IDeate-Esophageal01: A Phase 3, randomized, open-label study of ifinatamab deruxtecan (I-DXd) in patients with pretreated advanced/metastatic esophageal squamous cell carcinoma

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OBJECTIVES

- IDeate-Esophageal01 (NCT06644781) is a global, multicenter, randomized, open-label, Phase 3 trial in ~510 adults with unresectable locally advanced/metastatic ESCC[1]
- The study will evaluate the efficacy and safety of I-DXd compared with investigator's choice of chemotherapy (paclitaxel, docetaxel, or irinotecan) in patients with unresectable locally advanced/metastatic ESCC, who have PD after a maximum of 1 prior line of systemic therapy with platinum-based chemotherapy (PBC) and an ICI[1]

INTRODUCTION

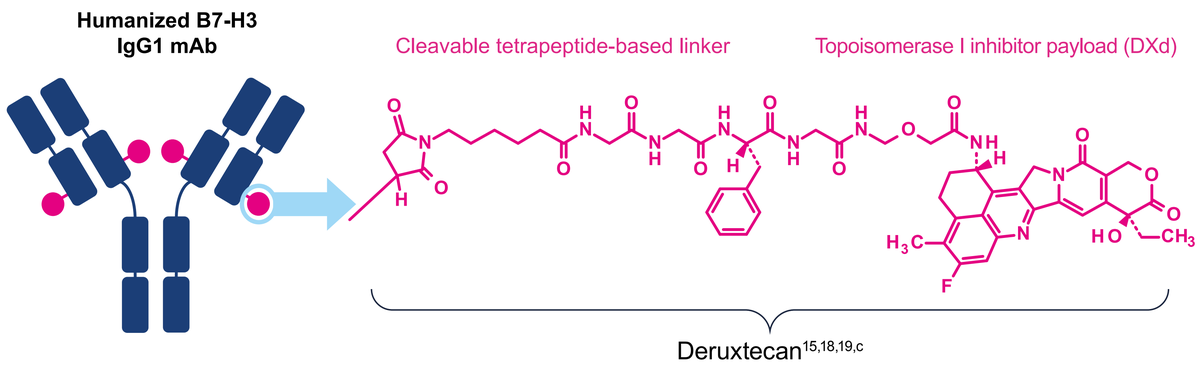
- ESCC accounts for 85–90% of esophageal cancers and is most prevalent in Eastern Asia, where mortality rates are also the highest[2,3]
- Standard-of-care 1L treatment for ESCC includes PBC + ICI, which is associated with median OS of only ~13–15 months[4–7]
- Prognosis in the 2L setting is even poorer, and treatment for patients with progression on 1L ICI-containing regimens is limited to chemotherapy alone (median OS, 6.3–8.4 months)[4,5,8–10]
- B7-H3 (CD276), a type 1 transmembrane protein belonging to the B7 family, is highly expressed in many solid tumors but shows minimal or no expression in normal tissues[11–13]
  - Patients with ESCC tumors with high B7-H3 expression had reduced survival rates compared with patients with ESCC tumors with low B7-H3 expression[13,14]
- I-DXd is a B7-H3–directed ADC comprising a B7-H3 mAb linked to a topoisomerase I inhibitor payload (DXd) via a stable cleavable linker, designed to enhance selective tumor-cell death and reduce systemic exposure to the payload[15] (**Figure 1**)
- In the Phase 1/2 IDeate-PanTumor01 study (NCT04145622), which enrolled 10 different solid tumor types, I-DXd 4.8–12.0 mg/kg demonstrated promising efficacy among 28 patients with pretreated ESCC (median 4 prior lines of therapy [LOTs]) with an ORR of 21.4% and median OS of 7.0 months (median follow-up, 14.9 months)[16,17]
  - I-DXd showed a manageable safety profile that was consistent across tumor types in IDeate-PanTumor01[17]
- Here, we describe IDeate-Esophageal01 (NCT06644781), a Phase 3, global, multicenter, randomized, open-label study evaluating the efficacy and safety of I-DXd compared with investigator's choice of chemotherapy (paclitaxel, docetaxel, or irinotecan) in patients with unresectable locally advanced/metastatic ESCC[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[15,a,b]

The **linker** binds the mAb to the payload
2. Plasma-stable linker–payload[15,a]
3. Tumor-selective cleavable linker[15,a]

The **payload** induces cell death when delivered to the tumor
4. Topoisomerase I inhibitor[15,18,a]
5. High potency[15,a]
6. Short systemic half-life[15,a,b]
7. Bystander antitumor effect[18,19,a]



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

METHODS

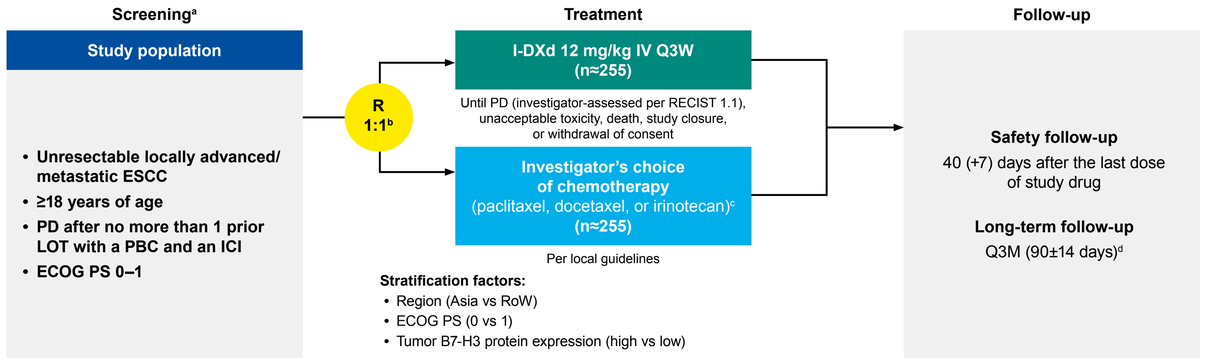
- IDeate-Eosphageal01 (NCT06644781) is a global, multicenter, randomized, open-label, Phase 3 trial in patients with unresectable locally advanced/metastatic ESCC who have PD after a maximum of 1 prior line of systemic therapy with a PBC and an ICI
- Approximately 510 adult patients with unresectable locally advanced/metastatic ESCC will be enrolled
- The study will be divided into three parts: Screening, Treatment, and Follow-up (**Figure 2**)
- Screening: patient eligibility will be confirmed within 28 days following signing the informed consent form; select enrollment criteria are presented in **Table 1**
- Treatment: enrolled patients will be randomized 1:1 to receive either I-DXd 12 mg/kg IV Q3W or investigator's choice of chemotherapy (paclitaxel, docetaxel, or irinotecan; selected prior to randomization and administered as monotherapy)
  - Randomization is stratified by region (Asia vs RoW), ECOG PS (0 vs 1), and tumor B7-H3 protein expression (high vs low)
  - Enrolled patients will receive I-DXd 12 mg/kg IV Q3W until radiographic disease progression (investigator-assessed per RECIST 1.1), unacceptable toxicity, death, or another reason per protocol
  - Radiographic tumor assessments will occur at baseline and every 6 weeks (±7 days) from C1D1 for the first 48 weeks and every 12 weeks (±7 days) thereafter
- Follow-up: upon permanent discontinuation of the study drug, patients will have a safety follow-up visit 40 (+7) days after the last treatment dose, followed by long-term follow-up visits at least Q3M (±14 days)

Table 1. Select enrollment criteria

Select inclusion criteria	Select exclusion criteria
• ≥18 years of age	• Prior treatment with orlotamab, enoblituzumab, or other B7-H3–targeted agents, including I-DXd
• ECOG PS 0–1 within 7 days prior to C1D1	• Received any topoisomerase inhibitor
• Has histologically or cytologically documented unresectable locally advanced/metastatic ESCC	• Histologically or cytologically confirmed adenosquamous carcinoma subtype
• PD after a maximum of 1 prior LOT with PBC and an ICI	• Ineligible for all investigator's choice of chemotherapy due to prior progression or intolerance
• A pretreatment tumor biopsy not previously irradiated or an archival tumor sample collected following completion of most recent systemic therapy; the sample must be evaluable for B7-H3 expression	• Clinically active brain metastasis, spinal cord compression, or leptomeningeal carcinomatosis, defined as untreated or symptomatic
• ≥1 measurable lesion according to RECIST 1.1 on CT or MRI as assessed by the investigator	• History of ILD/pneumonitis that required corticosteroids; current or suspected ILD/pneumonitis
• Patients with asymptomatic brain metastases (untreated or previously treated) are eligible	• Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses

- Study endpoints are presented in **Table 2**
  - An interim analysis will be conducted for OS
  - The OS for each treatment group will be compared using a stratified log-rank test and Kaplan–Meier estimates; median OS will be analyzed using the Brookmeyer and Crowley method to determine 95% CIs

Figure 2. Study design



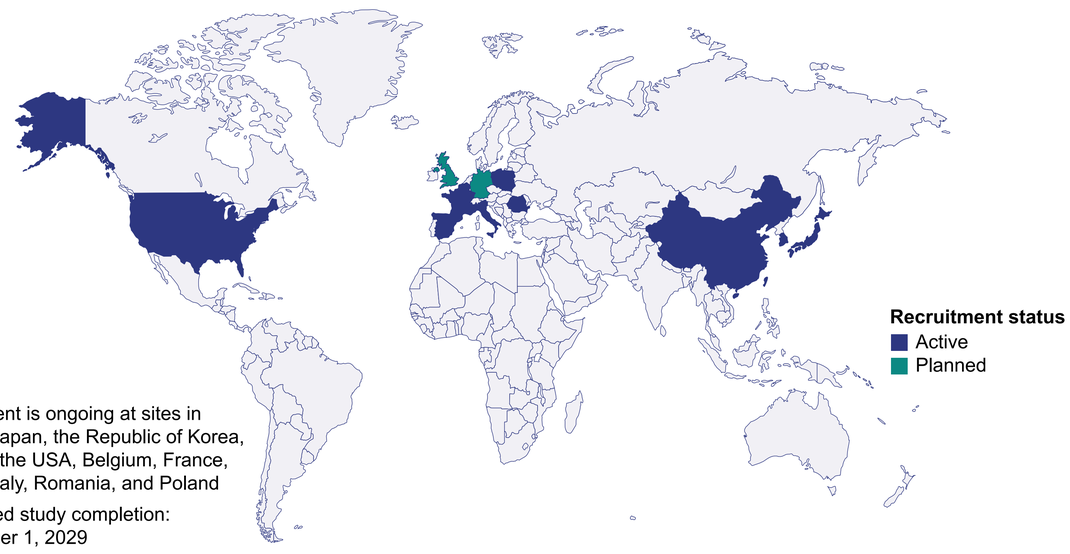
[a]28-day screening can be extended up to 42 days for patients with an initial B7-H3 result of NE who require retesting and/or a new biopsy. [b]A maximum of 3 days will be allowed between randomization and C1D1. [c]Dosing regimen as per SOC according to local and/or country-specific guidelines. [d]Long-term follow-up will commence after the safety follow-up, and will assess survival and collect further anticancer treatment data until death, withdrawal of consent, or a criterion for withdrawal from the study is met.

Table 2. Study endpoints

Primary endpoint	
• OS	
Key secondary endpoints	
• PFS	Assessed by BICR per RECIST 1.1
• ORR	
Secondary endpoints	
• DOR	Assessed by BICR per RECIST 1.1
• DCR	
• Patient-reported outcomes	
• Incidence of TEAEs, serious TEAEs, and AESIs	
• Immunogenicity	
• Biomarker analysis	
• Pharmacokinetics	

- Patients are currently being enrolled in China, Japan, the Republic of Korea, Taiwan, the USA, Belgium, France, Spain, Italy, Romania, and Poland (**Figure 3**)

Figure 3. Study site locations



Enrollment is ongoing at sites in China, Japan, the Republic of Korea, Taiwan, the USA, Belgium, France, Spain, Italy, Romania, and Poland

Estimated study completion: November 1, 2029

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ABBREVIATIONS

1L, first-line; **2L**, second-line; **ADC**, antibody–drug conjugate; **AESI**, adverse event of special interest; **B7-H3**, B7 homolog 3; **BICR**, blinded independent central review; **C1D1**, Cycle 1 Day 1; **CD**, cluster of differentiation; **CI**, confidence interval; **CT**, computed tomography; **DCR**, disease control rate; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ESCC**, esophageal squamous cell carcinoma; **ESMO**, European Society for Medical Oncology; **ICI**, immune checkpoint inhibitor; **I-DXd**, ifinatamab deruxtecan; **IgG1**, immunoglobulin G1; **ILD**, interstitial lung disease; **IV**, intravenous; **LOT**, line of therapy; **mAb**, monoclonal antibody; **MRI**, magnetic resonance imaging; **NE**, not evaluable; **ORR**, objective response rate; **OS**, overall survival; **PBC**, platinum-based chemotherapy; **PD**, progressive disease; **PFS**, progression-free survival; **Q3M/W**, every 3 months/weeks; **R**, randomization; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours, version 1.1; **RoW**, rest of world; **SOC**, standard of care; **TEAE**, treatment-emergent adverse event.

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DISCLOSURES

Dr Kato is a member of boards and/or advisory boards and has financial interests in AstraZeneca, BeiGene, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, MSD, Oncolys BioPharma, Ono Pharmaceutical, and Taiho Pharmaceutical. He has served on speaker bureaus for Bristol Myers Squibb, Eli Lilly, MSD, Ono Pharmaceutical, and Taiho Pharmaceutical. Dr Kato has personal and institutional relationships with BeiGene, Bristol Myers Squibb, MSD, Oncolys BioPharma, Ono Pharmaceutical, and Taiho Pharmaceutical; institutional relationships with AstraZeneca and Daiichi Sankyo; and a personal relationship with Eli Lilly.

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