# Neoadjuvant chemotherapy backbone, which is the optimal option?

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Neoadjuvant therapy has become a standard approach not only for large, primarily inoperable or inflammatory breast cancer but also for primarly operable eBC. In general for TNBC and HER2+ early breast cancer this is even the preferred treatment. In general whenever the systemic therapy can be decided based on the clinical and biological information available after core biopsy, the systemic treatment can be given as preoperative/neoadjuvant therapy, mainly chemotherapy plus targeted agents. Another more general aspect is that all chemotherapy regimen tested as adjuvant therapy can be used as neoadjuvant therapy and vice versa. Whether the chemotherapy backbone improves the efficacy of targeted agents is a current and probably never ending debate.

HER2+

The standard chemotherapy backbone is an anthracycline/taxane containing regimen, e.g. EC followed by paclitaxel. In parallel anthracycline free regimen have been used especially in combination with trastuzumab/pertuzumab (docetaxel plus carboplatinum plus anti-HER2 therapy). The neoadjuvant TRYPHAENA trial investigated different chemotherapy backbones in combination with trastuzumab/pertuzumab with respect to cardiac toxicity. The study showed that there was no statistically significant difference between FEC-Doc in combination with dual anti-HER2 therapy, FEC-Doc plus dual anti-HER2 therapy, and TCbHP with regards to cardiac toxicity. The neoadjuvant phase II BERENICE study showed that dose-dense chemotherapy with dual anti HER2 therapy is feasible in terms of cardiac toxicity. The pCR rate seemed to be higher with the dose-dense regimen in the HR-negative group. The GeparOCTO study conducted in all comers, showed no significant different pCR rates when dd chemotherapy was given as backbone. The pCR rate in the dose-dense arm was 60% which is almost identical to the one in BERENICE. The GeparSEPTO study investigating paclitaxel or nab-paclitaxel as neoadjuvant chemotherapy showed a significant higher pCR rate and improved DFS in the ITT overall population but only a small trend in the HER2+ subgroup in favour of nab-paclitaxel. The recent TRAIN-2 trial investigated the role of an anthracycline free chemotherapy (FEC-PacliCb vs PacliCb) in combination with trastuzumab and pertuzumab. The pCR rate was 67 and 68% respectively also the long-term outcome although not powered for that was not significantly different. Overall, in the aera of trastuzumab and pertuzumab as anti-HER2 therapy the chemotherapy backbone seems less important. It should be a standard regimen, proven efficacy and safet in phase III or larger randomised phase II trials with a known safety and efficacy profile.

TNBC

The targeted agents in TNBC in the treatment of eBC is quite new. The only available therapy is pembrolizumab in addition to paclitaxel plus carboplatinum followed by AC. A phase I/II study investigated different chemotherapy regimen in addition to pembrolizumab as neoadjuvant therapy. It seemed that the chemotherapy backbone chosen for the phase III KN522 study, had the highest pCR rate. The neoTRIP trial used an anthracycline free chemotherapy. The GeparNUEVO trial used nab-paclitaxel followed by EC q2weeks as chemotherapy backbone. In the TONIC trial in metastatic breast cancer it was shown that the highest efficacy and immune response was achieved with doxorubicin. Today, it is not known whether the choice of the chemotherapy backbone in combination with pembrolizumab or atezolizumab is important.

In summary, in the context of targeted agents the chemotherapy chosen seems to be less important than when used alone. However, data from phase III or at least randomised phase II studies should guide the decision which chemotherapy is optimal for the given targeted agent and the individual patient.