Clinical Study Report Synopsis	
Drug Substance	Trastuzumab Deruxtecan (T-DXd, DS-8201a)
Study Code	D967MC00001
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A Phase II, Multicenter, Open-label Study to Evaluate the Efficacy and Safety of Trastuzumab Deruxtecan (T-DXd) for the Treatment of Unresectable and/or Metastatic Solid Tumors Harboring HER2 Activating Mutations Regardless of Tumor Histology

Study dates:
First patient enrolled: 30 December 2020
Last patient enrolled: 24 May 2022
The analyses presented in this report are based on a data cut-off date of 25 January 2023 and a clinical data lock date of 26 April 2023

Phase of development: Therapeutic exploratory (II)

International Co-ordinating Investigator: PPD
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Sponsor's Responsible Medical Officer: PPD
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study sites

The study was conducted at study sites in Asia, Europe, and North America. In total, 29 study sites in 9 countries enrolled patients, and patients were assigned to treatment at 29 study sites in 9 countries.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary and secondary study objectives and endpoints are presented in **Table S1**. Results for all primary and secondary endpoints are presented in this Synopsis.

Table S1 Objectives and endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of T-DXd in patients with metastatic or unresectable tumors harboring specific HER2 activating mutations across tumor types	Confirmed ORR according to RECIST 1.1, as assessed by ICR
Secondary	
To further evaluate the efficacy of T-DXd in patients with metastatic or unresectable tumors harboring pre-specified HER2 activating mutations across tumor types	ICR and Investigator assessments, based on RECIST 1.1, to allow the calculation of: DoR DCR PFS Proportion of patients alive and progression-free at 6 and 12 months Confirmed ORR (Investigator assessment)
To further investigate the efficacy of T-DXd on tumors with pre-specified HER2 mutations as measured by OS across tumor types	OS Proportion of patients alive at 6 and 12 months
To assess the safety and tolerability of T-DXd	Assessed by the occurrence of AEs, SAEs, and changes from baseline in laboratory parameters, vital signs, ECG and ECHO/MUGA results
To assess the PK of T-DXd, total anti-HER2 antibody and MAAA-1181a in serum	Serum concentration of T-DXd, total anti-HER2 antibody and MAAA-1181a
To investigate the immunogenicity of T-DXd [a]	Presence of ADAs for T-DXd

As no patients were ADA-positive post-baseline, immunogenicity data are not presented in this Synopsis.

Exploratory objectives are described in the body of the Clinical Study Report.

ADA, anti-drug antibodies; AE, adverse event; DCR, disease control rate; DoR, duration of response; ECG, electrocardiogram; ECHO, echocardiogram; HER2, human epidermal growth factor receptor 2; ICR, independent central review; MAAA-1181a, deruxtecan; MUGA, multigated acquisition; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PK, pharmacokinetic(s); RECIST 1.1, Response Evaluation Criteria In Solid Tumours version 1.1; SAE, serious adverse event; T DXd, trastuzumab deruxtecan.

Study design

This was an open-label, multi-center, single arm, Phase II study to evaluate the efficacy and safety of trastuzumab deruxtecan (T-DXd) for the treatment of unresectable and/or metastatic

solid tumors harboring specific human epidermal growth factor receptor 2 (HER2) activating mutations regardless of tumor histology.

Eligible patients were assigned via interactive response technology to receive treatment with T-DXd 5.4 mg/kg every 3 weeks (q3w) until Response Evaluation Criteria In Solid Tumours version 1.1 (RECIST 1.1)-defined disease progression, withdrawal of consent, or until any other of the discontinuation criteria was met.

Patients had tumor assessments per RECIST 1.1 performed using computed tomography or magnetic resonance imaging scans of the chest, abdomen, and pelvis at screening (within 28 days before the first dose of investigational product [IP]) and every 6 (± 1) weeks relative to the date of first dose of IP until RECIST 1.1 objective disease progression, withdrawal of consent, or death by any cause. Any other sites at which disease was suspected or known at baseline were also imaged and additional sites of disease not covered by the Clinical Study Protocol (CSP)-specified anatomy were followed at the same scheduled visits as other RECIST assessments. All radiological examinations performed during the study were retained at site as source data and were made available for independent central review (ICR).

Target subject population and sample size

The study planned to assign approximately 100 patients with unresectable and/or metastatic solid tumors carrying pre-specified HER2 activating mutations, who had progressed following prior treatment or who had no satisfactory alternative treatment options to study treatment. To ensure adequate representation across multiple tumor types, it was planned to treat a maximum of approximately 20 patients per tumor type, but there was no pre-specified requirement for representation of any individual tumor type.

The final analysis was planned to be performed when the last patient had had the opportunity for approximately 32 weeks of follow-up after treatment assignment. A sample size of 100 patients was determined to provide sufficient precision for the estimation of the objective response rate (ORR) in the study population and to allow wider representation of tumor types and selected mutations. The overall target was an CCI (95% exact confidence interval [CI]: 30.3, 50.3).

Investigational product and comparator(s): dosage, mode of administration and batch numbers

T-DXd was supplied by the Sponsor as a CCI lyophilized powder for drug infusion after reconstitution and dilution.

T-DXd was administered from the following batches: 9A010A, 9B001A, 9J003A, and CN20060N01.

Duration of treatment

Patients continued to receive study treatment until RECIST 1.1-defined disease progression, withdrawal of consent, or another criterion for discontinuation was met. After disease progression or discontinuation of IP, patients were followed for survival every 3 months (± 14 days) up to the time of the final analysis. Patients were contacted in the week following the final data cut-off (DCO) for analysis of survival to provide complete survival data.

Statistical methods

The final analysis was performed with a DCO of 25 January 2023.

Efficacy

The Full Analysis Set (FAS), defined as all patients who received at least 1 dose of study treatment, was used for all efficacy analyses in the final analysis. All efficacy endpoints are presented across all tumor types with RECIST 1.1 assessments included in the calculation of each efficacy variable following the methods described in the statistical analysis plan.

The primary study endpoint was confirmed ORR assessed by ICR per RECIST 1.1 across all tumor types. Objective response rate, defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) as assessed by ICR per RECIST 1.1, is presented with associated 2-sided 95% exact Clopper-Pearson CI.

A sensitivity analysis was performed summarizing confirmed ORR assessed by ICR per RECIST 1.1 based on a subset of patients in the FAS with measurable disease at baseline by ICR. A further sensitivity analysis was performed to investigate consistency of treatment effect by tumor type, and selected mutations and other subgroups for confirmed ORR by ICR and Investigator assessment.

Progression-free survival (PFS) was reported as Kaplan-Meier median estimates and their corresponding 2-sided 95% CIs and the proportion of patients who were progression-free at 6 and 12 months by ICR and Investigator assessment. Duration of response (DoR) and overall survival (OS) is presented using the same approach as for PFS. Disease control rate (DCR) is presented as the proportion of patients that achieved disease control with corresponding 2-sided 95% CIs. A sensitivity analysis to investigate consistency of treatment effect by tumor type and selected mutations was also performed for DoR by ICR and Investigator assessment.

Pharmacokinetics

Serum concentrations of T-DXd, total anti-HER2 antibody, and MAAA-1181a (deruxtecan) were summarized.

Immunogenicity

The number and percentage of patients who developed detectable anti-drug antibodies (ADAs) to T-DXd was summarized by ADA category for the ADA-evaluable Set.

Safety

Safety and tolerability were assessed in terms of adverse events (AEs) (including serious adverse events [SAEs] and adverse events of special interest [AESI]), exposure to IP, deaths, laboratory measurements, vital signs/saturation of peripheral oxygen, electrocardiograms (ECGs), physical examination, World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status, pulmonary assessments in the event of suspected interstitial lung disease (ILD)/pneumonitis, and left ventricular (LV) dysfunction based on echocardiogram (ECHO)/multi-gated acquisition (MUGA) scans.

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Study population

The study population was representative of the intended target population of patients with unresectable and/or metastatic solid tumors harboring specific HER2 activating mutations, who had progressed following prior treatment or had no satisfactory alternative treatment options.

Of 131 patients enrolled in the study, 102 (77.9%) were assigned to treatment with IP and all 102 patients received IP.

At baseline, the median age of patients in the FAS was 66.5 years CCI [redacted] with 58 (56.9%) patients aged 65 years and above. Most patients were female (62 patients; 60.8%), 51 (50.0%) patients were White, 38 (37.3%) patients were Asian, and approximately one-third of patients came from each of Asia (34 patients; 33.3%), Europe (40 patients; 39.2%), and North America (28 patients; 27.5%).

At screening, overall disease classification was metastatic for 101 (99.0%) patients and CCI [redacted] The distribution of tumor types reflected the natural prevalence of solid tumors: 17 different tumor types were represented (16 different tumor types when esophagogastric and esophageal tumors are considered as one type rather than separate tumor types). Fifty-nine (57.8%) patients had either breast, colorectal, or hepatobiliary tumors.

The median number (range) of prior anti-cancer regimens was 3.0 (1 to 13), primarily cytotoxic chemotherapy and platinum compounds; 58 (56.9%) patients had received 3 or more prior regimens of anti-cancer therapy. Eighteen (17.6%) patients had received prior

HER2-targeted therapy, ie, therapy with either a HER2 inhibitor and/or a HER2 tyrosine kinase inhibitor. Thirty-three (32.4%) patients had received a prior topoisomerase I inhibitor (irinotecan).

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All 102 patients assigned to IP received treatment with IP.

At the final DCO, 87 (85.3%) patients had discontinued IP, most frequently due to objective disease progression (63 patients; 61.8%) or AEs (10 patients; 9.8%).

At the final DCO, 33 (32.4%) patients remained on-study, including 15 (14.7%) patients who were still receiving IP. All patients who were still on-study at the final DCO were considered to have completed the study.

Summary of efficacy results

All efficacy analyses were performed at the DCO and, except where indicated, were performed for the FAS.

Primary efficacy endpoint: confirmed ORR assessed by ICR per RECIST 1.1

The confirmed ORR based on ICR per RECIST 1.1 across all tumor types was 29.4%, (95% CI: 20.8, 39.3), with 30 patients achieving a confirmed response. Results based on Investigator assessment (secondary endpoint) were similar: 32.4% (95% CI: 23.4, 42.3).

Sensitivity analysis: Confirmed ORR by ICR per RECIST 1.1 performed on the subset of 92 patients in the FAS with measurable disease at baseline by ICR was 31.5% (95% CI: 22.2, 42.0).

Sensitivity analyses: Interpretation of confirmed ORR by ICR per RECIST 1.1 by subgroup was limited by small patient numbers and wide CIs in some subgroups. CCI

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Across all subgroup analyses, confirmed ORR per RECIST 1.1 by ICR and by Investigator assessment were generally similar, and where differences were observed, they typically involved subgroups with small patient numbers.

Secondary efficacy endpoints

Best objective response (BoR): Thirty (29.4%) patients achieved a BoR of either confirmed CR or confirmed PR by ICR per RECIST 1.1, including 2 (2.0%) patients with CR and 28 (27.5%) with PR. An additional 45 (44.1%) patients had stable disease (SD) ≥ 5 weeks based on ICR per RECIST 1.1.

The proportion of patients who achieved a BoR of either confirmed CR or confirmed PR by Investigator assessment per RECIST 1.1 was higher (33 patients; 32.4%) and the proportion of patients with SD ≥ 5 weeks (39 patients; 38.2%) was lower.

Duration of response: Median DoR from onset of response based on ICR per RECIST 1.1 for patients with an objective response was not evaluable (NE) (95% CI: 6.8, NE). Data for several patients were censored before the median, indicating that the median DoR was immature at the DCO and therefore not reached when assessed by ICR. Median DoR based on Investigator assessment was 11.0 months (95% CI: 7.9, 18.1).

For patients who achieved an objective response by ICR per RECIST 1.1, responses were generally long and durable, with 65.0% and 54.2% of patients still in response at 12 and 18 months, respectively.

Disease control rate: More than 70% of patients achieved disease control (ie, either confirmed CR, confirmed PR, or SD [without subsequent therapy]) per RECIST 1.1 at 6 weeks (75.5% by ICR and 70.6% by Investigator assessment). At 12 weeks, disease control was achieved by 53.9% and 55.9% by ICR and Investigator assessment, respectively.

Progression-free survival: At the DCO, 61 (59.8%) patients had PFS events (RECIST 1.1 progression by ICR or death in the absence of progression). Median PFS per RECIST 1.1 was 5.4 months (95% CI: 2.7, 7.1) by ICR and 4.4 months (95% CI: 2.8, 5.6) by Investigator. By ICR, 41.4% and 30.9% of patients were progression-free at 6 and 12 months, respectively.

Overall survival: Fifty-eight (56.9%) patients had died at the DCO. Median OS was 10.9 months (95% CI: 8.3, 14.9). At 6 and 12 months, 67.6% and 46.3% of patients were alive, respectively.

Summary of pharmacokinetic results

Overall concentration levels for T-DXd and total anti-HER2 antibody were similar. The arithmetic mean post-infusion concentration was 116.5 µg/mL (standard deviation [StD] 50.85 µg/mL) vs. 123.8 µg/mL (StD 52.80 µg/mL) at Cycle 1 15 mins post-infusion and 121.7 µg/mL (StD 40.09 µg/mL) vs. 122.1 µg/mL (StD 37.30 µg/mL) at Cycle 4 15 mins post-infusion for T-DXd and total anti-HER2 antibody, respectively, and in the same range as previously reported for patients dosed at T-DXd 5.4 mg/kg q3w. Steady state was reached around Cycle 2 to 4.

At 5 hours post-infusion Cycle 1, the arithmetic mean concentration of MAAA-1181a was 10.5 ng/mL (StD 5.12 ng/mL), which was similar to previously reported maximum concentration (Cmax) levels for patients dosed at T-DXd 5.4 mg/kg q3w and higher than the value 15 mins post-infusion (4.7 ng/mL; StD 2.86 ng/mL). First cycle arithmetic mean concentrations of MAAA-1181a at 15 mins post-infusion were slightly higher than in later cycles (4.7 ng/mL, 2.2 ng/mL, and 1.5 ng/mL for Cycles 1, 2, and 4, respectively).

For the 9 patients with suspected ILD/pneumonitis, concentrations of T-DXd or MAAA-1181a did not exceed exposure levels observed in the rest of the population.

Summary of immunogenicity results

No patients were ADA-positive post-baseline, thus ADA incidence (the percentage of patients who were evaluable for ADA and were treatment-emergent ADA-positive) was 0%.

Summary of safety results

All safety data are presented for the Safety Analysis Set (SAF).

Exposure

The median duration (range) of exposure to IP was 3.45 months (0.7 to 22.1 months) and the median number (range) of treatment cycles received was 5.0 (1 to 29). Fifty-two (51.0%) patients received at least 5 cycles of IP. Dose modifications (ie, dose delays and/or dose reductions) affected fewer than half the patients:

- 41 (40.2%) patients had dose delays, typically 1 or 2 dose delays, most of which were attributed to AEs.
- 14 (13.7%) patients had 1 or 2 dose reductions, all due to AEs.
- 45 (44.1%) patients experienced dose modifications. Most patients had ≤ 3 dose modifications; 1 (1.0%) patient had 10 dose modifications.

Safety findings

The observed safety profile of T-DXd monotherapy was consistent with the known safety profile for patients with solid tumors dosed with T-DXd 5.4 mg/kg. No new safety signals were observed.

Adverse events are summarized in **Table S2**.

Table S2 Overview of adverse events (SAF)

AE category	No. (%) of patients [a] T-DXd 5.4 mg/kg N = 102
Any AE	102 (100)
Any AE possibly related to IP [b]	79 (77.5)
Any AE of CTCAE Grade ≥ 3	52 (51.0)
Any AE of CTCAE Grade ≥ 3, possibly related to IP [b]	26 (25.5)
Any AE with an outcome of death	4 (3.9)
Any AE with an outcome of death, possibly related to IP [b]	2 (2.0)
Any SAE (including events with an outcome of death)	36 (35.3)
Any SAE (including events with an outcome of death), possibly related to IP [b]	10 (9.8)
Any AE leading to discontinuation of IP	10 (9.8)
Any AE leading to discontinuation of IP, possibly related to IP [b]	8 (7.8)
Any AE leading to dose modification of IP [c]	43 (42.2)
Any AE leading to dose modification of IP, possibly related to IP [b, c]	24 (23.5)
Any AE leading to dose reduction of IP [c]	14 (13.7)
Any AE leading to dose reduction of IP, possibly related to IP [b]	13 (12.7)
Any AE leading to dose interruption of IP [c]	37 (36.3)
Any AE leading to dose interruption of IP, possibly related to IP [b]	15 (14.7)
Any AE leading to hospitalization	35 (34.3)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.

As assessed by the Investigator. Missing causalities were counted as possibly related.

Dose modification includes AEs with action taken of dose reduced or drug interrupted.

Includes AEs with onset date or worsening on or after the first dose of IP up to and including 47 days after the last dose of IP, or before the initiation of the first subsequent anti-cancer therapy following discontinuation of IP, whichever occurred first.

MedDRA version 25.1.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; IP, investigational product; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SAF, Safety Analysis Set; T-DXd, trastuzumab deruxtecan.

Safety findings are summarized below:

- The most common AEs (reported in > 20% of patients) were nausea, anaemia, fatigue, diarrhoea, decreased appetite, and asthenia. These events were mostly Grade 1 or 2 and were manageable through routine clinical practice. None of these events resulted in discontinuation of IP.
- The maximum reported Common Terminology Criteria for Adverse Events (CTCAE) grade was Grade ≥ 3 for 52 (51.0%) patients and Grade 1 or 2 for 50 (49.0%) patients.

- CTCAE Grade ≥ 3 AEs were primarily hematologic, including anaemia, neutrophil count decreased, and platelet count decreased in 16 (15.7%), 8 (7.8%), and 5 (4.9%) patients, respectively. An additional 4 (3.9%) patients had events of Grade ≥ 3 neutropenia (3 [2.9%] patients) or febrile neutropenia (1 [1.0%] patient) and an additional 3 (2.9%) patients had events of Grade ≥ 3 thrombocytopenia.
- Four (3.9%) patients had an AE with a fatal outcome: 2 (2.0%) patients had pneumonitis events that were considered IP-related by the Adjudication Committee and the Investigator, and events of COVID-19 pneumonia and pneumonia, each reported by 1 (1.0%) patient, neither of which was considered related to IP by the Investigator.
- Thirty-six (35.3%) patients had a treatment-emergent SAE. SAEs reported in > 1 patient were pneumonitis in 4 (3.9%) patients and acute kidney injury, anaemia, asthenia, biliary tract infection, bone pain, cholangitis, constipation, dyspnoea, pneumonia, and vomiting, all in 2 (2.0%) patients. Ten (9.8%) patients had a treatment-related SAE as assessed by the Investigator.
- Adverse events resulting in discontinuation of IP occurred in 10 (9.8%) patients, and most were CTCAE Grade 1 or 2. Discontinuations were primarily due to events of adjudicated ILD/pneumonitis (pneumonitis and interstitial lung disease in 5 (4.9%) and 3 (2.9%) patients, respectively), driven in part by the CSP-defined dose modification criteria for ILD/pneumonitis to permanently discontinue IP for any CTCAE Grade 2 ILD/pneumonitis event as assessed by the Investigator.
- The most common AE associated with dose reduction was nausea in 5 (4.9%) patients. No other AE resulted in a dose reduction in > 1 (1.0%) patient.
- The most common AEs associated with interruption of IP were COVID-19 and neutrophil count decreased in 6 (5.9%) patients, anaemia in 5 (4.9%) patients, and fatigue in 3 (2.9%) of patients.
- Adjudicated ILD/pneumonitis was reported in 11 (10.8%) patients. All such events were considered related to IP and 7 (6.9%) patients discontinued IP due to adjudicated IP-related ILD/pneumonitis. Most cases were CTCAE Grade 1 or 2. Three (2.9%) patients had adjudicated IP-related ILD that was CTCAE Grade ≥ 3, 1 patient with a Grade 3 event and 2 patients with a Grade 5 event. The preferred term for all 3 events was pneumonitis. Most events were manageable with either a dose modification or by discontinuing IP following established treatment guidelines.
- LV dysfunction was reported in 5 (4.9%) patients. All events were CTCAE Grade 1 or 2, and none resulted in discontinuation of IP.
- Changes and grade shifts from baseline in laboratory data were consistent with reported AEs.
- Overall, no significant changes were observed over time in vital signs, ECGs, ECHO/MUGA, or WHO/ECOG performance status.

Conclusions

The current study is the first tumor-agnostic global study of T-DXd in a range of solid tumors with pre-specified HER2 mutations. In this heavily pre-treated patient population with limited

treatment options, T-DXd monotherapy 5.4 mg/kg q3w demonstrated encouraging anti-cancer activity as evidenced by:

- A confirmed ORR by ICR per RECIST 1.1 of 29.4% and favorable DoR across multiple tumor types (median not reached, 95% CI: 6.8, NE).
- A manageable safety and tolerability profile consistent with the known safety profile of T-DXd monotherapy in patients with solid tumors, with no new safety signals.
- Serum concentrations of T-DXd, total anti HER2 antibody, and MAAA-1181a that were consistent with those previously reported for patients treated with T-DXd 5.4 mg/kg q3w.

Translational research will help to characterize the population of patients who may derive the greatest benefit from treatment with T-DXd.