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Letter to the Editor

Bevacizumab Added to Neoadjuvant Chemotherapy in HER2-Negative Non-Metastatic Breast Cancer

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To the Editor,

Recombinant humanized monoclonal antibody bevacizumab binding and inactivating VEGF-A has recently been a particularly attractive focus of research in anti-angiogenic treatment strategy for breast cancer especially the HER-2 negative subtype [1]. Three recently published phase III randomized controlled trials-ARTemis [2], GBG 44- GeparQuinto [3] and SWOG S0800 trial [4]-have showed that adding bevacizumab to neoadjuvant chemotherapy (NAC) increased the pathological complete response (pCR) but did not favor the survival of HER-2 negative non-metastatic breast cancer (NMBC), while NSABP B-40 trial [5] contradicted the findings by demonstrating an improved survival particularly disease-free survival (DFS). To settle the disputes, we therefore performed a meta-analysis to evaluate the survival benefit and risk of this treatment strategy.

Involving 4122 participants with a median follow-up from 3 to 4.7 year, the pooled data suggested no significant effect of bevacizumab on either DFS or overall survival (OS). Similar results on DFS were also found according to the hormone receptor (HR) status. Unexpectedly, a significantly reduced DFS was indicated in patients achieving a pCR (hazard ratio, 2.36; 95%CI, 1.33-4.19) while not in patients without a pCR. The stratification analyses by HR status regarding OS showed no significant effect as well (Figure 1). Involving two trials with a total of 1897 participants, the result showed significantly increased risk of any surgical complications (risk ratio, 1.39; 95%CI, 1.20-1.62) in patients receiving NAC and neoadjuvant bevacizumab (Figure 1).

Although an individual patient-level meta-analysis would be ideal, our results highlighted that adding bevacizumab to NAC for HER-2 negative NMBC did not provide survival benefit but significantly increased the risk of surgical complications. Also, the results did not support the role of HR status in discriminating the effect of bevacizumab, which contradicted the finding from NSABP-B40 that addition of bevacizumab resulted in improved survival especially in HR-positive patients. In NSABP B40 but not in other trials, patients received bevacizumab not just preoperatively but also postoperatively, such substantial differences may have contributed to the discordant results because bevacizumab was able to affect not only the primary tumor but also dormant micrometastases. Although most previous trials incorporating the currently included trials showed consistently an increased pCR rate with neoadjuvant bevacizumab, reduced DFS was revealed in patients achieving pCR in the present study, suggesting that the pCR advantage seemed not always to be translated into a survival advantage. Our analysis failed to demonstrate this benefit while confirmed increased toxicity, supporting utmost cautions against the adoption of neoadjuvant bevacizumab in this setting.

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Competing Interests

The authors have declared that no competing interest exists.

Characteristics	ARTemis[2]	NSABP B-40[5]	GBG 44–GeparQuinto[3]	SWOG0800[4]
Clinicaltrial number	NCT01093235	NCT00408408	NCT 00567554	NCT00856492
Design	phase III, RCT, open label	phase III, RCT, open label	phase III, RCT, open label	phase III, RCT, open label
Country	UK	Canada and USA	USA	USA
Baseline NAC	T-FEC	T→AC or TX→AC or TG→AC	EC→T	Nab-paclitaxel→AC
Setting	T⩾2cm, Node(±)	T1c-T3,N0-N2a	T1-4,Node(+)	Locally advanced/inflammatory
Bev dose(cycles)	15 mg/kg iv,q3w(×4)	15 mg/kg iv,q3w(×6)	15 mg/kg iv,q3w(×8)	10 mg/kg iv,q2w(×6)
Postoperative use of Bev	no	yes	no	no
Median follow-up	3.5 years	4.7 years	3.8 years	3 years
No. of Patients(Bev vs. no Bev)	399 vs. 401	592 vs. 594	956 vs. 969	98 vs. 113
Age	⩽50 years(68%) >50 years(32%)	<50 years(52%) ⩾50 years(48%)	<40 years(16%) ⩾40 years(84%)	Median 51.5 (22-75) years
Hazard ratio(95%CI) for Bev	1.18 (0.89-1.57)	0.80 (0.63-1.01)	1.03 (0.84-1.25)	0.89 (0.48-1.65)
P value for DFS	0.25	0.06	0.784	0.71
Hazard ratio(95%CI) for Bev	1.26 (0.90-1.76)	0.65 (0.49-0.88)	0.97 (0.75-1.26)	0.84 (0.41-1.73)
P value for OS	0.19	0.004	0.842	0.64
Any surgical complications(%)	-	40.0% vs. 28.6%	14.7% vs. 10.9%	-

Pooled analysis

Outcome	No. of participants (No. of trials)	Hazard Ratio or Risk Ratio(95%CI) *	Heterogeneity test
Disease-free survival	4120(4 trials)	0.98 (0.85-1.11)	P=0.19, I^2=37%, F
pCR(yes)	449(2 trials)	2.36 (1.33-4.19)	P=0.51, I^2=0%, F
pCR(no)	2153(2 trials)	0.98 (0.82-1.17)	P=0.88, I^2=0%, F
HR(+)	2112(3 trials)	1.03 (0.66-1.60)	P=0.04, I^2=69%, R
HR(-)	1208(3 trials)	0.93 (0.76-1.15)	P=0.23, I^2=33%, F
Overall survival	4122(4 trails)	0.91 (0.67-1.23)	P=0.03, I^2=68%, R
HR(+)	851(2 trials)	0.94 (0.34-2.59)	P=0.09, I^2=66%, R
HR(-)	546(2 trials)	0.74 (0.52-1.05)	P=0.36, I^2=0%, F
Surgical complications	1897(2 trials)	1.39 (1.20-1.62)	P=0.87, I^2=0%, F

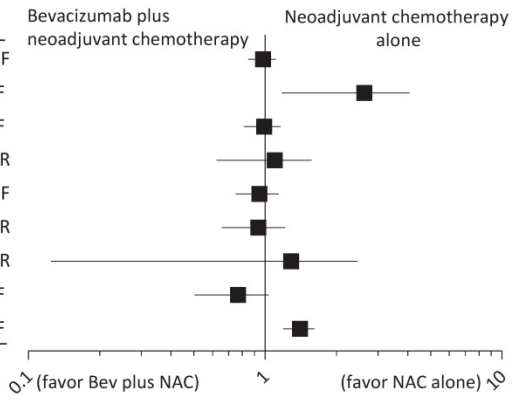

Figure 1. Survival and surgical complications for bevacizumab plus neoadjuvant chemotherapy versus neoadjuvant chemotherapy alone. Bev, bevacizumab; NAC, neoadjuvant chemotherapy; RCT, randomized controlled trial; T, docetaxel; FEC, fluorouracil plus epirubicin plus cyclophosphamide; AC, doxorubicin plus cyclophosphamide; TX, docetaxel plus capecitabine; TG, docetaxel plus gemcitabine; EC, epirubicin plus cyclophosphamide; q3w, every third week; iv, intravenously; DFS, disease-free survival; OS, overall survival; pCR, pathological complete response; HR, hormone receptor * A hazard ratio or risk ratio less than 1 favors the outcome by Bev plus NAC, while a hazard ratio or risk ratio greater than 1 favors the outcome by NAC alone. F, fixed-effect model; R, random-effect model.

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