Ifinatamab deruxtecan (I-DXd) + atezolizumab ± carboplatin as first-line therapy for extensive-stage small cell lung cancer

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*At the time of the design of the study

OBJECTIVES

- IDeate-Lung03 (NCT06362252) is a multicenter, open-label Phase 1b/2 trial enrolling patients with ES-SCLC in the US, Europe, and Japan[1]
- The study is designed to evaluate the safety and efficacy of I-DXd in combination with atezolizumab with or without carboplatin in patients with ES-SCLC in the 1L setting

INTRODUCTION

- The current 1L SOC therapy for patients with ES-SCLC includes carboplatin + etoposide + atezolizumab,[2] but prognosis remains poor with this combination, with median PFS of 5.2 months and median OS of 12.3 months[3]
  - Patients with brain metastases have worse survival outcomes (median PFS and OS of 4.2 and 8.5 months, respectively)[3] and their treatment remains a clinical challenge[4]
- B7-H3 (CD276), a transmembrane protein belonging to the B7 family, is expressed in many solid tumors but is absent or expressed at low levels in normal tissue[5–7]
- B7-H3 is highly expressed in SCLC,[8,9] with consistent expression across all molecular subtypes[8]; high B7-H3 expression has been associated with a shorter median OS (7.4 months vs 23.8 months in patients with low or absent B7-H3)[10]
- I-DXd is a B7-H3–directed ADC comprising a B7-H3 mAb linked to a potent topoisomerase I inhibitor payload (DXd) via a stable cleavable linker, designed to enhance selective tumor-cell death and reduce systemic exposure[11] (**Figure 1**)
- In the dose-optimization part of the Phase 2 IDeate-Lung01 study (NCT05280470), I-DXd 12 mg/kg demonstrated promising efficacy among 42 patients with pretreated ES-SCLC (ORR, 54.8%; median DOR, 4.2 months; median PFS, 5.5 months; median OS, 11.8 months)[12]
- I-DXd is being investigated further in a Phase 3 trial comparing I-DXd with physician's choice of topotecan, lurbinectedin, or amrubicin in patients with relapsed SCLC who have received only 1 prior line of platinum-based chemotherapy (IDeate-Lung02 [NCT06203210])[13]
- Here, we describe IDeate-Lung03 (NCT06362252), a Phase 1b/2, multicenter, open-label study of I-DXd in combination with atezolizumab and carboplatin as 1L induction, and I-DXd + atezolizumab as 1L maintenance, in patients with ES-SCLC[1]

Figure 1. I-DXd was designed with 7 key attributes

The **mAb** directs the DXd ADC to the tumor cell

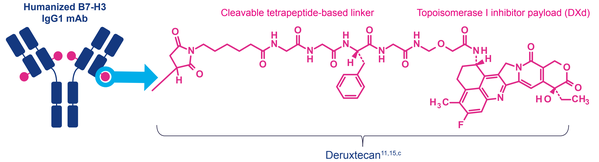
1. Optimized drug-to-antibody ratio of ~4[11,14,a,b]

The **linker** binds the mAb to the payload

2. Plasma-stable linker–payload[11,14,a]
3. Tumor-selective cleavable linker[11,14,a]

The **payload** induces cell death when delivered to the tumor

4. Topoisomerase I inhibitor[11,14,15,a]
5. High potency[11,14,a]
6. Short systemic half-life[11,14,a,b]
7. Bystander antitumor effect[14–16,a]



[a]The clinical relevance of these features is under investigation. [b]Based on animal data. [c]Refers to the linker and payload.

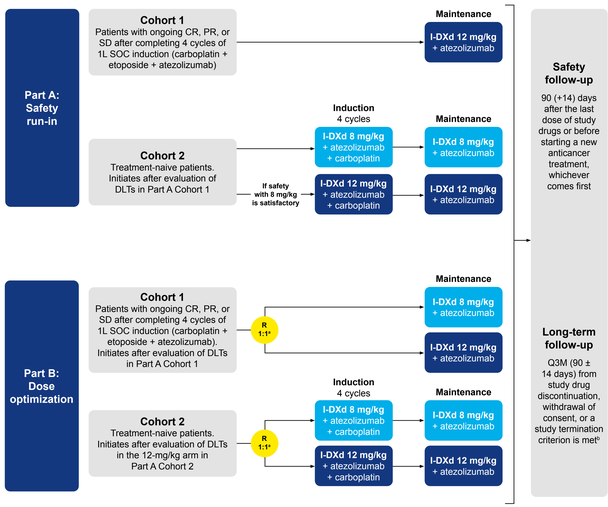
METHODS

- IDeate-Lung03 (NCT06362252) is a multicenter, open-label Phase 1b/2 trial evaluating the safety and efficacy of I-DXd in combination with atezolizumab with or without carboplatin in patients with ES-SCLC in the 1L setting
- A total of ~123 patients with ES-SCLC will be included; key enrollment criteria are presented in **Table 1**
- The study comprises 2 parts, each with 2 cohorts (Part A [Phase 1b; safety run-in] and Part B [Phase 2; dose optimization])
- The study will investigate I-DXd + atezolizumab as maintenance therapy in patients who have completed 1L SOC induction, and induction with I-DXd + atezolizumab + carboplatin followed by maintenance with I-DXd + atezolizumab in treatment-naive patients (**Figure 2**)
- The primary endpoint is safety; study endpoints are presented in **Table 2**
- Patients are enrolling in the US, Japan, France, and Spain (**Figure 3**)

Table 1. Key enrollment criteria

General key inclusion criteria	Key exclusion criteria
• Histologically or cytologically confirmed diagnosis of ES-SCLC requiring 1L therapy	• Prior treatment with orlotamab, enoblituzumab, or other B7-H3–targeted agents, including I-DXd
• Aged ≥18 years or minimal legal adult age (whichever is greater)	• Prior discontinuation of an ADC that consists of an exatecan derivative (eg, trastuzumab deruxtecan) due to treatment-related toxicities
• ECOG PS 0–1	• Prior treatment with CD137 agonists or ICIs, except for atezolizumab for Part A Cohort 1 and Part B Cohort 1
• Patients with asymptomatic brain metastases (untreated or previously treated) are eligible	• Clinically active brain metastases, spinal cord compression, or leptomeningeal carcinomatosis
Cohort-specific key inclusion criteria	• Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses
• Part A Cohort 1 and Part B Cohort 1: – Received 4 cycles of 1L induction therapy with carboplatin, etoposide, and atezolizumab for ES-SCLC without progression per RECIST 1.1 as assessed by the investigator	• History of ILD/pneumonitis that required corticosteroids; current or suspected ILD/pneumonitis
	• Uncontrolled or significant cardiovascular disease
• Part A Cohort 2 and Part B Cohort 2: – Received no prior treatment for ES-SCLC – ≥1 measurable lesion according to RECIST 1.1 on CT or MRI as assessed by the investigator – ≥1 lesion amenable to core biopsy	• Known, uncontrolled HIV infection; active or uncontrolled HBV or HCV infection; uncontrolled systemic bacterial, fungal, or viral infection; or active, known, or suspected autoimmune disease

Figure 2. Study design



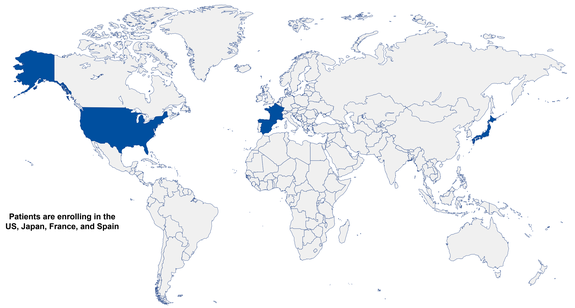
At both doses (8 mg/kg and 12 mg/kg), I-DXd is administered as an IV infusion Q3W[c]

[a]Randomization stratified by lactate dehydrogenase (≤ULN vs ULN) and ECOG performance status (0 vs 1), as determined at induction baseline. [b]Long-term follow-up will occur to assess survival and tumor progression until PD for patients who discontinue treatment for reasons other than PD, and to collect information on further anticancer treatments. [c]Atezolizumab is administered as an IV infusion Q3W at a dose of 1,200 mg; carboplatin is administered as an IV infusion Q3W, AUC 5; etoposide is administered as an IV infusion Q3W on Day 1 to Day 3 at a dose of 100 mg/m^2.

Table 2. Study endpoints

Primary endpoints	
• Safety (DLTs [Part A] and TEAEs [Parts A and B])	
Secondary endpoints	
• PFS	Assessed by BICR and investigator per RECIST 1.1
• ORR	
• DCR	
• DOR	
• CBR	
• TTR	
• Best percentage change in the sum of diameters of measurable tumors	
• OS	
• Pharmacokinetics	
• Immunogenicity	

Figure 3. Enrollment status



ACKNOWLEDGMENTS

This study is sponsored by Daiichi Sankyo, Inc. In October 2023, Daiichi Sankyo entered into a global development and commercialization collaboration agreement with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA for ifinatamab deruxtecan (I-DXd).

Medical writing support was provided by Sultana Jahan, PhD, on behalf of BOLDSCIENCE©, Inc., and was funded by Daiichi Sankyo, Inc. and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Editorial support was provided in accordance with Good Publication Practice guidelines (https://www.ismpp.org/gpp-2022).

These data were previously presented at the 2024 European Society for Medical Oncology Congress.

ABBREVIATIONS

1L, first-line; **ADC**, antibody–drug conjugate; **AUC**, area under the curve; **B7-H3**, B7 homolog 3; **BICR**, blinded independent central review; **CBR**, clinical benefit rate; **CD**, cluster of differentiation; **CR**, complete response; **CT**, computed tomography; **DCR**, disease control rate; **DLT**, dose-limiting toxicity; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ES**, extensive-stage; **HBV**, hepatitis B virus; **HCV**, hepatitis C virus; **HIV**, human immunodeficiency virus; **ICI**, immune checkpoint inhibitor; **I-DXd**, ifinatamab deruxtecan; **IgG1**, immunoglobulin G1; **ILD**, interstitial lung disease; **IV**, intravenous; **mAb**, monoclonal antibody; **MRI**, magnetic resonance imaging; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **PR**, partial response; **Q3M**, every 3 months; **Q3W**, every 3 weeks; **R**, randomization; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours, version 1.1; **SCLC**, small cell lung cancer; **SD**, stable disease; **SOC**, standard of care; **TEAE**, treatment-emergent adverse event; **TRAE**, treatment-related adverse event; **TTR**, time to response; **ULN**, upper limit of normal; **US**, United States.

REFERENCES

1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06362252. Accessed February 11, 2025.
2. Mathieu L, et al. *Oncologist*. 2021;26:433–438.
3. Horn L, et al. *N Engl J Med*. 2018;379:2220–2229.
4. Althoff FC, et al. *Front Oncol*. 2023;13:1273478.
5. Getu AA, et al. *Mol Cancer*. 2023;22:43.
6. Dong P, et al. *Front Oncol*. 2018;8:264.
7. Wang L, et al. *Tumour Biol*. 2016;37:2961–2971.
8. Gay CM, et al. *J Clin Oncol*. 2024;42(Suppl 16). Abstract 8088.
9. Miller CD, et al. *Cancer Res Commun*. 2024;4:1369–1379.
10. Qiu MJ, et al. *Front Oncol*. 2021;11:600238.
11. Yamato M, et al. *Mol Cancer Ther*. 2022;21:635–646.
12. Rudin CM, et al. Oral presentation at the World Conference on Lung Cancer. September 7–10, 2024; San Diego, CA, USA. Presentation OA04.03.
13. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06203210. Accessed February 11, 2025.
14. Daiichi Sankyo. Data on file.
15. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173–185.
16. Ogitani Y, et al. *Cancer Sci*. 2016;107:1039–1046.

Presented at the Japanese Society of Medical Oncology Annual Meeting; March 6–8, 2025; Kobe, Japan.

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