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DEVELOPMENTAL THERAPEUTICS—IMMUNOTHERAPY

Phase 1A clinical trial of the first-in-class fascin inhibitor NP-G2-044 evaluating safety and anti-tumor activity in patients with advanced and metastatic solid tumors.

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Abstract

2548

Background: Fascin inhibitors block tumor metastasis and increase antigen uptake in intra-tumoral dendritic cells. Filopodia, finger-like protrusions on cell surfaces, are necessary for migration of metastatic tumor cells and intra-tumoral dendritic cells. Fascin is the primary actin cross-linker in filopodia and elevated levels correlate with increased risk of metastasis, disease progression and mortality. NP-G2-044 is a novel small molecule that inhibits function of fascin. Pre-clinical data demonstrate drug-associated reductions in tumor growth and metastasis, enhanced immune response and survival in treated animals, and drug-drug synergism when combined with anti-PD-1 antibodies. **Methods:** This multicenter phase 1A clinical trial was designed to evaluate safety and tolerability of NP-G2-044 and to identify the drug's recommended phase 2 dose (RP2D) using a 3+3 dose escalation design. NP-G2-044 was administered to patients (pts.) with treatment-refractory solid tumor malignancies as a single oral daily dose for 6-week cycles that included 4 weeks on (daily dosing) and 2 weeks off (rest). **Results:** A total of 23 pts. were enrolled in 7 dose cohorts ranging from 200-2100 mg. QD. Overall, NP-G2-044 appeared well-absorbed and distributed with Tmax of 4 hrs and T1/2 of 20-24 hrs. Across all cohorts, no DLTs, drug-related SAEs or patient deaths were observed. Based on PK and safety findings, 1600 mg. daily was selected as the provisional RP2D. While no formal RECIST-based objective responses were observed, consistent with the drug's non-cytotoxic mechanism of action, preliminary signals of anti-

tumor and anti-metastatic activity were observed. These include dose proportional increases in duration of treatment, progression-free-survival, and metastasis-free interval, in particular for 4/4 late-stage ovarian cancer patients (table). Comparison of time on treatment (TOT) for ovarian cancer patients. **Conclusions:** In this first-in-human clinical trial, the novel fascin inhibitor, NP-G2-044, appeared safe and well tolerated. Signals of single-drug anti-tumor and anti-metastatic activity were observed. A phase 2A clinical trial with a particular focus on Ovarian Cancer will seek to elucidate signals of RP2D activity in both monotherapy and the combination of NP-G2-044 with anti-PD-(L)1 immune checkpoint inhibitors. Clinical trial information: NCT03199586.

Patient	Cancer Type	Last Prior Therapy	Time on Last Prior Therapy	Time on NP-G2-044	TOT Improvement	Metastatic Sites Prior to NP-G2-044	New METS on NP-G2-044
023	Ovary	CSF1R Inhibitor	~60 days	170 days	~183%	Liver, Colon, Pancreas, Bladder	No
027	Ovary	Doxorubicin	~105 days	170 days	~62%	Lung, Lymph Node, Peritoneum	No
028	Fallopian Tube	Anti-LIF1	~90 days	158 days	~76%	Lung, Lymph Node	No
031	Ovary	Liposomal Doxorubicin	~90 days	251 days	~179%	Peritoneum, Liver, Abdominal wall, Ilium	No

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