Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: a dose-expansion, phase 1 study

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Summary

Background Trastuzumab deruxtecan (DS-8201a) is a novel HER2-targeted antibody–drug conjugate with a humanised anti-HER2 antibody, cleavable peptide-based linker, and potent topoisomerase I inhibitor payload. A phase 1, non-randomised, open-label, multiple-dose study was done to assess the safety, tolerability, and activity of trastuzumab deruxtecan in HER2-expressing, advanced solid tumours. The dose escalation (part 1) has previously been reported and the recommended doses for expansion of 5·4 mg/kg or 6·4 mg/kg were established. In this Article, we report the safety and preliminary activity results from this phase 1 trial in all patients with HER2-positive advanced-stage breast cancer with previous trastuzumab emtansine treatment who received trastuzumab deruxtecan at the recommended doses for expansion.

Methods We did an open-label, dose-escalation and dose-expansion phase 1 trial at eight hospitals and clinics in the USA and six in Japan. Eligible patients were at least 18 years old in the USA and at least 20 years of age in Japan and had advanced solid tumours (regardless of HER2 expression in dose escalation or HER2 expression or mutation in dose expansion). The recommended doses for expansion of 5·4 mg/kg or 6·4 mg/kg trastuzumab deruxtecan were administered intravenously to patients once every 3 weeks until withdrawal of consent, unacceptable toxicity, or progressive disease. In this Article, all patients with HER2-positive advanced-stage breast cancer with previous trastuzumab emtansine treatment who received trastuzumab deruxtecan at the recommended doses for expansion were analysed together. The primary endpoints of the study were safety and preliminary activity (proportion of patients who achieved an objective response as assessed by the investigators). The activity evaluable set included all patients who received at least one dose of trastuzumab deruxtecan at the recommended doses for expansion, and for whom both baseline and post-treatment activity data were available. The safety analysis set included all patients who received at least one dose of trastuzumab deruxtecan at the recommended doses for expansion. Enrolment for patients with HER2-positive breast cancer has been completed. This trial is registered at ClinicalTrials.gov, number NCT02564900, and ClinicalTrials.jp, number JapicCTI-152978.

Findings Between Aug 28, 2015, and Aug 10, 2018, 115 of 118 patients with HER2-positive breast cancer were treated with at least one dose of trastuzumab deruxtecan at the recommended doses for expansion. All patients had at least one treatment-emergent adverse event. Frequent grade 3 or worse treatment-emergent adverse events included anaemia (19 [17%] of 115) and decreased neutrophil (16 [14%]), white blood cell (ten [9%]), and platelet (nine [8%]) counts. At least one serious treatment-emergent adverse event occurred for 22 (19%) patients. Investigators reported 20 cases of interstitial lung disease, pneumonitis, or organising pneumonia, including one grade 3 event and two treatment-related deaths due to pneumonitis. One death unrelated to study treatment was due to progressive disease. 66 (59·5%; 95% CI 49·7–68·7) of 111 patients had a confirmed objective response.

Interpretation Trastuzumab deruxtecan had a manageable safety profile and showed preliminary activity in trastuzumab emtansine-pretreated patients with HER2-positive breast cancer. These results suggest that further development in phase 2 and 3 clinical trials for HER2-positive breast cancer is warranted.

Funding Daiichi Sankyo Co, Ltd.

Introduction

About 15–20% of breast cancers show HER2 over-expression or amplification, an attribute that is generally associated with aggressive disease.[1–3] Recommended first-line therapy for patients with metastatic HER2-positive breast cancer is dual blockade with anti-HER2 humanised monoclonal antibody therapies trastuzumab and pertuzumab, in combination with chemotherapy.[4–6] At the

Research in context

Evidence before this study

We searched PubMed to identify studies assessing treatment options for HER2-positive breast cancer following progression on trastuzumab. The search terms used included "HER2-positive" and "breast" and "HER2-targeted therapy" with publication dates between Jan 1, 1980, and Sept 6, 2018, and filtered for English language only. We also examined relevant published congress abstracts. On the basis of results from the CLEOPATRA trial, current guidelines recommend the use of dual blockade with the HER2-targeted therapies trastuzumab and pertuzumab, in combination with a taxane, for the first-line treatment of patients with advanced or metastatic HER2-positive breast cancer. The EMILIA and TH3RESA studies provided evidence for use of trastuzumab emtansine, a HER2-tageted antibody–drug conjugate with a tubulin inhibitor payload, as the recommended HER2-targeted therapy for HER2-positive metastatic breast cancer after progression on a trastuzumab-based regimen. Although the continuation of HER2 therapy is recommended, there is no clear standard of care for HER2-targeted therapy after disease progression on trastuzumab emtansine.

Added value of this study

This is the first-in-human clinical study for trastuzumab deruxtecan (DS-8201a), a HER2-targeting antibody–drug conjugate with a topoisomerase I inhibitor payload, for the treatment of patients with advanced solid tumours, including a large cohort of patients with advanced HER2-postive breast cancer previously treated with trastuzumab emtansine. In patients with breast cancer who received a median of seven previous cancer therapies, 60% of patients achieved an objective response and the safety profile of trastuzumab deruxtecan was consistent with what is expected from a HER2-targeted antibody–drug conjugate that uses a topoisomerase I inhibitor as its payload.

Implications of all the available evidence

The results of the present study show a manageable safety profile and preliminary anti-tumour activity of trastuzumab deruxtecan in heavily treated patients with advanced HER2-positive breast cancer. If confirmed in ongoing clinical trials, trastuzumab deruxtecan might become a new treatment option for patients with refractory HER2-positive breast cancer.

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time of disease progression, treatment with trastuzumab emtansine, a HER2-targeted-DM1 antibody–drug conjugate with a tubulin inhibitor payload, is recommended on the basis of improvements in progression-free survival and overall survival observed in clinical trials.[7–9] Although continuation of HER2-targeted therapies is recommended, no standard of care has been established for HER2-targeted therapy in patients with metastatic HER2-postive breast cancer whose disease has progressed on or after trastuzumab emtansine.[7] Thus, a substantial need remains unmet in this patient population.

Trastuzumab deruxtecan (DS-8201a) is a novel, HER2-targeted antibody–drug conjugate comprised of a humanised monoclonal antibody attached by a cleavable peptide-based linker to a potent topoisomerase I inhibitor payload. The anti-HER2 antibody in this antibody–drug conjugate has the same amino acid sequence as trastuzumab.[10] The unique linker of trastuzumab deruxtecan is stable in plasma and selectively cleaved by lysosomal cathepsins that are upregulated in cancer cells.[10] The topoisomerase I inhibitor payload of trastuzumab deruxtecan was ten times more potent than the active metabolite of the topoisomerase I inhibitor, irinotecan, in cell-free inhibition assays, and trastuzumab deruxtecan exhibited 99% tumor growth inhibition at a dose of 4 mg/kg in xenograft models.[10] Together with a high drug-to-antibody ratio of about eight, these features are designed for efficient delivery of the payload to tumour cells while reducing the potential for systemic toxicities.[10–12] Furthermore, the payload is cell membrane permeable and has shown a short systemic half-life in preclinical in-vivo studies in animal models.[13] These characteristics could allow for a potent cytotoxic bystander effect, whereby the released topoisomerase I inhibitor diffuses across the target-cell membrane, affecting nearby cells regardless of their HER2-expression.[12] Together, these unique properties might explain the broad anti-tumour activity of trastuzumab deruxtecan observed in preclinical studies across a variety of tumour types, including those with lower HER2 expression by immunohistochemistry.[10]

A phase 1, first-in-human study[14] was started in August, 2015, with the primary objectives of selecting the recommended dose for expansion and evaluating the safety, tolerability, and activity of trastuzumab deruxtecan in advanced HER2-expressing or HER2-mutated solid tumours, including breast cancer. In the dose-escalation part of the study, doses of 5·4 mg/kg and 6·4 mg/kg administered intravenously every 3 weeks were selected as the recommended doses for expansion on the basis of the observed preliminary anti-tumour activity and safety results.[14] No dose-limiting toxicities were observed and the maximum tolerated dose was not reached during dose escalation.[14] In this Article, we report the safety and preliminary activity results from this phase 1 trial in all patients with HER2-positive advanced-stage breast cancer with previous trastuzumab emtansine treatment who received trastuzumab deruxtecan at the recommended doses for expansion.

Methods

Study design and participants

We did a two-part, first-in-human, non-randomised, open-label, phase 1 study at eight hospitals and clinics in

See Online for appendix

the USA and six in Japan (appendix p 3). Detailed methods and preliminary safety and activity as well as pharmacokinetic results of the dose escalation part (part 1) of the phase 1 study were previously published.[14] Briefly, patients with advanced breast or gastric cancer in whom previous therapy had failed were enrolled in part 1 of the study and treated with doses of 0·8–8·0 mg/kg of trastuzumab deruxtecan intravenously once every 3 weeks. Dose escalation was done using the modified continuous reassessment method to determine the dose-limiting toxicities, maximum tolerated dose, and recommended doses for expansion. A full protocol can be found in the appendix (pp 16–142).

In the dose-expansion part (part 2) of the study, the safety, tolerability, and activity of trastuzumab deruxtecan at the recommended doses for expansion (5·4 mg/kg and 6·4 mg/kg every 3 weeks) were further assessed in five patient cohorts: advanced, unresectable, or metastatic HER2-positive breast cancer after trastuzumab emtansine (defined as immunohistochemistry 3+ or in-situ hybridisation-positive; part 2a), HER2-positive gastric or gastro-oesophageal junction cancer after trastuzumab (defined as immunohistochemistry 3+ or immunohistochemistry 2+ and in-situ hybridisation-positive; part 2b), HER2-low-expressing breast cancer (defined as immunohistochemistry 1+ or 2+, in-situ hybridisation-negative; part 2c), other HER2-expressing (defined as immunohistochemistry 3+, 2+, or 1+ or amplified) or HER2-mutated solid tumours (as determined by next-generation sequencing or other methods; part 2d), and a pharmacokinetic cohort that included patients with HER2-expressing advanced, unresectable, or metastatic breast cancer (defined as immunohistochemistry 3+, 2+, 1+, or in-situ hybridisation-positive; part 2e; appendix p 4). The data in this analysis includes all patients with HER2-positive advanced, unresectable, or metastatic breast cancer previously treated with trastuzumab emtansine and who received trastuzumab deruxtecan doses of 5·4 mg/kg or 6·4 mg/kg from parts 1, 2a, and 2e. The combination of patients by cancer type from multiple cohorts was decided post hoc.

Eligible patients were at least 18 years of age (or at least 20 years in Japan), with an Eastern Cooperative Oncology Group performance status of zero or one, measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 at baseline, documented HER2-positive (immunohistochemistry 3+, immunohistochemistry 2+ and in-situ hybridisation-positive, or in-situ hybridisation-positive) advanced, unresectable, or metastatic breast cancer that was refractory to standard treatment or for which standard treatment was intolerable or unavailable, a life expectancy of at least 3 months, and previous treatment with trastuzumab emtansine. Tumour HER2 status was locally assessed using archival samples; new biopsy before treatment was not required. Full eligibility criteria are in the appendix (pp 5–6).

Independent ethics committees or institutional review boards at each site approved the study protocol. The study was done in compliance with the protocol and in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent before study enrolment.

Procedures

The study drug, trastuzumab deruxtecan, was supplied by the study sponsor as single-use glass vials (Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; Daiichi Sankyo Co, Ltd, Tokyo, Japan). The number of treatment cycles was not fixed; 5·4 mg/kg or 6·4 mg/kg trastuzumab deruxtecan was administered intravenously to patients once every 3 weeks until withdrawal of consent, unacceptable toxicity, or progressive disease. Patients were assigned to a dose by use of a non-randomised, ad-hoc sequential block method, in which one dose was assigned for a period of time before switching to the other dose. This process was repeated, with the goal of assigning a similar number of patients to each dose. Patients remained on study until withdrawal for reasons including progressive disease, clinical progression, adverse events, withdrawal of consent, loss to follow-up, protocol violation, study termination, or for other reasons at the discretion of the investigator. Dose interruptions of up to 4 weeks from the planned date of study drug administration were allowed (appendix p 7). Up to two dose reductions were permitted, but doses lower than 0·8 mg/kg were not allowed (appendix pp 67–68).

In the initial 24 weeks after the first dose was administered, tumour assessments (CT or MRI) were done every 6 weeks, and then every 12 weeks thereafter. Tumour response was evaluated by the investigators using RECIST version 1.1. At each study visit, treatment-emergent adverse events were documented and graded according to the Common Terminology Criteria for Adverse Events version 4.0. Left ventricular ejection fraction was determined by echocardiography or multigated acquisition scanning at screening, before infusion on the first day of cycles 2 and 3, and every two cycles thereafter until the end of treatment. When interstitial lung disease, pneumonitis, or organising pneumonia was suspected, early diagnosis through appropriate imaging, laboratory tests, and pulmonary consultation as well as withdrawal of study medication and management with steroids for moderate to severe cases was recommended, in accordance with the guidelines from the Japanese Respiratory Society.[15] An independent adjudication committee was established to review reported cases of interstitial lung disease, pneumonitis, and organising pneumonia.

Outcomes

The primary endpoints of the study were safety and preliminary activity. Safety endpoints included

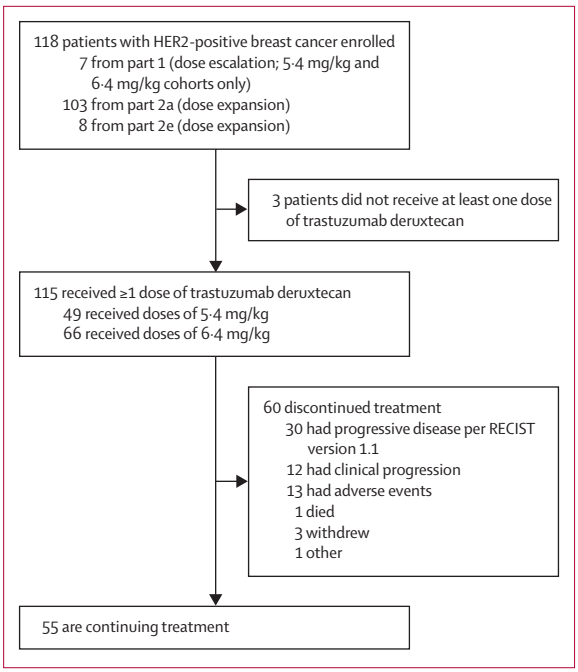

Figure 1: **Study profile**
RECIST=Response Evaluation Criteria in Solid Tumors.

	HER2-positive breast cancer, n=115
Age, years	55·0 (47·0–66·0)
Sex	
Female	114 (99%)
Male	1 (1%)
Country	
Japan	62 (54%)
USA	53 (46%)
Eastern Cooperative Oncology Group performance status	
0	72 (63%)
1	43 (37%)
Time from initial diagnosis, months*	69·7 (48·0–117·2)
Previous anticancer regimens†	7·0 (5·0–11·0)
≥5 previous anticancer regimens	94 (82%)
Trastuzumab	114 (99%)
Pertuzumab	99 (86%)
Trastuzumab emtansine	115 (100%)
Lapatinib	62 (54%)
Other HER2 therapy	6 (5%)
Previous cancer surgery	88 (77%)
Previous radiotherapy	94 (82%)
HER2 expression (immunohistochemistry)	
3+	79 (69%)
2+ (in-situ hybridisation-positive)	31 (27%)
1+ (in-situ hybridisation-positive)	1 (1%)
0	0
Missing or not examined	4 (3%)
Hormone receptor status	
Positive	81 (70%)
Negative	33 (29%)
Missing	1 (1%)
Tumour size, cm	
Sum of diameters‡	6·0 (3·6–10·0)
<5	47 (41%)
≥5 to <10	37 (32%)
≥10	29 (25%)

Data are median (IQR) or n (%). Baseline was defined as the last available value taken before the first dose of study drug. Safety analysis set included all patients who received at least one dose of trastuzumab deruxtecan at 5·4 mg/kg or 6·4 mg/kg. RECIST=Response Evaluation Criteria in Solid Tumors. *Time from initial diagnosis was calculated as: (date of first dose of study drug – date of initial diagnosis + 1) × 12 ÷ 365·25. †Includes hormone therapies for breast cancer and treatments received in the (neo)adjuvant setting. ‡Median sum of diameters of target lesions per RECIST version 1.1.

Table 1: **Patient demographics and baseline characteristics (safety analysis set)**

treatment-emergent adverse events, serious treatment-emergent adverse events, treatment-emergent adverse events leading to discontinuation, physical examination assessments, vital sign measurements, and standard clinical laboratory parameters. Treatment-emergent adverse events of special interest included interstitial lung disease or pneumonitis, organising pneumonia, ejection fraction decrease, electrocardiogram QT prolongation, hepatic events, and infusion-related reactions. In this study, progressive disease was an endpoint, and thus, was not to be reported as an adverse event; however, if a patient died from progressive disease with no other immediate causes, progressive disease was to be reported as a serious adverse event.

The primary activity endpoint was the proportion of patients who achieved an objective response (defined as patients who achieved a complete response or partial response) as assessed by the investigators. Other activity endpoints were overall survival, progression-free survival, proportion of patients achieving disease control (defined as complete response, partial response, or stable disease for a minimum of 5 weeks from the first dosing date), percentage change of the sum of target lesion diameters, duration of response, time to response, duration of stable disease, time on therapy for trastuzumab deruxtecan, and growth modulation index ratio. Activity endpoints were not centrally reviewed for this analysis. A retrospective, blinded, independent review is ongoing.

Progression-free survival was defined as the time from the date of the first dose to the first objective documentation of radiographic progressive disease or death due to any cause, whichever was earlier. Overall survival was defined as the time from the date of the first dose to the date of death from any cause. Time to response was measured from the date of the first dose to the date at which criteria for complete response or partial response were first met. Duration of response was measured from the time at which complete response or

	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Haematological				
Anaemia	26 (23%)	18 (16%)	1 (1%)	0
Neutrophil count decreased*	16 (14%)	13 (11%)	3 (3%)	0
Platelet count decreased†	23 (20%)	7 (6%)	2 (2%)	0
White blood cell count decreased‡	15 (13%)	8 (7%)	2 (2%)	0
Gastrointestinal				
Nausea	87 (76%)	4 (3%)	0	0
Vomiting	55 (48%)	5 (4%)	0	0
Diarrhoea	41 (36%)	2 (2%)	0	0
Constipation	41 (36%)	1 (1%)	0	0
Stomatitis	24 (21%)	0	0	0
Dyspepsia	14 (12%)	0	0	0
Abdominal pain	13 (11%)	0	0	0
Other				
Decreased appetite	62 (54%)	2 (2%)	0	0
Alopecia	54 (47%)	0	0	0
Fatigue	46 (40%)	5 (4%)	0	0
Pyrexia	24 (21%)	2 (2%)	0	0
Malaise	24 (21%)	0	0	0
Cough§	22 (19%)	0	0	0
Hypokalaemia	16 (14%)	3 (3%)	0	0
Dysgeusia	17 (15%)	0	0	0
Rash	15 (13%)	0	0	0
Oedema peripheral	14 (12%)	0	0	0
Hypoalbuminaemia	12 (10%)	1 (1%)	0	0
Headache	12 (10%)	1 (1%)	0	0
Weight decreased	12 (10%)	1 (1%)	0	0
Epistaxis	12 (10%)	0	0	0
Nasopharyngitis	12 (10%)	0	0	0
Upper respiratory tract infection	12 (10%)	0	0	0
Hyponatraemia	7 (6%)	3 (3%)	0	0
Adverse events of interest				
Aspartate aminotransferase increased	28 (24%)	1 (1%)	0	0
Alanine aminotransferase increased	23 (20%)	0	0	0
Blood bilirubin increased	4 (3%)	0	0	0
Ejection fraction decreased	0	0	0	0
Electrocardiogram QT prolonged	10 (9%)	0	0	0
Interstitial lung disease¶	5 (4%)	1 (1%)	0	0
Organising pneumonia¶	6 (5%)	0	0	0
Pneumonitis¶	6 (5%)	0	0	2 (2%)
Infusion-related reactions	2 (2%)	0	0	0

Data are presented as n (%). This table shows all grade 1 or 2 adverse events occurring in at least 10% of patients, grade 3–5 events occurring in at least 2% of patients, and all adverse events of special interest regardless of incidence. The complete list of all grade 3–5 treatment-emergent adverse events is in the appendix (pp 14–15). Patients might experience more than one event per system organ class and preferred term. At each level of patient summarisation, the patient is counted once at the worst Common Terminology Criteria for Adverse Events grade. System Organ Class was coded with Medical Dictionary for Regulatory Activities version 18.0. Safety analysis set included all patients who received at least one dose of trastuzumab deruxtecan at 5·4 mg/kg or 6·4 mg/kg. *Includes preferred terms of neutropenia (n=6) and neutrophil count decreased. †Includes preferred terms of thrombocytopenia (n=6) and platelet count decreased. ‡Includes preferred terms of leucopenia (n=1) and white blood cell count decreased. §Grade was missing for one patient. ¶As assessed by the investigator before independent adjudication.

Table 2: **Treatment-emergent adverse events (n=115; safety analysis set)**

partial response criteria were first met to the first date of objectively documented progressive disease or death due to any cause. Progressive disease was defined as an increase in the sum of diameters of target lesions of at least 20% and an absolute increase of at least 5 mm, or the appearance of at least one new lesion.

Secondary endpoints were to assess the pharmacokinetic profile of trastuzumab deruxtecan, total anti-HER2 antibody and the free payload, and the incidence of anti-drug antibody against trastuzumab deruxtecan. Results for the secondary endpoints will be reported separately.

Statistical analysis

For dose escalation (part 1), sample size was determined by practical considerations and did not include formal statistical assessments.[14] The planned sample size for dose expansion (part 2a) was 100 patients, providing at least 90% power to exclude a proportion of patients who achieved an objective response of 15% or less at the 5% type I error (one-sided), when the true proportion of patients achieving an objective response was 35%. An objective response of 35% was thought to be clinically meaningful based on historical reports of efficacy in this setting.[8] For part 2e, the planned sample size was 20 patients, which would provide at least 75% power to exclude a proportion of patients who achieved an objective response of 15% or less at the 20% type I error (one-sided), when the true proportion was 30%. The probability values for the sample size were derived from binomial distribution using SAS (version 9.2).

The activity evaluable and safety analysis populations were defined by the study protocol. The activity evaluable set included all patients with HER2-postive breast cancer after trastuzumab emtansine who received at least one dose of trastuzumab deruxtecan at 5·4 mg/kg or 6·4 mg/kg regardless of cohort and had both baseline and post-treatment activity data available. The safety analysis set included all HER2-positive breast cancer patients who received at least one dose of trastuzumab deruxtecan at the recommended doses for expansion. Other activity populations that were not defined in the protocol were also analysed, including a modified intention-to-treat population of all patients who received at least one dose of trastuzumab deruxtecan at the recommended doses for expansion. Patients evaluable for a confirmed response had two or more postbaseline scans, had progressive disease, or discontinued treatment before a second postbaseline scan. Exploratory analyses of outcomes by previous pertuzumab treatment, hormone receptor status, and dose were done post hoc.

SAS (version 9.3) was used for statistical analyses. Point estimates and 95% exact binomial CIs were computed for objective response and disease control. The Kaplan-Meier method was used to describe time-to-event variables with confidence intervals calculated using

the Brookmeyer-Crowley method. Descriptive statistics were used to summarise the best percentage change in the sum of the longest diameters of measurable tumours and demographic and safety data. Treatment duration in months was defined as: (the date of the last dose of study drug−the date of the first dose of study drug+21 days)×12÷365·25. Missing or dropout data were not imputed unless otherwise specified. No formal interim analyses were planned. This trial is registered at ClinicalTrials.gov, number NCT02564900, and ClinicalTrials.jp, number JapicCTI-152978.

Role of the funding source

The study was funded by the sponsor, Daiichi Sankyo Co, Ltd, which was involved in study design, data collection, data analysis, and data interpretation, provided the study drug, assisted in writing the report, and approved the final version of the manuscript for publication in conjunction with the authors. The authors had full access to all data in the study and provided final approval to submit the manuscript for publication.

Results

Between Aug 28, 2015, and Aug 10, 2018, 259 of 274 patients enrolled received at least one dose of trastuzumab deruxtecan at the recommended doses for expansion of 5·4 mg/kg or 6·4 mg/kg every 3 weeks (12 in the dose escalation and 247 in the dose expansion). Of these 274 patients, 118 patients with HER2-positive breast cancer were enrolled. As of Aug 10, 2018, the data cutoff point, 115 of these patients had received at least one dose of trastuzumab deruxtecan at the recommended doses for expansion every 3 weeks (seven from part 1, 100 from part 2a, and eight from part 2e; figure 1). Among treated patients, 49 received the 5·4 mg/kg dose and 66 received the 6·4 mg/kg dose. Median duration of treatment was 8·3 months (IQR 4·4–12·0). At the time of data cutoff, trastuzumab deruxtecan treatment was ongoing for 55 (48%) of 115 patients. Study treatment was discontinued for 60 (52%) of 115 patients, most commonly due to progressive disease per RECIST in 30 (26%) patients, clinical progression in 12 (10%), or adverse events in 13 (11%; figure 1).

Most patients with HER2-positive breast cancer were female with a median age of 55 years (IQR 47·0–66·0) and a median of seven previous cancer therapies (5·0–11·0; table 1). In 113 patients with tumour size available at baseline, the median sum of target lesion longest diameters was 6·0 cm (3·6–10·0). Overall, 81 (70%) of 115 patients had hormone receptor-positive tumours (table 1), with 78 (68%) oestrogen receptor-positive and 56 (49%) progesterone receptor-positive.

All 115 patients had one or more treatment-emergent adverse event of any grade, 22 (19%) had one or more serious treatment-emergent adverse event, and 57 (50%) had a treatment-emergent adverse event of grade 3 or worse (appendix p 13). Drug-related treatment-emergent adverse events leading to treatment discontinuation occurred in 13 (11%) patients, which included interstitial lung disease or pneumonitis in nine patients as well as organising pneumonia, radiation pneumonitis, radiation necrosis, and anaemia (each in one patient). Drug-related serious treatment-emergent adverse events occurred for 13 (11%) patients (appendix p 13). Drug-related serious treatment-emergent adverse events occurring in more than one patient included interstitial lung disease or pneumonitis (n=4) and vomiting (n=2). Treatment interruption due to a treatment-emergent adverse event

	Total evaluable, n=114	Received previous pertuzumab (post-hoc analysis), n=99
Treatment duration, months		
N for modified intention to treat*	115	99
Median (IQR)	8·3 (4·4–12·0)	8·3 (4·4–12·0)
Median (IQR) follow-up for modified intention to treat, months*	9·9 (6·9–14·3)	9·7 (7·0–14·1)
Confirmed best overall response, n/N (%)†		
Complete response	3/111 (3%)	3/96 (3%)
Partial response	63/111 (57%)	57/96 (59%)
Stable disease	38/111 (34%)	30/96 (31%)
Progressive disease	6/111 (5%)	6/96 (6%)
Non-evaluable	1/111 (1%)	0/96
Confirmed objective response, n/N (%; 95% CI)†	66/111 (59·5%; 49·7–68·7)	60/96 (62·5%; 52·0–72·2)
Confirmed disease control, n/N (%; 95% CI)†‡	104/111 (93·7%; 87·4–97·4)	90/96 (93·8%; 86·9–97·7)
Confirmed objective response in modified intention to treat, n/N (%; 95% CI)*	66/115 (57·4%; 47·8–66·6)	60/99 (60·6%; 50·3–70·3)
Confirmed disease control in modified intention to treat, n/N (%; 95% CI)*	105/115 (91·3%; 84·6–95·8)	91/99 (91·9%; 84·7–96·4)
Time to response, months§		
n	73¶	65
Median (95% CI)	1·6 (1·4–2·8)	1·4 (1·4–2·7)
Range	1·2–9·0	1·2–8·5
Duration of response, months‖		
n	73¶	65
Median (95% CI)	20·7 (not estimable)	Not estimable
Range	0**–21·8**	0**–21·8**
Progression-free survival, months		
Event, n (%)	33 (29%)	30 (30%)
Median (95% CI)	22·1 (not estimable)	16·4 (not estimable)
Range	0·8**–27·9**	1·0–27·9**

The activity evaluable set included all patients who received at least one dose of trastuzumab deruxtecan at 5·4 mg/kg or 6·4 mg/kg and for whom both baseline and post-treatment activity data were available. *The modified intention-to-treat set included patients who received at least one dose of trastuzumab deruxtecan at either 5·4 mg/kg or 6·4 mg/kg. †Evaluable patients for confirmed response had two or more postbaseline scans, had progressive disease, or discontinued treatment for any reason before second postbaseline scan. ‡Disease control was calculated as the proportion of patients demonstrating complete response, partial response, or stable disease for a minimum of 5 weeks from the first dosing date. §Time to response was measured from the date of the first dose to the date at which criteria for complete response or partial response are first met. ¶Includes seven cases of unconfirmed response. ‖Duration of response was measured from the time at which complete response or partial response criteria are first met until the first date of objectively documented progressive disease. **Censored observation.

Table 3: **Anti-tumour activity outcomes (activity evaluable set)**

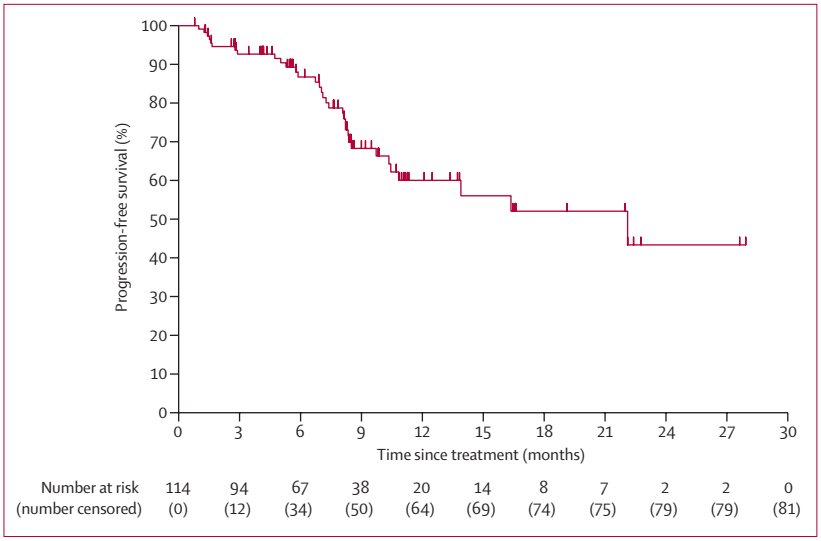

Figure 2: **Progression-free survival for trastuzumab deruxtecan (5·4 mg/kg or 6·4 mg/kg) in patients with HER2-positive breast cancer**
Progression-free survival is based on investigator assessment. Vertical tick marks indicate where data were censored.

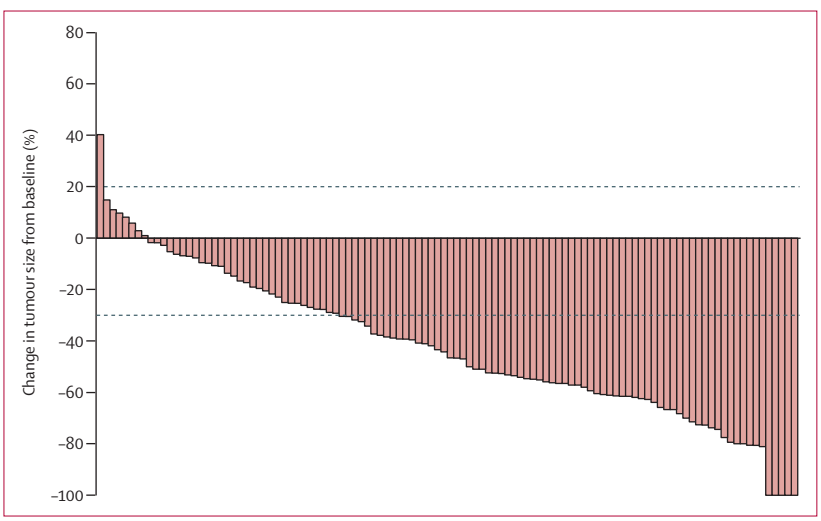

Figure 3: **Best percentage change in tumour size from baseline in individual patients with HER2-positive breast cancer treated with trastuzumab deruxtecan (5·4 mg/kg or 6·4 mg/kg doses; n=110)**
Dotted lines denote 20% increase or 30% reduction in tumour size. For this plot, one subject was excluded due to no post-baseline sum of diameters.

occurred for 34 (30%) patients—including pneumonitis in five patients and organising pneumonia in two—and 21 (18%) had dose reductions due to a treatment-emergent adverse event. The frequency of grade 3 or worse treatment-emergent adverse events, serious treatment-emergent adverse events, dose reductions, and treatment discontinuations for the 6·4 mg/kg dose compared with the 5·4 mg/kg dose is presented in the appendix (p 13). At the time of this analysis, there were three deaths due to treatment-emergent adverse events: one from progressive disease and two from pneumonitis. Both cases of pneumonitis were considered drug-related.

Two of the most common classes of treatment-emergent adverse events were gastrointestinal and haematological (table 2; appendix pp 14–15). The most common grade 3 or worse events were anaemia (19 [17%] of 115) and decreased counts of neutrophils (16 [14%]), platelets (nine [8%]), and white blood cells (ten [9%]; table 2). One case of grade 3 febrile neutropenia was reported (appendix pp 14–15); the patient was hospitalised, medication was initiated, and the dose of trastuzumab deruxtecan was reduced, resulting in resolution after 12 days.

No cases of decreased ejection fraction were recorded. Nine patients experienced a grade 1 and one patient experienced a grade 2 electrocardiogram QT prolongation (table 2), and all patients maintained the same dose. Alanine aminotransferase increased in 23 (20%; all grade 1 or 2) patients and aspartate aminotransferase in 29 (25%; one grade 3 or worse; table 2). Infusion-related reactions occurred in two patients, both grade 1. Investigators reported eight cases of pneumonitis (four grade 1, two grade 2, and two grade 5), six cases of interstitial lung disease (four grade 1, one grade 2, and one grade 3), and six cases of organising pneumonia (two grade 1 and four grade 2) in patients with HER2-positive breast cancer (table 2). Of the 20 cases of interstitial lung disease, pneumonitis, or organising pneumonia, six were observed with 5·4 mg/kg (six [12%] of 49) and 14 with 6·4 mg/kg doses (14 [21%] of 66). The median time to onset of pneumonitis was 251·5 days (95% CI 83·0–290·0) and 187·0 days (95% CI 82·0–341·0) for interstitial lung disease. An independent adjudication committee assessed the cases of interstitial lung disease or pneumonitis and organising pneumonia. On the basis of their review, 13 cases were confirmed as interstitial lung disease related to trastuzumab deruxtecan; one was considered interstitial lung disease, but not related to trastuzumab deruxtecan; two cases were not interstitial lung disease; and four cases were pending adjudication.

As of Aug 10, 2018, 111 (97%) of the 115 patients were evaluable for confirmed response. Of patients who were not included, one received study treatment but had no record of prebaseline or postbaseline tumour assessment data, one had no second postbaseline tumour assessment without progressive disease, and two had no baseline measurable disease. 66 (59·5%, 95% CI 49·7–68·7) of 111 patients achieved a confirmed objective response and 104 (93·7%, 95% CI 87·4–97·4) of 111 patients achieved confirmed disease control, with a median follow-up of 9·9 months (IQR 6·9–14·3; table 3). The median time to response was 1·6 months (95% CI 1·4–2·8) and the median duration of response was 20·7 months (95% CI not estimable, range 0–21·8 [with censoring]; table 3). The median progression-free survival was 22·1 months (95% CI not estimable, range 0·8–27·9 [with censoring]; table 3; figure 2), and the median overall survival has not been reached (appendix p 8).

Tumour shrinkage was observed in 102 (93%) of 110 patients with measurable lesions who had at least one postbaseline scan (figure 3); 91 (89%) of 102 had tumour shrinkage by the first 6-week postbaseline tumour assessment (appendix p 9).

In the post-hoc subgroup analysis of patients who had received previous pertuzumab treatment, 60 (62·5%, 95% CI 52·0–72·2) of 96 patients achieved a confirmed objective response, 90 (93·8%, 86·9–97·7) of 96 achieved disease control, and median progression-free survival was 16·4 months (95% CI not estimable, range 1·0–27·9; table 3). In the post-hoc analysis of trastuzumab deruxtecan by dose group, 26 (56·5%, 95% CI 41·1–71·1) of 46 patients achieved an objective response and 42 (91·3%, 79·2–97·6) of 46 achieved disease control in the 5·4 mg/kg dose group, and 40 (61·5%, 48·6–73·3) of 65 achieved an objective response and 62 (95·4%, 87·1–99·0) of 65 achieved disease control in the 6·4 mg/kg group (appendix pp 10–11). Activity was also assessed by hormone receptor status post hoc. In hormone receptor-positive patients, 47 (59·5%, 47·9–70·4) of 79 achieved an objective response and 73 (92·4%, 84·2–97·2) of 79 achieved disease control. In hormone receptor-negative patients, 19 (61·3%, 42·2–78·2) of 31 achieved an objective response and 30 (96·8%, 83·3–99·9) of 31 achieved disease control. Additional activity outcome data are in the appendix (pp 10–12).

Discussion

To our knowledge, trastuzumab deruxtecan is the first HER2-targeted antibody–drug conjugate with a topoisomerase I inhibitor payload to be investigated in patients with advanced, unresectable, or metastatic HER2-positive breast cancer. The results of the dose-escalation part of the study were previously reported.[14] In this phase 1 study, trastuzumab deruxtecan treatment had a manageable safety profile and resulted in clinically significant preliminary responses with durable benefits in this patient population. In a post-hoc analysis, anti-tumour activity was also observed in the subgroup of patients who previously received pertuzumab, in addition to trastuzumab and trastuzumab emtansine. The effect of trastuzumab deruxtecan on overall survival for this patient population has yet to be determined; however, a large proportion of patients achieved an objective response or disease control, and a long duration of response occurred. Along with the high response in breast cancer reported here, promising preliminary anti-tumour activity has also been observed in HER2-positive gastric cancer by Shitara and colleagues,[16] in non-archetype HER2-expressing tumour types (ie, non-breast or non-gastric), as well as in breast cancer with low HER2 expression levels.[17,18]

Metastatic HER2-positive breast cancer is challenging to treat. In clinical trials, trastuzumab, pertuzumab, and trastuzumab emtansine have shown clinical anti-tumour activity as monotherapy or in combination.[8,9,19,20] However, most patients will eventually progress on trastuzumab emtansine, with the median duration of response ranging from 7·2 months to 12·6 months across multiple studies, and approved options for these patients are scarce.[9,21–23] Our trial enrolled patients who were heavily pretreated and received multiple lines of previous therapy, including trastuzumab and trastuzumab emtansine as well as pertuzumab in most cases. Although not clearly defined, several mechanisms of resistance to trastuzumab emtansine have been proposed, including reduced tumour HER2 overexpression, changes in the intracellular concentrations of the trastuzumab emtansine payload, altered expression of drug efflux proteinsides, and resistance to the cytotoxic effect of the released tubulin inhibitor payload.[24] Trastuzumab deruxtecan delivers a topoisomerase I inhibitor payload by a highly stable linker-payload system at a consistently higher drug-to-antibody ratio (about 8) compared with trastuzumab emtansine (drug-to-antibody ratio of 3·5).[10,24] Therefore, trastuzumab deruxtecan might circumvent resistance to the cytotoxicity of the tubulin inhibitor in trastuzumab emtansine by efficiently delivering a higher concentration of a cytotoxic payload of a different class and mechanism of action (ie, a topoisomerase I inhibitor).

Patients who have received previous pertuzumab are of great clinical interest, because guidelines suggest that dual HER2-blockade with trastuzumab and pertuzumab in combination with chemotherapy is the standard of care for the first-line treatment of metastatic HER2-positive breast cancer.[4–6] Thus, many patients who receive second-line or greater therapies are likely to have had pertuzumab treatment, and it is important to understand if the anti-tumour effect of new treatments is different in this patient population. Some evidence suggests the efficacy of trastuzumab emtansine in patients who have received a first-line pertuzumab plus trastuzumab regimen is lower than in patients who received first-line trastuzumab without pertuzumab.[25,26] In our study, 62·5% of patients who received previous pertuzumab treatment achieved an objective response.

Hormone receptors for oestrogen and progesterone are additional markers that might alter the effectiveness of therapies for HER2-positive breast cancer.[27] In our study, trastuzumab deruxtecan showed preliminary anti-tumour activity in patients with advanced HER2-positive breast cancer regardless of hormone receptor status.

Further studies are needed to better understand the mechanism of action for trastuzumab deruxtecan. It can be hypothesised that the unique structural characteristics of the compound, such as its potent payload with stable linker-payload system, high drug-to-antibody ratio, and potential bystander effect,[12] contribute to the promising observed anti-tumour activity of trastuzumab deruxtecan. Moreover, the anti-tumour activity does not appear to be limited to conventionally defined HER2-positive breast cancer,[10,17,18] suggesting that trastuzumab deruxtecan might affect HER2-expressing tumours even if the HER2

pathway is not the primary oncogenic driver for the disease. How much of the anti-tumour effect observed with trastuzumab deruxtecan can be attributed to HER2-targeted delivery of the cytotoxic payload versus blockade of the HER2 pathway itself remains to be seen. Additionally, further studies are needed on the mechanism of resistance to trastuzumab deruxtecan, as well as on the discovery of potential predictors of response outside the conventional HER2 immunohistochemistry or in-situo hybridisation status.

The overall safety profile of trastuzumab deruxtecan was consistent with what would be expected for a HER2-targeted antibody–drug conjugate that utilises a topoisomerase I inhibitor as its payload. Two common classes of treatment-emergent adverse events were gastrointestinal and haematological. Cardiac dysfunction, including severe congestive heart failure and left ventricular ejection fraction decrease, is a serious side-effect of treatment with trastuzumab,[28] pertuzumab,[29] and, to a lesser extent, trastuzumab emtansine.[9,30] For patients with HER2-positive breast cancer in this study, there were no reported cases of ejection fraction decrease. Additionally, hepatotoxicity is also reported as a potential side-effect of trastuzumab emtansine.[9,20] In this study, treatment-emergent adverse events involving the liver were mainly grade 1 increases in alanine aminotransferase and aspartate aminotransferase.

Treatment-induced pulmonary adverse events, including interstitial lung disease, have been reported as rare, potentially life-threatening adverse events associated with trastuzumab and trastuzumab emtansine.[31,32] Drug-related interstitial lung disease or pneumonitis, including fatal cases, were reported in this study.[18] The proportion of patients who had this complication was lower for those who received the 5·4 mg/kg dose than those who received the 6·4 mg/kg dose; further investigation is needed to establish the relative risk by dose. A robust monitoring and management plan has been established and implemented across all studies of trastuzumab deruxtecan. Independent adjudication of these cases, increased awareness of investigators, proactive monitoring for and investigation or treatment of suspect cases, and further research will help better characterise and mitigate the risk of pulmonary toxicities associated with trastuzumab deruxtecan. Additionally, these efforts will help identify potential risk factors and optimise clinical management for such events.

This study had some limitations that might affect generalisation of the results. It was a non-randomised, phase 1 study with a heterogeneous patient population and a small sample size. The study was not designed to capture detailed information on the patients' status at the time of previous treatments; thus, the data for both relapsed and de-novo metastatic breast cancer are pooled. Conflicting reports exist about whether this distinction might affect clinical outcome,[33–35] and further studies are needed to investigate whether response to trastuzumab deruxtecan is different in patients with de-novo versus relapsed metastatic breast cancer. Additionally, HER2 immunohistochemistry status was determined using archival samples, which might have over-represented the number of patients with HER2-positive breast cancer at study entry, because HER2-expression has been shown to change in some tumours in response to neoadjuvant chemotherapy or sequential trastuzumab regimens.[36] Archival samples were processed and analysed by local facilities, not centrally, potentially leading to variation in assessment of tumour HER2 status due to differences in local practices. Another limitation is that the reported radiographic tumour responses were based on local radiology review; however, a retrospective, blinded, independent review of responses is ongoing and will be reported subsequently.

Trastuzumab deruxtecan showed preliminary anti-tumour activity, with 59·5% of patients achieving an objective response and durable responses seen in heavily pretreated patients with advanced, unresectable, or metastatic HER2-positive breast cancer, giving rationale for further investigation of trastuzumab deruxtecan in this setting. In August, 2017, the US Food and Drug Administration granted breakthrough therapy designation to trastuzumab deruxtecan for treatment of patients with advanced HER2-positive breast cancer previously treated with trastuzumab and pertuzumab, and whose disease progressed after trastuzumab emtansine. The ongoing DESTINY-Breast01 study (NCT03248492), a pivotal, phase 2, multicentre, open-label trial, is further characterising the activity and safety of trastuzumab deruxtecan in patients with HER2-positive unresectable or metastatic breast cancer previously treated with trastuzumab emtansine. Additionally, two international, phase 3 studies of trastuzumab deruxtecan in advanced HER2-positive breast cancer have been initiated. DESTINY-Breast02 (NCT03523585) will assess the efficacy and safety of trastuzumab deruxtecan versus investigator's choice of treatment (trastuzumab plus capecitabine or lapatinib plus capecitabine) in patients whose disease progressed on trastuzumab emtansine. DESTINY-Breast03 (NCT03529110) will assess the efficacy and safety of trastuzumab deruxtecan compared with trastuzumab emtansine. Several other ongoing studies are investigating different tumour types with trastuzumab deruxtecan as monotherapy or in combination with other agents. DESTINY-Gastric01 (NCT03329690) is an ongoing phase 2 study that will enrol around 220 patients with advanced gastric or gastro-oesophageal junction cancer to assess the efficacy and safety of trastuzumab deruxtecan compared with physician's choice of treatment. Phase 2 studies of trastuzumab deruxtecan in advanced HER2-expressing colorectal cancer (NCT03384940) and HER2-overexpressing or HER2-mutated non-small cell lung cancer (NCT03505710) are also ongoing. These studies will further expand the understanding of trastuzumab deruxtecan efficacy and safety in various settings. The

results reported here suggest trastuzumab deruxtecan might offer an additional therapeutic option for advanced HER2-positive breast cancer.

Contributors

All authors were involved in the conception or design of the study and in drafting and revising the manuscript. KT, JT, ST, HI, IEK, CR, YS, TD, HP, RKM, RAR, and SM were involved in data collection. MS analysed the data. All authors were involved in the interpretation of data and approved the final version of the manuscript.

Declaration of interests

KT reports research funding from Daiichi Sankyo paid to his institution during the conduct of the study. JT received preclinical research funds from Daiichi Sankyo during the conduct of this study, and outside the submitted work, honorarium from Novartis, Taiho, Eisai, Chugai, and Kyowa Hakko Kirin, personal fees for participating in advisory boards for Eisai and Asahi Kasei, and support for travel expenses from Daiichi Sankyo. ST reports grants from Daiichi Sankyo during the conduct of the study, personal fees from Novartis, Merck Sharp & Dohme Corporation (MSD), Eisai, Taiho, Chugai, Daiichi Sankyo, Bayer, and AstraZeneca, and grants from MSD, Eisai, Taiho, Chugai, Daiichi Sankyo, Bayer, AstraZeneca, and Quintiles outside the submitted work. HI received grants and personal fees from Daiichi Sankyo during the conduct of this study, and, outside the submitted work, grants from Chugai, Pfizer, AstraZeneca, MSD, Kyowa Hako Kirin, GlaxoSmithKline, Lilly, Novartis, and Bayer, and personal fees from Chugai, Eisai, Pfizer, and AstraZeneca. IEK reports research support and consulting fees from Genentech and Roche and consulting fees from Daiichi Sankyo. CR owns stock in Pfizer. YS received honoraria from Pfizer, Novartis, Taiho, Eisai, Chugai, Kyowa Hakko Kirin, Lilly, and AstraZeneca. TD received grants from Daiichi Sankyo during the conduct of this study, and outside the submitted work, grants from Lilly, Chugai, Kyowa Hakko Kirin, MSD, Daiichi Sankyo, Taiho, Novartis, Merck Serono, Astellas, Janssen, Boehringer Ingelheim, Takeda, Pfizer, Sumitomo Group, Celgene, Bristol-Myer Squibb, AbbVie, and Quintiles, and personal fees from Lilly, Chugai, Kyowa Hakko Kirin, MSD, Daiichi Sankyo, and Amgen. HP reports non-financial support from Daiichi Sankyo. RKM reports research grants paid to University of Texas MD Anderson Cancer Center from Daiichi Sankyo, Genentech, and Cascadian Therapeutics outside the submitted work. RAR reports research grants paid to the University of Louisville from Merck, Bristol-Myers Squibb, Lilly, Pfizer, and Daiichi Sankyo. TJ, CL, MS, JS, and AY are full-time employees of Daiichi Sankyo. SM received personal and other fees from Daiichi Sankyo related to the submitted work, outside of the submitted work; she reports personal and other fees from Genentech and Seattle Genetics, personal fees from Carrick and Puma, and other fees from Novartis.

Data sharing

De-identified individual participant data and applicable supporting clinical trial documents may be available upon request at the Vivli website. In cases where clinical trial data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo, Inc, will continue to protect the privacy of our clinical trial participants. Details on data sharing criteria and the procedure for requesting access can be found at Vivli's Daiichi Sankyo web page. For more information, see appendix p 2.

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