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First-In-Human Phase 1 Study of INCAGN02385, a LAG-3 Monoclonal Antibody Antagonist, in Patients with Advanced Malignancies

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Introduction

- Lymphocyte-activation gene 3 (LAG-3) is a cell-surface immune checkpoint receptor
  - LAG-3 has a negative regulatory role on T-cell proliferation, activation, and cytokine secretion[1]
- INCAGN02385 is a humanized Fc-engineered immunoglobulin G1κ (IgG1κ) monoclonal antibody with selective and potent LAG-3 antagonist activity[2]
- INCAGN02385 disrupts LAG-3 binding to MHC class II receptors and restores production of T-cell receptor – nuclear factor of activated T-cell (TCR–NFAT) signaling, cytokine secretion, and T-cell cytolytic function in vitro[2]

Objective

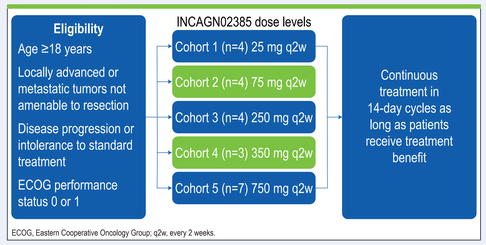
- To determine the safety and tolerability of INCAGN02385 monotherapy and to establish a maximum tolerated dose or pharmacologically active dose for future combination studies

Methods

Study Design

- Phase 1, multicenter, open-label, dose-escalation study to evaluate the safety and tolerability of INCAGN02385 in adults with advanced solid tumors that did not respond to available therapies, were intolerant to treatment, or refused noncurative standard treatment
- INCAGN02385 was administered intravenously every 2 weeks (q2w) at 5 dose levels between 25 and 750 mg in a 3+3 dose escalation design (**Figure 1**)

Figure 1. Study Design



Endpoints and Assessments

- The primary endpoint was safety and tolerability of INCAGN02385 based on the frequency and severity of adverse events
- Secondary and exploratory endpoints assessed pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of INCAGN02385 monotherapy
  - PK results: INCAGN02385 concentrations were measured from serum samples collected preinfusion on Day 1 of cycles 1, 2, 3, 4, 6, 7, 8, and 12; within 10 minutes and ≈4 hours postinfusion on Day 1 of cycles 1 and 6, 24 hours postinfusion on Day 2 of cycles 1 and 6, and untimed on Day 8 of cycles 1 and 6 and the safety follow-up visit
  - PD results included electrochemoluminescent immunoassay detection of antidrug antibodies (ADAs), Ki67 biomarker detection of changes in levels of circulating T cells, and flow cytometry detection of LAG-3 receptor occupancy in whole blood
  - Efficacy was measured by investigator assessment of tumor response via Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Statistical Analyses

- The full analysis set included all patients who received ≥1 dose of INCAGN02385 and was used for patient demographics, safety, and efficacy
- Populations evaluable for PK or PD included all patients in the full analysis set who had ≥1 postdose PK or PD serum sample collected and analyzed
- Progression-free survival was estimated with the Kaplan-Meier method

Results

Patients

- The study included a highly pretreated patient population (N=22); 68.2% had prior checkpoint inhibitor immunotherapy and 13.6% other immunotherapy (**Table 1**)

Table 1: Patient Demographics and Baseline Characteristics

	INCAGN02385 Treatment Group					
	25 mg (n=4)	75 mg (n=4)	250 mg (n=4)	350 mg (n=3)	750 mg (n=7)	Total (N=22)
Age, median (range), y	59 (46–61)	63 (46–74)	67 (58–86)	59 (53–77)	66 (49–74)	63 (46–86)
Male, n (%)	1 (25.0)	1 (25.0)	3 (75.0)	2 (66.7)	5 (71.4)	12 (54.5)
White, n (%)	4 (100)	3 (75.0)	3 (75.0)	3 (100)	7 (100)	20 (90.9)
ECOG PS 1, n (%)	4 (100)	3 (75.0)	3 (75.0)	3 (100)	5 (71.4)	18 (81.8)
Most common cancer types, n (%)						
Lung	2 (50.0)	0	2 (50.0)	0	0	4 (18.2)
Adenocarcinoma of the endometrium	0	1 (25.0)	0	0	1 (14.3)	2 (9.1)
Breast	1 (25.0)	0	0	0	1 (14.3)	2 (9.1)
Gastric	0	0	0	2 (66.7)	0	2 (9.1)
Melanoma	0	0	0	1 (33.3)	1 (14.3)	2 (9.1)
Ovarian	0	2 (50.0)	0	0	0	2 (9.1)
≥3 metastatic sites, n (%)	3 (75.0)	3 (75.0)	3 (75.0)	2 (66.7)	2 (28.6)	13 (59.1)
Visceral metastases present at study entry,* n (%)	4 (100)	3 (75.0)	4 (100)	2 (66.7)	4 (57.1)	17 (77.3)
≥3 lines of prior systemic therapy,† n (%)	4 (100)	3 (75.0)	4 (100)	0	3 (42.9)	14 (63.6)
Prior immunotherapy, n (%)						
Checkpoint inhibitor‡	3 (75.0)	2 (50.0)	4 (100)	1 (33.3)	5 (71.4)	15 (68.2)
Other immunotherapy§	1 (25.0)	0	1 (25.0)	0	1 (14.3)	3 (13.6)

ECOG PS, Eastern Cooperative Oncology Group performance status.
* Visceral metastases included all metastases other than bone, lymph nodes, and skin or subcutaneous tissue. † 22 patients (100%) received ≥1 prior line of any type of systemic therapy; prior therapies included chemotherapy (n=16), targeted (n=11), and hormonal (n=3). ‡ α–PD-(L)1 monotherapy (n=10), α–PD-1 + α–CTLA-4 (n=2), α–CTLA-4 followed by α–PD-1 (n=1), α–PD-1 followed by α–CTLA-4 + α–GITR (n=1), and α–PD-1 followed by α–PD-L1 + α–A2AR (n=1). § Bacillus Calmette-Guérin, TLR9 agonist, and OX40 agonist (n=1 each).

Safety

- All patients experienced treatment-emergent adverse events (TEAEs), and 14 (63.6%) experienced TEAEs that were grade ≥3 (**Table 2**)
  - No DLT was observed
  - No immune-related TEAEs were seen

Table 2: Summary of TEAEs

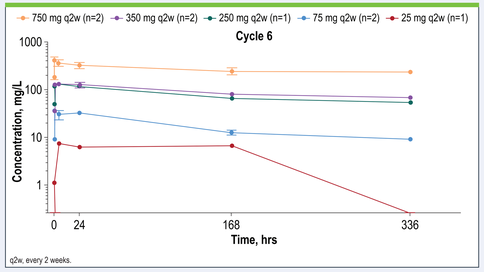
Event, n (%)	INCAGN02385 Treatment (N=22)	Events Description
TEAE	22 (100)	Most commonly fatigue (36.4%), cough (27.3%); hypokalemia, nausea, or tumor pain (each 22.7%)
Treatment-related TEAE	16 (72.7)	Most commonly fatigue (31.8%); blood creatinine increased, lymphopenia, myalgia, pruritus, or tumor pain (each 9.1%)
Grade ≥3 TEAE	14 (63.6)	None were experienced by >1 patient; one patient experienced lymphopenia (75-mg cohort) that was considered related to treatment
Serious TEAE	8 (36.4)	None were experienced by >1 patient; none were considered related to treatment
Fatal TEAE	1 (4.5)	Failure to thrive due to progression of underlying disease unrelated to treatment (250-mg cohort)
TEAE leading to discontinuation	1 (4.5)	Drug-unrelated stroke
TEAE leading to reduction	0	—
TEAE leading to interruption	6 (27.3)	6 patients experienced 9 TEAEs; no TEAEs occurred in >1 patient

TEAE, treatment-emergent adverse events.

Pharmacokinetics

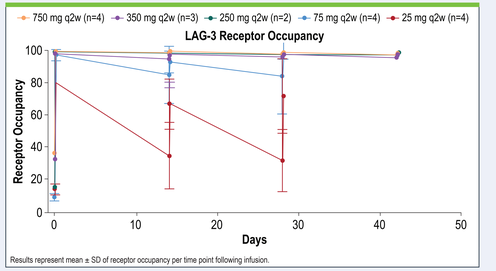
- In cycles 1 to 7 of treatment, trough concentrations of INCAGN02385 increased in all dose levels; steady-state trough concentrations were dose-proportional (**Figure 2**)

Figure 2. INCAGN02385 Steady-State Serum Predose Trough Concentration (mean ± SE)



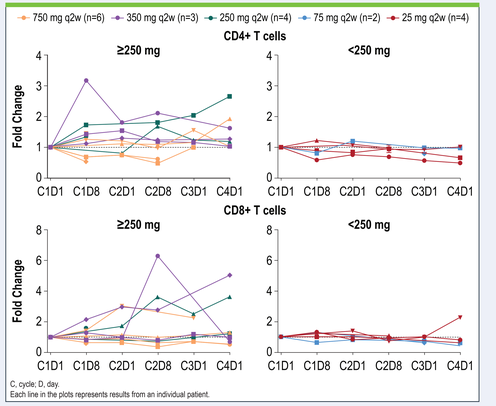
- Mean receptor occupancy levels of LAG-3 at cycle 2, Day 1 and all subsequent time points were ≥94.6% when INCAGN02385 was administered at doses ≥250 mg (**Figure 3**)

Figure 3. LAG-3 Receptor Occupancy



- Treatment with INCAGN02385 at doses ≥250 mg increased CD4+ and CD8+ T-cell proliferation in some individuals (**Figure 4**); no significant changes were observed in other activation markers (eg, CD38, human leukocyte antigen–DR isotope [HLA-DR])

Figure 4. Changes in the Frequencies of Proliferating T Cells in Individual Patients



- 10 patients had ≥1 treatment-emergent ADA-positive sample (**Table 3**)
  - ADAs appeared to impact the PK of 2 patients in the 25-mg cohort
  - ADAs did not appear to impact PK in subsequent cohorts based on increasing trough concentrations following multiple doses

Table 3: Immunogenicity

	INCAGN02385 Treatment Group				
	25 mg (n=4)	75 mg (n=4)	250 mg (n=2)	350 mg (n=3)	750 mg (n=6)
Patients with treatment-emergent positive immunogenicity status, n (%)	3 (75.0)	3 (75.0)	2 (100)	2 (66.7)	0

Efficacy

- Best overall response was stable disease, and disease control rate (complete response + partial response + stable disease) was 27.3% (**Table 4**).

Table 4: Preliminary Efficacy Results

Parameter	INCAGN02385 Treatment Group					
	25 mg (n=4)	75 mg (n=4)	250 mg (n=4)	350 mg (n=3)	750 mg (n=7)	Total (N=22)
Best overall response, n (%)						
CR	0	0	0	0	0	0
PR	0	0	0	0	0	0
SD*	2 (50.0)	0	1 (25.0)	1 (33.3)	2 (28.6)	6 (27.3)
PD	1 (25.0)	4 (100)	3 (75.0)	2 (66.7)	5 (71.4)	15 (68.2)
NE	1 (25.0)	0	0	0	0	1 (4.5)
Median PFS, month (95% CI)	9.3 (1.9, NE)	1.8 (1.7, NE)	2.2 (0.3, NE)	1.9 (1.9, NE)	1.9 (0.7, 7.0)	1.9 (1.9, 2.5)

CR, complete response; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
* 1 patient had SD >6 months (750 mg cohort); of the 6 patients who responded with SD, 5 had received another prior immunotherapy.

Conclusions

- **INCAGN02385 was generally well tolerated in adult patients with advanced malignancies**
  - **No dose-limiting toxicities were observed, and the maximum tolerated dose was not reached**
  - **No novel safety signals were seen**
- **Treatment with INCAGN02385 monotherapy was associated with linear PK; INCAGN02385 PK was typical of monoclonal antibodies**
- **Linear PK did not appear to be affected in limited instances of detectable ADAs at higher doses**
- **In this heavily pretreated population, the best response to INCAGN02385 monotherapy was stable disease**
- **A 350-mg q2w dose was selected as the recommended dose for future phase 1b/2 combination studies based on receptor occupancy, PK, and safety data**
- **Clinical trials in combination are ongoing**
  - **NCT05287113: INCAGN02390 (α–TIM-3), INCAGN02385 (α–LAG-3), and retifanlimab (α–PD-1) combined inhibition in PD-L1+ squamous cell carcinoma of the head and neck [ESMO 2022, poster 705TiP]**
  - **NCT04370704: INCAGN02390 (α–TIM-3), INCAGN02385 (α–LAG-3), and retifanlimab (α–PD-1) combined inhibition in select advanced malignancies**
  - **NCT04463771: INCAGN02390 (α–TIM-3), INCAGN02385 (α–LAG-3), and retifanlimab (α–PD-1) combined inhibition in advanced microsatellite instability high endometrial cancer (PODIUM-204)**
  - **NCT04586244: INCAGN02390 (α–TIM-3) plus INCAGN02385 (α–LAG-3) or INCAGN02385 (α–LAG-3) combined with retifanlimab (α–PD-1) in muscle-invasive urothelial carcinoma of the bladder (OPTIMUS)**

Disclosures

JDP is on the Board of Directors with ownership interest and intellectual property for: BioCytics Inc., Carolina BioOncology Institute, PLLC; consultant for: Aavocyte and Boxer Capital; principal investigator without financial interest in: AbbVie, Adagene, Alkermes, Apros, Arcus BioSciences, AstraZeneca/MedImmune, Atreca, BJ BioScience, Bristol-Myers Squibb, Calico Life Sciences, Conjupro BioTherapeutics, Cullinan, EMD Serono, Fate Therapeutics, FLX Bio, Genentech/Roche, I-MAB Pharma, Immune-Onc, Jounce Therapeutics, Macrogenics, Molecular Templates, NexCure, Nuvation, Repertoire Immune Medicines, Seattle Genetics, Sequenom, Tempest Therapeutics, Top Alliance Biosciences, Trethera, Xilio Therapeutics, Zenshine Pharma; institutional funding from: Merck, MT Group, Nuvation, Precision for Medicine, Replimmune, STEMCELL Technologies, Xilis; personal and institutional funding from PIONMA. LH is an employee and stockholder of AstraZeneca. JEJ, PH, ZD, WW, XC, and NB are employees and shareholders of Incyte Corporation (Wilmington, DE, USA). OH, MEG, and AB have nothing to disclose.

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