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Clinical Trial

HannaH phase III randomised study: Association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant–adjuvant trastuzumab after 2 years of treatment-free follow-up

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KEYWORDS
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Trastuzumab

Abstract ***Background:*** In the phase III, open-label, randomised HannaH study, fixed-dose neoadjuvant–adjuvant subcutaneous trastuzumab for human epidermal growth factor receptor 2 (HER2)-positive early breast cancer was non-inferior to standard weight-based intravenous infusion in terms of serum trough concentration and pathological complete response (pCR). Evidence suggests that pCR, particularly total pCR (tpCR), is likely to predict clinical benefit. We report associations between tpCR and event-free survival (EFS) from HannaH (the largest population from a single study of patients presenting with newly diagnosed HER2-positive breast cancer treated with neoadjuvant–adjuvant trastuzumab to date) plus long-term efficacy and safety.

Methods: Eligible patients received four cycles of neoadjuvant docetaxel followed by four cycles of fluorouracil/epirubicin/cyclophosphamide administered concurrently with 3-weekly subcutaneous (600 mg fixed dose) or intravenous trastuzumab (8 mg/kg loading, 6 mg/kg maintenance doses). Post-surgery, patients received adjuvant trastuzumab as randomised to complete 1 year of standard treatment. In exploratory analyses, we used Cox regression to assess associations between tpCR and EFS. EFS rates per subgroup were estimated using the Kaplan–Meier method.

Findings: Three-year EFS rates were 76% for subcutaneous and 73% for intravenous trastuzumab (unstratified hazard ratio [HR] 0.95, 95% confidence interval [CI] 0.69–1.30; intention-to-treat population). Three-year overall survival rates were 92% for subcutaneous and 90% for intravenous trastuzumab (unstratified HR 0.76, 95% CI 0.44–1.32). tpCR was associated with a reduced risk of an EFS event: subcutaneous arm HR 0.38 (95% CI 0.22–0.65); intravenous arm HR 0.32 (95% CI 0.18–0.60). Results were similar for subgroups, including oestrogen receptor status. The few additional adverse events occurring during treatment-free follow-up were balanced between arms.

Interpretation: Long-term efficacy supports the established non-inferiority of subcutaneous trastuzumab, and its safety profile remains consistent with the known intravenous profile. In each of HannaH's treatment arms, tpCR was associated with improved EFS, adding to evidence that tpCR is associated with clinical benefit in HER2-positive early breast cancer.

1. Introduction

One year of subcutaneous trastuzumab (Herceptin® SC; F. Hoffmann-La Roche Ltd, Basel, Switzerland) is approved in over 60 countries worldwide as neoadjuvant and adjuvant therapy for human epidermal growth factor receptor 2 (HER2)-positive early breast cancer, and its advantages over intravenous trastuzumab (Herceptin®, F. Hoffmann-La Roche Ltd) include time savings and convenience for patients and health care professionals [1–3]. Patients reported preference for subcutaneous trastuzumab because it saves time and, in contrast with clinically reported adverse events, causes less pain/discomfort/side-effects [3–5]. Approval of subcutaneous trastuzumab was based on results of the HannaH phase III study; with almost 600 patients, HannaH is the largest single study in patients with HER2-positive early breast cancer homogeneously treated with neoadjuvant–adjuvant trastuzumab. HannaH confirmed non-inferiority of subcutaneous versus intravenous trastuzumab in terms of the co-primary end-points of serum trough concentration (C_{trough}) and pathological complete response (pCR) [6]. Additional analyses at 20 months' median overall follow-up confirmed the 12-month analysis finding that subcutaneous trastuzumab was generally well tolerated, with adverse event and event-free survival (EFS) rates comparable to those seen with intravenous trastuzumab [7]. We now report per-protocol long-term efficacy (EFS and overall survival [OS]) and safety from the HannaH study with a median overall follow-up of approximately 40 months, after the last patient had completed 1 year of neoadjuvant–adjuvant treatment and at least 2 years of additional treatment-free follow-up (clinical cut-off). HannaH's study design also allowed exploratory analyses of the association between pCR and EFS. Prior studies have indicated that pCR, and in particular total pCR (tpCR; absence of invasive neoplastic cells in the breast and ipsilateral lymph nodes, regardless of ductal carcinoma in situ), is likely to predict clinical benefit in patients with HER2-positive early breast cancer [8–14]. Moreover, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) define pCR as the absence of cancer in the breast and ipsilateral (regional) lymph nodes [15,16]. This definition is equivalent to the definition of tpCR in HannaH. Thus, tpCR is used for the main association analyses here.

2. Methods

2.1. Study design, patients, randomisation, and masking

HannaH is an open-label, multicentre, international, randomised phase III study, the design of which has been described [6]. HannaH was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and all patients provided written informed consent. Approval for the study protocol and all accompanying material provided to the patients were obtained from independent ethics committees at participating institutions.

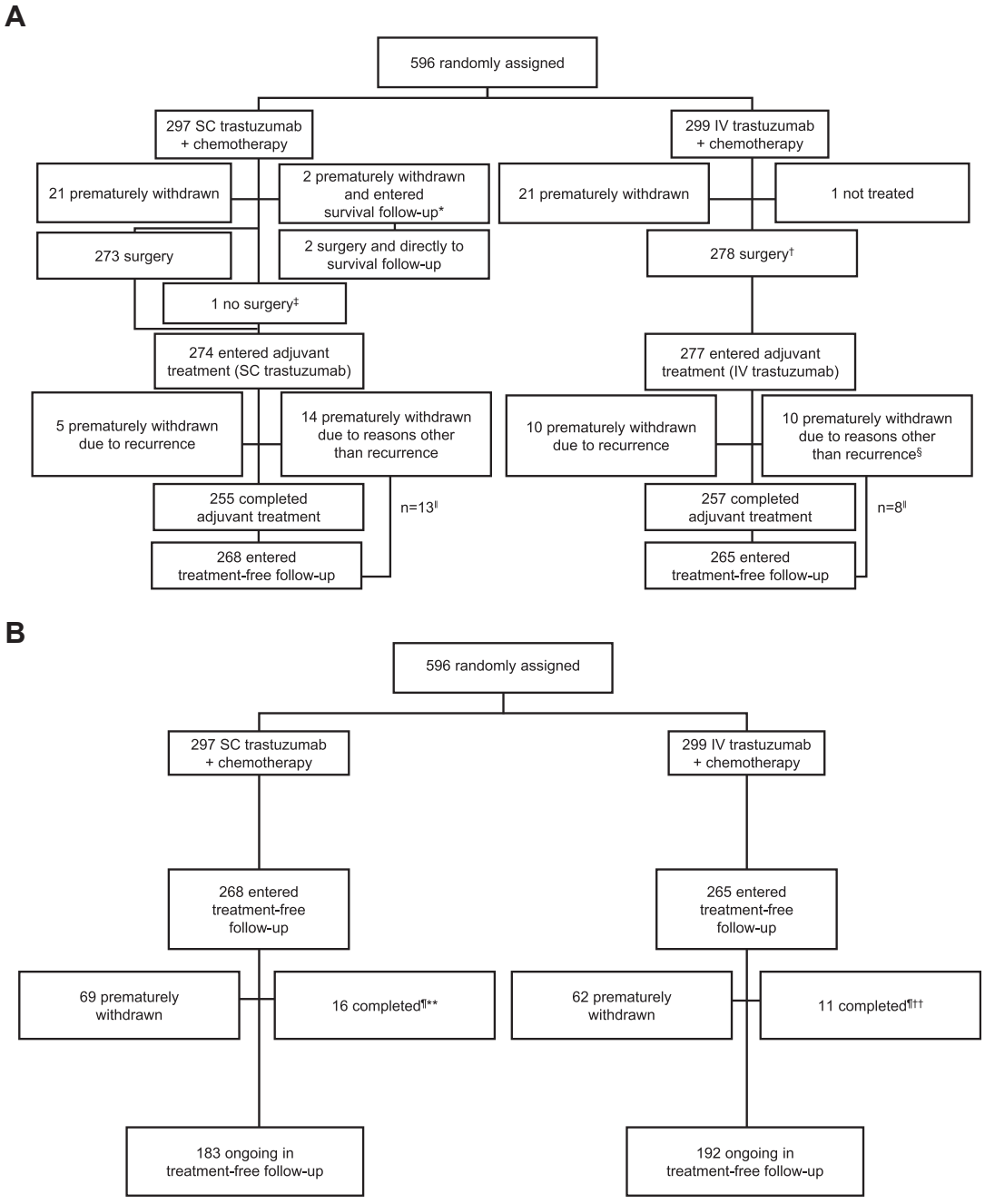


Fig. 1. Trial profile. '*', Two patients were prematurely withdrawn due to disease progression after completion of eight cycles of treatment but nevertheless underwent surgery and are included in the efficacy per-protocol population. '†', Includes one patient who discontinued treatment at the end of the neoadjuvant phase, did not receive adjuvant treatment, and underwent surgery in the treatment-free follow-up phase. '‡', One patient did not undergo primary surgery after completion of the neoadjuvant phase. '§', Includes one patient who withdrew due to insufficient therapeutic response. '‖', In the intravenous trastuzumab arm, two patients withdrew consent. In the subcutaneous trastuzumab arm, one patient withdrew consent. These patients did not enter treatment-free follow-up for event-free survival. '¶', Patients who consented to 2 years of follow-up under Protocol Amendment B only. '**', Includes seven patients with termination page missing at time of analysis. '††', Includes three patients with termination page missing at time of analysis. IV = intravenous; SC = subcutaneous.

Table 1
Baseline patient demographic and tumour characteristics for the intention-to-treat population.

	Subcutaneous trastuzumab (n = 294)	Intravenous trastuzumab (n = 297)
Age (years)	50.0 (25–81)	50.0 (24–77)
Body weight (kg)	68.0 (39.0–136.0)	66.2 (42.0–137.1)
Region		
Eastern Europe	114 (38.8%)	122 (41.1%)
Asia-Pacific	63 (21.4%)	59 (19.9%)
Western Europe and Canada	51 (17.3%)	56 (18.9%)
South America	50 (17.0%)	45 (15.2%)
South Africa	16 (5.4%)	15 (5.1%)
Ethnic origin		
White	197 (67.0%)	207 (69.7%)
Asian	64 (21.8%)	61 (20.5%)
Other	33 (11.2%)	29 (9.8%)
Left ventricular ejection fraction[a]	66.0% (53–87)	65.0% (55–82)
Breast cancer type[b]		
Operable[c]	151 (51.4%)	163 (54.9%)
Locally advanced[d]	123 (41.8%)	115 (38.7%)
Inflammatory	20 (6.8%)	19 (6.4%)
Breast cancer subtype[e]		
Ductal	272 (92.8%)	273 (91.9%)
Lobular	12 (4.1%)	17 (5.7%)
Other	9 (3.1%)	7 (2.4%)
Oestrogen receptor status[b]		
Negative	140 (47.6%)	148 (49.8%)
Positive	154 (52.4%)	148 (49.8%)
Unknown	0	1 (0.3%)
Histological grade		
Well differentiated	13 (4.4%)	8 (2.7%)
Moderately differentiated	152 (51.7%)	151 (50.8%)
Poorly differentiated	128 (43.5%)	137 (46.1%)
Anaplastic	0	1 (0.3%)
Unknown	1 (0.3%)	0
Clinical nodal status[e]		
cN0	71 (24.2%)	62 (20.9%)
cN1	129 (44.0%)	151 (50.8%)
cN2	60 (20.5%)	50 (16.8%)
cN3	33 (11.3%)	34 (11.4%)
Clinical tumour status[e]		
cT1b	2 (0.7%)	2 (0.7%)
cT1c	17 (5.8%)	21 (7.1%)
cT2	129 (44.0%)	130 (43.8%)
cT3	52 (17.7%)	49 (16.5%)
cT4abc	73 (24.9%)	76 (25.6%)
cT4d	20 (6.8%)	19 (6.4%)

Data are median (range) or number (%).
[a] n = 293 for the subcutaneous trastuzumab arm and n = 296 for the intravenous trastuzumab arm.
[b] Stratification factors.
[c] Clinical stage cT1b–cT3, cN0–cN1.
[d] Clinical stage cT1b–cT4c, cN2–cN3.
[e] n = 293 for the subcutaneous trastuzumab arm and n = 297 for the intravenous trastuzumab arm.

2.2. Procedures

Patients were randomised to receive eight cycles of neoadjuvant chemotherapy, administered concurrently with trastuzumab, every 3 weeks either intravenously (8 mg/kg loading dose, 6 mg/kg maintenance dose) or subcutaneously (fixed dose of 600 mg). Chemotherapy comprised four cycles of docetaxel (75 mg/m^2) followed by four cycles of fluorouracil (500 mg/m^2), epirubicin (75 mg/m^2), and cyclophosphamide (500 mg/m^2). Post-surgery, patients received ten cycles of trastuzumab to complete 1 year of neoadjuvant–adjuvant therapy [6]. For the present analysis, patients were followed for efficacy and safety for 2 years after the last dose of study medication. Reporting time windows for adverse events are listed in Supplementary Table S1.

2.3. Outcomes

The secondary end-points of EFS, OS, and safety were assessed at this clinical cut-off. EFS was defined as time from randomisation to the date of disease recurrence or progression (local, regional, distant, or contralateral), or death from any cause. OS was defined as time from randomisation to death and a final analysis will be carried out once 5 years of survival data have been collected. Adverse events and serious adverse events were recorded and graded according to standard criteria [17–19]. Safety for this analysis is focused on the treatment-free follow-up phase.

2.4. Statistical analyses

Target sample sizes and power calculations for the primary analysis have been reported [6]. Long-term efficacy analyses are focused on the intention-to-treat (ITT) population, which includes all patients who had at least one efficacy assessment after first study drug administration. Analyses were also conducted on the efficacy per-protocol (EPP) population (all randomised patients without major protocol violations: a full description of criteria is shown in the Supplementary Materials) [7]. Results for the EPP population are shown in the Supplementary Materials, as results are similar to the ITT population.

Exploratory EFS sub-analyses included EFS by age (cut-off: 65 years), oestrogen receptor status, C_{trough} quartiles at pre-dose cycle 8, body weight quartiles, tpCR, and pCR. The association between tpCR and EFS was also assessed according to oestrogen receptor status, a stratification factor in HannaH. For exploratory tpCR/pCR–EFS associations in the ITT population, patients withdrawn prior to surgery were counted as non-responders. EFS rates and unstratified hazard ratios (HRs)/confidence intervals (CIs) were estimated using the Kaplan–Meier method and Cox regression, respectively. tpCR/pCR–EFS associations were analysed using multivariable Cox modelling. To investigate if the association between tpCR/pCR and EFS was different in the two arms, a Cox regression model on EFS with a treatment–tpCR/pCR interaction term was used (interaction p-value <0.1 was used as indicator of

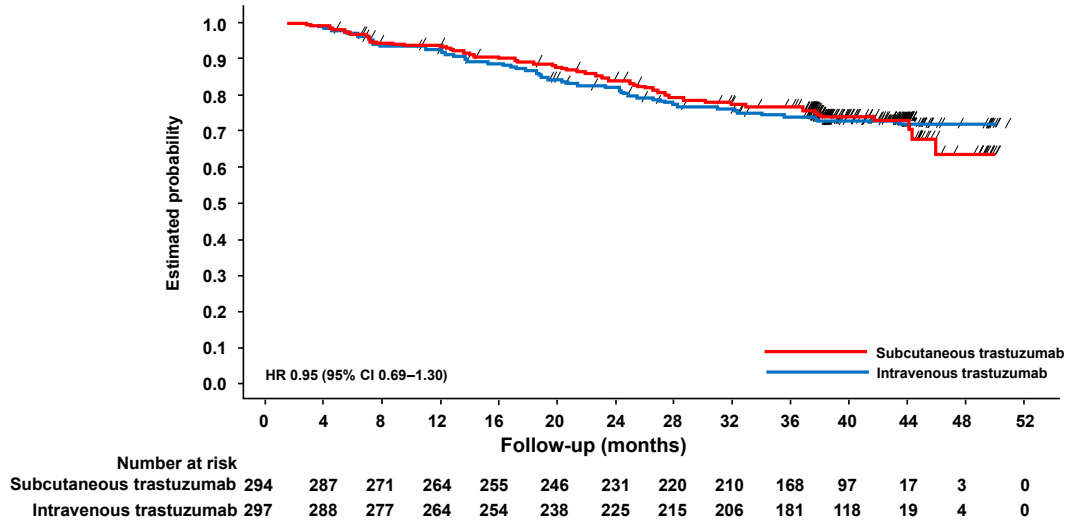


Fig. 2. Event-free survival for the intention-to-treat population. CI = confidence interval; HR = hazard ratio.

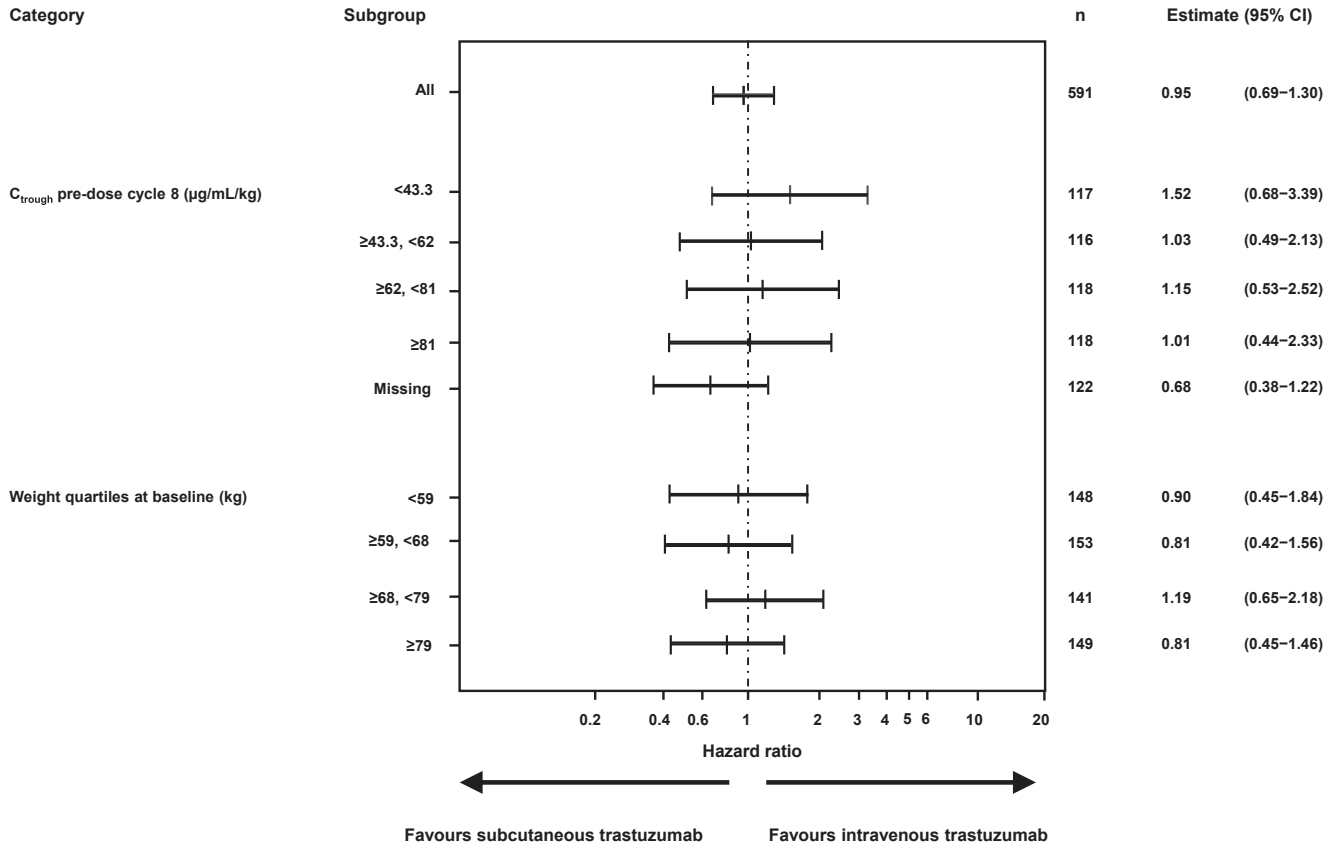


Fig. 3. Event-free survival for subgroups related to efficacy of the fixed subcutaneous dose in the intention-to-treat population. CI = confidence interval; C_{trough} = serum trough concentration.

differences in correlation between arms). Analyses were performed with SAS, v9.2 (SAS Institute Inc., Cary, NC, USA). The safety population included all patients who received at least one dose of study drug, and adverse events are described overall and during the treatment-free follow-up period.

HannaH is registered with ClinicalTrials.gov, number NCT00950300.

3. Results

In total, 596 eligible patients were enrolled between 19th October 2009 and 1st December 2010: 297 patients were randomised to receive subcutaneous trastuzumab and 299 were randomised to receive intravenous trastuzumab [6]. ITT populations were 294 and 297 patients,

respectively; EPP populations, 260 and 263 patients; safety populations, 297 and 298 patients [6]. Patient dispositions for the neoadjuvant–adjuvant and treatment-free follow-up phases are shown in Fig. 1. Demographic characteristics of the ITT population (Table 1) were balanced and consistent with those of the EPP population [6]. At clinical cut-off (17th January 2014), median follow-up was 40.3 months with subcutaneous trastuzumab (range 0.3–50.7) and 40.6 months with intravenous trastuzumab (range 1.0–51.0).

Median trastuzumab dose intensity was 196.4 mg/week (range 163.2–208.0) in the subcutaneous arm and 135.6 mg/week (range 86.9–234.6) in the intravenous arm; median relative dose intensities were >98% in both arms. Median relative dose intensities for all chemotherapy agents were 99% in both arms (Supplementary Table S2).

Of the ITT population, 154 of 294 patients in the subcutaneous arm and 148 of 297 patients in the intravenous arm had oestrogen receptor-positive tumours. Of these patients, 133 of 154 (86.4%) and 120 of 148 (81.1%) subsequently received at least one endocrine therapy, respectively; the most common being tamoxifen (99 of 154 patients [64.3%] in the subcutaneous arm and 79 of 148 [53.4%] in the intravenous arm) and aromatase inhibitors (37 of 154 patients [24.0%] in the subcutaneous arm and 42 of 148 patients [28.4%] in the intravenous arm). A complete list is shown in Supplementary Table S3.

At clinical cut-off, EFS rates 3 years after randomisation were 76% in the subcutaneous arm and 73% in the intravenous arm, and the resulting HR was 0.95 (95% CI 0.69–1.30) (Figs 2–4). HRs were similar in both arms across C_{trough} pre-dose cycle 8 and body weight quartiles (Fig. 3). Results were not affected by age, the HR for subcutaneous versus intravenous trastuzumab being 0.94 (95% CI 0.67–1.31) in patients aged <65 years and 1.03 (95% CI 0.39–2.72) in patients aged ≥65 years. EFS results were also similar between the arms by oestrogen receptor status (HR 0.86 [95% CI 0.54–1.38] for oestrogen receptor-positive disease and 1.04 [95% CI 0.68–1.59] for oestrogen receptor-negative disease/unknown disease status). In addition, 3-year EFS rates were higher in oestrogen receptor-positive disease versus oestrogen receptor-negative disease/unknown oestrogen receptor status for both subcutaneous and intravenous trastuzumab: 79% and 73% in the subcutaneous arm and 76% and 71% in the intravenous arm.

Patients who achieved tpCR had a >60% reduction in the risk of an EFS event compared with those who did not: HR 0.38 (95% CI 0.22–0.65) in the subcutaneous arm and 0.32 (95% CI 0.18–0.60) in the intravenous arm (Table 2). This finding was also reflected in the EFS Kaplan–Meier curves, graphically presented for each arm separately in Fig. 5A and B, translating into 3-year EFS rates which were approximately 20 percentage points higher for patients who achieved

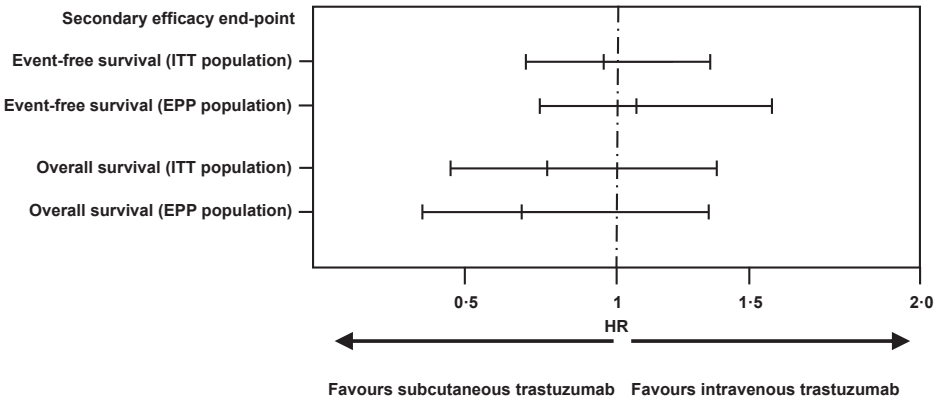


Fig. 4. Event-free and overall survival in the intention-to-treat population and efficacy per-protocol populations. EPP = efficacy per protocol; ITT = intention-to-treat; HR = hazard ratio.

Table 2
Event-free survival according to treatment and total pathological complete response status of the intention-to-treat population.

	Subcutaneous trastuzumab (n = 294)		Intravenous trastuzumab (n = 297)	
	tpCR (n = 108)	No tpCR (n = 186)[a]	tpCR (n = 94)	No tpCR (n = 203)[a]
Kaplan–Meier 3-year EFS rate (95% CI)	88% (82–94%)	69% (62–76%)	87% (80–94%)	67% (61–74%)
Cox regression HR (95% CI)	0.38 (0.22–0.65)		0.32 (0.18–0.60)	

CI = confidence interval; EFS = event-free survival; HR = hazard ratio; tpCR = total pathological complete response.
[a] Includes patients withdrawn before surgery.

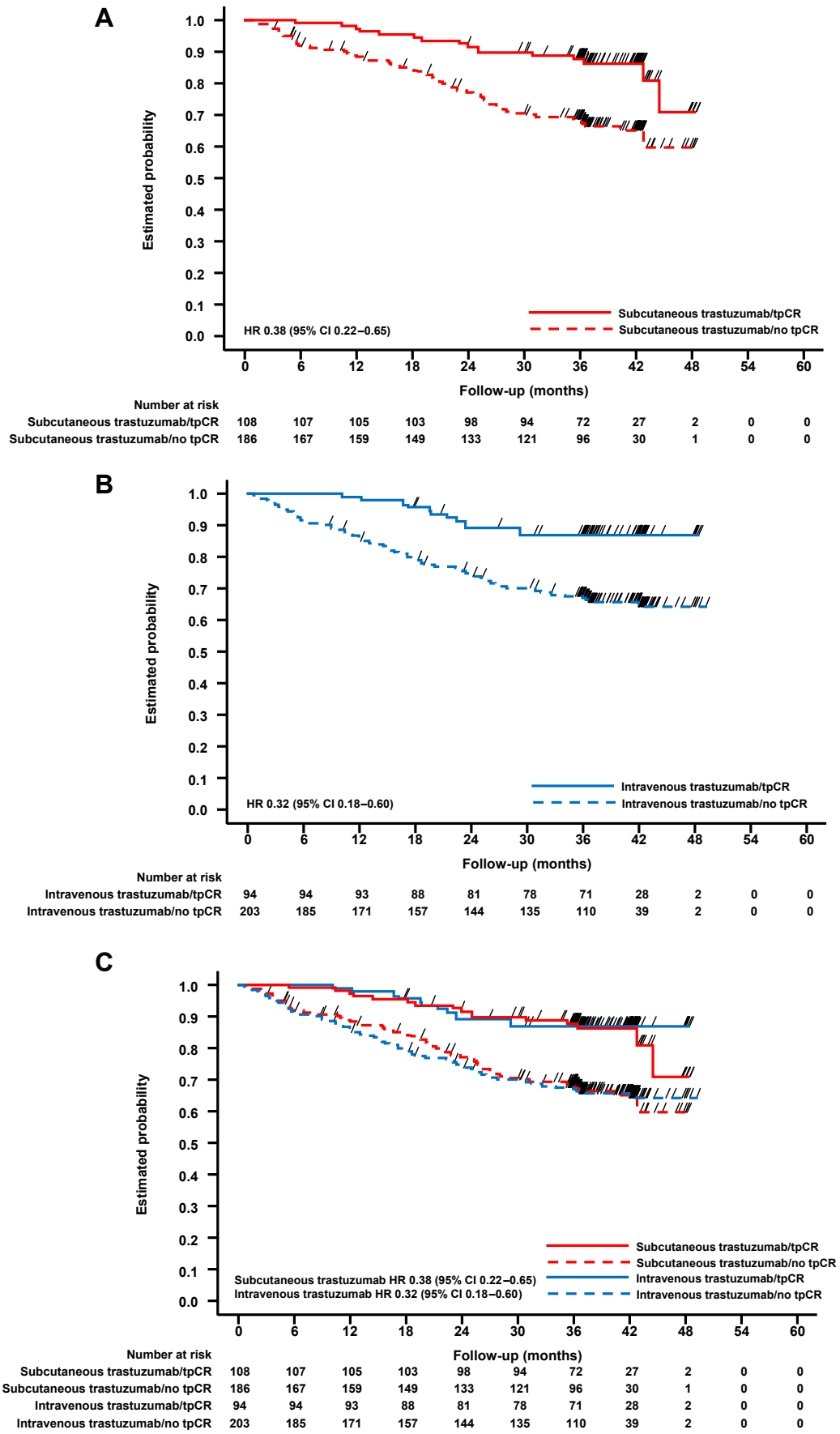


Fig. 5. Event-free survival according to tpCR status of the intention-to-treat population. CI = confidence interval; HR = hazard ratio; tpCR = total pathological complete response.

tpCR, compared with those who did not (Table 2). Fig. 5C shows a similar relationship of tpCR with EFS for both arms (treatment–tpCR interaction test: p = 0.67).

The benefit to 3-year EFS rates when achieving tpCR was similar between oestrogen receptor-positive disease and oestrogen receptor-negative disease/unknown oestrogen receptor status when study arms were pooled: HR 0.21 (95% CI 0.09–0.53) and 0.35 (95% CI 0.22–0.57), corresponding to 22 and 23 percentage point-higher 3-year EFS rates, respectively, when compared with those who did not achieve tpCR (Table 3). Kaplan–Meier plots of the oestrogen receptor-positive disease and oestrogen receptor-negative/unknown oestrogen receptor status groups according to tpCR status and study arm are shown in Fig. 6 and reveal consistent results.

At the data cut-off date, the 3-year OS rate was 92% for subcutaneous trastuzumab and 90% for intravenous trastuzumab (HR 0.76, 95% CI 0.44–1.32) (Fig. 4).

Efficacy results in the EPP population were consistent with those in the ITT population and pCR results were consistent with tpCR results in both the ITT and EPP populations (Fig. 4, Supplementary Tables S4–S9, Supplementary Figs. S1–S5).

Overall safety findings are summarised in Table 4 and are consistent with previous reports [6,7]. More patients reported serious adverse events in the subcutaneous arm, but no pattern in the types of events was identified that would account for different rates between the arms. During treatment-free follow-up, adverse event rates were balanced, with few serious events observed in the 2 years after completion of treatment (Table 5). During this period, one adverse event case (endometrial cancer) led to death with subcutaneous trastuzumab and two adverse event cases (emphysema and myeloid leukaemia) led to death with intravenous trastuzumab. Analysis of data from all phases of the study showed that the overall cardiac safety profiles of subcutaneous and intravenous trastuzumab remained comparable, with the percentage of patients with ≥1 cardiac event being similar in both arms (14.1% [42 of 297 patients] with subcutaneous trastuzumab and 13.4% [40 of 298 patients] with intravenous trastuzumab). The most common cardiac adverse events were left ventricular dysfunction (3.4% of patients [ten of 297] with subcutaneous trastuzumab [eight resolved] and 3.7% [11 of 298] with intravenous trastuzumab [nine resolved]) and tachycardia (2.0% of patients [six of 297] with subcutaneous trastuzumab [five resolved] and 3.0% [nine of 298] with intravenous trastuzumab [all resolved]). Two patients (0.7%) experienced congestive heart failure with subcutaneous trastuzumab; one case reported as resolved and one reported as resolved with sequelae. Few patients experienced cardiac adverse events during the treatment-free follow-up phase and proportions of those who did were comparable between treatment arms (1.7% with subcutaneous trastuzumab and 1.3% with intravenous trastuzumab). In the lower body weight quartiles, cardiac adverse events were well balanced between treatment arms (Table 6).

4. Discussion

The HannaH phase III study provides data from the largest homogeneous population of patients with HER2-positive early breast cancer. In HannaH, the secondary long-term efficacy end-points, EFS and OS, at a median follow-up of more than 40 months, support the established non-inferiority of subcutaneous trastuzumab relative to intravenous trastuzumab as per the co-primary end-points, pCR and C_{trough}. HannaH's results were robust and consistent across analysis populations, and in agreement with the neoadjuvant–adjuvant NeOAdjuvant Herceptin (NOAH) study of intravenous trastuzumab, where 3-year EFS was 71% for trastuzumab-treated patients [20]. In general, results were consistent across subgroups (including demographic and disease characteristics). In particular, EFS results for both arms were similar in patients in the higher body weight patient quartiles, as compared with the overall population, which is important as higher body weight patients may have reduced trastuzumab exposure from the 600 mg every 3 weeks subcutaneous fixed dose compared with weight-based intravenous dosing.

Table 3
Event-free survival according to oestrogen receptor and total pathological complete response status of the intention-to-treat population (pooled study arms).

	Oestrogen receptor-positive (n = 302)		Oestrogen receptor-negative or status unknown (n = 289)	
	tpCR (n = 71)	No tpCR (n = 231)[a]	tpCR (n = 131)	No tpCR (n = 158)[a]
Kaplan–Meier 3-year EFS rate	94%	72%	84%	61%
Cox regression HR (95% CI)	0.21 (0.09–0.53)		0.35 (0.22–0.57)	

CI = confidence interval; EFS = event-free survival; HR = hazard ratio; tpCR = total pathological complete response.
[a] Includes patients withdrawn before surgery.

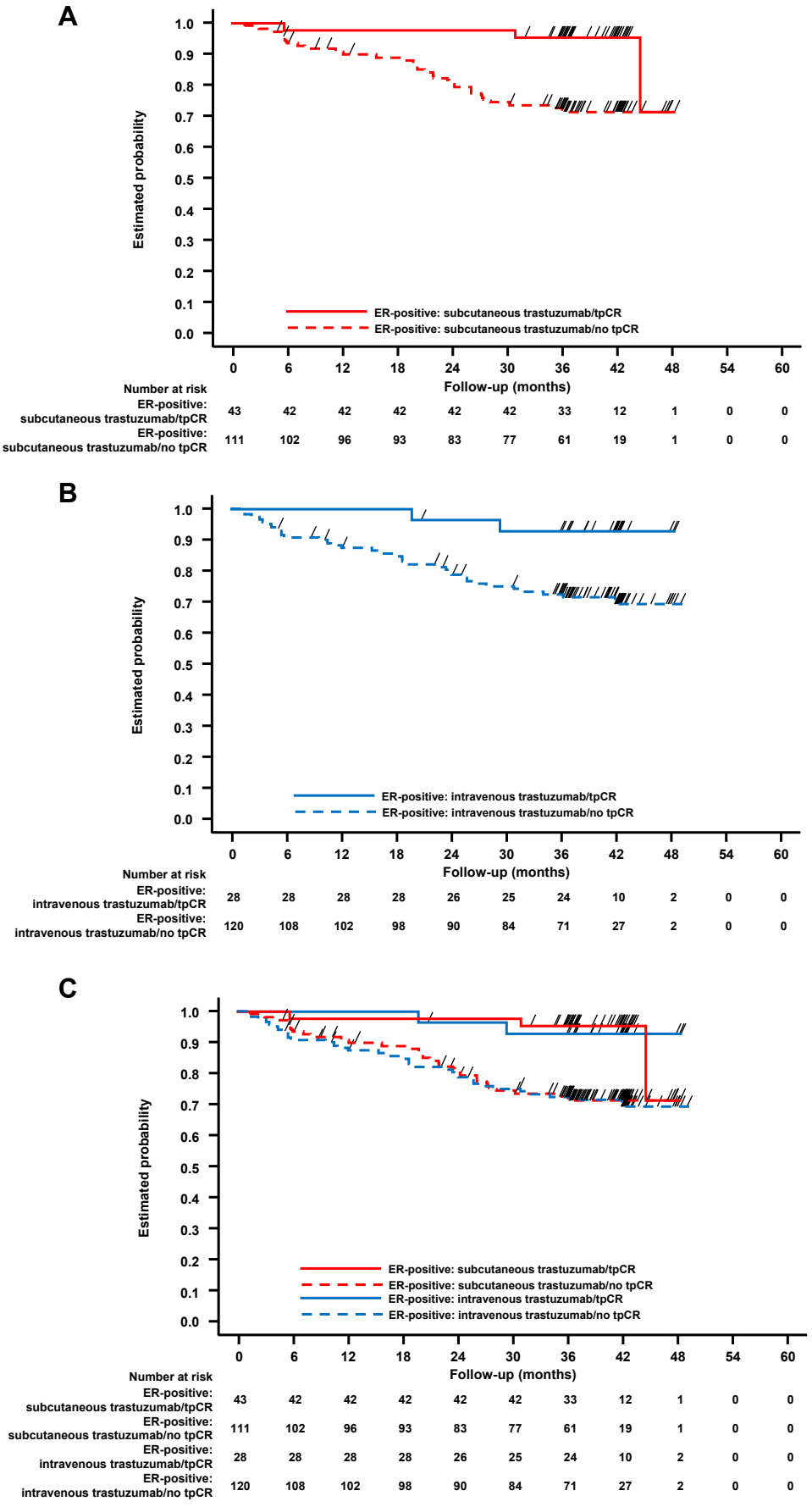
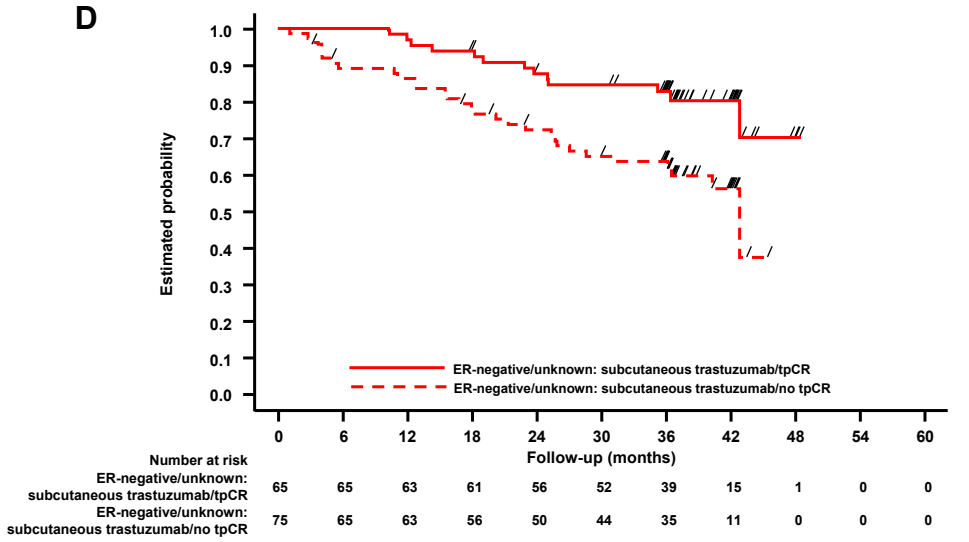
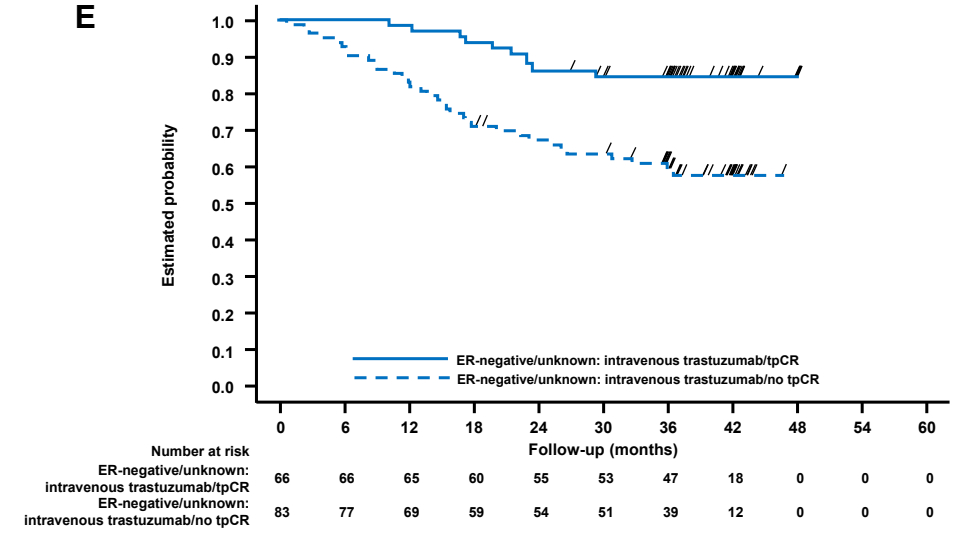


Fig. 6. Event-free survival according to oestrogen receptor and tpCR status of the intention-to-treat population. (A)−(C) Represent oestrogen receptor-positive disease and (D)−(F) represent oestrogen receptor-negative disease/unknown disease status. tpCR = total pathological complete response; ER = oestrogen receptor.





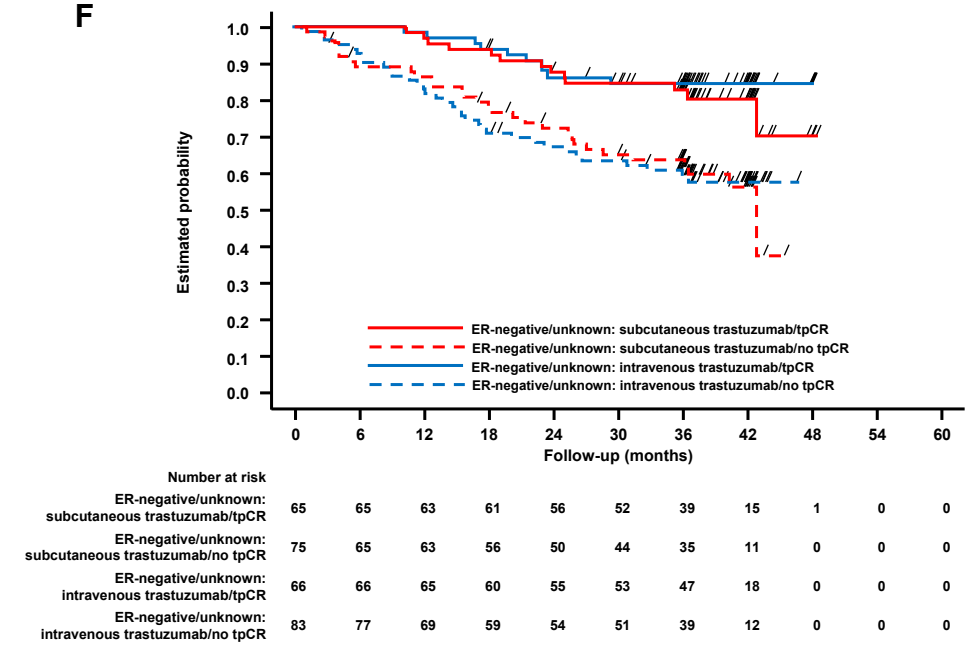


Fig. 6. (Continued)

Table 4
Safety overview (safety population).

	Overall		Treatment-free follow-up	
	Subcutaneous trastuzumab (n = 297)	Intravenous trastuzumab (n = 298)	Subcutaneous trastuzumab (n = 297)	Intravenous trastuzumab (n = 298)
Patients with ≥1 adverse event (any grade)	290 (97.6%)	282 (94.6%)	7 (2.4%)	7 (2.3%)
Patients with ≥1 grade 3–5 adverse event	158 (53.2%)	158 (53.0%)	2 (0.7%)	3 (1.0%)
Patients with ≥1 serious adverse event	65 (21.9%)	43 (14.4%)	2 (0.7%)	3 (1.0%)
Patients with ≥1 related serious adverse event	31 (10.4%)	24 (8.1%)	1 (0.3%)	0
Patients with adverse events leading to death	4 (1.3%)	3 (1.0%)	1 (0.3%)	2 (0.7%)

Data are number (%).

Table 5
Overview of serious adverse events during the treatment-free follow-up period (safety population).

	Subcutaneous trastuzumab (n = 297)	Intravenous trastuzumab (n = 298)
Total	2 (0.7%)	3 (1.0%)
Endometrial cancer	1 (0.3%)[a]	0
Myeloid leukaemia	0	1 (0.3%)[a]
Congestive heart failure	1 (0.3%)	0
Goitre	0	1 (0.3%)
Emphysema	0	1 (0.3%)[a]

Data are number (%).
[a] Led to death.

Table 6
Cardiac adverse events by body weight quartiles (safety population).

	Subcutaneous trastuzumab (n = 297)	Intravenous trastuzumab (n = 298)
<59 kg	6/71 (8.5%)	9/77 (11.7%)
≥59 kg, <68 kg	8/70 (11.4%)	9/84 (10.7%)
≥68 kg, <79 kg	14/71 (19.7%)	6/70 (8.6%)
≥79 kg	14/85 (16.5%)	16/67 (23.9%)

Data are n/N (%).

No new safety signals were observed at this data cut-off and only a limited number of additional adverse events were observed during the treatment-free follow-up phase, with no differences reported between the two treatment arms. Since the previous analysis [7], only one new adverse event leading to death has occurred in the treatment-free follow-up phase: emphysema in the intravenous trastuzumab arm. The overall cardiac safety profile of subcutaneous trastuzumab was consistent with intravenous trastuzumab [21], and cardiac adverse events were comparable between the treatment arms in the lower body weight quartiles.

Along with the confirmation of efficacy and safety data after a median follow-up of 40 months, which support previous analyses [6,7], a notable outcome of HannaH was the finding that in each of the two treatment arms (there being almost 300 patients in each arm), tpCR was associated with improved long-term efficacy outcomes (EFS) in patients who received neoadjuvant–adjuvant therapy for HER2-positive early breast cancer, the risk of an EFS event being reduced by >60%. The FDA has issued guidance on the subject, concluding that favourable pCR results are likely to predict clinical benefit [10,15]. The EMA concludes that pCR may be acceptable as an end-point for neoadjuvant early breast cancer trials under certain conditions [16]. Present results are consistent with other published studies in HER2-positive early breast cancer[8,9,11–14] particularly NOAH [12], which enrolled a more homogeneous population than the other studies [8,9,11,13,14] and is most similar to HannaH, albeit with a different concurrent neo-adjuvant chemotherapy regimen. In NOAH, an exploratory analysis also found a significant effect of tpCR for EFS in the trastuzumab group [12]. It should be noted that in HannaH the magnitude of EFS benefit was comparable within the oestrogen receptor sub-groups: achieving tpCR resulted in improved EFS regardless of oestrogen receptor status. The Neo-adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (NeoALTTO) study showed a significant improvement in pCR with neoadjuvant lapatinib plus trastuzumab versus trastuzumab [11], while the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) study reported no long-term efficacy (disease-free survival) benefit in the adjuvant setting [22]. However, it should be noted that the trial designs and patient populations were different, and a recent analysis of the two studies using the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) methodology did not show discordance

[23]. Indeed, applying the CTNeoBC methods demonstrated that ALTTO's results supported the relationship between pCR and long-term efficacy [23] Nevertheless, in HannaH, we demonstrate the tpCR–EFS relationship within the same patient population in the same study.

In light of the positive outcome in this HER2-positive population, neoadjuvant–adjuvant systemic treatment including at least trastuzumab every 3 weeks for 18 cycles (1 year) should be offered to patients regardless of their hormone receptor status. With this option, long-term survival might subsequently be increased. An additional option to improve tpCR further for patients with HER2-positive early breast cancer is the addition of pertuzumab to the neoadjuvant armamentarium, as was done in the NeoSphere and ToleRabilitY of Pertuzumab, Herceptin and AnthracyclinEs in NeoAdjuvant breast cancer (TRYPHAENA) studies [24–26] which led to the approval of neoadjuvant pertuzumab plus trastuzumab plus docetaxel by the FDA and the EMA. HannaH's results are consistent with recent NeoSphere results, where patients who achieved tpCR with trastuzumab plus docetaxel or trastuzumab plus pertuzumab plus docetaxel had a reduced risk of both progression-free and disease-free survival events [25]. HannaH's large population, which includes almost 600 patients treated with trastuzumab randomised into two separate study arms, adds further to the evidence that tpCR is associated with favourable clinical benefits.

Limitations of the present HannaH analysis include a still relatively short median follow-up in view of the long-term changes to the natural history of HER2-positive breast cancer with the advent of targeted treatments and improved prognosis over time. Moreover, the availability of newer anti-HER2 agents, including pertuzumab and trastuzumab emtansine, could impact survival in relapsing patients.

To conclude, in the present HannaH phase III analysis with a median follow-up time of more than 40 months, the secondary long-term efficacy end-points, EFS and OS, support the established non-inferiority of subcutaneous trastuzumab relative to intravenous trastuzumab as per the co-primary end-points, pCR and C_{trough} [6], and the safety profile of subcutaneous trastuzumab continues to be consistent with the known intravenous trastuzumab safety profile [21]. In each of HannaH's two treatment arms, comprising approximately 300 patients per arm, tpCR was associated with improved long-term efficacy outcomes (EFS) in patients who received neoadjuvant–adjuvant therapy for HER2-positive early breast cancer. HannaH provides the largest clinical dataset from a single study in HER2-positive early breast cancer to demonstrate the favourable association between tpCR and EFS to date, and these data add to the body of evidence on tpCR being associated with clinical benefit in HER2-positive early breast cancer.

Contributors

All authors have reviewed the data analyses, contributed to data interpretation, contributed to the writing of the report, approved the final version of the submitted report, and agree to be accountable for all aspects of the report. CJ, S-TC, and MS contributed to the conception/study design. CJ, RH, DS, J-SA, BM, S-CC, S-BK, ML, ES, GK, SF, S-TC, and XP enrolled patients. CJ, J-SA, BM, ES, GK, S-TC, and DH collected data. CJ and DH undertook literature searches. DH, AC-F and MS contributed to generation of tables/figures. AC-F and MS collated data. A full list of study investigators can be found in the Supplementary Materials.

Conflict of interest statement

CJ reports personal fees from Roche Pharma during the conduct of the study. BM reports personal fees and non-financial support from F. Hoffmann-La Roche Ltd, personal fees and non-financial support from Novartis, personal fees from BMS, personal fees from GSK, personal fees from Pfizer, personal fees and non-financial support from Merck, and personal fees from Lilly, outside the submitted work. SF reports personal fees. DH is an employee of, and holds shares in, F. Hoffmann-La Roche Ltd. AC-F is an employee of F. Hoffmann-La Roche Ltd. MS is an employee of Genentech, Inc. RH, DS, J-SA, S-BK, ML, ES, GK, S-TC, and XP have no interests to declare. None of the authors were paid by F. Hoffmann-La Roche Ltd for this work.

Disclosure of prior publication

These analyses have been presented in part:

Jackisch C, Hegg R, Stroyakovskiy D, Ahn JS, Melichar B, Chen S-C, Crepelle-Fléchais A, Heinzmann D, Shing M, Pivot X. Subcutaneous versus intravenous trastuzumab in early breast cancer: 2-year follow-up of HannaH. 14th St. Gallen International Breast Cancer Conference 2015, 18th–21st March 2015, Vienna, Austria; Abstract 227.

Jackisch C, Hegg R, Stroyakovskiy D, Ahn JS, Melichar B, Chen S-C, Crepelle-Fléchais A, Heinzmann D, Shing M, Pivot X. Total pathologic complete response (tpCR) and EFS with subcutaneous (SC) or intravenous (IV) trastuzumab in HER2-positive early breast cancer (EBC). American Society of Clinical Oncology Annual Meeting 2015, 29th May–2nd June 2015, Chicago, IL, USA; Abstract 585.

Research in context

Evidence before this study

Trastuzumab was originally given as a weight-based intravenous dose until subcutaneous trastuzumab was proven to be non-inferior in terms of serum trough concentration and pCR for the treatment of HER2-positive early breast cancer [6]. Guidance from the Food and Drug Administration (FDA) states that favourable pCR (particularly tpCR) results are likely to predict clinical benefit. To put the findings of the HannaH trial into context with respect to associations between tpCR and EFS (one of HannaH's long-term secondary efficacy end-points), we searched PubMed plus abstracts from the American Society of Clinical Oncology annual meetings, the San Antonio Breast Cancer Symposium annual meetings, the European Society for Medical Oncology biennial meetings, and the European Cancer Congress biennial meetings with the terms 'breast cancer', 'HER2', 'long term', and 'pathologic(al) complete response', selecting relevant English language publications within the last 5 years only. Studies indicated that pCR/tpCR is likely to predict clinical benefit in patients with HER2-positive early breast cancer [8–14].

Added value of this study

HannaH adds value to previous studies by virtue of its being the largest trial of patients with HER2-positive early breast cancer homogeneously treated with trastuzumab in the neoadjuvant–adjuvant setting to date: almost 600 patients in total across two study arms. This allowed us to add to the body of evidence comparing patients by tpCR status and confirm the similarity of subcutaneous and intravenous trastuzumab.

Implications of all the available evidence

In each of HannaH's two treatment arms, comprising approximately 300 patients per arm, tpCR was associated with improved long-term efficacy outcomes (EFS) in patients who received neoadjuvant–adjuvant therapy for HER2-positive early breast cancer. These data add to the body of evidence on tpCR being associated with clinical benefit in HER2-positive early breast cancer. HannaH also confirmed no difference between subcutaneous and intravenous trastuzumab in terms of efficacy or safety with longer follow-up.

Role of the funding source

The sponsor was involved in study design and data interpretation. Employees of the sponsor gathered and managed data and undertook statistical analyses. The principal investigator (CJ) had full access to all study data at the time of the trial and during the follow-up period, and had final responsibility for the decision to submit for publication.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.03.087.

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