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Clinical Practice Observation of Trastuzumab in Patients with Human Epidermal Growth Receptor 2-Positive Metastatic Adenocarcinoma of the Stomach or Gastroesophageal Junction

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Metastatic adenocarcinoma of the stomach or gastroesophageal junction • Trastuzumab • Human epidermal growth receptor 2 • Backbone chemotherapy • Noninterventional study • Real-world data

Abstract

Background. The observational study HerMES collected primary data on effectiveness and safety of trastuzumab in patients with human epidermal growth receptor 2 (HER2)-positive cancer of the stomach or gastroesophageal junction (GEJ) in routine clinical practice, exploring the treatment with trastuzumab, chemotherapy backbones used, and the HER2 testing in a real-world setting in Germany.

Subjects, Materials, and Methods. This noninterventional study observed patients with histologically confirmed, HER2-positive metastatic adenocarcinoma of the stomach or GEJ, who were treated with trastuzumab according to the physicians' judgement and clinical practice. The observation phase per patient took as long as the duration of the trastuzumab therapy, but for a maximum of 12 months. A subsequent extended follow-up phase lasted until the patient's death or the end of the study, that is, 2 years from start of the follow-up phase of the last patient. All data were analyzed descriptively.

Results. Between February 2010 and July 2016, 364 patients were observed at 171 sites throughout Germany. The median overall survival was 14.1 months and the median progression-free survival was 7.9 months. The overall response rate was 43%. Safety was in line with previous reports. This study observed a high diversity of chemotherapy regimens that were combined with trastuzumab. Post hoc subgroup analyses showed differences in outcomes according to the chemotherapy regimen used.

Conclusion. Trastuzumab treatment in everyday practice as observed in HerMES confirmed the positive results of the pivotal study ToGA in an observational, real-world setting. ***The Oncologist*** 2020;25:e1181–e1187

Implications for Practice: Real-world data of trastuzumab treatment of patients with gastroesophageal or gastric metastatic adenocarcinoma confirmed the positive results of the pivotal clinical trial. The observed median overall survival was 14.1 months and the median progression-free survival was 7.9 months. Although recommendations concerning administration of trastuzumab were well implemented, a high diversity of chemotherapy regimens were combined with trastuzumab. Regimens other than the in-label regimens, especially oxaliplatin-based doublets or 5-fluorouracil, leucovorin, oxaliplatin, taxane triplets, were used in 29% of patients. Observation of a second, marginal HER2-positivity population confirmed the benefit of trastuzumab predominantly for well-confirmed human epidermal growth receptor 2 (HER2)-positive tumors and the requirement of reliable HER2 testing.

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Introduction

Both gastric and esophageal carcinomas are frequent causes of cancer death in Germany [1]. Over the past 3 decades, evidence has accumulated suggesting a relationship between overexpression/amplification of the human epidermal growth receptor 2 (HER2) and adenocarcinomas of the stomach or gastroesophageal junction (GEJ) [2]. Trastuzumab (Herceptin; Roche Pharma AG, Grenzach-Wyhlen, Germany) is a monoclonal antibody binding specifically to HER2. Based on the pivotal study ToGA [3, 4], trastuzumab—in combination with cisplatin and 5-fluorouracil—is an established therapy for HER2-positive gastric and GEJ adenocarcinoma [5]. The objective of the present study HerMES was the observation of the use of trastuzumab in patients with gastric or GEJ carcinoma in the real-world setting in Germany. HerMES aimed to assess the effectiveness and tolerability of trastuzumab in routine clinical practice and to collect data on the choice of backbone chemotherapy combinations and implementation of recommendations for application of trastuzumab.

Subjects, Materials, and Methods

Patients and Study Design

The observational, postauthorization study HerMES (ClinicalTrials.gov identifier: NCT01220934) included adult patients with histologically confirmed metastatic adenocarcinoma of the stomach or GEJ in Germany. The tumors needed to be HER2 positive (immunohistochemistry [IHC] 2+ and in situ hybridization [ISH] positive, or IHC 3+) and the patients eligible for treatment with trastuzumab according to the physician's judgement. Exclusion criteria were contraindications, interactions, and incompatibilities as specified in the trastuzumab summary of product characteristics (SmPC) [5]. The observational plan, patient information, and informed consent form were approved by an independent ethics committee (Ethik-Kommission bei der Landesärztekammer Hessen; FF 107/2009).

The study was conducted at 171 institutions across Germany between February 2010 and July 2016. A total of 443 patients were screened; 364 patients met all selection criteria and were included in the analysis population (AP), which comprised all eligible patients who received trastuzumab at least once. Thirty-nine additional patients were only marginally HER2 positive (i.e., IHC 2+ without confirmation by ISH) and were included in the marginal HER2-positivity population that included all patients who met the selection criteria except that they had the less well-confirmed HER2 status indicated above and received trastuzumab at least once.

Documentation comprised two phases per patient, an observation phase and a follow-up phase. The start of the observation phase was documented as baseline followed by one documentation for each treatment cycle for as long as trastuzumab therapy continued, up to a maximum of 1 year. If the trastuzumab therapy lasted less than 12 months, the observation period was correspondingly shorter. If the trastuzumab therapy lasted longer than 12 months, the observation period nevertheless ended after 12 months, that is, independently of the continuation of the trastuzumab therapy after these 12 months. The follow-up phase, a quarterly status enquiry about survival and adverse events (AEs), lasted until the end of this study (2 years from start of the follow-up phase of the last patient) or until the patient's death. During the follow-up phase, patients could have already terminated or could continue trastuzumab treatment. The individual total duration of the study for each patient was approximately 3 to 6 years depending on study entry.

Table 1. Subgroups of patients by type of chemotherapy regimen: AP

Subgroup by type of chemotherapy	Combination of cancer drugs	No. of patients within the AP
In-Label	Trastuzumab +5-FU or capecitabine + cisplatin (+ other drugs)	172
FLOT[a]	Trastuzumab +5-FU + docetaxel + oxaliplatin (+leucovorin)[b]	37
Fluoropyrimidine	Trastuzumab +5-FU or capecitabine (+leucovorin)[b]	33
Oxaliplatin / Fluoropyrimidine	Trastuzumab +5-FU + oxaliplatin (+leucovorin)[b]	70
Other regimens	All other trastuzumab -containing combinations	52

[a]In the FLOT regimen, application takes place every 2 weeks; thus, deviating from the 3-weekly dose, the loading dose is 6 mg/kg and the therapy dose is 4 mg/kg trastuzumab.
[b]Leucovorin was not considered a chemotherapeutic substance per se and not used for the definition of subgroups.
Abbreviations: 5-FU, 5-fluorouracil; AP, analysis population; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, taxane (a specific regimen of chemotherapy).

Variables

Effectiveness variables were overall survival (OS), progression-free survival (PFS), and overall response rate (ORR) according to RECIST 1.1 [6]. Safety variables comprised occurrence and frequency of all AEs (including classification according to National Cancer Institute Common Terminology Criteria for Adverse Events, seriousness, severity, and relatedness to trastuzumab) and of AEs of special interest (AESIs) defined as cardiac events, infusion-related reactions, and pulmonary events. Other variables included treatment with trastuzumab and regimens for chemotherapy backbone treatment.

Because of a change in requirements for reporting of AEs not related to trastuzumab on December 23, 2013, unrelated AEs before that date were collected retrospectively, whereas unrelated AEs after that date were collected prospectively.

Table 2. Median PFS and OS: AP and marginal HER2-positivity population

Population or subgroup	*n*	No. of events[a,b]	Median PFS, months	95% CI for median PFS	12-months PFS	95% CI for 12-months PFS
Median PFS						
AP	364	294 (80.8%)	7.9	7.1–8.7	33%	28%–38%
Subgroups of AP by chemotherapy:						
In-Label	172	145 (84.3%)	8.0	7.1–8.9	33%	25%–40%
FLOT	37	30 (81.1%)	9.5	6.3–15.5	45%	28%–60%
Fluoro-pyrimidine	33	28 (84.8%)	6.4	4.1–7.8	21%	9%–37%
Oxaliplatin/ Fluoropyrimidine	70	51 (72.9%)	8.6	6.3–11.2	37%	25%–49%
Other regimens	52	40 (76.9%)	6.9	4.6–10.3	30%	17%–44%
Marginal HER2-positivity population	39	29 (74.4%)	7.1	4.8–9.3	29%	14%–45%
Median OS						
AP	364	230 (63.2%)	14.1	12.3–15.5	58%	52%–63%
Subgroups of AP by chemotherapy:						
In-Label	172	110 (64.0%)	13.9	10.9–17.9	55%	47%–63%
FLOT	37	23 (62.2%)	15.5	9.5–20.8	68%	49%–82%
Fluoro-pyrimidine	33	21 (63.6%)	14.4	8.9–27.2	59%	40%–74%
Oxaliplatin/ Fluoropyrimidine	70	40 (57.1%)	15.8	11.1–19.7	63%	49%–74%
Other regimens	52	36 (69.2%)	12.3	6.9–14.1	52%	36%–66%
Marginal HER2-positivity population	39	27 (69.2%)	9.1	5.1–15.4	40%	23%–57%

[a]Event = death or progression of cancer for PFS, and death for OS.
[b]Percentages refer to the total number of patients within the respective population or subgroup indicated in the second column of this table.
Abbreviations: AP, analysis population; CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, taxane (a specific regimen of chemotherapy); HER2, human epidermal growth receptor 2; OS, overall survival; PFS, progression-free survival.

Statistical Analysis

A formal sample size calculation was not performed. For comparability of the noninterventional study (NIS) HerMES with the pivotal ToGA study ([3], ClinicalTrials.gov Identifier: NCT01041404; trastuzumab arm: 294 patients), the sample size was to be larger than that of ToGA. Recruitment was continued until 364 patients were included as this number was deemed sufficiently high.

All data were analyzed descriptively. Time-to-event data such as OS and PFS time were analyzed using the method by Kaplan-Meier and include the corresponding 95% confidence intervals (CIs) for the median of the time until the occurrence of the events. Backbone chemotherapy combinations were coded according to World Health Organization drug dictionary version 2016.03. All AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 14.0). The recorded AEs and serious adverse events (SAEs) were summarized based on the system organ class (SOC) and preferred term (PT) with absolute and relative frequencies.

After database lock, new clinically relevant subgroups of observed patients by type of chemotherapy regimen of the first treatment cycle were defined (Table 1). Post hoc analyses of these subgroups were performed for the effectiveness parameters OS, PFS, and ORR. For the relative frequencies, 95% CIs were determined according to Clopper-Pearson.

Results

Patient Characteristics and HER2 Diagnosis at Baseline

The AP comprised 364 patients (271 [74.5%] male and 93 [25.5%] female). The median age was 66 years (range, 25–90 years). At baseline, the Eastern Cooperative Oncology Group performance status was 0 for 100 (30.6%) patients, 1 for 180 (55.0%) patients, 2 for 38 (11.6%) patients, 3 for 8 (2.4%) patients, and 4 for 1 (0.3%) patient (data for 37 patients missing).

The stomach/GEJ tumor present at baseline was newly diagnosed in 282 (77.5%) patients and a recurrence in 81 (22.3%) patients (data for one patient missing). One hundred eighty-seven (51%) patients had GEJ cancer and 188 (52%) patients stomach cancer, including 11 patients with both regions, GEJ and stomach, affected. Documented cancer treatment before start of trastuzumab therapy included chemotherapy for 165 (45.3%) patients, tumor-related surgery for 122 (33.5%) patients, and radiotherapy for 21 (5.8%) patients. The most frequent specific (i.e., not "X") values for TNM status were T3 in 119 (32.7%) patients and N1 in 93 (25.5%) patients. M1 was recorded for 329 (90.4%), M0 for 15 (4.1%), and MX for 11 (3.0%) patients (missing for 9 patients). Metastases were present in the following organs (≥5% of patients): for 191 (52.5%)

Table 3. ORR: AP and marginal HER2-positivity population

Population or subgroup	*n*	ORR[a] (patients)	95% CI for response rates
AP	364	43.4% (158)	38%–49%
Subgroups of AP by chemotherapy:			
In-Label	172	41.9% (72)	34%–50%
FLOT	37	54.1% (20)	37%–71%
Fluoropyrimidine	33	39.4% (13)	23%–58%
Oxaliplatin/ Fluoropyrimidine	70	48.6% (34)	36%–61%
Other regimens	52	36.5% (19)	24%–51%
Marginal HER2-positivity population	39	43.6% (17)	28%–60%

[a]Percentages refer to the total number of patients within the respective population or subgroup indicated in the second column of this table.
Abbreviations: AP, analysis population; CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, taxane (a specific regimen of chemotherapy); HER2, human epidermal growth receptor 2; ORR, overall response rate.

patients in the liver, for 140 (38.5%) in lymph nodes, for 88 (24.2%) in the peritoneum, for 54 (14.8%) in the lung, and for 28 (7.7%) in bones (metastases in several organs possible). The HER2 status was IHC 3+ for 321 (88.2%) patients and IHC 2+ plus a confirmation by ISH for 43 (11.8%) patients of the AP.

Treatment with Trastuzumab and Backbone Chemotherapy

The median duration of trastuzumab treatment was 5.9 months (mean ± SD was 6.9 months ±5.37 months). The median number of trastuzumab cycles per patient was 9.0 (range, 1–27; mean ± SD was 10.6 ± 7.43). The median trastuzumab dose without loading dose per patient was 6.00 mg/kg body weight; the interquartile range (Q1–Q3) was 4.40–6.00 mg/kg. The mean ± SD trastuzumab dose without loading dose per patient was 5.44 ± 1.791 mg/kg body weight. The median time of infusion was 90 minutes in treatment cycles 1 and 2, 65 minutes in cycle 3, and 60 minutes in later cycles.

Eighty-six (23.6%) patients of the AP received trastuzumab treatment for 12 months (i.e., the maximum duration of the observation period) whereas 272 (74.7%) patients received trastuzumab treatment for less than 12 months (data missing for 6 patients). The main reasons for early termination of trastuzumab treatment were progressive disease (41.2% of patients), death (16.8%), predefined number of cycles given (3.3%), surgery as resectability achieved (3.0%), cardiotoxicity (1.4%), other trastuzumab intolerance (1.1%), and other reason (13.7%). Sixty-one (16.8%) patients were recorded to have received subsequent trastuzumab treatment after the observation phase.

Based on the chemotherapy regimen in cycle 1, the AP was divided into five clinically relevant subgroups (Table 1); therapy changes in later cycles were not taken into account.

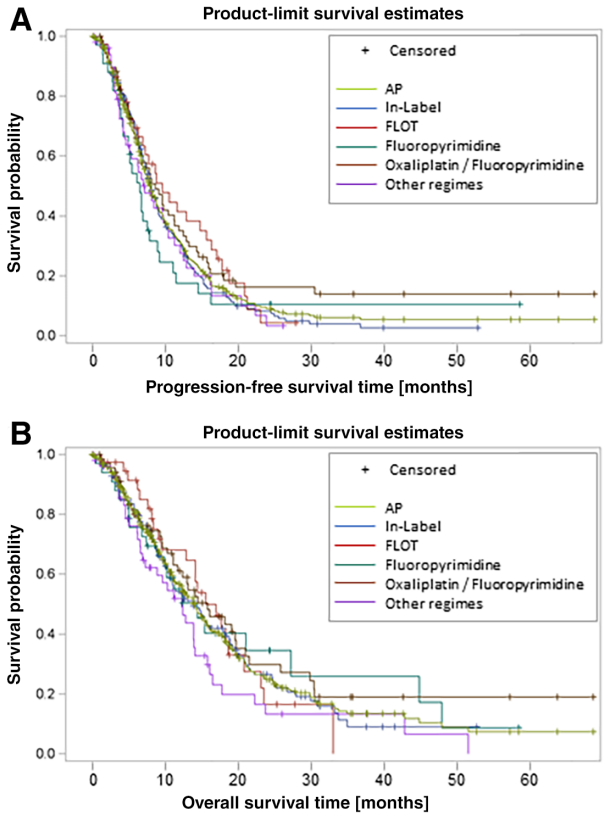

Figure 1. Kaplan-Meier curves for the AP and subgroups by chemotherapy. **(A):** Analysis of progression-free survival. **(B):** Analysis of overall survival.
Abbreviations: AP, analysis population; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, taxane.

Notably, although use of trastuzumab according to the SmPC was specified in the inclusion criteria, this observational study reflected a high proportion of different backbone combinations. One hundred seventy-two (47%) patients were treated in-label (i.e., trastuzumab in combination with capecitabine or 5-fluorouracil and cisplatin). Eighteen patients received additional radiotherapy.

Two hundred ninety-five (81.0%) patients received at least one treatment with concomitant medication; the number of treatments was 2,007. Concomitant medication received by ≥25% of patients were proton pump inhibitors (135 patients; 37.1%), serotonin (5HT3) antagonists (114; 31.3%), glucocorticoids (114; 31.3%), pyrazolones (104; 28.6%), and propulsives (99; 27.2%).

Progression-Free Survival

Two hundred ninety-four (80.8%) patients of the AP had an event (i.e., they died or experienced progression of cancer) during the study (Table 2). The median PFS, that is, time to the event, was 7.9 months. The 12-months PFS rate was 33%. In subgroups by chemotherapy, the median PFS ranged from 6.4 to 9.5 months and the 12-months PFS rate ranged from 21% to 45% (Table 2; Fig. 1A). In the marginal HER2-positivity population, 29 (74.4%) patients died or had cancer progression during the study. Median PFS was 7.1 months and the 12-months PFS rate was 29% and thus below the respective data of the AP (Table 2).

Table 4. Overview of adverse events during the observation phase: AP

Type of AE (at least one event)	No. of patients (*n* = 364)	CI, %	Total no. of AEs
AE	165 (45.3%)	40.1;50.6	686
SAE	73 (20.1%)	16.1;24.5	197
AE leading to discontinuation of the therapy	19 (5.2%)	3.2;8.0	28
AE leading to death	26 (7.1%)	4.7;10.3	45
Related AE	130 (35.7%)	30.8;40.9	448
Related SAE	43 (11.8%)	8.7;15.6	101
Related AE leading to the discontinuation of the therapy	15 (4.1%)	2.3;6.7	18
Related AE leading to death	6 (1.6%)	0.6;3.6	7
Unrelated AE (retrospective / prospective)	93 (25.5%) / 1 (2.9%)	21.1;30.4 / 0.1;14.9	248 / 1
Unrelated SAE (retrospective)[a]	44 (12.1%)	8.9;15.9	97
Unrelated AE leading to the discontinuation of the therapy (retrospective)[a]	5 (1.4%)	0.4;3.2	10
Unrelated AE leading to death (retrospective)[a]	22 (6.0%)	3.8;9.0	38

Multiple occurrences of the same preferred term in one individual counted only once.
[a]No prospective AE reported in this category.
Abbreviations: AP, analysis population; AE, adverse event; CI, confidence interval; SAE, serious adverse event.

Overall Survival

Two hundred thirty (63.2%) patients of the AP died. The median OS time was 14.1 months. The 12-months OS rate was 58%. In subgroups by chemotherapy, median OS ranged from 12.3 to 15.8 months and the 12-months OS rate ranged from 52% to 68% (Table 2; Fig. 1B). In the marginal HER2-positivity population, 27 (69.2%) patients died. Median OS was 9.1 months and the 12-months survival 40% (Table 2).

Overall Response Rate

The ORR, that is, complete or partial response, was 43.4% for the AP (Table 3). Subgroups by chemotherapy displayed higher or lower response rates than the AP (Table 3). The ORR of the marginal HER2-positivity population was similar to that of the AP (Table 3).

Safety Analyses

An overview of the AEs in the AP during the observation phase is provided in Table 4 for all events, events related, and events not related to trastuzumab treatment as judged by the treating physician. Unrelated AEs were evaluated "retrospective" unrelated AEs (for *n* = 364 patients) or "prospective" unrelated AEs (for *n* = 35 patients; see section 2.2).

Among the AEs, the two most frequent SOCs during observation phase were "gastrointestinal disorders" (189 events in 91 [25.0%] patients) with the predominant PTs "diarrhea," "nausea," and "vomiting" and "general disorders and administration site conditions" (107 events in 75 [20.6%] patients) with the predominant PT "fatigue" (Table 5). Overall, the reported AEs were aligned with the known safety profiles. No new safety signals were identified.

Related serious AESIs included 11 SAEs belonging to the SOC "cardiac disorders" in 11 patients, with PTs "cardiac failure" (4 patients), "arrhythmia" (2 patients), and five further PTs in single patients. Related serious AESIs of the SOC "respiratory, thoracic, and mediastinal disorders" included nine serious pulmonary events in seven patients such as "dyspnea" in three patients as well as "bronchospasm," "pulmonary fibrosis," and "pulmonary edema" in one patient each; "bronchopneumonia" (SOC: "infections and infestations") was recorded as a related SAE for one patient. No AESIs were reported as related nonserious AEs in >5% of the patients.

Eighteen related AEs in 15 patients led to the discontinuation of trastuzumab therapy. They belong to the SOC "cardiac disorders" (five events), "respiratory, thoracic, and mediastinal disorders" (four events), "gastrointestinal disorders" (four events), "general disorders and administration site conditions" (three events), "injury, poisoning, and procedural complications" (one event), and "psychiatric disorders" (one event). This list includes the following related AESIs (PTs) that led to the discontinuation of therapy: "cardiac failure" (two patients), "cardiotoxicity" (two patients), "arrhythmia," "infusion related reaction," "dyspnea," "pulmonary fibrosis," and "pulmonary edema" (one patient each).

Nine related AEs in eight (2.2%) patients had a fatal outcome (of which seven events in six patients occurred during the observation phase); these were "pericardial effusion," "gastrointestinal disorder"/"vomiting" (both recorded for one patient), "ill-defined disorder," "hepatic failure," "neoplasm progression," and "pulmonary fibrosis" during the observation phase as well as "death" and "acute myeloid leukemia" during follow-up.

Table 5. Adverse events by SOC and PT recorded for >2% of patients during treatment phase: AP

SOC PT	No. of patients with at least one AE (*n* = 364)	Total no. of AEs per SOC
Gastrointestinal disorders	91 (25.0%)	189
Diarrhea	43 (11.8%)	
Nausea	38 (10.4%)	
Vomiting	27 (7.4%)	
Abdominal pain	12 (3.3%)	
Constipation	12 (3.3%)	
Stomatitis	9 (2.5%)	
General disorders and administration site conditions	75 (20.6%)	107
Fatigue	26 (7.1%)	
General physical health deterioration	17 (4.7%)	
Pyrexia	10 (2.7%)	
Chills	9 (2.5%)	
Mucosal inflammation	9 (2.5%)	
Edema peripheral	8 (2.2%)	
Nervous system disorders	39 (10.7%)	55
Polyneuropathy	18 (4.9%)	
Dizziness	8 (2.2%)	
Respiratory, thoracic and mediastinal disorders	38 (10.4%)	48
Dyspnea	8 (2.2%)	
Epistaxis	8 (2.2%)	
Blood and lymphatic system disorders	34 (9.3%)	50
Anemia	16 (4.4%)	
Neutropenia	11 (3.0%)	
Leucopenia	10 (2.7%)	
Thrombocytopenia	8 (2.2%)	
Infections and infestations	31 (8.5%)	37
Skin and subcutaneous tissue disorders	25 (6.9%)	37
Metabolism and nutrition disorders	24 (6.6%)	31
Cardiac disorders	22 (6.0%)	24
Investigations	16 (4.4%)	20
Musculoskeletal and connective tissue disorders	14 (3.8%)	15
Psychiatric disorders	11 (3.0%)	11
Renal and urinary disorders	11 (3.0%)	11
Vascular disorders	11 (3.0%)	13
Neoplasms benign, malignant, and unspecified	8 (2.2%)	10

Abbreviations: AE, adverse event; AP, analysis population; PT, preferred term; SOC, system organ class.

Median changes of the body weight were ≤1 kg from baseline to treatment cycle 22. In cycles 23 and 24, when the numbers of patients were low (22 and 19 patients), changes were slightly higher but divergent (−1.2 kg and + 2.0 kg).

Discussion

Effectiveness results of HerMES were in line with the ToGA study [3]. Median OS was 14.1 and 13.8 months in HerMES and ToGA, respectively. Median PFS was 7.9 and 6.7 months in HerMES and ToGA, respectively. ORR was 43% and 47% in HerMES and ToGA, respectively. A cross trial comparison is difficult because of the different populations. The ToGA comprised slightly more patients with metastatic disease (97% vs. 90%) and more patients with moderate HER2 expression, but on the other hand, the HerMES was a real-life study with nearly no upfront selection of patients. Therefore, it is reassuring to see that survival was comparable, despite the use of diverse backbone regimens.

In HerMES, relatively few AEs were recorded. This may represent an underreporting, which is typical for retrospective reporting of unrelated AEs for most of the patients. Otherwise, safety results of HerMES were consistent with the ToGA study (ToGA results: 292/294 [99%] patients with any AE; 95/294 [32%] patients with SAEs; 48/294 [16%] patients who discontinued therapy for at least one treatment; 17/294 [6%] patients with fatal AEs). No new safety signals were identified by the NIS HerMES. Overall, the real-life data of HerMES confirm the data of ToGA.

Observation of the routine administration shows that overall, recommendations concerning dosage and application of trastuzumab were well implemented in everyday clinical routine practice at least for the median values. It was interesting to see that a relevant proportion of patients (53%) received trastuzumab in combination with regimens other than the in-label regimen. Especially oxaliplatin-based doublets or 5-fluorouracil, leucovorin, oxaliplatin, taxane (FLOT) triplets [7] were used in 29% of patients.

Because of the nonrandomized character of the study, it is impossible to draw conclusions regarding the optimal backbone therapy. The survival curves for PFS and OS show that the outcomes were largely similar, indicating that trastuzumab's activity does not depend on the backbone chemotherapy. This result could be of special interest to the oncologist as studies of trastuzumab with the more modern chemotherapy regimens, specifically the oxaliplatin-based ones, have been lacking. Interestingly, in the marginal HER2-positivity population, OS and PFS seemed to be inferior to the AP (Table 2), thereby confirming the benefit of trastuzumab predominantly for well-confirmed HER2-postitive tumors and the requirement of reliable HER2 testing.

The frequent observation of off-label use of trastuzumab with various different backbone chemotherapy combinations confirms the utility of observational research reflecting real-world praxis treatment decisions. Although the NIS HerMES was conducted in an unselected patient population, the observed effectiveness and safety results were in line with

the ToGA trial. Interestingly, the results of ToGA could be reproduced with diverse chemotherapy backbones.

Conclusion

Collectively, trastuzumab treatment in everyday clinical routine practice as observed by the large observational study HerMES confirmed the positive results of the pivotal clinical trial ToGA in the real-world setting in Germany. This was the case, even though more than half the patients received trastuzumab in combination with backbone chemotherapy regimens other than the in-label regimen, including oxaliplatin-based doublets or FLOT triplets.

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Disclosures

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