Challenges in Prognosis, Systemic Therapy, and Survival in Patients with HER2-Negative Metastatic Breast Cancer candidates to systemic chemotherapy

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ABSTRACT

In patients with HER2-negative metastatic breast cancer who are not candidates for endocrine therapy, several regimens are approved, but there is no consensus on which should be preferred. The impressive gains in progression-free survival achieved by combining two cytotoxic drugs or chemotherapy plus bevacizumab have not consistently translated into overall survival benefits. Survival in this population depends on a wide range of biological and clinical factors, some of which remain unclear. International guidelines recommend that combination regimens should be limited to clinically aggressive situations. However, an evidence-based definition that could help guide treatment decisions and trial design has not been established for so-called ‘poor-prognosis’ or ‘aggressive’ tumors. In this article, we summarize the current literature regarding prognosis and treatment of patients with no endocrine options for HER2-negative metastatic breast cancer. The choice of optimal systemic therapy should be based on robust prognostic factors, the biologic characteristics of the tumor, and the type and severity of comorbidities. Furthermore, we suggest that combination regimens (chemotherapy doublets or bevacizumab-based regimens) may be considered appropriate options for patients with well-defined criteria representing poor-prognosis disease.

Running Title: Treatment Options for Poor-prognosis MBC

Keywords: Metastatic breast cancer • Chemotherapy • Clinical Prognostic Factor
INTRODUCTION

Although metastatic breast cancer (MBC) remains largely incurable and its treatment is palliative in intent, overall survival (OS) has improved over the last three decades [1–3]. New diagnostic tools and better therapeutic strategies, including more effective cytotoxic and targeted agents, may explain this gain in OS [1, 2]. Nevertheless, many confounding factors, such as patient or tumor characteristics and prior therapies, as well as the expanding range of treatment options in subsequent lines, make it very difficult to correlate OS benefits with a specific therapeutic approach [4].

Currently, estrogen receptor (ER) and progesterone receptor (PR) expression and human epidermal growth factor receptor 2 (HER2) amplification and/or overexpression status are crucial factors in determining the optimal systemic therapeutic strategy for patients [5]. There are three major subtypes of breast cancer defined by these biomarkers that drive treatment decisions in clinical practice: (i) HER2-positive; (ii) HER2-negative and ER/PR-positive; and (iii) triple-negative breast cancer (TNBC), which is defined by an absence of all three markers.

The progressive gain in OS observed for patients with HER2-positive MBC appears to be directly related to the incorporation of anti-HER2 regimens into several lines of treatment [1]. Although the specific roles of cytotoxic and endocrine agents in the HER2-amplified subtype have not been fully elucidated, further improvements in OS have been observed with new anti-HER2 agents and combinations of HER2-directed therapies [6, 7].

Most patients with HER2-negative hormone receptor-positive tumors, are suitable candidates for endocrine therapy and many will gain long-term benefit from this strategy. In the first line setting, the standard treatment with aromatase inhibitors (AI) has been relegated following the communication of positive results of these drugs with cyclin inhibitors and fulvestrant as a single agent. In patients whose disease progresses on a non-steroidal aromatase inhibitor, the addition of everolimus, a mammalian target of rapamycin (mTOR) inhibitor, to exemestane has been shown to significantly improve progression-free survival (PFS) and overall response rate (ORR), but not OS [8, 9]. More recently, palbociclib, which inhibits CDK4 and CDK6, was shown to significantly improve PFS when combined with fulvestrant in patients with progression during prior endocrine therapy in the PALOMA-3 trial [10]. Ultimately, however, patients with HER2-negative endocrine-resistant MBC will require chemotherapy to control disease progression. Finally, in patients with TNBC, chemotherapy-based treatment is the standard first-line approach as neither HER2-directed therapy nor endocrine therapy is an option. In this article, we focus on patients with either TNBC or HER2-negative ER/PR-positive MBC with no further endocrine options available.

Although there is no clear gold-standard chemotherapy regimen, several agents or regimens have demonstrated improvements in ORR, clinical benefit rate, or PFS compared with other regimens. However, consistent gains in OS are absent in contemporary clinical trials. Consequently, international guidelines and consensus statements usually recommend limiting first-line combination regimens to patients with more aggressive disease, which includes ‘rapid clinical progression’, ‘life-threatening visceral metastases’, ‘visceral crisis’, or ‘need for rapid symptom or disease control’ [11]. These concepts are difficult to translate into precise definitions and consequently, in clinical trials, patients are often stratified based on the presence of visceral metastasis, ER status, tumor phenotype, or geographic region rather than disease aggressiveness. If clinicians are to succeed in demonstrating
OS gains leading to registration of new agents, innovative approaches for the design of clinical trials in HER2-negative MBC are needed.

During the past 30 years, a large number of clinical and biologic prognostic factors have been associated with clinical outcomes [12–15]. Factors that may influence the choice of treatment include Eastern Cooperative Oncology Group (ECOG) performance status, metastatic organ sites, extent of disease or tumor burden, disease-free interval, prior adjuvant therapy, and prior therapy for MBC. Unfortunately, the vast majority of series are single-institution long-term follow-up reports with wide variability due to changes in the standards of care over time.

The main purpose of the present article is to revisit clinical prognostic factors in patients with HER2-negative disease with no further endocrine options. Identification of strong clinical markers in the absence of molecular ones may help physicians make the best possible treatment decisions. In addition, systematic use of such clinical markers or combinations of markers to identify patient populations with a homogeneous prognosis could lead to more tailored selection of treatment regimens. A reasonable option is to limit regimens that are more aggressive but effective to patients with the worst OS prognosis. In this scenario, increased PFS and/or ORR may be easier to translate into an OS gain or at least into quality of life benefits through symptom control. Defining subgroups with consistently short OS might also have implications for the design of new prospective trials that target OS as the primary endpoint.

### ‘Classical’ Prognostic Factors in MBC

A wide range of prognostic markers has been described for patients with MBC following the first report by Hortobagyi and colleagues in 1983 [15]. These prognostic factors can be grouped according to dependence on the patient, the tumor, or the treatment (Table 1). Several prognostic factors related to patient characteristics, such as older age and the presence and type of comorbidities, have been associated with higher disease-specific mortality in patients with MBC [16–18]. ECOG performance status ≥2 has also been associated with decreased OS [19,20], but may depend upon the comorbidities of a patient rather than reflecting the disease itself. Furthermore, as both age and ECOG performance status have been associated with under-treatment in many series, their influence on treatment decision-making should be treated with caution.

A second set of prognostic factors includes clinical or laboratory markers related to the extent or degree of tumor burden [21]. These include the number of affected organs, size and number of metastases, presence of visceral disease, involvement of specific organs, such as the central nervous system or liver, or certain laboratory abnormalities (baseline albumin, hemoglobin, hepatic enzymes, or lactate dehydrogenase). Tumor markers, such as CA15-3, may also be included in this group, although their prognostic value remains questionable. The practical utility of CA15-3 is relegated to monitoring responses to systemic therapies [22,23]. More recently, the presence and number of circulating tumor cells was shown to represent a strong, independent predictor of OS among women with MBC, allowing differentiation of patients with indolent versus aggressive disease [24].
Table 1. Summary of ‘classical’ prognostic factors

<table>
<thead>
<tr>
<th>Patient-dependent factors</th>
<th>Age &gt;70 years</th>
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<tbody>
<tr>
<td></td>
<td>ECOG performance status ≥2</td>
</tr>
<tr>
<td>Disease-dependent factors</td>
<td>&gt;1 involved distant organ</td>
</tr>
<tr>
<td></td>
<td>Presence of liver metastases</td>
</tr>
<tr>
<td></td>
<td>Presence of CNS metastases</td>
</tr>
<tr>
<td></td>
<td>Total tumor burden</td>
</tr>
<tr>
<td>Tumor-dependent factors</td>
<td>Molecular</td>
</tr>
<tr>
<td></td>
<td>Triple-negative subtype</td>
</tr>
<tr>
<td></td>
<td>HER2-positive status</td>
</tr>
<tr>
<td></td>
<td>Hormone-receptor positive tumors with low ER status and high proliferative index</td>
</tr>
<tr>
<td>Circulating factors</td>
<td>Circulating tumor cells</td>
</tr>
<tr>
<td></td>
<td>CA15.3 serum levels</td>
</tr>
<tr>
<td>Treatment-dependent factors</td>
<td>No response to previous systemic treatment</td>
</tr>
<tr>
<td></td>
<td>Early relapse after adjuvant therapy (&lt;24 months)</td>
</tr>
<tr>
<td></td>
<td>Hormone resistance in patients with ER- and/or PR-positive disease</td>
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</tbody>
</table>

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

A third group of prognostic factors relates to the treatment administered. Well-established factors associated with poor prognosis in both retrospective series and prospective clinical trials include prior chemotherapy exposure in earlier stages, the type of drug (anthracycline and/or taxane), and the time to disease relapse from initial systemic treatment (disease-free interval of less than 1 or 2 years) [25]. The efficacy of systemic therapy in metastatic disease, defined as an objective radiological response to chemotherapy or clinical benefit with hormonal therapy, appears to be a determining prognostic factor in many series [26].

Most studies on prognostic factors are retrospective series examining the historical outcomes of patients. A major limitation of these studies is the use of chemotherapy-based schedules that are no longer
considered standard in contemporary oncology practice. For example, the first and most cited analysis on the impact of predictive and prognostic factors in MBC concerned a series of 619 patients treated between 1973 and 1976 with a first-line anthracycline-containing regimen for endocrine-resistant MBC [15]. Of note, only 10% had received prior chemotherapy for early breast cancer and options for subsequent lines of therapy were very limited or non-existent. Another limitation is the lack of information on modern molecular predictors such as HER2. Furthermore, OS was analyzed from the first diagnosis of MBC and not specifically from the time at which chemotherapy was needed. Consequently, the relevance of findings from this study to modern-day clinical practice may be modest.

**Therapy Options for Endocrine-Ineligible HER2-negative MBC**

Historically, very few trials comparing chemotherapy regimens have enrolled a purely HER2-negative population. However, the international community has assumed that results from trials conducted before stratification by HER2 status are valid for the scenario of HER2-negative disease. This assumption seems reasonable, as several studies have shown that ORR, PFS, and OS in HER2-positive patients before the introduction of trastuzumab were similar to (or worse than) those in HER2-negative populations.

The optimal first-line chemotherapy-based approach remains a matter of debate. Although anthracycline-based therapy was considered the standard first-line therapy for almost 30 years, the introduction of taxanes and the expanded use of anthracyclines in the adjuvant setting clearly changed practice in favor of taxanes [27]. The strategy of combining different active drugs to improve outcomes has been explored for several decades. The combination of anthracyclines and taxanes was studied in many randomized trials. However, a meta-analysis indicated that this option, although more active in terms of ORR and PFS, did not improve OS compared with non-taxane combinations [28]. Combination regimens excluding anthracyclines were also explored with similar results [29]. Adding gemcitabine or capecitabine to single-agent taxane therapy was shown to improve OS but also increased toxicity [30,31]. Subsequent exploratory analyses suggested that in patients who initially received single-agent docetaxel, post-study treatment with capecitabine improved OS, unlike other treatments [32]. In current practice, a sequential strategy is generally preferred to the combination schedule. The E1193 trial provided evidence that two different sequential approaches including doxorubicin and paclitaxel were less toxic and produced similar OS to the combination of the two agents [33]. Finally, the duration of chemotherapy has also been debated. A meta-analysis including 11 randomized trials suggested that prolonging first-line chemotherapy duration improves PFS and OS [34].

The combination of targeted therapies and chemotherapy has been widely explored in patients with triple-negative MBC with little success to date. Epidermal growth factor receptor (EGFR) and poly-adenosine diphosphate ribose polymerase (PARP) appear to be crucial players in TNBC [35]. However, the combination of cisplatin and the anti-EGFR monoclonal antibody cetuximab only modestly improved PFS, and no further development is foreseen with this approach [36]. Similarly, iniparib, a presumed inhibitor of PARP, was combined with carboplatin and gemcitabine in a large phase III trial but failed to meet the coprimary objectives of improving OS and PFS [37] despite impressive activity in a randomized phase II trial [38]. However, interest in true PARP inhibitors continues...
and several, including olaparib, veliparib, rucaparib, niraparib, and BMN 673, are under evaluation in phase II and III trials especially in patients with germline BRCA-mutated breast cancer.

Bevacizumab has been investigated extensively in combination with cytotoxic agents in HER2-negative MBC. Four randomized phase III trials demonstrated significantly improved PFS and ORR with the association of bevacizumab to first-line chemotherapy [39–42]. In addition, two randomized phase III trials in the first-line HER2-negative MBC setting compared different bevacizumab-containing regimens (combination with paclitaxel, capecitabine, ixabepilone, and nab-paclitaxel) [43,44]. An individual patient data meta-analysis including 2,447 patients from three of these first-line trials (E2100, AVADO, and RIBBON-1) demonstrated improved PFS and ORR with bevacizumab-containing regimens versus chemotherapy alone [45]. No OS benefit was observed (HR 0.97; 95% CI: 0.86%–1.08%) although the trials were not designed for this endpoint. The magnitude of clinical benefit associated with bevacizumab in patients with a short OS expectancy was similar to that seen in the overall population. However, 1-year OS rates consistently favored bevacizumab-containing therapy, suggesting that in those with the highest risk of rapid progression and short OS after starting chemotherapy for MBC, bevacizumab may have had a more marked effect [45]. However, findings from these exploratory subgroup analyses in poor-prognosis populations can be considered only hypothesis-generating.

**RISK FACTOR INDICES IN HER2-NEGATIVE MBC**

While the trials and meta-analysis described above focused on the impact of combining bevacizumab with chemotherapy, other investigators have performed subgroup analyses to explore prognostic factors in large and relatively homogeneous populations of patients treated with bevacizumab-containing therapy in two single-arm studies. An analysis of prognostic factors in the German ML21165 non-interventional study (n = 818) of first-line bevacizumab in combination with paclitaxel showed that factors associated with a significantly worse PFS were ≥3 metastatic sites, presence of visceral metastases, TNBC, ER- and PR-negative or unknown disease, and prior (neo)adjuvant chemotherapy (Table 2) [46]. Three of these factors (TNBC, negative/unknown ER/PR status, and prior [neo]adjuvant chemotherapy) were also associated with significantly worse OS.

In ATHENA, a prospective global study evaluating first-line bevacizumab-containing therapy in more than 2,000 patients treated in routine oncology practice, time to progression (TTP) did not differ according to ECOG performance status (median 9.6 months in patients with ECOG 2 versus 8.9 months in patients with ECOG 0 or 1) [47]. The elderly population was also analyzed, and no differences were observed in terms of toxicity and efficacy between the 175 patients aged ≥70 years and their younger counterparts [48].
More recently, a new analysis of the ATHENA dataset trying to identify prognostic factors for OS in patients with HER2-negative tumors receiving first-line chemotherapy plus bevacizumab was published [49]. To our knowledge, the single-arm ATHENA study is the largest trial examining first-line therapy in patients with MBC. At the time of the analysis, 1,171 (53%) of the 2,203 patients with HER2-negative MBC had died. Prognostic factors for OS were selected from a univariate Cox regression analysis. All marginally significant variables (p < .10) were entered in the multivariate analysis. The final model selected was that providing the best fit with least information lost according to the Akaike information criteria. The five factors most closely and robustly associated with worse OS were: (i) disease-free interval ≤24 months; (ii) prior (neo)adjuvant anthracycline and/or taxane chemotherapy; (iii) presence of liver metastasis and/or ≥3 involved organ sites; (iv) TNBC; and (v) ECOG performance status 2 and/or corticosteroid and/or analgesic treatment at the time of inclusion (Table 3). Some of the factors were combined (ECOG 2 and analgesic/corticosteroid use; liver metastases and ≥3 metastatic organ sites) because the combined factors showed similar prognostic value to either factor alone. These factors

### Table 2. Prognostic factors in the ML21165 trial evaluating first-line bevacizumab combined with paclitaxel (n = 818) [46]

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median PFS, months</th>
<th>p value</th>
<th>Median OS, months</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>9.4</td>
<td></td>
<td>20.8</td>
<td></td>
</tr>
<tr>
<td>&lt;3 metastatic sites</td>
<td>9.7</td>
<td>.034</td>
<td>21.6</td>
<td>NS</td>
</tr>
<tr>
<td>≥3 metastatic sites</td>
<td>9.0</td>
<td></td>
<td>18.9</td>
<td></td>
</tr>
<tr>
<td>Visceral metastases</td>
<td>9.1</td>
<td>&lt;.005</td>
<td>19.4</td>
<td>NS</td>
</tr>
<tr>
<td>No visceral metastases</td>
<td>11.0</td>
<td></td>
<td>21.6</td>
<td></td>
</tr>
<tr>
<td>Triple negative</td>
<td>8.0</td>
<td>&lt;.001</td>
<td>16.0</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Non-triple negative</td>
<td>10.1</td>
<td></td>
<td>22.9</td>
<td></td>
</tr>
<tr>
<td>ER and/or PR positive</td>
<td>10.2</td>
<td>.033</td>
<td>23.2</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>ER and PR negative (or unknown)</td>
<td>8.8</td>
<td></td>
<td>17.0</td>
<td></td>
</tr>
<tr>
<td>Prior (neo)adjuvant chemotherapy</td>
<td>9.0</td>
<td>&lt;.001</td>
<td>18.7</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>No prior (neo)adjuvant chemotherapy</td>
<td>11.2</td>
<td></td>
<td>24.2</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ER, estrogen receptor; OS, overall survival; PFS, progression-free survival; PR, progesterone receptor.
were then used to categorize the patient population according to the number of risk factors present, and OS was analyzed within these subgroups. Risk of death was increased three-fold in patients with >2 risk factors compared with those who had only one or no risk factors. Likewise, those with two risk factors had a significantly worse OS prognosis, with risk of death almost doubling compared with the subgroup that had <2 risk factors. Median OS was 16.0 months in patients with >2 risk factors, 23.8 months in those with two risk factors, and 38.8 months in those with <2 risk factors (Figure 1). The prognostic factor analysis was sufficiently powerful to detect similar effects within the smaller subgroups of patients according to hormone receptor status (TNBC or non-TNBC). Interestingly, TNBC was not the strongest prognostic factor: a subset of patients with hormone receptor-positive disease had a median OS even shorter than some subsets with TNBC (Table 4).

These findings from prognostic factor analyses of the ATHENA study triggered similar analyses in datasets from two randomized phase III trials of first-line bevacizumab-containing therapy: RIBBON-1 [41] and TURANDOT [43]. In the TURANDOT trial, which compared bevacizumab plus paclitaxel versus bevacizumab plus capecitabine, the results of subgroup analyses according to risk factors showed potential in guiding treatment decisions [50]. A simple risk factor index appeared to identify those patients with a particularly poor prognosis in whom bevacizumab plus paclitaxel was clearly a more appropriate option, whereas in those with hormone receptor-positive disease and fewer than two risk factors, there was a trend towards longer OS with bevacizumab plus capecitabine, despite more favorable PFS in patients treated with bevacizumab plus paclitaxel. The analysis of RIBBON-1 focused on the cohort of patients treated with capecitabine with or without bevacizumab. As in TURANDOT, efficacy was analyzed in subgroups according to hormone receptor status and risk factors. Interestingly, a subgroup of patients with hormone receptor-positive disease and more than two risk factors had a PFS outcome similar to the population of patients with TNBC [51].

Table 3. ATHENA trial: multiple analysis of overall survival according to prognostic factors (HER2-negative population; n = 2,203) [49]

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free interval ≤24 months</td>
<td>1.75 (1.53–1.98)</td>
</tr>
<tr>
<td>ECOG performance status 2 and/or prior analgesic treatment</td>
<td>1.65 (1.47–1.85)</td>
</tr>
<tr>
<td>and/or prior corticosteroid treatment</td>
<td></td>
</tr>
<tr>
<td>Liver metastases and/or ≥3 metastatic organ sites</td>
<td>1.61 (1.43–1.81)</td>
</tr>
<tr>
<td>Triple-negative breast cancer</td>
<td>1.58 (1.39–1.81)</td>
</tr>
<tr>
<td>Prior (neo)adjuvant anthracycline and/or taxane therapy</td>
<td>1.27 (1.12–1.44)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.
Table 4. ATHENA trial: overall survival in the TNBC subgroup \((n = 585)\) and hormone receptor-positive subgroup \((n = 1,517)\) according to number of prognostic factors present [49]

| Number of prognostic factors | TNBC subgroup \((n = 585)\) | | | Hormone receptor-positive subgroup \((n = 1,517)\) | | |
|-----------------------------|-----------------------------|---|-----------------------------|---|---|
| | Deaths/no. patients (%) | Median OS, mo. (95% CI) | | Deaths/no. patients (%) | Median OS, mo. (95% CI) | |
| 0 | _a_ | _a_ | 72/243 (30) | NE (34.2–NE) | |
| 1 | 24/80 (30) | NE (27.8–NE) | 199/494 (40) | 34.8 (32.3–37.3) | |
| | 77/151 | | 300/504 (60) | 23.9 (22.1–25.9) | |
| 2 | (51) | 24.8 (19.7–30.1) | 164/239 (69) | 18.5 (16.1–20.1) | |
| | 126/195 | | | | |
| 3 | (65) | 18.3 (16.1–21.6) | | 14.6 (8.2–21.6) | |
| | 97/119 | | | | |
| 4 | (82) | 11.2 (9.2–12.6) | | | |
| | 27/37 (73) | | | | |
| 5 | 38/40 (95) | 7.6 (6.4–9.8) | _a_ | _a_ | _a_ |

a By definition, all patients in the TNBC subgroup had at least one prognostic factor (TNBC) and none of the patients in the hormone receptor-positive subgroup had five prognostic factors (no TNBC).

Abbreviations: CI, confidence interval; mo, months; NE, not estimable (median OS and the upper limit of the 95% CI could not be estimated with events in substantially less than 50% of patients); OS, overall survival; TNBC, triple-negative breast cancer.

Figure 1. A predictive model stratifying the number of baseline prognostic factors in patients recruited to the ATHENA trial. Patients were categorized according to the number of prognostic factors present at baseline (<2 vs 2 vs >2) [49]
These findings from prognostic factor analyses of the ATHENA study triggered similar analyses in datasets from two randomized phase III trials of first-line bevacizumab-containing therapy: RIBBON-1 [41] and TURANDOT [43]. In the TURANDOT trial, which compared bevacizumab plus paclitaxel versus bevacizumab plus capecitabine, the results of subgroup analyses according to risk factors showed potential in guiding treatment decisions [50]. A simple risk factor index appeared to identify those patients with a particularly poor prognosis in whom bevacizumab plus paclitaxel was clearly a more appropriate option, whereas in those with hormone receptor-positive disease and fewer than two risk factors, there was a trend towards longer OS with bevacizumab plus capecitabine, despite more favorable PFS in patients treated with bevacizumab plus paclitaxel. The analysis of RIBBON-1 focused on the cohort of patients treated with capecitabine with or without bevacizumab. As in TURANDOT, efficacy was analyzed in subgroups according to hormone receptor status and risk factors. Interestingly, a subgroup of patients with hormone receptor-positive disease and more than two risk factors had a PFS outcome similar to the population of patients with TNBC [51].

Taken together, these results confirm that the TNBC subtype has a consistently poor behavior. More interestingly, among the hormone receptor-positive population, there exists a large subgroup, identifiable by clinical factors, with a prognosis as poor as that of the TNBC subgroup at the time when chemotherapy is required for disease control.

**DISCUSSION**

It is difficult to use evidence-based medicine to make decisions regarding the optimal choice of chemotherapy for patients with HER2-negative MBC who are not candidates for endocrine therapy. In the absence of biomarkers, the final therapeutic decision is governed by clinical characteristics of patients, the goals of therapy, and patients’ preferences. Although the most active therapies are recommended for more aggressive situations, guidelines and clinical consensus are not always helpful in defining these scenarios. Clinicians require robust clinical or biological prognostic factors to guide clinical practice and trial design for these populations.

The impressive gains in PFS and ORR obtained with some combination therapies and especially with regimens that incorporate bevacizumab initially sidestepped this debate, as benefits were obtained in patients with either aggressive or indolent disease. However, in the absence of bevacizumab-based trials specifically designed to clarify the impact on OS, and given the lack of validated biomarkers enabling selection of patients deriving the most substantial benefit from bevacizumab, the role of this compound has been a matter of debate and the risk–benefit balance is an important consideration. In some healthcare settings, the prioritization of bevacizumab regimens (and, to some extent, other combination regimens) is focused on situations or scenarios in which the most relevant absolute or clinically significant benefits can be gained and/or the most favorable risk–benefit is foreseen.

Analysis of prognostic factors in the ATHENA study indicated that significant subgroups of patients with hormone receptor-positive tumors as well as those with TNBC have a poor prognosis and very short OS expectancy. These OS findings related to prognostic factors may also be useful for patients treated with non-bevacizumab combination regimens. Consistent patterns were seen in similar analyses of datasets from randomized phase III trials and may help guiding treatment decisions. Identification and implementation of a clinical prognostic factor index may
lead to improved selection of patients with poorer OS expectancy that may require more intensive treatments. This has the potential to drive systemic treatment in the absence of well-defined biomarkers.

Based on the present evaluation of the data for treatment options in patients with poor-prognosis HER2-negative MBC, bevacizumab in combination with paclitaxel emerges as an active and valid treatment regimen that can be offered to these patients. Novel strategies aiming to build on the efficacy of bevacizumab in combination with taxane-based therapy include the use of metronomic chemotherapy instead of taxane regimens, and the use of maintenance chemotherapy in combination with bevacizumab after initial bevacizumab–taxane combination therapy. This latter innovative approach has recently shown how we might design future trials in this population. The phase III IMELDA trial explored a maintenance strategy in patients with HER2-negative MBC who responded or achieved stable disease with up to six cycles of docetaxel and bevacizumab [52]. A total of 185 patients were eligible for randomization to maintenance therapy with bevacizumab and capecitabine (n = 91) versus single-agent bevacizumab (n = 94). The bevacizumab plus capecitabine regimen was associated with statistically significant improvements in both PFS (primary endpoint; median 11.9 vs 4.3 months, respectively; HR 0.38; p < .0001) and OS (secondary endpoint; median 39.0 vs 23.7 months, respectively; HR 0.43; p = .0003). Although the trial has some weaknesses, such as use of docetaxel as induction therapy and the prematurely terminated accrual, the results are remarkable. They are also in line with the previously described meta-analysis of 11 maintenance chemotherapy trials including 2,269 patients, which showed a slight benefit in OS (HR 0.91; p = .046) in favor of maintenance strategies [34]. Trials focusing on patients sensitive to initial first-line therapy cannot be compared directly with standard first-line randomization trials and do not help in selecting patients most suited to combination regimens. Furthermore, some underlying questions remain unresolved, such as how to identify non-responding patients at the earliest opportunity. In the absence of molecular markers, early evaluation of circulating tumor cells or circulating tumor-DNA may be promising ways to preclude resistance, enabling an early switch from expensive and/or ineffective agents. Nevertheless, maintenance strategies are very encouraging in HER2-negative MBC.

Finally, the development of new drugs and treatment strategies is jeopardized in this scenario if a gain in OS becomes an essential requirement for regulatory authorities. Innovative study designs will be needed targeting OS as the (co)primary endpoint. In this situation, the selection of a well-defined patient population with an accurately estimated OS prognosis, enabling precise calculation of an appropriate sample size, is mandatory. Furthermore, such a design will minimize the impact of other confounding factors such as post-progression survival or the influence and number of subsequent therapies. Findings assessed here highlight some of the most important factors in identifying and defining such patient populations.

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