Early Proof of Concept of Safety and Clinical Activity of Clonal Neontantier Reactive T Cells (cNeT)

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Background

In NSCLC and melanoma, checkpoint inhibitors (CIIs) are included in first line therapy. Most patients, however, exhibit partial or complete resistance with time. There is a significant unmet need in patients in the post-checkpoint setting. Tumors that escape CD8 T lymphocytes (TLs) therapy have activity in a variety of malignancies, although a lack of understanding of their mechanism of action and impede possee assay development. The requirement for high doses of lymphocytotoxic checkpoint (CIIs) or CD8 TLs is yet to be applied to patients which is particularly restricted in NSCLC.

We have initiated trials evaluating T cells reacting against clonal neoantigens (cNeTs) in advanced, heavily pre-treated patients with NSCLC (CHIRON, NCT04032847) and melanoma (THETIS, NCT03997474). Clinical responses met early in trial development and are present in all tumour cells in contrast to subclinical mutations which occur later and are present in only subsets of tumour cells. Since neoantigen are not present on normal tissues, the chance of on-target off-tumour toxicities are limited. Our manufacturing process uses dendritic cell (DC) culture with low doses of IL-2 resulting in greater IL-2 responsiveness and allowing us to utilize lower dose lymphodepletion (LD) (2). Leukopenia is a potential risk (1) that also results in a limited toxicities and broad applicability. The use of highly selective proliferative-clonal neoantigen specific T cells therefore promises to add some of the current limitations with TIL therapies.

Methods

CHIRON: All patients had advanced or metastatic Stage III-IV NSCLC and had received prior anti-PD-L1/PD-1 treatment.

THETIS: All patients had recurrent or metastatic malignant melanoma and had received prior anti-PD-L1/PD-1 treatment.

Exclusion criteria: Key exclusion criteria (non-exhausted across both studies include 1) >18 years old, 2) Histologically confirmed diagnostic, 3) Medical/radiological abnormalities, 4) ECOG 3-5, 5) Adequate organ function as defined by blood count, clotting, liver function tests, GFR, 6) Accessible lesion, 7) Active life expectancy >6 months.

Study-specific exclusions: In CHIRON, never smokers and patients with EGFR+ or BRAF+ mutations were excluded. In THETIS, acute and mucosal melanomas were excluded.

Exclusion criteria across both studies: Key exclusions (non-exhausted) include 1) Known underlying autoimmune disorders (CIIs, CIIs, 2) Hep C, HIV, Thyroid dysfunction, 3) Active autoimmune disease requiring immunosuppressants, 4) Significant medical history (proliferation/drug day), 5) History of immunosuppressed CIIs that was caused by immunotherapy, 6) Concurrent cancer, 7) Confirmed history of allergic to morphine, benzylpenicillin or streptomycin

Pre-conditioning: Patients underwent low-dose lymphokine (L-K) (250-300Mg/m² x 4; cyclophosphamide 300Mg/m² x 4) days -6, -5, and 4 before the initial infusion.

IL-2: Patients received 10 daily doses of 0.2-2.5MUI/m² subcutaneously. No. of patients: 21 patients (17 in THETIS, 4 in CHIRON) were dosed at time of safety cut off (Sept 7th 2022). The 14th patient (CHIRON C-28) was dosed on December 5, 2021 after NOTP notification of expansion of abstract and thus included in the efficacy dataset, but not safety.

Results

Fourteen patients dosed (including three on VELOS® Process 2) Median cNeT dosed administered across the 14 patients was 18M, with median clonal reactivity of 16% (2M), and 2M% in CHIRON (n=10) and THETIS (n=4) respectively. The median dose in THETIS was 78M, one was naive and patients had a median of two prior lines of systemic anti-cancer therapy. Three patients in CHIRON were dosed on VELOS® Process 2, three patients had an median dose of 7M. Patients had a median of IL-D28 21μl/m², two metabolites, sum of target lesion diameter of 12.22m and 10 months on PD-L1 prior to dosing. cNeT was well tolerated. There were 25 treatment-emergent adverse events (AEs) with lymphopenia and neutropenia the most common (51 NSCLC, 10 melanoma respectively). There were four serious AEs (SAs) and two deaths related to the study treatments. The study was ongoing at the time of safety data cut off.

Efficacy: best responses of 1 PR, 9 SD and 4 PD

CHIRON: In the NSCLC study we observed the best responses of one partial response (PR), six stable diseases (SD) and one progressive disease (PD). There were several durable clinical benefit at 12 weeks in 5/7 evaluable patients (71%) and 4/7 at 18 weeks (57%). The partial responder showed total target lesion reduction of 56% at week 36 (Fig 2). T cell engraftment and cytokine profiles are supportive of cNeT driving anti-tumour activity in the PR (Fig 3-5). Six of thirteen patients dosed best responses were three SD, three PD.

Conclusions

• Encouraging safety and tolerability has been demonstrated for cNeT, with potential for deep and durable clinical responses in NSCLC with low doses of cNeT and reduced dose lymphokine and IL-2.PR. Forty patients received the full course of IL-2, and 95% of doses were delivered in total.

• Early proof of concept has been demonstrated in NSCLC with a disease control at 22 weeks observed in 5 of 7 evaluable patients (71%) including one PR (36 weeks).

• For the patient with PR, T cell engraftment and cytokine profiles were supportive of cNeT driving anti-tumour activity. In-depth characterization of the cNeT product biologic and active component is polycystin-dependent.

• Due to the lower dose lymphokine and IL-2 (vs. other TIL therapies) there is potential for wider applicability of cNeT including in melanoma.

• These data support the expansion in enrollment of subjects in ongoing Phase I/II trials.

• Ongoing use of proprietary translational platforms will allow further examination of parameters associated with clinical responses and inform development of the VELOS® process as well as forming the foundation of potency assay.

References

1. Maio M et al Oncology 2021

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