

PHASE 1 CLINICAL TRIAL EVALUATING THE SAFETY, BIOLOGIC AND ANTI-TUMOR ACTIVITY OF THE NOVEL STING AGONIST IMSA101 ADMINISTERED BOTH AS MONOTHERAPY AND IN COMBINATION WITH PD-(L)1 CHECKPOINT INHIBITORS

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Background Anti-tumor efficacy of immuno-oncology (IO) approaches remains limited to a minority of tumor subtypes and considerable efforts remain focused on strategies to improve IO activity in immune-refractory or ‘cold’ tumors. A recently discovered innate immunity pathway, cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING), plays a critical role in anti-tumor immunity. IMSA101 is a small molecule analogue of cGAMP that directly activates STING with high potency. Pre-clinical studies demonstrate provocative anti-cancer activity both with IMSA alone and in combination with ICI and radiotherapy.

Methods IMSA101–101 (NCT# 04020185) is a first-in-human phase 1 trial evaluating IMSA101 both as monotherapy and in combination with ICIs at 6 U.S. cancer centers. The study’s primary objective was to identify recommended phase 2 doses of IMSA101. Patients (pts.) \geq 18 yrs. with locally advanced or metastatic solid tumor malignancies were administered intra-tumoral IMSA at escalating dose levels (100–1200 mcg.) weekly (with cycle 1) and bi-weekly thereafter. For the combination cohort, ICI naive pts. or those with initial disease progression through ICI monotherapy were administered IMSA101 at escalating dose levels beginning at the monotherapy RP2D -1.

Results 22 pts. were enrolled across 5 monotherapy dose cohorts with no dose-limiting toxicities (DLTs) or drug-related serious adverse events (SAEs) observed. 31 study-drug related TEAEs were reported in 14 pts. (63.6%). IMSA101 appeared well-absorbed and distributed with Tmax of 0.7 hrs and t1/2 of 1.8 hrs. Both Cmax/AUC and cytokine levels increased in a dose proportional manner. In the combination cohort, 18 pts. were enrolled in 3 dose cohorts ranging from 800–2400 mcg. with a total of 23 TEAEs reported in 11 pts. (61.1%). A single Grade 1 TEAE of cytokine release syndrome (CRS) was reported at 800 mcg. and this resolved 1 day after onset. One pt. (1200 mcg.) experienced a DLT of G3 arthropathy. Based on PK/safety findings, 1200 mcg. was selected as the RP2D of IMSA101 for both mono and combination therapy. While no formal RECIST-based responses were observed in monotherapy, notable tumor regressions were observed in both injected and non-injected lesions. In the combination arm, a single and ongoing PR (66%) was observed in a pt. with refractory uveal melanoma.

Conclusions Intra-tumoral administered IMSA101 is safe and well tolerated. Notable efficacy signals with both monotherapy and in combination with ICI were observed. Phase 2 randomized trials evaluating the combination of IMSA101, ICI and pulsed radiotherapy (PULSAR) in the settings of oligometastatic and oligo-progressive disease are now underway.

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