The Oncologist®

Breast Cancer

Treatment of Metastatic Breast Cancer in a Real-World Scenario: Is Progression-Free Survival With First Line Predictive of Benefit From Second and Later Lines?

Marta Bonotto,[a] Lorenzo Gerratana,[a,b] Donatella Iacono,[a] Alessandro Marco Minisini,[a] Karim Rihawi,[a] Gianpiero Fasola,[a] Fabio Puglisi[a,b]

[a]Department of Oncology, University Hospital of Udine, Udine, Italy; [b]Department of Medical and Biological Sciences, University of Udine, Udine, Italy

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Breast neoplasms • Overall survival • Treatment outcome • Decision making

Abstract

Introduction. Despite the availability of several therapeutic options for metastatic breast cancer (MBC), no robust predictive factors are available to help clinical decision making. Nevertheless, a decreasing benefit from first line to subsequent lines of treatment is commonly observed. The aim of this study was to assess the impact of benefit from first-line therapy on outcome with subsequent lines.

Methods. We analyzed a consecutive series of 472 MBC patients treated with chemotherapy (CT) and/or endocrine therapy (ET) between 2004 and 2012. We evaluated progression-free survival (PFS) at first (PFS1), second, third, and fourth therapeutic lines, according to treatment (ET and/or CT) and tumor subtypes.

Results. In the whole cohort, median overall survival was 34 months, and median PFS1 was 9 months. A 6-month benefit was shown by 289 patients (63.5%) at first line, 128 (40.5%) at second line, 76 (33.8%) at third line, and 34 (23.3%) at fourth line. Not having a 6-month benefit at PFS1 was associated with less chance of benefit at second line (odds ratio [OR]: 0.48; 95% confidence interval [CI]: 0.29–0.77, $p = .0026$) and at any line beyond first (OR: 0.39; 95% CI: 0.24–0.62, $p < .0001$). In the total series, after stratification for tumor subtypes, a strong predictive effect was observed among HER2-positive tumors (OR: 0.2; 95% CI: 0.05–0.73, $p = .0152$).

Conclusion. Our results suggest that the absence of at least a 6-month benefit in terms of PFS with first-line therapy predicts a reduced probability of benefit from subsequent therapeutic lines, especially in HER2-positive disease. ***The Oncologist*** 2015; 20:719–724

Implications for Practice: This study supports evidence showing that the absence of a 6-month benefit in terms of progression-free survival with first-line therapy predicts a lack of benefit from subsequent therapeutic lines in metastatic breast cancer. The random distribution of benefit experienced by a subset of the cohort further spurs an interest in identifying predictive factors capable of identifying the most appropriate therapeutic strategy.

Introduction

Breast cancer (BC) is the most common cancer among women worldwide, with a total of 232,670 new cases of invasive BC and 40,000 deaths estimated to occur in the United States in 2014 [1]. In European countries, the total number of new cases and cancer deaths from BC estimated in 2012 was 364.4 and 90.6 per 100,000, respectively. About 1 in 8 (12%) women will develop invasive BC during their lifetime [1, 2].

Approximately 6%–10% of newly diagnosed BC cases are metastatic, whereas 20%–50% of patients with early BC will eventually develop metastatic disease [3].

In this setting, systemic treatment aims to maintain or enhance quality of life and to delay further spread of disease, prolonging survival. Nevertheless, metastatic breast cancer (MBC) remains an incurable disease [4].

Estimating overall survival (OS) for women with MBC is a compelling issue that oncologists have to face when dealing with this tumor type. The median OS for women with MBC is about 24 months, ranging from 6.3 months in the worst-case scenario to 55.8 months in the best-case scenario [5]. BC is a highly heterogeneous disease consisting of different subtypes, each exhibiting specific histopathological and biological features, and variable clinical outcome and response to different treatments. Based on these premises, it should come as no surprise that different levels of understanding and treatment of

Correspondence: Fabio Puglisi, M.D., Ph.D., Department of Oncology, University Hospital of Udine, Piazzale S.M. Misericordia, 33100 Udine, Italy. Telephone: 39-0-432-552754; E-Mail: fabio.puglisi@uniud.it Received January 2, 2015; accepted for publication March 5, 2015; published Online First on May 27, 2015. ©AlphaMed Press 1083-7159/2015/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2015-0002

these subtypes have been reached. HER2-positive disease is a stark example of this variability of outcomes: although a HER2-positive tumor used to be associated with poor prognosis, the development of anti-HER2 therapies has dramatically changed the prognosis of patients with HER2-positive disease [6–8].

Sequential use of single agents is considered a standard approach for patients with MBC and is preferred mainly because of reduced toxicity compared with combination chemotherapy, with most women treated with multiple lines of therapy. All therapeutic decisions are usually tailored, taking into account several variables such as tumor burden, sites of the disease (visceral vs. nonvisceral), HER2 status, hormone receptor (HR) status, disease-free interval, age, and menopausal status. Despite the availability of several therapeutic options for MBC, there are no validated predictive factors of benefit for treatments beyond first line that could help in choosing the most appropriate sequence of drugs to use in each different case [9, 10]. Moreover, although it is still unclear how the choice of a specific therapy can influence further treatments, data suggest that the duration of disease control achieved with initial lines of treatment may affect the duration of benefit from subsequent therapies [11]. Given the impact of cancer-care costs, this topic is increasingly important to promote the proper use of resources. Limiting further chemotherapy for patients not experiencing response to three consecutive regimens is among the strategies suggested by the American Society of Clinical Oncology (ASCO) to improve care and to reduce costs [12].

The aim of this study is to assess how the benefit gained from first-line treatment may influence the outcome with subsequent lines and to analyze and explore differences according to tumor subtypes.

Materials and Methods

We analyzed a consecutive series of 472 MBC patients treated at the Department of Oncology of the University Hospital of Udine, Italy, between 2004 and 2012. Pathological and clinical data were extracted from electronic medical records according to strict privacy standards and anonymized before analysis.

Based on this database, simplified BC profiles were defined as follows: HR positive (estrogen receptor [ER] or progesterone receptor [PR] positive, HER2 negative), HER2 positive (HER2 amplification or overexpression and any ER or PR status), and triple negative (ER and PR negative, HER2 negative). The threshold for HR positivity was set at 1% [13].

We collected data about chemotherapy (CT), endocrine therapy (ET), and anti-HER2 therapy.

OS was defined as the time elapsed between the start of treatment for metastatic disease and death or last follow-up. Progression-free survival (PFS) was defined as the time elapsed between treatment initiation and tumor progression or death from any cause, censoring patients who were lost to follow-up [14]. Three distinct analyses were conducted, first, by counting both CT and ET lines; second, by counting CT lines only; and third, by counting ET lines only. We evaluated progression-free survival at first (PFS1), second (PFS2), third (PFS3), and fourth (PFS4) lines of treatment, according to treatment (ET and/or CT) and tumor subtypes. Postprogression survival (PPS) was defined as the interval between progression at first line and death or last follow-up [15].

The clinical benefit achieved with each line of treatment was defined as progression or death more than 6 months after starting a specific treatment. We evaluated the distribution of clinical benefit for first, second, third, and fourth lines of treatment. The threshold of 6 months for disease-control duration was chosen arbitrarily on the basis of data in the literature about mean value for median PFS1 (7.6 months) [5] and its easy application in clinical practice. The analysis focused on odds ratio (OR) calculated to estimate the chance of having a 6-month benefit from a line beyond the first if a 6-month benefit was not observed at first line. Other potential predictors of therapeutic benefit beyond first line were also evaluated through univariate and multivariate analyses.

To evaluate the different impact of not having 6-month benefit according to tumor subtypes, a subgroup analysis was conducted.

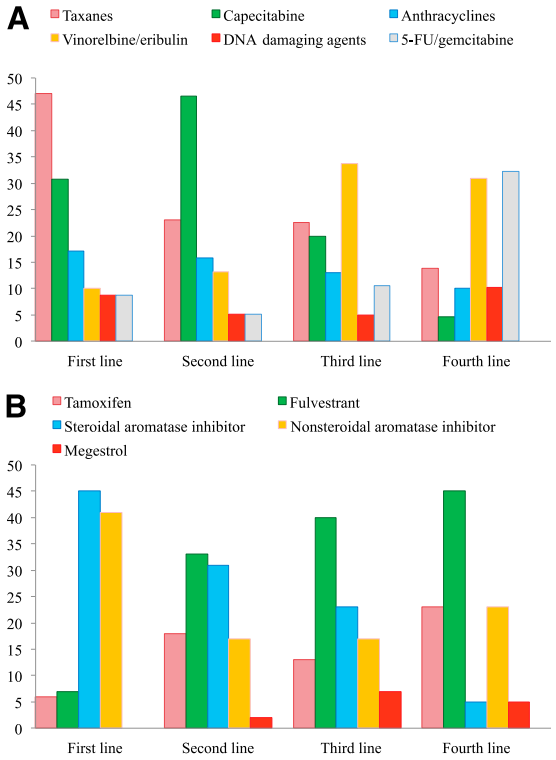

Figure 1. Class of antineoplastic agents according to line of treatment.

Abbreviation: 5-FU, 5-fluorouracil.

Results

Patient and disease characteristics are reported in Table 1. Data about treatment history, categorized according to the drug's mechanism of action, are presented in Figure 1. Overall, 62.9% of patients had HR-positive disease, 24.8% had HER2-positive disease, and 12.3% had triple-negative disease.

The median follow-up of the series was 46.7 months. One-third of patients were metastatic at diagnosis. Approximately 37% and 22% of patients had received anthracyclines and taxanes, respectively, as part of adjuvant or neoadjuvant treatment. Twenty-two patients had received trastuzumab in either the adjuvant or neoadjuvant setting.

The median number of treatment lines for MBC was 3 (range: 1–13). All patients included in this analysis received a first-line treatment, and 335 (71%), 246 (52%), and 158 (33%) received second, third, and fourth lines of therapy, respectively. The number of patients according to lines of treatment, distinguishing

Table 1. Patient and disease characteristics

Characteristic	*n*	%
ER status	433	
Positive (≥1%)	339	78.3
Negative (<1%)	94	21.7
PR status	434	
Positive (≥1%)	275	63.3
Negative (<1%)	159	36.6
HER2 status (IHC and/or FISH tests)	420	
Positive	89	21.2
Negative	328	78.1
Previous treatment for early disease	472	
Chemotherapy	234	49.6
Endocrine therapy	234	49.6
Anti-HER2	22	4.7
Stage at diagnosis	471	
M0	324	68.8
M1	147	31.2
Sites of metastasis	472	
Bone only	123	26.1
Visceral	243	51.5
Lung	114	24.2
CNS	21	4.4
Liver	117	24.8
ECOG PS		
At first line	425	
≥2	44	10.4
0–1	381	89.6
At second line	325	
≥2	38	11.7
0–1	287	88.3
At third line	241	
≥2	32	13.3
0–1	209	86.7
At fourth line	153	
≥2	20	13.1
0–1	133	86.9

Age at diagnosis of metastatic breast cancer: median, 63 years; 25th to 75th percentile, 53–73.
Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; MBC, metastatic breast cancer.

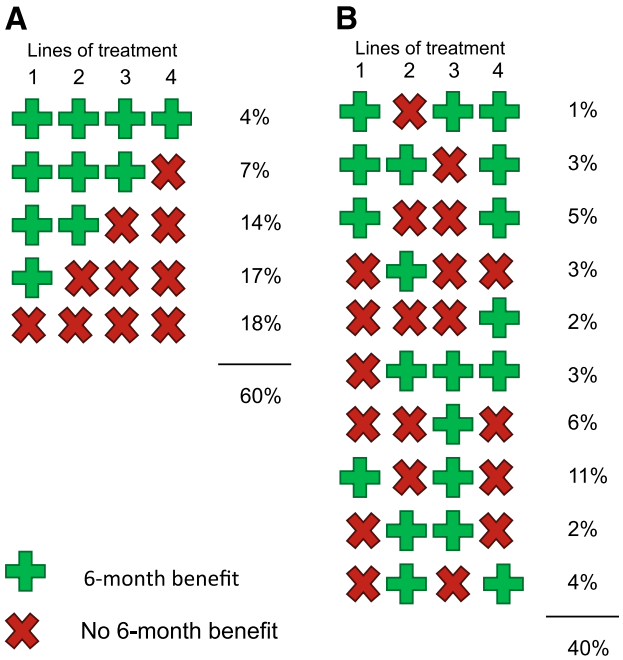

Figure 2. Clinical benefit for first, second, third, and fourth lines of treatment observed linear **(A)** and scattered **(B)** distribution.

the successive categories of treatments for the HR-positive population (endocrine treatment or chemotherapy), is shown in Figure 2. Combination chemotherapy was preferred in 82 patients (22.47%) as first-line treatment and subsequently in 28 patients (12%) at second line, in 10 patients (6.25%) at third line, and in 9 patients (10.47%) at fourth CT line. Among patients with HR-positive disease, endocrine maintenance treatment was received by 16.72% (57 of 341) in first-line, 5.22% (13 of 249) in second-line, 5.38% (10 of 186) in third-line, and 2.38% (3 of 126) in fourth-line treatment. In the HER2-positive population, an anti-HER2 drug was received by 94% at first line, 57% at second line, 54% at third line, and 42% at fourth CT line. Among patients with bone-only metastatic disease, 37% (45 of 123) received radiotherapy with palliative intent at one disease site or more.

In the whole cohort, median OS was 34 months, and median PFS1, PFS2, PFS3, and PFS4 were 9, 4.4, 4, and 3 months, respectively. Median PFS1 for CT was 7.1 months, whereas median PFS1 for ET was 9.5 months. Median PFS2, PFS3, and PFS4 were respectively 3.7, 3.3, and 4.2 months in CT lines and 4.7, 3.9, and 4.2 months in ET lines (Table 2).

As expected, subgroup analysis showed significantly shorter PFS1 for triple-negative disease compared with HR- or HER2-positive disease (3.8 vs. 9.9 months, $p < .0001$). PFS2 was also significantly different between HR- and HER2-positive populations (4.3 vs. 6.4 months, $p = .02$) and between patients with or without triple-negative disease (2.3 vs. 4.8 months, $p < .0001$).

A 6-month benefit was shown by 289 patients (63.5%) at first line, 128 (40.5%) at second line, 76 (33.8%) at third line, and 34 (23.3%) at fourth line (Table 2).

Among patients who received at least four lines of treatment, 60% exhibited a linear distribution of therapeutic effect (i.e., no benefit if there was no benefit in the previous line), with only 4% of patients experiencing a 6-month benefit across all four lines (supplemental online Fig. 1). In the total series, the lack of a 6-month benefit in PFS1 was associated with a lack of benefit at second line (OR: 0.48; 95% confidence interval [CI]: 0.29–0.77; $p = .0026$) and at any line beyond first (OR: 0.39; 95% CI: 0.24–0.62; $p < .0001$). When CT only was considered, patients who did not achieve a 6-month benefit had less chance of benefit from second line (OR: 0.45; 95% CI: 0.25–0.81; $p = .0072$) and from any other line beyond first (OR: 0.43; 95% CI: 0.2–0.7; $p = .0026$).

A lack of benefit at the first ET line did not affect the outcome with second or any subsequent ET line. Subgroup analysis based on tumor subtypes showed that not having a 6-month benefit from first-line treatment influenced the chance of having a 6-month benefit from subsequent lines only among patients with

Table 2. Progression-free survival according to different lines of treatment

Line	*n*[a]	Median PFS (months)	IQR (25th–75th percentile)	Patients presenting a 6-month benefit, *n/n* (%)[b]
All treatment				
First	472	9.0	4.2–18.2	289/455 (63.5)
Second	335	4.4	2.5–10.6	128/316 (40.5)
Third	246	4.0	2.2–8.4	76/225 (33.8)
Fourth	158	3.0	2.0–6.1	34/146 (23.3)
Endocrine therapy				
First	331	9.5	3.7–19.7	208/319 (65.2)
Second	180	4.7	2.7–10.4	66/170 (38.8)
Third	75	3.9	2.4–7.3	23/72 (31.9)
Fourth	22	4.2	1.5–10.6	8/14 (36.4)
Chemotherapy				
First	367	7.1	3.5–14.4	187/347 (53.8)
Second	234	3.7	2.1–8.4	78/219 (35.6)
Third	160	3.3	2.1–5.7	30/219 (21.1)
Fourth	87	2.5	1.8–4.2	6/80 (7.5)

[a]Sample includes censored and uncensored patients.
[b]Sample includes patients in whom the event (i.e., obtaining a 6-month benefit) occurred.
Abbreviations: IQR, interquartile range; PFS, progression-free survival.

HER2-positive tumors (Table 3). Supplemental online Figure 2 depicts the distribution of clinical benefit for first, second, third, and fourth line of treatment according to tumor types.

Variables predicting benefit from subsequent treatments maintained statistically significance in multivariate analysis (Table 4).

In the whole cohort, median PPS was 18.3 months (25th to 75th percentiles: 5.1–36.2 months). Stratifying the population by tumor subtypes, the median PPS was 18.7 months (25th to 75th percentiles: 6.8–38.3 months) among patients with HER2-positive disease, 19.4 months (25th to 75th percentiles: 6.4–36.8 months) among patients with luminal disease, and 6 months (25th to 75th percentiles: 0.8–12.1 months) among patients with triple-negative disease. Factors predicting PPS on multivariate analysis are reported in Table 5.

Discussion

Most women with MBC receive multiple lines of treatment, thanks to the wide availability of drugs beyond the first line. Although improvement of survival over time could be explained by the introduction of novel agents for MBC [16–18], choosing the most appropriate therapeutic sequence—and the opportunity of commencing a new treatment in advanced lines—is still largely outside evidence-based medicine. Moreover, no robust predictive factors are currently available. Consequently, in everyday clinical practice, decisions about treatment are usually based on rough estimation of the expected benefit.

Although clinical experience may provide some support for the use of lines beyond the first, data from the scientific literature are few. Furthermore, expected benefit from advanced lines of therapy is modest and even more unlikely to be achieved if previous lines have provided benefits of short duration. In fact, eribulin is the only chemotherapeutic agent

Table 3. Influence of not having a 6-month benefit from first-line treatment on chance of having a 6-month benefit from subsequent lines

	Probability of benefit at second line		Probability of benefit at any line beyond first	
	OR	95% CI	OR	95% CI
Overall				
Total	0.48	0.29–0.77	0.39	0.24–0.62
Chemotherapy	0.45	0.25–0.81	0.43	0.24–0.74
Endocrine therapy	0.80	0.41–1.56	0.91	0.47–1.75
HR-positive				
Total	0.89	0.49–1.64	0.58	0.32–1.05
Chemotherapy	0.67	0.30–1.49	0.59	0.27–1.26
Endocrine therapy	1.24	0.58–2.67	1.24	0.58–2.65
HER2-positive				
Total	0.20	0.05–0.73	0.14	0.04–0.53
Chemotherapy	0.24	0.06–0.90	0.21	0.06–0.79
Endocrine therapy	NA[a]	NA[a]	0.75	0.05–11.31
Triple negative				
Total	0.19	0.02–2.5	0.41	0.05–3.53
Chemotherapy	0.17	0.01–2.18	0.35	0.04–3.09
Endocrine therapy	NA	NA	NA	NA

Subgroup analysis is based on tumor types.
[a]Analysis not reliable because of small sample size.
Abbreviations: CI, confidence interval; HR, hormone receptor; NA, not applicable; OR, odds ratio.

Table 4. Variables predicting benefit from subsequent treatments (multivariate analysis)

Variable	OR	95% CI		*p* value
Overall lines				
Having 6-month benefit (no vs. yes)	0.47	0.28	0.81	.0065
HR status (negative vs. positive)	0.24	0.10	0.55	.0008
HER2 status (negative vs. positive)	0.18	0.07	0.43	.0001
Visceral localization (no vs. yes)	1.91	1.13	3.24	.0162
CT lines only				
Having 6-month benefit (no vs. yes)	0.40	0.22	0.75	.0065
HER2 status (negative vs. positive)	0.30	0.15	0.60	.0001

Abbreviations: CI, confidence interval; CT, chemotherapy; HR, hormone receptor; OR, odds ratio.

Table 5. Variables predicting postprogression survival (multivariate analysis)

Variable	Hazard ratio	95% CI		*p* value
Having 6-month benefit (no vs. yes)	1.25	0.90	1.73	.1790
HR-positive vs. HER2-positive	1.28	0.84	1.96	.2486
Triple negative vs. HER2-positive	**3.54**	**1.91**	**6.57**	**.0001**
ECOG PS at first line (1 vs. 0)	**1.49**	**1.07**	**2.07**	**.0176**
ECOG PS at first line (≥2 vs. 0)	1.08	0.55	2.09	.8313
Visceral localization (yes vs. no)	**1.55**	**1.13**	**2.12**	**.0064**

Bold values indicate statistically significant results.
Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hormone receptor.

that showed an OS gain in heavily pretreated patients with MBC, as reported in the phase III EMBRACE trial (13.1 vs. 10.6 months; hazard ratio: 0.81; 95% CI: 0.66–0.99; $p = .041$) [19]. Eribulin was not found to be cost effective in the treatment of advanced breast cancer relative to treatment of physician choice; however, in comparison to some more expensive branded drugs, eribulin appears to be cost effective [20].

In our cohort, 60% of patients presented a linear distribution of treatment effect showing no further benefit after PFS of short duration (i.e., less than 6 months). In contrast, 40% of patients gained benefit from treatment beyond first or second line despite a lack of benefit from previous lines. Interestingly, these results seem to question once more whether the decision-making process can be based on the performance observed with previous treatments. The random distribution of benefit, although experienced by a minority of patients, further spurs an interest in identifying predictive factors capable of driving toward the most appropriate therapeutic strategy.

Our findings support evidence showing that the absence of at least a 6-month benefit in PFS with first-line therapy predicts a lack of benefit from subsequent therapeutic lines; however, the results of our study have to be considered with caution because of some potential pitfalls. In particular, the sample size is small, and it is even smaller when considering patients progressing to subsequent lines of treatment. Despite these limitations, our analysis is one of the few evaluating outcome across multiple lines of treatment for MBC. Future studies following this approach could be used for proper allocation of resources, considering both ASCO's suggestions [12] and the growing number of reports in favor of early integration of supportive care for patients with advanced disease [21, 22].

Interestingly, in our study, the ability to predict therapeutic benefit on the basis of previous treatment performance does not seem to apply equally to the different subgroups (supplemental online Fig. 2) or to different treatments (CT or ET).

Patients with HR-positive disease who did not respond to first-line treatment might still gain benefit from subsequent therapies, although we cannot rule out that this effect is due to chance. The basis of endocrine therapy resistance has been well studied in luminal subtypes. Some resistance mechanisms that potentially influence treatment response have been identified. Several data are available about the activity of endocrine treatments in lines beyond the first. Fulvestrant and anastrozole demonstrated efficacy in women whose BC had progressed following tamoxifen [23, 24]. The phase III trial EFECT also demonstrated activity of fulvestrant or exemestane in patients who failed treatment with nonsteroidal aromatase inhibitors (NSAIs) [25]. More recently, data from the BOLERO-2 trial showed efficacy of exemestane in combination with everolimus in HR-positive, HER2-negative patients who progressed to NSAIs [26, 27].

Notably, patients with HER2-positive disease who did not show any response to first-line treatment were less likely to respond to subsequent lines; such behavior could be explained by the presence of de novo resistance. Our findings are in line with those recently reported by Murthy et al., who analyzed a series of 513 consecutive patients with HER2-positive MBC treated with trastuzumab as part of first-line treatment [28]. The authors observed that women with prior exposure to trastuzumab as part of their treatment for early BC had less clinical benefit from trastuzumab than trastuzumab-naive patients. In addition, in the phase III trial CLEOPATRA, patients with de novo disease had a median PFS of 21.6 months, whereas trastuzumab-pretreated patients had a median PFS of 16.9 months [29, 30].

In our series, the interpretation of the results about anti-HER2 treatment requires caution because of the marginal use of new agents potentially capable to overcome trastuzumab resistance [31, 32]. In fact, ado-trastuzumab emtansine [33, 34] or the combination of lapatinib and trastuzumab [35] has shown efficacy in patients with pretreated HER2-positive disease.

Moreover, because of the small sample size and the retrospective design, the present study does not allow testing the effect of maintenance endocrine therapy after chemotherapy. Because maintenance therapy is largely considered as an available strategy to improve OS [36], this represents an important need to explore prospectively.

In summary, in our study, the absence of at least a 6-month benefit for PFS with first-line therapy predicts a lack of benefit from subsequent therapeutic lines; however, PPS does not seem to be influenced by the benefit obtained at first line. Accordingly, it could be hypothesized that lines beyond the first may have an impact on subsequent outcome. These results may explain the low correlation between PFS with first line and OS when a long PPS is observed [15, 37].

Conclusion

In the era of precision medicine [38], this study provides further evidence of the lack of predictive factors that can be used for therapeutic choices in patients with metastatic breast cancer and emphasizes the urgent need to identify biomarkers that could optimize therapeutic strategy. Targeted and nontargeted agents should be tested in clinical trials with ad hoc translational design. To achieve medical utility, modern clinical trials should not only consider drug effectiveness. In fact, the identification of a companion diagnostic capable of driving benefit estimation and clinical decision making is necessary and equally relevant [39].

Sharpening the definition of the target population is of pivotal importance in adopting the optimal upfront therapy. Similarly, each subsequent treatment should be based on evaluation of agent- and line-specific predictive factors. Finally, to understand the ultimate effect of a therapeutic strategy (i.e., use of distinct drugs in the first line and beyond), a clinical trial should be built to provide adequate information about the treatment sequence. Results from such studies are eagerly awaited [40].

Author Contributions

Conception/Design: Marta Bonotto, Lorenzo Gerratana, Fabio Puglisi
Provision of study material or patients: Marta Bonotto, Lorenzo Gerratana, Gianpiero Fasola, Fabio Puglisi
Collection and/or assembly of data: Marta Bonotto, Lorenzo Gerratana, Donatella Iacono, Fabio Puglisi
Data analysis and interpretation: Marta Bonotto, Lorenzo Gerratana, Fabio Puglisi
Manuscript writing: Marta Bonotto, Lorenzo Gerratana, Donatella Iacono, Alessandro Marco Minisini, Karim Rihawi, Gianpiero Fasola, Fabio Puglisi
Final approval of manuscript: Marta Bonotto, Lorenzo Gerratana, Donatella Iacono, Alessandro Marco Minisini, Karim Rihawi, Gianpiero Fasola, Fabio Puglisi

Disclosures

Fabio Puglisi: Roche, Celgene (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

References

1. Siegel R, Ma J, Zou Z et al. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9–29.

2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374–1403.

3. Lu J, Steeg PS, Price JE et al. Breast cancer metastasis: Challenges and opportunities. Cancer Res 2009;69:4951–4953.

4. Cardoso F, Bischoff J, Brain E et al. A review of the treatment of endocrine responsive metastatic breast cancer in postmenopausal women. Cancer Treat Rev 2013;39:457–465.

5. Kiely BE, Soon YY, Tattersall MHN et al. How long have I got? Estimating typical, best-case, and worst-case scenarios for patients starting first-line chemotherapy for metastatic breast cancer: A systematic review of recent randomized trials. J Clin Oncol 2011;29:456–463.

6. Dawood S, Broglio K, Buzdar AU et al. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: An institutional-based review. J Clin Oncol 2010;28:92–98.

7. Bonotto M, Gerratana L, Poletto E et al. Measures of outcome in metastatic breast cancer: Insights from a real-world scenario. ***The Oncologist*** 2014;19:608–615.

8. Seah DSE, Luis IV, Macrae E et al. Use and duration of chemotherapy in patients with metastatic breast cancer according to tumor subtype and line of therapy. J Natl Compr Canc Netw 2014;12:71–80.

9. Roché H, Vahdat LT. Treatment of metastatic breast cancer: Second line and beyond. Ann Oncol 2011;22:1000–1010.

10. Cardoso F, Di LA, Lohrisch C et al. Second and subsequent lines of chemotherapy for metastatic breast cancer: What did we learn in the last two decades? Ann Oncol 2002;13:197–207.

11. Dufresne A, Pivot X, Tournigand C et al. Impact of chemotherapy beyond the first line in patients with metastatic breast cancer. Breast Cancer Res Treat 2008;107:275–279.

12. Schnipper LE, Smith TJ, Raghavan D et al. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: The top five list for oncology. J Clin Oncol 2012;30:1715–1724.

13. Harbeck N, Rody A. Lost in translation? Estrogen receptor status and endocrine responsiveness in breast cancer. J Clin Oncol 2012;30:686–689.

14. Saad ED, Katz A, Hoff PM et al. Progression-free survival as surrogate and as true end point: Insights from the breast and colorectal cancer literature. Ann Oncol 2010;21:7–12.

15. Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. J Natl Cancer Inst 2009;101:1642–1649.

16. Mauri D, Polyzos NP, Salanti G et al. Multiple-treatments meta-analysis of chemotherapy and targeted therapies in advanced breast cancer. J Natl Cancer Inst 2008;100:1780–1791.

17. Giordano SH, Buzdar AU, Smith TL et al. Is breast cancer survival improving? Cancer 2004;100:44–52.

18. Chia SK, Speers CH, D'yachkova Y et al. The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. Cancer 2007;110:973–979.

19. Cortes J, O'Shaughnessy J, Loesch D et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): A phase 3 open-label randomised study. Lancet 2011;377:914–923.

20. Lopes G, Glück S, Avancha K et al. A cost effectiveness study of eribulin versus standard single-agent cytotoxic chemotherapy for women with previously treated metastatic breast cancer. Breast Cancer Res Treat 2013;137:187–193.

21. Smith TJ, Temin S, Alesi ER et al. American Society of Clinical Oncology provisional clinical opinion: The integration of palliative care into standard oncology care. J Clin Oncol 2012;30:880–887.

22. Bruera E, Hui D. Integrating supportive and palliative care in the trajectory of cancer: Establishing goals and models of care. J Clin Oncol 2010;28:4013–4017.

23. Howell A, Robertson JFR, Quaresma Albano J et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol 2002;20:3396–3403.

24. Osborne CK, Pippen J, Jones SE et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: Results of a North American trial. J Clin Oncol 2002;20:3386–3395.

25. Chia S, Gradishar W, Mauriac L et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: Results from EFECT. J Clin Oncol 2008;26:1664–1670.

26. Baselga J, Campone M, Piccart M et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012;366:520–529.

27. Piccart M, Hortobagyi GN, Campone M et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: Overall survival results from BOLERO-2†. Ann Oncol 2014;25:2357–2362.

28. Murthy RK, Varma A, Mishra P et al. Effect of adjuvant/neoadjuvant trastuzumab on clinical outcomes in patients with HER2-positive metastatic breast cancer. Cancer 2014;120:1932–1938.

29. Baselga J, Cortés J, Kim S-B et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109–119.

30. Swain S, Kim S, Cortes J et al. Overall survival (os) analysis from the Cleopatra study of first-line (1l) pertuzumab (ptz), trastuzumab (t), and docetaxel (d) in patients (pts) with Her2-positive metastatic breast cancer (mbc). Ann Oncol 2014;25:mdu438.7.

31. Arteaga CL, Sliwkowski MX, Osborne CK et al. Treatment of HER2-positive breast cancer: Current status and future perspectives. Nat Rev Clin Oncol 2012;9:16–32.

32. Puglisi F, Minisini AM, De Angelis C et al. Overcoming treatment resistance in HER2-positive breast cancer: Potential strategies. Drugs 2012;72:1175–1193.

33. Verma S, Miles D, Gianni L et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367:1783–1791.

34. Krop IE, Kim S-B, González-Martín A et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): A randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:689–699.

35. Blackwell KL, Burstein HJ, Storniolo AM et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: Final results from the EGF104900 study. J Clin Oncol 2012;30:2585–2592.

36. Gligorov J, Doval D, Bines J et al. Maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-negative metastatic breast cancer (IMELDA): A randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:1351–1360.

37. Verma S, McLeod D, Batist G et al. In the end what matters most? A review of clinical endpoints in advanced breast cancer. ***The Oncologist*** 2011;16:25–35.

38. Ciardiello F, Arnold D, Casali PG et al. Delivering precision medicine in oncology today and in future-the promise and challenges of personalised cancer medicine: A position paper by the European Society for Medical Oncology (ESMO). Ann Oncol 2014;25:1673–1678.

39. Simon R. Clinical trial designs for evaluating the medical utility of prognostic and predictive biomarkers in oncology. Per Med 2010;7:33–47.

40. von Minckwitz G, Puglisi F, Cortes J et al. Bevacizumab plus chemotherapy versus chemotherapy alone as second-line treatment for patients with HER2-negative locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy (TANIA): An open-label, randomised phase 3 trial. Lancet Oncol 2014;15:1269–1278.

See http://www.TheOncologist.com for supplemental material available online.