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LUMINOS-102: Lerapolturev with and without α-PD- 1 in unresectable α-PD- 1 refractory melanoma

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A novel FLI1 expressing tumour cell population in melanoma

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Transcriptional heterogeneity and tumour cell plasticity drive melanoma therapy resistance and recurrence. Here, we are using zebrafish melanoma models to interrogate this heterogeneity and plasticity. Analysis of zebrafish melanoma single cell RNA-sequencing data revealed a subpopulation of tumour cells that unexpectedly express the transcription factor *fli1*, a marker of endothelial differentiation. FLI1 is a key oncogenic driver in Ewing's Sarcoma, however whilst aberrant FLI1 expression in melanoma is associated with more aggressive tumours, little is known of its functional significance. Therefore, we first validated these *fli1* + cells in zebrafish melanomas using multiplex immunohistochemistry with Fli1 and Sox10 antibodies. Next, we generated a *Tg(fli1:GFP, crestin:mCherry)* zebrafish line on our $BRAF^{V600E}$ p53 mutant melanoma background and used fluorescence activated cell sorting to isolate GFP+, mCherry+ cells from primary melanomas. Importantly, we have also detected these *fli1* + tumour cells in both human melanoma scRNA-sequencing data and in patient melanoma tissue samples at multiple disease stages. Moreover, our zebrafish melanoma model undergoes rapid regression following MITF depletion, and thus we next asked if this population is found in residual disease. Excitingly, our data suggest that *fli1* + melanoma cells are enriched within a subset of the rare persister cells in the regressed tumour, possibly as a means to promote survival and contribute to tumour recurrence. To follow these cells through melanoma disease stages, we are engineering a dual-lineage tracing reporter line to track *fli1* + , *sox10* + cells and their progeny. Presently, we are using RNA-sequencing to investigate the molecular mechanisms that underlie these *fli1* + tumour cells and ultimately plan to employ gene editing to functionally test the role of this population in melanoma progression, therapy resistance and recurrence.

LUMINOS-102: Lerapolturev with and without α-PD-1 in unresectable α-PD-1 refractory melanoma

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Lerapolturev (lera, formerly PVSRIPO) is a novel poliovirus based intratumoral immunotherapy that infects both cancer cells and antigen-presenting cells (APCs) via CD155, the poliovirus receptor. Lera has direct anticancer effects while also generating type I/III interferon-dominated inflammation and anti-tumor T-cell priming and activation via infection of local APCs.

LUMINOS-102 (NCT04577807) is a multi-center, open-label, two-arm randomized Phase 2 study investigating the efficacy and safety of lera ± α-PD-1 in patients with unresectable melanoma who failed prior α-PD-1 therapy. Cross-over to the α-PD-1 arm is permitted after progression, PR for ≥6 mo or 6 mo on treatment with SD. The maximum initial lera dose was $6x10^8$ $TCID_{50}$ /visit every 3 or 4 weeks (Q3/4 W). As of March 2022, the maximum lera dose was increased to 1.6 x 10^9 $TCID_{50}$/visit, every week (QW) for 7 weeks (induction), followed by Q3/4 W dosing (maintenance).

As of 20-Jun-2022, 21 participants (10 male, 11 female, median 64 yrs) received lera ($n = 14$ at initial dose, Q3/4 W; $n = 4$ at increased dose, Q3/4 W; $n = 3$ at increased dose, QW) ± αPD-1. Five patients are currently on treatment.

With the initial regimen, no objective responses and a CBR of 7% were observed. However, with the higher dose regimen, 1 complete response and a CBR of 71% (5/7) has been observed. Two of 4 participants with stable disease have evidence of response (1 with resolution of uninjected lung metastasis, 1 with decreased PET signal in injected and uninjected lesions receiving combination therapy). The only treatment related AE in >1 pt was fatigue (19%, all grade 1 or 2). No dose-limiting toxicities or treatment-related SAEs were reported. Multiplex-IF analysis of on-treatment tumor biopsies will be presented.

Lera ± αPD-1 is well tolerated, with early signs of efficacy at the higher dose level. Enrollment and randomization are ongoing.