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Phase 1/2 Trial of ASP1570, a Novel Diacylglycerol Kinase ζ Inhibitor, in Patients With Advanced Solid Tumors

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Conclusions

- In vitro, ASP1570 promoted human CD8+ T cell activation and restored human CD8+ T cell functions suppressed by multiple immunosuppressive signals
- In the phase 1/2 clinical study of ASP1570, exploratory biomarker analysis of tumor biopsy and blood samples supported that ASP1570 may promote T cell activation and enhance the effectiveness of cancer immunotherapy
- ASP1570 monotherapy had an acceptable safety profile and showed early signs of clinical activity
- These data support further study of ASP1570 in patients with advanced solid tumors

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Disclosures of Interest

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Background

- Therapeutic benefits of immune checkpoint inhibitors are limited by primary or adaptive resistance as T cells become suppressed by inhibitory mechanisms in the tumor microenvironment[1–3]
- During T cell receptor (TCR) activation, diacylglycerol (DAG) has been identified as critical for T cell downstream signaling[4,5]
- Diacylglycerol kinase ζ (DGKζ) negatively modulates DAG-mediated T cell activation by catalyzing the conversion of DAG to phosphatidic acid[4,5]
- ASP1570, a novel small-molecule DGKζ inhibitor, may represent a promising strategy to promote T cell activation and enhance the efficacy of cancer immunotherapy[6]

Objective

- To report nonclinical properties in cancer immunotherapy of ASP1570 and clinical results from the first-in-human study of ASP1570 oral monotherapy in patients with advanced solid tumors

Methods

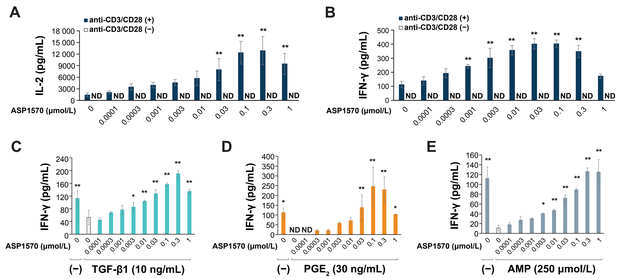
- In preclinical studies, TCR signaling and T cell function were evaluated under immunosuppressive conditions relevant to the tumor microenvironment, and antitumor efficacy was evaluated in the anti–PD-1-antibody–insensitive B16F1/F10 mouse model
  - Cell-based assays were constructed by Astellas Pharma Inc. (PD-1 co-culture assay system) or were from Promega (CTLA-4 Blockade Bioassay, Cat# JA3001; and TIGIT/CD155 Blockade Bioassay, Cat# J2201)
  - Mice bearing B16F1 tumors received oral ASP1570 (twice-daily [BID], 5 mg/kg/10 mL) or vehicle or intraperitoneal anti-PD-1 antibody (twice-weekly, 100 μg/head) from days 0–9; or oral ASP1570 (once-daily [QD], 3 mg/kg/10 mL) or vehicle from days 0–9, and intraperitoneal anti-CD8 antibody (200 μg/head) on days 0, 1, 2, 6, and 10
  - Statistical comparisons were performed with Dunnett's multiple comparison test, unless otherwise indicated
- In the phase 1/2, multicenter, open-label study (NCT05083481),[7] patients with locally advanced or metastatic solid tumors who had progressed or were no longer eligible to receive standard therapy were included
  - During dose escalation, cohorts (n ≥ 3) received escalating doses of ASP1570 10–75 mg orally QD or BID over a 21-day cycle until patients met discontinuation criteria
- The primary endpoint was safety
  - Adverse events, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) version 5.0, were monitored up to 45 days after the last dose of ASP1570 or until initiation of a new anticancer therapy, whichever came first
- Secondary endpoints included pharmacokinetics (PK) and efficacy; exploratory endpoints included biomarker analysis
  - For exploratory biomarker analysis, tumor biopsies at baseline (≤ 8 weeks prior to cycle 1 day 1 [C1D1]) and on C2D1 were obtained per investigator judgement
  - Blood samples were collected within 1 hour prior to each dose on D1, D2, D8, and D15 of C1 and C2
  - Analyses were summarized using descriptive statistics, and numeric differences were reported

Results

Preclinical Studies

- ASP1570 enhanced interleukin (IL)-2 and interferon (IFN)-γ production in human CD8+ T cells stimulated with anti-CD3/CD28 antibodies for 3 days (**Figure 1A–B**). These activations were not observed without TCR stimulation
- ASP1570 restored CD8+ T cell activation in the presence of TCR signaling suppressors, including transforming growth factor (TGF)-β1, prostaglandin (PG) E2, and adenosine monophosphate (AMP) (**Figure 1C–E**)

Figure 1. Activation of CD3/CD28-Stimulated T Cells In Vitro by ASP1570



Compared with the anti-CD3/CD28 (+) ASP1570 (–) group, ASP1570 increased (**A**) IL-2 and (**B**) IFN-γ production; ASP1570 restored T-cell responses compared with the (**C**) TGF-β1 (+) ASP1570 (–) groups, (**D**) PGE2 (+) ASP1570 (–) groups, and (**E**) AMP (+) ASP1570 (–) groups. *P < 0.05, **P < 0.01.
AMP, adenosine monophosphate; IFN, interferon; IL, interleukin; ND, not detected; PG, prostaglandin; TGF, transforming growth factor.
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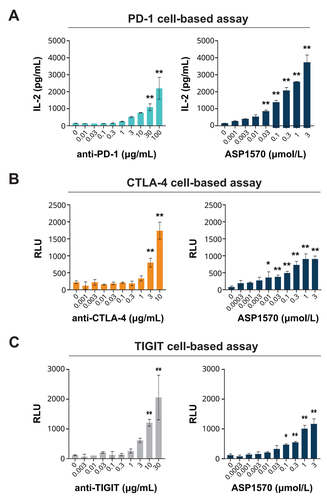
- ASP1570 completely reversed the inhibitory effect of the PD-1 signal and partially reversed the inhibitory effect of cytotoxic T-lymphocyte antigen (CTLA)-4 and T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (TIGIT) signals (**Figure 2**)

Figure 2. Restoration of T Cell Response In Vitro by ASP1570



ASP1570 restored T cell response in the presence of immune checkpoint inhibitors (**A**) PD-1, (**B**) CTLA-4, and (**C**) TIGIT. *P < 0.05, **P < 0.01.
CTLA, cytotoxic T-lymphocyte antigen; PD, programmed cell-death protein; RLU, relative light unit; TIGIT, T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif.
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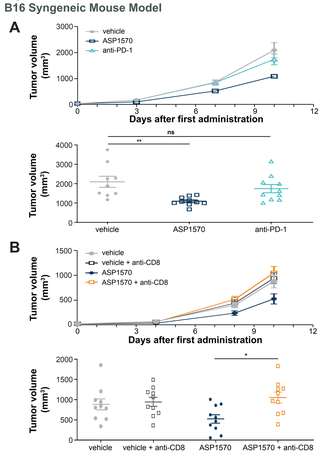
- ASP1570 suppressed tumor growth in an immune checkpoint inhibitor (CPI)-insensitive B16 syngeneic mouse model, while tumor growth was resistant to anti-PD-1 antibody treatment (**Figure 3A**)
- Although ASP1570 markedly inhibited tumor growth, CD8+ T cell depletion completely abolished this effect (P < 0.05; **Figure 3B**), indicating that the antitumor effect of ASP1570 is mediated by CD8+ T cell-dependent mechanisms

Figure 3. Antitumor Effect of ASP1570 in a CPI-Insensitive B16 Syngeneic Mouse Model



(**A**) ASP1570 suppressed tumor growth compared with anti-PD-1 antibody treatment; (**B**) inhibition of tumor growth by ASP1570 was abolished with anti-CD8 antibody treatment. Tumor volume of each group was plotted at each time point as mean ± SEM (n = 9 or 10). *P < 0.05, **P < 0.01.
CPI, immune checkpoint inhibitor; ns, not significant; PD, programmed cell-death protein; SEM, standard error of the mean.
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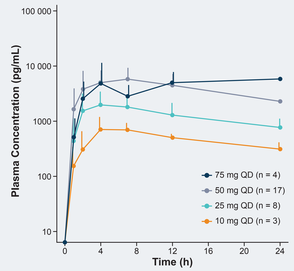
Clinical Studies

- As of July 15, 2024, 59 patients received ≥ 1 dose of ASP1570 (see patient demographics and baseline characteristics in **Supplementary Table 1**)

PK and Safety

- PK exposure to ASP1570 increased proportionally across 10–50 mg QD groups (**Figure 4**)

Figure 4. Mean Plasma Concentration-Time Profile of ASP1570



Single dose pharmacokinetics on C1D1 are shown. Data are presented as mean with SD.
C, cycle; D, day; QD, once daily; SD, standard deviation.

- All-grade treatment-related adverse events (TRAEs) occurred in 54 of 59 (91.5%) patients; grade 3 TRAEs occurred in 14 of 59 (23.7%) patients (**Table 1**)
  - TRAEs led to discontinuation of treatment in 4 of 59 (6.8%) patients
  - The most common all-grade TRAEs were diarrhea (57.6%), nausea (37.3%), rash (27.1%), and vomiting (27.1%)
- Dose-limiting toxicities occurred in 4 patients: 1 patient had diarrhea, and 3 patients had rash

Table 1. Adverse Events in the Safety Analysis Set[a,b]

Patients, n (%)	ASP1570 10 mg QD (n = 3)	ASP1570 25 mg QD (n = 15)	ASP1570 50 mg QD (n = 17)	ASP1570 75 mg QD (n = 5)	ASP1570 25 mg BID (n = 9)	ASP1570 35 mg BID (n = 8)	ASP1570 50 mg BID (n = 2)	Total (N = 59)
TRAEs								
All	3 (100.0)	13 (86.7)	16 (94.1)	5 (100.0)	7 (77.8)	8 (100.0)	2 (100.0)	54 (91.5)
Grade 3[c]	1 (33.3)	3 (20.0)	3 (17.6)	2 (40.0)	2 (22.2)	3 (37.5)	0	14 (23.7)
Serious	1 (33.3)	1 (6.7)	1 (5.9)	1 (20.0)	1 (11.1)	0	0	5 (8.5)
TRAEs[d] by preferred terms[e]								
Diarrhea	2 (66.7)	8 (53.3)	9 (52.9)	3 (60.0)	4 (44.4)	6 (75.0)	2 (100.0)	34 (57.6)
Nausea	0	1 (6.7)	7 (41.2)	3 (60.0)	4 (44.4)	6 (75.0)	1 (50.0)	22 (37.3)
Rash[f]	0	6 (40.0)	5 (29.4)	2 (40.0)	1 (11.1)	2 (25.0)	0	16 (27.1)
Vomiting	0	1 (6.7)	9 (52.9)	2 (40.0)	0	2 (25.0)	2 (100.0)	16 (27.1)
Decreased appetite	0	2 (13.3)	4 (23.5)	0	2 (22.2)	1 (12.5)	0	9 (15.3)
Fatigue	1 (33.3)	1 (6.7)	2 (11.8)	3 (60.0)	0	1 (12.5)	1 (50.0)	9 (15.3)

Twenty-two deaths occurred during the study period; none were considered related to the study drug by investigators.
[a]Data cutoff date: July 15, 2024.
[b]The safety analysis set comprised all patients who received at least 1 dose of study drug, and patients were analyzed by dose level.
[c]No grade 4 or 5 events. [d]The all-grade events reported here occurred in ≥ 15% of patients across all cohorts.
[e]Preferred terms were defined according to the Medical Dictionary for Regulatory Activities terminology version 26.0.
[f]Including the following system organ class preferred terms: rash, rash macular, and rash maculo-papular.
BID, twice daily; QD, once daily; TRAE, treatment-related adverse event.

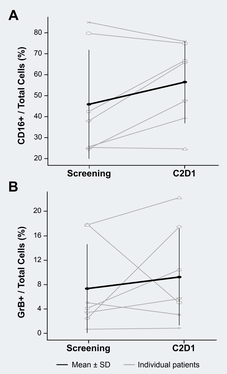
Efficacy

- Among efficacy-evaluable patients (n = 38), confirmed disease control rate per immune-based RECIST was 44.7% (17/38), including 1 patient with confirmed partial response

Tumor Biomarker Analysis

- Limited tumor biopsy data (n = 7) showed trends for increased CD16+ cells and Granzyme B (GrB)-expressing cells in the tumor microenvironment (**Figure 5**), aligning with the proposed mechanism of action of ASP1570

Figure 5. Immune Activation in the Tumor Microenvironment in Response to ASP1570

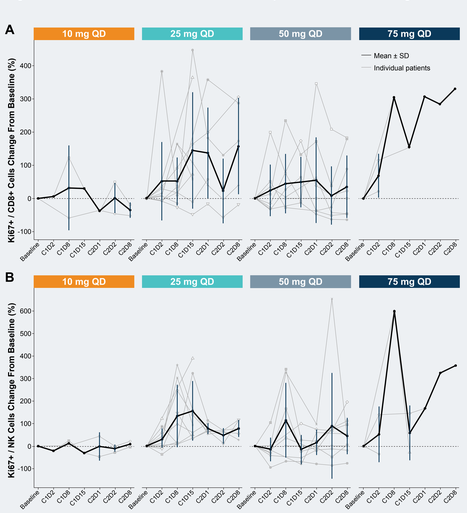


C, cycle; D, day; GrB, Granzyme B; SD, standard deviation.

Peripheral Biomarker Analysis

- ASP1570 promoted dose-dependent activation of CD8+ T cells and natural killer (NK) cells (**Figure 6**)

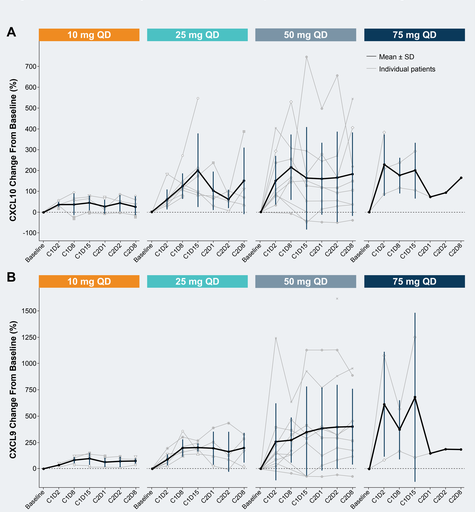
Figure 6. Activation of Immune Cells in Blood Samples of Patients Receiving ASP1570



Percent change of (**A**) Ki-67+ CD8+ T cells and (**B**) Ki-67+ NK cells trended higher after patients received ASP1570.
C, cycle; D, day; NK, natural killer; QD, once daily; SD, standard deviation.

- Dose-dependent increases in inflammatory cytokines C-X-C motif chemokine 10 (CXCL10) and CXCL9 were also observed (**Figure 7**)

Figure 7. Activation of Cytokines in Blood Samples of Patients Receiving ASP1570



Percent change of (**A**) CXCL10 and (**B**) CXCL9 trended higher after patients received ASP1570.
C, cycle; CXCL, C-X-C motif chemokine ligand; D, day; QD, once daily; SD, standard deviation.