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SPECIAL ARTICLE

National Cancer Institute Breast Cancer Steering Committee Working Group Report on Meaningful and Appropriate End Points for Clinical Trials in Metastatic Breast Cancer

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ABSTRACT

Purpose
To provide evidence-based consensus recommendations on choice of end points for clinical trials in metastatic breast cancer, with a focus on biologic subtype and line of therapy.

Methods
The National Cancer Institute Breast Cancer Steering Committee convened a working group of breast medical oncologists, patient advocates, biostatisticians, and liaisons from the Food and Drug Administration to conduct a detailed curated systematic review of the literature, including original reports, reviews, and meta-analyses, to determine the current landscape of therapeutic options, recent clinical trial data, and natural history of four biologic subtypes of breast cancer. Ongoing clinical trials for metastatic breast cancer in each subtype also were reviewed from ClinicalTrials.gov for planned primary end points. External input was obtained from the pharmaceutic/biotechnology industry, real-world clinical data specialists, experts in quality of life and patient-reported outcomes, and combined metrics for assessing magnitude of clinical benefit.

Results
The literature search yielded 146 publications to inform the recommendations from the working group.

Conclusion
Recommendations for appropriate end points for metastatic breast cancer clinical trials focus on biologic subtype and line of therapy and the magnitude of absolute and relative gains that would represent meaningful clinical benefit.

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INTRODUCTION

Significant heterogeneity exists in the natural history of metastatic breast cancer (MBC), particularly with regard to overall prognosis, treatment options, and benefits of therapy in biologic subtypes. Survival outcomes in clinical trials depend on many variables, including number and type of prior therapies, sites and extent of disease, and toxicity. The expected postprogression survival (PPS) after completion of protocol-specific therapy has implications for the choice of optimal end point: When overall survival (OS) is measured in years and patients receive multiple lines of therapy, progression-free survival (PFS) may be the most meaningful metric of treatment outcome. Conversely, in poor prognosis settings, such as triple-negative metastatic breast cancer (TNMBC), where expected PPS is short, OS is likely the most appropriate end point.[1] The balance between incremental gain in PFS and encountered toxicity is crucial, although data are scant on this topic.[2] In this context, several recent randomized trials have yielded statistically significant improvements in the primary end point with experimental therapy but did not lead to regulatory approval or practice change[3] primarily because of toxicity. This highlights the need for guidance on appropriate end points for both clinical trials in the setting of MBC and incorporation of patient-reported outcomes (PROs) and toxicities into the discussion of clinical trial design, conduct, and interpretation.

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Formal guidance for industry on clinical trial end points was provided by the US Food and Drug Administration (FDA) in 2007[4] but was not disease specific. Patient-focused drug development is mandated by the Prescription Drug User Fee Act V,[5] and the integration of PROs in the assessment of benefit of new treatments is evolving. Our working group (WG) sought to create a specific consensus on end points for MBC clinical trials by focusing on biologic subtype and line of therapy with sensitivity to various stakeholders, including medical oncologists, patients, the FDA, the National Cancer Institute, biostatisticians, and industry.

METHODS

The National Cancer Institute Breast Cancer Steering Committee[6] formed a WG and obtained external input from the pharmaceutic/biotechnology industry, real-world clinical data specialists, and experts in quality of life (QoL) and PROs (see Acknowledgment). We conducted a detailed curated systematic review of the literature in quarter 3 of 2016 through quarter 1 of 2017 to determine the current landscape of clinical trial data and natural history of four biologic subtypes of breast cancer: hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2–), HR–/HER2– (TNMBC), HR+/HER2+, and HR–/HER2+. The literature review was performed through PubMed using the search terms metastatic or advanced breast cancer, and clinical trial end points and included original reports, reviews, meta-analyses, and editorials (Fig 1), yielding 146 publications. Ongoing trials in each subtype also were reviewed from ClinicalTrials.gov, with particular attention to the planned primary end point of each study. External expertise was provided through Web-based teleconference. The WG achieved consensus by discussion and anonymous electronic polling/voting. Because other groups are examining the topics of brain metastases, bone metastases, immunotherapy, and cost of care,[7] we did not focus on these issues. For each biologic subtype, the WG reviewed biology and prognosis, current standard treatments, recent drug approvals, and ongoing phase III trials and end points. We sought to achieve consensus on the appropriate end point and magnitude of absolute and relative gains that would represent meaningful clinical benefit. In this context, the WG critically assessed current knowledge and perception of the balance between incremental PFS gain and encountered toxicity/effect on QoL, with consideration of both categorical and combinatorial approaches. The WG examined optimal strategies to best capture toxicity and integration of PROs into such clinical benefit analysis.

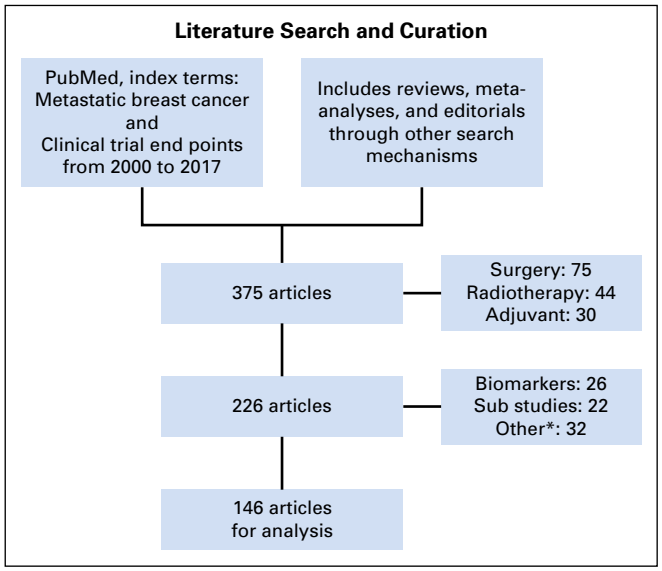

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram for literature analysis. Flow diagram illustrates the selection of articles for analysis. (*) Not relevant on end point issue for randomized controlled trials.

RESULTS

Consensus on Definitions

The most objective and validated end point for clinical trials is OS, which is defined as the time from random assignment to the time of patient death as a result of any cause. The development of surrogate end points, which would allow for smaller and shorter trials, has been influenced by the pragmatic desire to reduce both the cost of trials and the timeline for an effective drug to reach the marketplace. Minor differences in definitions can have a significant effect on the reported treatment outcomes and can lead to difficulty in making cross-trial comparisons. The WG recognized the value in providing robust definitions for clinical trial end points, as was done for early-stage breast cancer in the STEEP guidelines.[8] The Definition for the Assessment of Time to Event Endpoints in Cancer Trials (DATECAN) project aimed to standardize definitions of time-to-event end points to facilitate comparisons of trial results and improve the quality of trial design and reporting.[9] The DATECAN group used a formal consensus (Delphi) methodology to reach agreement on appropriate end points and definitions for both metastatic and nonmetastatic disease in breast, sarcoma/GI stromal tumor, and pancreatic cancer. This group identified PFS and time to progression as the most commonly used primary end points in randomized clinical trials of MBC. For PFS, the recommended clinical events for inclusion in the definition were death as a result of breast cancer, death as a result of nonbreast cancer cause, death related to protocol treatment, death as a result of any cause, death as a result of unknown cause, regional invasive recurrence/progression, and appearance/occurrence of metastases/distant recurrence. For time to progression, the recommendation was to include death as a result of breast cancer, regional invasive recurrence/progression, and appearance/occurrence of metastases/distant recurrence.

The WG believed that the DATECAN guideline definitions were appropriate and that the appropriate starting point for time-to-event determinations is time of random assignment or registration to a study rather than time of treatment initiation. We achieved consensus (defined as $\geq$ 80% of WG members agreeing or strongly agreeing with the statement) on definitions for several end points believed to be pertinent to MBC clinical trials (Table 1).

One consideration in trial design is the question of evaluating the sequencing of agents versus their combination. When new agents are being assessed, clinical trials commonly compare standard-of-care therapy with standard of care plus an investigational agent. In the absence of a compelling preclinical/biologic rationale, which often exists in investigating combinations, it may be valuable to compare the strategy that combines the standard of care and the investigational therapy versus the sequential receipt of them. The end point of time to treatment failure (TTF) spurred additional discussion. TTF usually is defined as the time since random assignment/registration to treatment discontinuation for any reason, including disease progression, treatment

Table 1. Summary of End Point Definitions

End Point Definition	Strength of Agreement
Progression-free survival: the time between random assignment/registration and tumor progression or death as a result of any cause	High
Time to progression: the time between random assignment/registration and tumor progression (does not include deaths)	High
Time to treatment failure: the time between random assignment/registration and either tumor progression, death, or discontinuation for toxicity or any reason	High
Overall survival: the time between random assignment/registration and death as a result of any cause	High
Duration of disease control: the time between random assignment/registration and tumor progression, including time after treatment discontinued, stopped before progression of disease, and no other treatment started	High
Time to treatment cessation: a composite end point that would require validation and could be used as additional supportive data	Moderate

NOTE. Voting working group member consensus: ≥ 80% indicates high agreement, and ≥ 60% indicates moderate agreement.

toxicity, patient preference, or death. The FDA has noted that TTF is a composite end point that is seldom useful for regulatory purposes because discontinuation of a drug for toxicity is not a direct reflection of its efficacy.[10] The FDA posits that separate analyses of safety and efficacy are required for regulatory approval. However, given that in clinical practice patients may stop a given therapy for a multitude of reasons, TTF may have some relevance to patients. The WG believed that a composite end point that considers reasons for treatment discontinuation, such as patient preference and toxicity, although perhaps challenging to operationalize, could be clinically meaningful and useful in treatment decision making for patients and clinicians. The WG also considered several scenarios in which objective progression defined by Response Evaluation Criteria in Solid Tumors (RECIST) might not indicate treatment failure or the need to change therapy. Some examples include focal progression amenable to local therapy, indolent or asymptomatic progression, and progression while receiving immunotherapy. This issue was addressed by Oxnard et al,[11] who recommended a more-detailed collection of progression characteristics, additional prospective study of treatment beyond progression, and exploration of alternate progression end points in clinical trials as potential ways to facilitate development of more-meaningful criteria for objective progression. The validated Prostate Cancer Working Group 2 guidelines for assessing progression in bone metastases, as they relate to the correlation between PFS and OS, is one recent example that breaks with traditional RECIST criteria.[12]

Critical Review of the Literature: Consideration of End Points by Biologic Subtype

The WG's recommendations for preferred primary, coprimary, and secondary end points are detailed in this section and summarized in Figure 2A, with an illustration of how these recommendations were reached shown in Figure 2B. The WG strove to link recommendations for preferred end points primarily to expected PPS, which we recognize as a moving target with serial introduction of new therapeutic agents that have and will continue to increase PFS progressively and in certain circumstances, OS.

HR+/HER2–. More than one half of all patients with MBC have HR expression, yet both intrinsic and acquired resistance limit the efficacy of anti-estrogen therapy. Loss of estrogen receptor expression, estrogen receptor mutations, altered expression of coregulators, and upregulation of alternative signal transduction pathways are all mechanisms of resistance that currently are being targeted. The development of rationally designed therapeutics has led to randomized trials that demonstrate that when added to anti-estrogen therapy, these agents can significantly extend PFS. For this population, given the expected long PPS, the WG regards PFS as the most robust and appropriate end point; the detection of an OS benefit is regarded as nice to have but not as need to have for such an approach to be clinically meaningful (Fig 2A). The FDA agreed that PFS was an acceptable primary end point and that it would be important to demonstrate no detriment in OS. When such patients have disease that is refractory to endocrine therapy and have been exposed to several lines of chemotherapy, where PPS is expected to be much shorter, OS may emerge as the preferred end point (Fig 2A).

The addition of CDK4/6 inhibitors palbociclib, ribociclib, or abemaciclib to an aromatase inhibitor (AI) as first-line therapy for postmenopausal woman with MBC yields a clinically and statistically improved PFS (Table 2). Although additional toxicities were more common with CDK4/6 inhibitors, they were uncommonly grade > 2. The addition of everolimus to exemestane significantly improved PFS without improvement in OS (Table 2). Everolimus use was associated with more grade ≥ 3 toxicity.

Some trials that have not led to regulatory approval nevertheless were informative for the WG in the consideration of optimal end points in this population. Two randomized trials examined the addition of bevacizumab to endocrine therapy for MBC.[3,19] In CALGB 40503 (Alliance), the experimental arm had a modest, but statistically significantly improved PFS, but grade ≥ 3 adverse events (AEs) were approximately three-fold higher with bevacizumab (Table 2). Similarly, in the Letrozole/Fulvestrant and Avastin trial, more-serious toxicities and several toxicity-related deaths occurred in the bevacizumab arm (Table 2).

The WG agreed that proportional and absolute gains in PFS need to be balanced carefully against toxicity. In the future, metrics that capture toxicity over time may be more meaningful and complement conventional worst-grade reporting.[25,26] The multisymptom spider plot used by Woo et al[27] is a useful tool for visualizing the levels of multiple AEs at specific time points in a composite manner. Thanarajasingam et al[25] developed a toxicity over time approach to assess AEs longitudinally. Toxicity over time provides clinically meaningful data that can be visualized in several ways, such as by butterfly plot that displays side by side the mean grade for multiple AEs over all treatment cycles for two agents or by area under the curve to overlay the mean grades over treatment cycles for a specific AE for two agents. The WG regards the integration of PROs[28-30] as especially relevant for patients with HR +/HER2– breast cancer as new agents with significant potential toxicities, such as phosphoinositide 3-kinase inhibitors and histone deacetylase inhibitors, are evaluated.

A

Line of Therapy	TNMBC	HR–/HER2+	HR+/HER2+	HR+/HER2–
First	1^0: OS 2^0: RR, PRO	1^0: PFS, OS 2^0: RR, PRO	1^0: PFS, OS 2^0: RR, PRO	1^0: PFS 2^0: OS, RR, PRO
Second	1^0: OS 2^0: RR, PRO	1^0: PFS, OS 2^0: RR, PRO	1^0: PFS, OS 2^0: RR, PRO	1^0: PFS 2^0: OS, RR, PRO
Third or more	1^0: OS 2^0: RR, PRO	1^0: PFS, OS 2^0: RR, PRO	1^0: PFS, OS 2^0: RR, PRO	1^0: PFS, OS 2^0: RR, PRO

B

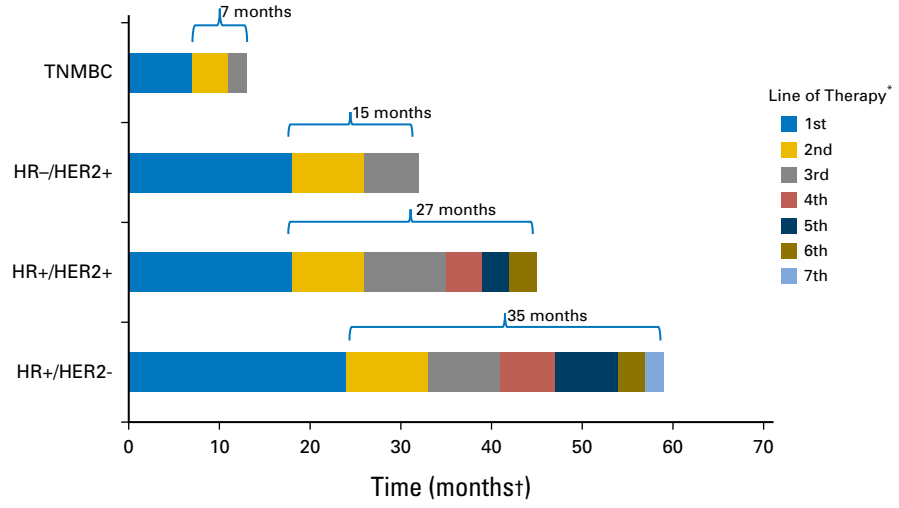

Fig 2. (A) Working group consensus on preferred end points by biologic subtype and line of therapy. (B) Hypothetical scenarios for expected postprogression survival (PPS) and choice of preferred end point. In settings such as first-line treatment of triple-negative metastatic breast cancer (TNMBC) where expected PPS is < 12 months, overall survival (OS) is the preferred primary end point. In settings such as hormone receptor–negative (HR–)/human epidermal growth factor receptor 2–positive (HER2+) or HR+/HER2+ MBC where PPS is > 12 months, in both the first- and later-line settings, progression-free survival (PFS) is the end point of choice, and OS could be considered as a coprimary end point. In settings such as HR+/HER2– MBC, given the expected long PPS, PFS is the most appropriate end point. When such patients have disease that is refractory to endocrine therapy and have been exposed to several lines of chemotherapy, where PPS is expected to be much shorter, OS may be the most meaningful and appropriate end point. (*) Line of therapy may be endocrine therapy, chemotherapy, HER2-targeted therapy, combinations, and so forth. (†) Months shown are for illustrative purposes only. 1°, primary end point; 2°, secondary end point; PRO, patient-reported outcome; RR, response rate.

HR–/HER2– (TNMBC). Approximately 15% to 20% of breast cancers are triple negative; however, this subgroup of breast cancers is quite heterogeneous by gene expression analysis.[31,32] The prognosis of TNMBC is poor, with an estimated median OS of 10 to 18 months and PPS after first-line therapy of 6 months.[1,32] Current standard treatment is primarily cytotoxic chemotherapy, but the development of novel biomarkers (eg, homologous recombination deficiency, androgen receptors) and novel therapeutic approaches (eg, antibody-drug conjugates, immunotherapy, targeted agents) likely will change the treatment landscape. Given limited prognosis, OS has been suggested as a valid primary end point for this patient population, irrespective of line of therapy[1] (Fig 2A). The WG examined the magnitude of benefit considered to be clinically significant in simulations; an OS improvement of 4.5 to 6 months with a hazard ratio of 0.75 to 0.8 with acceptable toxicity was believed to be a reasonable target in the first-line TNMBC setting. This recommendation may change with the advent of effective novel therapies that prolong expected PPS.

HR–/HER2+. HER2 is amplified in approximately 25% of breast cancers, and HRs are co-expressed in approximately 50% of these.[33,34] Although treated similarly, some key differences exist between HR+ and HR–/HER2+ disease. HR–/HER2+ breast cancer is more likely to metastasize to viscera than HR+/HER2+ disease. In the registHER study, distant disease-free interval (defined as the time between the end of nonhormonal adjuvant treatment and metastatic diagnosis) was 26.1 months for HR+ disease and 13.1 months for HR– disease.[35] PFS and OS are somewhat better for patients with HR+ disease.[35,36]

The prognosis for HER2+ breast cancer has dramatically improved with the standard use of HER2-targeted therapies in both the adjuvant and the metastatic setting. In the CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) trial, the addition of pertuzumab to docetaxel and trastuzumab in the first-line setting significantly improved both PFS and OS[37] (Table 2). These data led to FDA approval of pertuzumab in the first-line treatment of HER2+ MBC and sets the benchmark by which future treatments in the first-line setting should be measured. The EMILIA (Trastuzumab Emtansine Versus Capecitabine + Lapatinib in Participants With HER2-Positive Locally Advanced or Metastatic Breast Cancer) trial compared ado-trastuzumab emtansine (T-DM1) with capecitabine and lapatinib in patients with prior taxane and trastuzumab treatment.[20] Treatment with T-DM1 resulted in improved OS and PFS (Table 2).

In CLEOPATRA, the primary end point was PFS; OS was a secondary end point. In EMILIA, PFS and OS were coprimary end points. As of April 2017, there were eight phase III clinical trials of HER2-targeted therapies in the metastatic setting; three of these studies have OS as a coprimary end point (Table 3). In both first- and later-line settings, we conclude that PFS is the end point of choice for this patient population and that OS could be considered as a coprimary end point (Fig 2A). Studies of new agents or those that seek to move an agent from later to earlier lines of therapy should target at least a 6-month improvement in PFS. In

Table 2. Pivotal Phase III Clinical Trials in MBC

Study	Setting/Population	Primary End Point/Result	Comments	First Author
HR+/HER2–				
BOLERO-2: exemestane + everolimus *v* exemestane + placebo	Second line (n = 724; postmenopausal) 2:1 randomization	PFS, 10.6 *v* 4.1 months (hazard ratio, 0.36; 95% CI, 0.27 to 0.47; $P < .001$)	OS (secondary end point), 31.1 *v* 26.6 months (hazard ratio, 0.89; 95% CI, 0.73 to 1.10; $P = .14$)	Baselga[13]
PALOMA-2: letrozole + palbociclib *v* letrozole + placebo	First line (n = 666; postmenopausal) 2:1 randomization	PFS, 24.8 *v* 14.5 months (hazard ratio, 0.58; 95% CI, 0.46 to 0.72; $P < .001$)	No mature OS data from PALOMA-2 No OS difference in PALOMA-1	Finn[14]
PALOMA-3: fulvestrant ± goserelin + palbociclib *v* fulvestrant ± goserelin + placebo	Second line (n = 521; pre- and postmenopausal) 2:1 randomization	PFS, 9.5 *v* 4.6 months (hazard ratio, 0.46; 95% CI, 0.36 to 0.59; $P < .001$)		Turner[15]
MONALEESA: letrozole + ribociclib *v* letrozole + placebo	First line (n = 668; postmenopausal)	18-month PFS rate, 63% *v* 43.3% (hazard ratio, 0.56; 95% CI, 0.43 to 0.72; $P < .001$)		Hortobagyi[16]
MONARCH 2: fulvestrant + abemaciclib *v* fulvestrant + placebo	Second line (n = 669; pre- and postmenopausal) 2:1 randomization	PFS, 16.4 *v* 9.3 months (hazard ratio, 0.55; 95% CI, 0.45 to 0.68; $P < .001$)	OS data not mature at time of publication	Sledge[17]
MONARCH 3: nonsteroidal AI + abemaciclib *v* nonsteroidal AI + placebo	First line (n = 493; postmenopausal) 2:1 randomization	PFS (hazard ratio, 0.54; 95% CI, 0.41 to 0.72; $P < .001$)	At median follow-up of 17.8 months, PFS for the abemaciclib arm was not reached PFS was 14.7 months in placebo arm OS data not mature at time of publication but similar between arms	Goetz[18]
CALGB 40503: letrozole ± bevacizumab	First line (n = 343; postmenopausal)	PFS, 20.2 *v* 15.6 months (hazard ratio, 0.75; 95% CI, 0.59 to 0.96; $P = .016$)	No difference in OS (43.9 *v* 47.2 months) 47% of patients treated with bevacizumab had grade ≥ 3 adverse events	Dickler[3]
LEA: letrozole or fulvestrant ± bevacizumab	First line (n = 374; postmenopausal)	PFS, 19.3 *v* 14.4 months (hazard ratio, 0.83; 95% CI, 0.65 to 1.06; $P = .126$)	No difference in OS Significant increase in grade 3/4 hypertension, liver function test abnormalities, and proteinuria 4.2% of bevacizumab-treated patients died as a result of toxicity-related cause	Martin[19]
HER2+ (any HR status)				
CLEOPATRA: docetaxel + trastuzumab + pertuzumab *v* docetaxel + trastuzumab + placebo	No prior chemotherapy (n = 808)	PFS, 18.5 *v* 12.8 months (hazard ratio, 0.62; 95% CI, 0.51 to 0.75; $P < .001$)	OS (secondary end point) improved (56.5 *v* 40.8 months; hazard ratio, 0.68; 95% CI, 0.56 to 0.84; $P < .001$) No difference in benefit of pertuzumab in HR+ *v* HR–	Swain[37]
EMILIA: T-DM1 *v* capecitabine + trastuzumab	Previous treatment with taxane/trastuzumab (n = 991)	PFS, 9.6 *v* 6.4 months (hazard ratio, 0.65; 95% CI, 0.55 to 0.77; $P < .001$) OS, 30.9 *v* 25.1 months (hazard ratio, 0.68; 95% CI, 0.55 to 0.85; $P < .001$)	PFS and OS were coprimary end points	Verma[20]
HR+/HER2+				
EGF30008: letrozole + lapatinib *v* letrozole + placebo	First line, HR+ (n = 1,280; postmenopausal) HR+/HER2+ subset (n = 219)	PFS in HER2+, 8.2 *v* 3.0 months (hazard ratio, 0.71; 95% CI, 0.53 to 0.96; $P = .019$) No improvement in HER2–		Johnston[21]
TAnDEM: anastrozole + trastuzumab *v* anastrozole alone	No prior AI and no prior chemotherapy in metastatic setting (prior tamoxifen in metastatic setting ok; n = 207; postmenopausal)	PFS, 4.8 *v* 2.4 months (hazard ratio, 0.63; 95% CI, 0.47 to 0.84; $P = .0016$)		Kaufman[22]
ALTERNATIVE: AI + trastuzumab + lapatinib *v* AI + trastuzumab *v* AI + lapatinib	HR+/HER2+ MBC progressing on chemotherapy (n = 355; postmenopausal)	PFS (trastuzumab + lapatinib *v* trastuzumab), 11 *v* 5.7 months (hazard ratio, 0.71; 95% CI, 0.51 to 0.98; $P = .0361$)		Johnston[23]
PERTAIN: AI + trastuzumab + pertuzumab *v* AI + trastuzumab	First line (prior endocrine therapy allowed; n = 258; postmenopausal)	PFS, 18.9 *v* 15.8 months (hazard ratio, 0.65; 95% CI, 0.48 to 0.89; $P = .007$)	148 of the 258 enrolled patients received discretionary induction chemotherapy	Arpino[24]

Abbreviations: AI, aromatase inhibitor; ALTERNATIVE, Alternate Approaches for Clinical Stage II or III Estrogen Receptor Positive Breast Cancer Neoadjuvant Treatment; CLEOPATRA, Clinical Evaluation of Pertuzumab and Trastuzumab; EMILIA, Trastuzumab Emtansine Versus Capecitabine + Lapatinib in Participants With HER2-Positive Locally Advanced or Metastatic Breast Cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LEA, Letrozole/Fulvestrant and Avastin; MBC, metastatic breast cancer; MONALEESA, Efficacy and Safety of LEE011 in Postmenopausal Women With Advanced Breast Cancer; OS, overall survival; PERTAIN, Pertuzumab in Combination With Trastuzumab Plus an AI in Participants With Metastatic HER2+ and HR+ Advanced Breast Cancer; PFS, progression-free survival; TAnDEM, Trastuzumab and Anastrozole Directed Against ER-Positive HER2-Positive Mammary Carcinoma; T-DM1, ado-trastuzumab emtansine.

a later-line setting, a lower benefit in PFS could be considered acceptable if the adverse event profile of the experimental therapy is significantly better than the currently approved agents. Although cost is not currently a consideration used for evaluation and drug approval by the FDA, this factor may be considered by the patient, payer, and prescriber for drugs with modest clinical benefit.[5]

HR+/HER2+. For patients with HR+/HER2+ MBC, one FDA-approved regimen and at least two other approaches may be considered for postmenopausal patients for whom chemotherapy is deemed not indicated. The addition of lapatinib to letrozole significantly improves PFS at the expense of more dermatologic and GI toxicity (Table 2). The addition of trastuzumab to anastrozole also has been shown to prolong PFS (Table 2). In CLEOPATRA, the benefit of adding pertuzumab to taxane and trastuzumab did not seem to vary by HR status. The role of dual inhibition of HER2 with endocrine therapy and no chemotherapy for first-line treatment in selected patients is examined in two studies: the ALTERNATIVE (Alternate Approaches for Clinical Stage II or III Estrogen Receptor Positive Breast Cancer Neoadjuvant Treatment) trial, which met its primary objective of an improved PFS with the addition of lapatinib to AI and trastuzumab compared with AI and trastuzumab alone,[23] and the randomized phase II PERTAIN (Pertuzumab in Combination With Trastuzumab Plus an AI in Participants With Metastatic HER2+ and HR+ Advanced Breast Cancer) trial in which a 3-month improvement in median PFS for the addition of pertuzumab to AI plus trastuzumab was observed for the intention-to-treat population[24] (Table 2). In PERTAIN, 148 of the 258 enrolled patients received discretionary induction chemotherapy, a decision driven by patient attributes such as disease burden, symptoms, and patient preference. In terms of primary end point selection, consideration of the expected PPS still remains paramount in trial design, regardless of the choice of whether to lead with chemotherapy for such patients who have broad options. For this population, the WG consensus is that in both first- and later-line settings, PFS is the preferred end point and OS could be considered a coprimary end point (Fig 2A).

End Point Selection by Line of Therapy and/or Expected PPS

In consideration of novel primary end points other than OS (particularly PFS but also even earlier end points such as response rate), it is useful to consider both their intrinsic importance with respect to clinical benefit for the patient, which may allow approval without proven surrogacy, and their possible value as validated surrogate end points for OS. Sargent et al[38] discussed the validation of such end points. Early-phase evaluation involves the establishment of the correlation of end points with established outcome

Table 3. Ongoing Trials in HER2+ Breast Cancer

Trial	ClinicalTrials.gov Identifier	Treatment	Line	Primary	Secondary
PRECIOUS	NCT02514681	TPC chemotherapy + trastuzumab or pertuzumab *v* trastuzumab	Fewer than four prior regimens; no pertuzumab in latest treatment	PFS	PFS (independent review), PFS in patients with prior T-DM1, RR, DOR, OS, PRO, safety, biomarkers
Neratinib	NCT01808573	Neratinib + capecitabine *v* lapatinib + capecitabine	Third or more	PFS, OS	PFS (investigator), ORR, CBR (24 weeks), DOR, time to intervention for CNS metastasis, safety, QoL, population PK
SOPHIA	NCT02492711	Margetuximab + chemotherapy *v* trastuzumab + chemotherapy	Second to fourth, must have prior anti-HER2/ pertuzumab and T-DM1	PFS, OS	PFS (investigator), ORR
MM302	NCT01304797	MM302 + trastuzumab *v* TPC chemotherapy + trastuzumab	Second or more; must have prior pertuzumab and T-DM1; no prior anthracycline	PFS	PFS (investigator), OS, TTF, DOR, safety, PK
Danish	NCT00430001	Vinorelbine + trastuzumab *v* docetaxel + trastuzumab	First line	DFS	RR, OS
TOP	NCT00637325	Responders: trastuzumab *v* trastuzumab + chemotherapy Second line: trastuzumab + chemotherapy *v* chemotherapy alone	First and second	Responders: PFS Second line: OS	Responders: OS Second line: PFS
Kadcyla (Asian cohort)	NCT01702571	T-DM1	Second or more	Safety	PFS, OS, OR, CBR, DOR, TTR
CHEVENDO	NCT02344472	Chemotherapy *v* endocrine therapy in combination with dual HER2-targeted therapy	First to third	No. of participants with AEs	Quality-adjusted survival, ORR, CNS metastasis, QoL, CTCs, DCR, PFS, OS

Abbreviations: AE, adverse event; CBR, clinical benefit rate; CHEVENDO, Chemo Versus Endo; CTC, circulating tumor cell; DCR, disease control rate; DFS, disease-free survival; DOR, duration of response; HER2, human epidermal growth factor receptor 2; OR, overall response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRECIOUS, Pertuzumab Retreatment in Previously Pertuzumab Treated HER2-Positive Advanced Breast Cancer; PRO, patient-reported outcome; QoL, quality of life; RR, response rate; SOPHIA, Margetuximab Plus Chemotherapy Versus Trastuzumab Plus Chemotherapy in the Treatment of HER2+ Metastatic Breast Cancer; T-DM1, ado-trastuzumab emtansine; TOP, Trastuzumab Optimization Trial in Breast Cancer; TTF, time to treatment failure; TTR, time to response.

variables, particularly OS, on the patient level, which can be done in the context of individual randomized or nonrandomized trials or even outside the context of formal clinical trials. After such correlation has been established, the end points can be used in individual patient management. However, to establish such end points as appropriate for the primary outcome assessment in clinical trials, it must be established that the new end point captures a substantial portion of the treatment benefit (on the trial level) associated with an established end point, such as OS.[39] In other words, a meta-analysis across randomized trials that involve related treatments must be conducted to establish that the treatment benefit (eg, OS) seen across the trials is highly correlated with that of the new end point.

When PFS Is the Preferred End Point, What Are Meaningful Relative and Absolute Gains?

The WG considered a series of hypothetical case simulations to assess our internal level of consensus on the magnitude of incremental PFS gain that would be meaningful/acceptable in the context of various degrees of toxicity. Table 4 depicts one such experiment. As expected, with increasing expected toxicity, the threshold incremental PFS gain desired for meaningful benefit increases. Ultimately, it is the patients' perspective, rather than that of this WG, that matters most in this trade-off analysis. Hurvitz et al[2] used the Metastatic Breast Cancer Progression Questionnaire to assess how patients value PFS in the context of MBC, with hypothetical scenarios presented and patient feedback provided. Patients associated longer PFS with improved QoL, physical functioning, and emotional well-being and preferred a treatment that prolonged PFS from 12 to 16 months, even when adverse effects and OS were proposed to be identical. Unfortunately, a paucity of meaningful information remains on this important subject, one that begs for rigorous future investigation.

PFS/Toxicity-QoL Burden: The Balance and Meaningful Benefit

Meaningful benefit is a term used in both drug regulatory approval and patient treatment decisions. All treatment decisions in metastatic cancer depend on an informed benefit/risk (PFS or OS/toxicity) ratio. Substantial toxicities, whether short or long term, reversible, financial, or temporal, can counterbalance improvements in PFS and even OS for patients. Patients who are adjusting to an incurable illness show great variability in tolerance to treatment toxicities and QoL issues. Unique patient life experiences and different philosophical/spiritual beliefs result in a wide spectrum of value decisions about the benefit/risk balance. Patients and their clinicians must weigh the trade-off between effectiveness of treatment and QoL; a few extra months of symptomatic life prolongation may be insignificant to some and highly prized by others. Explaining and understanding the concept of average PFS improvement with unclear OS benefit and contrasting with likely toxicities pose a challenge to physicians and patients and frequently fall short of clarity. The WG considered and evaluated external attempts to quantify levels of toxicity for comparison with antitumor activity to define meaningful benefit but found this challenging. Measures that could improve toxicity reporting in clinical trials include commitment of both financial resources and statistical rigor to the study of QoL and PROs, attention to reporting of both the time course and the severity of toxicities, and visual methods for educating patients and clinicians about QoL results from clinical trials. Such measures are crucial for the evaluation and communication of meaningful benefit in the context of drug development.

Regulatory Perspective

Approval of drugs in the United States requires substantial evidence of clinical benefit, including safety and effectiveness, on the basis of adequate and well-controlled trials.[40] The accelerated approval regulations[41] subsequently have allowed for additional end points to support the approval of drugs or biologic products that are reasonably likely to predict clinical benefit, with postapproval trials verifying that benefit. There is no comparative efficacy requirement for regular approval. However, to meet accelerated approval requirements, a drug should demonstrate a benefit over available therapy.

The appropriate end point to support approval, therefore, depends on the pathway being sought. For regular approval, the end point should reflect direct clinical benefit, and for accelerated approval, it should be reasonably likely to predict clinical benefit. The FDA Guidance for Industry (2007) provides details of clinical

Table 4. Balance Between Incremental PFS Gain and Degree of Encountered Toxicity

Variable	Hazard Ratio				
	0.8	0.7	0.6	0.5	< 0.5
Median PFS in control arm = 6 months	7.5 months	8.6 months	10 months	12 months	> 12 months
Minimal toxicity, % of WG votes	40	33	20	7	0
Moderate toxicity, % of WG votes	0	27	53	13	7
Major toxicity, % of WG votes*	7	0	20	20	33
Median PFS in control arm = 12 months	15 months	17.1 months	20 months	24 months	> 24 months
Moderate toxicity	0	40	47	13	0

NOTE. Representative patient. Question: Mrs Smith is enrolling in a trial of a new agent for second-line treatment of her estrogen receptor–positive/human epidermal growth factor receptor 2–positive metastatic breast cancer. What is the minimal threshold gain in PFS that you would want to see for a meaningful benefit when faced with either minimal, moderate, or major toxicity? Working group members voted anonymously. Percentages represent working group members who voted for a specific item (n = 14).

Abbreviation: PFS, progression-free survival; WG, working group.

*The remaining 20% of WG members selected "Hazard ratio much less than 0.5, desire a more than doubling of PFS or an OS benefit" when median PFS in control arm = 6 months and major toxicity.

trial end points for the approval of cancer drugs and biologics.[4] This guidance does not include specific considerations related to breast cancer but does delineate certain statistical concepts related to preferred FDA definitions of end points, including OS, PFS, and objective response rate (ORR). These end points have factored into both regular and accelerated breast cancer approvals.[42-45]

OS can be challenging to assess in MBC, given that patients may receive multiple subsequent therapies after progression that can affect OS, thereby confounding its relevance as the most robust end point. However, OS should be considered as a primary or coprimary end point when expected survival is short (< 6 to 12 months).[46] In many cases, the FDA has accepted PFS and ORR supported by long duration of response, especially in rare biomarker-defined subsets, as the primary end point, and depending on the context, these end points could support either regular or accelerated approval. For any end point, the magnitude of benefit that is clinically meaningful needs to be considered in the context of the safety/tolerability profile of the agent and the available therapy. The FDA does not specify a requirement for absolute or relative gains in PFS or ORR because each application is viewed independently.

From a regulatory perspective, use of alternative end points, such as TTF, could be challenging because the end point is confounded by factors unrelated to efficacy, including toxicity, patient preference, and physician reluctance to continue therapy. Nevertheless, alternative end points could be examined in concert with PFS and should track in the same direction to be viewed as supportive information.

In real-world breast cancer clinical practice, progression events by RECIST may not result in therapy discontinuation, and thus, with a prespecified plan and rationale, the continuation of treatment beyond progression in clinical trials may be acceptable from a regulatory standpoint and should be discussed with the FDA during trial design. This approach could allow patients to continue therapy if their treating physicians believe that they are deriving clinical benefit while still allowing for end point evaluation. In addition, the FDA routinely provides advice about collection of PROs to aid in the assessment of clinical benefit for new treatments.[25,26,28,47]

In conclusion, recognition of the heterogeneity in biology, and thus, the expected variable outcomes of patients who enroll in clinical trials of systemic therapy for MBC, mandates careful consideration of situation-sensitive and appropriate choice of primary outcome measures. The WG considered a series of key position statements related to this to assess our internal level of consensus (Table 5). In scenarios where PFS is the more appropriate end point, careful consideration of the balance between incremental PFS gain and encountered toxicity and QoL and PROs will enable stakeholders to avoid the expenditure of resources in trials that yield statistically significant *P* values but not clinically meaningful results. However, when outcomes are poor and PPS is short, OS is the most appropriate end point. The future development and validation of composite metrics that capture both efficacy and toxicity/effect on QoL and PROs collectively may afford a valuable means to prospectively define clinical benefit upfront in the trial design phase rather than out back after its conclusion.[48,49] In addition, a more patient-centered approach to the conduct of clinical trials would provide more meaningful data to patients to inform their decision making on an individual level.

Table 5. Summary of Key Position Statements

Position Statement	Strength of Agreement
In MBC trials, toxicity can outweigh small PFS gains.	High
In MBC trials, toxicity can outweigh small OS gains.	High
When PFS is the preferred end point, the balance of PFS gain and toxicity burden and PRO/QoL effect should be considered individually, in parallel.	High
When PFS is the preferred end point, the balance of PFS gain and toxicity burden and PRO/QoL effect may be considered collectively; development of a composite metric that captures all domains is warranted.	Moderate
Insufficient patient-based research exists to gauge how patients regard incremental PFS gain versus toxicity burden.	High
Reporting the area under the time-toxicity curve may provide a more meaningful assessment of tolerability than reporting percentage with worst grade experienced.	High
Graphic displays of toxicity over time, such as the ToxT[25] method can communicate complex ideas with precision and clarity.	High
The ASCO conceptual framework to assess the value of cancer treatment options[7] that captures clinical benefit, toxicity, and cost, if validated, may provide a valuable metric to compare treatments in arms of future RCTs.	Moderate
The PRO version of CTCAE yields direct insight into patient experience and provides a comprehensive perspective of the benefits and risks of treatment and should be considered in RCTs with FDA discussion; attention to frequency and timing of missing data and concomitant medications are important for interpretation.	High
The ability to capture and report data for patients who receive a specific therapy after approval in the real world of clinical practice, outside of a clinical trial, will help to inform clinical trial end points in the future.	Moderate
Systemic therapy changes guided by clinician interpretation (clinical assessment, radiology, laboratory, pathology) and judgment correlate better with OS than those that rely on Response Evaluation Criteria in Solid Tumors (RECIST).	Moderate
Governmental approval to extend and fund the Prescription Drug User Fee Act beyond September 2017 will facilitate multidisciplinary action to better incorporate PROs in the evaluation of new drugs and biologics.	High

NOTE. Voting working group member consensus: ≥ 80% indicates high agreement, and ≥ 60% indicates moderate agreement.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; FDA, Food and Drug Administration; MBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; QoL, quality of life; RCT, randomized controlled trial; ToxT, toxicity over time.

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