Multimodal mechanism of action of the GSK-3 inhibitor 9-ING-41 (elraglusib) includes an immunomodulatory component: preliminary results from the 1801 phase 1/2 trial

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Abstract: #CT222

ABSTRACT

9-ING-41 (elraglusib) is a potent and selective GSK-3 inhibitor that has shown anti-tumor activity in patient-derived xenograft models and phase1/2 clinical studies in patients (pts) with advanced solid tumors. Preclinical studies have demonstrated that elraglusib downregulates PD-1, TIGIT and LAG-3, upregulates expression of MHC class I proteins in tumor cells from “cold tumors”, and shows synergy when combined with PD-1 blockade in mouse xenografts. Clinical activity has been observed both as a single agent and in combination with standard of care chemotherapies in several advanced cancer histologies. Here we present initialomics data from our phase 1/2 study (NCT03678883; ACT1801) spanning >100 pts with advanced cancer evaluating both single agent and chemotherapy combinations. The patients (pts) included in this study received elraglusib as a 3rd line therapy for advanced disease. Most pts with melanoma treated with elraglusib monotherapy (8/9; 89%) stayed on study for >2 cycles. One patient with melanoma refractory to checkpoint inhibitors achieved a confirmed and durable CR. Clinical benefit was also observed among pts with colorectal cancer with 4/12 (33.3%) pts treated with monotherapy and 12/15 (80%) that received elraglusib plus irinotecan rechallenge stayed on study for >2 cycles reaching median overall survival of 106 and 211 days, respectively. Based on emerging in vivo and in vitro results demonstrating that elraglusib activates T and NK cells promoting anti-tumor immune responses, we hypothesize immunomodulation by elraglusib may be contributing to anti-tumor immune response in the 1801 trial. We have acquired TCRseq and RNAseq profiles of PBMC samples from seven patients in 1801 during the first two weeks of treatment with elraglusib monotherapy. In these pts, reduced TCR clonality was observed and specific TCR clonotypes expanded after treatment, indicating T cell activation and expansion. These pts also showed changes in PBMC populations during elraglusib therapy as measured by immune deconvolution of PBMC RNAseq. Taken together, these data support a novel, previously unrecognized immunomodulatory mechanism of action for elraglusib and could provide rationale for future clinical development of elraglusib in pts with advanced malignancies. Additional analysis from TCRseq, immune profiling and cytokine analysis from expanded cohort of pts is ongoing.

RESULTS

CONCLUSIONS

- Elraglusib (9-ING-41) shows initial evidence of clinical benefit in multiple histologies and provides durable responses for some patients.
- Elraglusib administration is associated with specific drug clonotypes even after just 1-2 doses.
- Patients demonstrated changes in peripheral blood monocyte composition during therapy.
- Chemokines associated with cancer progression decreased during elraglusib treatment.

OTHER WORK FROM ACTUATE:

Determinants of Elra Response in Panc. Cancer

Section 15 Poster 7 April 18th 9-12 AM

Predicting Elra Response and Biomarkers using Machine Learning

Section 31 Poster 4 April 18th 1:30-5:00 PM