The Oncologist®

Breast Cancer

Comparative Effectiveness of an mTOR-Based Systemic Therapy Regimen in Advanced, Metaplastic and Nonmetaplastic Triple-Negative Breast Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. mTOR inhibitor • Mesenchymal • Metaplastic breast cancer • Triple-negative breast cancer

Abstract

Background. Triple-negative breast cancer (TNBC) is a heterogeneous disease with subtypes having different "targetable" molecular aberrations. Metaplastic breast cancers (MpBCs) are typically TNBCs and commonly have alterations in the PI3K/Akt/mTOR pathway. We previously reported efficacy for an mTOR-based chemotherapy regimen in MpBC. To determine if tumor subtype influences prognosis, we compared treatment outcomes of patients with MpBC with those of patients with nonmetaplastic TNBC receiving an mTOR-based systemic therapy regimen.

Patients and Methods. Patients with advanced MpBC and nonmetaplastic TNBC were treated at our institution from April 16, 2009, through November 4, 2014, using mTOR inhibition (temsirolimus or everolimus) with liposomal doxorubicin and bevacizumab (DAT/DAE). Median progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan-Meier method. Cox regression analyses were used to evaluate associations between tumor histology and outcomes. Multivariable models were adjusted for all covariates.

Results. Fourteen patients with nonmetaplastic TNBC and 59 patients with advanced MpBC were treated with DAT/-DAE. MpBC patients were older (p = .002) and less likely to have a history of bevacizumab use (p = .023). Median PFS for the nonmetaplastic TNBC and MpBC patients was 2.5 months and 4.8 months, respectively. This difference in PFS was statistically significant on univariable (p = .006) but not multivariable analysis (p = .087). Median OS for the nonmetaplastic TNBC and MpBC patients was 3.7 months and 10.0 months, respectively (p = .0003). MpBC remained significantly associated with improved OS on multivariable analysis (p < .0001).

Conclusion. In our study, DAT/DAE appeared to be more effective in MpBC compared with nonmetaplastic TNBC. These data support patient selection for targeted therapy in TNBC. ***The Oncologist*** 2018;23:1300–1309

Implications for Practice: Metaplastic breast cancers (MpBCs) represent <1% of all breast cancers, demonstrate mesenchymal differentiation, and are typically resistant to chemotherapy. Patients with advanced MpBC treated with an mTOR-based systemic therapy regimen had better long-term outcomes compared with patients with nonmetaplastic triple-negative breast cancer treated with the same regimen, suggesting that metaplastic histology may predict benefit from agents targeting the PI3K/Akt/mTOR pathway.

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Introduction

Metaplastic breast cancers (MpBCs) are a group of histologically heterogeneous breast cancers demonstrating various combinations of poorly differentiated adenocarcinoma, sarcomatoid, and/or squamous components within the same tumor [1–6]. These tumors are rare, representing <1% of all breast malignancies [7], and are typically triple-negative breast cancers (TNBCs) with dismal prognosis [8, 9].

The molecular signature of MpBCs most closely resembles the claudin-low and mesenchymal subtypes of TNBC with an enrichment of genes involved in epithelial-to-mesenchymal transition and other stem cell-associated genes [10, 11]. TNBCs as a group have demonstrated greater sensitivity to cytotoxic chemotherapy compared with non-TNBCs [12]. However, compared with the basal-like 1 subtype of TNBC, which has been reported to have a pathologic complete response (pCR) rate of 52% when treated with standard neoadjuvant chemotherapy, the mesenchymal and mesenchymal stem-like subtypes of TNBC are less sensitive to cytotoxic chemotherapy, with reported pCR rates of only 23%–31% in the neoadjuvant setting [13].

Given the molecular similarities between MpBCs and the mesenchymal and mesenchymal stem-like subtypes of TNBC, it is therefore not surprising that MpBCs have been reported to be comparatively resistant to cytotoxic chemotherapy [8]. We previously reported the results of a phase I trial evaluating the novel combination of liposomal doxorubicin, bevacizumab, and mammalian target of rapamycin (mTOR) inhibition with temsirolimus or everolimus (DAT or DAE, respectively). We observed promising signs of activity in MpBC, especially in patients who had a molecular aberration affecting the phosphatidylinositol-3-kinase (PI3K) pathway [14–17].

Here we report the results of a post hoc analysis of a clinical trial, comparing outcomes of 14 patients with advanced nonmetaplastic TNBC and 59 patients with advanced MpBC treated with targeted therapy using DAT or DAE.

Materials and Methods

Patients

We previously reported our clinical experience with DAT and DAE in MpBC [14, 15, 17, 18]. We identified patients who received DAT or DAE at the University of Texas MD Anderson Cancer Center (MDACC) and compared outcomes in patients with advanced, MpBC to those with advanced, nonmetaplastic TNBC (considered an "unselected cohort" of patients with TNBC). Subspecialized breast pathologists at MDACC reviewed all available tumor material and rendered all histologic diagnoses prior to treatment initiation. MpBC was defined according to the World Health Organization Classification of Tumors of the Breast (4th edition) [19], with invasive breast carcinomas categorized as having metaplastic histology if the invasive carcinoma cells had morphologic evidence of squamous or mesenchymal differentiation, the latter including spindle cell, chondroid, or osseous differentiation. TNBC was defined as a tumor that was estrogen receptor (ER) negative, progesterone receptor negative, and human epidermal growth factor receptor 2 (HER2) negative. ER and progesterone receptor negativity was defined as <10% staining of invasive carcinoma cells of any intensity by immunohistochemistry. HER2 negativity was defined according to the American Society of Clinical Oncology/College of American Pathologists HER2 testing guidelines [20]. Sixty-three patients received therapy as part of an Institutional Review Board (IRB) approved clinical trial (#2008-0384), and 10 patients were treated on another IRB-approved clinical protocol (DR11-0039) that involved collecting data from patients treated with the same targeted therapy outside of the parent protocol (in this case, #2003-0384). The results of a dose escalation phase I trial determined the recommended phase II dose to be the following: liposomal doxorubicin, 30 mg/m^2 IV every 3 weeks; bevacizumab, 15 mg/kg IV every 3 weeks; and temsirolimus, 10 mg IV weekly, or everolimus, 7.5 mg by mouth daily, using 21-day cycles (NCT00761644) [15]. Eligibility criteria for protocol #2008-0384 has been previously described [15, 18]. Patients who had previously received a cumulative doxorubicin dose of greater than 300mg/m^2 were excluded from the study, and all patients underwent close cardiac monitoring, as previously described [15]. Treatment assignment to DAT or DAE was determined according to logistical considerations such as patient preference for oral agents, insurance approval, and availability of slots at the time of enrollment. Patients were enrolled from April 16, 2009, through November 4, 2014, and followed for survival outcomes through April 1, 2017.

Efficacy

Restaging scans were obtained every 6 weeks (two cycles) while on protocol and response was assessed using RECIST version 1.1 [21]. All complete and partial responses (CRs and PRs, respectively) were confirmed on at least one subsequent staging evaluation. In patients with a best response of stable disease (SD), the duration of SD was defined as the time from study enrollment to progression or exit from study, whichever occurred first. The overall response rate (ORR) was defined as the percentage of patients with a best response of either a confirmed CR or confirmed PR. The clinical benefit rate (CBR) was defined as the percentage of patients with a best response of a confirmed CR or confirmed PR or having at least 6 months of disease stability (SD ≥6 months).

Progression-free survival (PFS) was defined as the time from study enrollment to progression or death from any cause, whichever occurred first. For patients not known to have progressed or died, data for PFS were censored at the time of last follow-up. Overall survival (OS) was defined as the time from study enrollment to death from any cause. Information on the patient's vital status were obtained from our electronic medical records and supplemented by data from the MDACC tumor registry. For patients not known to have died, data for OS were censored at the time the patient was last known to be alive.

Table 1. Baseline characteristics and treatment regimens

Characteristics and treatment regimens	Nonmetaplastic TNBC (n = 14), n (%)	MpBC (n = 59), n (%)	Unadjusted odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
Age at enrollment, median (range), y	45 (33–67)	59 (38–79)	4.1[a] (1.8–9.0)	.0006	6.9[a] (2.0–23.6)	.002
Race						
White	12 (86)	52 (88)	1		1	
Nonwhite	2 (14)	7 (12)	0.8 (0.1–4.4)	.805	0.8 (0.07–9.0)	.833
Prior systemic therapy for metastatic disease						
No	2 (14)	29 (49)	1		1	
Yes	12 (86)	30 (51)	0.2 (0.04–0.8)	.029	0.2 (0.01–2.3)	.185
Prior anthracycline						
No	3 (21)	13 (22)	1		1	
Yes	11 (79)	46 (78)	1.0 (0.2–4.0)	.961	10.7 (0.9–124.5)	.058
Prior taxane						
No	1 (7)	11 (19)	1		1	
Yes	13 (93)	48 (81)	0.3 (0.04–2.8)	0.317	0.4 (0.01–9.5)	.554
Prior bevacizumab						
No	7 (50)	55 (93)	1		1	
Yes	7 (50)	4 (7)	0.1 (0.02–0.3)	.0004	0.1 (0.007–0.7)	.023
Prior mTOR inhibitor						
No	12 (86)	55 (93)	1		1	
Yes	2 (14)	4 (7)	0.4 (0.07–2.7)	.369	0.1 (0.005–2.3)	.154
ECOG performance status						
0	2 (14)	12 (20)	1.0 (0.3–2.8)	.934	1.21 (0.22–6.61)	.825
1	11 (79)	40 (68)				
2	1 (7)	7 (12)				
Study regimen						
DAT	12 (86)	38 (64)	1		1	
DAE	2 (14)	21 (35)	3.3 (0.7–16.2)	.139	1.1 (0.1–11.7)	.906

[a]Per 10-year increase in age.

Abbreviations: CI, confidence interval; DAE, liposomal doxorubicin, bevacizumab, everolimus; DAT, liposomal doxorubicin, bevacizumab, temsirolimus; ECOG, Eastern Cooperative Oncology Group; MpBC, metaplastic breast cancer; mTOR, mammalian target of rapamycin; TNBC, triple-negative breast cancer.

Statistical Analysis

Univariable and multivariable logistic regression was used to examine associations between baseline patient characteristics and histologic subtype. Confidence intervals (CI) of proportions were calculated using the exact binomial method. The effect of study covariates on the ORR and CBR were examined using univariable and multivariable logistic regression. Prior taxane and bevacizumab use were excluded from the regression models predicting ORR and CBR because of their joint distribution with outcomes. Estimates of median PFS and OS were calculated using the Kaplan-Meier method, and time-to-event distributions were compared using the log-rank test. Univariable and multivariable Cox regression analyses were used to determine the effect of study covariates on PFS and OS. Results are expressed as hazard ratios (HR) in univariable analyses and adjusted hazard ratios (aHR) in multivariable models with accompanying 95% CIs.

To account for multiplicity of testing, a two-sided p value of less than .02 was considered statistically significant when evaluating associations between histology (metaplastic vs. nonmetaplastic) and outcomes. All other comparisons are hypothesis generating, and p values should be interpreted with caution. All data were analyzed using R Statistical Software (version 3.5.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 73 patients were included in this study, of whom 14 patients had advanced nonmetaplastic TNBC (median age, 45 years; range, 33–67 years) and 59 patients had advanced MpBC (median age, 59 years; range, 38–79 years). Of the 59 patients with advanced MpBC, 98% (58/59) had TNBCs. The last patient was ER negative but HER2 positive based on in situ hybridization with an average HER2/Chromosome 17 ratio of 2.5 and an average number of HER2 signals/nucleus of 6.9. This testing was performed outside our institution, and additional archival tumor tissue was not available for repeat testing of HER2

Table 2. Baseline characteristics of patients treated on protocol #2008-0384 compared with patients treated on protocol DR11-0039

Baseline characteristics	2008-0384 (*n* = 63), *n* (%)	DR11-0039 (*n* = 10), *n* (%)
Histology		
Nonmetaplastic TNBC	11 (17)	3 (30)
MpBC	52 (83)	7 (70)
Age at enrollment, median (range), y	57 (33–79)	59 (39–69)
Race		
White	54 (86)	10 (100)
Nonwhite	9 (14)	0
Prior systemic therapy for metastatic disease		
No	25 (40)	6 (60)
Yes	38 (60)	4 (40)
Prior anthracycline		
No	13 (21)	3 (30)
Yes	50 (79)	7 (70)
Prior taxane		
No	10 (16)	2 (20)
Yes	53 (84)	8 (80)
Prior bevacizumab		
No	55 (87)	7 (70)
Yes	8 (13)	3 (30)
Prior mTOR inhibitor		
No	58 (92)	9 (90)
Yes	5 (8)	1 (10)
ECOG performance status		
0	14 (22)	0
1	43 (68)	8 (80)
2	6 (10)	2 (20)
Study regimen		
DAT	43 (68)	7 (70)
DAE	20 (32)	3 (30)

Abbreviations: DAE, liposomal doxorubicin, bevacizumab, everolimus; DAT, liposomal doxorubicin, bevacizumab, temsirolimus; ECOG, Eastern Cooperative Oncology Group; MpBC, metaplastic breast cancer; mTOR, mammalian target of rapamycin; TNBC, triple-negative breast cancer.

status at MDACC. Notably, this patient developed metastatic disease while receiving adjuvant trastuzumab and developed disease progression after only two cycles of docetaxel, pertuzumab, and trastuzumab as front-line therapy for metastatic disease. Because this clinical course suggested that her disease was resistant to HER2-directed therapy, the patient was included in these analyses. Of the 14 patients with advanced nonmetaplastic TNBC, 12 were treated with this regimen because of progression of disease on standard therapy, and the remaining 2 patients received this regimen because of physician and patient preferences. Baseline patient characteristics are summarized in Table 1. On univariable logistic regression, older age was associated with metaplastic histology (odds ratio [OR], 4.1; 95% CI, 1.8–9.0; $p = .0006$). In contrast, prior systemic therapy in the metastatic setting (OR, 0.2; 95% CI, 0.04–0.8; $p = .029$) and prior bevacizumab therapy (OR, 0.1; 95% CI, 0.02–0.3; $p = .0004$) were less likely to be associated with metaplastic histology. Patients with MpBC and nonmetaplastic TNBC received a median of one (range, 0–5) and three (range, 0–6) prior lines of systemic therapy for metastatic disease, respectively. On multivariable logistic regression, older age was associated with metaplastic histology (OR, 6.9; 95% CI, 2.0–23.6; $p = .002$), whereas prior treatment with bevacizumab was less likely to be associated with metaplastic histology (OR, 0.1; 95% CI, 0.007–0.7; $p = .023$). Table 2 summarizes and compares the baseline characteristics between the 63 patients who received therapy as part of protocol #2008-0384 with the 10 patients treated on protocol DR11-0039.

Table 3. Best response

Responses	Nonmetaplastic TNBC (n = 14), *n* (%)	MpBC (n = 59), *n* (%)	*p* value[a]
Best response			
CR	0	4 (7)	
PR	1 (7)	7 (12)	
SD ≥6 mo	0	10[b] (17)	
SD <6 mo	4 (29)	14 (24)	
PD	9 (64)	19 (32)	
NE	0	5 (8)	
Overall response[c]	1 (7)	11 (19)	.440
Clinical benefit[d]	1 (7)	21 (36)	.051

[a]The *p* values are from Fisher's exact test.
[b]One patient was able to obtain insurance approval to get treated with maintenance single agent everolimus closer to home after having SD on DAT for 5.79 months. This patient was counted as having SD ≥6 months. All other patients with a best response of SD but followed for <6 months ($n = 3$) were considered to have a best response of SD <6 months.
[c]Overall response is best response of CR or PR.
[d]Clinical benefit is best response of CR, PR, or SD ≥6 months. Abbreviations: CR, complete response; MpBC, metaplastic breast cancer; NE, nonevaluable; PD, progressive disease; PR, partial response; SD, stable disease; TNBC, triple-negative breast cancer.

Efficacy

Of the 14 patients with nonmetaplastic TNBC treated, there were no CRs, and one patient had a PR, for an ORR of 7% (95% CI, 0.2–34%; Table 3). In contrast, among the patients with MpBC, there were four CRs and seven PRs for an ORR of 19% (95% CI, 9.7–31%; Table 3). However, this difference was not statistically significant on both univariable (OR, 3.0; 95% CI, 0.4–25.2; $p = .317$; Table 4) and multivariable logistic regression (OR, 2.1; 95% CI, 0.1–38.4; $p = .625$; Table 4). Poorer performance status was associated with a lower likelihood of achieving an objective response on both univariable (OR, 0.1; 95% CI, 0.01–0.3; $p = .0002$; Table 4) and multivariable logistic regression (OR, 0.03; 95% CI, 0.004–0.2; $p = .0006$; Table 4). Among the 14 patients with nonmetaplastic TNBC, four patients had SD as their best response, but the duration of disease stability was less than 6 months in all four cases, and therefore the CBR was also

Table 4. Effect of baseline prognostic factors on overall response and clinical benefit

	Overall response (CR+PR)				Clinical benefit (CR+PR+SD ≥6 months)			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
Baseline prognostic factors	Unadjusted odds ratio (95% CI)	*p* value	Adjusted odds ratio (95% CI)	*p* value	Unadjusted odds ratio (95% CI)	*p* value	Adjusted odds ratio (95% CI)	*p* value
Histology								
Nonmetaplastic TNBC	1		1		1		1	
MpBC	3.0 (0.4–25.2)	.317	2.1 (0.1–38.4)	.625	7.2 (0.9–58.8)	.066	6.2 (0.4–91.9)	.182
Age at enrollment[a]	1.1 (0.6–2.0)	.778	1.3 (0.5–3.5)	.592	1.4 (0.8–2.3)	.213	1.7 (0.7–4.0)	.200
Race								
White	1		1		1		1	
Nonwhite	0.6 (0.1–5.3)	.648	2.1 (0.1–30.2)	.589	1.2 (0.3–5.2)	.824	2.6 (0.4–17.5)	.316
Prior systemic therapy for metastatic disease								
No	1		1		1		1	
Yes	0.5 (0.1–1.6)	.230	1.0 (0.2–5.0)	.993	0.3 (0.1–0.8)	**.019**	0.4 (0.1–1.8)	.260
Prior anthracycline								
No	1		1		1		1	
Yes	0.8 (0.2–3.4)	.778	0.3 (0.04–2.2)	.224	0.7 (0.2–2.1)	.469	0.4 (0.1–2.2)	.315
Prior mTOR inhibitor								
No	1		1		1		1	
Yes	1.0 (0.1–9.6)	.987	0.7 (0.03–13.9)	.795	1.2 (0.2–6.9)	.859	1.0 (0.1–18.9)	.986
ECOG performance status	0.1 (0.01–0.3)	**.0002**	0.03 (0.004–0.2)	**.0006**	0.1 (0.02–0.3)	**.0001**	0.02 (0.003–0.2)	**.0003**
Study regimen								
DAT	1		1		1		1	
DAE	1.1 (0.3–4.1)	.882	1.0 (0.2–5.5)	.996	0.8 (0.2–2.3)	.610	0.4 (0.1–1.9)	.238

Values in bold indicate statistically significant results, defined as $p < 0.02$.
[a]Per 10-year increase in age.
Abbreviations: CI, confidence interval; CR, complete response; DAE, liposomal doxorubicin, bevacizumab, everolimus; DAT, liposomal doxorubicin, bevacizumab, temsirolimus; ECOG, Eastern Cooperative Oncology Group; mTOR, mammalian target of rapamycin; MpBC, metaplastic breast cancer; PR, partial response; SD, stable disease; TNBC, triple-negative breast cancer.

7% (95% CI, 0.2–34%; Table 3). Ten patients with MpBC had SD lasting more than 6 months as their best response, and therefore the CBR in patients with MpBC was 36% (95% CI, 24–49%; Table 3). However, this difference did not reach statistical significance using both univariable (OR, 7.2; 95% CI, 0.9–58.8; $p = .066$; Table 4) and multivariable logistic regression (OR, 6.2; 95% CI, 0.4–91.9; $p = .182$; Table 4). On univariable logistic regression, prior systemic therapy for metastatic disease (OR, 0.3; 95% CI, 0.1–0.8; $p = .019$; Table 4) and worse performance status (OR, 0.1; 95% CI, 0.02–0.3; $p = .0001$, Table 4) were associated with a lower likelihood of clinical benefit. On multivariable analysis, only poorer performance status retained its statistical significance (OR, 0.02; 95% CI, 0.003–0.2; $p = .0003$; Table 4).

The median follow-up for all patients was 29.0 months (interquartile range, 21.3–51.6 months). The estimated median PFS of the patients with nonmetaplastic TNBC and the patients with MpBC was 2.5 months (95% CI, 1.0–4.2 months) and 4.8 months (95% CI, 3.0–6.9 months), respectively (Fig. 1A). On univariable analysis, MpBC (HR, 0.4; 95% CI, 0.2–0.8; $p = .006$; Table 5) was associated with improved PFS, whereas prior bevacizumab therapy (HR, 3.1; 95% CI, 1.5–6.5; $p = .002$; Table 5) and worse performance status (HR, 3.4; 95% CI, 2.0–6.1; $p < .0001$) were associated with worse PFS. On multivariable analysis, only worse performance status retained its statistical significance (aHR, 4.4; 95% CI, 2.3–8.2; $p < .00001$; Table 5).

The estimated median OS of the patients with nonmetaplastic TNBC and the patients with MpBC was 3.7 months (95% CI, 1.5–6.7 months) and 10.0 months (95% CI, 6.9–12.0 months), respectively (Fig. 1B). On univariable analysis, MpBC was associated with improved OS (HR, 0.3; 95% CI, 0.2–0.6; $p = .0003$; Table 6), whereas prior systemic therapy for metastatic disease (HR, 2.2; 95% CI, 1.3–3.8; $p = .005$; Table 6) and worse performance status (HR, 4.9; 95% CI, 2.5–9.7; $p < .00001$; Table 6) were associated with worse OS. On multivariable analysis, MpBC (aHR, 0.1; 95% CI, 0.03–0.3; $p < .0001$; Table 6), nonwhite ethnicity (aHR, 0.2; 95% CI, 0.1–0.5; $p = .0006$; Table 6), and prior taxane therapy (aHR, 0.3; 95% CI, 0.1–0.7; $p = .006$; Table 6) were associated with improved OS, whereas prior systemic therapy for metastatic disease (aHR, 2.2; 95% CI, 1.1–4.4; $p = .019$; Table 6), prior anthracycline therapy (aHR, 2.6; 95% CI, 1.2–5.6; $p = .020$; Table 6), and worse performance status (aHR, 7.4; 95% CI, 3.6–15.2; $p < .0000001$; Table 6) were associated with worse OS.

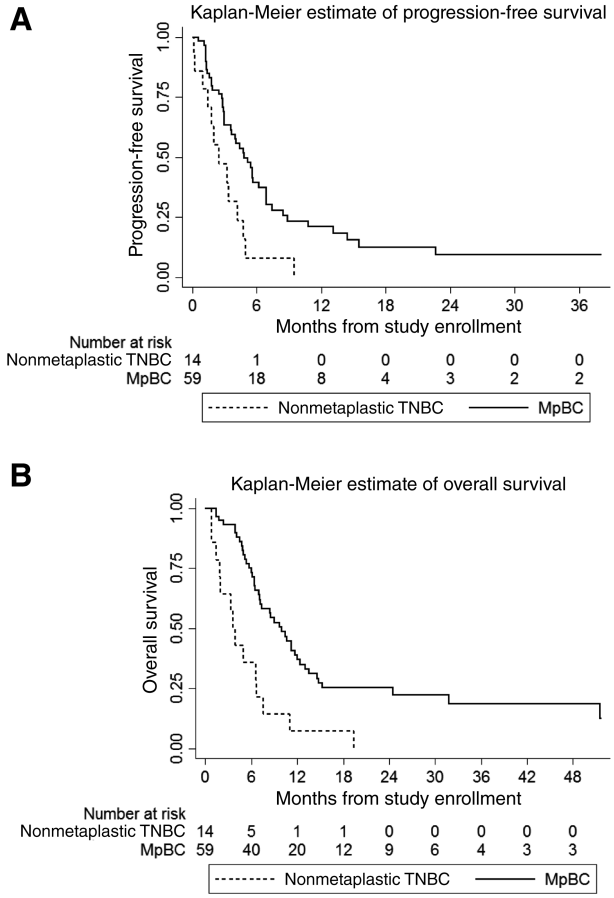

Figure 1. Compared with patients with MpBC, patients with nonmetaplastic TNBC had a shorter progression-free survival (PFS) and overall survival (OS). Kaplan-Meier plots of PFS **(A)** and OS **(B)** are shown, stratified by histologic subtype. Compared with patients with MpBC (n = 59, solid lines) treated with the combination of mTOR inhibition, liposomal doxorubicin and bevacizumab, patients with nonmetaplastic TNBC (n = 14, dashed lines) treated with the same regimen had a poorer PFS (p = .006) and OS (p = .0003) on univariable analysis. On multivariable analysis, the difference in OS between the two groups of patients remained statistically significant (p < .0001), whereas the difference in PFS was no longer statistically significant (p = .087).
Abbreviations: MpBC, metaplastic breast cancer; TNBC, triple-negative breast cancer.

Discussion

Although modern molecular profiling has identified subtypes of TNBC with different targetable molecular aberrations [22], there are limited data demonstrating that subtyping TNBC will improve clinical outcomes. Additionally, the simultaneous activation of multiple signaling pathways in a tumor may explain low clinical response rates when single-agent targeted therapeutic strategies are employed, and combining multiple agents may help overcome this therapeutic barrier.

In our study, patients with advanced MpBC treated with the combination of liposomal doxorubicin, bevacizumab, and mTOR inhibition had better OS compared with patients with nonmetaplastic or "unselected" TNBC patients treated with the same regimen on both univariable and multivariable analysis. On univariable analysis, patients with MpBC also had better PFS compared with patients with nonmetaplastic TNBC. However, the difference in PFS between the two groups was not statistically significant on multivariable analysis. In addition, although our data suggested that patients with MpBC had better ORR and CBR rates compared with patients with nonmetaplastic TNBC, these differences were not statistically significant on both univariable and multivariable analyses. Furthermore, the trend towards lower ORR and CBR in patients with nonmetaplastic TNBC compared with patients with MpBC could potentially be explained by differences in baseline characteristics between the two groups, including higher rates of prior systemic therapy in the metastatic setting and prior bevacizumab use in the 14 patients with nonmetaplastic TNBC.

Several reasons could potentially explain the better OS outcomes observed in patients with MpBC. First, MpBC could be inherently more sensitive to mTOR inhibition because of hyper-activation of PI3K/Akt/mTOR pathway components [11]. Notably, MpBCs have gene expression profiles resembling those of cancer stem cells (CSCs), in which increased activity of the PI3K pathway features prominently [11, 17, 23–27]. Additionally, preclinical data have suggested that breast CSC survival and tumorigenesis can be inhibited by administration of rapamycin [17, 26, 27]. Furthermore, MpBCs are commonly associated with *PI3KCA* mutations and loss of PTEN [11], which could also account for increased sensitivity to mTOR inhibitors. Second, the use of bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, in this novel combination could explain in part its higher efficacy in MpBCs, which are characterized by increased levels of angiogenesis and expression of VEGF as well as hypoxia-inducible factor 1 (HIF-1) [24, 25]. Additionally, in vitro studies have shown that inhibition of mTOR leads to decreased levels of HIF-1 and VEGF [28–31], which could potentially enhance the efficacy of bevacizumab when used in combination with mTOR inhibition. However, it is important to note that bevacizumab has not been shown to be more effective in patients with increased levels of angiogenesis markers, and our inferences regarding the utility of bevacizumab in MpBC remain hypothesis generating.

It could also be argued that factors other than appropriate selection of targeted therapy influenced patient outcomes in this study. Although survival data for MpBC are limited because of its rarity, this subtype of breast cancer has been associated with worse survival compared with TNBC [32] or cancers with ductal or lobular histologies [33], suggesting that the MpBC is, in general, more aggressive than nonmetaplastic TNBC, making it highly unlikely that the better PFS and OS observed in the MpBC cohort is the result of a more indolent biology in MpBC. Additionally, it is notable that prior bevacizumab use was significantly higher in the nonmetaplastic TNBC cohort and associated with poorer PFS on univariable analysis. Because bevacizumab was one of the three drugs used in this study, the development of compensatory pathways and resistance in patients previously treated with bevacizumab [34] could arguably be the cause of poorer survival outcomes in nonmetaplastic TNBC. However, prior bevacizumab use was

Table 5. Effect of baseline prognostic factors on progression-free survival

	Progression-free survival			
	Univariable analysis		Multivariable analysis	
Baseline prognostic factors	**HR (95% CI)**	***p* value**	**aHR (95% CI)**	***p* value**
Histology				
Nonmetaplastic TNBC	1		1	
MpBC	0.4 (0.2–0.8)	**.006**	0.4 (0.1–1.2)	.087
Age at enrollment[a]	0.9 (0.7–1.2)	.45	1.0 (0.7–1.4)	.888
Race				
White	1		1	
Nonwhite	0.8 (0.4–1.9)	.644	0.4 (0.1–1.0)	.054
Prior systemic therapy for metastatic disease				
No	1		1	
Yes	1.5 (0.9–2.5)	.149	1.1 (0.6–2.0)	.862
Prior anthracycline				
No	1		1	
Yes	1.3 (0.7–2.5)	.425	1.8 (0.8–3.7)	.143
Prior taxane				
No	1		1	
Yes	0.8 (0.4–1.7)	.626	0.6 (0.3–1.4)	.231
Prior bevacizumab				
No	1		1	
Yes	3.1 (1.5–6.5)	**.002**	1.2 (0.4–4.0)	.705
Prior mTOR inhibitor				
No	1		1	
Yes	1.7 (0.7–3.9)	.252	2.0 (0.8–5.0)	.131
ECOG performance status	3.4 (2.0–6.1)	**<.0001**	4.4 (2.3–8.2)	**<.00001**
Study regimen				
DAT	1		1	
DAE	0.7 (0.4–1.3)	.3	0.8 (0.4–1.5)	.458

Values in bold indicate statistically significant results, defined as $p < 0.02$.
[a]Per 10-year increase in age.
Abbreviations: aHR, adjusted HR; CI, confidence interval; DAE, liposomal doxorubicin, bevacizumab, everolimus; DAT, liposomal doxorubicin, bevacizumab, temsirolimus; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mTOR, mammalian target of rapamycin; MpBC, metaplastic breast cancer; TNBC, triple-negative breast cancer.

neither an independent predictor of PFS on multivariable analysis nor significantly associated with OS outcomes, consistent with most published trials in which the addition of bevacizumab to standard chemotherapy has not been shown to impact OS in breast cancer [35–37].

Although multivariable logistic regression did not reveal any statistically significant differences in Eastern Cooperative Oncology Group (ECOG) performance status or the use of prior systemic therapy in the metastatic setting between the MpBC and nonmetaplastic TNBC cohorts, poorer ECOG performance status and the use of prior systemic therapy in the metastatic setting independently predicted worse OS on multivariable analysis. In addition, poorer ECOG performance status was also an independent predictor of worse PFS on multivariable analysis. These findings are consistent with prior publications, suggesting that the patients studied displayed similar patterns of survival seen in advanced breast cancer. As previously published, the ECOG performance status predicts the efficacy of systemic therapy, as patients with poorer functional status are less likely to adhere to therapy and more likely to require dose interruptions or reductions while on therapy [38–41]. The observed association between prior systemic therapy for metastatic disease and poorer outcomes is also consistent with other studies evaluating systemic therapy in metastatic breast cancer [42–44] and is thought to be due to development of increasing resistance from sequential exposure to cytotoxic agents [45]. In support of this, a pooled analysis of four prospective trials of liposomal doxorubicin in patients with metastatic breast cancer found that patients who were less heavily pretreated had a higher CBR on univariable analysis but not on multivariable analysis [44], consistent with the findings from our study.

In this study, prior anthracycline use was found to be an independent predictor of poorer OS on multivariable analysis. We hypothesize that this finding is a reflection of anthracycline resistance and reduced efficacy of liposomal doxorubicin in this patient population. Interestingly, prior

Table 6. Effect of baseline prognostic factors on overall survival

	Overall survival			
	Univariable analysis		Multivariable analysis	
Baseline prognostic factors	**HR (95% CI)**	***p* value**	**aHR (95% CI)**	***p* value**
Histology				
Nonmetaplastic TNBC	1		1	
MpBC	0.3 (0.2–0.6)	**.0003**	0.1 (0.03–0.3)	**<.0001**
Age at enrollment[a]	1.0 (0.8–1.3)	.964	1.1 (0.8–1.6)	.564
Race				
White	1		1	
Nonwhite	0.6 (0.3–1.4)	.238	0.2 (0.1–0.5)	**.0006**
Prior systemic therapy for metastatic disease				
No	1		1	
Yes	2.2 (1.3–3.8)	**.005**	2.2 (1.1–4.4)	**.019**
Prior anthracycline				
No	1		1	
Yes	1.1 (0.6–2.2)	.69	2.6 (1.2–5.6)	**.020**
Prior taxane				
No	1		1	
Yes	0.7 (0.4–1.5)	.383	0.3 (0.1–0.7)	**.006**
Prior bevacizumab				
No	1		1	
Yes	2.0 (1.0–3.9)	.055	0.4 (0.1–1.1)	.064
Prior mTOR inhibitor				
No	1		1	
Yes	1.3 (0.5–2.9)	.594	1.6 (0.7–4.1)	.289
ECOG performance status	4.9 (2.5–9.7)	**<.00001**	7.4 (3.6–15.2)	**<.0000001**
Study regimen				
DAT	1		1	
DAE	0.7 (0.4–1.2)	.211	0.8 (0.4–1.6)	.606

Values in bold indicate statistically significant results, defined as $p < 0.02$.

[a]Per 10-year increase in age.

Abbreviations: aHR, adjusted HR; CI, confidence interval; DAE, liposomal doxorubicin, bevacizumab, everolimus; DAT, liposomal doxorubicin, bevacizumab, temsirolimus; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mTOR, mammalian target of rapamycin; MpBC, metaplastic breast cancer; TNBC, triple-negative breast cancer.

taxane use and nonwhite ethnicity were independently associated with improved OS in this study on multivariable but not univariable analyses. The significance of these observations is unclear and needs to be evaluated in future studies with larger patient cohorts.

Our study has a few limitations. First, there were several differences in baseline characteristics between patients with MpBC and nonmetaplastic TNBC. However, through multivariable modeling, we adjusted for all known study covariates to account for these baseline differences, and metaplastic histology remained a statistically significant predictor of improved OS. Second, our relatively small sample size, in particular the limited number of patients with nonmetaplastic TNBC in this study, may have restricted our ability to detect statistically significant differences in ORR or CBR. In addition, the observation that metaplastic histology was predictive of improved PFS on univariable but not multivariable analysis could also be due to our limited sample size. Third, the lack of a contemporary control group of patients with MpBC treated with alternative regimens limited our ability to draw conclusions on the relative benefit of this regimen in MpBC. Fourth, as all patients were treated with the combination of DAT or DAE, it was not possible to determine the relative contribution of each agent to efficacy in this study. However, to the best of our knowledge, our study is the largest series of patients with MpBC and nonmetaplastic TNBC treated with a targeted therapy regimen. Furthermore, despite the small sample size, we observed a statistically significant difference in OS between patients with MpBC and those with nonmetaplastic TNBC, which is intriguing, considering the aggressive clinical course and shortened OS associated with advanced MpBC.

Conclusion

The underlying molecular heterogeneity of TNBC has in part limited the success of targeted therapies [22], and

although small numbers limit the strength of inferences that can be drawn from this comparison, our results suggest that metaplastic histology is associated with improved OS as compared with "unselected" TNBC in patients with advanced disease receiving mTOR-based systemic therapy regimens. Additionally, in the absence of data from prospective randomized trials in MpBC, our results are among the best reported for patients with advanced MpBC. Because metaplastic histology has been associated with distinct mesenchymal molecular signatures [11], these interesting observations support the concept of molecular subtyping in TNBC for the purposes of clinical trial design. However, the utility of molecular subtyping needs to be confirmed in larger, prospective studies before becoming standard of care for patient management. The overlap and similarities between MpBC and the mesenchymal subtypes of TNBC also support testing agents targeting the PI3K/Akt/mTOR pathway in clinical trials for these subtypes of TNBC.

Acknowledgments

The authors acknowledge the support of the Triple-Negative Breast Cancer Foundation and the Conquer Cancer Foundation of the American Society of Clinical Oncology (to R.K.B), the Allison and Brian Grove Fellowship for Breast Medical Oncology (to C.Y.), the Susan Papizan Dolan Fellowship in Breast Oncology (to C.Y.), and the numerous private donors who contribute to research in metaplastic and triple-negative breast cancer at The University of Texas MD Anderson Cancer Center. The authors also wish to thank John M. Stewart, M.D., for his assistance in processing archival tumor specimens for this study.

G.N.H. was the principal investigator of the BOLERO-2 trial and received research funding from Novartis for conducting the trial and honoraria for chairing the protocol steering committee.

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Disclosures

Gabriel N. Hortobagyi: Novartis (RF, H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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