14. Thor AD, Edgerton SM, Jones FE. Subcellular localization of the HER4 intracellular domain, 4ICD, identifies distinct prognostic outcomes for breast cancer patients. Am J Pathol 2009; 175: 1802–1809.
15. Naresh A, Long W, Vidal GA et al. The ERBB4/HER4 intracellular domain 4ICD is a BH3-only protein promoting apoptosis of breast cancer cells. Cancer Res 2006; 66: 6412–6420.
16. Eralp Y, Derin D, Ozluk Y et al. MAPK overexpression is associated with anthracycline resistance and increased risk for recurrence in patients with triple-negative breast cancer. Ann Oncol 2008; 19: 669–674.
17. Ellis MJ, Lin L, Crowder R et al. Phosphatidyl-inositol-3-kinase alpha catalytic subunit mutation and response to neoadjuvant endocrine therapy for estrogen receptor positive breast cancer. Breast Cancer Res Treat 2010; 119: 379–390.
18. Ginestier C, Hur MH, Charafe-Jauffret E et al. ALDH1 is a marker of normal and malignant human mammary stem cells and a predictor of poor clinical outcome. Cell Stem Cell 2007; 1: 555–567.
19. Fu P, Ibusuki M, Yamamoto Y et al. Insulin-like growth factor-1 receptor gene expression is associated with survival in breast cancer: a comprehensive analysis of gene copy number, mRNA and protein expression. Breast Cancer Res Treat 2011; 130: 307–317.
20. Derin D, Eralp Y, Ozluk Y et al. Lower level of MAPK expression is associated with anthracycline resistance and decreased survival in patients with hormone receptor negative breast cancer. Cancer Invest 2008; 26: 671–679.
21. Aleskandarany MA, Rakha EA, Ahmed MA et al. Clinicopathologic and molecular significance of phospho-Akt expression in early invasive breast cancer. Breast Cancer Res Treat 2011; 127: 407–416.

Annals of Oncology 25: 1979–1987, 2014
doi:10.1093/annonc/mdu364
Published online 28 July 2014

Patients' preferences for subcutaneous trastuzumab versus conventional intravenous infusion for the adjuvant treatment of HER2-positive early breast cancer: final analysis of 488 patients in the international, randomized, two-cohort PrefHer study

X. Pivot[1]*, J. Gligorov[2,3], V. Müller[4], G. Curigliano[5], A. Knoop[6], S. Verma[7], V. Jenkins[8], N. Scotto[9], S. Osborne[9] & L. Fallowfield[8] on behalf of the PrefHer Study Group

[1]Department of Medical Oncology, University Hospital Jean Minjoz, Besançon; [2]Medical Oncology Department, APHP Hôpital Tenon, Paris; [3]UPMC, Institut Universitaire de Cancérologie, Paris, France; [4]Department of Gynecology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [5]Early Drug Development for Innovative Therapies Division, European Institute of Oncology, Milan, Italy; [6]Department of Oncology, Copenhagen University Hospital, Copenhagen, Denmark; [7]Division of Medical Oncology, Sunnybrook Odette Cancer Centre, Toronto, ON, Canada; [8]Sussex Health Outcomes Research & Education in Cancer (SHORE-C), Brighton and Sussex Medical School, University of Sussex, Falmer, UK; [9]Global Medical Affairs, F. Hoffmann-La Roche Ltd, Basel, Switzerland

Received 10 May 2014; revised 16 July 2014; accepted 24 July 2014

Background: Patients with HER2-positive early breast cancer (EBC) preferred subcutaneous (s.c.) trastuzumab, delivered via single-use injection device (SID), over the intravenous (i.v.) formulation (Cohort 1 of the PrefHer study: NCT01401166). Here, we report patient preference, healthcare professional satisfaction, and safety data pooled from Cohort 1 and also Cohort 2, where s.c. trastuzumab was delivered via hand-held syringe.

Patients and methods: Patients were randomized to receive four adjuvant cycles of 600 mg fixed-dose s.c. trastuzumab followed by four cycles of standard i.v. trastuzumab, or vice versa. The primary endpoint was overall preference proportions for s.c. or i.v., assessed by patient interviews in the evaluable ITT population.

Results: A total of 245 patients were randomized to receive s.c. followed by i.v. and 243 received i.v. followed by s.c. (evaluable ITT populations: 235 and 232 patients, respectively). s.c. was preferred by 415/467 [88.9%; 95% confidence interval (CI) 85.7–91.6; $P < 0.0001$; two-sided test against null hypothesis of 65% s.c. preference]; 45/467 preferred i.v. (9.6%; 95% CI 7–13); 7/467 indicated no preference (1.5%; 95% CI 1–3). Clinician-reported adverse events occurred in 292/479 (61.0%) and 245/478 (51.3%) patients during the pooled s.c. and i.v. periods, respectively ($P < 0.05$; $2 \times 2\ \chi^2$); 16 patients (3.3%) in each period experienced grade 3 events; none were grade 4/5.

*Correspondence to: Prof. Xavier Pivot, Department of Medical Oncology, University Hospital Jean Minjoz, 1 Boulevard Fleming, Besançon Cedex 03, 25030 France. Tel: +33-381-669-212; Fax: +33-381-668-858; E-mail: xavier.pivot@univ-fcomte.fr

Conclusions: PrefHer revealed compelling and consistent patient preferences for s.c. over i.v. trastuzumab, regardless of SID or hand-held syringe delivery. s.c. was well tolerated and safety was consistent with previous reports, including the HannaH study (NCT00950300). No new safety signals were identified compared with the known i.v. profile in EBC. PrefHer and HannaH confirm that s.c. trastuzumab is a validated and preferred option over i.v. for improving patients' care in HER2-positive breast cancer.

Clinicaltrials.gov registration number: NCT01401166.

Key words: breast cancer, HER2/neu, patient preference, subcutaneous, trastuzumab

introduction

Trastuzumab-containing regimens are standard of care for HER2-positive early breast cancer (EBC) and metastatic breast cancer (MBC) [1–3]. A 600 mg fixed-dose manual injection of subcutaneous (s.c.) trastuzumab (Herceptin® SC, F. Hoffmann-La Roche Ltd, Basel, Switzerland) given via hand-held syringe is approved by the European Medicines Agency for EBC and MBC as an alternative to conventional intravenous (i.v.) infusion, based on noninferiority of trough serum concentration (geometric mean ratio of 1.33) and pathologic complete response (40.7% and 45.4% in the i.v. and s.c. groups, respectively) in the phase III HannaH study (NCT00950300) [4]. An s.c. single-use injection device (SID), which automatically delivers a pre-inserted s.c. dose via a button press when attached to the thigh, has comparable pharmacokinetics and safety to the hand-held syringe [5].

Intuitively, s.c. trastuzumab should be more convenient for patients as administration requires only 2–5 min [6]. Objectively, reductions in patients' infusion chair time, healthcare professionals' time, and other hospital resources have been demonstrated [7, 8]. The international, open-label, randomized, PrefHer study (NCT01401166) examined patients' preferences in the adjuvant breast cancer setting for i.v. or s.c. delivery via two cohorts using both methods of s.c. trastuzumab administration (SID or hand-held syringe) [9]. We present additional and final results of patient preferences in the overall study population (data pooled from both cohorts).

methods

patients

Patient eligibility criteria have been described previously [9] and are available in the supplementary material at *Annals of Oncology* online.

study design

After surgery and completion of (neo)adjuvant chemotherapy, patients were randomized to receive four adjuvant cycles of s.c. trastuzumab (600 mg fixed dose injected into the thigh over ~5 min) every 3 weeks followed by four cycles of i.v. (8 mg/kg loading dose if the patient was randomized to receive i.v. trastuzumab first, 6 mg/kg maintenance doses) every 3 weeks or vice versa (the crossover period, which was assessed in this report) as part of their standard trastuzumab [9]. Stratification was by *de novo* and non-*de novo* trastuzumab groups. Patients received s.c. trastuzumab via the SID in Cohort 1 and the hand-held syringe in Cohort 2. Following the crossover period, patients received i.v. trastuzumab in Cohort 1 (unless participating in SID self-administration) and s.c. trastuzumab via hand-held syringe in Cohort 2. The primary endpoint was the proportion of patients indicating an overall preference for s.c. or i.v. in each cohort, assessed by two study-specific telephone patient interviews (PINTs): one before randomization and one after the crossover period. PINTs were conducted by experienced telephone interviewers and were stringently quality-controlled to ensure impartial questioning. The first interview (PINT1) probed factors that could potentially influence preferences, such as previous experiences with drug delivery methods, needle phobias, and expected preferences for s.c. or i.v. trastuzumab. The second interview (PINT2) probed patients' experiences with each administration method on-study, final preference, strength of the preference, and reasons for it. Factors influencing preference, strength of the preference, and reasons for it were exploratory endpoints. Patients in the SID cohort with ≥2 cycles remaining after crossover had the option to self-administer the SID, their satisfaction being assessed by questionnaire after first and last self-administrations as an exploratory endpoint. Secondary endpoints were safety and tolerability (assessed using standard methods [10–12]), event-free survival, immunogenicity (anti-trastuzumab and anti-recombinant human hyaluronidase [rHuPH20] antibodies in blood samples, taken at baseline and pre-dose cycle 5; assessed due to inclusion of rHuPH20 in the s.c. formulation and the potential for Langerhans cell-mediated immune reactions with s.c. injection) in the SID cohort, healthcare professional satisfaction (assessed by responses of gynecologists, oncologists, oncology/specialist chemotherapy nurses, and other healthcare professionals to the questionnaire question, 'All things considered with which method of administration were you most satisfied?' after the crossover period), and healthcare professional-perceived time savings with s.c. trastuzumab, also assessed by questionnaire.

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

statistical analyses

Preference for s.c. was compared in a nonprotocol-specified analysis with a two-sided test against a null hypothesis value of 65% [9]. Each cohort was powered independently. Factors potentially influencing preference were assessed in terms of their effect on the primary endpoint using logistic regression (forward selection by stepwise regression with α 0.05) in an exploratory manner.

Differences in adverse event (AE) rates were assessed using a 2×2 χ^2 test.

Statistical analyses were carried out with SAS (version 9.1.3).

results

patients

From 27 October 2011 to 3 December 2012, 488 patients were randomized (Figure 1). The safety population included 483 patients (five randomized patients did not receive study treatment): 243 s.c. → i.v. and 240 i.v. → s.c. Twenty-four treated

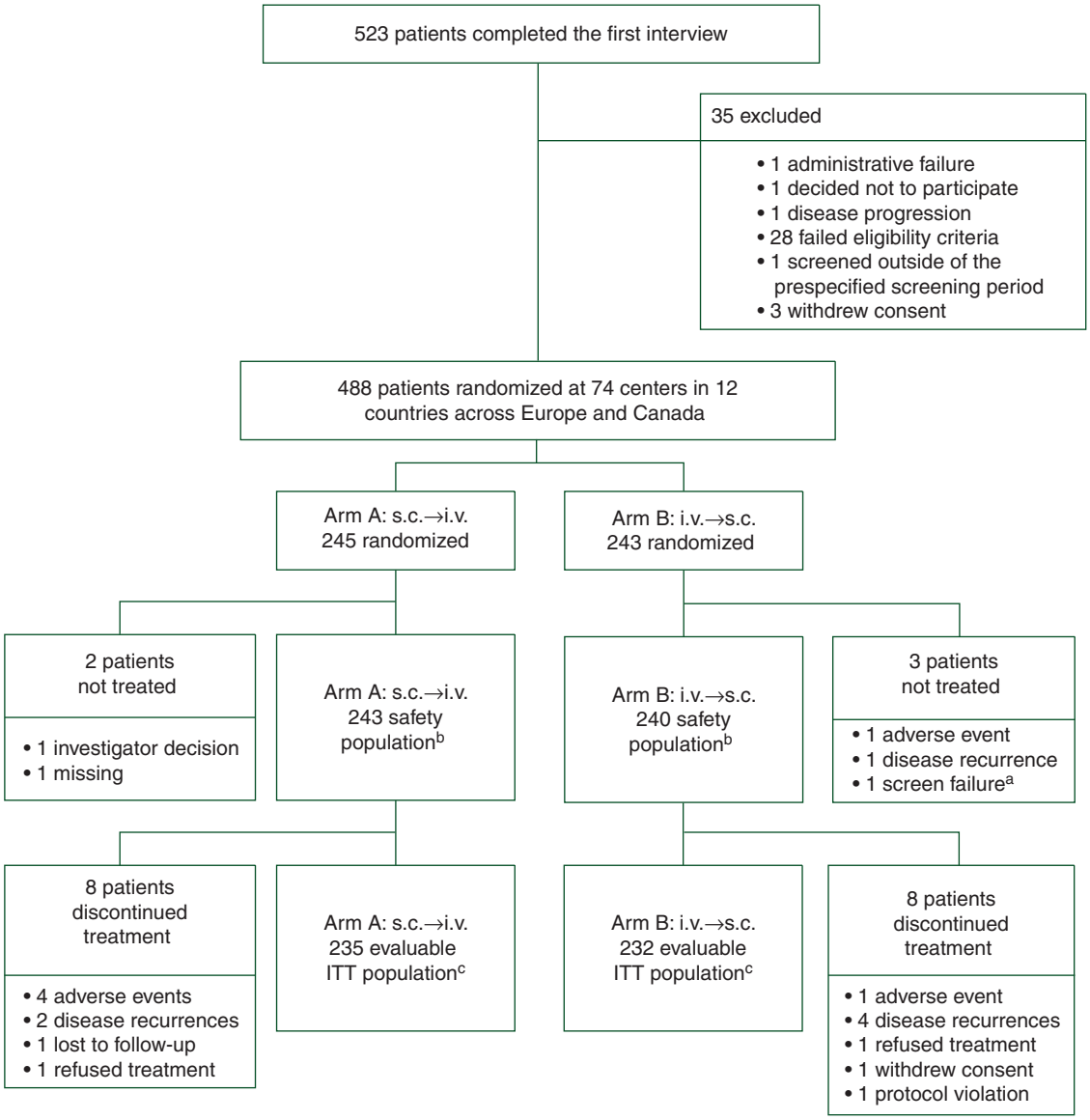

Figure 1. Trial profile. [a]Patient was screened and randomized but was later found to have a left ventricular ejection fraction of 53%. No treatment was given on-trial. [b]Patients who received at least one dose of study treatment. [c]Patients who received at least one dose of s.c. trastuzumab and i.v. trastuzumab and completed PINT1 and the primary endpoint question in PINT2. ITT, intention-to-treat; i.v., intravenous; PINT, patient interview; s.c., subcutaneous.

patients did not complete all eight trastuzumab cycles during crossover owing to disease recurrence (nine patients), AEs [grade 2 congestive heart failure (one patient), left ventricular dysfunction (five patients: two grade 1, three grade 3), grade 2 arthralgia (one patient), grade 3 generalized erythema (one patient)], refusal of treatment (three patients), withdrawal of consent (two patients), loss to follow-up (one patient), and protocol violation (one patient in the hand-held syringe cohort with lung metastases was erroneously randomized and was withdrawn after receiving one trastuzumab cycle). Of these patients, eight received s.c. and i.v. and completed the primary endpoint question in PINT2; therefore, they were included in the evaluable ITT population. The remaining 16 patients did not complete the primary endpoint question; therefore, the evaluable ITT population comprised 467 patients (235 patients s.c. → i.v. and 232 i.v. → s.c.). No data were missing as all evaluable ITT patients completed both PINTs.

Baseline patient demographics, tumor characteristics, and treatment history were balanced between study arms (Table 1).

patient preference

primary endpoint. At PINT2, 88.9% of patients (415/467) preferred s.c. [95% confidence interval (CI) 85.7–91.6; $P < 0.0001$, two-sided test against the null hypothesis of 65% s.c. preference], 9.6% (45/467, 95% CI 7.1–12.7) preferred i.v., and 1.5% (7/467, 95% CI 0.6–3.1) had no preference (Figure 2). Results were consistent in both study arms: s.c. → i.v. arm, 89.8% of patients (211/235, 95% CI 85.2–93.3) preferred s.c., 8.9% (21/235, 95% CI 5.6–13.3) preferred i.v., and 1.3% (3/235,

Table 1. Patient demographics, tumor characteristics, and treatment history (evaluable intention-to-treat population)

	Arm A s.c. → i.v. *n* = 235	Arm B i.v. → s.c. *n* = 232
Age, years[a]		
Median	53.0	52.0
(min–max)	(29–78)	(27–76)
Weight, kg		
Median	68.0	66.0
(min–max)	(35.0–120.0)	(41.0–131.8)
ECOG at screening, *n* (%)		
0	194 (82.6)	187 (80.6)
1	41 (17.4)	44 (19.0)
Not done	0	1 (0.4)
TNM classification at diagnosis, *n* (%)		
Primary tumor[b]		
T0–T2	208 (88.5)	195 (84.1)
T3–T4	22 (9.4)	37 (15.9)
Not assessable/unknown	5 (2.1)	0
Lymph node status, *n* (%)		
Negative	119 (50.6)	110 (47.4)
Positive	109 (46.4)	118 (50.9)
Not assessable/unknown	7 (3.0)	4 (1.7)
Trastuzumab before enrollment, *n* (%)		
De novo	47 (20.0)	47 (20.3)
Non-*de novo*	188 (80.0)	185 (79.7)
Previous treatment, *n* (%)		
Chemotherapy	234 (99.6)	232 (100)
Radiotherapy	145 (61.7)	141 (60.8)
Hormonal therapy	96 (40.9)	95 (40.9)
Lapatinib	0	2 (0.9)

All patients received prior surgery. Two hundred twenty-four patients (48.0%) received prior i.v. chemotherapy via cannula, 206 (44.1%) received prior i.v. chemotherapy via a venous access device, and 37 (7.9%) received prior i.v. chemotherapy via both methods.

[a]There were 331 patients who were younger than 60 years and 136 who were 60 years or older.

[b]Patients with T4 tumors received (neo)adjuvant chemotherapy and were eligible for the study.

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; i.v., intravenous; s.c., subcutaneous.

95% CI 0.3–3.7) had no preference; i.v. → s.c. arm, 87.9% of patients (204/232, 95% CI 83.0–91.8) preferred s.c., 10.3% (24/232, 95% CI 6.7–15.0) preferred i.v., and 1.7% (4/232, 95% CI 0.5–4.4) had no preference.

exploratory analysis: strength of preferences. Overall preference for s.c. was 'very strong' in 64.9% of patients (303/467; 95% CI 60.4–69.2), 'fairly strong' in 17.3% (81/467, 95% CI 14.0–21.1), and 'not very strong' in 6.6% (31/467, 95% CI 4.6–9.3). Overall preference for i.v. was 'very strong' in 5.1% of patients (24/467, 95% CI 3.3–7.6), 'fairly strong' in 2.1% (10/467, 95% CI 1.0–3.9), and 'not very strong' in 2.4% (11/467, 95% CI 1.2–4.2).

exploratory analysis: reasons for patients' preferences. The two main reasons that patients gave for preferring s.c. when asked in an open-ended question were that it saved time and that it resulted in less pain/discomfort/side effects (Table 2). When specifically asked about pain and bother from bruising or irritation to the injection site, patients reported that s.c. was the least painful [60.6% (283/467 patients) versus 17.3% for i.v. (81/467); 22.1% (103/467) reported no difference], and caused less bother from bruising [41.1% (192/467) versus 16.1% (75/467); 42.8% (200/467) reported no difference], or irritation to the injection site [33.0% (154/467) versus 14.6% (68/467); 52.5% (245/467) reported no difference].

predefined exploratory endpoint: factors influencing preference. There was a high preference by patients for s.c. trastuzumab regardless of whether they had received i.v. trastuzumab before enrollment (Figure 2).

Four terms were found to be significant and therefore kept in the final stepwise logistic regression model to select factors that potentially influence preference (supplementary Table S1, available at *Annals of Oncology* online): expected preferences given at PINT1 [odds ratio (OR) 2.98, 95% CI 1.51–5.88], weight (OR 0.41, 95% CI 0.17–0.97), needle phobia/anxiety (OR 0.31, 95% CI 0.14–0.68), and i.v. delivery type for prior chemotherapy (OR 2.31, 95% CI 1.21–4.41). However, these results should be interpreted with caution due to the low number of patients who expressed a preference for i.v. or expressed no preference.

Hypothetical preference from PINT1 was a factor that influenced final preferences. Of the patients who expressed a prior preference for s.c., 94.0% (203/216) expressed a final preference for s.c. (Table 3). Of the patients who expressed a prior preference for i.v. or expressed no prior preference, 84.5% (212/251) expressed a final preference for s.c.

Preference for s.c. was 91.5% (95% CI 87.4–94.6) for patients receiving i.v. trastuzumab by cannula (236/258 patients), 85.8% (95% CI 80.2–90.3) for those with a venous access device (175/204 patients), and 80.0% (95% CI 28.4–99.5) for those who received i.v. trastuzumab by both venous access methods (4/5 patients). Patients also preferred s.c. over i.v. regardless of their country (supplementary Table S2, available at *Annals of Oncology* online).

exploratory analysis: hypothetical preferred location and route of trastuzumab administration. Overall, 60.4% of patients (282/467, 95% CI 55.8–64.9) expressed a hypothetical preference to receive s.c. at home [65.7% in the SID cohort (155/236, 95% CI 59.2–71.7) and 55.0% in the hand-held syringe cohort (127/231, 95% CI 48.3–61.5)] when asked during PINT2 (supplementary Table S3, available at *Annals of Oncology* online).

secondary endpoint: healthcare professional satisfaction. Two hundred thirty-five healthcare professional questionnaires were completed. Responses indicated that most respondents were more satisfied with s.c. administration [77.0% (181/235), 95% CI 71.1–82.2] than with i.v. [3.0% (7/235), 95% CI 1.2–6.0]. The remaining 20.0% [(47/235), 95% CI, 15.1–25.7] indicated no preference for either route.

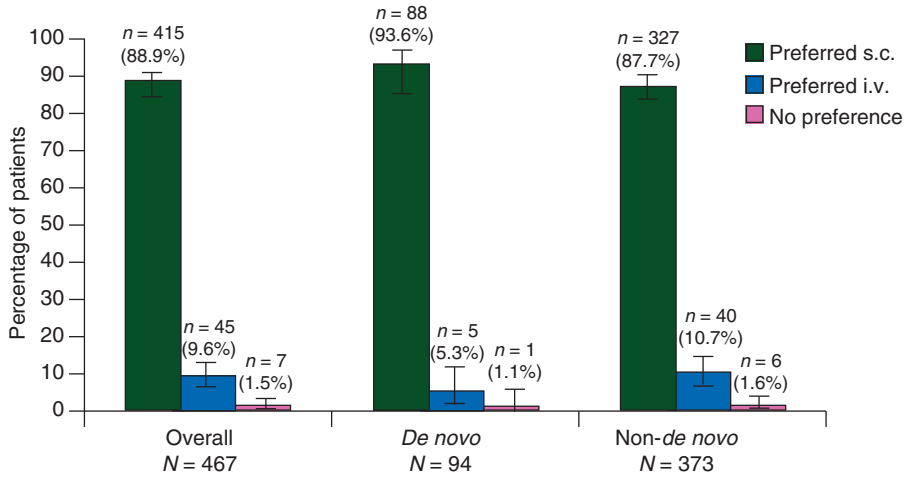

Figure 2. Patients' preferences (evaluable intention-to-treat population). Responses to the question 'All things considered, which method of administration did you prefer?' Error bars represent 95% confidence intervals. i.v., intravenous; s.c., subcutaneous.

Table 2. Primary reasons for patients' preferences (evaluable intention-to-treat population)

Reason category	Total, *n* (%)[a]	Example
s.c. preferred, *n* = 756 reasons given by 415 patients		
Time saving	375 (80.3)	'It does affect me being there so many hours. With this it was 'Hello' and 'Bye' without having to spend hours with patients'
Less pain/discomfort/side effects	160 (34.3)	'The s.c. method was a lot less painful to me and my bruises faded faster than in the case of the intravenous method'
Ease of administration	62 (13.3)	'Nurses can take care of many patients at the same time'
Convenience to patient	57 (12.2)	'Busy mum with four young children — want to get on with life'
Problems with i.v.	51 (10.9)	'No veins to be found as my veins are collapsing'
Less stress/anxiety	35 (7.5)	'i.v. reminds one of chemo and isn't very pleasant for the head'
Other	20 (4.3)	'Safer — less risk of infections'[b]
i.v. preferred, *n* = 64 reasons given by 45 patients		
Fewer reactions (less pain, bruising, irritation, etc.)	33 (7.1)	'Irritation due to the s.c.'
Other/don't know	10 (2.1)	'Had to have the port flushed through when attending for s.c. sessions, so would have been easier just to use it anyway'
Psychological	9 (1.9)	'When you have i.v., you arrive, settle yourself. You have about 30 minutes. You can discuss with the nurses and other patients. It's a feeling of being "at home."'
Perceived efficacy	6 (1.3)	'I'm not quite convinced that s.c. has the same effect as i.v.'[b]
Environment/staff	5 (1.1)	'One has to go there anyway and one can sit there with other women and exchange experience'
Ecological considerations	1 (0.2)	'Device is not environmentally sustainable. It is all thrown away after use'

Responses to the question 'What are the two main reasons for your preference?' were recorded verbatim by the interviewer. Four experienced researchers independently scrutinized the dataset and provided overarching themes or core categories for coding. When broad consensus about these had been reached, each researcher independently coded every patient's response; the researchers then reconciled codings with each other and determined if any thematic categories could reasonably be collapsed together or if a new category was required.

[a]Some patients gave only one reason or no reason. Percentages were calculated on a per-patient basis (*N* = 467).

[b]Statement based on patient preference and not reflective of clinical data.

i.v., intravenous; s.c., subcutaneous.

secondary endpoint: AE profile. The AE profile obtained during the crossover period at this interim safety analysis is shown in Table 4. Differences between rates in the pooled s.c. and i.v. periods were driven by grade 1 events occurring more frequently during the s.c. period. Influenza, dermatitis, syncope, hypertension, left ventricular dysfunction, and dyspnea were the most common grade 3 AEs [0.4% of patients (two) each]. No patients had a grade 4 or 5 AE. No serious AEs were considered

Table 3. Expected and actual preferences (evaluable intention-to-treat population)

	PINT1: preferred method of administration			
	i.v.	s.c.	No preference	Overall
	n = 46	*n* = 216	*n* = 205	*N* = 467
PINT2: preferred method of administration, *n* (%)				
i.v.	11 (23.9)	12 (5.6)	22 (10.7)	45 (9.6%)
s.c.	33 (71.7)	203 (94.0)	179 (87.3)	415 (88.9%)
No preference	2 (4.3)	1 (0.5)	4 (2.0)	7 (1.5%)
s.c. preferred (exact binomial)				
Estimated proportion	71.7	94.0	87.3	88.9
95% CI	56.5–84.0	89.9–96.8	82.0–91.5	85.7–91.6

CI, confidence interval; i.v., intravenous; PINT, patient interview; s.c., subcutaneous.

to be related to trastuzumab and each was resolved without sequelae. Twenty-four of 483 patients experienced cardiac events, but only two instances were recorded as grade 3 (both were left ventricular dysfunction). No cardiac events were reported as serious and there was one case of congestive heart failure (grade 2; resolved without sequelae).

secondary endpoint: immunogenicity. In the s.c. → i.v. and i.v. → s.c. arms, anti-trastuzumab antibody rates were 0% [0/114 evaluable patients (any patient with a pre-dose cycle 5 trastuzumab or rHuPH20 antibody result regardless of baseline result)] and 3.4% (4/119), respectively, and the anti-rHuPH20 antibody rates were 2.6% (3/115) and 7.6% (9/119), respectively (supplementary Table S4, available at *Annals of Oncology* online). No association between AEs and the presence of anti-trastuzumab or -rHuPH20 antibodies was observed (data not shown).

discussion

Final preference results from PrefHer showed that patients strongly preferred s.c. trastuzumab, regardless of SID or hand-held syringe delivery. These data provide an impetus for a change in practice regarding trastuzumab administration, and patients should be offered the choice of route. Patients should be provided with timely, accurate and easily understandable information regarding the available routes of administration, and with the evidence base accumulated showing the experiences and preference of patients who received both i.v. and s.c. Future trial designs (including in MBC) might use the methodology employed in PrefHer, where appropriate, with patient preferences and the reasons for them assessed as an essential part of the protocol.

Patients consistently gave 'time saving' as their main reason for s.c. preference [9, 13, 14], which was confirmed by quantitative data from a time-and-motion sub-study [7, 8]. The SID may save patients further time by potentially allowing self-administration at home: the location hypothetically preferred by almost two-thirds of the patients in the SID cohort.

s.c. trastuzumab was well tolerated and no new safety signals were identified compared with the known i.v. profile in EBC. Additional analyses of PrefHer have shown that the safety profile combined from both cohorts is not affected by switching from s.c. to i.v. or vice versa [15], further supporting a change for patients who prefer this method. As with HannaH [16], trastuzumab and rHuPH20 anti-drug antibody rates were low and there was no correlation with safety; however, results should be interpreted with caution as anti-trastuzumab antibody rates may have been underestimated due to the presence of trastuzumab in the serum affecting detection of anti-trastuzumab antibodies in the assay, and due to the fact that assessment was carried out after only four cycles of exposure. HannaH will assess immunogenicity up to 60 months post-treatment [17] and SafeHer will further assess immunogenicity with the SID [18].

Interpretation of safety analyses should also take into account the limitations of having a short period of time during which the events were recorded for this analysis (eight 3-weekly cycles). Future analyses will assess data from the continuation periods once all patients have completed follow-up.

The apparent discrepancy between increased clinician-reported AEs during the s.c. period and patients' reports of s.c. producing less pain, bruising, and irritation may have resulted from a more conservative approach to reporting due to inexperience with the s.c. formulation [4].

Healthcare professionals were more satisfied with s.c. regardless of administration method. The time-and-motion sub-study has shown that healthcare professional time and center costs may be substantially reduced using the SID or the hand-held syringe [7, 8], and that healthcare professional-perceived clinical management and efficiency was increased with either s.c. method, to the benefit of different stakeholders [8, 19]. Combined with the totality of the clinical and patient preference data, s.c. trastuzumab has been shown to provide benefits to both patients and healthcare systems.

In conclusion, PrefHer revealed compelling and consistent patient preference for s.c. trastuzumab, regardless of delivery method (SID or hand-held syringe). Healthcare professionals were also more satisfied with s.c. over i.v. administration and s.c. was well tolerated. Safety data, including immunogenicity, were consistent with previous reports and no new safety signals were identified compared with the known i.v. profile in EBC.

Table 4. Adverse event profile during the crossover period (four cycles of s.c. trastuzumab and four cycles of i.v. trastuzumab, safety population)

	s.c. period (all arms pooled) *n* = 479	i.v. period (all arms pooled) *n* = 478
Adverse events (all NCI-CTCAE grades), *n* (%)	292 (61.0)[a]	245 (51.3)[a]
Grade 1 (mild)	253 (52.8)	195 (40.8)
Grade 2 (moderate)	116 (24.2)	106 (22.2)
Grade 3 (severe)	16 (3.3)	16 (3.3)
Grade 4 (life-threatening)	0	0
Grade 5 (death)	0	0
Most frequent adverse events (≥5% of patients in the s.c., i.v., or crossover periods, all NCI-CTCAE grades), *n* (%)		
Arthralgia	24 (5.0)	27 (5.6)
Grade 1 (mild)	20 (4.2)	22 (4.6)
Grade 2 (moderate)	4 (0.8)	5 (1.0)
Asthenia	27 (5.6)	23 (4.8)
Grade 1 (mild)	15 (3.1)	18 (3.8)
Grade 2 (moderate)	12 (2.5)	5 (1.0)
Hot flush	23 (4.8)	16 (3.3)
Grade 1 (mild)	16 (3.3)	10 (2.1)
Grade 2 (moderate)	7 (1.5)	6 (1.3)
Fatigue	19 (4.0)	18 (3.8)
Grade 1 (mild)	13 (2.7)	12 (2.5)
Grade 2 (moderate)	6 (1.3)	6 (1.3)
Grade 3 (severe)	0	1 (0.2)
Nausea	25 (5.2)	14 (2.9)
Grade 1 (mild)	20 (4.2)	12 (2.5)
Grade 2 (moderate)	4 (0.8)	2 (0.4)
Grade 3 (severe)	0	0
Missing	1 (0.2)	0
Headache	20 (4.2)	16 (3.3)
Grade 1 (mild)	14 (2.9)	12 (2.5)
Grade 2 (moderate)	6 (1.3)	3 (0.6)
Grade 3 (severe)	0	1 (0.2)
Injection site pain	32 (6.7)	0
Grade 1 (mild)	28 (5.8)	0
Grade 2 (moderate)	4 (0.8)	0
Injection site reaction	30 (6.3)[b]	0
Grade 1 (mild)	29 (6.1)	0
Grade 2 (moderate)	4 (0.8)	0
Injection site erythema	27 (5.6)	0
Grade 1 (mild)	24 (5.0)	0
Grade 2 (moderate)	3 (0.6)	0
Diarrhea	16 (3.3)[c]	12 (2.5)
Grade 1 (mild)	12 (2.5)	10 (2.1)
Grade 2 (moderate)	5 (1.0)	2 (0.4)
Pain in extremity	18 (3.8)	7 (1.5)
Grade 1 (mild)	17 (3.5)	2 (0.4)
Grade 2 (moderate)	1 (0.2)	5 (1.0)
Serious adverse events (ICH E2A), *n* (%)[d]	4 (0.8)	4 (0.8)
Study drug discontinued due to adverse events, *n* (%)	5 (1.0)	6 (1.3)

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.
Patients could be counted in both the s.c. and i.v. period columns.
[a]$2 \times 2\ \chi^2$, $P < 0.05$.
[b]Three patients had both grade 1 (mild) and grade 2 (moderate) injection site reactions and so are counted once in each NCI-CTCAE grade and once overall.
[c]One patient had both grade 1 (mild) and grade 2 (moderate) diarrhea and so is counted once in each NCI-CTCAE grade and once overall.
[d]Breast expander infection, axilla abscess, benign breast adenoma, and hematoma (not at the injection site) during the s.c. period and wound infection, influenza, cholelithiasis, suture-related complication (post-laparotomy), and mental disorder during the i.v. period. All were reported in one patient each (0.2%), none were related to study treatment, and all resolved fully without sequelae.
ICH, International Conference on Harmonisation; i.v., intravenous; NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events; s.c., subcutaneous.

Based on data from HannaH and PrefHer, s.c. trastuzumab is the validated and preferred option over i.v. for improving patients' care in HER2-positive breast cancer.

acknowledgements

We thank the individuals who contributed to the design of the study instruments, the patients, their families, the nurses, the interviewers, and the investigators who participated in this study. We also thank Rebecca Elliot of Genentech, Inc. (South San Francisco, CA) for immunogenicity analyses. Support for third-party writing assistance for this manuscript, furnished by Daniel Clyde, PhD, was provided by F. Hoffmann-La Roche Ltd.

funding

This work was supported by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

disclosure

XP has held consultant/advisory roles for F. Hoffmann-La Roche Ltd, GlaxoSmithKline, and Teva, and has received honoraria from Sanofi-Aventis and Eisai. JG has held consultant/

advisory roles for F. Hoffmann-La Roche Ltd, Teva, and Eisai, and has received honoraria from F. Hoffmann-La Roche Ltd, GlaxoSmithKline, and Novartis. VM has held consultant/advisory roles for Amgen, Celgene, and F. Hoffmann-La Roche Ltd, and has received honoraria from Amgen, Celgene, Pierre-Fabre, F. Hoffmann-La Roche Ltd, and Janssen-Cilag. AK has held consultant/advisory roles for, and has received honoraria from, F. Hoffmann-La Roche Ltd. SV has held consultant/advisory roles for, and has received honoraria from, F. Hoffmann-La Roche Ltd, Novartis, and Amgen, and has received research funding from F. Hoffmann-La Roche Ltd and Sanofi-Aventis. NS is an employee of, and holds stocks in, F. Hoffmann-La Roche Ltd. SO is an employee of F. Hoffmann-La Roche Ltd. LF has held consultant/advisory roles for, and has received honoraria and research funding from, F. Hoffmann-La Roche Ltd. GC and VJ have no conflicts of interest to disclose.

references

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 2014. V3.2014. http://www.nccn.org/ (14 April 2014, date last accessed).
2. Senkus E, Kyriakides S, Penault-Llorca F et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24: vi7–vi23.
3. Goldhirsch A, Winer EP, Coates AS et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 2013; 24: 2206–2223.
4. Ismael G, Hegg R, Muehlbauer S et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I–III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. Lancet Oncol 2012; 13: 869–878.
5. Wynne C, Ellis-Pegler RB, Waaka DS et al. Comparative pharmacokinetics of subcutaneous trastuzumab administered via handheld syringe or proprietary single-use injection device in healthy males. Cancer Chemother Pharmacol 2013; 72: 1079–1087.
6. Herceptin 600 mg/5 ml solution for injection summary of product characteristics. Roche Products Limited. http://www.medicines.org.uk/emc/medicine/28179/SPC/Herceptin+600+mg+5+ml+Solution+for+Injection/ (25 March 2014, date last accessed).
7. De Cock E, Knoop A, Jakobsen EH et al. Manual injection of subcutaneous trastuzumab vs intravenous infusion for HER2-positive early breast cancer: a time-and-motion study. Eur J Cancer 2013; 49: S432. Abstract 1955.
8. Burcombe R, Chan S, Simcock R et al. Subcutaneous trastuzumab (Herceptin®): a UK time and motion study in comparison with intravenous formulation for the treatment of patients with HER2-positive early breast cancer. Adv Breast Cancer Res 2013; 2: 133–140.
9. Pivot X, Gligorov J, Müller V et al. Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study. Lancet Oncol 2013; 14: 962–970.
10. National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. 2009. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (31 January 2014, date last accessed).
11. The Criteria Committee for the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 9th edition. New York: Little, Brown and Company, 1994.
12. ICH Harmonised Tripartite Guideline. Clinical safety data management: definitions and standards for expedited reporting E2A. 1995.
13. Pivot X, Gligorov J, Müller V et al. Patient preference for subcutaneous trastuzumab via handheld syringe versus intravenous infusion in HER2-positive early breast cancer: cohort 2 of the PrefHer study; abstract P4-12-11. Cancer Res 2013; 73 (24 Suppl).
14. Fallowfield L, Jenkins V, Kilkerr J et al. Reasons for patients' preferences for subcutaneous or intravenous trastuzumab in the PrefHer study. Eur J Cancer 2013; 49: S385. Abstract 1759.
15. Gligorov J, Curigliano G, Müller V et al. Assessment of adverse events in patients switching between trastuzumab administration routes (subcutaneous to intravenous and intravenous to subcutaneous) in the PrefHer study. In: 9th European Breast Cancer Conference, Glasgow, Scotland, 2014. Abstract 229.
16. Hegg R, Pienkowski T, Chen S-C et al. Immunogenicity of trastuzumab intravenous and subcutaneous formulations in the Phase III HannaH study; abstract 273P. Ann Oncol 2012; 23: ix95–ix115.
17. A study to compare subcutaneous versus intravenous administration of herceptin (trastuzumab) in women with HER2-positive early breast cancer. Hoffmann-La Roche; http://clinicaltrials.gov/ct2/show/NCT00950300 (14 July 2014, date last accessed).
18. Gligorov J, Azim HA, Ataseven B et al. SafeHer: A study of assisted- and self-administered subcutaneous trastuzumab (H-SC) as adjuvant therapy in patients with early HER2-positive breast cancer (EBC). Ann Oncol 2012; 23: ix95–ix115. Abstract 315TiP.
19. De Cock E, Pan I, Sandoval M et al. Healthcare professionals' perceptions of the impact on clinical management of switching from the intravenous to the subcutaneous formulation of trastuzumab. In: 9th European Breast Cancer Conference, Glasgow, Scotland, 2014. Abstract 42.

appendix

Sussex Health Outcomes Research & Education in Cancer (SHORE-C) PrefHer study team

Lesley Fallowfield; Valerie Jenkins; Justine Kilkerr; Carolyn Langridge; Kathryn Monson.

PrefHer study investigators

Europe

Denmark. Erik Hugger Jakobsen (Vejle Sygehus)
Mette Holck Nielsen (Odense Universitetshospital)
Soeren Linnet (Regionshospitalet Herning)
Ann Knoop (Copenhagen University Hospital)

France. Xavier Pivot (University Hospital Jean Minjoz).
Herve Bonnefoi (Institut Bergonié)
Mireille Mousseau (Hôpital Albert Michallon)
Laurent Zelek (Hôpital Avicenne)
Hugues Bourgeois (Clinique Victor Hugo)
Claudia Plesse Lefeuvre (Centre Eugène Marquis)
Thomas Bachelot (Centre Léon Bérard)
Thierry Petit (Centre Paul Strauss)
Etienne Brain (Centre René Huguenin)
Christelle Levy (CRLCC-François Baclesse)
Joseph Gligorov (APHP Hôpital Tenon)

Germany. Doris Augustin (Donauisar Klinikum Deggendorf)
Heiko Graf (Klinikum Meiningen Klinik für Gynäkologie und Geburtshilfe)
Georg Heinrich (Schwerpunktpraxis Dr. med. Georg Heinrich)
Hendrik Kroening (Onkologische Gemeinschaftspraxis)
Sherko Kuemmel (Klinikum Essen-Mitte Ev. Huyssens-Stiftung/Knappschafts GmbH)

Volkmar Müller (University Medical Center Hamburg-Eppendorf)
Friedrich Overkamp (Praxis für Onkologie und Hämatologie)
Tjoung-Won Park-Simon (Medizinische Hochschule Hannover, Klinik für Frauenheilkunde und Geburtshilfe)
Marcus Schmidt (Uniklinik Mainz)
Lidia Perlova-Griff (Sankt Gertrauden-Krankenhaus Brustzentrum)
Christopher Wolf (Dres. Christopher Wolf und Alfred Wolf)

Italy. Marco Colleoni (IRCCS Istituto Europeo Di Oncologia (IEO))
Alberto Ballestrero (Uni Degli Studi Di Genova)
Antonio Bernardo (IRCCS Fondazione Maugeri)
Angela Stefania Ribecco (Azienda Sanitaria di Firenze–Ospedale Santa Maria Annunziata, SC Oncologia Medica)
Luca Gianni (Oncologia Medica, Ospedale San Raffaele)
Giuseppe Curigliano (European Institute of Oncology)

Poland. Elżbieta Brewczynska (Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology)
Jacek Jassem (Uniwersyteckie Centrum Kliniczne, Klinika Onkologii i Radioterapii)

Russia. Vadim Shirinkin (State Institute of Healthcare Orenburg Regional Clinical Oncology Dispensary)
Alexey Manikhas (City Oncology Dispensary)
Victoria Dvornichenko (Regional Oncology Hospital)
Mikhail Lichinitser (Blokhin Cancer Research Center)
Vladimir Semiglazov (NN Petrov Research Institute of Oncology)
Guzel Mukhametshina (Republican Clinical Oncologic Dispensary of Republic of Tatarstan)
Irina Bulavina (Sverdlovsk Regional Oncology Dispensary)

Spain. Enrique Espinosa Arranz (Hospital Universitario La Paz)
Francisco Carabantes Ocon (Hospital Regional Universitario Carlos Haya)
Guillermo López Vivanco (University Hospital Cruces, San Vicente de Barakaldo, Vizcaya)
Javier Salvador Bofill (Hospital Universitario Nuestra Señora de Valme)
Ignacio Porras Quintela (Hospital Universitario Reina Sofia)
Alfonso Sanchez Muñoz (Hospital Clínico Universitario Virgen de la Victoria)
Yolanda Fernández Pérez (Hospital Univ. Central de Asturias)
Javier Cassinello Espinosa (Hospital General Universitario de Guadalajara)
José Valero Alvarez (Complejo Hospitalario Zamora – Hospital Virgen de la Concha)
Rodrigo Lastra del Prado (Hospital General de San Jorge)
Luis De La Cruz Merino (Hospital Universitario Virgen Macarena)
José Manuel Pérez García (Hospital Quirón Barcelona)
Santos Enrech Frances (Hospital Universitario de Getafe)

Sweden. Per Edlund (Gävle Sjukhus)
Bengt Norberg (Länssjukhuset Ryhov)
Anna-Karin Wennstig (Länssjukhuset Sundsvall)
Pehr Lind (Mälarsjukhuset)

Switzerland. Nik Hauser (Kantonsspital Baden AG)
Christoph Tausch (Brustzentrum)

Turkey. Celalettin Camci (Gaziantep University Medical Faculty)
Fikret Arpaci (GATA)
Huseyin Abali (Adana Baskent University Hospital)
Ruchan Uslu (Ege University Medical Faculty)

United Kingdom. Saad Tahir (Broomfield Hospital)
Duncan Wheatley (Royal Cornwall Hospital)
Stephen Chan (Nottingham City Hospital)
Peter Barrett-Lee (Velindre Cancer Centre)
Karen McAdam (Peterborough District Hospital)
Richard Simcock (Brighton and Sussex University Hospital)
Russell Burcombe (Maidstone and Tunbridge Wells Hospital)

Canada

Robert El-Maraghi (Royal Victoria Regional Health Centre)
Nadia Califaretti (Grand River Regional Cancer Centre)
Silvana Spadafora (Algoma Regional Cancer Program, Sault Area Hospital)
Sandeep Sehdev (William Osler Health System Brampton Civic Hospital)
Amer Sami (Saskatoon Cancer Centre, University of Saskatoon Campus)
Sunil Verma (Sunnybrook Odette Cancer Centre)