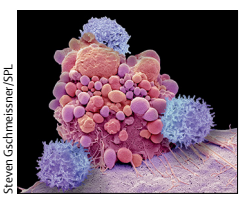
CD19-directed CAR T cells gain traction



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Anti-CD19 chimeric antigen receptor (CAR) T-cell therapy has changed the prognosis of patients with relapsed or refractory large B-cell lymphoma. In the past 12 months, two products have been approved by both the US Food and Drug Administration and the European Medicines Agency for use in this setting: axicabtagene ciloleucel, which was approved in the USA in late 2017 on the basis of results of the ZUMA-1 trial,[1,2] and tisagenlecleucel, which was initially approved in the USA for relapsed or refractory paediatric or young adult B-cell precursor acute lymphoblastic leukaemia in 2017, and subsequently approved for adults with relapsed or refractory diffuse large B-cell lymphoma in early 2018 on the basis of results of the JULIET trial.[3,4]

In *The Lancet Oncology,* Frederick Locke and colleagues[5] present a follow-up analysis of the ZUMA-1 trial[1] to assess long-term activity and safety of axicabtagene ciloleucel. The new results extend median follow up by 12 months, from 15·4 months (IQR 13·7–17·3) to 27·1 months (25·7–28·8). These results represent the longest reported follow-up so far from a large, multicentre study of anti-CD19 CAR T-cell therapy in patients with relapsed or refractory diffuse large B-cell lymphoma. Most importantly, the safety profile of axicabtagene ciloleucel and the durability of responses remain unchanged with an additional year of follow-up. The response duration reported by Locke and colleagues is identical to what was previously reported:[1] median duration of response remains 11·1 months (95% CI 4·2–not estimable), and was not reached for complete responders, which shows sustained activity. These findings build on the previously reported single-institution study by Kochenderfer and colleagues[6] in which the same anti-CD19 CAR construct was used in relapsed or refractory diffuse large B-cell lymphoma: four of the five patients who had complete responses remained in remission at 56, 51, 44, and 38 months' follow-up, respectively. Thus, there is reason for optimism about long-term outcomes for patients with relapsed or refractory diffuse large B-cell lymphoma who achieve complete remission after anti-CD19 CAR T-cell therapy.

Cross-trial comparisons of the activity and toxicity of clinically available CD19-directed CAR T-cell therapies are precluded by differences in anti-CD19 CAR T-cell constructs (CD28 co-stimulatory domain for axicabtagene ciloleucel, 4-1BB for tisagenlecleucel), clinical trial designs, time from apheresis to enrolment and infusion, patient selection and characteristics, use of bridging chemotherapy after apheresis and before CAR T-cell infusion, lymphodepleting chemotherapy regimens received, and even the grading systems used for cytokine release syndrome. However, irrespective of these differences, what is remarkable across anti-CD19 CAR T-cell trials in relapsed or refractory diffuse large B-cell lymphoma is the consistent durability of responses, with ongoing responses in 39 (39%) of 101 patients at a median of 27·1 months' follow-up in ZUMA-1[5] and 35 (35%) of 99 patients at a median of 19·3 months' follow-up in JULIET;[3] the emergence of plateaus in curves for response duration and progression-free survival beyond 6 months; the absence of late or unexpected gene-therapy-related events; and the unique but manageable toxicities (ie, cytokine release syndrome and neurotoxicity[1,3,5,7]). Investigators at the University of Pennsylvania previously reported[7] a cohort of 14 patients with relapsed or refractory diffuse large B-cell lymphoma (NCT02030834), with a median follow up of 28·6 months, who were treated with a 4-1BB-driven CAR T-cell product. For seven (50%) of the 14 patients who were responders (six complete responses and one partial response), median follow-up is now 46·8 months, with the longest follow-up reaching 54·6 months. Of the six patients with complete responses, only one had a relapse (after 32·2 months in continuous remission). In addition to long-term safety, evidence of B-cell recovery during these sustained remissions was also noted (as in Locke and colleagues' study[5]), with evidence of immunoglobulin recovery in some patients too.[7]

When assessing the potential therapeutic effects of CD19-directed CAR T-cell therapies on prognosis for relapsed or refractory diffuse large B-cell lymphoma, it will be necessary to identify the subsets of patients who will benefit from this treatment. To discern this population, sponsors of clinical trials will need to be as transparent as possible when reporting results, and should report the number of patients screened who met eligibility requirements but were not enrolled (stating the reasons for non-enrolment, which are generally unavailable) and the number of patients enrolled and treated or not

treated (with reasons for not receiving treatment, which are generally available). It is also important to keep in mind that available anti-CD19 CAR T-cell products are only the beginnings of progress in this field and that, together with the addition of B-cell targets other than CD19, CAR T cells will be amenable to modulation of their function to improve efficacy and enhance safety.

The current status of CD19-directed CAR T-cell therapies brings to mind a quote from the late Carroll Shelby, an innovative American automotive designer, who said, "I've always been asked, 'what is my favorite car?', and I've always said 'the next one.'"

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I have received personal fees for consultancy, and the University of Pennsylvania has received research grants on my behalf, from Novartis.

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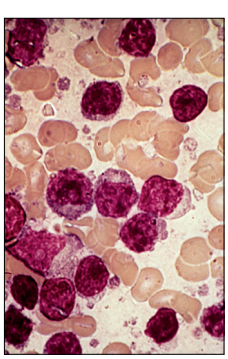
Ibrutinib: searching for a partner drug

Although ibrutinib has become the treatment of choice for patients with relapsed or refractory chronic lymphocytic leukaemia, its position as a first-line regimen is less clear. As ibrutinib prevents homing and migration of leukaemic cells to their microenvironmental niche, it induces quiescence but not apoptosis of chronic lymphocytic leukaemia cells. As a consequence, complete responses are rare and require a prolonged duration of treatment with concomitant high costs, toxicities and side-effects, and the risk of selecting resistant clones.[1–4] For these reasons, and because of its high tolerability and long progression-free survival and overall survival, many physicians still prefer a 6-month regimen of chlorambucil plus obinutuzumab for elderly patients.[5] Improvement of ibrutinib-based therapy can therefore be achieved by reducing side-effects or achieving deep remissions that allow treatment cessation, thereby potentially decreasing the development of resistance. To achieve these desired effects, ibrutinib needs a partner drug. Logical as it sounds, simultaneously combining ibrutinib with rituximab has not shown a progression-free survival benefit,[6] which might be related to the in-vitro observation that ibrutinib inhibits antibody-dependent cellular cytotoxicity.[7] Obinutuzumab might be a more effective alternative because of its higher potency in inducing this cytotoxicity in the presence of ibrutinib.[7]

In *The Lancet Oncology*, Carol Moreno and colleagues[8] present the results of the iLLUMINATE study. They combined ibrutinib with six cycles of obinutuzumab and compared this regimen to standard chlorambucil plus obinutuzumab in patients with untreated chronic lymphocytic leukaemia who were aged at least 65 years, or younger patients with a high cumulative illness rating scale score or a tumour protein p53 mutation. The study ultimately enrolled a fit elderly population in whom the preferred chemoimmunotherapy regimen is arguably bendamustine plus rituximab rather than chlorambucil plus obinutuzumab. Nonetheless, Moreno and colleagues[8] accrued patients remarkably rapidly, with 229 patients enrolled in less than a year, showing the strong interest in chemotherapy-free regimens. With a median follow-up of 31·3 months (IQR 29·4–33·2), iLLUMINATE met its primary endpoint, with significantly longer progression-free survival in the ibrutinib plus obinutuzumab group than in the chlorambucil plus obinutuzumab group (median not reached [95% CI 33·6–non-estimable] *vs* 19·0 months [15·1–22·1]; hazard ratio [HR] 0·23; 95% CI 0·15–0·37; p<0·0001).

Several considerations need to be made. First, as with most chronic lymphocytic leukaemia studies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