Efficacy and safety of subcutaneous trastuzumab and intravenous trastuzumab as part of adjuvant therapy for HER2-positive early breast cancer: Final analysis of the randomised, two-cohort PrefHer study

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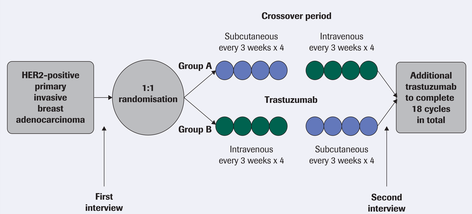
Background

- A 600 mg fixed-dose manual injection of subcutaneous trastuzumab (Herceptin® SC [H SC], F. Hoffmann-La Roche Ltd, Basel, Switzerland), given via hand-held syringe from an H SC Vial, was approved following demonstrated non-inferiority compared with intravenous trastuzumab (Herceptin® [H IV], F. Hoffmann-La Roche Ltd) based on pathological complete response and serum trough concentration in the HannaH study.[1]
- The international, open-label, randomised, crossover PrefHer study (NCT01401166) revealed overwhelming patient preferences for H SC, given by single-use injection device (SID) or hand-held syringe from an H SC Vial, over H IV as adjuvant therapy for HER2-positive early breast cancer.[2,3]
  - Preferences were due to 'time saving' and 'less pain/discomfort/side effects,' and there was a high preference for H SC irrespective of whether or not patients received H IV prior to study enrolment.[2,3]
- We present here the efficacy results and final safety data from the PrefHer study.

Methods

- Patients with histologically confirmed primary invasive breast adenocarcinoma with no evidence of residual, locally recurrent or metastatic disease after completion of surgery and neoadjuvant or adjuvant chemotherapy (with or without H) were randomised to receive either four cycles of H SC every 3 weeks (q3w), then four cycles of H IV, or the reverse sequence (Figure 1).

Figure 1. Overall study design[2]



Randomisation was stratified according to whether or not patients had already received intravenous trastuzumab.

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- During the crossover period, patients in Cohort 1 received H SC via SID and patients in Cohort 2 received H SC via hand-held syringe from an H SC Vial. Following the crossover period, i.e., the H continuation period, it was planned for patients in Cohort 1 to receive H IV (unless participating in SID self-administration), and for patients in Cohort 2 to receive H SC via hand-held syringe from an SC Vial.
- Patients could have been either H-naive (*de novo*) or could have already started H treatment for early breast cancer prior to study entry (non-*de novo*), but needed to receive at least eight more cycles to complete 1 year (18 cycles) of H treatment in the adjuvant setting.
- The primary endpoint, patient preference for H SC or H IV, has been reported elsewhere as described in the Background section, along with safety data from the crossover period.[2,3] We report here a secondary endpoint, 3-year event-free survival (EFS), defined as time from randomisation to local, regional or distant disease recurrence, contralateral breast cancer or death from any cause, as well as safety across both groups of the study in the crossover and H continuation periods.
- EFS was assessed using the Kaplan–Meier approach and is shown for the overall evaluable intention-to-treat (ITT) populations of each cohort, and overall.
- Adverse events (AEs) and serious AEs (SAEs) were reported according to NCI-CTCAE v4 and New York Heart Association criteria.

Results

- Of 488 patients randomised, 483 received at least one dose of study treatment and were evaluated for safety.[3] A total of 467 patients who received at least one dose of H IV and H SC and completed patient interviews before randomisation and at the end of crossover treatment for the primary endpoint (patient preference) were included in the evaluable ITT population.[3]
- The *de novo* group comprised 98/483 patients (20.3%) and the non-*de novo* group 385/483 patients (79.7%).
- A total of 409 patients completed follow-up according to protocol. Baseline characteristics were balanced between treatment groups, as previously described.[3]

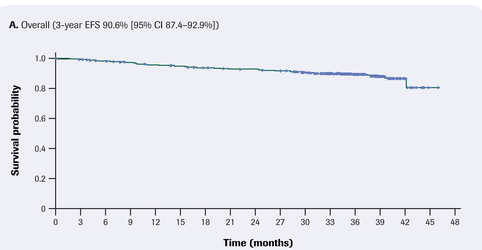
Treatment exposure

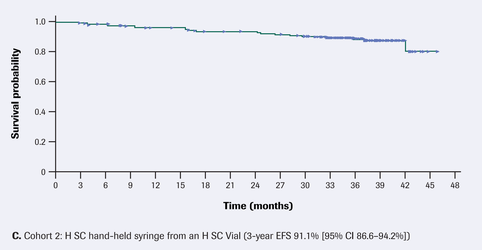
- Taking into account the H cycles received prior to randomisation, a total of 425/483 (88.0%) patients in the safety population received all 18 cycles of H, with a median of 13 cycles on-study.
- The majority of patients in the *de novo* group (89/98, 90.8%) completed all 18 cycles of H.
- Taking into account H cycles received before randomisation, the majority of non-*de novo* patients (336/385, 87.3%) also completed all 18 cycles of H.

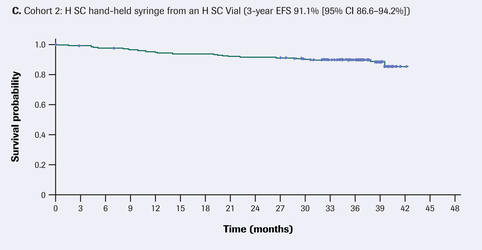
Event-free survival

- After median follow-up of 36.1 months, 3-year EFS across both groups in the evaluable ITT population was 90.6% overall (Figure 2A), 89.9% in Cohort 1 (Figure 2B) and 91.1% in Cohort 2 (Figure 2C).

Figure 2. EFS in the evaluable ITT population (both study groups combined)







EFS is defined as time from randomisation to local, regional or distant disease recurrence, contralateral breast cancer or death from any cause.

CI, confidence interval; EFS, event-free survival; H, trastuzumab (Herceptin®); SC, subcutaneous; SID, single-use injection device.

Safety

- Safety by treatment period is shown in Table 1.

Table 1. Summary of safety by treatment period (both cohorts combined)

Patients with ≥ 1 AE, n (%)*	H SC period during crossover n = 479	H IV period during crossover n = 478	H continuation n = 440	H SC SID self-administration during H continuation n = 43	Overall n = 483
Median H cycles, n	4.0	4.0	5.0	2.0	13.0
Any AE	300 (62.6)	258 (54.0)	223 (50.7)	12 (27.9)	388 (80.3)
Grade 1	262 (54.7)	206 (43.1)	175 (39.8)	10 (23.3)	360 (74.5)
Grade 2	119 (24.8)	110 (23.0)	85 (19.3)	5 (11.6)	214 (44.3)
Grade 3	17 (3.5)	16 (3.3)	16 (3.6)	1 (2.3)	45 (9.3)
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Treatment-related AE	163 (34.0)	53 (11.1)	60 (13.6)	4 (9.3)	207 (42.9)
Discontinuation for AE	5 (1.0)	6 (1.3)	10 (2.3)	0	21 (4.3)
Any SAE	4 (0.8)	4 (0.8)	11 (2.5)	1 (2.3)	19 (3.9)
Treatment-related SAE	0	0	1 (0.2)	0	1 (0.2)

* Could be counted once per grade but ≥ once overall.

AE, adverse event; H, trastuzumab (Herceptin®); IV, intravenous; SAE, serious adverse event; SC, subcutaneous; SID, single-use injection device.

- The most common AEs across both cohorts (all grades) were arthralgia (13.7%), asthenia (13.7%) and headache (10.4%), with no other AEs occurring in ≥ 10% of patients.
  - Differences in AE rates between H SC and H IV periods during crossover were driven by injection site reactions, and rates were comparable between H SC and H IV periods when injection site reactions were excluded.
- Most AEs were Grade 1 or 2, with Grade 3 AEs in 45 patients (9.3%). No Grade 3 AE occurred in more than 1% of patients. There were no Grade 4 or 5 AEs.
- AEs considered by the investigator to be related to H treatment were reported in 213 patients (44.1%), and at Grade 3 severity in 14 patients (2.9%). Left ventricular dysfunction and dyspnoea (two patients each) were the only H-related Grade 3 AEs that occurred in more than one patient.
- SAEs were reported in 19 patients (3.9%). Only one of 19 (left ventricular dysfunction in one patient) was considered by the investigator to be related to H treatment. All SAEs had resolved by clinical cut-off.

Cardiac events

- Cardiac AEs are summarised in Table 2.
- Most were Grade 1 or 2, and only one serious cardiac AE was reported (left ventricular dysfunction, above).
- Only four patients had Grade 3 cardiac AEs (three left ventricular dysfunction, one congestive heart failure).
- Congestive heart failure was reported in five patients (1.0%), none serious.

Table 2. Cardiac AEs

Patients with ≥ 1 AE, n (%)*	H SC period during crossover n = 479	H IV period during crossover n = 478	H continuation n = 440	H SC SID self-administration during H continuation n = 43	Overall n = 483
Any cardiac AE	12 (2.5)	15 (3.1)	17 (3.9)	0	40 (8.3)
Grade 1	9 (1.9)	11 (2.3)	11 (2.5)	0	28 (5.8)
Grade 2	2 (0.4)	3 (0.6)	6 (1.4)	0	10 (2.1)
Grade 3	1 (0.2)	2 (0.4)	1 (0.2)	0	4 (0.3)
Cardiac disorders†	8 (1.7)	14 (2.9)	14 (3.2)	0	33 (6.8)
Left ventricular dysfunction	2 (0.4)	5 (1.0)	4 (0.9)	0	11 (2.3)
Palpitations	3 (0.6)	2 (0.4)	2 (0.5)	0	7 (1.4)
Congestive heart failure	2 (0.4)	0	3 (0.7)	0	5 (1.0)
Investigations‡	4 (0.8)	3 (0.6)	3 (0.7)	0	9 (1.9)

* Could be counted once per grade but ≥ once overall.

† Cardiac disorders not listed: bradycardia (three patients), extrasystoles (two patients), angina pectoris, cardiomyopathy, diastolic dysfunction, heart valve incompetence, left ventricular hypertrophy, mitral valve incompetence, sinus bradycardia, tachycardia (one patient each).

‡ Ejection fraction decreased (seven patients), ejection fraction abnormal, electrocardiogram change (one patient each).

AE, adverse event; H, trastuzumab (Herceptin®); IV, intravenous; SC, subcutaneous; SID, single-use injection device.

Conclusions

- Overall, the 3-year EFS rates observed in both cohorts of the PrefHer study were consistent with those observed in previous clinical trials of H therapy for patients with HER2-positive early breast cancer.[4–8]
- No new safety signals were identified with longer follow-up, with only one cardiac SAE reported in 483 patients.
- The overall safety profile during adjuvant treatment was as expected.
- Consistent results from both cohorts of PrefHer, combined with data from the HannaH study, demonstrate that H SC is a valid and well tolerated option for patients and healthcare professionals, regardless of H SC delivery method (SID or hand-held syringe from an H SC Vial).

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