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A Phase 1 Study Exploring the Safety and Tolerability of the Small-Molecule PD-L1 Inhibitor, INCB086550, in Patients With Select Advanced Tumors

Christophe Le Tourneau,[1,*] Sarina A. Piha-Paul,[2] Hans Prenen,[3] Brant Delafontaine,[4] David J. Pinato,[5] Armando Santoro,[6] Rebecca Kristeleit,[7] Kristen R. Spencer,[8] Tara C. Mitchell,[9] Howard Burris,[10] Nuria Kotecki,[11] Bristi Basu,[12] Donna M. Graham,[13] Anna Maria Di Giacomo,[14] Solmaz Sahebjam,[15] Massimo Di Nicola,[16] Carolos Gomez-Roca,[17] Pascale Tomasini,[17] Paolo A. Ascierto,[18] Giuseppe Curigliano,[19,20] Thomas Karasic,[21] Ryan Geschwindt,[22] Jeannie Daniel,[22] Eric Van Cutsem[23]

[1]Institut Curie, Paris, France; [2]University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [3]UniversityHospital Antwerp, Edegem, Belgium; [4]Drug Research Unit Ghent, UZ Ghent, Ghent, Belgium; [5]Imperial College London, Hammersmith Hospital, London, UK; [6]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele; IRCCS Humanitas Research Hospital - Humanitas Cancer Center, Rozzano, Milan, Italy; [7]Guy's and St. Thomas NHS Foundation Trust, London, UK; [8]Perlmutter Cancer Center of NYU Langone Health and NYU Grossman School of Medicine, New York, NY, USA; [9]Abramson Cancer Center, Hospital of the University of Pennsylvania, Philadelphia, PA, USA; [10]Tennessee Oncology, Nashville, TN, USA; [11]Institut Jules Bordet, Brussels, Belgium; [12]University of Cambridge and Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; [13]The Christie NHS Foundation Trust, Manchester, UK; [14]University of Siena, Center for Immuno-Oncology, Siena, Italy; [15]Moffitt Cancer Center, Tampa, FL, USA; [16]Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [17]Assistance Publique Des Hôpitaux de Marseille, Marseille, France; [18]Istituto Nazionale Tumori, Milan, Italy; [19]European Institute of Oncology, IRCCS and University of Milan, Milan, Italy; [20]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy [21]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [22]Incyte Corporation, Wilmington, DE, USA; [23]University Hospitals Gasthuisberg, Leuven & University of Leuven, Leuven, Belgium

* Presenting author

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
- INCB086550 is a novel, orally administered small-molecule inhibitor of PD-L1, disrupting the PD-1/PD-L1 interaction
- Previously, preliminary data from this phase 1 study of INCB086550 in patients with advanced solid tumors revealed objective responses and a safety profile similar to typical monoclonal antibody PD-1/PD-L1 inhibitors, with the exception of peripheral neuropathy[2]
- We report here updated study results, including data from patients with lower dose levels and intermittent treatment schedules

Objectives

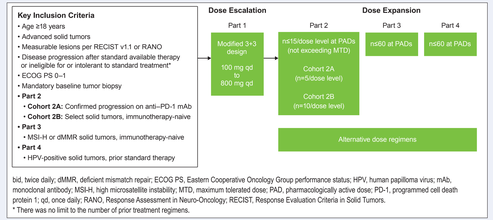
- This ongoing phase 1 study (NCT03762447) evaluates the safety, tolerability, and efficacy of INCB086550 in advanced solid tumors and aims to identify a pharmacologically active dose or maximum tolerated dose (MTD), whichever is lower

Methods

Patients and Study Design

- This phase 1, open-label, dose-finding study is evaluating INCB086550 in adults whose disease had previously progressed on available therapy, using a modified 3+3 dose escalation design (part 1) to determine MTD followed by dose expansion (parts 2–4; **Figure 1**)
- Patients received INCB086550 as an oral tablet, either in continuous 21-day or 28-day cycles or on alternative schedules
  - Intermittent schedule with treatment cycles of 1 week, followed by a 1-week off-treatment period
  - Intermittent schedules with treatment cycles of 1 or 2 weeks, followed by 1- or 2-week stepdown dosing
  - Alternative dose administration was explored in the dose expansion cohorts; the short half-life of INCB086550 (8.62 hours) enabled intermittent dosing and optimization of benefit/risk

Figure 1. Study Design



bid, twice daily; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papilloma virus; 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; RANO, Response Assessment in Neuro-Oncology; 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 INCB086550, measured by monitoring frequency and severity of adverse events
- Secondary 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 or Response Assessment in Neuro-Oncology (RANO)

Statistical Analyses

- Descriptive statistics were used for all analyses in this exploratory study
- The efficacy-evaluable population consists of patients who have received ≥1 dose of INCB086550, completed a baseline scan, and have met ≥1 of the following criteria: ≥1 postbaseline scans, a follow-up of ≥63 days, or have discontinued study

Results

Patient Characteristics and Disposition

- A total of 138 patients were treated before data cutoff on April 1, 2022; 27 patients (19.6%) were enrolled in dose escalation (part 1) and 111 (80.4%) in dose expansion (parts 2A, 2B, 3, and 4; **Table 1**)
- The majority of patients had previously received 1–2 lines of anticancer therapy (**Table 2**)
- 121 patients (87.7%) discontinued INCB086550 treatment, 90 due to disease progression

Table 1. Number of Patients per Assigned Dose Level

	Dose Level	Number of Patients (N=138)
Dose escalation		
Part 1	100 mg qd	6
	200 mg qd	3
	200 mg bid	3
	400 mg qd	4
	400 mg bid	4
	800 mg qd	1
	800 mg bid	6
Dose expansion		
Part 2	Cohort A 200 mg bid	3
	Cohort A 400 mg bid	7
	Cohort B 200 mg bid	14
	Cohort B 400 mg bid	17
	Cohort B 400 mg bid 1 wk; off 1 wk	5
	Cohort B 400 mg bid 1 wk; 100 mg qd 1 wk	11
	Cohort B 400 mg bid 2 wk; 100 mg qd 2 wk	4
Part 3 (MSI-H or dMMR)	200 mg bid	8
	400 mg bid	5
	400 mg bid 1 wk; off 1 wk	13
	400 mg bid 1 wk; 100 mg qd 1 wk	7
Part 4 (HPV+)	400 mg bid	1
	400 mg bid 1 wk; off 1 wk	9
	400 mg bid 1 wk; 100 mg qd 1 wk	7

bid, twice daily; dMMR, deficient mismatch repair; HPV, human papilloma virus; MSI-H, high microsatellite instability; qd, once daily.

Table 2. Patient Demographics

	Total (N=138)
Age, median (range), y	65 (31–86)
Female, n (%)	84 (60.9)
Race, n (%)	
White	111 (80.4)
Black	5 (3.6)
Asian	3 (2.2)
Other	15 (10.9)
Missing	4 (2.9)
ECOG status, n (%)	
0	55 (39.9)
1	83 (60.1)
Prior IO treatment, n (%)	14 (10.1)
Previous lines of therapy, n (%)	
0	15 (10.9)
1	45 (32.6)
2	35 (25.4)
≥3	43 (31.2)

ECOG, Eastern Cooperative Oncology Group; IO, immuno-oncology.

Safety

- A total of 135 patients (97.8%) experienced a treatment-emergent adverse event (TEAE) (**Table 3**); the most frequent TEAEs and treatment-related TEAEs (TRAEs) were fatigue and nausea (**Tables 4** and **5**)
  - Treatment-related serious TEAEs that occurred in >1 patient was immune-mediated neuropathy (n=2)
  - No protocol-specified dose-limiting toxicities (DLTs) were observed

Table 3. Safety

n (%)	Total (N=138)
Any-grade TEAE	135 (97.8)
Treatment-related TEAE	88 (63.8)
Grade ≥3 treatment-related TEAE	18 (13.0)
Treatment-related serious TEAE	9 (6.5)
Treatment-related death	0

TEAE, treatment-emergent adverse event.

Table 4. Very Common TEAEs (≥15% [n≥21] Patients) by MedDRA Preferred Term

n (%)	Total (N=138)	
	Any grade	Grade ≥3
Fatigue	46 (33.3)	4 (2.9)
Nausea	42 (30.4)	0
Decreased appetite	38 (27.5)	1 (0.7)
Vomiting	33 (23.9)	1 (0.7)
Constipation	32 (23.2)	2 (1.4)
Diarrhea	29 (21.0)	1 (0.7)
Anemia	23 (16.7)	10 (7.2)

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

Table 5. Common Any-Grade TRAEs (≥5% [n≥7] Patients) by MedDRA Preferred Term

n (%)	Total (N=138)	
	Any grade	Grade ≥3
Nausea	26 (18.8)	0
Fatigue	24 (17.4)	2 (1.4)
Decreased appetite	13 (9.4)	0
Vomiting	13 (9.4)	1 (0.7)
Pruritus	11 (8.0)	1 (0.7)
Lipase increased	10 (7.2)	1 (0.7)
Peripheral sensory neuropathy	10 (7.2)	1 (0.7)
Diarrhea	9 (6.5)	1 (0.7)
Headache	8 (5.8)	0
Eosinophilia	7 (5.1)	0
Rash	7 (5.1)	2 (1.4)

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

- Sponsor-defined immune-related TEAEs (irTEAEs) occurred in 36 patients (26.1%); the most common irTEAEs, including their management, are presented in **Table 6**
  - irTEAEs were observed at 200 mg twice daily (bid; n=4), 400 mg once daily (qd; n=1), 400 mg bid (including intermittent schedules; n=28), and 800 mg bid (n=3)
  - In total, 22 irTEAEs (15.9%) were peripheral neuropathies; stepdown/intermittent dose regimens did not mitigate these events

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

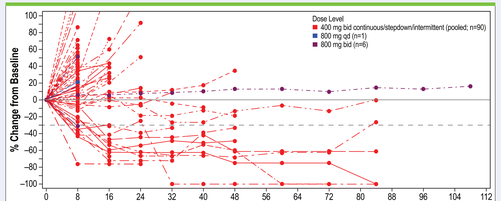
			Management¶ (N=138)			
irTEAE, n (%)	Any grade (N=138)	Grade ≥3 (N=138)	Dose Reduction	Dose Interruption	Discontinuation	Corticosteroid Treatment
Any	36 (26.1)	12 (8.7)	7 (5.1)	13 (9.4)	5 (3.6)	—
Most common group terms*						
Peripheral neuropathy†	22 (15.9)	3 (2.2)	4 (2.9)	4 (2.9)	3 (2.2)	6 (4.3)
Peripheral sensory neuropathy	10 (7.2)	1 (0.7)	3 (2.2)	2 (1.4)	1 (0.7)	—
Neuropathy peripheral	5 (3.6)	0	0	0	0	—
Paresthesia	3 (2.2)	0	1 (0.7)	0	0	—
Immune-mediated neuropathy	2 (1.4)	2 (1.4)	0	0	2 (1.4)	—
Peripheral motor neuropathy	2 (1.4)	0	0	2 (1.4)	0	—
Skin reactions‡	7 (5.1)	2 (1.4)	1 (0.7)	2 (1.4)	0	5 (3.6)
Musculoskeletal§	9 (6.5)	2 (1.4)	0	3 (2.2)	0	3 (2.2)
Colitis	5 (3.6)	2 (1.4)	0	3 (2.2)	1 (0.7)	1 (0.7)

irTEAE, immune-related treatment-emergent adverse event.
* Includes any-grade irTEAEs that occurred in >3 patients and grade ≥3 irTEAEs that occurred in >1 patient. † Peripheral neuropathies listed occurred in >1 patient; peripheral neuropathies that occurred in only 1 patient included Bell's palsy, facial pain, neuralgia, polyneuropathy, restless legs syndrome, and sensory loss. ‡ Skin reactions that occurred in >1 patient included pruritus (n=4) and rash (n=2). § Musculoskeletal reactions that occurred in >1 patient included myalgia (n=6), arthralgia (n=2), and muscular weakness (n=2). ¶ Patients may have been counted in multiple management categories.

Efficacy

- 2 complete responses to INCB086550 were observed at 400 mg bid (squamous cell anal cancer, high microsatellite instability [MSI-H] colorectal cancer)
  - 10 patients overall achieved a partial response
- Dose levels ≥400 mg bid showed anti-tumor activity (**Figure 2**)

Figure 2. Percentage Change From Baseline in Diameters of Target Lesions (for Patients Treated With ≥400 mg bid)*



bid, twice daily; qd, once daily.
Plot includes all patients in the efficacy-evaluable population treated with at least 400 mg bid, including patients with only baseline assessments (n=97). Unscheduled visits have been removed.
* Either in sum of diameters of target lesions by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) or sum of product of diameters (perpendicular diameters of all measurable enhancing lesions per visit) by Response Assessment in Neuro-Oncology (RANO).

Conclusions

- **No protocol-specified DLTs occurred with INCB086550 doses between 100 mg qd and 800 mg bid**
- **INCB086550 has a safety profile consistent with monoclonal antibody immune checkpoint inhibitors, except for an observed increased rate of immune-mediated peripheral neuropathy**
- **Encouraging antitumor activity has been observed, including 2 complete responses in patients with squamous cell anal cancer and MSI-H colorectal cancer**
- **Alternative dosing strategies were evaluated, but the dose-limiting immune-mediated peripheral neuropathy was not mitigated; development of INCB086550 has been discontinued, and further development is proceeding with the oral PD-L1 inhibitors INCB099280 and INCB099318 [SITC 2022 Posters 622 and 734]**

Disclosures

CLT has participated in advisory boards from MSD, BMS, Astra Zeneca, ALX Oncology, Rakuten, Merck Serono, Roche, MaxiVax, Seagen, Seattle Genetics, Celgene.

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HP has received honoraria from Amgen, Astra Zeneca, Bayer, Roche, and Sanofi.
TCM serves on scientific advisory boards for BMS, GigaGen, Instill Bio., Merck, and OncoSec.HB.

GC has received honoraria for speaker's engagement from Roche, Seattle Genetics, Novartis, Lilly, Pfizer, Foundation Medicine, NanoString, Samsung, Celltrion, BMS, MSD; honoraria for providing consultancy from Roche, Seattle Genetics, and NanoString; honoraria for participating in advisory boards from Roche, Lilly, Pfizer, Foundation Medicine, Samsung, Celltrion, and Mylan; honoraria for writing engagements from Novartis and BMS; honoraria for participation in Ellipsis Scientific Affairs Group; research/grant funding from Pfizer, Roche, Novartis, Sanofi, Celgene, Servier, Orion, AstraZeneca, Seattle Genetics, AbbVie, Tesaro, BMS, Merck Serono, Merck Sharp Dome, Janssen-Cilag, Philogen, Bayer, Medivation, and Medimmune.

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RG and JD are employees and shareholders of Incyte Corporation (Wilmington, DE, USA).

BD, DJP, AS, RK, KRS, NK, BB, DMG, AMDG, SS, MDN, CG-R, PT, PAA, and EVC declare no disclosures.

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