

Abstract 529

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Phase 1 Study of INCB086550, an Oral PD-L1 Inhibitor, in Immune Checkpoint–Naïve Patients With Advanced Solid Tumors

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Drug & Presenting Author Disclosures

- INCB086550 is an investigational product in phase 1 development and is not currently approved by any regulatory authority
- Dr Van Cutsem has served on advisory boards for AbbVie, Array, Astellas, AstraZeneca, Bayer, Beigene, Biocartis, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Daiichi, GlaxoSmithKline, Halozyme, Helsinn, Incyte Corporation, Ipsen, Janssen Research, Lilly, Merck KGaA, Merck Sharp & Dohme, Mirati, Novartis, Pierre Fabre, Roche, Seattle Genetics, Servier, Sirtex, Terumo, Taiho, TRIGR, and Zymeworks; and has received institutional research grants from Amgen, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Ipsen, Lilly, Merck KGaA, Merck Sharp & Dohme, Novartis, Roche, and Servier

INCB086550 MOA & Rationale

- Intravenous anti–PD-(L)1 mAbs prevent PD-1/PD-L1 interaction, reducing immune system evasion by cancer cells and reactivating T-cell–mediated tumor cell death¹
 - Overall survival benefit has been demonstrated in a variety of cancers
- INCB086550 is a novel orally administered small molecule that binds PD-L1, inhibiting the PD-1/PD-L1 interaction
- Markers of immune activation were identified in patients treated with INCB086550 in a previously-reported translational analysis from the phase 1 study²
- Preliminary clinical data from this phase 1 study (NCT03762447) are presented

Study Design and Objectives

Phase 1, Open-Label, Dose-Finding Study (NCT03762447)

Key Inclusion Criteria

- Age ≥ 18 years
- Advanced solid tumors
- Measurable lesions per RECIST v1.1 or RANO
- Disease progression after standard available therapy* including anti-PD-(L)1 mAb if locally approved
- ECOG score 0–1
- Mandatory baseline tumor biopsy
- **Part 2**
 - **Cohort 2A:** Confirmed progression on anti-PD-1 mAb
 - **Cohort 2B:** Select solid tumors, immunotherapy naive
- **Part 3**
 - MSI-H or dMMR solid tumors, immunotherapy naive
- **Part 4**
 - HPV-positive solid tumors, prior standard therapy

Dose Escalation

Part 1

Modified 3+3
design

100 mg QD
to
800 mg BID

Part 2 Expansion

$n \leq 15$ /dose level
at PADs (not
exceeding MTD)

Cohort 2A
($n=5$ /dose level)

Cohort 2B
($n=10$ /dose level)

Dose Expansion

Part 3 Expansion

$n \leq 60$ at PADs

Part 4 Expansion

$n \leq 60$ at PADs

Cohort 2B Expansion
($n \leq 20$ per tumor type)[†]

Primary Endpoints

- Safety and tolerability
- Identification of a PAD and/or MTD
- Identification of the RP2D

Secondary Endpoints

- PK
- PD
- Preliminary efficacy including ORR, DCR, and DOR

BID, twice daily; DCR, disease control rate; dMMR, mismatch repair deficient; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HPV, human papilloma virus; MSI-H, microsatellite instability-high; MTD, maximum tolerated dose; ORR, objective response rate; PADs, pharmacologically active doses; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; RANO, response assessment in neuro-oncology; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, Recommended Phase 2 Dose.

* There was no limit to the number of prior treatment regimens. [†] If preliminary responses are observed, further expansion in ≤ 3 tumor types may be undertaken.

Patient Demographics and Clinical Characteristics

- 79 patients received treatment in study parts 1–3 before data cutoff on 09 April 2021
- These included 27 patients (34.2%) enrolled in dose escalation (part 1) and 52 patients (65.8%) enrolled in dose expansion phases (parts 2A, 2B, and 3)

| Characteristic | Total (N=79) |
|----------------------------------|------------------|
| Age, y | |
| Mean (SD) | 64.0 (11.2) |
| Median (range) | 65.0 (31.0–84.0) |
| Female, n (%) | 45 (57.0) |
| Race, n (%) | |
| White | 71 (89.9) |
| Black | 3 (3.8) |
| Asian | 2 (2.5) |
| Other | 3 (3.8) |
| ECOG status, n (%) | |
| 0 | 29 (36.7) |
| 1 | 50 (63.3) |
| Previous lines of therapy, n (%) | |
| 0 | 6 (7.6) |
| 1 | 24 (30.4) |
| ≥2 | 49 (62.0) |
| Previous IO treatment | 13 (16.5) |

Number of Patients per Assigned Dose Level

| Dose Level, n (%) | Total (N=79) |
|---|-----------------|
| 100 mg QD | 6 (7.6) |
| 200 mg QD | 3 (3.8) |
| 200 mg BID | 24 (30.4) |
| 400 mg QD | 4 (5.1) |
| 400 mg BID | 32 (40.5) |
| 800 mg QD | 1 (1.3) |
| 800 mg BID | 6 (7.6) |
| 400 mg BID 1 week; 100 mg QD 1 week; repeat | 1 (1.3) |
| 400 mg BID 2 weeks; 100 mg QD 2 weeks; repeat | 2 (2.5) |

Tumor types in the study included adrenal, anal, anal canal, angiosarcoma, basal cell, breast, cancer of unknown primary, carcinoma of parotid gland, castrate-resistant prostate cancer, cervical, cholangiocarcinoma, colorectal, endometrial, esophageal, fallopian, gall bladder, gastric, gastroesophageal junction, glioblastoma, hepatocellular, melanoma, mesothelioma, myoepithelial, neuroendocrine, ovarian, pancreatic, penile, pleomorphic sarcoma, prostate, prostate adenocarcinoma with neuroendocrine differentiation, renal cell, salivary gland, sarcoma, small cell lung cancer, squamous cell carcinoma of the head and neck, urothelial, vaginal, and well-differentiated liposarcoma

Safety

Summary of TEAEs and Treatment-Related TEAEs

- 46 patients (58.2%) had treatment-related TEAEs (Grade ≥ 3 related in 10 patients, 12.7%)

| Characteristic, n (%) | Total (N=79) |
|-----------------------------------|--------------|
| Any TEAE | 75 (94.9) |
| Treatment-related TEAE | 46 (58.2) |
| Serious TEAE | 28 (35.4) |
| Grade ≥ 3 TEAE | 39 (49.4) |
| TEAE leading to discontinuation | 13 (16.5) |
| TEAE leading to dose reduction | 5 (6.3) |
| TEAE leading to dose interruption | 21 (26.6) |
| Fatal TEAE* | 5 (6.3) |
| Dose limiting toxicity | 0 |

| Treatment-Related TEAEs, n (%) | Any Related (N=79) | Grade ≥ 3 Related (N=79) | Serious Related (N=79) |
|--------------------------------|--------------------|-------------------------------|------------------------|
| Any | 46 (58.2) | 10 (12.7) | 6 (7.6) |
| Most common [†] | | | |
| Nausea | 13 (16.5) | 0 | 0 |
| Fatigue | 8 (10.1) | 1 (1.3) | 0 |
| Decreased appetite | 7 (8.9) | 0 | 0 |
| Vomiting | 7 (8.9) | 1 (1.3) | 1 (1.3) |
| Diarrhea | 6 (7.6) | 0 | 0 |
| Lipase increased | 6 (7.6) | 0 | 0 |
| Headache | 5 (6.3) | 0 | 0 |
| Peripheral sensory neuropathy | 5 (6.3) | 2 (2.5) | 1 (1.3) |
| Pruritus | 5 (6.3) | 1 (1.3) | 0 |
| Rash | 5 (6.3) | 1 (1.3) | 0 |

TEAE, treatment-emergent adverse event.

* All considered unrelated to study drug (cerebrovascular accident, dyspnea, general physical health deterioration, intestinal obstruction, intracranial hemorrhage [each n=1]).

[†] Occurring in $\geq 5\%$ of patients.

Safety

Immune-Related TEAEs and Management

- irTEAEs (based on sponsor clinical review) occurred in 15 patients (19.0%)
 - 2/24 patients at 200 mg BID had irTEAEs (Grade 2 peripheral neuropathy, Grade 2 pruritus)
 - 13/40 patients at 400 mg BID and above had irTEAEs
- In total, 10 patients (12.7%) had irTEAEs of peripheral neuropathy; all were Grade ≤ 3
 - All Grade 2 or 3 TEAEs of peripheral neuropathy resolved or improved
- The most common irTEAEs are presented with corresponding management in the table below

| Immune-Related TEAEs, n (%) | Any Related (N=79) | Grade ≥ 3 Related (N=79) | Management [§] (N=79) | | | |
|------------------------------------|-----------------------|-------------------------------------|-----------------------------------|----------------------|-----------------|-----------------------------|
| | | | Dose Reduction | Dose Interruption | Discontinuation | Corticosteroid Treatment |
| Any | 15 (19.0) | 7 (8.9) | 3 (3.8) | 5 (6.3) | 3 (3.8) | 6 (7.6) |
| Most common* | | | | | | |
| Peripheral neuropathy [†] | 10 (12.7) | 4 (5.1) | 2 (2.5) | 2 (2.5) | 2 (2.5) | 4 (5.1) |
| Pruritus | 3 (3.8) | 1 (1.3) | 1 (1.3) | 0 | 0 | 2 (2.5) |
| Rash [‡] | 3 (3.8) | 1 (1.3) | 0 | 1 (1.3) | 0 | 2 (2.5) |

irTEAE, immune-related treatment-emergent adverse event.

* Occurring in >1 patient.

[†] TEAEs of peripheral neuropathy included peripheral sensory neuropathy (n=5), immune-mediated neuropathy (n=2), peripheral motor neuropathy (n=2), Bell's palsy (n=1), paresthesia (n=1), peripheral neuropathy (n=1), polyneuropathy (n=1), and sensory loss (n=1).

[‡] TEAEs of rash included rash (n=1), rash maculopapular (n=1), and rash pruritic (n=1).

[§] Patients may have been counted in multiple management categories.

Efficacy

- Among 68 patients in the efficacy-evaluable population, ORR was 11.8% (95%CI, 5.2%–21.9%) and DCR was 19.1% (95%CI, 10.6%–30.5%)

| Best Overall Response, ^{*,†} n (%) | Efficacy-Evaluable Population [‡] (n=68) | Part 2B | Part 3 |
|---|---|--|--|
| | | IO Treatment-Naive Expansion 400 mg BID (n=14) | MSI-H/dMMR IO Treatment-Naive Expansion 400 mg BID (n=5) |
| ORR (CR+PR) [§] | 8 (11.8) | 3 (21.4) | 3 (60.0) |
| CR | 1 (1.5) | 1 (7.1) | 0 |
| PR | 7 (10.3) | 2 (14.3) | 3 (60.0) |
| DCR (CR+PR+SD ≥12 weeks) | 13 (19.1) | 5 (35.7) | 3 (60.0) |
| SD (≥12 weeks) | 5 (7.4) | 2 (14.3) | 0 |
| PD | 39 (57.4) | 7 (50.0) | 2 (40.0) |
| Not evaluable [¶] | 8 (11.8) | 1 (7.1) | 0 |
| Not assessed | 8 (11.8) | 1 (7.1) | 0 |

* Assessed by RECIST v1.1 or RANO; † 1 patient with GBM was assessed by RANO and had best overall response of progressive disease. ‡ The efficacy-evaluable population included all solid tumor participants enrolled in the study who received at least 1 dose of INCB086550, completed a baseline scan, and met at least 1 of the following criteria: ≥1 postbaseline scan, participant had been on the study for a minimum of 63 days of follow-up, or participant had discontinued from treatment. § No objective responses were observed below 400 mg BID. ¶ “Not evaluable” indicates participants in the efficacy-evaluable population that did not have valid postbaseline overall response assessments by RECIST or RANO. || “Not assessed” indicates participants in the efficacy-evaluable population that did not have any postbaseline overall response assessments by RECIST or RANO.

Response by Histology and MSI Status

- 8 objective responses were observed at doses ≥ 400 mg BID
 - 3 of these responses were noted among the 5 IO treatment-naive patients with MSI-H/dMMR tumors who received 400 mg BID

| Tumor Type | IO Treatment -Naive | Dose | Best Overall Response | Duration of Response (Months) |
|-----------------------------------|--------------------------------|-------------|----------------------------------|--|
| Squamous cell anal cancer | Yes | 800 mg BID | PR | 4.17 |
| Squamous cell anal cancer | Yes | 400 mg BID | CR | 5.78 |
| MSI-H colon adenocarcinoma | No | 400 mg BID | PR | 5.78+ |
| Clear cell ovarian cancer | Yes | 400 mg BID | PR | 3.35+ |
| MSI-H colon adenocarcinoma | Yes | 400 mg BID | PR | 3.71+ |
| dMMR gastric cancer | Yes | 400 mg BID | PR | 1.87+ |
| MSI-H neuroendocrine colon cancer | Yes | 400 mg BID | PR | 1.87 |
| Squamous cell vaginal cancer | Yes | 400 mg BID | PR | 0.03+ |

Conclusions

- Immune-related AEs observed in this ongoing phase 1 study are consistent with those seen with mAb immune checkpoint inhibitors, with the exception of an increased rate of peripheral neuropathy
 - All Grade 2 or 3 TEAEs of peripheral neuropathy were manageable and resolved or improved
- Preliminary efficacy of INCB086550 in tumor types known to be responsive to anti-PD-(L)1 mAb therapy is encouraging and warrants further investigation