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Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial

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assisted with data interpretation, writing of the report, reviewing the manuscript, and the decision to submit for publication.

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Running head (65 characters or fewer including spaces): Efficacy and safety of T-DXd in HER2-expressing solid tumors

Previous presentation of study: Interim analysis (data cutoff, Nov 2022) presented at the American Society of Clinical Oncology 2023 *(Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-expressing solid tumors: DESTINY-PanTumor02 (DP-02) interim results. JCO. 2023;41(17_suppl):LBA3000).*

Context Summary:

Key objective: What is the efficacy and safety of trastuzumab deruxtecan (T-DXd; 5.4 mg/kg once every 3 weeks) in previously treated patients with locally advanced or metastatic human epidermal growth factor 2 (HER2)-expressing (immunohistochemistry [IHC] 3+/2+) solid tumors?

Knowledge generated: DESTINY-PanTumor02 demonstrated that treatment with T-DXd resulted in durable responses across multiple tumor types, alongside clinically meaningful rates of progression-free survival and overall survival, with the greatest benefit observed in the HER2 IHC 3+ population. The safety profile was consistent with the known profile for T-DXd, including incidence of interstitial lung disease.

Relevance: Trastuzumab deruxtecan provides meaningful benefit for patients with multiple types of solid tumors that express HER2, particularly for those whose tumors express HER2 at the 3+ level on central review.

Relevance section written by JCO Associate Editor Gini Fleming, MD.

ABSTRACT

PURPOSE

Trastuzumab deruxtecan (T-DXd) is a human epidermal growth factor 2 (HER2)-directed antibody-drug conjugate approved in HER2-expressing breast and gastric cancers and HER2-mutant non-small cell lung cancer. Treatments are limited for other HER2-expressing solid tumors.

PATIENTS AND METHODS

This open-label phase II study evaluated T-DXd (5.4 mg/kg Q3W) for HER2-expressing (immunohistochemistry [IHC] 3+/2+ by local or central testing) locally advanced or metastatic disease after ≥1 systemic treatment, or without alternative treatments. Primary endpoint was investigator-assessed confirmed objective response rate (ORR). Secondary endpoints included safety, duration of response (DOR), progression-free (PFS), and overall survival (OS).

RESULTS

At primary analysis, 267 patients received treatment across seven tumor cohorts: endometrial, cervical, ovarian, bladder, biliary tract, pancreatic, and other. Median follow-up was 12.75 months. In all patients: ORR, 37.1% (n=99; 95% CI, 31.3–43.2) with responses in all cohorts; median DOR, 11.3 months (95% CI, 9.6–17.8); median PFS, 6.9 months (95% CI, 5.6–8.0); median OS, 13.4 months (95% CI, 11.9–15.5). In patients with central HER2 IHC 3+ expression (n=75): ORR, 61.3% (95% CI, 49.4–72.4); median DOR, 22.1 months (95% CI, 9.6–not reached); median PFS, 11.9 months (95% CI, 8.2–13.0); median OS, 21.1 months (95% CI, 15.3–29.6). Grade ≥3 drug-related adverse events were observed in 40.8% of patients; 10.5%

experienced adjudicated drug-related interstitial lung disease (ILD), with three deaths.

CONCLUSION

Our study demonstrates durable clinical benefit, meaningful survival outcomes, and safety consistent with the known profile (including ILD) in pre-treated patients with HER2-expressing tumors receiving T-DXd. Greatest benefit was observed for the IHC 3+ population. These data support the potential role of T-DXd as a tumor-agnostic therapy for patients with HER2-expressing solid tumors.

INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine kinase receptor involved in the stimulation of cell proliferation, differentiation, and survival.[1] HER2 overexpression can occur in a range of solid tumors, including breast, gastric, biliary tract, bladder, pancreatic, and gynecological tumors.[2] HER2 overexpression is associated with a biologically aggressive tumor phenotype, poor prognosis, increased risk of disease recurrence, and limited benefit from chemotherapy.[1,3–5] HER2-directed therapy is standard-of-care for HER2-expressing unresectable or metastatic breast cancer, HER2-positive locally advanced or metastatic gastric cancers, colorectal and gastroesophageal junction adenocarcinomas, and HER2-mutant non-small cell lung cancer.[6–9] However, many patients with other HER2-expressing solid tumors will progress on standard therapy, with poor prognosis and limited alternatives.[5,10–13] This represents an opportunity to improve outcomes for such patients with novel HER2-targeted therapeutics.

Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody-drug conjugate composed of a humanized immunoglobulin G1 anti-HER2 monoclonal antibody, a tetrapeptide-based cleavable linker, and a potent topoisomerase I inhibitor payload.[14] T-DXd is currently approved in the USA and EU for treatment of HER2-expressing breast cancer, HER2-positive gastric or gastroesophageal junction adenocarcinoma, and in the USA and Japan for HER2-mutant non-small cell lung cancer.[15–17] In early-phase studies, T-DXd demonstrated antitumor activity in a range of HER2-expressing malignancies, including colorectal, salivary gland, biliary tract, and endometrial cancer.[18] In August 2023, T-DXd was granted breakthrough therapy designations in the USA for adult patients with unresectable or metastatic HER2-positive (immunohistochemistry [IHC] 3+) solid tumors that have progressed

following prior treatment and have no satisfactory alternatives, and for patients with HER2-positive (IHC 3+) metastatic colorectal cancer who have received ≥2 prior treatment regimens.[19] The aim of this study (NCT04482309) was to assess efficacy and safety of T-DXd in patients with selected, locally advanced, metastatic, or unresectable HER2-expressing solid tumors.

METHODS

Study Design and Participants

This open-label, multicenter, phase II study (NCT04482309) evaluated the efficacy and safety of T-DXd 5.4 mg/kg Q3W in patients with previously treated HER2-expressing solid tumors in seven cohorts.

Eligible patients were ≥18 years, had histologically confirmed locally advanced, unresectable, or metastatic biliary tract, bladder, cervical, endometrial, ovarian, pancreatic, or other solid cancers (excluding breast, colorectal, gastric, and non-small cell lung cancers), who progressed after ≥1 systemic treatment, or had no satisfactory alternative treatment options; Eastern Cooperative Oncology Group performance status of 0–1;[20] HER2-overexpressing tumors with IHC 3+/2+ (local or central testing) scored using current American Society of Clinical Oncology/College of American Pathology guidelines for scoring HER2 in gastric cancer;[21] and had ≥1 investigator-assessed measurable lesion on the basis of Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).[22] Patients with non-infectious interstitial lung disease (ILD)/pneumonitis requiring steroids, or if suspected ILD/pneumonitis could not be ruled out by imaging at screening, were excluded. HER2 expression for eligibility was based on local assessment, where available. Otherwise, eligibility was determined by central testing. HER2 IHC status was assessed centrally using HER2 HercepTest™ (DAKO) and scored according to gastric-specific criteria. Prior HER2-targeted therapy was permitted. Eligibility criteria are provided in the Appendix Methods.

The study protocol was approved by the institutional review board at each site and was conducted in accordance with the International Conference on Harmonization

Good Clinical Practice, the Declaration of Helsinki, and local regulations on the conduct of clinical research. All patients provided written informed consent before study participation.

Procedures

T-DXd was administered intravenously every 3 weeks at 5.4 mg/kg of body weight. RECIST scans were performed at screening and every 6 weeks until documented disease progression (RECIST 1.1) or withdrawal of consent. Treatment continued until documented disease progression (RECIST 1.1), withdrawal of consent, or when discontinuation criteria were met. Dose interruptions and/or reduction and supportive therapy were permitted for clinically significant and/or unacceptable toxicity. For suspected ILD/pneumonitis, treatment was interrupted pending evaluation, and all events were followed until resolution (including after discontinuation) regardless of severity (Appendix Methods).

Endpoints

The primary endpoint was investigator-assessed confirmed objective response rate (ORR), defined as the proportion of patients with a confirmed complete or partial response by RECIST 1.1 (Appendix Methods). Secondary efficacy endpoints included duration of response (DOR; time from date of first documented response [complete or partial] until the date of documented progression, or death in the absence of disease progression); disease control rate (percentage of patients with a best objective response of confirmed complete response or partial response, or with stable disease for at least 5 weeks after first dose); progression-free survival (PFS; time from first dose until date of objective disease progression or death regardless of withdrawal or receipt of another cancer therapy); and overall survival (OS; time from

date of first dose until death due to any cause). An independent central review per RECIST 1.1 was performed and reported alongside the investigator-assessed results for secondary outcomes.

Secondary safety endpoints included the occurrence of adverse events (including drug-related adverse events, serious adverse events, adverse events of special interest [ILD/pneumonitis and left ventricular dysfunction]), and changes in vital sign measurements and standard clinical laboratory parameters. Adverse events were coded and graded according to the Medical Dictionary for Regulatory Activities (version 26.0) and National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). Potential cases of ILD/pneumonitis were evaluated by an independent adjudication committee.

Statistical Analysis

A sample size of 40 patients per cohort was determined to provide sufficient precision for the estimation of objective response in each cohort (eg, for ORR 35%, exact CI would be [20.6–51.7]). Efficacy and safety results are presented by cohort and overall based on the full analysis set (patients who received at least one dose of study medication). Outcomes are reported in all patients enrolled by local and central testing; subgroup analyses by HER2 status are reported as confirmed by central testing alone. Descriptive statistics were used to summarize each endpoint. Kaplan-Meier estimations were used to describe DOR, PFS, and OS. Exact 95% CIs for binomial proportions were calculated using the Clopper-Pearson method.

RESULTS

Patients

Between October 7, 2020, and July 7, 2022, a total of 268 patients with HER2-expressing solid tumors were enrolled from >120 sites across 15 countries. Of these, 267 (99.6%) patients received at least one dose of study treatment and were included in the full analysis set; one patient withdrew before receiving treatment (Fig A1).

Median age was 62 (range 23–85) years. Patients had received a median of two lines of prior therapy (range 0–12; Table 1). Across all cohorts, 40.8% had received ≥3 prior lines, and 14.2% had received prior HER2 therapy (trastuzumab [12.4%], pertuzumab [1.9%], zanidatamab [1.5%], trastuzumab emtansine [1.1%], trastuzumab duocarmazine [0.4%], and/or tucatinib [0.4%]). The other tumors cohort included patients with salivary gland cancer (n=19), malignant neoplasm of unknown primary site (n=5), extramammary Paget's disease (n=3), cutaneous melanoma (n=2), oropharyngeal neoplasm (n=2), adenoid cystic carcinoma, head and neck cancer, lip and/or oral cavity cancer, esophageal adenocarcinoma, intestinal adenocarcinoma, appendiceal adenocarcinoma, esophageal squamous cell carcinoma, testicular cancer, and vulvar carcinoma (all n=1).

In total, 202 patients were enrolled based on local HER2 testing, and 65 patients were enrolled based on central HER2 testing. According to HER2 testing for eligibility, 111 patients were enrolled with IHC 3+ expression, 151 with IHC 2+ expression, and five with IHC 1+ expression (Table 1). Based on central testing, there were 75 patients with IHC 3+ expression, 125 with IHC 2+ expression, 25 with

IHC 1+ expression, 30 with IHC 0 expression, and 12 patients were unknown, owing to unavailable/unevaluable samples for central testing (Table A1).

At data cutoff (June 8, 2023), median follow-up duration across all cohorts was 12.75 months (range 0.4–31.6); 235 patients had discontinued treatment (progressive disease [n=167, 62.5%], any adverse event [n=32, 12.0%], death during study [n=18, 6.7%], patient decision [n=11, 4.1%], investigator decision [n=4, 1.5%], unknown [n=2, 0.7%], lost to follow-up [n=1, 0.4%]), and 32 (12.0%) patients remained on treatment. The median number of 21-day treatment cycles for all patients was eight.

Among the 267 patients, 99 patients (37.1%) [95% CI, 31.3–43.2] had a confirmed objective response by investigator assessment. Investigator-assessed ORRs in all patients by cohort (Fig 1 and Table A2) were 57.5% (95% CI, 40.9–73.0) endometrial; 50.0% (95% CI, 33.8–66.2) cervical; 45.0% (95% CI, 29.3–61.5) ovarian; 39.0% (95% CI, 24.2–55.5) bladder; 30.0% (95% CI, 16.6–46.5) other tumors; 22.0% (95% CI, 10.6–37.6) biliary tract; and 4.0% (95% CI, 0.1–20.4) pancreatic. In patients with centrally confirmed HER2 IHC 3+ expression (n=75), investigator-assessed ORRs by cohort (Fig 1) were 84.6% (n=13; 95% CI, 54.6–98.1) endometrial; 75.0% (n=8; 95% CI, 34.9–96.8) cervical; 63.6% (n=11; 95% CI, 30.8–89.1) ovarian; 56.3% (n=16; 95% CI, 29.9–80.2) bladder; 44.4% (n=9; 95% CI, 13.7–78.8) other tumors; 56.3% (n=16; 95% CI, 29.9–80.2) biliary tract; and 0% for pancreatic cancer (n=2). In the pancreatic cohort, no objective response was observed in the first 15 patients, and the cohort was closed for further recruitment according to prespecified futility criterion, by which time 25 patients had been enrolled. Investigator-assessed ORRs by central IHC 3+/2+ status are provided in Fig 1.

Responses were observed in patients who received (n=38; 36.8% [95% CI, 21.8–54.0]) or did not receive (n=227; 37.4% [95% CI, 31.1–44.1]) prior HER2 therapy. Across all tumor types, 100 patients (37.5%; 95% CI, 31.6–43.6) had a confirmed ORR by independent central review. By cohort, ORRs by independent central review in all patients were 57.5% (95% CI, 40.9–73.0) endometrial; 37.5% (95% CI, 22.7–54.2) cervical; 42.5% (95% CI, 27.0–59.1) ovarian; 41.5% (95% CI, 26.3–57.9) bladder; 35.0% (95% CI, 20.6–51.7) other tumors; 26.8% (95% CI, 14.2–42.9) biliary tract; and 12.0% (95% CI, 2.5–31.2) pancreatic.

Investigator-assessed median DOR (Fig 1C and Table A2) across all cohorts was 11.3 months (95% CI, 9.6–17.8), ranging from 5.7 months in the pancreatic cohort to 22.1 months in the other tumors cohort; median DOR was not reached in the endometrial cohort. In all HER2 subgroups, the longest median DOR was in patients with IHC 3+ (22.1 months [95% CI, 9.6–not reached]).

Investigator-assessed median PFS (Fig 2 and Table A2) was 6.9 months (95% CI, 5.6–8.0), ranging from 3.2 months in the pancreatic cohort to 11.1 months in the endometrial cohort. In all HER2 subgroups, the longest median PFS was in patients with IHC 3+ (11.9 months [95% CI, 8.2–13.0]). PFS by tumor cohort and HER2 status is provided in Fig 2 and Table A2.

Across all cohorts, median OS (Fig 3 and Table A2) was 13.4 months (95% CI, 11.9–15.5; 66% maturity), ranging from 5.0 months in the pancreatic cohort to 26.0 months in the endometrial cohort. In all HER2 subgroups, the longest median OS

was in patients with IHC 3+ (21.1 months [95% CI, 15.3–29.6]). OS by tumor cohort and HER2 status is provided in Fig 3 and Table A2.

Percentage change of target lesion size from baseline and a full breakdown of efficacy in the other tumors cohort are shown in Fig A2 and Table A3, respectively.

Among 267 treated patients (median follow-up of 12.75 months), ≥1 investigator-assessed drug-related adverse event was experienced by 226 (84.6%) patients (Table 2), with the most common being nausea (55.1%), anemia (27.7%), diarrhea (25.8%), vomiting (24.7%), and fatigue (24.7%; Table A4). Grade 3 or higher drug-related adverse events occurred in 109 (40.8%) patients, with the most common being neutropenia (10.9%) and anemia (10.9%). Serious drug-related adverse events occurred in 36 (13.5%) patients. Drug-related adverse events led to discontinuation in 23 (8.6%) patients and dose reduction in 54 (20.2%) patients. Drug-related adverse events and non-drug-related adverse events resulting in death occurred in four (1.5%) and 19 (7.1%) patients, respectively. Adjudicated drug-related events of ILD/pneumonitis occurred in 28 (10.5%) patients, with the majority as low grade (grade 1, n=7 [2.6%]; grade 2, n=17 [6.4%]). There was one (0.4%) grade 3 event and three (1.1%) fatal adjudicated drug-related cases of ILD/pneumonitis, one each in the biliary tract, endometrial, and other tumors cohorts.

DISCUSSION

In this phase II study, T-DXd demonstrated durable responses across multiple tumor types, alongside clinically meaningful PFS and OS in pre-treated patients. The highest response rates, and longest DOR, PFS, and OS were observed in tumors with IHC 3+ expression. Responses were also observed irrespective of prior HER2 therapy.

HER2 protein expression, gene amplification, and gene mutation have been identified as therapeutic targets in multiple tumor types.[23] However, HER2-targeted therapy is not currently approved beyond breast, gastric, colorectal, and lung cancer.[5,15,24] The tumor types investigated here were predefined based on epidemiological frequency, prevalence of HER2 expression and unmet medical need.[2,5] Investigations are supported by phase I clinical data of T-DXd and encouraging results from the HERALD phase II basket trial which assessed T-DXd in advanced solid tumors with HER2 amplification.[18,25]

Of note are the magnitudes of benefit observed in the endometrial, cervical, and ovarian cohorts; the highest ORRs were observed in these cohorts across all studied tumor types (57.5% endometrial; 50.0% cervical; 45.0% ovarian). To the best of our knowledge, this is the first report of a HER2-directed antibody-drug conjugate in these gynecological tumors. In the endometrial cohort, 77.5% of patients had ≥2 prior lines of therapy. The ORR in patients with HER2 IHC 3+ expression was 84.6%. In all patients with endometrial cancer, median PFS and OS were 11.1 months and 26.0 months, respectively. The clinically significant response and survival rates observed in this study are encouraging for HER2-expressing endometrial cancers, which are typically associated with high risk for progression

and poor survival rates.[10] In the cervical cohort, 85.0% of patients had ≥2 prior lines of therapy, and the ORR in patients with HER2 IHC 3+ expression was 75.0%. Median OS in this cohort was 13.6 months in all patients, not reached in IHC 3+ patients, and 11.5 months in IHC 2+ patients. These data are promising in a cohort with few treatment options and a typically low response rate to treatment.[11] The median number of prior treatments in the ovarian cohort was three, and 35.0% of patients had five or more prior lines of therapy; the median OS was 13.2 months in all patients and 20.0 months in patients with HER2 IHC 3+ expression. Results from the present study further support use of a HER2 antibody-drug conjugate for treating ovarian cancer, and the outcomes are promising for a disease subgroup with a high mortality rate.[12,26]

Although there was only one investigator-assessed responder in the pancreatic cohort (4.0%; closed to recruitment with 25 patients enrolled), when assessed by independent central review, three responses were observed (12.0%). PFS and OS results showed potential in the late-line pancreatic cancer setting; however, it is challenging to draw conclusions from this cohort owing to the low patient numbers, particularly in the IHC 3+ group.

Biliary tract cancer is uncommon[12] but has a high mortality rate[13] and limited clinical benefit from second-line chemotherapy.[27] The phase II trial of T-DXd in patients with unresectable or recurrent HER2-expressing biliary tract cancers showed promising activity in patients with HER2-positive (IHC 3+ and IHC 2+/in-situ hybridization+) biliary tract cancer.[28] The data in the DESTINY-PanTumor02 trial further support HER2 as a therapeutic target in biliary tract cancer where an ORR of 56.3% and OS of 12.4 months were observed in patients with IHC 3+ tumors.

Safety findings for T-DXd in this trial were consistent with the established safety profile.[15] A risk of pulmonary adverse events, primarily ILD/pneumonitis, has been observed in patients receiving T-DXd and is an important consideration for these patients.[29,30] While most cases of adjudicated drug-related ILD in this trial were low-grade and manageable, and overall incidence was consistent with that in previous studies,[31] three adjudicated drug-related ILD/pneumonitis-related deaths occurred. Multidisciplinary guidelines for diagnosing and managing T-DXd-related ILD/pneumonitis have been published.[29] T-DXd-related ILD/pneumonitis can be safely managed with a multidisciplinary team, who should manage the ILD/pneumonitis jointly with the medical oncologist and may include a primary care physician, nurse practitioner, pulmonologist, pathologist, pharmacist, infectious disease specialist, and radiologist. Patients should be proactively monitored for ILD/pneumonitis, and suspected cases should be actively managed by a multidisciplinary team; T-DXd treatment should be interrupted in the event of grade 1 ILD/pneumonitis, and the event must resolve before treatment may resume.[29]

This tumor-agnostic biomarker-driven approach represents an innovative application of the principles of precision medicine.[5] Despite the prospects of the tumor-agnostic strategy, only six drugs have received US FDA approval on this basis: pembrolizumab for microsatellite instability high, mismatch repair deficient, or tumor mutational burden high tumors; dostarlimab for mismatch repair deficient tumors; larotrectinib or entrectinib for tumors with *NTRK* gene fusions; dabrafenib plus trametinib for tumors with *BRAF* V600E mutations; and selpercatinib for tumors with *RET* gene fusions.[32] As with those studies, this trial has a clear rationale based on

preclinical/clinical data, and demonstrates meaningful antitumor activity across endometrial, cervical, ovarian, bladder, biliary tract, and other tumor cohorts.

A tumor-agnostic investigative approach has some limitations, most notably the single-arm nature of the studies. It was not possible to include a single comparator, given the range of tumor types that were included. Another potential limitation is the few patients included with HER2 IHC 1+ tumors. The protocol allowed for recruitment of patients with HER2 IHC 1+ tumors once 3/15 responders within a cohort had been observed in centrally confirmed HER2 IHC 3+ or IHC 2+ tumors. However, only the cervical cohort prospectively opened enrollment to patients with IHC 1+ tumors, as recruitment in other cohorts was complete by the time response rate data were available on the first 15 patients. There is limited evidence available from this study in HER2-low patients, a population of growing clinical interest following the approval of T-DXd in HER2-low breast cancer.[15] The few responses in patients who were determined to be IHC 1+/0 on retrospective central testing suggest that further exploration in patients with IHC 1+ tumors is warranted beyond breast cancer.

In this global, multicenter phase II study, treatment with T-DXd demonstrated robust clinical activity providing durable clinical benefit for pre-treated patients with selected HER2-expressing solid tumors. The observed safety profile, including ILD, was consistent with that in previously reported studies of T-DXd. These data provide clinical evidence for antitumor activity of T-DXd across multiple tumor types, suggesting potential tumor-agnostic activity in patients with HER2-expressing solid tumors.

CLINICAL TRIAL INFORMATION

NCT04482309

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI [TBC]

DATA SHARING STATEMENT

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at: https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available, outlining further details: https://vivli.org/ourmember/astrazeneca/.

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Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

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FIGURE LEGENDS

FIG 1. Investigator-assessed responses as per RECIST 1.1. (A) ORR across tumor cohorts, according to HER2 status by central testing. [a]Responses in the other tumors cohort include responses in extramammary Paget's disease, oropharyngeal neoplasm, head and neck, and salivary gland cancers. (B) The maximum change in tumor size, according to tumor type. Patients with IHC 3+ status (central testing) are marked with a dot. The other tumors cohort includes responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer. (C) DOR in patients with an objective response, according to tumor type. DOR was defined as the time from the date of first documented response (complete response or partial response) until the date of documented progression, or death in the absence of disease progression. Response was determined by investigator assessment according to RECIST 1.1 and required confirmation after the first observed response at least 4 weeks later. Censored patients are marked with a rounded dot, patients who stopped responding are marked with a triangular dot, and patients with a complete response are marked with a square dot. BTC, biliary tract cancer; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

FIG 2. Kaplan-Meier estimates of PFS, according to tumor type. (A) Endometrial cancer, (B) cervical cancer, (C) ovarian cancer, (D) bladder cancer, (E) other tumors, (F) biliary tract cancer, and (G) pancreatic cancer. IHC, immunohistochemistry; NR, not reached; PFS, progression-free survival.

FIG 3. Kaplan-Meier estimates of OS, according to tumor type. (A) Endometrial cancer, (B) cervical cancer, (C) ovarian cancer, (D) bladder cancer, (E) other tumors, (F) biliary tract cancer, and (G) pancreatic cancer. IHC, immunohistochemistry; NR, not reached; OS, overall survival.

FIG A1. Patient disposition. DCO, data cutoff.

FIG A2. Target lesions size, percentage change from baseline over time (full analysis set). CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

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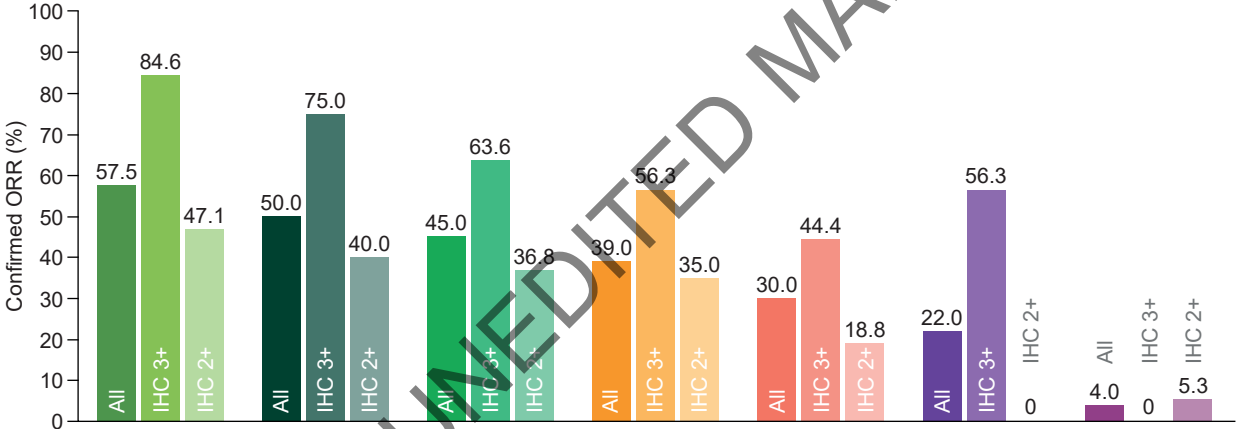
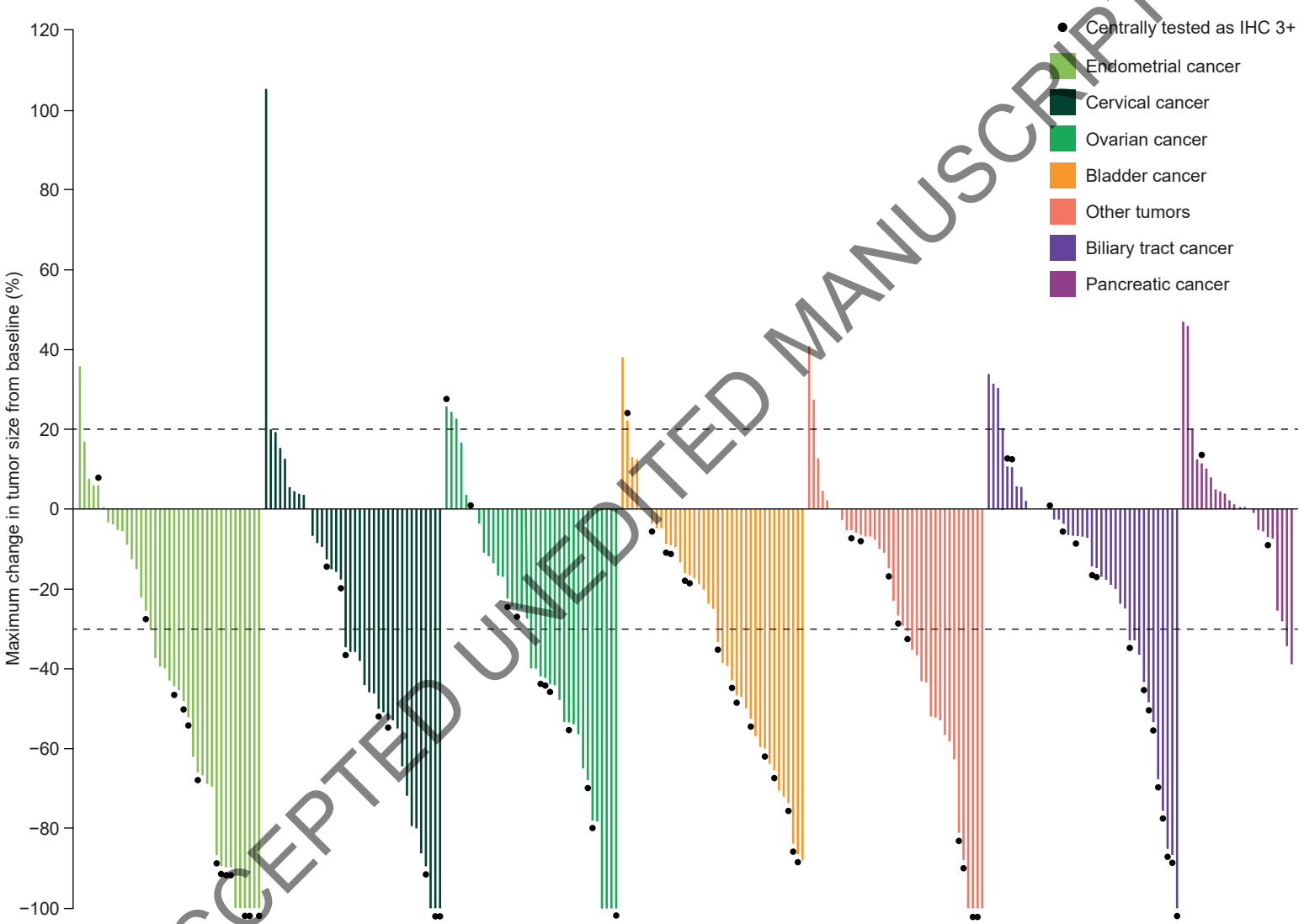
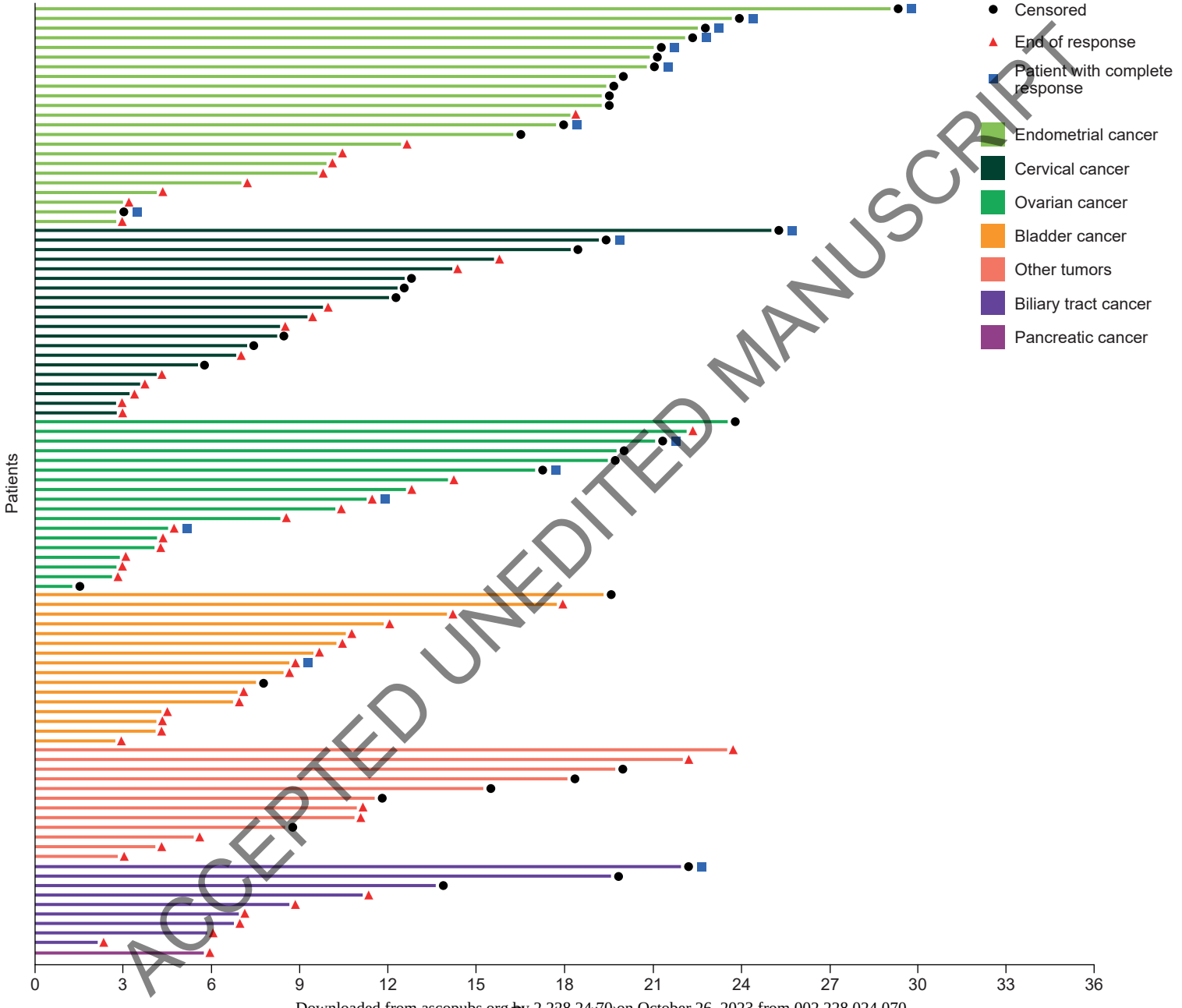
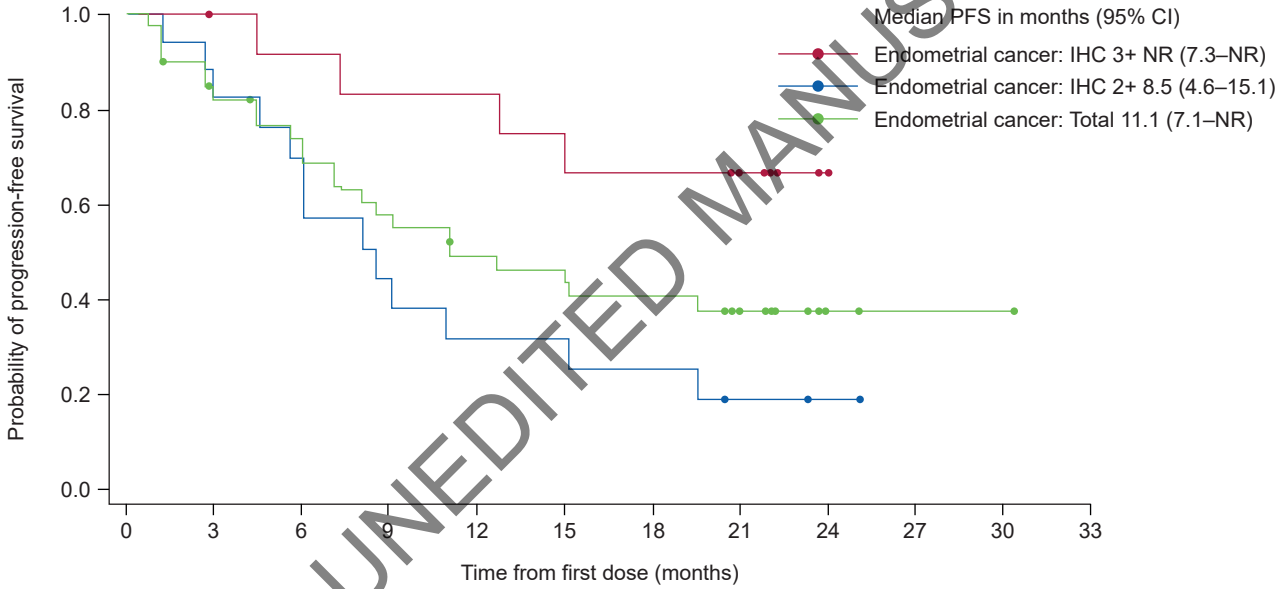
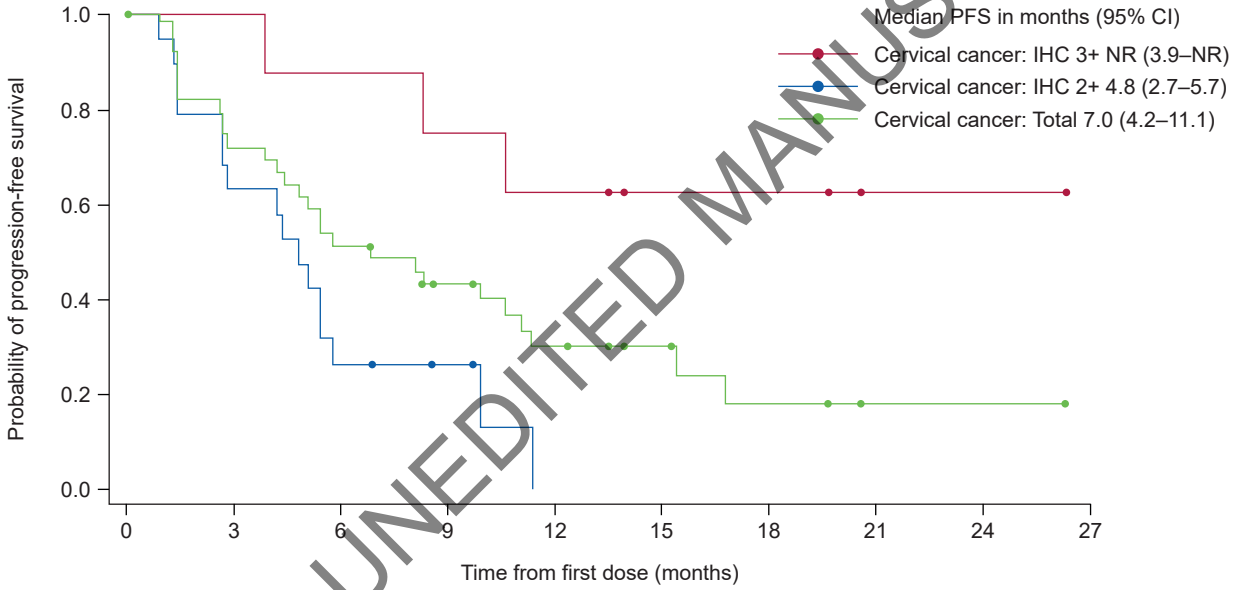




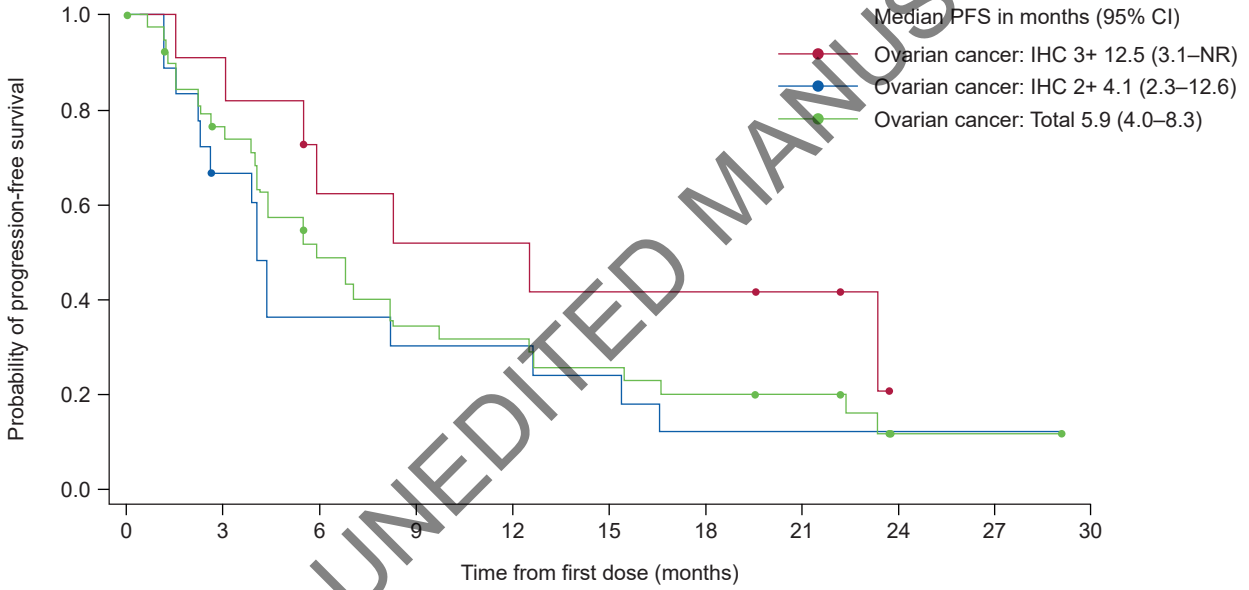




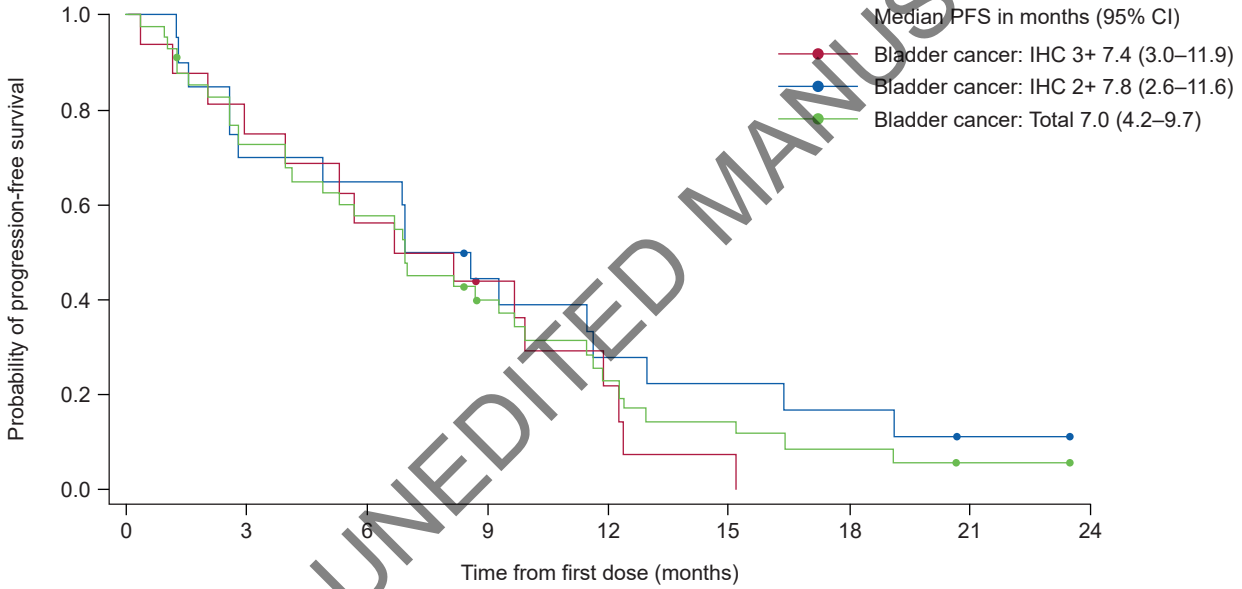
Number of patients at risk, month	0	3	6	9	12	15	18	21	24	27	30	33
Endometrial cancer: IHC 3+	13	12	11	10	10	9	8	5	0			
Endometrial cancer: IHC 2+	17	14	11	7	5	5	4	2	1	0		
Endometrial cancer: Total	40	31	27	21	17	16	14	8	2	1	1	0



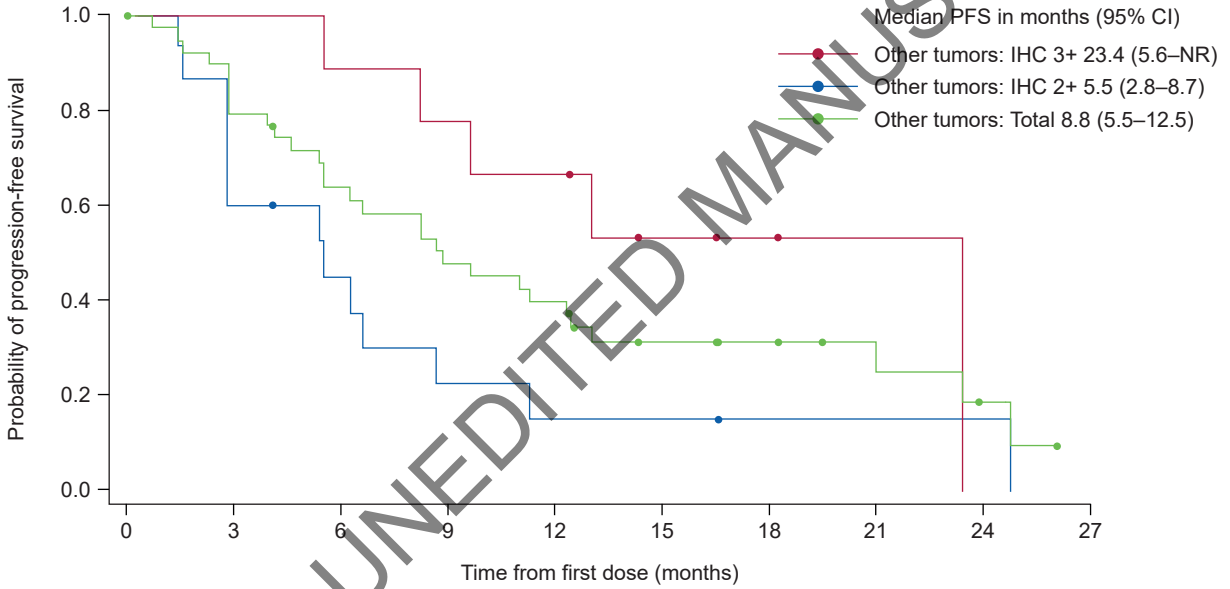
Number of patients at risk, month	0	3	6	9	12	15	18	21	24	27
Cervical cancer: IHC 3+	8	8	7	6	5	3	3	1	1	0
Cervical cancer: IHC 2+	20	12	5	3	0					
Cervical cancer: Total	40	28	20	14	9	6	3	1	1	0



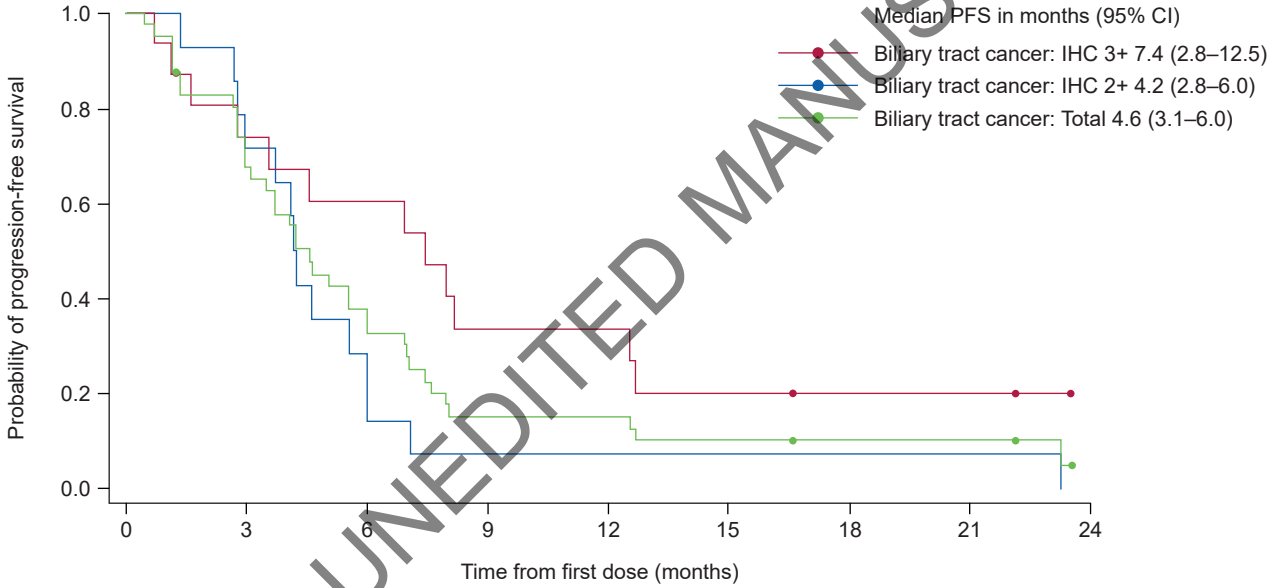
Number of patients at risk, month	0	3	6	9	12	15	18	21	24	27	30
Ovarian cancer: IHC 3+	11	10	6	5	5	4	4	3	0		
Ovarian cancer: IHC 2+	19	11	6	5	5	4	2	2	1	1	0
Ovarian cancer: Total	40	28	17	12	11	9	7	6	1	1	0



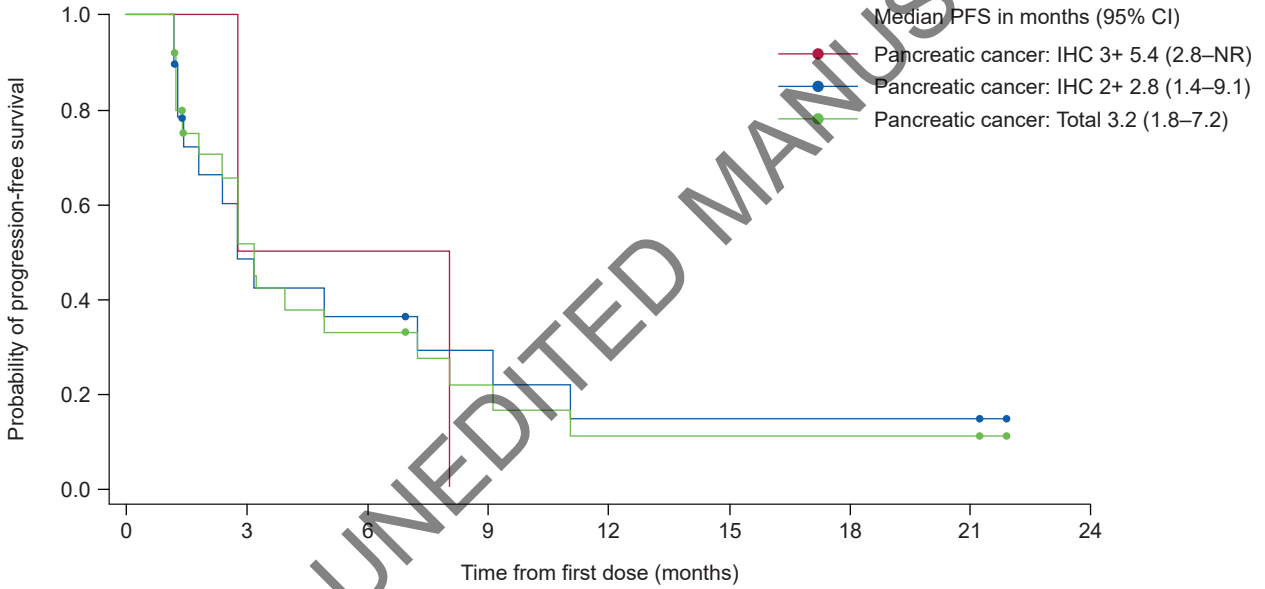
Number of patients at risk, month	0	3	6	9	12	15	18	21	24
Bladder cancer: IHC 3+	16	12	9	6	3	1	0		
Bladder cancer: IHC 2+	20	14	13	8	5	4	3	1	0
Bladder cancer: Total	41	29	23	14	8	5	3	1	0



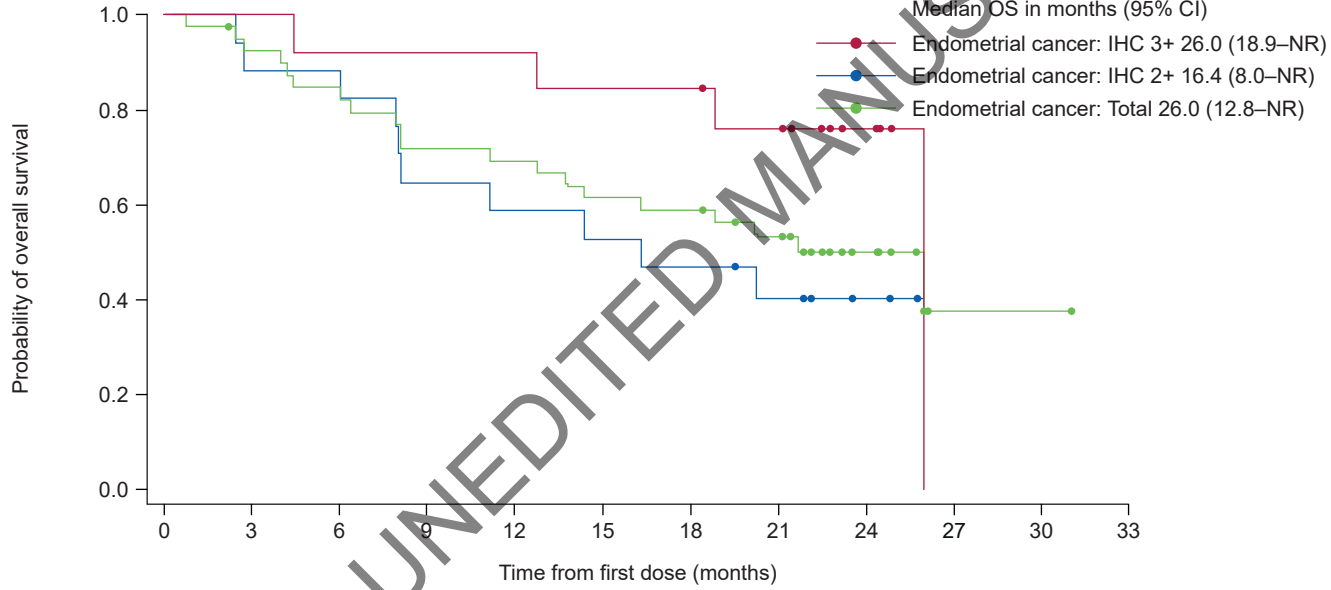
Number of patients at risk, month	0	3	6	9	12	15	18	21	24	27
Other tumors: IHC 3+	9	9	8	7	6	3	2	1	0	
Other tumors: IHC 2+	16	9	6	3	2	2	1	1	1	0
Other tumors: Total	40	31	24	18	15	9	7	4	2	0



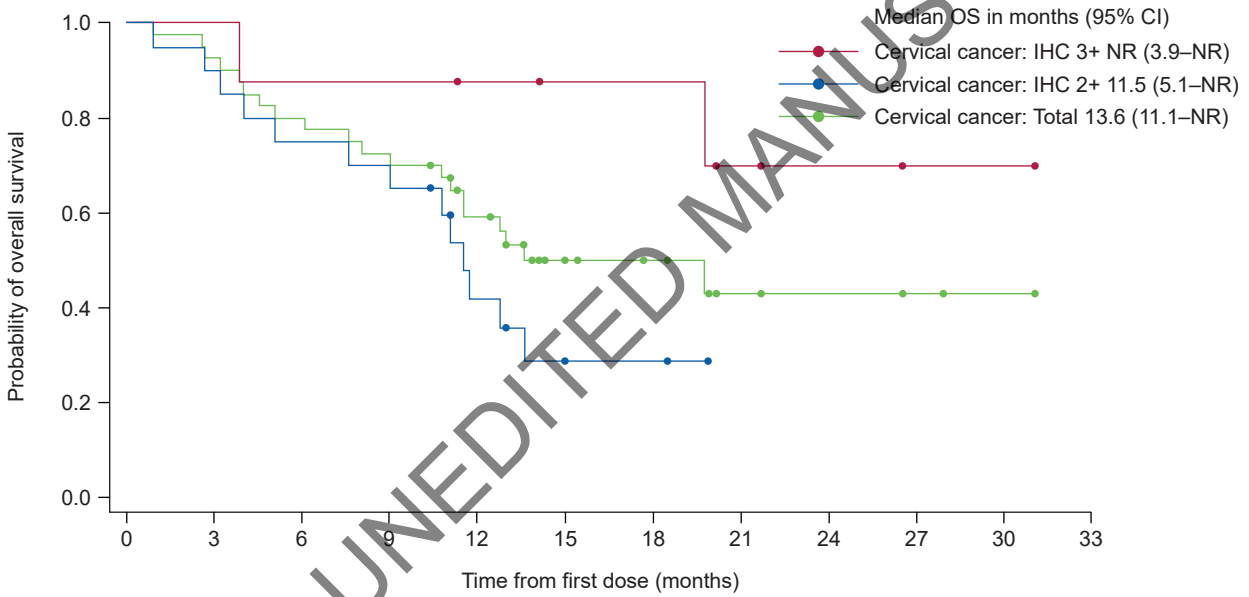
Number of patients at risk, month	0	3	6	9	12	15	18	21	24
Biliary tract cancer: IHC 3+	16	11	9	5	5	3	2	2	0
Biliary tract cancer: IHC 2+	14	10	3	1	1	1	1	1	0
Biliary tract cancer: Total	41	27	14	6	6	4	3	3	0



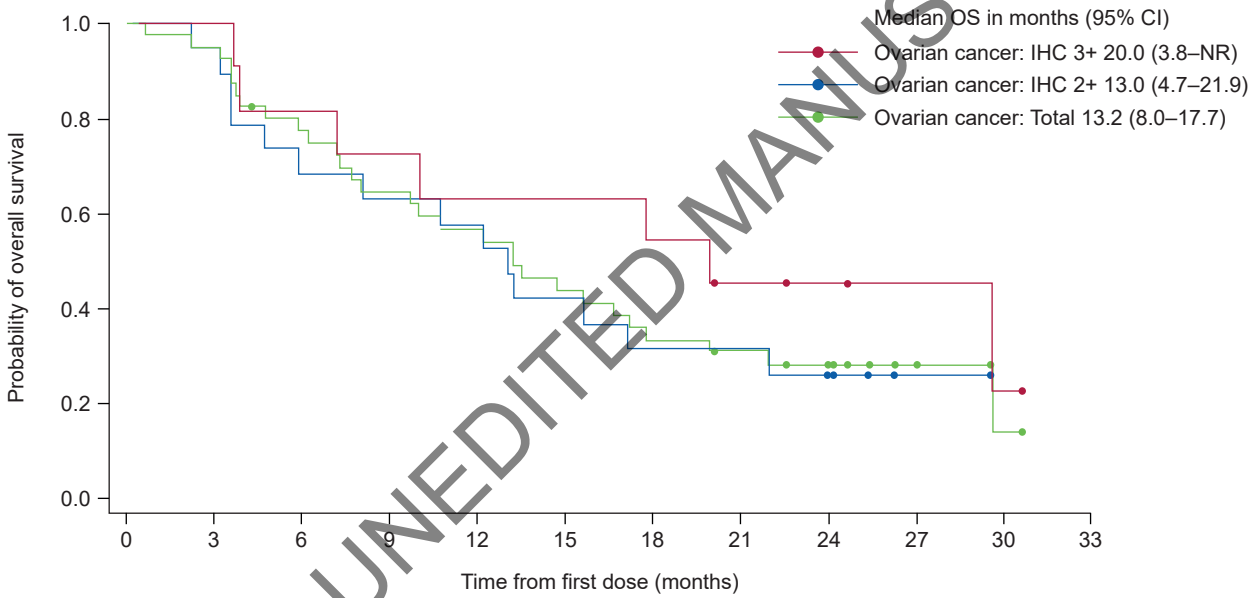
Number of patients at risk, month	0	3	6	9	12	15	18	21	24
Pancreatic cancer: IHC 3+	2	1	1	0					
Pancreatic cancer: IHC 2+	19	8	6	4	2	2	2	2	0
Pancreatic cancer: Total	25	11	7	4	2	2	2	2	0



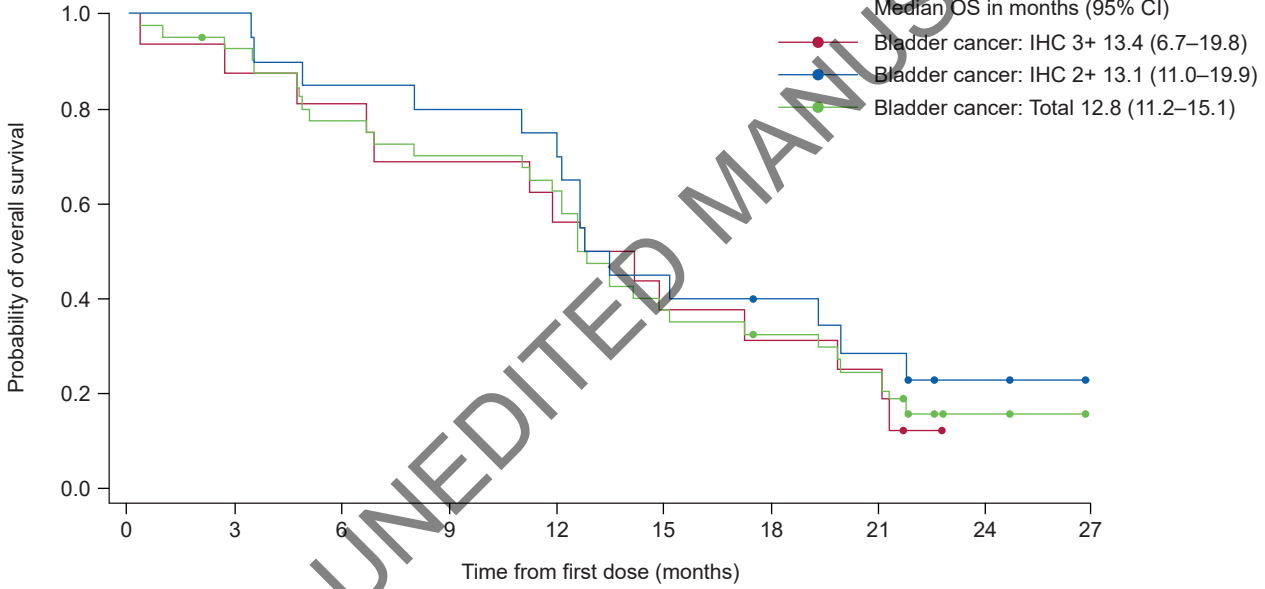
Number of patients at risk, month	0	3	6	9	12	15	18	21	24	27	30	33
Endometrial cancer: IHC 3+	13	13	12	12	12	11	11	9	4	0		
Endometrial cancer: IHC 2+	17	15	15	11	10	9	8	6	3	0		
Endometrial cancer: Total	40	36	33	28	27	24	23	19	9	1	1	0



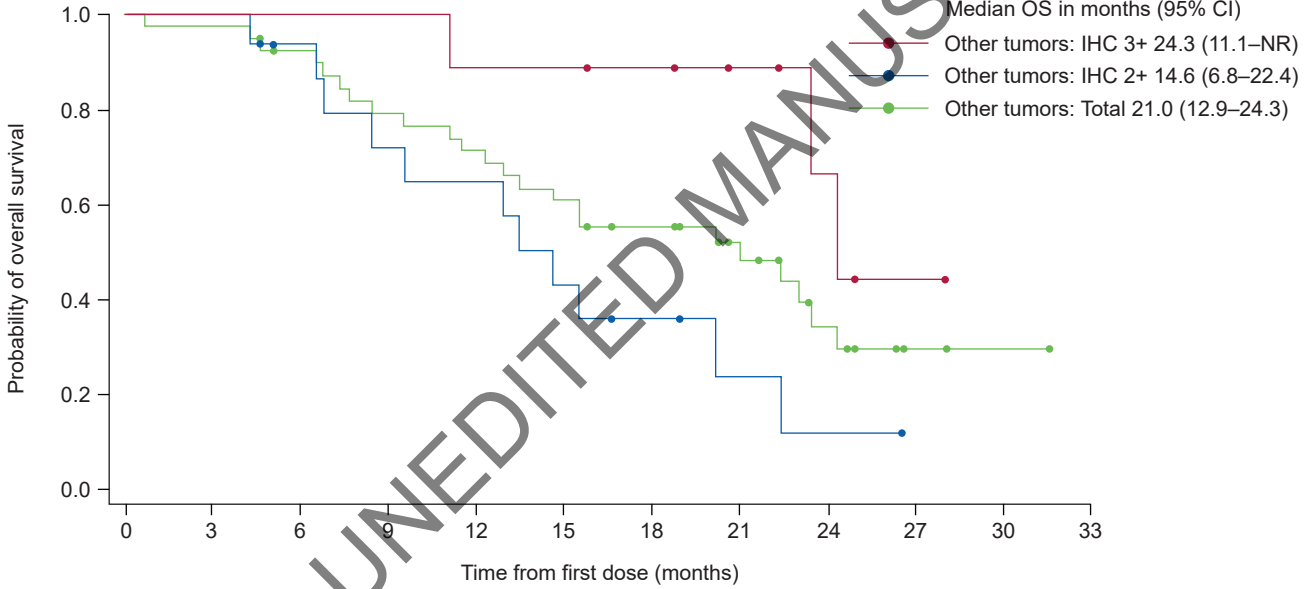
Number of patients at risk, month	0	3	6	9	12	15	18	21	24	27	30	33
Cervical cancer: IHC 3+	8	8	7	7	6	5	5	3	2	1	1	0
Cervical cancer: IHC 2+	20	18	15	14	7	3	3	0				
Cervical cancer: Total	40	37	32	29	21	11	9	4	3	2	1	0



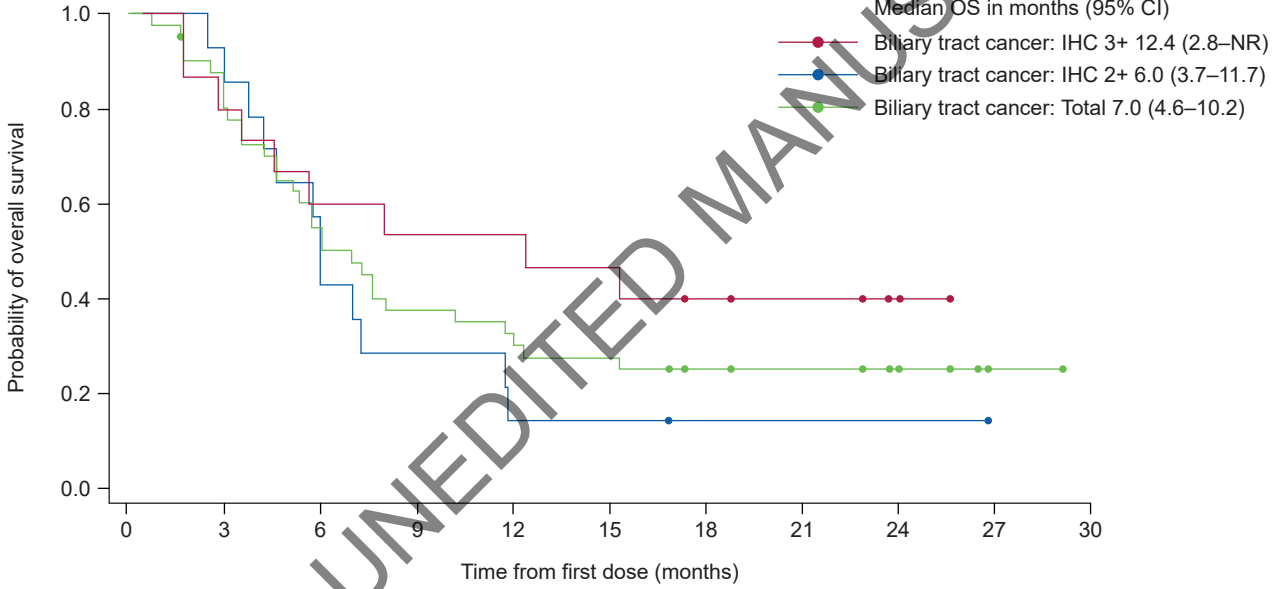
Number of patients at risk, month	0	3	6	9	12	15	18	21	24	27	30	33
Ovarian cancer: IHC 3+	11	11	9	8	7	7	6	4	3	2	1	0
Ovarian cancer: IHC 2+	19	18	13	12	11	8	6	6	4	1	0	
Ovarian cancer: Total	40	38	30	25	22	17	13	11	8	3	1	0



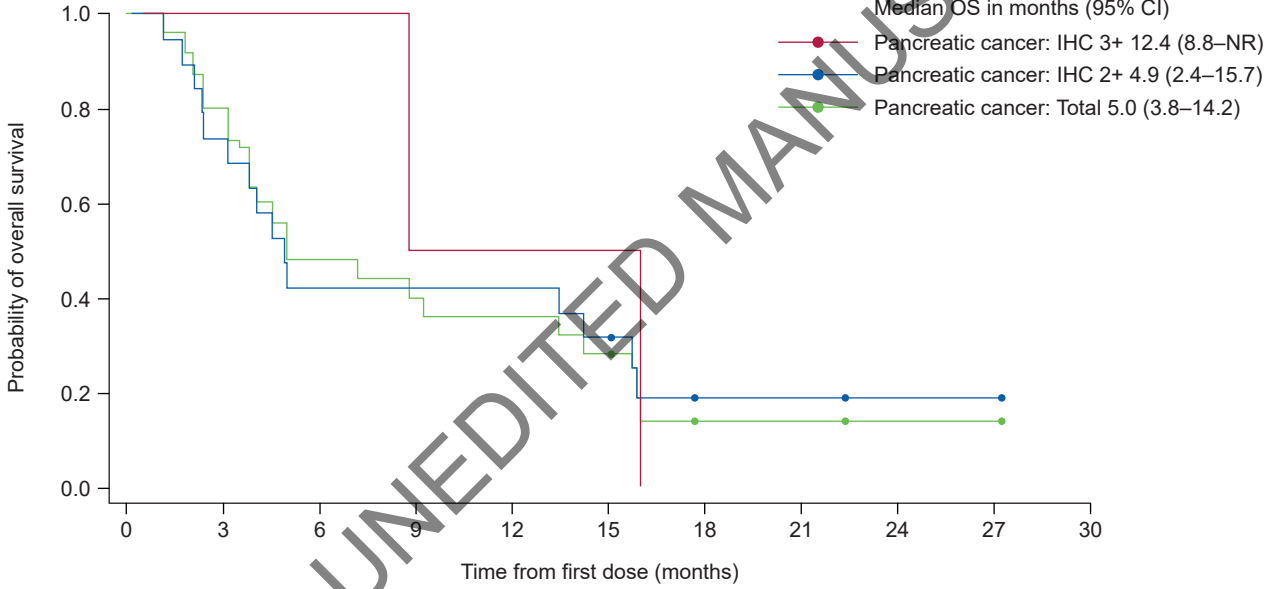
Number of patients at risk, month	0	3	6	9	12	15	18	21	24	27
Bladder cancer: IHC 3+	16	14	13	11	9	6	5	4	0	
Bladder cancer: IHC 2+	20	20	17	16	15	9	7	5	2	0
Bladder cancer: Total	41	37	31	28	25	15	12	9	2	0



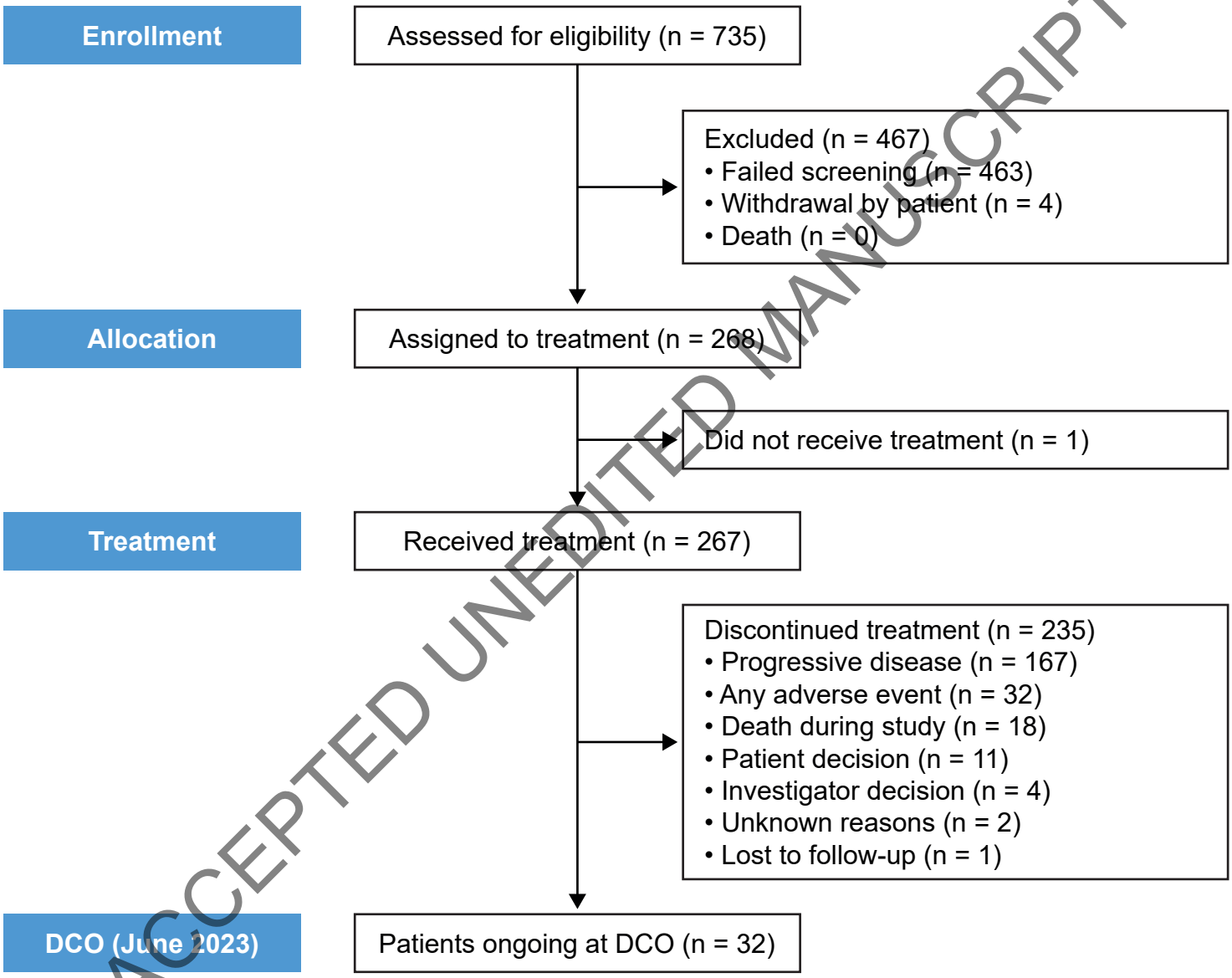
Number of patients at risk, month	0	3	6	9	12	15	18	21	24	27	30	33
Other tumors: IHC 3+	9	9	9	9	8	8	7	5	3	1	0	
Other tumors: IHC 2+	16	16	13	10	9	6	4	2	1	0		
Other tumors: Total	40	39	35	30	27	23	19	13	7	2	1	0



Number of patients at risk, month	0	3	6	9	12	15	18	21	24	27	30
Biliary tract cancer: IHC 3+	16	12	9	8	8	7	5	4	1	0	
Biliary tract cancer: IHC 2+	14	12	7	4	2	2	1	1	1	0	
Biliary tract cancer: Total	41	32	21	15	12	11	8	7	4	1	0



Number of patients at risk, month	0	3	6	9	12	15	18	21	24	27	30
Pancreatic cancer: IHC 3+	2	2	2	1	1	1	0				
Pancreatic cancer: IHC 2+	19	14	8	8	8	6	2	2	1	1	0
Pancreatic cancer: Total	25	20	12	10	9	7	2	2	1	1	0



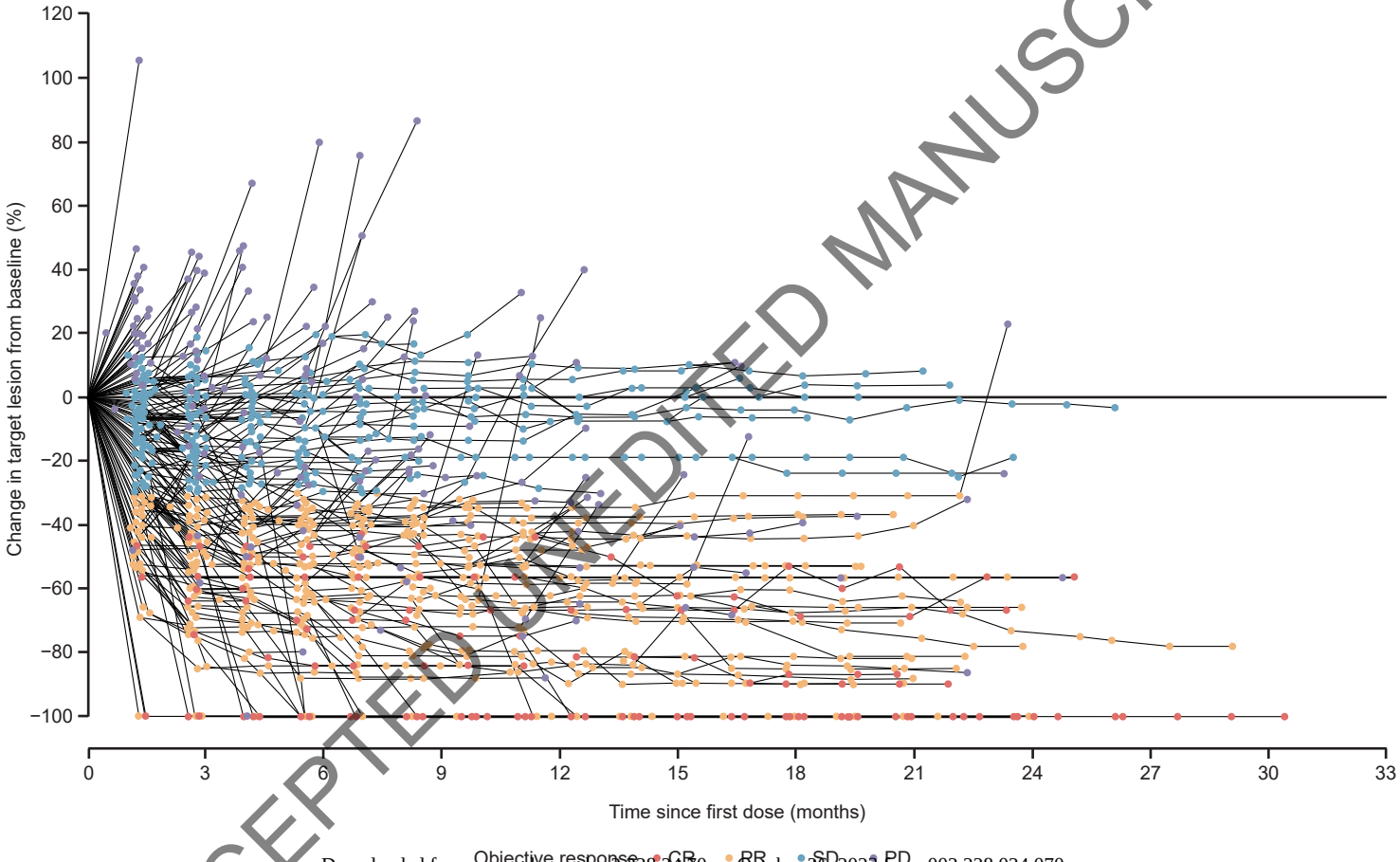


TABLE 1. Demographics and Baseline Clinical Characteristics

	Endometrial Cancer (n = 40)	Cervical Cancer (n = 40)	Ovarian Cancer (n = 40)	Bladder Cancer (n = 41)	Other Tumors (n = 40)	Biliary tract Cancer (n = 41)	Pancreatic Cancer (n = 25)
Median Age, Years (Range)	67 (37–79)	49 (28–78)	56 (34–72)	67 (43–85)	61 (38–81)	64 (31–80)	62 (23–80)
Female, No. (%)	40 (100.0)	40 (100.0)	40 (100.0)	14 (34.1)	13 (32.5)	21 (51.2)	10 (40.0)
Race, No. (%)							
White	23 (57.5)	29 (72.5)	22 (55.0)	25 (61.0)	27 (67.5)	20 (48.8)	17 (68.0)
Black or African American	4 (10.0)	0	1 (2.5)	0	0	0	1 (4.0)
Asian	10 (25.0)	7 (17.5)	17 (42.5)	16 (39.0)	10 (25.0)	21 (51.2)	6 (24.0)
Other	0	3 (7.5)	0	0	2 (5.0)	0	1 (4.0)
Not reported	3 (7.5)	1 (2.5)	0	0	1 (2.5)	0	0
ECOG Performance Status,[a] No. (%)							
0	23 (57.5)	22 (55.0)	26 (65.0)	19 (46.3)	15 (37.5)	13 (31.7)	8 (32.0)
HER2 Testing for Eligibility,[b] No. (%)							
Local	31 (77.5)	23 (57.5)	37 (92.5)	33 (80.5)	29 (72.5)	34 (82.9)	15 (60.0)
Central	9 (22.5)	17 (42.5)	3 (7.5)	8 (19.5)	11 (27.5)	7 (17.1)	10 (40.0)
HER2 IHC Status (Eligibility),[c] No. (%)							
IHC 3+	16 (40.0)	10 (25.0)	15 (37.5)	27 (65.9)	16 (40.0)	22 (53.7)	5 (20.0)
IHC 2+	24 (60.0)	25 (62.5)	25 (62.5)	14 (34.1)	24 (60.0)	19 (46.3)	20 (80.0)
IHC 1+[c]	0	5 (12.5)	0	0	0	0	0
Centrally Confirmed HER2 IHC Status, No. (%)							
IHC 3+	13 (32.5)	8 (20.0)	11 (27.5)	16 (39.0)	9 (22.5)	16 (39.0)	2 (8.0)
IHC 2+	17 (42.5)	20 (50.0)	19 (47.5)	20 (48.8)	16 (40.0)	14 (34.1)	19 (76.0)
IHC 1+	4 (10.0)	8 (20.0)	5 (12.5)	2 (4.9)	2 (5.0)	3 (7.3)	1 (4.0)
IHC 0	5 (12.5)	4 (10.0)	5 (12.5)	2 (4.9)	4 (10.0)	7 (17.1)	3 (12.0)
Unknown[d]	1 (2.5)	0	0	1 (2.4)	9 (22.5)	1 (2.4)	0
Prior Therapy Lines							
Median (range)	2 (0–7)	2 (1–6)	3 (1–12)	2 (0–9)	2 (0–8)	2 (1–5)	2 (1–4)
0, No. (%)	1 (2.5)	0	0	1 (2.4)	1 (2.5)	0	0
1, No. (%)	8 (20.0)	6 (15.0)	8 (20.0)	13 (31.7)	15 (37.5)	14 (34.1)	7 (28.0)
2, No. (%)	18 (45.0)	15 (37.5)	8 (20.0)	8 (19.5)	9 (22.5)	15 (36.6)	11 (44.0)
3, No. (%)	6 (15.0)	9 (22.5)	5 (12.5)	10 (24.4)	10 (25.0)	9 (22.0)	6 (24.0)
4, No. (%)	3 (7.5)	6 (15.0)	5 (12.5)	4 (9.8)	0	2 (4.9)	1 (4.0)
≥5, No. (%)	4 (10.0)	4 (10.0)	14 (35.0)	5 (12.2)	5 (12.5)	1 (2.4)	0
Prior HER2 Therapy, No. (%)	9 (22.5)	1 (2.5)	2 (5.0)	3 (7.3)	14 (35.0)	7 (17.1)	2 (8.0)
Trastuzumab	5 (12.5)	1 (2.5)	2 (5.0)	3 (7.3)	14 (35.0)	6 (14.6)	2 (8.0)
Pertuzumab	0	1 (2.5)	0	1 (2.4)	2 (5.0)	1 (2.4)	0
Zanidatamab	2 (5.0)	0	0	0	1 (2.5)	1 (2.4)	0
Trastuzumab emtansine	1 (2.5)	1 (2.5)	0	1 (2.4)	0	0	0

Trastuzumab duocarmazine	1 (2.5)	0	0	0	0	0	0
Tucatinib	0	0	0	0	0	0	1 (4.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

[a]ECOG performance status scores range from 0 to 5, with higher scores indicating greater disability.

[b]HER2 expression for eligibility was based on local assessment where available, or local testing.

[c]In the cervical cohort, five patients with IHC 1+ status were included following the protocol-specified interim analysis (Supplementary Methods).

[d]Includes patients whose samples were not evaluable and may have included patients who did not provide a sample for central testing.

TABLE 2. Incidence of Drug-Related Adverse Events

	Endometrial Cancer (n = 40)	Cervical Cancer (n = 40)	Ovarian Cancer (n = 40)	Bladder Cancer (n = 41)	Other Tumors (n = 40)	Biliary Tract Cancer (n = 41)	Pancreatic Cancer (n = 25)
Drug-Related Adverse Events, No. (%)	36 (90.0)	36 (90.0)	34 (85.0)	38 (92.7)	34 (85.0)	33 (80.5)	15 (60.0)
Grade ≥3	14 (35.0)	19 (47.5)	21 (52.5)	17 (41.5)	15 (37.5)	16 (39.0)	7 (28.0)
Serious adverse events	4 (10.0)	3 (7.5)	11 (27.5)	4 (9.8)	6 (15.0)	5 (12.2)	3 (12.0)
Leading to discontinuation	3 (7.5)	3 (7.5)	1 (2.5)	4 (9.8)	6 (15.0)	5 (12.2)	1 (4.0)
Leading to dose modification[a]	13 (32.5)	13 (32.5)	18 (45.0)	15 (36.6)	13 (32.5)	13 (31.7)	0
Associated with death	2 (5.0)	0	0	1 (2.4)	1 (2.5)	0	0
Most Common Drug-Related Adverse Events (> 10% of Total Patients), No. (%)							
Nausea	29 (72.5)	26 (65.0)	22 (55.0)	21 (51.2)	23 (57.5)	19 (46.3)	7 (28.0)
Anemia	7 (17.5)	15 (37.5)	15 (37.5)	12 (29.3)	11 (27.5)	10 (24.4)	4 (16.0)
Diarrhea	16 (40.0)	15 (37.5)	8 (20.0)	13 (31.7)	6 (15.0)	8 (19.5)	3 (12.0)
Fatigue	10 (25.0)	9 (22.5)	11 (27.5)	11 (26.8)	12 (30.0)	9 (22.0)	4 (16.0)
Vomiting	16 (40.0)	10 (25.0)	7 (17.5)	6 (14.6)	15 (37.5)	9 (22.0)	3 (12.0)
Neutropenia	4 (10.0)	8 (20.0)	5 (12.5)	11 (26.8)	9 (22.5)	9 (22.0)	4 (16.0)
Decreased appetite	8 (20.0)	7 (17.5)	8 (20.0)	8 (19.5)	7 (17.5)	7 (17.1)	2 (8.0)
Asthenia	11 (27.5)	9 (22.5)	6 (15.0)	3 (7.)	8 (20.0)	6 (14.6)	3 (12.0)
Alopecia	9 (22.5)	8 (20.0)	5 (12.5)	5 (12.2)	7 (17.5)	9 (22.0)	2 (8.0)
Thrombocytopenia	2 (5.0)	2 (5.0)	5 (12.5)	6 (14.6)	7 (17.5)	5 (12.2)	3 (12.0)

[a]Dose modification includes adverse events with action taken of dose reduced or drug interrupted. Adverse events associated with death included pneumonia (n = 1), organizing pneumonia (n = 1), pneumonitis (n = 1), and neutropenic sepsis (n = 1).

Appendix to: Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results from the DESTINY-PanTumor02 Phase II Trial

Funda Meric-Bernstam, Vicky Makker, Ana Oaknin, Do-Youn Oh, Susana Banerjee, Antonio González-Martín, Kyung Hae Jung, Iwona Ługowska, Luis Manso, Aránzazu Manzano, Bohuslav Melichar, Salvatore Siena, Daniil Stroyakovskiy, Anitra Fielding, Yan Ma, Soham Puvvada, Norah Shire, Jung-Yun Lee

TABLES A1–A4

TABLE A1. HER2 Status at Baseline, Local versus Central Test Results

Group	Local Results	Patients, No. (%)					
		Central HER2 IHC Results					
		IHC 3+	IHC 2+	IHC 1+	IHC 0	Unknown	Total
Endometrial Cancer	IHC 3+	9 (22.5)	3 (7.5)	1 (2.5)	1 (2.5)	0	14 (35.0)
	IHC 2+	2 (5.0)	7 (17.5)	3 (7.5)	4 (10.0)	1 (2.5)	17 (42.5)
	IHC 1+	0	0	0	0	0	0
	No local result	2 (5.0)	7 (17.5)	0	0	0	9 (22.5)
	Total	13 (32.5)	17 (42.5)	4 (10.0)	5 (12.5)	1 (2.5)	40 (100)
Cervical Cancer	IHC 3+	6 (15.0)	1 (2.5)	1 (2.5)	0	0	8 (20.0)
	IHC 2+	0	7 (17.5)	3 (7.5)	3 (7.5)	0	13 (32.5)
	IHC 1+	0	1 (2.5)	0	1 (2.5)	0	2 (5.0)
	No local result	2 (5.0)	11 (27.5)	4 (10.0)	0	0	17 (42.5)
	Total	8 (20.0)	20 (50.0)	8 (20.0)	4 (10.0)	0	40 (100)
Ovarian Cancer	IHC 3+	7 (17.5)	6 (15.0)	0	0	0	13 (32.5)
	IHC 2+	2 (5.0)	12 (30.0)	5 (12.5)	5 (12.5)	0	24 (60.0)
	IHC 1+	0	0	0	0	0	0
	No local result	2 (5.0)	1 (2.5)	0	0	0	3 (7.5)
	Total	11 (27.5)	19 (47.5)	5 (12.5)	5 (12.5)	0	40 (100)
Bladder Cancer	IHC 3+	12 (29.3)	8 (19.5)	1 (2.4)	2 (4.9)	1 (2.4)	24 (58.5)
	IHC 2+	1 (2.4)	7 (17.1)	1 (2.4)	0	0	9 (22.0)
	IHC 1+	0	0	0	0	0	0
	No local result	3 (7.3)	5 (12.2)	0	0	0	8 (19.5)
	Total	16 (39.0)	20 (48.8)	2 (4.9)	2 (4.9)	1 (2.4)	41 (100)
Other Tumors	IHC 3+	4 (10.0)	2 (5.0)	0	1 (2.5)	5 (12.5)	12 (30.0)
	IHC 2+	1 (2.5)	7 (17.5)	2 (5.0)	3 (7.5)	4 (10.0)	17 (42.5)
	IHC 1+	0	0	0	0	0	0
	No local result	4 (10.0)	7 (17.5)	0	0	0	11 (27.5)
	Total	9 (22.5)	16 (40.0)	2 (5.0)	4 (10.0)	9 (22.5)	40 (100)
Biliary Tract Cancer	IHC 3+	12 (29.3)	4 (9.8)	1 (2.4)	1 (2.4)	0	18 (43.9)
	IHC 2+	0	7 (17.1)	2 (4.9)	6 (14.6)	1 (2.4)	16 (39.0)
	IHC 1+	0	0	0	0	0	0
	No local result	4 (9.8)	3 (7.3)	0	0	0	7 (17.1)
	Total	16 (39.0)	14 (34.1)	3 (7.3)	7 (17.1)	1 (2.4)	41 (100)
Pancreatic Cancer	IHC 3+	1 (4.0)	2 (8.0)	0	1 (4.0)	0	4 (16.0)
	IHC 2+	0	8 (32.0)	1 (4.0)	2 (8.0)	0	11 (44.0)
	IHC 1+	0	0	0	0	0	0
	No local result	1 (4.0)	9 (36.0)	0	0	0	10 (40.0)
	Total	2 (8.0)	19 (76.0)	1 (4.0)	3 (12.0)	0	25 (100)

Unknown central HER2 test results include patients whose samples were unevaluable (for various technical reasons) and may include patients who did not provide a sample for central testing. Abbreviations: HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

TABLE A2. Efficacy by Tumor Cohort

	Endometrial Cancer	Cervical Cancer	Ovarian Cancer	Bladder Cancer	Other Tumors	Biliary Tract Cancer	Pancreatic Cancer
All Patients	40	40	40	41	40	41	25
Confirmed ORR (Investigator)	23 (57.5)	20 (50.0)	18 (45.0)	16 (39.0)	12 (30.0)	9 (22.0)	1 (4.0)
95% CI	40.9–73.0	33.8–66.2	29.3–61.5	24.2–55.5	16.6–46.5	10.6–37.6	0.1–20.4
Best Overall Response							
CR, No. (%)	8 (20.0)	2 (5.0)	4 (10.0)	1 (2.4)	0	1 (2.4)	0
PR, No. (%)	15 (37.5)	18 (45.0)	14 (35.0)	15 (36.6)	12 (30.0)	8 (19.5)	1 (4.0)
SD, No. (%)	12 (30.0)	11 (27.5)	14 (35.0)	16 (39.0)	20 (50.0)	23 (56.1)	16 (64.0)
PD, No. (%)	4 (10.0)	7 (17.5)	7 (17.5)	7 (17.1)	3 (7.5)	7 (17.1)	7 (28.0)
NE, No. (%)	0	1 (2.5)	1 (2.5)	0	1 (2.5)	0	0
Median DOR,[a] n	23	20	18	16	12	9	1
Median, months	NR	14.2	11.3	8.7	22.1	8.6	5.7
95% CI	9.9–NR	4.1–NR	4.1–22.1	4.3–11.8	4.1–NR	2.1–NR	NR–NR
DCR at 12 Weeks, No. (%)	32 (80.0)	27 (67.5)	28 (70.0)	29 (70.7)	30 (75.0)	27 (65.9)	9 (36.0)
95% CI	64.4–90.9	50.9–81.4	53.5–83.4	54.5–83.9	58.8–87.3	49.4–79.9	18.0–57.5
Kaplan-Meier Estimate of Patients With Extended DOR							
≥12 months	68.3%	50.6%	47.1%	20.8%	56.3%	33.3%	0
Median PFS, Months	11.1	7.0	5.9	7.0	8.8	4.6	3.2
95% CI	7.1–NR	4.2–11.1	4.0–8.3	4.2–9.7	5.5–12.5	3.1–6.0	1.8–7.2
PFS, 6 Months	74.0	51.3	48.9	57.6	63.7	35.1	32.8
95% CI	57.0–85.1	34.8–65.5	32.1–63.7	41.0–71.1	46.5–76.6	20.9–49.7	14.8–52.3
PFS, 12 Months	49.2	29.9	31.6	22.8	39.8	15.1	10.9
95% CI	32.4–64.0	15.8–45.4	17.4–46.9	11.0–37.2	24.4–54.7	6.1–27.7	1.9–28.9
Median OS, Months	26.0	13.6	13.2	12.8	21.0	7.0	5.0
95% CI	12.8–NR	11.1–NR	8.0–17.7	11.2–15.1	12.9–24.3	4.6–10.2	3.8–14.2
OS, 6 Months	84.7	80.0	77.3	77.6	92.4	52.6	48.0
95% CI	69.0–92.8	64.0–89.5	61.0–87.5	61.4–87.7	78.3–97.5	36.2–66.6	27.8–65.6
OS, 12 Months	69.3	59.1	56.7	62.6	71.3	30.0	36.0
95% CI	52.3–81.2	42.0–72.7	39.9–70.5	45.8–75.5	54.2–83.0	16.8–44.4	18.2–54.2

Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a]DOR includes only patients with an objective response.

TABLE A3. Efficacy by Tumor Type in the Other Tumors Cohort

	Group Term	All Patients	Confirmed ORR (Investigator) *95% CI*	Median DOR, n Median, Months *95% CI*	Median PFS, Months *95% CI*
Adenocarcinoid tumor of the appendix	Appendix	1	0	..	NR *NR–NR*
Adenoid cystic carcinoma	Salivary gland	1	0	..	8.3 *NR–NR*
Salivary gland cancer		19	8 (42.1%) 20.3–66.5	6 20.1 *5.6–NR*	12.5 *8.8–NR*
Extramammary Paget's disease	Extramammary Paget's disease	3	2 (66.7%) 9.4–99.2	2 12.4 *5.4–NR*	15.7 *6.6–NR*
Head and neck	Head and neck (other)	1	1 (100.0%) 2.5–100	1 NR *NR–NR*	NR *NR–NR*
Lip and/or oral cavity cancer		1	0	..	4.7 *4.2–NR*
Oropharyngeal neoplasm		2	1 (50.0%) *1.3–98.7*	1 NR *NR–NR*	NR *4.2–NR*
Intestinal adenocarcinoma	Small intestine	1	0	1 5.6 *NR–NR*	8.3 *NR–NR*
Malignant neoplasm of unknown primary site	Cancer of unknown primary site	5	0	1 NR *NR–NR*	2.8 *2.4–NR*
Cutaneous melanoma	Cutaneous melanoma	2	0	..	1.5 *1.4–NR*
Esophageal adenocarcinoma	Esophageal	1	0	1 2.8 *NR–NR*	6.3 *NR–NR*
Esophageal squamous cell carcinoma		1	0	..	0.7 *NR–NR*
Testis cancer	Testis	1	0	..	NR *NR–NR*
Vulva cancer	Vulva	1	0	1 2.6 *NR–NR*	5.6 *NR–NR*
Total other tumors	..	40	12 (30.0%) 16.6–46.5	14 19.4 *5.4–NR*	8.8 5.5–12.5

Abbreviations: DOR, duration of response; NR, not reached; ORR, objective response rate; PFS, progression-free survival.

TABLE A4. Safety (Non-Drug-Related Adverse Events)

	Endometrial Cancer	Cervical Cancer	Ovarian Cancer	Bladder Cancer	Other Tumors	Biliary Tract Cancer	Pancreatic Cancer
Number of Patients	40	40	40	41	40	41	25
Any AE, No. (%)	39 (97.5)	40 (100.0)	38 (95.0)	41 (100.0)	38 (95.0)	41 (100.0)	24 (96.0)
Any AE of CTCAE grade 3 or higher	26 (65.0)	26 (65.0)	25 (62.5)	26 (63.4)	22 (55.0)	30 (73.2)	14 (56.0)
Any with outcome of death	3 (7.5)	1 (2.5)	1 (2.5)	3 (7.3)	3 (7.5)	6 (14.6)	2 (8.0)
Any serious AE (including events with outcome of death)	15 (37.5)	15 (37.5)	16 (40.0)	17 (41.5)	19 (47.5)	23 (56.1)	9 (36.0)
Any AE leading to discontinuation of T-DXd	3 (7.5)	4 (10.0)	3 (7.5)	4 (9.8)	7 (17.5)	8 (19.5)	3 (12.0)
Any AE leading to dose modification of T-DXd	20 (50.0)	22 (55.0)	23 (57.5)	26 (63.4)	22 (55.0)	17 (41.5)	3 (12.0)
Any AE leading to dose reduction of T-DXd	12 (30.0)	9 (22.5)	17 (42.5)	7 (17.1)	6 (15.0)	10 (24.4)	0
Any AE leading to dose interruption of T-DXd	14 (35.0)	17 (42.5)	19 (47.5)	24 (58.5)	21 (52.5)	13 (31.7)	3 (12.0)
Any AE leading to hospitalization	15 (37.5)	15 (37.5)	14 (35.0)	17 (41.5)	17 (42.5)	21 (51.2)	8 (32.0)
Most Common Adverse Events (>10% of Total Patients), No. (%)							
Nausea	32 (80.0)	30 (75.0)	25 (62.5)	23 (56.1)	28 (70.0)	23 (56.1)	12 (48.0)
Anemia	14 (35.0)	21 (52.5)	25 (62.5)	19 (46.3)	17 (42.5)	16 (39.0)	8 (32.0)
Diarrhea	19 (47.5)	16 (40.0)	13 (32.5)	18 (43.9)	10 (25.0)	10 (24.4)	4 (16.0)
Vomiting	19 (47.5)	13 (32.5)	9 (22.5)	7 (17.1)	16 (40.0)	12 (29.3)	7 (28.0)
Fatigue	12 (30.0)	10 (25.0)	14 (35.0)	12 (29.3)	17 (42.5)	10 (24.4)	6 (24.0)
Decreased appetite	12 (30.0)	8 (20.0)	13 (32.5)	15 (36.6)	9 (22.5)	11 (26.8)	5 (20.0)
Asthenia	14 (35.0)	11 (27.5)	10 (25.0)	5 (12.2)	8 (20.0)	11 (26.8)	5 (20.0)
Constipation	12 (30.0)	14 (35.0)	4 (10.0)	9 (22.0)	10 (25.0)	5 (12.2)	3 (12.0)
Neutropenia	5 (12.5)	8 (20.0)	6 (15.0)	11 (26.8)	9 (22.5)	9 (22.0)	6 (24.0)
Alopecia	12 (30.0)	9 (22.5)	5 (12.5)	5 (12.2)	7 (17.5)	11 (26.8)	2 (8.0)
Neutrophil count decreased	5 (12.5)	4 (10.0)	10 (25.0)	10 (24.4)	7 (17.5)	4 (9.8)	1 (4.0)
Abdominal pain	6 (15.0)	6 (15.0)	10 (25.0)	6 (14.6)	5 (12.5)	6 (14.6)	1 (4.0)
Hypokalemia	8 (20.0)	9 (22.5)	8 (20.0)	5 (12.2)	2 (5.0)	6 (14.6)	1 (4.0)
Aspartate aminotransferase increased	7 (17.5)	4 (10.0)	9 (22.5)	3 (7.3)	5 (12.5)	4 (9.8)	4 (16.0)
COVID-19	5 (12.5)	6 (15.0)	7 (17.5)	7 (17.1)	7 (17.5)	2 (4.9)	1 (4.0)
Thrombocytopenia	3 (7.5)	3 (7.5)	5 (12.5)	7 (17.1)	8 (20.0)	6 (14.6)	3 (12.0)
Alanine aminotransferase increased	5 (12.5)	3 (7.5)	7 (17.5)	4 (9.8)	5 (12.5)	4 (9.8)	4 (16.0)
Urinary tract infection	6 (15.0)	7 (17.5)	8 (20.0)	6 (14.6)	2 (5.0)	2 (4.9)	0
Pyrexia	4 (10.0)	3 (7.5)	11 (27.5)	4 (9.8)	5 (12.5)	1 (2.4)	0
Hypoalbuminemia	1 (2.5)	4 (10.0)	7 (17.5)	5 (12.2)	4 (10.0)	1 (2.4)	5 (20.0)
Platelet count decreased	2 (5.0)	2 (5.0)	9 (22.5)	6 (14.6)	5 (12.5)	3 (7.3)	0
Weight decreased	4 (10.0)	2 (5.0)	5 (12.5)	6 (14.6)	4 (10.0)	4 (9.8)	2 (8.0)

Data are n (%). Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; T-DXd, trastuzumab deruxtecan. Adverse events associated with death included COVID-19 (n = 1), COVID-19 pneumonia (n = 1), neutropenic sepsis (n = 1), pneumonia (n = 3), sepsis (n = 1), cerebrovascular accident (n = 1), cardiac arrest (n = 2), hypotension (n = 1), organizing pneumonia (n = 1), pneumonitis (n = 1), pulmonary embolism (n = 1), and general disorders and administration site conditions (n = 5).

Appendix to: Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results from the DESTINY-PanTumor02 Phase II Trial

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METHODS

Patients

Male and female patients were at least 18 years of age at the time of giving signed informed consent. Patients with locally advanced, unresectable, or metastatic solid tumors with histology specific to respective cohorts, who have progressed following at least one prior systemic treatment for metastatic or advanced disease, or who have no satisfactory alternative treatment option, were recruited; patients with prior human epidermal growth factor receptor 2 (HER2)-targeted therapy were permitted. The respective cohorts for patient inclusion were:

- Cohort 1 (biliary tract cancer): metastatic or advanced biliary tract cancers, including intra- or extrahepatic cholangiocarcinoma and tumors arising in the ampulla of Vater or gallbladder
- Cohort 2 (bladder cancer): metastatic or advanced urothelial carcinoma, including transitional cell or predominantly transitional cell carcinoma of the renal pelvis, ureter, urinary bladder, or urethra
- Cohort 3 (cervical cancer): metastatic or advanced cervical carcinoma
- Cohort 4 (endometrial cancer): metastatic or advanced endometrial carcinoma
- Cohort 5 (ovarian cancer): metastatic or advanced epithelial ovarian carcinoma
- Cohort 6 (pancreatic cancer): metastatic or advanced pancreatic cancer
- Cohort 7 (other tumors): metastatic or advanced rare tumors with HER2 overexpression (immunohistochemistry [IHC] 3+ and 2+), excluding the tumors mentioned above, and breast, non-small cell lung, gastric, and colorectal cancer

Patients must have had HER2 overexpression (IHC 3+ or IHC 2+) as determined by local or central assessment scored using current American Society of Clinical Oncology/College of American Pathologists guidelines for scoring HER2 in gastric cancer. Central assessment may have been offered based on site need. For each cohort, 1–6, up to ten IHC 1+ patients may have been included if ≥3 objective responses were observed in the first 15 patients with confirmed HER2 overexpression (IHC 3+ or IHC 2+) by central testing. For the other tumors cohort (Cohort 7), only patients with HER2 overexpression (IHC 3+ or IHC 2+) were enrolled. Patients must have provided an existing formalin-fixed paraffin-embedded (FFPE) tumor sample for tissue-based IHC staining to centrally determine HER2 expression and other correlatives. The mandatory FFPE tumor sample needed to have been obtained at the time of diagnosis of metastatic or locally advanced, unresectable, solid tumors (most recent pre-enrollment tumor sample must have been provided). Specimens with limited tumor content and fine needle aspirates were inadequate for defining tumor HER2 status. Patients were also required to have measurable target disease assessed by the Investigator based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), an Eastern Cooperative Oncology Group performance status of 0–1, left ventricular ejection fraction ≥50% by either echocardiography or multiple-gated acquisition scan within 28 days before treatment assignment, adequate organ function within 14 days before trastuzumab deruxtecan administration, and adequate treatment washout period before study drug treatment.

Patients were excluded from the study if they had a known somatic DNA mutation of *HER2* (*ERBB2*) without tumoral HER2 expression, primary diagnosis of adenocarcinoma of the breast, adenocarcinoma of the colon or rectum, adenocarcinoma of the gastric body or gastroesophageal junction, or non-small cell lung cancer. Substance abuse or any other medical conditions (eg, clinically significant cardiac or psychological conditions) that may, in the opinion of the Investigator, have interfered with the patient's participation in the clinical study or evaluation of the clinical study results also warranted exclusion from the study.

Central HER2 Testing

Tumor tissue samples collected from patients will be analyzed for HER2 status by a central laboratory designated by the sponsor using a validated assay. Tumor lesions used to acquire samples for HER2 testing were not target lesions, unless there were no other lesions suitable for biopsy. Samples with limited tumor content and fine needle aspirate specimens were considered not acceptable.

Treatment and Responses

Patients received a dose of 5.4 mg/kg every 3 weeks, and the number of treatment cycles with trastuzumab deruxtecan until RECIST 1.1 disease progression and withdrawal of consent parameters were not fixed. Upon commencing study treatment, patients continued receiving trastuzumab deruxtecan until RECIST 1.1 disease progression, withdrawal of consent, or any of the discontinuation criteria were met.

Trastuzumab deruxtecan was administered using an intravenous bag containing 5% (w/v) Dextrose Injection infusion solution and delivered through an intravenous administration set with a 0.2 or 0.22 µm filter. The standard infusion time for trastuzumab deruxtecan was approximately 90 minutes for the first infusion. If the first infusion was well tolerated and the participant did not experience an infusion-related reaction, the minimum infusion time for subsequent cycles was at least 30 minutes. If there were interruptions during the infusion, the total infusion time was not allowed to exceed 3 hours at room temperature. The participant's weight at screening (baseline) was used to calculate the initial dose. If, during treatment, the participant's weight changed by ≥10%, the participant's dose was recalculated based on the participant's updated weight.

All dose modifications (interruption, reduction, and/or discontinuation) should be based on the worst preceding toxicity. Dosing was interrupted (or discontinued in the case of a dose-limiting toxicity), and supporting therapy was administered as required. Upon improvement of an adverse event leading to dose interruption, trastuzumab deruxtecan therapy could be resumed at the same dose. If a further episode of the same adverse event, or a different adverse event, required dose interruption, therapy could be restarted at a reduced dose upon improvement (dose

level 1: 4.4 mg/kg of body weight; dose level 2: 3.2 mg/kg of body weight). Treatment-emergent adverse events were assessed by the Study Investigator as related use of trastuzumab deruxtecan.

Interstitial Lung Disease/Pneumonitis

Interstitial Lung Disease is considered an important identified risk-based on a comprehensive cumulative review of potential ILD/pneumonitis cases reviewed by the independent ILD Adjudication Committee, the available safety data from the clinical development program, available data from recent epidemiology/literature, biological plausibility, and safety information from drugs of similar class. High resolution CT and pulmonary function were measured at baseline and at the time of suspected ILD/pneumonitis events. Pulmonologist consultation, and pulse oximetry (SpO2), arterial blood gases if clinically indicated, and one blood sample were collected for PK as soon as ILD/pneumonitis was suspected, if feasible.

Multidisciplinary guidelines for diagnosing and managing T-DXd-related ILD/pneumonitis have been published and are available here: https://www.cancertreatmentreviews.com/article/S0305-7372(22)00042-1/fulltext

Visit Responses

For all patients, the RECIST tumor response data were used to determine each patient's visit response according to RECIST 1.1. They were also used to determine if a patient had progressed in accordance with RECIST and their best objective response to study treatment.

Baseline radiological tumor assessments were performed no more than 28 days before the start of study treatment and were performed as close as possible to the start of study treatment. Post-baseline tumor assessments by the Investigator were performed at the following timepoints:

- Every 6 weeks (±1 week) relative to the date of first dose of trastuzumab deruxtecan, until RECIST 1.1-defined radiological disease progression

- Tumor assessment scans continued if patients discontinued trastuzumab deruxtecan owing to toxicity without progression until progressive disease was detected

If an unscheduled assessment was performed, and the patient had not progressed, every attempt should have been made to complete the subsequent assessments at their scheduled visits. This schedule was followed to minimize any unintentional bias caused by some patients being assessed at a different frequency from other patients.

At each visit, patients were assigned a RECIST 1.1 visit response of complete response, partial response, stable disease, or progressive disease, using the information from target lesions, non-target lesions, and new lesions, and depending on the status of their disease compared with baseline and previous assessments. If a patient had a tumor assessment that could not be evaluated, then the patient was assigned a visit response of not evaluable unless there was evidence of progression, in which case the response was assigned as progressive disease.

Interim Analyses

Interim efficacy analyses were performed using the centrally determined analysis set after 15 centrally determined HER2-eligible patients within a cohort had the opportunity to complete two scheduled post-baseline scans according to RECIST 1.1. Safety data were reviewed alongside efficacy to support any decision to expand the inclusion criteria or size of a cohort. No adjustment for multiple testing was planned for this study.

Once 15 patients within a cohort were centrally determined as having HER2 IHC 3+ or IHC 2+ and had the opportunity to complete at least two scheduled post-baseline scans according to RECIST 1.1, the following applied:

- For each tumor-specific cohort (Cohorts 1–6), the inclusion criteria were expanded to include up to 10 IHC 1+ patients, if three or more responses were observed in the first 15 patients. If one or two responses were observed in the first 15 patients, the cohort continued recruiting without change. If zero responses

were observed in the first 15 patients, the cohort was closed to further recruitment

- For the other tumors cohort (Cohort 7), if one or more responses were observed in the first 15 patients, the cohort continued recruiting without change. If zero responses were observed in the first 15 patients, the cohort was closed to further recruitment
- During the study, both the bladder and cervical cohorts met the protocol-specified criteria to open recruitment of IHC 1+ patients, and only the cervical cohort prospectively recruited patients who were 1+ after this point, and so available data for 1+ patients are very limited. The cohorts for biliary tract cancer, endometrial cancer, and ovarian cancer had almost fully enrolled to 40 patients at the time the first 15 centrally confirmed patients were evaluable for response. Recruitment to the pancreatic cohort was closed (March 24, 2022) as zero responses in the first 15 patients had been observed

Target Lesion Visit Responses	**Description**
Complete response	Disappearance of all target lesions. Any pathological lymph nodes selected as target lesions must have had a reduction in short axis to <10 mm
Partial response	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters as long as criteria for progressive disease were not met
Stable disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease
Progressive disease	A ≥20% increase in the sum of diameters of target lesions and an absolute increase of ≥5 mm, taking as reference the smallest sum of diameters since treatment started, including the baseline sum of diameters
Not evaluable	Only relevant in certain situations (ie, if any of the target lesions were not assessed, or not evaluable, or had a lesion intervention at this visit, and scaling up could not be performed for lesions with interventions). Note: if the sum of diameters met the progressive disease criteria, progressive disease was overridden (ie, the lesions were not evaluable as a target lesion response)
Not applicable	No target lesions recorded at baseline

Non-Target Lesion Visit Responses	Description
Complete response	Disappearance of all non-target lesions present at baseline with all lymph nodes non-pathological in size (<10 mm short axis)
Non-complete response/ non-progressive disease	Persistence of one or more non-target lesions with no evidence of progression
Progressive disease	Unequivocal progression of existing non-target lesions. Unequivocal progression may have been due to an important progression in one lesion only or in several lesions. In all cases, the progression must have been clinically significant for the physician to consider changing (or stopping) therapy
Not evaluable	Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: for patients without target lesions at baseline, this was relevant if any of the non-target lesions were not assessed at this visit, and the progression criteria were not met
Not applicable	Only relevant if there were no non-target lesions at baseline

Overall Visit Response

Target	Non-Target	New Lesions	Overall
Complete response	Complete response or not applicable	No (or not evaluable)	**Complete response**
Complete response	Non-complete response, non-progressive disease, or not evaluable	No (or not evaluable)	**Partial response**
Partial response	Non-progressive disease, not evaluable, or not applicable	No (or not evaluable)	**Partial response**
Stable disease	Non-progressive disease, not evaluable, or not applicable	No (or not evaluable)	**Stable disease**
Progressive disease	Any	Any	**Progressive disease**
Any	Progressive disease	Any	**Progressive disease**
Any	Any	Yes	**Progressive disease**
Not evaluable	Non-progressive disease, not evaluable, or not applicable	No (or not evaluable)	**Not evaluable**
Not applicable	Complete response	No (or not evaluable)	**Complete response**
Not applicable	Non-complete response or non-progressive disease	No (or not evaluable)	**Stable disease**
Not applicable	Not evaluable	No (or not evaluable)	**Not evaluable**

Statistical Analyses

All RECIST 1.1 assessments, whether scheduled or unscheduled, were included in the calculation of efficacy variables, regardless of whether a patient discontinued study treatment or received another anticancer therapy. At the time of final analysis, all efficacy endpoints were summarized by cohort for the full analysis set. Selected efficacy endpoints were also summarized by cohort for the centrally determined efficacy analysis set.

Endpoints Analyzed	**Notes**
Confirmed ORR	Number and percentage of patients achieving confirmed objective response as determined by the Investigator according to RECIST 1.1 (with the associated two-sided 95% exact CI)
DOR	A Kaplan-Meier plot of DOR will be presented. The Kaplan-Meier estimate of median response and the corresponding two-sided 95% CIs will be reported
Disease control rate	Number and percentage of patients achieving disease control (with the associated two-sided 95% exact CI)
PFS	A Kaplan-Meier plot of PFS will be presented. The Kaplan-Meier estimate of median PFS and the corresponding two-sided 95% CIs will be reported. The proportion of patients alive and progression free at 6 and 12 months (Kaplan-Meier estimates) will be presented
OS	A Kaplan-Meier plot of OS will be presented. The Kaplan-Meier estimate of median OS and the corresponding two-sided 95% CIs will be reported. The proportion of patients alive at 6 and 12 months (Kaplan-Meier estimates) will be presented
Safety	Summary statistics for adverse events, serious adverse events, laboratory findings, vital signs, and echocardiography, electrocardiography, or multiple-gated acquisition results, Eastern Cooperative Oncology Group/World Health Organization performance status, and deaths

Abbreviations: DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Appendix to: Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results from the DESTINY-PanTumor02 Phase II Trial

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