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A Phase 1, First-in-Human, Open-Label, Multicenter Study of INCA32459, a Bispecific Anti–PD-1 and Anti–LAG-3 Antibody, in Patients With Select Advanced Malignancies

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Introduction

- Anti–programmed cell death protein (PD)-ligand (L)1 therapies have improved clinical outcomes in patients with various cancers[1]
- However, many patients either do not respond or develop resistance, partly due to additional immune checkpoint receptors including lymphocyte activation gene-3 (LAG-3), which is frequently co-expressed with PD-1 on tumor-infiltrating lymphocytes[2-4]
- Combined anti–PD-1 and anti–LAG-3 therapy has demonstrated improvements in clinical outcomes compared with anti–PD-1 alone[5]
- INCA32459, a human Fc-silenced IgG1 bispecific PD-1 × LAG-3 antibody, may enhance clinical activity compared with individual monoclonal antibodies
  - In 2 human primary immune cell assays, INCA32459 treatment resulted in higher interleukin-2 and interferon-γ induction, respectively, compared with a combination of nivolumab and relatlimab analog antibodies[6]

Objective

- This trial in progress will assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary clinical efficacy of INCA32459 in patients with advanced malignancies

Methods

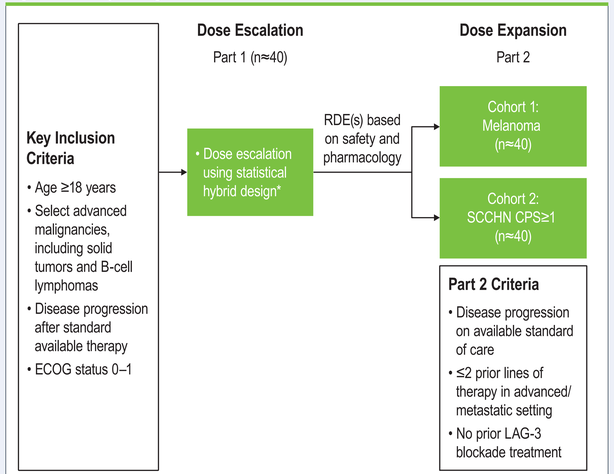
Patients

- Part 1 (dose escalation): Patients with select advanced malignancies
- Part 2 (dose-expansion) cohort 1: Patients with unresectable or metastatic melanoma who have experienced disease progression after standard therapy
- Part 2 (dose-expansion) cohort 2: Patients with recurrent or metastatic PD-L1+ (combined positive score ≥1) squamous cell carcinoma of the head and neck who have experienced disease progression after standard therapy (**Figure 1**)

Study Design

- First-in-human, multicenter, open-label, dose-escalation, dose-expansion phase 1 clinical study (NCT05577182; **Figure 1** and **2**)
- INCA32459 will be administered intravenously to patients with select advanced malignancies

Figure 1. Study Design



CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; LAG-3, lymphocyte activation gene-3; RDE, recommended dose for expansion; SCCHN, squamous cell carcinoma of the head and neck.
* The 3-step design is a hybrid of the modified toxicity probability interval design and a dose-toxicity model.[7]

- Following the first 2 INCA32459 dose levels in part 1 (dose escalation), a statistical hybrid design[7] will be used to assess safety and tolerability and to identify the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE; **Figure 1**)
  - The dose will not be increased by more than 1 dose level at a time
- Part 2 (dose expansion) will enroll 2 tumor-specific cohorts (**Figure 1**)
- The estimated duration of study includes ≤28 days of screening, continuous treatment in 3-week cycles for ≤2 years as long as patients receive benefit from treatment, and 90±7 days for safety follow-up

Endpoints and Assessments

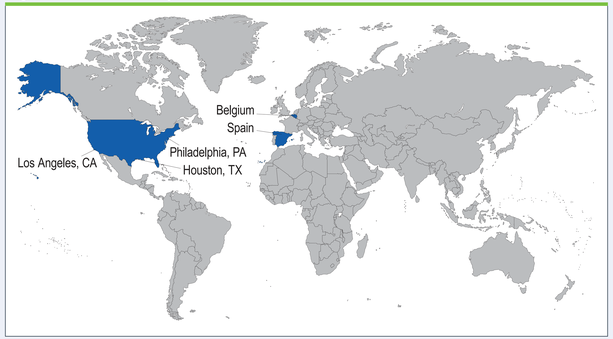
- The primary endpoints are occurrence of dose-limiting toxicities and incidence of treatment-emergent adverse events (TEAEs) to evaluate safety and tolerability of INCA32459 and determine the MTD and/or RDE (**Table 1**)
- TEAE assessments will be performed on days 1, 2, 8 (±1), and 15 (±3) of cycle 1; days 1 (±3) and 8 (±3) of cycles 2–3; day 1 (±3) of cycles ≥4; end of treatment; and at 30 (±7) and 90 (±7) days after end of treatment
  - Adverse events include any safety assessments (eg, electrocardiogram, vital signs, clinically meaningful laboratory tests) that worsen from baseline and are considered clinically significant (ie, not related to underlying disease progression)
  - Adverse event severity will be assessed using the Common Terminology Criteria for Adverse Events v5.0 grades 1–5
- Radiologic tumor assessments will be performed every 9 (±1) weeks for the first year of study, then every 12 (±1) weeks; solid tumors will be assessed by contrast-enhanced computed tomography (CT) or magnetic resonance imaging; B-cell lymphomas will be assessed by positron emission tomography/CT

Table 1. Study Endpoints

Endpoints
Primary: safety, tolerability, MTD, and/or RDE(s)
• Occurrence of DLTs • TEAEs • TEAEs leading to interruptions of INCA32459 or withdrawal from treatment
Secondary: efficacy
• Objective response (CR or PR)* • Disease control (CR, PR, and SD)* • DOR (earliest date of disease response to earliest date of disease progression)*
Secondary: pharmacokinetics
• C_{max}, t_{max}, C_{min}, AUC, CL, V_z, $t_{1/2}$
Secondary: target engagement of INCA32459
• PD-1 receptor occupancy in peripheral blood samples

AUC, area under the curve; CL, total systemic clearance; C_{max} (or C_{min}), maximum (or minimum) observed plasma or serum concentration; CR, complete response; DLT, dose-limiting toxicity; DOR, duration of response; MTD, maximum tolerated dose; PD-1, programmed cell death protein 1; PR, partial response; RDE, recommended dose for expansion; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; $t_{1/2}$, apparent terminal-phase disposition half-life; TEAE, treatment-emergent adverse event; t_{max}, time to maximum concentration; V_z, volume of distribution during the elimination phase.
* Objective response, disease control, and disease response/progression are determined by investigator assessment of radiographic evidence per RECIST v1.1 or, if B-cell lymphoma, Lugano criteria.

Figure 2. Current Study Locations Map



Disclosures

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NB, RS, Y-oY, WW, and PM are employees and shareholders of Incyte Corporation (Wilmington, DE, USA).

TCM serves on scientific advisory boards for BMS, GigaGen, Instill Bio., Merck, and OncoSec.

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