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BISPECIFIC ANTIBODIES AND CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY FOR INDOLENT LYMPHOMA

Introduction

Classic follicular (FL) and marginal zone (MZL) lymphomas are the primary indolent non-Hodgkin lymphomas (iNHL). Once first-line therapy is initiated, the majority of patients eventually experience treatment failure and face progressively shorter disease-free periods following subsequent lines of conventional chemotherapy.[1] Patients with progressive disease within 24 months of first-line therapy (POD24) represent a significant unmet need. The five-year overall survival (OS) for patients with FL and POD24 is only 50% vs 90% for those without POD24.[2] The three-year OS for patients with MZL is 53% and 95% respectively.[3]

Chimeric antigen receptor T cells (CAR-T) and bispecific T-cell engagers (BiTEs) are designed to improve patients' outcome by redirecting their polyclonal T cells against a lymphoma-associated antigen, independently of the major histocompatibility complex. Multicenter Phase II trials with CAR-T and BiTEs in patients with relapse/refractory (R/R) FL and MZL have been published. Key results are summarized in **Table 1**.

CAR-T cells

CAR-T cells are engineered ex vivo to gain a chimeric receptor generated by fusing a single-chain variable fragment derived from a monoclonal antibody, a hinge region, a transmembrane section, and an intracellular domain combining T cell activating and co-stimulatory features.[4] Most CAR-T cells studied in iNHL target CD19 and have one co-stimulatory domain, either CD28 or 4-1BB, and are therefore known as second-generation CAR-T. CD28 and 4-1BB exhibit distinct properties and a distinct toxicity profile.

The manufacturing process involves local non-mobilized leukapheresis and central manufacturing. Following viral transduction, expansion and quality control procedures, cryopreserved CAR-T cells are returned. Bridging therapy (BT) may be needed to facilitate the manufacturing time and may influence CAR-T cell therapy efficacy.[5] Lymphodepleting therapy (LT) precedes CAR-T infusion and contributes to CAR-T expansion and persistence.[5] Three days of fludarabine and cyclophosphamide is the preferred LT regimen over a bendamustine alternative.

CAR-T cells are infused in specialized centres that handle typical early CAR T-related toxicities, namely cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).[6] Although largely reversible, these syndromes may be severe and fatal, and mandate timely management based on clinical evaluation. CRS presents with fever and constitutional symptoms and may be associated with varying intensities of organ failure. ICANS typically presents with aphasia, impaired fine motor skills and/or reduced level of awareness and may rarely culminate in seizures and/or cerebral edema. CRS and ICANS result from the activation of CAR-T, in addition to bystander immune and nonimmune cells. CAR-T may also be associated with hemophagocytic lymphohistiocytosis-like syndromes.[7]

Hypogammaglobulinemia related to CD19 off-tumor effect and myelosuppression of unpredictable duration may occur. Myelosuppression recovery is expected, but underlying differential diagnosis includes myelodysplastic syndrome.

Nonetheless, we learned from real-world reports in large B-cell lymphoma that CAR-T cell therapy can be safely administered to a broad range of patients with preserved efficacy, including some patients deemed ineligible for the pivotal trial and/or unfit for high-dose chemotherapy and autologous stem cell transplant (HDT-ASCT), but with preserved performance status and no significant organ dysfunction.

Axicabtagene ciloleucel (axi-cel) is a CD28-based CAR-T studied in the ZUMA-5 trial that led to its approval by the FDA.[8] A total of 181 patients with R/R FL and MZL after at least two lines of therapy (LoT), including an anti-CD20 combined with an alkylating agent or with high-risk features were screened; 153 were leukapheresed and 148 were infused. No manufacturing failure occurred. Median time from leukapheresis to axi-cel delivery was 17 days (interquartile range [IQR]: 16–20). Four patients with FL and two with MZL received BT. Hospitalization for seven days following infusion was mandatory. The updated overall response rate (ORR) was 90% and the complete remission rate (CRR) was 75%.[9] Median progression-free survival (PFS) was 40 months and three-year PFS was 54%. CAR-T expansion appeared slightly higher in patients with MZL although outcomes seemed similar with three-year PFS of 56% in patients with MZL and 54% with FL. Outcomes of patients with POD24 were better than expected with a three-year PFS of 59% among patients with POD24 vs 52% without POD24.

Tisagenlecleucel (tisa-cel) is a 4-1BB-based CAR-T cell therapy evaluated in the ELARA trial that led to its approval by the FDA.[10] A total of 119 patients with R/R FL following at least two LoT including an anti-CD20 combined with an alkylating agent, with relapse within six months of second or later LoT or with R/R FL after HDT-ASCT were screened; 98 were enrolled and 97 were infused. Four patients received a lower dose and two received an out-of-specification CAR-T infusion (one low cell viability and one higher cell count). Time from leukapheresis to

infusion was not reported and median time from enrollment to infusion was 46 days (IQR: 38–57); 45% received BT. At the investigator's discretion, 18% of the patients were managed as outpatients and one-third did not require hospitalization. The Independent Review Committee assessed a CRR by independent review (CRRi) of 68% and an objective response rate (ORRi) of 86%.[11] CRR was 59% for patients with POD24. Two-year PFS reached 57%. High tumor burden as measured by the metabolic tumor volume (MTV) was associated with significantly shorter PFS.

Lisocabtagene maraleucel (liso-cel) is a 4-1BB-based CAR-T and is infused in a fixed 1:1 ratio of CD4:CD8. It was studied in patients with R/R FL and MZL in the TRANSCEND-FL trial. In the efficacy set including patients with R/R FL after at least two LoT, 114 patients were leukapheresed, 107 infused and 101 evaluable.[12] Four were excluded due to non-conforming product; 41% received BT. Primary analysis of the efficacy set reports a 97% ORRi, a 94% CRRi, and a 12-month PFS of 81%.

Bispecific T-cell engagers (BiTEs)

BiTEs are recombinant proteins designed to bind simultaneously to T cells and a malignant antigen. They force an immune synapse triggering cell-mediated cytotoxicity. BiTEs with the most mature data in iNHL target CD3 on T cells and CD20 on B cells. They use a full-length IgG-like structure allowing for intermittent dosing. CRS mitigation strategies with an initial step-up dosing and corticosteroid premedication led to a significant reduction in incidence and severity of CRS and neurotoxicity vs CAR-T cell therapy.

Mosunetuzumab was studied in a Phase II trial that led to its approval by the FDA.[13] A total of 90 patients with R/R FL after at least two LoT including an anti-CD20 combined with an alkylating agent received mosunetuzumab intravenously. Dosing was every week (qw) for the first 21-day cycle without mandatory hospitalization and then q3w. Patients with a complete response (CR) at cycle 8 ended their treatment, whereas patients with partial response or stable disease were able to complete 17 cycles. The best ORRi was 80% with a 60% CRRi.[14] Patients with POD24 had an 85% ORRi and a 57% CRRi. The two-year duration of CR was 63% and the two-year PFS was 48%. The median PFS with mosunetuzumab was 24 months whereas it was only 12 months with the last prior therapy. No association between the timing of the first CR and the duration of the response was observed. Two patients discontinued therapy due to related toxicities. Grade ≥2 CRS was greater in patients with bone/bone marrow metabolic disease burden, occurring in 33.3% of patients vs 13.8% if there was no involvement. No correlation was observed between the occurrence of CRS and tumor response. Tumor burden, as measured by the total MTV, did not correlate with response, a finding typically associated with a poorer response rate to CAR-T cell therapy.[15]

Odronextamab was evaluated in the Phase I trial ELM-1 in R/R B-cell NHL.[16] Patients with R/R FL received odronextamab intravenously. CRR was 72% among the 32 patients who received the active dose of odronextamab, with an estimated probability of maintained CR at four years of 54%. The Phase II ELM-2 trial evaluated patients with R/R FL[17] after at least two LoT including an anti-CD20 combined with an alkylating agent. Following the first cycle step-up, odronextamab was dosed qw for the subsequent three 21-day cycles and thereafter q2w until disease progression or significant toxicity. An inpatient 24-hour monitoring period was mandatory after each dosing of cycle 1 and after day 1 of cycle 2. A prespecified analysis of 121 patients reported an 82% ORRi, the primary endpoint, and a 75% CRRi. Median duration of CR was 20.5 months. Ten patients discontinued odronextamab due to related toxicities.

Epcoritamab evidence of single-agent efficacy was observed in 10 patients with R/R FL in the EPCORE NHL-1 trial with a 90% ORR and a 50% CRR.[18] Epcoritamab was administered subcutaneously. Epcoritamab was further evaluated in combination with rituximab and lenalidomide (R2) in patients with R/R FL after at least one LoT in the Phase I/II EPCORE NHL-2 trial.[19] Arm 2a dosed epcoritamab qw in the first three 28 days cycles, then q2w for six cycles and q4w thereafter for a total duration of two years. Arm 2b dosed epcoritamab qw in the first two 28 days cycles then q4w for a total duration of two years. Hospitalization for 24 hours after a full dose at day 15 cycle 1 was mandatory. The primary objective was safety and antitumor activity. The median number of prior LoT was one (range: 1–7). The ORR was 98% with 87% CR in the 104 evaluable patients. This was substantially improved compared to the 85% ORR and 58% CR with immediate prior therapy. Among POD24, the ORR was 98% and the CRR was 75%. The nine-month PFS was 85%. The safety cohort included 111 patients. The incidence of CRS was 48% with only 2% grade 3 and the peak onset was at day 15 cycle 1, corresponding to the first full dose.

Glofitamab is a BiTE unique in its bivalent binding to CD20 and is administered as one infusion of the anti-CD20 obinutuzumab one week prior to initiating BiTE infusion as a CRS mitigation strategy. It is administered intravenously for a fixed duration for up to twelve 21 day cycles. In the Phase I study of 171 R/R B-cell NHL, glofitamab achieved an ORR of 71%, a CR of 48% and a median PFS of 11.8 months in 44 patients with R/R FL.[20]

CAR-T or BiTE?

Retrospective analysis comparing CAR-T cell therapy and BiTE with conventional chemotherapies suggest improvement in PFS and/or OS.[14,21,22]Access, toxicities, sequencing and the financial burden of these novel immunotherapies represent their main challenges. CAR-T cell therapies are logistically more complex than BiTEs and are offered only in limited centres throughout Canada, involving travel considerations for patients and their caregiver(s). Patients in need of rapid treatment initiation may achieve more timely benefit from BiTEs as their toxicity mitigation

	CAR T			BiTE		
	Axicabtagene ciloleucel[8,9]	Tisagenlecleucel[10,11]	Lisocabtagene maraleucel[12]	Mosunetuzumab[13,14]	Odronextamab[17]	Epcoritamab + R2[19]
	CD28	4-1BB	4-1BB	IV fixed-duration C1: qw C2-17: q3w 21d cycle	IV indefinite C1: step-up C2-4: qw 21d cycle C≥5 : q2w 14d cycle	SC fixed-duration 2 arms 28d cycle 2 years total
Pivotal trial	ZUMA-5 NCT03105336	ELARA NCT03568461	TRANSCEND FL NCT04245839	NCT02500407	ELM-2 NCT03888105	EPCORE NHL-2 NCT04663347
Histology	FL and MZL	FL	FL and MZL	FL	FL	FL
N	Efficacy: 127 FL 31 MZL Safety: 124 FL 28 MZL	Efficacy: 94 Safety: 97	FL cohort: Efficacy: 101 Safety: 130	90	Efficacy: 121 Safety: 131	Efficacy: 104 Safety: 111
POD24	81/148 (55%)	61/97 (63%)	58/107 (54%)	47/90 (52%)	60/121 (50%)	42/111 (38%)
Median follow up (m)	40.5	28.9	17.5 for PFS	28.3	22.4	11.4
ORR	90% (94% FL/77% MZL)	86%	97%	80%	82%	98%
CR	75% (79% FL/65% MZL)	68%	94%	60%	75%	87%
PFS	3y PFS 54% FL/56% MZL	2 y PFS 57%	1y PFS 81%	2y PFS 48%	18-month PFS 55%	9-month PFS 85%
OS	3y OS 76% FL/74% MZL	2 y OS 88%	Not reported	2y OS 87%	18-month OS 76%	-
All grade CRS	82% (78% FL/100% MZL)	49%	58%	44%	57%	48%
Grade 3+ CRS	7% (6% FL/8% MZL)	0	1%	2%	2%	2%
All grade ICANS	59% (56% FL/71% MZL)	4%	15%	3%	None with optimized step-up dosing	2%
Grade 3+ ICANS	19% (15% FL/38% MZL)	1%	2%	None	None	None
Infections grade ≥ 3	18%	9%	5%	14%	32%	-
Treatment related mortality (n)	1	None	2	None	3	4

Table 1. *Summary of pivotal Phase II trials of chimeric antigen receptor T cell (CAR T) and bispecific T cell engagers (BiTE) for refractory or relapsing follicular (FL) and marginal zone (MZL) lymphomas, with no direct cross-trial comparison; courtesy of Isabelle Fleury, MD and Eva Laverdure, MD.*
C: Cycle, ***d:*** Days, ***IV:*** Intravenous, ***m:*** months, ***POD24:*** Progression within 24 months of first-line therapy, ***SC:*** Subcutaneous, ***qw:*** Every week.

strategies allow greater availability across Canada in cancer centres in which CRS and ICANS management algorithms are implemented. CAR-T cell therapy, however, offers the opportunity for a single-dose therapy with less care time required, and prolonged remission.

As per the Health Canada product monographs, both axi-cel and tisa-cel are indicated for patients with R/R grade 1–3a FL after at least 2 LoT.[23,24] At the time of writing, Canadian Agency for Drugs and Technologies in Health (CADTH) has published its recommendation to support Canadian access to tisa-cel in this setting and to draft a report to support access to axi-cel as well. Evaluation by Institut national d'excellence en santé et services sociaux (INESSS) for Quebec has not yet been published and access is still, however, pending. Health Canada approval for liso-cel and BiTEs for R/R are not yet available.

The most favourable sequence for recruiting patients' T cells through CAR-T cell therapy or BiTE along the patient's journey has yet to be defined. From large B cell and mantle cell lymphoma studies, we know that BiTE therapy has demonstrated efficacy irrespective of prior CAR T-cell therapy exposure and response, and that recent exposure to bendamustine may hamper CAR-T cell therapy efficacy.[25,26] Data on BiTE rechallenge after response loss will also contribute to guiding our therapeutic choice.

Both CAR-T and BiTE are being evaluated in combination with other agents and are being studied in earlier LoT. Clinical studies with new BiTE and immune effector cells are also ongoing. The design of these trials and the better understanding of the resistance mechanism will be paramount in optimizing their use.

CAR-T and BiTE have launched a new era for patients with R/R FL and MZL with a rapidly evolving treatment landscape and a promising future for patients in Canada.

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References:

1. *Link BK, Day BM, Zhou X, et al. Second-line and subsequent therapy and outcomes for follicular lymphoma in the United States: data from the observational National LymphoCare Study. Br J Haematol. 2019;184(4):660-663. doi:https://doi.org/10.1111/bjh.15149*
2. *Casulo C, Byrtek M, Dawson KL, et al. Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. J Clin Oncol. 2015;33(23):2516-2522. doi:https://doi.org/10.1200/JCO.2014.59.7534*
3. *Luminari S, Merli M, Rattotti S, et al. Early progression as a predictor of survival in marginal zone lymphomas: an analysis from the FIL-NF10 study. Blood. 2019;134(10):798-801. doi:https://doi.org/10.1182/blood.2019001088*
4. *Sterner RC, Sterner RM. CAR-T Cell therapy: Current Limitations and Potential Strategies. Blood Cancer Journal. 2021;11(4):1-11. doi:https://doi.org/10.1038/s41408-021-00459-7*
5. *Amini L, Silbert SK, Maude SL, et al. Preparing for CAR T cell therapy: patient selection, bridging therapies and lymphodepletion. Nature Reviews Clinical Oncology. 2022;19(5):342-355. doi:https://doi.org/10.1038/s41571-022-00607-3.*
6. *Morris EC, Neelapu SS, Giavridis T, Sadelain M. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. Nature Reviews Immunology. 2021;22(2). doi:https://doi.org/10.1038/s41577-021-00547-6 .*
7. *Hines MR, Knight TE, et al.. Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome. Transplant Cell Ther. 2023 Jul;29(7):438.e1-438.e16.*
8. *Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. The Lancet Oncology. 2022;23(1):91-103. doi:https://doi.org/10.1016/S1470-2045(21)00591-X*
9. *Chavez J, Sehgal AR, et al. 3-year follow-up analysis of ZUMA-5: a phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL). Blood (2022) 140 (Supplement 1): 10380–10383.*
10. *Fowler NH, Dickinson M, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. Nat Med 2022 Feb;28(2):325-332.*
11. *Dreyling M, Dickinson M, Martinez Lopez J, et al. Long-Term Clinical Outcomes and Correlative Efficacy Analyses in Patients (Pts) with Relapsed/Refractory Follicular Lymphoma (r/r FL) Treated with Tisagenlecleucel in the Elara Trial. Blood. 2022;140(Supplement 1):1459-1463. doi:https://doi.org/10.1182/blood-2022-158024.*
12. *Morschhauser F, Dahiya S, et al. TRANSCEND FL: Phase 2 study results of lisocabtagene maraleucel (LISO-CEL) in patients (PTS) with relapsed/refractory (R/R) follicular lymphoma (FL). Hematol Oncol. 2023;41(S2):877-880.*
13. *Budde LE, Sehn LH, Matasar M, et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. The Lancet Oncology. 2022;23(8):1055-1065. doi:https://doi.org/10.1016/S1470-2045(22)00335-7*
14. *Bartlett NL, Sehn LH, Matasar MJ, et al. Mosunetuzumab monotherapy demonstrates durable efficacy with a manageable safety profile in patients with relapsed/refractory follicular lymphoma who received ≥2 prior therapies: updated results from a pivotal phase II study. Blood. 2022;140(Supplement 1):1467-1470. doi:https://doi.org/10.1182/blood-2022-157691.*
15. *Dean EA, Mhaskar RS, Lu H, et al. High metabolic tumor volume is associated with decreased efficacy of axicabtagene ciloleucel in large B-cell lymphoma. Blood Advances. 2020;4(14):3268-3276. doi:https://doi.org/10.1182/bloodadvances.2020001900.*
16. *Bannerji R, Arnason JE, Advani RH, et al. Odronextamab, a human CD20×CD3 bispecific antibody in patients with CD20-positive B-cell malignancies (ELM-1): results from the relapsed or refractory non-Hodgkin lymphoma cohort in a single-arm, multicentre, phase 1 trial. The Lancet Haematology. 2022;9(5):e327-e339. doi:https://doi.org/10.1016/s2352-3026(22)00072-2.*
17. *Novelli S, S. Luminari, M. Taszner, et al. Odronextamab in patients with relapsed/refractory follicular lymphoma (FL) Grade 1-3A: results from a prespecified analysis of the pivotal phase II study ELM-02. Hematol Oncol. 2023 June 9;41(S2):121-122.*
18. *Hutchings M, Mous R, Clausen MR, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. The Lancet. 2021;398(10306):1157-1169. doi:https://doi.org/10.1016/S0140-6736(21)00889-8.*
19. *Merryman R, Belada D, Sureda A, et al. 2023 ASCO Annual Meeting; Abstract. J Clin Oncol;41(16 suppl):750.*
20. *Hutchings M, Morschhauser F, Iacoboni G, et al. Glofitamab, a novel, bivalent CD20-targeting T-cell–engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-cell lymphoma: a phase I trial. J Clin Oncol. 2021;39(18):1959-1970. doi:https://doi.org/10.1200/jco.20.03175.*
21. *Ghione P, Palomba ML, Patel AR, et al. Comparative effectiveness of ZUMA-5 (axi-cel) vs SCHOLAR-5 external control in relapsed/refractory follicular lymphoma. Blood. 2022;140(8):851-860. doi:https://doi.org/10.1182/blood.2021014375.*
22. *Salles G, Schuster SJ, Dreyling M, et al. Efficacy comparison of tisagenlecleucel vs usual care in patients with relapsed or refractory follicular lymphoma. Blood Advances. 2022;6(22):5835-5843. doi:https://doi.org/10.1182/bloodadvances.2022008150.*
23. *Kymriah. [cited 2023 Oct 12]. Available from: https://pdf.hres.ca/dpd_pm/00047188.PDF*
24. *Yescarta. [cited 2023 Oct 12]. Available from: https://pdf.hres.ca/dpd_pm/00067754.PDF*
25. *Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2022;387(24):2220-2231. doi:https://doi.org/10.1056/nejmoa2206913.*
26. *Wang M, Munoz J, Goy A, et al. Three-Year Follow-Up of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma, Including High-Risk Subgroups, in the ZUMA-2 Study. J Clin Oncol. 2022;41(3). doi:https://doi.org/10.1200/jco.21.02370.*