Phase I study of GCC CAR-T therapy IM96 in patients with advanced colorectal cancer

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Background

The clinical outcomes of metastatic colorectal cancer (mCRC) therapies are limited. Guanylyl cyclase 2C (GCC) is ectopically expressed in mCRC and intestinally-restricted. A GCC-targeted CAR-T (IM96) was developed and phase I study was conducted to evaluate the safety and efficacy (NCT05287165).

Methods

In this open-label, 3+3 dose-escalation study, IM96 was evaluated in GCC-positive mCRC patients (pts) failed to ≥3 lines of therapies. Bridging therapies were allowed. Pts were pre-treated with fludarabine and cyclophosphamide, and received a single infusion of IM96 at the dose of 3×10⁸ (DL1), 6×10⁸ (DL2), 12×10⁸ (DL3), or 20×10⁸ (DL4) CAR-T cells. The primary objectives were safety and toxicity, and the secondary objectives were efficacy and pharmacokinetic profile.

Results

As of December 2022, 9 pts were enrolled and infused with IM96. The median age was 52.6, and 5/9 cases were male. Bridging therapies were used in 8 pts. Neurotoxicity and ≥grade 3 cytokine release syndromes (CRS) were not observed. Grade 1-2 CRS occurred in 5/9 pts (55.6%) with dramatic increase of interleukin-6. In 4/9 pts (44.4%), grade 1-3 diarrhea and rash were observed. Grade 3 diarrhea occurred in 2/9 pts (22.2%), and grade 2-3 oral mucositis occurred in 3/9 pts (33.3%), only in DL2 and DL3 groups. Dose-limiting toxicity and maximum tolerated dose were not achieved. The disease control rate (DCR) was 66.7%, and the objective response rate (ORR) was 11.1%. After CAR-T infusion, 5/9 (55.6%) patients showed a significant decrease in CEA level which was aberrantly high in all pts at baseline. CAR-T proliferated in all pts and reached peak at 7-10 days after infusion. Two pts showed persisting tumor reduction and declination of CEA level within 3 months, coinciding with CAR-T expansion to 10⁸/L. The response in pts with moderate-to-strong GCC expression in ≥30% of tumor cells was 100% DCR, and with this prerequisite, tumor reduction was observed in 100% pts when the IM96 dose was ≥6×10⁸.

Conclusions

IM96 was well tolerated and showed encouraging efficacy. The clinical response is correlated with tumor GCC expression, infusion dose, and CAR-T expansion level. This study is ongoing, and dose extensive investigation will also be performed.

Clinical trial identification

NCT05287165.

Legal entity responsible for the study

Peking University Cancer Hospital and Institute.

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Disclosure

All authors have declared no conflicts of interest.

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