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Trastuzumab in the treatment of elderly patients with early breast cancer: Results from an observational study in Germany

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ABSTRACT

Background: In elderly patients with HER2-positive breast cancer, few data on efficacy and toxicity of adjuvant trastuzumab treatment exists since older patients were in general excluded from large randomized studies. This prospective observational study aimed to confirm the beneficial findings from pivotal trials in age cohorts ≥65 years.

Materials and Methods: There were no restrictions for recruitment with respect to age or concomitant/sequential adjuvant medication. Long-term relapse/survival status of the patients was assessed once a year.

Results: Among the 3940 evaluable patients enrolled between 2006 and 2012 at 339 institutions, 507 were aged between 65 and 69 years, with another 507 patients ≥70 years. Elderly patients suffered from significantly more advanced primary tumors. Preceding or concomitant chemotherapy showed decreasing aggressiveness with patient's age. Trastuzumab treatment was stopped prematurely in only 11% of the elderly, but more often than in younger patients ($p = 0.0008$). With 453 events hitherto reported, elderly patients did not exhibit an

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inferior relapse-free survival when adjusted for other relevant prognostic factors (hazard ratio: 1.01 per year; $p = 0.24$). Three-year overall survival was significantly lower in the population older than 64 years than in younger patients (94.2% vs. 96.8%, $p = 0.0011$).

Conclusions: To our knowledge, our population of elderly patients treated with adjuvant trastuzumab is the largest analyzed so far. The beneficial long-term results were comparable to those in the younger cohorts. Although the risk of cardiotoxicity increased significantly with age, it also remained manageable in older patients. Thus, chronological age alone should not preclude HER2 antibody treatment.

1. Introduction

More than 30% of patients diagnosed with breast cancer worldwide are beyond the age of 65 years, and this proportion is even distinctly higher (up to more than 50%) in developed countries with a longer overall life expectancy.[1–3] This corresponds to incidence rates of about 400 per 100,000 in Western European countries and the USA. Nevertheless, the evidence base for aggressive antineoplastic treatment of elderly patients is limited, although it is generally accepted that specific aspects have to be taken into account in this subpopulation, such as comorbidity, concomitant medication, susceptibility to toxic effects, and compliance.[4,5] The lack of data in elderly patients with breast cancer results from the trend to exclude older and/or comorbid patients from randomized phase III trials, especially those focusing on newly developed treatments.[4–8] Therefore, recommendations, such as those compiled by the International Society of Geriatric Oncology (SIOG) mostly have to rely on the extrapolation of data from younger patients, with respect to efficacy, and to toxicity-driven contraindications, precautions, or usage restrictions.[4]

In elderly patients, the introduction and consecutive improvement of adjuvant chemotherapy seems to have a smaller impact on outcome, especially on mortality.[5,9] This finding may, however, be explained by the fact that this patient group received less systemic treatment.[2,5,10] This attitude corresponds to the assumption that in older patients breast cancer may be in general less aggressive, and usually hormone receptor–positive and human epidermal growth factor receptor 2 (HER2)–negative.[2] Moreover, it certainly reflects toxicity concerns. On the other hand, as recently shown in SEER (Surveillance, Epidemiology, and End Results) database research, adjuvant treatment-related mortality was very low in the elderly population.[11] It is now generally accepted that age, by itself, should not be a barrier to aggressive tumor therapy, and that the treatment objectives (e.g. improving quality of life, preserving functional autonomy, or avoiding hospitalization rather than achieving relapse-free survival) may differ between elderly and younger patient populations.[2,4]

In the last decade, treatment of HER2-positive, localized breast cancer was revolutionized by the early results from large pivotal studies of adjuvant chemotherapy combined with the HER2-directed monoclonal antibody trastuzumab[12–17] convincingly underpinned by several meta-analyses.[18–20] However, because the number of elderly patients in these large trials was rather small, treatment guidelines are less well established in this population.[6,21] In fact, the incidence of HER2-positivity in elderly patients is still not well described,[3,6,10] although the National Comprehensive Cancer Network (NCCN) recently reported 26% of patients with HER2-positive, early breast cancer to be 60 years or older.[22] Current estimates indicate that the proportion of HER2-positive cases among elderly patients with breast cancer is 10% to 20%, which is not much different from the incidences reported for the entire breast cancer population.[10]

After approval of trastuzumab (Herceptin®) for the treatment of early breast cancer in Germany in 2006 (without any restrictions with respect to age), we embarked on this non-interventional observation study to obtain data on the clinical management of the overall population of HER2-positive patients with early breast cancer. The only selection criterion was the decision to receive adjuvant trastuzumab treatment, and we made no restrictions on age, comorbidity, or treatment regimen, which permitted the inclusion of patients receiving endocrine combinations or trastuzumab monotherapy.

The definition of "elderly" is somewhat controversial. The cutoff at 65 years is in line with a statement by the International Conference on Harmonization,[23] also reflecting that physicians usually treat patients differently from this age onwards.[5] However, 70 years might be a clinically more useful threshold, as relevant age-related changes seem to sharply increase only between 70 and 75 years.[5] Therefore, we analyzed the data for the patient groups aged 65 to 69 years and aged ≥70 years separately, which was justified because the number of patients in our cohort was large.

2. Methods

2.1. Patient Population and Methods of Observation

This non-interventional observation study focused on patients with early breast cancer who received trastuzumab after its approval in Germany. Investigators were asked to report on a pre-specified number of consecutive patients fulfilling this criterion. All types of previous or concomitant adjuvant treatments (endocrine or chemotherapy) were acceptable. For inclusion, HER2 positivity had to be confirmed, usually defined as 3+ staining in immunochemistry or a positive result of fluorescence *in situ* hybridization (FISH) in case of 2+ staining. Patients were treated in accordance with routine practices of the respective institution, and findings were prospectively documented on standardized case report forms (CRF). There were no further restrictions with respect to individual diagnostic and therapeutic procedures before and after patient registration. Course of disease and treatment were closely monitored, either until (premature) trastuzumab therapy

stop for whatever reason, or for the recommended antibody treatment period of 12 months. Thereafter, key long-term data on surviving patients were regularly retrieved via fax forms. Adverse drug reactions (ADRs), as defined in the CRF, were recorded according to the regulations of German drug laws. Database closure for the present analysis was October 2013. Long-term follow-up is still ongoing.

2.2. Endpoint Evaluation and Statistical Aspects

Rates of baseline and treatment characteristics as well as toxicity were compared using Fisher's exact test or the Cochran–Armitage trend test, respectively. The post-therapeutic disease course, including disease recurrence, was assessed, based on standard clinical procedures at the discretion and routine of the investigators/participating institutions, without formal requirements on re-staging procedures. Relapse-free survival (RFS) and overall survival (OS) were calculated as the time between the baseline assessment before the first trastuzumab administration and the respective event. Surviving patients without relapse were censored at the last valid observation point. Safety data were collected during the 12-month period of detailed documentation, but events reported afterwards were also included in the analysis.

Event-related endpoints were analyzed using the Kaplan–Meier method, providing 95% confidence intervals (CIs) for event-free proportions at specific time points. Univariate analyses comparing subgroups were performed using the log rank test [24]; hazard ratios (HR) with 95% CIs were derived from Cox proportional hazards models.[25] All prognostic factors with an associated p value < 0.1 in univariate analysis were included in a multivariate Cox proportional hazards model of RFS. By backward selection, all "unnecessary" variables were removed step-by-step, so that the final model only contained covariates with a p value ≤ 0.05. All statistical analyses were of an exploratory nature, with no adjustment of p values for multiplicity made. The term "significant" was used for $p \leq 0.05$. All reported p values are two-sided.

3. Results

Overall, 4027 case documentation forms were prospectively obtained from 339 clinics and practices across Germany for patients starting adjuvant trastuzumab treatment between 2006 and 2011. After exclusion of clearly ineligible cases (26 patients with M1 disease; 64 patients subsequently assessed as HER2-negative; 3 patients meeting both of these criteria), 3940 patients with HER2-positive breast cancer remained for this analysis. Among these, 2926 (74%) were below 65 years of age, and the remaining 1014 patients were categorized as "elderly", equally distributed to the two subgroups, i.e. 65–69 years (n = 507; "elderly I") and ≥ 70 years (n = 507; "elderly II"). Twenty-nine (1%) patients were ≥80 years old.

3.1. Baseline Characteristics

Table 1 shows the patient and tumor characteristics by age subgroup. As expected, performance status was more impaired in patients aged ≥65 years than in younger patients (ECOG 0: 53% vs. 65%, $p < 0.0001$). In this group, there were more advanced cases with respect to the primary tumor (pT ≥ 2: 56% vs. 48%, $p < 0.0001$), while lymph node involvement exhibited no clear trend. Histopathologic characteristics did not indicate a more favorable profile in elderly patients. Hormone receptor positivity (both estrogen and progesterone) tended to be even lower in

Table 1 – Patient and tumor characteristics by age group.

Parameter	Age group		
	<65 years (n = 2926)	65–69 years (n = 507)	≥70 years (n = 507)
Body weight			
Median (range) [kg]	69 (40–178)	70 (46–168)	70 (44–121)
ECOG performance status			
0	1878 (65%)	283 (56%)	250 (50%)
1	977 (34%)	204 (41%)	231 (46%)
2	34 (1%)	14 (3%)	18 (4%)
3	–	–	3 (1%)
4	1 (0%)	–	–
Primary tumor stage			
pTis	243 (9%)	33 (7%)	30 (6%)
pT1	1190 (42%)	187 (38%)	182 (36%)
pT2	1105 (39%)	227 (46%)	227 (45%)
pT3	154 (5%)	21 (4%)	30 (6%)
pT4	80 (3%)	20 (4%)	24 (5%)
TX	81 (3%)	9 (2%)	11 (2%)
Lymph node stage			
pN0	1550 (53%)	282 (56%)	233 (46%)
pN1	799 (27%)	120 (24%)	137 (27%)
pN2	313 (11%)	53 (10%)	73 (14%)
pN3	182 (6%)	42 (8%)	48 (9%)
NX	69 (2%)	9 (2%)	16 (3%)
Involved nodes, mean number	2.1	2.3	3.1
AJCC stage			
Stage I	964 (35%)	149 (31%)	130 (26%)
Stage II	1277 (46%)	232 (48%)	234 (48%)
Stage III	541 (19%)	106 (22%)	128 (26%)
Grading			
G1	89 (3%)	13 (3%)	7 (1%)
G2	1294 (44%)	222 (44%)	231 (46%)
G3	1501 (51%)	268 (53%)	261 (52%)
GX	31 (1%)	–	5 (1%)
Hormone receptor status			
Estrogen receptor–positive	1789 (61%)	300 (59%)	275 (54%)
Progesterone receptor–positive	1539 (53%)	228 (45%)	224 (44%)
At least one positive	1890 (65%)	312 (62%)	288 (57%)
IHC staining for HER2			
2+/FISH/CISH positive	319 (11%)	50 (10%)	53 (11%)
Pathological finding in echocardiography and/or ECG	144 (5%)	49 (10%)	67 (13%)
LVEF, median (range) [%] *	65 (25–98)	65 (37 -87)	65 (40–87)
LVEF ≤ 50%	51 (2.7%)	13 (4.1%)	12 (3.8%)

Total patient numbers may deviate from n = 3940 in case of missing values in individual parameters.
ECOG: Eastern Cooperative Oncology Group; ECG: electrocardiogram; LVEF: left ventricular ejection fraction.
* Quantitative data available in 2508 patients only.

the elderly groups (overall, $p = 0.0006$, test for trend). Baseline echocardiography was performed in 83% of patients. However, while quantitative data on cardiac function (documented in 64% of patients only) did not reveal any major differences, the overall rate of pathologic findings in cardiac diagnosis was clearly increasing with age.

3.2. Adjuvant Therapy

The vast majority of patients (94%) received trastuzumab concomitantly with (neo)adjuvant chemotherapy or afterwards. The rate of patients receiving HER2 antibody treatment only (with or without hormone therapy) increased with age from 5% in younger patients to 7% in elderly I, and to 9% in elderly II patients ($p = 0.0003$). Most patients (80%) received chemotherapy after surgery, including only 74 patients (2%) who had likewise received neoadjuvant treatment before. Overall, 14% of patients had received chemotherapy in a neoadjuvant setting only. The rate of pre-surgical cytotoxic treatment decreased from 19% in younger patients to 10% and 7% in the elderly I and II groups, respectively ($p < 0.0001$). The proportion of patients receiving anthracycline-containing chemotherapy was only slightly smaller in the elderly I group (86%) than in younger patients (90%), but was markedly lower in the elderly II group (70%). The fractions of patients receiving taxanes as part of the adjuvant treatment were 69%, 57%, and 61% in the three age groups, respectively. The most pronounced differences between age cohorts were seen for the combination of anthracyclines and taxanes, amounting to 59%, 44%, and 36%, respectively ($p < 0.0001$). In contrast, only minor differences in the number of (neo)adjuvant chemotherapy cycles administered were seen, with a median of 6 cycles calculated for the total population and mean values of 6.9, 6.6, and 6.3 for younger, elderly I, and elderly II groups, respectively. Use of platinum derivatives steadily increased during the period of recruitment and was more prevalent in older patients (8%, 10%, and 17%, respectively; $p < 0.0001$).

In line with the hormone receptor expression, adjuvant endocrine treatment was no more frequent in elderly I (53%) and elderly II (50%) patients than in the younger group (58%). However, the class of agents differed distinctly, with tamoxifen (58% of patients with endocrine therapy) used most frequently in younger patients, followed by aromatase inhibitors (45%) and LHRH (luteinizing hormone-releasing hormone) analogues (13%). The respective rates in patients aged ≥65 years were 25%, 79%, and 1%. In total, 79% of younger patients received adjuvant irradiation, compared to 73% of patients in the group of older patients.

Trastuzumab was given simultaneously with chemotherapy in 16% of patients with no major difference according to age. Likewise, no relevant differences were detected with respect to antibody dosage and duration. Mean treatment period was 50.9, 49.7, and 49.0 weeks in the three age cohorts. Overall, 95% of patients received the planned dose throughout the treatment course in all groups, while dose delays (20%, 21%, and 24%) were only slightly more common in the oldest patients.

3.3. Toxicity

Within the framework of this observational study, trastuzumab was generally well tolerated with predictable and manageable ADRs when given as monotherapy or in combination with or subsequent to other treatments. Table 2 presents the incidence of cardiac toxicity of all National Cancer Institute Common Toxicity Criteria (NCI CTC) grades, with the maximum grade experienced by each patient stated. The rates of all-grade cardiac function toxicity ranged from 3.7% in younger patients to 3.9% in elderly I and 5.7% in elderly II patients ($p = 0.057$). The trend was more pronounced if only grade 3 to 4 events were taken into account (0.6%, 1.2%, and 2.0%, respectively; $p = 0.0040$). In the subgroup of patients receiving adjuvant anthracyclines, the overall cardiac dysfunction rates were not much different, with 3.5%, 3.6%, and 4.6%, in the respective three age cohorts, a finding probably influenced by the almost unselective usage of anthracyclines in younger patients. Quantitative data on left ventricular ejection fraction (LVEF) at the time of antibody treatment stop were reported in only about half of the patients across all age groups. Mean and median values of 63.5%/64% in younger patients and 62.3%/62% in elderly I and 61.6%/61% in elderly II patients indicated that most patients did not experience any deterioration of cardiac function. When all qualitative reports on echocardiography and electrocardiography (ECG) were taken into account, abnormal findings were recorded at the end of trastuzumab therapy in 6%, 12%, and 13% of patients in the three age groups. The corresponding rates for at least one pathological finding during the entire antibody-treatment period were 16%, 26%, and 28%. No additional signal of specific toxic effects other than cardiac was detected in the elderly cohorts.

Trastuzumab was stopped prematurely in 8% of the younger patients, compared to 10% and 13% in elderly I and II patients, respectively ($p = 0.0008$). However, adverse events, mostly of a cardiac type, as the reason to terminate trastuzumab therapy were no more frequent in elderly patients, but the absolute numbers were too small for any definitive conclusions.

Table 2 – Frequency of cardiac adverse reactions (highest NCI CTC grade per category and patient) by age group.

Adverse reaction/age group	Patients with NCI CTC grade [*n* (%)]			
	1	2	3	4
Arrhythmia *				
<65 years	6 (0%)	3 (0%)	–	–
65–69 years	1 (0%)	–	–	1 (0%)
≥70 years	3 (1%)	–	2 (0%)	1 (0%)
Heart function **				
<65 years	50 (2%)	41 (1%)	18 (1%)	1 (0%)
65–69 years	4 (1%)	10 (2%)	5 (1%)	1 (0%)
≥70 years	8 (2%)	11 (2%)	10 (2%)	–
Heart, other *				
<65 years	12 (0%)	4 (0%)	–	–
65–69 years	1 (0%)	–	–	–
≥70 years	3 (1%)	1 (0%)	–	–

NCI CTC: National Cancer Institute Common Toxicity Criteria.
* Grade 1: mild, 2: moderate; 3: severe; 4: life-threatening; disabling.
** Grade 1: Asymptomatic, resting ejection fraction (EF), <60–50%; shortening fraction (SF), <30–24%. Grade 2: Asymptomatic, resting EF <50–40%; SF <24–15%. Grade 3: Symptomatic CHF responsive to intervention; EF <40–20%; SF <15%. Grade 4: Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated.

3.4. *Efficacy*

After a median follow-up period of 38.7 months overall, with no relevant differences between the age groups (39.1, 37.8, and 38.7 months), 453 RFS events (11.5%) were observed in the total study population, resulting in estimated relapse-free survival of 90.0% after three years (95% confidence interval [CI], 88.9%–91.1%) and 82.8% after five years (81.2%–84.4%). Fig. 1 shows Kaplan–Meier curves for RFS for patients aged <65 years and ≥65 years. In patients aged <65 years, the RFS rate at three years amounted to 90.3% (95% CI, 89.0%–91.5%), which was rather similar to the rate calculated for the elderly population (89.3%, 95% CI, 87.1%–91.5%). However, due to some separation of the curves after longer follow-up periods, the logrank test detected an overall difference of borderline significance ($p = 0.049$). HR for relapse amounted to 1.23 (95% CI, 1.00–1.50) for patients aged ≥65 years. If the elderly group was split, the group aged ≥70 years appeared to have a higher frequency of events during the first 36 months, but this finding is preliminary because of limited event counts at this stage (hazard ratio for elderly I vs. elderly II: 1.16, 95% CI, 0.81–1.67). If age was examined as a continuous variable in a univariate Cox model, HR was 1.01 per year (95% CI, 1.00–1.02; $p = 0.036$). However, when age was included in a multivariate regression model for RFS including other established, univariately significant prognostic factors (data not shown), age lost its independent impact on RFS (Table 3).

Based on the actual documentation of 249 deaths (6.3%), OS for the whole study population amounted to 96.2% after three years (95% CI, 95.4%–96.9%) and 90.0% after five years (95% CI, 88.6%–91.4%). As shown in Fig. 2, OS at three years was higher in patients aged <65 years (96.8% [95% CI, 96.1%–97.6%]) than in those aged ≥ 65 years (94.2% [95% CI, 92.5%–95.9%]). This difference was statistically significant ($p = 0.0011$). A similar trend by age is also detected when comparing the elderly I and II groups (hazard ratio: 1.51; 95% CI, 0.95–2.4), without hitherto reaching statistical significance.

4. Discussion

Despite the high prevalence of geriatric patients in the breast cancer population, decisions on their appropriate treatment suffer from the lack of prospective trials specifically designed for this subgroup, and therefore, from the lack of generally accepted, evidence-based therapy recommendations. As a result, the physician's, patient's, or family members' fears often lead to suboptimal treatment strategies based on the numerical age alone, rather than considering life expectancy, comorbidity, and functional status.[8] Although many thousands of patients have been recruited in adjuvant breast cancer trials during the last two decades, data on elderly patients remain sparse because most clinical trials tend to exclude the elderly population, or specific analyses are not publicly available. For example, six large randomized trials including about 10,000 patients receiving adjuvant antibody treatment in HER2-positive breast cancer were performed. Although the cutoff for "elderly" was defined as 60 years, only about 1000 of these patients could be included in recent systematic reviews on this important subpopulation.[7,20,21] In the HERA study, only 16% of patients were aged ≥60 years.[12] Thus, prospective patient series as described in our non-interventional observation study still seem to provide the most reliable information on patient groups older than 65 years or even 70 years. With a proportion of more than one out of four patients being over 65 years of age, we provide data on this, to our knowledge, largest hitherto published group of elderly patients treated with adjuvant trastuzumab.

Albeit this still remains a controversial topic, most of the reviews on breast cancer in elderly patients conclude that this age group typically suffers from biologically less aggressive, predominantly hormone receptor–positive disease.[2,5,21,26] For example, Montroni et al.[27] reported that in a retrospective series of 422 patients aged ≥70 years, only 23% had G3 grading, and only 11% were hormone receptor–negative. Large US datasets, derived from US registries starting in the 1970s, show a steady

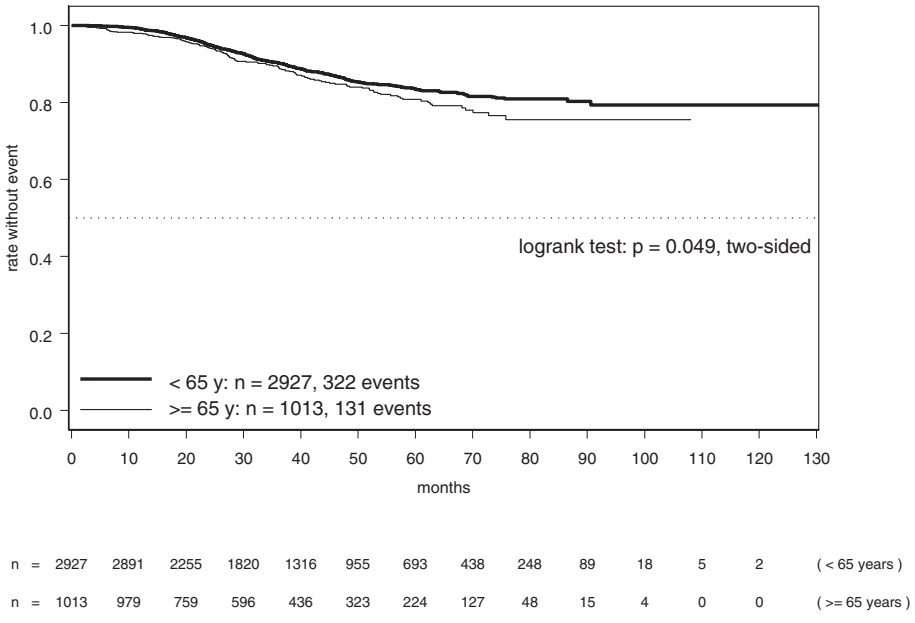

Fig. 1 – Relapse-free survival in patients aged <65 years and ≥65 years.

Table 3 – Multivariate regression analysis of prognostic factors for relapse-free survival.

Prognostic factor (first group mentioned is reference; –, not in model)	Multivariate model HR (95% CI) *p*
Age: per year, continuous	1.01 (0.997–1.01) $p = 0.24$
Primary tumor: pT1/cis vs. pT2–4	1.93 (1.55–2.40) $p < 0.0001$
Lymph nodes: pN0 vs. pN+	2.11 (1.71–2.61) $p < 0.0001$
Grading: G1/2 vs. G3	1.19 (0.97–1.47) $p = 0.092$
Hormone receptor status: neg. vs. pos.	0.58 (0.47–0.71) $p < 0.0001$
ECOG performance: 0 vs. 1–4	1.11 (0.91–1.36) $p = 0.29$

HR: hazard ratio; CI: confidence interval.

increase of hormone receptor positivity, diploidy, and low S-phase fraction with rising age.[28] However, our data (Table 1) suggest that this does not hold true in the sub-subpopulation of elderly patients with HER2-positive disease, as the respective proportions with G3 and hormone receptor–negative tumors were similar to or even slightly higher than those in the younger cohort. This discrepancy may be explained by the fact that only 6% of patients participating in the study reported by Montroni et al. were HER2-positive according to the usual standards. It is also in line with SEER-Medicare data on patients ≥66 years who had received adjuvant trastuzumab treatment, documenting a high prevalence (42%) of hormone receptor negativity (although the respective findings on the corresponding younger population are not provided).[29] Obviously, the fact is that HER2 overexpression levels off differences in tumor biology otherwise detected between older and younger patients. On the other hand, our finding of more advanced T and N stages in the elderly subgroups is in line with other patient series that disregarded HER2 status.[5]

There is no major prospective study on the comparison of trastuzumab-related cardiotoxicity between younger and elderly patients with early breast cancer. Again, the large pivotal, randomized studies produced no relevant data on this issue due to the age limit at selection, and, more importantly, due to the strict exclusion of patients with cardiac risk factors. An age trend for cardiotoxicity among the younger patients was not consistently shown in these trials. While the US studies revealed an increasing risk of cardiotoxicity with age, this trend was not evident in HERA,[5,30] possibly due to the investigators' option to individually tailor the chemotherapy according to age and/or comorbidity. A recent SEER database study in women aged 67 to 94 years (constituting only 1.9% of the study cohort) revealed a rather high rate (>15%) of administrative code claims of "heart failure" or "cardiomyopathy" after one year of treatment with adjuvant trastuzumab.[31] This contrasts with the low incidence of cardiac function toxicity (approx. 5%, all grades) in the elderly patients of our prospective observation. On the other hand, our data significantly show a comparatively higher, and increasing risk in patients beyond 65 years, remaining, however, within acceptable limits. Thus, our data confirm the general recommendations hitherto based on small patient series from individual institutions only, that adjuvant trastuzumab is feasible also in elderly/comorbid patients, if carefully managed and monitored.[6,21]

Two meta-analyses of the randomized studies of trastuzumab vs. control addressed the age-dependent efficacy of trastuzumab with respect to RFS.[7,20] The Cochrane review included meta-regression analyses of some prognostic factors. When both the HERA and the joint analysis of NCCTG N9831 and NSABP B-31 were combined, age above 60 years was associated with an only weak trend towards decreased treatment benefit (relative HR = 1.14; 95% CI, 0.63–2.09). However, the individual results from the two trial analyses were extremely heterogeneous; relative HR was 0.82 in favor of elderly patients in the US studies compared to 1.52 in HERA (i.e. no significant treatment effect detected in the elderly group). This discrepancy was not further discussed by the

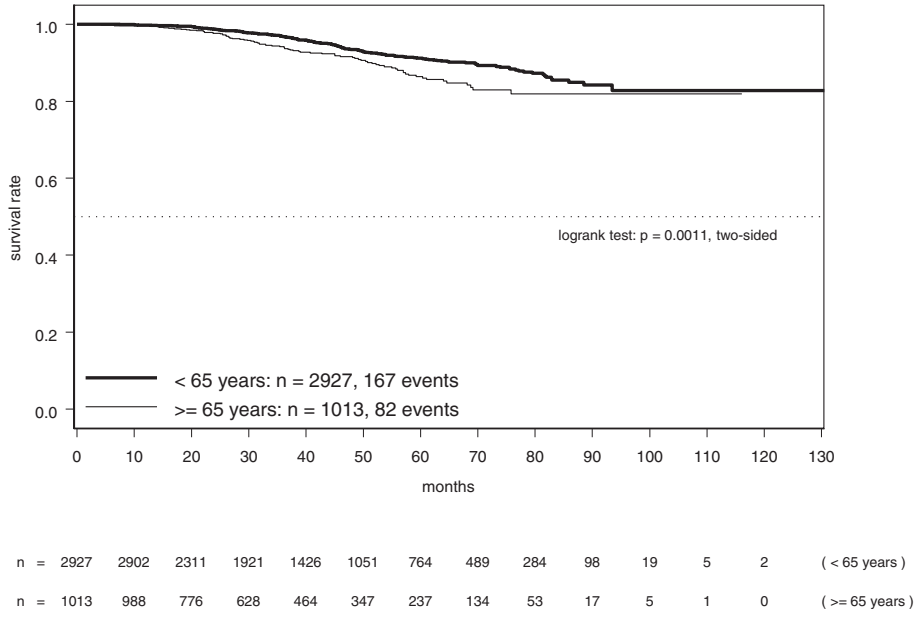

Fig. 2 – Overall survival in patients aged <65 years and ≥65 years.

Cochrane reviewers, possibly due to the limited absolute numbers and the wide CIs. The second meta-analysis[7] of the same trials confirmed this discrepancy, albeit to a lower extent. The latter is due to the fact that the second overview, although published more recently, used the earliest data from HERA published[12] instead of the updated ones.[13] Thus, the randomized trials remain rather inconclusive with respect to age effects. However, our data clearly suggest a comparable benefit of adjuvant trastuzumab treatment in elderly and younger patients. The slight difference detected in the univariate RFS analysis (Fig. 1) might be attributable to confounding factors, and consequently vanished in the multivariate model. The significant disadvantage exhibited in the overall survival curves can be easily explained by the expected different background mortality in older patients, regardless of the tumor disease, especially since our oldest patient was 100 years of age.

There are several limitations in our study. Most importantly, we neither have data on a comparable patient cohort without trastuzumab treatment nor information on an imaginable process of excluding specific patients from the targeted antibody treatment despite of HER2 positivity. With respect to toxicity, our records show the frequency of cardiac assessments in routine practice to be clearly lower than recommended, possibly leading to an underestimation of risks. Moreover, the scope of our recorded data did not allow any quantified geriatric assessment, which would probably be more appropriate for treatment decisions than chronological age.

In summary, our study comprises a representative data set, reflecting the routine treatment decisions and outcome assessments in patients receiving trastuzumab in Germany, without any restriction by protocol requirements and procedures. It shows the underlying biological aggressiveness of HER2-overexpressing tumors, even when diagnosed in old age. Although cardiotoxicity increased significantly with age, we consider antibody treatment feasible in the vast majority of elderly patients. Our long-term outcome data seem to confirm the beneficial findings from the pivotal studies also in a large group of elderly patients who are not, or only marginally, represented in the randomized trials. Nevertheless, results from ongoing randomized studies of HER2-targeted therapies, specifically focusing on elderly patients, e.g. the RESPECT trial,[32] are eagerly awaited.

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Disclosures and Conflict of Interest Statements

T. Wohlfarth is Senior Medical Manager at Roche Pharma AG. H. Tesch serves as an advisor to Roche Pharma AG. P. Dall and H. Tesch have received honoraria from Roche Pharma AG.

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