In the End What Matters Most? A Review of Clinical Endpoints in Advanced Breast Cancer

SUNIL VERMA,^a DEANNA MCLEOD,^b GERALD BATIST,^c ANDRÉ ROBIDOUX,^d ILÍDIO R. S. MARTINS,^b
JOHN R. MACKEY^e

^aSunnybrook Odette Cancer Centre, University of Toronto, Toronto, Ontario, Canada; ^bKaleidoscope Strategic, Toronto, Ontario, Canada; ^cSegal Cancer Centre/Jewish General Hospital/Lady Davis Institute, McGill University, Montréal, Québec, Canada; ^dCentre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada; ^eCross Cancer Institute, University of Alberta, Edmonton, Alberta, Canada

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ABSTRACT

Many agents are being studied for the treatment of metastatic breast cancer (MBC), yet few studies have demonstrated longer overall survival (OS), the primary measure of clinical benefit in MBC. This paper examines the key endpoints in clinical trials and U.S. Food and Drug Administration (FDA) approvals of drugs for MBC.

PubMed was searched (1980 to October 2009) for reports of phase III trials investigating chemotherapy and/or targeted therapy agents in MBC. FDA approval histories (1996–2009) for cytotoxic and biological agents indicated for MBC were reviewed.

Of the 73 phase III MBC trials reviewed, a strikingly small proportion of trials demonstrated a gain in OS duration (12%, $n = 9$). OS gains were less frequently noted in first-line trials (8%) than in trials of second-line plus

other lines of therapy (22%). Few trials were designed with the capacity to detect OS effects. Among 37 phase III trials conducted in the last 15 years, only three systemic therapies were approved for first-line use and nine were approved for use as second-line or other lines of therapy. Of these, only four were supported by results showing longer survival times.

There is substantial discordance among the design and conduct of clinical trials, FDA drug approval, and the current view of OS as the ultimate measure of clinical benefit. There is an urgent need to reassess standards for clinical benefit in MBC and to establish guidelines for study design and conduct and drug approval. In the end, what matters most is ensuring rapid access to safe and effective oncology treatments. *The Oncologist* 2011;16:25–35

Figure 1. The cycle of NME development for metastatic breast cancer.

Abbreviations: FDA, U.S. Food and Drug Administration; NME, new molecular entity.

INTRODUCTION

Despite the availability of an unprecedented number of clinically active antitumor agents for the treatment of metastatic breast cancer (MBC), the disease remains incurable. Current clinical goals are to prolong life while maintaining optimal quality of life, underscoring the importance of earlier access to safe and effective new treatments.

Clinical Trial Design and Endpoints

The process by which clinicians gain access to new molecular entities (NMEs) is complex, involves multiple stages and stakeholders, and is somewhat cyclical (Fig. 1). Clinical trial results, particularly those from phase III trials, form the basis for regulatory review, reimbursement review, and ultimately adoption or rejection by the medical community. Therefore, clinical trial design, and specifically the selec-

tion of the primary endpoint, is pivotal because it defines how the clinical benefit will be measured, determines the size of the trial, and determines the length of follow-up required.

Survival as an Endpoint

Overall survival (OS) is defined as the time from randomization to death from any cause [1, 2] and has historically been regarded as the gold standard measure of clinical benefit [3]. OS is favored due to its objectivity, clear indication of benefit, and ease and reliability of measurement. However, determination of OS also requires a larger sample size, requires a prolonged follow-up period, and may be influenced by therapies used after patient participation in a given trial has ended, including crossover to the experimental arm. This has been of increasing concern because, over the last decade, significant advances in the systemic treatment

Table 1. Meta-analyses of randomized controlled trials evaluating PFS or TTP as surrogates for OS

Study	n of patients	n of RCTs	Nature of intervention	Surrogate endpoint	True endpoint	Individual patient data (yes/no)	Measure of treatment effect	Results (effects and criteria for correlation)	Study outcome
Hackshaw et al. (2005) [4]	9,163	42	FEC or FAC versus other chemotherapy	TTP	OS	No	HR (OS), OR (TTP)	TTP-logOR versus OS-logHR: $m = 0.51$, $R^2 = 56\%$, $SE = 0.0928$; $p = .0001$	Positive (TTP)
Burzykowski et al. (2008) [7]	3,953	11	Anthracycline-containing regimens versus taxane or taxane + anthracycline	PFS, TTP	OS	Yes	logHR (PFS, TTP, OS)	PFS-logHR versus OS-logHR: $CC = 0.48$, 95% CI, 0.34–1.30; TTP-logHR versus OS-logHR: $CC = 0.49$, 95% CI, 0.32–1.30	Negative (PFS, TTP)
Miksad et al. (2008) [5]	10,216	31	FEC or FAC and taxane-containing regimens	PFS	OS	No	HR (PFS, OS)	κ (ant): 0.71, 95% CI, 0.36–1.00, $p = .0029$; κ (tax): 0.75, 95% CI, 0.42–1.00, $p = .0028$; PFS-HR versus OS-HR (ant): $p = .0019$, $R^2 = 0.49$; PFS-HR versus OS-HR (tax): $p = .012$, $R^2 = 0.35$	Positive (PFS)
Sherrill et al. (2008) [6]	17,081	67	Chemotherapy, hormonal therapy, and targeted therapy	PFS or TTP	OS	No	HR (PFS/TTP, OS); $Effect_{TTP} = HR_{TTP} - 1$; $Effect_{OS} = HR_{OS} - 1$	$Effect_{OS} = 0.32$ (95% CI, 0.20–0.43) $\times Effect_{TTP}$; $R^2 = 0.30$	Positive (PFS or TTP)

Abbreviations: CC, R^2 , linear correlation coefficient; CI, confidence interval; FAC, fluorouracil, doxorubicin, cyclophosphamide; FEC, fluorouracil, epirubicin, cyclophosphamide; HR, hazard ratio; OR, odds ratio; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; SE, standard error; TTP, time to progression.

of MBC have dramatically altered the number and variety of available treatments that are used sequentially. The usefulness of OS as a trial endpoint in an era of effective subsequent-line agents must now be reconsidered.

Progression-Free Survival and Time to Progression as Endpoints

Time-to-event endpoints, such as progression-free survival (PFS) and the related endpoint time to progression (TTP), focus on progression of disease and were previously considered of secondary significance compared with OS. Initial interest in PFS and TTP as measures of clinical benefit in MBC began with their potential as surrogate endpoints for survival. Although some degree of association has been detected between PFS/TTP and OS [4–6] (Table 1), results remain inconsistent [4–7], and the nature of the relationship is uncertain. Nevertheless, these endpoints have been increasingly used as primary endpoints and are now the most frequently used endpoints in ongoing randomized MBC trials. Although their definitions are not standardized [5, 8], the U.S. Food and Drug Administration (FDA) defines PFS as the time elapsed between randomization and tumor progression or death from any cause and defines TTP as the time elapsed between randomization and disease progression [1, 2]. The merits of using PFS and TTP as measures of clinical benefit are that they are reached faster than OS, are not influenced by subsequent treatments [1, 9], and many consider these endpoints direct measures of clinical benefit [10–12]. One reservation has been that measurement of PFS/TTP is more involved, and therefore more susceptible

to error and bias, although the direction of bias is not always evident [1, 9, 13].

Clinical Trial Endpoints and Regulatory Drug Approval

The basis for FDA approvals of New Drug Applications or Biologics Licensing Applications is the sponsor's ability to demonstrate clinical benefit in adequate and well-controlled studies [14, 15]. According to the FDA, clinical benefit can be established through improvements in OS, patient-reported outcomes such as symptom improvement, or an established surrogate endpoint [1, 16].

Two types of approval exist for drugs or biological products: regular approval and accelerated approval (AA). Regular approval requires evidence of clinical benefit or improvement in an established surrogate endpoint for clinical benefit, whereas AA requirements are less stringent [17]. The FDA established AA regulations in 1992. These regulations were designed to improve access to therapeutics for life-threatening diseases by allowing sponsors to begin marketing relevant drugs on the basis of trials that identify improvements in surrogate outcomes that are reasonably likely to predict clinical benefit, such as the response rate (RR) or PFS interval [18]. The use of AA was expanded to include NMEs for oncology through an initiative of the office of the President of the U.S. in 1996 [19] and the Food and Drug Administration Modernization Act of 1997 [20] (Fig. 2). Under the revised AA regulation, registration trials can be phase II or phase III; however, the sponsors are required to conduct confirmatory studies to verify clinical efficacy [17, 21]. In 1999, the Oncol-

Figure 2. Changes in FDA regulatory approval from 1990 through 2008 [18].

Abbreviations: AA, accelerated approval; FDA, U.S. Food and Drug Administration; NME, new molecular entity.

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ogy Drug Advisory Committee (ODAC) voted to maintain OS as the gold standard for regular approval of NME applications in MBC [22]. In 2003 and 2005, in response to recommendations made by the ODAC regarding AA applications, the FDA advised sponsors that single-arm, phase II studies would only be interpretable in the setting of refractory disease, whereas interim analyses of phase III trials could support AAs in a broad range of settings; additional follow-up of these trials could provide evidence of clinical benefit [15, 23].

In view of the key role played by endpoints in the drug development cycle and regulatory process, we sought to assess the effects of primary endpoint selection on clinical outcomes and regulatory approval.

CLINICAL TRIAL REVIEW

Clinical Trial Methods

PubMed was searched for English language reports of phase III trials investigating chemotherapy and/or targeted therapy agents for MBC published between 1980 and October 2009. In total, 485 randomized clinical trials were identified using the terms “breast,” “cancer,” “advanced,” and “therapy,” and of these, 73 were confirmed as phase III trials reporting efficacy outcomes (Fig. 3). Randomized phase II trials and studies reporting pooled analyses were excluded. Because the intention of our analysis was to compare trends in FDA policy and practice with trends in study design, and it was believed that only phase III trials would be influential at the regulatory level, we opted to include only those trials with a phase III study-level designation. Studies without an explicit statement relative to trial phase were excluded from the analysis.

Data relating to the primary endpoint, line of treat-

Figure 3. CONSORT diagram summarizing literature search eligibility criteria.

Abbreviation: LABC, locally advanced breast cancer.

ment, number of patients, and study start date were extracted from full source articles. In the absence of a clear statement regarding primary endpoint designation, endpoints used for sample size calculations were considered the primary endpoints. When multiple primary efficacy endpoints were identified, the primary endpoint was designated as not reported (NR). The studies were parsed

into four primary endpoint categories: OS, PFS/TTP, RR (overall response rate [ORR] and/or complete response), and other endpoints. First-line MBC trials were defined as those trials with patient populations that had not received any prior chemotherapy or biologic therapy for metastatic disease. All other trials, including those with mixed populations of first-line patients and patients receiving prior therapy for MBC were categorized as second-line plus (second-line+) trials.

In order to control for publication bias [24], study start dates were used for the historical analysis. Start dates were determined based on explicit statements in the original reports or through reference to secondary sources such as the ClinicalTrials.gov database. Start dates were not available in three studies and these were excluded from all point-in-time analyses. Data were categorized into two time periods based on the median start year of our population of trials (1995). Two of the studies for which the start date could not be determined were published before 1995 [25, 26] and were included in the pre-1995 group. Significant improvement in an endpoint was defined as $p < .05$. In the analysis of trials with a 2×2 factorial design ($n = 2$), only the main comparisons were considered. For trials with more than two arms and without a factorial design, group p -values were used. When the number of “randomized” patients was not reported, we used the enrolled or registered population in the calculation of the number of randomized patients per arm. In the assessment of study results, we used the values reported for the intent-to-treat population preferentially.

Clinical Trial Findings

In total, 73 trials, corresponding to 152 trial arms, met the eligibility criteria for this review and were included in the analysis. These trials were conducted over three decades, with the first trial initiated in July 1978 and the last trial initiated in March 2004. A plot of phase III trials by start date (Fig. 4A) revealed a substantial increase in the number of trials initiated between 1994 and 1996, with the greatest number of trials initiated in 1996. A chronological analysis of the average number of patients randomized by arm showed that trial size increased substantially over the last three decades (Fig. 4B).

Of the 72 trials that could be unambiguously assigned to before or after 1995, 47 trials in total, or approximately two thirds (65%) of the phase III trials, were first-line trials (Fig. 5A), whereas 23 trials in total, or approximately one third (32%), were second-line+ trials, of which the majority ($n = 21$) were a mix of first- and second-line patient populations. The line of treatment could not be determined in the remaining studies ($n = 2$, 3%).

OS was reported as the primary endpoint in only 7% ($n = 5$) (Fig. 5B) of trials, whereas the PFS/TTP and RR primary

Figure 4. Chronological analysis of advanced breast cancer trials by start year ($n = 70$). (A): Phase III trials initiated by year. (B): Plot of number of patients per arm in phase III trials.

endpoints were considerably more common (38%, $n = 27$ and 32%, $n = 23$, respectively). Primary study endpoints were NR in 21% ($n = 15$) of trials. Of the trials initiated prior to 1995, the majority of studies selected either RR as the primary endpoint or had an NR designation. After 1995, the proportion of NR designated trials decreased (18% versus 3%), whereas the proportion of trials reporting time-to-event endpoints, either PFS or TTP, increased (6% versus 32%). Survival was infrequently reported as a primary endpoint either before or after 1995 (3% or 4%, respectively).

Patterns of endpoint reporting for both first-line and second-line+ trials mirrored those of trials overall. Studies reporting PFS and RR as primary endpoints were most common, followed by NR designated studies, whereas trials reporting OS as the primary endpoint were among the least common (Fig. 5C).

When outcomes from all phase III trials ($n = 73$) were reviewed, only a small proportion of trials demonstrated an OS gain (12%, $n = 9$) (Fig. 6A). Of the trials reporting OS as a primary endpoint ($n = 5$), only one trial (20%) reported a significant OS gain [27] (Fig. 6B). Of the 27 studies reporting PFS/TTP as the primary endpoint, approximately half of the trials (52%) reported significantly longer PFS/TTP.

When outcomes were considered for first-line trials ($n = 48$), regardless of primary endpoint selection, OS gains were

Figure 5. Trials started before and after 1995 ($n = 72$) categorized by line of treatment (A) or primary endpoint (B); (C): Frequency of primary endpoints in first-line trials or trials of second-line plus other lines of therapy (second-line+).

Abbreviations: NR, not reported; OS, overall survival; PFS, progression-free survival; RR, response rate; TTP, time to progression.

observed in four trials (8%), whereas PFS/TTP gains were observed in 14 trials (29%) (Fig. 6C). Of the 23 second-line+ trials, five (22%) reported longer OS times whereas 10 (43%) reported longer PFS/TTP (Fig. 6D).

FDA REGULATORY APPROVAL

FDA Methods

We reviewed the approval history of cytotoxic and biological NMEs for MBC approved by the FDA in 1996–2009. Data included: agent approved, year of approval, description of indication, type of approval (AA versus regular), trial design (phase III versus phase II), and endpoint used as

Figure 6. Frequency of significant improvements in OS and PFS/TTP of (A): All trials ($n = 73$); (B): Trials reporting OS ($n = 5$) or PFS/TTP ($n = 27$) as the primary endpoint; (C): First-line trials ($n = 48$); and (D): Trials of second-line plus other lines of therapy (second-line+) ($n = 23$).

Abbreviations: NR or ND, not reported or nondeterminable; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

the basis for FDA approval. Data sources included documents publicly available on the FDA website (approval letters, medical and statistical reviews) [28], peer-reviewed or conference reports summarizing FDA findings [14–16, 29], transcripts from FDA advisory committee meetings [3, 22, 23], and package inserts. Cytotoxic and/or targeted systemic therapies approved by the FDA were classified as first-line or second-line+ using the same definition as was used to classify clinical trials.

FDA Findings

In 1996–2003, a period governed by early AA policy, two applications were granted AA for second-line+ disease and two applications were granted regular approval, one for second-line+ and one for first-line disease (Table 2). In 1996 and 1998, respectively, docetaxel (Taxotere®; sanofi-aventis, Bridgewater, NJ) and capecitabine (Xeloda®; Hoffmann-La Roche) were granted AA based on higher ORRs reported by phase II registration trials that enrolled patients who were resistant to specified treatments [15, 28]. Regular approval was granted in 1998 and 2001, respectively, for the use of these agents in patients having failed prior therapy based on confirmatory phase III trials demonstrating survival benefits. In 1998, two trastuzumab (Herceptin®; Genentech, San Francisco, CA) applications were granted tandem regular approval for use in patients with human epidermal growth factor receptor (HER)-2⁺ disease. Trastuzumab in combination with paclitaxel (Taxol®; Bristol-Myers Squibb, New York) was approved for first-line disease based on a phase III registration trial demonstrating an independently reviewed longer TTP and a statistically significant greater 12-month survival rate for patients receiving trastuzumab and chemotherapy [3]. Patients in the trastuzumab and paclitaxel subgroup had a longer TTP with a trend toward longer survival [28]. Single-agent trastuzumab was approved for use in patients with relapsed disease based on a phase II registration trial demonstrating a higher ORR and supported by the first-line breast cancer approval [3, 28].

In 2004–2009, a period governed by current AA policy, five applications were granted regular approval and one application was granted AA. Of the six approvals, four applications were for second-line+ disease, and two were for first-line disease. Two applications for the use of ixabepilone (Ixempra®; Bristol-Myers Squibb, New York) in resistant disease were granted tandem regular approval in 2007; the use of ixabepilone in combination with capecitabine in resistant disease was approved based on an independently confirmed longer PFS interval in a phase III registration trial [28], and the use of ixabepilone monotherapy in highly resistant patients was approved based on a greater ORR in a phase II registration trial and supported by the first-line approval [3]. Nab-paclitaxel (Abraxane®; American Bioscience, Blauvelt, NY) and lapatinib (Tykerb®; GlaxoSmithKline, Philadelphia) were also granted regular approval for the treatment of relapsed MBC patients; in 2005, nab-paclitaxel monotherapy was approved under regulation 505(b)(2) based on the results of a phase III, noninferiority trial demonstrating a higher target lesion response rate than with paclitaxel; lapatinib in combination with capecitabine was approved in 2007 for use in patients with

HER-2⁺ tumors based on the results of an independent review of a phase III registration trial demonstrating a longer TTP [28]. Finally, applications for gemcitabine (Gemzar®; Eli Lilly, Indianapolis) and bevacizumab (Avastin®; Genentech, San Francisco) were approved for use in first-line disease; in 2004, gemcitabine in combination with paclitaxel was granted regular approval based on interim phase III data demonstrating an independently confirmed longer TTP and a strong trend toward longer survival ($p = .0489$), whereas bevacizumab in combination with paclitaxel was granted AA in 2008 for first-line use in patients with HER-2[−] disease based on independently confirmed phase III data demonstrating a longer PFS interval in the absence of longer OS [28].

DISCUSSION

MBC Studies and Sensitivity to Detect OS Gain

Our review of outcomes from 73 phase III MBC trials, conducted over the last three decades, reveals considerable discordance between regulatory standards for outcomes in MBC and clinical trial design. Although demonstration of a longer OS time is considered the primary measure of clinical benefit in MBC, especially for first-line trials, only five of 73 trials overall (7%) and four of 48 first-line trials (8%) reported OS as a primary endpoint. These findings indicate that only a very small number of trials had the capacity to detect improvements in survival. Not surprisingly, when trial outcomes were reviewed, a strikingly small proportion of trials overall (12%, $n = 9$) and even fewer first-line trials (8%, $n = 4$) demonstrated OS gains. These findings suggest that OS is not used by investigators as a primary endpoint and most trials are not powered to detect OS benefits.

Similar observations were recently published by Saad et al. [30] as well as by Wilcken and Dear [31]. Although there were differences in the prospective, systematic, trial selection criteria applied in our study, observations regarding OS outcomes were comparable. Saad et al. reviewed eligible trials ($n = 76$) that investigated systemic therapy, including predominantly cytotoxic, biological, and endocrine therapy, published in selected journals over the last decade (1998–2007) and found that 19.7% of trials demonstrated OS gains. Wilcken and Dear reviewed 63 studies obtained from the Cochrane Breast Cancer Group database and American Society of Oncology abstracts for 2000–2007 and reported that 13% of trials demonstrated significant OS gains. Although differences in trial selection may explain differences in the proportions of trials reporting OS effects (12% versus 19.7% versus 13%), the findings overall support a lack of an OS effect in individual MBC trials.

Although some have begun to question the rigor of clin-

Table 2. Regulatory approval of agents in advanced breast cancer [3, 28]

Drug	Year	Line of therapy ^a	Approved indication	Approval type	Trial design (supporting endpoint)
First period (1996–2003)					
Docetaxel (Taxotere®)	1996	Second-line +	Taxotere® (docetaxel) for injection concentrate is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy	Accelerated	Phase II (ORR)
	1998	Second-line +	Taxotere® (docetaxel) for injection concentrate for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy	Regular	Phase III (survival)
Capecitabine (Xeloda®)	1998	Second-line +	Xeloda® (capecitabine) tablets for the second-line treatment of patients with anthracycline- and paclitaxel-resistant metastatic disease	Accelerated	Phase II (ORR)
	2001	Second-line +	Xeloda® (capecitabine) tablets in combination with Taxotere® (docetaxel) for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline-containing chemotherapy	Regular	Phase III (survival)
Trastuzumab (Herceptin®)	1998	Second-line +	Trastuzumab is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER-2 protein and who have received one or more chemotherapy regimens for their metastatic disease	Regular	Phase II (ORR)
	1998	First-line	Trastuzumab in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress HER-2 protein and who have not received chemotherapy for their metastatic disease	Regular	Phase III HCT versus CT (TTP, by independent review, and 1-year survival rate)
Second period (2004–2008)					
Ixabepilone (Ixempra®)	2007	Second-line +	Ixempra® (ixabepilone) for injection in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated	Regular	Phase III (PFS, by independent review)
	2007	Second-line +	Ixempra® (ixabepilone) for injection as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine	Regular	Phase II (ORR, by independent review)
Nab-paclitaxel (Abraxane®)	2005	Second-line +	Abraxane® for injectable suspension (paclitaxel protein-bound particles for injectable suspension) for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy; prior therapy should have included an anthracycline unless clinically contraindicated	Regular	Phase III noninferiority (TLRR)
Lapatinib (Tykerb®)	2007	Second-line +	Tykerb® in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER-2 (ErbB-2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab	Regular	Phase III (TTP, by blinded independent review)
Gemcitabine (Gemzar®)	2004	First-line	Gemzar® (gemcitabine HCl) for injection in combination with paclitaxel for the <i>first-line</i> treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated	Regular	Phase III (TTP, by independent review, and survival)
Bevacizumab (Avastin®)	2008	First-line	Bevacizumab for use in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER-2 ⁻ breast cancer	Accelerated	Phase III (PFS, by independent review, and no survival)
^a Anthracycline resistance is defined as progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting. Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting. Abbreviations: CT, chemotherapy; HCT, Herceptin plus chemotherapy; HER-2, human epidermal growth factor receptor 2; ORR, overall response rate; PFS, progression-free survival; Second-line+, mixed populations of first-line patients and patients receiving prior therapy for metastatic breast cancer; TLRR, target lesion response rate; TTP, time to progression.					

ical trial design, others have begun to question the feasibility of detecting OS effects in an era of multiple lines of

MBC therapy. Recent modeling by Broglio and Berry [32] has focused attention on the relationship between OS and

postprogression survival (PPS). The model assumes that the investigational drug has a PFS benefit but no effect on PPS, and that the treatment-related improvement in PFS is carried over to a treatment-related improvement in OS. According to this model, the probability of detecting a statistically significant difference in OS is dependent on the length of the median PPS interval and the magnitude of difference in the PFS interval. Therefore, OS was found to be an appropriate primary endpoint when the median PPS interval was short; however, it was not considered to be an optimal endpoint when the PPS interval was >12 months, because of the greater likelihood that the effect would be diluted by subsequent lines of therapy. A recent study by Saad and colleagues [30] explored the relationship between OS and PPS in MBC patients and found that the average median PPS interval for cytotoxic or targeted MBC trials published in the last decade was 11.4 months overall—12.9 months for first-line trials and 8.5 months for second-line trials. These findings suggest that, in contrast to regulatory policy, OS may be a more appropriate endpoint for second-line trials, in which the PPS interval is shorter (8.5 months, second-line disease), whereas PFS and TTP may be more appropriate endpoints in first-line disease, in which the PPS interval is longer (12.9 months). Consistent with these findings, when we analyzed the occurrence of significant OS improvements in first-line disease regardless of primary endpoint ($n = 48$), only four studies reported gains in OS (8%), whereas 14 trials (29%) reported gains in PFS/TTP. In second-line+ disease ($n = 23$), five trials in total reported OS gains (22%), whereas 10 trials (43%) reported gains in PFS/TTP.

Furthermore, there is evidence to suggest that survival may be improving for MBC patients overall [33–35]. Recent data from a population-based analysis of survival trends in 2,150 MBC patients treated at the British Columbia Cancer Agency in Canada published by Chia and colleagues confirmed previously reported survival trends in MBC and linked these to the use of new agents. A significantly longer survival time was observed for patients diagnosed in 1991–1995 than for those diagnosed in 1997–1998 ($p = .002$), as well as for patients diagnosed in 1999 and 2001 versus those diagnosed in 1997–1998 ($p = .05$) [36]. The study found that the longer survival times corresponded to greater use of systemic therapy for MBC; 75% of patients diagnosed in 1991–1992 were administered therapy whereas >90% of patients diagnosed in 1994–2001 received therapy. Moreover, improvements in survival appeared to be associated with differences in the use of agents or combinations over time. For instance, the largest median OS gain (~4 months; $p = .002$) was observed in patients diagnosed in 1997–1998, the period corresponding

to the introduction of aromatase inhibitors, docetaxel, and trastuzumab, all agents that demonstrated longer survival times in individual trials. The findings may be explained, in part, by changes in the use of diagnostic or imaging technology and the safety of newer agents; however, they also support the notion that widespread access to newer therapies that have demonstrated superior outcomes, either gains in OS or PFS/TTP, can translate into greater population-based survival benefits in MBC patients.

Use of Non-OS Endpoints in Regulatory Approval

FDA regulatory policy holds that an improvement in OS or an established surrogate of OS is the gold standard for full approval of NMEs in MBC, although in recent years the introduction of AA policy has allowed for NME approval based on non-OS endpoints that are likely to predict OS [3]. Our review of the regulatory history revealed that, of the 37 phase III trials conducted in the last 15 years, only 12 new systemic therapies were approved for the treatment of MBC since 1995. Of these, eight systemic therapies in total were approved based on non-OS outcomes (Table 2). Of the 26 phase III trials conducted in first-line disease, only three new systemic therapies were approved for first-line treatment—two based on OS-outcomes and one based on non-OS outcomes [28].

The debate regarding appropriate measures of clinical benefit in MBC patients is ongoing [3]. Proponents of non-OS measures of clinical benefit argue that, in an era of multiple lines of subsequent therapy, PFS and TTP should be considered true endpoints because they are not affected by subsequent lines of therapy, and that slowing disease progression has intrinsic clinical and psychological value from the patient's perspective. However, the recent ODAC recommendation [37] to withdraw the breast cancer indication from the bevacizumab label despite a modest and statistically significant PFS effect has raised questions regarding the magnitude of effect that should be considered clinically significant as well as whether assessment of PFS should be based on median values or hazard ratios. The lack of reproducibility of the PFS benefit seen in initial studies underscores the importance of rigorous, blinded clinical trial design and independent review of treatment outcomes when considering non-OS outcomes.

The question of which endpoints are of intrinsic value was recently addressed in a survey conducted by Sheikh-Yousouf and colleagues at the University of Toronto, Toronto, Canada [10]. In total, 28 Canadian breast cancer oncologists responded to the survey. When asked to state the most important endpoint in selecting a therapy for their MBC patients, 54% of clinicians reported that OS was most

important whereas 46% felt that PFS and TTP were important. When asked what magnitude of effect would make treatment worthwhile, clinicians indicated that an absolute gain in OS of 2–6 months would be warranted to justify treatment. These results are limited by a small sample size; however, the findings indicate that clinicians were divided between PFS/TTP and OS as the most important endpoint, underscoring the intrinsic clinical value of PFS/TTP.

The question of measuring clinical benefit becomes even more complex in light of our evolving understanding of the molecular heterogeneity of breast cancer. The ability to group tumors based on molecular signatures indicates varied tumor biology and the potential for divergent responses to a specific therapy. Important examples are studies that appear to be negative with regard to OS in unselected populations, but with biological understanding, subgroups are subsequently identified that have significant benefits; for example, cetuximab (Erbix®; ImClone and Bristol-Myers Squibb) [38–40] and panitumumab (Vectibix®; Amgen, Thousand Oaks, CA) [41] in wild-type (nonmutated) *K-ras* colorectal cancers. Given the emergence of molecular pathology and personalized medicine, there is an even greater urgency for collaboration between researchers and regulators.

CONCLUSIONS

Taken together, our findings have identified multiple important causes and implications of the current lack of efficiency in drug development for MBC. We have identified substantial discordance between the conduct and design of clinical trials and historical measures of clinical benefit. Although regulatory approvals continue to hold OS as the gold standard, few phase III trials have the capacity to detect OS effects, especially in the first-line setting. These findings underscore the importance of a unity of vision and better collaboration between clinical researchers and regulators worldwide in planning and implementing clinical trials in the MBC setting.

There is increasing evidence to suggest that population-based survival is improving for MBC patients overall,

which supports the notion that widespread access to newer therapies can prolong OS, even though only a few regimens have been associated with longer OS times in individual trials. These findings should be validated and, if confirmed, factored into the debate on how standards of clinical benefit in MBC are determined.

In the End, What Matters Most?

In the end, what matters most is that safe and effective treatments that benefit patients be made available in a timely fashion. To this end, we urge patients, clinicians, researchers, and regulators to reach a consensus on how best to measure clinical benefit in MBC therapy, and to work together to ensure that this standard forms the foundation of study design, conduct, analysis, drug approval, and drug reimbursement for new MBC agents.

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AUTHOR CONTRIBUTIONS

Conception/Design: Sunil Verma, André Robidoux, John R. Mackey
Administrative support: Sunil Verma, Deanna McLeod, André Robidoux, John R. Mackey
Collection and/or assembly of data: Sunil Verma, Deanna McLeod, André Robidoux, Ilídio R. S. Martins, John R. Mackey
Data analysis and interpretation: Sunil Verma, Deanna McLeod, André Robidoux, Ilídio R. S. Martins, John R. Mackey
Manuscript writing: Sunil Verma, Deanna McLeod, Gerald Batist, André Robidoux, Ilídio R. S. Martins, John R. Mackey
Final approval of manuscript: Sunil Verma, Deanna McLeod, Gerald Batist, André Robidoux, Ilídio R. S. Martins, John R. Mackey
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