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

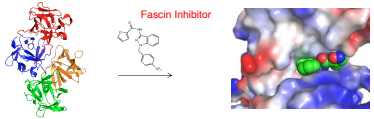
BACKGROUND: Fascin inhibitors block tumor metastasis and increase antigen uptake in intra-tumoral dendritic cells. Filopodia, finger-like protrusions on cell surfaces, are necessary for migration of metastatic tumor cells and intra-tumoral dendritic cells. Fascin is the primary actin cross-linker in filopodia, and elevated fascin levels correlate with increased risk of metastasis, disease progression and mortality. NP-G2-044 is a novel small molecule that inhibits the functions of fascin. Pre-clinical data demonstrate drug-associated reductions in tumor growth and metastasis, enhanced immune responses and survivals 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 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 patients 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-metastasis activity were observed. These include dose proportional increases in duration of treatment, progression-free-survival, and metastasis-free interval, in particular for 4 out of 4 late-stage ovarian cancer patients.

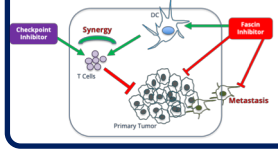
CONCLUSIONS: In this first-in-human clinical trial, the novel fascin inhibitor, NP-G2-044, appeared safe and well tolerated. Signals of single-drug anti-tumor and anti-metastasis activity were observed. A Phase 2A clinical trial will seek to elucidate signals of RP2D activity in both monotherapy and the combination of NP-G2-044 with anti-PD-1 immune checkpoint inhibitors.

Background



Fascin inhibitors are small molecule compounds that can occupy the actin-binding site on fascin, thus blocking fascin from bundling actin filaments.

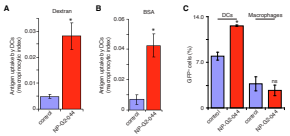
A Multi-Faceted Attack on Cancer

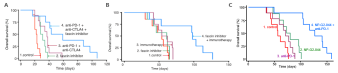


- NP-G2-044 is a first-in-class fascin inhibitor with multiple anti-tumor activities
- Simultaneously targets tumor cells and dendritic cells within the tumor microenvironment
- Decreases tumor growth and blocks tumor metastasis
- Activates dendritic cells and increases antigen uptake
- Functions synergistically with immune checkpoint inhibitors
- Effective on many cancer types

Pre-Clinical Data

NP-G2-044 increases antigen uptake by intra-tumoral dendritic cells in cultured cells and in mice





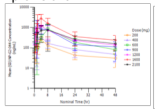
NP-G2-044 synergistically increases survival when combined with anti-PD-1 antibody

Methods and Study Design

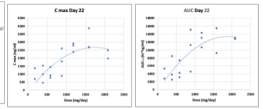
- Phase 1 clinical trial conducted at 3 U.S. centers: City of Hope; Honor Health; and MSKCC
- Late-stage pts. with advanced solid tumor malignancies
- 20 cancer patients finished at least 1 cycle of treatments, 8 of these patients completed 2 cycles, 3 patients completed 4 cycles, 1 patient completed 6 cycles.
- 7 orally bio-available dose cohorts evaluated: 200, 400, 600, 900, 1200, 1600, 2100 mg QD

Safety and Pharmacokinetics

- A total of 23 pts. were enrolled in 7 dose cohorts ranging from 200-2100 mg QD.
- Overall, NP-G2-044 was well-absorbed and distributed with T_{max} of ~4 hrs and $T_{1/2}$ of 20-24 hrs.
- Across all cohorts, no DLTs, drug-related SAEs or patient deaths were observed.
- Drug concentration/exposure increase in dose proportional fashion (through 1600 mg QD)
- Based on PK and safety findings, 1600 mg daily was selected as the provisional RP2D.



Mean (SD) concentration following single dose oral NP-G2-044 administration

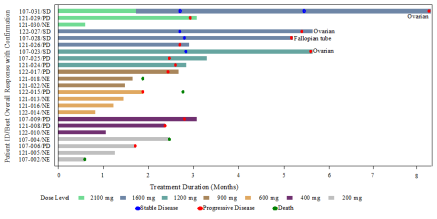


Individual subject exposure parameters vs dose level following daily dose oral NP-G2-044 administration

Efficacy

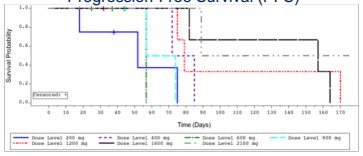
- No formal RECIST-based objective responses were observed, consistent with the drug's non-cytotoxic mechanism of action
- Preliminary signals of anti-tumor and anti-metastatic activities were observed.
- Tumor regressions in multiple pre-treated refractory solid tumor patients were observed.
- Of particular note, signals of efficacy were observed in 100% (4/4) ovarian cancer patients.

Dose-dependent Increase of Time-on-Treatment

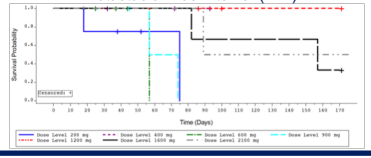


Dose-Dependent Increases in PFS and MFI

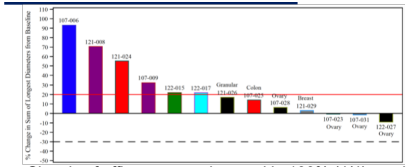
Progression-Free Survival (PFS)



Metastasis-Free Interval (MFI)



Inhibition of Ovarian Cancer Growth



- Signals of efficacy were observed in 100% (4/4) ovarian cancer patients.

Time-On-Treatment (TOT) Increases for Ovarian Cancer Patients

Patient	Dose Level	Cancer Type	Cancer Stage	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	Best Response
107-023	1200 mg	Ovary	Unknown	CSF1R inhibitor	~60 Days	170 Days	~183%	Liver, Colon, Pancreas, Bladder	No	Stable Disease
122-027	1600 mg	Ovary	IV	Doxorubicin	~105 Days	170 Days	~62%	Lung, Lymph Node, peritoneum	No	Stable Disease
107-028	1600 mg	Fallopian tube	IV	anti-LIF1	~ 90 Days	158 Days	~76%	Lung, Lymph Node	No	Stable Disease
107-031	2100 mg / 1600 mg	Ovary	III	Doxorubicin	~ 80 Days	251 Days	~179%	peritoneum, Liver, abdominal wall, Brain	No	Stable Disease

Summary and Next Steps

- NP-G2-044 is the first fascin inhibitor used in clinical studies.
- Anti-cancer activity achieved through tandem ability to block tumor metastasis and activate dendritic cells in the TME
- Phase 1 clinical trial demonstrates that the drug is well tolerated and generates provocative signals of anti-tumor activity
- Phase 2A clinical trial will be conducted at 15-20 U.S. cancer centers and further evaluate NP-G2-044 as both monotherapy and in combination with anti-PD-1 agents.
- The Sponsor wishes to thank the patients and families who participated on this clinical trial.