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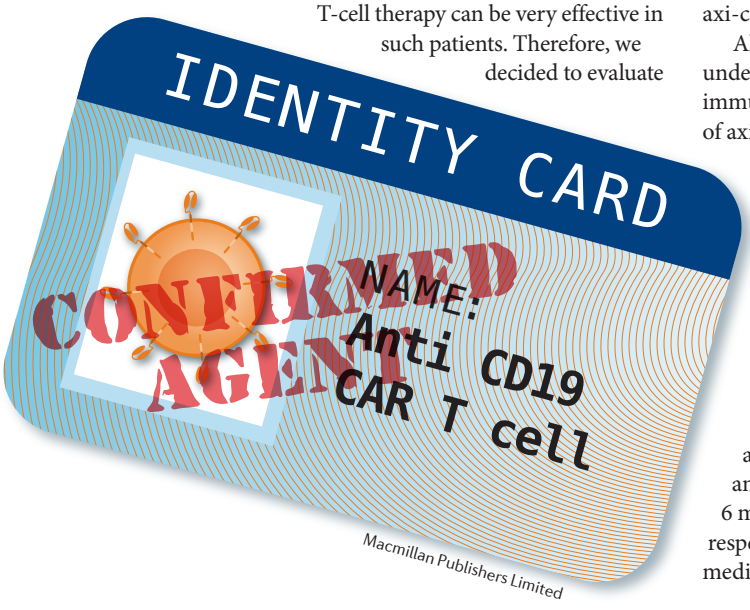
HAEMATOLOGICAL CANCER

Favourable outcomes with CAR T cells

> The oncology community will probably not be surprised if new CAR T cell therapies are approved in the next few months

Promising results of clinical trials of CAR-T-cell-based therapies for patients with haematological malignancies have been increasingly reported in the past few years. Two studies presented in the 2017 American Society of Hematology annual meeting and published in the *New England Journal of Medicine* confirm the favourable outcomes associated with CAR-T-cell therapies in patients with refractory B-cell lymphomas.

"Patients with aggressive B-cell non-Hodgkin lymphomas — including diffuse large B-cell lymphoma (DLBL), primary mediastinal B-cell lymphoma, and transformed follicular lymphoma — who are refractory to chemotherapy have an extremely poor prognosis, with a median survival of approximately 6 months. Prior single-institution studies showed that anti-CD19 CAR-T-cell therapy can be very effective in such patients. Therefore, we decided to evaluate the efficacy of axicabtagene ciloleucel (axi-cel) in a multicentre trial," explains Sattva Neelapu, the main investigator of ZUMA-1. The number of patients enrolled in this phase II trial was 111, of which 77 patients with DLBL and 24 with primary mediastinal B-cell lymphoma or transformed follicular lymphoma received the CAR-T-cell product axi-cel. The second trial involved a smaller cohort of patients, also with non-responsive or chemorefractory disease; of 38 patients enrolled, 14 with follicular lymphoma and 14 with DLBL received CTL019.



Both axi-cel and CTL019 have a single-chain variable fragment extracellular domain that targets CD19, and a CD3ζ intracellular domain. One of the main differences in design between these CAR-T-cell products is the intracellular co-stimulatory domain: CD28 in axi-cel, and CD137 in CTL019.

All patients enrolled in ZUMA-1 underwent leukapheresis to collect immune cells for the manufacture of axi-cel, which was achieved in all but one patient. "Importantly, the average turnaround time from apheresis to the delivery of axi-cel to the clinical site, 17 days, was short," highlights Neelapu. In the second study, T-cell manufacturing was unsuccessful for five patients.

For patients receiving axi-cel, the objective response and complete response rate at 6 months were 82% and 54%, respectively. At 6 months, the median duration of response was 8.1 months, and at longer follow-up durations (median 15.4 months) it was 11.1 months. Similar outcomes were reported in the second study, with a complete response rate of 57% and a median duration of response of 29.3 months at 6 months. At longer follow-up durations (median 28.6 months), 57% of patients remained free from disease progression.

Among patients receiving axi-cel, 95% had grade ≥3 adverse events. Cytokine release syndrome (CRS) was reported by 93% of patients, including 13% with grade ≥3 CRS. Among patients receiving CTL019, 57% had any-grade CRS, including 18% with grade ≥3 CRS.

"The long-term durability observed in ZUMA-1 and in prior single-institution studies with CD19 CAR-T-cell therapy products suggests that this approach could be potentially curative for a significant proportion of these patients," indicates Neelapu.

The results of ZUMA-1 led to the FDA approval of axi-cel for adult patients with large B-cell lymphomas with no response or disease relapse after at least two lines of therapy. This second approval of a CAR-T-cell-based therapy, on 18 October 2017, occurred less than 2 months after the first of such products was approved. The oncology community will probably not be surprised if new CAR-T-cell therapies are approved in the next few months — whether the success of these therapies is replicated once they become available to all patients who could benefit from them remains to be determined.

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ORIGINAL ARTICLES Neelapu, S. S. *et al.* Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1707447 (2017) | Schuster, S. S. *et al.* Chimeric antigen receptor T cells in refractory B-cell lymphomas. *Journal N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1708566 (2017)

FURTHER READING Brudno, J. N. & Kochenderfer, J. N. Chimeric antigen receptor T-cell therapies for lymphoma. *Nat. Rev. Clin. Oncol.* **15**, 31–46 (2017)