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IMMUNOTHERAPY

New or second CARs for ALL

Anti-CD19 chimeric antigen receptor (CAR) T cells have remarkable clinical activity against B-cell acute lymphoblastic leukaemia (B-ALL); indeed, the first approval of such agents was for this disease. Nevertheless, relapses can occur, often owing to emergence of $CD19^-$ leukaemic blasts. Novel CAR T cells targeting CD22, expression of which is usually retained after anti-CD19 immunotherapy, have now been evaluated in a phase I trial.

Terry Fry *et al.* treated 21 children or adults with relapsed and/or refractory B-ALL with autologous anti-CD22 CAR T cells. Notably, 17 patients had received prior anti-CD19 therapy (15 with CAR T cells), and 10 had $CD19^-$ or $CD19^{dim}$ blasts. The complete remission (CR) rate among 15 patients who received $\geq 1 \times 10^6$ anti-CD22 CAR T cells per kg was 73% — comparable to that reported with anti-CD19 CAR T cells. All five patients with $CD19^-$ or $CD19^{dim}$ disease treated at this dose achieved a CR. The median duration of remission was 6 months; however, one CR was ongoing at 21 months. As with other CAR-T-cell therapies, cytokine-release syndrome was common, but manageable.

"Our findings demonstrate, for the first time, that targeting a second antigen can overcome immunotherapeutic resistance," Fry explains. "We also demonstrated a novel form of immune escape caused by a decrease in target antigen density [CD22] on cancer cells, rather than complete loss of that antigen as has been seen with CD19," he adds.

"With a novel second target for effective CAR-T-cell therapy, but similar issues with antigen-negative escape, the goal is to develop multiantigen-targeting strategies in order to reduce the likelihood of relapse — similar to the paradigm of multiagent chemotherapy," states co-author Nirali Shah. Indeed, the investigators showed that bispecific anti-CD19/CD22 CAR T cells have promising activity against B-ALL cell lines with mixed CD19/CD22 expression and patient-derived xenografts. "We are currently conducting clinical trials testing this approach," Fry concludes.

David Killock

ORIGINAL ARTICLE Fry, T. J. *et al.* CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. *Nat. Med.* http://dx.doi.org/10.1038/nm.4441 (2017)