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Benefit-Risk Assessment of Bevacizumab in the Treatment of Breast Cancer

Rodrigo Dienstmann,[1] *Felipe Ades*,[2] *Kamal S. Saini*[3] and *Otto Metzger-Filho*[2]

1 Molecular Therapeutic Research Unit, Medical Oncology Department, Vall d'Hebron Institute of Oncology, Barcelona, Spain
2 Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
3 Breast International Group, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

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Abstract

An evaluation of the benefit-versus-risk of bevacizumab in the treatment of advanced breast cancer is timely and relevant. Recently, the US FDA has withdrawn the approval of bevacizumab as a therapeutic option for the treatment of advanced breast cancer, generating controversy in the scientific community. Although the pivotal study (Eastern Cooperative Oncology Group 2100 trial [E2100]) had shown doubling of the progression-free survival when bevacizumab was added to chemotherapy, this magnitude of benefit could not be replicated in subsequent studies. Furthermore, individual studies and meta-analyses failed to demonstrate an overall survival benefit with the addition of bevacizumab to different chemotherapy regimens. In addition, this agent is associated with an increased incidence of serious adverse events such as hypertension, congestive heart failure and thromboembolism, and its cost is likely to be a consideration in its use for many patients worldwide. Retrospective biomarker-based studies aiming to identify the subpopulation of patients most likely to benefit from the addition of bevacizumab to standard chemotherapy in breast cancer should be a research priority.

Much progress has been made in antiangiogenic therapy since the publication of Judah Folkman's seminal hypothesis on this topic about 40 years ago.[1] The prototype antiangiogenic drug is bevacizumab, a humanized monoclonal antibody against the vascular endothelial growth factor

(VEGF). A synergistic effect has been observed in multiple preclinical models when an antiangiogenic agent is combined with a cytotoxic chemotherapeutic drug.[2,3] In addition, the toxicity profile of bevacizumab is distinct from that of most cytotoxic agents.[4] Therefore, there has been much interest in testing the combination of bevacizumab and chemotherapy in clinical trials. To date, this combination has been tested in five phase III studies and one large observational study in metastatic breast cancer patients.

Since publication of the first randomized trial showing impressive doubling of response rate (RR) and time to progression, there have been more questions than answers regarding the role of bevacizumab in advanced breast cancer. After the US FDA rescinded approval of this drug, a firestorm of criticism was prompted by some members of the medical community and breast cancer patients. It is now clear that survival and quality of life are not improved when this agent is added to standard chemotherapy in the general population of breast cancer patients. In addition, despite being a targeted therapy, bevacizumab lacks a robust, predictive, biological or clinical marker of activity. With the concerns about increased toxicity and the high costs of antiangiogenic therapy, it seems reasonable to critically assess the benefit-risk ratio and the role of bevacizumab in advanced breast cancer.

1. Benefits of Bevacizumab in the Treatment of Breast Cancer

1.1 Advanced Disease: First-Line Setting

The Eastern Cooperative Oncology Group 2100 trial (E2100) randomized 722 patients with locally recurrent or metastatic breast cancer to receive paclitaxel (90 mg/m^2/week for 3 weeks in a 4-week cycle) alone or in combination with bevacizumab (10 mg/kg every 2 weeks).[5] Treatment was continued until unacceptable toxicity or disease progression, with no crossover allowed. As shown in table I, the addition of bevacizumab significantly increased the overall RR and doubled the progression-free survival (PFS) – which was the primary endpoint of the trial – compared with single-agent weekly paclitaxel. However, the difference in overall survival (OS) was not statistically significant. An independent review of the E2100 trial by Gray et al.[10] confirmed the improvement in both RR (50% vs 22%) and PFS (median 11.3 vs 5.8 months; hazard ratio [HR] 0.48) in favour of the drug combination. Based on these results, the US FDA and other regulatory agencies worldwide approved the combination for this indication.[11]

The Avastin And Docetaxel (AVADO) study was a three-arm, phase III study that recruited 736 patients with human epidermal growth factor receptor 2 (HER-2)-negative metastatic breast cancer.[6] Patients received docetaxel 100 mg/m^2 in combination with bevacizumab at two dose levels (7.5 mg/kg or 15 mg/kg) or placebo every 3 weeks. Treatment was continued for up to nine cycles, progression or unacceptable toxicity. Authors reported the results after a median of 25 months' follow-up. In the unsupervised analysis, in agreement with improvement in overall RR, PFS was superior in the combination arm with the 15 mg/kg dose level (median 10.1 vs 8.2 months; HR 0.77; p = 0.006), but not statistically different in the 7.5 mg/kg arm (9.0 vs 8.2 months; HR 0.86; p = 0.12). These data suggest that the optimal dose of bevacizumab in breast cancer is 5 mg/kg/week. OS was similar in all treatment arms. Importantly, about 40% of patients in the placebo arm received bevacizumab in the second-line setting.

The largest trial testing bevacizumab in breast cancer was Regimens in Bevacizumab for Breast Oncology (RIBBON)-1.[7] A total of 1237 patients were randomized (in a 1 : 2 ratio) to receive chemotherapy as per physician's choice, combined with placebo or bevacizumab (15 mg/kg every 3 weeks). Investigators could choose between capecitabine (2000 mg/m^2/day for 2 weeks of a 3-week cycle), taxane (nanomolecule albumin-bound paclitaxel [260 mg/m^2] or docetaxel [75–100 mg/m^2] every 3 weeks), or anthracycline-based chemotherapy (doxorubicin [adriamycin] or epirubicin plus cyclophosphamide with or without fluorouracil every 3 weeks). Most patients received capecitabine (n = 615) followed by anthracyclines (n = 315) and taxanes (n = 307). As shown in table I, the same

Table I. Phase III studies with bevacizumab (BEV) and chemotherapy in advanced breast cancer

Study (y)	Treatment line	Treatment arms	No. of pts	Response rate (%)	Progression-free survival (HR [95%CI])	Overall survival (HR [95%CI])
E2100 (2007)[5]	First	PTX q1w + BEV 10 mg/kg q2w vs PTX q1w	722	36.9 vs 21.2 ($p < 0.001$ vs PTX q1w)	11.8 vs 5.9 mo (0.6 [0.51, 0.7])	26.7 vs 25.2 mo (0.88 [$p = 0.16$])
AVADO (2008)[6]	First	DTX q3w + BEV 15 mg/kg vs BEV 7.5 mg/kg vs PL q3w	736	64 ($p < 0.001$ vs PL q3w), 55 ($p = 0.07$ vs PL q3w) vs 46	10.1 (0.77 [0.64,0.93]) vs 9.0 (0.86 [0.72,1.04]) vs 8.2 mo	30.2 (1.03 [0.7, 1.3]) vs 30.8 (1.05 [0.81,1.36]) vs 31.9 mo
RIBBON-1 (2009)[7]	First	CAP q3w + BEV 15 mg/kg q3w vs PL q3w	1237	35.4 vs 23.6 ($p = 0.009$ vs PL q3w)	8.6 vs 5.7 mo (0.69 [0.56,0.84])	29.0 vs 21.2 mo (0.85 [0.63,1.14])
		ATC[a]/TX[b] q3w + BEV 15 mg/kg q3w vs PL q3w		51.3 vs 37.9 ($p = 0.005$ vs PL q3w)	9.2 vs 8.0 mo (0.64 [0.52,0.80])	25.2 vs 23.8 mo (1.03 [0.77,1.38])
Miller et al. (2005)[8]	Second or third	CAP q3w + BEV 15 mg/kg q3w vs CAP q3w	462	19.8 vs 9.1 ($p = 0.001$ vs CAP q3w)	4.8 vs 4.2 mo (0.98 [0.77,1.25])	15.1 vs 14.5 mo (p = NS)
RIBBON-2 (2009)[9]	Second	TX[c]/GCB[d]/CAP q3w/VNB q1w + BEV 10 mg/kg q2w or 15 mg/kg q3w vs TX[c]/GCB[d]/CAP q3w/VNB q1w + PL q2–3w	684	39.5 vs 29.6 ($p = 0.02$ vs PL q2-3w)[e]	7.2 vs 5.1 mo (0.78 [0.64,0.93])[e]	18.0 vs 16.4 mo (0.9 [0.71,1.14])[e]

a DOX or EPR + CTX ± 5-FU q3w.

b DTX or nab-PTX q3w.

c PTX q1w or q3w, DTX q3w, nab-PTX q3w.

d Days 1 and 8 q3w.

e Data for response rate, PFS and OS are overall values for bevacizumab-containing treatment arms versus those without bevacizumab.

5-FU = fluorouracil; **ATC** = anthracycline; **AVADO** = Avastin And Docetaxel; **CAP** = capecitabine; **CTX** = cyclophosphamide; **DOX** = doxorubicin; **DTX** = docetaxel; **E2100** = Eastern Cooperative Oncology Group 2100 trial; **EPR** = epirubicin; **GCB** = gemcitabine; **HR** = hazard ratio; **nab-PTX** = nanoparticle albumin-bound paclitaxel; **NS** = non-significant; **OS** = overall survival; **PFS** = progression-free survival; **PL** = placebo; **pts** = patients; **PTX** = paclitaxel; **qxw** = every *x* week; **RIBBON-1** = Regimens in Bevacizumab for Breast Oncology; **RIBBON-2** = Regimens in Bevacizumab for Breast Oncology Second-Line; **TX** = taxane; **VNB** = vinorelbine.

pattern of benefit with the addition of bevacizumab in the first-line setting was observed. With a median follow-up of 15.6 months for the capecitabine cohort and 19.2 months for the taxane and anthracycline cohorts, RR and PFS were higher in the bevacizumab combination arms. No difference in OS was observed. At progression, about half of the patients in the placebo arms received bevacizumab with second-line chemotherapy.

Although the AVADO and RIBBON-1 trials produced statistically significant increases in RR and PFS, the outcomes were arguably not clinically compelling. The smaller magnitude of benefit observed in these studies compared with the pivotal E2100 trial, the absence of survival advantage with long-term follow-up, and the incomplete or superficial quality-of-life benefit analysis led to withdrawal of bevacizumab approval for the treatment of metastatic breast cancer by the US FDA and other agencies.[11,12]

Subsequently, results of the Avastin Therapy for Advanced Breast Cancer (ATHENA) study were presented. This large observational study aimed to evaluate the efficacy and toxicity of bevacizumab in combination with a taxane regimen in the first-line metastatic setting.[13] A total of 2251 patients were treated, with single-agent paclitaxel (35%) and docetaxel (33%) being the most common regimens added to bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks). RR in the intent-to-treat population was 52%. With a follow-up of 12.7 months, time to disease progression was 9.5 months (95% CI 9.1, 9.9). The authors concluded that these results were consistent with those from randomized studies.

1.2 Advanced Disease: Second-Line Setting

The first phase III trial, which evaluated the addition of bevacizumab to chemotherapy after failure to respond to first-line treatment of advanced breast cancer, randomized patients to receive capecitabine (2500 mg/m^2/day for 2 weeks of a 3-week cycle) alone or in combination with bevacizumab (15 mg/kg on day 1 every 3 weeks).[8] A total of 462 patients were enrolled. Despite a significant increase in RR, no PFS or OS benefit was observed. In addition, time to deterioration in quality of life was similar in both arms (2.86 vs 2.92 months; $p = 0.633$).

In the Regimens in Bevacizumab for Breast Oncology Second-Line (RIBBON-2) trial, 684 patients were randomized in a 1 : 2 ratio to chemotherapy alone or in combination with bevacizumab at 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks.[9] Prior to randomization, investigators chose one of the following chemotherapy agents: taxane (paclitaxel [90 mg/m^2/week for 3 weeks in a 4-week cycle or 175 mg/m^2 every 3 weeks], nanoparticle albumin-bound paclitaxel 260 mg/m^2 or docetaxel 75–100 mg/m^2 every 3 weeks), gemcitabine (1250 mg/m^2 on days 1 and 8 every 3 weeks), capecitabine (2000 mg/m^2/day for 2 weeks of a 3-week cycle) or vinorelbine (30 mg/m^2/week every 3 weeks). At the last interim analysis, in addition to the increment in RR, PFS was also significantly higher in patients who received bevacizumab; however, no difference in OS was observed.

1.3 Meta-Analysis in Advanced Disease Setting

Up until the publication of this review, two meta-analyses evaluating the benefit of the addition of bevacizumab to chemotherapy in advanced breast cancer have been published.[14,15] Both included data from the first-line E2100, AVADO and RIBBON-1 trials, as well as the capecitabine trial in the second-line setting. A combination of bevacizumab and chemotherapy resulted in a statistically significant improvement in RR (relative risk 1.26, 95% CI 1.17, 1.37; and 1.53, 95% CI 1.37, 1.71) and PFS (HR 0.70, 95% CI 0.60, 0.82; and 0.69, 95% CI 0.58, 0.81). The pooled analysis for OS did not show significant advantage for the use of bevacizumab compared with placebo (HR 0.90, 95% CI 0.80, 1.03; and 0.92, 95% CI 0.82, 1.03).[14,15] In addition, the combined analysis of the E2100 and AVADO trials of taxane-based chemotherapy plus bevacizumab in the first-line treatment of advanced breast cancer confirmed these findings.[16]

1.4 Neoadjuvant Setting

In the GeparQuinto study, 1889 patients with untreated HER-2-negative breast cancer clinically

staged cT3/4a-d, or estrogen and progesterone receptor-negative, or estrogen/progesterone-positive tumours with clinically positive lymph nodes were randomized to receive four cycles of epirubicin/cyclophosphamide (90/600 mg/m^2) every 3 weeks followed by four cycles of docetaxel (100 mg/m^2) every 3 weeks, with or without concomitant bevacizumab 15 mg/kg added to chemotherapy cycles.[17] One-third of the patients had triple-negative disease (estrogen, progesterone, HER-2 negative). Efficacy results presented so far showed no apparent benefit at the time of surgery for patients who received bevacizumab. Pathological complete responses with no invasive residual cancer in breast and lymph node rates were 20.3% with bevacizumab and 18.5% without bevacizumab, the difference not being statistically significant.

2. Risks of Bevacizumab in the Treatment of Breast Cancer

The most common adverse events (AEs) directly associated with bevacizumab therapy, probably 'on target' side effects related to inhibition of VEGF activity and deficient blood vessel formation, include hypertension, bleeding, proteinuria, increased risk of arterial and venous thromboembolic events and gastrointestinal perforation. Table II summarizes grade 3 and 4 events in the phase III trials that tested the addition of bevacizumab to standard chemotherapy in advanced breast cancer.

In general, an increase in the incidence of severe AEs is observed with the addition of the antiangiogenic agent. Grade 3 and 4 hypertension occurred in 4–18% of patients who received bevacizumab compared with <2% in those who had standard chemotherapy. A recent meta-analysis demonstrated a relative risk of 18.83 (95% CI 1.23, 292.29) of developing significantly raised blood pressure in breast cancer patients who received bevacizumab 5 mg/kg/week, the recommended dose for breast cancer patients based on the published phase III trials.[18] Incidence varied greatly in all clinical studies and the reasons for the considerably lower frequencies of grade 3–4 hypertension in the AVADO study compared with E2100 could be the blinded nature of the first study, reducing reporting bias. In addition, the lower rate of severe hypertension reported in more recent trials may be due to increased awareness of the problem and more aggressive management for early hypertension.

Regarding bleeding, all-grade events (primarily epistaxis) occur in up to 50% of patients receiving bevacizumab plus chemotherapy.[6] Grade 3 and 4 events were reported in <2% of patients in breast cancer trials (with the exception of 5.4% in the taxane plus bevacizumab arm of the RIBBON-1 study).[7] The risk of fatal bleeding with bevacizumab in combination with chemotherapy appears to be increased only in patients with lung cancer.[19] Importantly, it is now clear that the incidence of intracranial haemorrhages in the bevacizumab-treated patients is not higher than the general oncology population, as demonstrated in meta-analyses and large retrospective series.[19,20]

Clinically significant proteinuria has been reported in about 2–4% of patients with breast cancer receiving bevacizumab in combination with chemotherapy. This toxicity is not seen with standard cytotoxic agents. The relative risk of developing proteinuria is 11.03 (95% CI 2.09, 58.21), according to a meta-analysis.[15] As was seen with hypertension and bleeding, proteinuria risk is higher with increasing doses of bevacizumab.[6] In the second-line capecitabine plus bevacizumab trial, the incidence of proteinuria was higher in patients who received concurrent pamidronic acid (pamidronate) [33.9% vs 18.5%; $p = 0.026$].[7] In addition, there appears to be a positive association between proteinuria and hypertension, i.e. patients with proteinuria are more likely to develop hypertension, even though it is not clear that one causes the other.[8]

Venous thromboembolism is an important toxicity related to antiangiogenic agents. A meta-analysis that included patients with different tumour types treated with bevacizumab showed a significantly increased risk of venous thromboembolism, with a relative risk of 1.33 (95% CI 1.13, 1.56) compared with controls.[21] In the subgroup analysis of breast cancer trials, the incidence of venous thromboembolism was 7.3%, with a non-significant relative risk of 1.30 (95%

Table II. Reported toxicities in phase III studies with bevacizumab (BEV) in combination with chemotherapy in advanced breast cancer

Reported toxicities (% pts)[a]	E2100[5]		AVADO[6]			RIBBON-1[7]						Miller et al.[8]		RIBBON-2[9]	
						CAP		TX		ATC					
	no BEV (n=346)	BEV (n=365)	no BEV (n=231)	BEV 7.5 mg/kg (n=252)	BEV 15 mg/kg (n=247)	no BEV (n=201)	BEV (n=404)	no BEV (n=102)	BEV (n=203)	no BEV (n=100)	BEV (n=210)	no BEV (n=215)	BEV (n=229)	no BEV (n=221)	BEV (n=458)
Serious/grade 3–4 adverse events	NR	NR	**67**	**78**	**75**	19	24	**26**	**41**	16	22	NR	NR	**18**	**25**
Discontinuation due to adverse event	**36**	**51**	12	9	14	12	12	**8**	**24**	**4**	**14**	13	12	**7.2**	**13.3**
Treatment-related mortality	NR	NR	3	2	2	2.5	1.5	3	2.5	3	1.4	NR	NR	2.3	1.3
Hypertension[b]	**0**	**14.8**	**1.3**	**0.8**	**4.5**	**1.0**	**9.4**	**2.0**	**8.9**	**0**	**10.0**	**0.5**	**17.9**	**0.5**	**9.0**
Bleeding[b]	0	0.5	0.9	1.2	0.8	0.5	0.2	**0**	**5.4**	0	0	0.5	0.4	0	1.7
Proteinuria[b]	**0**	**3.5**	**0**	**0.8**	**2.0**	**0**	**3.2**	**0**	**3.4**	**0**	**1.9**	**0**	**0.9**	**0.5**	**3.1**
Thromboembolism[b]	1.5	2.1	3.0	1.6	2.0	3.5	4.8	4.9	2.0	1.0	2.9	**3.7**	**6.9**	NR	NR
Cardiac failure[b]	0.3	0.8	0	1.2	0	0.5	1.0	0	2.0	0	2.9	**1.0**	**3.0**	NR	NR
Gastrointestinal perforation[b]	0	0.5	0.9	0.4	0.4	0	0	1.0	2.0	0	0	NR	NR	NR	NR
Neutropenia[b]	0.3	0	17.3	19.8	19.8	1.0	1.2	**4.9**	**9.4**	4.0	4.3	2.8	2.6	14.5	17.7
Febrile neutropenia[b]	0	0.8	**11.3**	**15.1**	**16.2**	0	0	**2.0**	**7.9**	5.0	3.8	0.9	0.4	2.7	2.2
Infection[b]	**2.9**	**9.3**	2.2	1.2	0.4	NR	NR	NR	NR	NR	NR	0.5	0.9	NR	NR
Fatigue[b]	**4.9**	**9.1**	**5.2**	**9.5**	6.5	NR	NR	NR	NR	NR	NR	6.6	7.4	NR	NR
Neuropathy[b]	**17.7**	**23.5**	1.7	2.8	1.6	0.5	3.0	8.8	8.4	0	0.5	NA	NA	5.9	6.3
Mucositis[b]	0.6	1.1	**0.4**	**4.0**	**4.9**	NR	NR	NR	NR	NR	NR	0.5	1.7	NR	NR

a Values highlighted in bold indicate events that were statistically more frequent in the bevacizumab-containing arms (as compared with control arms without bevacizumab).

b Individual toxicities are grade 3–4 events only.

ATC = anthracycline; **AVADO** = Avastin And Docetaxel; **CAP** = capecitabine; **E2100** = Eastern Cooperative Oncology Group 2100 trial; **NA** = not applicable; **NR** = not reported; **pts** = patients; **RIBBON-1** = Regimens in Bevacizumab for Breast Oncology; **RIBBON-2** = Regimens in Bevacizumab for Breast Oncology Second-Line; **TX** = taxane.

CI 0.64, 2.67) compared with chemotherapy without bevacizumab. Regarding the risk of cardiac ischaemia and arterial thromboembolic events, the meta-analysis of randomized controlled trials in multiple tumours demonstrated an increased risk in patients receiving bevacizumab compared with controls, with a relative risk of 1.44 (95% CI 1.08, 1.91).[22] The risk appeared to be higher in renal cell carcinoma and colorectal cancer patients. An additional study found an incidence of arterial thromboembolism of 0.7% in breast cancer patients treated with bevacizumab, not significantly higher than chemotherapy alone (relative risk 1.47; 95% CI 0.27, 7.95).[23] Nevertheless, there was a significant increase in cerebrovascular ischaemia among patients receiving combined therapy with paclitaxel and bevacizumab in the E2100 trial (1.9% vs 0%; $p = 0.02$).[5]

Congestive heart failure (CHF) associated with bevacizumab has been sporadically reported in several trials of bevacizumab in advanced solid tumours. Breast cancer patients may have prior or current exposure to known cardiotoxic agents, including anthracyclines and/or trastuzumab and chest wall radiation therapy. In a recently published, large, comprehensive report that analyzed data from more than 2300 breast cancer patients treated with bevacizumab, the overall incidence of high-grade CHF was 1.6% (95% CI 1.0, 2.6) compared with 0.4% (95% CI 0.2, 1.0) in the control or placebo-treated groups.[24] Relative risks for patients treated with taxanes, capecitabine and anthracyclines were 5.42 (95% CI 1.25, 23.52), 2.77 (95% CI 0.78, 9.88) and 6.22 (95% CI 0.35, 109.4), respectively. The authors could not correlate the incidence of CHF with secondary hypertension or arterial thromboembolic events. On the other hand, in the ATHENA study of bevacizumab plus taxane-based chemotherapy in more than 2000 patients, a low rate of grade 3–4 CHF (0.4%) was observed in a community-based setting, in which a higher prevalence of cardiac risk factors might be anticipated.[13] However, it is important to point out that the incidence of CHF could have been underestimated as these expanded access programmes are not usually designed to sensitively capture rare events.

The estimated incidence of gastrointestinal perforation in breast cancer patients treated with bevacizumab was 0.8%, with a non-significant relative risk of 1.63 (95% CI 0.43, 6.2) compared with conventional chemotherapy, according to a meta-analysis of clinical trials involving multiple solid tumours.[25] This incidence is low compared with ovarian, renal and colorectal tumours, which usually have more extensive peritoneal metastatic involvement and previous abdominal surgeries.[25]

In addition to the potentially severe AEs reported above, the addition of bevacizumab to chemotherapy in advanced cancer patients was associated with an increased risk of fatal AEs, with a relative risk of 1.46 (95% CI 1.09, 1.94).[26] This association varied significantly with chemotherapeutic agents (higher with taxanes or platinum agents) but not with tumour types or bevacizumab doses. The most common causes of death were haemorrhage (23.5%), neutropenia (12.2%) and gastrointestinal tract perforation (7.1%).[26]

Bevacizumab also increases the incidence of some frequent chemotherapy-related toxicities, as shown in table II. Infection and fatigue were more common in the combination arm of the E2100 trial.[5] Incidence of grade 3–4 neutropenia and febrile neutropenia was slightly increased in the bevacizumab arms of the AVADO trial.[6] In the taxane arm of the RIBBON-1 trial, neutropenia and febrile neutropenia were more common with the addition of bevacizumab.[7] Additionally, in the neoadjuvant GeparQuinto trial of epirubicin and cyclophosphamide followed by docetaxel with or without bevacizumab, some grade 3–4 toxicities were more frequent in the combination arms: leukopenia (62.6% vs 47.2%) during the anthracycline-based regimen, and mucositis (15.3% vs 4.5%) during treatment with the taxane agent.[27] Of note, the incidence of osteonecrosis of the jaw was not increased with the addition of bevacizumab to chemotherapy and bisphophonate therapy.[28]

In the phase III trials of bevacizumab in breast cancer, the mean delivered dose intensity for the cytotoxic agents was usually similar in the chemotherapy and combination therapy arms. In the E2100 trial, paclitaxel discontinuation at least 3 weeks before disease progression was higher in the bevacizumab arm, probably because patients

in the experimental arm continued treatment for a longer period and therefore had an increased risk of cumulative toxic effects of the chemotherapy, such as neuropathy.[5] In the ATHENA observational study, bevacizumab was discontinued permanently in 19% of patients because of AEs, most commonly hypertension (1.8%), fatigue (1.2%), proteinuria (1.0%), epistaxis (0.8%) and thromboembolism (0.8%).[13]

3. Discussion

In advanced disease, the first large study that evaluated the addition of bevacizumab to chemotherapy in breast cancer (capecitabine in the second- and third-line setting) showed disappointing negative results.[8] The next combination tested in the clinic (weekly paclitaxel in the first-line E2100 trial) demonstrated an impressive PFS benefit.[5] Improvements in RR and PFS, which are standard measures of antitumour activity, were qualitatively and quantitatively smaller in the later trials than in E2100. The AVADO and RIBBON-1 studies were also positive for the primary endpoint of PFS, but again showed no OS benefit.[6,7] The RIBBON-2 trial results appear to be similar.[9]

The main objective of the treatment of metastatic solid tumours is to improve the quality and quantity of the patient's survival. OS has been the gold-standard endpoint for demonstrating clinical benefit in cancer treatment. It is accurate, measured daily and reflects efficacy and safety.[29] However, compulsions related to statistical designs dictate that studies that have OS as the primary endpoint need to be larger and have longer follow-up periods. There are also concerns about the effect of crossover, the impact of subsequent therapies, and non-cancer-related deaths that can contaminate the accuracy of this endpoint. On the other hand, PFS could be a surrogate marker of treatment effect, not being influenced by subsequent treatments or crossover.[30] As PFS events occur more often, sample size is reduced and quicker results are generated, which indirectly accelerates drug development.[31] Interestingly, Ocaña et al.[32] analysed several studies using bevacizumab in the metastatic setting across different solid tumours. They observed that, although similar gains in terms of survival endpoints were observed among the trials, results were reported differently. In the particular case of bevacizumab in metastatic breast cancer, despite the lack of OS benefit, final results were reported as positive. This inconsistency is related to the use of PFS as a primary endpoint in some clinical trials. In addition, the current treatment paradigm, which includes multiple lines of therapy, suggests that time to progression in first-line treatment may not be a very important endpoint for evaluating novel regimens in the absence of strong considerations of toxicity and quality of life. In fact, some authors believe that the E2100 study overestimated the magnitude of benefit of bevacizumab in metastatic breast cancer; therefore, the results could not be replicated in subsequent trials.[33]

The most frequent toxicities of bevacizumab are grade 1–2 hypertension, proteinuria and bleeding, events that are manageable with medical therapy. The toxic effects particular to antiangiogenic agents (hypertension, bleeding, thrombosis, gastrointestinal perforation) occurred less frequently in phase III studies in breast cancer than in the pivotal trials of bevacizumab in colorectal and non-small-cell lung cancer.[34,35] Excluding pregnant women and those at risk of hypersensitivity reactions, bevacizumab is not contraindicated in any subgroup of patients, although caution should be exercised when treating certain patients, such as those with clinically significant cardiovascular disease or a history of arterial thromboembolism. Before starting bevacizumab therapy, pre-existing hypertension should be controlled. Treatment should be discontinued permanently in patients who experience gastrointestinal perforation, arterial thromboembolism, pulmonary embolism, significant hypertension that cannot be medically controlled, grade 3–4 bleeding, fistulas or proteinuria.

With regard to the risk of CHF with bevacizumab in breast cancer patients, the results of trials with more extensive cardiac monitoring are awaited. Preliminary safety data of phase II studies showed that the addition of bevacizumab to dose-dense anthracycline plus cyclophosphamide in the adjuvant setting is not associated with early clinically significant cardiac toxicity, although the number of patients with decline in ejection fraction >10% was higher in the bevacizumab arm, and

long-term follow-up data are still pending.[36-38] Additionally, data on bevacizumab cardiotoxicity with concurrent or prior trastuzumab exposure are limited as the vast majority of patients enrolled in the five large, randomized trials of bevacizumab in metastatic breast cancer were HER-2-negative. Phase III trials evaluating the addition of bevacizumab to trastuzumab-based therapy in the adjuvant and advanced settings are underway.[39-42]

Importantly, preclinical studies have suggested the existence of a rebound phenomenon during treatment with or after withdrawal of some antiangiogenic agents, leading to accelerated tumour growth and increased local invasion and distant metastasis.[43-45] These preclinical findings have raised general questions about accelerated disease course and more aggressive metastasis pattern in the clinical setting after cessation of antiangiogenic therapy. However, a recently reported pooled analysis of patients with several tumour types enrolled in randomized clinical trials who discontinued bevacizumab prematurely as a result of AE or disease progression did not show a decreased time from discontinuation to death in the bevacizumab group compared with the placebo group.[46]

4. Conclusions

While the correct bar for success of bevacizumab in breast cancer is unclear in an unselected population (different endpoints might be of interest to clinicians, patients and regulators), the identification of the proper patients, tumours or clinical settings has the potential to eradicate this ambiguity.[47] To date, subset analyses have failed to convincingly identify which patients or tumour types warrant, or could be spared, bevacizumab-based therapy. The HRs for PFS among patients with triple-negative breast cancers were similar to those for patients with estrogen/progesterone-positive tumours in the largest studies of metastatic disease. In the neoadjuvant setting, subgroup analysis of the GeparQuinto study suggests that triple-negative patients might have higher benefit in terms of pathological complete response with the addition of bevacizumab to standard chemotherapy (40.1% vs 32.7% of patients; $p = 0.059$).[48] There are no meaningful data for use of this agent in HER-2-overexpressing breast cancers.

There is a great need to identify and validate biomarkers to aid clinical decisions in the treatment with targeted therapies. Attempts to discover molecular or pathological predictive factors for efficacy of bevacizumab have not been successful. Additionally, the number of studies in which an active search for biomarkers of bevacizumab efficacy in breast cancer has been performed is very limited. Germline polymorphisms of the main players in the VEGF pathway can have major effects on bevacizumab pharmacokinetics and pharmacodynamics. Retrospective analysis of tumour samples in the E2100 trial showed that specific VEGF genotypes were associated with a superior median OS in the bevacizumab arm.[49] Validation of these findings is necessary for definite conclusions. In addition, incorporation of on-treatment pharmacodynamic markers of activity of bevacizumab, including changes in imaging parameters, such as diffusion contrast-enhanced magnetic resonance imaging in the neoadjuvant setting, is a good strategy for rational drug development of this agent. Studies focused on the identification of subgroups of breast cancer patients most likely to benefit from bevacizumab should be a research priority and should include triple-negative, locally advanced and inflammatory tumours.

A definite conclusion about the use of antiangiogenic therapy for breast cancer cannot be made with the available literature and discussion around the benefit-risk ratio will likely continue for the next few years as additional data from the (neo) adjuvant setting become available.

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Correspondence: *Otto Metzger Filho*, Institut Jules Bordet, Université Libre de Bruxelles, Boulevard de Waterloo, 121, 1000 Brussels, Belgium.
E-mail: otto.metzger@bordet.be