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PODCAST

ESMO20 YO for YO: highlights on immune checkpoint blockade for triple-negative breast cancer

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Available online 4 January 2021

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Important news for immune therapy in breast cancer was presented at the European Society for Medical Oncology (ESMO) Virtual Congress 2020.

In the early setting, the primary analysis of IMpassion031 (ClinicalTrials.gov identifier: NCT03197935) was presented. In this trial, 333 patients with stage II or III triple-negative breast cancer were randomized to atezolizumab or placebo, combined with 12 weekly administrations of nab-paclitaxel followed by 4 cycles of dose-dense doxorubicin-cyclophosphamide in the neoadjuvant setting. After surgery, patients and investigators were unblinded and patients in the experimental arm continued for an additional 11 cycles of atezolizumab. The trial met its primary endpoint with a significantly higher rate of pathological complete response (pCR) in the atezolizumab arm (+16.5% pCR). Both the programmed death-ligand 1 (PD-L1)-positive and the PD-L1-negative patients had comparable benefit from the addition of atezolizumab, while there was a higher difference in pCR rate in the node-positive compared with the node-negative patients. Compared with PD-L1-negative patients, PD-L1-positive patients had higher pCR rates in both arms. Trends in immature event-free, disease-free and overall survival analyses support the pCR benefit seen with atezolizumab. With this trial, the potential of immune checkpoint blockade to improve pCR rates in early triple-negative breast cancer is confirmed after earlier phase III data from KEYNOTE-522 with pembrolizumab added to platinum-containing neoadjuvant chemotherapy (ClinicalTrials.gov identifier: NCT03036488). Despite these promising results of immune checkpoint blockade in early triple-negative breast cancer, several questions remain on the magnitude of long-term benefit, toxicity, prognostic and predictive biomarkers, the optimal treatment duration and chemotherapy backbone.

In the advanced setting, the first results of IMpassion131 (ClinicalTrials.gov identifier: NCT03125902) and the final analysis of IMpassion130 (ClinicalTrials.gov identifier: NCT02425891) were released. In IMpassion131, 631 patients with previously untreated advanced triple-negative breast cancer were randomized between paclitaxel with atezolizumab or placebo. The co-primary endpoint was progression-free survival (PFS) in the PD-L1-positive and intent-to-treat (ITT) population and was tested first in the PD-L1-positive subgroup. Surprisingly, the trial did not meet its primary endpoint, with similar PFS in both PD-L1-positive and ITT populations. Overall survival (OS) was a secondary endpoint and an updated analysis showed a numerically lower median OS in the experimental arm in both PD-L1-positive patients and in the overall population. These trends of worse OS were not statistically significant.

In the same session, the final overall survival analysis from IMpassion130 was presented, which investigated atezolizumab in the same setting in combination with nab-paclitaxel. In this trial, a small but statistically significant PFS benefit was seen in the ITT and PD-L1-positive patients. The 2.3 months' difference in OS in the ITT population in this final analysis did not met the prespecified boundary. The OS difference in the PD-L1-positive patients, a co-primary endpoint in this trial, could not be formally tested due to the hierarchical design. The numerical difference in median OS between both arms was 7.5 months, which can be considered clinically relevant. Subgroup analysis revealed that patients without prior exposure to taxanes had the highest benefit.

The exact reasons for the discordance between both trials are unknown. Several factors can contribute, but differences in chemotherapy backbone and corticosteroid use are unlikely to explain everything. The difference in median OS of the PD-L1-positive patients between the control arms of both trials reflects the heterogeneity of advanced triple-negative breast cancer and suggests enrichment of more indolent triple-

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negative breast cancer subtypes in IMpassion131. Many questions remain unanswered regarding the optimal use of immune checkpoint blockade for triple-negative breast cancer in the advanced setting. Awaiting further data, atezolizumab combined with nab-paclitaxel remains a standard treatment option for PD-L1-positive patients with advanced triple-negative breast cancer.

FUNDING

None declared.

DISCLOSURE

KP's institution received honoraria for advisory/consultancy roles for Astra Zeneca, Eli Lilly, Novartis, Pfizer, Pierre Fabre, Hoffmann/La Roche and Vifor Pharma (paid to institution, outside the submitted work); speaker fees for Eli Lilly, Mundi Pharma, Novartis, Pfizer, Hoffmann/La Roche and Teva (paid to institution, outside the submitted work); research funding from Sanofi (paid to institution, outside the submitted work). KP received travel support from Astra Zeneca, Novartis, Pfizer, PharmaMar and Hoffmann/La Roche. AM has no conflicts of interest to disclose.