PATIENT PREFERENCE FOR SUBCUTANEOUS VERSUS INTRAVENOUS ADJUVANT TRASTUZUMAB: RESULTS OF THE PREFHER STUDY

PrefHer
PREFERENCE FOR HERCEPTIN SC OR IV ADMINISTRATION

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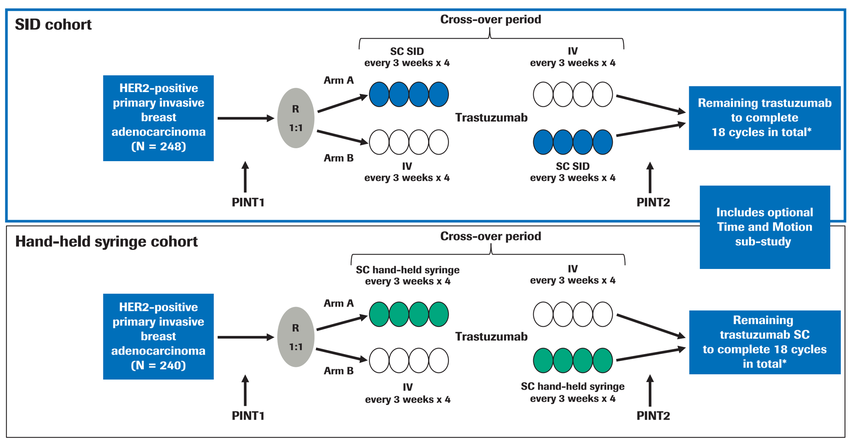
Background

- Intravenous (IV) trastuzumab-containing regimens are the foundation of care for the treatment of human epidermal growth factor receptor 2 (HER2)-positive early and advanced/metastatic breast cancer.
- A subcutaneous (SC) formulation (fixed dose of 600 mg trastuzumab and 10 000 U recombinant human hyaluronidase [rHuPH20] as an excipient) has been developed for 3-weekly use as an alternative to the IV formulation.
  - Trastuzumab SC could potentially improve patient convenience/compliance (injection time less than 5 minutes; important in long-term trastuzumab therapy) and reduce the use of hospital resources.[1–3]
  - A single-use injection device (SID) is currently in development as an alternative to manual SC injection via hand-held syringe. Pharmacokinetic bioequivalence between the two methods of SC administration, with consistently high SID performance, has been shown.[4]
  - The pivotal Phase III HannaH study met its co-primary endpoints of non-inferior trastuzumab SC serum trough concentration (C_{trough}) and pathological complete response (pCR) with (neo)adjuvant trastuzumab SC (manual injection) vs. IV.[1,5]
    - The geometric mean ratio of trastuzumab SC to IV C_{trough} was 1.33 (90% confidence interval [CI] 1.24 to 1.44).[5]
    - pCR rates were 45.4% in the SC group and 40.7% in the IV group: a difference of 4.7% (95% CI –4.0 to 13.4).[5]
    - The overall safety profile of trastuzumab SC was consistent with the known safety profile of trastuzumab in early breast cancer, with new safety signals identified at 20 months' median follow-up.[6]
- **To investigate benefits of the trastuzumab SC formulation, the international, multi-centre, open-label, randomised, two-cohort, two-arm PrefHer study was designed to assess patients' preferences for trastuzumab SC or IV in the adjuvant breast cancer setting.** Patients with HER2-positive early breast cancer were randomised to receive 4 cycles of trastuzumab SC followed by 4 of IV (Arm A), or the reverse sequence (Arm B) (the 'cross-over' period) as part of their standard 18 cycles of adjuvant trastuzumab therapy, following completion of surgery and (neo)adjuvant chemotherapy.
  - Randomisation was stratified by pre-study trastuzumab IV therapy (*de novo* and non-*de novo* subgroups).
- The PrefHer study contains two cohorts, differing in trastuzumab SC administration method:
  - Cohort 1: trastuzumab SC administered via SID (presented here).
  - Cohort 2: trastuzumab SC administered via hand-held syringe and manual injection (enrolment was completed in December 2012; data collection is ongoing and results will be presented at a later date).

Methods

- The overall study design is shown in Figure 1.

Figure 1: Study design



Patients completed surgery and (neo)adjuvant chemotherapy (concurrent or sequential with trastuzumab IV) and had at least 8 out of the total of 18 planned trastuzumab cycles remaining in their adjuvant trastuzumab therapy. Stratification factor: *de novo* vs. non-*de novo* trastuzumab (to balance the sequence groups for the proportion of patients with prior trastuzumab IV treatment). * Initially, 22 cycles were planned; however, the protocol was amended to 18 once non-inferiority of trastuzumab SC was demonstrated.[5]
HER2, human epidermal growth factor receptor 2; IV, intravenous; PINT, Patient Interview; R, randomised; SC, subcutaneous; SID, single-use injection device

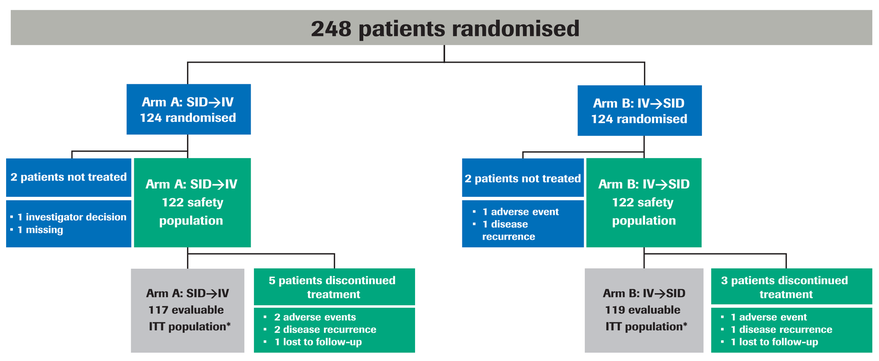
- Trastuzumab IV was administered 3-weekly as an 8 mg/kg loading dose (patients who received trastuzumab IV first in the *de novo* group only) and a 6 mg/kg maintenance dose over 30 to 90 minutes.
- Trastuzumab SC was administered 3-weekly as a 600 mg/5 mL fixed dose, injected into the thigh over approximately 5 minutes.
- **Primary endpoint: proportion of patients indicating an overall preference for the SC or IV route of trastuzumab administration, assessed by a single direct question ("All things considered, which method of administration did you prefer?").**
  - Secondary endpoints: safety and tolerability,[7–9] event-free survival (time to local, regional or distant recurrence, contralateral breast cancer or death due to any cause), immunogenicity (anti-trastuzumab and -rHuPH20 antibodies in blood samples, Cohort 1 only), and healthcare professional (HCP) satisfaction/perceived time savings with trastuzumab SC.
    - Follow-up is ongoing, and efficacy, immunogenicity, HCP-perceived time savings and additional safety results will be presented at a later date.
  - Exploratory endpoints: factors that influenced patients' preferences for SC or IV administration, and patient satisfaction with SID self-administration (Cohort 1 only).
  - A Time and Motion pharmacoeconomic sub-study will assess Medical Care Utilisation, including collection of time of administration and resource data, at selected sites in both cohorts (see poster #209).[10]
- Patient-reported outcomes were assessed by two telephone Patient Interviews (PINTs) during the study, conducted in local languages by experienced, trained interviewers and developed specifically for PrefHer using an iterative process.
  - Questions investigated factors potentially influencing preferences such as experiences during administration.
  - Patients' final preferences, reasons for these and strength of preference were directly elicited in PINT2.
  - Interviews were quality-controlled to ensure impartial questioning.
- Safety was assessed by physical examination and vital signs every 3 months, with cardiac monitoring by echocardiogram or multi-gated acquisition scan every 4 cycles of trastuzumab. Following cessation of treatment, monitoring was performed at 6, 12 and 24 months, or according to institutional practice.
  - Patients will be followed up until 3 years after the last patient is randomised, or until disease recurrence (whichever occurs first).
- Primary patient preference analyses will be carried out independently in each cohort on the evaluable intention-to-treat (ITT) populations: patients who received at least one dose of trastuzumab SC and IV and completed PINT1 and the primary endpoint question in PINT2, once the last patients have completed the cross-over periods. In the current analysis of Cohort 1:
  - The proportion of patients preferring trastuzumab SC and the 95% CIs for this proportion (exact binomial method) were calculated.
  - It was determined that the primary endpoint would be met if at least 65% of patients preferred trastuzumab SC.
  - The margin of error within which the estimated proportion is given was chosen to be 7.5%; therefore, a sample size of 160 patients was needed for the 95% CIs to be within 57.5% and 72.5%.
  - Preference for SC administration was compared with a two-sided test against the null hypothesis value of 65%.
  - The potentially influencing factors: pre-study trastuzumab treatment, patient demographics/characteristics, tumour/treatment characteristics and PINT1-expected preferences were assessed in terms of their impact on the primary endpoint.
- The safety population comprised all patients who received at least one dose of study treatment. Overall adverse event rates are reported in this poster for the combined 4 cycles of trastuzumab SC and IV cross-over period only; additional analyses will be reported at a later date.

Cohort 1 results

Patients and treatment characteristics

- Two hundred and forty-eight patients were randomised at 74 centres in 11 countries between October 2011 and March 2012. The evaluable ITT and safety populations comprised 236 and 244 patients, respectively (Figure 2).

Figure 2: Patient disposition



N = 265 patients competed PINT1. * Patients who received at least one dose of trastuzumab SC and IV and completed both PINT1 and the primary endpoint question in PINT2.
ITT, intention-to-treat; IV, intravenous; PINT, Patient Interview; SID, single-use injection device.

- The median number of trastuzumab cycles received during the cross-over period was 8.
- Baseline patient demographics, tumour characteristics and treatment history were generally balanced between study arms (evaluable ITT population; Table 1).

Table 1: Patient demographics, tumour characteristics and treatment history (evaluable ITT population)

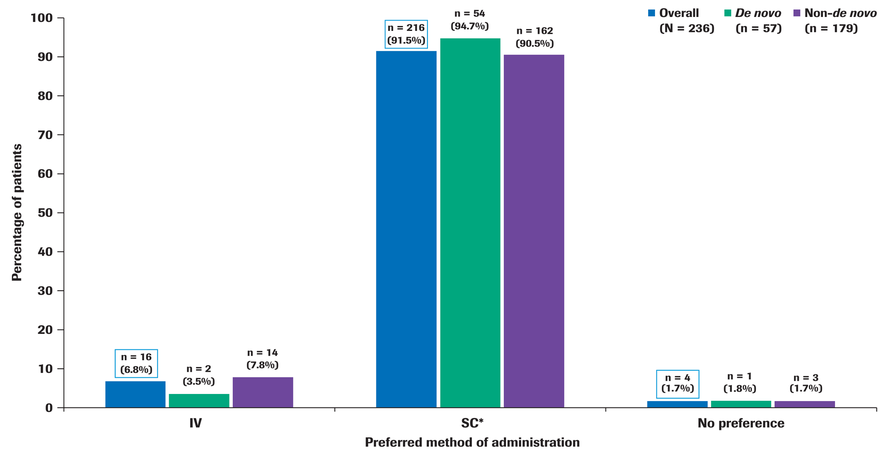
	Arm A SID→IV n = 117	Arm B IV→SID n = 119	Overall N = 236
Age (years)			
Median	54.0	51.0	53.0
Min, max	32, 76	28, 75	28, 76
Weight (kg)			
Median	68.6	66.0	68.0
Min, max	35.0, 120.0	45.0, 131.8	35.0, 131.8
ECOG at screening, n (%)			
0	95 (81.2)	96 (80.7)	191 (80.9)
1	22 (18.8)	23 (19.3)	45 (19.1)
TNM classification at diagnosis			
Primary tumour, n (%)*	2 (1.7)	4 (3.4)	6 (2.5)
T0	60 (51.3)	39 (32.8)	99 (41.9)
T1	38 (32.5)	57 (47.9)	95 (40.3)
T2	9 (7.7)	11 (9.2)	20 (8.5)
T3	6 (5.1)	8 (6.7)	14 (5.9)
T4	2 (1.7)	0	2 (0.8)
Unknown			
Lymph node status, n (%)			
Negative	63 (53.8)	51 (42.9)	114 (48.3)
Positive	48 (41.0)	66 (55.5)	114 (48.3)
Unknown	6 (5.1)	2 (1.7)	8 (3.4)
HER2-positive, n (%)	117 (100.0)	119 (100.0)	236 (100.0)
Stratification factor: adjuvant trastuzumab, n (%)			
De novo	29 (24.8)	28 (23.5)	57 (24.2)
Non-*de novo*	88 (75.2)	91 (76.5)	179 (75.8)
Previous treatment, n (%)			
Chemotherapy	117 (100.0)	119 (100.0)	236 (100.0)
Radiotherapy	72 (61.5)	71 (59.7)	143 (60.6)
Hormonal therapy	50 (42.7)	50 (42.0)	100 (42.4)
Lapatinib	0	1 (0.8)	1 (0.4)

All patients received prior surgery. * No tumours were metastatic. Patients with T4 tumours received (neo)adjuvant chemotherapy and were eligible for the study.
ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IV, intravenous; SID, single-use injection device

Patients' preferences (evaluable ITT population)

- **Overall, 91.5% of patients preferred trastuzumab SC (95% CI 87.2% to 94.7%; p < 0.0001); 6.8% preferred IV (95% CI 3.9% to 10.8%) and 1.7% had no preference (95% CI 0.5% to 4.3%) (Figure 3).**
  - Arm A: 95.7% preferred SC (95% CI 90.3% to 98.6%) and 4.3% preferred IV.
  - Arm B: 87.4% preferred SC (95% CI 81.1% to 92.8%), 9.2% preferred IV and 3.4% had no preference.
  - High preference for trastuzumab SC was maintained, irrespective of whether patients were *de novo* or non-*de novo* trastuzumab IV prior to study enrolment (Figure 3).
  - Primary reasons for patients' preferences for trastuzumab SC were time saving and less pain/discomfort (Table 2).

Figure 3: Patients' preferences (evaluable ITT population)



PINT2, Q53: "All things considered, which method of administration did you prefer?"; * SC preferred (exact binomial): Overall = 91.5% (95% CI 87.2% to 94.7%); *de novo* trastuzumab = 94.7% (95% CI 85.4% to 98.9%); non-*de novo* trastuzumab = 90.5% (95% CI 85.2% to 94.4%); CI, confidence interval; IV, intravenous; PINT, Patient Interview; SC, subcutaneous.

Table 2: Primary reasons for patients' preferences (evaluable ITT population)

Reason category	Total, n*
SC preference, n = 216	
Time saving	195
Less pain/discomfort	88
Convenience to patient	35
Ease of administration	33
Problems with IV	25
Less stress/anxiety	15
Other	6
IV preference, n = 16	
Fewer perceived reactions (less pain, bruising, irritation, etc.)	11
Other	5
Environment/staff	2
Perceived efficacy	1
Ecological considerations	1
No preference, n = 4	

* Some patients gave >1 reason for preference. IV, intravenous; SC, subcutaneous.

- Overall preference for trastuzumab SC was 'very strong' in 159 patients (67.4%, 95% CI 61.0% to 73.3%), 'fairly strong' in 45 (19.1%) and 'not very strong' in 12 (5.1%). Overall preference for IV was 'very strong' in eight patients (3.4%), 'fairly strong' in three (1.3%) and 'not very strong' in five (2.1%).
- None of the potentially influencing factors impacted the primary endpoint results.

HCP satisfaction

- HCPs (n = 103) were more satisfied with trastuzumab SC (73.8%, 95% CI 64.2% to 82.0%) compared with IV (1.9%). The remaining 24.3% did not indicate a preference.

Adverse event profile

- The adverse event profile is shown in Table 3 and represents the overall profile for the cross-over period (4 cycles of trastuzumab SC and 4 of IV; median of 8 cycles).
  - Adverse events of any grade (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE], v4.0) were reported in 67.2% of 244 patients; 4.5% were reported at NCI-CTCAE grade 3 and 0% were reported at NCI-CTCAE grades 4 or 5 during this period.
  - No congestive heart failure was reported during this period.
  - Serious adverse events were reported in 2.5% of patients during this period (six events were reported in six patients); none was considered to be related to trastuzumab and each was fully resolved without sequelae.

Table 3: Adverse event profile during the cross-over period (safety population)

	Overall, n (%) N = 244
Adverse events (all NCI-CTCAE grades)	164 (67.2)
Grade 1 (mild)	148 (60.7)
Grade 2 (moderate)	78 (32.0)
Grade 3 (severe)	11 (4.5)
Grade 4 (life-threatening)	0
Grade 5 (death)	0
Unknown	4 (1.6)
Serious adverse events	6 (2.5)
Relationship to study treatment	
Yes	0
No	6 (2.5)

If a patient had multiple events of the same CTCAE grade or relationship category, they were counted only once in that CTCAE grade or relationship category. However, patients could be counted more than once overall. CTCAE, Common Terminology Criteria for Adverse Events.

Conclusions

- In Cohort 1 of the PrefHer study, patients overwhelmingly (91.5%) preferred fixed-dose trastuzumab SC over standard IV for the treatment of HER2-positive early breast cancer.
  - Preference for trastuzumab SC was irrespective of SC/IV sequence, and of potentially influencing factors.
  - Time saving and reduced pain/discomfort compared with IV administration were the most common reasons for SC preference in an exploratory analysis.
- The overall safety profile of 4 cycles of trastuzumab SC and 4 cycles of trastuzumab IV observed during the cross-over period of Cohort 1 in the PrefHer study was consistent with the known safety profile of trastuzumab IV in early breast cancer.[11] Safety data did not raise any safety concerns thus far.
- Patient preference results from PrefHer, combined with efficacy and pharmacokinetic results from HannaH, suggest that a fixed dose of 600 mg trastuzumab SC every 3 weeks may be considered a valid and preferred option for the treatment of HER2-positive breast cancer.

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