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Plasma cytokine profiles and survival outcomes in the 1801 phase 1/2 clinical trial of 9-ING-41 (elraglusib) in patients with advanced cancer.

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Background: 9-ING-41 (elraglusib) is a novel inhibitor of GSK-3β that has shown early signs of clinical benefit in a phase 1/2 clinical trial (ACT1801; NCT03678883). Early data support a multi-modal mechanism of action for elraglusib that targets both the tumor and immune system. Thus, the discovery and validation of biomarkers of drug sensitivity to elraglusib is a high priority. Here, we take inspiration from the literature on checkpoint inhibitor therapy and explore the potential of cytokines to predict elraglusib clinical response. **Methods:** Peripheral plasma samples from 59 patients enrolled in the 1801 phase 1/2 trial of elraglusib were assayed for 40 circulating cytokine levels. Patients advanced solid tumors refractory to standard treatments and received either elraglusib (1.0-15.0 mg/kg) as a single agent or in combination with other chemotherapies. Samples were taken from time points prior to elraglusib administration (pre-dose), after cycle 1, or after cycle 2. Each cytokine time point combination was used to stratify patients into high and low categories using an optimal cut-point determined using maximally selected rank statistics. Kaplan Meier and Cox Proportional Hazards analysis was used to determine the efficacy of each cytokine as a biomarker. The change in cytokine values between pre-dose and cycle 1 or pre-dose and cycle 2 was evaluated in a similar manner. **Results:** A total of 142 samples spanning eight different tumor histologies were collected and analyzed. A total of 240 cytokine-timepoint combinations were evaluated, and 53 significantly stratified patients by overall survival (p-value < 0.05). Of those, 35 showed that higher levels of the given cytokine correlated with a survival benefit and 18 a survival decrease. Notable among the cytokines demonstrating survival benefits were Granzyme B at Cycle 1 Day 4 (HR: 9.54, p-value:0.015) and TGF β at Cycle 1 Day 4 (HR: 8.48, p-value:0.0063). Strong hazard ratios were also observed for cytokines that correlated with survival decreases including TRAIL-R2 at Cycle 1 Day 2 (HR: 9.56e-02, p-value:0.0001), and IL-10 at Cycle 1 Day 4 (HR: 8.77e-02, p-value:0.007). Delta between timepoints was also able to stratifying patients by overall survival. **Conclusions:** Plasma cytokine profiling is a promising approach for discovery and validation of biomarkers prognostic for elraglusib clinical benefit. Numerous cytokines measured pre-dose stratified patients into significant survival groups suggesting a potential strategy for patient enrichment in clinical trials of elraglusib. These initial findings are being expanded by 1) increasing the cohort to accommodate histology specific investigations; 2) examining which cytokines are elraglusib response-specific versus drug-agnostic; and 3) combining cytokines in multivariate and machine learning models for optimal predictive capacity. Clinical trial information: NCT03678883. Research Sponsor: Actuate Therapeutics Inc.