

First-in-human phase 1 study of INCAGN02390, a TIM-3 monoclonal antibody antagonist, in patients with advanced malignancies

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DECLARATION OF INTERESTS

Martin E. Gutierrez

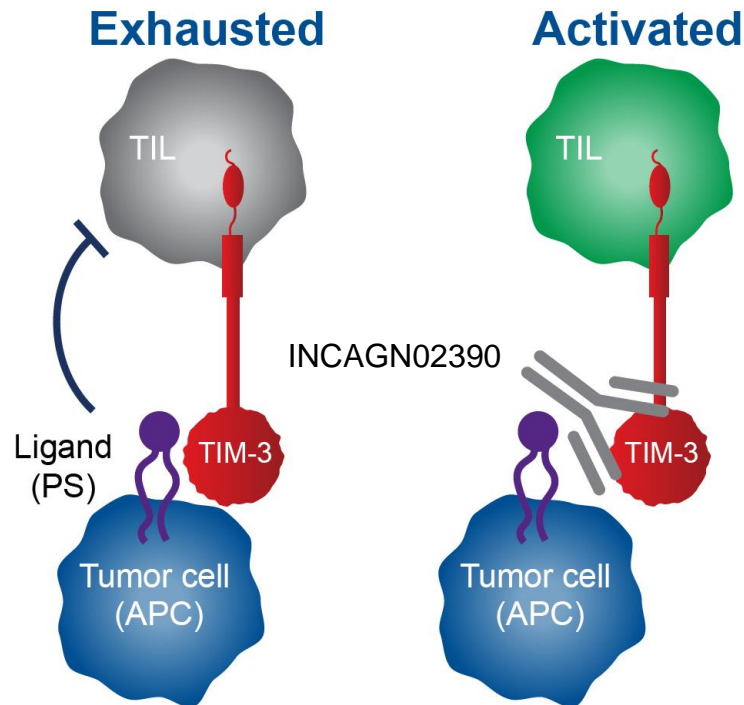
Consulting & Advisory Board: Celularity and Guardant360

Introduction

TIM-3 is a transmembrane checkpoint receptor expressed on multiple immune cells¹

INCAGN02390 is a fully human Fc-silenced IgG1k monoclonal antibody that stimulates immune cell function through inhibition of TIM-3 interaction with immunosuppressive ligands (eg, PS) as well as induction of TIM-3 receptor internalization²

INCAGN02390 enhances antitumor responses in preclinical mouse tumor models when combined with α -PD1 and α -LAG-3 antibodies²

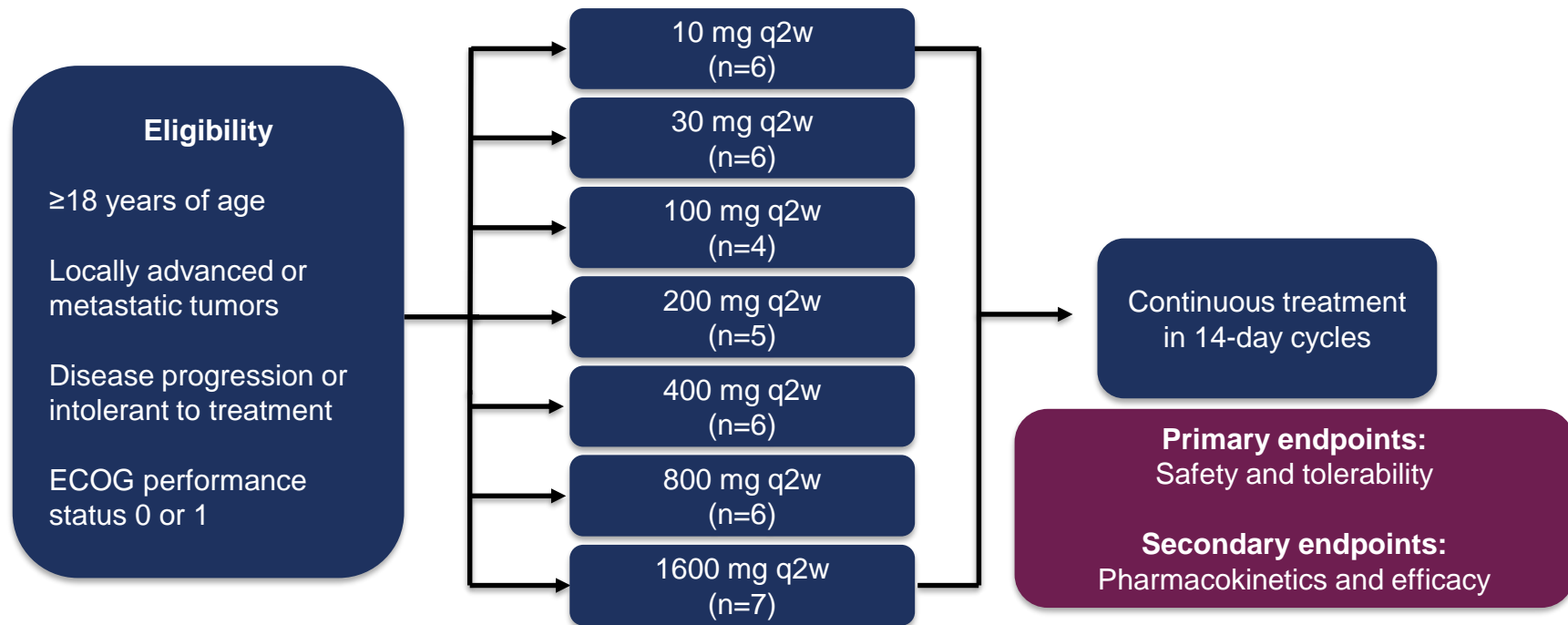


Objective: To determine the safety and tolerability and define the MTD or PAD of INCAGN02390 monotherapy

APC, antigen presenting cell; IgG1, immunoglobulin G1; Fc, fragment crystallizable region; LAG-3, lymphocyte activation gene 3; MTD, maximum tolerated dose; PAD, pharmacologically active dose; PD-1, programmed cell death protein 1; PS, phosphatidylserine; TIL, tumor-infiltrating T cell; TIM-3: T-cell immunoglobulin and mucin domain 3.

¹Du W, et al *Int J Mol Sci.* 2017;18:645. ²Waight J, et al AACR 2018. Poster 3825.

NCT03652077 Study Design: 3 + 3 Dose Escalation



ECOG, Eastern Cooperative Oncology Group; q2w, every 2 weeks.

Demographics and Baseline Characteristics

	INCAGN02390 Treatment Group							
	10 mg q2w (n=6)	30 mg q2w (n=6)	100 mg q2w (n=4)	200 mg q2w (n=5)	400 mg q2w (n=6)	800 mg q2w (n=6)	1600 mg q2w (n=7)	Total (N=40)
Age, median (range), y	64 (40–66)	62 (26–65)	62 (53–70)	63 (43–72)	67 (55–77)	65 (32–90)	63 (44–75)	63 (26–90)
Male, n (%)	5 (83.3)	4 (66.7)	3 (75.0)	1 (20.0)	2 (33.3)	2 (33.3)	4 (57.1)	21 (52.5)
ECOG PS 0 / 1, n	1 / 5	1 / 5	1 / 3	1 / 4	1 / 5	1 / 5	1 / 6	7 / 33
Most common cancer types, n (%)								
Breast	1 (16.7)	1 (16.7)	0	1 (20.0)	1 (16.7)	0	2 (28.6)	6 (15.0)
Lung	0	1 (16.7)	1 (25.0)	1 (20.0)	1 (16.7)	1 (16.7)	0	5 (12.5)
Colorectal	1 (16.7)	0	1 (25.0)	1 (20.0)	0	0	1 (14.3)	4 (10.0)
≥3 metastatic sites,* n (%)	4 (66.7)	6 (100)	1 (25.0)	3 (60.0)	2 (33.3)	4 (66.7)	5 (71.4)	25 (62.5)
Visceral metastases,† n (%)	5 (83.3)	6 (100)	3 (75.0)	5 (100)	5 (83.3)	6 (100)	7 (100)	37 (92.5)
Prior immunotherapy, n (%)	5 (83.3)	3 (50.0)	2 (50.0)	1 (20.0)	5 (83.3)	4 (66.7)	3 (42.9)	23 (57.5)
≥3 prior lines of systemic treatment, n (%)	2 (33.3)	6 (100)	1 (25.0)	4 (80.0)	5 (83.3)	2 (33.0)	4 (57.1)	24 (60.0)

The study included a heavily pretreated patient population: 57.5% had prior immunotherapy

* Metastatic sites reported as “lymph nodes” without further location specification were counted as one site. † Visceral metastases included all metastases other than bone, lymph nodes, breast, and skin or subcutaneous tissue.

ECOG PS, Eastern Cooperative Oncology Group performance status; q2w, every 2 weeks.

Safety

Event, n (%)	INCAGN02390 (N=40)	Events description
TEAE*	40 (100)	Most commonly anemia (35%), back pain (30%), fatigue (28%)
Treatment-related TEAE	12 (30.0)	Most commonly fatigue (7.5%), pruritus (7.5%), diarrhea, myalgia, and rash (5% each)
Treatment-related grade ≥ 3 TEAE	3 (7.5)	One each and all grade 3: adrenal insufficiency (the only drug-related serious TEAE, 1600-mg cohort), anemia, elevated amylase
Serious TEAE	18 (45.0)	Pleural effusion (n=4), acute respiratory failure (n=3), sepsis (n=2) [†]
Immune-related TEAE [‡]	4 (10.0)	Adrenal insufficiency, hypothyroidism, acute kidney injury, dermatitis, pruritus (n=1 each)
Fatal TEAE	1 (2.5)	Multi-organ failure (unrelated to study drug, 800-mg dose)

- There were no consistent differences between adverse events across dose cohorts
- No DLTs or infusion-related reactions were observed
- All patients discontinued treatment, mostly due to progressive disease (67.5%); 6 (15%) TEAEs led to treatment discontinuation

* TEAEs are adverse events either reported for the first time or worsening of a pre-existing event after first dose of study drug (until ≥ 30 days after the last dose of study drug or until the start of new anticancer therapy, whichever occurs first); [†] All other serious TEAEs were reported in 1 patient each; [‡] Immune-related TEAE per sponsor assessment based on a predetermined list based on data with immune checkpoint inhibitors. DLT, dose-limiting toxicity; TEAE, treatment-emergent adverse event.

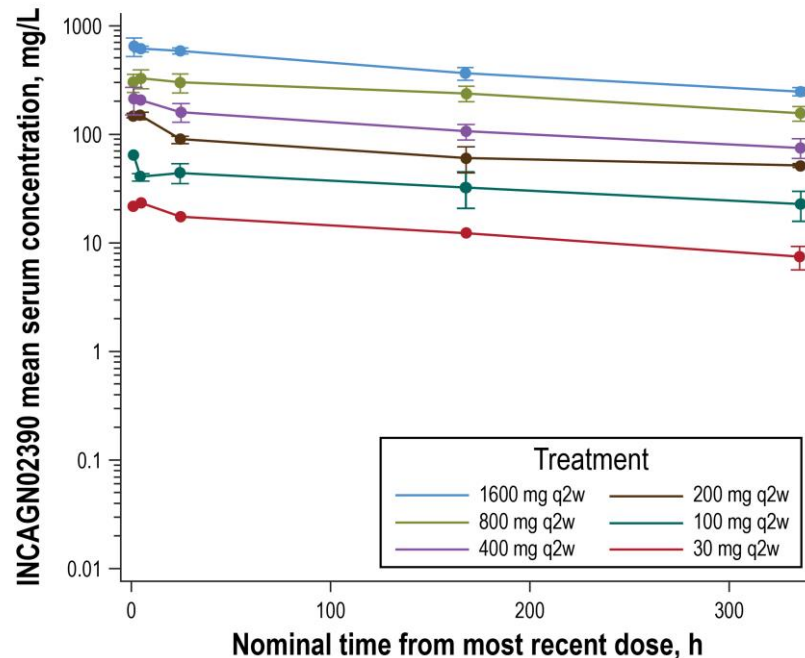
Pharmacokinetics

Serum Concentration

- INCAGN02390 trough serum concentrations achieved steady state around cycles 4–6
- Maximum serum concentration and area under serum concentration-time curve were linear across most dose levels
- PK profile of INCAGN02390 was typical of monoclonal antibodies

PK, pharmacokinetics; q2w, every 2 weeks.

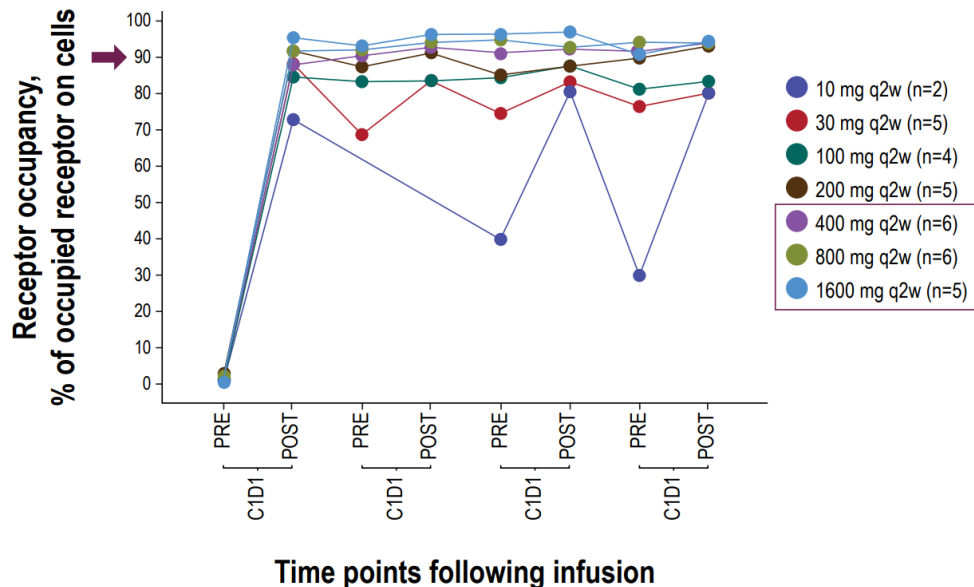
Steady-state INCAGN02390 serum concentration



Antidrug Antibodies (ADA) and Receptor Occupancy

- 5 patients had at least 1 ADA-positive sample, 2 of whom were positive at baseline
 - No treatment-boostered ADAs were observed
- Linear PK was not affected by ADA across dose levels
- TIM-3 receptor occupancy levels were $\geq 90\%$ in peripheral blood in doses ≥ 400 mg

INCAGN02390 Receptor Occupancy



Notes: 1) Receptor occupancy presented here was assessed in peripheral blood monocytes.
2) No changes in T-cell activity or immune-related cytokines were observed as a result of INCAGN02390 treatment.

C, cycle; D, day; PK, pharmacokinetics; PRE, pre-dose; POST, post-dose; TIM-3: T-cell immunoglobulin and mucin domain 3.

Efficacy

Best overall response, n (%)	INCAGN02390 Treatment Group							
	10 mg q2w (n=6)	30 mg q2w (n=6)	100 mg q2w (n=4)	200 mg q2w (n=5)	400 mg q2w (n=6)	800 mg q2w (n=6)	1600 mg q2w (n=7)	Total (N=40)
CR	-	-	-	-	-	-	-	-
PR	-	-	-	1 (20.0)	-	-	-	1 (2.5)
SD	-	-	-	2 (40.0)	2 (33.3)	2 (33.3)	-	6 (15.0)
PD	2 (33.3)	6 (100)	4 (100)	2 (40.0)	3 (50.0)	2 (33.3)	5 (71.4)	24 (60.0)
NE	4 (66.7)	-	-	-	1 (16.7)	2 (33.3)	1 (14.3)	8 (20.0)
Missing	-	-	-	-	-	-	1 (14.3)	1 (2.5)

- Disease control rate (CR+PR+SD per RECIST v1.1) was 17.5%
- 1 confirmed PR (adenoid cystic carcinoma in lung) with a duration of 5.65 months

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; q2w, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Conclusions

INCAGN02390 monotherapy was generally well tolerated. There were no DLTs, and MTD and MNTD were not reached

Treatment with INCAGN02390 monotherapy was associated with linear PK

Linear PK was not affected in limited instances of detectable ADA

In this heavily pretreated population (N=40), there was 1 PR and 6 patients with SD

INCAGN02390 400 mg q2w achieved $\geq 90\%$ RO and was selected for investigation in phase 1b/2 studies in combination with other immunotherapies

- NCT05287113; TIM-3, LAG-3, and retifanlimab [α -PD-1] combined inhibition in PD-L1+ SCCHN [ESMO 2022, poster 705TiP]
- NCT04370704; TIM-3, LAG-3, and retifanlimab [α -PD-1] combined inhibition in select advanced malignancies
- NCT04463771; TIM-3, LAG-3, and retifanlimab [α -PD-1] combined inhibition in advanced MSI-H endometrial cancer
- NCT04586244; TIM-3 plus LAG-3 or LAG-3 combined with retifanlimab [α -PD-1] in MIBC (OPTIMUS)

ADA, antidrug antibody; DLT, dose-limiting toxicity; MIBC, muscle-invasive bladder cancer; MNTD, maximum number of tolerated doses; MSI-H, microsatellite instability high; MTD, maximum tolerated dose; PK, pharmacokinetics; PR, partial response; RO, receptor occupancy; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease.

Thank you!

