Objective response of first-line chemotherapy of triple-negative breast cancer translates into survival benefit: an analysis in an independent, prospective clinical trial and a real-world setting

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This study sought to assess whether the objective response (OR, including complete response and partial response) of first-line chemotherapy can predict overall survival (OS) for patients with metastatic triple-negative breast cancer (mTNBC) in both clinical trial and a real-world setting. The survival predictable parameters were assessed in two independent cohorts, the training cohort of 236 patients as part of a phase 3 trial (CBCSG006, Trial registration number NCT0128762) and the validation cohort of 360 patients from the real-world setting. Univariable and multivariable Cox proportional hazard models were applied to explore associations with progression-free survival and OS in the training cohort and then in the validation cohort. OR (OR vs non-OR, HR, 0.438, p<0.001) together with Eastern Cooperative Oncology Group (ECOG) performance status, disease-free survival, number of metastatic organ sites and platinum-based chemotherapy used as first-line chemotherapy were observed to be independent prognostic factors for progression-free survival (PFS), and OR (OR vs non-OR, HR, 0.602, p=0.002) together with ECOG score, disease-free survival, number of metastatic organ sites and previous anthracycline and/or taxane treatment were observed to be independent predictive factors for OS in the training cohort. These predictors were confirmed in the validation cohort. For OR and non-OR group, median OS was 23.72 and 13.83 months in the training cohort (HR, 0.637, p=0.002), and 21.95 and 13.80 months in the validation cohort (HR, 0.608, p<0.001), respectively. By adding OR in the OS predictors, the concordance index (C-index) improved from 0.622 to 0.645 in the training cohort and 0.653 to 0.675 in the validation cohort. PFS and OS of mTNBC can be predicted by OR status with any regimen of first-line chemotherapy in an independent prospective clinical trial and a real-world setting. Therefore, TNBC, not like other subtypes of breast cancer, may be in need of combination chemotherapy or intense chemotherapy to achieve a high response rate for survival.

Key words: first-line chemotherapy, metastatic triple-negative breast cancer, objective response, overall survival

Triple-negative breast cancer (TNBC) is a special subtype of breast cancer with poor prognosis. It is defined as the absence of estrogen receptor (ER) and progesterone receptor (PR) as well as human epidermal growth factor receptor 2 (HER-2) amplification. TNBC comprises about 15% of all invasive breast cancers and is characterized by larger tumors, higher-grade tumors, more rapid growth of tumors, and more frequent metastasis to viscera such as lungs and brain. Patients with TNBC are not eligible to be treated with endocrine therapies or anti-HER2 targeted therapies [1]. For patients with a germline breast cancer susceptibility gene (BRCA) mutation, Olaparib monotherapy provided an option. However, the mutation rate was low, and no overall

survival (OS) prolongation was achieved [2]. Therefore, cytotoxic chemotherapy currently remains the main systemic therapy. Patients with TNBC attain pathologic complete response (pCR) rates of 30–40% in the neoadjuvant setting, which is known as a predictor for long-term survival [3]. Despite the significant impact of pCR rates on outcomes, no standard and, more importantly, effective therapy exists for this population when metastasis occurs. A vast majority of deaths occur in the first 5 years after treatment, indicating that TNBC, as a whole group, still has a poor outcome [1].

Patients with continued complete response (CR) following the first-line treatment had longer survival [4], and the longer duration of first-line chemotherapy was associated

with prolonged OS and progression-free survival (PFS) [5]. However, objective response (OR) predicting survival in metastatic triple-negative breast cancer (mTNBC) in a first-line setting has not been well studied. Therefore, a better understanding of the relationship between response and survival in this setting is urgently required.

This study investigated the clinical characteristics of patients in both clinical trial and a real-world setting with the intention to determine the OR (including CR and PR) in the risk prognostication of OS for patients with metastatic TNBC (mTNBC) receiving first-line chemotherapy. The results might provide a strategy for choosing combination chemotherapy or sequential single-agent chemotherapy in the first-line treatment of mTNBC.

Patients and methods

Patient selection. The risk prognostic parameters were assessed in two independent cohorts of patients with mTNBC receiving first-line chemotherapy. The training cohort was derived from the randomized CBCSG006 trial in Fudan University Shanghai Cancer Center, recruiting 236 patients between January 2011 and November 2013. The flow chart was described as previously and its primary results had already been published [6]. The outcome data of the original CBCSG006 trial were updated in this study. The validation cohort was from a breast cancer population of 360 patients with mTNBC recruited between April 2005 and November 2013 in the real-world setting. All data were collected from electronic patient records and hospital charts. The flow chart of the validation cohort was shown in Figure 1. The study procedures were approved by the institutional ethical board of the Fudan University Shanghai Cancer Center. The eligible patients were ≥18 years old, had TNBC histologically confirmed as the primary tumor, and had clinical, imaging, histological, or cytological evidence of metastatic disease. Patients were classified as TNBC based on their surgical or biopsy results. ER and PR were considered negative if less than 1% of tumor cells exhibited nuclear staining, and HER2 negative was defined as having an immunohistochemistry (IHC) score of 0 or 1+ or fluorescence in situ hybridization (FISH) non-amplified score according to the American Society of Clinical Oncology (ASCO) guidelines [7, 8]. Patients with an incomplete receptor status or a changed status in metastatic lesions inconsistent with the aforementioned definition were excluded.

Data collection. The efficacy was analyzed according to the overall response rate (ORR), PFS, and OS. Tumor response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guidelines by computed tomography scanning or magnetic resonance imaging every two cycles or as clinically indicated [9]. The date of disease progression was determined from the clinical notes. OR was defined as CR and partial response (PR) using RECIST, version 1.1. The ORR was defined as the percentage of patients who achieved a CR and a PR using RECIST, version 1.1. PFS was defined as the time from the start of the first-line treatment until disease progression or death by any cause. OS was calculated from the start of the first-line treatment to death by any cause or the last date when the patient was
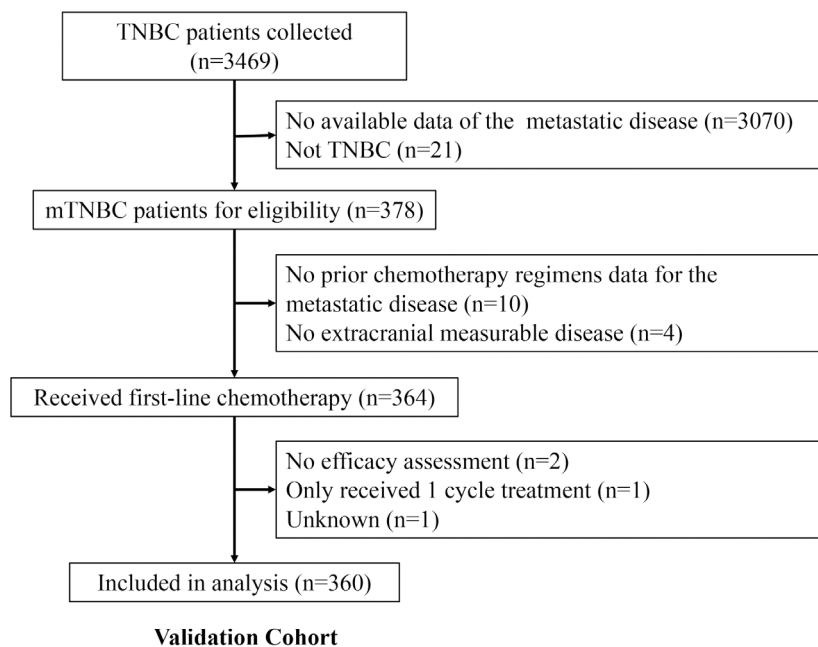

Figure 1. Flow chart of 360 enrolled patients with mTNBC. TNBC, triple-negative breast cancer; mTNBC, metastatic TNBC.

known to be alive. Potential prognostic variables, including age, Eastern Cooperative Oncology Group (ECOG) performance status, menstruation status, details about neoadjuvant and adjuvant chemotherapy, disease-free interval (DFI), number and sites of metastatic disease, and OR status, were collected at the time of diagnosis of distant metastases or the beginning of treatment.

Statistical analysis. The risk prognostic parameters were assessed in two independent cohorts. First, univariate and multivariate Cox proportional hazards models were applied to explore associations with PFS and OS in the training cohort. Then, the prognostic parameters were validated in the validation cohort. The results were analyzed using SPSS 16.0 (SPSS, IL, USA). The statistical analysis of 2×2 contingency tables of categorical variables in the two cohorts was performed using the Pearson's chi-square test. Factors with p<0.1 in the univariate analysis were examined with the Cox proportional hazards model, which defined independent predictive factors, hazard ratios (HRs), and 95% CIs. The median PFS and OS were estimated by the Kaplan-Meier method and compared using a log-rank test. All p-values were two sided, and a p-value <0.05 was considered to indicate a statistically significant difference. Additionally, the C-index (Harrell) was calculated for prognostic discrimination using the statistical software R (version 3.1.0) and the R-package rms (version 1.0.1).

Results

Patients' characteristics. The characteristics of the study participants are presented in Table 1. The training and validation cohorts comprised of 236 and 360 patients, respectively. No significant difference was found in the distribution of age, menstruation status, number of metastatic sites, and anthracyclines and taxanes in prior neoadjuvant/adjuvant chemotherapy between the two cohorts. In the training cohort, the participants had a better ECOG performance status (p=0.003) and a longer DFI (p=0.001) compared with the validation cohort. Further, more patients had visceral metastases in the training cohort (70.8% vs. 57.2%, p=0.001). The metastatic sites were well balanced between the two cohorts except for the metastatic site in the lung (56.8% vs. 44.7%, p=0.004). Fewer patients used platinum-based chemotherapy (PBCT) as first-line chemotherapy in the training cohort compared with the validation cohort (50.0% vs. 60.0%, p=0.016).

Training cohort: survival and predictors of survival. By the time of data lock, the median PFS was 6.54 months (95% CI 5.83–7.25 months) and the median OS was 18.86 months (95% CI 15.14–22.58 months), with the ORR of 56.8% (12 CR and 122 PR) for the training cohort (Figures 2A, 2B). The results of the univariate analysis are listed in Table 2. OR (p<0.001, Figure 2C) together with DFI (p=0.015), number of metastatic organ sites (p<0.001), and PBCT used as first-line chemotherapy (p=0.003, Figure 2D) were observed to be predictive factors for better PFS. OR (p=0.002, Figure 2E)

Table 1. Characteristics of study participants in the training and validation cohorts.

Characteristics	Training (n=236)		Validation (n=360)		p-value
	n	%	n	%	
Age (median, range), years	47, 26–72		49, 25–76		
<40	40	16.9	72	20.0	0.351
≥40	196	83.1	288	80.0	
Menstruation status					
Postmenopausal	117	49.6	186	51.7	0.618
Premenopausal	119	50.4	174	48.3	
ECOG performance status					
0	81	34.3	84	23.3	0.003
≥1	155	65.7	276	76.7	
Number of metastatic sites					
<3	152	64.4	253	70.3	0.133
≥3	84	35.6	107	29.7	
Metastatic sites					
Lymph nodes	144	61.0	224	62.2	0.767
Liver	60	25.4	78	21.7	0.288
Bone	56	23.7	98	27.2	0.341
Lung	134	56.8	161	44.7	0.004
Chest wall	52	22.0	100	27.8	0.116
Pleura	22	9.3	32	8.9	0.857
Brain	10	4.2	11	3.1	0.444
Contralateral breast	10	4.2	7	1.9	0.100
Visceral metastasis					
Yes	167	70.8	206	57.2	0.001
No	69	29.2	154	42.8	
Disease-free interval, month					
>12	171	72.5	205	56.9	0.001
≤12	65	27.5	155	43.1	
Prior adjuvant chemotherapy					
Anthracyclines	195	82.6	286	79.4	0.336
Taxanes	152	64.4	207	57.5	0.092
Both	139	58.9	183	50.8	0.053
PBCT used as first-line chemotherapy					
Yes	118	50.0	216	60.0	0.016
No	118	50.0	144	40.0	

Abbreviations: ECOG – Eastern Cooperative Oncology Group; PBCT – platinum-based chemotherapy

together with DFI (p<0.001) and number of metastatic organ sites (p<0.001) were observed to be predictive factors for better OS. For OR and non-OR groups, the median OS was 23.72 and 13.83 months in 134 and 102 patients, respectively (HR, 0.637, p=0.002, Figure 2E). No difference was found in the OS between the PBCT and non-PBCT groups (Figure 2F).

All significant factors in the univariate analysis were included in the multivariate analysis based on Cox regression. OR (OR vs. non-OR, HR, 0.438, 95% CI 0.324–0.592, p<0.001) together with the ECOG performance status (p=0.001), DFI (p=0.023), number of metastatic organ
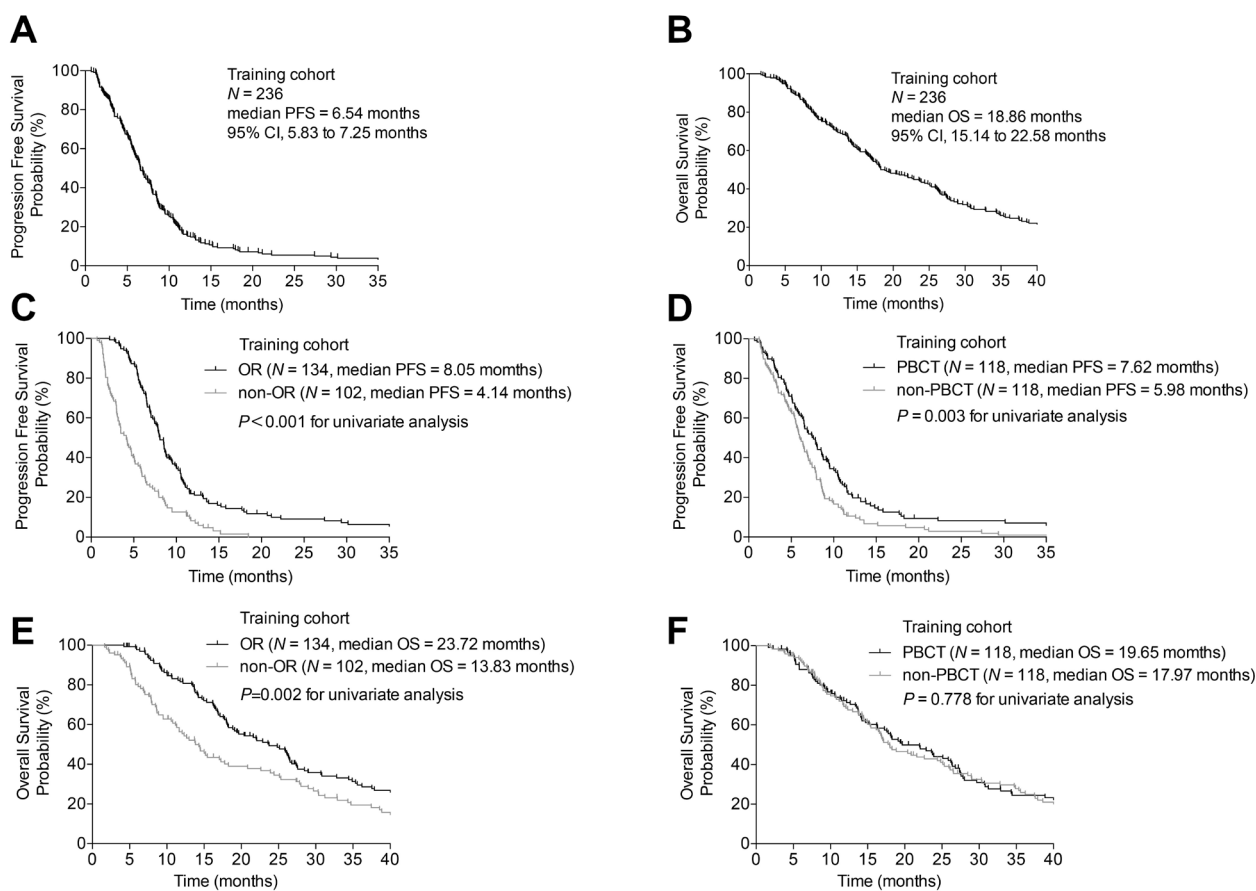
Figure 2. Survival and predictors of survival in the training cohort: Kaplan–Meier plot of PFS (A) and OS (B) for all patients; Kaplan–Meier plot of PFS (C) and OS (E) in patients with OR versus non-OR; Kaplan–Meier plot of PFS (D) and OS (F) in patients with PBCT versus non-PBCT.

sites (p<0.001), and PBCT used as first-line chemotherapy (p=0.004) remained independent prognostic factors for PFS. OR (OR vs. non-OR, HR, 0.602, 95% CI 0.440–0.824, p=0.002) together with ECOG (p=0.029), DFI (p<0.001), number of metastatic organ sites (p<0.001), and previous treatment (anthracycline and/or taxane) (p=0.022) remained independent prognostic factors for OS (Table 3). The predictive accuracy and discriminative ability were measured using the concordance index (C-index). By adding OR in the OS predictors, including age, menstruation status, ECOG status, DFI, number of metastatic sites, visceral metastasis, PBCT, and previous treatment (anthracycline and/or taxane), the C-index improved from 0.622 to 0.645 in the training cohort.

Validation cohort: survival and predictors of survival. By the time of data lock, the median PFS was 6.54 months (95% CI 5.80–7.28 months) and the median OS was 17.05 months (95% CI 15.23–18.87 months), with the ORR of 47.8% (23 CR and 149 PR) for the validation cohort (Figures 3A, 3B). The parameters estimated from the training cohort were verified in the independent valida-

tion cohort. The results of univariate analyses are listed in Table 2. In the univariate analyses, longer PFS was observed in patients with ECOG performance status for 0 (p=0.005), DFI ≥12 (p=0.012), number of metastatic organ sites <3 (p<0.001), OR (p<0.001, Figure 3C), and PBCT used as first-line chemotherapy (p<0.001, Figure 3D). Longer OS was observed in patients with postmenopausal status (p=0.026), DFI (p<0.001), number of metastatic organ sites <3 (p<0.001), no visceral metastasis (p=0.036), and OR (p<0.001, Figure 3E). For the OR and non-OR groups, the median OS was 21.95 and 13.80 months in 172 and 188 patients, respectively (HR, 0.608, p<0.001, Figure 3E). The results were consistent with those from the training cohort. No difference in OS was observed between the PBCT and non-PBCT groups (Figure 3F).

A Cox proportional hazards model was used to determine the independent predictive factors of the aforementioned variables of survival for patients with mTNBC in the first-line setting. OR (OR vs. non-OR, HR, 0.448, 95% CI 0.353–0.568, p<0.001) together with ECOG score (p=0.024), DFI (p=0.021), number of metastatic organ sites (p=0.002),

Table 2. Univariate analyses results of study participants in the training and validation cohorts.

	Univariate analysis results of PFS					
Variables	**Training (n=236)**			**Validation (n=360)**		
	Hazard ratio	**95% CI**	**p-value**	**Hazard ratio**	**95% CI**	**p-value**
Age, years						
<40	1.528	0.757–1.528	0.683	1.089	0.833–1.424	0.533
≥40	Reference			Reference		
ECOG						
0	0.793	0.599–1.050	0.106	0.685	0.526–0.893	0.005
≥1	Reference			Reference		
Menopausal status						
Premenopausal	1.223	0.936–1.598	0.140	1.199	0.968–1.486	0.097
Postmenopausal	Reference			Reference		
DFI						
<12	1.515	1.084–2.119	0.015	1.339	1.066–1.683	0.012
≥12	Reference			Reference		
Number of metastatic sites						
<3	0.517	0.390–0.686	<0.001	0.614	0.484–0.779	<0.001
≥3	Reference			Reference		
Visceral metastasis						
No	0.820	0.608–1.105	0.191	0.805	0.647–1.002	0.053
Yes	Reference			Reference		
Anthracycline and/or taxane						
No	1.030	0.785–1.351	0.833	0.977	0.715–1.335	0.884
Yes	Reference			Reference		
PBCT used as first-line chemotherapy						
No	1.498	1.145–1.959	0.003	1.544	1.240–1.921	<0.001
Yes	Reference			Reference		
Objective response status						
OR	0.406	0.308–0.535	<0.001	0.447	0.360–0.555	<0.001
Non-OR	Reference			Reference		
	Univariate analysis results of OS					
Variables	**Training (n = 236)**			**Validation (n = 360)**		
	Hazard ratio	**95% CI**	**p–value**	**Hazard ratio**	**95% CI**	**p–value**
Age, years						
<40	0.929	0.625–1.381	0.715	1.087	0.823–1.434	0.558
≥40	Reference			Reference		
ECOG						
0	0.922	0.684–1.244	0.596	0.874	0.674–1.132	0.307
≥1	Reference			Reference		
Menopausal status						
Premenopausal	1.231	0.924–1.640	0.156	1.284	1.031–1.600	0.026
Postmenopausal	Reference			Reference		
DFI						
<12	1.950	1.365–2.785	<0.001	1.836	1.449–2.326	<0.001
≥12	Reference			Reference		
Number of metastatic organ site						
<3	0.466	0.345–0.630	<0.001	0.495	0.390–0.628	<0.001
≥3	Reference			Reference		
Visceral metastasis						
No	0.743	0.536–1.030	0.074	0.787	0.630–0.984	0.036
Yes	Reference			Reference		
Anthracycline and/or taxane						
No	0.830	0.617–1.118	0.220	0.751	0.540–1.043	0.087
Yes	Reference			Reference		
PBCT used as first-line chemotherapy						
No	1.042	0.782–1.387	0.778	0.906	0.723–1.134	0.387
Yes	Reference			Reference		
Objective response status						
OR	0.637	0.477–0.851	0.002	0.608	0.488–0.759	<0.001
Non-OR	Reference			Reference		

Abbreviations: DFI – disease-free interval; ECOG – Eastern Cooperative Oncology Group; HR – hazard ratio; MBC – metastatic breast cancer; OR – objective response; OS – overall survival; PBCT – platinum-based chemotherapy; PFS – progression-free survival
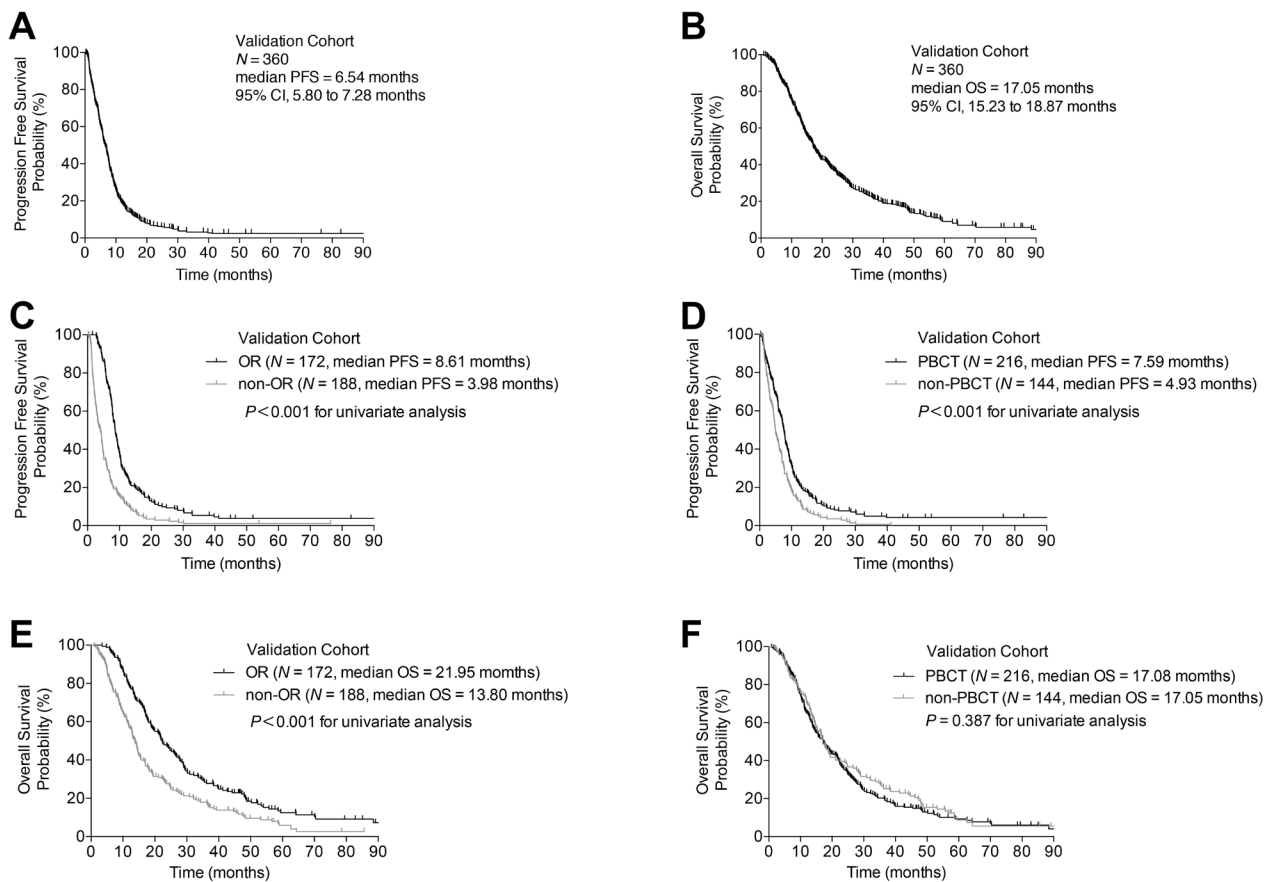
Figure 3. Survival and predictors of survival in the validation cohort: Kaplan–Meier plot of PFS (A) and OS (B) for all patients; Kaplan–Meier plot of PFS (C) and OS (E) in patients with OR versus non-OR; Kaplan–Meier plot of PFS (D) and OS (F) in patients with PBCT versus non-PBCT.

menopausal status (p=0.010), and PBCT used as first-line chemotherapy (p=0.008) were observed to be independent predictive factors for PFS. OR (OR vs. non-OR, HR, 0.561, 95% CI 0.440–0.715, p<0.001) together with DFI (p<0.001), number of metastatic organ sites (p<0.001), and previous treatment (anthracycline and/or taxanes; p=0.027) were observed to be independent predictive factors for OS. The C-index improved from 0.653 to 0.675 by adding OR in the OS predictors, including age, menstruation status, ECOG status, DFI, number of metastatic sites, visceral metastasis, PBCT, and previous treatment (anthracycline and/or taxane).

Discussion

TNBC is aggressive breast cancer with poor prognosis. No benefit from endocrine therapy or trastuzumab and the lack of a preferred standard form of chemotherapy has made the treatment of patients with TNBC more difficult, especially when recurrence or metastasis occurs [10, 11]. Improvement in survival becomes a critical issue. The present study revealed

that the first-line OR status with any regimen could predict the PFS and OS of patients with mTNBC in an independent prospective clinical trial and a real-world setting.

pCR was proposed as a surrogate for survival in early TNBC. Compared with other subtypes of breast cancer, patients with TNBC showed high pCR with neoadjuvant treatment, but those who did not achieve pCR had a six-to-nine times higher risk for relapse [3, 12]. Recently, increasing pCR in TNBC has been a major focus. Adding either carboplatin or bevacizumab to neoadjuvant chemotherapy increased pCR rates in patients with stage II–III TNBC [13, 14]. Although patients with pCR had improved survival, especially in aggressive tumor subtypes, such as TNBC, the validation of pCR as a surrogate endpoint for improved event-free survival and OS was not proved [15, 16]. In renewed data, the GeparSixto study reported that the addition of carboplatin to a neoadjuvant regimen significantly increased not only the proportion of patients achieving pCR, but also the DFI [17].

The combination chemotherapy showed a statistically significant advantage for survival compared with the sequen-

Table 3. Cox regression results of study participants in the training and validation cohorts.

	Cox regression results of PFS					
Variables	**Training (n=236)**			**Validation (n=360)**		
	Hazard ratio	**95% CI**	**p-value**	**Hazard ratio**	**95% CI**	**p-value**
Age, years						
<40	0.989	0.651–1.503	0.960	1.033	0.747–1.430	0.843
≥40	Reference			Reference		
ECOG						
0	0.594	0.433–0.815	0.001	0.721	0.543–0.958	0.024
≥1	Reference			Reference		
DFI						
<12	1.520	1.060–2.179	0.023	1.319	1.043–1.669	0.021
≥12	Reference			Reference		
Number of metastatic sites						
<3	0.508	0.369–0.699	<0.001	0.651	0.497–0.854	0.002
≥3	Reference			Reference		
Visceral metastasis						
No	1.082	0.764–1.532	0.657	0.880	0.690–1.122	0.302
Yes	Reference			Reference		
Anthracycline and/or taxane						
No	0.749	0.547–1.026	0.072	0.992	0.637–1.547	0.973
Yes	Reference			Reference		
Menopausal status						
Premenopausal	1.185	0.854–1.645	0.310	1.434	1.089–1.899	0.010
Postmenopausal	Reference			Reference		
PBCT used as first-line chemotherapy						
No	1.532	1.142–2.056	0.004	1.391	1.092–1.773	0.008
Yes	Reference			Reference		
Objective response status						
OR	0.438	0.324–0.592	<0.001	0.448	0.353–0.568	<0.001
Non-OR	Reference			Reference		
	Cox regression results of OS					
Variables	**Training (n=236)**			**Validation (n=360)**		
	Hazard ratio	**95% CI**	**p-value**	**Hazard ratio**	**95% CI**	**p-value**
Age, years						
<40	0.718	0.455–1.132	0.154	0.864	0.618–1.207	0.390
≥40	Reference			Reference		
ECOG						
0	0.695	0.501–0.964	0.029	0.931	0.707–1.226	0.612
≥1	Reference			Reference		
DFI						
<12	2.126	1.445–3.128	<0.001	1.888	1.477–2.413	<0.001
≥12	Reference			Reference		
Number of metastatic sites						
<3	0.439	0.311–0.620	<0.001	0.497	0.376–0.656	<0.001
≥3	Reference			Reference		
Visceral metastasis						
No	0.962	0.666–1.390	0.836	0.907	0.703–1.169	0.449
Yes	Reference			Reference		
Anthracycline and/or taxane						
No	0.684	0.495–0.946	0.022	0.581	0.360–0.939	0.027
Yes	Reference			Reference		
Menopausal status						
Premenopausal	1.123	0.794–1.588	0.510	1.305	0.99–1.726	0.058
Postmenopausal	Reference			Reference		
PBCT used as first-line chemotherapy						
No	0.968	0.710–1.320	0.839	0.816	0.637–1.046	0.108
Yes	Reference			Reference		
Objective response status						
OR	0.602	0.440–0.824	0.002	0.561	0.440–0.715	<0.001
Non-OR	Reference			Reference		

Abbreviations: DFI – disease-free interval; ECOG – Eastern Cooperative Oncology Group; HR – hazard ratio; MBC – metastatic breast cancer; OR – objective response; OS – overall survival; PBCT – platinum-based chemotherapy; PFS – progression-free survival

tial single-agent chemotherapy because of its high response rate [18], but it also produced more toxicity. In the metastatic breast cancer settings, the achievement of an OR to chemotherapy was associated with a true survival benefit [19, 20]. However, the results differed [21] and made the clinical practice difficult. No clinical trial or literature to date has demonstrated that the OR of first-line chemotherapy in mTNBC could predict the OS. The results of the present study showed that the OR was an independent prognostic factor for not only PFS but also OS. Although the first-line chemotherapy differed, the OR was still associated with greatly improved survival, confirming the validity of the OR to different treatment modalities. The OS surprisingly improved with almost 8–10 months in both the training cohort (OR vs non-OR, 23.72 vs 13.83 months, HR, 0.637, p=0.002) and the validation cohort (OR vs non-OR, 21.95 vs 13.80 months, HR, 0.608, p<0.001). This improvement indicated that TNBC, not like other subtypes of breast cancer, might be in need of combination chemotherapy or intense chemotherapy to achieve a high response rate for survival.

TNBC may harbor a dysfunctional BRCA pathway and thus may be sensitive to agents such as platinum that selectively target cells deficient in homologous recombination DNA repair [22, 23]. The present study showed that PBCT used as first-line chemotherapy was an independent prognostic factor for PFS, but not for OS, which was in accordance with the data from the prospective phase III trial CBCSG006 [6] and the retrospective study by Zhang et al. in the Center [24]. TNBC is a heterogeneous disease divided into six intrinsic molecular subtypes: two basal-like subtypes (BL1 and BL2) sensitive to cisplatin, an immunomodulatory (IM) subtype, a mesenchymal (M) subtype, a mesenchymal stem-like subtype, and a luminal androgen receptor subtype [25]. The unselected mTNBC treated with platinum may lead to clinical heterogeneity. Furthermore, the second-line or subsequent line treatment in the present study differed, and some patients might have crossed over to platinum-based chemotherapy when the disease progressed in first-line chemotherapy. All these reasons might have narrowed down the differences in OS between the two groups.

This study had limitations due to its retrospective nature and treatment selection biases as follows. The validation cohort included only one institution, and some of the baseline information in the two cohorts was different. The comparison of survival by OR might also be biased because patients needed to live long enough to see a response to the treatment. Patients who died earlier before they had had a chance to respond to the treatment might be classified as non-responders and had an impact upon the survival estimates. A long-term observation might narrow the bias gap.

In summary, the present study comprehensively investigated the predictive value of OR in the first-line setting of mTNBC patients. It provided evidence that patients who achieved their best response of CR or PR in any first-line treatment would have prolonged survival. Therefore, it was assumed that in clinical practice, maximum tumor shrinkage and combination chemotherapy or intense chemotherapy in the first-line treatment should be considered for this aggressive subtype of breast cancer, which might help improve patients' prognosis and prolong their survival.

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