Editorial

A new paradox for pCR in BRCA mutation carriers

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Pathologic complete response (pCR) in neoadjuvant chemotherapy (NACT) in breast cancer and especially in the triple negative subtype (TNBC) is considered an important surrogate end point for disease free survival (DFS), event free survival (EFS) and overall survival (OS) (1). Breast tumors of patients carrying a germline BRCA1/2 mutation represent a subgroup with unique biological characteristics (2). A subgroup analysis of the previously reported GeparQuinto study (3) was recently published by Fasching *et al.* in the *Journal of Clinical Oncology* (4) of the TNBC patients who carried a germline BRCA1/2 mutation, and found that the addition of bevacizumab to the NACT regimen of anthracycline/cyclophosphamide followed by weekly paclitaxel, significantly increased pCR rates (ypT0/is-ypN0) to 61.5% *vs.* 41.2% in the non-bevacizumab arm. However, this increase in pCR was not translated into an improved DFS (HR, 0.74; 95% CI, 0.32–1.69; P=0.472) (4).

So far, the clinical trials that have studied the addition of bevacizumab to NACT in breast cancer have yielded conflicting results. GeparQuinto and CALGB 40603 showed that the addition of bevacizumab in the neoadjuvant setting of HER-2 negative and triple negative breast cancer patients, respectively, produced an increased rate of pCR of about 10% (3,5). The effect from the addition of bevacizumab in the GeparQuinto study was more pronounced in the triple negative subgroup. The updated results of CALGB 40603 presented at the 2015 San Antonio Breast Cancer Symposium showed that despite the fact that the patients who achieved pCR had improved RFS and OS, these clinical benefits lacked a significant association with the addition of bevacizumab, thus rendering the study underpowered (6). In the NSABP B40 study the addition of bevacizumab to a NACT regimen consisting of docetaxel/doxorubicin and capecitabine or gemcitabine (depending on the study arm) showed benefit for pCR and OS only in women with hormone receptor–positive disease, with negative findings in the TNBC subgroup (7,8). The ARTemis study randomized women with HER2-negative breast cancer receiving NACT with 3 cycles of docetaxel followed by 3 cycles of cyclophosphamide, epirubicin, and fluorouracil, with or without bevacizumab. Initially, the patients of the bevacizumab arm had increased rates of pCR, an effect that was more pronounced in the TNBC subgroup (45% *vs.* 31%) (9). However, after 3.5 years of follow up, there was no clear benefit in terms of PFS and OS in the cohort of patients who received bevacizumab although pCR in the non-bevacizumab group was associated with an increased PFS and OS (10). These results were explained by the researchers with the hypothesis that micrometastatic breast cancer may grow in an angiogenesis-independent manner. In the GeparSixto trial 595 patients with TNBC were randomized into 2 groups, with both groups receiving 18 weeks of weekly paclitaxel in combination with weekly non-pegylated liposomal doxorubicin, and bevacizumab every 3 weeks. The experimental arm additionally received weekly carboplatin. A total of 333 women completed treatment in the both arms. The addition of carboplatin resulted in a significantly improved pCR rate over control (53% *vs.* 37%; P=0.005). This increase in pCR was translated into an absolute benefit in 3-year EFS for the addition of carboplatin over control of 9.7% [85.8% *vs.* 76.1%, respectively; HR, 0.56 (95% CI, 0.33–0.96)]. Due to the addition of carboplatin it is not feasible to determine any possible benefit from the addition of bevacizumab (11). Summarizing all the previous data, there is no clear and proven clinical benefit from the addition of bevacizumab in

TNBC in the neoadjuvant setting.

In the GeparQuinto study, 1,984 patients with HER-2 negative breast cancer were initially enrolled and 678 of them had TNBC. Genotype data were obtained for 493 patients. Amongst them 90 patients had germline mutations in *BRCA1/2* genes, 74 in the *BRCA1* gene and 16 in the *BRCA2* gene. Fifty-one BRCA mutation carriers were randomized in the non-bevacizumab arm (40 had BRCA1 mutation and 11 BRCA2 mutation) and 39 mutation carriers were randomized in the bevacizumab arm (34 with BRCA1 mutation and 5 with BRCA2 mutation). In the TNBC subgroup of the study, the BRCA1/2 mutations carriers had increased rates of pCR compared to non-carriers 50% *vs*. 31.5% irrespectively of the administration of bevacizumab [odds ratio (OR), 2.17; 95% CI, 1.37–3.46; P=0.001]. The pCR rates were similar for BRCA1 (48.6%) and BRCA2 (56.3%) mutation carriers. BRCA1/2 mutations carriers had a significantly improved DFS (HR, 0.644; 95% CI, 0.415–0.998; P=0.047) than those with no mutations. The addition of bevacizumab in BRCA mutation carriers lead to pCR in 61.5% of them *vs*. 41.2% for the BRCA mutation carriers that were randomized in the non-bevacizumab arm. Interestingly enough though, the increased pCR rate in patients with BRCA1/2 mutations was not significantly associated with an improved DFS (HR, 0.74; 95% CI, 0.32–1.69; P=0.472). Due to the increased risk of this specific patient population for contralateral breast cancer development the researchers analyzed the data also with distant DFS (DDFS) as the outcome variable and the analysis yielded similar results. As expected, the patients without BRCA1/2 mutations derived substantial benefit from pCR (HR, 0.18; 95% CI, 0.11–0.31; P<0.001) (4).

Although we must interpret with caution the results of the GeparQuinto study due to the small number of patients enrolled who had BRCA1/2 mutations and especially the very few patients harboring BRCA2 mutations, it seems that the addition of bevacizumab in the NACT regimen in BRCA mutation carriers increases the pCR rate. This effect was explained by the researchers due to the synthetic lethality phenomenon caused by angiogenesis inhibition and the lack of a functional homologous recombination machinery in BRCA mutant cells (12). In addition, BRCA mutation carriers had a higher pCR rate compared with non-carriers regardless of bevacizumab administration and improved DFS. However, TNBC BRCA mutation carriers do not seem to have a better prognosis than the non-carriers based on the largest prospective cohort study conducted so far by Copson *et al*. (13).

Is pCR a surrogate marker for better clinical outcome for BRCA mutation carriers? Paluch-Shimon *et al*. in a single institution prospective study using a smaller number of patients (34 BRCA mutation carriers) who received neoadjuvant therapy with dose dense doxorubicin/cyclophosphamide followed by paclitaxel found no difference in relapse-free survival regardless of pCR status (log-rank P=0.25). In contrast, in the non-carrier cohort, the achievement of pCR seemed to retain its expected prognostic significance (log-rank P=0.0001) (14). The results of this study are in concordance with the results of GeparQuinto as they both demonstrate lack of prognostic value for pCR in BRCA mutation carriers. On the contrary in the GeparSixto trial, the data did not show a differential effect of pCR in the prognosis of patients with and without BRCA1/2 mutation. However, the number of BRCA mutation carriers was small (n=50) and due to the effect of carboplatin the possible beneficial role in EFS from the addition of bevacizumab remains uncertain.

Is there an explanation for the results of GeparQuinto? The increased pCR rates in BRCA mutation carriers irrespectively from the addition of bevacizumab can be attributed to the unique biologic characteristics conferred to the tumor by the lack of a functional *BRCA1/2* gene. The increased capacity of chemotherapy with anthracycline/taxane/cyclophosphamide combination to induce pCR in BRCA mutant tumors was also shown by Paluch-Shimon *et al*. (14). BRCA mutation carriers have an intrinsic defect in homologous DNA recombination. This defect possibly confers greater chemosensitivity to treatments with DNA damage inducing agents such as anthracyclines and cyclophosphamide (15). More importantly however, is to explain the lack of correlation between pCR after NACT for BRCA1/2 mutation carriers and an improved prognosis. We can postulate that the answer lies in the unique genetic characteristics of the tumors that bear mutations in the *BRCA* genes and how these affect the interaction of the malignant cells with the host's immune system. The defect in homologous recombination may increase tumor neoantigen load due to the inability of these cells to correct the DNA damage properly. Lin studied tumors from 82 patients with early onset breast cancer and found using whole exome sequencing that tumors with mutations in the genes that control homologous recombination or MMR have higher number of neopeptides with high binding affinity and immunogenicity than wild type tumors (16). Moreover, possibly due to the increased neoantigen load these tumors have been associated in some studies with increased

number of tumor infiltrating lymphocytes (17). The higher immunogenicity of these tumors may lead to a more effective immunosurveillance by the host's immune system in the setting of micrometastatic disease thus obscuring the possible beneficial effect of a pCR after NACT on patients' clinical outcome.

In conclusion the role of bevacizumab in NACT for BRCA mutation carriers remains controversial because although it seems to increase pCR rates, it does not improve clinical outcome for these patients. In the era of immune checkpoint inhibitors and PARP inhibitors and the promising results of the addition of these agents in the neoadjuvant setting (18,19) it may be difficult for bevacizumab to find its place. This study showed us a new paradox for the achievement of pCR in a patient who carries a BRCA mutation since the implication on prognosis was not what we would have expected.

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Footnote

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