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Trastuzumab duocarmazine (SYD985) in locally advanced and metastatic solid tumours and HER2-expressing breast cancer: a phase 1 dose-escalation with expansion study

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Summary

Background

Trastuzumab duocarmazine is a novel HER2-targeting antibody-drug conjugate comprised of trastuzumab covalently bound to a linker-drug containing duocarmycin. Preclinical studies showed impressive antitumour activity in various models. In this first-in-human study we evaluated the safety and activity in patients with solid tumours.

Methods

In the dose-escalation part, patients aged 18 years or older with locally advanced or metastatic solid tumours with variable HER2 status and refractory to standard therapy were enrolled. The expansion cohorts included patients with breast, gastric, urothelial, or endometrial cancer with at least HER2 immunohistochemistry 1+ expression and measurable disease according to RECIST. Trastuzumab duocarmazine was administered intravenously on day 1 of each 3-week cycle at doses of 0·3 to 2·4 mg/kg until disease progression or unacceptable toxicity. A 3+3 design was used in the dose-escalation part and the primary endpoint was to evaluate safety and determine the recommended phase 2 dose. The primary endpoint of the expansion part was the proportion of patients who achieved an objective response. This ongoing study is registered with ClinicalTrials.gov, number NCT02277717, and is fully recruited.

Findings

Between October 30, 2014 and April 2, 2018, 39 patients were enrolled and treated in the dose-escalation part and 146 patients in the expansion part of the study. One dose-limiting toxicity (fatal pneumonitis) occurred at the highest administered dose. Grade ≥ 3 treatment-related adverse events reported more than once were keratitis (three patients) and fatigue (two patients). Based on all available data, the recommended phase 2 dose was set at 1·2 mg/kg. In de expansion part of the study, treatment-related serious adverse events were reported in 16 (11%) of 146 patients. The most common treatment-related adverse events were fatigue (48 [33%] of 146 patients), conjunctivitis (45 [31%]), and dry eye (45 [31%]). The majority of patients had one or more ocular adverse events, with grade 3 events in 10 (7%) of 146 patients. In the breast cancer expansion cohorts, 16 (33%, 95% CI 20·4-48·4) of 48 evaluable patients with HER2-positive breast cancer achieved an objective response. The proportion of patients with HER2-low, HR-positive breast cancer who achieved an objective response was 28% (95% CI 13·8-46·8; nine of 32 patients) and for patients with HER2-low, HR-negative breast cancer 40% (95% CI 16·3-67·6; six of 15 patients). Responses were also observed in one (6%; 95% CI 0·2-30·2) of 16 gastric cancer, four (25%; 95% CI 7·3-52·4) of 16 urothelial cancer, and five (39%; 95% CI 13·9-68·4) of 13 endometrial cancer patients.

Interpretation

Trastuzumab duocarmazine has shown important clinical activity in heavily pretreated patients with HER2-expressing metastatic cancer, including HER2-positive trastuzumab emtansine-resistant and HER2-low breast cancer, with a manageable safety profile.

Funding

Synthon Biopharmaceuticals BV

Introduction

The human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine kinase receptor protein that promotes cell proliferation and inhibits apoptosis. HER2 overexpression and/or amplification is frequently found across different tumour types[1] and is associated with more aggressive disease and lower overall survival.[2,3] During the last two decades, multiple drugs targeting HER2 have been developed for HER2-positive breast cancer, including (bispecific) antibodies, small molecules, vaccines, and antibody-drug conjugates (ADCs).[4,5] However, HER2-positive metastatic breast cancer is still incurable and resistance to these therapies is inevitable. Further, trastuzumab failed to improve the outcome of patients with HER2-low expressing breast cancer, defined as HER2 immunohistochemistry (IHC) 1+ or IHC 2+ and in-situ hybridisation (ISH) negative, [6] and there are currently no HER2-targeting drugs specifically licensed for the treatment of any cancer with low HER2 levels. Thus, new drugs targeting also HER2-low expressing cancers will address an unmet need in multiple tumour types.

Antibody-drug conjugates (ADC) are designed for selective delivery of potent cytotoxic drugs to tumour cells by linking the cytotoxins to monoclonal antibodies. Trastuzumab emtansine, a HER2-targeting ADC that contains trastuzumab covalently linked to a microtubule inhibitor, significantly prolonged progression-free survival (PFS) and overall survival (OS) with less toxicity in patients with HER2-positive metastatic breast cancer.[7,8] Trastuzumab emtansine is currently recommended as second-line therapy in breast cancer patients who progressed through at least one line of trastuzumab-based therapy. Several new HER2-targeting ADCs with different linkers and payloads are currently in clinical development for multiple tumour types with promising results.[9, 10]

Trastuzumab duocarmazine (also known as SYD985) is a novel HER2-targeting ADC comprising the monoclonal IgG1 antibody trastuzumab covalently bound to a linker-drug containing duocarmycin, with a drug-to-antibody ratio (DAR) of 2·8.[11–13] The linker-drug contains a cleavable linker and the prodrug *seco*-duocarmycin-hydroxybenzamide-azaindole (*seco*-DUBA). After binding to HER2 and internalization, the linker is cleaved in the lysosome by proteases which releases the active toxin (DUBA). The active toxin alkylates DNA resulting in DNA damage in both dividing and nondividing cells and ultimately cell death. Additionally, proteases such as cathepsin B can be active extracellularly through secretion by malignant cells.[14] Extracellular cleavage of the linker-drug may therefore induce a bystander cell-killing effect which is not HER2-mediated.[17] Trastuzumab duocarmazine showed impressive preclinical antitumour activity in breast, ovarian, and other cancers with varying (low to high) HER2 expression and was more potent than trastuzumab emtansine.[13,15,16]

In this first-in-human study we evaluated safety, pharmacokinetics, and preliminary antitumour activity of trastuzumab duocarmazine in patients with locally advanced or metastatic solid tumours. Here, we present data of the completed dose-escalation part, and safety and activity data for the fully recruited expansion cohorts.

Methods

Study design and participants

In the dose-escalation part, patients with locally advanced or metastatic solid tumours refractory to standard therapy and regardless of HER2 status were eligible. Patients were recruited in three sites in Belgium, the Netherlands and the United Kingdom. In the expansion cohort part, patients with HER2-expressing breast, gastric (including adenocarcinomas of the gastro-oesophageal junction), urothelial, or endometrial cancer were recruited in a total of 15 sites in Belgium, the Netherlands, the United Kingdom, and Spain.

In a standard 3+3 dose-escalation design, doses were initially doubled for subsequent dose cohorts if no dose-limiting toxicity (DLT) was observed in the first treatment cycle. If a DLT was observed in one patient during the first cycle, at least three additional patients were to be treated at that dose level. The highest dose level at which no more than one out of six patients experienced a DLT was determined to be the maximum tolerated dose. The recommended phase 2 dose was determined based on all available safety, pharmacokinetic and activity data. This dose was used in the expansion part of the study, in which breast, gastric, urothelial, and endometrial cancer patient cohorts were evaluated (figure 1).

Eligible patients were aged 18 years or older, had Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, estimated life expectancy of at least 12 weeks, and adequate organ function. In the expansion part, patients had to have at least one measurable tumour lesion as defined by the Response Evaluation Criteria for Solid Tumours (RECIST version 1·1), and centrally assessed tumour HER2 expression should have been at least IHC 1+. Key exclusion criteria were anthracycline treatment within three months or any other cancer therapy within four weeks; history of infusion-related reaction and/or hypersensitivity to trastuzumab or trastuzumab emtansine; left ventricular ejection fraction (LVEF) <55%; and symptomatic brain metastases or therapy for brain metastases within four weeks. Further details can be found in the protocol (appendix pp 8-90).

The study protocol, amendments, and informed consent forms were reviewed and approved by local authorities and independent ethics committee at each study site. All patients provided written informed consent before any protocol-related activities started. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.

Procedures

Trastuzumab duocarmazine (Synthon Biopharmaceuticals BV, Nijmegen, the Netherlands) was administered intravenously on day 1 of each 3-week cycle (Q3W) with a first-in-human starting dose of 0·3 mg/kg. First infusion was given over one hour and if well tolerated, subsequent infusions could be given over 30 minutes. Intra-patient dose escalation was not permitted, but dose reductions and delays were allowed by protocol. Patients were treated until disease progression or unacceptable toxicity.

Patients were evaluated at least weekly in the first two cycles and once during subsequent cycles for toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. Vital signs, haematology, blood chemistry, 12-lead electrocardiograms, cardiac biomarkers, and urinalysis were assessed at each visit. Weight, physical and ophthalmological examinations, and LVEF assessments were done at each or every other cycle. Blood samples were collected at each visit for pharmacokinetic evaluation, and before each infusion for immunogenicity (anti-drug antibodies) analyses.

After completion of the dose-escalation part, several prophylactic measures were introduced, as per approved protocol amendment, to evaluate the effect on ocular toxicity. Lubricating eye drops were to be prescribed to all patients enrolled in the expansion part of the study. Vasoconstrictive phenylephrine and anti-inflammatory dexamethasone eye drops were to be administered one hour before start of the infusion and the latter to be continued up to 2 days after infusion in the HER2-low breast cancer cohorts and the non-breast cancer cohorts. In the HER2-positive breast cancer expansion cohort, patients were randomised to either 1·2 mg/kg Q3W continuously, 1·2 mg/kg Q3W for four cycles followed by 0·9 mg/kg Q3W, or 1·2 mg/kg Q3W for four cycles followed by 1·2 mg/kg Q6W to explore the effect of different dosing regimens on ocular toxicity (figure 1).

HER2 tumour expression was assessed by IHC and ISH on archival or fresh tissue according to the ASCO/CAP guidelines for breast and gastric cancer. Fresh tissue was obtained just before start study treatment when no archival tissue was available. HER2-positive was defined as IHC 3+ or ISH-positive. In the dose-escalation part, analysis was performed by the local site laboratory whereas in the expansion part analysis was done centrally using the Ventana HER2 IHC (4B5) and Dual ISH assays. Patients with HER2 IHC 3+ or ISH-positive breast cancer were enrolled in the HER2-positive breast cancer cohort; patients with IHC 2+ or 1+ and ISH-negative breast cancer were enrolled in either the HER2-low, hormone receptor (HR)-positive cohort or the HER2-low, HR-negative cohort, in order to evaluate these patient populations separately in view of the substantially different biology, natural history, and treatment recommendations. The non-breast cancer cohorts included patients with HER2-low and HER2-positive tumours. Validated ELISA-based methods were used to measure the plasma concentration of total antibody (irrespective of the amount of conjugated toxins, i.e. DAR≥0)) and conjugated antibody (antibodies that have at least one conjugated toxin, i.e. DAR≥1). A validated LC/MS-MS-based method was used for quantification of DUBA (free toxin) in plasma.

Tumour response was assessed by the investigator at baseline and every six weeks during treatment according to RECIST version 1·1.

Outcomes

The primary endpoint of the dose-escalation part was to evaluate safety and to determine the maximum tolerated dose and recommended phase 2 dose for trastuzumab duocarmazine. The classification of dose-limiting toxicity is provided in the appendix (p 1). The primary endpoint of the expansion cohort part was the proportion of patients who achieved an objective response (complete response (CR) or partial response (PR)). Secondary endpoints included safety, pharmacokinetics, immunogenicity (data

not shown), and activity endpoints including best percent change in target lesion measurements, progression-free survival (PFS; defined as the time from first day of treatment to tumour progression or death from any cause), clinical benefit rate (data not shown), duration of response (data not shown), overall survival (data not shown), and quality of life (data not shown).

Statistical analysis

It was estimated that a total of up to 24 patients would need to be enrolled in the dose-escalation part to determine the recommended phase 2 dose. In the expansion part, initially up to 128 patients would be enrolled in six patient cohorts, i.e. 48 in the HER2-positive breast cancer cohort and 16 in each other cohort. A Simon's two-stage design was applied to all cohorts except for the HER2-positive breast cancer cohort. The null hypothesis that the true response rate was 5% or less was to be tested against the one-sided alternative of a response rate of 20%. In case the null hypothesis could be rejected, i.e. if two or more responders were found in the initial 16 enrolled patients, a maximum of 14 additional patients could be enrolled in that cohort. This design had a type I error rate of 5% and a power of 80% when the true response rate was 20%.

The safety population, defined as all patients who received at least one dose of study treatment, was used for the evaluation of safety and activity endpoints, except for tumour response analysis which excluded patients without measurable disease at baseline and/or a post-baseline RECIST assessment. The pharmacokinetic analysis set included all patients for whom at least one pharmacokinetic parameter could be calculated. Descriptive statistics were used to summarise patient demographics, baseline characteristics and safety data. Activity proportions were summarised with exact binomial 95% confidence intervals (CIs) and PFS was analysed using Kaplan-Meier quartile estimates along with two-sided 95% CIs. Data were censored at the date of last RECIST assessment when no documented date of progression (by RECIST 1·1) or death was available, or when death or progression occurred after two or more consecutive missed assessments. Statistical analysis was performed with SAS version 9·4. Pharmacokinetic analysis was performed with software Phoenix™WinNonlin version 8.1. Actual blood sampling times relative to the time of dose were used to determine the pharmacokinetic parameters. Values below the limit of quantification were imputed as zero. This study is registered with ClinicalTrials.gov, number NCT02277717.

Role of funding source

The study sponsor was involved in study design, data collection, data analysis, interpretation of data, and writing of the report. UB, CvH, EM, NK, and PA had full access to all study data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Between October 30, 2014 and April 2, 2018, 39 patients were enrolled and treated in the dose-escalation part of the study and 146 patients in the expansion part of the study. At the data cut-off date of July 5, 2018, three patients with HER2-positive breast cancer, two patients with endometrial cancer, and one patient with urothelial cancer were still on treatment. The overall median follow-up time for all patients was 5·0 months (IQR 2·9-7·6) until last safety evaluation. Patient demographics and baseline characteristics are provided in table 1 and appendix (p 2). Patients were heavily pretreated with anticancer therapies with an overall median of five treatment lines. In the HER2-positive breast cancer expansion cohort, 40 (80%) of 50 patients had received prior trastuzumab emtansine.

In the dose-escalation part, initial doses were doubled from 0·3 mg/kg up to 2·4 mg/kg as no DLTs occurred in the first treatment cycles. One of three patients dosed with 2·4 mg/kg developed pneumonitis in cycle 2 which was considered possibly related to study drug and became fatal after the third infusion. Although the event did not occur during the first cycle, it was considered a DLT. Due to the seriousness of this toxicity and because promising activity was already observed at the 1·2 mg/kg dose level, it was decided not to enroll three additional patients at the 2·4 mg/kg dose but to evaluate lower doses in more detail. Therefore, the protocol defined maximum tolerated dose has not been defined. No DLTs occurred at doses of 1·8 mg/kg (n=12), 1·5 mg/kg (n=12), and 1·2 mg/kg (n=6). One additional fatal event (general physical health deterioration) occurred in the dose-escalation part which was related to disease progression. The overall median duration of trastuzumab duocarmazine exposure was 3·5 months (IQR 1·4-5·4) and was longest at the 1·2 mg/kg dose (8·1 months; IQR 5·9-9·8). An overview of treatment-related adverse events is provided in table 2 and divided per dose level in the appendix (p 3). In the dose-escalation part, grade 3 or 4 treatment-related adverse events occurred in 13 (33%) of 39 patients and events reported more than once were keratitis (three patients) and fatigue (two patients). Most commonly observed treatment-related adverse events of any grade were conjunctivitis (12 [31%] of 39 patients), fatigue (11 [28%]) and dry skin (10 [26%]) during the dose-escalation. Reversible decrease of ejection fraction was reported as adverse event for two (5%) of 39 patients and for 3 (8%) patients, an absolute worst decrease from baseline of at least 10% to a value below 50% was reported during treatment. Eleven (28%) of 39 patients discontinued the study due to treatment-related toxicity, most commonly due to ocular adverse events after five to ten cycles (n=5) or pneumonitis after two to six cycles (n=4). The ocular toxicity improved after treatment discontinuation and was reported as recovered at the cut-off date for four patients. All four events of pneumonitis occurred at doses of 1·5 mg/kg or higher and three events without respiratory symptoms (of which one grade 1 and two grade 2) resolved within one month after study discontinuation. Overall, doses up to 1·8 mg/kg were tolerated well without a clear dose-related occurrence of adverse events, although ocular toxicity seemed to occur earlier at higher doses and increased with increasing exposure. Based on these data in combination with the observed treatment duration and activity data (see below), the recommended phase 2 dose was set at 1·2 mg/kg as the 1.5 or 1.8 mg/kg dose seemed not to improve the benefit-risk for the patients. The 1.2 mg/kg dose was used in the expansion patient cohorts.

In the expansion cohorts, the most common treatment-related adverse events were fatigue (48 [33%] of 146 patients), conjunctivitis (45 [31%]), and dry eye (45 [31%]) (table 2). 104 (71%) of 146 patients had

one or more ocular adverse events, with grade 3 events in 10 (7%) of 146 patients. Ocular toxicity occurrence and severity generally increased with prolonged exposure with a median time to grade 3 events of 7·6 months (IQR 4·3-8·9). Reduced dosing after four infusions of trastuzumab duocarmazine, i.e. to 0·9 mg/kg Q3W or 1·2 mg/kg Q6W, and/or the use of prophylactic eye drops did not markedly improve the tolerability, although several patients seemed to benefit from dose delays and/or dose reduction and could continue with study drug beyond one year. The majority of the ocular events improved and/or recovered with treatments such as eye drops/ointments, although recovery sometimes took several months. Decrease of ejection fraction was reported as adverse event in 11 (8%) of 146 patients, of which eight were reported as resolved before the data cut-off date. For eight (5%) of 146 patients, an absolute worst decrease from baseline of at least 10% to a value below 50% was reported during treatment. Treatment-related serious adverse events were reported in 16 (11%) of 146 patients, most commonly infusion related reaction (two [1%]) and dyspnea (two [1%]. Four fatal events were reported in the expansion cohorts (hepatic failure, upper gastrointestinal haemorrhage, neurological decompensation, and renal failure) which were all related to disease progression. Overall, 62 (43%) of 146 patients had at least one treatment-related adverse event leading to one or more dose delays and/or dose reductions, and 27 (19%) of 146 patients discontinued the study due to treatment-related toxicity, of which 15 (10%) due to ocular toxicity. The majority of these events were reported as resolved at the cut-off date.

Total antibody, conjugated antibody, and DUBA (free toxin) pharmacokinetics after intravenous infusion followed a mono-phasic log-linear decline and were time independent. Concentrations were generally close to or below the limit of quantification at three weeks after dosing at all dose levels with minimal accumulation across consecutive cycles (appendix p 4). Pharmacokinetics of all analytes were dose proportional within the dose range of 1·2 mg/kg to 2·4 mg/kg. Dose levels below 1.2 mg/kg had faster elimination of total and conjugated antibody which is indicative for target mediated drug disposition. Elimination half-life was two to three days for conjugated antibody at doses of 1·2 mg/kg or higher. Free toxin exposure was generally 3000-times lower compared to conjugated antibody (on a molar basis) with peak concentrations in the pg/ml range. The pharmacokinetic parameters for conjugated antibody and DUBA (free toxin) are presented in the appendix (p 5). None of the patients were found positive for anti-drug antibodies at any time point.

Eleven (32%, 95% CI 17·4-50·5) of 34 evaluable patients in the dose-escalation part had a partial response, of whom ten (six confirmed) with breast cancer and one (unconfirmed) with oesophageal cancer. Responses were seen in both HER2-positive and HER2-low tumours and all occurred at doses of 1·2 mg/kg or higher (figure 2). Five of the 39 patients were not evaluable due to non-measurable disease (three patients) or missing post-baseline RECIST evaluation (two patients). In the expansion part of the study, six of the 146 patients were not evaluable due to missing post-baseline RECIST evaluation (five patients) or non-measurable disease at baseline (one patient) (figure 1). In the three breast cancer expansion cohorts, 67 (71%) of 95 evaluable patients showed a reduction in target lesions, 31 (33%) of 95 patients had a partial response of which 23 confirmed responses (figure 2). The proportion of patients with an objective response was 33% (95% CI 20·4-48·4; 16 of 48 patients) for patients with HER2-positive breast cancer, 28% (95% CI 13·8-46·8; nine of 32 patients) for patients with HER2-low, HR-

positive, and 40% (95% CI 16·3-67·6; 6 of 15 patients) for HER2-low, HR-negative breast cancer patients. The median progression-free survival in the safety population was 7·6 months (95% CI 4·2-10·9), 4·1 months (95% CI 2·4-5·4), and 4·9 months (95% CI 1·2-not evaluable), respectively. Of the 50 patients with HER2-positive breast cancer, 28 (56%) received trastuzumab duocarmazine beyond six months and seven (14%) beyond one year; six of these seven patients had received prior trastuzumab emtansine (figure 3).

In the non-breast cancer expansion cohorts, 25 (57%) of 44 evaluable patients had a reduction in target lesions (appendix pp 6-7). The proportions of patients with an objective response were 6% (95% CI 0·2-30·2; one of 16 patients) for gastric cancer, 25% (95% CI 7·3-52·4; four of 16 patients) for urothelial cancer, and 39% (95% CI 13·9-68·4; five of 13 patients) for endometrial cancer. The median progression-free survival was 3·2 months (95% CI 1·6-5·3), 4·0 months (95% CI 1·3-not evaluable), and 4·3 months (95% CI 2·4-9·9), respectively.

Discussion

To our knowledge, this is the first report of a novel ADC with a DNA-alkylating duocarmycin payload. In this phase 1 study, trastuzumab duocarmazine was administered to heavily pretreated patients with locally advanced or metastatic solid tumours. Trastuzumab duocarmazine showed a manageable safety profile with a limited number of grade ≥3 adverse events and the determined recommended phase 2 dose was set at 1·2 mg/kg. Responses were observed across all tumour types, not only in HER2-positive tumours but also in tumours expressing lower levels of HER2. Of the HER2-positive metastatic breast cancer patients, of whom 80% had previously received trastuzumab emtansine and 30% pertuzumab, 33% achieved an objective response with a median PFS of 7.6 months. In the HER2-low breast cancer cohorts, 28% (HR-positive) and 40% (HR-negative) of the patients achieved an objective response with a median PFS of 4·1 months and 4·9 months, respectively.

The side effect profile of trastuzumab duocarmazine has similarities and differences with other HER2-targeting ADCs. The most common side effects seen with trastuzumab duocarmazine was ocular toxicity. Although this toxicity has been described with other ADCs, it is less common in HER2-targeting ADCs and the pathophysiology of these events is not yet well understood.[17] Interestingly, planned dose reductions, reducing the frequency of administration, or prophylactic eye drops did not remarkably alter long-term tolerability of trastuzumab duocarmazine overall, but several patients could continue with study drug beyond one year and the majority of ocular events was reported as recovered or improving at the cut-off date. However, in view of the relative scarcity of the data additional observations especially over a prolonged treatment period are necessary for drawing more definitive conclusions. Importantly, less than 1% grade 3 or 4 thrombocytopenia and 6% grade 3 or 4 neutropenia were observed with trastuzumab duocarmazine, which is lower than for other HER2-targeting ADCs.[8,18] This could be of importance while exploring future combination strategies. Pneumonitis was observed as dose-limiting toxicity at the 2·4 mg/kg dose, but seems to be a dose-related toxicity with reduced risk at the recommended phase 2 dose of 1·2 mg/kg. This type of toxicity has also been reported for trastuzumab emtansine[19] and trastuzumab deruxtecan, a HER2-targeting topoisomerase ADC in development.[18,20] The underlying mechanism or risk factors are yet unclear.

The pharmacokinetic profile in combination with the DNA-alkylating mode of action of trastuzumab duocarmazine supports a 3-weekly dosing schedule by receptor binding and subsequent intracellular release of the toxin. Systemically free toxin levels were substantially lower compared to other ADC's such as trastuzumab emtansine[21] and trastuzumab deruxtecan.[18] The ADC drug levels achieved in patients are consistent with drug levels achieved in mice that showed significant xenograft growth delay with trastuzumab duocarmazine.[13]

This study was performed in patients who completed several late-line therapy options for metastatic disease. Pertuzumab was not yet commonly prescribed for patients with HER2-positive breast cancer in Europe when the study started due to pending reimbursement discussions following approval of this drug in 2013, so less than half of the patients was pretreated with pertuzumab in this study. Another potential limitation of this study was that tumour assessments were not centrally evaluated. Resulting estimates should be viewed with this limitation in mind but are convincing in a phase 1 setting.

Trastuzumab duocarmazine showed meaningful single agent clinical activity in three areas of unmet need. Firstly, relevant clinical activity was observed in HER2-positive metastatic breast cancer patients. This is particularly important as trastuzumab emtansine treatment is set to move to adjuvant treatment paradigms following the results of the KATHERINE study.[22] This increases the need for novel treatment options in HER2-positive breast cancer for patients with metastatic disease after progression on trastuzumab emtansine. A pivotal randomised phase 3 study (TULIP®) comparing trastuzumab duocarmazine to standard of care chemotherapy combinations in patients with HER2-positive breast cancer is ongoing (NCT03262935). Importantly, trastuzumab duocarmazine single agent activity was also observed in patients with HER2-low (IHC 1+ or 2+/ISH-negative) HR-negative disease where no HER2-targeted drugs and ADCs are currently approved. These triple-negative breast cancers (TNBC) are a highly diverse group of cancers[23] for which several ADCs targeting different antigens are in development, such as the anti-trop-2 ADC sacituzumab govitecan that showed impressive activity in a phase 1 study.[24] Moreover, the prolonged PFS observed with atezolizumab in combination with nab-paclitaxel in a selective group of TNBC patients is promising.[25] Nevertheless, there is still a high unmet need to improve the outcome for these patients for which trastuzumab duocarmazine could potentially be of benefit. The third area in which trastuzumab duocarmazine could be of relevance is non-breast HER2-expressing metastatic cancers with limited treatment options and poor prognoses, such as urothelial and endometrial cancers. Trastuzumab duocarmazine showed several responses in these patients of whom the majority had HER2-low expressing tumours. Although HER2 expression data is variable between different studies[1,26], it would be interesting to further investigate HER2-targeting drugs in these subsets of patients.

To conclude, this phase 1 study of trastuzumab duocarmazine has shown important and relevant clinical activity and a manageable safety profile in heavily pretreated patients with HER2-expressing metastatic cancer, including HER2-positive trastuzumab emtansine-resistant and HER2-low breast cancer.

Contributors

UB, CvH, EM, NK, and PA conceived and designed the study. All authors except EM and NK treated patients and collected data. UB, CvH, EM, NK, and PA made substantial contributions to the analyses and interpretation of the data. All authors contributed to the writing and review of the manuscript and approved the final version of the manuscript.

Declaration of interests

UB reports grants from Chugai, Onyx Pharmaceuticals, BTG International, Verastem, AstraZeneca, and personal fees from Lilly, Phoenix Solutions, Novartis, Astex Pharmaceuticals, Karus Therapeutics, Vernalis, and Astellas outside the submitted work. CH reports grants from BMS, MSD, Regeneron, Astra Zeneca, Merck, Ipsen, Novartis, Sanofi, and Bayer outside the submitted work. CS reports grants from AstraZeneca, Roche, Genentech, Macrogenics, Novartis, Pfizer, Piqur Therapeutics, Puma, and Synthon during the conduct of the study, and personal fees AstraZeneca, Celgene, Daiichi Sankyo, Eisai, Roche, Genomic health, Novartis, Pfizer, Pierre Fabre, Piqur Therapeutics, Puma, and Synthon outside the submitted work. IM reports personal fees from Roche Products UK Ltd, Pierre Fabre, and Daiichi Sankyo outside the submitted work. CR reports personal fees from MSD, Novartis, Guardanthealth, and Mylan, grants from Novartis and Sanofi, and non-financial support from Oncompass, OncoDNA, IASLC, ISALB (International Society of Liquid Biopsy), ESMO, ASCO, and OLA (Oncology Latin America Association) outside the submitted work. EV reports grants from Synthon Biopharmaceuticals BV during the conduct of the study, grants from Amgen, Genentech, Roche, Chugai Pharma, CytomX Therapeutics, Nordic Nanovector, G1 Therapeutics, AstraZeneca, Radius Health, and Bayer outside the submitted work, and consulting/advisory fees from NSABP, Daiichi Sankyo, Pfizer, Sanofi, Synthon Biopharmaceuticals BV, and Merck. EM and NK are employees of Synthon Biopharmaceuticals BV and NK has a pending SYD985 clinical application patent. PA reports personal fees from Boehringer Ingelheim, Macrogenics, Synthon, Amgen, Novartis, Roche, and Novartis, and non-financial support from MSD, Roche, Pfizer, and Amgen outside the submitted work. All other authors have nothing to disclose.

Data sharing statement

Synthon Biopharmaceuticals BV shares patient-level and study-level data after de-identification for trastuzumab duocarmazine when approved in both the European Union and the USA. These data will be shared with qualified non-commercial, scientific and medical researchers, upon researcher's request. Requests for data sharing can be made to NK including a detailed proposal for data meta-analysis that must be approved by Synthon. When Synthon has agreements related to joint research, development, or commercialisation, or when the product has been out-licensed, the responsibility for disclosure might be dependent on these agreements. Under these circumstances, Synthon will endeavour to gain agreement with its contractual parties to share data in response to approved research requests.

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Legends Figures and Tables

Figure 1 Study profile

DLT=dose-limiting toxicity. Q3W=every 3 weeks. Q6W=every 6 weeks. MBC=metastatic breast cancer. HR=hormone receptor. IHC=immunohistochemistry. ISH=in-situ hybridization. *Three patients were added at the same time that enrolment started for cohort 6. † Cohort was expanded from 16 to 30 patients when two of the initial 16 patients had a partial response (Simon two-stage design). ‡ Patients were randomised to one of the subgroups in order to explore the effect of different dosing regimens on ocular toxicity.

Table 1 Patient demographics and baseline characteristics

Data are median (IQR) or n (%). MBC=metastatic breast cancer. HR=hormone receptor. Pos=positive. Neg=negative. ECOG =Eastern Cooperative Oncology Group. IHC=immunohistochemistry. ISH=in-situ hybridization. * In expansion part, breast cancer patients were allocated to a cohort based on centrally assessed HER2 status on most recent available tumour tissue which in some patients deviated from prior locally assessed HER2 status. † Tumour tissue was HER2 ISH-positive for these patients.

Table 2: Adverse events considered related to trastuzumab duocarmazine

Data are presented as n(%). Included in this table are maximum grade adverse events by preferred term considered related to study drug of grade 1 or 2 in at least 10% of all patients, and all grade 3, 4, and 5 events.

Figure 2: Best percentage change in tumour size from baseline in target lesions for evaluable patients in (A) dose-escalation part by cancer type, HER2 expression, and dose (in mg/kg), (B) HER2-positive breast cancer expansion cohort, (C) HER2-low, hormone receptor-positive breast cancer expansion cohort, and (D) HER2-low, hormone receptor-negative breast cancer expansion cohort.

A: B=breast cancer. C=colon/rectal cancer. G=gastric/oesophageal cancer. O=other cancer.

B: *Best percentage change is 0%.

C: *Best percentage change is 0%.

Figure 3: Duration of treatment for HER2-positive breast cancer expansion cohort.

Cross indicates the time of first partial response. Arrows indicate patients still on treatment at the cut-off date.

Research in context

Evidence before this study

We searched PubMed on Dec 20, 2018 with the terms metastatic breast cancer, HER2, antibody-drug conjugate, and ADC in several combinations for articles written in English without restrictions to the publication date. Retrieved literature showed that treatment options beyond the first two lines of standard HER2-targeting treatment for metastatic breast cancer (i.e. taxane+trastuzumab+pertuzumab followed by trastuzumab emtansine) comprised of various combinations of trastuzumab plus chemotherapy or the oral combination of lapatinib with capecitabine. These treatments generally result in a median progression-free survival of about 4 months. Additionally, there are currently no HER2-targeting drugs specifically licensed for the treatment of breast or any other cancer with low HER2 levels. Antibody-drug conjugates may be considered as targeted chemotherapy using a single agent and may provide a novel, potentially more effective, treatment option for these patients.

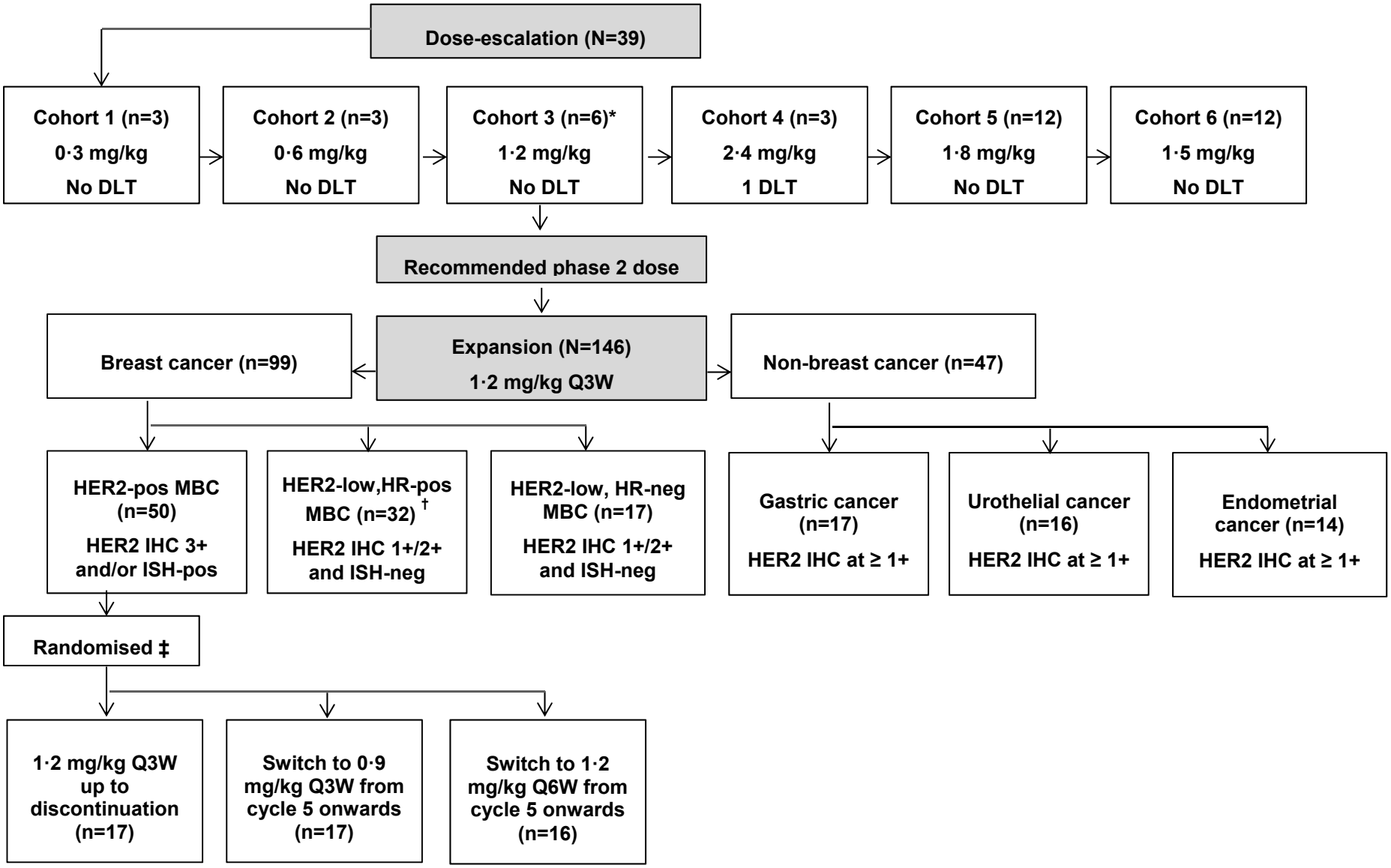
Added value of this study

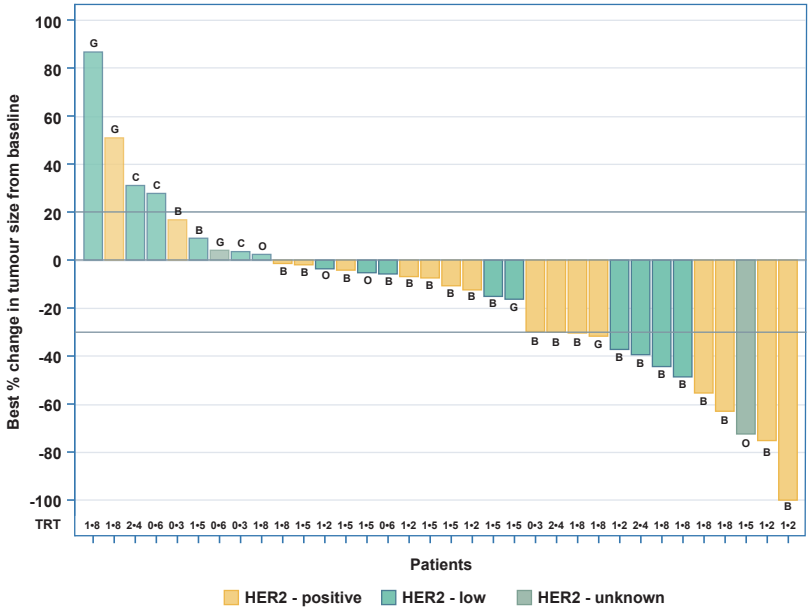
This is the first study that reports on the clinical profile of trastuzumab duocarmazine (SYD985) and its activity and safety in HER2-expressing metastatic breast and other cancers, including triple-negative breast cancer.

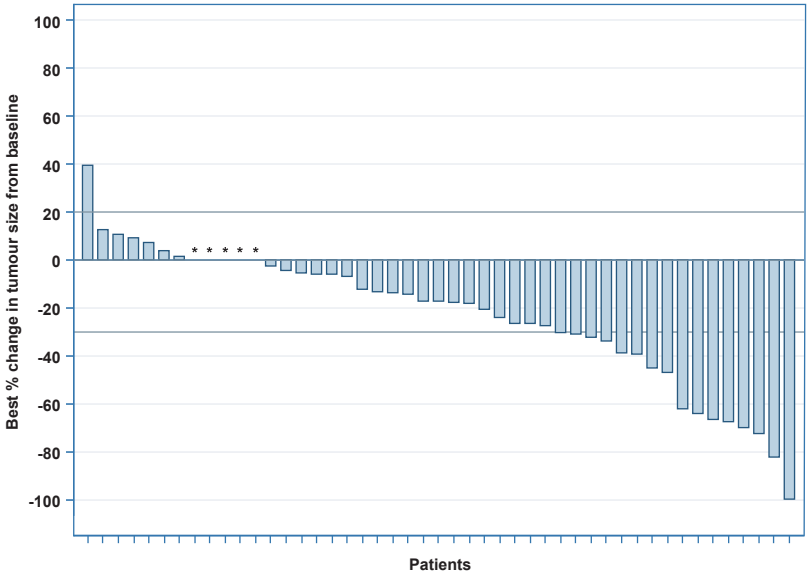
Implications of all available evidence

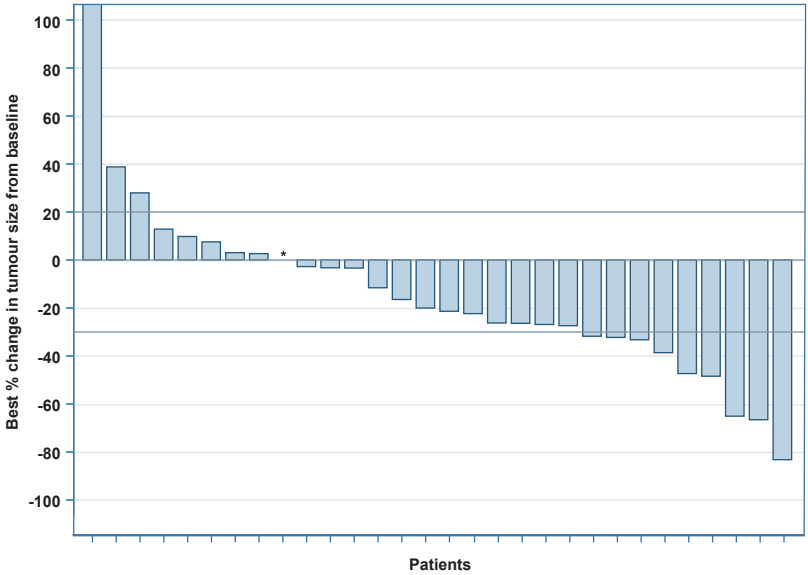
Results of this study demonstrate that trastuzumab duocarmazine warrants further investigation and may provide a novel treatment option for patients with HER2-positive breast cancer who have previously been treated with trastuzumab plus pertuzumab and/or trastuzumab emtansine and, enable this HER2-targeting ADC to be explored for patients with lower levels of HER2-expression in multiple tumour types.

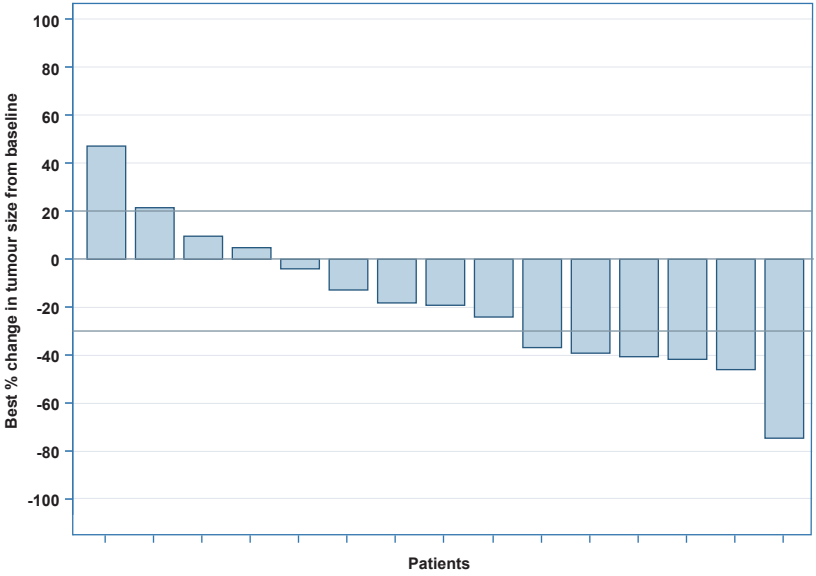
Figure 1


Dose-escalation (N=39)
Cohort 1 (n=3)
0·3 mg/kg
No DLT
Cohort 2 (n=3)
0·6 mg/kg
No DLT
Cohort 3 (n=6)*
1·2 mg/kg
No DLT
Cohort 4 (n=3)
2·4 mg/kg
1 DLT
Cohort 5 (n=12)
1·8 mg/kg
No DLT
Cohort 6 (n=12)
1·5 mg/kg
No DLT
Recommended phase 2 dose
Expansion (N=146)
1·2 mg/kg Q3W
Breast cancer (n=99)
Non-breast cancer (n=47)
HER2-pos MBC (n=50)
HER2 IHC 3+ and/or ISH-pos
HER2-low,HR-pos MBC (n=32) †
HER2 IHC 1+/2+ and ISH-neg
HER2-low, HR-neg MBC (n=17)
HER2 IHC 1+/2+ and ISH-neg
Gastric cancer (n=17)
HER2 IHC at ≥ 1+
Urothelial cancer (n=16)
HER2 IHC at ≥ 1+
Endometrial cancer (n=14)
HER2 IHC at ≥ 1+
Randomised ‡
1·2 mg/kg Q3W up to discontinuation (n=17)
Switch to 0·9 mg/kg Q3W from cycle 5 onwards (n=17)
Switch to 1·2 mg/kg Q6W from cycle 5 onwards (n=16)


Best % change in tumour size from baseline
100
80
60
40
20
0
-20
-40
-60
-80
-100
TRT
1•8 1•8 2•4 0•6 0•3 1•5 0•6 0•3 1•8 1•8 1•5 1•2 1•5 1•5 0•6 1•2 1•5 1•5 1•2 1•5 1•5 0•3 2•4 1•8 1•8 1•2 2•4 1•8 1•8 1•8 1•8 1•5 1•2 1•2
Patients
HER2 - positive
HER2 - low
HER2 - unknown


100
80
60
40
20
0
-20
-40
-60
-80
-100
Best % change in tumour size from baseline
Patients


100
80
60
40
20
0
-20
-40
-60
-80
-100
Best % change in tumour size from baseline
*
Patients


100
80
60
40
20
0
-20
-40
-60
-80
-100
Best % change in tumour size from baseline
Patients

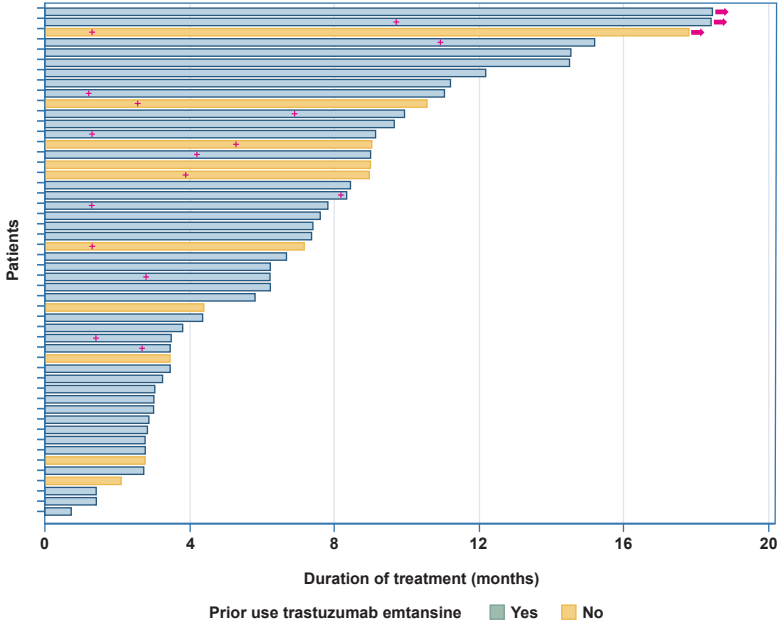

Patients
0
4
8
12
16
20
Duration of treatment (months)
Prior use trastuzumab emtansine
Yes
No

Table 1

	Dose-escalation (n=39)	Expansion cohorts Total (n=146)	Breast cancer expansion cohorts			Non-breast cancer cohorts (n=47)
			HER2-pos MBC (n=50)	HER2-low, HR-pos MBC (n=32)	HER2-low, HR-neg MBC (n=17)	
Age, years	55 (47-63)	57 (49-65)	54 (47-63)	53 (47-61)	53 (45-62)	64 (54-71)
Sex						
Female	30 (77%)	120 (82%)	50 (100%)	32 (100%)	17 (100%)	21 (45%)
Male	9 (23%)	26 (18%)	0	0	0	26 (55%)
Race						
White	38 (97%)	140 (96%)	47 (94%)	32 (100%)	17 (100%)	44 (94%)
Other	1 (3%)	6 (4%)	3 (6%)	0	0	3 (6%)
ECOG performance status						
0	22 (56%)	69 (47%)	26 (52%)	19 (59%)	5 (29%)	19 (40%)
1	17 (45%)	77 (53%)	24 (48%)	13 (41%)	12 (71%)	28 (60%)
Time since initial diagnosis, months	67 (33-143)	53 (27-100)	78 (47-107)	94 (55-136)	43 (23-84)	25 (16-45)
Cancer type						
Breast	26 (67%)	99 (68%)	50 (100%)	32 (100%)	17 (100%)	0
Gastric/Oesophageal	6 (15%)	17 (12%)	0	0	0	17 (36%)
Colon/Rectal	3 (8%)	0	0	0	0	0
Urothelial	0	16 (11%)	0	0	0	16 (34%)
Endometrial	1 (3%)	14 (10%)	0	0	0	14 (30%)
Other	3 (8%)	0	0	0	0	0
Number of metastatic sites	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-3)	3 (2-4)	3 (2-4)
Known brain metastasis	3 (8%)	8 (5%)	5 (10%)	0	0	3 (6%)
HER2 expression						
IHC 3+	15 (39%)	57 (39%)	41 (82%)	0	0	16 (34%)
IHC 2+	12 (31%)	37 (25%)	3 (6%)	10 (31%)	7 (41%)	17 (36%)
ISH-positive	2 (5%)	6 (4%)	3 (6%)	0	0	3 (6%)
ISH-negative	8 (20%)	27 (18%)	0	10 (31%)	7 (41%)	10 (21%)
ISH-equivocal	1 (3%)	3 (2%)	0	0	0	3 (6%)
ISH-unevaluable	1 (3%)	1 (1%)	0	0	0	1 (2%)
IHC 1+	6 (15%)	51 (35%)	5 (10%)[†]	22 (69%)	10 (59%)	14 (30%)
IHC 0	4 (10%)	1 (1%)	1 (2%)[†]	0	0	0
Missing	2 (5%)	0	0	0	0	0
Number of previous systemic therapies						
Median (IQR)	6 (2-8)	4 (3-7)	6 (4-8)	7 (5-9)	4 (3-5)	2 (2-3)
1-3	13 (33%)	50 (34%)	5 (10%)	3 (9%)	6 (35%)	36 (77%)
4-6	9 (23%)	55 (38%)	24 (48%)	11 (34%)	9 (53%)	11 (23%)
>6	17 (44%)	41 (28%)	21 (42%)	18 (56%)	2 (12%)	0
Previous HER-2 targeting therapy*	20 (51%)	62 (42%)	47 (94%)	6 (19%)	1 (6%)	8 (17%)
Trastuzumab	20 (51%)	61 (42%)	46 (92%)	6 (19%)	1 (6%)	8
Trastuzumab emtansine	16 (41%)	43 (29%)	40 (80%)	3 (9%)	0	0
Lapatinib	9 (23%)	26 (18%)	23 (46%)	2 (6%)	1 (6%)	0
Pertuzumab	2 (5%)	17 (12%)	15 (30%)	2 (6%)	0	0
Previous CDK 4/6 inhibitors	2 (5%)	5 (3%)	0	5 (16%)	0	0
Previous PD-1/PD-L1 inhibitors	0	14 (10%)	1 (2%)	2 (6%)	1 (6%)	10 (21%)

Table 2

Adverse Event	Dose=escalation (n=39)				Expansion cohorts (n=146)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Fatigue	9 (23%)	2 (5%)	0	0	43 (29%)	5 (3%)	0	0
Conjunctivitis	11 (28%)	1 (3%)	0	0	41 (28%)	4 (3%)	0	0
Dry eye	6 (15%)	0	0	0	44 (30%)	1 (1%)	0	0
Lacrimation increased	8 (21%)	0	0	0	29 (20%)	0	0	0
Dry skin	10 (26%)	0	0	0	26 (18%)	0	0	0
Decreased appetite	6 (15%)	1 (3%)	0	0	27 (18%)	2 (1%)	0	0
Keratitis	3 (8%)	3 (8%)	0	0	25 (17%)	3 (2%)	0	0
Alopecia	8 (21%)	0	0	0	26 (18%)	0	0	0
Nausea	6 (15%)	0	0	0	27 (18%)	0	0	0
Stomatitis	8 (21%)	1 (3%)	0	0	24 (16%)	0	0	0
Skin hyperpigmentation	5 (13%)	0	0	0	23 (16%)	0	0	0
Neutropenia	3 (8%)	1 (3%)	0	0	14 (10%)	9 (6%)	0	0
Vomiting	5 (13%)	0	0	0	17 (12%)	0	0	0
Anaemia	6 (15%)	1 (3%)	0	0	13 (9%)	2 (1%)	0	0
Pyrexia	9 (23%)	0	0	0	9 (6%)	0	0	0
Dysgeusia	7 (18%)	0	0	0	11 (8%)	0	0	0
Infusion related reaction	3 (8%)	0	0	0	13 (9%)	2 (1%)	0	0
Vision blurred	0	0	0	0	15 (10%)	1 (1%)	0	0
Ejection fraction decreased	1 (3%)	1 (3%)	0	0	10 (7%)	1 (1%)	0	0
Diarrhoea	1 (3%)	0	0	0	9 (6%)	1 (1%)	0	0
Thrombocytopenia	2 (5%)	0	0	0	7 (5%)	1 (1%)	0	0
Aspartate aminotransferase increased	1 (3%)	0	0	0	7 (5%)	1 (1%)	0	0
Lymphopenia	0	0	0	0	7 (5%)	2 (1%)	0	0
Dyspnoea	4 (10%)	0	0	0	2 (1%)	2 (1%)	0	0
Asthenia	0	1 (3%)	0	0	7 (5%)	0	0	0
Mouth ulceration	1 (3%)	0	0	0	5 (3%)	1 (1%)	0	0
Pericardial effusion	0	1 (3%)	0	0	2 (1%)	2 (1%)	1 (1%)	0
Gamma-glutamyltrans-ferase increased	0	0	0	0	4 (3%)	0	2 (1%)	0
Rash maculo-papular	1 (3%)	0	0	0	4 (3%)	1 (1%)	0	0
Blood alkaline phosphatase increased	1 (3%)	0	0	0	3 (2%)	1 (1%)	0	0
Pneumonitis	3 (8%)	0	0	1 (3%)*	0	0	1 (1%)	0
Transaminases increased	1 (3%)	0	0	0	3 (2%)	1 (1%)	0	0
White blood cell count decreased	0	0	0	0	4 (3%)	1 (1%)	0	0
Episcleritis	0	1 (3%)	0	0	4 (3%)	0	0	0
Lymphocyte count decreased	0	0	0	0	1 (1%)	3 (2%)	0	0
Platelet count decreased	0	0	1 (3%)	0	1 (1%)	2 (1%)	0	0

Palmar-plantar erythrodysaesthesia syndrome	0	0	0	0	3 (2%)	1 (1%)	0	0
Neutrophil count decreased	0	1 (3%)	0	0	2 (1%)	0	0	0
Hepatic enzyme increased	0	0	0	0	1 (1%)	1 (1%)	0	0
Injection site reaction	0	1 (3%)	0	0	1 (1%)	0	0	0
Pleural effusion	0	0	0	0	1 (1%)	1 (1%)	0	0
Pancytopenia	0	0	0	0	0	1 (1%)	0	0
Ocular toxicity	0	0	0	0	0	1 (1%)	0	0
Retinal haemorrhage	0	0	0	0	0	1 (1%)	0	0
Ventricular dysfunction	0	0	0	0	0	1 (1%)	0	0
Haemoptysis	0	0	0	0	0	1 (1%)	0	0
Conjunctivitis bacterial	0	0	0	0	0	1 (1%)	0	0
Pain in extremity	0	0	0	0	0	1 (1%)	0	0
Delirium	0	0	0	0	0	0	1 (1%)	0
Haematuria	0	0	0	0	0	1 (1%)	0	0