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ESMO20 YO for YO: highlights on new drugs in advanced breast cancer focusing on sacituzumab govitecan and alpelisib

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Important news in the field of advanced breast cancer was presented at the European Society for Medical Oncology (ESMO) Virtual Congress 2020. Among them, the highly awaited results from the ASCENT trial (ClinicalTrials.gov identifier: NCT02574455) and the overall survival data from SOLAR-1 (ClinicalTrials.gov identifier: NCT02437318) were released.

The ASCENT phase III trial investigated the new first-in-class antibody-drug conjugate sacituzumab govitecan in heavily pretreated patients with advanced triple-negative breast cancer. Sacituzumab govitecan is an anti-Trop-2 antibody coupled to SN-38 (the active metabolite of irinotecan) via a hydrolysable linker; this agent is characterized by a high drug-to-antibody ratio and an important bystander effect. Prior results from a phase I/II trial in heavily pretreated patients with advanced triple-negative breast cancer showed promising activity with manageable safety, leading to an accelerated approval by the Food and Drug Administration of sacituzumab govitecan. In ASCENT, 529 patients with advanced triple-negative breast cancer who received a median number of four prior anticancer regimens were randomized 1:1 to sacituzumab govitecan or single-agent chemotherapy (capecitabine, eribulin, vinorelbine, or gemcitabine) of physician's choice. In the primary efficacy analysis in 468 patients without baseline brain metastases, a clinically relevant and statistically significant improvement in progression-free survival (PFS), overall survival (OS), objective response rate (ORR) and clinical benefit rate (CBR) favoring sacituzumab govitecan was observed. No alarming toxicity signals were observed. The most common adverse events were neutropenia, anemia, diarrhea, nausea, fatigue and alopecia. Based on these results, sacituzumab govitecan can be considered a new standard treatment option for patients with advanced triple-negative breast cancer who have received $\geq$2 treatment lines. Many trials are ongoing to investigate the role of this agent in the early setting of triple-negative breast cancer, its possible combination with other targeted agents and immunotherapy as well as the possible use in other breast cancer disease subtypes or different solid tumors.

The SOLAR-1 phase III trial investigated the role of the α-specific phosphatidylinositol 3-kinase (PI3K) inhibitor alpelisib added to fulvestrant in patients with advanced hormone receptor-positive/HER2-negative breast cancer progressing on or after an aromatase inhibitor. The trial randomly allocated 572 patients to fulvestrant plus alpelisib or placebo in two cohorts based on tumor-tissue *PIK3CA* mutation status. First results of the trial were previously reported showing that the combination of fulvestrant plus alpelisib was associated with better PFS, ORR and CBR in the cohort of patients with *PIK3CA* mutations, with no benefit in the cohort of patients without *PIK3CA* mutations. The main toxicities of alpelisib were hyperglycemia, diarrhea, nausea, decreased appetite and rash. Updated results of the trial showed in the *PIK3CA*-mutated cohort a clinically relevant but not statistically significant improvement in OS and a longer median time to chemotherapy. Notably, at the time of this analysis, more than 10% of the patients were still on active treatment and OS events were recorded in approximately half of the included patient population. In the SOLAR-1 trial, only 6% of the patients received prior treatment with CDK4/6 inhibitors. Full results of the BYLieve trial (ClinicalTrials.gov identifier: NCT03056755) will shed more light on the activity of alpelisib in patients progressing on prior CDK4/6 inhibitor-based treatment.

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