Circulating Tumor DNA and Association with CAR-T Cell Therapy Response in Gastric and Pancreatic Cancer Patients

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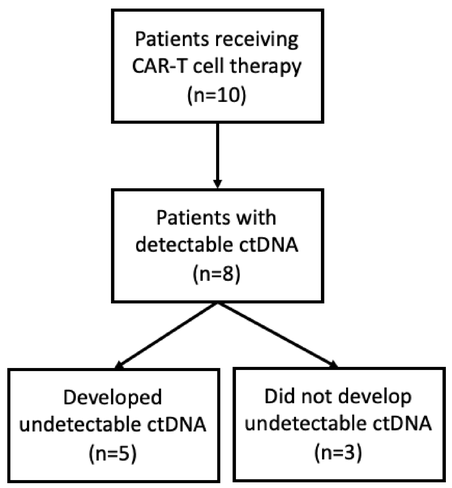
Background:

- Circulating tumor DNA (ctDNA) is a form of cell free DNA that can be used to detect and measure cancer molecular residual disease (MRD) before and after systemic therapy. There are no data pertaining to the assessment of MRD in patients with solid tumors treated with chimeric antigen receptor T-cell (CAR-T) therapy.
- Claudin18.2 (CLDN18.2)-targeted CAR-T cells have demonstrated efficacy in gastrointestinal cancers in early clinical trials.
- We evaluated a tumor-informed ctDNA assay in the setting of gastric and pancreatic malignancies treated with CLDN18.2-targeted CAR-T cells (CT041), NCT04404595.

Methods:

- A single-center review between 7/1/2021 – 1/1/2023 identified 10 patients with pancreatic or gastric carcinoma who received CAR-T CT041 cell therapy. Eight patients were ctDNA positive prior to treatment .
- Data was collected through serial blood samples drawn before and after CAR-T cell therapy. Banked plasma was analyzed for ctDNA using a tumor-informed SignateraTM, mPCR-NGS ctDNA assay (Natera, Inc.).
- The correlative prognostic value of ctDNA to predict response after CAR-T cell therapy was analyzed by RECIST 1.1 criteria.

Figure 1. Flow diagram of study



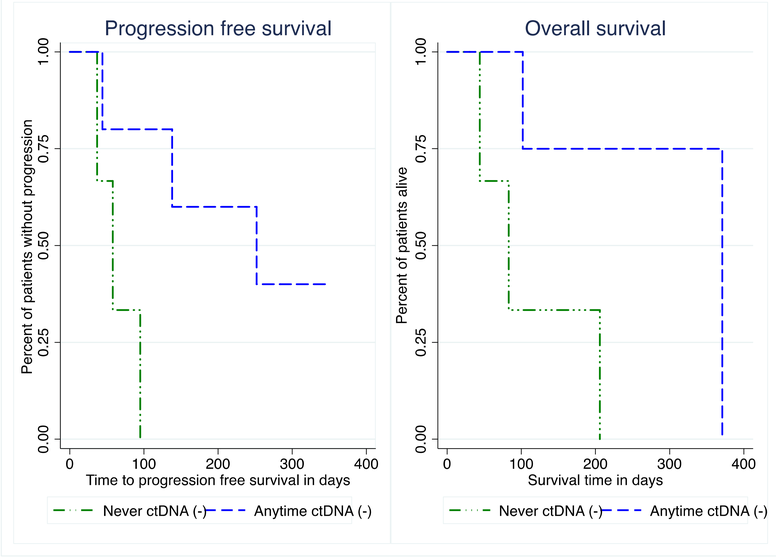
Results:

- Pre- and post-treatment serial ctDNA was available for 8 of 10 (3/5 gastric and 5/5 pancreatic cancer) patients and all 8 were ctDNA positive prior to CAR-T CT041 cell therapy. Of the 8, 5 (62.5%) became undetectable at some time after CT041 therapy, while 3 (37.5%) remained ctDNA positive throughout treatment.
- The median nadir of ctDNA was on day 14 after CT041 infusion for these 8 patients.
- The disease control rate (DCR) was 80% for anytime negative ctDNA patients (4/5).
- Of patients with responsive disease after CT041 , 2/3 (67%) achieved undetectable ctDNA and 1/3 (33%) had a ctDNA reduction by 95%. Both patients with stable disease developed undetectable ctDNA.
- In those patients with progressive disease, 1/3 (33%) had a negative ctDNA at some point during treatment.
- One patient with a target lesion complete response (CR) had undetectable ctDNA, then later developed progressive disease detectable by ctDNA 3 months prior to radiography.
- Overall survival was higher (9.1 months vs. 3.7 months) in those who achieved anytime undetectable ctDNA.

Figure 2. Characteristics of initially ctDNA positive patients receiving CAR-T therapy

	Never ctDNA (-) (N=3)	Anytime ctDNA (-) (N=5)
Age (years) – mean (SD)	53 (5.3)	55 (17.5)
Female sex – no. (%)	3 (100)	2 (40)
Primary disease – no. (%)		
Gastric	1 (33.3)	2 (40)
Pancreatic	2 (66.7)	3 (60)
Progression Free Survival – no. (%)		
Disease Control Rate = Stable, Partial, and Complete Response	1 (33)	4 (80)
Progressive Disease	2 (66)	1 (20)
Overall Survival (months) – mean (SD)	3.7 (2.8)	9.1 (3.8)

Figure 3. Kaplan-Meier survival estimates based on anytime ctDNA negativity



Progression-free survival and overall survival estimates for patients getting CAR-T cell therapy, stratified based on ctDNA negativity at any time. P value for the log-rank test for equality of survivor functions were 0.046 and 0.065, respectively.

Conclusions:

Overall, we concluded that tumor-informed ctDNA enables early response assessment to CAR-T cell therapy with a median of 14 days for ctDNA nadir.

- In this examination of eight patients, ctDNA - specifically achieving negative ctDNA - appears to correlate with response to CAR-T cell therapy.
- The statistics reveal a positive correlation, although not always statistically significant given the sample size. Eventual progression of disease may be expected in the setting of metastatic cancer.
- Ongoing clinical trials of CT041 CAR-T cell therapy will continue ctDNA analysis prospectively.

References:

1. Qi, C., Gong, J., Li, J., Liu, D., Qin, Y., Ge, S., ... & Shen, L. (2022). Claudin18. 2-specific CAR T cells in gastrointestinal cancers: phase 1 trial interim results. Nature Medicine, 28(6), 1189-1198.
2. Villaruz, L. C., & Socinski, M. A. (2013). The clinical viewpoint: definitions, limitations of RECIST, practical considerations of measurement. Clinical cancer research, 19(10), 2629-2636.
3. Frank, M. J., Hossain, N. M., Bukhari, A., Dean, E., Spiegel, J. Y., Claire, G. K., ... & Miklos, D. B. (2021). Monitoring of circulating tumor DNA improves early relapse detection after axicabtagene ciloleucel infusion in large B-cell lymphoma: results of a prospective multi-institutional trial. Journal of Clinical Oncology, 39(27), 3034-3043.
4. Mencel J., Slater S., Cartwright E., & Starling, N. (2022). The role of ctDNA in gastric cancer. Cancers, 14(20), 5105.
5. Jiang, H., Shi, Z., Wang, P., Wang, C., Yang, L., Du, G., ... & Li, Z. (2019). Claudin18. 2-specific chimeric antigen receptor engineered T cells for the treatment of gastric cancer. JNCI: Journal of the National Cancer Institute, 111(4), 409-418.

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