A phase 2 study of ifinatamab deruxtecan (I-DXd; DS-7300) in patients with previously treated ES-SCLC

#1561

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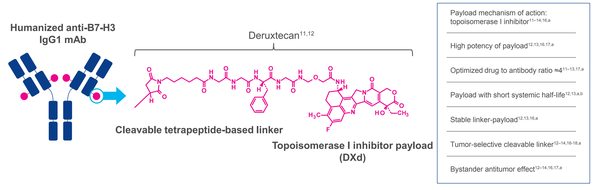
INTRODUCTION

- Patients with extensive-stage small cell lung cancer (ES-SCLC) rapidly progress on available therapies and have a significant unmet need for more effective options that can provide durable clinical benefit
  - SCLC is an aggressive neuroendocrine lung malignancy in which >70% of patients are diagnosed with ES disease and in which the 5-year survival rate is as low as <10%[1–4]
  - Despite high initial response rates to combination platinum-based chemotherapy and immunotherapy in the first-line setting, median progression-free survival is only 5.1 – 5.2 months, and median overall survival is 12.3 – 13 months[5,6]
- B7 homolog 3 (B7-H3 [CD276]), a type 1 transmembrane protein belonging to the B7 family, is overexpressed in SCLC and is associated with higher tumor volume and lower overall survival
  - B7-H3 is overexpressed in SCLC; 65% of patients exhibit moderate-to-high expression,[7] whereas normal lung tissue biopsies have shown no B7-H3 staining[8,9]
  - B7-H3 overexpression is an independent prognostic indicator of worse overall survival[10]: median overall survival is 7.4 months in patients with high expression vs 23.8 months in patients with low expression[7]
- I-DXd (DS-7300) is a novel B7-H3–directed antibody–drug conjugate (ADC) that leverages the clinically validated deruxtecan (DXd) technology and is a promising new therapy with the potential to offer clinical benefit in patients with ES-SCLC
  - I-DXd is an ADC composed of 3 components (**Figure 1**): a humanized anti–B7-H3 immunoglobulin G1 monoclonal antibody covalently linked to a potent topoisomerase I inhibitor payload (an exatecan derivative) via a plasma-stable linker[11–14,a]
  - The first-in-human dose-escalation study of I-DXd (DS7300-A-J101, NCT04145622) demonstrated promising clinical activity in heavily pretreated patients with ES-SCLC[15]
  - Patients with ES-SCLC treated with I-DXd 6.4 – 16.0 mg/kg demonstrated a 52% objective response rate (ORR) (data cutoff: January 31, 2023)

[a]The clinical relevance of these features is under investigation.

Figure 1: I-DXd Is a B7-H3–Directed ADC Composed of Three Components



[a]The clinical relevance of these features is under investigation. [b]Based on animal data.
ADC, antibody–drug conjugate; B7-H3, B7 homolog 3; DXd, deruxtecan; I-DXd, ifinatamab deruxtecan; IgG1, immunoglobulin G1; mAb, monoclonal antibody.

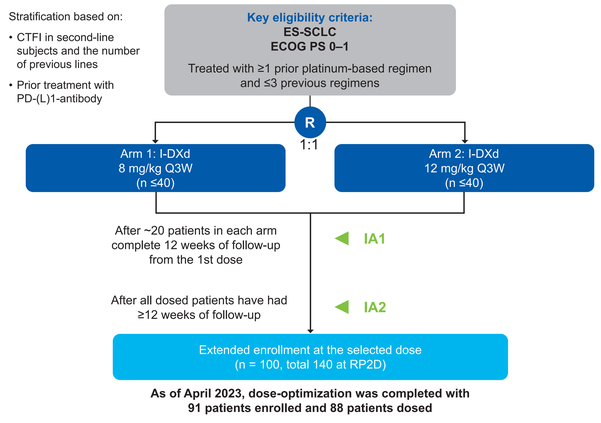
PURPOSE

- The objectives of this study are to optimize the dose of I-DXd based on efficacy, safety, and pharmacokinetics and to investigate I-DXd antitumor activity in patients with previously treated ES-SCLC

METHODS

- A phase 2, dose-optimization study evaluating I-DXd in patients with previously treated ES-SCLC is in progress (NCT05280470)
- A sample size of approximately 40 patients per dose level will provide sufficient statistical precision for the inference of ORR (**Figure 2**)
- Study endpoints and patient eligibility criteria are provided in **Table 1** and **Table 2**, respectively

Figure 2: Study Design



CTFI, chemotherapy-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small cell lung cancer; IA, interim analysis; I-DXd, ifinatamab deruxtecan; ORR, objective response rate; PD-(L)1, programmed death-(ligand) 1; Q3W, every 3 weeks; R, randomization; RP2D, recommended phase 2 dose.

Table 1: Study Endpoints[a]

Primary
• Objective response rate[b]
Secondary
• Overall safety
• Progression-free survival
• Duration of response
• Overall survival
• Time to response
• Objective response rate[c]
• Disease control rate
• Pharmacokinetic parameters
• Treatment-emergent antidrug antibodies

[a]For endpoints that included tumor response/disease progression assessments, RECIST v1.1[20] was used.
[b]Assessed by blinded independent central review. [c]Assessed by the investigator.
RECIST, Response Evaluation Criteria In Solid Tumors.

Table 2: Patient Eligibility Criteria

Key inclusion criteria
• ≥1 lesion, not previously irradiated, amendable to core biopsy
• Histologically or cytologically documented ES-SCLC
• ≥1 measurable lesion according to RECIST v1.1[20]
• Prior therapy with ≥1 platinum-based line as systemic therapy for ES-SCLC with ≥2 cycles of therapy (except in the case of early objective PD)
• Documentation of radiological disease progression on or after the most recent systemic therapy

Key exclusion criteria
• Prior treatment with orlotamab, enoblituzumab, or other B7-H3–targeted agents
• Prior treatment with an ADC that contains an exatecan derivative
• Clinically active brain metastasis, spinal cord compression, or leptomeningeal carcinomatosis
• Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses
• History of ILD/pneumonitis that required corticosteroids; current or suspected ILD/pneumonitis
• Active, known, or suspected autoimmune disease

ADC, antibody–drug conjugate; B7-H3, B7 homolog 3; ES-SCLC, extensive-stage small cell lung cancer; ILD, interstitial lung disease; PD, progressive disease; RECIST, Response Evaluation Criteria In Solid Tumors.

Figure 3: Enrollment Status

*Planned
First patient first visit: June 2022
Dose-optimization completion: April 2023
Estimated primary completion: May 2024

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