Pharmacokinetic results of a subcutaneous injection of trastuzumab into the thigh versus into the abdominal wall in patients with HER2-positive primary breast cancer treated within the neo-/adjuvant GAIN-2 study

P 5-20-09

V. Möbus[1], R. Mahlberg[2], W. Janni[3], O. Tomé[4], F. Marmé[5], H. Forstbauer[6], T. Reimer[7], A. von der Assen[8], M. Reinisch[9], R. Lorenz[10], S. Schmatloch[11], M. Schmidt[12], B. Sinn[13], N. Klutinus[14], E. Stickeler[15], M. Untch[16], S. Seiler[17], N. Burchardi[17], G. von Minckwitz[17], S. Loibl[17]

[1]Klinik für Gynäkologie und Geburtshilfe, Klinikum Frankfurt, Germany, [2]Klinikum Mutterhaus Mitte, Trier, Germany, [3]Frauenheilkunde und Geburtshilfe, Universitätsklinikum Ulm, Germany, [4]St. Vincentius-Kliniken gAG, Karlsruhe, Germany, [5]Allgemeine Frauenheilkunde und Geburtshilfe, Universitätsklinikum Heildelberg, Germany, [6]GOSPL - Gesellschaft für onkologische Studien, Troisdorf, Germany, [7]Universitätsfrauenklinik und Poliklinik am Klinikum Südstadt Rostock, Germany, [8]Niels-Stensen-Kliniken, Franziskus-Hospital Harderberg, Georgsmarienhütte, Germany, [9]Brustzentrum, Kliniken Essen-Mitte, Essen,Germany, [10]Frauenärztl. Gemeinschafts- u. Schwerpunktpraxis Onkologie, Braunschweig, Germany, [11]Brustzentrum, Elisabeth Krankenhaus Kassel, Germany, [12]Universitätsmedizin Mainz, Germany, [13]Institut für Pathologie, Charité - Universitätsmedizin Berlin, Germany, [14]HELIOS Klinikum Pforzheim GmbH Brustzentrum, Pforzheim, Germany, [15]Klinik für Gynäkologie und Geburtsmedizin, Universitätsklinikum Aachen, Germany, [16]HELIOS Klinikum Berlin Buch, Germany, [17]German Breast Group, Neu-Isenburg, Germany

Background

A subcutaneous (s.c.) formulation of trastuzumab became available in 2013 based on equivalent efficacy, pharmacokinetics (PK) and safety with standard intravenous (i.v.) administration. In this study, s.c. trastuzumab was administered into the thigh only.[1] As an s.c. injection into the abdominal wall (abdw) might be more convenient for patients (pts) and health care professionals, the PK profile of s.c. trastuzumab injected into the thigh vs into the abdw in pts with HER2-positive early breast cancer needs to be evaluated.

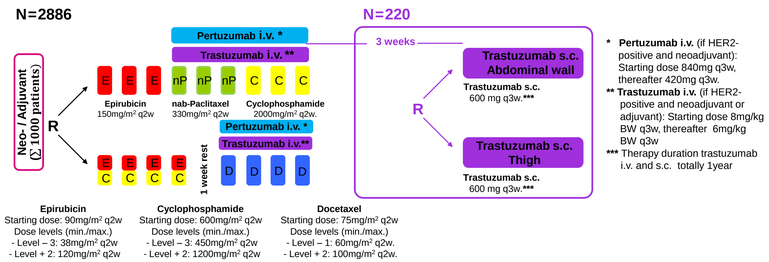
Patients and Methods

Study design of the GAIN-2 main trial including the s.c. trastuzumab substudy is shown in Figure 1.
Based on the variability observed in the HannaH study[1] and using a total sample size of 30 (15 per group) pts, the estimated two-sided 90% confidence interval (CI) of the area under the plasma concentration-time curve ($AUC_{0\text{-}21d}$) was (0.79-1.27) and (0.77-1.30) of the peak drug concentration (C_{max}). Allowing for a dropout rate of 15%, 18 pts per group were planned to be included in the PK substudy. For the PK profile of s.c. trastuzumab, blood samples collected before cycle 7, on days (d) 2, 4, 8, 15 and 21 of cycle 7 were evaluated.
One-way analyses of covariance were performed to compare PK parameters between the two routes of administration and adjusted for body weight at baseline including stratification factors based on the per protocol (pp) analysis set. Routes of administration could be considered comparable if the observed two-sided 90% CIs of the geometric mean ratio (GMR) are similar to the estimated CIs.

Objectives

- **Primary objective:** to assess the PK profile of s.c. trastuzumab injected into the thigh vs into the abdw using the peak exposure C_{max} (taken directly from the data without interpolation) and the extent of exposure $AUC_{0\text{-}21d}$ from day 0 to day 21.
- **Secondary objectives:** to assess time-to-peak drug plasma concentration T_{max}, drug concentration at the end of the dosage interval C_{trough}, safety and tolerability.

Figure 1: Study design of the GAIN-2 main trial and s.c. trastuzumab substudy



* **Pertuzumab i.v.** (if HER2-positive and neoadjuvant): Starting dose 840mg q3w, thereafter 420mg q3w.
** **Trastuzumab i.v.** (if HER2-positive and neoadjuvant or adjuvant): Starting dose 8mg/kg BW q3w, thereafter 6mg/kg BW q3w
*** Therapy duration trastuzumab i.v. and s.c. totally 1year

Results

Table 1. Baseline characteristics of patients

Parameter	Category	Thigh (N=17) N (%)	Abdominal wall (N=13) N (%)	Overall (N=30) N (%)	p-value
Age group (year)*	≤50	11 (64.7)	8 (61.5)	19 (63.3)	1.000
	>50	6 (35.3)	5 (38.5)	11 (36.7)	
pT	pT1	9 (52.9)	6 (46.2)	15 (50.0)	0.873
	pT2	5 (29.4)	5 (38.5)	10 (33.3)	
	pT3	3 (17.6)	2 (15.4)	5 (16.7)	
	pT4	0 (0.0)	0 (0.0)	0 (0.0)	
pN	pN0	4 (23.5)	2 (15.4)	6 (20.0)	0.011
	pN1	1 (5.9)	7 (53.8)	8 (26.7)	
	pN2	9 (52.9)	1 (7.7)	10 (33.3)	
	pN3	3 (17.6)	3 (23.1)	6 (20.0)	
ER/PgR	both ER, PgR negative	4 (23.5)	3 (23.1)	7 (23.3)	1.000
	ER and/or PgR positive	13 (76.5)	10 (76.9)	23 (76.7)	
Tumor grading	G1	0 (0.0)	0 (0.0)	0 (0.0)	0.376
	G2	4 (23.5)	5 (38.5)	9 (30.0)	
	G3	13 (76.5)	8 (61.5)	21 (70.0)	
Histological tumor type	ductal or ductal-lobular invasive	13 (76.5)	10 (76.9)	23 (76.7)	0.977
	lobular invasive	0 (0.0)	0 (0.0)	0 (0.0)	
	other	4 (23.5)	3 (23.1)	7 (23.3)	
Treatment arm in main study*	EnPC	9 (52.9)	7 (53.8)	16 (53.3)	1.000
	dtEC-dtD	8 (47.1)	6 (46.2)	14 (46.7)	
Weight (kg)	Median	69.0	75.0	73.0	0.098
	Min; Max	53.0; 92.0	55.0; 130.0	53.0; 130.0	
BMI	Median	25.4	26.2	25.9	0.161
	Min; Max	18.8; 32.0	20.7; 42.0	18.8; 42.0	

*stratification factor; pT, pathological tumor stage; pN, pathological nodal status; BMI, body mass index; ER, estrogen receptor; PgR, progesteron receptor

Table 2. The most frequent adverse events (AE)

AE	Grade	Thigh N (%)	Abdominal wall N (%)	Overall N (%)	p-value
Any AE	any	16 (94.1)	13 (100.0)	29 (96.7)	1.00
	3-4	2 (11.8)	3 (23.1)	5 (16.7)	0.628
Any hematological AE	any	16 (94.1)	11 (84.6)	27 (90.0)	0.565
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Anemia	any	12 (70.6)	8 (61.5)	20 (66.7)	0.705
Leukopenia	any	14 (82.4)	10 (76.9)	24 (80.0)	1.00
Any non-hematological AE	any	16 (94.1)	13 (100.0)	29 (96.7)	1.00
	3-4	2 (11.8)	3 (23.1)	5 (16.7)	0.628
Increased ASAT	any	5 (29.4)	4 (30.8)	9 (30.0)	1.00
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Increased ALAT	any	6 (35.3)	5 (38.5)	11 (36.7)	1.00
	3-4	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Fatigue	any	8 (47.1)	10 (76.9)	18 (60.0)	0.141
	3-4	1 (5.9)	0 (0.0)	1 (3.3)	1.00
Alopecia	any	6 (35.3)	3 (23.1)	9 (30.0)	0.691
Peripheral neuropathy (PNP)	any	9 (52.9)	7 (53.8)	16 (53.3)	1.00
	3-4	1 (5.9)	1 (7.7)	2 (6.7)	1.00
Serious AE (SAE)	n.a.	2	4	6	n.a.

Figure 2. Mean plasma concentration-time profile of the s.c. trastuzumab

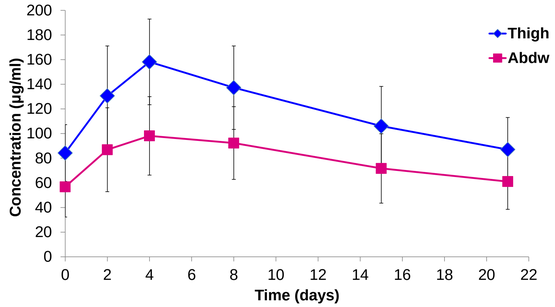


Table 3. PK parameters of the s.c. trastuzumab

Parameter	Category	Thigh	Abdominal wall
C_{max} (µg/ml)	Mean (SD)	150.73 (44.81)	100.00 (31.14)
	CV%	29.73	31.14
	Geo-Mean (SD)	142.08 (1.49)	94.00 (1.49)
	GLSM (95%CI)	129.70 (113.77; 147.87)	100.48 (85.96; 117.47)
$AUC_{(0\text{-}21d)}$ (µg*day/ml)	Mean (SD)	2377.05 (639.24)	1589.95 (568.96)
	CV%	26.89	35.78
	Geo-Mean (SD)	2246.41 (1.50)	1468.45 (1.57)
	GLSM (95%CI)	2060.38 (1777.64; 2388.32)	1595.50 (1338.29; 1902.35)
T_{max} (day)	Mean (SD)	5.18 (2.24)	5.23 (2.39)
	Median	4	4
	Min; Max	2; 8	2; 8
$C_{(trough)}$ (µg/ml)	Mean (SD)	87.02 (26.05)	58.67 (23.23)
	CV%	29.94	39.60
	Geo-Mean (SD)	81.24 (1.56)	54.31 (1.52)
	GLSM (95%CI)	76.67 (64.34; 91.38)	58.26 (47.27; 71.79)

Geo-Mean, geometric mean; GLSM, model-adjusted geometric least square means; CV, coefficient of variation; SD, standard deviation

- The pp-set consisted of 30 pts (17 in the thigh and 13 in the abdw group). Baseline characteristics are shown in Table 1. The mean plasma concentration-time profiles of the s.c. trastuzumab administered into the thigh and into the abdw are presented in Figure 2.
- The geo-means of C_{max} and $AUC_{0\text{-}21d}$ were higher in the thigh than in the abdw group (GMR 1.29 [90 %CI 1.05; 1.58] and GMR 1.29 [90%CI 1.03; 1.63], respectively) with the higher limit of the 90% CI being greater than the estimated (Table 3).
- Similarly, the geo-mean of C_{trough} were higher in the thigh than in the abdw group (GMR 1.32 [90%CI 1.00; 1.73]), whereas the mean T_{max} did not differ between the two groups (Table 3). Variability as measured by CV% for C_{max}, $AUC_{0\text{-}21d}$ and C_{trough} was higher in the abdw than in the thigh group (Table 3).
- Overall delay of the s.c. trastuzumab application within the first 7 cycles of the substudy was observed in 19 pts (10 in the thigh and 9 in the abdw group) mainly due to organizational reasons, no delay due to toxicity was reported.
- Overall 29 pts (96.7%) reported AEs of any grade (grades 1-4) and 5 pts (16.7%) of high grade (grades 3-4). The most frequent hematological AEs of any grade were leukopenia (80.0%) and anemia (66.7%), and the most common non-hematological AEs of any grade were fatigue (60.0%) and peripheral neuropathy (53.3%) (Table 2).

Conclusions

- **Bioavailability of the s.c. trastuzumab as reflected by peak and total exposure measured in cycle 7 was approximately 30% higher if administered into the thigh than into the abdominal wall in pts with HER2-positive primary breast cancer treated with dose-dense CT plus i.v. trastuzumab.**
- **PK parameters of the s.c. trastuzumab administered into the thigh were in line with those from the HannnaH study[1].**
- **No increased toxicity was observed in both treatment groups.**
- **Study limitations were that no cross-over design was used and the number of patients satisfying criteria for pp-set were different in the groups.**

References

1. 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; 3:869-78.

Presented at: San Antonio Breast Cancer Symposium - December 5-9, 2017

The study was financially supported by Roche