

Maximizing the Benefit of CAR T-Cell Therapy in Lymphoma and Multiple Myeloma



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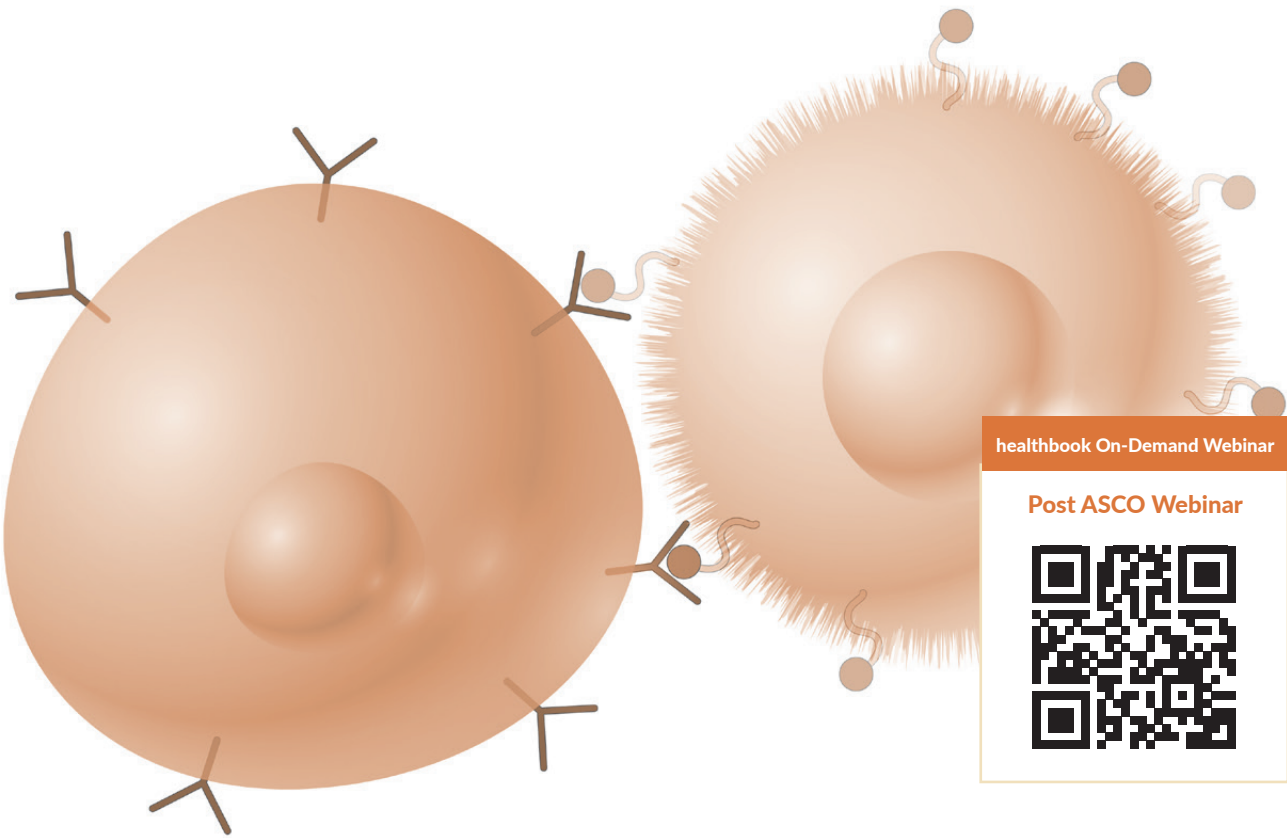
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CAR T-cell therapy in DLBCL

CD19-directed chimeric antigen receptor (CAR) T-cell therapies have shown remarkable success in the treatment of diffuse large B-cell lymphoma (DLBCL). In Switzerland, tisagenlecleucel (tisa-cel)¹, axicabtagene ciloleucel (axi-cel)², and lisocabtagene maraleucel (liso-cel)³ are approved as third- or later-line therapies for adult patients with relapsed or refractory (R/R) DLBCL based on results from the pivotal clinical studies JULIET⁴, ZUMA-1⁵, and TRANSCEND^{6,7}, respectively. The progression-free survival (PFS) rate with the three products reached a plateau and at 2 years was approximately 40%. One strategy to improve the efficacy is to use them earlier in disease management, thus their efficacy was explored in the second-line setting in the BELINDA⁸, ZUMA-7⁹, and TRANSFORM¹⁰ trials, respectively. These phase III studies included patients with refractory disease or who had relapsed within 12 months of first-line therapy and compared CAR T-cell therapy versus standard of care (SOC), which was salvage platinum-based chemotherapy, followed by high-dose chemotherapy with autologous stem cell transplantation (ASCT) in responders. The primary endpoint was event-free survival (EFS), which BELINDA trial (tisa-cel) failed to meet. At a median follow-up of 24.9 months, axi-cel significantly improved EFS compared with SOC (median, 8.3 months vs 2.0 months; hazard ratio (HR): 0.40 [95% CI: 0.31–0.51]; p<0.001), with a 2-year EFS rate of 41% and 16%, respectively.⁹ With less mature data at a median follow-up of 6.2 months, liso-cel demonstrated similar results (median, 10.1 months vs 2.3 months; HR: 0.35 [95% CI: 0.23–0.53]; p<0.0001), with estimated 1-year EFS rates of 45% with liso-cel and 24% with SOC.^{10,11} As a result, both axi-cel¹² and liso-cel¹¹ were recently approved for the treatment of patients with refractory or early relapsed (≤12 months) large B-cell lymphoma (LBCL) after first-line chemoimmunotherapy by Food and Drug Administration (FDA).

ZUMA-7: Superiority of axi-cel over SOC in second-line DLBCL regardless of tumor burden, LDH level, or target expression

In an exploratory analysis of ZUMA-7, the association between pretreatment tumor characteristics and clinical outcomes with axi-cel was assessed.¹⁴ Investigated parameters included elevated lactate dehydrogenase (LDH) level, defined as greater than the upper limit of normal (ULN); tumor burden, calculated as the sum of product diameters (SPD) of ≤6 reference lesions; as well as tumor CD19 expression, assessed by immunohistochemistry (H-score). Baseline tumor characteristics were generally balanced between the axi-cel (n=170) and SOC (n=168) arms, with elevated LDH seen in 54% of patients (23% with LDH ≥2 x ULN), a median tumor burden of 2,115 mm², and a median CD19 H-score of 150. Axi-cel remained superior over SOC in terms of EFS in patients with high (>median) and low (≤median) tumor burden, with an HR of 0.289 (p<0.0001) and 0.486 (p=0.0003), respectively. No impact of tumor burden on EFS was observed within the axi-cel arm (high vs low, HR: 0.915; p=0.6778), whereas a negative association was demonstrated within the SOC arm (high vs low, HR: 1.507; p=0.0240). Similarly, axi-cel improved EFS compared with SOC irrespective of baseline LDH level (elevated, HR: 0.324; p<0.0001; normal, HR: 0.496; p=0.0006), with the worst outcome observed in patients with an elevated LDH receiving SOC (elevated vs normal, with SOC, HR: 1.556; p=0.0119; with axi-cel, HR: 1.108; p=0.6132). When stratified according to CD19 protein expression, patients with high (>median) CD19 levels who received axi-cel achieved the greatest benefit (axi-cel vs SOC, HR: 0.283; p<0.0001; within axi-cel, high vs low CD19, HR: 0.627; p=0.0341). Of note, EFS favored axi-cel over SOC even in patients with low CD19 expression (HR: 0.572; p=0.0044).



PILOT: High response rates with second-line liso-cel in patients with RR LBCL ineligible for ASCT

The phase II PILOT trial enrolled patients with LBCL who had received one prior line of therapy, including an anthracycline and an anti-CD20 agent and who were not intended for ASCT while having an adequate organ function.¹⁵ Eligibility criteria included (≥1 parameter for entry): age ≥70, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2, diffusing capacity for carbon monoxide (DLCO) ≤60%, left ventricular ejection fraction (LVEF) <50% (but ≥40%), creatinine clearance (CrCl) <60 mL/min (but >30); and/or elevated alanine/aspartate aminotransferases (ALT/AST) (2 x ULN < ALT/AST ≤5 x ULN). The primary endpoint was the overall response rate (ORR). In total, 61 patients received liso-cel, of whom 79% were elderly, 26% had an ECOG PS of 2, and 25% had impaired renal function. In this frail population, liso-cel demonstrated an ORR of 80% and a complete response (CR) rate of 54%. At a median follow-up of 13.0 months, the median progression-free survival (PFS) was 9.03 months. Based on these findings, liso-cel was approved by FDA for adult patients with relapsed or refractory LBCL after first-line chemoimmunotherapy who are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age.¹¹

ZUMA-2: 3-year follow-up shows durable responses with brexu-cel in RR MCL

Brexucabtagene autoleucel (brexu-cel), a CD19-directed CAR T-cell therapy, is approved by Swissmedic for the treatment of patients with R/R mantle cell lymphoma (MCL) after ≥2 lines of systemic therapy, including a Bruton tyrosine kinase (BTK) inhibitor.¹⁶ The regulatory decision was based on data from the pivotal phase 2 trial ZUMA-2, in which patients with heavily

pretreated R/R MCL underwent leukapheresis and optional bridging therapy, followed by conditioning chemotherapy and a single infusion of brexu-cel.¹⁷ In the first 60 efficacy-evaluable patients, the objective response rate (ORR) was 93%, with a CR achieved by 67% of patients. With about 2 years of additional follow-up, brexu-cel efficacy remained high at an ORR and CR rate of 91% and 68% (n=68), respectively.¹⁸ The median PFS was 25.8 months, with a 2-year PFS rate of 52.9%. The median OS was 46.6 months, with a 30-month OS rate of 60.3%. Thus, brexu-cel demonstrated durable benefit in this setting. As a bendamustine-based regimen is a standard approach in MCL¹⁹ and the associated prolonged lymphopenia may impact CAR T-cell manufacturing²⁰, the influence of prior bendamustine exposure on CAR T-cell levels was assessed in an exploratory analysis, including propensity score matching.¹⁸ Overall, 54% of patients in ZUMA-2 had been previously treated with bendamustine. Compared with patients who had not received bendamustine, those with bendamustine use within 6 months prior to CAR T-cell infusion had significantly lower peak CAR T cells (p=0.032). The difference was lower but not significant when patients received bendamustine >6 months before CAR T-cell therapy (p=0.13). As peak CAR T cell numbers have been associated with clinical response^{21,22} and thus might be used as a surrogate endpoint, extending the period following bendamustine use might maximize brexu-cel benefit and generally, if patients might be eligible for brexu-cel in a short timeframe, its use must be carefully considered.

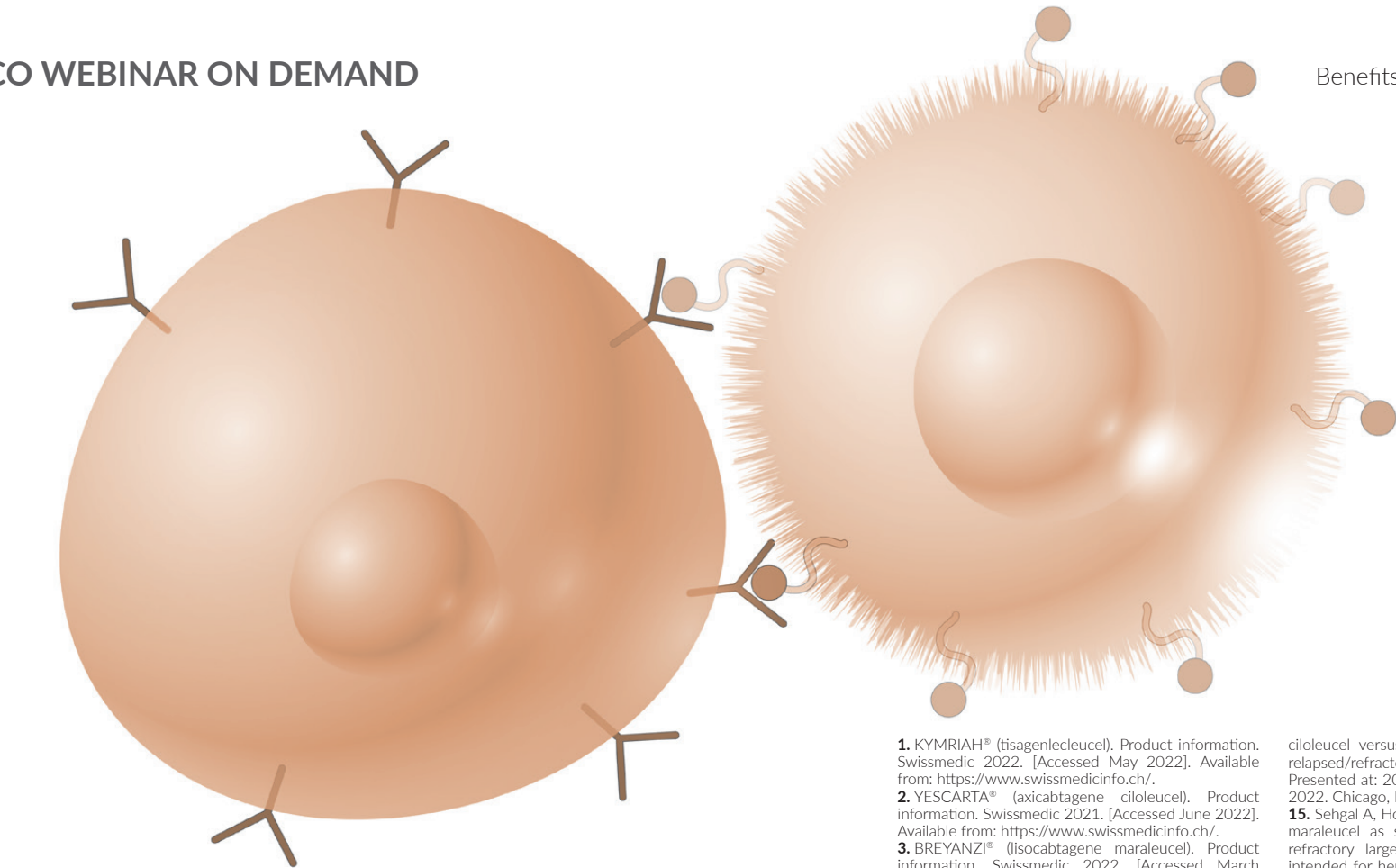
CAR T-cell therapy in multiple myeloma

B-cell maturation antigen (BCMA) has emerged as a promising target in multiple myeloma (MM), as it is selectively and highly expressed in plasma cells and also MM cells from patients at all

stages.²³ Two CART-T-cell therapies targeting BCMA, idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), have been explored for the treatment of RRMM and have shown potent antimyeloma activity.^{24,25} In the phase II KarMMa trial, ide-cel demonstrated an ORR of 73% (n=128) and CR rate of 33%, minimal residual disease (MRD) negativity rate (threshold: 10⁻⁵) of 26% and a median PFS of 8.8 months.²⁴ Based on this data, Swissmedic approved ide-cel for the treatment of adult patients with RRMM after ≥3 prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody.²⁶ In the phase Ib/II CARTITUDE-1 study of cilta-cel, ORR was 98% (n=97), with a stringent (s) CR and MRD negativity achieved by 80% and 58% of patients, respectively, and the median PFS was 22.8 months.²⁷ As a result, cilta-cel was approved for the same indication by EMA²⁸ and after ≥4 prior lines of therapy by FDA²⁹ but not yet by Swissmedic³⁰.

Real-world data shows comparable efficacy and safety of ide-cel in patients with RRMM ineligible for KarMMa inclusion

In this first real-world study of ide-cel, 196 heavily pretreated patients with RRMM underwent leukapheresis, of whom 77% did not meet the KarMMa eligibility criteria.³¹ For example, 31% had organ failure, 22% had received prior anti-BCMA therapy and 6% had an allogeneic hematopoietic stem cell transplantation. Nevertheless, the best ORR was 86% (n=141). CR or better (>CR) was achieved by 42% of patients, of whom 78% were MRD negative. At a median follow-up of 6.5 months, the median PFS was 10.3 months and the estimated 6-month OS rate was 92%.³² In a multivariable analysis for response, prior BCMA-directed therapy was associated with inferior outcomes, with a median PFS and OS in those patients (n=33) of 5.8 months and 7.43 months, respectively.^{31,32} The antibody-drug conjugate (ADC) belantamab mafodotin (n=25) did not impact PFS probability compared with no prior anti-BCMA use.³² In contrast, worse median PFS (2.7 months) was observed in patients receiving a BCMA bi-specific T-cell engager (BiTE) (n=4). Albeit those patients were too few to draw any solid conclusion, the sequence of BCMA-targeting therapies should be carefully considered. Overall, real-world outcomes with ide-cel were similar to the reported KarMMa data and support its use in RRMM.



CARTITUDE-1: Deep and durable responses with cilta-cel in heavily pretreated patients with RRMM

In this phase Ib/II study, patients with progressive MM double refractory or following ≥3 lines of prior therapy underwent apheresis and bridging therapy, as needed, before receiving a single infusion of cilta-cel.²⁵ In the 2-year post last-patient-in (LPI) analysis, ORR remained at 97.9%, with sCR of 82.5% at a median follow-up of 27.7 months.³³ Both median PFS and OS were not reached, with 27-month rates of 54.9% and 70.4%, respectively.

As in DLBCL, there are efforts to move CAR T-cell therapies upfront to improve outcomes in MM. They are explored in high-risk (KarMMA-4 study with ide-cel)³⁴ or transplant-ineligible (CARTITUDE-5 study with cilta-cel)³⁵ patients with newly diagnosed MM.³² Other strategies include using different BCMA-directed CAR T cells³⁶, dual targeting with CD19³⁷, exploring different targets such as GPRC5D³⁸, or using an allogeneic platform³⁹.

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