing clinical trials, including the EudraCT 2016-002293-12 project, aim to evaluate the validity and safety of individually adjusting the duration of treatment to the response achieved.

In patients with mantle cell lymphoma (MCL) who have experienced disease progression during or after treatment with Bruton's tyrosine kinase inhibitors (BTKIs), the prognosis remains very poor. The efficacy of available regimens in this group is limited, creating a need for new, more targeted treatments. One of the most promising approaches is chimeric antigen receptor T-cell (CAR-T) therapy against CD19, known as KTE-X19, designed to eliminate CD19-expressing B-cell tumours. The ZUMA-2 Brexucabtagene autoleucel in relapsed or refractory mantle cell lymphoma, intention -to-treat use in the DESCAR-T registry (2024), a multicentre phase II study, evaluated the efficacy and safety of KTE-X19 in patients with relapsed or refractory MCL after prior BTKi therapy. Patients could have had up to five prior lines of therapy. After leukapheresis, some patients received bridging therapy, followed by conditioning chemotherapy and a single infusion of KTE-X19 at a dose of 2×10^6 CAR-T cells per kilogram of body weight. The primary endpoint was the objective response rate, including complete and partial responses, as assessed by an independent review committee according to the Lugano criteria. Seventy-four patients were enrolled in the study, of whom 71 were successfully CAR-T cell-engaged and 68 ultimately received treatment. In the primary efficacy analysis, which included 60 patients followed for at least 7 months, 93% achieved an objective response and 67% achieved complete remission. In the intention-to-treat analysis (including all 74 patients), these percentages were 85% and 59%, respectively. After a median follow-up of 12.3 months, 57% of patients remained in remission. The estimated 1-year progression-free survival (PFS) and overall survival (OS) rates were 61% and 83%, respectively, indicating the durability of the responses obtained. The most commonly observed grade 3 or higher adverse events were cytopenias (94%) and infections (32%). Fifteen per cent of patients experienced cytokine release syndrome (CRS) grade ≥3, and 31% experienced neurological events of similar severity. No deaths directly related to CRS or neurotoxicity were reported, but two patients died as a result of severe infections (grade 5). The safety profile of KTE-X19 was comparable to other approved CAR-T therapies. The study results indicate that the use of KTE-X19 leads to durable remission in a significant proportion of patients with relapsed or refractory MCL after failure of BTKi therapy. Although this treatment is associated with the risk of severe haematological, infectious and neurological complications, its clinical efficacy and the possibility of long-term disease control confirm its therapeutic value in this high-risk group.

According to the study Seven-year results of venetoclax and ibrutinib therapy in mantle cell lymphoma: Durable responses and treatment-free remissions (2024) in patients with mantle cell lymphoma (MCL) who have completed therapy with a Bruton's tyrosine kinase inhibitor (BTKi) such as ibrutinib due to disease progression or intolerance, the median overall survival (OS) ranges from 2.5 to 14.2 months. The ZUMA-2 study was a landmark clinical trial evaluating the efficacy of autologous T-cell therapy with chimeric antigen receptor CD19 (CAR-T) brexucabtagene autoleucel (brexu-cel, KTE-X19) in patients with heavily pretreated, relapsed or refractory MCL (R/R) who had progressed after prior therapies, including BTKi (ibrutinib or acalabrutinib). The primary efficacy analysis showed a 93% overall response rate (ORR) according to an independent radiology committee, including 67% complete responses (CR). Similar ORR values were achieved in clinical practice, but the duration of response (DOR) was shorter. These results, analysed from the time of leukapheresis, led the French health agency to grant access to brexu-cel under an early access programme for patients with relapsed or refractory MCL after failure of at least one line of chemoimmunotherapy and BTKi therapy. The aim of the study was to present the first results of treatment with brexu-cel in an intention-to-treat (ITT) regimen in a group of patients with relapsed or refractory MCL after the decision to use CAR-T therapy.

The study included all patients with MCL in France for whom the decision to treat with brex-cel was made during an oncology consultation (TBR) after the therapy was approved by the European Medicines Agency. A prerequisite was the prior failure of at least one chemoimmunotherapy and one BTKi. Patients were enrolled in the DESCAR-T registry. The study protocol (ClinicalTrials.gov identifier: NCT04328298) was approved by national bioethics committees and the Data Protection Authority, and the procedures were conducted in accordance with the principles of the Declaration of Helsinki. The first patient was enrolled on

20 December 2019, and data were exported from the registry on 1 September 2023. The ITT analysis included all patients for whom a decision to use CAR-T therapy was made, except for three cases in which the manufacturing process was ongoing at the time of database closure. Survival was analysed from the time of the TBR (ITT) decision or from the date of CAR-T cell infusion (modified ITT – mITT). The 'treated' group included patients who received brexu-cel infusion, while the 'untreated' group included those who did not receive the preparation. Response was assessed according to the Lugano 2014 criteria using FDG-PET. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were classified according to the guidelines of the American Society for Transplantation and Cellular Therapy (ASTCT). CAR-T cell expansion in the blood was monitored by flow cytometry (MFC) in 21 patients at various time points after infusion. Statistical analyses were performed using SAS v9.3 software.

A total of 181 patients from 24 centres in France were registered, of whom 71.8% did not meet the eligibility criteria for the ZUMA-2 study. The most common reasons for exclusion were the need for bridging therapy other than corticosteroids or BTKis (61.1%), deteriorated general condition (PS ≥2, 12%) and previous malignancy (8.3%). Three patients were excluded due to ongoing manufacturing, resulting in 152 patients in the treated group and 26 in the untreated group. Detailed clinical data are presented in Table 1. Among the treated patients, five did not receive BTKi and two did not undergo prior chemotherapy. The most common reasons for not administering brex-cel were disease progression (N=15, including 7 deaths prior to infusion) and manufacturing failure (N=5). Three patients required repeat leukapheresis, but they were not included in the manufacturing failure group.

In the ITT analysis (n=178) and with a median follow-up of 14.2 months, the median overall survival (OS) was 19.8 months. In the untreated group, the median OS was 1.8 months, while in the treated group it was not reached (55.6% of patients were alive after 24 months). The median time from enrolment to leukapheresis was 20 days (IQR 11–31), and from leukapheresis to infusion was 39 days (IQR 33–53). In the treated group, 82.2% of patients received bridging therapy, of which 61.1% included chemotherapy. The median follow-up time from the date of infusion (mITT) was 12.2 months (95% CI: 11.8–13.4). The highest overall response rate (ORR) among 144 patients with at least one efficacy assessment was 84.7%, including CR in 72.2%. The median progression-free survival (PFS) from infusion was 9.5 months (95% CI: 6.2–15.1), with 61.3% of patients progression-free at 6 months and 45.6% at 12 months. Median OS from infusion was not reached (51.1% at 24 months), and the median duration of CR was 21.9 months (95% CI: 10.7–NR).

Among 149 patients with safety assessment, CRS was reported in 87.9% of subjects and ICANS in 55%. Grade ≥3 CRS or ICANS reactions occurred in 12.1% and 15.4% of patients, respectively. The median time to onset of CRS was 5 days and its duration was 6 days. For ICANS, these values were 7 days and 7 days, respectively. The main treatments used for CRS and ICANS were tocilizumab (74.8%), corticosteroids (64.9%), anakinra (11.5%) and siltuximab (5.3%, always with tocilizumab). Persistent cytopenia was observed in 19.7% of patients after three months, including grade ≥3 neutropenia in 13 patients and thrombocytopenia in one patient. Grade ≥3 infections occurred in 25.5% of patients, mainly of bacterial aetiology (16.8%). Hospitalisation in the intensive care unit was required in 34.3% of patients, with a median stay of 6 days. The main indications were CRS (44 cases) and/or ICANS (36 cases). With the exception of two grade 5 CRS cases, all patients were discharged after clinical improvement. Among the 152 individuals who received the infusion, 46 died, and the mortality rate unrelated to disease recurrence was 11.2%. The most common cause of death was disease progression (N=29), followed by infections (N=11: seven cases of bacterial sepsis, three deaths due to COVID-19 and one due to cerebral toxoplasmosis), CRS (N=2), myelodysplastic syndrome (N=2) and two deaths of unknown aetiology. Nine patients had previously undergone allogeneic stem cell transplantation, with no evidence of graft-versus-host disease (GVHD).

Exploratory analyses showed that the need for bridging therapy and lack of response to it were associated with shorter OS after infusion. The 12-month survival rate was 58% in patients who did not respond to bridging therapy, 79.9% in patients who responded, and 84.3% in those who did not require bridging therapy. Higher concentrations of C-reactive protein (>30 mg/l) and ferritin above the upper limit of normal at the time of infusion correlated with shorter OS. No differences in OS or PFS were observed based on age, duration of bridging therapy, or lactate dehydrogenase activity.

CAR-T cell expansion parameters (AUC, CMAX, TMAX) were measured in 21 patients. Both CMAX and AUC were higher in patients who developed CRS or ICANS, while TMAX did not differ between groups. The adopted thresholds (60 cells/ml and/or 500 AU) for CMAX and AUC were predictive of PFS but not OS. The study had limitations due to its retrospective nature and missing data. Nevertheless, this is the first ITT analysis from a national consultation on the use of brex-cel in routine practice in patients with relapsed or

refractory MCL. The most common reasons for not administering the therapy were disease progression and manufacturing failures. The results obtained (mITT) were consistent with observations from the ZUMA-2 study and other clinical projects, although PFS appeared to be shorter and the incidence of severe ICANS lower. This may be due to the higher number of patients who had undergone intensive treatment and lower T-cell functionality. The data collected confirm the efficacy of brexu-cel in the population of patients with R/R MCL after BTKi failure, especially in cases where disease control is achieved prior to infusion. In addition, it has been shown that monitoring CAR-T cell expansion in clinical practice is feasible and may be of prognostic significance.

The SYMPATICO study was an international, randomised, double-blind, placebo-controlled phase 3 study conducted at 84 centres in Europe, North America and the Asia-Pacific region. Adult patients (≥18 years of age) with histopathologically confirmed MCL who had relapsed or failed to respond after one to five prior lines of therapy were eligible for participation. Eastern Cooperative Oncology Group (ECOG) performance status 0–2. Participants were randomly assigned (1:1) to one of two groups: the first received oral ibrutinib (560 mg once daily) in combination with venetoclax (dose escalation over 5 weeks to 400 mg daily), the second received ibrutinib with placebo. The combination therapy lasted two years, after which patients continued treatment with ibrutinib alone until disease progression or the occurrence of adverse events preventing further treatment.

Randomisation was performed using an interactive response system based on a stratified permuted block scheme (block sizes 2 and 4). ECOG performance status, number of prior lines of therapy, and risk of tumour lysis syndrome were taken into account. Neither the patients nor the investigators were aware of the treatment group assignment. The primary endpoint was progression-free survival (PFS) as assessed by the investigator in the intention-to-treat (ITT) population. Safety was assessed in all cases where at least one dose of the study drug was administered. The study was registered in the ClinicalTrials.gov database under number NCT03112174 and has completed recruitment. Between April 2018 and August 2019, 267 participants were enrolled in the study, of whom 134 were assigned to the ibrutinib-venetoclax group and 133 to the ibrutinib-placebo group. In the overall population, 211 (79%) were men and 56 (21%) were women.

After a median follow-up of 51.2 months (IQR 48.2–55.3), the median PFS was 31.9 months (95% CI 22.8–47.0) in the ibrutinib-venetoclax group and 22.1 months (95% CI 16.5–29.5) in the ibrutinib–placebo group. This corresponded to a hazard ratio of 0.65 (95% CI 0.47–0.88; p = 0.0052), indicating a statistically significant advantage for combination therapy. The most commonly observed grade 3–4 adverse events were neutropenia (42 [31%] in the ibrutinib–venetoclax group vs 14 [11%] in the control group), thrombocytopenia (17 [13%] vs 10 [8%]) and pneumonia (16 [12%] vs 14 [11%]). Serious adverse events occurred in 81 (60%) of 134 patients treated with combination therapy and in 79 (60%) of 132 patients in the control group. Treatment-related deaths were reported in three patients (2%) in the ibrutinib -venetoclax group (due to COVID-19 infection, cardiac arrest and respiratory failure) and in two patients (2%) in the ibrutinib-placebo group (due to heart failure and COVID-19-related pneumonia). Combination therapy with ibrutinib and venetoclax prolonged progression-free survival compared to ibrutinib monotherapy in patients with relapsed or refractory MCL. The adverse event profile was consistent with that known for both drugs. The results indicate that the combination of these two drugs may provide a favourable efficacy-to-safety ratio in this patient population. In patients with relapsed or refractory mantle cell lymphoma (R/R MCL), clinical trials conducted in recent years have confirmed the efficacy and safety of modern targeted therapies, which has translated into improved outcomes for the treatment of this chronic disease. Ibrutinib, the first Bruton's tyrosine kinase inhibitor (BTKi), has been approved as a continuous treatment for R/R MCL and has shown an overall response rate (ORR) of 77%, a complete remission rate (CRR) of 23% and a median progression-free survival (PFS) of 15.6 months. Subsequent generations of BTKis, such as acalabrutinib and zanubrutinib, have achieved comparably high response rates and favourable PFS values in single-arm studies. Venetoclax, a BH3 protein mimetic, has also shown activity as monotherapy in this patient group, achieving an ORR of 75%, a CRR of 21% and a median PFS of 11.3 months, while retrospective analyses showed a response rate of 40%. Despite these advances, maintaining durable remission in R/R MCL remains difficult, and disease progression remains the leading cause of death.

Based on earlier preclinical observations indicating a synergistic effect of the combination of both drugs in MCL and their different toxicity profiles, a single-centre phase II study (AIM) was conducted combining ibrutinib with venetoclax. After 16 months of follow-up, the overall remission rate assessed by computed tomography was 42%, which exceeded the historical results of ibrutinib monotherapy (9%) at the same time point. On PET/FDG assessment, complete remissions were achieved in 60% of patients after 16 weeks and in

71% over the entire study period. No minimal residual disease (MRD) was detected in flow cytometry in 67% of patients and in allele-specific PCR analysis in 38%. Achieving MRD negativity correlated with improved immunological parameters.

After 88 months of observation, long-term treatment results were presented, assessing response durability, treatment safety, and the possibility of planned treatment interruptions (ETI) in selected patients. The study design and eligibility criteria have been described previously. In short, it was an open-label phase II single-arm trial in which 24 patients with MCL received ibrutinib (560 mg/day) in combination with venetoclax (400 mg/day). Patients with relapsed or refractory MCL and those who were not eligible for first-line treatment with chemoimmunotherapy were included. Initially, treatment was continued until progression or unacceptable toxicity.

Following the publication of results from studies on chronic lymphocytic leukemia, which confirmed the possibility of achieving long-term remission without treatment using venetoclax-based regimens, the protocol was modified to allow treatment discontinuation (ETI) after at least 56 weeks in patients with confirmed complete remission without MRD. Relapse was defined as the presence of MRD in the blood or bone marrow confirmed in two consecutive tests, or radiological progression. Efficacy was assessed, among other things, by analyzing PFS, overall survival (OS), and duration of response. In addition, a modified PFS indicator was used, which excluded progression events during the ETI period, thus defining the time to treatment failure (TTF). The safety assessment included all participants. In addition, a modified PFS indicator was used, which excluded progression events during the ETI period, thus defining the time to treatment failure (TTF). Safety assessment included all study participants. Disease response was assessed by computed tomography, FDG-PET (Deauville scale), bone marrow analysis, and MRD using 8-color flow cytometry with a sensitivity of 10^{-3}–10^{-4}[1]. Survival data were obtained from medical records.

The study was approved by the Peter MacCallum Cancer Centre Bioethics Committee and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Statistical analyses were performed using IBM SPSS Statistics 28.0.1.1(14) using the Kaplan-Meier method, and confidence intervals were calculated using logarithmic transformation. The data collection closure date was September 15, 2023, and all authors had access to the raw data. Between July 2015 and September 2016, 24 individuals were enrolled in the study, 23 of whom had refractory or recurrent MCL after a median of two prior therapies (range 1–6). The median age was 68 years (range, 47–81), TP53 aberrations were found in 48% of patients, and NF-κB pathway mutations in 26%. The median PFS was 28 months (95% CI, 13–82), and the seven-year PFS rate was 30% (95% CI, 14–49). The median OS was 32 months (95% CI, 15–NE), and the seven-year OS rate was 43% (95% CI, 23–62). Seven-year OS rate – 43% (95% CI, 23–62). Seventeen patients achieved complete remission confirmed by PET scan, with a median time to CR of 4 months. The median duration of response was 81 months (95% CI, 22–NE). In this group, four patients died in remission during treatment, three experienced progression, two remain in CR, and eight progressed to ETI.

A total of 15 patients died, 9 of whom died due to disease progression. Two deaths were due to infection in patients with active MCL. Four disease-unrelated deaths occurred in remission—three due to secondary malignancies (small cell lung cancer, myelodysplastic syndrome transformed to AML, glioblastoma multiforme) and one due to heart failure. No new cardiac events were observed after 56 weeks of treatment. The most common adverse events were grade 3 diarrhea (3 cases) and lung infections (2 cases, including one cryptococcal infection). A total of four secondary malignancies were reported, including three fatal ones. After more than seven years of follow-up, the combination therapy of ibrutinib and venetoclax continues to benefit some patients with R/R MCL. Comparison with the results of other single-arm studies suggests that the median PFS of 28 months and OS of 32 months exceed the effects of monotherapy with these drugs[1,4] and the results of sequential use of both preparations, where the median PFS was 3.2 months and OS was 9.4 months. In the SYMPATICO phase III study, the combination of ibrutinib and venetoclax in the SYMPATICO phase III trial, the combination of ibrutinib and venetoclax resulted in longer PFS (31.9 vs. 22.1 months) and prolonged time to next treatment (not reached vs. 35.4 months) compared with ibrutinib plus placebo. Other studies evaluating combinations involving ibrutinib and venetoclax, such as OASIS, showed similar ORR and CRR results, with 4-year PFS and OS rates of 50%. Other regimens containing ibrutinib achieved CRR rates of 37–56% and median PFS of 16 to 24 months. In studies involving venetoclax in first-line treatment, the combination with lenalidomide and rituximab resulted in an ORR of 96% and a CRR of 86%[23]. In a phase II study using venetoclax, umbralisib, and ublituximab, it was possible to discontinue treatment after achieving complete remission. To the best of our knowledge, this analysis is the first description of treatment interruptions (ETI) in patients with MCL treated with a combination of venetoclax and ibrutinib who achieved deep remission

without MRD. The median duration of ETI was 58 months. Although the number of patients included in ETI was small, the results suggest that in selected patients, long-term disease control can be maintained without continuous treatment, and in case of progression, therapy can be effectively resumed. However, the concept of ETI requires further validation in prospective studies. This possibility may also apply to other regimens with BTKi inhibitors and BH3 mimetics. The AIM2 study (NCT05864742) is currently underway, analyzing short-term targeted therapies. This possibility may also apply to other regimens with BTKi inhibitors and BH3 mimetics. The AIM2 trial (NCT05864742) is currently underway, analyzing short-term targeted therapies in patients with relapsed or refractory MCL.

New clinical data from 2025 (including Results of treatment with BTK inhibitors and venetoclax with or without anti-CD20 monoclonal antibody in relapsed or refractory mantle cell lymphoma) confirm that MCL is becoming an increasingly controllable disease. The study aimed to evaluate the efficacy of Bruton's tyrosine kinase inhibitor-based therapy used with venetoclax in patients with refractory or relapsed mantle cell lymphoma, including regimens with or without the addition of anti-CD20 antibody. The analysis included 49 patients treated in China between June 2018 and February 2022.

All patients received Bruton's tyrosine kinase inhibitors in combination with venetoclax (200 mg daily), and some of them also received anti-CD20 monoclonal antibody. Before the combination therapy was implemented, the median number of previous lines of treatment was three (range 2–7). The mean age of patients was 62 years, with a male-to-female ratio of 3.08:1. The study group was dominated by high-risk cases: Ki-67 ≥ 30% (89.8%), blastoid or pleomorphic type (36.7%), high risk according to the International Prognostic Index for mantle cell lymphoma (42.9%), complex karyotype (27.7%), and TP53 mutations (71.4%). In 57.1% of patients, TP53 mutations were present along with other high-risk genes (KMT2D, NSD2, CCND1, NOTCH1, CDKN2A, NOTCH2, SMARCA4), and in 65.3% disease progression was observed within 24 months. Treatment efficacy and survival outcomes were similar in the two-drug and three-drug treatment groups ($p > 0.05$).

The overall response rate was 67.4% and the complete remission rate was 53.1%. Three-year progression-free survival was achieved in 37.5% of patients, and overall survival was achieved in 50.8%. An independent factor worsening the prognosis for progression-free survival was Eastern Cooperative Oncology Group (ECOG) performance status ≥2. In the case of overall survival, both ECOG ≥2 and the co-occurrence of TP53 mutations with other high-risk genes had a negative impact. The most commonly observed adverse events were hematological and pulmonary infections, and the main cause of death was disease progression (19 out of 22 cases). Therapy based on Bruton's tyrosine kinase inhibitors and venetoclax proved effective, especially in the earlier stages of treatment. The addition of anti-CD20 antibody did not provide additional benefits in terms of efficacy and survival. Patients in the very high-risk group require more intensive therapeutic strategies.

Discussion

The introduction of molecularly targeted therapies, such as ibrutinib and venetoclax, has resulted in longer remissions compared to previous treatment standards based mainly on chemotherapy and immunotherapy. The combination of these two drugs uses different mechanisms of action — inhibition of the BTK pathway and induction of apoptosis by BCL-2 blockade — which translates into higher clinical efficacy and a higher percentage of complete responses.

In turn, the use of CAR-T cell therapy, such as KTE-X19, offers the possibility of achieving durable remissions even in patients with refractory disease and after numerous previous lines of treatment. The results of the studies indicate a high response rate with a simultaneous risk of serious adverse events, which emphasizes the need for appropriate patient selection and treatment in specialized centers. Despite clear progress, challenges remain regarding the long-term efficacy and safety of new methods. Not all clinical responses are sustained over time, as confirmed by cases of relapse after achieving complete remission. This requires further research into the mechanisms of resistance and into sequential and combination treatment strategies. It remains equally important to determine the role of minimal residual disease as a potential indicator for therapeutic decisions, including the possible shortening of treatment duration.

Personalization of therapy is certainly an area that requires further development. Identification of response biomarkers may enable better tailoring of treatment to the biological profile of the tumor and the individual characteristics of the patient. In the future, the combination of targeted therapies, immunotherapy, and potentially new forms of treatment may enable more effective and controlled management of MCL.

The SYMPATICO study confirmed that the combination of ibrutinib and venetoclax prolongs progression-free survival compared to ibrutinib monotherapy, with an acceptable safety profile. These results represent a step forward in therapy based on understanding the biology of the cancer and the interactions between lymphoma cell signaling pathways. Furthermore, it can be concluded that the possibility of achieving deep remission with negative minimal residual disease (MRD) opens up the prospect of time-limited treatment, which has so far been characteristic mainly of chronic lymphocytic leukemia. At the same time, the results of the ZUMA-2 study on CAR-T therapy (KTE-X19) show that even in patients with MCL resistant to BTK inhibitor treatment, it is possible to achieve durable remissions. Although associated with toxicity risks, cell therapies are now becoming a viable option for treating patients with advanced or relapsed disease. In light of these observations, future studies should focus on further optimizing treatment sequences, including the role of next-generation BTKs (e.g., zanubrutinib,

Cell therapies, although associated with toxicity risks, are now becoming a viable option for treating patients with advanced or recurrent forms of the disease. In light of these observations, future studies should focus on further optimizing treatment sequences, including the role of next-generation BTKs (e.g., zanubrutinib, pirtobrutinib) and evaluating the efficacy of combination therapies in different biological patient groups. There is also an opportunity to identify predictive biomarkers that will allow for better determination of which patients can safely forego ASCT or shorten treatment time while maintaining a durable response.

Thanks to the integration of targeted therapies, immunotherapy, and advanced cellular strategies, it is possible to create personalized treatment models in which the goal is no longer just to achieve remission, but also to maintain it long-term without the need for intensive chemotherapy. Modern therapeutic approaches offer real hope for changing the natural course of the disease. However, they require long-term observation, further clinical trials, and the creation of treatment algorithms that will enable the optimal use of available methods in clinical practice.

Conclusions

Advances in mantle cell lymphoma therapy are the result of the development of targeted therapies, which enable high response rates even in patients with relapsed or refractory disease. BTK inhibitors, such as ibrutinib, have changed the clinical course of the disease by effectively inhibiting proliferation pathways and prolonging disease control. The combination of ibrutinib and venetoclax exploits the synergistic effects of these drugs, resulting in higher complete remission rates and longer progression-free survival compared to BTK inhibitor monotherapy. The SYMPATICO study reported a clear difference in median time to progression between the study groups, indicating the superiority of combination therapy in this patient population. In turn, CAR-T cell therapy with KTE-X19 enabled durable remissions in a significant proportion of patients with unfavorable disease, including those who had failed BTK inhibitor therapy. The rates of complete remission and progression-free survival observed in this study are higher than those seen with previous standard treatment options for this patient group. Although this therapy is associated with serious risks of toxicities, including cytokine release syndrome and neurological complications, most events were manageable in a clinical setting.

The combination of targeted therapies and cell therapy opens up new possibilities for patients with mantle cell lymphoma, especially in populations with limited treatment options. The data obtained indicate a real chance of achieving deep and durable remissions in patients with relapsed or refractory disease, as well as the possibility of better tailoring therapeutic strategies to individual clinical courses. The use of modern therapeutic strategies may change the clinical picture of mantle cell lymphoma from a disease with a very unfavorable course to a form that can be effectively controlled for a long time. To achieve this goal, future research should focus on identifying predictive markers of response, analyzing the maintenance of remission after the end of therapy, and developing strategies to reduce adverse effects while maintaining high treatment efficacy.

Author's Contributions Statement:

Conceptualization: Hanna Pietruszewska, Katarzyna Kleszczewska, Agnieszka Pruska, Natalia Senatorska, Julia Rarok, Daria Godlewska, Monika Banaszek, Agata Panfil, Julia Błocka, Agata Lurka

Methodology: Hanna Pietruszewska, Katarzyna Kleszczewska, Agnieszka Pruska, Natalia Senatorska, Julia Rarok, Daria Godlewska, Monika Banaszek, Agata Panfil, Julia Błocka, Agata Lurka

Investigation: Hanna Pietruszewska, Katarzyna Kleszczewska, Agnieszka Pruska, Natalia Senatorska, Julia Rarok, Daria Godlewska, Monika Banaszek, Agata Panfil, Julia Błocka, Agata Lurka

Formal analysis: Hanna Pietruszewska, Katarzyna Kleszczewska, Agnieszka Pruska, Natalia Senatorska, Julia Rarok, Daria Godlewska, Monika Banaszek, Agata Panfil, Julia Błocka, Agata Lurka

Writing-rough preparation: Hanna Pietruszewska, Katarzyna Kleszczewska, Agnieszka Pruska, Natalia Senatorska, Julia Rarok, Daria Godlewska, Monika Banaszek, Agata Panfil, Julia Błocka, Agata Lurka

Writing-review and editing: Hanna Pietruszewska, Katarzyna Kleszczewska, Agnieszka Pruska, Natalia Senatorska, Julia Rarok, Daria Godlewska, Monika Banaszek, Agata Panfil, Julia Błocka, Agata Lurka

Resources: Hanna Pietruszewska, Katarzyna Kleszczewska, Agnieszka Pruska, Natalia Senatorska, Julia Rarok, Daria Godlewska, Monika Banaszek, Agata Panfil, Julia Błocka, Agata Lurka

Supervision: Hanna Pietruszewska, Katarzyna Kleszczewska, Agnieszka Pruska, Natalia Senatorska, Julia Rarok, Daria Godlewska, Monika Banaszek, Agata Panfil, Julia Błocka, Agata Lurka

All authors have read and agreed with the published version of the manuscript.

Funding Statement: The study did not receive external funding.

Informed Consent Statement: Not applicable.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article's bibliography.

Acknowledgements: Not applicable.

Conflict of Interest Statement: The authors report no conflict of interest.

REFERENCES

1. E. Silkenstedt , M. Dreyling *To consolidate or not to consolidate: the role of autologous stem cell transplantation in mantle cell lymphoma (MCL*). Hematology Am Soc Hematol Educ Program 2024; 2024 (1): 42–47. doi: https://doi.org/10.1182/hematology.2024000546
2. ESMO Clinical Practice Guidelines — Mantle Cell Lymphoma (current guidelines, ESMO/2024–2025).
3. Flinn, I. W., van der Jagt, R., Kahl, B., Wood, P., Hawkins, T., MacDonald, D., Simpson, D., Kolibaba, K., Issa, S., Chang, J., Trotman, J., Hallman, D., Chen, L., & Burke, J. M. (2019). First-Line Treatment of Patients With Indolent Non-Hodgkin Lymphoma or Mantle-Cell Lymphoma With Bendamustine Plus Rituximab Versus R-CHOP or R-CVP: Results of the BRIGHT 5-Year Follow-Up Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, *37*(12), 984–991. https://doi.org/10.1200/JCO.18.00605
4. Handunnetti, S. M., Anderson, M. A., Burbury, K., Thompson, P. A., Burke, G., Bressel, M., Di Iulio, J., Hicks, R. J., Westerman, D., Lade, S., Pott, C., Agarwal, R., Koldej, R., Ritchie, D., Dreyling, M., Dawson, M. A., Dawson, S.-J., Seymour, J. F., Roberts, A. W., & Tam, K. S. (2024). *Seven-year results of venetoclax and ibrutinib therapy in mantle cell lymphoma: Durable responses and treatment-free remissions*. *Blood, 144*(8), 867–872. https://doi.org/10.1182/blood.2023023388
5. Herbaux C, Bret C, Bachy E, Bories P, Di Blasi R, Cuffel A, Gastinne T, Lamy T, Roussel M, Bouabdallah K, Beauvais D, Cartron G, Bay JO, Blaise D, Rubio MT, Mohty M, Le Bras F, Casasnovas O, Guy J, Guidez S, Llorente CC, Hermine O, La Rochelle LD, Carras S, Guffroy B, Caillat-Zucman S, Houot R, Le Gouill S. Brexucabtagene autoleucel in relapsed or refractory mantle cell lymphoma, intention-to-treat use in the DESCAR-T registry. Haematologica. 2024 Nov 1;109(11):3745-3750. doi: 10.3324/haematol.2023.284786. PMID: 38899352; PMCID: PMC11532701.
6. Kamdar M, Li H, Chen RW, Rimsza LM, Leblanc ML, Fenske TS, Shea TC, Barr PM, Phillips TJ, Leonard JP, Kahl BS, Friedberg JW, Smith SM. Five-year outcomes of the S1106 study of R-hyper-CVAD vs R-bendamustine in transplant-eligible patients with mantle cell lymphoma. Blood Adv. 2019 Oct 22;3(20):3132-3135. doi: 10.1182/bloodadvances.2019000526. PMID: 31648328; PMCID: PMC6849956.
7. Song Y, et al. Zanubrutinib in relapsed/refractory mantle cell lymphoma — Long-term registration results. Blood / Phase II publication and analysis. 2022.
8. Swerdlow SH, Campo E, Harris NL et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Revised 4th Edition. Lyon: International Agency for Research on Cancer (IARC); 2017.

9. Tam CS, O'Connor OA, et al. (Ibrutinib studies in relapsed/refractory MCL) *N Engl J Med* / key phase II studies.
10. Tam, C. S., Anderson, M. A., Pott, C., Agarwal, R., Handunnetti, S., Hicks, R. J., Burbury, K., & Roberts, A. W. (2018). *Ibrutinib and venetoclax for mantle-cell lymphoma. The New England Journal of Medicine, 378*(13), 1211–1223. https://doi.org/10.1056/NEJMoa1715519
11. Wang M., et al. Ibrutinib + venetoclax in MCL — long-term/new results and randomizations (Lancet Oncology; 2024–2025 reports).
12. Wang M., et al. Three-year follow-up of KTE-X19 in relapsed/refractory MCL (ZUMA-2 follow-up / J Clin Oncol 2023).
13. Wang M., Munoz J., Goy A., et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med.* 2020;382:1331–1342. (ZUMA-2 pivotal).
14. Wang, M., Munoz, J., Goy, A., Locke, F. L., Jacobson, C. A., Hill, B. T., Timmerman, J. M., Holmes, H., Jaglowski, S., Flinn, I. W., McSweeney, P. A., Miklos, D. B., Pagel, J. M., Kersten, M. J., Milpied, N., Fung, H., Topp, M. S., Houot, R., Beitinjaneh, A., Peng, W., … Reagan, P. M. (2020). KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. *The New England journal of medicine*, *382*(14), 1331–1342. https://doi.org/10.1056/NEJMoa1914347
15. Yang, P., Li, C., Liu, S., Wang, J., Chen, Y.-T., Zhang, W.-L., & Jing, H.-M. (2025). *Results of treatment with BTK inhibitors and venetoclax with or without anti-CD20 monoclonal antibody in relapsed or refractory mantle cell lymphoma*. Annals of Hematology, 104(4), 2361–2371. https://doi.org/10.1007/s00277-025-06379-x