A PHASE 1/2 STUDY OF ASP1570 IN PARTICIPANTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS WHO HAVE PROGRESSED ON, OR ARE INELIGIBLE FOR, ALL AVAILABLE STANDARD THERAPIES

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Background Cancer immunotherapies target immune checkpoints and have been transformative in the treatment practices of oncology. However, only a subset of all patients in most cancer types effectively respond to these therapies. It has been established that approximately 60% to 70% of patients who receive anti–programmed cell death protein-1 (anti–PD-1) or anti–cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) do not respond to treatment. Furthermore, acquired resistance is common, causing some patients who initially responded to the therapy to later experience disease progression. Therefore, there is a significant opportunity for immunotherapy expansion in cancer treatment.

Diacylglycerol kinase (DGK) is a large enzyme family of 10 mammalian isoenzymes that catalyzes the conversion of diacylglycerol (DAG) to phosphatidic acid (PA). In T cells, DGK (such as DGKz) inhibits DAG-mediated signals following T-cell receptor engagement by catalyzing the conversion of DAG to PA. Even when PD-1 is blocked by anti–PD-1 antibodies, there may be partial inactivation by DGK. Therefore, DGK inhibitors have the potential to enhance DAG downstream signaling, leading to T-cell activation regardless of PD-1 signaling. ASP1570 is a novel inhibitor against DGKz and has the potential to enhance DAG downstream signaling which can activate T cells regardless of PD-1 signaling and lead to tumor killing. ASP1570 restored T-cell functions suppressed by multiple immunosuppressive signals (PD-1, transforming growth factor beta, prostaglandin E2, and adenosine) and induced tumor growth inhibition in mice models of MC38 (anti–PD1 sensitive) and B16-F1 (tumor-infiltrating lymphocyte poor, anti–PD-1 insensitive). Taken together, ASP1570 treatment as a single agent and/or in combination with anti–PD-1 therapy for locally advanced or metastatic solid tumors may result in clinical benefit.

Methods This is a phase 1/2, open-label, multicenter, multiple-dose, dose-escalation/expansion study of ASP1570 in participants with locally advanced or metastatic solid tumors. The study will enroll approximately 168 participants into 2 phases, dose escalation and dose expansion, to assess safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics (figure 1). The study will consist of the following periods: screening, treatment with ASP1570 daily oral dosing in 21-day cycles, end of treatment, follow-up (safety and survival follow-up), and end of study (figure 2). The study is open for enrollment.

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Trial Registration NCT05083481

REFERENCES

Ethics Approval This study received IRB approval from Advarra (Pro00055357), and all participants must provide informed consent before taking part.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Part 1: Dose Escalation

Stage 1

Cohort 1 (20 mg qd) n = 3
Cohort 2 (30 mg qd) n = 3
Cohort 3 (75 mg qd) n = 3
Cohort 4 (150 mg qd) n = 3
Cohort 5 (200 mg qd) n = 3
Cohort 6 (100 mg bid) n = 3
Cohort 7 (200 mg bid) n = 3
Cohort 8 (150 mg bid) n = 3

Part 2: Dose Expansion

Stage 1

Cohort 1 (10 mg bid) n = 3
Cohort 2 (25 mg bid) n = 3
Cohort 3 (10 mg bid) n = 3
Cohort 4 (15 mg bid) n = 3
Cohort 5 (20 mg bid) n = 3
Cohort 6 (15 mg bid) n = 3
Cohort 7 (20 mg bid) n = 3
Cohort 8 (10 mg bid) n = 3

Stage 2

Cohort Type 1 RPD Expansion Melanoma (n = 6
Cohort Type 1 RPD Expansion Melanoma (n = 6
Cohort Type 2 RPD Expansion NODC (n = 12)
Cohort Type 2 RPD Expansion NODC (n = 12)
Cohort Type 3 Response-tolerant Expansion/ Type A (n = 6)
Cohort Type 3 Response-tolerant Expansion/ Type A (n = 6)
Cohort Type 3 Response-insensitive Expansion/ Type B (n = 6)
Cohort Type 3 Response-insensitive Expansion/ Type B (n = 6)


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Abstract 754 Figure 2 Study Visit Schema