**Clinical outcome in women with HER2-positive de novo or recurring stage IV breast cancer receiving trastuzumab-based therapy.**

# Clinical outcome in women with HER2-positive de novo or recurring stage IV breast cancer receiving trastuzumab-based therapy

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## Abstract

Background

Five to 10% of women with newly diagnosed breast cancer have synchronous metastases (de novo stage IV). A further 20% will develop metastases during follow-up (recurring stage IV). We compared the clinical outcomes of women with HER2-positive metastatic breast cancer (MBC) receiving first-line trastuzumab-based therapy according to type of metastatic presentation.

Patients and methods

Retrospective analysis of 331 MBC patients receiving first-line trastuzumab-based treatment. Response rates (RR) were compared by the chi-square test. Time-to progression (TTP) and overall survival (OS) curves were compared by the log-rank test. Cox-proportional hazards models were used to study predictors of PFS and OS, including the type of metastatic presentation.

Results

Seventy-seven patients (23%) had de novo stage IV disease. Forty-six of these patients underwent surgery of the primary ("de novo/surgery"). Response rates to first-line trastuzumab-based therapy and median progression-free survival did not differ in patients with "recurring", "de novo/surgery" and "de novo" without surgery ("de novo/no surgery) stage IV breast cancer. However, women with "de novo/surgery" stage IV breast cancer had the longest median OS (60 months), and those with "de novo/no surgery" stage IV breast cancer the shortest (26 months). For women with recurring metastatic breast cancer median OS was 40 months (overall log-rank test, $p < 0.01$). Multivariate analysis confirmed these findings.

Conclusion

Our analysis shows that response rates and PFS to first-line trastuzumab-based therapy do not differ significantly between de novo and recurring stage IV, HER2 positive breast cancer. The observed difference in OS favoring women with de novo stage IV disease submitted to surgery of the primary tumor could be the result of a selection bias.

**Keywords:** Breast cancer, HER2, Trastuzumab, De novo, Recurring, Metastases.

## Introduction

Metastatic (stage IV) breast cancer remains a virtually incurable disease, despite encouraging improvements brought by newer and more active anticancer compounds [1]. Clinically overt metastatic disease emerges usually during follow-up after surgery of loco-regional disease (recurring stage IV). However, approximately 5–10% of women with newly diagnosed breast cancer have synchronous metastases (de novo stage IV) [[2], [3]]. Early systemic spread characterizingde novo stage IV breast cancer might be perceived as a more aggressive form of disease. This may acquire a particular importance when

occurring concomitantly with other markers of tumor aggressiveness like human epidermal growth factor receptor 2 (HER2)-overexpression or amplification (positivity) [4].

Some reports in unselected patients suggest that the prognosis of de novo stage IV disease is not different or even better than that of patients with recurring stage IV disease [5]. To our knowledge, no such comparison focusing on patients with HER2-positive disease receiving first-line trastuzumab-based therapy has been published in a peer reviewed journal. In this disease subset, prognosis has dramatically improved since the introduction of the monoclonal antibody trastuzumab [[6], [7]], and further improvements are expected from the introduction in the clinic of other anti HER2-compounds [[8], [9],[10]].

Such analysis would be interesting for a number of reasons and the survival findings may inform the decision to perform local surgery or other forms of locoregional treatment as part of the management of patients with de novo stage IV disease. Furthermore, comparison of patterns of metastatic spread may suggest a different underlying biology of de novovs recurrent stage IV disease that can be exploited clinically. On these premises, we set out to compare clinical outcomes of patients with de novo and recurring stage IV breast cancer receiving first-line trastuzumab-based therapy in a large multi-institutional database.

**Patients and method**

Patients were selected from a multi-institutional database containing the clinical data of women with HER2-positive breast cancer receiving trastuzumab-based therapy for metastatic disease and treated at two Italian Institutions (the European Institute of Oncology in Milan, Italy, and the Institute for Cancer Research and Treatment in Candiolo, Italy). For all consecutive patients who received at least one infusion of trastuzumab as first-line treatment for HER2-positive metastatic breast cancer we collected clinical and pathological characteristics, prior treatments for breast cancer and details of the first trastuzumab-based treatment (drugs and doses, best response to the initial trastuzumab-based treatment, date of progression, and date of death or of last follow-up visit). Patients with central nervous system (CNS) metastases as the only site of first tumor progression were excluded.

All patients had their specimens reviewed for HER2, ER and PgR at their respective treating Institution before trastuzumab-based therapy. Whenever possible, assessments were performed on the most recent tumor material, either the primary tumor or a biopsy of metastatic disease. HER2 positivity was defined as a 3 + score by immunohistochemistry (IHC) in >10% of invasive tumor cells using the HercepTest (Dako, Glostrup, Denmark). Equivocal cases at IHC (2 + score), were submitted to Fluorescence in situ hybridization (FISH) analysis. A ratio of HER2 gene signals to chromosome 17 signals of ≥2 was used as cutoff to define HER2-gene amplification. The assessment of HR status was carried out by IHC using the 1D5 monoclonal antibody (MAb) to ER (Dako, at 1/100 dilution), and the 1A6 MAb to PgR (Dako, 1/800 dilution). Only nuclear reactivity was taken into account for ER and PgR. Positivity was defined as immunostaining in ≥1% of invasive tumor cells.

**Statistical analysis**

The Kaplan Meier method was used to estimate Progression-free survival (PFS), which was defined as the interval between the date of the first administration of trastuzumab and the date of tumor progression or death, which ever occurred first, and overall survival (OS), which was defined as the interval between the date of the first administration of trastuzumab and death from any cause. Disease-free interval (DFI) was defined as the time between the diagnosis of primary breast cancer and the date of the first confirmed metastatic progression. For patients with de novo stage IV disease DFI was considered to be 0 months. Furthermore, for some patients in this series the diagnosis of metastatic disease was not exactly synchronous with that of the primary tumor because of the time elapsing between a suspected metastasis and the confirmation through additional imaging and/or biopsy. We therefore established that a diagnosis of metastatic disease within 3 months from that of a primary breast tumor could reasonably considered

“de novo” stage IV disease. Also for these patients DFI was considered to be 0 months in the analyses. Patients alive were censored at the date of the last follow-up contact. For each patient, tumor response, which was recorded according to the WHO criteria [11], was assessed at the treating Institution every 2–3 months during the first year of treatment and every 6 months from the second year onward. For the scope of this analysis, each patient's imaging was reviewed.

Comparisons between patient characteristics were studied by the Chi Square or the Fischer's exact test (dichotomous variables), and by the Kruskal–Wallis test (continuous variables). Survival curves were compared by the log-rank test. Univariate and multivariate logistic regression and Cox-proportional hazards analysis models were studied to identify variables that were independently associated with clinical outcomes of interest, including the modality of stage IV presentation. All the factors, regardless of their significance at the univariate analysis, were included in a saturated model and removed each at a time based on their significance (removed if $p > 0.05$). At each step, the modality of presentation was allowed to re-enter the model. The proportionality of hazards assumption was checked by the log-minus-log survival plot method. All the analyses were conducted by the SPSS 17.0 statistical package (Chicago, IL, USA).

Being a retrospective analysis of clinical outcomes, no specific written informed consent was required for this study. However, the process of data collection was conducted in compliance with the Ethical requirements of each of the participating Institutions.

**Results**

A total of 331 consecutive patients, 77 of whom (23%) with de novo stage IV and 254 (77%) with recurring stage IV disease, were identified for this analysis. Forty-six (14% of the total) of the patients with de novo stage IV disease underwent surgery of the primary tumor (de novo/surgery), either before, or after the initiation of first-line trastuzumab-based therapy, whereas no surgery of the primary tumor (de novo/no surgery) was performed in the remaining 31 patients (9% of the total). Table 1 summarizes the main demographic characteristics of these patients. Most of the patients with recurring stage IV disease were previously exposed to neoadjuvant or adjuvant chemotherapy, which consisted mainly of anthracycline-containing regimens. Four patients with de novo stage IV disease had started anthracycline-based adjuvant chemotherapy (range 1–3 cycles), which was stopped and changed with a trastuzumab-based regimen when synchronous metastases were confirmed. Another 2 patients received one cycle of an anthracycline-containing regimen at the time of the diagnosis of metastasis. When HER2-positivity was confirmed, these patients started an anthracycline-free, trastuzumab-based regimen. Finally, 8 patients with co-expression of HER2 and hormone receptors received chemotherapy and trastuzumab after failing first-line endocrine therapy. Although not statistically significant, women withde novo stage IV disease who did not undergo surgery of the primary tumor (de novo/no surgery) tended to display more adverse clinical features compared to the other groups, with 81% of visceral involvement and more frequent multiple sites of metastases (Table 1).

**Table 1:** Patient characteristics according to type of metastatic presentation.

| | *De novo* MBC, no surgery *N* = 31 (%) | *De novo* MBC, surgery of primary tumor 46 (%) | Recurring MBC*N* = 254 (%) | *P* |
|---|---|---|---|---|
| Median age, years (range) | 56 (27–80) | 49 (32–80) | 52 (27–81) | 0.22 |
| ER positive | 12 (39) | 17 (37) | 127 (50) | 0.04 |
| PgR positive | 8 (25) | 12 (26) | 91 (36) | 0.39 |
| Prior adjuvant/neoadjuvant chemotherapy | 2 (6) | 3 (6) | 220 (87) | <0.01 |
| Prior anthracyclines[a] | 3 (10) | 5 (11) | 190 (75) | <0.01 |
| Prior taxanes[a] | 1 (3) | 1 (2) | 65 (26) | <0.01 |
| Prior endocrine therapy[b] | 5 (16) | 3 (6) | 130 (51) | <0.01 |
| Median DFS in months (range)[c] | 0 (0–3) | 0 (0–3) | 27 (3–152) | <0.01 |
| Sites of metastatic disease | | | | |
| Liver | 18 (58) | 23 (50) | 106 (42) | 0.16 |
| Lung | 10 (32) | 9 (20) | 81 (32) | 0.24 |
| Bone | 18 (58) | 16 (35) | 116 (46) | 0.13 |
| Soft-tissue/nodes | 21 (68) | 26 (56) | 140 (55) | 0.41 |
| Visceral involvement (lung + liver + CNS) | 25 (81) | 27 (59) | 159 (63) | 0.11 |
| Number of metastatic sites | | | | |
| 1 | 8 (26) | 25 (54) | 101 (40) | 0.09 |
| 2 | 10 (32) | 13 (28) | 73 (29) | |
| ≥3 | 13 (42) | 8 (17) | 79 (31) | |
| Type of chemotherapy with trastuzumab | | | | |
| Taxane-based | 18 (58) | 26 (56) | 135 (53) | 0.97 |
| Vinorelbine-based | 10 (32) | 15 (33) | 94 (37) | |
| Single agent trastuzumab | 2 (6) | 4 (9) | 15 (6) | |
| Other regimens | 1 (3) | 1 (3) | 10 (4) | |

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor; DFI, disease-free interval; CNS, central nervous system; NS, non significant at the 0.05 level; NA, not applicable.

aExposure occurred in the adjuvant or neoadjuvant setting.

bEither in the adjuvant and/or in the metastatic setting.

cFrom the initial diagnosis of breast cancer to the first occurrence of metastatic disease. For patients with stage IV disease at the onset of breast cancer, DFI was assumed to be equal to 0.

The median follow-up time for patients still alive at the time of this analysis was 27 months. A total of 241 patients developed tumor progression during first-line trastuzumab-based treatment and 161 died.

Overall response rates (ORR) to the initial trastuzumab-based treatment was 61%, 56% and 59% for patients with de novo/no surgery, de novo/surgery and recurring stage IV breast cancer, respectively (p = 0.91).

Overall, PFS and OS did not differ according to whether patients had de novo stage IV (with or without surgery) or recurring stage IV breast cancer (Figs. 1 and 2). Kaplan Meier estimates of PFS and OS according to type of metastatic progression and to surgery of the primary tumor in women with de novo stage IV breast cancer are represented in Figs. 3and 4. While median progression-free survival was fairly similar in the three groups of patients, a difference in OS was observed. De novo/surgery stage IV women had the longest median OS (60 months), whereas those with de novo/no surgery stage IV breast cancer the shortest (median OS 26 months). Women with recurring stage IV breast cancer had intermediate median OS (40 months).

**Fig. 1 : PFS according to type of metastatic progression.** De novo stage IV (dashed line, median 14 months, 95% C.I. 9–18 months), recurring stage IV (solid line, median 13 months, 95% C.I. 10–15 months). Overall log-rank test, p = 0.37.

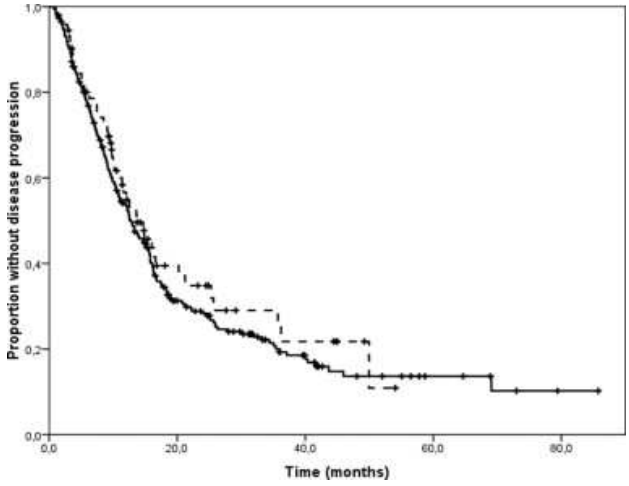



**Fig. 2: OS according to type of metastatic progression**. *De novo* metastatic breast stage IV (dashed line, median 37 months, 95% C.I. 27–48 months), recurring stage IV (solid line, median 40 months, 95% C.I. 37–43 months). Overall log-rank test, *p* = 0.88.

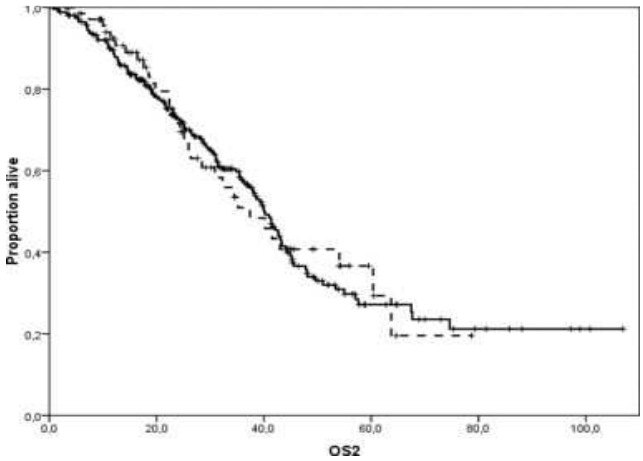


**Fig. 3: PFS according to type of metastatic progression and receipt of surgery of the primary tumor.** De novo stage IV submitted to surgery of primary breast cancer (dashed line, median 15 months, 95% C.I. 8–22 months), de novo stage IV not submitted to surgery of primary breast cancer (dotted line, median 12 months, 95% C.I. 7–18 months), recurring stage IV (solid line, median 13 months, 95% C.I. 10–15 months). Overall log-rank test, p = 0.26.

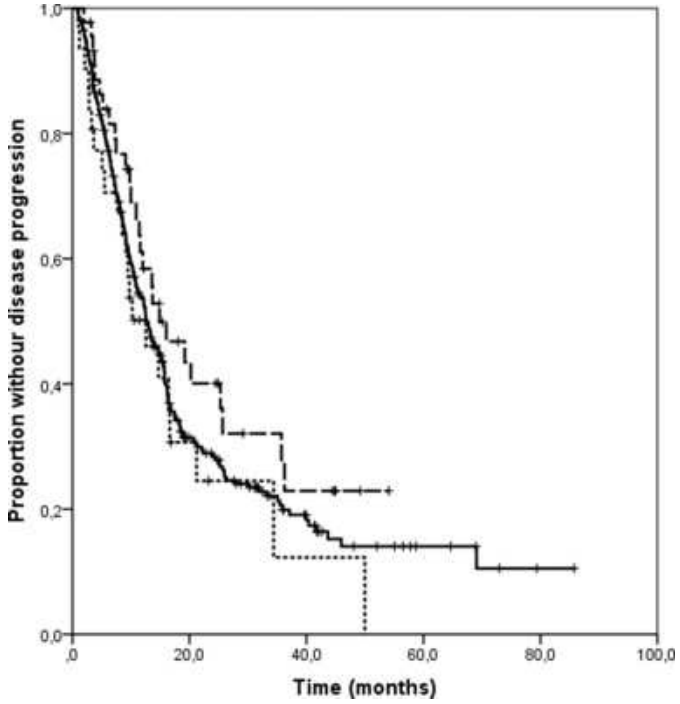
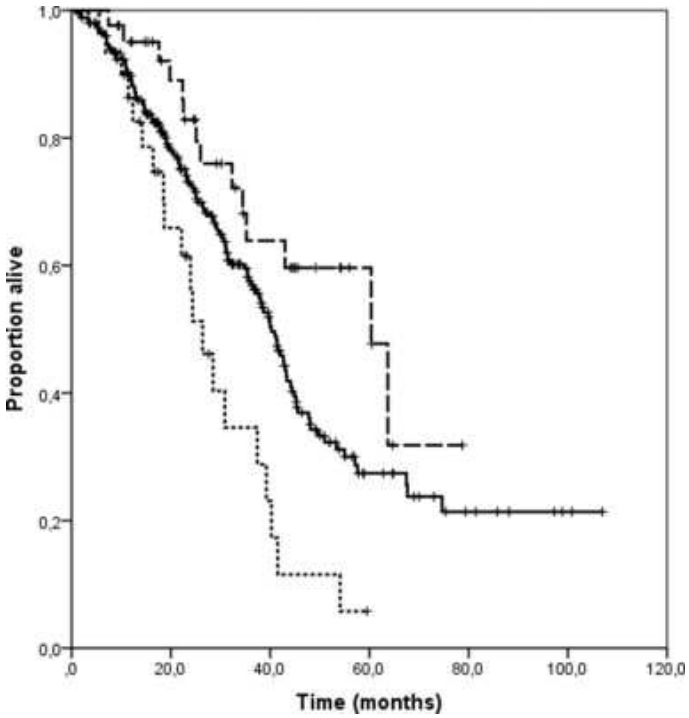



**Fig. 4: OS according to type of metastatic progression and receipt of surgery of the primary tumor**. De novo stage IV submitted to surgery of primary breast cancer (dashed line, median 60 months, 95% C.I. 41–79 months), de novo stage IV not submitted to surgery of primary breast cancer (dotted line, median 26 months, 95% C.I. 20–32 months), recurring stage IV (solid line, median 40 months, 95% C.I. 37–43 months). Overall log-rank test, p < 0.01.



Univariate and multivariate analyses of factors associated with progression-free and overall survival, including type of metastatic presentation, are summarized in Tables 2 and 3. We found a non-linear relationship between disease-free interval and the hazard of progression and death. DFI was therefore treated as a categorical variable and divided into 6-month intervals. Patients developing tumor progression beyond 60 months from surgery had a significantly better clinical outcome. Other factors significantly associated with increased risk of either progression, survival or both, were prior exposure to taxanes, multiple sites of metastasis (vs single site), visceral and liver involvement, type of trastuzumab-based regimen and response to the initial trastuzumab-based regime which was associated with PFS, but not with OS. Multivariate analyses results are summarized in Table 3. Progression-free survival was significantly predicted by DFI, prior exposure to a taxane in the adjuvant setting, number of metastatic sites, liver involvement, type of treatment associated with trastuzumab and response to trastuzumab-based therapy. In the final model, type of metastatic presentation was not independently associated with PFS, although a trend towards reduced risk of progression was observed favoring patients with *de novo* stage IV disease. Overall survival was significantly predicted by type of metastatic presentation, DFI, liver involvement, number of metastatic sites and response to trastuzumab-based therapy.

**Table 2:** Univariate analysis of progression-free and overall survival.

| HR for progression | *P* | HR for death | *P* |
|---|---|---|---|
| Type of presentation | | | |
| Recurring MBC | 1 | | 1 | |
| *De novo* MBC, surgery | 0.753 | 0.17 | 0.578 | 0.05 |
| *De novo* MBC, no surgery | 1.173 | 0.48 | 1.984 | <0.01 |
| Age ≤52 years | 0.959 | 0.75 | 0.734 | 0.05 |
| DFI (months) | | | |
| 0–6 | 1 | | 1 | |
| 6.1–24 | 1.620 | <0.01 | 1.527 | 0.04 |
| 24.1–60 | 0.922 | 0.65 | 0.839 | 0.42 |
| >60 | 0.795 | 0.35 | 0.443 | 0.02 |
| Prior adjuvant or neoadjuvant CT | 1.030 | 0.83 | 1.057 | 0.75 |
| Prior anthracycline | 0.962 | 0.77 | 1.172 | 0.33 |
| Prior taxane | 1.562 | <0.01 | 1.388 | 0.10 |
| Number of sites of metastases | | | |

| | | | | |
|---|---|---|---|---|
| Single site | 1 | | 1 | 1 |
| Two sites | 1.597 | <0.01 | 1.456 | 0.07 |
| Three or more sites | 1.924 | <0.01 | 2.291 | <0.01 |
| ER positive (vs negative) | 0.999 | 0.56 | 1.001 | 0.40 |
| PgR positive (vs negative) | 0.999 | 0.12 | 1.000 | 0.92 |
| Visceral involvement (liver + lung + CNS) | 1.806 | <0.01 | 2.177 | <0.01 |
| Liver involvement | 1.709 | <0.01 | 2.064 | <0.01 |
| Type of treatment associated with T | | | | |
| Taxane-based | 1 | | 1 | |
| Vinorelbine-based | 0.967 | 0.74 | 0.904 | 0.54 |
| Other regimens | 2.175 | <0.01 | 0.752 | 0.37 |
| Response to first-line trastuzumab-based therapy | | | | |
| CR + PR vs no response | 0.613 | <0.01 | 0.802 | 0.17 |

*Abbreviations: OR, odds ratio; HR, hazard ratio; DFI, disease-free interval from initial diagnosis to metastatic progression (by definition, this is 0 months for patients with stage IV as first presentation of breast cancer); CT, chemotherapy; ER, estrogen receptor, PgR, progesterone receptor; MBC, metastatic breast cancer; CNS central nervous system; ER, estrogen receptor PgR, progesterone receptor; T, trastuzumab; SD, stable disease; PD, progressing disease; NE, non evaluable for response; CR complete remission; PR, partial remission.*

**Table 3:** Multivariate analysis of progression-free and overall survival.

| **HR for progression** | **95% C.I.** | ***P*** | **HR for death** | **95% C.I.** | ***P*** | |
|---|---|---|---|---|---|---|
| Type of presentation | | | | | | |
| Recurring MBC | 1 | – | – | 1 | | |
| *De novo* MBC, surgery | 0.405 | 0.153–1.071 | 0.068 | 0.320 | 0.104–0.982 | 0.05 |
| *De novo* MBC, no surgery | 0.567 | 0.210– | 0.264 | 0.995 | 0.338– | 0.99 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | 1.535 | | | 2.928 | |
| DFI (months) | | | | | | |
| 0–6 | 1 | | | 1 | | |
| 6.1–24 | 0.728 | 0.291–1.817 | 0.50 | 0.858 | 0.311–2.363 | 0.77 |
| 24.1–60 | 0.399 | 0.159–1.004 | 0.05 | 0.467 | 0.166–1.313 | 0.15 |
| >60 | 0.296 | 0.09–0.802 | 0.02 | 0.242 | 0.077–0.768 | 0.02 |
| Prior taxane | 1.475 | 1.064–2.046 | 0.02 | – | – | – |
| Number of sites of metastases | | | | | | |
| Single site | 1 | | | | | |
| Two sites | 1.735 | 1.254–2.399 | <0.01 | 1.517 | 1.004–2.293 | 0.05 |
| Three or more sites | 2.292 | 1.627–3.229 | <0.01 | 2.072 | 1.372–3.131 | <0.01 |
| Liver involvement | 1.673 | 1.271–2.204 | <0.01 | 1.831 | 1.308–2.564 | <0.01 |
| Type of treatment associated with T | | | | | | |
| Taxane-Based | 1 | | | – | – | – |
| Vinorelbine-Based | 0.987 | 0.746–1.307 | 0.93 | – | – | – |
| Other regimens | 2.668 | 1.677–4.244 | <0.01 | – | – | – |
| Response to first-line trastuzumab-based therapy (CR or PR vs no response) | 0.442 | 0.334–0.585 | <0.01 | 0.622 | 0.447–0.866 | <0.01 |

*Abbreviations: OR, odds ratio; HR, hazard ratio; DFI, disease-free interval from initial diagnosis to metastatic progression (by definition, this is 0 months for patients with stage IV as first presentation of breast cancer); CT, chemotherapy; ER, estrogen receptor, PgR, progesterone receptor; MBC, metastatic breast cancer; CNS central nervous system; ER, estrogen receptor PgR, progesterone receptor; T, trastuzumab.*

**Discussion**

In this retrospective analysis, the type of metastatic presentation (de novo vs recurring) was not associated with clinical outcome in women receiving first-line trastuzumab-based therapy for HER2-positive disease. However, when women withde novo stage IV disease were stratified according to surgical treatment of the primary tumor, we found a significant association between type of metastatic presentation and overall survival. In particular, patients with de novo stage IV breast cancer who had their primary tumor removed had an almost 70% reduction in the risk of death compared with the other two subgroups. The association between surgery of the primary tumor and improved survival has been observed by other investigators [[12], [13], [14]]. This has led to the widespread practice of treating primary breast cancer in women with synchronous metastases, when feasible, even in the absence of a documented efficacy from a randomized trial. In accordance with other previous observations [[15], [16]], we believe that surgery may have acted, at least in part, as a surrogate of lower metastatic burden. In fact, women with de novo stage IV disease who did not receive surgery of the primary tumor tended to have more frequent visceral involvement and multiple sites of disease, compared with the other two groups of patients. The fact that women whose primary tumor was surgically treated had frequently a single site of metastatic involvement (often a single metastasis, data not shown), suggests that stage migration could have occurred, resulting in a surprisingly long median OS.

In a recent study, Dawood et al. found that the median OS of “de novo” stage IV patients disease was significantly longer than that of those with recurring breast cancer [5]. In that study, less than half of the patients with de novo stage IV disease underwent surgery of the primary tumor (309 out of 643), but the results were not reported according to the local treatment. Differently from Dawood's study, we did not find differences in outcome when patients with de novo stage IV disease were grouped and compared with those with recurring stage IV disease (Figs. 1 and 2). There are several possible reasons for the discrepancy in these two retrospective analyses. First, the number of patients with de novo stage IV disease was 77 in our study, compared with more than 600 in the study by Dawood et al. Second, we focused on patients receiving trastuzumab-based therapy as first-line treatment for metastatic disease. The increased efficacy of systemic treatments with trastuzumab and, more recently, lapatinib may have smoothened a possible overall survival difference according to the metastatic presentation. Third, and most likely, a significantly longer OS in women with de novo stage IV disease receiving surgery of the primary tumor may have influenced the survival of the entire de novo stage IV group to a different extent in Dawood's study and in our own. We believe, however, that beyond possible explanations for discordant results, both Dawood's and our study consistently show that at least some patients with de novo stage IV disease may experience a particularly favorable course. The issue that becomes crucial, at this point, is whether the therapeutic approach should differ in de novo vs recurring stage IV breast cancer patients. In fact, while there is substantial agreement that the treatment of recurring stage IV disease is aimed to prolong the natural course of the disease [[1], [17]], the optimal treatment of de novo stage IV disease is undefined. This disease subset is likely to become a distinct entity due to the diffusion of imaging methods with higher sensitivity for distant metastases in the workup of clinically localized breast cancer. In the past, a number of reports have suggested that the incidence of distant metastases in breast cancer patients candidates to surgery could be as high as 20% when CT-PET scanning is used [[18], [19]]. More recently, a prospective study involving 254 women with clinical stages II and III breast cancer evaluated the diagnostic yield of CT-PET scanning [20]. Distant metastases were detected in 53 patients, with an incidence ranging from 2.3% to 47.1% according to clinical stage (IIA through IIIC). Undoubtedly, progress has been made in the treatment of metastatic breast cancer [21]. this has been probably due to the introduction of newer drugs, with particularly striking results in the treatment of HER2 positive breast cancer [22]. This progress has involved also patients with de novo stage IV disease, as shown by Andrè and colleagues in a retrospective analysis involving 724 patients treated between 1987 and 2000. [23]

Our study has obvious limitations due to its retrospective nature and the relatively small numbers involved. For example, we could not collect information on whether the diagnosis of metastatic disease was made on account or symptoms or was incidental (i.e. tumor marker raise in asymptomatic patients or imaging

performed for other causes). This may have masked differences in OS due a different natural history of low-burden, asymptomatic disease compared to symptomatic metastatic involvement. Additionally, treatment choices were diversified according to factors that are impossible to control for in a retrospective analysis, and that could be themselves related to outcome. In fact, it is possible that surgery of the primary tumor was encouraged in some patients by the achievement of optimal control of metastatic disease with trastuzumab-based therapy. Conversely, less responsive metastatic disease could have discouraged performing surgery of the primary tumor. Therefore, factors influencing the pursuit of surgery of the primary tumor could explain outcomes, rather than surgery by itself.

In conclusion, we found that response rates and PFS to first-line trastuzumab based therapy did not differ between patients with de novo or recurrent stage IV breast cancer. This finding suggests that the "de novo stage IV" presentation does not necessarily identify a biologically more aggressive variant of HER2-positive breast cancer and does not require a different medical management, compared with the "recurring" presentation. We also found that median OS was longer for de novo stage IV breast cancer patients who, at some point during the course of the disease, underwent surgery of the primary tumor. However, because of inherent potential biases and the limitations of our analysis that we have discussed, this finding must be interpreted with caution.

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**Conflict of interest statement**

Filippo Montemurro has served as a consultant for GlaxoSmithKline and Hoffmann La Roche SPA.

All the other authors of this manuscript have no conflict of interest.

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