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BREAST CANCER

Combining bevacizumab with chemotherapy—from maintenance to second-line treatment

Bevacizumab is a VEGF-neutralizing antibody that blocks angiogenesis, a crucial process in the growth of both primary tumours and metastases. Bevacizumab has been used for the treatment of several cancer types, including colon and breast cancer.

The combination of bevacizumab with chemotherapy, in the first-line or second-line setting, results in improved progression-free survival (PFS) in patients with HER2-negative, locally recurrent or metastatic breast cancer. However, no study has shown an improvement in overall survival, possibly because the patients with breast cancer did not receive bevacizumab for a long enough period to achieve a survival benefit: preclinical studies demonstrate that tumour blood vessels can regrow once bevacizumab administration is terminated.

In the multicentre phase III TANIA trial, von Minckwitz *et al.* recruited patients with HER2-negative locally recurrent or metastatic breast cancer whose disease had progressed after receiving 12 weeks or more of first-line bevacizumab plus chemotherapy. Overall, 494 patients were randomly assigned in a 1:1 ratio to receive second-line single-agent chemotherapy either alone or in combination with bevacizumab. Importantly, second-line treatment was continued until disease progression, excessive toxicity or consent to withdrawal, and crossover was not allowed. If disease progression occurred, patients were then assigned to third-line chemotherapy alone (if they were in the chemotherapy group) or to bevacizumab (if they were in the combination group). At a median follow-up of ~16 months, PFS—the primary end point of the study—was significantly longer for patients in the combination arm (6.3 months versus 4.2 months), and as von Minckwitz highlights, "the rate of primary progressions is lower in the bevacizumab group". Of note, the improved PFS was not accompanied by an increase in the number of patients achieving responses. However, the overall survival and third-line PFS data are not yet mature. Pending final analysis, the primary data of the TANIA trial highlight that further treatment with bevacizumab improves PFS and that bevacizumab could be a valid option for patients responding to and tolerating first-line bevacizumab therapy.

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In parallel with the publication of the TANIA trial, the results of the IMELDA study were also published in *The Lancet Oncology*. IMELDA was an open-label randomized phase III trial that investigated the efficacy of maintenance therapy with capecitabine and bevacizumab versus bevacizumab alone until disease progression in patients with HER2-negative metastatic breast cancer who received initial bevacizumab and docetaxel treatment. The rationale for such a trial was that, according to a meta-analysis of 11 randomized trials, longer first-line chemotherapy is associated with longer PFS and overall survival. However, prolongation of docetaxel until disease progression is not feasible owing to its high level of toxicity. Capecitabine is a more tolerable chemotherapeutic agent, hence the efficacy of the capecitabine plus bevacizumab combination was investigated in the IMELDA study. Gligorov and co-authors randomly assigned 185 patients to receive bevacizumab alone or in combination with capecitabine. Both PFS and overall survival were significantly longer in the combination arm—11.4 months versus 4.3 months for PFS and 39.0 months versus 23.7 months for overall survival. These results are impressive considering the early discontinuation of enrolment and randomization, which resulted in a smaller sample size and fewer PFS events than expected. The study was not designed to compare overall survival, as it was terminated 24 months after the last patients were randomized, and no information of post-progression treatment was available.

An increasing body of evidence, including data from the TANIA and IMELDA trials, indicate an improved efficacy of continued antiangiogenic therapy. Furthermore, the IMELDA trial data suggest that an early switch to maintenance therapy might be beneficial, challenging the current treatment paradigms for HER2-negative metastatic breast cancer.

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Original articles von Minckwitz, G. *et al.* Bevacizumab plus chemotherapy versus chemotherapy alone as second-line treatment for patients with HER2-negative locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy (TANIA): an open-label, randomised phase 3 trial. *Lancet Oncol.* doi:10.1016/S1470-2045(14)70439-5 | Gligorov, J. *et al.* Maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-negative metastatic breast cancer (IMELDA): a randomised, open-label, phase 3 trial. *Lancet Oncol.* doi:10.1016/S1470-2045(14)70444-9