

## Lymphoma immunotherapy - Section 3

# Lymphoma immunotherapy: Efficacy, safety, and accessibility to CAR-T therapy for lymphomas

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### Take Home Messages

- CAR T-cell therapy has shown preliminary high efficacy for relapsed or refractory aggressive non-Hodgkin lymphoma, including diffuse large B-cell lymphoma in different phase II studies.
- The safety profile in this setting includes potentially life-threatening cytokine release syndrome (CRS) and neurologic events (NE), which requires specific arrangements for centers implementing CAR T-cell therapy.
- Accessibility to this novel treatment might be limited by health care resources considering high costs for the cell-product, hospitalization, and numerous ancillary processes required for CAR T-cell therapy.

### Principles of CAR T-cell therapy

T-cells cannot recognize and attack malignant cells without antigen-presentation via the HLA complex. An important and frequently observed mechanism of malignant growth is loss of major histocompatibility complex (HLA) expression. Chimeric antigen receptor T-cells (CAR T-cells) have been developed in order to circumvent both immune tolerance of the T-cell repertoire and MHC restriction. The development has been reviewed by Carl June recently.<sup>1</sup> The CAR T-cells are generated by (usually, but not necessarily, autologous and viral-based) transfection with the CAR construct, which contains several domains. First, the antigen binding site, which is generally derived from single-chain variable fragments (scFv) of an antibody. This domain allows the transduced T-cells to recognize the tumor cell with a high specificity. Second, the hinge domain, which is followed by the transmembrane domain. These domains link the antigen-binding domain to the, third, intracellular signaling domain. This domain is crucial for T-cell activation, expansion, and persistence. The approved CAR constructs are called “second generation” CARs, which refers to the signaling domains. In contrast to the first generation of CAR constructs, which included only CD3 as an intracellular signaling domain, second-generation CARs added one costimulatory domain. For the constructs discussed in this brief overview, this is derived from either CD28 or 4-1BB. With the introduction of these costimulatory domains, the expansion and persistence and thus the efficacy of CAR T-cells could be improved substantially. CAR T-cell therapy in clinical practice requires several steps to be taken. Autologous T-cells must be harvested by leukapheresis first, then T-cells must be selected, transfected, cultured and expanded *ex vivo*, and finally the cell-product must be re-transfused into the patient. Depending on the production technique used, this process may take between 14 to 28 days (turn-around time).

### Efficacy of CAR T-cell therapy in lymphomas

The efficacy of conventional genotoxic chemotherapy could be substantially improved with the introduction of the anti-CD20 antibody rituximab into the first-line treatment. However, patients failing R-chemo with either relapsed or refractory (r/r) disease face a dismal prognosis.<sup>2</sup> This is especially true for r/r diffuse large B-cell lymphoma (DLBCL) and other more aggressive B-NHL subtypes. Three-year progression-free survival (PFS) is around 20% for transplant eligible patients nowadays, whereas the majority of patients are transplant-ineligible and have an even poorer outcome.<sup>3,4</sup> Therefore, the development of CAR T-cell therapy has been focused on r/r aggressive B-NHL. For the purpose of this summary, we will report only on anti-CD19 directed constructs in r/r aggressive B-NHL, as those are most advanced for clinical use.

Axicabtagene ciloleucel (YESCARTA, Kite Pharma, Inc.), a construct using CD28 as co-stimulatory domain, has been approved by the FDA in October 2017 for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Approval was granted based on the results of the single-arm, multicenter, pivotal ZUMA-1 trial enrolling 111 patients with refractory disease to the most recent therapy or relapse within one year after autologous hematopoietic stem cell transplantation.<sup>5,6</sup> Patients received a single infusion of axicabtagene ciloleucel at a target dose of  $2 \times 10^6$  anti-CD19 CAR T-cells per kilogram of body weight after receiving a conditioning regimen of low-dose cyclophosphamide and fludarabine. Turn-around time was short with a median of 17 days and a cell product was successfully manufactured for 110 patients (99%) and administered to 101 patients (91%). The objective response rate was 82%, and the complete response rate was 54%. With a median

follow-up of 15.4 months, 42% of the patients continued to have a response, with 40% continuing to have a complete response. Accordingly, partial remissions were short-lived (2.1 months). The overall rate of survival at 18 months was 52%. Response rates were observed across key covariates, including age, disease stage, or other established baseline risk-factors. CAR T-cell expansion was associated with durable responses.

Another pivotal phase-II trial (JULIET) has been conducted with tisagenlecleucel (CTL019, Kymriah, Novartis), the first approved CAR therapy.<sup>7</sup> This construct uses 4-1BB (CD137) as co-stimulatory domain.<sup>8</sup> The international multicenter JULIET trial was presented in December 2017 at the ASH meeting with 147 patients enrolled, of whom 99 were infused and 88 were evaluable for response.<sup>9</sup> 90% of patients were infused between 30 and 96 days of enrollment with a target dose of  $1.5 \times 10^8$  cells. The best overall response rate (ORR) was 53% (CR, 40%), 38% (CR, 32%) at 3 months; and 37% (CR, 30%) at 6 months. The product was FDA approved for r/r DLBCL after two prior lines of treatment in May 2018. In the clinical trial setting, production turn-around time of this product exceeded 100 days in some patients, so conventional bridging therapy was mandatory. However, in the commercial setting, time to delivery of the product should be shortened to less than four weeks, which would allow treatment of most patients without bridging therapies.

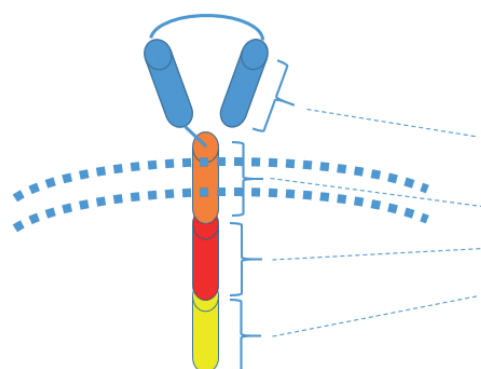
Finally, a third construct currently under development in the same indication named JCAR017 (Juno Therapeutics), should be mentioned (Figure 1). The construct is similar to tisagenlecleucel with regard to the binding and co-stimulatory domain; however, the final cell product differs in terms of a predefined CD4:CD8 ratio of 1 and a target dose of  $10^8$  cells. Preliminary results from an ongoing study (TRANSCEND) showed a 3-month ORR of 74% (14/19) and a 3-month CR rate of 68% (13/19). Again, expansion of CD8 positive cells was correlated to durable remissions.<sup>10</sup>

In summary, CD19 targeting second generation CAR T-cell therapy has proven very high efficacy with different constructs, production technologies, and cell doses. Established baseline risk-factor are not predictive for responsiveness to this new adoptive T-cell therapy, so far.

### Safety of CAR T-cell therapy in lymphomas

The most frequently reported severe adverse event in all studies is related to the hematopoietic system with neutropenia, anemia,

and thrombocytopenia. However, cytopenia might be related to lymphodepleting chemotherapy (usually  $3 \times 30$  mg/m<sup>2</sup> fludarabine and  $3 \times 300$ -500 mg/m<sup>2</sup> cyclophosphamide) within a week before re-transfusion. After re-transfusion, CAR T-cells recognize CD19 expressing cells (both malignant and non-malignant), are activated and expand rapidly. The expansion is often accompanied by massive release of pro-inflammatory cytokines, the so-called cytokine-release syndrome (CRS). CRS may become symptomatic by mild fevers only, starting within the first week after re-transfusion and usually lasting for less than one week. However, CRS may become severe and patients may develop life-threatening symptoms including hypotension requiring vasopressors and/or hypoxemia with the need for mechanical ventilation. With axicabtagene ciloleucel, which uses CD28 as co-stimulatory domain, fatal outcomes have been described (one event of hemophagocytic lymphohistiocytosis and one event of grade 5 cardiac arrest while CRS was ongoing).<sup>6</sup> No treatment-related fatality has been reported with tisagenlecleucel in the JULIET study so far.<sup>9</sup> The frequency of grade  $\geq 3$  CRS should be compared between the different studies with caution, as they used different classifications systems. Importantly, severe CRS can be usually controlled or even terminated by blocking the IL-6 pathway with the anti-IL-6 receptor antibody tocilizumab. Another important CD19 CAR T-cell specific adverse event affects the central nervous system (neurologic events, NE), which includes encephalopathy with cerebral edema, confusional state, aphasia, and somnolence. Early clinical signs of encephalopathy include word-finding difficulties, attention or calculation defects, and difficulty executing complex commands (e.g. handwriting). In the pivotal studies, no patient died due to NE and all events resolved ad integrum. However, Kite Pharmaceuticals reported that one patient enrolled in the safety expansion phase of ZUMA-1 died from cerebral edema. Grade  $\geq 3$  NE were observed with axicabtagene ciloleucel in 28% of patients and with tisagenlecleucel in 12%, respectively. In contrast to CRS, NE do not respond to tocilizumab and require the use of high-dose corticosteroids. Overall, the potentially life-threatening adverse events of CD19 CAR T-cell therapy in aggressive B-NHL requires the implementation of "Risk Evaluation and Mitigation Strategies (REMS)", which ensure that hospitals administering these therapeutics are specially certified and have on-site, immediate access to tocilizumab. In addition, prescribing physicians must be trained in the management of CRS and NE.



domain	Axicabtagene ciloleucel (KTE-C19)	Tisagenlecleucel (CTL019)	JCAR017
anti-CD19-antibody single chain variable fragment	FMC63	FMC63	FMC63
transmembrane	CD28	CD8	IgG4
co-stimulatory	CD28	4-1BB	4-1BB
TCR signaling	CD3ζ	CD3ζ	CD3ζ

Figure 1. Structure of different anti-CD19 CAR constructs for the treatment of B-NHL.

## Accessibility to CAR-T therapy for lymphomas

Obviously, CD19 targeting CAR T-cell therapy for r/r aggressive B-NHL is different from conventional therapies in many aspects. Costs of both the cell-product and the treatment and management of adverse events cannot be exactly appointed yet; however, the list price for tisagenlecleucel in its approved indication (r/r childhood acute lymphoblastic leukemia) has been set at \$ 475,000, whereas the list price of axicabtagene ciloleucel for r/r aggressive B-NHL is \$373,000. Additional costs will arise from adverse event management. About a third of all patient will need intensive care monitoring including tocilizumab, vasopressors, and oxygen supply. The additional costs for individual patients has been estimated to reach half a million US dollar.<sup>11</sup> Although reliable numbers are not available yet, prices by far exceed any other approved treatment for B-NHL and may cause specific regulations. In addition, the industry still has to implement sufficient production capacities, if all patients with r/r aggressive B-NHL should get the chance of being treated with this promising approach. Finally, centers and CAR T-cell teams still need to be qualified. For the time being, treatment capacities of qualified centers might not be sufficient to meet the needs. Overall, there are many difficulties to overcome before CAR T-cell therapy for malignant lymphoma can be called “established” and it will take major efforts from the national authorities, the respective health care system, and the physicians to make it available to our patients.

## Future perspectives

Certainly, CAR T-cell therapy holds promise to have relevant impact on the survival r/r B-NHL patients. However, we should be aware that this still is a promise, but no proven evidence. Longer follow-up of the published phase II data is necessary for definite conclusions. Implementation into daily routine must be established. Trials are already ongoing to investigate the efficacy of the above mentioned – and other – constructs for additional CD19 expressing lymphoma subtypes like mantle-cell lymphoma or follicular lymphoma. Competition in the field may hopefully result in prices, which make this treatment option easier acceptable for the society. An alternative option might be the individual on-site production of CAR T-cells by academic institutions, which would allow production without the need for profit as it has been the case for stem-cell transplantation for many decades now.

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