Update – Novelties in neoadjuvant therapy of breast cancer

Neoadjuvant chemotherapy (NACT) has become a mainstay of treatment for patients with triple-negative breast cancer (TNBC), and human epidermal growth factor 2 (HER2) positive BC. In these patients pathological complete response (pCR) is correlated with long term outcome and allows to adapt adjuvant treatment. Some patients with hormone receptor (HR) positive HER2-negative BC also require NACT, mainly because of locoregionally advanced disease or aggressive biology.

Neoadjuvant pembrolizumab in TNBC: 5-year event-free survival in Keynote-522

The Keynote-522 study randomized 1'174 patients with higher risk TNBC (cT1c cN1-2 or cT2-4 cN0-2) to either neoadjuvant chemotherapy (NACT) with pembrolizumab followed by adjuvant pembrolizumab (n = 784) or NACT with placebo (n = 390). The event-free survival (EFS) at 60-months was 81.3 % (95 %CI 78.4-83.9) in the pembrolizumab arm, and 72.3 % (95 % CI: 67.5-76.5) in the placebo arm, representing a significant (HR: 0.63; 95 % CI: 0.49–0.81) and sustained difference compared to the last interim-analysis after 36-months (HR 0.63; 95 % CI: 0.48–0.82). The benefit was irrespective of PD-L1 status and a difference between the two arms seems to emerge even in the patients having reached pCR (HR: 0.65; 95 % CI:0.39–1.08). Overall survival results were not presented (1).

Neoadjuvant immunotherapy in HR positive and HER2 negative breast cancer

The rationale to use PD-1/PD-L1 inhibitors in patients with HR+/HER2- BC stems from the I-Spy2 study suggesting improved pCR rates with these agents (2–5). Two studies investigating immune checkpoint inhibitors in these patients were presented at ESMO 2023. In the Keynote-756 study 1'278 patients with grade 3, ER ≥1 % and cT1c-2 cN1-2 or cT3-4 cN0-2 BC were randomized 1:1 (6). In the CheckMate 7FL study 510 patients with grade 3 and ER ≥1 % or grade 2 and ER 1-10 % BC and a tumor stage of cT1c-T2 cN1-2 or cT3-4 cN0-2 were randomized 1:1 (7). The patients received neoadjuvant pembrolizumab/placebo or nivolumab/placebo with NACT and post-surgical pembrolizumab/placebo or nivolumab/placebo with endocrine therapy, respectively. Both studies reported significantly improved pCR rates (Keynote-756: 24.3 % vs. 15.6 %; CheckMate 7FL: 24.5 % vs. 13.8 %). Discontinuation rates were higher in the immunotherapy arms compared to placebo (Keynote-756: 19.1 % vs. 10.1 %; CheckMate7FL: 10 % vs. 3 %). One treatment-related death occurred in the pembrolizumab arm and two deaths in the nivolumab arm. In the CheckMate 7FL cohort, no higher proportion of breast-conserving surgery was observed (38 % vs. 39 %).

Omission of breast surgery in breast cancer patients with excellent response to neoadjuvant chemotherapy

Three-year follow-up data of a phase-2 multicenter prospective trial examining the omission of breast surgery after NACT in TNBC and HER2+ BC were presented. Patients had to have radiological complete or partial response and confirmed pCR on image-guided biopsy (8). Of 50 enrolled patients with cT1-2 cN0-1, 31 (62 %) showed a pCR and breast surgery was subsequently omitted, with all patients undergoing adjuvant whole breast radiotherapy and tumor bed boost. At a median follow-up of 38.4 months zero events were registered, resulting in an in-breast recurrence-free survival of 100 %.

Conclusions

In TNBC, EFS results were confirmed. Next, overall survival results are eagerly awaited. Other studies may potentially open completely new treatment paths for high-risk ER+/HER2- BC. It will be incremental to see, whether the presented increased pCR rates translate to improved survival also in this cohort. And finally, further de-escalation of surgical treatment after NACT was shown to harbor excellent oncologic results in a small cohort after 3-years of follow-up being highly relevant for the Swiss-initiated SAKK 23/18 VISION-1 trial (clinicaltrials.gov NCT04289935).

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