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CLINICAL TRIAL

Impact of clinical trial on survival outcomes

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Abstract The number of patients with breast cancer who participate in therapeutic clinical trials remains low. One reason is a lack of opportunity; another is health care providers who do not recommend trials because they fear poorer outcome from the use of new drugs. Thus, we compared survival outcome in patients with metastatic breast cancer (MBC) who participated in first-line therapeutic clinical trials with outcome in patients who had never enrolled in a clinical trial and received only standard care. We hypothesized that first-line therapeutic clinical trials does not have a negative survival outcome. We reviewed the records of patients with MBC who were treated at MD Anderson Cancer Center between January 2000, and December 2010. The medical records of 5501 patients with MBC were screened, and 652 patients—285 in the trial arm and 367 in the control arm—met our specific eligible criteria. The median follow-up of our cohort was 7.16 years (95 % confidence interval [CI] 6.53–7.64 years). Among the global population, no significant differences in progression-free survival (PFS) or overall survival (OS) were observed between the treatment arms: for the clinical trial cohort, median PFS was 7 months (95 % CI 5.72–8.71 months), and median OS was 28.48 months (95 % CI 22.70–34.60 months). For the control cohort, median PFS was 10.02 months (95 % CI 7.13–11.99 months), and median OS was 28.71 months (95 % CI 24.41–31.31 months) ($P = .089$ and .335, respectively). Enrollment in first-line MBC therapeutic clinical trials does not result in less favorable survival outcome than that in MBC patients who never enrolled in a clinical trial.

Keywords Breast neoplasms · Clinical trial · Survival · Disease-free survival · Overall survival · Triple-negative breast cancer

Introduction

Developing clinical trials and enrolling patients are critical to improve standard care and understand the biology of cancer. However, participation in clinical trials remains low, even in breast cancer trial [1, 2].

There are several reasons for the current low rate of patients' participation in clinical trials: Lack of *awareness*, defined as a lack of education regarding clinical trials and inappropriate knowledge about cancer, is a barrier for enrollment. The lack of *opportunity* to participate due to geographical location, socioeconomic status, ethnic status, and/or health insurance status is a second barrier. Once patients are advised and eligible to participate in a protocol, *mistrust* in clinical research remains the last barrier [3, 4].

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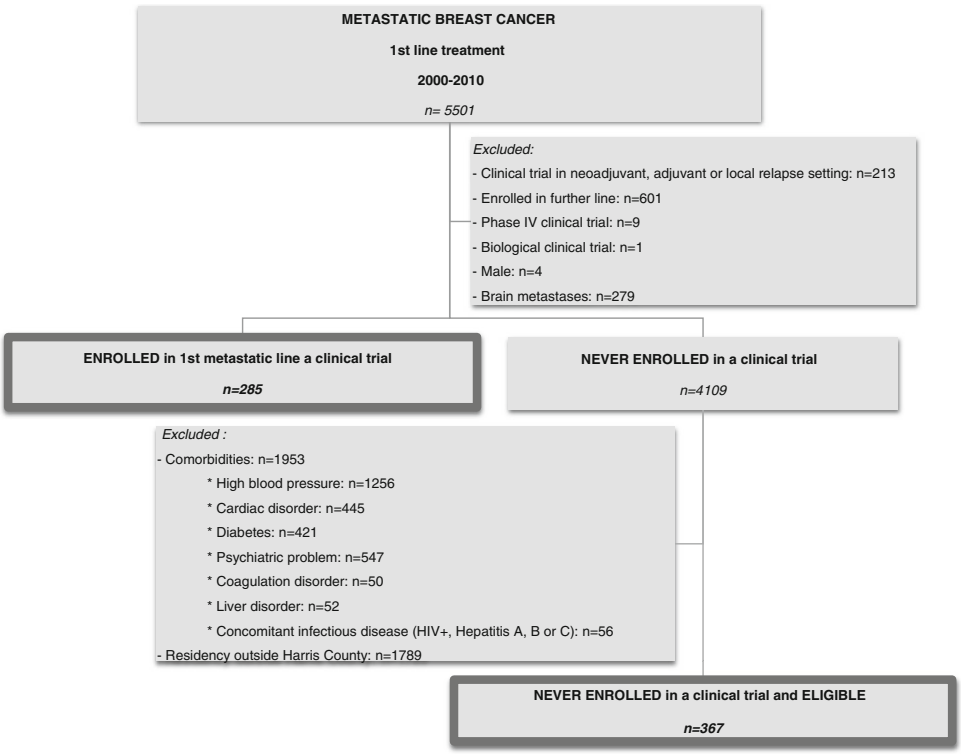


Fig. 1 Patient flow diagram

Even if the ethical committee ensures that there is no lack of opportunity for each patient enrolled, a few studies have evaluated the impact of enrollment on outcome in clinical trials. Only a few high-quality studies support the widespread belief that cancer trial participation can lead to improved outcomes (trial effect), as demonstrated in the Peppercorn et al. [5] review. Such a trial effect could be due to an *experimental treatment effect* (e.g., trastuzumab), a *protocol effect* (the way the treatments are delivered), a *care effect* (incidental aspects of care), a *Hawthorne effect* (awareness of being under observation), or a *placebo effect*. Such discrepancy could also be biased by *confounding* in baseline characteristics as trial participants must have good performance status and are often a subset of patients with favorable prognosis [5]. For example, the recently submitted first US population-based study predicted lower overall and cancer-specific mortality for cancer patients enrolled in clinical trial, but it likely reflected the favorable characteristics of patients who were enrolled in clinical trials [1].

In patients with breast cancer, data regarding the impact of participation in clinical trials are still limited. In early-stage breast cancer, enrollment in clinical trials was shown to improve survival in a univariate analysis but not after adjustment of prognosis markers (e.g., tumor size, node status, estrogen receptor, endocrine therapy) [6]. A retrospective descriptive analysis on locally advanced and metastatic breast cancer from MD Anderson Cancer Center revealed an overall survival (OS) of 6.7 months for patients enrolled in a phase I trial, without comparison to a control arm [7]. To date, no comparative data on outcome have been published on metastatic breast cancer (MBC). This study compared survival outcomes in two MBC populations: patients enrolled versus patients never enrolled in a clinical trial. With this regard, whether participation in clinical trials may affect negative or positive is still not known. Some patients are concerned about negative impact of clinical trials on survival outcomes, and revealing the impact may accelerate the enrollment in clinical trials.

Based on results obtained for other neoplasms [8], *we hypothesized that survival outcomes in patients with MBC who participated in first-line therapeutic clinical trials would not be poorer than the outcome in patients who had never enrolled in a clinical trial and received standard care*. The primary objective is to compare survival outcomes of patients who were treated in clinical trials in their first-line treatment for metastatic disease and with those of patients who has never been on clinical trials. The long-term goal of this study was to provide an objective argument to help alleviate patients' mistrust in clinical research.

Table 1 Baseline demographic and clinical characteristics

		Protocol		*P* value
		No 367	Yes 285	
Age at first distant mets	Median (q1, q3)	50 (42, 59)	51 (43, 61)	0.3103
Race				
Asian	29 (4.4 %)	24 (6.5 %)	5 (1.8 %)	*<.0001**
Black	122 (18.7 %)	81 (22.1 %)	41 (14.4 %)	
Hispanic	101 (15.5 %)	68 (18.5 %)	33 (11.6 %)	
Other	10 (1.5 %)	8 (2.2 %)	2 (0.7 %)	
White	399 (59.8 %)	186 (50.7 %)	204 (71.6 %)	
ER				
Negative	259 (44 %)	129 (39.9 %)	130 (49.1 %)	*.0267*
Positive	329 (56 %)	194 (60.1 %)	135 (50.9 %)	
Missing	64	44	20	
PR				
Negative	325 (56.7 %)	166 (53.2 %)	159 (60.9%)	*.0634*
Positive	248 (43.3 %)	146 (46.8 %)	102 (39.1 %)	
Missing	79	55	24	
HER2				
Negative	368 (74 %)	205 (75.6 %)	163 (72.1 %)	.3725
Positive	129 (26%)	66 (24.4 %)	63 (27.9 %)	
Missing	155	96	59	
Neoadjuvant chemotherapy				
No	507 (77.8 %)	282 (76.8 %)	225 (78.9 %)	.5208
Yes	145 (22.2 %)	85 (23.2 %)	60 (21.1 %)	
Adjuvant chemotherapy				
No	379 (58.1 %)	238 (64.9 %)	141 (49.5 %)	*.0001*
Yes	273 (41.9 %)	129 (35.1 %)	144 (50.5 %)	
Radiation				
No	383 (58.7 %)	215 (58.6 %)	168 (58.9 %)	.9253
Yes	269 (41.3 %)	152 (41.4 %)	117 (41.1 %)	
Previous chemotherapy regimen				
Anthracycline	129 (35.8 %)	61 (33 %)	68 (38.9 %)	.2720
Anthracycline-Taxane	179 (49.7%)	98 (53 %)	81 (46.3 %)	
Others	35 (9.7 %)	15 (8.1 %)	20 (11.4 %)	
Taxanes	17 (4.7 %)	11 (5.9 %)	6 (3.4 %)	
Missing	298	182	116	
The number of metastatic organs				
1	377 (58 %)	223 (61.1 %)	154 (54 %)	.0703
>1	273 (42 %)	142 (38.9 %)	131 (46 %)	
Missing	2	2	0	
Bone metastasis				
No	320 (49.1 %)	162 (44.1 %)	158 (55.4 %)	*.0042*
Yes	332 (50.9 %)	205 (55.9 %)	127 (44.6 %)	
Lung metastasis				
No	456 (69.9 %)	278 (75.7 %)	178 (62.5 %)	*.0002*
Yes	196 (30.1 %)	89 (24.3 %)	107 (37.5 %)	

Table 1 continued

		Protocol		*P* value
		No 367	Yes 285	
Liver metastasis				
No	474 (72.7 %)	281 (76.6 %)	193 (67.7 %)	*.0119*
Yes	178 (27.3 %)	86 (23.4 %)	92 (32.3 %)	
Distant lymph nodes				
No	459 (70.4 %)	277 (75.5 %)	182 (63.9 %)	*.0013*
Yes	193 (29.6 %)	90 (24.5 %)	103 (36.1 %)	
Bone marrow metastasis				
No	638 (97.9 %)	356 (97 %)	282 (98.9 %)	.1067
Yes	14 (2.1 %)	11 (3 %)	3 (1.1 %)	
Spinal cord or meninges metastasis				
No	648 (99.4 %)	364 (99.2 %)	284 (99.6 %)	.6357
Yes	4 (0.6 %)	3 (0.8 %)	1 (0.4 %)	
Pleura or pericardium metastasis				
No	576 (88.3 %)	321 (87.5 %)	255 (89.5 %)	.4281
Yes	76 (11.7 %)	46 (12.5 %)	30 (10.5 %)	
Skin metastasis				
No	614 (94.2 %)	351 (95.6 %)	263 (92.3 %)	.0693
Yes	38 (5.8 %)	16 (4.4 %)	22 (7.7 %)	
Intra-abdominal metastasis				
No	613 (94 %)	344 (93.7 %)	269 (94.4 %)	.7273
Yes	39 (6 %)	23 (6.3 %)	16 (5.6 %)	
Kidney or adrenal metastasis				
No	638 (97.9 %)	357 (97.3 %)	281 (98.6 %)	.2879
Yes	14 (2.1 %)	10 (2.7 %)	4 (1.4 %)	
Rare metastasis				
No	648 (99.4 %)	364 (99.2 %)	284 (99.6 %)	.6357
Yes	4 (0.6 %)	3 (0.8 %)	1 (0.4 %)	

* *P* value comparing among Asian, Black, Hispanic, and White only

Methods

Patients

The Institutional Review Board of The University of Texas MD Anderson Cancer Center approved this study (PA13-0779) and waived the requirement for informed consent. We used MD Anderson's electronic health record system and the database of the Breast Medical Oncology Department to address research questions. We conducted a retrospective analysis of the medical records of all patients with MBC who had undergone treatment at MD Anderson between January 1, 2000 and December 31, 2010, for at least their first line of systemic treatment.

We extracted two cohorts from these MBC patients. The first cohort included patients who were enrolled in a therapeutic clinical trial for the first time for first-line MBC systemic treatments. Patients enrolled in further lines (second line and later) were excluded. The second cohort, referred to as the *control population*, included patient who did not participate in a clinical trial at any stage of their disease.

To limit confounding factors in baseline characteristics, we excluded male patients and patients with known brain metastasis from two cohorts. These exclusion criteria consisted of the usual exclusion criteria on MBC clinical trials.

To obtain an eligible control cohort, patients with the following criteria were excluded from the control population: patients with comorbidities defined as high blood pressure, diabetes, psychiatric problem, coagulation disorder, liver disorder, cardiac disorder (including congestive heart failure and coronary artery disease), and concomitant infectious disease [human immunodeficiency virus (HIV); hepatitis A, B, or C]. In addition, to reduce a bias linked to socioeconomic factors, we limited the control cohort to

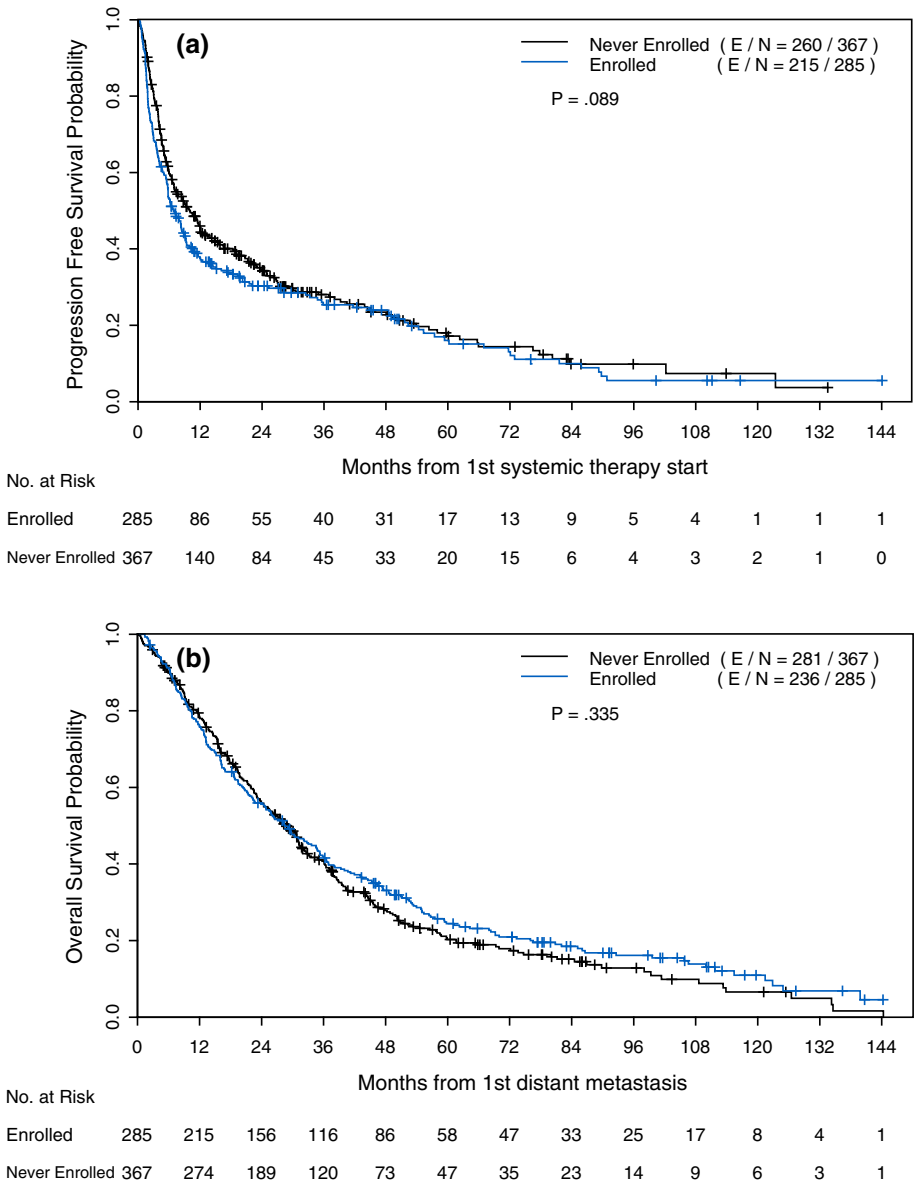


Fig. 2 Kaplan–Meier plots for progression-free survival (**a**) and overall survival (**b**) in global population. Curves: *blue*, clinical trial cohort; *black*, control cohort. The number of patients at risk is provided below each part of the figures

patients living in the Harris County (where MD Anderson is located) who would be eligible for a clinical trial at MD Anderson and could benefit from the MD Anderson financial assistance program support.

Study design and end points

Our objective is to compare the long-term outcome between clinical trial participants and non-participants.

Our primary end point is *overall survival,* defined as the interval between the time of metastatic diagnosis and the date of death.

Our secondary end point is *progression-free survival* (PFS), defined as the interval between the time of first systemic treatment and the date of progressive disease or death. Lost to follow-up is considered as censoring.

Statistical analysis

We summarized descriptive statistics such as median and interquartile range for age at first distant metastasis, frequency, and percentage for categorical variables such as patients' demographic and clinic-pathological characteristics. The Wilcoxon rank-sum test and χ^2-test or Fisher exact test, when appropriate, are used to determine the difference in age and categorical variables, respectively, by status of clinical trial participation. Kaplan–Meier survival analyses, including the log-rank test, and Cox regression analysis are used to assess the effect of categorical and continuous covariates on time-to-event variables (PFS and OS), respectively. The multicovariate Cox model is used to assess the impact on PFS and OS of being treated by protocol, adjusting for other important

Table 2 Multi-covariate survival analysis on progression-free survival (**a**) and overall survival (**b**) in the overall population

Covariate for PFS	Level	Hazard ratio (95% CI)	*P* value
A			
Hormone receptor	Positive vs. negative	0.715 (0.559–0.916)	0.0079
HER2	Positive vs. negative	0.479 (0.365–0.628)	<.0001
Nuclear grade	I vs. III	0.784 (0.343–1.793)	0.0277
	II vs. III	0.704 (0.544–0.911)	
Neoadjuvant chemotherapy	Yes vs. no	1.699 (1.339–2.155)	<.0001
Adjuvant chemotherapy	Yes vs. no	1.391 (1.104–1.753)	0.0052
Number of metastatic organs	>1 vs. 1	1.493 (1.202–1.853)	0.0003
Protocol	Yes vs. no	1.145 (0.915–1.432)	*0.2363*
B			
Race	Asian vs. Black	0.936 (0.543–1.615)	0.0045
	Hispanic vs. Black	0.687 (0.489–0.964)	
	White vs. Black	0.633 (0.489–0.821)	
Hormone receptor	Positive vs. negative	0.425 (0.34–0.531)	<.0001
HER2	Positive vs. negative	0.465 (0.36–0.601)	<.0001
Neoadjuvant chemotherapy	Yes vs. no	1.926 (1.537–2.415)	<.0001
Adjuvant chemotherapy	Yes vs. no	1.331 (1.074–1.649)	0.0089
Number of metastatic organs	>1 vs. 1	1.85 (1.507–2.27)	<.0001
Protocol	Yes vs. no	0.894 (0.724–1.105)	*0.30*

covariates. Adjustments in multicovariate model are selected either due to clinical reasons or based on univariate analysis results with significance level of .1, and remain significant in the multicovariate model with significance level of .05.

All computations were carried out in SAS 9.3 (SAS Institute Inc., Cary, NC, USA) and Splus 8.2 (TIBCO Software Inc, Palo Alto, CA).

Results

Patient demographics

The medical records of 5501 patients with MBC, who were treated at MD Anderson between January 1, 2000 and December 31, 2010, were screened. Based on our exclusion criteria, we excluded 213 patients due to their participation in clinical trials in a neoadjuvant, adjuvant, or local relapse setting; 601 patients due to their participation in a clinical trial in a metastatic setting other than first line; 10 patients due to participation in a phase IV clinical trial or a biological non-therapeutic clinical trial; 4 males; and 279 patients with known brain metastasis. In the control population, 1953 patients were excluded due to comorbidities, and 1789 patients were excluded due to where they lived. Thus, we finally selected 652 patients: 285 for the trial arm and 367 for the control arm (Fig. 1).

Discrepancies between two arms are observed for race (minorities were less represented in the clinical trial arm as previously reported) [2, 9, 10], estrogen receptor (ER) status (more ER-positive patients participated in clinical trials compared to ER-negative patients), and site of metastatic disease (fewer patients with bone metastasis participated in clinical trials, on the other hand, more patients with either lung, liver, or distant lymph node metastasis participated in clinical trials). In addition, patients enrolled in a clinical trial in a metastatic setting more frequently received adjuvant chemotherapy than did patients not enrolled (Table 1).

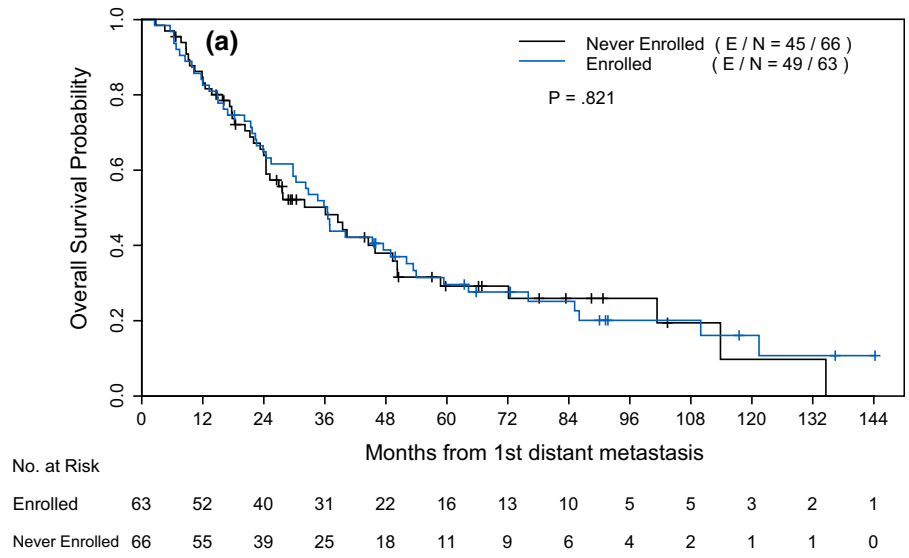
Progression-free survival

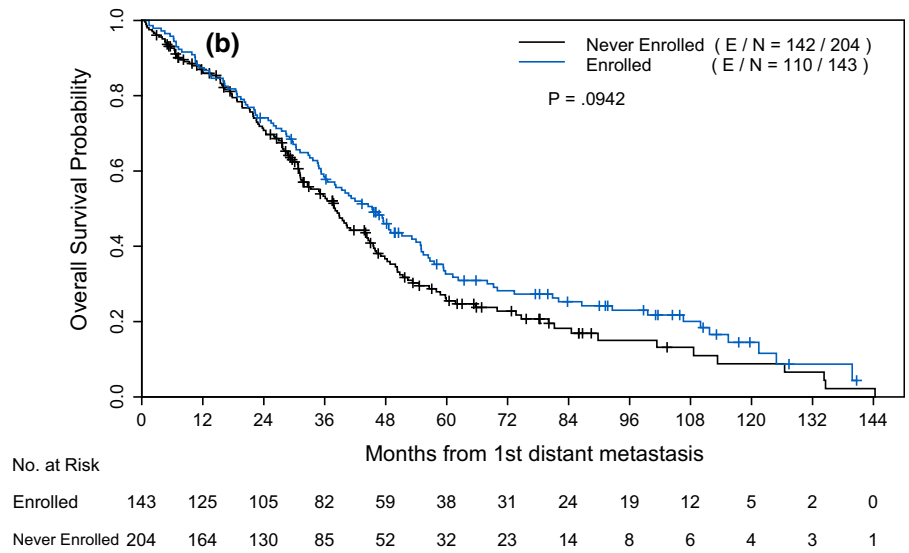
In Kaplan–Meier survival estimates, there is no significant difference of PFS rate between the clinical trial cohort (median PFS, 7 months; 95 % confidence interval [CI] 5.72–8.71 months) and the control cohort (median PFS, 10.02 months; 95 % CI 7.13–11.99 months) ($P = .089$) (Fig. 2a).

In multicovariate cox progression hazard models, being treated on protocol is not a significant prognostic factor of PFS (HR 1.145, 95 % CI .915–1.432, $P = .236$) after adjusting for hormone receptor status, HER2 status, nuclear grade, neoadjuvant and adjuvant chemotherapy, and number of metastatic organs (Table 2a).

Overall survival

The median follow-up time for the entire cohort was 7.16 years (95 % CI 6.53–7.64 years). A total of 236 deaths were observed in the clinical trial cohort and 281





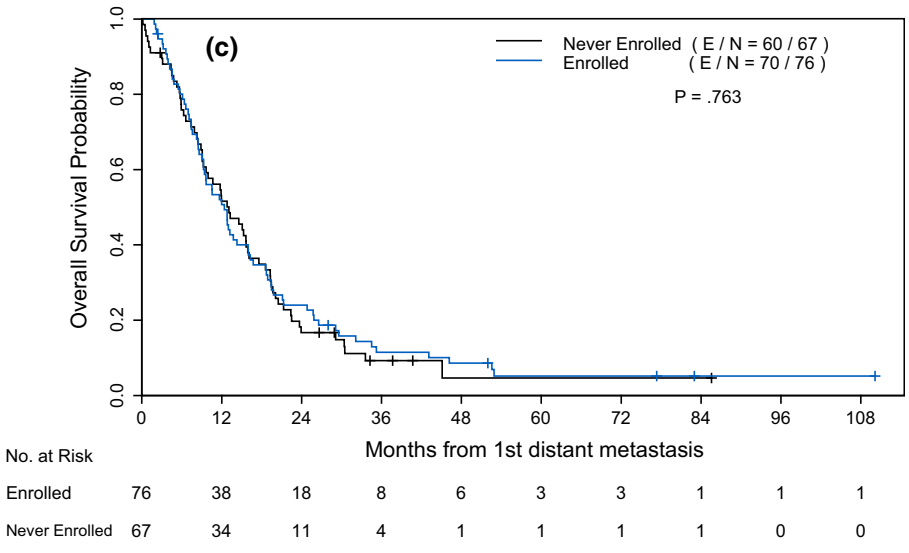


Fig. 3 Kaplan–Meier plots for overall survival in breast cancer subgroups: **a** HER2-positive BC; **b** ER-positive BC; **c** triple-negative BC. *Curves*: *blue*, clinical trial cohort; *black*, control cohort. The number of patients at risk is provided below each part of the figures

deaths in the control cohort. OS is not significantly different between the clinical trial cohort (median OS, 28.48 months; 95 % CI 22.70–34.60 months) and the control cohort (median OS, 28.71 months; 95 % CI 24.41–31.31 months) ($P = .335$) (Fig. 2b).

Being treated on protocol is not a significant prognostic factor of OS (HR .894, 95 % CI .724–1.105, $P = .300$) after adjusting for race, hormone receptor status, HER2 status, neoadjuvant and adjuvant chemotherapy, and number of metastatic organs (Table 2b).

Survival analysis for each subtype

In the HER2-positive cohort, OS does not differ between clinical and control arms (36.5 vs. 36.1 months; $P = .821$). The same results are observed for the ER-positive population (45.3 vs. 38.1 months; $P = .095$) and the TNBC cohort (12.4 vs. 13.1 months; $P = .763$) (Fig. 3a–c).

Discussion

The major challenge in this study was to separate true from false trial effects by identifying an appropriate comparison group. The best way to answer our question was first to direct a prospective randomized controlled study in which patients would be offered a clinical trial, but such a study could raise ethical issue. Moreover, the "not enrolled" patient arm would be finally enrolled in a clinical trial that could lead to major bias.

Thus, our final option was to *retrospectively* compare a group of trial participants with a group of non-trial patients. This study design may have had limitations including difficulty in controlling for baseline imbalances between groups and the possibility of inside bias. Our design was strengthened by a systematic method for identifying appropriate controls to those who would have met eligibility criteria and by careful adjustment for potential confounders, previously reported in some retrospective analyses (e.g., comorbid conditions, problems with transportation, health insurance) [11–14]. In a meta-analysis, published in 2004, a few studies controlled adequately for covariates (performance status, socioeconomic status) and only a few restricted the controlled arm to patients who meet eligible criteria [5].

All clinical trials do not have the same impact on OS. For example, from 2000 to 2010, some HER2-positive patients were enrolled in a trastuzumab protocol that substantially modified their prognosis, and, of course, could have biased our study. We also do know that impact of phase III clinical trial is better and phase I clinical trial may be more tough.

Conclusions

To better understand the reasons for the low participation of MBC patients in clinical trials, researchers of the BRIDGE survey studied the relationship between MBC patients, clinicians, and clinical studies. Of 950 MBC patients from more than 9 countries who were analyzed, 78 % did not participate in a clinical trial. The top two reasons for non-participation were that the patients were not invited to participate (56 %) or the health care provider did not recommend enrollment (30 %). On the contrary, among those patients who did participate, encouragement from the clinician was a key factor in driving their participation [15].

Another prospective study of more than 208 patients who were undecided after they received an invitation to participate in a clinical trial suggested that additional interventions and strategies are needed to increase participation. Physician recommendation was also demonstrated as an important factor related to participation [16]. Another prospective study of African American patients, often underrepresented in clinical trials, found that few patients received positive recommendations from their health care provider about joining a clinical trial, and most of the patients refused as a result of fears of additional adverse effects. Many patients and patients' families misunderstood the clinical trial information, and as a consequence, family members typically recommend against trial enrollment [17]. Physicians' influence and the quality of their information are the most important factors influencing patient enrollment.

In conclusion, our study should reassure the health care provider in showing that enrollment in a clinical trial of first-line therapeutic clinical trials of metastatic disease is not a matter of chance for MBC patients. This result is in accordance with those observed in the adjuvant setting [18]. The long-term goal of this study was to provide an objective argument to help alleviate patients' and advocates' mistrust in clinical research [4, 10].

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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