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Original article

Long term survival of HER2-positive early breast cancer treated with trastuzumab-based adjuvant regimen: A large cohort study from clinical practice

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ABSTRACT

Trastuzumab-based regimens for the adjuvant treatment of HER2-positive early breast cancer significantly prolonged overall survival (OS) and disease free survival (DFS) in large randomized trials, with sustained benefits at four-year follow-up. We assessed long-term survival estimates and predictors in a large cohort of Italian women with early breast cancer treated with trastuzumab in clinical practice. Through a record linkage between five regional healthcare databases, we identified women treated with trastuzumab for early breast cancer in Lombardy (2006–2009). DFS and OS were estimated using the Kaplan–Meier method, and independent predictors were assessed using proportional hazard models. 2046 women received trastuzumab in early breast cancer adjuvant setting. Overall, the proportion of patients surviving free of disease was 93.9% at one year, 85.8% at 2 years, 79.4% at 3 years, and 75.0% at 4 years. OS estimates were 98.7%, 95.4%, 91.5% and 89.4% at 1, 2, 3 and 4 years, respectively. Significant independent predictors of worse survival outcomes were age <40 or ≥70 years compared to age 40–69 years, positive nodal status, radical breast surgery, combination therapy with paclitaxel, having at least one comorbidity (i.e. diabetes, cardiovascular disease), and a trastuzumab-based regimen lasting less than six months. Long term survival rates of women treated with trastuzumab for early breast cancer in clinical practice were consistent with estimates from clinical trials testing the drug in the adjuvant setting.

Introduction

Human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine kinase receptor, involved in cell growth, differentiation and survival [1]. Gene amplification or protein overexpression of HER2 occur in 15%–20% of breast cancers [2], leading to a poor prognosis and a worse response to treatment [3,4].

Trastuzumab (Herceptin®), a recombinant humanized monoclonal antibody that selectively targets extra-cellular domain of the HER2 receptor, benefits patients with HER2-positive breast cancer, and has become the standard of care for the treatment of metastatic disease, as well as, more recently, of the earlier stages. Following approval by the European Medicines Agency (EMA) in 2004 [5], in 2006 the Italian Medicine Agency (Agenzia Italiana del Farmaco, AIFA) granted first approval for trastuzumab treatment in HER2-positive early breast cancer when administered "after breast surgery, chemotherapy (neoadjuvant/adjuvant) and radiotherapy (if applicable)".

Large phase III trials evaluating trastuzumab-based regimens for the adjuvant treatment of HER2-positive early breast cancer

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showed significant improvements in both overall survival (OS) and disease free survival (DFS) when trastuzumab was added to standard chemotherapy, with sustained benefits at four-year follow-up [6–8]. A recent systematic review of eight randomized clinical trials from the Cochrane Collaboration concluded that "trastuzumab significantly improves OS and DFS in HER2-positive women with early and locally advanced breast cancer" [9]. However, there are concerns on the reproducibility of results derived from selected populations in clinical trials in routine clinical practice [10]. Therefore, it is of interest to obtain survival estimates from HER2-positive early breast cancer trastuzumab users outside experimental studies.

Our group has recently assessed the cardiac safety profile of trastuzumab using regional healthcare databases in a cohort of 2046 Italian women with HER2-positive early breast cancer who first received the drug between 2006 and 2009, providing information on short- and long-term implications [11]. The aim of the present study is to analyze survival in the same cohort of women. In particular, our objectives are: i) to evaluate DFS and OS at 1, 2, 3 and 4 years after first trastuzumab administration, overall and by age; ii) to identify potential demographical and clinical predictors of DFS and OS; iii) to evaluate the association between duration of trastuzumab-based therapy and survival endpoints.

Materials and methods

Data sources

Data were retrieved from five regional healthcare administrative databases of Lombardy, the largest Italian region with 9.5 million of inhabitants, on the basis of the same cohort of women we used to estimate trastuzumab cardiotoxicity [11].

The first database is the File F registry (2006–2010), including all prescriptions of drugs administered directly in the outpatient setting and of selected novel high-cost drugs administered both in the outpatient setting and in day hospital (DH), and reimbursed by the National Health Service (NHS) [12]. It includes information on the date and the dosage of drug prescription, as well as on the hospital and the physician administering the drug.

The second source of data is the regional hospital discharge forms (Scheda di Dimissione Ospedaliera, SDO) database (2001–2010), which contains clinical information about patients and their hospitalizations both ordinary and in DH, including demographic characteristics, admission and discharge dates, main and five secondary diagnoses (coded according to the International Classification of Diseases 9, ICD-9), date and type of interventions, and hospitalization-related costs (coded according to the national Diagnosis Related Groups system, DRGs) [13]. The SDOs referring to chemotherapy included also information on whether the cost of the drug was compensated through the File F scheme.

The third data source is the Outpatients' Services database (2002–2010), which stores all services provided to NHS recipients in the outpatient setting (outside of ordinary hospitalization or DH), including chemotherapy or radiotherapy administration.

The fourth dataset is the Registry Office database of Lombardy, updated to April 2011, which includes information on vital status and, in case, date of death of Lombardy residents.

The fifth database is the regional outpatient drug prescription database (2000–2009), which stores all drug prescriptions reimbursed by the NHS and dispensed by a pharmacy in Lombardy.

Study population and data analysis

A computerized record linkage between the File F registry and the SDO database was carried out through a unique anonymous patient identification code. We selected all women residents in Lombardy who received the first prescription of trastuzumab between August 2006 and December 2009 and had at least one hospitalization between 2001 and 2009 reporting a breast cancer diagnosis (ICD-9 174.0–174.6, 174.8–174.9, 175.0, 175.9, V103) prior or concurrent with the first trastuzumab prescription. We defined the date of breast cancer diagnosis as the date of the first SDO where breast cancer was reported. We restricted the cohort to trastuzumab users in the adjuvant setting by excluding all patients with at least one hospitalization reporting distant recurrence (ICD-9 196.0–196.2, 196.5–196.6, 196.8–196.9, 197.0–197.8, 198.0–198.7, 198.81–198.82, 198.89, 199.0) prior or within 90 days from the first trastuzumab prescription.

Information about breast cancer-related care interventions was extracted from the SDO database and the Outpatients' Services database identifying codes related to breast surgery, neoadjuvant/adjuvant chemotherapies and radiotherapy in the period between the first breast cancer diagnosis and the first trastuzumab prescription. We also searched in the File F registry for any prescription of the oncologic drugs usually employed in early breast cancer treatment in the same period. The combination of paclitaxel was defined as the presence of a prescription of paclitaxel in the File F registry within two days from each trastuzumab prescription, on the basis of the approved regimen reported on the drug information technical dossier.

Duration of therapy was considered as time from the first to the last trastuzumab prescription or prior to recurrence, if any (up to the end of 2010). To assess the frequency of severe cardiac adverse events, we extracted SDOs reporting selected cardiac diseases (myocardial infarction/ischemia, heart failure, rhythm disorders, cardiac dysfunctions) as main diagnosis after the first trastuzumab administration.

To identify patients with prior selected chronic conditions (i.e. diabetes, dyslipidemia, obesity, cardiovascular, renal, respiratory, neurological and hepatic chronic diseases) we used two sources. We retrieved hospitalizations prior to first trastuzumab administration reporting these diseases in the SDO database, and we looked for prescriptions of drugs related to these diseases in the outpatient drug prescription database, relying on a previously developed algorithm [14–16].The classes of drugs we considered were antidiabetic, antihypertensive and lipid lowering drugs.

From the diagnostic codes in the SDOs, we evaluated also nodal status at surgery and type of surgery.

DFS was defined as time from the first trastuzumab prescription to the first occurence of any of the following events: local, regional or distant recurrence, contralateral breast cancer, second primary cancer, death from any cause. OS was defined as time from the first trastuzumab prescription to death from any cause. Patients were followed up until the occurrence of an event or the end of April 2011, whichever came first.

Statistical analysis

DFS and OS were estimated using the Kaplan–Meier method. The effect of potential predictors on survival endpoints was estimated by Cox proportional hazards models and expressed as hazard ratio (HR). The model included the following variables: age (<40, 40–69, ≥70 years), nodal status (positive, negative), type of surgery (conservative, radical, unknown), combination with paclitaxel (yes, no), presence of at least one of the selected comorbidities (yes, no). We also evaluated the interaction between combination therapy and tumor features as surrogates to T stage (positive/negative nodal status and radical/conservative surgery).

We estimated the association of duration of therapy (≤6, >6 months) with OS and DFS, starting follow-up one year after the first

trastuzumab administration, and excluding patients who experienced any event (i.e. recurrence, second primary cancer or death) and/or a cardiac adverse event during the first year of follow-up.

Results

Out of 2879 Lombardy residents who had at least one trastuzumab prescription during the study period, 2046 women received the drug in early breast cancer adjuvant setting and their baseline clinical characteristics are listed in Table 1. Overall, 38.8% were aged below 50 years, and the median age at breast cancer diagnosis was 54 years. Node-positive status was reported for 43.6% of cases, conservative breast surgery (57.3%) was performed more often than the radical procedure (32.2%), the majority of patients (91.8%) received previous chemotherapy, mainly in the adjuvant setting, and 60.4% underwent a course of radiotherapy.

Median follow-up was 2.6 years. Overall, we registered 154 deaths (7.5%) and 342 DFS events (16.7%): 240 distant recurrence (11.7%), 49 local recurrence (2.4%), 23 primary tumors (1.1%) and 30 deaths without prior recurrences (1.5%). The median number of trastuzumab prescriptions was 17.

Fig. 1 (A–D) shows Kaplan–Meier estimates of DFS and OS, overall (A–B) and stratified by age (C–D). Overall, patients surviving free of disease were 93.9% at one year, 85.8% at 2 years, 79.4% at 3 years, and 75.0% (95% Confidence Interval, [CI] 71.8–77.8) at 4 years. OS estimates were 98.7% after the first year, 95.4% after the second year, 91.5% after the third year, 89.4% (95% CI 87.4–91.1) at 4 years. For the analyses stratified by age (<40, 40–69, ≥70 years), data were censored at 3 year, due to the small number of subjects in subgroups. After three years, the DFS estimates were 73.6% in women aged <40 years, 81.5%, in women aged 40–69 years, and 65.2% in older women. The corresponding estimates for OS were 91.8%, 92.8% and 76.0%.

Table 1
Baseline characteristics of 2046 trastuzumab users for early-stage invasive breast cancer. Lombardy, Italy, 2006–2009.

	Breast cancer N (%)
Overall	2046
Age[a] (years)	
<40	237 (11.6)
40–49	557 (27.2)
50–59	585 (28.6)
60–69	493 (24.1)
≥70	174 (8.5)
Nodal status	
Positive	892 (43.6)
Negative	1154 (56.4)
Year of first administration	
2006	203 (9.9)
2007	403 (19.7)
2008	746 (36.5)
2009	694 (33.9)
Extent of surgery	
Conservative	1173 (57.3)
Radical	659 (32.2)
Unknown	214 (10.5)
Chemotherapy	
Yes	1878 (91.8)
Adjuvant	1630
Neoadjuvant	155
Undefined	93
No	168 (8.2)
Radiotherapy	
Yes	1235 (60.4)
No	811 (39.6)

[a] Age at first breast cancer diagnosis reported in regional hospital discharge form database.

Table 2 gives HRs of DFS and OS according to selected baseline characteristics and association with paclitaxel estimated from proportional hazard models. Women aged <40 years or ≥70 years had a worse DFS and OS compared to those aged 40–69 years: the HRs for DFS and OS were, respectively, 1.31 (95% CI 0.96–1.79) and 1.62 (95% CI 1.02–2.59) in patients <40 years and 1.37 (95% CI 0.97–1.94) and 2.59 (95% CI 1.68–4.00) in patients ≥70 years. A positive nodal status was associated with a significantly worse DFS and OS (respectively, HR 1.40, 95% CI 1.13–1.74, and HR 1.66, 95% CI 1.19–2.30), as well as radical breast surgery (respectively, HR 1.65, 95% CI 1.31–2.08, and HR 2.04, 95% CI 1.43–2.92) as compared to conservative breast surgery. Other significant independent predictors of worse survival outcomes were combination therapy with paclitaxel (respectively, HR 3.56, 95% CI 2.73–4.65, and HR 3.31, 95% CI 2.25–4.86) and, to a lesser extent, at least one comorbidity (respectively, HR 1.23, 95% CI 0.99–1.54, and HR 1.51, 95% CI 1.06–2.13). No statistically significant association was found between combination therapy and tumor features as surrogates to T stage (positive/negative nodal status and radical/conservative surgery).

The association between duration of therapy and DFS and OS was estimated among 1870 patients. Compared to women who were treated for ≤6 months, those treated for a longer period had a borderline better DFS (HR = 0.73, 95% CI 0.53–1.02) and a significantly better OS (HR = 0.44, 95% CI 0.27–0.69). The percentage of women treated for less than six months was 16% below age 70 years and 25% in women aged ≥70 years.

Discussion

In this unselected cohort study of women treated with trastuzumab-based adjuvant regimen for HER2-positive early breast cancer in clinical practice, the survival rate within the fourth year of follow-up (89.4%) was consistent with estimates from the main clinical trials testing trastuzumab in the adjuvant setting (89.3% in the HERA trial [6], 93% in the NCCTG N9831 and NSABP B-31 trials combined [7], and 93% and 94% in the two trastuzumab arms of the BCIRG-006 trial [8]). The proportion of patients surviving free of disease after 4 years was slightly lower (75.0%) in our study than previously reported (78.6% in HERA trial [6], 85.7% in NCCTG N9831 and NSABP B-31 [7] and 84% and 86% in BCIRG-006 [8]). However, in another population cohort of trastuzumab-treated women from the South East Wales Cancer Network (SEWCN) [17], three year OS was 98.5% and DFS 90.3%, much higher than our three year OS (91.8%) and DFS (79.4%), and also higher than the one reported in clinical trials.

Our results are similar to those of the HERA trial. Despite most of the women in the control group of the HERA trial crossed over to trastuzumab treatment after early stopping of the trial, the OS (87.7%) and DFS (72.2%) in the control arm were worse than those observed in our cohort. These estimates further decreased to 71.7% for DFS and 81.5% for OS when women that crossed over were censored in the analysis [6]. In the HERA trial, women were randomized only after completion of different types of neoadjuvant or adjuvant chemotherapies, while in the other trials randomization occurred at diagnosis/surgery, prior to any form of treatment, and the subsequent therapeutic regimen was strictly defined, not only with regard to trastuzumab. This renders the HERA trial more comparable to our cohort. Also, when computing our survival estimates, we started from first trastuzumab administration, as did the HERA trial, and not from time of surgery, like in the SEWCN cohort. Our 4-years survival rates were based on part of the cohort only, since the median follow up in this study was 2.6 years, compared to about 4 years in the HERA trial. However, the Kaplan Meier curve adjusts for variable length and provides an unbiased

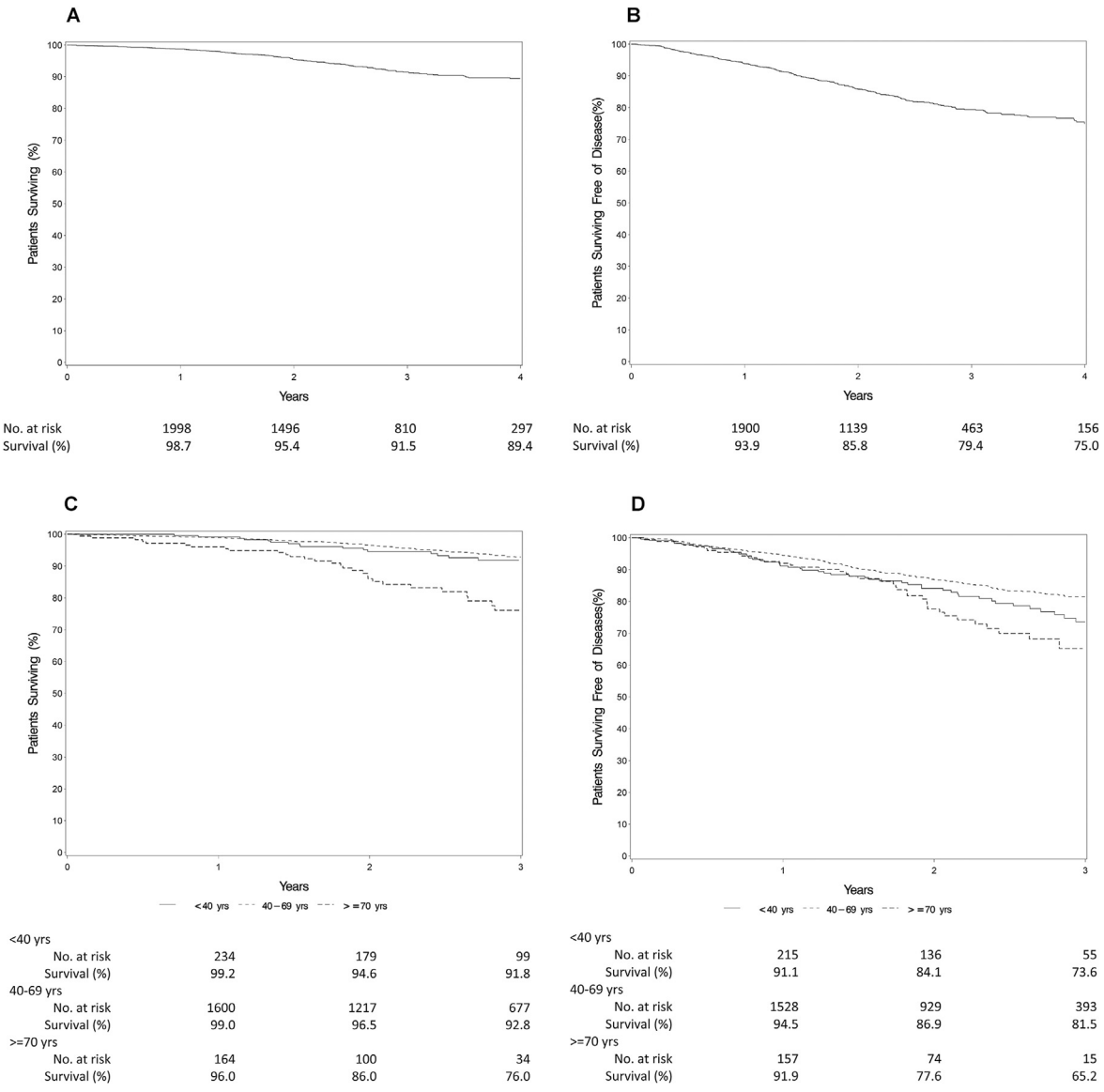

Fig. 1. A–D Kaplan–Meier estimates of disease free survival and overall survival among trastuzumab users for HER2 early breast cancer adjuvant treatment, overall (A–B) and by age (C–D). Disease events include local or distant recurrence, contralateral breast cancer, second primary cancers or death as a result of any cause. Overall survival is measured from the time of study enrollment to death or the end of April 2011.

estimate of the true target population survival curve if competing losses are uninformative [18].

The median age of this cohort was 54 years, and that of the SEWCN cohort 56 years, as compared to 49 years in the HERA trial [19] and in the pooled population from the eight studies [9]. In this study, both women below age 40 and women above age 70 years had worse OS and DFS than women aged 40–69 years. A worse OS in older women is expected. It is also possible that, due to higher comorbidity, older women receive a less intensive drug regimen [20]. In fact, the percentage of women treated for less than 6 months was higher above age 70 years. Concerning young women, in the HERA trial too, women below age 35 years had a worse OS and DFS [6]. Women below age 40 years are known to have a relatively poor prognosis compared with older women, which is not explained by a different distribution of pathological features, including HER2 status [21]. We could not distinguish between breast cancer-related death and death from other causes. However, the risk of non breast cancer related death in women aged less than 40 years is low. Thus, the excess death in younger women is likely due to the worse breast cancer prognosis.

Other independent predictors of worse survival outcomes were, as expected, a positive nodal status, and a radical surgical procedure. The worse survival associated to combination therapy with paclitaxel may indicate the use of a more intensive approach in women with a more extensive disease. However, no significant association was found between combination therapy and tumor features used as surrogates to disease extent (i.e. nodal status and type of surgery).

Finally, having at least one comorbidity was associated with a 50% increased HR of death. By design, women with cardiac risk factors were excluded from the HERA and other trials, because of the cardiotoxicity of trastuzumab. The incidence of severe cardiac heart failure in this cohort (1.4%) was more than 3 times higher than in the HERA trial (0.4%) [11], reflecting the older and less healthy general condition of women in our cohort [22] or a more sustained cardiotoxic effect of trastuzumab in clinical practice.

Table 2
Hazard ratios (HR) and corresponding 95% confidence intervals (CI) of overall survival (OS) and disease free survival (DFS) according to selected baseline characteristics and association with paclitaxel among 2046 trastuzumab users for early breast cancer.

		DFS		OS	
	No.	No. of events	HR[a] (95% CI)	No. of events	HR[a] (95% CI)
Age (yrs)					
<40	237	49	1.31 (0.96–1.79)	23	1.62 (1.02–2.59)
40–69	1635	253	1[b]	101	1[b]
≥70	174	40	1.37 (0.97–1.94)	30	2.59 (1.68–4.00)
Nodal status					
Negative	1154	159	1[b]	66	1[b]
Positive	892	183	1.40 (1.13–1.74)	88	1.66 (1.19–2.30)
Extent of surgery					
Conservative	1173	149	1[b]	54	1[b]
Radical	659	151	1.65 (1.31–2.08)	73	2.04 (1.43–2.92)
Unknown	214	42	1.42 (1.00–2.02)	27	2.45 (1.52–3.95)
Association with paclitaxel					
No	1875	270	1[b]	118	1[b]
Yes	171	72	3.56 (2.73–4.65)	36	3.31 (2.25–4.86)
Comorbidity					
No	1068	164	1[b]	63	1[b]
Yes	978	178	1.23 (0.99–1.54)	91	1.51 (1.06–2.13)

[a] Estimated through multiple Cox model including terms for age, nodal status, association with paclitaxel, type of surgery and previous comorbidity.
[b] Reference category.

In this cohort, 301 (16.1%) women received the trastuzumab-based adjuvant regimen for six months or less. The OS and DFS of women treated for shorter periods were significantly worse than those of women treated for more than 6 months. When contrasting the outcome of women treated for different duration, the issue of comparability of various groups must be carefully considered. In order to avoid immortal time bias [23] when comparing women receiving trastuzumab treatment for a different length of time, we excluded from the analysis the first year after starting trastuzumab administration. Since the occurrence of an event could have led drug discontinuation, to render the two groups more comparable we also excluded all patients who experienced any event (death or recurrence) and/or a cardiac adverse event (requiring hospitalization) in the first year of observation. However, we had no data on decline in left ventricular ejection fraction or symptomatic cardiac heart failure not requiring hospitalization. Thus, we missed less severe cardiac events that likely led to discontinuation of therapy. However, a worse prognosis for shorter duration of trastuzumab treatment was suggested by the PHARE non inferiority trial, which compared 6–12 months trastuzumab in adjuvant early breast cancer, and failed to show that 6 months of therapy was non inferior to 12 months [24].

Another aspect that may be considered is the reliability of HER2-testing in clinical practice. A central review of HER2 positivity of the first 104 patients enrolled in the NSABP B-31 trial found that 18% of the community based HER2+ assays were not confirmed in the central laboratory [25]. Thus, performance of HER2 testing with immunohistochemistry is less than optimal, and it is possible that an undefined number of HER2-negative women were treated with trastuzumab in our cohort. Given that HER2-negative women have generally a better prognosis, this may have inflated OS and DFS.

Potential limitations in our study can derive from the use of databases created for administrative purposes. A major issue is the completeness and reliability of the available data. Given that reimbursement to hospitals and other health structures by the NHS is based on data reported in these databases, it is in their interest to provide complete information. These data have been widely used for epidemiological research in various fields [26]. We used information from at least two different sources (the File F and the SDO database) to identify trastuzumab users (File F) with breast cancer (SDO) and there was an excellent consistency between these two sources. In general, the concordance between and within the five databases, as well as the substantial consistence with data from published literature are reassuring in terms of reliability and validity of results. Another important limitation is the lack of information on potential covariates and relevant tumor characteristics, such as stage and grade, number of positive nodes and hormonal receptor status. Moreover, we were also unable to exactly identify drugs previously administered in the adjuvant context. This might limit the comparison with the randomized clinical trial populations. Strengths of this study are the representativeness of routine clinical practice, the large sample size, the length of follow up, and the coverage of various age groups.

Conclusion

In spite of the several potential factors that can affect external validity of clinical trials, we found similar long-term survival rates of trastuzumab users for HER2-positive early breast cancer in clinical practice, suggesting that results from experimental studies are applicable to usual practice [27]. In this cohort, trastuzumab regimen lasting less than six months resulted in a worse prognosis, but, given the observational nature of this study, the causality of this association is unproven.

Conflict of interest statement

The authors declare no conflict of interest.

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