RHEALITY: Recurrence of HER2+ patients: evaluation of long term outcome in patients receiving trastuzumab therapy

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Abstract

Background: Despite improved prognosis of HER2+ eBC since the introduction of trastuzumab in the adjuvant setting in 2006, disease recurrences still occur in some patients after a few years. We aimed to describe in real life the long-term follow-up to assess disease-free and metastasis-free survival of patients with HER2+ eBC treated with adjuvant trastuzumab.

Methods: This was a multicenter, retrospective, cohort study assessing HER2+ eBC patients diagnosed between 2009 and 2010 and treated with adjuvant trastuzumab. Data were collected from patient’s medical charts. Disease-free survival (DFS), and metastatic-free survival (MFS) were evaluated in the overall population and within subgroups according to hormonal and nodal status.

Results: In the overall population (n=2,513) at 7 years, the DFS rate was 75.8% [95%CI 74.0%-77.6%), and the MFS rate was 84.1% [82.5%-85.6%]. According to hormonal status, the 7-year DFS rate was significantly higher for HR+ than for HR- patients [80.0% vs. 68.6%; p <0.001], and the 7-year MFS rate [87.9% for HR+ vs. 77.5% HR-]. According to nodal status, the 7-year DFS rate was significantly higher for N- than for N+ patients [86.7% vs. 66.4%; p <0.001], and the 7-year MFS rate [94.7% for N- vs. 74.9% for N+].

Conclusions: Despite introduction of adjuvant trastuzumab, prognosis of HER2+ eBC is still a matter above all in subgroups associated with a higher risk of disease recurrence. Our real-world study pointed out a particularly aggressive profile of N+ and HR- subgroups and the need for more efficient approaches for these particular group of patients.

Keywords: early breast cancer, adjuvant trastuzumab, cohort study, disease recurrence
Background

In breast cancer, Human Epidermal Growth Factor Receptor-2 (HER2) overexpression is independently associated with aggressive disease, poorer disease-free survival (DFS) and overall survival (OS) compared with tumors that do not overexpress HER2 [1,2]. The current standard treatment of patients with HER2-positive (HER2+) breast cancer involves chemotherapy combined with the HER2-targeted monoclonal antibody trastuzumab, followed by trastuzumab continued for a full year. Trastuzumab was approved approximately two decades ago for the treatment of patients with HER2+ positive metastatic breast cancer by the Federal food and Drug Administration and the European Medicines Agency (EMA) and in early breast cancer (eBC) in 2006 [3]. In eBC, the approval was based on the results of the early analyses of the large, international, open-label, multicenter, randomized phase III HERA (HERceptin Adjuvant) study, designed to compare one year of three-weekly trastuzumab (n=1694) to observation (n=1693) following surgery, established chemotherapy and radiotherapy in patients with HER2+ eBC. Trastuzumab significantly improved disease-free survival, recurrence-free survival and distant disease-free survival [4].

Other international, randomized, controlled phase III trials in the adjuvant setting (NSABP B-31, NCCTG N9831), confirmed the survival advantage conferred by the addition of trastuzumab to chemotherapy regimens in HER2+ eBC [5-7].

Long-term results of the HERA study after 11 years of median follow-up showed that adding a 1-year trastuzumab treatment to standard chemotherapy in HER2+ eBC led to an absolute gain of 6.8% improvement in 10-year DFS compared to the observation group [HR= 0.76, 95% CI 0.68-0.87]. This benefit was observed even though 52% of the patients in the observation group crossed over and received trastuzumab after publication of the initial results [8]. These
results also indicate that some patients are more prone to long-term recurrence than other patients.

Subgroups analyses of DFS showed differences. In the 1-year trastuzumab cohort, DFS at 10 years was greater in hormone-receptor positive (HR+) than hormone-negative (HR-) patients (72% versus 67%). In the same cohort, differences were even more marked when looking at nodal involvement. In the node negative subgroup (N-), DFS at 10 years was 80%, compared to 75% in the 1-3 positive nodes (N+) subgroup and 55% in the 4 or more N+ subgroup.

These results did not question the undisputable benefit of adding trastuzumab but brings to attention the need for improved DFS in specific subgroups associated with a higher risk of disease recurrence, notably HR- and N+. This consequently led to the conduct of phase III randomized clinical trials such as ALTTO assessing adjuvant lapatinib and trastuzumab for early HER 2 + eBC [9] and APHINITY assessing adjuvant pertuzumab and trastuzumab in HER2+ eBC [10] aiming to find new ways to improve DFS.

Even though trastuzumab was used in France as early as October 2005 in the adjuvant treatment of patients with HER2+ eBC, owing to a temporary use authorization granted by the French healthcare authorities prior to the EMA approval, there are no long-term real-life data available for trastuzumab in adjuvant eBC in France. This retrospective observational cohort study was carried out to collect long-term outcomes data and particularly to assess disease-free and metastasis-free survival in the HR- and N+ subgroups.

**Methods**

This real-world multicenter, retrospective chart review study was conducted in a cohort of patients diagnosed with HER2+ eBC, between 1\textsuperscript{st} January 2009 and 31\textsuperscript{th} December 2010 and treated with adjuvant trastuzumab (Fig. 1). Participating centers were selected among the 200
centers that prescribed 87% of adjuvant trastuzumab in HER2+ eBC in France in 2010 [11].

These centers were selected to be representative in terms of hospital setting and region. As control quality parameter, each center needed to treat at least 15 patients per year.

The main objective of the study was to assess disease recurrence within 7 years after the start of adjuvant trastuzumab in patients with eBC HER2+ treated in real-world practice, in the overall population and in subgroups according to hormonal (H) and nodal (N) status.

Eligible patients had to be ≥18 years old, presenting with a diagnosis of HER2+ eBC (non-metastatic) occurring between 1 January 2009 and 31 December 2010 and treated with at least one infusion of adjuvant trastuzumab regardless of the duration of the treatment. Hormonal status and regional lymph nodes involvement had to be documented at diagnosis. HER2 overexpression was defined as either 3+ by IHC and/or positive in situ hybridization testing according to local guidelines. Patients who received a neo-adjuvant treatment (regardless of the composition of this treatment) and male patients with breast cancer were excluded from the study.

A standardized one-page case report form was used for collecting data from patient medical charts. Data included patient’s characteristics (age, menopausal status), clinical profile (tumor size and nodal status) at diagnosis and anti-tumor adjuvant treatments (chemotherapy and/or radiotherapy and/or endocrine therapy). Patients’ status and events occurring before or on 31st December 2017 were collected.

The primary endpoint was disease-free survival, defined as the time elapsed from the first trastuzumab administration to the first occurrence of any of the following events: recurrence of breast cancer at any site (local, regional or metastatic), contralateral breast cancer, development of second non-breast cancer, death from any cause, in the overall population and within subgroups according to hormonal and nodal status.
Secondary endpoints included patients and disease characteristics overall and according to hormonal (HR+/HR-) and nodal (N+/N-) status, the characterization of the type of recurrence and the assessment of the metastasis-free survival of the patients.

The study protocol was submitted and approved by the INDS (Institut National des Données de Santé/National Institute for Health Data) based on a standardized methodology for a retrospective study (MR003/not requiring patient consent) and was submitted to the CNIL (Commission Nationale de l'Informatique et des Libertés/French data protection authority) which authorized the data processing of the study (DR-2018-072).

**Statistical analysis**

Statistical analyzes were mainly descriptive and exploratory using basic summary statistics. Continuous data were described by mean +/- standard deviation, median [range: minimum and maximum]. Nominal data, including some categories of continuous data, are presented in frequency tables.

Comparisons between subgroups were using two types of bilateral tests (Chi-square test or Student's test). A significant difference was considered for a p-value ≤ 5%. No multiple tests were performed.

Disease-free survival and metastasis-free survival (MFS) were assessed using the Kaplan-Meier method. The reference dates used to determine DFS and MFS were the date of the first trastuzumab administration to the date of the first event diagnosis (regardless of the site of recurrence for DFS and any distant recurrence for MFS). For each time point, the cumulative probabilities of disease recurrence were calculated as follows: 100 minus the disease-free or metastatic-free survival rate.
Data were analyzed by Kantar Health France using COSI software version 4.7.1. build 2 (MLI, Bourg-en-Bresse, France) for descriptive analyses and the R software version 3.0.2 (Foundation for Statistical Computing, Vienna, Austria) for Kaplan-Meier analyses.

Results

A total of 147 centers were contacted and about half of them participated in the study between May and July 2018. Among the 76 centers, offering a good representativeness, 27 (36%) were private clinics, 20 (26%) were public non-university hospitals, 17 (22%) were university hospitals and 12 (16%) were comprehensive cancer centers. The reasons for refusal to participate in the study for the 71 centers were mainly related to the impossibility or difficulty of ensuring the accrual of cases that met inclusion criteria.

A total of 2,524 patients were included in the study. Eleven patients were excluded from the analysis, 3 because they had received a neo-adjuvant treatment, 7 had undocumented lymph nodes status at diagnosis and 1 had missing follow-up information. Therefore, the final analyse was performed on 2,513 cases.

Overall, 62.8% (1,577) of patients had HR+ tumor (ER+ and/or PgR+) and 37.2% (936) had HR- disease.

A total of 1179 patients had no lymph node involvement (46.9%) and 965 patients had 1 to 3 lymph nodes invaded (38.4%), 369 patients (14.7%) had ≥4 or more positive lymph nodes, for a total of 1334 patients (53.1%) with N + cancer (Table 1).

Regardless of hormonal and nodal status, almost all patients received chemotherapy and adjuvant radiation (Table 2). Almost all HR+ patients (98.4%) received adjuvant endocrine
therapy, mostly aromatase inhibitor only (61.1%), anti-estrogen only (26.5%) or a sequence of anti-estrogen followed by aromatase inhibitor (11.8%).

More N+ patients received a combination of anthracyclines + taxanes than N- patients (81.6% vs. 66.8%) and had a radiation (96.9% vs. 91.9%). Conversely, more N- patients were treated with taxanes without anthracyclines than N+ patients (26.5% vs. 15.3%).

Disease-free survival and metastatic-free survival results for the overall population and for each subgroup (HR+/HR-, N+/N-), according to the number of positive nodes (1-3 vs. ≥ 4) and according to the combination of nodal and hormonal status (N-HR+, N-HR-, N+HR+, N+HR-) are shown in Table 4, Fig.2 and Fig. 3.

In the overall population at 7 years, the DFS rate was 75.8% [95%CI 74.0%-77.6%], and the MFS rate 84.1% [82.5%-85.6%] (Table 4). The most frequently reported events were metastatic recurrence (63.8%), local/regional recurrences (17.8%), death without evidence of disease progression (6.3%), second malignancy (6.1%) and contralateral breast cancer (5.9%).

The 7-year DFS rate according to hormonal status was significantly higher for HR+ than for HR- patients (80.0% vs. 68.6%; HR of HR+ patients vs HR- patients: 0.61 (95% CI:0.52-0.71); p <0.001), and according to nodal status, the 7-year DFS rate was significantly higher for N- than for N+ patients (86.7% vs. 66.4%; HR of N+ patients vs N- patients: 2.84 (95% CI:2.37-3.40); p <0.001). The percentage of 7-year DFS was higher in patients with 1-3 positive nodes, compared to ≥4 positive nodes (72.4% vs. 50.9%; HR of 1-3 positive nodes vs 4 positive nodes: 0.4324 (95%CI: 0.3594-0.5203); p <0.001). The 7-year-DFS in the HR-/N+ and the HR+/N- subgroups was 55.4% and 88.8%, respectively and it was 72.8% and 83.3% in the HR+/N+ and HR-/N-subgroups, respectively (Fig. 2).

The 7-year MFS rate according to hormonal status was significantly higher for HR+ than for HR- patients (87.9% vs. 77.5%; HR of HR+ patients vs HR- patients: 0.51 (95% CI:0.42-0.62); p
<0.001), and according to nodal status, the 7-year MFS rate was significantly higher for N- than for N+ patients (94.7% vs. 74.9%; HR of N+ patients vs N- patients: 4.98 (95% CI:3.82-6.50) ; p<0.001). The percentage of 7-year MFS was higher when 1-3 positive nodes were present, compared to ≥4 positive nodes (80.6% vs. 60.0 ; HR of 1-3 positive nodes vs 4 positive nodes: 0.3738 (95%CI: 0.3010-0.4642) ; p<0.001). The 7-year MFS was the lowest in the HR-/N+ subgroup and the highest in the HR+/N- subgroup (63.3% and 95.7%, respectively). The results of the other subgroups, HR+/N+ and HR-/N-, were 81.4% and 92.9%, respectively (Fig. 3).

Overall, at 7 years, the main sites of metastases were visceral +/- other metastases and brain +/- other metastases (45.1% and 41.7%, respectively) (Table 3). In the HR+ subgroup, 47.3% of patients presented with visceral +/- other metastases and 35.3% with brain +/- other metastases. In the N- subgroup, 60.7% of patients presented with visceral +/- other metastases and 37.5% with brain +/- other metastases. Differences between sites of metastases in the HR- and HR+ subgroups were significant (p=0.020) as well as differences between the N- and N+ subgroups (p=0.007) (Table 3).

Discussion

This retrospective cohort chart review study conducted in France assesses the long-term outcomes of patients with HER2+ eBC treated with adjuvant chemotherapy and trastuzumab, in a real-world setting. The number of cases collected as well as the representativeness of the centers that participated, provides a unique dataset for evaluating the long-term efficacy of adjuvant trastuzumab.

Among the 11,185 patients who were treated with adjuvant trastuzumab in 2010 in France, it is difficult to precisely evaluate the percentage of eligible patients that were included in our analysis (n=2,513 cases) because we excluded women treated with neo-adjuvant trastuzumab.
and men with HER2+ eBC, and these patients were not identifiable in the French medicalized information system program (PMSI). While the differences in eligibility criteria between patients in this study and in phase III interventional trials, assessing adjuvant trastuzumab such as HERA and APHINITY, excluded direct comparison [4,10], the general demographic and clinical characteristics of the patients in our cohort and these studies appeared very close, except for a higher rate of older patients aged 60 years or older in our cohort, i.e. 36% compared to 16% in the HERA trial, and 21% aged 65 years or older versus 13% in the APHINITY trial [4,10]. These differences reflect the exclusion of older patients from clinical trial as well as the propensity of physicians to propose participation in clinical trials to few elderly patients even if the protocol does not exclude them. The difference in the proportion of patients aged 60 years or over explains that the percentage of postmenopausal patients was higher in our cohort (57%) than in interventional trials where this criterion was described (45% in the HERA trial). The ratio HR+/HR- observed (63/37) is close to 60/40 usually found in an incident breast cancer population, and notably in the APHINITY trial (64/36) [4,10].

The 7-year DFS in the overall population was 75.8%, but it varied significantly according to both hormonal status and nodal involvement. The same observation can be made for the 7-year MFS which was 84.1% in the overall population, 87.9% in the HR+ subgroup and 74.9% in the N+ subgroup.

In France, the usual recommendation in real-world practices is to regularly follow-up patients with disease-free eBC during a period of 5 years, and then to space out or even discontinue the follow-up. The impact of this recommendation can be observed in the rate of patients who no longer consult at 5 years after the initiation of trastuzumab. The overall cumulative proportion of these patients is 6.9% (8.2% based on disease-free patients) but increase to 14.6% and 17.6% respectively at 6 years.
Although the number of patients with disease-free eBC documented at least 6 years after the start of trastuzumab remains high, the significant drop at 5 years follow-up may impact the population still documented over this period (less N+ patients lost to follow-up at 6 years, 11.8% versus N- 17.8%). Therefore, we also assessed outcomes at 5 years in the overall population even if the results at 7 years remain relevant for each subgroup. At 5 years, DFS for the overall population was 84.5% and MFS was 89.2% explaining 70% of all the recurrences documented. In both the N+ and the HR- subgroups the cumulative risk of recurrence at 5 years was 22.0%. In the N+ subgroup, patients with 4 or more positive nodes stand out with a high probability of recurrence at 5 years (35.8%) (Table 4).

Again, it is both in the N+ and HR- subgroups that the percentage of metastatic recurrence (16.9%) and the ratio of metastatic recurrence/total recurrence were the highest (77%). The overall rates mask important differences according to the nodal status and to the hormonal status of the tumor. The evaluation of DFS and MFS at 5 years in HER2+ eBC is of real interest, because most clinical trials limit the observation period to 3 or 4 years of follow-up.

Due to the differences in the characteristics of the population included, patient management, follow-up process and time elapsed until assessment, it is hazardous to compare the DFS and MFS rates of this study with those of other studies in a similar population. The final analysis of the HERA study at 11 year-follow-up showed that the addition of 1 year of adjuvant trastuzumab resulted in a constant 24% relative reduction in the risk of DFS event [8]. In the PHARE trial, a large phase III multicenter randomized French clinical trial assessing 6 months versus 12 months of adjuvant trastuzumab for patients with HER2+ eBC, the 3-year MFS in the N+ subgroup (88.9%) was very close to those observed in this study at the same time point (88.2%). Beyond the fact that the 3-year MFS in the PHARE trial confirm our result, it shows that during the 4th and 5th year following the start of trastuzumab treatment, an extra 5% of
N+ patients have a metastatic recurrence [12]. The trend pointed out by the Kaplan-Meier analysis seems to indicate a similar tendency in the 6th and 7th year.

The classification of the N+ subgroup between patients with 1-3 positive nodes and patients with 4 or more positive nodes was also particularly interesting. At 5-year follow-up, the DFS of patients with 1-3 positive nodes was 83.3% and the MFS 87.8%, while for patients with 4 or more positive nodes this was 64.2% and 70.8% respectively, showing 29.2% of metastatic recurrence.

Regarding the hormonal status, the differences between the 2 subgroups were less pronounced, but remained significant (p < 0.001): the 5-year DFS was 78.0% (22.0% of cumulative risk of event) and the 5-year MFS was 83.1% for HR- patients (versus 88.3% and 92.8% respectively in the HR+ subgroup). The 7-year DFS for HR- patients was 68.6% and the 7-year MFS was 77.5% (versus 80.0% and 87.9% respectively in the HR+ subgroup).

Indirectly, these figures point out the difference in the nature of the recurrence between the clinical profiles. For N+ patients most of recurrences were metastatic, especially in cases with 4 or more positive nodes, whereas in the N- subgroup, the main recurrences were non-metastatic.

Overall, the main category was brain +/- other sites of metastatic involvement (48%) and the second was visceral +/- other, excluding brain metastases (41%). There was a higher percentage of brain metastases in the HR- subgroup than in the HR+, and more in the N+ subgroup than in the N-. These differences have to be interpreted with caution, because in the N- subgroup the rate of distant recurrence was the lowest.

The limitations of this retrospective cohort study are inherent to the design of all real-life studies, data interpretation should be taken cautiously. For instance, the rate of lost to follow-up patients after the end of the treatment may include both discontinuations based on patient
decision and discontinuations decided by the sites for patients with no events. A comparison between the characteristics of the overall population and those of patients not lost to follow-up shows that the population not lost to follow-up at 8 years can be extrapolated to all patients and therefore that the cumulative rates of recurrence (whatever its nature) and metastatic recurrences observed at this time do not include any evaluation bias. Moreover, the comparison related to the N+ subgroup shows no difference between the distribution of the characteristics of all the patients included and that of the patients not lost to follow-up at 8 years. Although the slightly larger proportion of N+ patients not lost to follow-up at 8 years is likely to have a slight impact on the probability of recurrence for the entire population, there is no potential impact on the analysis on subgroups.

Since the publication of the results of the three phases III (NSABP B-31, NCCTG N9831, HERA) a decade ago, which provided solid evidence that adding trastuzumab to adjuvant treatment was indisputably increasing the progression-free survival, time to first distant recurrence and overall survival in patients with HER2+ eBC, the prognostic paradigm has definitively changed for this population [4-7]. HER2+ eBC, certainly, remains associated with aggressive behavior in breast cancer, but the fact that a targeted therapy was able to significantly improve the outcomes of the disease tends to alleviate the burden associated with this characteristic.

The results of this study slightly modify this optimistic opinion. In the HR+ and N- subgroups it is true that the 5-year probability of a recurrence (respectively 11.7% and 8.2%) and distant recurrence (7.2% and 3.8%) is relatively low but in the two other subgroups (HR- and N+) the outcomes are not the same, with 22.0% of 5-year probability of a recurrence, including 16.9% of distant recurrence for both HR- and N+ subgroups. Both quantitatively, by the frequency of events, and qualitatively, by the nature of the recurrence observed, the HR- and the N+ are two subgroups for whom the 5-year outcomes are relatively poor.
Conclusion

Despite improved prognosis of HER2+ eBC since the introduction of trastuzumab in the adjuvant setting, this population is heterogeneous, with a particularly aggressive profile for the N+ and HR- subgroups. This real-world study conducted in France, points out, as other international clinical trials, these particularities and the need for more efficient approaches. Taking into account our results on the rates of DFS, especially in the subgroups, we can conclude that there is still an important unmet medical need in the HER2+ eBC patient population.
**List of abbreviations:**

| Abbreviation | Description |
|--------------|-------------|
| HER2         | Human Epidermal growth factor Receptor-2 |
| HER2+        | HER2 positive |
| eBC          | Early Breast Cancer |
| IHC          | Immunohistochemistry |
| HR+          | Hormone-receptor positive |
| HR-          | Hormone-receptor negative |
| N+           | Node positive |
| N-           | Node negative |
| DFS          | Disease-free survival |
| MFS          | Metastatic-free survival |
| OS           | Overall survival |
| HR           | Hazard ratio |
| CI           | Confident interval |
| EMA          | European Medicines Agency |
| INDS         | Institut National des Données de Santé/National Institute for Health Data |
| CNIL         | Commission Nationale de l'Informatique et des Libertés/French data protection authority |
| PMSI         | Programme de Médicalisation des Systèmes d'Information/Medicalized information system program |
Declarations:

Ethical approval and consent to participate
The study protocol was submitted and approved by the INDS (Institut National des Données de Santé/National Institute for Health Data) based on a standardized methodology for a retrospective study (MR003/not requiring patient consent) and was submitted to the CNIL (Commission Nationale de l'Informatique et des Libertés/French data protection authority) which authorized the data processing of the study (DR-2018-072).

Consent for publication
Not applicable

Availability of data and material
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing Interests
Competing interest for MS: Roche
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Competing interest for DC: Roche
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Competing interest for CL: Roche

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Authors contributions
MS: study design, data interpretation and manuscript writing
EC: data interpretation and manuscript writing
DC: study design and data interpretation
AF: study design, data analyzing, data interpretation and manuscript writing
CL: data interpretation and manuscript writing

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Table 1: Patients and disease characteristics overall and according to hormonal and nodal status

|                           | Overall (n=2513) | HR- (n=936) | HR+ (n=1577) | N- (n=1179) | N+ (n=1334) |
|---------------------------|-----------------|-------------|--------------|-------------|-------------|
| N (%)                     |                 |             |              |             |             |
| Age at diagnosis (years)  |                 |             |              |             |             |
| < 35                      | 120 (4.8)       | 53 (5.7)    | 67 (4.2)     | 53 (4.5)    | 67 (5.0)    |
| 35-49                     | 722 (28.7)      | 277 (29.6)  | 445 (28.2)   | 313 (26.5)  | 409 (30.7)  |
| 50-59                     | 766 (30.5)      | 309 (33.0)  | 457 (29.0)   | 360 (30.5)  | 406 (30.4)  |
| ≥ 60                      | 904 (36.0)      | 297 (31.7)  | 607 (38.5)   | 452 (38.3)  | 452 (33.9)  |
| Missing data              | 1 (0.0)         | -           | 1 (0.1)      | 1 (0.1)     | -           |
| p-value                   |                 |             | p=0.007      |             | p=0.058     |
| Median age (Min-Max)      | 55 (22-89)      | 54 (22-89)  | 56 (22-84)   | 56 (22-83)  | 55 (22-89)  |
| Menopausal status at diagnosis |         |             |              |             |             |
| Premenopausal             | 675 (26.9)      | 262 (28.0)  | 413 (26.2)   | 295 (25.0)  | 380 (28.5)  |
| Uncertain (pre or per)    | 407 (16.2)      | 175 (18.7)  | 232 (14.7)   | 185 (15.7)  | 222 (16.6)  |
| Postmenopausal            | 1427 (56.8)     | 496 (53.0)  | 931 (59.0)   | 698 (59.2)  | 729 (54.6)  |
| Missing data              | 4 (0.2)         | 3 (0.3)     | 1 (0.1)      | 1 (0.1)     | 3 (0.2)     |
| p-value                   |                 |             | p=0.005      |             | p=0.066     |
| Tumor size (cm)           |                 |             |              |             |             |
| 0 à 1 cm                  | 378 (15.0)      | 144 (15.4)  | 234 (14.8)   | 238 (20.2)  | 140 (10.5)  |
| 1 à 2 cm                  | 949 (37.8)      | 315 (33.7)  | 634 (40.2)   | 562 (47.7)  | 387 (29.0)  |
| 2 à 5 cm                  | 1049 (41.7)     | 414 (44.2)  | 635 (40.3)   | 356 (30.2)  | 693 (51.9)  |
| > 5 cm                    | 124 (4.9)       | 58 (6.2)    | 66 (4.2)     | 17 (1.4)    | 107 (8.0)   |
| Missing data              | 13 (0.5)        | 5 (0.5)     | 8 (0.5)      | 6 (0.5)     | 7 (0.5)     |
| p-value                   |                 |             | P<0.001      |             | P=0.008     |
| Median size (Min-Max)     | 2.0 (0-1.5)     | 2.1 (0-1.5) | 2.0 (0-1.5)  | 1.7 (1-1.5) | 2.4 (0-1.5) |
| Nodal status              |                 |             |              |             |             |
| Negative                  | 1179 (46.9)     | 440 (47.0)  | 739 (46.9)   | 1179 (100)  |
| 1-3 positive nodes        | 965 (38.4)      | 336 (35.9)  | 629 (39.9)   | 965 (72.3)  |
| ≥ 4 positive nodes        | 369 (14.7)      | 160 (17.1)  | 209 (13.3)   | 369 (27.7)  |
| p-value                   |                 |             |             | p=0.015     |             |
|                               | Overall (n=2513) | HR- (n=936) | HR+ (n=1577) | N- (n=1179) | N+ (n=1334) |
|-------------------------------|-----------------|-------------|--------------|-------------|-------------|
| **Adjuvant chemotherapy**     |                 |             |              |             |             |
| Anthracycline + taxane        | 1876 (74.7)     | 728 (77.8)  | 1148 (72.8)  | 788 (66.8)  | 1088 (81.6) |
| Anthracycline w/o taxane      | 82 (3.3)        | 32 (3.4)    | 50 (3.2)     | 53 (4.5)    | 29 (2.2)    |
| Taxane w/o anthracycline      | 517 (20.6)      | 166 (17.7)  | 351 (22.3)   | 313 (26.5)  | 204 (15.3)  |
| Other regimens*               | 7 (0.3)         | 6 (0.6)     | 1 (0.1)      | 4 (0.3)     | 3 (0.2)     |
| No adjuvant chemotherapy      | 31 (1.2)        | 4 (0.4)     | 27 (1.7)     | 21 (1.8)    | 10 (0.7)    |
| **p value**                   |                 |             |              |             |             |
| Adjuvant radiotherapy         |                 |             |              |             |             |
| Yes                           | 2376 (94.5)     | 875 (93.5)  | 1501 (95.2)  | 1083 (91.9) | 1293 (96.9) |
| No                            | 131 (5.2)       | 61 (6.5)    | 70 (4.4)     | 93 (7.9)    | 38 (2.8)    |
| Missing data                  | 6 (0.2)         | -           | 6 (0.4)      | 3 (0.3)     | 3 (0.2)     |
| **p value**                   |                 |             |              |             |             |

*other regimens = neither anthracycline nor taxane
Table 3: Metastasis localization classification at 7 years

| Metastasis localization       | Overall (n=355) | HR- (n=188) | HR+ (n=167) | N- (n=56) | N+ (n=299) |
|-------------------------------|----------------|-------------|-------------|-----------|-----------|
| Brain +/- other sites         | 148 (41.7)     | 89 (47.3)   | 59 (35.3)   | 21 (37.5) | 127 (42.5) |
| Visceral +/- other sites      | 160 (45.1)     | 81 (43.1)   | 79 (47.3)   | 34 (60.7) | 126 (42.1) |
| Bones only                    | 43 (12.1)      | 15 (8.0)    | 28 (16.8)   | -         | 43 (14.4)  |
| Lymphatic only                | 4 (1.1)        | 3 (1.6)     | 1 (0.6)     | 1 (1.8)   | 3 (1.0)   |
| p value                       |                |             |             | p=0.020   | p=0.007   |
Table 4: Cumulative probability of occurrence (%) of events related to the disease or metastatic recurrences

| Events related to the disease | 12 months | 24 months | 36 months | 48 months | 60 months | 72 months | 84 months | 96 months |
|------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Total                        | 1.1       | 4.0       | 8.2       | 12.3      | 15.5      | 18.8      | 24.2      | 28.2      |
| HR+                          | 0.4       | 2.1       | 5.7       | 9.2       | 11.7      | 14.4      | 20.0      | 24.9      |
| HR-                          | 2.2       | 7.3       | 12.4      | 17.6      | 22.0      | 26.2      | 31.4      | 33.9      |
| N-                           | 0.4       | 2.1       | 4.1       | 6.5       | 8.2       | 10.1      | 13.3      | 15.9      |
| N+                           | 1.7       | 5.7       | 11.8      | 17.5      | 22.0      | 26.4      | 33.6      | 38.7      |

| Metastatic recurrences       | 12 months | 24 months | 36 months | 48 months | 60 months | 72 months | 84 months | 96 months |
|------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Total                        | 0.9       | 2.9       | 5.8       | 8.6       | 10.8      | 13.0      | 15.9      | 18.5      |
| HR+                          | 0.3       | 1.1       | 3.5       | 5.7       | 7.2       | 8.8       | 12.1      | 14.9      |
| HR-                          | 1.9       | 5.9       | 9.7       | 13.6      | 16.9      | 20.2      | 22.5      | 24.5      |
| N-                           | 0.1       | 0.9       | 1.8       | 3.0       | 3.8       | 4.5       | 5.3       | 6.6       |
| N+                           | 1.6       | 4.6       | 9.4       | 13.5      | 16.9      | 20.4      | 25.1      | 28.8      |
FIGURE LEGENDS

Fig. 1 Study design

Fig. 2 Kaplan-Meier disease-free survival curves for subgroups

Fig. 3 Kaplan-Meier metastatic-free survival curves for subgroups
Fig. 1: Study design

- Diagnosis of early (non metastatic) Breast Cancer with HER2 overexpression (3+ by IHC and/or ISH positive)
- Observation period from 1st January 2009 to 31st December 2010
- End of observation period on 31st December 2017
- Data collection from medical records from 25th May to 17th July 2018
Fig. 2: Kaplan-Meier disease-free survival curves for subgroups
Fig. 3: Kaplan-Meier metastatic-free survival curves for subgroups
Supplemental Material

Fig. 4 Kaplan-Meier disease-free survival and metastatic-free survival curves (overall population)

A

7-year DFS: 75.8% (95% CI: 74.0%-77.6%)

B

7-year MFS: 84.1% (95% CI: 82.5%-85.6%)