IDeate-PanTumor02: A Phase 1b/2 study to evaluate the efficacy and safety of ifinatamab deruxtecan (I-DXd) in patients with recurrent or metastatic solid tumors

TPS3157

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OBJECTIVES

- IDeate-PanTumor02 (NCT06330064)[1] is a global, multicenter, open-label, single-arm, parallel-cohort, Phase 1b/2 study in up to 530 adults with recurrent or metastatic solid tumors
- The study will evaluate the efficacy and safety of I-DXd in patients with recurrent or metastatic solid tumors who have received ≥1 prior line of systemic therapy for the selected tumor indication[1]

INTRODUCTION

- B7-H3 (CD276), a type 1 transmembrane protein belonging to the B7 family, shows minimal or no expression in normal tissues but is highly expressed in many solid tumors[2–4]
- High B7-H3 expression is associated with poorer prognosis and shorter OS compared with absent or low B7-H3 levels in multiple tumor types[4–11]
- 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[12] (**Figure 1**)

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

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

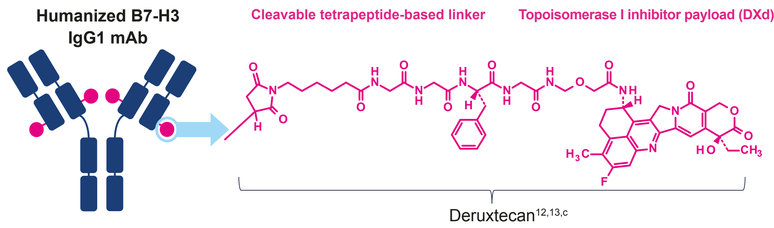
1. Optimized drug-to-antibody ratio of ~4[12,13,a,b]

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

2. Plasma-stable linker–payload[12,13,a]
3. Tumor-selective cleavable linker[12,13,a]

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

4. Topoisomerase I inhibitor[12–14]
5. High potency[12,13,a]
6. Short systemic half-life[12,13,a,b]
7. Bystander antitumor effect[13–15,a]



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

- In the Phase 1/2 IDeate-PanTumor01 study (NCT04145622), which included 10 different solid tumor types, I-DXd demonstrated promising efficacy among 139 heavily pretreated patients treated at doses of 4.8–16.0 mg/kg, with an ORR of 27.3%[16]
  - Objective responses to I-DXd were observed in 6 of the 7 tumor types in which ≥5 patients were enrolled (SCLC, ESCC, mCRPC, sqNSCLC, HNSCC, and endometrial cancer), with stable disease being the best overall response observed in the seventh tumor type (sarcoma)[13,16]
- In the dose-optimization part of the Phase 2 IDeate-Lung01 study (NCT05280470), I-DXd demonstrated promising efficacy in 88 patients with pretreated ES-SCLC, with better outcomes at the 12-mg/kg than the 8-mg/kg dose level[17]:
  - 8 mg/kg (n=46): ORR, 26.1%; median OS, 9.4 months (median follow-up, 14.6 months)
  - 12 mg/kg (n=42): ORR, 54.8%; median OS, 11.8 months (median follow-up, 15.3 months)
- In both studies, I-DXd showed a manageable safety profile, and this was consistent across tumor types in IDeate-PanTumor01[16,17]
- We describe IDeate-PanTumor02, a Phase 1b/2 study evaluating the efficacy and safety of I-DXd in patients with recurrent or metastatic solid tumors[1]

METHODS

- IDeate-PanTumor02 (NCT06330064) is a global, multicenter, open-label, single-arm, parallel-cohort, Phase 1b/2 study in patients with recurrent or metastatic solid tumors who have received ≥1 prior line of systemic therapy for the selected tumor indication
- The study includes 13 cohorts: Endometrial cancer; HNSCC; PDAC; CRC; HCC; adenocarcinoma of the esophagus, GEJ, or stomach; urothelial carcinoma; ovarian cancer; cervical cancer; biliary tract cancer; HER2-low BC (defined as IHC 2+/ISH− or IHC 1+ [ISH− or untested]); HER2-negative BC (defined as IHC 0 [ISH− or untested]); and cutaneous melanoma
- Key enrollment criteria for all patients are presented in **Table 1**, and select cohort-specific enrollment criteria are presented in **Table 2**
- The study will include up to 530 adult patients and be divided into 2 parts: Stage 1 (≈20 patients per tumor type) and Stage 2 (≈40 patients per tumor type; **Figure 2**)
  - Each cohort begins with Stage 1 and may progress to Stage 2 if suitable safety and efficacy data are observed, based on the totality of data, including the benefit–risk assessment, duration and depth of response, and the observed safety profile
- All cohorts except the HCC cohort will receive I-DXd 12 mg/kg Q3W
- The HCC cohort includes a safety run-in part to assess tolerability and the potential need for dose adjustment
- The primary endpoints are ORR per investigator (all cohorts) and safety (HCC safety run-in only); study endpoints are presented in **Table 3**
- Patients are being enrolled across sites in Asia, Australia, Europe, North America, and South America (**Figure 3**)

Table 1. Key enrollment criteria

General key inclusion criteria
• Recurrent or metastatic: Endometrial cancer; HNSCC; PDAC; CRC; HCC; adenocarcinoma of the esophagus, GEJ, or stomach; urothelial carcinoma; ovarian cancer; cervical cancer; biliary tract cancer; HER2-low BC; HER2-negative BC; or cutaneous melanoma
• Age ≥18 years
• ≥1 prior line of systemic therapy for the selected tumor indication[a]
• ≥1 measurable lesion per RECIST 1.1
• Radiologically documented PD on or after previous SOC regimen in the advanced/metastatic setting
• ECOG PS 0–1
• Patients with asymptomatic brain metastases (untreated or previously treated) are eligible
General key exclusion criteria
• Prior treatment with orlotamab, enoblituzumab, or other B7-H3–targeted agents, including I-DXd
• Prior discontinuation of an ADC that consists of an exatecan derivative (eg, T-DXd) due to treatment-related toxicities
• Clinically active brain metastasis, spinal cord compression, or leptomeningeal carcinomatosis
• History of ILD/pneumonitis that required corticosteroids; current or suspected ILD/pneumonitis

[a]Prior treatments and LOTs may vary by tumor type – see Table 2 for details.

Table 2. Select cohort-specific enrollment criteria

Prior therapy requirements for each cohort (additional enrollment criteria may apply)
• **Endometrial cancer:** Relapse or progression after a platinum-containing systemic treatment and an ICI-containing regimen (combination or sequential)[a]
• **HNSCC:** Progression after platinum-based and ICI therapy (combination or sequential)[a]
• **PDAC:** Relapse or progression after 1 prior line of gemcitabine-based systemic therapy[b,c,d]
• **CRC:** Relapse or progression after 1 prior line of systemic therapy including a fluoropyrimidine + oxaliplatin ± anti-VEGF or anti-EGFR mAb therapy; pathologically or cytologically documented unresectable or metastatic CRC with microsatellite stable status[b,d]
• **HCC:** Relapse or progression after 1 prior line of an ICI-containing regimen (combination or monotherapy)[a,c]
• **Adenocarcinoma of the esophagus, GEJ, or stomach:** Relapse or progression after 1 prior line of systemic therapy[c,e]
• **Urothelial carcinoma:** Relapse or progression after ≥1 prior line of ICI-containing regimen, and 1 prior line of systemic chemotherapy (in combination with other anticancer therapy or separately)[a,f]
• **Ovarian cancer:** ≥1 prior line of platinum-based therapy and bevacizumab (if eligible)[a]
• **Cervical cancer:** ≥1 prior line of systemic therapy[a,c,g]
• **Biliary tract cancer:** Relapse or progression after ≥1 prior line of systemic therapy[b]
• **HER2-low BC:** Progression on or after T-DXd; relapse or progression after 2–3 prior lines of systemic therapy[a,h]
• **HER2-negative BC:** Relapse or progression after 2–3 prior lines of systemic therapy[a,h]
• **Cutaneous melanoma:** Progression on or after ≥1 prior line of ICI-based therapy[i]

[a]In addition to the required LOTs listed, patients with actionable target mutations should have received prior treatment with targeted therapy (with ≤3 prior LOTs for patients with endometrial carcinoma or carcinosarcoma, urothelial carcinoma, HER2-low BC, or HER2-negative BC, and ≤2 prior LOTs for patients with unresectable or metastatic HNSCC or HCC). [b]Two prior LOTs in patients with PDAC, CRC, or biliary tract cancer who have received prior targeted therapy. [c]In the locally advanced or metastatic setting. [d]Patients with prior treatment with topoisomerase I inhibitors (irinotecan or topotecan) are not eligible. [e]Patients with PD-L1–positive or MSI-H/dMMR tumors should receive ICIs (if eligible) if SOC in the country; patients with a known history of HER2 positivity or other actionable target mutations must have received prior targeted therapy. [f]Patients must have received ≥1 prior line of enfortumab vedotin in countries where it is approved and available. [g]Patients must have received anti–PD-L1 therapy (if eligible) if part of SOC in the country. [h]Including patients with HR+ BC who have received endocrine therapy and an additional 2–3 prior lines of systemic therapy in the metastatic setting. [i]Patients with *BRAF*-mutated melanoma or other actionable target mutations must have also had progression on targeted therapy.

Table 3. Study endpoints

Primary endpoints	
• ORR assessed by investigator per RECIST 1.1	
• DLTs and TEAEs in the HCC cohort (safety run-in part only)	
Secondary endpoints	
• Incidence of TEAEs, serious TEAEs, and AESIs	
• DOR	• Assessed by investigator per RECIST 1.1
• PFS	
• DCR	
• OS	
• PK	
• Immunogenicity	

Figure 3. Study site locations

Enrollment is planned in study sites in 18 countries across Asia, Australia, Europe, North America, and South America

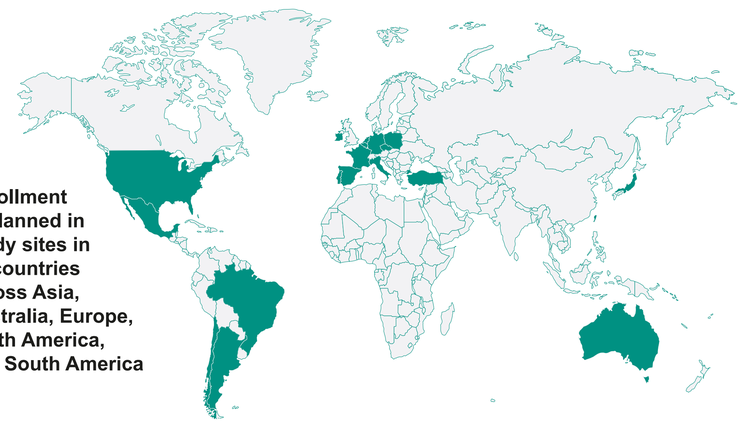


Figure 2. Study design

[a]Prior treatments and LOTs may vary by tumor type – see Table 2 for details. [b]The safety run-in will determine the dose used to further treat this cohort. [c]Comprising patients treated in the safety run-in part and an additional 11–17 patients. [d]Long-term follow-up will commence after the safety follow-up and will assess survival and tumor progression until PD for patients discontinuing treatment for other reasons and collect further anticancer treatment data until the sponsor deems survival data sufficient.

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ABBREVIATIONS

ADC, antibody–drug conjugate; **AESI**, adverse event of special interest; **B7-H3**, B7 homolog 3; **BC**, breast cancer; ***BRAF***, B-Raf proto-oncogene; **CD**, cluster of differentiation; **CRC**, colorectal cancer; **DCR**, disease control rate; **DLT**, dose-limiting toxicity; **dMMR**, deficient mismatch repair; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **EGFR**, epidermal growth factor receptor; **ESCC**, esophageal squamous cell carcinoma; **(ES-)SCLC**, (extensive-stage) small cell lung cancer; **GEJ**, gastroesophageal junction; **HCC**, hepatocellular carcinoma; **HER2**, human epidermal growth factor receptor 2; **HNSCC**, head and neck squamous cell carcinoma; **HR+**, hormone receptor-positive; **ICI**, immune checkpoint inhibitor; **I-DXd**, ifinatamab deruxtecan; **IgG1**, immunoglobulin G1; **IHC**, immunohistochemistry; **ILD**, interstitial lung disease; **ISH**, in situ hybridization; **LOT**, line of therapy; **mAb**, monoclonal antibody; **mCRPC**, metastatic castration-resistant prostate cancer; **MSI-H**, microsatellite instability-high; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PDAC**, pancreatic ductal adenocarcinoma; **PD-L1**, programmed death ligand 1; **PFS**, progression-free survival; **PK**, pharmacokinetics; **Q1Y**, annually; **Q3M**, every 3 months; **Q3W**, every 3 weeks; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours, version 1.1; **SOC**, standard of care; **sqNSCLC**, squamous non-small cell lung cancer; **T-DXd**, trastuzumab deruxtecan; **TEAE**, treatment-emergent adverse event; **VEGF**, vascular endothelial growth factor.

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