A phase 1b/2 study of gocatamig and ifinatamab deruxtecan for relapsed or refractory extensive-stage small cell lung cancer

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INTRODUCTION

- Delta-like ligand 3 (DLL3) and B7-H3 are two proteins highly expressed on the surface of small cell lung cancer (SCLC) cells[1,2]
- Gocatamig (MK-6070, HPN328) is a DLL3-directed T-cell engager developed using the TriTAC® platform[3] (**Figure 1**)
- Ifinatamab deruxtecan (I-DXd) is a B7-H3–directed antibody–drug conjugate (ADC) composed of a humanized anti–B7-H3 IgG1 monoclonal antibody covalently linked to a topoisomerase I inhibitor by a tetrapeptide-based cleavable linker[4] (**Figure 1**)
- Both gocatamig and I-DXd have shown promising clinical activity and manageable safety profiles when administered as monotherapy in participants with pretreated extensive-stage (ES)-SCLC[5,6]
- Durvalumab is a programmed death ligand 1 (PD-L1) inhibitor approved for use in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of ES-SCLC[7] (**Figure 1**)
- Because of their distinct mechanisms of action and minimally overlapping toxicities, combining gocatamig with an ADC or a checkpoint inhibitor may enhance efficacy without compromising tolerability
- We describe the ongoing phase 1b/2 study 6070-002 (NCT06780137) that is evaluating the combination of gocatamig with I-DXd or durvalumab, as well as gocatamig monotherapy and I-DXd monotherapy, for the treatment of relapsed or refractory ES-SCLC

Poster presented

https://bit.ly/4IZXOFJ

Poster slides

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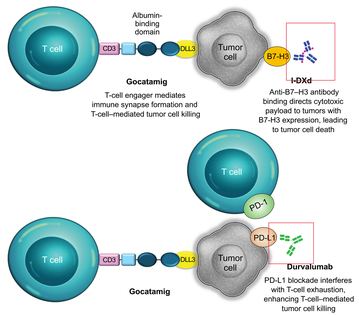
Plain language summary

http://bit.ly/47DIaxx

Figure 1. Mechanisms of action of gocatamig, I-DXd, and durvalumab



OBJECTIVES

Primary

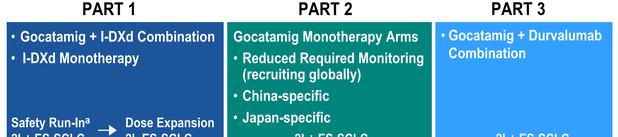
- Part 1: Evaluate the objective response rate (ORR), safety, and tolerability of gocatamig in combination with I-DXd or I-DXd alone
- Part 2: Evaluate the safety and tolerability of gocatamig monotherapy
- Part 3: Evaluate the safety and tolerability of gocatamig in combination with durvalumab

Secondary

- Part 1: Evaluate the duration of response (DOR) and progression-free survival (PFS), characterize the pharmacokinetic profile, and evaluate the immunogenicity of I-DXd alone or in combination with gocatamig
- Part 2: Evaluate the ORR, DOR, and PFS; characterize the pharmacokinetic profile; and evaluate the immunogenicity of gocatamig monotherapy
- Part 3: Evaluate the ORR, DOR, and PFS; characterize the pharmacokinetic profile; and evaluate the immunogenicity of gocatamig in combination with durvalumab

METHODS

Figure 2. The 6070-002 study design



2L, second line; 2L+, second line or later. [a]Bayesian optimal interval dosing.

- Gocatamig and I-DXd combination doses, the gocatamig monotherapy doses, and the gocatamig dose to be used in combination with durvalumab will depend on the results of the ongoing dual dose escalation and monotherapy cohorts of study 6070-001 (NCT04471727)
- Dose expansion in part 1 will depend on findings of the safety run-in period

Table 1. Key participant eligibility criteria

Inclusion criteria

- Age 18 years or older
- Stage IV ES-SCLC (T any, N any, M1a/b/c) following:
  - Part 1 safety run-in, part 2, and part 3: at least one prior line of platinum-based chemotherapy with or without PD-(L)1 inhibitors
  - Part 1 dose-expansion: only one prior line of platinum-based chemotherapy with or without PD-(L)1 inhibitors
- Measurable disease by RECIST 1.1 outside the CNS
- ECOG performance status 0 or 1
- Available tumor tissue sample
- Adequate organ function

Exclusion criteria

- Pleural effusion, pericardial effusion, or ascites requiring drainage procedures
- History of pneumonitis or interstitial lung disease
- Clinically severe pulmonary compromise
- Active or history of autoimmune disease or immune deficiency
- Uncontrolled or significant (or history of significant) cardiovascular disease
- Unresolved grade ≥2 AEs (per NCI CTCAE 5.0) from prior anticancer therapy
- Last systemic anticancer treatment or other investigational agent/device within 3 weeks of scheduled dosing
- Severe, life-threatening immune-mediated AEs or IRRs with prior immune-oncology agents
- Radiotherapy within 2 weeks of study treatment (parts 1 and 2), or radiation to the lung within 6 months or the abdominal area within 4 weeks of study treatment (part 1)
- Prior treatment with a DLL3-targeted agent (except part 1 safety run-in period for the I-DXd monotherapy arm)
- Other malignancy within 3 years of screening (except basal cell or squamous cell carcinoma of the skin or carcinoma in situ)
- Prior treatment with B7-H3–targeted agents (part 1)
- Prior discontinuation of an ADC that consists of an exatecan derivative due to treatment-related toxicities (part 1)
- Untreated or symptomatic brain metastases or leptomeningeal disease

AE, adverse event; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; IRR, infusion-related reaction; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; RECIST, Response Evaluation Criteria In Solid Tumors.

Assessments

- The incidence and causality of AEs, including serious AEs, will be collected from the time of treatment allocation through the last dose of study treatment and during the safety follow-up period
- Dose-limiting toxicities (DLTs; **Table 2**) will be assessed during the safety run-in period and graded using the NCI CTCAE v5.0 or the American Society for Transplant and Cellular Therapy (ASTCT) criteria
- ORR, DOR, and PFS will be assessed by the investigator per RECIST v1.1
- Pharmacokinetic and immunogenicity analyses for gocatamig alone or in combination with I-DXd or durvalumab will be performed

Table 2. Dose-limiting toxicities

Hematologic

- Grade 4 hematologic AE lasting ≥7 days
- Grade 4 thrombocytopenia of any duration
- Grade 3 thrombocytopenia associated with clinically significant bleeding
- Grade 3 or grade 4 febrile neutropenia

Nonhematologic

- Any grade ≥3 nonhematologic AE is considered a DLT, except:
  - Grade 3 fatigue lasting ≤7 days
  - Grade 3 diarrhea, nausea, or vomiting lasting <72 hours
  - Grade 3 diarrhea, nausea, or vomiting lasting >72 hours but <120 hours without use of antiemetics or antidiarrheals per standard of care
  - Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care
  - Grade 3 or 4 events of increased or decreased blood pressure if associated with symptoms of CRS/IRR and resolve in concordance with CRS symptom resolution and do not result in additional safety events
  - Grade 3 or 4 nonhematologic laboratory that is asymptomatic and/or rapidly reversible (returned to baseline or to grade ≤1 within 7 days) unless identified as clinically relevant by the investigator
- Drug-induced liver injury, defined as serum chemistry values and clinical presentation with the following features:
  - ALT or AST ≥3 × ULN
  - Total bilirubin ≥2 × ULN
  - Alkaline phosphatase <2 × ULN
  - No other cause for abnormalities, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury
- Grade ≥2 interstitial lung disease or pneumonitis
- Grade 5 toxicity

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRS, cytokine release syndrome; ULN, upper limit of normal.

Statistical analyses

- The safety analysis population will consist of all participants who received at least one dose of study treatment
- The efficacy analysis population for will consist of all participants with a baseline scan who received at least one dose of study treatment
- The per-protocol population for pharmacokinetic and immunogenicity analyses will consist of the subset of participants who complied with the protocol sufficiently to ensure that their data are likely to show the effects of treatment

Current status

- Recruitment is currently ongoing at sites worldwide in Argentina, Australia, Chile, China, Israel, Japan, South Korea, Spain, Taiwan, Türkiye, and the United States
- Enrollment is estimated to be approximately 242 participants across all treatment arms

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