Neo-adjuvant and/or Adjuvant Subcutaneous Trastuzumab (Herceptin®) in Patients With Early HER2-positive Breast Cancer: Real World Data from a German Observational Study - (NIS HerSCin)

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Abstract. *Background/Aim:* Subcutaneous Herceptin (HER SC) has been shown to be equally effective and safe compared to intravenous Herceptin (HER i.v.) application in early HER2-positive breast cancer (HER2+ BC). However, real-world data from the subcutaneous application are currently limited. *Patients and Methods:* Based on a non-interventional study (NIS), data from routine clinical use of HER SC have been gathered between 2013 and 2018 in 135 hospitals and open-care practices throughout Germany. *Results:* A total of 265 patients were recruited in the neo-adjuvant and 605 patients in the adjuvant setting. Primary effectiveness endpoint in the neo-adjuvant treatment setting was pathological complete response rate, which was achieved in 41.5%. Primary endpoint in the adjuvant setting was disease free survival rate after 2 years (94.9%). *Safety results from the study were comparable to the well-known safety profile of HER i.v. including preferred terms, incidence, severity, including cardiac events. No new safety*

signals were detected. Conclusion: Effectiveness and safety of HER SC were comparable to data from HER i.v. in early HER2+ BC.

Breast cancer is the most frequent cancer diagnosis in women, affecting over 2 million patients per year and 627,000 women died from this malignant disease in 2018 (1). Over the past decades, breast cancer has been described as an inhomogeneous disease with different histologies and target structures. One entity is HER2-positive breast cancer (HER2+ BC), characterized by overexpression of human epidermal growth factor receptor 2 (HER2) (2). HER2+ has been identified to be a negative prognostic factor in about 20% of breast cancer patients (3). In 2000, trastuzumab, a monoclonal antibody directed against the extracellular domain of HER2, was registered for the treatment of HER2-positive metastatic breast cancer and soon became a decisive constituent for the treatment standard in HER2+ BC (4, 5). Efficacy of the anti-HER2 antibody Herceptin (HER) has also been demonstrated in early HER2+ BC (6-8). In 2006, HER was registered in the adjuvant setting of breast cancer together with chemotherapy (CTX), as well as in the neo-adjuvant therapy setting (9-13). Unlike most chemotherapeutic regimens, treatment with HER may be deployed over months and even re-therapy with HER has been demonstrated to be effective as first line treatment for patients with advanced HER2+ BC after relapse-free (neo)adjuvant HER therapy (14, 15). Furthermore, continued treatment beyond progression of

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advanced disease is an accepted therapeutic option (16). HER together with new developments, like dual targeted anti-HER2-therapies (17), substantially improved prognosis of women with HER2+ BC (18, 19). As treatment of early HER2+ BC with the antibody is routinely continued over a period of one year (20), efforts have been made to reduce application time and optimize application route. This led to the development of a subcutaneous formulation, which was registered based on the results of the HannaH-study in the neo-adjuvant and adjuvant treatment of early HER2+ BC in 2013 (21). The SC formulation of Herceptin allows a fast and simple administration within 2-5 min without the need for a venous access. Effectiveness, safety, and applicability including physicians' assessment of this application mode in clinical routine was documented in our non-interventional study (NIS) 'HerSCin' in Germany and is registered in ClinicalTrials.gov under the identifier: NCT01959386.

Patients and Methods

HerSCin was designed as a merely observational study conducted as a non-interventional study (NIS) according to § 67 Abs. 6 German Medicinal Products Act (20) in patients with early HER2+ BC. Design and content of this NIS were submitted to the Ethical Committee of the State Chamber of Medicine in Rheinland-Pfalz. The NIS captures in-label data on the use of subcutaneously administered Herceptin (HER) from routine clinical practice in Germany. Inclusion into the NIS was based on the physician's decision to treat the patient with HER SC. Treatment was designed according to the specifications of the respective actual summary of product characteristics (SmPC) for HER SC. The primary objective of this NIS was to document the clinical effectiveness of HER SC. The evaluation for patients with early HER2+ BC with neo-adjuvant treatment was primarily assessed through documentation of the pathological complete response (pCR) rate. As neo-adjuvant treatment with HER is to be continued after surgery for an adjuvant treatment period, event-free survival (EFS) as well as disease-free survival rate after 2 years (DFS_{neo}) were also evaluated as a secondary outcome parameter for patients in the neoadjuvant treatment setting. For patients receiving adjuvant treatment, disease-free survival rate after 2 years (DFS_{adj}) was documented. Additional secondary objectives included safety, tolerability, quality of life of patients as assessed by patient questionnaires EORTC QLQ-C30 (version 3.0) and module QLQ-BR23 (breast cancer update QLQ-BR23) and physician's judgement of the overall compliance, effectiveness and tolerability of HER SC treatment for both treatment groups. The planned sample sizes were 240 patients in the neo-adjuvant and 120 patients in the adjuvant setting, to reach a precision of $\pm 7.5\%/\pm 6.8\%$ for the 95% CIs of pCR/ DFS after 2 years. However, a considerable oversampling with 720 adjuvant patients was expected. The primary analyses for both treatment settings and analyses of all other variables were performed descriptively. Results are presented in tables of descriptive summary statistics or result tables of Kaplan-Meier analyses. Continuous variables are displayed with arithmetic mean (mean), standard deviation (sd), median, minimum (min) and maximum (max) as applicable. Categorical variables present absolute and relative frequencies.

Results

Patient disposition and baseline characteristics. A total of 135 open-care and clinical sites across Germany enrolled a total of 1,001 patients with early HER2+ BC. According to actual SmPC at each time, 870 patients with early HER2+ BC were eligible and received at least one dose of HER SC. Details are displayed in Figure 1.

Allocation of patients to either the neo-adjuvant or adjuvant treatment group, followed the overall treatment perspective (including chemotherapy and possible additional anti-cancer therapies) instead of following the timing of the HER SC treatment. In total, 265 patients were treated in the neo-adjuvant treatment setting and 605 patients received adjuvant treatment for EBC. Three male patients were included into this NIS. Patients in the neo-adjuvant setting tended to be younger with larger tumor size and higher grading. Details of baseline and disease characteristics are displayed in Table I.

Treatment patterns. During the course of the study, neo-adjuvant patients concomitantly received a mean of 2.41 ± 2.38 (sd) cycles of chemotherapy. Adjuvant patients were treated with a mean of 1.85 ± 2.18 (sd) cycles of chemotherapy. Chemotherapies included epirubicin, doxorubicin, cyclophosphamide, 5-fluorouracil, (nab)-paclitaxel, docetaxel, carboplatin and other chemotherapeutic agents. For patients with endocrine treatment, mean duration of antihormonal therapy according to substance-administered during the course of the study (which might not reflect the complete treatment duration) was 0.9-24.5 months in the neoadjuvant setting and 10.0 to 20.7 months in the adjuvant treatment situation. Antihormonal treatment included letrozole, anastrozole, tamoxifen and exemestane besides others. Median cumulative dose of radiotherapy was documented in 176 neo-adjuvant patients with 50.4 Gray (GY) (range=10.0-666.0 Gy) and in 347 adjuvant patients with 58.8 GY (range=4.0-211.6 Gy).

Treatment with Herceptin. Median overall duration of total treatment with Herceptin (SC and *i.v.*), median overall duration of HER SC treatment, and median overall number of HER SC treatment cycles was comparable between the two patient groups treated either in the neo-adjuvant or adjuvant setting (Table II).

Treatment interruptions of HER SC in both treatment settings did not occur frequently. A comparable portion of patients had HER *i.v.* therapy at baseline. Less than 6% of patients in either treatment setting changed from subcutaneous to intravenous HER or *vice versa* (Table III).

The three most common reasons for discontinuation or interruption of HER SC were "Decision by the Physician", "Termination by the patient", and "Adverse event" in both treatment settings (Table IV).

Figure 1. Patient disposition. EBC: Early breast cancer; IHC: immune histochemistry; ISH: in situ hybridization.

Effectiveness in the neo-adjuvant patient population. Documentation of the primary effectiveness parameter pCR followed two distinct eCRF entries, with the first entry documenting pCR -“yes”, “no”, or “not assessable” and the second entry recording the patient’s remission status [“pCR in the breast achieved (ypT0/is ypNx)”, “total pCR in breast and axilla achieved (ypT0/is ypN0), or “not assessable”]. According to the first entry 110 [41.5%, (95%CI=35.5%-47.7%)] patients achieved pCR, whereas 65 (24.5%) patients did not achieve pCR, and for 90 patients, pCR-assessment was missing. Regarding the specification of remission status of the 110 patients with documented pCR, 55 (20.8%) patients achieved total pCR in breast and axilla (ypT0/is ypN0) and 54 (20.4%) patients achieved pCR in the breast (ypT0/is ypNx).

Figure 2 presents an overview on pCR assessment in general and remission status for patients with pCR.

Secondary effectiveness was assessed by EFS defined as the interval from start of first therapy with HER (SC or *i.v.*) to the earlier of either documentation of disease progression (based on the response assessments collected at the last visit and at the follow-up visit) or death from any cause and DFS_{neo} after 2 years, defined as the interval from surgery to disease progression or death from any cause.

After two years, EFS rate was 90.8% (95%CI=85.9-94.0%) and DFS_{neo} was 89.6% (95%CI=84.3-93.2%). Table V depicts DFS_{neo} dependent on achievement of pCR (see Figure 2), demonstrating a somewhat longer DFS_{neo} for patients with pCR. According to a *post hoc*-analysis after 30

Table I. Baseline patient and disease characteristics.

Parameter	Neo-adjuvant n=265	Adjuvant n=605
Age		
Mean (sd)	52.3 (11.56)	59.2 (12.32)
Median	51.0	59.0
Min-Max	20-90	21-95
Gender		
Female	264 (99.6%)	603 (99.7%)
Male	1 (0.4%)	2 (0.3%)
BMI by categories		
<25	119 (45.8%)	261 (44.4%)
≥25	141 (54.2%)	327 (55.6%)
missing	5	17
ECOG PS		
Grade 0	162 (66.4%)	352 (67.6%)
Grade 1	79 (32.4%)	154 (29.6%)
Grade 2	3 (1.2%)	14 (2.7%)
Grade 3	0	1 (0.2%)
Missing	21	84
Hormone receptor (estrogen or/and progesterone)		
Positive	178 (67.2%)	452 (74.7%)
Negative	86 (32.5%)	151 (25.0%)
Unknown	1 (0.4%)	2 (0.3%)
Grading		
G1	1 (0.4%)	17 (2.8%)
G2	114 (43.0%)	279 (46.1%)
G3	142 (53.6%)	302 (49.9%)
G4	1 (0.4%)	0
GX/unknown	7 (2.7%)	7 (1.2%)
TNM-T		
T0	14 (5.7%)	3 (0.5%)
T1	77 (31.3%)	329 (54.7%)
T2	116 (47.2%)	215 (35.7%)
T3	16 (6.5%)	27 (4.5%)
T4	13 (5.3%)	20 (3.3%)
Tis	4 (1.6%)	7 (1.2%)
Tx	6 (2.4%)	1 (0.2%)
missing	19	3
TNM- N		
N0	133 (54.3%)	354 (59.0%)
N1	78 (31.8%)	145 (24.1%)
N2	18 (7.3%)	52 (8.7%)
N3	6 (2.4%)	30 (5.0%)
Nx	10 (4.1%)	19 (3.2%)
Missing	20	5
TNM-M		
M0	246 (100%)	602 (100%)
Missing	19	3
Patients with cardiac disorder in medical history	10 (3.8%)	33 (5.5%)
Patients with vascular disorder in medical history	59 (22.3%)	167 (27.6%)

BMI: Body mass index; ECOG PS: Eastern Cooperative Oncology Group performance status; sd: standard deviation; IHC: immune histochemistry; ISH: *in situ* hybridization; TNM: tumor, nodes, metastases; G1: well differentiated; G2: moderately differentiated; G3: poorly differentiated; G4: undifferentiated; Gx: grade cannot be determined.

Table II. Duration of HER treatment (overall, treatment cycles and treatment duration).

	Neo-adjuvant (n=265)	Adjuvant (n=605)
Overall duration of total HER treatment, SC and <i>i.v.</i> [months]		
Mean (sd)	10.2 (4.76)	10.0 (3.64)
Median	10.8	11.2
Min-Max*	0.7-41.2	0.0-37.2
Overall number of treatment cycles, HER SC only		
Mean (sd)	14.1 (4.55)	14.6 (4.33)
Median	16.0	17.0
Min-Max	1.0-18.0	1.0-18.0
Overall duration of HER SC treatment [months]		
Mean (sd)	9.8 (4.54)	9.8 (3.53)
Median	10.7	11.2
Min-Max	0.0-41.2	0.0-37.2

N: Number; *i.v.*: intravenous; SC: subcutaneous; sd: standard deviation; min: minimum; max: maximum. *Treatment could be documented from start of neo-adjuvant therapy to finalization of HER-treatment.

months, stability of results for EFS and DFSneo is demonstrated (Table V).

Effectiveness in the adjuvant patient population. Primary effectiveness parameter for adjuvant patients was DFS_{adju} rate after 2 years, defined as the interval from surgery to the earlier of either disease progression (based on the response assessments collected at the last visit and the last follow-up visit) or death from any cause. The DFS_{adju} rate after 2 years was 94.9% (95%CI=92.6-96.5%). An additional analysis examined the effectiveness outcome according to age, tumor size, nodal status, and hormone receptor positivity as well as to the *post hoc* analysis of results after 30 months (Table VI).

Physician's evaluation of the subcutaneous HER application. Compliance, effectiveness, and tolerability of the subcutaneous application was assessed by the physicians at the last visit. A "very good" or "good" compliance was documented in over 90% of the votes [247 (93.2%) in neoadjuvant patients; 571 (94.4%) in adjuvant patients]. Effectiveness was assessed as "very good" or "good" in about 75% [210 (79.2%) for neoadjuvant and 450 (74.4%) for adjuvant patients]. For this rating, a large portion of patients was "not assessable" (51 neoadjuvant and 149 adjuvant patients). Predominantly "very good" or "good" tolerability for subcutaneous Herceptin resulted in over 90% of the assessments [242 (91.3%) in neoadjuvant, and 551 (91.1%) in adjuvant patients].

Table III. Changes in Herceptin SC treatment n (%).

	Neo-adjuvant (n=265)	Adjuvant (n=605)
Patients with at least one interruption in HER SC treatment		
Yes	25 (9.4%)	44 (7.3%)
No	240 (90.6%)	561 (92.7%)
Patients with HER <i>i.v.</i> therapy at baseline		
Yes	126 (47.5%)	254 (42.0%)
No	0 (0.0%)	2 (0.3%)
Missing	139 (52.5%)	349 (57.7%)
Patients with at least one change from HER SC. to <i>i.v.</i> administration		
Yes	15 (5.7%)	19 (3.1%)
No	250 (94.3%)	586 (96.9%)

N: Number; *i.v.*: intravenous; SC: subcutaneous.

Table IV. Reason for treatment discontinuation or interruption of HER SC (*s.c.* treatment only).

	Neo-adjuvant (n=64)	Adjuvant (n=105)
Decision by physician	16 (25.0%)	32 (30.5%)
Terminated by patient	18 (28.1%)	20 (19.0%)
Adverse event	11 (17.2%)	20 (19.0%)
Lost to Follow-Up	4 (6.3%)	8 (7.6%)
Metastatic disease	4 (6.3%)	3 (2.9%)
Informed consent withdrawn	3 (4.7%)	3 (2.9%)
Additional disease	1 (1.6%)	4 (3.8%)
Death	0 (0.0%)	4 (3.8%)
Recurrent/progressive disease (radiological)	1 (1.6%)	2 (1.9%)
Treatment never started/ Screening Failure	1 (1.6%)	1 (1.0%)
Other	5 (7.8%)	8 (7.6%)

n: Number.

Quality of life assessment. In this HerSCin-NIS, quality of life (QoL) was assessed by patient questionnaires EORTC QLQ-C30 and module QLQ-BR23. Analysis of the QoL endpoint was impaired by the relatively small amount of evaluable data already at baseline. The highest number of evaluable responses during the study was obtained at visit 5 (78 of 265 neoadjuvant and 185 of 605 adjuvant patients regarding “Global Health Status/QoL”). For the “All-Treated set”, the median change from baseline at Visit 5 was 0.0 for all scales. For all other visits, no meaningful analysis was feasible.

Safety results. Assessment of safety refers to all patients treated (n=971, see Figure 1, 315 neo-adjuvant, 654 adjuvant, and 2 patients in unspecified setting), *i.e.* all patients that received at least one dose of HER. Table VII gives an overview of the different (serious) adverse events (AEs/SAEs) in the two treatment groups. Overall AE incidences were comparable, with a somewhat higher incidence of AEs (17.1% vs. 13.9%) leading to treatment withdrawal, or treatment interruption in the neo-adjuvant treatment group, whereas more SAEs (10.2% vs. 15.9%) and SAEs >Grade 3 (6.7% vs. 11.2%) were documented for the adjuvant treatment group.

“Fatigue” (11.1% and 12.8%), “diarrhea” (8.6% and 7.0%), and “arthralgia” (7.0% and 8.0 %) were the most frequently reported preferred terms (PTs) in the neo-adjuvant as well as in the adjuvant treatment setting.

Documentation within this NIS HerSCin paid special attention to cardiac AEs (Table VIII). The percentage of patients with cardiac AEs (7.9% in the neo-adjuvant and 8.3% in the adjuvant setting) and SAEs (1.9% neo-adjuvant and 2.1% adjuvant) and related cardiac AEs ≥grade 3 (1.3%

neo-adjuvant and 1.1% adjuvant) was similar in both the neoadjuvant and the adjuvant setting. The most frequently reported PTs slightly differed between the neo-adjuvant and the adjuvant setting.

Altogether 12 patients (1.2%) stopped HER treatment due to cardiac AEs, some with pre-existing heart diseases some without any previously reported cardiac anamnesis. Cardiac events with NCI CTC AE grade >3 related to HER were “ejection fraction decreased” (4 events in 4 neoadjuvant patients, 3 events in 3 adjuvant patients) “cardiac failure” (4 events in 4 adjuvant patients), and “atrial fibrillation” (2 events in 2 adjuvant patients).

SAEs usually occurred as single PTs. All SAEs occurring in 2 patients and more either in the neo- or adjuvant setting are displayed in Table IX.

Fifteen patients (1.6%) died of a fatal AE during the course of the NIS, and 6 of these deaths were related to secondary carcinomas (1 patient with acute myeloid leukemia and 1 patient with acute leukemia, 2 patients with glioblastoma, bile duct cancer and endometrial adenocarcinoma with 1 patient each). For all these events – with the exception of the patient with acute leukemia and one patient with fatal atrial fibrillation and cardiac failure, where reporting physicians assumed a possible relation to HER - the physicians did not report a causal relationship to HER, or the relationship was unknown.

Discussion

The results from the NIS HerSCin seem to reflect treatment situation for early HER2+ BC in daily practice regarding patient numbers, selection, type, and geographic distribution

Figure 2. pCR-assessments (general and remission status). pCR: Pathologic complete response; n: number. Green frame indicates groups containing patients for whom achieved pCR is documented.

Table V. pCR Status and EFS and DFS_{neo} for neo-adjuvant patients.

pCR status	Endpoint	Rate [%] after 2 years (95%CI)	Rate [%] after 30 months (95%CI)
Any	EFS	90.8 (85.9-94.0)	88.8 (83.4-92.6)
Any	DFS _{neo}	89.6 (84.3-93.2)	88.7 (83.1-92.6)
pCR achieved	DFS _{neo}	90.4 (80.8-95.4)	88.1 (77.1-94.0)
pCR not achieved	DFS _{neo}	84.8 (72.8-91.8)	84.8 (72.8-91.8)

DFS_{neo}: Disease-free survival in the neoadjuvant setting; EFS: event-free survival; pCR: pathologic complete response; CI: confidence interval.

of the 135 participating centers in hospitals and open care practices all over Germany. HER SC had been registered in the (neo)adjuvant setting based on the results of the open label HannaH trial (21). Patients with early HER2+ BC received 8 neo-adjuvant cycles of HER SC or HER *i.v.* concurrently with chemotherapy, followed by surgery and completed HER SC or HER *i.v.* respectively, for up to one-year therapy duration. pCR was achieved in 45.4% of the patients receiving HER SC. In the neo-adjuvant treatment group within our NIS, 41.5% of the patients achieved pCR. Although a cross trial comparison must be regarded with great caution, as HerSCin was a mere observational study without specific inclusion and exclusion criteria and no specific documentation requirements, results for the neo-adjuvant treatment group were within expected range resulting from randomized clinical trials with HER *i.v.* or *s.c.* [as is *e.g.* HannaH (21), NOAH (13), GEPAR4 (25), TECHNO (26)]. Patients with documented pCR showed higher DFS_{neo} rates compared to those without pCR [patients

with pCR: 90.4% (95%CI=80.8-95.4) vs. patients not achieving pCR: 84.8% (95%CI=72.8-91.8)]. This difference in percentage already appears after 24 months, underlining the relevance of achieving pCR after effective neoadjuvant treatment, which has been demonstrated in several meta-analyses (27, 28) and is reflected by the support for the neoadjuvant therapy in all relevant guidelines and recommendations (29-31). Surprisingly, pCR assessment was lacking for more than 30% of the neo-adjuvant patients in our NIS. This high rate of missing values is possibly due to the non-interventional character of our study.

The pivotal trial HannaH has documented an EFS rate of 76% after three years in the patient group treated with subcutaneous HER (32). EFS rate of the neo-adjuvant patient population in our NIS was in a similar range with 91% after two years and 89% after 30 months (*post hoc* analysis). Side effects for the subcutaneous application for the neo-adjuvant treatment group from HerSCin ranged below the incidences

Table VI. Disease-free survival rate after 24 months and after 30 months (post hoc analysis) for adjuvant patients.

Adjuvant patients	n	Disease-free survival [%]	
		After 2 years (95%CI)	After 30 months (95%CI) ^a
All	605	94.9 (92.6-96.5)	92.5 (89.7-94.5)
Age category [years]			
<50	129	99.1 (94.0-99.9)	96.9 (90.7-99.0)
≥50-<70	335	97.6 (95.0-98.9)	94.2 (90.6-96.5)
≥70	141	83.3 (74.6-89.3)	83.3 (74.6-89.3)
Tumor staging			
T1	339	97.2 (94.4-98.6)	93.2 (89.3-95.8)
≥T2	262	92.0 (87.6-94.9)	91.4 (86.8-94.5)
Nodal status			
N0	354	96.7 (93.9-98.2)	94.6 (91.2-96.7)
N1	145	95.9 (90.3-98.3)	91.8 (84.7-95.7)
N2	52	84.8 (70.6-92.5)	84.8 (70.6-92.5)
N3	30	84.8 (64.3-94.0)	84.8 (64.3-94.0)
Nx	19	100.0 (100.0-100.0)	85.7 (33.4-97.9)
Hormone receptor status for estrogen and/or progesterone			
Positive	452	97.0 (94.7-98.3)	95.4 (92.6-97.1)
Negative	151	88.7 (81.7-93.2)	83.6 (75.4-89.3)

n: Number; CI: confidence interval. ^apost hoc analysis.

Table VII. Synopsis of adverse events.

Patients with	Neoadjuvant (n=315)	Adjuvant (n=654)	Treated patients* (n=971)
Any AE	208 (66.0%)	430 (65.7%)	638 (65.7%)
AEs of grade ≥3	44 (14.0%)	114 (17.4%)	158 (16.3%)
SAEs	32 (10.2%)	104 (15.9%)	136 (14.0%)
SAEs of grade ≥3	21 (6.7%)	73 (11.2%)	94 (9.7%)
AEs related to Herceptin SC	63 (20.0%)	127 (19.4%)	190 (19.6%)
AEs related to Herceptin SC of grade ≥3	9 (2.9%)	16 (2.4%)	25 (2.6%)
SAEs related to Herceptin SC	6 (1.9%)	11 (1.7%)	17 (1.8%)
AESIs	0 (0.0%)	0 (0.0%)	0 (0.0%)
AEs resulting in withdrawal/interruption of Herceptin SC	54 (17.1%)	91 (13.9%)	145 (14.9%)
AEs resulting in death	3 (1.0%)	12 (1.8%)	15 (1.5%)

AE: Adverse event; AESI: adverse event of special interest; SAE: serious adverse event; n: number. *2 patients in an unspecified setting.

that were reported in the pivotal trial (any AE 97.6% HannaH vs. 66.0% in HerSCin, AEs > Grade 3 HannaH 53.2% vs. 14.0% in HerSCin, SAEs 21.9% in HannaH vs. 10.2% in HerSCin, cardiac AEs 14.8% in HannaH vs. 7.9% in HerSCin). A certain extent of underreporting seems to be characteristic for observational studies. As a consequence, overall dimension of effectiveness and safety outcomes for the neo-adjuvant treatment group ranges within an expected scope.

The PrefHER study has documented patient preference and satisfaction of healthcare professionals with the subcutaneous use of HER in female patients with early HER2+ BC in the adjuvant treatment setting as primary endpoints. Secondary outcome parameters included EFS rate after 3 years (33),

Table VIII. Most frequently reported PTs within the SOC cardiac disorders.

	Neo-adjuvant n=315 patients (%) - events	Adjuvant n=654 patients (%) - events
Palpitations	3 (1.0%)-3	7 (1.1%)-8
Atrial fibrillation	1 (0.3%)-1	6 (0.9%)-9
Left ventricular dysfunction	5 (1.6%)-5	5 (0.8%)-5
Cardiomyopathy	1 (0.3%)-1	7 (1.1%)-7
Cardiac failure	2 (0.6%)-2	6 (0.9%)-6
Tachycardia	4 (1.3%)-4	3 (0.5%)-3

n: Number.

Table IX. SAEs per PT occurring more than in 2 patients.

SAE -SOC	SAE-PT	Neo-adjuvant patients n=315	Adjuvant patients n=654
General disorders and administration site conditions	General physical health deterioration	2 (0.7%)	14 (2.1%)
	Pyrexia	(6 events)	(15 events)
			5 (0.8%)
			(6 events)
	Impaired healing	2 (0.6%)	
Infections and infestations	Pneumonia	2 (0.6%)	5 (0.8%)
	Urinary tract infection	2 (0.6%)	
Blood and lymphatic system disorders	Anemia		5 (0.8%)
			(6 events)
	Leucopenia		5 (0.8%)
Respiratory, thoracic and mediastinal disorders	Dyspnea	2 (0.6%)	
	Dyspnea exertional	2 (0.6%)	
	Pulmonary embolism	2 (0.6%)	
Gastrointestinal disorders	Constipation	2 (0.6%)	
	Stomatitis		3 (0.5%)
			(6 events)
Psychiatric disorders	Depression		4 (0.6%)
			(5 events)
Vascular disorders	Hypertension		4 (0.6%)
			(5 events)
Cardiac disorders	Mitral valve incompetence	2 (0.6%)	
Neoplasms benign, malignant and unspecified	Metastases to central nervous system	2 (0.6%)	

SAE: Serious adverse event; SOC: system organ class; PT: preferred term; n: number. Number of events only given, if different from SAE-incidence.

which is different from the assessment within our NIS, evaluating the DFS_{adju} rate at 24 months for the adjuvant treatment group. EFS in PrefHER was defined as the time from randomization to local, regional, or distant disease recurrence, contralateral breast cancer or death from any cause. EFS for the overall evaluable ITT (intent to treat) population was 90.6% (95%CI=87.4-92.9%) (31). DFS_{adju} rates in our NIS were 94.91% (95%CI=92.59-96.52) after 2 years and 92.46% (95%CI=89.66-94.53) after 2.5 years. So, overall effectiveness results from both the randomized controlled study and our NIS range were about the same magnitude.

In PrefHER, the vast majority [91.5% (n=216/236)] of the patients preferred subcutaneous administration over intravenous application for reasons of time saving, less pain and discomfort during injection (33), which was also confirmed by Sanford *et al.* in his review of subcutaneous HER (34). The patient reported data from our NIS did not discover any change in quality of life - although patient participation rate in QoL assessments was modest at best throughout the NIS and did not allow to draw valid conclusions. Data from our NIS, however, reflect physician's positive assessment of compliance, tolerability, and effectiveness of subcutaneous HER.

Data for safety and tolerability from SafeHer, another phase III study evaluated the safety and tolerability of the Herceptin

SC 600 mg fixed dose for 1 year as (neo-) adjuvant therapy with concurrent or sequential chemotherapy for HER2-positive EBC. AE-rate in patients receiving chemotherapy in parallel compared to sequential administration of HER was higher. Cardiac disorders > Grade 3 (irrespective of relationship) were observed in 0.9% of patients (35), which somehow corresponds to the 1.1% of adjuvant patients with related > grade 3 cardiac events in our NIS.

Recently published data from a French NIS HERmione assessed the safety profile of subcutaneous Herceptin in 505 patients with early HER2+ BC in the neoadjuvant and adjuvant setting. The three most frequently reported AEs besides "radiation induced skin injury" were "asthenia" (in 27.5%), "arthralgia" (in 23.6%) and "myalgia" in 14.7% of the HERmione safety population (36). Most frequently reported PTs in PrefHER under HER SC (first treatment period) were "hot flushes" (7.0%), "nausea" and "asthenia" with 6.6% each (37). This largely matches with "fatigue (12.3%)", "diarrhea (7.5%)" and "arthralgia (7.6%)" being the most frequently reported AEs in our NIS HerSCin. Overall, safety results from the PrefHer study were in principle comparable to safety outcomes of the adjuvant patient population in our NIS (37).

Cardiac safety represents an essential aspect of safety as HER2 is also known to play a role in the development of

new and the repair of damaged myocardium (38, 39). Therefore, cardiac AEs were observed in our NIS for the neo-adjuvant and the adjuvant patient population, however, there were no signs, that cardiac toxicity occurred more frequently or in more severe intensity in day-to-day routine. During our NIS, six patients (0.6%) were reported to have died from secondary carcinoma of different kind. In this context we reviewed incidences of secondary carcinoma in HERA, where 3.5% of the patients treated with HER for 2 years and 2.8% when treated with HER over 1 year and 2.4% when treated without HER developed secondary carcinoma (40). So, incidence of secondary carcinoma in our NIS was below the range that has been documented in HERA.

There are several limitations to our NIS, which - first of all - refer to the mere observational character of the study, without specific in- or exclusion criteria, no strict regulations as to treatment documentation and adherence to regular check-up intervals. One specific limitation in this NIS, however, concerns the way of patient allocation into either the neo-adjuvant or adjuvant treatment group. This either follows the sole perspective of HER treatment, or considers the prior, parallel, or sequential chemotherapy backbone, which was the perspective that was considered for the final analysis of this NIS. Furthermore, pCR documentation was impaired by a double entry possibility for pCR in the eCRF, one for the overall pCR assessment (yes or no) and one for the detailed pathological remission status. As the observational plan did not exactly specify the intended pCR definition, the entries were made at the documenter's best judgement. This resulted in many patients without adequate pCR documentation, thus giving no exact pCR rate from the neo-adjuvant treatment group due to missing entries. For the adjuvant treatment group, it needs to be considered, that DFS is documented as a rate after 2 years. As a consequence, most of the patients were censored with respect to this percentage. A *post hoc* analysis after 2.5 years showed, that DFS rate minimally declined at this time.

Another common finding within NIS settings was a tendency of AE-underreporting, which may be also applied for HerSCin. Frequency of AEs and SAEs were relatively low when compared with controlled clinical trials. Likewise, QoL data were received at a low response rate in our NIS, preventing a detailed analysis of the results.

Based on patient choice and preferences - as reported in PrefHER - subcutaneous trastuzumab represents a progress in the concept of cancer management. Subcutaneous administration allows a quicker and for many patients more convenient HER regimen, especially in the maintenance phase (41, 42), after finalization of *i.v.* treatment with concomitant or precedent chemotherapy. Several randomized trials established the comparable efficacy and safety profiles between the subcutaneous and the intravenous application mode. This includes the results from FEDERICA, where

pertuzumab and trastuzumab were applied subcutaneously in early HER2+ BC, demonstrating comparable pharmacokinetic and pharmacodynamic results (43). Real world data from our NIS, as well as judgement from physicians about overall effectiveness, tolerability, and safety data from our NIS support these previous findings.

In summary, the subcutaneous formulation of Herceptin with its similar efficacy and safety profile compared to the intravenous route of administration can optimize the use of medical resources and thus offer a potential economic benefit. Results from this non-interventional study are in line with other trials, where Herceptin SC was administered in the neoadjuvant and adjuvant setting.

Conflicts of Interest

Dr. Schmidt reports personal fees from Amgen, AstraZeneca, Lilly, and Novartis, grants and personal fees from Pantarhei Bioscience, grants, personal fees, and non-financial support from Pfizer, grants and personal fees from Pierre-Fabre, personal fees from MSD, grants, personal fees, and non-financial support from Roche, personal fees from Seattle Genetics, other from Sividon, and grants and non-financial support from BioNTech outside the submitted work; in addition, Dr Schmidt has a patent to EP 2951317 B1: A method for predicting the benefit from inclusion of a taxane in a chemotherapy regimen in patients with breast cancer issued and a patent to EP 2390370 B1: A method for predicting the response of a tumor in a patient suffering from or at risk of developing recurrent gynecologic cancer towards a chemotherapeutic agent issued. Dr. Schmatloch received honoraria from Roche, Novartis, and Polytech for lecturing activities.

Dr. Kümmel received consulting fees (*e.g.* advisory boards) from Roche, Genomic Health, Novartis, Amgen, Celgene, Daiichi Sankyo, Astra Zeneca, Somatex, MSD, Pfizer, PFM Medical, Lilly, Sonoscape. Dr. Kümmel conducts contracted research with Roche, Somatex – Research Grant /Funding Institution, holds ownership interests in WSG Study Group – minority ownership and received Travel/Accommodation/Expenses from Roche/Daiichi Sankyo/Sonoscape.

Dr. Lüdtk-Heckenkamp received personal fees (lectures, advisory boards and travel and accommodation expenses for congresses) from Astra Zeneca, Celgene, Eisai, Novartis, Pfizer, Roche (in alphabetical order). Dr. Ruf-Doerdelmann reports personal fees from Amgen, Novartis, Genomic Health, Novartis and Roche. Dr. Busch-Liles holds stocks and is an employee of Roche Pharma Germany. Dr. Distelrath and Dr. Wacker reported to not have received personal fees.

Authors' Contributions

Primary drafting of the manuscript and review, and submission was performed by Marcus Schmidt and Kerstin Lüdtk-Heckenkamp. All Authors of the manuscript, *i.e.* M. Schmidt, K. Lüdtk-Heckenkamp, A. Distelrath, S. Kümmel, A. Ruf-Doerdelmann, S. Schmatloch, J Wacker and S. Busch-Liles contributed to the conception and design of the study, to the generation, collection, assembly, analysis and/or interpretation of data and to the drafting of the manuscript. All Authors approved the final version and submission of the manuscript.

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References

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 68(6): 394-424, 2018. PMID: 30207593. DOI: 10.3322/caac.21492
- Ross JS, Fletcher JA, Linette GP, Stec J, Clark E, Ayers M, Symmans FW, Pusztai L and Bloom KJ: The Her-2/neu gene and protein in breast cancer 2003: biomarker and target of therapy. *Oncologist* 8(4): 307-325, 2003. PMID: 12897328. DOI: 10.1634/theoncologist.8-4-307
- Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, Dowsett M, Fitzgibbons PL, Hanna WM, Langer A, McShane LM, Paik S, Pegram MD, Perez EA, Press MF, Rhodes A, Sturgeon C, Taube SE, Tubbs R, Vance GH, van de Vijver M, Wheeler TM and Hayes DF: American Society of Clinical Oncology; College of American Pathologists: American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol* 25(1): 118-145, 2007. PMID: 19548375. DOI: 10.1043/1543-2165(2007)131[18:ASOCCO]2.0.CO;2
- Spigel DR and Burstein HJ: Trastuzumab regimens for HER2-overexpressing metastatic breast cancer. *Clin Breast Cancer* 4(5): 329-337; discussion 338-339, 2003. PMID: 14715107. DOI: 10.3816/cbc.2003.n.038
- Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J and Norton L: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *New Engl J Med* 344(11): 783-792, 2001. PMID: 11248153. DOI: 10.1056/NEJM200103153441101
- Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Láng I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Rüschoff J, Suto T, Gatrex V, Ward C, Strahle C, McFadden E, Dolci MS and Gelber RD: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *New Engl J Med* 353(16): 1659-1672, 2005. PMID: 16236737. DOI: 10.1056/NEJMoa052306
- Kim MM, Allen P, Gonzalez-Angulo AM, Woodward WA, Meric-Bernstam F, Buzdar AU, Hunt KK, Kuerer HM, Litton JK, Hortobagyi GN, Buchholz TA, and Mittendorf EA: Pathologic complete response to neoadjuvant chemotherapy with trastuzumab predicts for improved survival in women with HER2-overexpressing breast cancer. *Ann Oncol* 24(8): 1999-2004, 2013. PMID: 23562929. DOI: 10.1093/annonc/mdt131
- Semiglazov V, Eiermann W, Zambetti M, Manikhas A, Bozhok A, Lluch A, Tjulandin S, Sabadell MD, Caballero A, Valagussa P, Baselga J and Gianni L: Surgery following neoadjuvant therapy in patients with HER2-positive locally advanced or inflammatory breast cancer participating in the NeOAdjuvant Herceptin (NOAH) study. *Eur J Surg Oncol* 37(10): 856-863, 2011. PMID: 21843921. DOI: 10.1016/j.ejso.2011.07.003
- Paik S, Kim C and Wolmark N: HER2 status and benefit from adjuvant trastuzumab in breast cancer. *New Engl J Med* 358(13): 1409-1411, 2008. PMID: 18367751. DOI: 10.1056/NEJMc0801440
- Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, Mackey J, Glaspy J, Chan A, Pawlicki M, Pinter T, Valero V, Liu MC, Sauter G, von Minckwitz G, Visco F, Bee V, Buyse M, Bendahmane B, Tabah-Fisch I, Lindsay MA, Riva A and Crown J: Adjuvant trastuzumab in HER2-positive breast cancer. *New Engl J Med* 365(14): 1273-1283, 2011. PMID: 21991949. DOI: 10.1056/NEJMoa0910383
- Perez EA, Romond EH, Suman VJ, Jeong JH, Sledge G, Geyer EC, Martino S, Rastogi P, Gralow J, Swain SM, Winer EP, Colon-Otero G, Davidson NE, Mamounas E, Zujewski JA and Wolmark N: Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol* 32(33): 3744-3752, 2014. PMID: 25332249. DOI: 10.1200/JCO.2014.55.5730
- Okamoto M, Tajiri W, Ueo H, Masuda T, Ijichi H, Koga C, Nakamura Y, Taguchi K, Ohno S and Tokunaga E: Efficacy of adjuvant combination therapy with trastuzumab and chemotherapy in HER2-positive early breast cancer: A Single Institutional Cohort Study from Clinical Practice. *Anticancer Res* 40(6): 3315-3323, 2020. PMID: 32487627. DOI: 10.21873/anticancer.14314
- Gianni L, Eiermann W, Semiglazov V, Lluch A, Tjulandin S, Zambetti M, Moliterni A, Vasquez F, Byakhov ML, Lichinitser M, Climent M, Angel M, Ciruelos E, Ojeda B, Mansutti M, Bozhok A, Magazzù D, Heinzmann D, Steinseifer J, Valagussa P and Baselga J: Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet Oncol* 15(6): 640-647, 2014. PMID: 24657003. DOI: 10.1016/S1470-2045(14)70080-4
- Hanker LC, Förster F, Schröder J, Grafe A, Hitschold T, Hesse T, Lattrich CR, and Rody A: Resumption of trastuzumab in patients with disease recurrence after (neo-) adjuvant anti-HER2-therapy in patients with HER2-positive breast cancer. *Anticancer Res* 40(7): 3973-3981, 2020. PMID: 32620640. DOI: 10.21873/anticancer.14390
- Láng I, Bell R, Feng FY, Lopez RI, Jassem J, Semiglazov V, Al-Sakaff N, Heinzmann D and Chang J: Trastuzumab retreatment

- after relapse on adjuvant trastuzumab therapy for human epidermal growth factor receptor 2-positive breast cancer: final results of the Retreatment after HErceptin Adjuvant trial. *Clin Oncol (R Coll Radiol) (Great Britain)* 26(2): 81-89, 2014. PMID: 24051172. DOI: 10.1016/j.clon.2013.08.011
- 16 von Minckwitz G, Du Bois A, Schmidt M, Maass N, Cufer T, Jongh FE, Maartense E, Zielinski C, Kaufmann M, Bauer W, Baumann KH de, Clemens MR, Duerr R, Uleer C, Andersson M, Stein RC, Nekljudova V and Loibl S: Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. *J Clin Oncol* 27(12): 1999-2006, 2009. PMID: 19289619. DOI: 10.1200/JCO.2008.19.6618
 - 17 Thomssen C, El Saghir NS, Francis AP, Jassem J, Rugo HS and Untch M: Dual HER2 blockade. *Breast Care (Basel, Switzerland)* 12(5): 345-349, 2017. PMID: 29234257. DOI: 10.1159/000484226
 - 18 Wang J and Xu B: Targeted therapeutic options and future perspectives for HER2-positive breast cancer. *Signal Transduct Target Ther* 4: 34, 2019. PMID: 31637013. DOI: 10.1038/s41392-019-0069-2
 - 19 Russillo, Ferretti G, Vidiri A, Gasparo S, Cognetti F, Pilegrini D and Fabi A: Impressive long-term response with pertuzumab and trastuzumab in HER2-positive breast cancer with brain metastasis. *In Vivo* 32(4): 839-842, 2018. PMID: 29936468. DOI: 10.21873/invivo.11317
 - 20 Chen L, Zhou W, Hu X, Yi M, Ye C and Yao G: Short-duration versus 1-year adjuvant trastuzumab in early HER2 positive breast cancer: A meta-analysis of randomized controlled trials. *Cancer Treat* 75: 12-19, 2019. PMID: 30856373. DOI: 10.1016/j.ctrv.2019.02.003
 - 21 Ismael G, Hegg R, Muehlbauer S, Heinzmann D, Lum B Kim SB, Pienkowski T, Lichinitser M, Semiglazov V, Melichar B and Jackisch C: 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* 13(9): 869-878, 2012. PMID: 22884505. DOI: 10.1016/S1470-2045(12)70329-7
 - 22 Medicinal Products Act (Arzneimittelgesetz – AMG) (2019). Available at: http://www.gesetze-im-internet.de/englisch_amg/index.html [Last accessed on June 30, 2020]
 - 23 Fayers P and Bottomley A: Quality of life research within the EORTC—the EORTC QLQ-C30. *Eur J Cancer* 38: 125-133, 2002. PMID: 11858978. DOI: 10.1016/S0959-8049(01)00448-8
 - 24 Breast Cancer (update of QLQ-BR23) | EORTC – Quality of Life (2019). Available at: <https://qol.eortc.org/questionnaire/update-qlq-br23> [Last accessed on June 30, 2020]
 - 25 Untch M, Rezaei M, Loibl S, Fasching PA, Huober J, Tesch H, Bauerfeind I, Hilfrich J, Eidtmann H, Gerber B, Hanusch C, Kühn T, Du Bois A, Blohmer JU, Thomssen C, Dan Costa S, Jackisch C, Kaufmann M, Mehta K and von Minckwitz G: Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. *J Clin Oncol* 28(12): 2024-2031, 2010. PMID: 20308670. DOI: 10.1200/JCO.2009.23.8451
 - 26 Untch M, Fasching PA, Konecny GE, Hasmüller S, Lebeau A, Kreienberg R, Camara O, Müller V, Du Bois A, Kühn T, Stickeler E, Harbeck N, Höss C, Kahlert S, Beck T, Fett W, Mehta KM, von Minckwitz G and Loibl S: Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. *J Clin Oncol* 29(25): 3351-3357, 2011. PMID: 21788566. DOI: 10.1200/JCO.2010.31.4930
 - 27 Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnefoi H, Cameron D, Gianni L, Valagussa P, Swain SM, Prowell T, Loibl S, Wickerham DL, Bogaerts J, Baselga J, Perou C, Blumenthal G, Blohmer J, Mamounas EP, Bergh J, Semiglazov V, Justice R, Eidtmann H, Paik S, Piccart M, Sridhara R, Fasching PA, Slaets L, Tang S, Gerber B, Geyer CE, Pazdur R, Ditsch N, Rastogi P, Eiermann W and von Minckwitz G: Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 384(9938): 164-172, 2014. PMID: 24529560. DOI: 10.1016/S0140-6736(13)62422-8
 - 28 von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, Gerber B, Eiermann W, Hilfrich J, Huober J, Jackisch C, Kaufmann M, Konecny GE, Denkert C, Nekljudova V, Mehta K and Loibl S: Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 30(15): 1796-1804, 2012. PMID: 22508812. DOI: 10.1200/JCO.2011.38.8595
 - 29 Glöggler: Diagnosis and treatment of patients with early and advanced Breast Cancer - Neoadjuvant (primary) Systemic Therapy. Available at: https://www.ago-online.de/fileadmin/ago-online/downloads/_leitlinien/kommission_mamma/2020/PDF_EN/2020E%2012_Neoadjuvant%20%28Primary%29%20Systemic%20Therapy_with%20References.pdf [Last accessed on July 14, 2020]
 - 30 Burstein H J, Curigliano G, Loibl S, Dubsy P, Gnant M, Poortmans P, Colleoni M, Denkert C, Piccart-Gebhart M, Regan M, Senn HJ, Winer EP and Thurlimann B: Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. *Ann Oncol* 30(10): 1541-1557, 2019. PMID: 31373601. DOI: 10.1093/annonc/mdz235
 - 31 Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, Zackrisson S and Senkus E: Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 30(8): 1194-1220, 2019. PMID: 31161190. DOI: 10.1093/annonc/mdz173
 - 32 Jackisch C, Hegg R, Stroyakovskiy D, Ahn JS, Melichar B, Chen SC, Kim SB, Lichinitser M, Staroslawska E, Kunz G, Falcon S, Chen ST, Crepelle-Fléchais A, Heinzmann D, Shing M and Pivot X: 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. *Eur J Cancer* 62: 62-75, 2016. PMID: 27208905. DOI: 10.1016/j.ejca.2016.03.087
 - 33 Pivot X, Verma S, Fallowfield L, Müller V, Lichinitser M, Jenkins V, Sánchez Munos A, Machackova Z, Osborne S and Gligorov J: Efficacy and safety of subcutaneous trastuzumab and intravenous trastuzumab as part of adjuvant therapy for HER2-positive early breast cancer: Final analysis of the randomised, two-cohort PreHer study. *Eur J Cancer* 86: 82-90, 2017. PMID: 28963915. DOI: 10.1016/j.ejca.2017.08.019
 - 34 Sanford M: Subcutaneous trastuzumab: a review of its use in HER2-positive breast cancer. *Target Oncol* 9(1): 85-94, 2014. PMID: 24664187. DOI: 10.1007/s11523-014-0313-1

- 35 Gligorov J, Ataseven B, Verrill M, Laurentiis, M de, Jung KH, Azim HA, Al-Sakaff N, Lauer S, Shing M and Pivot X: Safety and tolerability of subcutaneous trastuzumab for the adjuvant treatment of human epidermal growth factor receptor 2-positive early breast cancer: SafeHer phase III study's primary analysis of 2573 patients. *Eur J Cancer* 82: 237-246, 2017. PMID: 28625777. DOI: 10.1016/j.ejca.2017.05.010
- 36 Jacquin JP, Uwer L, Savignoni A, Ferrero JM, Lortholary A, Solub D, Delaporte F, Chalabi N, Pibre S and Belkacemi Y: Safety profile of subcutaneous trastuzumab in patients with HER2-positive early breast cancer: The French HERmione non-interventional prospective study. *Breast* 49: 1-7, 2020. PMID: 31670262. DOI: 10.1016/j.breast.2019.10.002
- 37 Gligorov J, Curigliano G, Müller V, Knoop A, Jenkins V, Verma S, Osborne S, Lauer S, Machakova Z, Fallowfield L and Pivot X: Switching between intravenous and subcutaneous trastuzumab: Safety results from the PrefHer trial. *Breast* 34: 89-95, 2017. PMID: 28549309. DOI: 10.1016/j.breast.2017.05.004
- 38 Suter TM, Cook-Bruns N and Barton C: Cardiotoxicity associated with trastuzumab (Herceptin) therapy in the treatment of metastatic breast cancer. *Breast* 13(3): 173-183, 2004. PMID: 15177418. DOI: 10.1016/j.breast.2003.09.002
- 39 Zhao YY, Sawyer DR, Baliga RR, Opel DJ, Han X, Marchionni MA and Kelly RA: Neuregulins promote survival and growth of cardiac myocytes. Persistence of ErbB2 and ErbB4 expression in neonatal and adult ventricular myocytes. *Int J Biol Chem* 273(17): 10261-10269, 1998. PMID: 9553078. DOI: 10.1074/jbc.273.17.10261
- 40 Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A and de Azambuja E, Castro G Jr, Untch M, Smith I, Gianni L, Baselga J, Al-Sakaff N, Lauer S, McFadden E, Leyland-Jones B, Bell R, Dowsett M and Jackisch C; Herceptin Adjuvant (HERA) Trial Study Team: 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet* 389(10075): 1195-1205, 2017. PMID: 28215665. DOI: 10.1016/S0140-6736(16)32616-2
- 41 Melichar B, Študentová H, Kalábová H and Vitásková D: Role of subcutaneous formulation of trastuzumab in the treatment of patients with HER2-positive breast cancer. *Immunotherapy* 6(7): 811-819, 2014. PMID: 25290414. DOI: 10.2217/imt.14.50
- 42 Heo YA and Syed YY: Subcutaneous trastuzumab: a review in HER2-positive breast cancer. *Target Oncol* 14(6): 749-758, 2019. PMID: 31686307. DOI: 10.1007/s11523-019-00684-y
- 43 Tan AR, Im SA, Mattar A, Colomer R, Stroyakovskii D, Nowecki Z, De Laurentiis M, Pierga JY, Jung KH, Schem C, Heeson S, Shivhare M, Kirschbrown MP, Restuccia E, Badovinac Crnjevic T and Jackisch C. (02152020): Abstract PD4-07: Subcutaneous administration of the fixed-dose combination of trastuzumab and pertuzumab in combination with chemotherapy in HER2-positive early breast cancer: Primary analysis of the phase III, multicenter, randomized, open-label, two-arm FeDeRiCa study. In: Poster Spotlight Session Abstracts. Abstracts: 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, Texas: American Association for Cancer Research, PD4-07-PD4-07.

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