HHS Public Access

Author manuscript

Breast Cancer Res Treat. Author manuscript; available in PMC 2022 November 01.

Published in final edited form as:

Breast Cancer Res Treat. 2022 November ; 196(1): 153–162. doi:10.1007/s10549-022-06700-6.

Clinical subtype, treatment response, and survival in *De Novo* and recurrent metastatic breast cancer

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Abstract

Purpose—This study evaluated whether patients with *de novo* metastatic breast cancer (MBC) have superior outcomes compared to those with recurrent MBC in a contemporary treatment era and examined factors related to outcome differentials.

Methods—Using an institutional database, we examined patient and tumor characteristics, treatment response, and outcome among 232 patients with *de novo* and 612 patients with recurrent MBC diagnosed between 2011 and 2017.

Results—*De novo* MBC had 9-month (m) longer overall survival (OS) than recurrent MBC (36.4 vs 27.4 m, $p < 0.001$). Contributions to this difference included nearly twofold more HER2-positive (29.3% vs 15.2%) and significantly fewer triple-negative breast cancers (20.3% vs 32.4%, both $p < 0.001$) in *de novo* compared with recurrent MBC cohorts. Stratified by clinical subtype, progression-free survival (PFS) on first-line therapy was significantly longer in *de novo* MBC in all but the triple-negative subtype, 25.5 vs 11.6 m ($p < 0.001$) among 390 patients with hormone receptor-positive, HER2-negative, 11.4 vs 5.4 m ($p = 0.002$) among 142 patients with HER2-positive, and 4.0 vs 3.0 m ($p = 0.121$) among 162 with triple-negative MBC.

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Author contributions Conceptualization: DMF, TP, ECD, CMP, and LAC. Formal Analysis: DMF and AMD. Investigation: DMF. Data Curation: AW. Writing–Original Draft: DMF. Writing–Review & Editing: DMF, TP, AMD, ECD, CMP, and LAC. Visualization: DMF and TP. Supervision: ECD and LAC. Funding Acquisition: ECD and LAC.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-022-06700-6.

Conflict of interest CMP is an equity stockholder and consultant of BioClassifier LLC; CMP is also listed as an inventor on patent applications for the Breast PAM50 Subtyping assay. The other authors report no disclosures in relation to this work.

Ethical approval The study was approved by the institutional review board at the University of North Carolina Office of Human Research Ethics Institutional Review Board.

Consent for publication The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health, the NCI, or the other study sponsors. The funding agencies had no role in the design or conduct of the study, collection, management, analysis, and interpretation of the data, preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

In multivariable analysis, *de novo* status remained independently associated with improved OS (hazard ratio 0.63, 95% CI 0.49–0.80), regardless of subtype and other features.

Conclusion—Patients with *de novo* MBC have better outcomes than those with recurrent MBC. Differences in clinical subtype and response to therapy in the metastatic setting contribute to, but do not fully explain, this difference. Longer PFS to first-line therapy in *de novo* MBC suggests biologic differences compared to recurrent MBC, which may be intrinsic or due to acquired resistance from treatment for prior localized breast cancer in recurrent disease.

Keywords

Breast cancer; *De novo* metastatic disease; Clinical subtypes; Breast cancer outcomes

Introduction

Metastatic breast cancer (MBC) is a leading cause of cancer-associated death among women. Metastases are most commonly identified months to years after initial breast cancer diagnosis, termed “recurrent” MBC (rMBC); however, some patients are found to have metastases before or shortly after their primary breast tumor is identified, termed “*de novo*” MBC (dnMBC). *De novo* MBC affects 6–10% of patients presenting with a new breast cancer diagnosis, a figure that has remained stable for decades [1–3]. Of patients with MBC, the relative proportion of patients with dnMBC has increased over time, as treatment advances for initially localized breast cancer have resulted in fewer patients experiencing recurrence [4].

Differences in clinical outcomes, including median overall survival (mOS), have been described between patients with dnMBC compared to rMBC and observed in subset analyses of clinical trials [4–9]. A recent recursive partitioning analysis of 16,187 patients with *de novo MBC* diagnosed between 2010 and 2013 in the National Breast Cancer Database (NCDB) found that key contributors to outcome within dnMBC included > 1 metastatic sites, clinical subtype, and other clinicopathologic features, supporting the need to address these features in any analysis of contributors to improved outcomes in dnMBC [10].

Potential contributors to differences in outcomes of dnMBC and rMBC may include heterogeneity in these clinicopathologic features as well as treatment type and response to therapy. Treatment type and response are particularly important given that drug sensitivity or resistance (either intrinsic or acquired), which is generally not available in non-trial databases, is crucial to outcome and is the reason that PFS is an intermediate endpoint for OS in drug trials. Using the UNC Metastatic Breast Cancer Database (MBCD), which includes the relevant clinicopathologic features as well as treatment details, response to therapy, and outcome, we were able to more deeply examine all of these variables and identify factors contributing to clinical outcome differences in the metastatic setting.

Methods

Patient population

All clinical and pathological data were obtained from the University of North Carolina (UNC) Metastatic Breast Cancer Database, which is a prospective observational registry for which data entry began in June 2011. All patients with MBC seen at UNC are enrolled into this database and followed for treatment and clinical outcomes. For patients who received treatment for metastatic disease prior to evaluation at UNC, data on prior therapy are collected retrospectively with subsequent clinical course followed prospectively. Patients were treated according to physician's choice and were monitored according to UNC Breast Center procedures, which includes regular restaging scans to assess for disease progression. In this cohort, patients diagnosed with MBC prior to January 2011 were excluded to minimize bias toward non-representative longer survival created by patients who had already lived with MBC for more than 1 year prior to the start of database enrollment. Patients diagnosed with metastatic disease after December 2017 were excluded to reduce a bias toward shorter survival as only patients with the worst outcomes had survival events prior to the cut-off for data analysis on January 10, 2020.

Clinical subtype was determined from pathology reports from the primary breast tumor, classified as hormone receptor-positive or negative (HR +, HR−) and human epidermal growth factor receptor 2-positive or negative (HER2 +, HER2−) according to ASCO/CAP guidelines in place at the time of diagnosis [11–13]. Patients with estrogen receptor and/or progesterone receptor positivity were classified as hormone receptor-positive. Pathologic stage was used when available, otherwise clinical stage was used. At the time of analysis, there were 1921 patients in the database; 1203 diagnosed with metastatic disease within the specified time interval. Additional exclusion criteria are shown in Fig. 1. Patients were excluded if they had more than one primary breast cancer due to inability to distinguish which primary tumor resulted in metastatic disease, making the designation as dnMBC vs rMBC unclear and the subtype of the primary tumor uncertain. Patients who did not receive treatment in the metastatic setting were excluded. Patients with rMBC who did not receive systemic treatment for localized disease (neoadjuvant or adjuvant) prior to metastatic diagnosis were also excluded given the objective of comparing treated, recurrent metastatic disease to untreated *de novo* metastatic disease (not germane for dnMBC since those patients have no time in which the disease is localized and treated with curative intent).

De novo MBC was defined by the detection of metastatic disease (classified as stage IV according to the American Joint Committee on Cancer (AJCC) TNM staging criteria) within three months of initial breast cancer diagnosis. Recurrent MBC was defined as any patient with an initial stage I–III breast cancer prior to metastatic relapse at least three months after diagnosis, a cut-off selected to allow for comparison to prior studies. Patients were not required to have biopsy-proven distant metastatic disease if imaging features and clinical history were highly consistent with this diagnosis.

Data analysis and interpretation

Patient and tumor characteristics were compared between dnMBC and rMBC cohorts using chi-square testing, with a two-sided *p*-value of < 0.05 used to define statistical significance. These included age at initial breast cancer and MBC diagnosis, race, clinical subtype, T stage, nodal status, grade, number, and type (visceral, non-visceral, bone) of metastatic sites at diagnosis as well as year of metastatic diagnosis. Number of metastatic sites was defined as the number of organ systems involved, with each visceral site counted separately and bone, skin, soft tissue, and distant lymph nodes each representing additional possible sites. Type of metastatic disease was classified as visceral if any visceral site was involved, bone if the patient had bone disease without visceral disease, with, or without non-visceral disease, and non-visceral only if the patient had neither visceral nor bone involvement but had metastatic disease limited to skin, soft tissue, or a distant lymph node. According to AJCC TNM staging, nodal status at diagnosis is limited to regional lymph nodes (axillary, internal mammary, and/or ipsilateral supraclavicular lymph nodes). Distant lymph nodes are categorized as metastatic (M1) disease. Treatment was assessed by line of therapy after metastatic diagnosis, for example, first-line therapy is the first systemic treatment given for metastatic disease.

Using Cox proportional hazards modeling, univariable and multivariable analyses were performed, and hazard ratios for death were calculated, as were 95% confidence intervals. Univariable analysis included all patients with known values and independently assessed the effect of *de novo* versus recurrent MBC, age at initial diagnosis, race, primary tumor clinical subtype, tumor size, nodal status, tumor grade, number of metastatic sites, type of metastatic disease, and year of metastatic diagnosis on survival from time of metastatic diagnosis. To account for improved treatment options over time, the year of metastatic diagnosis was divided into two roughly equal groups, 2011–2014 and 2015–2017. Multivariable analysis was performed including the same features, excluding patients with unknown race, T stage, nodal status, and/or grade. Kaplan–Meier curves were generated to assess median progression-free survival (mPFS) on first-line treatment in the metastatic setting and median overall survival (mOS) from date of metastatic diagnosis to death. Patients who pursued care outside of UNC were followed electronically as able, through uploaded provider notes and records from health systems with shared electronic medical records. Patients without survival events were censored at the time of last contact with any UNC clinic or hospital encounter. 1-year, 2-year, and 5-year OS estimates were obtained. In order to assess the impact of duration of first-line PFS on OS in the multivariable model, a landmark analysis was performed in which the landmark time point was set as the end of first-line treatment which became the new start time for measuring time to death. All analyses were performed using RStudio version 3.6.3.

In order to address the potential for lead-time bias, an exploratory analysis limited to patients with dnMBC whose primary tumor size and nodal status would not have prompted routine scans based on current guidelines, and who thus likely presented with symptoms, was performed as a comparison to rMBC which is most commonly detected due to symptoms [14].

Results

The CONSORT diagram illustrates the determination of the included cohort (Fig. 1). Of 844 patients, 232 had dnMBC (median follow-up 42 months (m)) and 612 had rMBC (median follow-up 41.3 m). With event rates greater than 65% in both cohorts, the mOS from metastatic diagnosis was 33% longer for dnMBC versus rMBC at 36.4 m (range 1.0 m to 101.0 m) versus 27.4 m (range 0.82 m to 105.9 m) ($p < 0.001$), with differences apparent within the first year after metastatic diagnosis and persistent thereafter (Fig. 2).

Patient and tumor characteristics

Table 1 illustrates baseline patient and tumor characteristics of the dnMBC and rMBC cohorts. The most common clinical subtype was hormone receptor-positive/HER2-negative (HR + /HER2−), followed by triple-negative (TNBC) and HER2-positive (HER2 +) breast cancer. Nearly 84% of patients had biopsy-proven metastatic disease. On average, patients with dnMBC were older at time of initial diagnosis, but there was no difference in age at metastatic diagnosis. There was no difference in racial distribution, with 23% of patients identifying as Black, nor time period of diagnosis, body mass index, visceral versus non-visceral metastases, or number of metastatic sites. Approximately 12% of patients with known germline mutational status had a pathogenic mutation in BRCA1 or BRCA2, in both the dMBC and rMBC cohorts. In patients with rMBC, the median interval from initial non-metastatic breast cancer diagnosis to metastatic diagnosis was 36.4 m.

There were significant differences between dnMBC and rMBC in clinical subtype and in primary tumor and nodal burden. A higher proportion of dnMBCs were HER2 + (dnMBC 29.3% vs rMBC 15.2%) and lower proportion were TNBC (dnMBC 20.3% vs rMBC 32.4%). Of patients with HER2 + MBC, which carries a relatively good prognosis, more than 40% had dnMBC, while fewer than 20% of patients with the poorest prognosis triple-negative MBC had dnMBC. *De novo* MBC was associated with significantly higher T stage (more than twofold more T3/4 tumors) and axillary nodal involvement, but fewer grade 3 tumors.

Treatment and progression-free survival by clinical subtype

Four hundred and thirty-eight patients with HR + /HER2− MBC were included, 321 with rMBC and 117 with dnMBC. Nearly all (93.8%) rMBC had received or were receiving adjuvant endocrine therapy at the time of metastatic diagnosis (Supplementary Table 1), with a median time to recurrence of 58.4 m (interquartile range, IQR, 29.8 m—95.0 m). Of patients who recurred within 5 years of their initial diagnosis and were thus predicted to be on endocrine therapy at the time of recurrence, the median time to recurrence was 30.4 m ($n = 165$, IQR 18.1 m–45.8 m). There was no difference between *de novo* and recurrent MBC in use of endocrine therapy in the first line (dnMBC 67.6%, rMBC 70.5%), although a higher proportion of patients with dnMBC who received first-line endocrine therapy also received a cyclin-dependent kinase (CDK) 4/6 inhibitor (dnMBC 42.5% vs rMBC 27.3%, $p = 0.017$), which is current standard of care. mPFS on any first-line therapy was 13.9 m longer for patients with dnMBC (dnMBC 25.5 m vs rMBC 11.6 m, $p < 0.001$) and was 19.5 m longer when considering only those treated with first-line endocrine therapy plus

CDK 4/6 inhibitor (Supplementary Fig. 1). Fewer patients with dnMBC were enrolled in a clinical trial as part of their first-line chemotherapy or medical therapy, compared to those with rMBC (dnMBC 1.7% vs rMBC 7.8%, $p = 0.019$). Changes in treatment patterns during this study period are reflected in Supplementary Table 2.

Among patients with HER2 + rMBC, 88% had received prior neoadjuvant and/or adjuvant HER2-targeting agents (Supplementary Table 1) and the median time to recurrence was 41.6 m (IQR 26.0–78.8 m) for HR + /HER2 + MBC and 25.7 m (IQR 19.8–35.9 m) for HR−/HER2 + MBC. 4.3% of patients recurred within one year and over half recurred within 3 years of initial diagnosis. More patients with HER2 + dnMBC received a first-line regimen that included pertuzumab (dnMBC 54.4% vs rMBC 37.6%, $p = 0.034$). mPFS on any first-line therapy was 6.0 m longer for patients with dnMBC (dMBC 11.4 m vs rMBC 5.4 m, $p = 0.002$) and was nearly ten months longer when considering only those whose first-line regimen contained the current standard of care taxane, trastuzumab, and pertuzumab (dnMBC 15.2 m vs rMBC 5.4 m, $p = 0.017$, Supplementary Fig. 1). Only one patient with dnMBC was treated on a clinical trial in the first-line metastatic treatment setting compared to seven patients with rMBC (dnMBC 1.5% vs rMBC 7.5%, $p = 0.081$).

All patients with triple-negative rMBC had previously received neoadjuvant or adjuvant chemotherapy (Supplementary Table 1). Median time to recurrence was 21.4 m (IQR 13.0–34.9 m), with 24.2% recurring within 1 year and 77.8% within the first 3 years. A higher proportion of patients with dnMBC received multiagent chemotherapy in the first-line setting (dnMBC 51.1% vs rMBC 27.5%, $p = 0.002$). Approximately 13% of patients in each cohort received an immune checkpoint inhibitor within the first three lines of therapy. No difference in mPFS on first-line chemotherapy was observed between dnMBC and rMBC (dnMBC 4.0 m vs rMBC 3.0 m, $p = 0.121$, Supplementary Fig. 1) regardless of single or multiagent chemotherapy (data not shown). There was no difference in rate of discontinuation due to toxicity among dnMBC and rMBC (data not shown). Similar proportions of patients with dnMBC and rMBC were treated on clinical trials in the first-line metastatic setting (dnMBC 19.1% vs rMBC 21.2%, $p = 0.754$).

Overall survival

Compared to rMBC, dnMBC was associated with superior survival from time of metastatic diagnosis in both univariable and multivariable analyses (Table 2). In multivariable analysis, dnMBC remained significantly and independently associated with OS (hazard ratio 0.63, 95% CI 0.49–0.80), with 37% of the difference in survival outcomes unaccounted for by variables in the model. Age, race, triple-negative clinical subtype, T stage, grade, number of metastatic sites, and year of metastatic diagnosis also remained independently associated with OS. Each subtype demonstrated a trend toward superior survival among dnMBC (Fig. 3). When PFS on first-line therapy was added to the multivariable model in a landmark analysis in which OS was measured as time from end of first-line treatment to death, PFS to first-line therapy significantly correlated with subsequent survival (hazard ratio 0.97, 95% CI 0.96–0.99, for each one month increase in first-line PFS). Differences in survival by race were identified with a 12.4-m inferior mOS among Black patients compared to white

patients (18.9 m vs 31.3 m, $p < 0.001$) which persisted within each subtype and is being further explored in a separate analysis.

Overall survival approximates disease-specific survival in this study population, with > 97% of deaths confirmed to be secondary to breast cancer. The 1-year and 2-year OS were superior among patients with dnMBC compared to rMBC, few patients in either cohort survived 5 years (1-year OS: dnMBC 84.0% vs rMBC 75.0%, $p = 0.004$; 2-year OS: dnMBC 66.1% vs rMBC 53.9%, $p = 0.001$; 5-year OS: dnMBC 28.9% vs 18.9%, $p = 0.119$). These differences between dnMBC and rMBC were seen to a variable degree in all subtypes (Fig. 3).

In an exploratory analysis stratifying rMBC by disease-free interval (DFI), outcomes for patients with dnMBC were similar to those seen in patients with rMBC who experienced at least a 3-year DFI (Supplementary Fig. 2). Given that symptoms prompt the diagnosis of MBC for most patients in the recurrent setting, a separate exploratory analysis inclusive only of patients with dnMBC predicted to have presented with symptomatic disease (T0-2N0-1 and T3N0 tumors) was performed and again demonstrated superior survival for patients with dnMBC (dnMBC 37.7 m vs rMBC 27.9 m, $p = 0.017$).

Discussion

This study found superior outcomes in dnMBC compared to rMBC diagnosed between 2011 and 2017 which was independent of clinicopathologic features. Superior survival from time of metastatic diagnosis of patients with dnMBC has been noted in several older series, although generally in eras not reflecting current treatment algorithms, rarely separated by clinical subtype, and not previously examined in context of type and responsiveness to therapy [4, 6–8]. Differences in mOS in the most recent comparable studies range from 8.3 to 12.0 months, consistent with our findings [6, 15].

We found several contributors to this difference in outcome between dnMBC and rMBC. Nearly twice as many patients with dnMBC had HER2 + MBC and a significantly lower proportion had TNBC than those with rMBC, a subtype differential that has also been observed in the British Columbia registry and the POSH young patient cohort [6, 16] and that has clear prognostic implications for the cohort as a whole. Although some of the survival disparity was attributable to varying proportions of prognostically relevant subtypes, 37% of the difference in outcome between dnMBC and rMBC was unaccounted for by clinicopathologic features.

Differences in treatment patterns and response revealed that PFS to first-line therapy was significantly longer among dnMBC than rMBC, even when the analysis was limited to patients who received National Cancer Center Network (NCCN) guideline-based optimal first-line regimens [14]. For example, within HR + /HER2− MBC, more patients with dnMBC received a CDK4/6 inhibitor concurrently with endocrine therapy in the first-line setting; however, within this stratum there remained a nearly 20-month superior mPFS for dnMBC. This suggests a biologic contribution to better outcomes in dnMBC. All patients with rMBC had received prior systemic therapy for localized breast cancer, with

the potential for acquired drug resistance and variations in both tumor biologic features and the tumor immune microenvironment. While still an emerging area of research, data in TNBC suggest that immune activation affects response to multiple types of therapy and that distinct immune profiles exist pre- and post-systemic therapy [9, 17–23].

Better understanding of *de novo* metastatic disease is increasingly important. With improved treatments contributing to fewer recurrences in patients with localized breast cancer, the proportion of MBC that is *de novo* has been rising and may someday constitute the majority of MBC since they are unaffected by improvements in early breast cancer treatment and have no opportunity for curative intent therapy at this time. Additionally, the incidence of dnMBC has not improved since the introduction of screening mammography [2]. Increased enrollment of patients with dnMBC in clinical trials is critical. It is also true that studying *de novo* disease is important in understanding the biology underlying metastasis since in these tumors, unlike in recurrent disease, the primary and the metastatic lesions are treatment naïve and contemporaneous.

Limitations of this study include those of any retrospective study. Data regarding duration on adjuvant therapy and whether rMBC were diagnosed while a patient was on adjuvant therapy was not captured. Similarly, whether patients with rMBC had systemic staging studies at the time of their initial diagnosis is unknown, genomic information obtained from somatic sequencing is not linked to this database. Clinical subtype of metastatic biopsies was not taken into account for this study as they were available only for approximately half of the patients and rates of discordance relative to primary breast tumors have been well reported in the literature. From a clinical perspective, the ability to diagnosis *de novo* versus recurrent MBC is likely to improve over time with the development of novel tools to detect microscopic metastatic disease through blood-based assays and/or increasingly sensitive imaging technologies. Currently, it is believed that most cases of rMBC occur in the setting of residual micrometastatic disease after initial treatment; however, identification of cases of local–regional recurrence with subsequent metastases is important as it represents another possible opportunity for curative intervention. Analysis of datasets that capture rates of local–regional recurrence prior to metastatic diagnosis would be helpful for making this distinction and continued development of tools to determine which patients are at the highest risk of distant recurrence remains critical.

In conclusion, while differences in clinical subtype distribution, grade, and first-line treatment type contribute to the superior mOS observed in patients with dnMBC compared to rMBC, they do not fully explain it. A striking feature we found is the difference in treatment responsiveness, which may relate to acquired resistance to therapy in recurrent disease or other unmeasured biologic variables. As novel therapies continue to improve outcomes in early breast cancer, rMBC is expected to become increasingly challenging to treat, with only the most treatment-refractory tumors recurring. This may lead to further disparities in outcomes between rMBC and dnMBC, which should be considered when designing clinical trials and selecting therapies for patients in each clinical situation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank all the patients and their family members for participating in the University of North Carolina Metastatic Breast Cancer Clinical Database.

Funding

This work was supported by funds from the National Cancer Institute (NCI) Breast-Specialized Program of Research Excellence (SPORE) (P50-CA58223), Susan G Komen for the Cure (ECD, LAC, CMP), the Breast Cancer Research Foundation (LAC, CMP), Fundación Sociedad Española de Oncología Médica (SEOM), Becas SEOM para Formación en Investigación en Centros de Referencia en el Extranjero (TP), the John William Pope Foundation (DMF), and by the National Institutes of Health T32 Integrated Training in Cancer Model Systems (DMF).

References

1. American Cancer Society (2019) Breast cancer facts & figures 2019–2020. American Cancer Society, Inc., Atlanta
2. Bleyer A, Welch G (2012) Effect of three decades of screening mammography on breast-cancer incidence. N Engl J Med 367:1998–2005. 10.1056/NEJMoa1206809 [PubMed: 23171096]
3. Welch G, Gorski D, Albertsen P (2015) Trends in metastatic breast and prostate cancer-lessons in cancer dynamics. N Engl J Med 373:1685–1687. 10.1056/NEJMp1510443 [PubMed: 26510017]
4. Malmgren J, Mayer M, Atwood MK, Kaplan HG (2018) Differential presentation and survival of *de novo* and recurrent metastatic breast cancer over time: 1990–2010. Breast Cancer Res Treat 167:579–590. 10.1007/s10549-017-4529-5 [PubMed: 29039120]
5. Dawood S, Broglio K, Ensor J, Hortobagyi GN, Giordano SH (2010) Survival differences among women with *de novo* stage IV and relapsed breast cancer. Ann Oncol 21:2169–2174. 10.1093/annonc/mdq220 [PubMed: 20427349]
6. Den Brok WD, Speers CH, Gondara L, Baxter E, Tyldesley SK, Lohrisch CA (2017) Survival with metastatic breast cancer based on initial presentation, *de novo* versus relapsed. Breast Cancer Res Treat 161:549–556. 10.1007/s10549-016-4080-9 [PubMed: 28000014]
7. Güth U, Magaton I, Huang DJ, Fisher R, Schötzau A, Vetter M (2014) Primary and sceondary distant metastatic breast cancer: two sides of the same coin. The Breast 23:26–32. 10.1016/j.breast.2013.10.007 [PubMed: 24215983]
8. Finn RS, Martin M, Rugo HS et al. (2016) Palbociclib and Letrozole in advanced breast cancer. N Engl J Med 375:1925–1936. 10.1056/NEJMoa1607303 [PubMed: 27959613]
9. Cortes J, Cescon DW, Rugo HS et al. (2020) Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. The Lancet 396:1817–1828. 10.1016/S0140-6736(20)32531-9
10. Plichta J, Thomas SM, Sergesketter A et al. (2020) A novel staging system for *de novo* metastatic breast cancer refines prognostic estimates. Ann Surg. 10.1097/SLA.0000000000004231
11. Hammond MEH, Hayes DF, Dowsett M et al. (2010) American society of clinical oncology/college of american pathologists guideine recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 28:2784–2795. 10.1200/JCO.2009.25.6529 [PubMed: 20404251]
12. Wolff AC, Hammond EH, Schwartz JN et al. (2007) American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 25(1):118–45. 10.1200/JCO.2006.09.2775 [PubMed: 17159189]

13. Wolff AC, Hammond EH, Hicks EC et al. (2013) Recommendation for human epidermal growth factor receptor 2 testing in breast cancer: American society of clinical oncology/college of American pathologists clinical practice guideline update. J Clin Oncol 31(31):3997–4013. 10.1200/JCO.2013.50.9984 [PubMed: 24101045]
14. National Comprehensive Cancer Network. Breast Cancer (Version 4.2021).
15. Lebbezoo DJA, van Kampen RJW, Voogd AC et al. (2015) Prognosis of metastatic breast cancer: are there differences between patients with *de novo* and recurrent metastatic breast cancer? Br J Cancer 112:1445–1451. 10.1038/bjc.2015.127 [PubMed: 25880008]
16. McKenzie HS, Maishman T, Simmonds P, Durcan L, Eccles D, Copson E (2020) Survival and disease characteristics of *de novo* vs recurrent metastatic breast cancer in a cohort of young patients. Br J Cancer 122:1618–1629. 10.1038/s41416-020-0784-z [PubMed: 32231292]
17. Loi S, Sirtaine N, Piette F et al. (2013) Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02–98. J Clin Oncol 31(7):860–867. 10.1200/JCO.2011.41.0902 [PubMed: 23341518]
18. Garcia-Recio S, Thennavan A, East MP et al. (2020) FGFR4 regulates tumor subtype differentiation in luminal breast cancer and metastatic disease. J Clin Invest 130(9):4871–4887. 10.1172/JCI130323 [PubMed: 32573490]
19. Loi S, Drubay D, Adams S et al. (2019) Tumor-infiltrating lymphocytes and prognosis: a pooled individual patient analysis of early-stage triple-negative breast cancers. J Clin Oncol 37(7):559–569. 10.1200/JCO.18.01010 [PubMed: 30650045]
20. King TA, Liu MC, McClure MB, et al. (2019) Multiplatform analysis of matched primary and metastatic breast tumors from the AURORA US Network. Oral Presentation. San Antonio Breast Cancer Symposium.
21. Schmid P, Cortes J, Pusztai L et al. (2020) Pembrolizumab for early triple-negative breast cancer. N Engl J Med 382:810–821. 10.1056/NEJMoa1910549 [PubMed: 32101663]
22. Mittendorf EA, Zhang H, Barrios CH et al. (2020) Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (Impassion031): a randomised, double-blind, phase 3 trial. The Lancet 396:1090–1100. 10.1016/S0140-6736(20)31953-X
23. Schmid P, Adams S, Rugo HS et al. (2018) Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 379:2108–2121. 10.1056/NEJMoa1809615 [PubMed: 30345906]

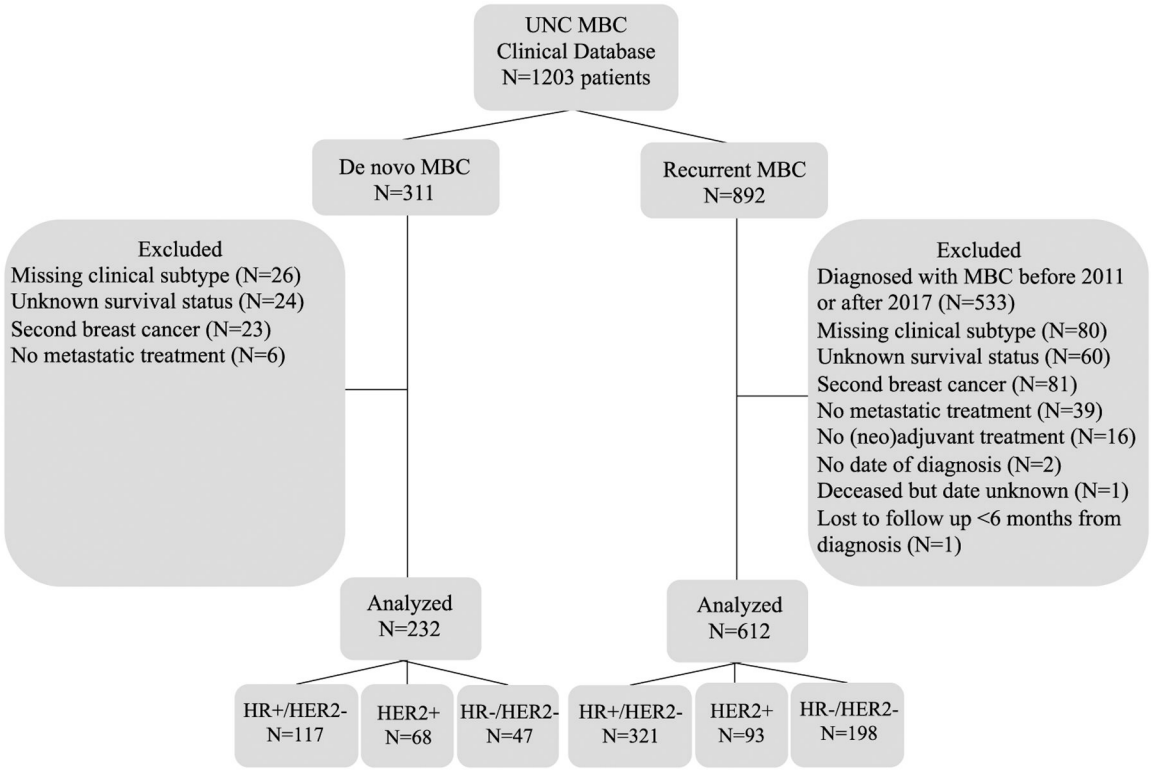

Fig. 1.

Consort diagram. *UNC* University of North Carolina, *MBC* metastatic breast cancer, *HR* hormone receptor; *HER2* human epidermal growth factor receptor 2

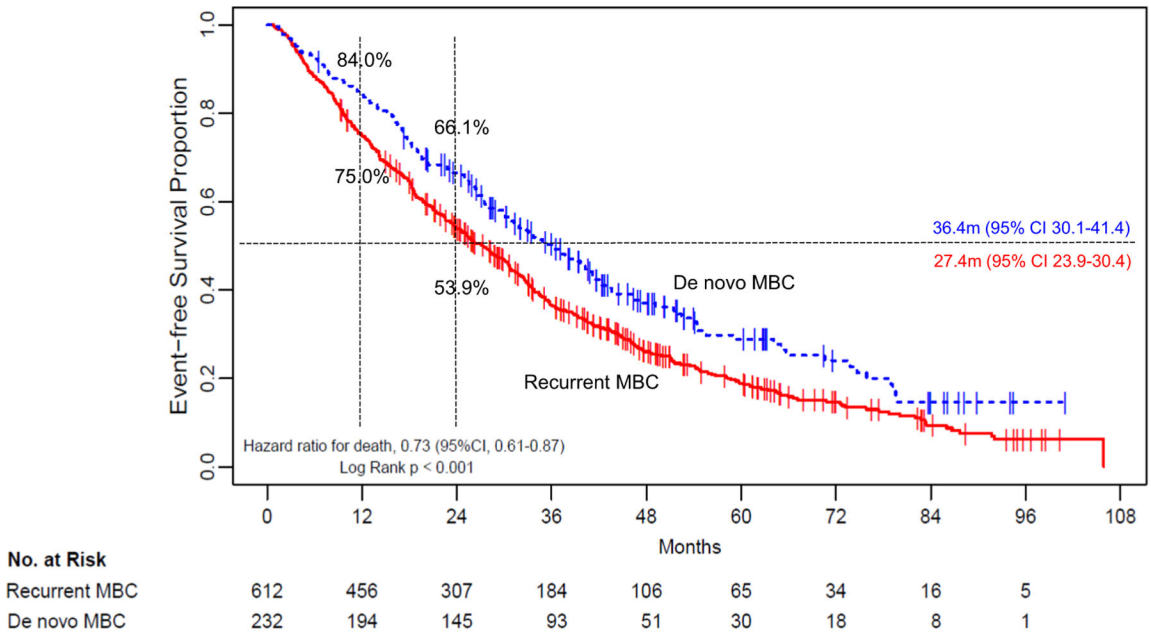

Fig. 2.

Overall survival among entire metastatic breast cancer study population by *de novo* or recurrent status. Estimates of overall survival were from Kaplan–Meier curves and tests of differences by two-sided log-rank test. Black-dashed line = *de novo* metastatic breast cancer. Gray solid line = recurrent metastatic breast cancer

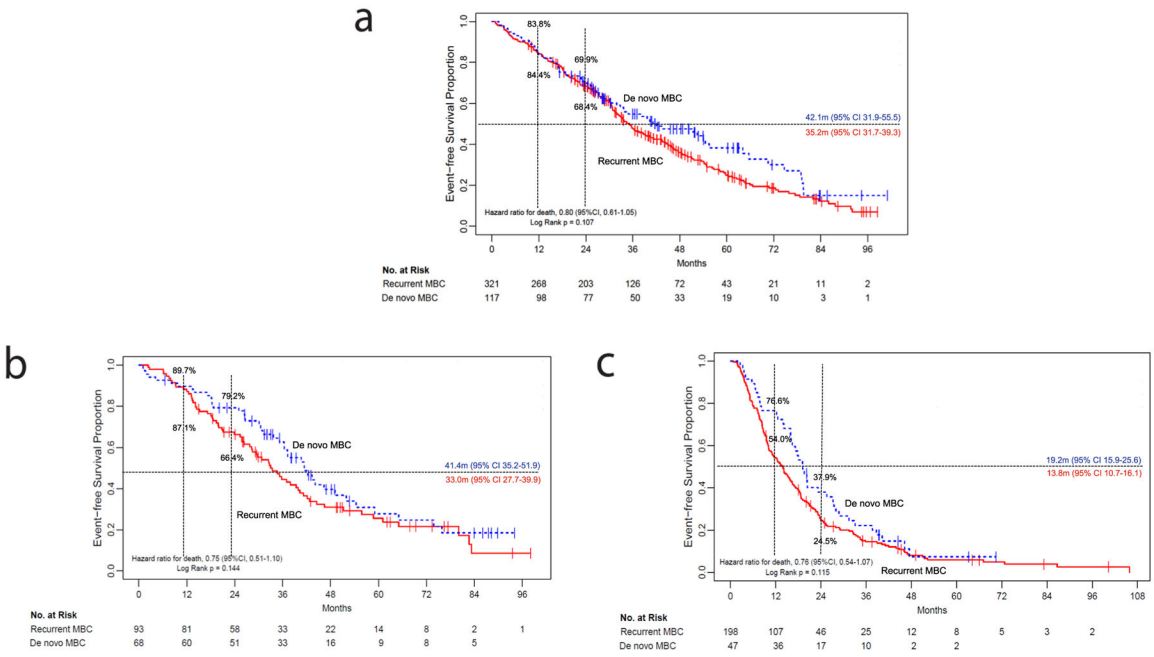

Fig. 3.

Overall survival curves among patients with metastatic breast cancer by *de novo* or recurrent status and by clinical subtype of the primary breast cancer. **a** Hormone receptor-positive/HER2-negative. **b** HER2-positive. **c** Hormone receptor-negative/HER2-negative. Estimates of overall survival were from Kaplan–Meier curves and tests of differences by two-sided log-rank test. Black-dashed line = *de novo* metastatic breast cancer. Gray solid line = recurrent metastatic breast cancer. *MBC* metastatic breast cancer, *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2

Breast Cancer Res Treat. Author manuscript; available in PMC 2022 November 01.

Table 1

Cohort characteristics, overall, by de novo, and recurrent metastatic breast cancer of patients diagnosed with metastatic disease between 2011 and 2017

Variable	All Patients (*N* = 844) No. (%)	*De Novo* MBC (*N* = 232) No. (%)	Recurrent MBC (*N* = 612) No. (%)	*p*-value
Median age at initial diagnosis, yr (range)	51.7 (23.9–92.9)	55.6 (26.7–87.4)	50.7 (23.9–92.9)	
Age at initial diagnosis				0.004 *
< 50	381 (45.1)	86 (37.1)	295 (48.2)	
≥ 50	463 (54.9)	146 (62.9)	317 (51.8)	
Age at metastatic diagnosis				0.539
< 50	299 (35.4)	86 (37.1)	213 (34.8)	
≥ 50	545 (64.6)	146 (62.9)	399 (65.2)	
Race [a]				0.107
White	570 (69.9)	147 (64.8)	423 (71.8)	
Black	193 (23.7)	65 (28.6)	128 (21.7)	
Other	53 (6.5)	15 (6.6)	38 (6.5)	
Unknown	28	5	23	
Clinical subtype				< 0.001 *
HR +/HER2−	438 (51.9)	117 (50.4)	321 (52.5)	
HER2 +	161 (19.1)	68 (29.3)	93 (15.2)	
HR−/HER2−	245 (29.0)	47 (20.3)	198 (32.4)	
T stage [a]				< 0.001 *
T0/T1/T2	539 (68.5)	102 (48.3)	437 (75.9)	
T3/T4	248 (31.5)	109 (51.7)	139 (24.1)	
Unknown	57	21	36	
Nodal status [a]				< 0.001 *
Node negative	245 (30.8)	34 (16.1)	211 (36.1)	
Node positive	551 (69.2)	177 (83.9)	374 (63.9)	
Unknown	48	21	27	
Grade [a]				0.017 *
1/2	279 (40.4)	93 (47.4)	186 (37.6)	
3	412 (59.6)	103 (52.6)	309 (62.4)	

Variable	All Patients (*N* = 844) No. (%)	*De Novo* MBC (*N* = 232) No. (%)	Recurrent MBC (*N* = 612) No. (%)	*p*-value
Unknown	153	36	117	
No. of metastatic sites [b]				0.741
1	301 (35.7)	78 (33.6)	223 (36.4)	
2	281 (33.3)	79 (34.1)	202 (33.0)	
3 +	262 (31.0)	75 (32.3)	187 (30.6)	
Type of metastases [b]				0.082
Bone	228 (27.0)	70 (30.2)	158 (25.8)	
Visceral	528 (62.6)	146 (62.9)	382 (62.4)	
Non-visceral only	88 (10.4)	16 (6.9)	72 (11.8)	
Yr of metastatic diagnosis				0.135
2011–2014	439 (52.0)	111 (47.8)	328 (53.6)	
2015–2017	405 (48.0)	121 (52.2)	284 (46.4)	

[*] Statistically significant

[a] Patients with unknown feature excluded from analysis

[b] At metastatic diagnosis; yr = year

MBC metastatic breast cancer, *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2

Breast Cancer Res Treat. Author manuscript; available in PMC 2022 November 01.

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Table 2

Univariable and multivariable Cox proportional hazard regression analyses for overall survival including *de novo* versus recurrent metastatic breast cancer and clinicopathological features

Feature	No	Events	mOS, m	Univariable analysis	*p*-value	Multivariable analysis	*p*-value
				Hazard Ratio (95% CI)		**Hazard Ratio (95% CI)**	
Metastatic presentation							
Recurrent MBC	612	473	27.4	–		–	
De novo MBC	232	152	36.4	0.73 (0.61–0.87)	< 0.001 *	0.63 (0.49–0.80)	< 0.001 *
Age at initial diagnosis							
< 50	381	273	31.7	–		–	
≥ 50	463	352	26.6	1.1 (0.98–1.34)	0.090	1.4 (1.13–1.67)	0.001 *
Race [a]							
White	570	412	31.3	–		–	
Black	193	160	18.9	1.6 (1.36–1.96)	< 0.001 *	1.6 (1.31–2.03)	< 0.001 *
Other	53	34	42.1	0.88 (0.62–1.25)	0.463	0.98 (0.65–1.47)	0.913
Clinical subtype							
HR + /HER2−	438	293	35.7	–		–	
HER2 +	161	108	37.0	0.97 (0.78–1.21)	0.796	0.76 (0.57–1.01)	0.057
HR−/HER2−	245	224	15.2	2.6 (2.18–3.11)	< 0.001 *	1.7 (1.38–2.18)	< 0.001 *
T stage [a]							
T0/T1/T2	539	394	30.5	–		–	
T3/T4	248	188	24.4	1.2 (1.02–1.44)	0.030 *	1.3 (1.06–1.62)	0.014 *
Nodal status [a]							
Node negative	245	180	26.1	–		–	
Node positive	551	409	30.5	0.92 (0.77–1.10)	0.344	0.96 (0.78–1.19)	0.715
Grade [a]							
1/2	279	158	47.6	–		–	
3	412	339	20.9	2.3 (1.93–2.84)	< 0.001 *	1.9 (1.55–2.41)	< 0.001 *
No. of metastatic sites [b]							

Feature	No	Events	mOS, m	Univariable analysis	*p*-value	Multivariable analysis	*p*-value
				Hazard Ratio (95% CI)		**Hazard Ratio (95% CI)**	
1	301	188	35.2	–		–	
2	281	232	27.3	1.5 (1.27–1.87)	< 0.001 *	1.4 (1.14–1.84)	0.003 *
3 +	262	205	20.4	1.7 (1.36–2.02)	< 0.001 *	1.5 (1.15–1.92)	0.003 *
Type of metastases [b]							
Bone	228	137	44.8	–		–	
Visceral	528	417	24.0	2.0 (1.64–2.41)	< 0.001 *	1.2 (0.94–1.57)	0.128
Non-visceral only	88	71	25.3	1.8 (1.37–2.43)	< 0.001 *	1.1 (0.73–1.50)	0.789
Year of metastatic diagnosis							
2011–2014	439	377	31.5	–		–	
2015–2017	405	248	26.3	1.2 (0.99–1.39)	0.065	1.3 (1.04–1.55)	0.021 *

*Statistically significant

[a]Patients with unknown feature excluded from analysis

[b]At metastatic diagnosis

MBC metastatic breast cancer, *m* months, *yr* year, *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2