

# New CAR Designs: Highlights From SOHO 2020



**Kelly Valla, PharmD, BCOP**, of Winship Cancer Institute of Emory University, considers exciting research on novel chimeric antigen receptor designs presented by Renier J. Brentjens, MD, PhD, of Memorial Sloan Kettering Cancer Center, at the 2020 SOHO Annual Meeting.

**P**atients with acute lymphocytic leukemia (ALL) or diffuse large B-cell lymphoma (DLBCL) can look forward to tremendous benefits with the approval of chimeric antigen receptor (CAR) T-cell therapy. Often touted are the exceptional response rates in heavily pretreated patients along with meaningful durability of response and ultimately progression-free survival that were found in the ZUMA-1 and JULIET studies for axicabtagene ciloleucel (axicel, Yescarta) and tisagenlecleucel (tisa-cel, Kymriah), respectively (Neelapu et al., 2017; Schuster et al., 2019).

However, these pivotal studies also illustrate that patients achieving less than a complete response (CR) are not enjoying the same benefits compared with those meeting the criteria for CR after CAR T-cell therapy. Additionally, providers must be aware of the potential emergence of CD19 escape variants that have been described in patients relapsing after CAR T-cell therapy (Xu et al., 2019). These disparate outcomes based on depth of response and challenges with CD19-negative

relapses demonstrate an unmet need that have investigators eager to build a better CAR.

## Key Points

- Although there have been successes with CAR T-cell therapies, some patients relapse or do not respond to treatment.
- New CAR T-cell designs aimed at improving efficacy include the development of armored CAR T cells that can secrete costimulatory ligands.
- Advanced practitioners should stay up to date on CAR T-cell therapy research and be aware of ongoing clinical trials at their institutions or nearby.

## NEXT GENERATION OF CAR T CELLS

Design of third-generation or later CAR T cells focuses on improving a few specific key elements, namely, cytotoxicity, persistence, ability to recruit endogenous immune mediators, and modulation/exploitation of the tumor microenvironment. Persistence is felt to be an important factor tied to the durability of CAR T-cell therapy. Immune recruitment and exploitation of the tumor microenvironment serve to impede the ability of tumor cells to interact with immune effectors in a way that suppresses host immunity. This will allow for non-CAR T cells to participate in the elimination of malignant cells.

Including two costimulatory domains, CD28 plus either 4-1BB or OX40, as opposed to selecting only one of these components, is a key differentiator of third-generation CAR T cells (Park & Brentjens, 2010). Furthermore, researchers have found that genetic manipulations of the CD28 costimulatory domain provide some insight into how to enhance cytotoxicity and persistence of CAR T cells (Feucht et al., 2019). The addition of constitutively active 4-1BB ligand has led to rapid tumor

elimination (Zhao et al., 2015). Murine studies have also shown a benefit of adding CD40L to the CD28 costimulatory backbone with eradication of lymphoma and significantly longer survival in a murine model, even in the absence of lymphodepleting therapy (Kuhn et al., 2019).

Armored CAR T cells are designed to not only incorporate these improvements to costimulation but also add new features that improve performance by promoting persistence as well as recruiting the host immune system. Options that have been explored include cytokine or single-chain fragment variable-linked antibody (scFv)-secreting CAR T cells. Interleukin (IL-18 or IL-36 $\gamma$ )-secreting CAR T cells have demonstrated excellent antitumor activity and survival outcomes in murine models (Avanzi et al., 2018; Li et al., 2020). Interestingly, the IL-18-secreting CAR T cells were also effective at eradicat-

ing CD19-negative tumor cells, which is notable given the concerns for CD19-negative relapses in patients receiving currently approved CAR T-cell products (Avanzi et al., 2018). Although IL-36 $\gamma$ -secreting CAR T cells also enhance tumor kill and persistence, mice treated with these cells ultimately had a profound and protracted B-cell aplasia (Li et al., 2020). However, these mice also had a clear endogenous immune response via T-cell recruitment, and these experiments revealed that this approach was able to thwart tumor rechallenge. Designing CAR T cells to secrete a PD-1-blocking scFv antibody, on the other hand, can result in benefits linked to autocrine- and paracrine-mediated effects that increase antitumor activity and, in some ways, give a two-for-one treatment option utilizing effects of both the CAR T-cell therapy and checkpoint inhibition (Rafiq et al., 2018). ●

### The Advanced Practitioner Perspective

Although these new CAR T-cell therapy models are not yet ready for prime time, it is important for advanced practitioners to stay up to date on research in this rapidly advancing field and be ready to work with the multidisciplinary team and patients if (or more likely, when) new cellular therapies come to market. Enhancements to CAR T-cell structure and function may ultimately impact the safety profile, which should be reviewed when the time comes.

Until then, advanced practitioners should know if their institutions are participating in any trials of new CAR T-cell therapies that may be appropriate for patients with multiply relapsed or refractory cancers. If institutions do

not offer commercial CAR T-cell therapy or have open clinical trials, patients may be referred to another institution for treatment.

Finally, although there are already FDA-approved CAR T-cell constructs available for patients with B-cell ALL, DLBCL, and mantle cell lymphoma, research continues to be active in this type of cellular therapy across many disease states, including multiple myeloma, chronic lymphocytic leukemia, Hodgkin lymphoma, and solid tumors. Advanced practitioners of all hematology/oncology specialties would benefit from a foundational understanding of this type of therapy.

### Disclosure

Dr. Valla has no conflicts of interest to disclose.

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