Exploratory Analysis of Peripheral Pharmacodynamic (PD) Biomarkers After Sitravatinib (Sitra) and Tislelizumab (TIS) in Advanced Solid Tumors: SAFFRON-103

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Background: Sitra is a spectrum-selective tyrosine kinase inhibitor targeting multiple receptors, including VEGFR2. Here, we present an exploratory analysis of PD biomarkers in SAFFRON-103, a phase 1b study investigating Sitra with TIS, an anti-PD-1 antibody, in patients (pts) with solid tumors including advanced non-squamous-non-small cell lung cancer (NSCLC), squamous-NSCLC, melanoma, or ovarian cancer.

Methods: Peripheral blood samples were collected at Cycle (C) 1 Day (D) 1, C2D1, and C3D1 prior to Sitra dosing, to investigate changes in cytokines (Meso Scale Discovery [MSD] multiplexing), plasma proteins (ELISA), and immune cell populations (fluorescence-activated cell sorting [FACS]). Generalized linear mixed models were used to estimate fold change and analyze biomarker changes; Wald tests were used to generate *P*-values.

Results: Baseline characteristics were balanced across pts with evaluable biomarker results (n=186 cytokines/plasma proteins, n=113 immune cell populations) and in the overall population (N=216). For all pts, changes in individual biomarker levels were consistent from C1D1 to both C2D1 and C3D1, with significant increases in VEGFA (*P*<0.0001; both) and CXCL10 (*P*<0.0001; both) and significant decreases across soluble (s) VEGFR2 (*P*<0.0001; both), peripheral G-MDSCs (*P*=0.0005; *P*=0.0002), and monocytes (*P*<0.0001; both). Estimated fold changes of PD biomarkers across tumor types are shown (Table). Changes in VEGFA (increased) and monocytes (decreased) after treatment (C2D1/C1D1) were associated with improved objective response rates (odds ratio [OR] 4.67, *P*=0.0005; OR 5.82, *P*<0.0001).

Conclusions: VEGFA increased and sVEGFR2 decreased consistently and significantly after Sitra plus TIS therapy, demonstrating the on-target anti-angiogenesis effect of Sitra. Decrease of G-MDSCs and monocytes in peripheral blood indicates a potential immune-modulating role for Sitra with TIS.

Table

Estimated fold change from C1D1	Non-squamous-NSCLC		Squamous-NSCLC		Melanoma		Ovarian cancer	
	C2D1	**C3D1**	**C2D1**	**C3D1**	**C2D1**	**C3D1**	**C2D1**	**C3D1**
ELISA/MSD eligible	**n=60**		**n=48**		**n=22**		**n=54**	
VEFGA	2.77	2.65	2.53	2.53	2.89	2.38	2.16	2.14
sVEFGR2	0.67	0.63	0.61	0.59	0.65	0.66	0.70	0.69
CXCL10	1.70	1.97	1.65	1.43	1.75	1.44	2.21	1.90
FACS eligible	**n=44**		**n=21**		**n=10**		**n=28**	
G-MDSCs	0.74	0.71	0.59	0.60	0.83	0.74	0.81	0.84
Monocytes	0.70	0.72	0.72	0.64	0.73	0.72	0.81	0.85

Abbreviations: G-MDSC, granulocyte-like myeloid derived suppressor cells; NSCLC, non-small cell lung cancer; VEFGA, vascular endothelial growth factor A; sVERGR2, soluble vascular endothelial growth factor receptor 2