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A Phase 1/2 Study of Retifanlimab (INCMGA00012, Anti–PD-1), INCAGN02385 (Anti–LAG-3), and INCAGN02390 (Anti–TIM-3) Combination Therapy in Patients With Advanced Solid Tumors

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Introduction

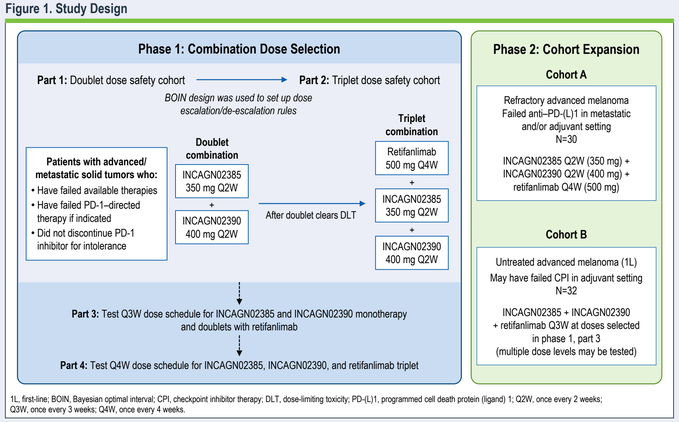
- Resistance and relapse post–programmed cell death protein (ligand)-1 [PD-(L)1] inhibitor therapy is a high unmet need
- Loss of T-cell function is associated with progressive expression of checkpoint molecules
- Lymphocyte activation gene (LAG)-3 and T-cell immunoglobulin and mucin-domain containing (TIM)-3 are key checkpoint pathways implicated in resistance to PD-1 inhibitors
- LAG-3/PD-1 combinations have shown clinical benefit in patients with advanced solid tumors, including as first-line therapy in patients with melanoma[1]
- Triple inhibition of PD-1, LAG-3, and TIM-3 has shown synergistic effects in a PD-1–naive murine model[2]
- INCAGN02385 is an Fc-modified IgG1κ monoclonal antibody that inhibits LAG-3 binding to major histocompatibility complex class II, and attenuates inhibitory signals to enhance T-cell immunity[3]
- INCAGN02390 is a recombinant, aglycosylated, fully human IgG1κ monoclonal antibody that antagonizes the TIM-3 pathway by inducing rapid receptor internalization and preventing ligand binding[4]
- Retifanlimab is a humanized IgG4 monoclonal antibody that targets human PD-1[5]
- This open-label, nonrandomized phase 1/2 study (NCT04370704) aims to determine optimal doses and preliminary safety and efficacy for the monoclonal antibody combinations of INCAGN02385 (anti–LAG-3), INCAGN02390 (anti–TIM-3), and retifanlimab in select advanced malignancies
- Here, we report initial safety and efficacy results of doublet anti–LAG-3 + anti–TIM-3 and triplet anti–LAG-3 + anti–TIM-3 + retifanlimab regimens

Methods

Study Objectives

- To confirm safety of combination doses chosen for recommended phase 2 doses for study drugs to be used in the following regimens in phase 1:
  - Part 1 (every 2 weeks [Q2W]): INCAGN02385 + INCAGN02390
  - Part 2: INCAGN02385 (Q2W) + INCAGN02390 (Q2W) + retifanlimab (every 4 weeks [Q4W])
  - Part 3 is ongoing to test safety of an every-3-week dosing schedule for both INCAGN02385 and INCAGN02390
  - Part 4 will test safety of a Q4W dosing schedule for the triplet combination
- To determine preliminary safety and efficacy for the monoclonal antibody combinations of INCAGN02385, INCAGN02390, and retifanlimab
- Phase 2 consists of expansion cohorts in patients with systemic therapy–naive (planned) or anti–PD-(L)1-relapsed/refractory advanced melanoma (currently ongoing)

Figure 1. Study Design



1L, first-line; BOIN, Bayesian optimal interval; CPI, checkpoint inhibitor therapy; DLT, dose-limiting toxicity; PD-(L)1, programmed cell death protein (ligand) 1; Q2W, once every 2 weeks; Q3W, once every 3 weeks; Q4W, once every 4 weeks.

Results (Phase 1, Parts 1 and 2)

Patients

- As of March 21, 2023, 21 patients were enrolled in parts 1 (n=10) and 2 (n=11)
- Patient demographics and disease characteristics are presented in **Table 2**, and patient tumor types are listed in **Table 3**
  - Median age was 61.0 years, and 62% of patients were women
  - Patients had a median of 3 (range, 1-11) prior lines of therapy including prior anti–PD-(L)1
  - A total of 12 patients had ≥3 lines of prior therapy
- At data cutoff, all enrolled patients had discontinued treatment, 1 patient due to toxicity
- One patient had a confirmed partial response maintained in the first follow-up post-treatment completion

Table 2. Baseline Demographics and Disease Characteristics

Variable	Part 1 Doublet (n=10)	Part 2 Triplet (n=11)
Age, median (range), years	65.5 (27-85)	54.0 (30-72)
Sex, n (%)		
Women	6 (60.0)	7 (63.6)
Men	4 (40.0)	4 (36.4)
ECOG PS, n (%)		
0	2 (20.0)	2 (18.2)
1	8 (80.0)	9 (81.8)
Time since initial diagnosis, median (range), years	2.6 (0.7-11.8)	1.4 (0.7-18.1)
Prior systemic therapy, n (%)	10 (100.0)	11 (100.0)
Number of prior systemic cancer therapy regimens, n (%)		
1	1 (10.0)	0
2	3 (30.0)	5 (45.5)
≥3	6 (60.0)	6 (54.5)
Number of prior systemic cancer therapy regimens with anti–PD-(L)1 therapy, n (%)		
0	2 (20.0)	0
1	5 (50.0)	2 (18.2)
2	3 (30.0)	6 (54.5)
≥3	0	3 (27.3)
Prior adjuvant therapy, n (%)	1 (10.0)	1 (9.1)
Prior therapies for advanced/metastatic disease, n (%)	10 (100.0)	11 (100.0)
Number of prior therapy regimens for advanced/metastatic disease, n (%)		
1	1 (10.0)	0
2	3 (30.0)	5 (45.5)
≥3	6 (60.0)	6 (54.5)

Prior lines of therapy were determined by clinical review as follows: any regimen that was discontinued due to progressive disease, recurrence, or insufficient response, or for which the date of progression occurred during or after treatment completion and before the start of the next regimen was counted as a line of therapy. In cases where the regimen was given with curative intent (adjuvant) and was discontinued due to progression or recurrence, it was calculated as a separate (palliative) line of treatment. Hormonal therapy was counted as a separate line of therapy, distinct from the rest of the regimen; nonhormonal maintenance therapy was not considered a separate line of therapy. If maintenance immunotherapy was given in combination with a new drug and upon disease progression, this was counted as a new regimen and line.
ECOG PS, Eastern Cooperative Oncology Group performance status; PD-(L)1, programmed cell death protein (ligand) 1.

Table 3. Cancer Types of Patients Enrolled in Study Phase 1, Parts 1 and 2

Tumor Type	Part 1 Doublet (n=10)	Part 2 Triplet (n=11)	Total (N=21)
Melanoma	3	5	8
Cervical	1	1	2
Renal	1	1	2
Prostate	2	0	2
Anal	1	0	1
Appendiceal	1	0	1
Colorectal	0	1	1
Head and neck	0	1	1
Lacrimal gland and duct	0	1	1
Lung	0	1	1
Pancreatic	1	0	1

Exposure, Safety, and Tolerability

- Patients received a median (range) of 5.0 (2-16) infusions in part 1 and 4.0 (2-52) infusions in part 2 for both INCAGN02385 and INCAGN02390, and 2.0 (1-26) infusions of retifanlimab in part 2
- Adverse events are summarized in **Table 4**
- Nine of 10 patients in part 1 and 11 of 11 patients in part 2 had treatment-emergent adverse events (TEAEs)
  - The most common TEAEs were anemia and diarrhea (each 3/10) in part 1 and anemia, fatigue, and pyrexia (each 4/11) in part 2 **(Table 5)**
- Six patients in part 1 and 6 patients in part 2 had grade ≥3 TEAEs
  - The only grade ≥3 TEAE occurring in more than 1 patient was treatment-unrelated grade 3 anemia (part 1, 2 patients; part 2, 3 patients) **(Table 5)**
- Serious TEAEs occurred in 1 patient in part 1 (grade 3 vasculitis) and 1 patient in part 2 (grade 3 myocarditis and pericardial effusion)
- One patient in part 1 had a fatal TEAE of sepsis unrelated to treatment—the patient had concurrent COVID-19 infection

Table 4. Summary of Adverse Events

Number of Patients With Adverse Event, n (%)	Part 1 Doublet (n=10)	Part 2 Triplet (n=11)
TEAEs (all grade, treatment-related and -unrelated)	9 (90.0)	11 (100.0)
Treatment-related TEAEs	5 (50.0)	6 (54.5)
Grade ≥3 TEAEs (treatment-related and -unrelated)	6 (60.0)	6 (54.5)
Grade ≥3 treatment-related TEAEs	1 (10.0)	1 (9.1)
Serious TEAEs (all grade, treatment-related and -unrelated)	5 (50.0)	2 (18.2)
Serious treatment-related TEAEs	1 (10.0)	1 (9.1)
TEAEs leading to dose interruption	3 (30.0)	5 (45.5)
TEAEs leading to discontinuation	0	2 (18.2)*
TEAEs leading to death	1 (10.0)†	0
Immune-related TEAEs assessed by the investigator	0	2 (18.2)
Grade ≥3 immune-related TEAEs	0	1 (9.1)
Infusion-related TEAEs assessed by the investigator	1 (10.0)	2 (18.2)
Grade ≥3 infusion reaction TEAEs	0	0

*Myocarditis with pericardial effusion (n=1), dyspnea (n=1). †Sepsis with concomitant COVID-19 infection.
TEAE, treatment-emergent adverse event.

Table 5. Summary of Most Common Adverse Events (Occurring in ≥10% of Patients in Parts 1 and 2 Combined) and Corresponding Grade ≥3 Events by MedDRA Preferred Term

Number of Patients With Adverse Event, n (%)	Part 1 Doublet (n=10)		Part 2 Triplet (n=11)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anemia	3 (30.0)	2 (20.0)	4 (36.4)	3 (27.3)
Fatigue	2 (20.0)	0	4 (36.4)	0
Pyrexia	2 (20.0)	1 (10.0)	4 (36.4)	0
Diarrhea	3 (30.0)	0	2 (18.2)	0
Back pain	1 (10.0)	0	3 (27.3)	1 (9.1)
Blood creatinine increased	2 (20.0)	0	2 (18.2)	0
Abdominal pain	0	0	3 (27.3)	0
Arthralgia	0	0	3 (27.3)	0
Dyspnea	1 (10.0)	1 (10.0)	2 (18.2)	0
Infusion-related reaction	1 (10.0)	0	2 (18.2)	0
Pain in extremity	2 (20.0)	0	1 (9.1)	1 (9.1)
Tumor pain	2 (20.0)	0	1 (9.1)	0

MedDRA, Medical Dictionary for Regulatory Activities version 25.0.

- In part 2, 1 patient had an immune-related TEAE of infusion reaction and 1 patient had immune-related TEAEs of grade 3 pericardial effusion and grade 3 myocarditis, which resolved after steroid therapy and treatment discontinuation **(Table 6)**

Table 6. Immune-Related Adverse Events by MedDRA Preferred Term as Assessed by the Investigator*

Number of Patients With Immune-Related Adverse Event, n (%)	Part 1 Doublet (n=10)	Part 2 Triplet (n=11)
Myocarditis	0	1 (9.1)
Pericardial effusion	0	1 (9.1)
Infusion-related reaction	0	1 (9.1)

*Patients were counted once under each MedDRA system organ class and preferred term.
MedDRA, Medical Dictionary for Regulatory Activities version 25.0.

Antitumor Activity

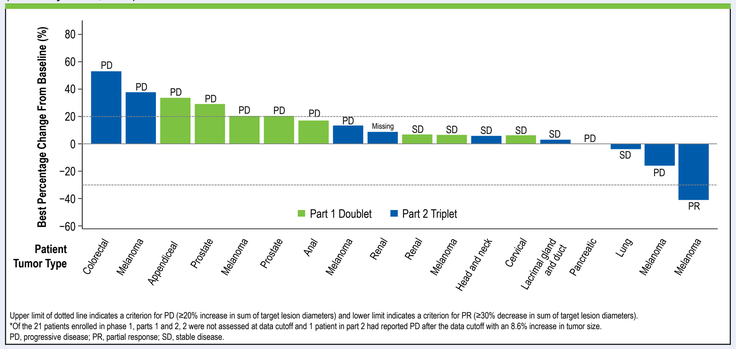
- Overall response is summarized in **Table 7**
  - The objective response rate was 4.8%
  - Best overall response in part 1 was stable disease, and in part 2 was a confirmed and durable partial response in 1 patient with melanoma refractory to checkpoint inhibitor therapy (failed both pembrolizumab in adjuvant and ipilimumab plus nivolumab in first-line settings)
    - This patient completed 2 years of triplet therapy and was ongoing with a sustained response at the data cutoff in the first follow-up assessment
- The best percentage change from baseline in target lesion size among patients assessable for response is shown in **Figure 2**

Table 7. Summary of Overall Response as Assessed by the Investigator per RECIST v1.1

Variable	Part 1 Doublet (n=10)	Part 2 Triplet (n=11)
Objective response rate (95% CI), %	0 (0.0-30.8)	9.1 (0.2-41.3)
Best overall response, n (%)		
Partial response	0	1 (9.1)
Stable disease	3 (30.0)	3 (27.3)
Progressive disease	6 (60.0)	5 (45.5)
Not assessed*	1 (10.0)	2 (18.2)
Disease control,† n (%)	3 (30.0)	4 (36.4)

*Not assessed or no postbaseline response data available; 1 patient in part 2 had reported progressive disease after the data cutoff. †Disease control was defined as patients having complete response, partial response, or stable disease on or after day 42.
CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 2. Best Percentage Change From Baseline in Target Lesion Size (Sum of Diameters) for Individual Patients by Investigator* (Full Analysis Set, N=21)



Upper limit of dotted line indicates a criterion for PD (≥20% increase in sum of target lesion diameters) and lower limit indicates a criterion for PR (≥30% decrease in sum of target lesion diameters).
*Of the 21 patients enrolled in phase 1, parts 1 and 2, 2 were not assessed at data cutoff and 1 patient in part 2 had reported PD after the data cutoff with an 8.6% increase in tumor size.
PD, progressive disease; PR, partial response; SD, stable disease.

Table 1. Key Eligibility Criteria (Phase 1, Part 1s and 2)

Inclusion	Exclusion
• Patients ≥18 years of age	• Previous organ transplant or LAG-3– or TIM-3–directed therapy
• Failed available therapies, including anti–PD-(L)1 therapy if indicated, that are known to confer clinical benefit, or who are intolerant to or ineligible for standard treatment	• Receipt of colony-stimulating factors ≤14 days before study day 1, anticancer therapy ≤21 days before first administration of study treatment, live vaccine within 30 days of planned start of study treatment, or chronic systemic corticosteroids (>10 mg/day of prednisone or equivalent)
• ECOG PS 0 or 1	• Radiation therapy ≤1 week of first dose of study treatment, or radiation therapy in the thoracic region >30 Gy ≤6 months before the first dose
	• Interstitial lung disease or active, noninfectious pneumonitis
	• Active brain or CNS metastases, except previously treated and clinically stable brain or CNS metastases with no evidence of new or enlarging brain metastases or CNS edema
	• Active autoimmune disease requiring systemic immunosuppression, or chronic or current active infections requiring systemic antibiotics, antifungal treatment, or antiviral treatment
	• Impaired cardiac function or clinically significant cardiac disease, or history or presence of abnormal ECG
	• History of immune-related toxicity during prior checkpoint inhibitor therapy for which permanent discontinuation of therapy is recommended, or immune-related toxicity requiring intensive or prolonged immunosuppression

CNS, central nervous system; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; Gy, gray; LAG-3, lymphocyte activation gene-3; PD-(L)1, programmed cell death protein (ligand) 1; TIM-3, T-cell immunoglobulin and mucin-domain containing-3.

Conclusions

- The phase 1 portion of this study primarily aimed to assess safety of the doublet anti–LAG-3 + anti–TIM-3 and triplet anti–LAG-3 + anti–TIM-3 + retifanlimab combination regimens in tumor-agnostic and heavily pretreated patients
- Both combination regimens were generally well tolerated with a safety profile consistent with that of the immune checkpoint inhibitor class
  - No novel toxicities were observed
  - Immune-related TEAEs were reported in 2 patients on the triplet regimen (1 with grade 3 myocarditis and pericardial effusion, and 1 with infusion-related reaction), and none on the doublet regimen; no grade ≥3 infusion-related adverse events were reported with either regimen
- In this phase 1 population, best response was stable disease on the doublet regimen and partial response (1 patient) on the triplet regimen
  - The one patient with checkpoint inhibitor therapy–refractory advanced melanoma with confirmed partial response completed 2 years of triplet therapy and maintains a response at last follow-up assessment (duration of response, >15 months and ongoing)
  - Disease control rates were 30.0% and 36.4% for the doublet and triplet regimens, respectively
- Optimal doses of the triplet combinations as well as alternative treatment schedules are currently being evaluated in phase 1, parts 3 and 4 of the study
- Cohort B of phase 2 will assess the activity of the triplet combination as first-line treatment in patients with advanced melanoma

Disclosures

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