short review

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Selection of phase II/III breast cancer study highlights at the 2022 ESMO annual meeting

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Summary The ESMO annual meeting 2022 was held in Paris from September 9th to September 13th 2022. This article aims at presenting highlights of phase II and III clinical trials reported at this meeting.

Keywords Breast cancer · Chemotherapy · Immunotherapy · Metastatic breast cancer · Early breast cancer

Introduction

The 2022 European Society for Medical Oncology (ESMO) Annual Meeting was held in Paris from 9–13 September 2022. Although no practice-changing data were presented for breast cancer, various interesting studies were presented that warrant further discussion. Therefore, this article aims at identifying and summarizing the most clinically relevant research in the field of breast cancer presented at this meeting.

Early breast cancer

As presented by Vivianne Tjan-Heijnen and colleagues, results from DATA, a phase III trial of extended adjuvant aromatase inhibitor (AI) treatment with letrozole after tamoxifen, showed no significant improvement in disease-free survival (DFS) after a median follow-up of 10.1 years (DFS 69% for 6 years vs. 66% for 3 years, hazard ratio [HR] 0.86, $p=0.073$) [1]. Subgroup analyses, however, showed a significant difference in DFS for patients exhibiting lymph node metastasis (69% vs. 61%, HR 0.74). Furthermore, in another subgroup analysis, tumor size greater than 2 cm in combination with nodal positivity yielded the highest benefit in terms of DFS (absolute benefit 13.6%, $p=0.005$) and showed a nonsignificant trend towards ameliorated overall survival (OS, HR 0.71, $p=0.084$). Of note, no significant OS benefit was reported for any subgroup for longer AI treatment. Still, the effects shown are clinically relevant and reflect data reported from the phase III ABCSG16 trial [2] in the sense that patients with high risk for recurrence should be offered and counseled about extended adjuvant endocrine treatment beyond 5 years. Individual factors such as bone density, tolerability and quality of life, however, should be taken into account when discussing therapy escalation.

In the phase II BELLINI trial, a study of checkpoint inhibitor (CI) treatment with ipilimumab and nivolumab or nivolumab alone in early triple-negative breast cancer (eTNBC) exhibiting tumor-infiltrating lymphocytes, objective radiological response rates (ORR) of up to 23% were reported [3]. Activation of the immune system was detected in 58% of patients and interestingly, in the 3 patients who underwent surgery after investigational CI treatment, one pathological complete response (pCR) and one near-pCR was observed. Adverse events of grade 3 or higher were seen in only 6% of patients. Even though preliminary and not ready for immediate implementation in the clinical routine, these results indicate activity of checkpoint inhibitor therapy in eTNBC without combination with chemotherapy. This is a thought-provoking notion that may create ground for the design of de-escalation strategies in this setting.

Dose-dense adjuvant chemotherapy for node-positive breast cancer was evaluated in the phase III trial GIM2 of the Gruppo Italiano Mammella [4] and the trial's final (15 year) analysis was presented at ESMO 2022 [5]. According to the data presented, the ini-

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tially reported benefits in OS and iDFS were sustained for the dose-dense (2-week) regimen when compared to conventional 3-week chemotherapy (61% vs. 52% iDFS, HR 0.77, $p<0.001$ and 76% vs. 69% OS, HR 0.72, $p<0.001$).

Metastatic breast cancer

An interim overall survival analysis of the phase III MONARCH3 [6] trial of a nonsteroidal aromatase inhibitor with/without the cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) abemaciclib in patients with hormone receptor (HR)-positive, Her2-negative advanced breast cancer was one of the highlights presented at ESMO 2022 [7]. This second interim analysis at approximately 70 months of follow-up showed a clinically relevant benefit for the treatment with the CDK4/6i when compared to endocrine treatment alone in terms of OS (67 vs. 55 months, HR 0.75, $p=0.0301$) in the intention-to-treat population. While the reported robust and statistically significant benefit in terms of progression-free survival (PFS) remained (28.2 vs 14.8 months, HR 0.54, $p=0.000021$), a potential OS benefit, however, did not meet the threshold for formal statistical significance. Therefore, the final analysis of the trial, expected for the end of 2023, remains of special interest.

TROPICS-02, a phase III study of sacituzumab–govitecan (SG), an antibody–drug conjugate already approved for the treatment of advanced/metastatic TNBC, in heavily pretreated HRpos/Her2neg breast cancer yielded positive results in terms of an overall survival benefit for SG when compared to treatment of physicians' choice (TPC) of either capecitabine, gemcitabine, vinorelbine or eribulin (14.4 vs 11.2 months, HR 0.79, $p=0.020$) [8]. Based on these findings, SG was approved as treatment in this setting by the US Food and Drug Administration (FDA) and approval by European Medicines Agency (EMA) is pending. Patients included in this study exhibited a median of three prior lines of chemotherapy for metastatic breast cancer. SG should hence be considered a novel treatment alternative in patients progressing after two or more chemotherapeutic regimen in this setting.

The Synergy trial, a phase II study of the chemotherapy/immunotherapy backbone of paclitaxel/carboplatin and the CI durvalumab with or without the CD73-directed antibody oleclumab as first-line therapy in advanced or metastatic TNBC reported no benefit in clinical benefit rate (CBR) or PFS for the addition of oleclumab (6 vs. 7.7 months PFS, approx. 43% CBR in both arms, n.s.) [9]. The rationale to target CD73 stems from its immunosuppressive effects on cytotoxic T-cells via adenosine level regulation and its potential direct oncogenic functions that mediate cancer invasive and metastatic properties [10, 11].

Another phase II trial, however, the monarcHER trial presented by Fabrice André at the meeting, gained a lot of attention through its positive signals. In this trial in patients suffering from HRpos/Her2pos ("triple-positive") advanced/metastatic breast cancer, treatment with abemaciclib with/without fulvestrant plus trastuzumab (arms A and B) versus chemotherapy plus trastuzumab (arm C) led to a numerical benefit in overall survival for the regimen containing the CDK4/6i (approx. 30 months for arms A+B vs. 20 months for arm C) [12]. Although the difference for this secondary endpoint of the phase II study was not statistically significant, this combination therapy warrants further examination as treatments targeting this entity beyond progression on Her2-directed therapies are dearly needed. This is substantiated through the fact that prior to ESMO 2022, progression-free survival, the primary endpoint of this study, had already been met [13]. Further, interestingly, in an explanatory analysis, patients with luminal intrinsic subtypes exhibited superior median PFS and OS than patients with non-luminal subtypes.

Another study providing a thought-provoking but not statistically significant trend was ELAINE-1, a phase II study of the estrogen receptor-modulator (SERM) lasofoxifene versus fulvestrant in advanced and pretreated HRpos/Her2neg breast cancer with an ESR1-mutation progressing on AI and CDK4/6i [14]. ELAINE-1 showed numerically improved PFS of 6 vs. 4 months for lasofoxifene vs. fulvestrant (HR 0.70, $p=0.138$) as well as numerically improved CBR and ORR.

Lastly, trials evaluating oral selective estrogen-receptor degraders (SERDs) failed to meet their primary endpoints: acelERA, a phase II study testing giredestrant versus physicians' choice of fulvestrant or aromatase inhibitors in patients with HRpos/Her2neg metastatic/advanced breast cancer who progressed after up to two lines of treatment showed no benefit in PFS for giredestrant vs. TPC (HR 0.81, $p=0.18$) [15]. A further phase II trial, AMEERA-3, showed no benefit in PFS for the SERD amcenestrant versus endocrine TPC in endocrine-resistant breast cancer, again in the advanced HRpos/Her2neg setting with up two previous lines of therapy allowed (HR 1.05, $p=0.64$) [16]. Both results are somewhat discouraging given the hope the community had developed for SERDs to play a role in overcoming endocrine resistance. Further studies with careful patient selection are needed to find optimal treatment settings for SERDs in advanced breast cancer.

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