Safety and Tolerability of a Novel Anti-HER2 Antibody–Drug Conjugate (PF-06804103) in Patients with HER2-Expressing Solid Tumors: A Phase 1 Dose-Escalation Study

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ABSTRACT

PF-06804103 is an anti-HER2 antibody–drug conjugate with auristatin payload. We evaluated its safety, tolerability, and antitumor activity in patients with advanced/unresectable or metastatic breast and gastric cancers. This multicenter, open-label, first-in-human, phase 1 study (NCT03284723) comprised dose escalation (P1) and dose expansion (P2). In P1, adults with HER2+ breast or gastric cancer received PF-06804103 0.15–5.0 mg/kg intravenously once/21 days (Q3W); in P2, patients with HER2+ or HER2-low (IHC 1+ or IHC 2+/ISH−) breast cancer received 3.0 or 4.0 mg/kg Q3W. The primary endpoints were dose-limiting toxicities (DLT) and safety (P1), and objective response rate (ORR) assessed using RECIST v1.1 (P2). Ninety-three patients enrolled in P1 ($n = 47$: HER2+ gastric cancer = 22, HER2+ breast cancer = 25) and P2 [$n = 46$: HER2+ breast cancer = 19, hormone receptor (HR)+ HER2-low breast cancer = 27] received PF-06804103. Four patients (3.0- and 4.0-mg/kg groups, $n = 2$ each) had DLTs (mostly Grade 3). Safety and efficacy results showed a dose–response relationship. Adverse events (AE) leading to treatment discontinuation (44/93, 47.3%) included neuropathy (11/93, 11.8%), skin toxicity (9/93, 9.7%), myalgia (5/93, 5.4%), keratitis (3/93, 3.2%), and arthralgia (2/93, 2.2%). Two (2/79, 2.5%) patients (P1, 4.0- and 5.0-mg/kg groups, $n = 1$ each) achieved complete response; 21 (21/79, 26.6%) achieved partial response. In P2, ORR was higher in HER2+ compared with HR+ HER2-low breast cancer [3.0 mg/kg: 16.7% (2/12) vs. 10.0% (1/10); 4.0 mg/kg: 47.4% (9/19) vs. 27.3% (3/11)]. PF-06804103 demonstrated antitumor activity; however, AEs led to discontinuation in 47.3% of patients. Safety and efficacy were dose-dependent.

Introduction

Aberrant activation of receptor tyrosine kinase *HER2* has been implicated in tumorigenesis and a driving factor in cancer progression (1–3). *HER2* amplification/overexpression in breast and gastric cancers was associated with decreased survival and clinicopathologic features of tumor progression (4, 5). After failure of approved therapies, HER2-expressing cancers constitute an unmet clinical need (6, 7).

Antibody–drug conjugates (ADC) are a class of drugs using antibodies specifically targeting tumor-associated antigens as vehicles to deliver covalently attached small-molecule toxins into cancer cells (8, 9). Experience in ado-trastuzumab emtansine (T-DM1), an ADC for the treatment of HER2-positive breast cancer (10–12), showed that in spite of its activity, intrinsic and acquired resistance to T-DM1 remains a major challenge, and further, its activity is limited in tumors expressing low levels of HER2. A second ADC, trastuzumab deruxtecan (T-DXd), has been approved more recently (13, 14). T-DXd is now considered the second-line agent of choice for patients with unresectable or metastatic HER2-positive (HER2 IHC 3+ or IHC 2+/ISH+) and HER2-low (HER2 expression is IHC 1+ or IHC 2+/ISH−) breast cancer, locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma and unresectable or metastatic non–small cell lung cancer (NSCLC) with activating *HER2* (ERBB2) mutations (13). Bystander activity is a key attribute engineered into the designs of a new generation of anti-HER2 ADC, such as T-DXd, that is beneficial in treating tumors with HER2 heterogeneity not responsive to T-DM1 (15).

PF-06804103 is an anti-HER2 immunoglobulin G1 ADC comprising an anti-HER2 mAb (trastuzumab) conjugated to the cytotoxic agent Aur0101 at specifically engineered reactive cysteine sites, allowing for

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a near homogeneous (drug–antibody ratio = 4) ADC preparation. PF-06804103 uses at least two different mechanisms of action. The primary mechanism is the targeted delivery of the cytotoxic anti-microtubule auristatin payload to HER2-positive, or HER2-low–expressing cells. An additional mechanism of action is the inhibition of HER2-mediated signaling by trastuzumab in HER2-expressing cancer cells (16).

Significant tumor growth control has been observed in PF-06804103 preclinical studies using various tumor models, including breast cancer and gastric and gastroesophageal cancer (GC) with HER2-low. In HER2-expressing patient-derived xenografts, PF-06804103 showed efficacy in mice with tumors expressing low to moderate levels of HER2 (17). These findings indicated that PF-06804103 may have the potential to provide therapeutic benefit to patients with HER2-low expressing tumors.

This phase 1 study (NCT03284723) of PF-06804103 was carried out in adult patients with HER2-positive and HER2-low breast cancer and HER2-positive GC to characterize the dose-limiting toxicity (DLT), assess the safety and tolerability, determine the recommended phase 2 dose as monotherapy, and investigate preliminary antitumor activity of PF-06804103. To identify patients with lower levels of HER2 protein who might respond to PF-06804103, patients with tumors expressing HER2 IHC 1+ and HER IHC 2+/ISH− were included and patients with HER2 IHC 0 tumors were excluded. This study was conducted in two parts, dose escalation and dose expansion.

Materials and Methods

This study was conducted in accordance with the protocol, legal and regulatory requirements, and general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Council on Harmonization Guideline for Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the Institutional Review Board or Ethics Committee of study centers. All patients provided written informed consent.

Study design

This was a phase 1, open-label, multicenter, multiple-dose, safety, pharmacokinetic (PK), and pharmacodynamics study investigating PF-06804103 in adult patients with HER2-positive solid tumors [breast cancer and GC (Part 1A only) and in patients with hormone receptor (HR)–positive HER2 IHC 1+ or IHC 2+/ISH− (HR+ HER2-low)] breast cancer (Supplementary Fig. S1). This study was planned to have a dose-escalation portion (Parts 1A and 1B) and a dose-expansion portion (Parts 2A and 2B); PF-06804103 was to be investigated as monotherapy in Parts 1A and 2A, and as part of a combination-treatment regimen in Parts 1B and 2B. The study started on November 1, 2017, and patients were enrolled at 21 study centers in 6 countries. On February 10, 2021, the study sponsor decided to terminate the study due to strategic consideration. The study was completed on August 31, 2021.

Dose escalation of PF-06804103 was performed using a modified toxicity probability interval (mTPI) design (18, 19). In Part 1A, patients with HER2-positive breast cancer or HER2-positive GC received PF-06804103 (intravenously) at 0.15, 0.5, 1.2, 2.0, 3.0, 4.0 or 5.0 mg/kg once every 3 weeks (Q3W) in a 21-day cycle to determine the dose level of PF-06804103 for Part 2A. Because of early termination, Part 1B only included two postmenopausal women with HR+ HER2-low breast cancer who received study treatment, that is, PF-06804103 (IV) at 2.0 mg/kg once every 2 weeks in a 28-day cycle in combination with oral palbociclib and letrozole (Supplementary File S1).

For the dose-expansion part, the combination regimen planned for Part 2B was not tested as Part 2B was not initiated as a result of the early termination decision, whereas PF-06804103 monotherapy was investigated in Part 2A. In Part 2A, patients with HER2-positive breast cancer in third-line therapy setting and those with HR+ HER2-low breast cancer in second-line therapy setting received PF-06804103 3.0 or 4.0 mg/kg administered as monotherapy Q3W.

Treatment with PF-06804103 continued until disease progression, patient withdrawal of consent or occurrence of unacceptable toxicity occurs, whichever occurred first, unless the investigator and medical monitor agreed to treatment beyond progression based on individual benefit/risk assessments.

Patients

Inclusion criteria

Eligible patients were: Adult male (Part 1A only) or female patients ages ≥18 years (≥19 years where required by local regulations); histologically or cytologically confirmed advanced/unresectable or metastatic HER2-positive breast cancer or GC (Part 1A only) that was refractory to or intolerable with standard therapy or for which no standard therapy was available; Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1; adequate bone marrow function, renal function and liver function; resolution of acute effects of any prior therapy; and not pregnant at screening.

Patients in Part 1A were also required to have hemoglobin-adjusted diffusing capacity for carbon monoxide (DL_{CO}) ≥60% and documentation of HER2 IHC 3+ or ISH+ status. For Part 2A, the additional inclusion criteria were documentation of HER2 IHC 3+ or ISH+ status and HER2 IHC 1+ or IHC 2+/ISH− status (having progressed on ≥1 prior systemic therapy, including a hormonal-based regimen and histologically or cytologically confirmed diagnosis of estrogen receptor-positive or progesterone receptor-positive breast cancer) that was advanced/unresectable or metastatic; ≥1 measurable lesion without previous irradiation, as defined by the RECIST version 1.1; and with archival or fresh tumor biopsy sample for retrospective assessment for HER2 expression.

Exclusion criteria

The key exclusion criteria included: HER2 IHC 0; symptomatic brain metastases requiring steroid treatment; radiotherapy within 4 weeks, hormonal therapy <7 days, or trastuzumab, trastuzumab emtansine, or pertuzumab therapy and/or lapatinib <21 days before registration; systemic anticancer therapy within 4 weeks before study entry; Grade 3 hypersensitivity reaction to prior receipt of any antibody therapy; previous high-dose chemotherapy requiring stem cell rescue; prior irradiation to >25% of the bone marrow; history of intolerance, including Grade 3 infusion reaction or hypersensitivity to trastuzumab, murine proteins, or docetaxel/paclitaxel or known or suspected hypersensitivity to recombinant human or murine proteins; and participation in other studies involving investigational drugs within 30 days, 5 half-lives or twice the duration of the biological effect of the investigational drug (whichever was longer) before study entry.

Endpoints and assessments

Endpoints

The primary endpoints for Part 1 were DLTs in the first cycle and safety findings, including adverse events (AE), serious AEs (SAE), and clinically meaningful abnormalities in laboratory values and vital signs. For Part 2, the primary endpoints were objective response (OR) assessed using RECIST version 1.1, and time-to-event endpoints such as duration of response (DoR) and progression-free survival (PFS).

Secondary endpoints included PK parameters of PF-06804103 ADC, total antibody, and unconjugated payload (PF-06380101) at single dose and multiple doses; incidence and titers of antidrug–antibody (ADA)

and neutralizing antibody (NAb) against PF-06804103; OR rate (ORR), time to response, DoR, PFS, and time-to-progression for Part 1; and HER2 expression levels in pretreatment tumor biopsies using IHC and ISH.

Exploratory endpoints included HER2 expression levels using IHC and ISH, and soluble HER2 levels in the blood.

Assessments

Study visits were scheduled for screening/baseline; Days 1, 4, 8, and 15 of Cycles 1 and 4; Days 1, 8, and 15 of Cycles 2, 3, 5, and subsequent cycles; end of treatment (EOT); and follow-up visit.

Safety assessments included the type, incidence, severity [graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03], timing, seriousness, and relatedness of assessment of AEs. Hematology and blood chemistry samples, and physical examination, including vital signs and assessment of ECOG PS, triplicate 12-lead electrocardiogram (ECG; with a 10-second rhythm strip) tracing, were collected at certain study visits. ECG (recorded before PK samples were obtained) or multigated acquisition scan were carried out on screening/baseline; Day 1 of Cycles 3, 6, and every 3 cycles thereafter; and EOT.

Tumor response was assessed using RECIST version 1.1. Radiological tumor assessments with CT or MRI scans, bone scan, and/or bone x-rays for all known or suspected disease sites were conducted at baseline, every 6 weeks (Part 1A and 2A) starting at Cycle 3 during treatment until disease progression was suspected (e.g., symptomatic deterioration), and EOT (if no radiological assessment in the previous 6 weeks).

PK, immunogenicity, biomarker, and pharmacodynamic assessments were also performed. Blood samples for PF-06804103, total antibody, and unconjugated payload (PF-06380101) PK were collected at pre-dose, 1 and 4 hours post-dose on Day 1; Days 2 (i.e., 24 hours post-dose), 4, 8 (Part 1A only on these 3 days), and 15 of Cycles 1 and 4; pre-dose and 1-hour post-dose on Day 1 of Cycles 2 and 3, and every cycle after Cycle 4; and EOT. Blood samples for soluble HER2 were collected at the same time points as for PK except 1-hour post-dose on Day 1 of Cycles 2 and 3, and every cycle after Cycle 4. Blood samples for immunogenicity of PF-06804103 (ADA and NAb against PF-06804103) were collected at pre-dose of Day 1 of each cycle, Day 15 of Cycle 1, and EOT.

For Part 1, tumor biopsy at pretreatment (screening) and on Day 1 of Cycle 3 (±5 days) was optional. For Part 2, a mandatory pretreatment biopsy (archived sample acceptable if no anti-HER2 treatment between sample collection and study start) was carried out for all patients at screening. In Part 2, a mandatory on-treatment biopsy was collected at Day 1 Cycle 3 (±5 days) from up to 10 patients in each arm to obtain paired pretreatment and on-treatment biopsies. Bone biopsies, cytological specimens, and fine-needle aspiration samples were excluded. Biopsy samples were also used to assess HER2 expression.

Details of the primary diagnosis and treatment history were collected within 28 days before the start of treatment. Past medical history, concurrent illness, and concomitant medications were collected.

Statistical analysis

An mTPI design (18, 19) was used for Part 1 dose escalation, which targeted a DLT rate of approximately 27.5% with an equivalence interval of 22.5%–32.5% using a Bayesian statistics framework with the prior distribution of DLT rate set as a beta (0.5–0.5).

Analysis sets included the full analysis set (all enrolled), the safety analysis set (received ≥1 dose of treatment), the DLT-evaluable set (received ≥1 dose of treatment without major treatment deviations during the DLT observation period), the modified intent-to-treat population (received ≥1 dose of treatment with baseline assessment and ≥1 post baseline assessment, disease progression or death before the first tumor assessment), the PK parameter analysis population (received ≥1 dose of treatment, had ≥1 of the PK parameters and had no major protocol deviations influencing the PK assessment), the immunogenicity analysis set (received ≥1 dose of treatment and had ≥1 ADA sample collected), the biomarker analysis population (with ≥1 of the biomarkers evaluated at pre- and/or post-dose), and the soluble HER2 concentration analysis set (a subset of the biomarker analysis set, including those who had ≥1 soluble HER2 concentration above the lower limit of quantification).

Concentrations of PF-06804103, total antibody, and unconjugated payload (PF-06380101) were measured using validated methods. PK parameters were determined from the respective concentration–time data using standard noncompartmental methods. Findings were summarized with descriptive statistics by dose and cycle. For immunogenicity, the percentage of patients with positive ADA and NAb were summarized by the dosing group. The time of onset of ADA or NAb response were described previously.

The occurrence of DLTs observed in the dosing cohorts was described and used to estimate the MTD. AEs were graded by the investigator according to the CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA) v24.1. The number and percentage of patients who experienced any AE, SAE, treatment-related AE (TRAE), and treatment-related SAE were summarized.

The ORR, PFS, DoR, duration of treatment, and best percentage of change from baseline in sum of diameters for target lesions were assessed.

Availability of data

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Results

Patients

A total of 93 patients enrolled in Parts 1A ($n = 47$: HER2+ GC = 22, HER2+ breast cancer = 25) and 2A ($n = 46$: HER2+ breast cancer = 19, HR+ HER2-low breast cancer = 27) received various doses of PF-06804103 (Supplementary Fig. S1, **Table 1**). In Part 1B, 2 patients with HR+ HER2-low breast cancer were enrolled and received PF-06804103 2.0 mg/kg in combination with palbociclib and letrozole. Findings of Part 1B are presented in the Supplementary File S1 and not included in the overall analysis. No patients were enrolled in Part 2B.

Part 1A enrolled 18 male patients, and the remaining 75 (in Parts 1A and 2A) were female patients. The mean (standard deviation) and median (range) age was 55.6 (11.3) and 58.0 (32–74) years for Part 1A, and 53.5 (10.3) and 52.5 (38–77) years for Part 2A, respectively. Most patients were White (62/93, 66.7%). All 93 patients received ≥1 regimen of prior cancer therapies; the median (range) number of regimens was 6.0 (1.0–18.0). Seventy-three (78.5%) patients (Parts 1A, $n = 47$; Part 2A, $n = 26$) received prior HER2-targeted antibody therapy; all 73 (78.5%) received trastuzumab, 30 (32.3%) received pertuzumab, 41 (44.1%) received T-DM1, and none received trastuzumab deruxtecan (fam-trastuzumab deruxtecan-nxki, DS-8201a). Of

Table 1. Patient demographics and baseline characteristics (the safety analysis set).

	Part 1A									Part 2A					Parts 1A and 2A		
	HER2+ BC or HER2+ GC							HER2+ GC		HER2+ BC		HR+ HER2-low BC		Total	HER2+ BC		Total
Dose, mg/kg	0.15 *n* = 2	0.5 *n* = 2	1.2 *n* = 2	2.0 *n* = 4	3.0 *n* = 16	4.0 *n* = 15	5.0 *n* = 6	Total *N* = 47	3.0 *n* = 7	4.0 *n* = 6	3.0 *n* = 5	4.0 *n* = 14	3.0 *n* = 12	4.0 *n* = 15	Total *N* = 46	3.0 *n* = 14	4.0 *n* = 23	Total *N* = 93
Sex																		
Male	2 (100.0)	1 (50.0)	1 (50.0)	2 (50.0)	5 (31.3)	5 (33.3)	2 (33.3)	18 (38.3)	—	—	0	0	0	0	0	—	—	—
Female	0	1 (50.0)	1 (50.0)	2 (50.0)	11 (68.8)	10 (66.7)	4 (66.7)	29 (61.7)	—	—	5 (100.0)	14 (100.0)	12 (100.0)	15 (100.0)	46 (100.0)	—	—	—
Race																		
White	1 (50.0)	1 (50.0)	2 (100.0)	2 (50.0)	10 (62.5)	10 (66.7)	5 (83.3)	31 (66.0)	—	—	4 (80.0)	4 (28.6)	11 (91.7)	12 (80.0)	31 (67.4)	—	—	—
Black	1 (50.0)	0	0	0	0	0	0	1 (2.1)	—	—	0	1 (7.1)	0	0	1 (2.2)	—	—	—
Asian	0	0	0	2 (50.0)	4 (25.0)	5 (33.3)	1 (16.7)	12 (25.5)	—	—	1 (20.0)	9 (64.3)	1 (8.3)	3 (20.0)	14 (30.4)	—	—	—
Not reported	0	1 (50.0)	0	0	0	0	0	1 (2.1)	—	—	0	0	0	0	0	—	—	—
Median (range) age (y)	49.0 (35–63)	65.5 (65–66)	58.0 (50–66)	65.0 (64–74)	56.5 (36–70)	55.0 (32–70)	58.5 (39–71)	58.0 (32–74)	—	—	52.0 (43–57)	50.5 (38–67)	56.0 (42–77)	51.0 (40–72)	52.5 (38–77)	—	—	—
ECOG PS																		
0	0	0	2 (100.0)	0	7 (43.8)	6 (40.0)	4 (66.7)	19 (40.4)	2 (28.6)	4 (66.7)	2 (40.0)	3 (21.4)	5 (41.7)	8 (53.3)	18 (39.1)	7 (50.0)	5 (21.7)	37 (39.8)
1	2 (100.0)	2 (100.0)	0	4 (100.0)	9 (56.3)	9 (60.0)	2 (33.3)	28 (59.6)	5 (71.4)	2 (33.3)	3 (60.0)	11 (78.6)	7 (58.3)	7 (46.7)	28 (60.9)	7 (50.0)	18 (78.3)	56 (60.2)
Primary diagnosis																		
GC	2	2	1	2	7	6	2	22	7	6	0	0	0	0	0	0	0	22
BC	0	0	1	2	9	9	4	25	0	0	5	14	12	15	46	14	23	71
Number of regimens																		
1	1 (50.0)	0	0	0	1 (6.3)	0	1 (16.7)	3 (6.4)	1 (14.3)	0	0	0	0	0	0	0	0	3 (3.2)
2	1 (50.0)	0	1 (50.0)	0	3 (18.8)	1 (6.7)	0	6 (12.8)	3 (42.9)	1 (16.7)	2 (40.0)	0	0	1 (6.7)	3 (6.5)	2 (14.3)	0	9 (9.7)
3–5	0	0	1 (50.0)	4 (100.0)	3 (18.8)	6 (40.0)	2 (33.3)	16 (34.0)	1 (14.3)	4 (66.7)	1 (20.0)	5 (35.7)	3 (25.0)	5 (33.3)	14 (30.4)	3 (21.4)	7 (30.4)	30 (32.3)
≥6	0	2 (100.0)	0	0	9 (56.3)	8 (53.3)	3 (50.0)	22 (46.8)	2 (28.6)	1 (16.7)	2 (40.0)	9 (64.3)	9 (75.0)	9 (60.0)	29 (63.0)	9 (64.3)	16 (69.6)	51 (54.8)
Median (range)	1.5 (1.0–2.0)	6.0 (6.0–6.0)	2.5 (2.0–3.0)	4.0 (3.0–5.0)	6.5 (1.0–18.0)	6.0 (2.0–10.0)	5.5 (1.0–7.0)	5.0 (1.0–18.0)	2.0 (1.0–9.0)	3.0 (2.0–7.0)	5.0 (2.0–8.0)	7.0 (3.0–12.0)	7.5 (3.0–16.0)	6.0 (2.0–13.0)	6.0 (2.0–16.0)	6.5 (2.0–18.0)	7.0 (3.0–12.0)	6.0 (1.0–18.0)
Had prior radiotherapy	1 (50.0)	2 (100.0)	1 (50.0)	2 (50.0)	8 (50.0)	12 (80.0)	4 (66.7)	30 (63.8)	1 (14.3)	4 (66.7)	3 (60.0)	11 (78.6)	10 (83.3)	14 (93.3)	38 (82.6)	10 (71.4)	19 (82.6)	68 (73.1)
Had prior surgery	2 (100.0)	1 (50.0)	1 (50.0)	4 (100.0)	15 (93.8)	15 (100.0)	6 (100.0)	44 (93.6)	6 (85.7)	6 (100.0)	4 (80.0)	12 (85.7)	10 (83.3)	14 (93.3)	40 (87.0)	13 (92.9)	21 (91.3)	84 (90.3)
Prior anti-microtubulin therapies																		
Yes	0	1 (50.0)	2 (100.0)	3 (75.0)	14 (87.5)	12 (80.0)	5 (83.3)	37 (78.7)	5 (71.4)	3 (50.0)	5 (100.0)	14 (100.0)	10 (83.3)	12 (80.0)	41 (89.1)	14 (100.0)	23 (100.0)	78 (83.9)
Median (range) of number of regimens	- (-, -)	1.0 (1.0–1.0)	1.5 (1.0–2.0)	1.0 (1.0–1.0)	2.0 (1.0–5.0)	2.0 (1.0–4.0)	3.0 (1.0–3.0)	2.0 (1.0–5.0)	1.0 (1.0–1.0)	1.0 (1.0–2.0)	2.0 (1.0–4.0)	3.0 (2.0–5.0)	2.5 (1.0–4.0)	1.5 (1.0–5.0)	2.0 (1.0–5.0)	3.0 (1.0–5.0)	3.0 (2.0–5.0)	2.0 (1.0–5.0)
Prior chemotherapy																		
Yes	2 (100.0)	2 (100.0)	2 (100.0)	4 (100.0)	16 (100.0)	15 (100.0)	6 (100.0)	47 (100.0)	7 (100.0)	6 (100.0)	5 (100.0)	14 (100.0)	12 (100.0)	14 (93.3)	45 (97.8)	14 (100.0)	23 (100.0)	92 (98.9)
Median (range) of number of regimens	1.5 (1.0–2.0)	5.0 (5.0–5.0)	2.0 (2.0–2.0)	3.5 (2.0–4.0)	3.5 (1.0–10.0)	4.0 (2.0–7.0)	4.0 (1.0–6.0)	4.0 (1.0–10.0)	2.0 (1.0–5.0)	3.0 (2.0–6.0)	3.0 (2.0–7.0)	5.5 (2.0–8.0)	4.5 (1.0–12.0)	3.0 (1.0–9.0)	4.0 (1.0–12.0)	4.5 (2.0–10.0)	5.0 (2.0–8.0)	4.0 (1.0–12.0)
Prior HER2-targeted antibody therapies																		
Yes	2 (100.0)	2 (100.0)	2 (100.0)	4 (100.0)	16 (100.0)	15 (100.0)	6 (100.0)	47 (100.0)	7 (100.0)	6 (100.0)	5 (100.0)	14 (100.0)	2 (16.7)	5 (33.3)	26 (56.5)	14 (100.0)	23 (100.0)	73 (78.5)
Trastuzumab	2 (100.0)	2 (100.0)	2 (100.0)	4 (100.0)	16 (100.0)	15 (100.0)	6 (100.0)	47 (100.0)	7 (100.0)	6 (100.0)	5 (100.0)	14 (100.0)	2 (16.7)	5 (33.3)	26 (56.5)	14 (100.0)	23 (100.0)	73 (78.5)
Pertuzumab	0	0	1 (50.0)	2 (50.0)	7 (43.8)	5 (33.3)	2 (33.3)	17 (36.2)	1 (14.3)	0	4 (80.0)	7 (50.0)	1 (8.3)	1 (6.7)	13 (28.3)	10 (71.4)	12 (52.2)	30 (32.3)
Ado-trastuzumab emtansine (T-DM1)	0	0	1 (50.0)	2 (50.0)	9 (56.3)	7 (46.7)	3 (50.0)	22 (46.8)	0	0	3 (60.0)	13 (92.9)	2 (16.7)	1 (6.7)	19 (41.3)	12 (85.7)	20 (87.0)	41 (44.1)
Prior HER2-targeted small-molecule drugs																		
Yes	0	0	0	2 (50.0)	5 (31.3)	6 (40.0)	1 (16.7)	14 (29.8)	0	0	3 (60.0)	10 (71.4)	1 (8.3)	0	14 (30.4)	8 (57.1)	16 (69.6)	28 (30.1)
Lapatinib	0	0	0	2 (50.0)	5 (31.3)	6 (40.0)	1 (16.7)	14 (29.8)	0	0	2 (40.0)	10 (71.4)	1 (8.3)	0	13 (28.3)	7 (50.0)	16 (69.6)	27 (29.0)
Tucatinib	0	0	0	0	0	0	0	0	0	0	1 (20.0)	1 (7.1)	0	0	2 (4.3)	1 (7.1)	1 (4.3)	2 (2.2)

Note: Values are *n* (%) unless stated otherwise.

All patients had prior cancer therapies. No patient received trastuzumab deruxtecan (fam-trastuzumab deruxtecan-nxki, ds-8201a) as prior HER2-targeted antibody therapy. For all groups in Parts 1A and 2A, PF-06804103 was administered once every 3 weeks. Part 1B enrolled 2 patients with HR+ HER2-low BC who received PF-06804103 2.0 mg/kg once every 2 weeks in combination with SOC doses of palbociclib and letrozole (see Supplementary File S1 for more details of Part 1B). No patients were enrolled in Part 2B.

Abbreviations: BC, breast cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gastric and gastroesophageal cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; SOC, standard of care.

27 patients with HR+ HER2-low breast cancer in Part 2A, 20 (74.1%) did not have prior HER2-targeted antibody therapy, 7 had prior HER2-targeted therapy (all received trastuzumab, 2 received pertuzumab, 3 received T-DM1). Of 13 patients with HER2+ GC in Part 1A who received PF-06804103 3.0 or 4.0 mg/kg, 1 received pertuzumab and none received T-DM1. Prior HER2-targeted small-molecule drugs were used in 28 (30.1%) patients, 27 (29.0%) received lapatinib, 2 (2.2%) received tucatinib, none of whom had HER2+ GC (**Table 1**).

All patients discontinued PF-06804103. The main reasons for discontinuation were AEs (44/93, 47.3%) and progressive disease (35/93, 37.6%). In total, 56 (56/93, 60.2%) patients completed the follow-up phase.

Safety

Exposure

The median (range) duration of treatment for all patients in Parts 1A and 2A was 16.0 (3.0–89.3) and 12.0 (3.0–49.4) weeks, and the mean relative dose intensity was 88.5% and 86.0%, respectively. For all patients, the median (range) duration of PF-06804103 treatment was 13.0 (3.0–89.3) weeks and the actual dose intensity was 3.0 (0.1–5.0) mg/kg/cycle (1 cycle = 3 weeks; Supplementary Fig. S2). In Parts 1A and 2A, 21 (44.7%) and 20 (43.5%) patients had dose delays, most (93.6% and 93.5%) did not skip treatment cycle, whereas 19 (40.4%) and 26 (56.5%) had dose reductions.

DLTs

In Part 1A, 4 patients experienced DLTs. Two patients received PF-06804103 3.0 mg/kg, one had Grade 3 non-serious TRAE of arthralgia and Grade 3 serious TRAE of neuralgia; the second patient had Grade 3 treatment-related musculoskeletal pain, which was associated with drug withdrawal. Two patients were in the PF-06804103 4.0 mg/kg group, one had Grade 2 treatment-related ejection fraction decreased and the other had Grade 3 TRAEs of arthralgia, myalgia, and fatigue. All DLTs were resolved.

AEs

All 93 (100%) patients had all-causality treatment-emergent AEs. In Parts 1A and 2A, 2 (4.3%) and 5 (10.9%) patients discontinued from study due to AEs, and 12 (25.5%) and 26 (56.5%) discontinued study drug due to AEs. SAEs were reported in 38 (40.9%) patients, of whom, 19 (20.4%) had serious TRAEs. The incidences of SAEs were generally higher in PF-06804103 ≥3.0 mg/kg groups in Part 1A and comparable across different populations in Part 2A.

Eighty-seven (93.5%) patients had TRAEs, the most frequently reported (≥30%) TRAEs were alopecia ($n = 42$ [45.2%], Grades 1 or 2 for all), fatigue ($n = 32$ [34.4%], Grade 3 in 7), peripheral sensory neuropathy [$n = 29$ (31.2%), Grade 1 in 11, Grade 2 in 13, Grade 3 in 5], and myalgia [$n = 28$ (30.1%), Grade 3 in 3; **Table 2**; Supplementary Table S1]. Grade 3 and 4 TRAEs were reported in 43 (46.2%) and 2 (2.2%) patients. One patient in Part 1A receiving PF-06804103 5.0 mg/kg had Grade 4 neutropenia and one patient with HER2+ breast cancer in Part 2A PF-06804103 4.0 mg/kg group had Grade 4 increased amylase and lipase. No Grade 5 TRAE was reported (**Table 2**; Supplementary Table S1).

Twenty-six (28.0%) patients experienced arthralgia, of whom, 22 (23.7%) had treatment-related arthralgia, and 2 (2.2%) resulted in drug withdrawal. The median onset of arthralgia was 3–70.5 days in different dose groups. Myalgia (including preferred terms of muscular weakness, musculoskeletal pain, myalgia, tendonitis, and musculoskeletal discomfort) was seen in 38 (40.9%) patients, 36 (38.7%) of whom were treatment-related, and 5 (5.4%) led to drug withdrawal. The median onset of myalgia was 5–166 days across groups. Neuropathy (including preferred terms of neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, and dysesthesia) was reported in 52 (55.9%) patients, 51 (54.8%) were treatment-related, and 11 (11.8%) led to drug withdrawal. Among all dose groups, the median onset of myalgia was 9–133.5 days. Sixty-four (68.8%) patients experienced skin toxicity (including AEs with high level group terms of epidermal and dermal conditions, pigmentation disorders, skin and subcutaneous tissue disorders NEC [not elsewhere classified] and skin appendage conditions; or high level term of acnes; or preferred terms of blepharitis, eyelid rash, cellulitis, rash pustular, skin infection, blister infected, injection site rash, infusion site ulcer, and lichenoid keratosis), 58 (62.4%) were treatment-related, and 8 (8.6%) led to drug withdrawal. The median onset of skin toxicity ranged 3.5–166 days across all dose groups. Nine (9.7%) participants experienced keratitis (including preferred terms of keratopathy and keratitis), all were treatment-related, and 3 (3.2%) led to drug withdrawal (all 3 patients were in Part 2A and received PF-06804103 4.0 mg/kg, 1 with HER2+ breast cancer had Grade 1 keratopathy, 1 with HER2+ breast cancer had Grade 2 keratopathy, and 1 with HR+ HER2-low breast cancer had Grade 2 keratitis). The median onset of keratitis was 26–65 days across dose groups. Most of the events of arthralgia, myalgia, neuropathy, skin toxicity, and keratitis were Grade 1 or 2.

In addition, 4 (4.3%) patients (all in Part 2A with HR+ HER2-low breast cancer) had QTcF >500 msec. No trend of clinically significant changes was observed in laboratory results.

Deaths

Eight (8.6%) deaths were recorded. One patient with HR+ HER2-low breast cancer in Part 2A who received 1 dose of PF-06804103 3.0 mg/kg died due to nontreatment-related disease progression within 28 days after dosing. All other 7 deaths were due to disease progression and occurred beyond 28 days after last dose.

Clinical efficacy

A total of 79 patients (43 in Part 1A, 36 in Part 2A) were evaluable for OR (**Table 3**). Best changes from baseline in the target lesions are shown in **Fig. 1**. Two (2/79, 2.5%) patients achieved complete response (CR), both were in Part 1A, one received PF-06804103 4.0 mg/kg and the other received PF-06804103 5.0 mg/kg. Twenty-one (21/79, 26.6%) patients achieved partial response (PR) as their best response, 11 of whom were in Part 1A (11/43, 25.6%) and 10 in Part 2A (10/36, 27.8%). In Part 1A, higher proportion of patients achieved OR (CR plus PR) in the PF-06804103 4.0 mg/kg group (6/14, 42.9%) versus 3.0 mg/kg group (3/14, 21.4%). In Part 2A, 2 of 14 (14.3%) and 8 of 22 (36.4%) patients treated with PF-06804103 3.0 and 4.0 mg/kg achieved PR. In patients with breast cancer enrolled in Parts 1A and 2A, 22 patients received PF-06804103 3.0 mg/kg, of whom, 2 of 12 (16.7%) with HER2+ breast cancer and 1 of 10 (10.0%) with HR+ HER2-low breast cancer achieved OR; 30 patients received PF-06804103 4.0 mg/kg, of whom, 9 of 19 (47.4%) with HER2+ breast cancer and 3 of 11 (27.3%) with HR+ HER2-low breast cancer achieved OR (**Table 3**; Supplementary Fig. S2).

Twenty-three patients in Parts 1A and 2A with confirmed CR or PR were assessed for DoR (Supplementary Fig. S3). In Part 1A, the median DoR was 7.6 months in 3 responders with GC, and 7.0 months in 5 responders with breast cancer. In Part 2A, median DoR was 2.9 months in 2 responders with HER2+ breast cancer, and 4.4 months in 2 responders with HR+ HER2-low breast cancer.

Table 2. Treatment-related adverse events in ≥15% patients by PF-06804103 doses (the safety analysis set).

	Part 1A							Part 2A				
	HER2+ BC or GC						Total	HER2+ BC		HR+ HER2-Low BC	Total	Total
PF-06804103 doses, mg/kg	0.15	0.5	1.2	2.0	3.0	4.0	5.0	0.15–5.0	3.0	4.0	3.0	4.0	3.0–4.0	0.15–5.0
N	2	2	2	4	16	15	6	47	5	14	12	15	46	93
With any adverse event	1 (50.0)	1 (50.0)	1 (50.0)	4 (100.0)	15 (93.8)	15 (100.0)	6 (100.0)	43 (91.5)	5 (100.0)	14 (100.0)	10 (83.3)	15 (100.0)	44 (95.7)	87 (93.5)
Alopecia	0	0	0	4 (100.0)	4 (25.0)	10 (66.7)	3 (50.0)	21 (44.7)	1 (20.0)	5 (35.7)	6 (50.0)	9 (60.0)	21 (45.7)	42 (45.2)
Fatigue	0	0	1 (50.0)	2 (50.0)	9 (56.3)	4 (26.7)	4 (66.7)	20 (42.6)	2 (40.0)	5 (35.7)	4 (33.3)	1 (6.7)	12 (26.1)	32 (34.4)
Neuropathy peripheral	0	0	0	0	8 (50.0)	3 (20.0)	3 (50.0)	14 (29.8)	0	1 (7.1)	2 (16.7)	4 (26.7)	7 (15.2)	21 (22.6)
Peripheral sensory neuropathy	0	0	0	2 (50.0)	3 (18.8)	6 (40.0)	2 (33.3)	13 (27.7)	1 (20.0)	7 (50.0)	3 (25.0)	5 (33.3)	16 (34.8)	29 (31.2)
Decreased appetite	0	0	0	1 (25.0)	4 (25.0)	5 (33.3)	2 (33.3)	12 (25.5)	2 (40.0)	2 (14.3)	3 (25.0)	2 (13.3)	9 (19.6)	21 (22.6)
Myalgia	0	0	0	0	5 (31.3)	5 (33.3)	2 (33.3)	12 (25.5)	0	7 (50.0)	4 (33.3)	5 (33.3)	16 (34.8)	28 (30.1)
Rash	0	0	0	0	3 (18.8)	5 (33.3)	2 (33.3)	10 (21.3)	2 (40.0)	6 (42.9)	3 (25.0)	3 (20.0)	14 (30.4)	24 (25.8)
Weight decreased	0	0	0	0	3 (18.8)	4 (26.7)	3 (50.0)	10 (21.3)	1 (20.0)	4 (28.6)	2 (16.7)	3 (20.0)	10 (21.7)	20 (21.5)
Arthralgia	0	1 (50.0)	0	0	3 (18.8)	4 (26.7)	1 (16.7)	9 (19.1)	1 (20.0)	3 (21.4)	4 (33.3)	5 (33.3)	13 (28.3)	22 (23.7)
Stomatitis	0	1 (50.0)	0	0	2 (12.5)	4 (26.7)	2 (33.3)	9 (19.1)	1 (20.0)	4 (28.6)	3 (25.0)	2 (13.3)	10 (21.7)	19 (20.4)
Anemia	0	0	1 (50.0)	0	3 (18.8)	2 (13.3)	2 (33.3)	8 (17.0)	0	3 (21.4)	2 (16.7)	2 (13.3)	7 (15.2)	15 (16.1)
Diarrhea	1 (50.0)	0	1 (50.0)	0	2 (12.5)	2 (13.3)	2 (33.3)	8 (17.0)	1 (20.0)	1 (7.1)	0	5 (33.3)	7 (15.2)	15 (16.1)
Nausea	0	0	0	1 (25.0)	2 (12.5)	2 (13.3)	2 (33.3)	7 (14.9)	0	3 (21.4)	2 (16.7)	3 (20.0)	8 (17.4)	15 (16.1)

Note: Values are *n* (%). MedDRA v24.1 coding dictionary applied.
Abbreviations: BC, breast cancer; GC, gastric and gastroesophageal cancer; MedDRA, Medical Dictionary for Regulatory Activities; *N*, number of patients in each group.

Among the 93 patients in Parts 1A and 2A, 45 (48.4%) had an event of disease progression. The estimated median PFS was 5.5 (95% CI, 4.2–7.0) months.

Other analysis

PK

PK parameters of PF-06804103, total antibody, and unconjugated payload (PF-06380101) are summarized in **Table 4**; Supplementary Table S2. Serum concentration–time profiles of the three analytes are presented in **Fig. 2**. Following a 1-hour intravenous infusion of PF-06804103 administered Q3W at doses ranging from 0.15 to 5.0 mg/kg in patients with advanced solid tumors, serum concentrations of PF-06804103 ADC exhibited a multi-phasic decline following attainment of maximum serum concentration (C_{max}). Arithmetic mean half-life ($t_{1/2}$) ranged 4–5 days at dose levels ≥3.0 mg/kg. Exposure based on geometric mean area under the serum concentration–time curve (AUC), AUC from time 0 to infinity (AUC_{inf}; Cycle 1) and to end of the dosing period (AUC_{tau}; Cycle 4), and C_{max} increased in a dose-dependent manner across the dose range following single and multiple dosing. The mean clearance (CL) was 0.017–0.021 L/h at dose levels ≥2.0 mg/kg, and lower dose levels showed generally higher CL. Mean volume of distribution at steady-state (V_{ss}) where evaluable was 3.037–3.467 L, indicating that distribution of PF-06804103 ADC was mainly limited to the vascular compartment. Drug accumulation was minimal following repeated dosing with mean R_{ac} values ≤1.16. Inter-participant variability for PF-06804103 ADC exposure was moderate with coefficient of variation ranging from 11% to 38% for AUC_{inf} (Cycle 1), 23% to 33% for AUC_{tau} (Cycle 4), and 7% to 29% for C_{max}.

For total antibody, serum concentrations exhibited a multi-phasic decline following attainment of C_{max}, $t_{1/2}$ was 4–6 days for doses ≥3.0 mg/kg, mean CL was 0.015–0.020 L/h at doses ≥2.0 mg/kg, mean V_{ss} was 2.180–3.520 L, mean R_{ac} was ≤1.12, and the inter-participant variability was 38%–62% for AUC_{inf} (Cycle 1), 18%–32% for AUC_{tau} (Cycle 4), and 9%–34% for C_{max}.

For unconjugated payload (PF-06380101), serum concentrations exhibited a multiphasic decline following attainment of C_{max} with the median time to C_{max} 3–6 days; mean $t_{1/2}$ was 4–6 days for doses ≥3.0 mg/kg, suggesting linker cleavage is the rate limiting step for payload disposition; the exposure increased in a generally dose-dependent manner following single and multiple dosing; R_{ac} was ≤1.08; and the inter-participant variability was 43%–83% for AUC_{inf} (Cycle 1), 19%–124% for AUC_{tau} (Cycle 4), and 15%–108% for C_{max}.

Biomarkers

All patients had HER2 assessment from their pathological reports (Supplementary Table S3). Of the 91 patients included in the biomarker analysis population, 67.0% (61/91) of patients were HER2-positive before enrollment based on diagnostic IHC and/or fluorescence ISH testing. For 10 patients, samples were collected on Cycle 3 Day 1 and analyzed for post-treatment HER2 expression, and HER2 expression status did not change from screening. The serum soluble HER2 levels were mostly below baseline at Cycle 4 with PF-06804103 treatment. No clear relationship between baseline soluble HER2 and PF-06804103 exposure was identified.

Immunogenicity

Among 86 patients from Parts 1A and 2A who were evaluable for ADA or NAb, 6 (7.0%) were ADA-positive at baseline, 2 (2.3%) of whom were NAb-positive; 16 (18.6%) were positive for treatment-induced ADA post-treatment, 4 (4.7%) of whom tested NAb-positive

Table 3. Best overall response and confirmed objective response based on RECIST v1.1 (the mITT population).[a]

	Part 1A						Part 2A					Parts 1A and 2A		
	HER2+ BC or HER2+ GC						HER2+ BC		HR+ HER2-low BC		Total	HER2+ BC		Total
Dose, mg/kg	<2.0 *n* = 6	2.0 *n* = 4	3.0 *n* = 14	4.0 *n* = 14	5.0 *n* = 5	Total *N* = 43	3.0 *n* = 4	4.0 *n* = 11	3.0 *n* = 10	4.0 *n* = 11	*N* = 36	3.0 *n* = 12	4.0 *n* = 19	*N* = 79
CR	0	0	0	1 (7.1)	1 (20.0)	2 (4.7)	0	0	0	0	0	0	1 (5.3)	2 (2.5)
PR	1 (16.7)	0	3 (21.4)	5 (35.7)	2 (40.0)	11 (25.6)	1 (25.0)	5 (45.5)	1 (10.0)	3 (27.3)	10 (27.8)	2 (16.7)	8 (42.1)	21 (26.6)
SD	2 (33.3)	4 (100.0)	6 (42.9)	8 (57.1)	2 (40.0)	22 (51.2)	3 (75.0)	5 (45.5)	3 (30.0)	8 (72.7)	19 (52.8)	7 (58.3)	9 (47.4)	41 (51.9)
Non-CR/Non-PD	1 (16.7)	0	1 (7.1)	0	0	2 (4.7)	0	0	0	0	0	1 (8.3)	0	2 (2.5)
PD	2 (33.3)	0	3 (21.4)	0	0	5 (11.6)	0	1 (9.1)	6 (60.0)	0	7 (19.4)	1 (8.3)	1 (5.3)	12 (15.2)
NE[b]	0	0	1 (7.1)	0	0	1 (2.3)	0	0	0	0	0	1 (8.3)	0	1 (1.3)
OR (CR+PR)	1 (16.7)	0	3 (21.4)	6 (42.9)	3 (60.0)	13 (30.2)	1 (25.0)	5 (45.5)	1 (10.0)	3 (27.3)	10 (27.8)	2 (16.7)	9 (47.4)	23 (29.1)
95% CI[c] of OR	0.4–64.1	0.0–60.2	4.7–50.8	17.7–71.1	14.7–94.7	17.2–46.1	0.6–80.6	16.7–76.6	0.3–44.5	6.0–61.0	14.2–45.2	2.1–48.4	24.4–71.1	19.4–40.4
DC (CR+PR+SD+ Non-CR/Non-PD)	4 (66.7)	4 (100.0)	10 (71.4)	14 (100.0)	5 (100.0)	37 (86.0)	4 (100.0)	10 (90.9)	4 (40.0)	11 (100.0)	29 (80.6)	10 (83.3)	18 (94.7)	66 (83.5)
95% CI of DC	22.3–95.7	39.8–100.0	41.9–91.6	76.8–100.0	47.8–100.0	72.1–94.7	39.8–100.0	58.7–99.8	12.2–73.8	71.5–100.0	64.0–91.8	51.6–97.9	74.0–99.9	73.5–90.9

Note: Values are *n* (%) unless stated otherwise.

Abbreviations: BC, breast cancer; CI, confidence interval; CR, complete response; DC, disease control; GC, gastric and gastroesophageal cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mITT, modified intent-to-treat; NE, not evaluable; OR, objective response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SOC, standard of care.

[a]The mITT population included patients who received ≥1 dose of PF-06804103 with adequate baseline assessment and ≥1 post baseline assessment (for SD or Non-CR/Non-PD, ≥5 weeks after treatment start date), disease progression, or death before the first tumor assessment. For all groups in Parts 1A and 2A, PF-06804103 was administered once every 3 weeks. Part 1B enrolled 2 patients with HR+ HER2-low BC who received PF-06804103 2.0 mg/kg once every 2 weeks in combination with SOC doses of palbociclib and letrozole. One patient in Part 1B was evaluable for OR and was assessed as achieved PR (see Supplementary File S1 for more details of Part 1B). No patients were enrolled in Part 2B.

[b]The reason for NE was SD too early, that is, <5 weeks of treatment.

[c]Clopper–Pearson method used.

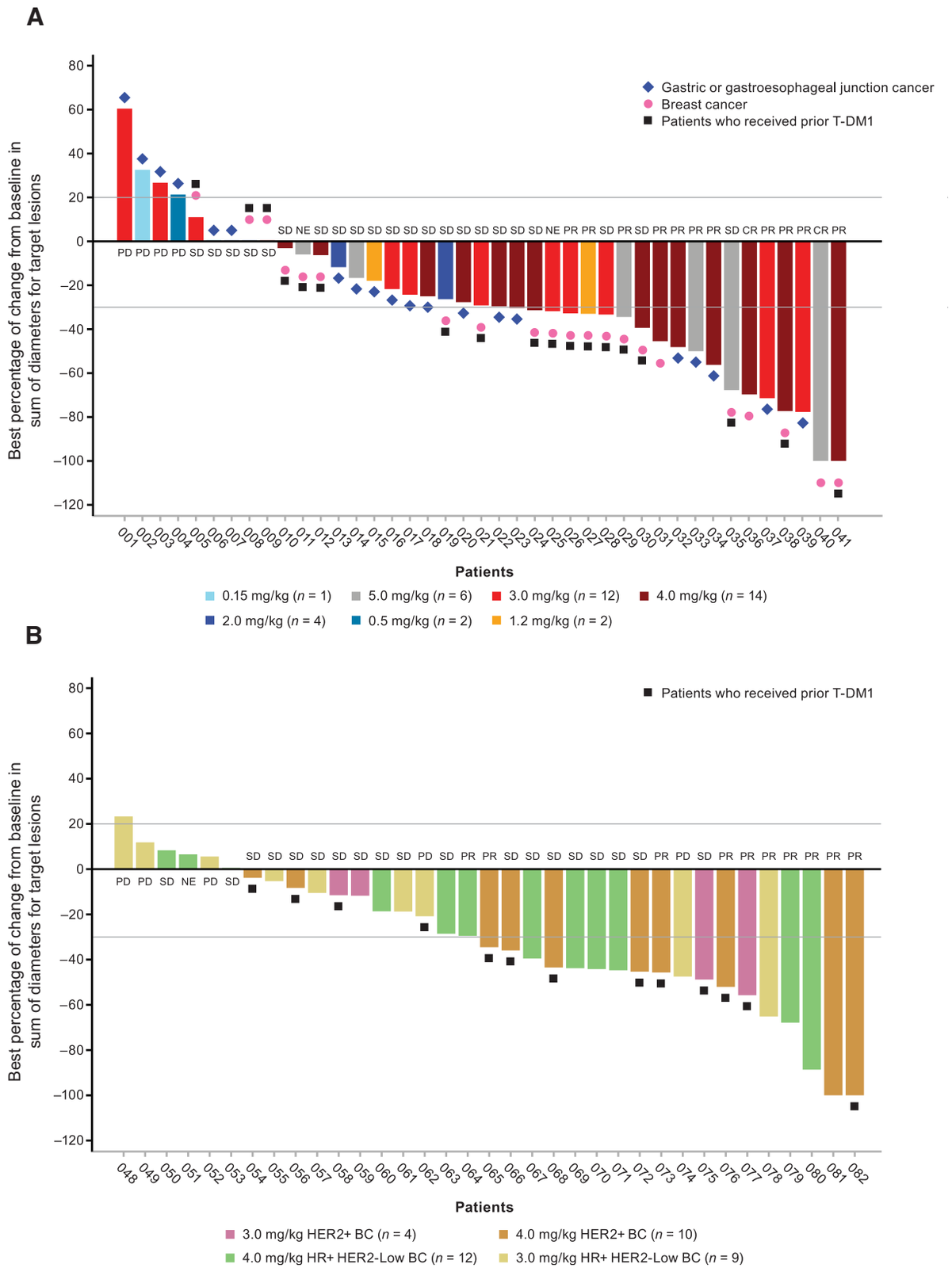

Figure 1.
Waterfall plot for best the percentage of change from baseline in sum of diameters for target lesions based on investigator assessment (the full analysis set). **A,** Individual patients in Part 1. **B,** Individual patients in Part 2. BC, breast cancer; CR, complete response; HER2, human epidermal growth factor receptor 2; HR, human receptor; NE, not evaluable/indeterminate; PD, progressive disease; PR, partial response; SD, stable disease.

Table 4. PK parameters for PF-06804103 ADC (PK parameter analysis population).

	Part 1A, PF-06804103 ADC						
PF-06804103, mg/kg, Q3W	**0.15** ***N*** **= 2**	**0.5** ***N*** **= 2**	**1.2** ***N*** **= 2**	**2.0** ***N*** **= 4**	**3.0** ***N*** **= 16**	**4.0** ***N*** **= 15**	**5.0** ***N*** **= 6**
Cycle 1							
n	2	2	2	4	16	15	6
AUC_{inf}, μg·h/mL	296	720; 969	2,080; 2,540	5,120 (11)	9,498 (32)	12,940 (31)	16,550 (38)
AUC_{inf}(dn), μg·h/mL/(mg/kg)	1,960	1,400; 1,950	1,740; 2,150	2,566 (11)	3,167 (32)	3,234 (31)	3,313 (38)
AUC_{last}, μg·h/mL	30.4; 288	667; 965	2,040; 2,500	5,026 (11)	8,263 (35)	12,290 (29)	15,480 (39)
AUC_{last}(dn), μg·h/mL/(mg/kg)	215; 1,910	1,300; 1,940	1,700; 2,110	2,520 (11)	2,748 (35)	3,071 (29)	3,099 (39)
CL, L/h	0.0405	0.0516; 0.0611	0.0282; 0.0373	0.02073 (32)	0.01970 (27)	0.01884 (24)	0.01975 (40)
C_{max}, μg/mL	1.96; 2.61	9.96; 12.6	16.3; 22.0	36.97 (24)	71.24 (21)	78.91 (21)	103.1 (28)
C_{max}(dn), μg/mL/(mg/kg)	13.9; 17.3	19.4; 25.3	13.6; 18.6	18.50 (24)	23.69 (21)	19.74 (21)	20.64 (28)
$t_{1/2}$, mean ± SD (d)	4.21	1.75; 2.09	3.63; 3.67	3.495 ± 0.76081	4.257 ± 1.1289	5.001 ± 1.2963	4.962 ± 1.3623
T_{max}, median (range; h)	1.00; 1.08	1.05; 3.60	1.00; 1.10	3.91 (3.67–22.9)	3.82 (0.967–4.03)	3.67 (0.967–24.0)	2.42 (0.967–24.0)
V_z, L	5.93	3.13; 4.43	3.54; 4.74	2.462 (26)	2.807 (15)	3.165 (24)	3.281 (25)
Cycle 4							
n	0	1	2	4	9	12	4
AUC_{last}, μg·h/mL	—	966	1,990; 2,790	2,970 (105)	7,432 (31)	10,990 (33)	11,740 (23)
AUC_{last}(dn), μg·h/mL/(mg/kg)	—	1,880	1,660; 2,360	1,543 (109)	2,758 (20)	3,412 (34)	3,491 (47)
AUC_{tau}, μg·h/mL	—	980	1,990; 2,800	4,260; 4,950	7,504 (28)	10,730 (33)	11,990 (23)
AUC_{tau}(dn), μg·h/mL/(mg/kg)	—	1,910	1,660; 2,370	2,450; 2,500	2,785 (19)	3,396 (34)	3,563 (49)
CL, L/h	—	0.0449	0.0256; 0.0391	0.0196; 0.0217	0.02069 (28)	0.01731 (27)	0.01971 (49)
C_{max}, μg/mL	—	10.3	16.9; 29.3	43.00 (15)	53.29 (29)	76.52 (24)	82.13 (7)
C_{max}(dn), μg/mL/(mg/kg)	—	20.0	14.1; 24.8	22.32 (20)	19.76 (10)	23.76 (20)	24.43 (23)
R_{ac}	—	1.34	0.972; 1.12	0.887; 1.07	1.007 (20)	1.164 (22)	1.114 (15)
$t_{1/2}$, mean ± SD (d)	—	2.34	2.95; 3.46	2.98; 3.42	4.177 ± 1.1648	5.185 ± 1.1855	5.278 ± 2.2199
T_{max}, median (range; h)	—	1.00	0.917; 1.02	2.43 (1.08–3.83)	1.10 (0.883–4.05)	3.81 (0.967–4.17)	4.00 (3.65–4.00)
V_{ss}, L	—	3.93	2.76; 4.82	1.94; 2.77	3.037 (15)	3.106 (24)	3.467 (24)

Note: Values are geometric mean (geometric %CV) unless otherwise stated. Individual values are listed when there were less than 3 evaluable measurements. dn was calculated on the basis of reported actual dose (mg)/baseline body weight (kg).

Abbreviations: %CV, percentage coefficient of variation; ADC, antibody–drug conjugate; AUC_{inf}, area under the concentration-time curve from time 0 to infinity; AUC_{last}, area under the serum concentration-time profile from time 0 to the time of the last quantifiable concentration; AUC_{tau}, area under the concentration-time profile from time 0 to time tau (τ), the dosing interval, where tau = 504 hours for the Q3W dosing; C_{max}, maximum serum concentration; CL, clearance; dn, dose normalization; *n*, number of patients contributing to the summary statistics; *N*, total number of patients in the treatment group in the PK parameter population; PK, pharmacokinetics; Q3W, once every 3 weeks; R_{ac}, observed accumulation ratio based on AUC_{tau}, $t_{1/2}$, elimination half-life; T_{max}, time for C_{max}; V_{ss}, volume of distribution at steady state; V_z, volume of distribution based on the terminal phase.

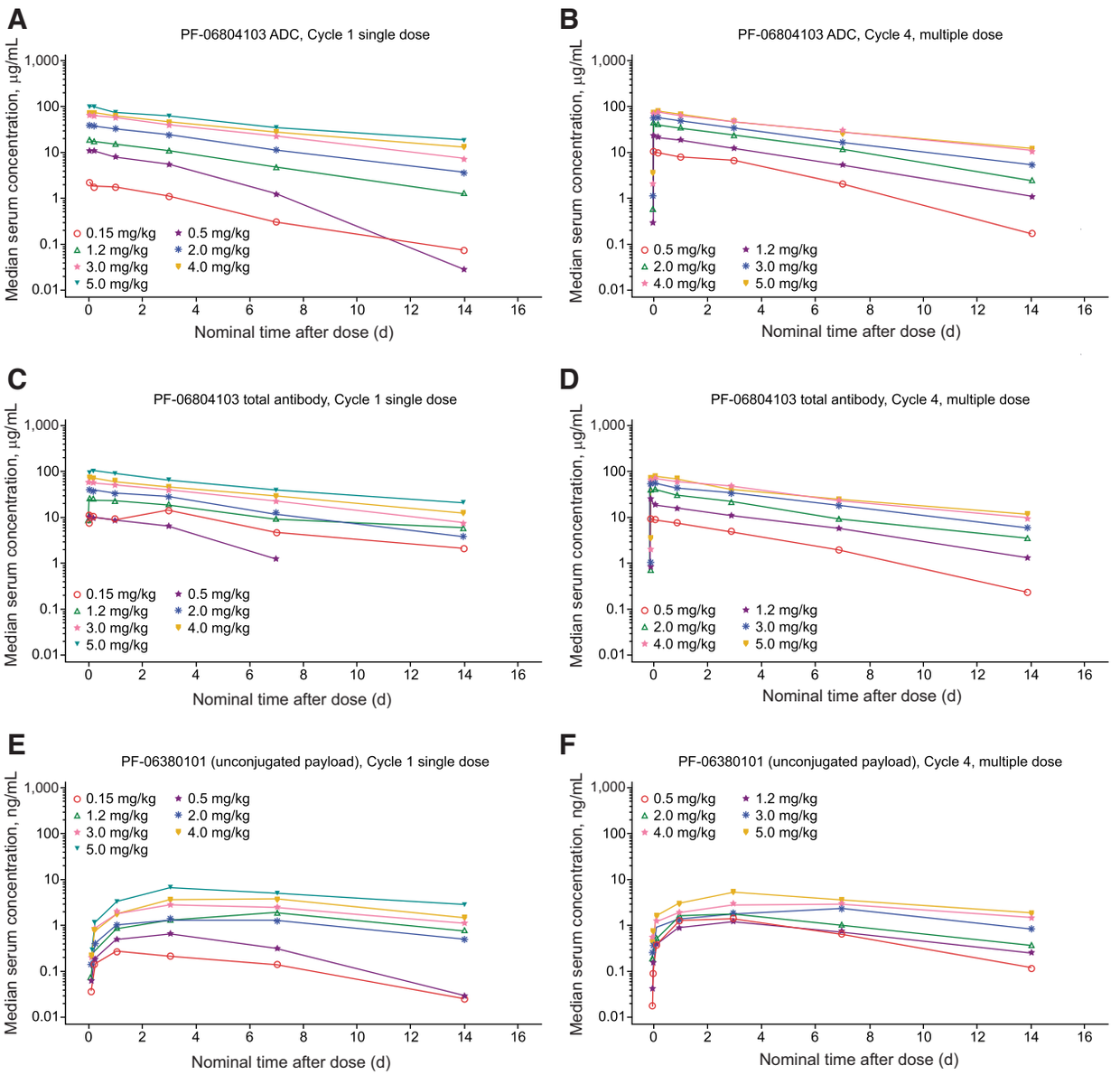

Figure 2.
PK profiles of PF-06804103 ADC, total antibody, and unconjugated payload (PF-06380101; the PK parameter analysis population). ADC, antibody–drug conjugate; PK, pharmacokinetic.

(Supplementary Table S4). The overall mean onset of ADA incidences was approximately 6 weeks post-treatment. The onset time of NAb was 15, 42, 77, and 105 days for each of the 4 NAb-positive participants. With the limited sample size, there was no consistent trend between ADA status and Cycle 4 pre-dose PF-06804103 concentrations. The presence of ADA did not appear to be associated with hypersensitivity or infusion reactions.

Discussion

For PF-06804103, there was in general a strong trend for a dose–response relationship for both safety and efficacy. The 3.0-mg/kg dose was better tolerated but appeared less efficacious and was vice versa for 4.0-mg/kg dose in both HER2+ breast cancer and HR+ HER2-low breast cancer. Notable AEs leading to study treatment discontinuation included skin toxicity, neuropathy, myalgia, and arthralgia. Peripheral neuropathy is a common TRAE for ADC therapies that is related to ADC exposure and duration of treatment (20, 21). In the current study, the incidence of treatment-related peripheral sensory neuropathy was 31.6%, and no clear trend was seen with the dosage of PF-06804103. The toxicity profile of PF-06804103 differentiates it from the other ADCs having different constructs or payloads (22).

PF-06804103 PK properties were measured in three analytes, including PF-06804103 ADC, total antibody, and PF-06380101

unconjugated payload. The exposure of all three analytes increased generally in a dose-dependent manner with minimal dose accumulation, and the inter-participant variability was moderate. Only observations in the study population were reported; exposure–response comparison with other molecules was not conducted. Among all evaluable patients, 20% were positive for ADA post-treatment and 5% tested positive for NAb. All ADA and NAb cases were treatment-induced. No clear relationship between ADA status and exposure was found on the basis of our preliminary analysis.

There were four patients with DLT in the PF-06804103 3.0 mg/kg (arthralgia and neuralgia in one patient, musculoskeletal pain in another) and 4.0 mg/kg (ejection fraction decreased in one; arthralgia, myalgia, and fatigue in another) dosing groups. An MTD was not reached on the basis of the DLT criteria; 3.0 mg/kg lacked a relative degree of activity and 5.0 mg/kg was determined to be intolerable, although no DLTs were reported at 5.0 mg/kg dosing. Therefore, 4.0 mg/kg was initially selected to be the Part 2 dose, with flexibility in the protocol to reduce to a lower dose (e.g., 3.0 mg/kg) if the observed toxicity of 4.0 mg/kg was determined to be too high. As the trial enrolled, a data-driven decision was made to explore both 3.0 and 4.0 mg/kg PF-06804103 doses in Part 2.

Compared with other ADCs approved for these indications (9, 23), PF-06804103 showed potential for improvement in efficacy that needed to be balanced with overall treatment benefit. In this study, the longest DoR observed was 18.9 months in one patient with HER2+ breast cancer who received 3.0 mg/kg PF-06804103, whereas the median (range) DoR was 7.0 (2.4–18.7) months for five confirmed responders receiving 4.0 mg/kg PF-06804103. Furthermore, in Part 2A, a higher percentage of patients in the 4.0-mg/kg dose group achieved OR than in the 3.0-mg/kg dose group for both HER2+ breast cancer and HR+ HER2-low breast cancer. At equivalent dose level, the ORR was higher in HER2+ breast cancer than HR+ HER2-low breast cancer [16.7% (2/12) vs. 10.0% (1/10) at PF-06804103 3.0 mg/kg; 47.4% (9/19) vs. 27.3% (3/11) at PF-06804103 4.0 mg/kg]. This may be partly attributable to higher HER2 receptor expression on HER2+ breast cancer tumors that allows greater binding of PF-06804103 and therefore killing of cancer cells.

There is great interest in extending the benefit of HER2-targeted therapies to HER2-low patients. Indeed T-DXd has shown striking activity in HER2-low breast cancer, leading to its approval by the FDA. Furthermore, disitamab vedotin (RC48), another HER2 ADC with an anti-tubulin (monomethyl auristatin E, MMAE) payload has been reported to have antitumor activity in HER2-low patients (24). In our study, response to PF-06804103 was observed in patients with HER2-low breast cancer in this study. HER2+ is commonly defined by current clinical practice as HER2 IHC 3+ or 2+/ISH+. HER2 expression in the patients in the HER2-low population was analyzed retrospectively using a novel, more sensitive IHC assay with the ability to detect a more granular expression level of HER2. As this new assay detected expression levels of HER2 that the IHC assay could not detect, further analysis is needed to confirm the responses for the HER2-low population.

The study included a relatively well-sized group of patients with HER2+ breast cancer who received 4.0 mg/kg PF-06804103 in Parts 1A and 2A. The ORR observed in Part 1A appeared better than in Part 2A. PF-06804103 4.0 mg/kg showed very encouraging efficacy in this heavily pretreated breast cancer population, that is, who had been treated with >2 prior anti-microtubule agents (same mechanism of action as PF-06804103 payload). However, this was limited by poor tolerability with TRAEs, resulting in shorter duration of treatment and possibly impacting PFS.

Despite the prevailing dogma that ADCs increase the MTD of potent cytotoxin payloads while lowering the minimum effective dose, mounting clinical evidence argues that AEs are a major limitation in ADC development (25). PF-06894103 is a drug–antibody ratio (DAR) of 4, site-specific conjugate of the Aur0101 linker payload, which displayed a significant improvement in therapeutic index compared with a conventional HER2–vc0101 conjugate, in exploratory toxicity studies in Sprague–Dawley rats and cynomolgus monkeys (16). Compared with HER2–vc0101 conjugate, PF-06894103 had almost a doubling of the highest clinically tolerated dose in cynomolgus monkeys, longer half-life, and higher exposure rates, but with reduction in neutropenia as off-target toxicity. Although in our clinical trial, bone marrow toxicity was not a major limitation, several other AEs leading to study treatment discontinuation occurred, including skin toxicity, neuropathy, myalgia, and arthralgia. This highlights a limitation of preclinical data to predict clinical safety of ADCs.

In Part 1A, PF-06804103 also demonstrated a high potential for treatment benefits in gastric/gastroesophageal cancer. Future development of PF-06804103 in the tested indications and other solid tumors, including NSCLC, may consider threading a balance between its superiority in tumor ORR balanced with selecting the right patient population, combination partner, and adhering to data or model driven dose modification strategies for early management of drug-related AEs. Such a strategy may include taking advantage of the likely absence of a pneumonitis risk and targeting a patient population with no or less heavily pretreated anti-microtubulin or neuropathy-causing agents.

Over the course of our study, multiple additional HER2-targeted therapies advanced in clinical development. Of these, the most notable is T-DXd, a mAb with a cleavable linker. T-DXd is different from PF-06804103 also because of its higher DAR (DAR of 8 vs. DAR of 4). Furthermore, PF-06804103 has an anti-tubulin agent payload Aur0101, whereas T-DXd has a different and quite potent payload, topoisomerase inhibitor deruxtecan (DXd). Over the past few years, T-DXd has shown compelling activity in not only HER2-positive breast and gastric cancers, but also in HER2-low breast and HER2-mutant lung cancers. Although we have been able to show antitumor activity of PF-06804103 in patients with HER2-positive breast cancer with prior T-DM1 therapy, because of the timing of our study, none of our patients had been treated with T-DXd. Therefore, we were unable to determine the activity of PF-06804103 in patients with intrinsic or acquired resistance to T-DXd.

In conclusion, PF-06804103 demonstrated clinical benefit and a generally manageable toxicity profile in treating patients with heavily pretreated HER2-expressing solid tumors and has the potential to be successfully developed as monotherapy or in combination, including with checkpoint inhibitors, in the right clinical setting and applying data-driven dosing strategies. However, new therapies are becoming available or under development for these indications (13, 26–28). The study sponsor made a decision to terminate the development of PF-06804103 to adapt to the changing treatment landscape.

Authors' Disclosures

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Note

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References

1. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2001;2:127–37.
2. Tagliabue E, Balsari A, Campiglio M, Pupa SM. HER2 as a target for breast cancer therapy. Expert Opin Biol Ther 2010;10:711–24.
3. Roskoski R Jr. The ErbB/HER family of protein–tyrosine kinases and cancer. Pharmacol Res 2014;79:34–74.
4. Ross JS, Fletcher JA. The HER-2/neu oncogene in breast cancer: prognostic factor, predictive factor, and target for therapy. Stem Cells 1998;16:413–28.
5. Jørgensen JT, Hersom M. HER2 as a prognostic marker in gastric cancer—a systematic analysis of data from the literature. J Cancer 2012;3:137–44.
6. Sapna F, Athwal PSS, Kumar M, Randhawa S, Kahlon S. Therapeutic strategies for human epidermal receptor-2–positive metastatic breast cancer: a literature review. Cureus 2020;12:e9522.
7. Agostinetto E, Montemurro F, Puglisi F, Criscitiello C, Bianchini G, Del Mastro L, et al. Immunotherapy for HER2-positive breast cancer: clinical evidence and future perspectives. Cancers 2022;14:2136.
8. Sievers EL, Senter PD. Antibody–drug conjugates in cancer therapy. Annu Rev Med 2013;64:15–29.
9. Criscitiello C, Morganti S, Curigliano G. Antibody–drug conjugates in solid tumors: a look into novel targets. J Hematol Oncol 2021;14:20.
10. Lambert JM, Chari RV. Ado-trastuzumab emtansine (T-DM1): an antibody–drug conjugate (ADC) for HER2-positive breast cancer. J Med Chem 2014;57:6949–64.
11. US Food and Drug Administration, Genentech. Kadcyla (ado-trastuzumab emtansine) prescribing information. 2013 (last update: February 2022). [cited 2022 December 15]. Available from: https://www.gene.com/download/pdf/kadcyla_prescribing.pdf.
12. European Medicines Agency. Kadcyla (ado-trastuzumab emtansine) summary of product characteristics. 2013 (last update: February 2022). [cited 2022 December 15]. Available from: https://www.ema.europa.eu/en/documents/product-information/kadcyla-epar-product-information_en.pdf.
13. US Food and Drug Administration, Daiichi Sankyo Inc. ENHERTU® (fam-trastuzumab deruxtecan-nxki) prescribing information. 2019 (last update:

December 2019). [cited 2022 December 15]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761139s000lbl.pdf.
14. European Medicines Agency. Enhertu (trastuzumab deruxtecan) summary of product characteristics. 2021 (last update: November 2022). [cited 2022 December 15]. Available from: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf.
15. Ogitani Y, Hagihara K, Oitate M, Naito H, Agatsuma T. Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody–drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity. Cancer Sci 2016;107:1039–46.
16. Graziani EI, Sung M, Ma D, Narayanan B, Marquette K, Puthenveetil S, et al. PF-06804103, a site-specific anti-HER2 antibody–drug conjugate for the treatment of HER2-expressing breast, gastric, and lung cancers. Mol Cancer Ther 2020;19:2068–78.
17. Sung MS, Hopf C, Upeslacis E, Golas J, Kaplan M, Khandke K, et al. Abstract 818: NG-HER2 ADC (PF-06804103) is superior to trastuzumab emtansine in a mouse 'avatar' head-to-head clinical trial. Cancer Res 2018;78:818.
18. Ji Y, Liu P, Li Y, Bekele BN. A modified toxicity probability interval method for dose-finding trials. Clin Trials 2010;7:653–63.
19. Ji Y, Wang SJ. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. J Clin Oncol 2013;31:1785–91.
20. Wolska-Washer A, Robak T. Safety and tolerability of antibody–drug conjugates in cancer. Drug Saf 2019;42:295–314.
21. Kågedal M, Samineni D, Gillespie WR, Lu D, Fine BM, Girish S, et al. Time-to-event modeling of peripheral neuropathy: platform analysis of eight valine-citrulline-monomethylauristatin e antibody–drug conjugates. CPT Pharmacometrics Syst Pharmacol 2019;8:606–15.
22. McKertish CM, Kayser V. Advances and limitations of antibody–drug conjugates for cancer. Biomedicines 2021;9:872.
23. Fu Z, Li S, Han S, Shi C, Zhang Y. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. Signal Transduct Target Ther 2022;7:93.
24. Shi F, Liu Y, Zhou X, Shen P, Xue R, Zhang M. Disitamab vedotin: a novel antibody–drug conjugates for cancer therapy. Drug Deliv 2022;29:1335–44.
25. Colombo R, Rich JR. The therapeutic window of antibody drug conjugates: a dogma in need of revision. Cancer Cell 2022;40:1255–63.
26. The Antibody Society. Therapeutic monoclonal antibodies approved or in review in the EU or US. 2022. [cited 2022 December 15]. Available from: www.antibodysociety.org/resources/approved-antibodies, www.antibodysociety.org/antibodies-in-late-stage-clinical-studies.
27. Xu J, Ying J, Liu R, Wu J, Ye F, Xu N, et al. KN026 (anti-HER2 bispecific antibody) in patients with previously treated, advanced HER2-expressing gastric or gastroesophageal junction cancer. Eur J Cancer 2022;178:1–12.
28. Meric-Bernstam F, Beeram M, Hamilton E, Oh DY, Hanna DL, Kang YK, et al. Zanidatamab, a novel bispecific antibody, for the treatment of locally advanced or metastatic HER2-expressing or HER2-amplified cancers: a phase 1, dose-escalation and expansion study. Lancet Oncol 2022;23:1558–70.