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Phase 1 results of XmAb819, a novel ENPP3 x CD3 bispecific, in advanced clear cell renal cell carcinoma (ccRCC)

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Background

There is an unmet need in advanced ccRCC for differentiated treatment options following exposure to immune checkpoint inhibition (ICI), VEGFR-TKIs, and HIF2 α inhibition. The tumor-associated antigen ENPP3 has high expression in ccRCC and low expression in normal tissues. XmAb819 (ENPP3 x CD3) is a 2+1 bispecific antibody engineered for tumor-selective T-cell engagement that is being investigated in patients with advanced ccRCC.

Methods

XmAb819-01 is a phase 1 multicenter study in patients with advanced ccRCC previously treated with ≥ 1 ICI and ≥ 1 VEGFR-TKI, with or without prior HIF2 α inhibitor therapy. XmAb819 was administered as an intravenous (IV) or subcutaneous weekly priming regimen, then Q2W in Cycle 2 and onward until progression or unacceptable toxicity. Adverse events (AEs) were graded per CTCAE v5.0; cytokine release syndrome (CRS) graded per ASTCT; efficacy assessed per RECIST v1.1.

Results

As of 02 Apr 2026, 101 patients received XmAb819 IV; median age 61 years, median 3 prior lines of therapy (range, 1-10), 60% with ≥ 2 prior lines of VEGFR-TKIs, 34% with prior HIF2 α inhibitor therapy. For patients administered XmAb819 at the target dose range with ≥ 1 postbaseline scan (n=60), objective response rate (ORR) was 27% (confirmed and unconfirmed), disease control rate (DCR) was 68%, and median time to response was 12 weeks; ORR and DCR were consistent in patients with ≥ 2 prior VEGFR-TKIs (n=33; 30%, 73%) and prior HIF2 α inhibitor exposure (n=23; 26%, 70%). Fifteen of 16 responding patients remained on treatment at data cut, with a median follow-up of 21 weeks (range, 7-87) for ongoing responders. In the safety population (n=101), Grade ≥ 3 treatment-related AEs occurred in 61% of patients; AEs led to treatment discontinuation in 7%; no Grade 5 events occurred. Further follow-up and biomarker data, including ENPP3 expression, will be presented at the meeting.

Conclusions

XmAb819 demonstrates durable antitumor activity in heavily pretreated ccRCC, including patients with prior HIF2 α inhibition. CRS is manageable and does not prevent patients from receiving target doses with antitumor activity. These data support continued development in ccRCC and other ENPP3-expressing tumors, including pRCC, CRC, and NSCLC.

Clinical trial identification

NCT05433142.

Legal entity responsible for the study

Xencor, Inc.

Funding

Xencor, Inc.

Disclosure

S.K. Pal: Financial Interests, Institutional, Local PI: Eisai, Genentech, Roche, Exelixis, Pfizer, CRISPR Therapeutics, Allogene Therapeutics, Xencor, Novartis; Non-Financial Interests, Member: ASCO; Non-Financial Interests, Leadership Role: SWOG; Other, Other, Travel reimbursement: CRISPR, Roche. B. 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