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185P Safety, tolerability, and antitumor activity of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2+ metastatic breast cancer (mBC) and active brain metastases (BM) in DESTINY-Breast07 (DB-07)

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184MO First-in-human phase I/IIa study of the first-in-class, next-generation CDK4-selective inhibitor PF-07220060 in combination with endocrine therapy (ET) in patients (pts) with HR+/HER2− metastatic breast cancer (mBC) who progressed on prior CDK4/6 inhibitors (CDK4/6i): Safety and efficacy update

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Background: PF-07220060 is a novel potent oral CDK4i with significant sparing of CDK6. Preliminary safety and dose escalation data from this phI/IIastudy were previously presented. Here we report updated safety and efficacy data in pts with HR+/HER2− mBC, who progressed on prior CDK4/6i and ET, treated with PF-07220060 + ET.

Methods: This study in pts with advanced solid tumors was enriched for pts with HR+/HER2− mBC who received ≥2 lines of treatment including ET and CDK4/6i. Prior fulvestrant and chemotherapy were allowed. Study objectives were to assess safety, tolerability, and antitumor activity of PF-07220060 alone and in combination with ET.

Results: At data cutoff (Nov 1, 2023), 33 pts received PF-07220060 (300mg/400mg BID) in combination with letrozole or fulvestrant (Parts 1B + 1C). Median age was 62.0y (range 41−82); ECOG PS was 0 (36.4%) or 1. Median prior lines of systemic therapy (advanced setting) was 4.0 (range 1−11). All pts had prior CDK4/6i treatment, 24 (72.7%) had prior fulvestrant, and 22 (66.7%) had prior chemotherapy in the advanced/metastatic setting. Most frequent treatment-emergent adverse events (TEAEs) were neutropenia (54.5%; 18.2% Grade 3 [G3]), diarrhea (42.4%; 0% G3), and nausea (42.4%; 3.0% G3), with no >G3 TEAEs. Dose modifications due to TEAEs included: 1 (3.0%) pt discontinued PF-07220060, 5 (15.2%) pts had dose reduction, and 10 (30.3%) pts had dose interruptions. In 25 pts with measurable disease who progressed on prior CDK4/6i + ET, 8 (32.0%) had confirmed RECIST v1.1 objective responses (1 CR, 7 PR). Clinical benefit response (CR, PR, or ≥24 wks stable disease) was seen in 20/33 (60.6%) pts. Median progression-free survival was 8.1 months (95% CI: 5.3, 10.9). Confirmed objective responses (PRs) were observed irrespective of ESR1 or PI3K pathway mutations.

Conclusions: PF-07220060 + ET showed a favorable safety profile with few hematologic adverse events and infrequent dose modifications, and promising efficacy despite prior CDK4/6i treatment, irrespective of key mutations.

Clinical trial identification: NCT04557449.

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185P Safety, tolerability, and antitumor activity of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2+ metastatic breast cancer (mBC) and active brain metastases (BM) in DESTINY-Breast07 (DB-07)

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Background: DEBBRAH, ROSET-BM, TUXEDO-1, and a pooled DB-01, -02, -03 analysis indicate robust efficacy of T-DXd in pts with stable/active BM; however, efficacy in pts with BM is not yet fully established. DB-07 is a phase Ib/II, multicenter, open-label study exploring the safety, tolerability, and antitumor activity of T-DXd alone or in combination with other anticancer agents (NCT04538742). Results are from an interim analysis of the dose-expansion phase of T-DXd monotherapy in pts with active BM.

Methods: Pts had locally assessed HER2+ mBC with measurable disease. No or one prior line of therapy for mBC was allowed; a disease-free interval of ≥12 months from (neo)adjuvant HER2-directed therapy or chemotherapy was required. Pts had untreated BM not requiring local therapy or progressing BM after treatment with local therapy. Ongoing use of systemic corticosteroids (>2 mg dexamethasone daily or equivalent) for control of BM symptoms was exclusionary. Pts received T-DXd 5.4 mg/kg intravenously every 3 weeks. Primary endpoints were safety and tolerability; secondary endpoints included objective response rate (ORR) and progression-free survival (PFS) per RECIST 1.1 and Response Assessment in Neuro-Oncology (RANO)-BM.

Results: Thirty-five pts with active BM were treated (median age 49 years); median follow up was 11.5 months (range 5.3−24.6). As of August 1, 2023, the most common any-grade adverse events (AEs) were nausea (74.3%; Grade 3, 5.7%) and vomiting (45.7%; Grade 3, 2.9%); no Grade ≥4 nausea or vomiting was reported. By RANO-BM, confirmed ORR was 57.1% and PFS rate at 12 months was 74.6% (Table).

Conclusions: The safety profile is consistent with the known profile for T-DXd and data confirm promising efficacy in pts with active BM; a median PFS has not been reached after 11.5 months. Ongoing analyses will provide more mature data.

Clinical trial identification: NCT04538742.

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186P Exploratory pooled safety analysis of trastuzumab deruxtecan (T-DXd) in patients With HER2+ or HER2-low unresectable and/or metastatic breast cancer (mBC) in DESTINY-Breast trials

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Background: T-DXd is approved as 2L+ treatment for pts with HER2+ or HER2-low (IHC 1+/IHC 2+/ISH−) mBC based on efficacy in DESTINY-Breast (DB)-01/02/03/04 trials. There are no published pooled safety data for T-DXd in pts with mBC.

Methods: Analysis included pts with HER2+ (DB-01/02/03) or HER2-low (DB-04) mBC. DB-01 was a single-arm study of T-DXd after trastuzumab emtansine (T-DM1). DB-02 compared T-DXd to treatment of physician's choice (TPC) after T-DM1. DB-03 compared T-DXd to T-DM1 after trastuzumab (± pertuzumab) + taxane. DB-04 compared T-DXd to TPC after 1 or 2 chemotherapy lines.

Results: Drug-related treatment-emergent adverse event (TEAE) rates for T-DXd were similar in DB-01/02/03/04 (Table). Median time (range) to T-DXd discontinuation due to any TEAE in DB-01/02/03/04 was 187.0 (8-783), 248.5 (2-759), 337.0 (104-1163), and 149.0 (3-740) d, respectively. Pooled T-DXd (N = 1216) adjudicated drug-related interstitial lung disease (ILD) rate was 12.7%; most grade 1 or 2 (11%); median (range) time to onset 176 (26-960) d; median (range) duration 56.5 (1-542) d. Rates of any-grade adjudicated drug-related ILD with T-DXd after <3/≥3 prior therapy lines were 14.3%/15.9% in DB-01, 7.1%/11.3% in DB-02, 17.9%/13.1% in DB-03, and 5.7%/13.2% in DB-04. Median treatment duration was ∼2-fold longer for pooled T-DXd (13.9 months; range, 0.2-45.1) vs comparators. Exposure-adjusted incidence rates of grade ≥3 TEAEs were 0.48 (T-DXd), 0.77 (TPC, DB-02), 0.65 (T-DM1), and 1.81 (TPC, DB-04) pt-years. Higher rates of drug-related nausea (72.4% vs 30.8%, 27.6%, 23.8%), vomiting (37.3% vs 11.8%, 5.7%, 9.9%), and fatigue (51.2% vs 31.3%, 29.1%, 42.4%) occurred with T-DXd vs TPC (DB-02), T-DM1 (DB-03), and TPC (DB-04).

Table: 185P Key safety and efficacy data

	T-DXd in pts with active BM (n=35)	
Any-grade AEs, n (%)	35 (100)	
AEs Grade ≥3, n (%)	18 (51.4)	
Serious AEs, n (%)	5 (14.3)	
Any-grade pneumonitis (adjudicated as interstitial lung disease related to study drug), n (%)	3 (8.6)	
Grade 2, n (%)	2 (5.7)	
Grade 5, n (%)	1 (2.9)	
Median actual treatment duration, months (range)	10.0 (2.6—24.3)	
	Overall response (RECIST 1.1 by investigator)	**Intracranial response (RANO-BM BICR)**
Confirmed ORR, % (80% CI)	77.1 (65.5, 86.2)	57.1 (44.9, 68.7)
PFS rate at 12 months, % (80% CI)	84.5 (74.1, 91.0)	74.6 (59.4, 84.8)

BICR, blinded independent central review; CI, confidence interval.