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Evolving options for the treatment of metastatic breast cancer: Progression-free survival as an endpoint

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Abstract

Because of its direct clinical relevance, overall survival is the gold standard endpoint for measuring clinical efficacy. However, achieving improvements in overall survival can be confounded by factors such as crossover to active treatment arms and subsequent treatment with non-experimental active therapies. Powering studies to detect significant overall survival increases requires prohibitively large patient numbers and long follow-up and may not always be practical. Trials incorporating progression free survival (PFS) or time to progression (TTP) as primary outcome measures are likely to be shorter, require fewer patients and are usually more affordable, which may ultimately translate into a more rapid evaluation of potentially effective experimental therapies. In heavily pretreated metastatic breast cancer, significant improvements in progression-free survival may indicate a clinically meaningful benefit for patients with otherwise limited salvage therapy options available. Approval for several newer agents in the advanced resistant or refractory metastatic breast cancer setting has been based on prolonged progression-free survival or time to progression as primary trial endpoints. In this paper, clinical trial data relating to OS, PFS and TTP endpoints are reviewed and the use of surrogate markers of survival for the evaluation of new drugs is considered.

Keywords

Overall survival; Progression-free survival; Metastatic breast cancer; Treatment options

Introduction

Overall survival (OS) remains the gold standard measure of clinical efficacy when evaluating experimental chemotherapy regimens for cancer.[1] The advantage of OS is that it is of direct clinical relevance to the patient. Furthermore, OS is an objective endpoint, whereas other endpoints such as response rate and progression free survival may be influenced by methods of evaluation and the drug schedules used, and may be biased by the knowledge of therapy.[2]

This review discusses the use of OS as a primary endpoint, particularly in the metastatic setting, and considers PFS as an alternative endpoint. PFS, TTP and OS data from recent,

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large, randomized trials of novel single agent or combination regimens for the treatment of patients with MBC are compared.

Obstacles to the interpretation of OS

A number of challenges exist in achieving an accurate assessment of survival in the randomized clinical trial setting. As the median survival for metastatic breast cancer is relatively long, patients who do not respond to one therapy are often well enough to go onto another regimen. Thus, at the time of disease progression, study participants with advanced breast cancer are able to switch to another active non-experimental treatment after coming off study. These subsequent treatments, which are not controlled by the study, may confound the interpretation of differences in OS between treatment arms.[2]

When a study drug shows promising efficacy in early phase studies, the randomized phase III clinical trial will sometimes allow patients in the control arm to crossover to the study drug arm at the time of disease progression. While this makes enrollment in the study more attractive to patients and allows more patients to have access to a potentially active new agent, it also blurs the ability to interpret survival data as this crossover may improve the rate of OS observed in the control arm. Despite this, some would argue that it is not ethically responsible to deny trial participants access to potentially effective experimental drugs in order to improve chances of detecting significant differences in OS. The Intergroup E1193 study demonstrated that a combination of doxorubicin plus paclitaxel as the first-line therapy did not improve survival compared to sequential single-agent therapy. As approximately 50% of patients receiving single-agent doxorubicin or paclitaxel were crossed over to the other agent at the time of progression, this study highlights the potential impact of crossover on survival.[3] By contrast, some notable studies have demonstrated an OS benefit in spite of substantial crossover. This was the case in the phase III pivotal study evaluating trastuzumab for HER2-overexpressing metastatic breast cancer. In this study, two-thirds of patients crossed over from the chemotherapy arm to receive trastuzumab and yet a substantial improvement in survival was observed. More recently, a phase II randomized trial evaluating the use of chemotherapy with or without a poly(ADP-ribose) polymerase-1 (PARP1) inhibitor for triple negative metastatic breast cancer was reported and showed a significant improvement in survival associated with the PARP-inhibitor.[4] It should be noted however that this study was not powered to detect a difference in overall survival. With only 116 patients randomized in this study, chance alone could have led to the observation of OS benefit.

Another factor that may be considered a disadvantage of OS is the inclusion of non-cancer deaths which could, by chance, skew the findings of the study., Furthermore, in contrast to PFS, trials aimed at detecting a difference in survival often require prohibitively large patient numbers and long follow up to be powered adequately.[2] In fact, the majority of trials in the metastatic setting have sample sizes which are too small to detect differences in survival.

Surrogate endpoints for survival: PFS and TTP

Given these challenges, investigators in oncology have begun to evaluate alternative clinical trial endpoints that better reflect the small gains that contribute positively to the quality of life of patients with previously treated MBC. PFS and TTP have become common primary endpoints in clinical trials, and the US Food and Drug Administration (FDA) has accepted both as surrogate endpoints for accelerated approval in cancer trials. PFS is defined as the time from randomization until objective tumor progression or death. It is a direct measure of the effect of treatment on the tumor burden process, and is sensitive to both cytostatic and cytotoxic intervention mechanisms.[5] TTP is defined as the time from randomization until

objective tumor progression, not including death. Because PFS incorporates death it is better able to detect important harmful drug effects than TTP. TTP censors death events and thus can introduce substantial bias to the analysis.[5] Measurement of PFS and TTP are also vulnerable to assessment bias in unblinded trials as the determination of progression has a subjective component. This may result in a trial reporting that a new treatment has an improved PFS when in fact the investigators were slower to declare disease progression in patients who were on the study drug arm.[6] This may also be the case in double-blinded studies if adverse events effectively unblind the physician. For this reason, PFS endpoints should be validated by independent review committees. Clinical trials incorporating PFS or TTP as primary outcome measures are likely to be shorter, need fewer patients, and therefore be more affordable. More rapid evaluation of experimental therapies can expedite access to effective new agents for which there is an unmet need. In addition, PFS and TTP endpoints are generally not affected by factors such as treatment crossover or subsequent therapies and include measurement of stable disease. While PFS and TTP have several advantages compared to OS, their utility relies upon frequent radiologic assessments, balanced timing of assessments between treatment arms and consistent definitions to characterize these endpoints across clinical trials.[7]

Clinical TTP/PFS and survival data in MBC: a review of the literature

Chemotherapy trials showing TTP and OS benefit

A small number of randomized phase III clinical trials were able to demonstrate significant improvements in both TTP and OS in MBC (Table 1A).[8-13] These have included trials of taxanes as single agents or in combination with anthracyclines, gemcitabine, or capecitabine.

A head-to-head comparison of q3 weekly single agent docetaxel (100 mg/m^2) vs. paclitaxel (175 mg/m^2) in patients with MBC whose disease had progressed after anthracycline therapy ($N = 449$) showed that docetaxel improved TTP (5.7 vs. 3.6 months, $P < 0.0001$) and OS (15.4 vs. 12.7 months, $P = 0.03$) compared with paclitaxel.[8] No crossover was allowed; however, taxanes were administered as salvage therapy in 33% of patients randomly assigned to docetaxel (20% received paclitaxel and 13% were retreated with docetaxel) and 36% of patients treated with paclitaxel (19% received docetaxel and 17% were retreated with paclitaxel).

The benefit of a combining taxanes with doxorubicin compared with a standard fluorouracil, doxorubicin, and cyclophosphamide (FAC) regimen was investigated in two randomized studies. In a phase II to III study in first-line MBC ($N = 216$), a combination of docetaxel plus doxorubicin resulted in a significantly longer TTP and OS than FAC (TTP: 8.0 vs. 6.6 months, $P = 0.004$; and OS: 22.6 vs. 16.2 months, $P = 0.019$).[9] No crossover was prespecified; however, post-study taxane therapy was administered to 23% of patients treated with docetaxel plus doxorubicin and 67% of patients treated with FAC. A phase III trial compared the efficacy of a combination of paclitaxel and doxorubicin with FAC, also as first-line therapy, for women with MBC ($N = 267$).[10] The benefit of paclitaxel plus doxorubicin vs. FAC with regards to TTP (8.1 vs. 6.2 months, $P = 0.036$) and OS (23.0 vs. 18.3 months, $P = 0.005$) was recently confirmed in a long-term analysis of this study.[11] No crossover was planned; however, post-study taxane therapy was administered to 2% of patients treated with paclitaxel plus doxorubicin and 24% of patients treated with FAC. These results may reflect the large impact of taxanes on breast cancer outcomes. When an agent has considerable efficacy in a number of patients, survival benefit is readily observed.[14]

Both capecitabine and gemcitabine are approved in combination with taxanes in anthracycline-pretreated MBC. Capecitabine is also approved as monotherapy or in

combination with ixabepilone for the treatment of patients with MBC resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen. Approvals of the gemcitabine–taxane and capecitabine–taxane combinations were based upon results from two phase III studies in which these regimens prolonged both TTP and OS over single-agent taxanes. Capecitabine in combination with docetaxel significantly prolonged TTP (6.1 vs. 4.2 months, $P = 0.0001$) and OS (14.5 vs. 11.5 months, $P = 0.0126$) relative to docetaxel alone in anthracycline-pretreated patients with advanced breast cancer ($N = 511$).[12] Poststudy docetaxel was administered more frequently in the capecitabine–docetaxel arm (20%) than in the docetaxel monotherapy arm (7%). Conversely, poststudy capecitabine was more common in the single-agent group (17%) than in the combination arm (3%). Gemcitabine in combination with paclitaxel improved TTP (6.14 vs. 3.98 months, $P = 0.0002$) and OS (18.6 vs. 15.8 months, $P = 0.0489$) compared with paclitaxel alone in women with MBC and prior anthracycline treatment ($N = 529$).[13] Off-study gemcitabine was administered to 15.6% of patients in the paclitaxel arm and 4.1% of patients in the gemcitabine plus paclitaxel arm. Neither of these studies allowed crossover and only a small number of patients went onto receive study drug outside the clinical trial.

Most of the above studies showing OS benefit did not allow prior taxane therapy. Moreover, these studies tended to include patients receiving first-line treatment. In contrast, those trials showing only TTP/PFS benefit (Table 1B).[15-21] typically included patients receiving therapy in the second-line setting or beyond. (Table 1A).[8-13]

One notable exception to this is a phase III study recently reported that evaluated the use of eribulin mesylate vs. treatment of physicians' choice in anthracycline- and taxane-pretreated metastatic breast cancer (Table 1C).[22] The primary endpoint in this study that enrolled 762 patients was overall survival. The median overall survival was statistically significantly better in the eribulin arm (13.1 months for eribulin vs 10.7 months, $P = 0.04$). Interestingly, in this study PFS was not statistically significantly improved (3.7 months for eribulin vs 2.3 months, $P = 0.09$). This study differs from all others reviewed herein as it compares a single agent with a variety of different agents depending on physician's choice of treatment. The physician's choice could include any monotherapy or supportive care alone; however, no patients received supportive care alone.

Chemotherapy trials showing TTP/PFS benefit but no OS benefit

In MBC, a number of randomized trials have demonstrated significantly prolonged TTP/PFS for one arm over the other, without demonstrating significant benefits in OS. In a study of women receiving first-line chemotherapy for MBC ($N = 429$), a combination of docetaxel (75 mg/m^2) and doxorubicin (50 mg/m^2) failed to demonstrate a difference in OS compared with a combination of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2). Median TTP, however, was significantly longer with docetaxel plus doxorubicin than doxorubicin plus cyclophosphamide (37.3 vs. 31.9 weeks; $P = 0.014$).[15] Crossover was not allowed; however, 29% of patients randomized to doxorubicin and cyclophosphamide received off study docetaxel compared with 6% randomized to doxorubicin and docetaxel. These results are in contrast to the two studies described above which, in spite of substantial crossover, were able to demonstrate a survival benefit with the use of a taxane–anthracycline combination. None of these three studies were powered for OS. Moreover, in this study, the dose of doxorubicin used in the taxane arm was lower than in the control (AC) arm, which may partly explain the difference in outcomes observed among these studies.

Trials of newer agents have also failed to demonstrate OS benefits in this population. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel), a novel formulation of paclitaxel encapsulated in albumin, improved TTP (23.0 vs. 16.9 weeks, $P = 0.006$) compared with paclitaxel in patients who had not received taxanes for MBC ($N = 460$), but OS was

similar.[16] Furthermore, the long-circulating formulation of doxorubicin, pegylated liposomal doxorubicin, significantly improved TTP from 7.0 to 9.8 months in combination with docetaxel ($P = 0.000001$) compared with docetaxel monotherapy in patients with advanced breast cancer previously treated with neoadjuvant–adjuvant anthracycline therapy ($N = 751$).[17] OS, however, was again similar between the two groups. No crossover was prespecified and there was comparable use of poststudy taxanes/microtubule targeting agents (34% vs. 29%), capecitabine (33% vs. 38%), and gemcitabine (13% vs. 8%) between the two arms.

When gemcitabine was added to vinorelbine as salvage therapy for patients with MBC previously treated with anthracyclines and taxanes ($N = 252$), an improved PFS was reported for the combination arm vs. vinorelbine alone (6.0 vs. 4.0 months, $P = 0.0028$), but there was no improvement in OS.[18] In addition, ixabepilone demonstrated improved PFS in combination with capecitabine vs. capecitabine alone in two phase III trials: in women with MBC resistant to anthracyclines and taxanes ($N = 752$; 5.3 vs. 3.8 months, $P = 0.0011$) and in a confirmatory trial in heavily pretreated MBC ($N = 1221$; 6.2 vs. 4.4 months, $P = 0.0005$).[19-21] Both studies reported a numerical improvement in OS that was not statistically significant and no crossover was allowed in either study.

Despite significant improvements in TTP or PFS, these studies including patients from all molecular subclasses, did not show improvements in OS. A variety of reasons may contribute to the lack of survival benefit in these trials. The majority of trials showing TTP/PFS benefit, but no OS benefit, allowed prior taxane therapy or included patients who were resistant to taxane therapy. This may be especially relevant for agents acting via a similar mechanism to the taxanes e.g. targeting microtubules. It is important to note that only one of these trials included OS as a primary endpoint and therefore were not powered to detect differences in OS.[21]

Trials of biological agents showing improvement in PFS but not OS - bevacizumab

The targeted anti-VEGF antibody, bevacizumab, inhibits the tumor neoangiogenesis that is essential for tumor growth.[23] It has been investigated in first-line and previously treated MBC in combination with a number of different chemotherapies. With the exception of one study of bevacizumab plus capecitabine vs. capecitabine alone in pretreated MBC[24] combining bevacizumab with chemotherapy in both the first and second line setting has yielded improved PFS. No studies, however, have demonstrated an improvement in OS following bevacizumab treatment. Table 2[4,25-37] lists survival data from recent randomized trials of biological agents in advanced breast cancer.

Three studies in first-line MBC have investigated bevacizumab in combination with standard chemotherapy. Bevacizumab in combination with paclitaxel prolonged PFS compared with paclitaxel alone in predominantly (91%) HER2/neu-negative disease ($N = 722$; 11.8 vs. 5.9 months, $P < 0.001$), but did not prolong overall survival.[25] While no crossover was allowed on this study, it is unknown how many patients went onto receive off study bevacizumab following FDA approval. The AVADO study investigated the combination of bevacizumab and docetaxel as first-line therapy in patients with locally recurrent or MBC ($N = 736$).[27] A mature analysis (median follow-up of 25 months) showed that bevacizumab in combination with docetaxel significantly increased PFS (placebo: 8.1 months; bevacizumab 7.5 mg/kg: 9.0 months, $P = 0.0450$; bevacizumab 15 mg/kg: 10 months, $P = 0.0002$); however, OS was similar across treatment arms.[28] It has been suggested that use of second-line bevacizumab with chemotherapy following progression may have influenced OS. In total, 90 patients in the placebo arm received bevacizumab on progression. In the RIBBON-1 trial ($N = 1237$), PFS was significantly prolonged when bevacizumab was used first-line in combination with standard chemotherapy (capecitabine:

8.6 vs. 5.7 months, $P = 0.0002$, or a taxane [nab-paclitaxel or docetaxel] or an anthracycline: 9.2 vs. 8.0 months, $P < 0.0001$) compared with chemotherapy plus placebo in women with HER2/neu-negative MBC or locally-recurrent disease. OS data was limited (33% of events), and the increase in OS with bevacizumab was not statistically significant.[29] All patients were eligible for second-line treatment with bevacizumab on progression; 60% of patients in the placebo group and 50% of patients in the bevacizumab arm received subsequent treatment with bevacizumab. It should be underscored that none of these trials were powered for an OS endpoint. A recent exploratory metaanalysis of E2100, AVADO and RIBBON-1 confirmed that although significant improvements in PFS were seen following addition of bevacizumab to first-line chemotherapy in these trials, there was no OS benefit.[26] We can hypothesize that one reason for the lack of benefit observed in the metaanalysis of these three trials may be a result of treatments received following progression and the fact that OS was not a primary endpoint for any of these studies individually.

In patients with previously treated MBC (77% HER2/neu-negative; $N = 462$), bevacizumab in combination with capecitabine did not prolong PFS or OS compared with capecitabine alone, despite a significant increase in the response rates (19.8% vs. 9.1%, $P = 0.001$).[31] Eligible patients in this study were allowed to have received up to two lines of chemotherapy for metastatic breast cancer and no crossover was allowed. Response rates (an objective measure of tumor response to chemotherapy) do not always correlate with survival benefits, although they may indicate symptomatic relief of clinical significance. Interim results from the RIBBON-2 trial ($N = 684$), however, showed that the addition of bevacizumab to chemotherapy (which included either capecitabine, gemcitabine, vinorelbine, or a taxane [paclitaxel, nab-paclitaxel, or docetaxel]) for second-line treatment of patients with HER2/neu-negative MBC significantly improved PFS (7.2 vs. 5.1 months, $P = 0072$) compared to chemotherapy plus placebo. The increase in median overall survival in the bevacizumab group was not statistically significantly.[30] However, this analysis was performed with only 57% of events having occurred. The mature analysis of OS is pending. Crossover to bevacizumab was not allowed in this study. It is not known how many patients in the control arm went onto receive bevacizumab off study in the third-line setting.

These studies did not prospectively evaluate the utility of bevacizumab in different molecular subtypes of breast cancer. Exploratory subset analyses in E2100, AVADO and RIBBON-1/2 did show that similar PFS benefits are derived in triple-negative breast cancer and/or hormone receptor positive breast cancer (Table 1).[8-13,15-22] Unfortunately, investigators have not yet successfully determined which tumor types are most likely to respond to bevacizumab. Identifying a molecular marker to predict for response to bevacizumab would allow a more focused approach to clinical trial design and may enable the detection of a survival benefit in a select group of patients.

Bevacizumab may have a role to play in the treatment of HER2/neu-positive breast cancer. There is preclinical evidence to suggest that tumors in this subgroup are highly reliant on angiogenesis for growth and typically have a high expression of VEGF.[38,39] In addition, a combination of bevacizumab plus trastuzumab has demonstrated promise in phase I and phase II studies of HER2/neu-positive MBC[40]and is being investigated in phase III studies in the adjuvant (BETH study) and metastatic (AVEREL study) settings.

Trials of biological agents showing improvement in PFS/TTP and OS

With advances in the molecular sub-classification of breast cancer and the emergence of targeted therapies, clinical trials in MBC are becoming more focused, enrolling carefully selected patient populations.

Trastuzumab

In contrast to bevacizumab, the monoclonal HER2-targeted antibody trastuzumab was specifically developed for one particular subtype of breast cancer in which amplification of the gene encoding HER2 results in HER2 overexpression. The overexpression of HER2 has been shown to drive tumor proliferation, diminished apoptosis, and increased metastatic potential.[41] Clinically, HER2-overexpression is associated with poorer outcome including worse median survival. Fortunately, early clinical trial evaluation of trastuzumab restricted eligibility to patients whose tumors overexpressed HER2. In a phase III trial of women with MBC over-expressing HER2/neu ($N = 469$), the addition of trastuzumab to chemotherapy was associated with a longer TTP (7.4 vs. 4.6 months; $P < 0.001$) and OS (25.1 vs. 20.3 months; $P = 0.046$).[32] It should be noted that in this study over two-thirds of the patients in the control arm subsequently received trastuzumab and yet a survival difference was still observed when comparing the arms using an intent to treat analysis. This supports genuine synergy between trastuzumab and chemotherapy. Furthermore, in a randomized phase II trial of 186 patients with HER2/neu-positive MBC, trastuzumab plus docetaxel was significantly superior to docetaxel alone in terms of OS (31.2 vs. 22.7 months; $P = 0.0325$) and TTP (11.7 vs. 6.1 months; $P = 0.0001$).[33] Had this targeted biologic agent been tested in all patients regardless of HER2 expression, the survival benefit would have been difficult if not impossible to detect without drastically increasing the number of patients enrolled.

Results of a study to determine the benefit of continuing trastuzumab in patients with HER2-positive locally advanced or MBC ($N = 156$) whose disease had become resistant to trastuzumab show that the combination of trastuzumab and capecitabine is more effective than capecitabine alone in terms of TTP, but not OS (TTP: 8.2 vs. 5.6 months, $P = 0.026$ and OS: 25.5 vs. 20.4 months, $P = 0.26$).[34] The primary endpoint of the study was time to progression and no crossover was allowed on study. However, the study closed early due to poor accrual with the approval of lapatinib and it is not clear how many patients went onto receive post-trial lapatinib.

Lapatinib

Lapatinib, in combination with capecitabine, is indicated for the treatment of patients with HER2/neu-overexpressing locally advanced or MBC whose disease has progressed after receiving previous treatment with an anthracycline, a taxane, and trastuzumab. The pivotal phase III trial ($N = 399$) showed prolonged TTP (6.2 vs. 4.3 months, $P < 0.001$) with combination therapy compared with capecitabine alone, but OS was not significantly different between the treatments.[35] Following discontinuation of accrual, crossover was offered to patients receiving monotherapy.

In another phase III trial of heavily pretreated women who had progressed on prior anthracycline-, taxane-, and trastuzumab-containing therapy ($N = 296$), lapatinib plus trastuzumab significantly prolonged PFS in comparison with lapatinib alone (12.0 vs. 8.4 months, $P = 0.029$).[36] Combination therapy also significantly prolonged OS (60.7 vs. 41.4 weeks, $P = 0.026$).[37] The survival benefit of combination therapy may be underestimated due to the high frequency of crossover in this trial. It is not clear why this study showed OS benefit, but the study of von Minckwitz et al.,[34] also looking at continuing trastuzumab after progression, did not. It is possible that differences in the power of these studies – the Blackwell et al.[37] study is double that of von Minckwitz et al.[34] – may have affected outcomes. Another theory is that a synergistic interaction takes place between lapatinib and trastuzumab that does not take place between capecitabine and lapatinib.

BSI-201

BSI-201 is a poly(ADP-ribose) polymerase-1 [PARP1] inhibitor, a novel class of agents that selectively targets cells with defects in double-strand DNA repair.[42] The PARP family plays an important role in DNA damage repair pathways. Inhibition of PARP activity may sensitize the cell to exogenous agents such as chemotherapy and radiation. PARP inhibitors also induce cell death through 'synthetic lethality' in patients with BRCA1/BRCA2 mutations. BRCA1/BRCA2-deficient tumors are deficient in BRCA-mediated DNA repair/ cell rescue pathways and rely more heavily on the PARP pathway for DNA repair.[43,44] This mechanism is thought to underlie the positive results of PARP inhibition in BRCA-associated tumors. Further, the triple-negative breast cancer subtype shares molecular and pathologic features with BRCA1-related breast cancers. Preliminary analysis from a recent phase II randomized trial in patients with triple-negative breast cancer demonstrate that, compared with gemcitabine/carboplatin alone, the addition of BSI-201 significantly improved median PFS (5.9 vs. 3.6 months, $P = 0.012$), and median OS (>12.2 vs. 7.7 months, $P = 0.014$).[4]Similar to trastuzumab, this study prospectively defined a target and specific patient population (i.e. patients with triple negative, who are more likely to be deficient in BRCA-mediated DNA repair/cell rescue pathways). While this impressive survival benefit may be confirmed in the phase III study which has completed enrollment, the difference observed in OS in this study may have also been attributed to chance alone given the small sample size. On the other hand, the fact that an improvement in survival was seen in spite of crossover is noteworthy.

Survival outcomes in MBC – progression free vs. overall

A recent analysis of phase III treatment trials in patients with advanced breast cancer (75 trials; 159 trial arms; $N = 28,973$) indicated that OS increased in trials of first-line hormone-based therapy and decreased with subsequent lines of any type of treatment. For trials of first-line chemotherapy (with or without targeted agents) and hormone therapy (with or without chemotherapy), the median OS was 20.7 and 31.1 months, respectively. With trials of second-line chemotherapy and hormone therapy, OS decreased to 15.2 and 23.2 months, respectively. Investigators concluded that although pretreatment has a major role in determining OS, first-line PFS/TTP was not convincing as a good surrogate for OS in the trials analyzed and, therefore, further studies are warranted in order to understand the role of PFS/TTP vs. post-progression survival in determining OS.[45]

Options for salvage therapy for patients that have progressed after or are resistant to anthracyclines and taxanes are still limited, and survival in this group of pretreated patients is generally discussed in terms of months rather than years. For randomized trials in pretreated patients with MBC, the use of endpoints other than OS has been assessed and discussed in two meta-analyses. In the first, Burzykowski and colleagues showed that in trials of first-line therapy with anthracyclines and taxanes, the relationship between tumor response and PFS was strong, but there was only a weak relationship between PFS/TTP and OS.[46] In the second meta-analysis, Sherrill and colleagues examined data from randomized controlled trials for MBC conducted between 1994 and 2007[47] and showed that the effect of treatment on TTP/PFS corresponded to an attenuated effect on OS ($R^2 = 0.30$). Investigators acknowledged there were limitations to the meta-analysis, including variability of patient characteristics and prognostic markers, inconsistent definitions for progression, lack of consistent summary statistics, and lack of identification of treatment options following progression (e.g. crossover to another study arm or further treatment with non-study agents). It is also not scientifically valid to directly compare studies with different inclusion criteria and variable patient populations.

Despite these data suggesting at best a weak relationship between PFS/TTP and OS, there are examples in other tumors of the use of PFS/TTP to predict OS. For example, in a metaanalysis of randomized trials of first-line treatment of metastatic colorectal cancer or non-small-cell lung cancer, TTP and response rate were shown to correlate to improvement in survival. TTP was the preferred surrogate as more modest and achievable differences were needed in order to predict a significant survival benefit in these patients.[48]

Until convincing evidence is demonstrated of a similar relationship existing between outcomes in MBC, clinical trials should continue to incorporate both OS and PFS/TTP endpoints. Ideally, in trials where OS is a primary endpoint, crossover designs should be avoided; however, given the ethical implications of withholding alternative potentially effective treatment following progression, in reality this may be difficult to achieve. The FDA advocates overall survival as the 'gold standard for a registration trial designed to gain marketing approval,' but acknowledges that other endpoints have been used in the approval of oncology drugs. It states that surrogate endpoints such as PFS/TTP may be acceptable for accelerated approval as long as the sponsor commits to providing evidence of clinical benefit in subsequent trials.[7] In cases where there is a clear unmet need, surrogate endpoints such as PFS or TTP may be appropriate in order to expedite the availability of the drug to the patient.

The studies listed in Tables 1 and 2,[9-28] showing recent trials in patients with advanced MBC together with the recent meta-analyses in MBC, indicate that for most trials significant improvements in PFS generally have a positive correlation with increases in OS, although OS improvements rarely reach statistical significance in these patient populations. The primary endpoint for most of these trials was not OS and they are therefore not powered to show differences in this endpoint. This may in part explain the lack of significant benefits in OS observed in these trials. Furthermore, crossover to active treatment arms and subsequent treatment with non-experimental active therapies may have masked OS differences in some of these studies. For many studies though, it seems that lack of OS benefit in some but not others may simply be due to a play of chance.

Despite the advantages of OS, in the majority of phase III trials in the metastatic setting OS is not the primary endpoint, although it is typically measured as a secondary objective. While most trials are designed with a primary endpoint of PFS or TTP, it is important to note that these are not yet validated surrogates for overall survival in MBC. Novel drug regimens need to demonstrate an improvement in meaningful outcomes relative to established therapies if they are to be approved for use as therapy for MBC. However, given the array of therapies available to patients beyond first-line treatment it may be challenging to show an improvement in OS with a new drug.

Conclusions

Although OS remains the gold standard for assessing efficacy, there is a need for more practical outcome measures. PFS and TTP are commonly used primary endpoints in MBC, but are not yet validated surrogates for overall survival in this setting. In heavily pretreated MBC in particular, significant PFS improvements may indicate a clinically meaningful benefit for patients with otherwise limited salvage therapy options available. Powering studies to detect significant OS increases may not be practical in advanced MBC. Requiring significant OS increases could result in potentially beneficial agents failing to be registered.

In otherwise difficult to treat patients, such as those who are triple-negative and those who are heavily pretreated and/or resistant to previous treatment options, newer approved drugs such as ixabepilone and lapatinib are providing additional therapeutic options where there

was previously little hope. Approval for several of these agents in the advanced resistant or refractory MBC setting has been based on prolonged PFS or TTP as primary trial endpoints.

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Table 1

(A) and (B) TTP/PFS and survival data from randomized trials of chemotherapy in advanced breast cancer. Showing (A) clinical trials with significant improvements in both TTP and OS, and (B) clinical trials with improvement in TTP/PFS only.

Drugs	Patients	Treatment	Study design	Median TTP/PFS	Median OS
A					
Docetaxel (D) vs. paclitaxel (P) (Jones et al., 2005[10])	Women with advanced breast cancer that had progressed after an anthracycline-containing chemotherapy regimen (n = 449). Any number of prior therapies for MBC permitted (more than 40% of patients receiving treatment first-line)	D, docetaxel 100 mg/m^2 (n = 225) or P, paclitaxel 175 mg/m^2 on day 1, every 21 days (n = 224)	Primary endpoints: ORR and toxicity. No crossover; however, post-study taxanes were administered to 33% in the D arm and 36% in the P arm	D vs. P: TTP 5.7 vs. 3.6 months; HR = 1.64 (95% CI: 1.33–2.02; P < 0.0001)	D vs. P: 15.4 vs. 12.7 months; HR = 1.41 (95% CI: 1.15–1.73; P = 0.03)
Doxorubicin + docetaxel (AD) vs. fluorouracil, doxorubicin, and cyclophosphamide (FAC). (Bontebal et al., 2005[11])	Women with MBC treated first-line (N = 216). No prior therapies for MBC	AT: doxorubicin 50 mg/m^2 + docetaxel 75 mg/m^2 or FAC: fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 500 mg/m^2. Both regimens were administered on day 1, every 3 weeks	Primary endpoint: ORR. No crossover; however, post-study taxanes were administered to 23% in the AD arm and 67% in the FAC arm	AD vs. FAC: TTP 8.0 vs. 6.6 months; HR = 1.50 (95% CI: 1.13–1.98; P = 0.004)	AD vs. FAC: 22.6 vs. 16.2 months; HR = 1.43 (95% CI: 1.06–1.92; P = 0.019)
Doxorubicin + paclitaxel (AP) vs. FAC. (Jassem et al., 2001; 2009[12,13])	Patients with MBC treated first line (N = 267). No prior therapies for MBC	AP: doxorubicin 50 mg/m^2 followed 24 h later by paclitaxel 220 mg/m^2 (n = 134) or FAC: 5-fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2, each administered every 3 weeks for up to eight cycles (n = 133)	Primary endpoint: TTP. No crossover; however, post-study taxanes were administered to 2% in the AP arm and 24% in the FAC arm	AP vs. FAC: TTP 8.1 vs. 6.2 months (P = 0.036)	AP vs. FAC: 23.0 vs. 18.3 months (P = 0.005)
Docetaxel (D) ± capecitabine (X). (O'Shaughnessy et al., 2002[14])	Women with anthracycline-pretreated MBC (N = 511). Prior therapies for MBC: 0–2 (approximately one third treated first-line)	XD: capecitabine 1250 mg/m^2 twice daily on days 1–14 + D: 75 mg/m^2 on day 1 (n = 255) + docetaxel 100 mg/m^2 on day 1 (n = 256) or D: docetaxel 100 mg/m^2 on day 1 (n = 256)	Primary endpoint: TTP. No crossover; however, poststudy D was administered to 20% in the XD arm and 7% in the D arm and poststudy X was given to 17% in the D arm vs. 3% in the XD arm	XD vs. D: TTP 6.1 vs. 4.2 months; HR = 0.652 (95% CI: 0.545–0.780; P = 0.0001)	XD vs. D: 14.5 vs. 11.5 months; HR = 0.775 (95% CI: 0.634–.947; P = 0.0126)
Paclitaxel (P) ± gemcitabine (G). (Albain et al., 2008[15])	Women with advanced breast cancer previously treated with anthracyclines in the adjuvant/ neoadjuvant setting (N = 529). No prior therapies for MBC	GP: gemcitabine 1250 mg/m^2 on days 1 and 8 of a 21-day cycle + paclitaxel 175 mg/m^2 on day 1 + (n = 266) or P: paclitaxel 175 mg/m^2 on day 1 of a 21-day cycle (n = 263)	Primary endpoint: OS. No crossover; however, off study G was administered to 15.6% in the P arm and 4.1% in the GP arm	GP vs. P: TTP 6.14 vs. 3.98 months; HR = .0.70 (95% CI: 0.59–0.85; P = 0.0002)	GP vs. P: 18.6 vs. 15.8 months; HR = .0.82 (95% CI: 0.67–1.00; P = 0.0489)
B					
Doxorubicin + docetaxel (AD) vs. doxorubicin + cyclophosphamide (AC). (Nabholtz et al., 2003[16])	Women with MBC treated first line (N = 429). No prior therapies for MBC	AD: doxorubicin 50 mg/m^2 + docetaxel 75 mg/m^2 (n = 214) or AC: doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 on day 1, every 3 weeks (n = 215)	Primary endpoint: TTP. No crossover; however, 29% in the AC arm received off study D vs. 6% in the AT arm	AD vs. AC: TTP 37.3 vs. 31.9 weeks; HR = 1.32 (95% CI: 1.06–1.66; P = 0.014)	AD vs. AC: 22.5 vs. 21.7 months (95% CI: 19.0–26.4 months; P = 0.26)

Drugs	Patients	Treatment	Study design	Median TTP/PFS	Median OS
Nab-paclitaxel (NabP) vs. paclitaxel (P). (Gradishar et al., 2005[17])	Women with pretreated MBC (N = 460). Prior therapies for MBC: 0 to ≥ 3 (approximately 40% treated first-line and 40% treated second-line)	NabP: nab paclitaxel 260 mg/m^2 every 3 weeks (n = 229) or P: paclitaxel 175 mg/m^2 every 3 weeks (n = 225)	Primary endpoint: ORR. No crossover	NabP vs. P: TTP 23.0 vs. 16.9 weeks; HR = 0.75 (P = 0.006).	NabP vs. P: 65.0 vs. 55.7 weeks (P = 0.374)
Docetaxel (D) ± pegylated liposomal doxorubicin (PLD). (Sparano et al., 2009[18])	Women with advanced breast cancer who had experienced relapse >1 year after prior adjuvant or neoadjuvant anthracycline therapy (N = 751). Prior therapies for MBC: 0 or 1 (majority treated first-line)	PLD + D: PLD 30 mg/m^2 followed by docetaxel 60 mg/m^2 every 21 days (n = 378) or D: 75 mg/m^2 (n = 373)	Primary endpoint: TTP. No crossover; however, there was comparable use of poststudy taxanes/ microtubule agents (D: 34% vs. PLD + D: 29%), capecitabine (D: 33% vs. PLD + D: 38%), and gemcitabine (D: 13% vs. PLD + D: 8%)	PLD + D vs. D: TTP 7.0 vs. 9.8 months; HR = .0.65 (95% CI: 0.55–0.77; P = 0.000001)	PLD + D vs. D: 20.5 vs. 20.6 months HR = 1.02 (95% CI: 0.86–1.22; P = 0.81)
Vinorelbine (V) ± gemcitabine (G). (Martin et al., 2007[19])	Women with LABC or MBC pretreated with anthracyclines and taxanes (N = 252). Prior therapies for MBC: 0–2 (approximately 50% treated second-line and 30% treated third-line)	VG: vinorelbine 30 mg/m^2 + gemcitabine 1200 mg/m^2 days 1 and 8 (n = 125) or V: vinorelbine 30 mg/m^2 days 1 and 8 (n = 126)	Primary endpoint: PFS. No crossover	VG vs. V 6.0 vs. 4.0; HR = 0.66 (0.50–0.88; P = 0.0028)	VG vs. V 15.9 vs. 16.4; HR = 1.04 (0.78–1.39; P = 0.8046)
Capecitabine (X) ± Ixabepilone (I). (Thomas et al., 2007; Hortobagyi et al., 2010[20,21])	Women with advanced breast cancer that were resistant to anthracyclines and taxanes (N = 752). Prior therapies for MBC: 0 to ≥ 3 (approximately 50% treated second-line and 40% treated third-line)	IX: ixabepilone 40 mg/m^2 on day 1 of a 21-day cycle + capecitabine 2000 mg/m^2/day on days 1–14 of a 21-day cycle (n = 375) orX: capecitabine 2500 mg/m^2/day on days 1–14 of a 21-day cycle (n = 377)	Primary endpoint: PFS. No crossover	IX vs. X: PFS 5.3 vs. 3.8 months; HR = 0.78 (0.67–0.91; P = 0.0011)	IX vs. X: 12.9 vs. 11.1 months; HR = 0.90 (0.77–1.05; P = 0.1936)
Capecitabine (X) ± Ixabepilone (I). (Sparano et al., 2010[22])	Women with advanced breast cancer that were resistant to anthracyclines and taxanes (N = 1221). Prior therapies for MBC: 0 to ≥ 3 (approximately 20% treated first-line and 60% treated second line)	IX: ixabepilone 40 mg/m^2 on day 1 of a 21-day cycle + capecitabine 2000 mg/m^2/day on days 1–14 of a 21-day cycle (n = 609) orX: capecitabine 2500 mg/m^2/day on days 1–14 of a 21-day cycle (n = 612)	Primary endpoint: OS. No crossover	IX vs. X: PFS 6.2 vs. 4.4 months; HR = 0.79 (0.69–0.90; P = 0.0005)	IX vs. X: 16.4 vs. 15.6; HR = 0.90 (0.78–1.03; P = 0.1162)

Abbreviations: LABC, locally advanced breast cancer; HR, hazard ratio.

Table 2

TTP/PFS and survival data from randomized trials of targeted biological agents in advanced breast cancer.

Drugs	Patients	Treatment	Primary endpoint(s)study design	Median TTP/PFS	Median OS
Paclitaxel (P) ± bevacizumab (B). (E2100; Miller et al., 2007; O'Shaughnessy et al. 2009[9,23])	Patients with MBC treated first line (patients with HER2-positive MBC were eligible only if they had received trastuzumab) (N = 722). No prior therapies for MBC	BP: bevacizumab 10 mg/kg on days 1 and 15 + paclitaxel 90 mg/m^2 on days 1, 8, and 15 every 4 weeks (n = 368) or P: paclitaxel 90 mg/m^2 on days 1, 8, and 15 every 4 weeks (n = 354)	Primary endpoint: PFS. No crossover	BP vs. P: PFS 11.8 vs. 5.9 months; HR =.0.60 (P < 0.001). In triple-negative breast cancer: 10.2 vs. 4.7 months; HR = 0.45. In ER+/PR + breast cancer: PFS 14.4 vs. 8.0 months; HR = 0.54	BP vs. P: 26.7 vs. 25.2 months; HR = 0.88 (P = 0.16)
Docetaxel (D) ± bevacizumab (B). (AVADO; Miles et al., 2008; 2009; O'Shaughnessy et al., 2009[23-25])	Patients with HER2-negative locally advanced or MBC treated first-line (N = 736). No prior therapies for MBC	Docetaxel 100 mg/m^2 every 3 weeks (n = 241) ± bevacizumab 7.5 mg/kg (n = 248) or 15 mg/kg (n = 247) every 3 weeks	Primary endpoint: PFS. No crossover; however, 90 patients in the placebo arm received B on progression	D + placebo vs. DB7.5 vs. DB15: PFS 8.1 vs. 9.0 vs. 10.0 months. D + placebo vs. DB7.5: HR = 0.80 (P = 0.0450). D + placebo vs. DB15: HR = 0.67 (P = 0.0002). In triple-negative breast cancer (D + placebo vs. DB15): PFS 8.1 vs. 6.0 months; HR = 0.60	D + placebo vs. DB7.5 vs. DB15: 31.9 vs. 30.8 vs. 30.2 months. D + placebo vs. DB7.5: HR = 1.05 (P = 0.7198). D + placebo vs. DB15: HR = 1.03 (P = 0.8528)
Bevacizumab (B) + chemotherapy (capecitabine [X], taxane [T], or anthracycline [A]) vs. placebo + chemotherapy. (RIBBON-1; Robert et al., 2009[26])	Patients with HER2-negative LABC or MBC (N = 1237). No prior therapies for MBC	B or placebo: 15 mg/kg every 3 weeks (BX: n = 206, placebo + X: n = 409, BAT: n = 415, placebo + AT: n = 207) + chemotherapy (capecitabine [X]: 2000 mg/m^2 × 14 days, nab-paclitaxel: 260 mg/m^2, or docetaxel: 75 or 100 mg/m^2 every 3 weeks or anthracycline-based chemotherapy every 3 weeks)	Primary endpoint: PFS. No crossover; however, 60% of patients in the placebo arm and 50% of patients in the B arm received B on progression	BX vs. placebo X: PFS 8.6 vs. 5.7 months; HR = 0.688 (95% CI: 0.564–0.840; P = 0.0002). BAT vs. placebo + AT: PFS 9.2 vs. 8.0 months; HR = 0.644 (95% CI: 0.522–0.795; P < 0.0001). In triple-negative breast cancer. BX vs. placebo X: PFS 6.1 vs. 4.2 months; HR = 0.72. BAT vs. placebo + AT: 14.5 vs. 8.2 months HR = 0.78	BX vs. placebo X: 29.0 vs. 21.2 months HR = 0.847 (95% CI: 0.631–1.138; P = 0.2706). BAT vs. placebo + AT: 25.2 vs. 23.8 months; HR = 1.032 (95% CI: 0.774–1.376; P = 0.8298)
Bevacizumab + chemotherapy or placebo + chemotherapy (RIBBON-2; Brufsky et al., 2009; 2010[27,28])	Patients with HER2-negative MBC treated second line (N = 684). Prior therapies for MBC: 1	Bevacizumab (B) or placebo: 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks, depending on the chemotherapy regimen (chemotherapy + B: n = 225, chemotherapy + placebo: n = 459) + chemotherapy (paclitaxel [P]: 90 mg/m^2/week for 3 of the 4 weeks, P: 175 mg/m^2 every 3 weeks, nab-paclitaxel [nabP]: 260 mg/m^2 every 3 weeks, docetaxel [D]: 75–100 mg/m^2 every 3 weeks, gemcitabine [G]: 1250 mg/m^2 on days 1 and 8 every 3 weeks, capecitabine [X]: 2000 mg/m^2 days 1–14 every 3 weeks, or vinorelbine [V] 30 mg/m^2/week	Primary endpoint: PFS. No crossover	Chemotherapy + B vs. chemotherapy + placebo: PFS 7.2 vs. 5.1 months; HR = 0.775 (P = 0.0072). In triple-negative breast cancer: PFS 6.0 vs. 2.7 months; HR = 0.49. In ER+/PR + breast cancer: PFS 7.4 vs. 6.0 months; HR = 0.89	Chemotherapy + B vs. chemotherapy + placebo: 18.0 vs. 16.4 months (P = 0.372)
Chemotherapy ± trastuzumab (H).	Women with HER2-positive MBC treated	Chemotherapy (doxorubicin: 60 mg/m^2 or epirubicin: 75 mg/m^2 + cyclophosphamide: 600 mg/m^2 for	Primary endpoint: TTP. Two thirds of patients in the chemotherapy alone arm	Chemotherapy + H vs. chemotherapy alone: TTP 7.4	Chemotherapy + H vs. chemotherapy alone: 25.1 vs. 20.3 months;

Drugs	Patients	Treatment	Primary endpoint(s)study design	Median TTP/PFS	Median OS
(Slamon et al., 2001[37])	first line (N = 469). No prior therapies for MBC	patients who had never before received an anthracycline; or paclitaxel: 175 mg/m^2 for patients who had received adjuvant) once every 3 weeks for 6 cycles (n = 234) ± H: trastuzumab 4 mg/kg followed by 2 mg/kg once a week until disease progression (n = 255)	received trastuzumab after disease progression	vs. 4.6 months; HR = 0.52 (95% CI: 0.41–0.63; P < 0.001)	HR = 0.80 (95% CI: 0.64–1.00; P = 0.046)
Docetaxel (D) ± trastuzumab (H). (Marty et al., 2005[38])	Women with HER2-positive MBC treated first line (N = 186). No prior therapies for MBC	HD: docetaxel 100 mg/m^2 every 3 weeks for 6 cycles + trastuzumab 4 mg/kg followed by 2 mg/kg weekly until disease progression (n = 92) or D: 100 mg/m^2 every 3 weeks for 6 cycles (n = 94)	Primary endpoint: ORR. 57% of patients in the docetaxel-alone arm crossed over to receive trastuzumab after disease progression or due to toxicity or other reasons	HD vs. D: TTP 11.7 vs. 6.1 months (P = 0.0001)	HD vs. D: 31.2 vs. 22.7 months (P = 0.0325)
Capecitabine (X) ± trastuzumab (H). (von Minckwitz et al. 2008[39])	Women with HER2-positive, LABC or MBC that progressed during treatment with trastuzumab ± adjuvant and/or 1st-line metastatic chemotherapy (N = 156). Prior therapies for MBC: 0 or 1	XH: capecitabine 2500 mg/m^2 on days 1–14, every 21 days + trastuzumab 6 mg/kg, every 3 weeks (n = 78) or X: capecitabine 2500 mg/m^2 on days 1–14, every 21 days (n = 78)	Primary endpoint: TTP. No crossover	XH vs. X: TTP: 8.2 vs. 5.6 months; HR = 0.69 (P = 0.026)	XH vs. X: 25.5 vs. 20.4 months; HR = 0.76 (P = 0.26)
Capecitabine (X) ± lapatinib (L). (Cameron et al., 2008[40])	Patients with advanced or metastatic HER2-positive breast cancer with prior therapy including an anthracycline, a taxane and trastuzumab (N = 399). Any number of prior therapies for MBC permitted	LX: lapatinib 1250 mg/day continuously + capecitabine 2000 mg/m^2 on days 1–14 of a 21-day cycle (n = 82) or X: capecitabine 2500 mg/m^2 on days 1–14 of a 21-day cycle (n = 102)	Primary endpoint: TTP. Crossover from X to LX allowed at study completion	LX vs. X. TTP 6.2 vs. 4.3 months, HR = 0.57 (95% CI: 0.43–0.77; P < 0.001)	LX vs. X. 15.6 vs. 15.3; HR = 0.78 (95% CI: 0.55–1.12; P = 0.177)
Lapatinib (L) ± trastuzumab (H). (O'Shaughnessy et al. 2008; Blackwell et al., 2009[41,42])	Women with heavily pretreated (prior anthracyclines and taxanes) HER2-positive MBC progressing on H (N = 296). Any number of prior therapies for MBC permitted	LH: lapatinib 1000 mg/day + trastuzumab 4 mg/kg followed by 2 mg/kg weekly (n = 148) or L: lapatinib 1500 mg/day (n = 148)	Primary endpoint: PFS. 52% of patients in the L arm crossed over to LH after disease progression	LH vs. L: PFS 12.0 vs. 8.4 months, HR = 0.77 (95% CI: 0.6–1.0; P = 0.029)	LH vs. L: 60.7 vs. 41.4 months, HR = 0.74 (95% CI: 0.57–0.97; P = 0.026)
Gemcitabine + carboplatin (GC) ± BSI-201. (O'Shaughnessy et al., 2008[41])	Patients with pre-treated triple-negative MBC who had received received ≤ 2 prior cytotoxic regimens (N = 86; planned N = 120). Any number of prior therapies for MBC permitted	GC: gemcitabine 1000 mg/m^2 and carboplatin AUC = 2 on days 1 and 8 (n = 57) ± BSI-201: 5.6 mg/kg on days 1, 4, 8, and 11 every 21 days (n = 59)	Primary endpoint: Clinical benefit rate. No crossover	GC + BSI-201 vs. GC: PFS 6.9 vs. 3.3 months; HR = 0.34 (95% CI: 0.20–0.58; P < 0.0001)	GC + BSI-201 vs. GC: 9.2 vs. 5.7 months; HR = 0.35 (95% CI: 0.19–0.65; P = 0.0005)