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A Phase 1 Trial of A Human Thymus-Expressed Apoptosis Factor in Pts with Advanced Solid Tumors: Interim Report

Background: This apoptosis factor (NEROFE™) is a 14-a.a. modified form of a hormone-like peptide present in the human thymus, which plays a key role in immune system regulation. In preclinical evaluation, it induced apoptosis in cancer cells, inhibited angiogenesis/metastasis, and showed in vivo efficacy with low toxicity.

Methods: This ongoing, single-center, first-in-human, 3+3 dose-escalation study of this factor given I.V. at 6 mg/m^2-96 mg/m^2 over 5 3-pt cohorts (3 times a week; 28-day cycle) examines the MTD, safety, PK profile, and anti-tumor activity in pts with advanced solid tumors. Pts undergo tumor assessments every other cycle. Samples for PK are taken on days 1 of cycles 1 and 2.

Results: To date, 14 previously treated (57% ≥3 lines) and 1 first line pts (M=8, F=7, median age: 63) with advanced/metastatic solid tumors have been enrolled. MTD has not been reached. Treatment was well-tolerated with no cumulative toxicity. The most frequently observed AEs (G≤2) in the first 4 cohorts were: hypertension (21%) and increased bilirubin (14%); 5 of 15 evaluable pts continued therapy beyond cycle 2. SD was noted in 2 pts: colorectal cancer (6M) and spinal cord neoplasia (+10M). PK was dose-dependent and approximately linear (Table). Factor administration was associated with orders of magnitude decreases in plasma levels of VEGF A, PDGF AA, PDGF BB, VEGF D, bFGF, aFGF and Angiopoeitin-1 in all pts in cohorts 3 and 4. Also, in 3 pts with elevated plasma EGF levels, it decreased the levels to below normal levels. In the 2 pts that achieved SD, tumor biopsies stained positive to ST2 receptor, had increased plasma TNF-alpha and IL-2.

Conclusions: This factor administered at doses up to 96 mg/m^2 is safe, well-tolerated, and demonstrates interesting anti-angiogenic activity in combination with increased immune cytokines. Tumor ST2 expression may be a biomarker for sensitivity to this factor. Dose-escalation continues in this trial.

	PK Parameters						
	Dose (mg/m^2)	**Auc0-t(ng h/mL)**		**Cmax (ng/ml)**		**T1/2 (hrs)**	
		Cycle 1Day1	**Cycle 2 Day1**	**Cycle 1Day1**	**Cycle 2 Day1**	**Cycle 1 Day1**	**Cycle 2 Day1**
Cohort 1	6	3813	9719	1209	1536	2.3	2.8
Cohort 2	12	12905	11452	6048	6048	2.1	2.0
Cohort 3	24	49630	57069	14609	14609	3.2	3.7
Cohort 4	48	79935	100093	18267	22113	4.9	4.6