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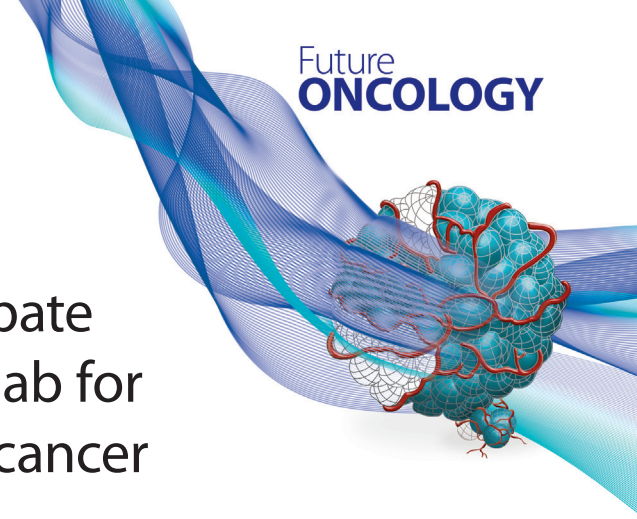

A Delphi consensus and open debate on the role of first-line bevacizumab for HER2-negative metastatic breast cancer

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To gain consensus on the role of bevacizumab plus paclitaxel as first-line treatment for HER2-negative metastatic breast cancer, a panel of expert oncologists experienced in treating patients with metastatic breast cancer in Italy participated in a Delphi consensus study. The panel reached a full consensus on the efficacy of bevacizumab plus paclitaxel and the clinical meaningfulness of the progression-free survival benefit compared with paclitaxel alone, despite the lack of an overall survival effect in clinical trials. The participants agreed that real-world data support the effectiveness and well-defined safety profile of the regimen. Views on the use of bevacizumab plus paclitaxel in specific patient populations were not unanimous and clinical judgment remains important. Nevertheless, a high level of agreement was reached.

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• angiogenesis • bevacizumab • breast cancer

In recent years, there has been controversy about the antiangiogenic agent bevacizumab as treatment for HER2-negative metastatic breast cancer (mBC) [1–4]. After initial accelerated approval by the US FDA, based on the results of the E2100 trial [5], regulatory approval was withdrawn in the USA. In Europe, however, regulatory authorities examined the same clinical trial results and reached a different conclusion. The European regulatory approval of bevacizumab plus paclitaxel was retained and indeed expanded to include the combination of bevacizumab plus capecitabine (based on results of the RIBBON-1 trial [6]), although approval of bevacizumab plus docetaxel, as investigated in the AVADO trial [7], was withdrawn. The controversy continued when randomized trials in the neoadjuvant setting consistently demonstrated a benefit from the addition of bevacizumab to preoperative chemotherapy for early breast cancer [8–12], although effects on disease-free survival and overall survival (OS) showed less homogeneous results [13–15].

Differences of opinions from regulatory authorities are also reflected in the medical community. In the complex treatment decision-making process, varying opinions on the scientific interpretation of end points, significance, applicability and clinical meaningfulness of results all play important roles in the overall decision to use – or not use – bevacizumab to treat a patient with mBC. To

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gain insight into the scientific rationale for such decisions, a Delphi consensus method was used to evaluate the degree of agreement and disagreement about the possible therapeutic role of bevacizumab in HER2-negative mBC. In challenging situations where scientific evidence is lacking or conflicting, the application of the Delphi consensus method enables a panel of independent experts to reach the most unanimous opinion possible on a given topic [16–19].

In this article, we present the statements defined in the consensus and the data supporting the conclusions drawn, but also expand on this by discussing some of the most recently published and presented data, as well as speculating on future directions and new and emerging strategies.

Method

The Delphi consensus model implemented in this study was developed over a period of 2 months and consisted of three key steps. In the first step, a scientific board comprising eight experts in mBC was convened to define the statements on which a broader panel would vote in later steps. The members of the scientific board were identified based on their publication record and participation in national and international medical congresses and meetings. The scientific board met in Rome on 2 April 2015, joined by a psychologist with expertise in qualitative research in the pharmaceutical sector, who moderated the meeting. During this session, the panelists discussed potential topics for future online voting and ultimately defined 12 statements related to the appropriateness and therapeutic role of the combination of bevacizumab plus paclitaxel in various populations of patients with HER2-negative mBC.

In the second step, the statements agreed upon in step 1 were distributed to 37 oncologists with expertise in breast cancer. These comprised 31 oncology specialists identified by the members of the scientific board based on their clinical experience in breast cancer and six members of the scientific board. The two remaining members of the scientific board were excluded from the vote as they were chosen to chair the third step described below.

Of the 37 oncologists invited to take part in the online survey, 31 (84%) accepted. The survey was administered using a commercial software program (SurveyMonkey®), which has been successfully used in other Delphi consensus surveys [16,20]. Using this platform, the 12 statements, along with results of supporting studies and publications from the literature, were sent to the 31 participating panelists on 7 May 2015. Panel members were asked to reply within 11 days. Panelists were asked, individually and anonymously, to express their level of agreement with each statement using a five-item Likert scale (where 1 = completely disagree; 2 = slightly disagree; 3 = partially agree; 4 = agree; 5 = completely agree) and the main reason for their chosen level of agreement from a series of prespecified options. A consensus was considered to have been reached if the sum of answers 1 and 2 (negative) or 3, 4 and 5 (positive) exceeded 66%, as described previously for similar projects using the Delphi method [19,21–22]. The survey results were collected and the final report was shared with all participants on 19 May 2015.

The third step (the Delphi plenary session) was conducted during two web conferences on 21 May and 26 May 2015, using the WebEx® system. All survey participants were invited to discuss the results shared previously and to vote again on those statements for which the criterion for consensus (at least 66% unanimity) had not been reached in step 2. It was decided to organize two separate web meetings according to geographical area (northern Italy chaired by F Puglisi and southern Italy chaired by P Marchetti) and the availability of the specialists, but most importantly to ensure that the number of participants did not prevent full engagement in the discussion and the opportunity to voice opinions. Members of the scientific board and the psychologist took part in both web conferences. Overall, 27 of the 31 panelists participated in the two web conferences.

Results

After the online survey in the second step, the predefined threshold for consensus (at least 66% unanimity) was reached for all statements and therefore all statements were approved **(Table 1)**. Because of the high level of agreement in step 2 (more than 90% consensus according to the prespecified criteria for all 12 statements), the two web conferences were used instead to discuss the results and the reasons for the answers given.

• Efficacy of first-line bevacizumab plus paclitaxel in HER2-negative mBC

1. Bevacizumab plus paclitaxel is an effective first-line option for HER2-negative mBC

In Italy, bevacizumab is indicated in combination with paclitaxel for the first-line treatment of

Table 1. Delphi model results.

Item	Statement	Degree of consensus
First-line efficacy of the combination of bevacizumab plus paclitaxel in HER2-negative mBC	1. Bevacizumab plus paclitaxel is an effective first-line option for HER2-negative mBC	100%
	2. The advantage in terms of PFS achieved with bevacizumab plus paclitaxel in the first-line treatment of HER2-negative mBC is clinically significant	100%
	3. The lack of a benefit in terms of OS of bevacizumab as first-line treatment for mBC does not justify not using the drug	100%
Special populations	4. In the first-line treatment of HER2-negative mBC, the bevacizumab plus paclitaxel combination is a valid treatment option for patients with high disease burden	97%
	5. Bevacizumab plus paclitaxel is an adequate first-line treatment option for TNBC	97%
	6. Bevacizumab plus paclitaxel is an appropriate first-line treatment option for hormone receptor (ER/PgR)-positive HER2-negative mBC	100%
	7. In elderly patients, the use of bevacizumab is efficacious and safe as first-line treatment for HER2-negative mBC	97%
	8. Bevacizumab is a valid treatment option also in patients pretreated with (neo)adjuvant taxanes in the early BC setting	91%
Real life	9. In the mBC setting, the data obtained in real-life studies confirm the efficacy of bevacizumab obtained in randomized clinical studies	100%
Treatment duration	10. It is useful to continue the first-line treatment of mBC with bevacizumab until progression even after the discontinuation of chemotherapy	94%
QoL and safety	11. Combining bevacizumab with paclitaxel as first-line treatment for mBC does not negatively impact on QoL	97%
	12. Bevacizumab has a well-defined safety profile	100%

BC: Breast cancer; ER: Estrogen receptor; mBC: Metastatic breast cancer; OS: Overall survival; PFS: Progression-free survival; PgR: Progesterone receptor; QoL: Quality of life: TNBC: Triple-negative breast cancer.

adult patients with HER2-negative mBC at the recommended dose of 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks [23]. There was unanimous agreement that bevacizumab plus paclitaxel is an effective first-line option in HER2-negative mBC, supported by the results of two randomized Phase III trials (the open-label E2100 trial [5,24] and, more recently, the double-blind placebo-controlled MERiDiAN trial [25]). Both trials showed that adding bevacizumab to first-line paclitaxel significantly improves progression-free survival (PFS; primary end point) and also overall response rate (ORR; secondary end point). The median PFS in both of these trials was approximately 11 months, although the hazard ratios (HRs) differed between the two trials. Of note, three additional randomized Phase III trials – TURANDOT, CALGB 40502 and TABEA – demonstrated almost identical median PFS durations with bevacizumab plus paclitaxel in this setting (11.0 months in TURANDOT, 11.0 months in CALGB 40502 and 11.3 months in TABEA) [26–28]. Similarly, ORRs with this regimen are very consistent (50% in E2100, 54% in MERiDiAN, 44% in TURANDOT, 38% in CALGB 40502 and 47% in TABEA), taking into account slight differences in trial design, study populations and tumor assessments.

PFS was the primary end point in all of these trials and its value is discussed in more detail below. However, in our opinion, ORR is also a very meaningful important end point in mBC. Responding patients have a better OS expectancy than those with stable or progressive disease, as shown in two large meta-analyses each including more than 2000 patients with mBC [29,30]. Furthermore, ORR is particularly important from the patient's perspective. Patients are reassured to know that their disease is responding and their lesions are shrinking during treatment. If a patient is responding to a given treatment, they can be advised that it is worth continuing with that regimen because their disease is under control. It is not difficult to imagine the psychological impact that such news will have on quality of life (QoL) and outlook for patients.

The statement discussed by the panelists relates to the combination of bevacizumab plus paclitaxel. It should also be noted that the double-blind randomized Phase III RIBBON-1 trial demonstrated significantly improved PFS (primary end point) with the addition of bevacizumab to capecitabine [6] and this regimen was compared with bevacizumab plus paclitaxel in the TURANDOT randomized Phase III trial mentioned above [26]. However, as the

bevacizumab plus capecitabine regimen is not available in Italy, the discussion focuses on the bevacizumab plus paclitaxel combination.

2. The advantage in terms of PFS achieved with bevacizumab plus paclitaxel in the first-line treatment of HER2-negative mBC is clinically significant

The Phase III E2100 and MERiDiAN trials mentioned above demonstrated statistically significant improvements in PFS with the addition of bevacizumab to paclitaxel. The clinical significance of the results represents a more subjective question. In E2100, the HR according to Independent Review Facility assessment was 0.48 [24], representing a 52% reduction in the risk of progression or death. In MERiDiAN the HR was 0.68 (32% reduction in the risk of progression or death). There was little doubt when the results from the E2100 trial were first presented that halving the risk of reduction of PFS and median PFS values of 11.3 months with bevacizumab plus paclitaxel versus 5.8 months with paclitaxel alone were clinically significant, important and relevant. More modest differences were observed in subsequent trials, not only in the MERiDiAN trial [25] but also in the AVADO [7] and RIBBON-1 [6] trials evaluating bevacizumab in combination with alternative chemotherapy backbones. These trials had the methodological advantage of being double-blind placebo-controlled trials whereas E2100 was an open-label trial. However, in E2100 an Independent Review Facility reported almost identical PFS results to the investigator-assessed PFS results [24].

There are at least three aspects to consider when assessing statement 2: first, is PFS a clinically significant (or relevant) end point? Second, what magnitude of difference is clinically significant? And third, what PFS improvement, if any, matters to a patient? In the authors' opinion, PFS is a clinically significant end point. From the patient's perspective, PFS (and ORR) are valuable (as mentioned elsewhere in this article). Regarding the relevance of this end point in formally defining treatment efficacy in prospective interventional clinical trials, we believe that PFS is more valuable than OS, interpretation of which can be confounded by postprogression survival and second and subsequent lines of therapy (see statement 3 below). The second question is also quite subjective, and an American Society of Clinical Oncology Cancer Research Committee convened specifically to examine and define 'clinical meaningfulness' could not reach a consensus in breast cancer [31]. For patients with triple-negative mBC, an improvement in median PFS of 4 months was considered clinically meaningful [31]. The European Society for Medical Oncology Magnitude of Clinical Benefit Scale also attempts to define 'clinically meaningful' [32]. Specifically in trials with a primary end point of PFS, an HR of ≤0.65 together with a median PFS gain of ≥1.5 months (if the control arm median is ≤6 months) or of ≥3 months (if the control arm median is >6 months) meets the criteria for the highest grade of benefit. Using these thresholds, E2100 but not MERiDiAN would be considered clinically meaningful, although it is important to note that the European Society for Medical Oncology Magnitude of Clinical Benefit Scale considers four additional aspects and should not be used to consider PFS in isolation. Moving beyond these theoretical and mathematical models, what are the views of a patient? In a survey of almost 300 women with mBC, 'extending PFS' was ranked the second most important treatment outcome after OS [33]. Importantly, results of the survey suggested that from a patient perspective, extending PFS is associated with improvement in QoL, physical functioning and emotional well-being.

3. The lack of a benefit in terms of OS of bevacizumab as first-line treatment for mBC does not justify not using the drug

OS is frequently cited as the 'gold standard' end point in trials of mBC [34,35]. However, in the first-line treatment setting in HER2-negative mBC, few if any trials have demonstrated a statistically significant improvement in OS and the factors contributing to this lack of OS difference, particularly postprogression survival and crossover, have been discussed intensely in the literature [35–38]. Although some postulate that antiangiogenic strategies may lead to a more aggressive tumor phenotype, evidence to support this hypothesis is limited to preclinical studies of tyrosine kinase inhibitors [39]. Furthermore, analyses of clinical trials of bevacizumab did not support these preclinical observations [40].

Although no evidence of OS benefit was observed in first-line clinical trials in HER2-negative mBC, a gradual improvement in OS has been reported in mBC [41] and the most likely explanations, beyond improved screening,

diagnosis and locoregional therapy, seem to be the incremental benefits in PFS with new therapies and the increasing number of regimens available to patients, enabling multiple lines of therapy. Thus, even if one specific treatment cannot be shown to significantly improve OS, the cumulative contribution of several different agents over the course of several lines of treatment can reasonably be expected to make a difference to OS. Therefore in the view of the panelists, it is difficult to exclude any particular therapy because of its lack of OS benefit demonstrated during use in a single treatment line. Indeed, if only treatments with proven OS benefit in contemporary clinical trials are to be used in the first-line setting of HER2-negative mBC, the options become extremely limited. Interestingly, there is a similar lack of evidence for a significant OS benefit in trials evaluating second and further lines of treatment [42].

- **Special populations**

4. In the first-line treatment of HER2-negative mBC, the bevacizumab plus paclitaxel combination is a valid treatment option for patients with high disease burden

One of the major challenges when selecting patients for bevacizumab-containing therapy is the lack of a predictive marker, or indeed a clinical marker, identifying patients most or least likely to derive benefit from bevacizumab. An extensive biomarker program has been undertaken, exploring a range of tumor markers [43]. However, despite initially encouraging signals for the utility of plasma VEGF-A as a predictive biomarker for bevacizumab efficacy, recently presented results of the MERiDiAN randomized Phase III trial, which was designed to evaluate this candidate biomarker prospectively, did not support use of baseline plasma VEGF-A to identify patients benefiting most from bevacizumab [25].

In the absence of a robust and reliable predictive biomarker for bevacizumab efficacy, we tend to resort to clinical parameters to try to identify those patients who may be most suitable for bevacizumab therapy. However, numerous retrospective, *post hoc*, and exploratory analyses provide no clear evidence that one subgroup of patients benefits more (or less) from bevacizumab than another [44]. In this scenario, arguably there is no reason to favor use of bevacizumab in one population versus another. However, in a healthcare system with limited resources, we may often be faced with the challenge of limiting a treatment to a smaller number of patients than those strictly eligible for the treatment. Thus, although bevacizumab plus paclitaxel is approved in Europe for all patients with HER2-negative mBC unless they have a contraindication for bevacizumab, reimbursement constraints pose different challenges. If bevacizumab can be offered to only a limited number of patients, many clinicians favor those with the most aggressive disease, as these patients typically require a rapid response, require intensive therapy and do not have time to try less effective therapies first. This pragmatic approach in a resource-limited setting is supported by results of an analysis recently published by Bonotto and colleagues, who showed that failure to reach PFS of 6 months may be associated with reduced probability of benefit from subsequent lines of therapy compared with patients whose first-line therapy resulted in a PFS duration of ≥6 months [45]. This brings us to the fourth statement in the Delphi consensus.

The first challenge is the definition of 'high disease burden'. Prospective trials of treatment in such a specific population are lacking, not least because there is no agreed definition of 'high disease burden'. However, Arpino and colleagues conducted a systematic review of the literature to identify the factors most commonly associated with aggressive mBC [46]. The highest levels of evidence to support associations with worse OS were observed for visceral metastases, number of metastatic sites, disease-free interval, presence of circulating tumor cells, triple-negative disease and tumor grade.

In a meta-analysis of the three pivotal trials of first-line bevacizumab for mBC (albeit only one of them – E2100 – evaluated bevacizumab plus paclitaxel), treatment effect was explored in various populations of patients considered to have a poor prognosis [44]. The PFS HRs in subgroups of patients with triple-negative breast cancer (TNBC), visceral disease or ≥3 metastatic organ sites were 0.63, 0.66 and 0.64, respectively, remarkably similar to the PFS HR of 0.64 in the overall population. The absolute improvement in median PFS of 2–3 months with bevacizumab did not differ dramatically between subgroups, although in populations with very short PFS expectancy, the relative difference is greater and therefore perhaps of greater clinical importance.

In another retrospective analysis, this time based on the single-arm ATHENA study

evaluating first-line bevacizumab plus the investigator's choice of chemotherapy in the setting of routine oncology practice [47], Llombart-Cussac and colleagues developed a simple prognostic index for OS [48]. Using five clinical parameters, they were able to differentiate a population at high risk of death with a median OS of only 16 months on bevacizumab-containing therapy versus a population with a threefold lower risk of death and median OS of 39 months on bevacizumab-containing therapy. The risk factors contributing to this prognostic factor index were: liver metastases/≥3 metastatic organ sites; triple-negative mBC; prior anthracycline and/or taxane therapy; Eastern Cooperative Oncology Group performance status 2 and/or prior analgesic and/or corticosteroid therapy; and a disease-free interval of ≤24 months. Subsequently, this prognostic factor index has been adopted in exploratory analyses of other bevacizumab mBC datasets and yielded supportive results. For example, in an exploratory analysis of the TURANDOT trial, which compared bevacizumab plus paclitaxel versus bevacizumab plus capecitabine [26], Brodowicz and colleagues concluded that in patients with triple-negative disease, a regimen of bevacizumab plus paclitaxel may be preferred to the bevacizumab plus capecitabine regimen based on the more favorable OS outcome despite shorter PFS [49].

5. Bevacizumab plus paclitaxel is an adequate first-line treatment option for TNBC

As already alluded to above, patients with TNBC – defined as negative estrogen receptor (ER), progesterone receptor (PgR) and HER2 status – generally have a poor prognosis. The population of patients with TNBC represents a heterogeneous subgroup, including at least six distinct subtypes (two basal-like, immunomodulatory, mesenchymal, mesenchymal stem-like and luminal androgen receptor) [50].

Considering the poor prognosis and limited treatment options for these patients, there has been particular interest in the role of bevacizumab in TNBC, not only in the metastatic setting but also as neoadjuvant and adjuvant therapy. Retrospective and subgroup analyses of Phase III trials demonstrated median PFS ranging from 8.8 to 10.6 months with bevacizumab plus paclitaxel [25,44,49]. In the subgroup of patients with TNBC in the ATHENA study, median time to disease progression with bevacizumab-containing therapy (not only paclitaxel) was 7.2 months [51]. These data led the panelists to conclude that bevacizumab plus paclitaxel is an adequate first-line treatment option for metastatic TNBC.

The importance of bevacizumab plus paclitaxel in triple-negative mBC is evidenced by the use of this regimen as the control arm in recent clinical trials, including the ongoing Dutch Triple-B randomized Phase IIB trial (NCT01898117) and a randomized Phase II trial of onartuzumab [52]. In this prospective trial in patients receiving first- or second-line therapy for TNBC, median PFS was 7.2 months with bevacizumab plus paclitaxel.

Although bevacizumab plus paclitaxel may be an adequate treatment option from the available choices, there is a need to find better treatments for patients with TNBC. Many ongoing clinical trials are evaluating new strategies for this difficult-to-treat population, with a particular focus on agents inhibiting PARP, such as veliparib, olaparib, niraparib and talazoparib [53,54]. Emerging data for immunotherapeutic approaches, such as the PD-1 inhibitor pembrolizumab [55] and PD-L1 inhibitor atezolizumab [56,57], highlight interest in this strategy for TNBC within an expansive range of tumor settings. The ongoing Phase III KEYNOTE-119 and IMpassion130 trials are evaluating pembrolizumab and atezolizumab, respectively, in metastatic TNBC. Other avenues of research include antiandrogenic therapies, MEK inhibition, PI3K inhibition, mTOR inhibition, heat-shock protein 90 inhibition and histone deacetylase inhibition [53,54].

The landmark paper by Lehmann and colleagues [50], together with a simplified model that may allow easier translation into the clinic [58], provide new means of classifying TNBC that may potentially improve patient selection and guide therapeutic decisions. It is time to dissect this subgroup of breast cancer into more specific molecular entities, which will improve our ability to estimate prognosis and allow more efficacious treatment of our patients.

6. Bevacizumab plus paclitaxel is an appropriate first-line treatment option for hormone receptor (ER/PgR)-positive HER2-negative metastatic BC

For patients with hormone receptor-positive HER2-negative mBC, bevacizumab plus paclitaxel was also considered to be an appropriate first-line treatment option. This is perhaps not

surprising given that the benefit in TNBC in terms of HR was no different from that in the population with hormone receptor-positive disease or in the overall population [44]. However, additional data in this setting perhaps merit attention when considering the broader range of treatment options for these patients. First, according to the Advanced Breast Cancer 2 guidelines, the preferred treatment for patients with ER-positive HER2-negative mBC is endocrine therapy, even in the presence of visceral metastases [59,60]. Chemotherapy should be reserved for cases of rapidly progressing disease or proven endocrine resistance. Therefore the panelists agreed unanimously that bevacizumab plus paclitaxel is an appropriate first-line therapy for hormone receptor-positive HER2-negative mBC if chemotherapy is the only possible treatment option (e.g., in patients with hormone-refractory disease or those with visceral crisis).

Within the population of patients with hormone receptor-positive mBC, there exist different populations with different prognoses. For example, in the analysis of the ATHENA dataset described above, patients with hormone receptor-positive disease could be classified according to the prognostic factor index into those with one or no risk factors (median OS of 38.8 months), those with two risk factors (median OS of 23.9 months) and those with three or four risk factors (median OS of 17.4 months) [48]. Of note, in the subgroup with three or four risk factors, the OS expectancy was worse than in many of the patients with TNBC. Based on these observations, bevacizumab plus paclitaxel seems an appropriate treatment option for patients with hormone receptor-positive mBC, particularly those with more aggressive disease.

When a very similar prognostic factor index was applied to the TURANDOT dataset, patients with hormone receptor-positive mBC had more favorable PFS and ORR outcomes with the combination of bevacizumab plus paclitaxel compared with bevacizumab plus capecitabine [49]. However, interestingly, in the population of patients defined as having low-risk hormone receptor-positive mBC, those treated with bevacizumab plus capecitabine appeared to have a more favorable OS outcome. These exploratory analyses in a small, retrospectively defined subpopulation should have no bearing on clinical practice, especially in Italy where bevacizumab plus capecitabine is not available; however, they further illustrate the complexities of treatment decision-making for these patients.

It is also worth mentioning three trials in hormone receptor-positive mBC evaluating the combination of bevacizumab and endocrine therapy. The LEA and CALGB 40602 randomized Phase III trials both evaluated the addition of bevacizumab to endocrine therapy and in both, the primary end point was PFS [61,62]. In the LEA trial, there was no statistically significant improvement in PFS with the addition of bevacizumab to letrozole or fulvestrant. In the CALGB 40503 trial, the primary objective was met, demonstrating a significant PFS improvement with the addition of bevacizumab to letrozole (PFS: HR: 0.75, 95% CI: 0.59–0.96; p = 0.016; median 15.6 months with letrozole alone vs 20.2 months with letrozole plus bevacizumab). However, the authors noted a marked increase in grade 3/4 toxicities with bevacizumab-containing therapy. Finally, the AROBASE trial compared continued bevacizumab plus taxane versus a switch to bevacizumab plus exemestane after initial response to bevacizumab plus taxane induction therapy [63]. The trial was prematurely terminated because of the low probability of significantly improving PFS with the investigational arm.

7. In elderly patients, the use of bevacizumab is efficacious & safe as first-line treatment for HER2-negative mBC

While chronological age *per se* is not a reason to withhold a treatment, additional factors should be considered when selecting treatment for biologically elderly patients. Importantly, age in years is not always a reliable predictor of frailty and the importance of geriatric assessments is widely underestimated. Common comorbidities in older patients that may influence treatment choice include hypertension, hyperlipidemia, anemia, ischemic heart disease, diabetes, heart failure and chronic kidney disease [64].

To the best of our knowledge, no trials have evaluated bevacizumab specifically in older patients with mBC and experience is limited to exploratory and retrospective subgroup analyses. However, particularly in the ATHENA study, extensive analyses were undertaken to understand outcomes in patients aged ≥70 years [65]. Both hypertension and proteinuria, known side effects of antiangiogenic therapies, were more common in patients aged ≥70 years than in those younger than 70 years. However, in the

older subgroup there was no excess of thromboembolic events, which are a particular concern in elderly patients. Overall, results from the ATHENA study provide no evidence for worse efficacy or tolerability in older compared with younger patients, although older age may influence chemotherapy choice [65].

8. Bevacizumab is also a valid treatment option in patients pretreated with (neo)adjuvant taxane in the early BC setting

Taxane rechallenge with a first-line taxane-containing regimen is generally a reasonable option for patients treated with taxane-containing therapy for early breast cancer, providing relapse has not occurred within 12 months of completing (neo)adjuvant taxane therapy [59,60]. In these patients, the addition of bevacizumab to first-line paclitaxel may be expected to improve efficacy based on the intent-to-treat results of Phase III trials of first-line bevacizumab [5,25,44]. The pooled analysis of three first-line trials (E2100, AVADO and RIBBON-1) suggested that taxane-pretreated patients may derive an OS benefit from the addition of bevacizumab but the lack of adjustment for multiplicity in these exploratory *post hoc* analyses is a major drawback when trying to interpret such findings [44].

• Real life

9. In the mBC setting, the data obtained in real-life studies confirm the efficacy of bevacizumab obtained in randomized clinical trials

There is no doubt that prospective randomized clinical trials remain the gold standard when determining the effect of a new treatment on patient outcomes. However, there is increasing interest in real-world data, in which outcomes are collected either prospectively or uniformly with a specific objective in mind or retrospectively from routine practice to address research questions in defined populations. Randomized clinical trials assess treatment effects within a specific carefully selected patient population and typically include strict eligibility criteria, rigorous monitoring for adherence to the protocol (including treatment administration and efficacy and safety assessment) and minimization of the risk of bias through randomization, stratification and usually double blinding. Although such trials undoubtedly provide the most rigorous evaluation of treatment effect, a limitation is their applicability to the populations of patients presenting in routine oncology practice, many of whom are ineligible for Phase III clinical trials.

Real-world data complement findings from randomized clinical trials and provide valuable information on the effectiveness of treatment, measuring the degree of clinical benefit in a real-world setting. Following release of results from the E2100 randomized Phase III trial evaluating first-line bevacizumab plus paclitaxel for mBC, the international ATHENA study was initiated. This large, open-label study evaluated first-line bevacizumab-containing therapy in a broader population of more than 2000 patients treated in 37 countries worldwide [47]. Importantly, the chemotherapy choice was at the investigator's discretion based on the clinical, disease and prior treatment characteristics of each patient. Approximately a third of patients (35%) received bevacizumab in combination with paclitaxel (17% in a weekly schedule, 13% in an every-3-week schedule; 6% other); 33% received bevacizumab with docetaxel, 10% with taxane-based combination regimens, and the remainder with nontaxane regimens, such as capecitabine or vinorelbine. Although the primary end point of ATHENA was safety, time to disease progression (interval between initiation of first-line therapy and recorded disease progression) was a predefined secondary end point. Median time to disease progression in ATHENA was 9.7 months in the entire population and 10.6 months in the subgroup of 325 patients treated with bevacizumab plus weekly paclitaxel [66]. Of specific interest to the panelists, median time to progression was 10.9 months in the subgroup of 278 patients treated in Italian clinical practice within the ATHENA trial [67].

Similar real-world studies have been undertaken in Hungary and Germany to evaluate the safety and efficacy of first-line bevacizumab plus paclitaxel in routine oncology practice. Median PFS was 9.3 months in 220 patients treated in the Hungarian AVAREG study [68] and 9.6 months in 865 patients treated in the German ML21165 study [69].

Turning to the second type of real-world data collection study mentioned above, very recently results were presented at the American Society of Clinical Oncology Annual Meeting from the Epidemio-Strategy-Medico-Economic database, assessing treatment outcomes in patients treated in routine oncology practice in France [70]. The study included 3426 patients starting first-line treatment with paclitaxel, with or without

bevacizumab, between 2008 and 2013. OS was longer in patients treated with bevacizumab plus paclitaxel compared with paclitaxel alone (HR adjusted for the main prognostic variables: 0.67, 95% CI: 0.60–0.75; median 27.7 vs 19.8 months, respectively). Sensitivity analyses and supporting analyses adjusting for propensity score showed consistent results.

Taking into account differences in data collection and follow-up as well as the broader patient populations included in real-world studies, the panelists all agreed that these results are consistent with results from the prospective randomized Phase III trials of first-line bevacizumab plus paclitaxel in more strictly defined patient populations and suggest that results from Phase III evaluation can be transferred to routine oncology practice.

• Treatment duration

10. It is useful to continue the first-line treatment of mBC with bevacizumab until progression even after the discontinuation of chemotherapy

In the randomized Phase III trials of first-line bevacizumab-containing therapy for mBC, bevacizumab was generally continued until disease progression, unacceptable toxicity or withdrawal of consent. Retrospective analyses attempting to assess the impact of continued single-agent bevacizumab have suggested improved outcomes if bevacizumab is continued as maintenance therapy versus discontinued at the same time chemotherapy is stopped [66,71]. However, comparing outcomes in patients who received maintenance bevacizumab versus prematurely discontinuing bevacizumab is extremely challenging because duration of treatment and outcome are not independent: those patients remaining alive and progression-free (in the case of PFS) or alive (in the case of OS) for longer have the opportunity to receive bevacizumab for longer, whereas those who have early progression will discontinue bevacizumab earlier. In the absence of data specifically comparing the two strategies, the approach adopted in clinical trials and stated in the prescribing information should be followed (i.e., treatment with bevacizumab until disease progression or unacceptable toxicity).

Although the panelists agreed on the statement that bevacizumab should be continued until disease progression even after interrupting chemotherapy, one participant expressed concern that a prolonged duration of bevacizumab treatment may result in cumulative cardiovascular risk and potentially increase the severity of side effects such as hypertension and proteinuria. Investigators from at least three trials of bevacizumab plus paclitaxel have reported safety results specifically in subgroups of patients treated for ≥1 year. In the ATHENA study, 473 patients (21%) continued bevacizumab for ≥1 year (99 of whom continued bevacizumab for ≥2 years). The mean number of grade ≥3 adverse events was 1.26 per treatment-year in patients treated for ≥1 year versus 4.13 events per treatment-year in those treated for less than 1 year. Proteinuria was more common in the post 1-year treatment period suggesting that this side effect is cumulative; however, there was no evidence that first onset of hypertension was more common in later than earlier cycles of treatment [66]. In the single-arm JO19901 study evaluating first-line bevacizumab plus paclitaxel in Japanese patients, both hypertension and proteinuria occurred occasionally in later cycles [72]. In the single-arm German noninterventional ML21165 study, the incidence of grade ≥3 hypertension was increased with prolonged bevacizumab exposure but this effect was described as manageable by the investigators [69].

In the context of maintenance bevacizumab, results of the randomized Phase III IMELDA trial deserve mention. This trial compared maintenance bevacizumab alone versus maintenance bevacizumab plus capecitabine in patients achieving disease control with initial bevacizumab plus docetaxel therapy [73]. Unfortunately, recruitment to the trial was prematurely terminated following withdrawal of regulatory approval for the bevacizumab plus docetaxel combination. Despite this, the trial provided intriguing results. Patients randomized to receive capecitabine with maintenance bevacizumab had longer PFS (primary end point) and, remarkably, longer OS (secondary end point) compared with patients receiving maintenance bevacizumab alone. The practical application of these results is challenging, particularly in Italy where bevacizumab plus capecitabine is not available, yet the concept of induction therapy with a taxane plus bevacizumab followed by a switch to a more tolerable chemotherapy regimen with continued bevacizumab certainly generates interesting hypotheses. The authors concluded that these results might inform future maintenance trials and current first-line treatment strategies for HER2-negative mBC.

- **Quality of life & safety**

11. Combining bevacizumab with paclitaxel as first-line treatment for mBC does not negatively impact on QoL

As mentioned above, improving PFS may improve QoL [33], which is an important treatment goal in patients with mBC, particularly when improvement in OS is so elusive. QoL is generally measured by self-reported questionnaires, such as the Functional Assessment of Cancer Therapy-Breast (FACT-B) instrument. FACT-B, which is specifically designed to evaluate patient-reported outcomes in breast cancer, includes the 27-item FACT-General questionnaire assessing overall physical, functional, emotional and social well-being and the 9-item Breast Cancer Subscale, which focuses specifically on concerns of particular relevance to patients with breast cancer.

In the E2100 study, analyses of FACT-B results indicated that the addition of bevacizumab to paclitaxel was not associated with additional side-effect burden from the patients' perspective. Furthermore, breast cancer-specific concerns were reduced to a greater extent with bevacizumab plus paclitaxel than with paclitaxel alone [74]. In the TURANDOT trial, patient-reported outcomes were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire 30 (EORTC QLQ-C30) at baseline, at each tumor assessment (every 12 weeks), and 28 days after discontinuation of study treatment. Analysis of mean global health status showed little change from baseline over time [26].

12. Bevacizumab has a well-defined safety profile

There can be little debate that bevacizumab has a well-defined safety profile after evaluation in a multitude of Phase III trials across a wide range of tumor types. Modest qualitative differences between tumor types have been noticed but overall, bevacizumab therapy is characterized by increased incidences of hypertension, proteinuria and low-grade bleeding. Specifically in mBC, the risk of hypertension, proteinuria, left ventricular dysfunction and hemorrhagic events is increased in patients receiving bevacizumab in combination with chemotherapy versus chemotherapy alone [75]. However, no statistically significant differences in the incidences of gastrointestinal perforation, vascular events or febrile neutropenia were observed. Adverse effects of bevacizumab have been analyzed in numerous meta-analyses in breast cancer and across tumor types: conclusions from these meta-analyses differ slightly according to the trial selection criteria but overall show quite similar results [44,75–77].

Conclusion

Despite the lack of consensus between regulatory authorities on either side of the Atlantic Ocean and even between European countries, the 31 Italian oncologists participating in this Delphi consensus reached a high level of agreement. These expert oncologists reached full (100%) consensus with regard to the efficacy of first-line bevacizumab plus paclitaxel, the clinical significance of the PFS benefit associated with this regimen despite the lack of OS benefit, translation of efficacy from clinical trials to the real-world setting and the well-defined safety profile of the regimen. Consensus was reached, but not unanimously, on topics related to the role of bevacizumab plus paclitaxel in specific populations of patients (those with high disease burden, TNBC, taxane-pretreated disease or advanced age), the continuation of bevacizumab until disease progression and the lack of negative impact of bevacizumab on QoL. Nevertheless, for these parameters the level of agreement with the statements exceeded 90% in all cases. Ultimately, in the absence of a clear predictive marker, treatment decisions regarding the administration of bevacizumab plus paclitaxel rest on the clinical judgement of the oncologist treating the patient, taking into consideration numerous factors related to patient, disease and medical history characteristics.

This consensus represents an Italian perspective. We believe that the consensus reached here could provide valuable insight for the development of practice guidelines at institutional or regional levels in Italy. It would be interesting to know whether similar consensus could be reached by surveying a pan-European panel of oncologists, which would be expected to reflect differences in treatment practice, local guidelines, regulatory status and reimbursement issues.

Ongoing and future research in mBC is focusing on newer strategies targeting a range of other pathways, including PI3K and MEK, and immunotherapy as well as vaccination strategies. Increasingly a more personalized approach to treatment and a more targeted approach to drug development are being embraced.

Future perspective

In the next few years, the first-line treatment of HER2-negative mBC is expected to change with new advances in our knowledge of tumor biology. Molecularly driven treatment could be of benefit if the right target is identified. Accordingly, for each line of treatment it is desirable to identify predictive factors that may influence the therapeutic strategy. Parsimonious use of chemotherapy is of value as well as integration of chemotherapy into regimens including different types of biologic agent (e.g., antiangiogenic agents, immunotherapy).

Financial & competing interests disclosure

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EXECUTIVE SUMMARY

- Bevacizumab plus paclitaxel is an effective first-line treatment option for HER2-negative metastatic breast cancer, providing a clinically meaningful benefit over paclitaxel alone.
- No subgroup deriving a particularly large or small benefit from bevacizumab has been identified; therefore patient selection for bevacizumab is typically based on clinical need and availability of treatments.
- Results from real-world studies, in particular from almost 3500 patients treated in routine oncology practice in France, demonstrate the effectiveness of first-line bevacizumab plus paclitaxel for HER2-negative metastatic breast cancer.
- In the absence of robust data comparing continuing versus discontinuing bevacizumab after cessation of chemotherapy, continuation of maintenance bevacizumab (ideally with capecitabine) until disease progression is advisable.
- The safety profile of bevacizumab has been extensively described; the characteristic adverse events of hypertension and proteinuria can be managed relatively easily, and side effects associated with bevacizumab do not appear to have a detrimental effect on quality of life.

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