Subcutaneous versus intravenous formulation of trastuzumab for HER2-positive early breast cancer: updated results from the phase III HannaH study


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Background: HannaH (NCT00950300) was a phase III, randomized, international, open-label study that compared pharmacokinetics (PK), efficacy, and safety of two different trastuzumab formulations [subcutaneous (s.c.) and intravenous (i.v.)] in HER2-positive, operable, locally advanced, or inflammatory breast cancer in the neoadjuvant/adjuvant setting. The co-primary end points, to show noninferiority of s.c. versus i.v. trastuzumab in terms of serum concentration (C_{TROUGH}) and pathologic complete response (pCR) were met; safety profiles were comparable at 12 months' median follow-up. Secondary end points included safety and tolerability, PK profile, immunogenicity, and event-free survival (EFS). We now report updated safety and efficacy data after a median follow-up of 20 months.

 Patients and methods: Patients (N = 596) were treated with eight cycles of neoadjuvant chemotherapy, administered concurrently with 3-weekly s.c. trastuzumab (fixed dose of 600 mg) or the standard weight-based i.v. method. Following surgery, patients continued trastuzumab treatment to complete 1 year of therapy. Updated analyses of PK, efficacy, safety, and immunogenicity data were carried out.

 Results: s.c. trastuzumab was generally well tolerated and the incidence of adverse events (AEs), including grade 3 or 4 AEs, between treatment groups was comparable. A slightly higher incidence of serious AEs (SAEs), mainly due to infections, was reported with s.c. treatment [64 (21.5%; 95% confidence interval (CI) 17.0%–26.7%) versus 42 (14.1%; 95% CI 10.4%–18.6%) in the i.v. group]; however, the differences were small and often based on rare events, with no observable pattern across reported events. An early analysis of EFS showed rates of 95% in both groups 1 year postrandomization. Exploratory analyses did not reveal an association between toxicity and body weight or exposure.

 Conclusions: Overall, the safety profile of s.c. trastuzumab was consistent with the previously published data from HannaH and the known safety profile of i.v. trastuzumab. EFS rates were comparable between the i.v. and s.c. groups.

 Clinical trial number: NCT00950300.

 Key words: breast cancer, chemotherapy, HER2/neu, neoadjuvant, subcutaneous, trastuzumab
introduction
The humanized monoclonal antibody trastuzumab (Herceptin®, F. Hoffmann-La Roche Ltd, Basel, Switzerland), delivered intravenously (i.v.), is the foundation of standard regimens used to treat patients with HER2-positive breast cancer [1–3]. A subcutaneous (s.c.) formulation (Herceptin® SC, F. Hoffmann-La Roche Ltd, Basel, Switzerland), containing 600 mg of trastuzumab and the excipient recombinant human hyaluronidase (rHuPH20), offers a fixed-dose alternative to the weight-adjusted i.v. formulation. s.c. trastuzumab can be administered using a handheld syringe (HHS; approved by the European Medicines Agency) or a bioequivalent single-use injection device (SID), which provides a self-administration option (SID under investigation) [4].

The phase III, open-label, randomized, international, HannaH study (NCT00950300) compared the pharmacokinetics (PK), efficacy, and safety of s.c. and i.v. trastuzumab in the neoadjuvant/adjuvant setting. s.c. trastuzumab was shown to be noninferior to i.v. with regard to the co-primary end points, serum trough concentration (C_{trough}) and pathologic complete response (pCR) [5]. The s.c. and i.v. safety profiles were, in general, similar, with comparable distributions and types of adverse events (AEs; including grade 3–5), although a numerically higher proportion of serious AEs (SAEs) was reported with s.c. [5, 6]. Anti-drug antibody (ADA) rates were higher with s.c. [5, 7], but anti-trastuzumab or r-HuPH20 ADAs did not affect C_{trough} pre-dose cycle 8, pCR, or administration-related reactions (ARRs) [5, 7]; neutralizing antibodies (nAbs) against trastuzumab were detected during the treatment or treatment-free follow-up phases in both the s.c. and i.v. groups [7].

s.c. and i.v. trastuzumab were also compared in the international, multicenter, open-label, randomized PrefHer study (NCT01401166). PrefHer demonstrated that patients with HER2-positive early breast cancer preferred s.c. over i.v., because it saved time and caused less pain/discomfort/side-effects [8–10]. s.c. was well tolerated, with no new safety signals compared with the known profile of i.v. [9, 10]. The results of HannaH and PrefHer demonstrated that s.c. trastuzumab is an efficacious and well tolerated treatment and the preferred option for patients and health care professionals [5, 8–10].

We now report updated safety data, along with efficacy data [event-free survival (EFS)] from HannaH after a median follow-up of ∼20 months. Specifically, exploratory analyses examined the potential correlation between PK and body weight in terms of safety and pCR with the fixed dose of s.c. trastuzumab. The relationships between ADAs and PK, pCR, and ARRs were also examined.

patients and methods

study design and treatment

The study design and treatment schedule for the HannaH study have been reported previously [5]. Briefly, patients with HER2-positive, operable, locally advanced, or inflammatory breast cancer were randomized to eight cycles of neoadjuvant docetaxel, fluorouracil, epirubicin, and cyclophosphamide administered concurrently with 3-weekly trastuzumab given either s.c. (fixed dose of 600 mg by HHS, no loading dose) or i.v. (8 mg/kg loading dose and 6 mg/kg maintenance dose). Following surgery, patients continued to receive up to 1 year of trastuzumab monotherapy, with the same formulation as presurgery. The co-primary end points were C_{trough}, at pre-dose cycle 8 before surgery and pCR. Secondary objectives included safety and tolerability, PK profile, immunogenicity, and EFS. Analyses were carried out earlier than at the originally planned 2 years of follow-up, as part of regulatory submission procedures.

The study was carried out in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and all patients provided written informed consent. Approval for the protocol and any accompanying material provided to the patient was obtained from independent ethics committees at participating institutions.

efficacy

pCR was defined as the absence of invasive neoplastic cells of the primary tumor in the breast after surgery. EFS was defined as the time from randomization to the date of disease progression (local, regional, distant, or contralateral), recurrence, or death of any cause. At the time of clinical cutoff EFS was still considered immature and median follow-up was limited.

pharmacokinetics

The primary pharmacokinetic variable was the observed trastuzumab C_{trough} at pre-dose cycle 8 (end of cycle 7). The observed C_{max}, T_{max}, and AUC_{21 days} following the dose at cycle 7 and cycle 12, as well as observed and predicted C_{trough} at pre-dose cycle 8 and cycle 13 (i.e. the C_{trough} following the cycle 7 dose or cycle 12 dose) were analyzed according the treatment group. The AUC values at cycle 7 and cycle 12 were calculated from trastuzumab concentration–time profiles using standard noncompartmental pharmacokinetic methods and the computer program WinNonlin Enterprise, Version 5.2.1 (Pharsight Corporation; Cary, NC).

immunogenicity

Samples for immunogenicity assessments (ADA and nAb) were collected at baseline, pre-dose on day 1 of cycles 2, 5 (presurgery), 13, and 18 (postsurgery), and following the last trastuzumab dose (months 3, 6, 12, 18, and 24) as previously described [7].

safety

Safety analyses were conducted on the safety population (all patients who received ≥1 dose of study drug). AEs and SAEs were graded and reported according to National Cancer Institute Common Toxicity Criteria (version 3.0), International Conference on Harmonisation E2A functional classification, and New York Heart Association criteria, as previously described [5].

statistical analysis

Primary PK and efficacy analyses were carried out in the per-protocol populations (all randomized patients without any major protocol violation). Correlation analyses of pCR and safety (SAEs and grade ≥3 AEs) versus body weight and the PK variables C_{trough} and AUC investigated the impact of these covariates on the selected efficacy and safety variables. Exploratory analyses of safety compared to PK included median AUC of cycles 7 and 12, while efficacy analyses of pCR versus PK comprised C_{trough} at pre-dose cycle 8, and body weight. The relationship between ARRs and occurrence of ADAs was investigated.

results

patients

Baseline characteristics were well balanced across the treatment groups [efficacy per-protocol (EPP) population] [5]. At data
cut-off for this analysis (9 July 2012), 512 patients had completed treatment [257 (86.0%) and 255 (85.9%) in the i.v. and s.c. groups, respectively].

**median follow-up**

At the time of this analysis, the median duration of follow-up was 19.7 months (range 1.0–31.3 months) in the i.v. and 20.4 months (0.3–31.9) in the s.c. group.

**PK profile (observed)**

The median trastuzumab \( C_{\text{trough}} \) concentrations (pre-dose cycle 8) for patients with a pCR response compared with those without a pCR response was similar in the i.v. group (50.3 and 49.6 µg/ml, respectively), with a slightly higher value in the s.c. group (75.1 versus 67.4 µg/ml, respectively). The median observed \( C_{\text{trough}} \) level at the end of cycle 7 (pre-dose cycle 8) was higher in the s.c. group (supplementary Table S1, available at *Annals of Oncology* online), while the median \( C_{\text{max}} \) following the dose at cycle 7 was ~40% higher in the i.v. group (198 µg/ml) when compared with the s.c. group (141 µg/ml). This was consistent with the median \( T_{\text{max}} \) for the s.c. group of ~3 days, due to prolonged absorption with the s.c. route, which resulted in the lower \( C_{\text{max}} \) following s.c. administration. The geometric mean ratio of the observed \( C_{\text{trough}} \) values (\( C_{\text{trough, s.c.}} / C_{\text{trough, i.v.}} \)) at pre-dose cycle 8 was consistent with pre-dose cycle 13 values. Overall PK exposure as reflected by AUC was comparable between the two treatment groups (supplementary Table S1, available at *Annals of Oncology* online).

**safety overview**

The total number of AEs was generally comparable between the two groups and in the neoadjuvant and adjuvant phases (Table 1), and the majority of the commonly reported AEs (alopecia, nausea, diarrhea, fatigue, and asthenia) were similar between treatment groups, with <5% difference (supplementary Table S2, available at *Annals of Oncology* online).

The proportion of patients experiencing a grade ≥3 AE was comparable in both groups, and the majority of AEs [92% (2835/3096) in the i.v. group versus 92% (2973/3222) in the s.c. group] were grade 1 or 2. Grade ≥3 AEs were balanced between groups in the neoadjuvant and adjuvant phases. More patients in the s.c. group than in the i.v. group experienced AEs that led to withdrawal from treatment (Table 1; supplementary Table S3, available at *Annals of Oncology* online). In contrast to the i.v. group, the majority of AEs leading to withdrawal in the s.c. group were grade 1 or 2 [61% (11/18) versus 50% (4/8) in the i.v. group]. Sixteen patients in the i.v. group and 11 patients in the s.c. group died following disease progression (during the neoadjuvant phase) or recurrence (during the adjuvant or follow-up phase); two patients in the i.v. group and four patients in the s.c. group died as the result of an AE.

Cardiac disorders contributed most to the imbalance in withdrawal from study treatment between groups [1.7% (5/298) in the i.v. group versus 3.0% (9/297) in the s.c. group]. The majority of cardiac AEs were grade 1 or 2 (94.2% of events in the i.v. group versus 90.2% in the s.c. group), and there was no imbalance in incidence between groups. The number of significant left ventricular ejection fraction decreases (a drop of ≥10% points to a value of <50%) was similar in each group.

The incidence of ARRs in the i.v. group was 37.2% (111/298) and 47.8% (142/297) in the s.c. group; the difference was primarily driven by disorders of the skin and s.c. tissue, and by the respiratory, thoracic, and mediastinal systems. The number of grade ≥3 ARRs was balanced between the i.v. (6/298) and s.c. (5/297) groups, while most ARRs were grade 1 or 2 (97.0% in the i.v. group versus 97.9% in the s.c. group). The majority occurred in the neoadjuvant phase (32.6% versus 38.4%) and no grade 4 or 5 ARRs were reported in either treatment group.

**efficacy**

At clinical cutoff, 43 patients (16.3%) in the i.v. group and 41 (15.8%) in the s.c. group had experienced an event, with an unstratified hazard ratio (HR) of 0.97 [95% confidence interval (CI) 0.63–1.49] in the EPP population. Event-free rates 1-year postrandomization were 95% in both groups. In the intent-to-treat population, 61 patients (20.5%) in the i.v. group and 53 patients (18.0%) in s.c. group experienced events (HR 0.88; 95% CI 0.61–1.27). Event-free rates 1-year postrandomization were 90% and 92% in the i.v. and s.c. groups, respectively.

**exploratory analyses**

**safety overview.** Infections contributed most to the imbalance in reported SAEs, comprising almost half of the overall differences reported. The imbalance in SAEs and grade ≥3 AE infection rates was driven by the number of events reported during the adjuvant phase (supplementary Table S4, available at *Annals of Oncology* online).

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**Table 1. Safety profile (safety population)**

<table>
<thead>
<tr>
<th>(n = 298)</th>
<th>(n = 297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 adverse events (any grade)</td>
<td>282 (94.6%)</td>
</tr>
<tr>
<td>Neoadjuvant phase</td>
<td>275 (92.3%)</td>
</tr>
<tr>
<td>Adjuvant phase</td>
<td>201 (67.4%)</td>
</tr>
<tr>
<td>Patients with ≥1 severe adverse events (grade 3–5)</td>
<td>156 (52.3%)</td>
</tr>
<tr>
<td>Neoadjuvant phase</td>
<td>146 (49.0%)</td>
</tr>
<tr>
<td>Adjuvant phase</td>
<td>31 (10.4%)</td>
</tr>
<tr>
<td>Patients with ≥1 serious adverse events</td>
<td>42 (14.1%)</td>
</tr>
<tr>
<td>Neoadjuvant phase</td>
<td>30 (10.1%)</td>
</tr>
<tr>
<td>Adjuvant phase</td>
<td>10 (3.4%)</td>
</tr>
<tr>
<td>Patients with adverse events leading to withdrawal of study treatment</td>
<td>8 (2.7%)</td>
</tr>
<tr>
<td>Neoadjuvant phase</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Adjuvant phase</td>
<td>4 (1.3%)</td>
</tr>
<tr>
<td>Patients with adverse events leading to death</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Neoadjuvant phase</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Adjuvant phase</td>
<td>0</td>
</tr>
<tr>
<td>Treatment follow-up phase</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

i.v., intravenous; s.c., subcutaneous.
Online), with postoperative wound infection representing the most frequent type.

effect of body weight on PK. Body weight influenced AUC\textsubscript{0-21} days to differing extents in s.c.- and i.v.-treated patients. Body weight-adjusted dosing for the i.v. formulation resulted in lower PK exposures in lower quartile body weight patients (<59 kg) versus the higher body weight patients (≥79 kg) (supplementary Table S5, available at Annals of Oncology online). In higher body weight patients, exposure in the fixed-dose s.c. group was comparable with that in the i.v. group. Lower body weight patients had higher PK exposure when treated with s.c. trastuzumab (supplementary Table S5, available at Annals of Oncology online).

effect of exposure on pCR. Differences in pCR rates were compared and, when presented by quartiles of body weight distribution, pCR rates were higher for s.c. compared with i.v. across all but one of the body weight quartiles (supplementary Table S6, available at Annals of Oncology online). Patients ≥79 kg had similar pCR rates across treatment groups, while there was a noticeable difference in pCR rates between groups for patients in the lowest body weight quartile.

To further investigate the potential relationship between pCR and C\textsubscript{trough} at pre-dose cycle 8, multiple logistic regression analyses of pCR were carried out with C\textsubscript{trough}, body weight, treatment group, and all interactions with treatment as covariates. None of the parameters impacted pCR rates and the estimated odds ratios were similar in each body weight quartile with increasing C\textsubscript{trough} at pre-dose cycle 8 values (Figure 1).

effect of exposure on safety profile. Rates of SAEs and grade ≥3 AEs were assessed by quartiles of body weights and AUC values. The frequency of SAEs was higher in the s.c. group, and this was reflected across the different quartiles for AUC value and body weight (supplementary Table S7, available at Annals of Oncology online). There was no indication or pattern suggestive of an increase in grade ≥3 AE rates (supplementary Table S8, available at Annals of Oncology online) with increasing AUC. Similarly, there was no increase of SAE rates or grade ≥3 AE rates with decreasing body weight in the s.c. group receiving a fixed dose and experiencing a higher PK exposure.

incidence of SAEs and grade ≥3 AEs in patients with very low body weights. Overall, the types of SAEs observed in very low body weight patients [≤25th percentile (<59 kg) and <10th percentile (<51 kg)] were consistent with those observed in the overall population (supplementary Table S9, available at Annals of Oncology online). SAE and grade ≥3 AE rates were comparable between treatment groups.

effect of ADAs on PK, efficacy, and safety. Overall trastuzumab ADA rates were 7.1% (21/296) with i.v. treatment and 14.6% (43/295) with s.c. treatment. Trastuzumab nAbs were detected in postbaseline (treatment-free) samples from one patient in the i.v. group and two patients in the s.c. group. The rate of rHuPH20 ADAs in the s.c. group was 16.3% (48/295) and rHuPH20 nAbs were not detected in any of the patients who received s.c.

Trastuzumab concentrations at pre-dose cycle 8 and cycle 13 were analyzed based on ADA results. Comparisons across cycles of treatment and trastuzumab formulation (i.v. versus s.c.) indicated that PK was not affected by the detection of anti-trastuzumab or rHuPH20 antibodies.

There was no association between the higher incidence of anti-trastuzumab antibody-positivity post-baseline in the s.c. group and reduced pCR. In fact, pCR rates were numerically lower for patients who were negative for anti-rHuPH20 antibodies [40.2%...
(96/239) compared with patients who were positive for anti-rHuPH20 antibodies [50.0% (24/48)]. Therefore, efficacy did not seem to be adversely affected by anti-rHuPH20 status.

Anti-trastuzumab ADAs did not appear to be associated with increased ARRs in either the i.v. or s.c. groups. In the i.v. group, 38.1% (8/21) of patients with ADA-positivity developed any ARR during treatment versus 38.0% (97/255) patients with ADA-negative results. This incidence was similar in the s.c. group, where 41.9% (18/43) of patients with ADA-positivity developed any ARR during treatment compared with 48.9% (115/235) patients with ADA-negative results.

discussion

HannaH, the pivotal clinical phase III study to evaluate s.c. trastuzumab, demonstrated that $C_{\text{trough}}$ before surgery and pCR were noninferior to standard i.v. administration, with a similar safety profile [5]. The present updated results, obtained with median follow-up of ~20 months, addressed several important questions regarding s.c. trastuzumab. In particular, the potential impact of administering a fixed dose, such as ‘under-’ or ‘over-dosing’ of patients with extremes of body weight, was investigated and, as previously reported [11], was shown not to alter efficacy or safety when compared with the standard i.v. formulation.

Although fixed dosing led to a higher exposure in low body weight patients treated with s.c. trastuzumab, exploratory analyses did not identify any clinically meaningful association between the incidence of SAEs or grade $\geq$ 3 AEs and exposure or body weight. Moreover, AE rates in very low body weight patients were consistent with those in the overall population for the s.c. group, providing further evidence that there is no increased safety risk in low body weight patients from the use of a fixed dose of s.c. trastuzumab. Serum trastuzumab exposure was comparable or higher between the i.v. and s.c. groups in the neoadjuvant phase and adjuvant phase, respectively.

The overall safety profile was consistent with that previously reported for the new s.c. formulation, and the known safety profile of i.v. trastuzumab in early breast cancer [12]. A slightly higher incidence of SAEs, serious infections, AEs leading to death, cardiac SAEs, and AEs leading to treatment withdrawal was observed with s.c. trastuzumab. However, these differences were comparable with the original analysis [5, 6], were small, and were often based on rare events, with no observable pattern in the SAEs reported. Thus, differences may be due, at least in part, to chance or reporting bias in this open-label study. In agreement with HannaH, the PrefHer study reported that s.c. trastuzumab was well tolerated, with no new safety signals [9, 10], and the safety profile of the s.c. formulation will be further investigated in the large, international phase IIIb SafeHER study (NCT01566721) [13].

Available data on ARRs did not indicate the emergence of a clinically significant immune response associated with the presence of anti-trastuzumab or anti-rHuPH20 antibodies. Injections of s.c. trastuzumab were generally well tolerated and, although more ARRs were reported in the s.c. group, these were manageable, not clinically significant, and consistent with previous analyses [5]. The occurrence of anti-trastuzumab or anti-rHuPH20 antibodies did not appear to have any clinical consequences with respect to efficacy, safety, or PK.

EFS results were comparable across the i.v. and s.c. groups, but follow-up was limited. Results of efficacy assessments based on pCR rates were robust and consistent across populations analyzed. Despite higher mean $C_{\text{trough}}$ values in the s.c. compared with the i.v. group, no relationship was found between $C_{\text{trough}}$ levels and pCR. Indeed, in higher body weight patients who receive a relatively lower exposure with fixed-dose s.c. trastuzumab compared with the weight-based i.v. dosing, similar pCR rates were demonstrated irrespective of the trastuzumab formulation.

The benefits of s.c. administration include improved patient convenience, increased patient preference and compliance, reduced pharmacy preparation times, and optimization of medical resources [10, 14, 15].

Limitations of the current analyses of secondary variables include the limited number of events for the time-to-events analyses, and the small number of ADA-positive patients.

In conclusion, in agreement with previously reported data from HannaH, the present analysis demonstrates that the overall safety profile of s.c. trastuzumab (including cardiac safety [5, 6]) is similar to the known safety profile of the approved i.v. formulation [5]. Overall, data from PK, efficacy, and safety outcomes are consistent with the well-established benefit-risk ratio of trastuzumab in the treatment of HER2-positive breast cancer and support the use of the s.c. formulation.

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disclosure

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references

Neoadjuvant treatment with docetaxel plus lapatinib, trastuzumab, or both followed by an anthracycline-based chemotherapy in HER2-positive breast cancer: results of the randomised phase II EORTC 10054 study

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Background: Neoadjuvant trials conducted using a double HER2 blockade with lapatinib and trastuzumab, combined with different paclitaxel-containing chemotherapy regimens, have shown high pathological complete response (pCR)