short review

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ESMO 2019: breast cancer

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Summary This articles reviews results of relevant breast cancer trials presented at the 2019 ESMO Meeting. In triple-negative disease, addition of pembrolizumab to standard neoadjuvant chemotherapy yielded a pathologic complete response (pCR) rate of 64.8%, the highest pCR rate reported to date in this setting; in addition, a trend towards improved event-free survival was observed in the immunotherapy group. In pretreated patients with metastatic triple-negative breast cancer, single-agent pembrolizumab was not superior to conventional chemotherapy. In metastatic hormone-receptor positive disease, an update of the MONARCH2 and MonaLEEsa-3 studies indicated an overall-survival benefit in favour of the respective CDK4/6 inhibitor groups emphasizing the clinical importance of this class of drugs.

Keywords Luminal breast cancer · Triple-negative breast cancer · CDK4/6-inhibitors · Pembrolizumab · Update

Introduction

At the 2019 ESMO Meeting, results from several clinically important studies in the field of breast cancer were presented, among them overall survival data of two CDK4/6 inhibitor trials in hormone-receptor positive, HER2-negative metastatic disease and results of studies with the immune checkpoint inhibitor pembrolizumab in the neoadjuvant and metastatic setting.

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Pembrolizumab in triple-negative breast cancer

In early stage triple-negative breast cancer (TNBC), neoadjuvant chemotherapy consisting of anthracyclines, cyclophosphamide, taxanes and carboplatin is regarded as a potential treatment standard based upon results of the phase III BrighTNess trial, where the quadruple combination achieved pathologic complete response (pCR) rates in excess of 50% [1]. The KEYNOTE-522 study evaluated the potential role of adding pembrolizumab to this regimen [2]. A total of 1174 patients were randomized to receive four cycles of paclitaxel plus carboplatin followed by doxorubicine/cyclophosphamide (AC) or epirubicine/cyclophosphamide (EC) in combination with pembrolizumab or placebo; placebo or immunotherapy were continued in the postneoadjvant part of the trial for another 27 weeks. Addition of pembrolizumab to neoadjuvant chemotherapy increased pCR rates from 51.2 to 64.8% (Δ13.6%; $p = 0.00055$). This effect was independent of PD-L1 expression as defined by CPS (combined positive score; 22C3 pharmDx assay). Patients with PD-L1 positive tumours had a higher pCR rate independent of treatment arm; of note, the additional benefit was most pronounced in patients with node-positive disease and those receiving weekly carboplatin as opposed to those receiving carboplatin once every three weeks. Event-free survival (EFS) was defined as co-primary endpoint; at the 18-month median follow-up, there was a nonsignificant 6% absolute difference in favour of the pembrolizumab group (EFS 91.3% vs. 85.3%; hazard ratio [HR] 0.63; 95% confidence interval [CI] 0.43–0.93). No new safety signals were observed. In summary, the pCR rate with quadruple chemotherapy combined with pembrolizumab is the highest reported in TNBC hitherto; in addition, early EFS data are intriguing and the size of the EFS difference suggests a benefit of im-

munotherapy beyond its effect on pCR. While longer follow-up needs to be awaited, pembrolizumab may eventually evolve as a clinically relevant addition to standard neoadjuvant therapy in TNBC.

KEYNOTE-119, on the other hand, was a negative trial [3]. Overall, 622 patients with metastatic TNBC were randomized to receive pembrolizumab monotherapy or chemotherapy by investigator's choice (including capecitabine, eribulin, vinorelbine, and gemcitabine). All patients had received prior treatment with anthracyclines and taxanes in the neoadjuvant, adjuvant, or metastatic setting. Overall survival (OS), which was defined as primary study endpoint, was not different in patients with CPS ≥10 or ≥1 tumours between the two groups; in a retrospective analysis, however, pembrolizumab was superior to chemotherapy in case of CPS ≥20 suggesting that only highly immunogenic TNBC may derive benefit from single-agent checkpoint inhibitors.

MONALEESA-3 and MONACRH2: overall survival update

In hormone-receptor (HR) positive breast cancer, OS data of two CDK4/6 inhibitor studies were presented. MONALEESA-3 randomized a mixed population of first- and second-line patients with HR-positive/HER2-negative locally advanced inoperable or metastatic breast cancer to the pure anti-oestrogen fulvestrant with ribociclib or placebo. Results of progression-free survival (PFS), which was defined as primary study endpoint, had already been published and combination therapy yielded a prolongation of median PFS from 12.8 to 20.5 months (HR 0.593; 95% CI 0.480–0.732; $p = 0.001$) [4]. At the 2019 ESMO Meeting, OS data were presented indicating a significant OS benefit in favour of the ribociclib group as well (median OS 40 months vs. not reached; HR 0.724; 95% CI 0.568–0.924; $p = 0.00455$); this effect was similar in first- and second-line patients (the latter group included patients with early relapse after adjuvant endocrine therapy) [5]. In MONARCH-2, patients progressing on adjuvant endocrine therapy or within one year since the end of prior adjuvant endocrine treatment as well as second-line patients were randomized to fulvestrant with abemaciclib or placebo. Again, PFS results have already been published and there was an expected prolongation of PFS in favour of the abemaciclib group observed (median PFS 16.4 vs. 9.3 months; HR 0.553; 95% CI 0.449–0.681; $p < 0.001$) [6]. OS data were presented at the ESMO Meeting and median OS was significantly prolonged from 37.3 months to 46.7 moths (HR 0.757; 95% CI 0.606–0.945; $p = 0.0137$); of note, a benefit was seen in patients with primary and secondary endocrine resistance [7]. These data are well in line with OS results from the MonaLEEsa-7 trial conducted exclusively in the first-line setting in premenopausal patients [8], while in heavily pretreated patients, no OS benefit was observed in PALOMA-3 [9]. Therefore, it appears beneficial to initiate CDK4/6 inhibitor therapy early. Before drawing any final conclusions, however, OS results from the first-line PALOMA-2, MonaLEEsa-2 and MONARCH-3 trials need to be awaited.

Take Home Message

Pembrolizumab when added to standard neoadjuvant chemotherapy increased pCR rates to >60% in early stage triple-negative breast cancer. Pembrolizumab was not superior to chemotherapy by physician's choice in pretreated patients with metastatic triple-negative breast cancer. The CDK4/6 inhibitors abemaciclib and ribociclib in combination with fulvestrant both prolonged overall survival over endocrine therapy alone in a mixed population of first- and second-line patients with metastatic hormone-receptor positive breast cancer.

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