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Review

CAR T-cell therapy for follicular lymphoma and mantle cell lymphoma

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***Abstract*:** Patients with relapsed and/or refractory (R/R) follicular lymphoma (FL) and mantle cell lymphoma (MCL) have a poor prognosis with anticipated short progression-free and overall survivals. Two CD19-directed chimeric antigen receptor T-cell (CAR T) therapies are approved in the United States for R/R FL, namely, axicabtagene ciloleucel (axi-cel) and tisagenlecleucel. The results of ZUMA-5 and ELARA studies led to the approval of axi-cel and tisagenlecleucel, respectively, after demonstrating high overall (ORR) and complete response (CR) rates in this high-risk population of FL patients who had received a median of 3 (range = 2–4) and 4 (range = 2–13) prior lines of therapies, respectively. For instance, the ORR for ZUMA-5 was 94% (CR = 79%), and for ELARA, it was 86% (CR = 69.1%). Pertaining to MCL, brexucabtagene autoleucel is approved for R/R MCL based on results of the ZUMA-2 study. In the latter study, despite the fact that all R/R MCL patients had been exposed to prior Bruton's tyrosine kinase inhibitors, the reported ORR was 91%, with 68% achieving a CR. These results undoubtedly demonstrate a strong efficacy of CAR T therapy in both R/R FL and MCL; yet, one must acknowledge the relatively short follow-up time of all aforementioned studies. Thus, longer follow-up showing durability of responses and long-term safety is definitely needed.

Keywords: CD19, chimeric antigen receptor T cell therapy, follicular lymphoma, mantle cell lymphoma, relapsed and refractory disease

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Introduction

Advances in T-cell engineering have brought chimeric antigen receptor T-cell therapy (CAR T) from the bench to the bedside. CAR Ts targeting CD19 have revolutionized the treatment of various B-cell lymphomas by demonstrating impressive and durable responses. CD19-targeted CAR Ts are approved for various relapsed and refractory (R/R) B-cell lymphomas, namely, diffuse large B-cell lymphoma (DLBCL), whether *de novo* or transformed, primary mediastinal B-cell lymphoma (PMBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL).[1–6] Two products, tisagenlecleucel and brexucabtagene autoleucel (brexu-cel), are also approved for patients with R/R B-cell acute lymphoblastic leukemia (B-ALL).[7,8]

Specifically for FL, axicabtagene ciloleucel (axi-cel) was approved by the US Food and Drug Administration (FDA) in March 2021 for treatment of adults with R/R FL after failing two or more lines of systemic therapy.[4] Similarly, in May 2022, the FDA also granted accelerated approval of tisagenlecleucel for a similar indication.[5] In addition, brexu-cel (formerly known as KTE-X19), also received USFDA approval for the treatment of adult patients with R/R MCL in June 2020 following a priority review and FDA breakthrough therapy designation based on the results of ZUMA-2.[6] In this study, almost all patients had failed to respond or progressed on Bruton's tyrosine kinase inhibitors (BTKis).[6]

Here, we provide a thorough review of the pivotal studies that led to the approval of these commercially available CAR Ts for FL and MCL, and we also summarize other studies that have evaluated other CAR T products for the treatment of these two diseases.

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Follicular lymphoma (FL)

FL represents the second most common lymphoma diagnosed in the Western Hemisphere, with a median age at presentation of approximately 65 years.[9,10] Over 80% of patients harbor the chromosomal abnormality t(14;18) with consequent overexpression of the B-cell lymphoma 2 (BCL-2) protein.[11] Most patients with low-grade FL (grade 1, 2, or 3A) present with advanced disease stage at initial diagnosis. Yet, treatment is not necessarily required unless patients develop symptomatic disease, impaired organ function, and symptomatic cytopenias, among other reasons.[12,13] When patients with advanced stage disease require treatment, several chemoimmunotherapeutic combinations can be used based on various studies including rituximab or obinutuzumab with cyclophosphamide, vincristine, and prednisone (CVP); or rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP-R); or bendamustine plus rituximab (BR) or obinutuzumab showing non-inferiority to conventional chemoimmunotherapy regimens.[14–17] The combination of lenalidomide and rituximab remains a valid option in many patients.[16] The outcomes of patients progressing early (within 24 months) after initial first-line containing anti-CD20 monoclonal antibody (POD24) remain very poor.[18]

The bulkiness and aggressive clinical presentation of the disease in patients with R/R FL requiring treatment could guide treatment choice, which is often tailored to the patient's performance status and existing comorbidities. Treatment options for second-line and beyond include chemoimmunotherapy, radioimmunotherapy, phosphoinositide 3-kinase inhibitors (PI3Kis), tazemetostat [an inhibitor of enhancer of zeste homolog 2 (*EZH2*)], and in some cases, autologous (auto-HCT) or an allogeneic (allo-HCT) hematopoietic cell transplant.[19–26] Several PI3Kis were withdrawn for the market because of safety concerns and pending results from phase III trial.[27] Unfortunately, as the disease progresses or becomes more refractory, the efficacy of conventional treatment options becomes more limited with a complete response (CR) rate of approximately 13%.[22]

Initial efforts to study the efficacy of CAR Ts in lymphoma date back to over one decade ago. In 2010, Kochenderfer *et al.*[28] treated a patient with advanced FL with a CD19 CAR T-cell product following a lymphodepleting regimen of cyclophosphamide 60 mg/kg/day × 2 days followed by fludarabine 25 mg/m^2/day × 5 days. The day following the fifth fludarabine dose, the patient received anti-CD19-CAR-transduced T cells in combination with interleukin-2 (IL-2).[28] The authors reported significant regression consistent with a partial response (PR) that lasted approximately 32 weeks. Moreover, the authors reported that B-cell precursors were selectively eliminated from the bone marrow after infusion of anti-CD19-CAR-transduced T cells.[28] This case highlighted a proof-of-concept and demonstrated the efficacy of CAR T-cell therapy even in the setting of bulky disease.[28] Nine years later, in a phase I/II study, Hirayama *et al.*[29] assessed the use of anti-CD19 CAR T-cell therapy in 21 patients with R/R FL ($n = 8$) or transformed FL ($n = 13$). CR was achieved in 7/8 patients with R/R FL (CR rate = 88%) who remained in remission after 24 months of follow-up. None of the patients developed severe (grade > 3) cytokine release syndrome (CRS) or neurological event (NE).

In 2021, axi-cel was approved for the treatment of patients with R/R FL after failing two or more lines of systemic therapy based on results of the ZUMA-5 study, a single-arm, phase II, multicenter international trial.[4] The primary endpoint of ZUMA-5 was overall response rate (ORR) as per assessment of an independent radiology review committee using the Lugano classification.[30] In ZUMA-5, 148 patients received axi-cel [FL = 124 (84%) and marginal zone lymphoma (MZL) = 24 (16%)].[4] The median age of patients with FL was 60 (range = 53–67) years, with 31% of cases being ⩾65 years of age. A total of 64 (52%) cases were reported as having a high tumor bulk using the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria.[12] The median number of prior lines of therapy was 3 (range = 2–4), and 78 (63%) had ⩾3 lines of therapy preceding axi-cel. At a median follow-up of 17.5 months, 84 (81%) patients with FL were eligible for the primary analysis: ORR was described in 79 (94%) patients and 66 (79%) patients achieved a CR.[4] Median time to initial and to CR were 1 month and 1 month, respectively. CRS was reported in 97 (78%) of 124 FL patients, with 8 (6%) cases being grade > 3. NEs were reported in 70 (56%) of 124 patients with FL; grade 1–2 and grade 3–4 NEs were reported in 51 (41%) and 19 (15%) FL cases, respectively. The median overall survival (OS) was not reached, and the 18-month OS was

94.1% in patients achieving a CR and 84.6% in those achieving a PR.[4] An updated analysis of ZUMA-5 presented at the annual meeting of the American Society of Hematology (ASH) in December 2021 showed that among FL patients progressing within less than 2 years (POD24) after initial chemoimmunotherapy the median duration of response (MDR) was 38.6 months *versus* reported as not reached in those without POD24.[31]

Tisagenlecleucel was granted accelerated approval by the FDA in May 2022 for the treatment of adults with R/R FL after failing two or more lines of systemic therapy. In the ELARA study, a phase II international study enrolling 98 patients, the median age of patients was 57 years, and the median number of prior lines of therapy was 4 (range = 2–13), including 36% that had failed a prior auto-HCT.[5] The primary endpoint was CR rate. A total of 97 out of 98 enrolled patients received tisagenlecleucel, and CR rate was reported at 69.1% with an ORR of 86.2%.[5] The CRS, NE, and the immune effector cell–associated neurotoxicity syndrome (ICANS) rates were 48.5% (grade ⩾3 = 0), 37.1% (grade ⩾3 = 3%), and 4.1% (grade ⩾3 = 1%), respectively, with no reported treatment-related deaths.[5] With a median follow-up of 17 months, a subgroup analysis of the ELARA study showed a 9-month duration of response (DOR) of 76% and a 1-year progression-free survival (PFS) of 67%.[32] The 9-month PFS in patients in CR was 85.5%.[32] The authors reported a lower 1-year PFS in patients with POD24 (60.8% *versus* 77.9%), those with a high baseline total metabolic tumor volume (TMTV, >510 cm^3) (54.5% *versus* 68.5%), and those who had received ⩾5 prior lines of therapy (59.6% *versus* 69.7%).[32] These and other patient-, disease- and treatment-related characteristics of the two studies that led to the approval of axi-cel and tisagenlecleucel in FL are summarized in Table 1.

Mantle cell lymphoma (MCL)

MCL is a rare subtype of B-cell non-Hodgkin lymphoma (NHL) defined by the presence of t(11;14)(q13; q32), resulting in cyclin D1 overexpression, while there are some cases of t(11;14) negative MCL.[33] Clinical presentation varies from an indolent to a more aggressive course. Several trials have established the role of high-dose cytarabine plus anthracycline-based

Table 1. Studies that led to the approval of CAR T-cell therapies for FL.

Clinical trials	CAR T-cell product	Study type	*N*	Median (range) age, years	Disease characteristics	Median (range), prior lines of therapy	Toxicities	Response	Survival
ZUMA-5 [4, 31]	Axicabtagene ciloleucel	Phase II, single-arm	124[a]	60 (53–67)	FLIPI high-risk ⩾ 3 = 44% High tumor bulk by GELF criteria = 52% Prior auto-HCT = 24% Refractory to last line of therapy = 68% POD24 = 55%	3 (2–4)	CRS Any grade = 78% Grade 3–4 = 15% NE Any grade = 56% Grade 3–4 = 6%	ORR = 94% CR = 79%	OS = 81% (2 years)
ELARA [5, 32]	Tisagenlecleucel	Phase II, single arm	97	57 (49–64)	FLIPI high-risk ⩾3 = 59.8% High tumor bulk by GELF criteria = 63.9% Prior auto-HCT = 36.1% Refractory to last line of therapy = 78.4% POD24 = 62.9%	4 (2–13)	CRS Any grade = 48% Grade 3–4 = 0 NE Any grade = 11.3% Grade 3–4 = 3%	ORR = 86% CR = 69.1%	PFS = 67% (1 year)

auto-HCT, autologous hematopoietic cell transplantation; CAR, chimeric antigen receptor; CR, complete remission; CRS, cytokine release syndrome; FLIPI, follicular lymphoma international prognostic index; GELF, The Groupe d'Etude des Lymphomes Folliculaires; *N*, number of patients; NE, neurologic events; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POD24, progression of disease within 2 years.
[a]This is the number of patients with FL.

chemoimmunotherapy regimens, like CHOP-R or alike, as backbone therapy for patients with advanced disease followed by auto-HCT in first complete remission in fit patients.[34,35–37] In the MCL Younger phase III trial, the use of R-DHAP (dexamethasone, cytarabine, and cisplatin) followed by auto-HCT improved PFS and OS after long-term follow-up compared with R-CHOP/auto-HCT.[38] Other non-aggressive therapy would be the combination of bendamustine and rituximab.[15] Various prospective and retrospective studies showed improved OS with the use of rituximab maintenance for 3 years after induction therapy with or without auto-HCT, with a survival advantage after auto-HCT.[39,40] BTKis have revolutionized the outcome of patients with R/R MCL. Targeted therapy was incorporated into conventional therapy with ibrutinib, a BTKi. In a study assessing the combination of ibrutinib and rituximab in patients with R/R MCL, the ORR and CR rates were high, but not in patients with high Ki-67 (>50%).[41] Patients relapsing after BTK inhibitors have poor survival of 6–10 months.[42]

In July 2022, brexu-cel was approved for the treatment of R/R MCL. This approval was based on the results of the ZUMA-2 multicenter phase II trial.[6] ZUMA-2 evaluated the use of brexu-cel for the treatment of R/R MCL. A total of 74 patients were enrolled, but only 68 received the product. Three patients had manufacturing failure and two died from disease progression before infusion. Median time from leukapheresis to delivery of brexu-cel was 16 days. All patients had received a BTKi, and had relapsed after or were refractory to this therapy. In the intent to treat population, the ORR was 85% ($n=63$ of 74), with 59% ($n=44$ of 74) achieving a CR. The 1-year estimated PFS and OS were 61% and 83%, respectively. PFS was similar in all subgroups including in patients with Ki-67 >50% ($n=37$), blastoid subtype ($n=17$), tumor protein P53 (TP53) mutation ($n=6$), POD24 ($n=33$), and minimal residual disease (MRD)-positive ($n=4$). The most common > grade 3 adverse events were cytopenias in 94% and infections in 32% of patients. CRS was seen in 91% of the patients, with 15% having grade ⩾3. Neurologic events occurred in 63% of the patients, with 31% of them having grade ⩾3. Median time from infusion to CRS and neurologic events occurrence were 2 and 8 days, respectively (Table 2).[6] Updated results after a median follow-up of 35.6 months showed a high ORR and CR rate of 91% and 68%, respectively. The median duration of response was 28.2 months. The median PFS and OS were 25.8 and 46.6 months, respectively. Nineteen patients were analyzed for MRD assessment at 6 months; 15 (79%) were MRD-negative with an ORR of 100%. Two patients had therapy-related myeloid diseases, one with myelodysplastic syndrome and another with acute myeloid leukemia at 25.2 and 37.5 months after therapy, respectively.[43] An exploratory analysis showed a trend toward attenuated T-cell functionality in patients who received prior bendamustine. Furthermore, patients who received bendamustine within 6 months of apheresis had lower CAR T peak compared with those who received it more than 6 months prior to undergoing apheresis. These results indicate that brexu-cel is safe and yields durable responses in patients with R/R MCL. The effect of bendamustine on T-cell functionality and CAR T peak should be further explored especially with the use of bendamustine as bridging therapy or a lymphodepleting agent.[44]

Iacoboni *et al.* reported a real-world study data of patients with R/R MCL treated with brexu-cel as part of the European Early Access Program in 11 European centers (Table 2).[45] A total of 39 patients underwent apheresis and 33 (85%) received the product. The remaining 6 patients did not receive the product due to progressive disease ($n=3$), achieving CR after bridging ($n=2$), and infection ($n=1$). The study included five patients who had failed an allo-HCT, a patient population that was not included in the ZUMA-2 trial. The median follow-up was 10.1 months. In this real-world study, 86% ($n=32$) of the patients received bridging therapy compared with 37% in the ZUMA-2 trial ($p<0.01$). The median time from apheresis to product delivery was 29 days, significantly longer than that reported in the ZUMA-2 trial (29 *versus* 16 days, $p<0.01$), without any reported death prior to the receipt of CAR T product.[6,45] The ORR was 91% ($n=30$), and CR was observed in 79% ($n=26$) of the patients, similar to what was reported in the ZUMA-2 trial. The 1-year PFS and OS were 51% and 61%, respectively, slightly lower than the ZUMA-2 trial results. The authors attributed this difference to the higher non-relapse mortality observed in the real-world data. In fact, five deaths were reported due to severe infections ($n=4$) or deconditioning related to prolonged steroid therapy ($n=1$). Thirty (91%) patients developed CRS, but only one patient had grade

Table 2. Studies evaluating CAR T-cell therapy for MCL.

Clinical trials	CAR T-cell product	Study type	*N*	Median (range) age, years	Disease characteristics	Median (range), prior lines of therapy	Toxicities	Response	Survival
Approved CAR T-cell therapy for MCL									
ZUMA-2 trial [6, 43]	Brexucabtagene autoleucel	Phase II, single arm	74	65 (38–79)	Blastoid morphology = 31% Ki67 >30% = 82% TP53 mutation = 17% Prior BKTi = 100%	3 (1–5)	CRS Any grade = 91% Grade 3–4 = 15% NE Any grade = 63% Grade 3–4 = 31%	ORR = 91% CR = 68%	PFS = 61% OS = 83% (1 year)
European Early Access Program [45]	Brexucabtagene autoleucel	Real-world data	39	67 (47–79)	Blastoid morphology = 27% Ki67 >30% = 49% TP53 mutation = 12% (Not available in 42%) Prior BKTi = 100%#	2 (1–8)	CRS Any grade = 91% Grade 3–4 = 2.6% NE Any grade = 64% Grade 3–4 = 36%	ORR = 91% CR = 79%	PFS = 51% OS = 61% (1 year)
US CAR T consortium [46]	Brexucabtagene autoleucel	Real-world data	189	67 (34–89)	Blastoid morphology = 45% Ki67 >30% = 77% TP53 mutation = 46% Prior BKTi = 82%	3 (1–9)	CRS Any grade = 91% Grade 3–4 = 8% NE Any grade = 61% Grade 3–4 = 32%	ORR = 89% CR = 80%	PFS = 63% OS = 85% (6 months)
Others non-approved CAR T-cell therapy for MCL									
TRANSCEND NHL 001 [47]	Lisocabtagene maraleucel	Phase I	41[a]	67 (36–80)	Blastoid morphology = 37.5% Ki67 >30% = 72% TP53 mutation = 22% Prior BKTi = 87.5%	3 (1–7)	CRS Any grade = 50%[b] Grade 3–4 = 3%[b] NE Any grade = 28%[b] Grade 3–4 = 9%[b]	ORR = 84% CR = 59%	NR

BTKi, Bruton's tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CR, complete remission; CRS, cytokine release syndrome; MCL, mantle cell lymphoma; NE, neurologic event; NHL, non-Hodgkin lymphoma; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TP53, tumor protein P53.
[a]This is the number of patients with MCL.
[b]Estimated from numbers published in the trial.

⩾3. Neurologic events were reported in 21 (64%) patients, with 12 (36%) having grade ⩾3.[45]

Another published real-world data of the use of brexu-cel in patients with R/R MCL were reported by the US lymphoma CAR T consortium from 16 participating centers (Table 2).[46] A total of 189 patients underwent leukapheresis, and 167 (88%) were infused. Interestingly, 10% of patients had central nervous system (CNS) involvement, and 78% ($n=130$) would not have met the eligibility criteria for ZUMA-2 trial. A total of 86% of patients were exposed to BTKi, and 68% received bridging therapy of BTKi, venetoclax, or chemo-immunotherapy. Median time from leukapheresis to lymphodepleting chemotherapy was 28 days (17–140), which was longer than in ZUMA-2. ORR and CR rates were 89% and 80%, respectively. ORR and CR were 89% and 79% for BTKi-exposed and 91% and 83% for BKTi-naïve patients. CRS and ICANS were seen in 91% and 61% of patients, with 8% and 32% being grade >3, respectively. Despite including a higher proportion of high(er)-risk patients, efficacy and safety results were comparable with ZUMA-2.

Lisocabtagene maraleucel (liso-cel) is a CD19-directed CAR T product currently approved for R/R large B-cell lymphoma after two or more lines of systemic therapy but not approved for MCL. Liso-cel has been studied in a small number of patients with MCL in the TRANSCEND NHL 001 phase I trial.[47] A total of 41 patients were included, but only 32 patients received liso-cel. High-risk features including blastoid morphology, Ki67 >30%, *TP53* mutation, and complex karyotype were seen in 37.5% ($n=12$), 72% ($n=23$), 22% ($n=7$), and 34% ($n=11$) of patients, respectively. Among patients c exposed to BTKi (87.5%), 34% were refractory. The ORR was 84%, and CR rate was 59%. CRS and neurologic events were seen in 50% and 28%, and 3% and 9% had grade >3 CRS and NE, respectively. These results indicate that liso-cel is associated with low rate of high-grade toxicity in patients with MCL with promising efficacy data. The study is still ongoing, and longer follow-up data are certainly awaited (NCT02631044).

Discussion

CD19 autologous CAR T treatments have demonstrated impressive efficacy in patients with R/R FL and MCL and have improved the adverse prognosis of these diseases, particularly in those with high-risk features/bulky disease. Consequently, modern treatment algorithms for FL, MCL, and other B-cell lymphoid malignancies nowadays incorporate CAR T-cell therapies as part of the recommended options for these patients.

In the case of FL, two products are commercially available in the United States, namely, axi-cel and tisagenlecleucel.[4,5] Studies leading to the approval of these two products, namely, ZUMA-5 and ELARA, share several similarities.[4,5] For instance, both represented single-arm phase II studies, the number of enrolled patients with FL was comparable at 124 and 97, respectively. Also, the median age of patients was also comparable 60 years *versus* 57 years, respectively.[4,5] Yet, notwithstanding the limitations of non-randomized comparisons between studies, the ELARA study appears to have enrolled a higher proportion of patients with high-risk disease features [follicular lymphoma international prognostic index (FLIPI) high risk = 59.8% *versus* 44%, high tumor bulk by GELF criteria = 63.9 *versus* 52%, refractory to last line of therapy = 78.4% *versus* 68%, and POD24 = 62.9% *versus* 55%] (Table 1). In addition, a higher proportion of patients in the ELARA study had also failed a prior auto-HCT (36.1% *versus* 24%).[5]

While acknowledging these differences, both ZUMA-5 and ELARA studies demonstrated impressive efficacy with ORR of 94% and 86% and CR rates of 79% and 69.1%, respectively (Table 1). These results show improved outcomes of patients with R/R FL refractory to two lines of treatment. The traditional ORRs with EZH2 inhibitors are approximately 69%. Yet, CR rates remains very low (13%) compared with those seen with axi-cel or tisagenlecleucel.[22] Given the high complete remission rates with CAR T therapy, we believe that treatments like axi-cel or tisagenlecleucel ought to be the preferred options in patients with R/R FL that failed two or more lines of systemic therapies. The optimal treatment following CAR T relapse/progression remains an area of future research. Although initial analysis of CAR T-cell therapies reported a beneficial effect of axi-cel and tisagenlecleucel across different disease prognostic risk factors, a recently presented update of the ELARA study during ASH 2021 showed an inferior 1-year PFS in patients treated with tisagenlecleucel with

POD24 (60.8% *versus* 77.9%), those with high baseline TMTV (>510 cm^3) (54.5% *versus* 68.5%), and those who had received ⩾5 prior lines of therapy (59.6% *versus* 69.7%) (Table 1).[32] These findings highlight the need to consider adjuvant treatment approaches to help reduce the risk of relapse or progression in this high-risk population. Potential approaches may include incorporating targeted therapies in the post-CAR T-cell consolidation/maintenance setting or, perhaps, considering an allo-HCT in patients with a suitable human leukocyte antigen (HLA)-compatible donor and who are deemed fit for the procedure.

In terms of toxicity, ZUMA-5 reported an apparently higher incidence of CRS (any grade = 78% *versus* 48%, grade ⩾3 = 15% *versus* 6%) and neurologic events (any grade = 56% *versus* 11.3%, grade ⩾3 = 6% *versus* 0) when compared with ELARA.[4,5] These findings appear consistent with other studies evaluating axi-cel and tisagenlecleucel in other histologies.[1,2] We believe that a better understanding of the pathogenesis of CRS and neurotoxicities have led to earlier diagnosis and more prompt treatment interventions of these unique toxicities.[48,49]

Pertaining to MCL, the results of ZUMA-2 showed safety and impressive efficacy of brexu-cel in R/R MCL. Three-year follow-up data showed high ORR of 91% with 68% CR rate (Table 2). These responses are much higher compared with standard of care, with ORR/CR rate of 66%/20% and a median PFS of 12.8 months with BTKi in patients relapsing after chemoimmunotherapy treatments.[50] Furthermore, real-world studies from Europe and the United States confirm results of ZUMA-2 showing comparable safety and efficacy in a population in which some patients would not have been eligible for inclusion in ZUMA-2. Furthermore, in the US consortium real-world study of brexu-cel in R/R MCL, patients BTKi-exposed and BKTi-naïve had comparable ORR (89% *versus* 91%) and CR rates (79% *versus* 83%). A third cohort of the ZUMA-2 trial is currently evaluating the safety and efficacy of brexu-cel in patients with R/R MCL who had received up to five lines of therapy but not a BTKi (NCT04880434) (Table 3).

Table 3. Summary of ongoing CAR T-cell therapy trials in follicular and mantle cell lymphoma.

Study disease	Treatment	Study type	ClinicalTrial.gov number
R/R LBCL, R/R FL	Allogeneic CAR T-cell, CD19 (ALLO-501)	Phase I	NCT03939026
R/R B-cell lymphoma	CD19 CAR T	Phase I/II	NCT05326243
R/R NHL	CD19 CAR T	Phase II	NCT04089215
R/R B-cell NHL	Third-generation CD19 CAR T	Phase I	NCT04049513
R/R B-cell lymphoma	Acalabrutinib and axi-cel	Phase I/II	NCT04257578
R/R B-cell NHL	CD19/CD20 CAR T	Phase II	NCT04007029
R/R NHL	CD20 CAR T	Phase I/II	NCT03277729
R/R NHL	BTKi and CD19 CAR T	Phase III	NCT05020392
R/R B-cell NHL	Third-generation CAR T	Phase I/II	NCT03676504
R/R B-cell malignancies	CD19/20 CAR T	Phase I/II	NCT04186520
R/R B-cell malignancies	JCAR017 combinations (durvalumab, CC-122, ibrutinib, CC-220, relatlimab, nivolumab, CC99282)	Phase I/II	NCT03310619
R/R B-cell NHL	Lisocabtagene maraleucel	Phase I	NCT02631044
R/R B-cell malignancies	Allogeneic CD20 gamma delta CAR T (ADI-001)	Phase I	NCT04735471

(Continued)

Table 3. (Continued)

Study disease	Treatment	Study type	ClinicalTrial.gov number
R/R MCL	BAFFR-targeting CAR T	Phase I	NCT05370430
R/R MCL	Acalabrutinib and CAR T	Phase II	NCT04484012
Previously untreated high-risk MCL	Acalabrutinib/rituximab followed by brexu-cel	Phase I	NCT05495464
R/R MCL	Cohort 3 of ZUMA-2, R/R MCL, no prior BTKi	Phase II	NCT04880434

Axi-cel, axicabtagene ciloleucel; BAFFR, B-cell activating factor-receptor; Brexu-cel, brexucabtagene autoleucel; BTKi, Bruton's tyrosine kinase inhibitor; CAR T, chimeric antigen receptor T-cell; FL, follicular lymphoma; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; R/R, relapsed and refractory.

A cost-effective Canadian analysis used data from ZUMA-2 trial and compared the use of brexu-cel with best supportive care. This study showed an incremental cost-utility ratio of 88,503 CAD per quality-adjusted life-year (QALY) gained with the use of brexu-cel compared with best supportive care.[51] Other targets are being investigated in MCL, including B-cell activating factor-receptor (BAFFR)-CAR T-cell in R/R disease (NCT05370430). Dual CD19 and CD20 CAR T-cells are also being investigated in the R/R setting (NCT04186520).

Although these CD19-directed CAR T-cell products have yielded impressive results in R/R FL and MCL, one must acknowledge the relatively short follow-up time of these studies. Accordingly, longer follow-up showing durability of responses in FL and MCL and long-term safety is undoubtedly needed.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Author contributions
Razan Mohty: Conceptualization; Writing – original draft; Writing – review & editing.

Mohamed A. Kharfan-Dabaja: Conceptualization; Writing – original draft; Writing – review & editing.

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