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Title: Switching between intravenous and subcutaneous trastuzumab: Safety results from the PrefHer trial

Author list: Joseph Gligorov [a,*], Giuseppe Curigliano [b], Volkmar Müller [c], Ann Knoop [d], Valerie Jenkins [e], Sunil Verma [f,**], Stuart Osborne [g], Sabine Lauer [g], Zuzana Machackova [g], Lesley Fallowfield [e], Xavier Pivot [h]

[a] *APHP Tenon, IUC-UPMC, Sorbonne University, Paris, France.* [b] *European Institute of Oncology, Milan, Italy.* [c] *University Medical Center, Hamburg, Germany.* [d] *Copenhagen University Hospital, Copenhagen, Denmark.* [e] *Sussex Health Outcomes, Research & Education in Cancer (SHORE-C), University of Sussex, East Sussex, UK.* [f] *Division of Medical Oncology, Sunnybrook Odette Cancer Centre, Toronto, ON, Canada.* [g] *F. Hoffmann-La Roche Ltd, Basel, Switzerland.* [h] *University Hospital Jean Minjoz, Besançon, France.*

***Current affiliation: Tom Baker Cancer Centre, Department of Oncology, University of Calgary, AB, Canada*

*** Corresponding author**

Joseph Gligorov MD, PhD

APHP Tenon, IUC-UPMC, Sorbonne University

4 Rue de la Chine

75020 Paris, France

Telephone: +33 15 601 6024

Fax: +33 15 601 6543

Email: joseph.gligorov@tnn.aphp.fr

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Abstract

Aim: To assess the safety and tolerability of switching between subcutaneous (SC) and intravenous (IV) trastuzumab in the PrefHer study (NCT01401166).

Patients and methods: Patients with HER2-positive early breast cancer completed (neo)adjuvant chemotherapy and were randomised to receive four cycles of SC trastuzumab, via single-use injection device (SID; Cohort 1) or hand-held syringe (Cohort 2), followed by four cycles of IV, or vice versa (the crossover period presented here) as part of their 18 standard cycles of adjuvant trastuzumab treatment. Adverse events (AEs) were reported using standard criteria.

Results: Overall, fewer AEs were reported during the IV treatment periods, regardless of administration sequence (IV→SC or SC→IV). Differences in AEs between the SC and IV periods were partly due to variances in grade 1 and 2 local injection site reactions (ISRs) and systemic administration-related reactions (ARRs) and these occurred mainly during SC treatment, as expected. When ISRs and ARRs were excluded, rates of AEs were higher during the first treatment period, compared with the second, in both treatment sequences; otherwise there was no clear pattern in the type of AEs reported. Rates of clinically important events, including grade ≥3 AEs, serious AEs, AEs leading to study drug discontinuation and cardiac AEs, were low and similar between treatment arms (<5%). There were no grade 4 or 5 AEs. No new safety signals for trastuzumab were observed.

Conclusions: PrefHer revealed that switching from IV to SC trastuzumab (hand-held syringe or SID) or vice versa did not impact the known safety profile of trastuzumab.

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Introduction

Trastuzumab (Herceptin®, F. Hoffmann-La Roche Ltd, Basel, Switzerland), is the standard of care for treating human epidermal growth factor receptor 2 (HER2)-positive breast cancer [1–3] and can be administered by intravenous (IV) infusion or subcutaneous (SC) injection. SC trastuzumab (Herceptin® SC, F. Hoffmann-La Roche Ltd) contains the recombinant human hyaluronidase enzyme as an excipient and offers a fixed-dose alternative to the conventional weight-adjusted IV dose. SC trastuzumab was approved by the European Medicines Agency based on data from the phase III, open-label, randomised, international HannaH study (NCT00950300) [4,5].

HannaH compared SC and IV trastuzumab in terms of pharmacokinetics, efficacy and safety in the neoadjuvant–adjuvant setting [4,5]. Analysis of the co-primary endpoints, serum trough concentration (C_{trough}) and pathological complete response (pCR), demonstrated that SC trastuzumab was non-inferior to IV [4]. Despite similar overall safety profiles, a numerical difference was reported in the rate of serious adverse events (SAEs) [4,5]. This imbalance was not reflected in the distribution of grade 3–5 AEs, and despite systematic analyses an underlying clinical explanation could not be identified [4,5]. An SC trastuzumab single-use injection device (SID) demonstrates pharmacokinetic bioequivalence with the hand-held syringe method [6].

Patients' preferences, for either SC administration or IV infusion, were investigated in the international, open-label, randomised, two-cohort, two-arm, PrefHer study (NCT01401166) in HER2-positive early breast cancer [7–9]. PrefHer incorporated a unique crossover period, comprising four cycles of SC

trastuzumab followed by four cycles of IV, or vice versa. This study design allowed a direct comparison of patients' preferences for SC or IV trastuzumab and evaluation of the safety profile associated with multiple, sequential administrations.

When compared with the known safety profile of IV trastuzumab, previous analyses from both cohorts of PrefHer indicated that SC trastuzumab was well tolerated, with no new safety signals [7–9]. Although an increase in clinician-reported AEs was noted with SC trastuzumab, this was not the case for patient-reported events [7,9]. Differences between AE rates in the combined SC and IV periods (Cohorts 1 and 2) were driven by grade 1 events and occurred more frequently during the SC period [7,9]. However, patients preferred SC over IV trastuzumab regardless of SID or hand-held syringe delivery, and patients reported SC trastuzumab to be less painful and to cause less bother from bruising or irritation than IV [7–9].

With consistent patient preference for SC over IV trastuzumab and the European approval of SC trastuzumab, patients may opt to switch from IV to SC trastuzumab during their treatment for early breast cancer. Due to its unique design, the PrefHer study offered the opportunity to assess the safety profile of patients switching between IV and SC trastuzumab, considering not only the influence of the treatment sequence, but also the impact of previous exposure to IV trastuzumab during (neo)adjuvant treatment. We report the results of this analysis here.

Patients and methods

Patients and study treatment

After completion of surgery and neoadjuvant or adjuvant chemotherapy, patients were randomised to receive four cycles of SC trastuzumab followed by four cycles of IV trastuzumab, or vice versa (the crossover period assessed here; **Fig. 1**) [7–9]. Patients then received trastuzumab to complete their standard 18 cycles of adjuvant treatment, planned to be via IV or SC SID in Cohort 1 and SC hand-held syringe in Cohort 2. Since (neo)adjuvant treatment could have included prior IV trastuzumab, randomisation was stratified by de novo (trastuzumab-naïve) or non-de novo (already receiving IV trastuzumab) treatment. Patients were enrolled if they still had at least eight out of their 18 planned cycles of trastuzumab remaining.

SC trastuzumab was administered either via SID (Cohort 1) or hand-held syringe (Cohort 2) and given every 3 weeks at a fixed dose of 600 mg, with no loading dose required. IV trastuzumab was administered every 3 weeks at a loading dose of 8 mg/kg (if the patient was not already receiving trastuzumab and was randomised to receive IV trastuzumab as the first cycle of treatment), followed by maintenance doses of 6 mg/kg.

The primary endpoint, previously reported, was the proportion of patients indicating an overall preference for SC or IV trastuzumab administration [7,9]. Secondary endpoints included safety and tolerability [7–9].

PrefHer was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. Approval for the protocol was obtained from appropriate local and national independent ethics committees.

Assessment of switching between SC and IV trastuzumab

AEs that occurred during the crossover period were summarised according to the primary system-organ class (SOC), and within each SOC by Medical Dictionary for Regulatory Activities (MedDRA)-preferred term; including overall AEs, grade ≥3 AEs, SAEs, systemic administration-related reactions (ARRs), localised injection site reactions (ISRs), AEs leading to discontinuation and cardiac AEs. AE incidences were summarised by treatment sequence (IV→SC or SC→IV) and route of administration (SC or IV); rates of AEs were then summarised by cohort (Cohort 1 or 2 and combined) and de novo or non-de novo trastuzumab. Analyses either included or excluded ARRs and ISRs.

AEs, SAEs and cardiac AEs were graded and reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE V4.0), International Conference on Harmonisation E2A guidance documentation (ICH E2A) and the New York Heart Association functional classification criteria, respectively.

Statistical considerations

Adverse event data are presented for the safety population, i.e., all patients who received ≥1 dose of trastuzumab during the crossover period. Data shown are the pooled (Cohort 1 [SID] and Cohort 2 [hand-held syringe]) or individual safety data from both cohorts during the crossover period. Results are descriptive.

AEs and patients' preferences were compared in the evaluable intention-to-treat (ITT) population (patients who completed both interviews and had ≥1 administration of both SC and IV trastuzumab).

Results

Patients

Baseline patient demographics, tumour characteristics and treatment histories of patients enrolled in Cohorts 1 and 2 of PrefHer have been reported previously [7–9]. A total of 488 patients (Cohorts 1 and 2 pooled), from 12 countries and 74 sites, participated, and the evaluable ITT population included 235 patients randomised to receive SC followed by IV (SC→IV arm), and 232 to receive IV followed by SC (IV→SC arm) (**Fig. 2**) [7–9]. The safety population comprised 483 patients (five randomised patients did not receive study treatment); most patients (459/483 [95.0%]) completed all eight cycles [7–9]. Of the safety population patients, 243 were randomised to receive four cycles of SC→IV trastuzumab, and 240 patients the alternate sequence. Of these, 242 patients were treated with SC trastuzumab using the SID and 237 using the hand-held syringe; 24 patients completed <8 cycles during the crossover period [9]. The majority of patients had prior trastuzumab treatment (194/243 [79.8%] in the SC→IV arm and 191/240 [79.6%] in the IV→SC arm).

Safety analysis during the crossover period (pooled cohorts)

Overall, the safety profiles of the pooled cohorts were similar between SC and IV trastuzumab during the crossover period, with no new safety signals observed (**Table 1**) [7–9].

Within the SC→IV arm, the rate of AEs during SC treatment was 65.4% (159/243 patients), compared with 48.7% during IV treatment (116/238 patients). The incidence of grade ≥3 AEs was 4.5% (11/243 patients) during

SC treatment and 2.9% (7/238 patients) during IV treatment. While there were a number of SOCs that were reported more frequently during SC administration (**Table 2**), the only preferred terms that accounted for any difference between treatment cycles were ISRs and ARRs (based on all AEs reported). Excluding ISRs and ARRs, the rate of AEs was 59.7% (145/243) during the SC period and 47.9% (114/238) during the IV period.

Among patients in the IV→SC arm, the rates of AEs were similar when switching from IV (129/240 [53.8%] patients) to SC (133/236 [56.4%] patients; **Table 1**). The incidence of grade ≥3 AEs was 2.1% (5/236 patients) during SC and 3.8% (9/240 patients) during IV treatment. When ISRs and ARRs were excluded, the rate of AEs was higher during IV (126/240 [52.5%]) than SC treatment (111/236 [47.0%]). ARR rates were similar between IV and SC.

Overall, the majority of ARRs were grade 1 or 2 and the frequency of grade 3 ARRs in both treatment arms was low (<2% in the SC→IV arm and <1% in the IV→SC arm). ISRs were observed exclusively during the SC periods in both treatment arms, except in one patient in the IV→SC arm who experienced an ISR during IV treatment (**Table 1**).

The proportion of patients experiencing a clinically important event, including grade ≥3 AEs, SAEs, AEs leading to study drug discontinuation or cardiac AEs, was similar between treatment groups (**Table 1**). Overall, eight patients reported nine SAEs during the SC or IV treatment periods (four patients during the SC treatment periods and four during the IV treatment periods; **Table 1**) and 11 patients withdrew from treatment due to AEs (five during the SC treatment periods and six during the IV treatment periods; **Table 1**).

Cardiac AE rates were low and similar between treatment arms (14 [2.9%] in the SC→IV treatment arm and 11 [2.3%] in the IV→SC arm; **Table 1**).

Differences in AE rates by grade between the SC and IV periods were observed only for grade 1 and 2 AEs (**Fig. 3**). Grade 3 AEs were reported for 17 patients (7.0%) in the SC→IV treatment arm (11 [4.5%] during the SC period and seven [2.9%] during IV treatment; one patient experienced a grade 3 AE during SC and IV treatment) and 14 patients (5.8%) in the IV→SC treatment arm (nine [3.8%] during SC treatment and five [2.1%] during the IV period). No grade 4 or 5 AEs were reported (**Fig. 3**) [7–9].

Safety analysis during the crossover period (individual cohorts)

Comparison of the SID and hand-held syringe methods of administering SC trastuzumab revealed a similar pattern of clinically important AEs to the overall analysis (**Tables 3 and 4**). No new safety signals specific to either method were observed.

AE rates in patients de novo or non-de novo for trastuzumab treatment (pooled cohorts)

The majority of patients (*n* = 385) received prior trastuzumab. Although the number of prior cycles varied (1–10), AE rates, excluding ISRs and ARRs for patients in each treatment arm, whether de novo or non-de novo for trastuzumab treatment, were higher during the first treatment period compared with the second, regardless of whether patients received SC or IV trastuzumab (**Table 5**).

In the IV→SC arm, AEs rates were similar between the IV and SC treatment periods for de novo and non-de novo patients. Patients in the non-de novo group reported a higher proportion of AEs for all AE categories compared with de novo patients.

Relationship between patients' preference and safety

There was no clear link between grade 3 and grade 1–2 AEs and patients' preferences for SC or IV trastuzumab (**Supplementary Table 1**). As previously reported, patients overwhelmingly preferred SC administration of trastuzumab [7–9].

Discussion

Trastuzumab has improved the prognosis of patients with HER2-positive breast cancer in both early and metastatic disease [12,13]. One year of trastuzumab is the standard of care in the adjuvant setting, providing consistent improvements in disease-free and overall survival [14,15]. The HannaH study compared SC and IV trastuzumab and reported that SC was non-inferior to IV in terms of pCR and C_{trough}; safety was similar [4,5]. Previously published PrefHer analyses found that SC trastuzumab was well tolerated and that patients preferred it over IV administration [7–9]. The SafeHer study (NCT01566721) showed consistent safety results with the hand-held syringe; SID data are anticipated [16].

Overall, the results from PrefHer's crossover period demonstrated a consistent safety profile with the known safety profile of IV trastuzumab [17]. This analysis revealed no clinically relevant differences when patients switched between trastuzumab routes. While fewer AEs were reported during the IV treatment periods regardless of sequence (IV→SC or SC→IV), when ISRs and ARRs were excluded the rate of AEs was higher during the first period, compared with the second, in both treatment arms. Importantly, when switching from IV→SC, the frequency of clinically important events (grade ≥3 AEs, SAEs, AEs leading to trial drug discontinuation and cardiac AEs) was <5% and similar between treatment arms. Differences in grade 1 and 2 AEs between the SC and IV periods were partly due to variances in ISRs and ARRs. These occurred mainly during SC treatment, as expected; otherwise, there was no clear pattern in the types of AEs reported.

The higher proportion of overall AEs in the non-de novo group could be explained by imbalanced subgroup sizes (de novo patients comprised 20% of the population). Also, considering that there were more AEs at the injection site with SC trastuzumab, particularly at the initiation of treatment, it is logical that these AEs are more marked during SC→IV treatment. Regardless, the important elements are that grade ≥3 AE rates were balanced, and that patients expressed a preference for SC trastuzumab regardless of whether they had received prior trastuzumab treatment [9]. As such, the difference in AE rates between de novo and non-de novo groups has no clinical impact. Combining the SC SID and hand-held syringe cohorts for the switching analysis was considered appropriate as the SID is pharmacokinetically bioequivalent to the hand-held syringe [6]. AE profiles for the individual cohorts were generally similar to those observed for the pooled cohorts. Previously reported analyses from PrefHer demonstrated that patients preferred SC trastuzumab, regardless of SID or hand-held syringe delivery [7–9]. The current analysis did not find any clear differences in AE profiles between the SID and the hand-held syringe.

This analysis was a safety review of the crossover period of PrefHer (four cycles of SC and four cycles of IV trastuzumab), and therefore does not take into consideration the overall safety profile. Following the crossover period, patients completed their remaining trastuzumab treatment (up to 18 cycles), and therefore AEs that may emerge with late onset are not reported.

Where several formulations may be available for the same drug, patient experience and preference may significantly affect treatment adherence and

quality of life [18]. Patient preference is particularly pertinent when considering IV versus SC administration [18]. Among trials that compared IV and SC routes of administration of the same drug, only two had patient preference as the primary objective: PrefHer [7–9] and SWITCH [19]. The SWITCH trial compared elective switching (IV→SC) between two anti-tumour necrosis factor treatments, adalimumab and infliximab, in Crohn's disease [19]. Overall, a clear preference for SC treatment was reported by patients in both studies [7–9,19]. European approval of SC trastuzumab, in combination with overwhelming patient preference, suggests that patients may opt to switch from IV to SC trastuzumab in early breast cancer. The results of this analysis demonstrate that AE rates were similar when switching from IV to SC trastuzumab, with no new safety concerns.

In conclusion, during the crossover period, the PrefHer study demonstrated no clinically relevant safety differences when patients switched from IV to SC trastuzumab, or vice versa. PrefHer is the only study to provide prospective data on switching from IV→SC treatment and the data from this trial support switching in clinical practice.

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Conflict of interest statement

JG has received travel grants, consultancy and speaker honoraria (Roche, Eisai, Teva, Genomic Health), consultancy honoraria (Sanofi-Aventis), consultancy and speaker honoraria (Novartis) and speaker honoraria (GlaxoSmithKline). VM has received speaker honoraria from Amgen, Celgene, Eisai, GlaxoSmithKline, Pierre Fabre, Roche and Janssen-Cilag. Consultancy honoraria from Roche, Pierre Fabre, Amgen and Eisai. AK has performed consultant/advisory roles for F. Hoffmann-La Roche Ltd, and received honoraria from F. Hoffmann-La Roche Ltd. SO and ZM are employed by F. Hoffmann-La Roche Ltd. SL has received consultancy honoraria from F. Hoffmann-La Roche Ltd. LF has received consultancy and speaker honoraria from Roche. XP has received consultancy honoraria from Roche, Amgen and GlaxoSmithKline. The other authors have no conflicts of interest to declare.

Highlights

- We assessed switching between subcutaneous (SC) and intravenous (IV) trastuzumab.
- Patients received 4 cycles of SC then 4 cycles of IV trastuzumab, or vice versa.
- Rates of clinically important events were low and similar (IV→SC versus SC→IV).
- No new safety signals for trastuzumab were observed.
- Switching did not impact the known trastuzumab early breast cancer safety profile.

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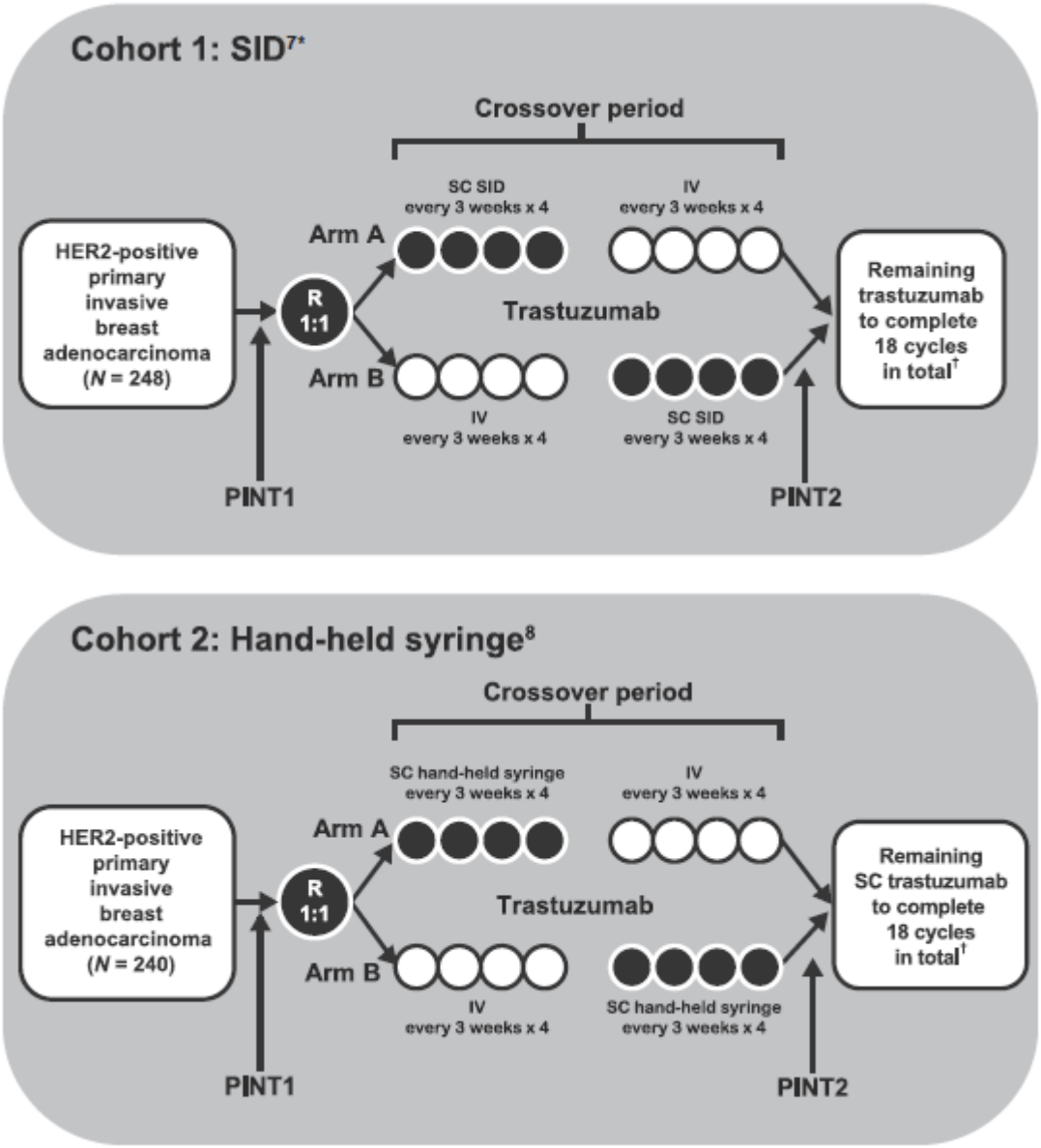
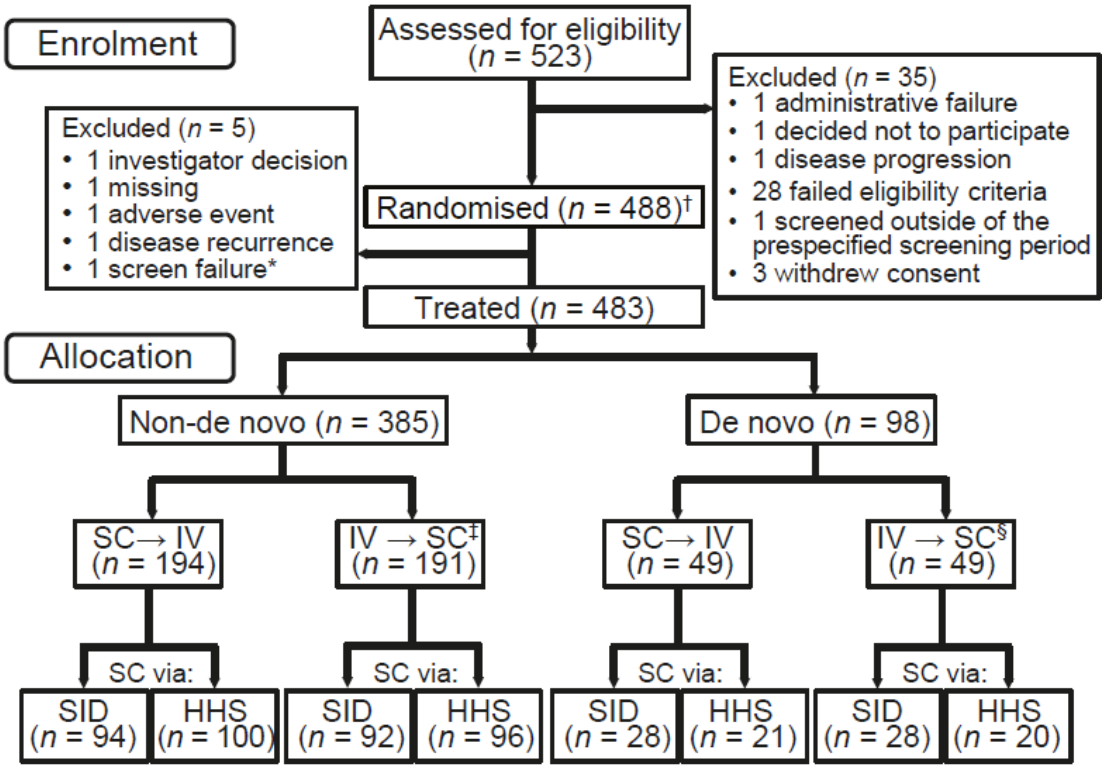
Fig. 1. PrefHer study design



Includes optional time-and-motion sub-study in both cohorts [10,11]. Patients completed surgery and (neo)adjuvant chemotherapy (concurrent or sequential with IV trastuzumab) and had at least eight out of the total of 18 planned trastuzumab cycles remaining in their adjuvant trastuzumab therapy. Stratification factor: de novo versus non-de novo trastuzumab (to balance the sequence groups for the proportion of patients with prior IV trastuzumab treatment). * * Reprinted from The Lancet Oncology, 14: Pivot X, Gligorov J, Müller V, Barrett-Lee P, Verma S, Knoop A, Curigliano G, Semiglazov V, López-Vivanco G, Jenkins V, Scotto N, Osborne S, Fallowfield L; PrefHer Study Group. Preference for

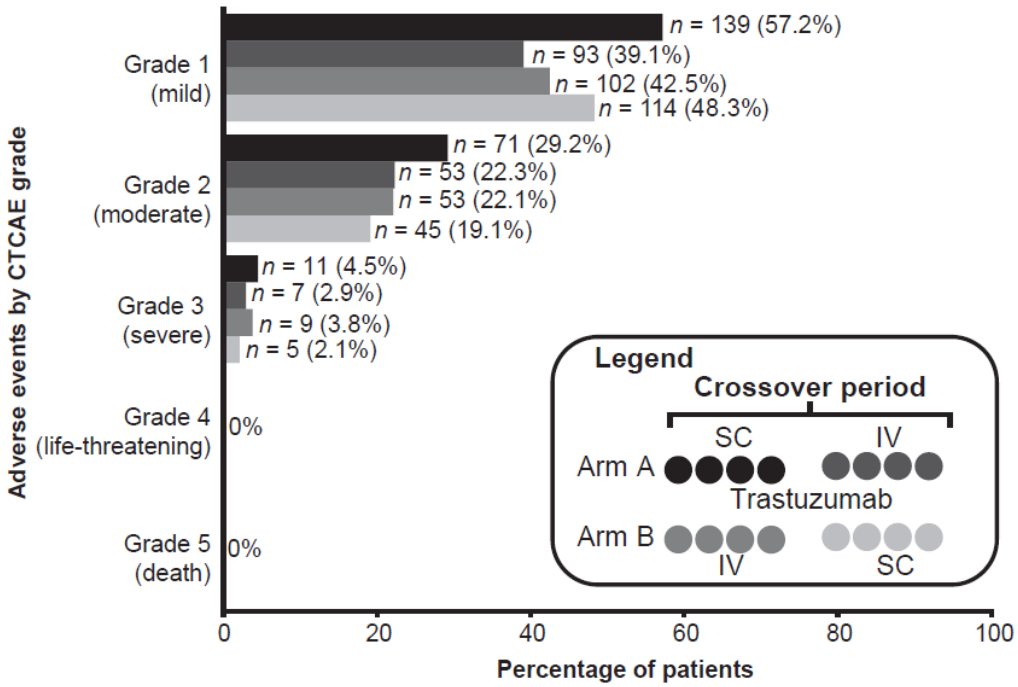
subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study, 962e970, Copyright (2013), with permission from Elsevier. † In the SID cohort, remaining trastuzumab was administered by IV infusion unless patients participated in SID self-administration. In the hand-held syringe cohort, remaining trastuzumab was planned to be administered subcutaneously by hand-held syringe. **Abbreviations:** HER2, human epidermal growth factor receptor 2; IV, intravenous; PINT, patient interview; R, randomised; SC, subcutaneous; SID, single-use injection device.

Fig. 2. PrefHer enrolment and allocation (pooled cohorts; safety population)



* No treatment was given on-trial as patient was screened and randomised but was later found to have an LVEF of 53%. † Patients who received at least one dose of study treatment. ‡ Three patients in non-de novo group (one in the SID cohort and two in the HHS cohort) and one patient in the de novo group (SID cohort) discontinued IV trastuzumab during IV→SC treatment. **Abbreviations:** HHS, hand-held syringe; IV, intravenous; LVEF, left ventricular ejection fraction; SC, subcutaneous; SID, single-use injection device.

Fig. 3. Adverse events by NCI-CTCAE grade in patients switching between trastuzumab administration routes during the crossover period (pooled cohorts; safety population)



All AEs, including SAEs, are included. If an AE start date was partially or fully missing, and it was unclear during which treatment period the AE started, the AE was assigned to all relevant treatment periods. If a patient had multiple events of the same NCI-CTCAE grade or relationship category, they were counted only once in that NCI-CTCAE grade or relationship category. AEs (all NCI-CTCAE grades) were reported in 65.4% (*n* = 159; Arm A: Cycles 1–4 SC), 48.7% (*n* = 116; Arm A: Cycles 5–8 IV), 53.8% (*n* = 129; Arm B: Cycles 1–4 IV) and 56.4% (*n* = 133; Arm B: Cycles 5–8 SC) of patients, respectively. Data was missing from 0.8% (*n* = 2; Arm A: Cycles 1–4 SC), 0.4% (*n* = 1; Arm B: Cycles 1–4 IV) and 0.8% (*n* = 2; Arm B: Cycles 5–8 SC) of patients, respectively. **Abbreviations:** AE, adverse event; IV, intravenous; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SAE, serious adverse event; SC, subcutaneous.

Table 1 Clinically relevant adverse events in patients switching between trastuzumab administration routes during the crossover period (pooled cohorts; safety population)

	SC→IV		**IV→SC**	
	Cycles 1–4: SC	**Cycles 5–8: IV**	**Cycles 1–4: IV**	**Cycles 5–8: SC**
	***N* = 243**	***N* = 238**	***N* = 240**	***N* = 236**
	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
AEs	159 (65.4)	116 (48.7)	129 (53.8)	133 (56.4)
AEs grade ≥3	11 (4.5)	7 (2.9)	9 (3.8)	5 (2.1)
SAEs	3 (1.2)	2 (0.8)	2 (0.8)	1 (0.4)
Systemic ARRs	39 (16.0)	12 (5.0)	18 (7.5)	18 (7.6)
Localised ISRs	57 (23.5)	0	1 (0.4)	40 (16.9)
AEs excluding ISRs and ARRs	145 (59.7)	114 (47.9)	126 (52.5)	111 (47.0)
AEs leading to study drug discontinuation	3 (1.2)	4 (1.7)	2 (0.8)	2 (0.8)
Cardiac AEs	6 (2.5)	8 (3.4)	6 (2.5)	5 (2.1)

If an AE start date was partially or fully missing, and it was unclear during which treatment period the AE started, the AE was assigned to all relevant treatment periods.

Abbreviations: AE, adverse event; ARR, administration-related reaction; ISR, injection site reaction; IV, intravenous; SAE, serious adverse event; SC, subcutaneous.

Table 2 Adverse events by SOC and specific adverse event in ≥5% of patients (any group) when switching between trastuzumab administration routes during the crossover period (pooled cohorts; safety population)

	SC→IV		**IV→SC**	
	Cycles 1–4: SC	**Cycles 5–8: IV**	**Cycles 1–4: IV**	**Cycles 5–8: SC**
	***N* = 243**	***N* = 238**	***N* = 240**	***N* = 236**
	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Musculoskeletal and connective tissue disorders	43 (17.7)	27 (11.3)	35 (14.6)	38 (16.1)
Arthralgia	10 (4.1)	11 (4.6)	16 (6.7)	14 (5.9)
General disorders and administration site conditions	87 (35.8)	31 (13.0)	38 (15.8)	58 (24.6)
Asthenia	16 (6.6)	10 (4.2)	13 (5.4)	11 (4.7)
Fatigue	14 (5.8)	8 (3.4)	10 (4.2)	5 (2.1)
Infections	25 (10.3)	35 (14.7)	23 (9.6)	16 (6.8)
Gastrointestinal disorders	33 (13.6)	25 (10.5)	17 (7.1)	25 (10.6)
Nausea	16 (6.6)	9 (3.8)	5 (2.1)	9 (3.8)
Nervous system disorders	32 (13.2)	21 (8.8)	20 (8.3)	17 (7.2)
Headache	13 (5.3)	4 (1.7)	12 (5.0)	7 (3.0)
Vascular disorders	31 (12.8)	16 (6.7)	19 (7.9)	22 (9.3)
Hot flush	17 (7.0)	10 (4.2)	6 (2.5)	6 (2.5)
Skin and SC tissue disorders	45 (18.5)	18 (7.6)	29 (12.1)	23 (9.7)
Respiratory, thoracic and mediastinal disorders	21 (8.6)	12 (5.0)	10 (4.2)	8 (3.4)
Injury, poisoning and procedural	13 (5.3)	9 (3.8)	9 (3.8)	2 (0.8)

complications

All AEs, including SAEs, were included. If an AE start date was partially or fully missing, and it was unclear during which treatment period the AE started, the AE was assigned to all relevant treatment periods.

Abbreviations: AE, adverse event; IV, intravenous; SAE, serious adverse event; SC, subcutaneous; SOC, system-organ class.

Table 3 Clinically relevant adverse events in patients switching between trastuzumab administration routes during the crossover period (Cohort 1; safety population)

	SC SID→IV		**IV→SC SID**	
	Cycles 1–4: SC SID ***N* = 122** ***n* (%)**	**Cycles 5–8: IV** ***N* = 119** ***n* (%)**	**Cycles 1–4: IV** ***N* = 122** ***n* (%)**	**Cycles 5–8: SC SID** ***N* = 120** ***n* (%)**
AEs	77 (63.1)	47 (39.5)	68 (55.7)	68 (56.7)
AEs grade ≥3	5 (4.1)	2 (1.7)	3 (2.5)	2 (1.7)
SAEs	3 (2.5)	1 (0.8)	1 (0.8)	1 (0.8)
Systemic ARRs	17 (13.9)	2 (1.7)	9 (7.4)	7 (5.8)
Localised ISRs	29 (23.8)	0	0	19 (15.8)
AEs excluding ISRs and ARRs	68 (55.7)	46 (38.7)	66 (54.1)	56 (46.7)
AEs leading to study drug discontinuation	2 (1.6)	0	1 (0.8)	0
Cardiac AEs	3 (2.5)	3 (2.5)	2 (1.6)	3 (2.5)

If an AE start date was partially or fully missing, and it was unclear during which treatment period the AE started, the AE was assigned to all relevant treatment periods.

Abbreviations: AE, adverse event; ARR, administration-related reaction; ISR, injection site reaction; IV, intravenous; SAE, serious adverse event; SC, subcutaneous; SID, single-use injection device.

Table 4 Clinically relevant adverse events in patients switching between trastuzumab administration routes during the crossover period (Cohort 2; safety population)

	SC HHS→IV		**IV HHS→SC**	
	Cycles 1–4: SC HHS	**Cycles 5–8: IV**	**Cycles 1–4: IV**	**Cycles 5–8: SC HHS**
	***N* = 121**	***N* = 119**	***N* = 118**	***N* = 116**
	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
AEs	82 (67.8)	69 (58.0)	61 (51.7)	65 (56.0)
AEs grade ≥3	6 (5.0)	5 (4.2)	6 (5.1)	3 (2.6)
SAEs	0	1 (0.8)	1 (0.8)	0
Systemic ARRs	22 (18.2)	10 (8.4)	9 (7.6)	11 (9.5)
Localised ISRs	28 (23.1)	0	1 (0.8)	21 (18.1)
AEs excluding ISRs and ARRs	77 (63.6)	68 (57.1)	60 (50.8)	55 (47.4)
AEs leading to study drug discontinuation	1 (0.8)	4 (3.4)	1 (0.8)	2 (1.7)
Cardiac AEs	3 (2.5)	5 (4.2)	4 (3.4)	2 (1.7)

If an AE start date was partially or fully missing, and it was unclear during which treatment period the AE started, the AE was assigned to all relevant treatment periods.

Abbreviations: AE, adverse event; ARR, administration-related reaction; HHS, hand-held syringe; ISR, injection site reaction; IV, intravenous; SAE, serious adverse event; SC, subcutaneous.

Table 5 Adverse events in patients de novo or non-de novo for trastuzumab administration prior to the crossover period (pooled cohorts; safety population)

	SC→IV		**IV→SC**	
	Cycles 1–4: SC	**Cycles 5–8: IV**	**Cycles 1–4: IV**	**Cycles 5–8: SC**
	***N* = 243**	***N* = 238**	***N* = 240**	***N* = 236**
Overall safety population	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
AEs excluding ISRs and ARRs	145 (59.7)	114 (47.9)	126 (52.5)	111 (47.0)
AEs grade ≥3	11 (4.5)	7 (2.9)	9 (3.8)	5 (2.1)
SAEs	3 (1.2)	2 (0.8)	2 (0.8)	1 (0.4)

	SC→IV		**IV→SC**	
	Cycles 1–4: SC	**Cycles 5–8: IV**	**Cycles 1–4: IV**	**Cycles 5–8: SC**
	***N* = 49**	***N* = 47**	***N* = 49**	***N* = 48**
De novo treatment	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
AEs excluding ISRs and ARRs	21 (42.9)	14 (29.8)	17 (34.7)	16 (33.3)
AEs grade ≥3	1 (2.0)	1 (2.1)	1 (2.0)	1 (2.1)
SAEs	0	1 (2.1)	0	0

	SC→IV		IV→SC	
	Cycles 1–4: SC	**Cycles 5–8: IV**	**Cycles 1–4: IV**	**Cycles 5–8: SC**
	***N* = 194**	***N* = 191**	***N* = 191**	***N* = 188**
Non-de novo treatment	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
AEs excluding ISRs and ARRs	124 (63.9)	100 (52.4)	109 (57.1)	95 (50.5)
AEs grade ≥3	10 (5.2)	6 (3.1)	8 (4.2)	4 (2.1)
SAEs	3 (1.5)	1 (0.5)	2 (1.0)	1 (0.5)

If an AE start date was partially or fully missing, and it was unclear during which treatment period the AE started, the AE was assigned to all relevant treatment periods.

Abbreviations: AE, adverse event; ARR, administration-related reaction; ISR, injection site reaction; IV, intravenous; SAE, serious adverse event; SC, subcutaneous.

Appendix A. Supplementary data

Supplementary Table 1: Comparison of adverse events and patients' preferred method of administration during the crossover period (pooled cohorts; ITT population)

Grade 3 AEs

	AE experienced during SC or IV period			
	IV and SC	**SC only**	**IV only**	**Neither**
	***N* = 1**	***N* = 11**	***N* = 13**	***N* = 442**
Preference	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
IV	0	3 (27.3)	2 (15.4)	40 (9.0)
SC	1 (100.0)	8 (72.7)	11 (84.6)	395 (89.4)
No preference	0	0	0	7 (1.6)

Grade ≤2 AEs

	AE experienced during SC or IV period			
	IV and SC	**SC only**	**IV only**	**Neither**
	***N* = 175**	***N* = 104**	***N* = 57**	***N* = 131**
Preference	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
IV	22 (12.6)	7 (6.7)	4 (7.0)	12 (9.2)
SC	150 (85.7)	97 (93.3)	50 (87.7)	118 (90.1)
No preference	3 (1.7)	0	3 (5.3)	1 (0.8)

Abbreviations: AE, adverse event; IV, intravenous; ITT, intention-to-treat; SC, subcutaneous.