A phase 2 clinical trial of first-in-class fascin inhibitor NP-G2-044 as monotherapy and in combination therapy with anti-PD-1 immunotherapy in patients with advanced solid tumor malignancies.

Abstract

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Background:

Fascin is the main actin cross-linker in filopodia and its elevated levels are correlated with increased risk of cancer metastasis, disease progression and mortality. Pre-clinical evidence shows that deletion of the fascin gene (FSCN1) delays tumor development, slows tumor growth, reduces metastatic colonization and increases overall survival. NP-G2-044 is a novel, small molecule antagonist of fascin that blocks tumor metastasis, inhibits cancer growth and increases antigen uptake by intra-tumoral dendritic cells. In a previously presented phase 1 clinical trial, the drug was well tolerated and demonstrated signals of anti-tumor and anti-metastatic activity.

Methods:

This open-label study was designed to establish the recommended phase 2 dose (RP2D) of orally administered NP-G2-044 administered as both monotherapy (MT) and in combination (CT) with anti-PD-1 immunotherapy (IO). Efficacy was assessed by RECIST 1.1 and iRECIST [CT patients (pts.) only]. Following MT-RP2D identification, additional treatment-refractory pts. with advanced/metastatic gynecologic (GYN) malignancies were evaluated at the MT-RP2D. The CT-RP2D was established by a 3+3 design followed by an expansion cohort in pts. experiencing stable disease (SD) or progressive disease (PD) on prior anti-PD(L)-1 therapy.

Results:

MT-RP2D of 2100mg QD was selected based on a 16-pt. comparative review of PK, safety, and efficacy between two highest doses previously identified in phase 1. No DLTs or drug-related SAEs were observed among MT-RP2D pts. Median PFS for 12 GYN pts. receiving the MT-RP2D was 20 weeks and greater than 70% of these pts did not develop new metastases while on study. One pt. (treatment-refractory ovarian cancer) continues on study with SD exceeding 24 months. A CT-RP2D of 1600 mg. QD was selected and enrollment is ongoing. Among 29 enrolled CT pts. evaluated to-date, no DLTs were observed. Multiple tumor bulk reductions were observed among CT pts. incl one confirmed RECIST PR (53% reduction in tumor bulk) for a pt. with cutaneous squamous cell cancer who progressed on prior anti-PD(L)-1 therapy. Most common TEAEs observed for CT were diarrhea, fatigue and nausea with the safety monitoring is ongoing.

Conclusions:

The first-in-class fascin inhibitor, NP-G2-044, appears safe and well tolerated administered both as MT and in CT with IO. Signals of anti-cancer and anti-metastatic activity were observed with both mono and combination therapy. A phase 3 randomized clinical trial evaluating NP-G2-044 in combination with chemo in pts. with platinum-resistant ovarian cancer is in development with enrollment anticipated to start later this year. Additionally, a phase 2 study to further evaluate NP-G2-044 in combination with anti-PD-1 therapy in IO-naïve pts is planned. Clinical trial information: NCT05023486.