Presented at the
Society for Immunotherapy of Cancer (SITC) 37th Annual Meeting
Boston, MA, or Virtual • November 8–12, 2022

A Phase 1 Study Exploring the Safety and Tolerability of the Small-Molecule PD-L1 inhibitor, INCB099280, in Patients With Select Advanced Solid Tumors

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Introduction

- Programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathway blockade, and subsequent T-cell activation, provides therapeutic benefit for many tumor types[1]
- Overall survival benefit has been demonstrated with intravenous monoclonal antibodies targeting PD-1/PD-L1 in a variety of cancers
- INCB099280 is a novel, orally administered small-molecule inhibitor of PD-L1, disrupting the PD-1/PD-L1 interaction
- We report here results from the ongoing phase 1 INCB099280 study

Objective

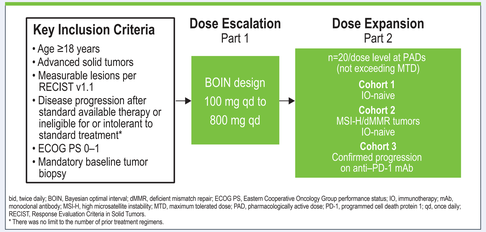
- This ongoing phase 1 study (NCT04242199) evaluates the safety, tolerability, and preliminary efficacy of INCB099280 in advanced solid tumors and aims to identify a pharmacologically active dose or maximum tolerated dose, whichever is lower

Methods

Patients and Study Design

- This phase 1, open-label, dose-finding study is evaluating INCB099280 in adults whose disease had previously progressed on available therapy
- Part 1 uses a Bayesian optimal interval dose escalation design (**Figure 1**)
- In part 2, two doses have been expanded for patients with various tumor types (**Figure 1**)

Figure 1. Study Design



bid, twice daily; BOIN, Bayesian optimal interval; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group performance status; IO, immunotherapy; mAb, monoclonal antibody; MSI-H, high microsatellite instability; MTD, maximum tolerated dose; PAD, pharmacologically active dose; PD-1, programmed cell death protein 1; qd, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.
* There was no limit to the number of prior treatment regimens.

Endpoints

- The primary endpoints were safety and tolerability of INCB099280, measured by monitoring frequency and severity of adverse events
- Exploratory endpoints included the objective response rate, defined as the percentage of patients with a best overall response of complete response or partial response per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Statistical Analyses

- Descriptive statistics were used for all analyses in this exploratory study
- The RECIST-evaluable population consists of patients who have received ≥1 dose of INCB099280, completed a baseline scan, and meet at least one of the following criteria: ≥1 postbaseline scan, a follow-up of ≥63 days, or have discontinued study

Results

Patient Characteristics and Disposition

- A total of 86 patients were treated before data cutoff on July 8, 2022; 47 patients (54.7%) were enrolled in dose escalation (part 1) and 39 (45.3%) in dose expansion (part 2; **Table 1**)
- The majority of patients had previously received 1–2 lines of anticancer therapy (**Table 2**)
- 59 patients (68.6%) discontinued treatment, 48 due to disease progression

Table 1. Number of Patients per Dose Level

	Dose Level	Number of Patients (N=86)
Dose escalation		
Part 1	100 mg qd	3
	200 mg qd	3
	200 mg bid	3
	300 mg bid*	9
	400 mg bid*	10
	600 mg qd*	9
	800 mg qd*	10
Dose expansion		
Part 2	Cohort 1 300 mg bid*	13
	Cohort 1 400 mg bid*	17
	Cohort 2 300 mg bid†	6
	Cohort 2 400 mg bid†	3

bid, twice daily; dMMR, deficient mismatch repair; IO, immunotherapy; MSI-H, high microsatellite instability; qd, once daily.
* Cancer types for patients enrolled in these dose levels (ie, IO naive patients) were: anal (n=13); breast (n=7), esophageal, colorectal (n=5); cervical (n=4); endometrial, neuroendocrine (n=3); gastric, cutaneous squamous cell carcinoma, prostate, sarcoma, thyroid (n=2); mesothelioma, basal cell carcinoma, ovarian, squamous cell carcinoma of the head and neck, cholangiocarcinoma, vaginal, vulvar, small intestine, ampulla of vater, cancer of unknown primary, peritoneal mesothelioma, sebaceous carcinoma of the scalp, sinuscarcinoma, squamous cell carcinoma of the rectovaginal septum, urachus carcinoma, porocarcinoma scalp, left temporal meningioma, other cutaneous carcinoma (n=1).
† Cancer types for patients enrolled in these dose levels (ie, IO naive patients with MSI-H/dMMR tumors) were: endometrial, prostate (n=3); colorectal (n=2), duodenum (n=1).

Table 2. Patient Demographics

	Total (N=86)
Age, median (range), y	63.0 (21.0–82.0)
Female, n (%)	48 (55.8)
Race, n (%)	
White	48 (55.8)
Black	2 (2.3)
Asian	1 (1.2)
Other	1 (1.2)
Not reported or missing	34 (39.5)
ECOG status, n (%)	
0	43 (50.0)
1	43 (50.0)
Prior IO treatment, n (%)	2 (2.3)
Previous lines of therapy, n (%)	
0	8 (9.3)
1	27 (31.4)
2	22 (25.6)
≥3	28 (32.6)
Missing	1 (1.2)

ECOG, Eastern Cooperative Oncology Group; IO, immunotherapy.

Safety

- A total of 82 patients (95.3%) experienced a treatment-emergent adverse event (TEAE) (**Table 3**); the most frequent TEAEs were decreased appetite, fatigue, nausea, asthenia, and diarrhea (**Table 4**); no grade ≥3 treatment-related TEAEs occurred in >1 patient (**Table 5**)
  - 2 patients experienced treatment-related serious TEAEs (hypophagia and confusional state, n=1 each)
- There was one protocol-defined dose-limiting toxicity (DLT); one patient in the 600-mg once-daily (qd) cohort was unable to receive ≥75% of the prescribed study drug dose due to vomiting
  - The 600-mg qd cohort completed enrollment, and none of the other 8 patients had a DLT

Table 3. Safety

n (%)	Total (N=86)
Any-grade TEAE	82 (95.3)
Treatment-related TEAE	62 (72.1)
Grade ≥3 treatment-related TEAE	6 (7.0)
Treatment-related serious TEAE	2 (2.3)
Treatment-related death	0

TEAE, treatment-emergent adverse event.

Table 4. Very Common TEAEs (≥15% [n≥13] Patients) by MedDRA Preferred Term

n (%)	Total (N=86)	
	Any Grade	Grade ≥3
Decreased appetite	27 (31.4)	2 (2.3)
Fatigue	23 (26.7)	3 (3.5)
Nausea	23 (26.7)	0
Asthenia	20 (23.3)	2 (2.3)
Diarrhea	20 (23.3)	1 (1.2)
Anemia	19 (22.1)	5 (5.8)
Vomiting	18 (20.9)	0
Constipation	17 (19.8)	0
Cough	14 (16.3)	0

MedDRA, Medical Dictionary for Regulatory Activities (v24.0); TEAE, treatment-emergent adverse event.

Table 5. Common Any-Grade TRAEs (≥5% [n≥5] Patients) by MedDRA Preferred Term

n (%)	Total (N=86)	
	Any Grade	Grade ≥3
Asthenia	16 (18.6)	1 (1.2)
Fatigue	15 (17.4)	1 (1.2)
Nausea	14 (16.3)	0
Decreased appetite	12 (14.0)	1 (1.2)
Diarrhea	10 (11.6)	1 (1.2)
Constipation	6 (7.0)	0
Dry mouth	6 (7.0)	0
Dry skin	6 (7.0)	0
Pruritus	6 (7.0)	0
Alanine aminotransferase increased	5 (5.8)	0
Arthralgia	5 (5.8)	0
Vomiting	5 (5.8)	0

MedDRA, Medical Dictionary for Regulatory Activities (v24.0); TRAE, treatment-related treatment-emergent adverse event.

- Sponsor-defined immune-related TEAEs (irTEAEs) occurred in 11 patients (12.8%); the most common irTEAEs, including their medical management, are presented in **Table 6**
  - irTEAEs were observed at 200 mg qd (n=1), 300 mg twice daily (bid; n=6), 400 mg bid (n=3), and 600 mg bid (n=1)
- No irTEAEs had a severity of grade ≥3, required a dose reduction, or resulted in study drug discontinuation
  - 3 cases of irTEAEs led to treatment interruption: blood creatinine increase (200-mg qd cohort), interstitial lung disease (400-mg bid cohort), and immune-mediated hepatitis (400-mg bid cohort)
- Unlike with the oral PD-L1 inhibitor INCB086550 [**SITC 2022 Poster 774**], no dose-limiting immune-mediated peripheral neuropathy has occurred to date with INCB099280
  - Peripheral sensory neuropathy occurred in 2 patients (a new onset and worsening of pre-existing neuropathy in 1 patient each) who received prior chemotherapy known to be associated with peripheral neuropathy
    - The cases were low-grade in severity and did not require an interruption in study drug nor medical intervention until they discontinued the study because of disease progression (**Table 6**)

Table 6. Summary of Sponsor-Defined irTEAEs and Their Management

			Management§ (N=86)			
irTEAE, n (%)	Any Grade (N=86)	Grade ≥3 (N=86)	Dose Reduction	Dose Interruption	Discontinuation	Corticosteroid Treatment
Any	11 (12.8)	0	0	3 (3.5)	0	—
Most common group term*						
Hypothyroidism	3 (3.5)	0	0	0	0	0
Peripheral neuropathy†	2 (2.3)	0	0	0	0	0
Musculoskeletal‡	2 (2.3)	0	0	0	0	2 (2.3)

irTEAE, immune-related treatment-emergent adverse event.
* Includes any-grade irTEAEs that occurred in ≥2 patients. † Peripheral neuropathies were peripheral sensory neuropathy (n=2).
‡ Musculoskeletal reactions included myalgia (n=1) and polymyalgia rheumatica (n=1). § Patients may have been counted in multiple management categories.

Efficacy

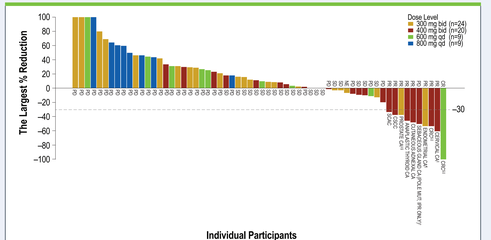
- 1 complete response (1.3%) was observed at 600 mg qd in colon adenocarcinoma with high tumor mutational burden (10.1 mut/Mb; **Figure 2**); 8 partial responses (10.0%) were observed, of which 6 were in the 400-mg bid dose level (**Table 7** and **Figure 2**)
- Dose levels ≥300 mg bid showed anti-tumor activity (**Figure 3**)

Table 7. Summary of Best Overall Response by RECIST v1.1

Best Overall Response, n (%)	RECIST-Evaluable Population* (N=80)	300 mg bid (n=28)	400 mg bid (n=24)	600 mg qd (n=9)	800 mg qd (n=10)
ORR (CR + PR)	9 (11.3)	2 (7.1)	6 (25.0)	1 (11.1)	0
CR	1 (1.3)	0	0	1 (11.1)	0
PR	8 (10.0)	2 (7.1)	6 (25.0)	0	0
DCR (SD + PR + CR)	33 (41.3)	13 (46.4)	12 (50.0)	3 (33.3)	1 (10.0)
SD (≥7 weeks)	24 (30.0)	11 (39.3)	6 (25.0)	2 (22.2)	1 (10.0)
PD	40 (50.0)	12 (42.9)	9 (37.5)	6 (66.7)	9 (90.0)
Not evaluable†	6 (7.5)	3 (10.7)	2 (8.3)	0	0
Not assessed‡	1 (1.3)	0	1 (4.2)	0	0

bid, twice daily; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; qd, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
* No anti-tumor activity was observed at doses below 300 mg bid; these doses were considered below pharmacologically active level and were therefore excluded from the dose breakdown columns to the right.
† "Not evaluable" indicates patients in the RECIST-evaluable population who did not have valid postbaseline overall response assessments by RECIST v1.1.
‡ "Not assessed" indicates patients in the RECIST-evaluable population who did not have any postbaseline overall response assessments by RECIST v1.1.

Figure 2. Best Percentage Change From Baseline in Diameters of Target Lesions (for Patients Treated With ≥300 mg bid)*


The Largest % Reduction
Individual Participants
Dose Level
300 mg bid (n=24)
400 mg bid (n=20)
600 mg qd (n=9)
800 mg qd (n=9)
CRC
SCAC
SCAC
SCA