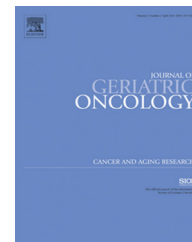


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## Trastuzumab in the treatment of elderly patients with early breast cancer: Results from an observational study in Germany

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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  $\geq 65$  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  $\geq 70$  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 inferior relapse-free survival when adjusted for other relevant prognostic factors (hazard ratio:

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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.

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## 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.<sup>1-3</sup> 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.<sup>4,5</sup> 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.<sup>4-8</sup> 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.<sup>4</sup>

In elderly patients, the introduction and consecutive improvement of adjuvant chemotherapy seems to have a smaller impact on outcome, especially on mortality.<sup>5,9</sup> This finding may, however, be explained by the fact that this patient group received less systemic treatment.<sup>2,5,10</sup> 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.<sup>2</sup> 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.<sup>11</sup> 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.<sup>2,4</sup>

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<sup>12-17</sup> convincingly underpinned by several meta-analyses.<sup>18-20</sup> However, because the number of elderly patients in these large trials was rather small, treatment guidelines are less well established in this population.<sup>6,21</sup> In fact, the incidence of HER2-positivity in elderly patients is still not well described,<sup>3,6,10</sup> although the National Comprehensive Cancer Network (NCCN) recently

reported 26% of patients with HER2-positive, early breast cancer to be 60 years or older.<sup>22</sup> 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.<sup>10</sup>

After approval of trastuzumab (Herceptin<sup>®</sup>) 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,<sup>23</sup> also reflecting that physicians usually treat patients differently from this age onwards.<sup>5</sup> 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.<sup>5</sup> Therefore, we analyzed the data for the patient groups aged 65 to 69 years and aged  $\geq 70$  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 immunohistochemistry 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

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