ORIGINAL RESEARCH

Is progression-free survival a more relevant endpoint than overall survival in first-line HR+/HER2− metastatic breast cancer?

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Background: Hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−), metastatic breast cancer (MBC) accounts for 73% of all MBCs. Endocrine therapy (ET) is the basis of first-line (1L) therapy for patients with HR+/HER2− MBC. Novel therapies have demonstrated improvements in progression-free survival (PFS) compared to ET. The clinical relevance of PFS is being debated, as there is no proven direct correlation with overall survival (OS) benefit to date. We reviewed studies of HR+/HER2− MBC to assess PFS and other factors that influence OS and treatment response, and health-related quality of life (HRQoL).

Methods: The Embase®, Medline®, and Cochrane databases were systematically searched to identify studies in adult women with HR+/HER2− MBC, published between January 2006 and January 2017, and written in English. Phase II and III randomized controlled trials (RCTs), observational, and retrospective studies were included.

Results: Seventy-nine RCTs were identified: 58 (73%) in the 1L+ setting and 21 (27%) in second-line or greater settings. PFS hazard ratios (HRs) were reported in 61 (77%) studies; 31 (39%) reported significant PFS improvements. OS was reported in 44 (41%) studies; 12 (15%) reported significant OS improvements. Significant improvements in both PFS and OS were reported in only 6 (8%) studies (1 Phase II; 5 Phase III). Patients with HER2− MBC received, on average, ≥5 lines of therapy, with no consistent treatment pathway. Baseline characteristics, prior therapies, and the type and number of post-progression therapies significantly impacted OS. PFS, response rates, and HRQoL decreased with each line of therapy (EuroQol 5 Dimensions: 0.78 1L vs. 0.70 post-progression).

Conclusion: Few RCTs in HR+/HER2− MBC have demonstrated significant improvements in OS. Factors other than choice of 1L therapy impact OS, including post-progression therapies, which cannot be controlled in RCTs. This study emphasizes the importance of PFS improvement in 1L treatment of HR+/HER2− MBC.

Keywords: breast cancer, overall survival, progression-free survival, health-related quality of life, systematic literature review

Introduction

Breast cancer is currently the most common malignancy diagnosed in women and is associated with the second-highest mortality rates, after lung cancer. In 2016, there were 246,660 confirmed diagnoses of breast cancer and an estimated 40,450 deaths attributed to the disease.[1] Approximately 12.4% of women will be diagnosed with breast cancer in their lifetime and,[2] though the malignancy is diagnosed at an early stage in 90% of patients, most tumors will progress to advanced or metastatic disease.[3,4] Progression to metastatic breast cancer (MBC) is associated with median survival times of

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18–24 months, and only 5% of patients are anticipated to be disease-free and alive at 5 years following tumor metastasis.[5] Approximately 30%–40% of women diagnosed with invasive breast cancer will eventually develop MBC;[6] in the USA, the 5-year survival rate for women with MBC is about 26%.[1]

The most common neoplasms of the breast, found in 74% of patients, are hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2−). This subset of breast cancer has the most favorable disease prognosis, as HR-negative tumors respond to therapy at a lower rate and HER2+ tumors are more aggressive.[7] The standard of care for post-menopausal women with HR+/HER2− breast cancer is endocrine therapy (ET).[8] The primary agents used are selective androgen receptor modulators, which include tamoxifen (TAM) and fulvestrant (FUL); and aromatase inhibitors, which include exemestane (EXE), letrozole (LET), and anastrozole (ANA).[9] Despite the variety of available therapies, only 20%–40% of patients will respond to these agents and most will develop resistance during their course of therapy.[10,11]

Management of resistance requires the use of drugs that target the resistance pathway and subsequently improve sensitivity to ET.[8] Drugs approved by the US Food and Drug Administration for the treatment of HR+/HER2− advanced breast cancer in combination with aromatase inhibitors are the mammalian target of rapamycin (mTOR) inhibitor everolimus (EVE) and the cyclin-dependent kinase (CDK) 4/6 inhibitors abemaciclib, palbociclib (PALBO), and ribociclib (RIBO). EVE and PALBO have been shown to improve progression-free survival (PFS) compared to ET alone in first- and second-line randomized controlled trials (RCTs).[12,13] RIBO, given as first-line (1L) therapy for post-menopausal women with HR+/HER2− advanced breast cancer in combination with LET, has demonstrated improvement in PFS compared with LET alone in a Phase III RCT.[14]

While the above-mentioned clinical trials reported improvements in PFS, data on overall survival (OS) with the use of some drugs, such as PALBO and RIBO, are limited, and it is uncertain whether improved PFS correlates with benefits in OS. To evaluate the available evidence for PFS and OS across Phase II and III RCTs of patients with HR+/HER2− MBC, we conducted a systematic literature review (SLR). In addition, we conducted a targeted literature search to identify factors that may influence OS in HR+/HER2− MBC and underlie treatment patterns. We also examined efficacy and health-related quality of life (HRQoL) changes relative to the line of therapy in HR+/HER2− MBC to determine if any trends were present.

Methods
SLR protocol
An SLR was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[15] The inclusion criteria for the literature search and the methods of analysis were specified in advance and documented in a protocol, details are provided in the following section.

SLR eligibility criteria
The SLR included original reports of Phase II and III RCTs in adult women with HR+/HER2− MBC, written in English and published between January 2006 and January 2017. Trials that enrolled both HER2− and HER2+ patients were included if >80% of the enrolled patients had HER2− disease, requiring that results were provided for the HER2− subgroup. The extracted outcome measures for efficacy included PFS or time-to-progression (TTP), and OS reported as either median survival (in months) or hazard ratios (HRs) vs. comparators. Publications reporting meta-analyses were also retained in the SLR for reference cross-checking.

Studies with fewer than 10 patients and those that lacked any of the measures of interest were excluded. No limitations were placed on therapies except that they must be systemic. Studies of surgical interventions, radiotherapy/chemoradiation, or adjuvant/neo-adjuvant therapies were excluded.

In cases of duplicate publications or conference abstracts reporting data from a study with an available manuscript, the most recent manuscript was prioritized unless an older manuscript or more recent abstract included data points that were missing in the later manuscript.

The targeted literature search also included a review of post hoc statistical analyses of factors influencing OS, non-randomized studies of treatment patterns, and studies reporting HRQoL in HR+/HER2− MBC. The search strategy was based on similar criteria as mentioned earlier; however, eligible study designs also included observational studies, retrospective chart reviews, and patient surveys, provided that data on outcomes of interest were reported.

Information sources
Studies were identified based on searches of the Embase, Medline, Daily Medline, and Medline In-Process electronic databases, Cochrane Central Register of Controlled Trials, Cochrane Database of Reviews of Effect, and Cochrane Database of Systematic Reviews. Additionally, congress abstracts from the American Society of Clinical Oncology, European Society of Medical Oncology, European Breast Cancer Conference, and San Antonio Breast Cancer Symposium

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libraries were identified. The literature search was conducted in January 2017 and included studies from January 2006 up to the date of the search. The full search strategy is available in Tables S1–S3.

Study selection

Following the database searches, two independent analysts reviewed and selected studies based on abstracts and titles. The eligibility of abstracts and full-text articles was then independently assessed by the two reviewers in a standardized manner. Discrepancies were resolved by consensus between both reviewers.

Data collection process

A data extraction sheet was developed to tabulate the studies' characteristics (detailed below). One reviewer extracted the data and a second checked the extracted data for accuracy. As above, discrepancies were resolved by consensus between the two reviewers.

Data items

The following data elements were extracted from each study: 1) trial characteristics included reference, name of trial, study design, phase of study, line of therapy (1L or second and later [2L+]), study interventions, class of intervention drug, and treatment arms; 2) population characteristics included total number of randomized participants, median age, number of patients with Eastern Cooperative Oncology Group performance status of 0 and 1, number of HER2− patients, number of HR+ patients, number of PR+ patients, endocrine status (resistant, sensitive, or mixed), number of premenopausal par-

ticipants, number of patients with visceral metastases, number of patients with 1, 2, or ≥3 metastatic sites, number of patients with prior ET, and number of patients with prior adjuvant/neo-adjuvant/metastatic-setting chemotherapy; 3) trial outcomes included type of primary endpoint, whether PFS/TTP and/or OS were reported, PFS/TTP and OS results (median months of survival, HRs, confidence intervals, and p-values).

For the targeted literature search, additional data elements extracted included any HRQoL outcomes, patient burden (humanistic), number of lines of therapies including duration, sequence and efficacy in each line, and factors associated with OS.

Results
Study selection

The database search returned 1017 records (Embase: 501, Cochrane: 272, Medline: 244). Of these, 636 were excluded due to failure to meet the inclusion criteria of population, intervention, outcomes, or study design. A further 274 duplicates were excluded, leaving a total of 107 full-text articles that were extracted and included in this SLR, 79 of which represent unique studies (58 1L, 21 2L+; Figure 1). The remaining 28 articles presented updated or interim data, the results of subgroup analyses, or were meta-analyses.

Study characteristics

The breakdown of study treatments included in this SLR is presented in Table 1 and Figure 2. In total, 58 1L studies and 21 2L+ studies were included. PFS HR data were reported in 61 of the 79 unique studies (77%); of these, 31 (51%) reported significant PFS improvements. OS HR data were
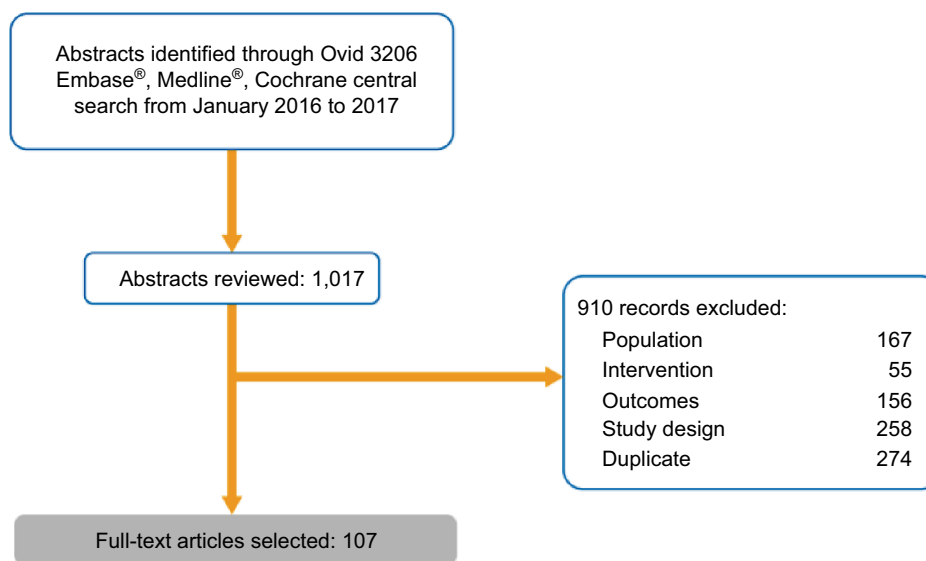

Figure 1 Randomized controlled trial evidence flow for systematic literature review of clinical evidence.

reported in 44 of the 79 studies (56%); of these, only 12 (27%) reported a significant OS improvement. Significant improvements in both PFS and OS were reported in only 6 (8%) studies (1 Phase II; 5 Phase III).

PFS

More Phase III than Phase II (15 vs. 4) RCTs reported statistically significant improvements in PFS in 1L therapy. Among the 19 1L studies that reported significant PFS improvement, 9 were of tyrosine kinase inhibitors (TKI) plus chemotherapy (CHEMO) and 3 were of CDK 4/6 inhibitor plus ET treatments.

We further evaluated PFS among RCTs that included ET as a control arm. Here, the greatest difference in PFS among arms was seen with the addition of a CDK4/6 inhibitor (PALBO or RIBO) to LET (HRs of 0.49 and 0.56, respectively) or mTOR inhibitor (EVE) to either EXE or TAM (HRs of 0.45 and 0.54, respectively). Of these, the PALBO+LET and EVE+TAM trials were 1L studies, while EVE+EXE included mostly 2L+ patients.[13–15] Statistically significant

Table 1 Systematic literature review results according to OS and PFS reporting

N	All studies	First-line studies	Second-line studies and beyond
Reported PFS months	67	47	20
Reported PFS hazard ratio	61	45	16
Reported significant PFS	31	19	12
Reported OS months	46	35	11
Reported OS hazard ratio	44	27	17
Reported significant OS	12	9	3
Reported PFS and OS months	39	29	10
Reported PFS and OS hazard ratio	40	31	9
Reported significant PFS and OS	6	5	1
Total unique studies	79	58	21

Abbreviations: OS, overall survival; PFS, progression-free survival.

improvements in PFS were also seen with the addition of bevacizumab (BEV) to LET vs. LET alone (HR =0.75) and BEV to LET or FUL (vs. either LET or FUL, HR =0.83).[16,17] Although the addition of ANA to FUL (vs. FUL alone) led to significant improvements in PFS (HR =0.80) in one study, this finding was not supported by another study (ANA+FUL vs. placebo + FUL, HR =1.0; Figure 3).[17]

Overall survival

Among the 79 RCTs, 46 (58%) reported incremental OS months, and 44 (56%) presented HRs for OS. However, only 12 studies (15%) reported statistically significant improvements in OS: 9 were 1L and 3 were 2L+.

Six Phase III RCTs reported statistically significant improvements in OS in 1L therapy compared to 3 Phase II trials. Among the 9 1L studies that reported significant OS improvement, 3 were of ET and 2 were of TKI+CHEMO treatments.

Among RCTs with ET as a control arm, only 1 of 9 studies reported statistically significant improvements in OS. The addition of EVE to TAM (vs. TAM alone) yielded a 55% reduction in risk of death, though this was reported in a small (n=111) Phase II study of patients receiving 1L therapy.[16] The addition of PALBO to LET vs. LET led to a 19% risk reduction (HR=0.81).[13] In 2 RCTs, the addition of ANA to FUL yielded HRs of 0.81 and 0.95, respectively.[18,19] The addition of BEV to either LET or LET+FUL did not yield consistent results with HRs of 0.87 and 1.13,[20,17] respectively (Figure 4).

PFS and OS by study phase and line of therapy

Among the 79 unique RCTs, only 6 studies (8%) reported statistically significant differences in both PFS and OS. Among these studies, the majority (5) were investigations of 1L
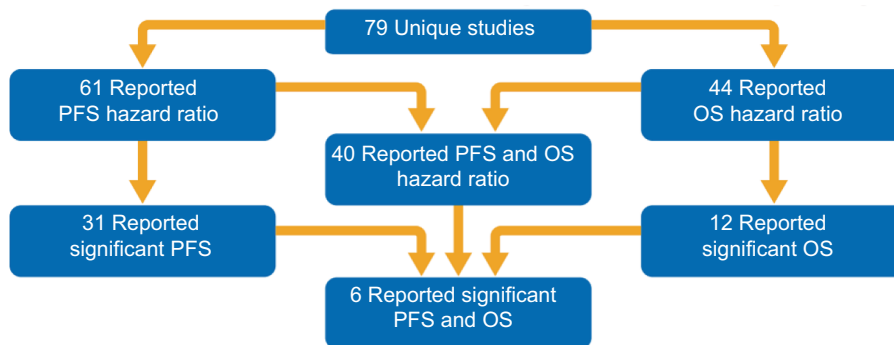

Figure 2 Systematic literature review results according to OS and PFS reporting.
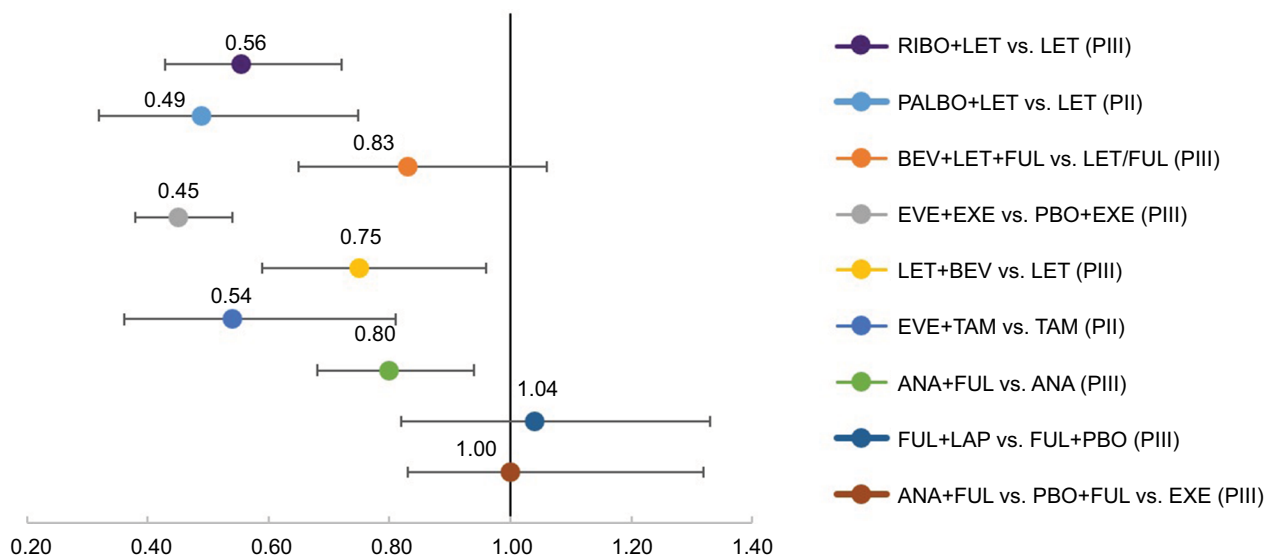**Abbreviations:** OS, overall survival; PFS, progression-free survival.

Figure 3 PFS HRs in selected randomized controlled trials
Notes: <1 favors experimental arm, >1 favors control arm.
Abbreviations: ANA, anastrole; BEV, bevacizumab; EXE, exemestane; EVE, everolimus; FUL, fulvestrant; HR, hazard ratio; LAP, lapatinib; LET, letrozole; PII, Phase II; PIII, Phase III; PALBO, palbociclib; PBO, placebo; PFS, progression-free survival; RIBO, ribociclib; TAM, tamoxifen.
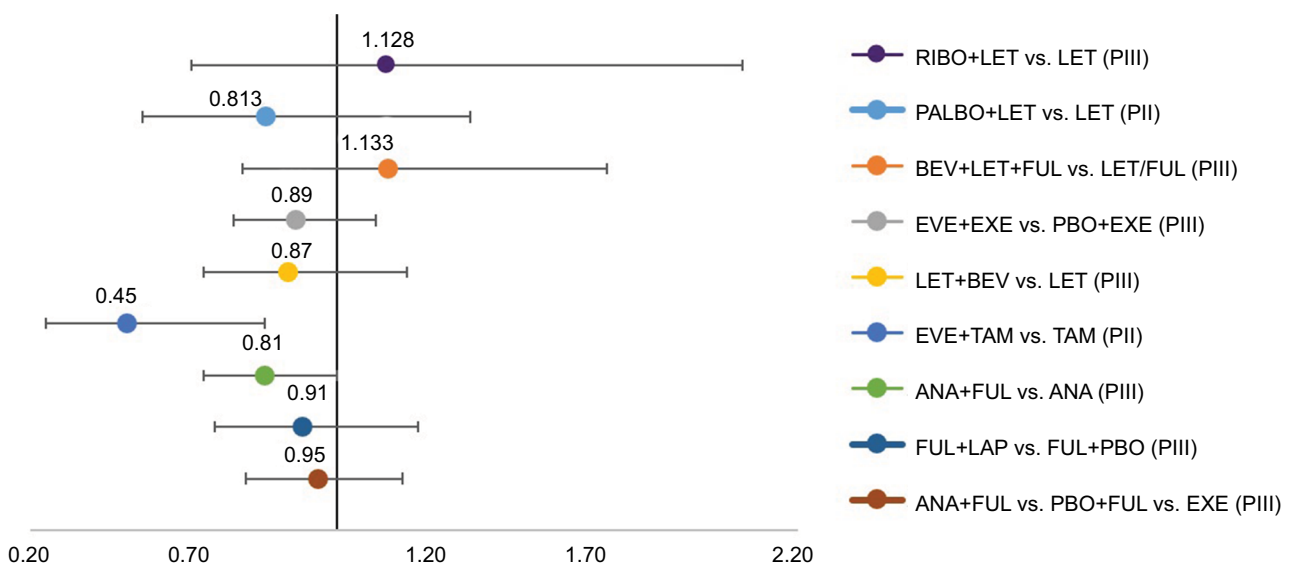

Figure 4 OS HRs in selected studies.
Notes: <1 favors experimental arm, >1 favors control arm.
Abbreviations: ANA, anastrole; BEV, bevacizumab; FUL, fulvestrant; EXE, exemestane; EVE, everolimus; HR, hazard ratio; LAP, lapatinib; LET, letrozole; OS, overall survival; PII, Phase II; PIII, Phase III; PALBO, palbociclib; TAM, tamoxifen; PBO, placebo; RIBO, ribociclib.

therapies, and Phase III RCTs (also 5). Among 4 Phase III 1L studies that reported statistical significance in PFS and OS, 2 were of TKI+CHEMO, 1 of TKI+ET, and 1 of ET combination.

Factors influencing overall survival

Multiple studies conducted subgroup analyses to identify clinical factors with an impact on OS. Park et al reported that median PFS of at least 7.6 months was associated with significantly longer OS (HR=0.34, confidence intervals:

0.25:0.46, $p<0.001$).[21] This and other studies also reported that demographic factors, baseline characteristics, prior adjuvant/neoadjuvant therapy as well as post-progression therapy, and the total number of lines of therapy have significant impact on final OS.[22–30]

Although RCTs can balance study populations on baseline characteristics and prior therapies, post-progression therapies or metastases cannot be controlled for in 1L studies. Factors demonstrated to affect OS are summarized in Table 2.

Table 2 Factors impacting OS in MBC

Demographics	Disease characteristics	Prior therapy	Post-progression therapy
Age ≥65 years	Measurable disease	Prior endocrine therapy	Type of post-progression
Region	ECOG (1–2 vs. 0)	Prior chemotherapy (adjust/neoadjuvant)	Lines of post-progression therapy
	Number of organs involved		
	Number of metastatic sites		
	Visceral involvement		
	CNS metastases		
	Liver metastases		
	Disease-free interval		

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; MBC, metastatic breast cancer, OS, overall survival.

Treatment patterns and HRQoL

Our targeted search found significant variability in the treatments used for 1L and 2L+ therapies, with no preferred treatment pathway and many patients receiving up to 6 lines of therapy.[31] The median length of PFS and response to treatment decreased with subsequent lines of therapy.[21] Park et al further reported that median PFS of >7.6 months in 1L treatment was an important predictor of longer PFS in 2L, and PFS of >5.1 months in 2L was associated with longer PFS in 3L.[21]

There were very limited data available on HRQoL associated with PFS. One abstract reported EuroQol 5 Dimensions (EQ-5D) data from a study of S1 (tegafur, gimeracil, and oteracil) vs. taxanes (paclitaxel or docetaxel), showing decline in EQ-5D scores from 1L therapy to post-progression (0.81 vs. 0.72). Additionally, a recent abstract presenting data from the MONALEESA-1 trial on RIBO and LET treatment in HR+/HER2− MBC reported that HRQoL declined post-progression.[32]

Discussion

OS, as a direct measurement of clinical benefit to a patient, has been a preferred measurement of efficacy in MBC RCTs. While no measurement can definitively gauge treatment efficacy, OS conforms to the standards of evidence-based medicine in that it is easily measured, and is considered unbiased and objective. However, our research has demonstrated that, overall, a minority of studies have reported significant OS improvements: among the 79 identified RCTs in HR+/HER2− MBC, only 12 reported improvements in OS. Besides the choice of treatment in 1L therapy, many factors influence OS. Multiple studies reported that patient demographics, baseline characteristics, prior adjuvant/neoadjuvant therapy as well as post-progression therapy, and the total number of lines of therapy have significant impacts on final OS. Though further removed from objectivity, PFS is commonly reported because it can be observed while respecting the time constraints that

often impinge on clinical trials. Most importantly, PFS in 1L was documented as a significant factor in OS.[33]

There is significant heterogeneity in MBC treatment, with many lines of therapies and no defined pathway. Macalalad et al documented variability in treatment patterns and over 5 lines of therapies among MBC patients.[31] Kantar Health CancerMpact 2016 also reported on variability of treatment choices and observed that a significant proportion of patients who progress on a previous line of therapy subsequently utilize the next line of treatment for up to 6 lines.[34] With the considerable variability in treatment patterns and many contributing factors to OS, there are concerns that the efficacy of 1L therapies measured by OS may be diluted or biased in clinical trials, thereby underestimating their true clinical benefit.

Both PFS and response rates decrease as MBC progresses. Park et al reported a decline in months of PFS and response rates by line of therapy among MBC patients.[21] Quality of life also decreases from 1L therapy to post-progression, as reported by Fukuda et al.[32] As such, improvement in PFS with maintained HRQoL may be a more suitable and robust endpoint in 1L RCTs of patients with HR+/HER2− MBC.

Conclusion

The goal of treatment in MBC is to prolong life while maintaining the quality of survival. As such, RCTs of MBC treatments ideally measure OS and HRQoL. In clinical trials of 1L therapies, OS is affected by multiple factors that cannot be controlled. This study examined important characteristics of RCTs in MBC and their relevance to OS. In addition to demographics, baseline characteristics, and prior adjuvant/neoadjuvant therapy, final OS is influenced by post-progression therapy and the total number of lines of therapy. This SLR found that ultimately very few 1L RCTs report OS improvement. PFS improvement is more often reported and its significance is perhaps understated. PFS, response rates, and QoL decrease as the disease progresses and with each line of therapy. PFS in

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1L is an important predictor of PFS in further lines of therapy. In 1L treatments for MBC, PFS improvement coupled with maintained HRQoL provides patients with more meaningful time and may be considered the best possible outcome.

Acknowledgments

Author contributions

A Forsythe and G Tremblay made substantial contributions to the conception and design, analyzed and interpreted the data, and helped to draft the article. A Shor acquired, analyzed, and interpreted data. D Chandiwana, J Barth, M Thabane, and J Baeck contributed to conception and development of this study and evaluation and interpretation of the data. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

D Chandiwana, J Barth, M Thabane and J Baeck are employees of Novartis. The authors report no other conflicts of interest in this work.

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Supplementary materials

Search strategy

Table S1 Ovid Medline® Epub ahead of print, in-process, and other non-indexed citations. Ovid Medline® daily and Ovid Medline® 1946 to present database

	Date: January 2017	
1	Exp breast neoplasms/	250,773
2	(Breast adj6 cancer$).af.	246,948
3	(Breast adj6 neoplas$).af.	252,542
4	(breast adj6 carcinoma$).af.	63,807
5	(Breast adj6 tumor$).af.	7401
6	(Breast adj6 tumor$).af.	48,416
7	1 or 2 or 3 or 4 or 5 or 6	336,672
8	Metasta$.mp. or exp neoplasm metastasis/	477,568
9	7 and 8	74,656
10	("Metastatic breast cancer" or "metastatic breast neoplasms").af.	11,972
11	9 or 10	74,661
12	"Hormone receptor positive".af.	2300
13	"Hormone receptor-positive".af.	2300
14	("Estrogen receptor-positive" or "oestrogen receptor-positive").af.	4218
15	"Progesterone receptor-positive".af.	732
16	"Hormone sensitive".af.	3719
17	12 or 13 or 14 or 15 or 16	10,513
18	11 and 17	1955
19	Exp randomized controlled trials/	111,704
20	Randomized controlled trial.pt.	448,501
21	Exp random allocation/or exp randomization/	89,826
22	Exp placebos/	34,191
23	Exp double-blind method/or double-blind$.af.	180,225
24	Exp multicenter study/or Multicent$.af.	279,405
25	Random$.ti,ab,kw,sh.	1,124,651
26	Blind$.ti,ab,kw,sh.	263,750
27	Placebo$.ti,ab,kw,sh.	203,823
28	Parallel$.ti,ab,kw,sh.	266,233
29	Exp clinical trial, phase 3/	13,116
30	Exp clinical trial, phase 2/	29,002
31	("Phase III" or "phase 2" or ("phase III" or "phase II")).af.	112,861
32	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	1,752,319
33	18 and 32	610
34	Limit 33 to yr="2006–Current"	422
35	Limit 34 to "review articles"	74
36	34 not 35	348
37	Limit 36 to humans	297
38	Remove duplicates from 37	**244**

Notes: Bold font indicates the total number of articles collect in each search.

Table S2 EBM Reviews, Cochrane Database of Systematic Reviews 2005 to June 9, 2017; Database Info Icon EBM Reviews, ACP Journal Club 1991 to May 2017; Database Info Icon EBM Reviews, Database of Abstracts of Reviews of Effects 1st Quarter 2016; Database Info Icon EBM Reviews, Cochrane Central Register of Controlled Trials April 2017; Database Info Icon EBM Reviews, Cochrane Methodology Register 3rd Quarter 2012; Database Info Icon EBM Reviews, Health Technology Assessment 4th Quarter 2016; Database Info Icon EBM Reviews, NHS Economic Evaluation Database 1st Quarter 2016

Date: January 2017

1	Exp breast neoplasms	9184
2	Breast adj6 cancer$	21,934
3	Breast adj6 neoplas$	10,989
4	Breast adj6 carcinoma$	2112
5	Breast adj6 tumor$	573
6	Breast adj6 tumor$	1851
7	1 or 2 or 3 or 4 or 5 or 6	23,744
8	Metasta$	21,265
9	Neoplasm Metastasis.sh.	2226
10	8 or 9	21,265
11	7 and 10	6121
12	"Hormone receptor positive"	607
13	Hormone receptor-positive' 588	607
14	Estrogen receptor-positive' or "oestrogen receptor-positive" 654	522
15	"Progesterone receptor-positive" 250	109
16	Hormone sensitive 986	210
17	12 or 13 or 14 or 15 or 16 2325	1318
18	11 and 17	453
19	Limit 18 to yr="2006–Current"	329
20	Limit 19 to english language	284
21	Limit 20 to humans	278
22	Remove duplicates from 21	**272**

Notes: Bold font indicates the total number of articles collect in each search.

Table S3 Embase database 1974 to 2017 June 09

Date: January 2017

1	Breast cancer'.af.	404,912
2	Exp breast tumor/	456,726
3	(Breast adj6 tumor*).mp	10,358
4	(Breast adj6 tumor*).mp	132,238
5	(Breast adj6 neoplas*).mp	22,949
6	(Breast adj6 cancer*).mp	446,177
7	(Breast adj6 carcinoma*).mp	95,202
8	1 or 2 or 3 or 4 or 5 or 6 or 7	513,111
9	Metastasis/	310,169
10	Metasta*	697,570
11	9 or 10	697,570
12	8 and 11	123,533
13	("metastatic breast neoplasms" or "metastatic breast neoplasm" or "metastatic breast cancer").mp	19,097
14	12 or 13	123,533
15	Hormone receptor positive' OR "hormone receptor-positive"	3917
16	Progesterone receptor-positive' OR "progesterone receptor positive"	1185
17	Estrogen receptor-positive' or "oestrogen receptor-positive"	7549
18	Hormone sensitive'	4924
19	Hormone adj3 positive	5460
20	15 or 16 or 17 or 18 or 19	17,999
21	14 and 20	4258
22	Exp "randomized controlled trial"/	481,221
23	Randomization/	84,943
24	Random*.ti,ab.	1,181,594
25	Parallel*.ti,ab	303,245

(Continued)

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Is PFS a more relevant endpoint than OS in 1L HR+, HER2– MBC?

Table S3 (*Continued*)

26	([Single or double or triple] adj3 [blind* or mask* or dummy]).ti,ab.	201,720
27	Double-blind' or "double-blinded"	219,339
28	Multicenter study' or multicent*	277,968
29	Blind*.ti,ab.	341,487
30	Placebo*.ti,ab	254,042
31	("Phase III" OR "phase II").ti,ab	40,098
32	("Phase III" OR "phase II").ti,ab	111,214
33	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	2,028,041
34	21 and 33	1173
35	Limit 34 to human	1094
36	Limit 35 to english language	1075
37	Limit 36 to yr="2006 -Current"	898
38	Limit 37 to embase	562
39	Limit 38 to (article or conference abstract)	**501**

Notes: Bold font indicates the total number of articles collect in each search.