Post San Antonio update—my top three abstracts!

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Summary Recent findings support the role of alpelisib in advanced HR-positive breast cancer harboring a *PIK3CA* mutation. A retrospective biomarker analysis on the intrinsic subtypes of HR-positive breast cancer reveals a subgroup that will not benefit under the addition of a CDK 4/6 inhibitor treatment. The detection of circulating tumor cells before start and during tumor treatment is associated with worse outcome in metastatic breast cancer patients.

Keywords Metastatic breast cancer · CDK 4/6 inhibitor · Endocrine resistance · *PIK3CA* mutations · Circulating tumor cells

The treatment of hormone-receptor (HR)-positive, HER2-negative metastatic breast cancer has changed over the past years and is an emerging field. Due to the development of new drugs and targeting *PIK3CA* mutations survival of patients may be prolonged.

Abstract 1: BYLieve study—Cohort B

After approval in the SOLAR-1 trial the phosphoinositide 3-kinase (PI3K) inhibitor alpelisib in combination with fulvestrant became a new treatment option in metastatic HR-positive breast cancer [1]. There was only a small number of cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitor pretreated patients in this study leading to the need of more studies investigating its role in this setting. The phase II BYLieve trial is a prospective trial enrolling 336 patients with HR-positive, HER2-negative, *PIK3CA*-mutated metastatic

breast cancer who progressed on a CDK 4/6 inhibitor in combination with antihormonal therapy. Patients were assigned to three cohorts on the basis of their pretreatment history. Cohort A received alpelisib and fulvestrant and had a CDK 4/6 inhibitor and an aromatase inhibitor (AI) as prior treatment. Patients in cohort B must have progressed on a CDK 4/6 inhibitor in combination with fulvestrant and were likely to receive alpelisib plus letrozole. Patients in cohort C must have had progress on an AI and recently received chemotherapy or endocrine therapy as immediate prior treatment and were intended for a treatment with alpelisib and fulvestrant. Results of cohort A have already been published and showed 61 of 121 patients (50.4%; 95% confidence interval [CI] 41.2–59.6) being alive without progressive disease at 6 months [2]. This primary endpoint was also met in cohort B ($n=112$) when 46.1% (95% CI 36.8–55.6%) of the patients were alive without disease progression at 6 months. The median progression-free survival (PFS) was 5.7 months (95% CI 4.5–7.2 months). Additional results included the overall response rate with 15.7% (95% CI 9.5–23.6) and the clinical benefit rate with 32.2% (95% CI 23.8–41.5%). More common grade ≥ 3 adverse events included hyperglycemia (25.4%), rash (9.5%), rash maculopapular (7.9%), diarrhea or fatigue (both 4%) [3]. These findings support the combination of alpelisib and letrozole in a CDK 4/6 inhibitor and fulvestrant pretreated patient population, thereby revealing an efficient treatment option for the future.

Abstract 2: Biomarker analysis of intrinsic subtypes across the MONALEESA studies

The phase 3 MONALEESA-2, -3 and -7 trials investigated the addition of the CDK 4/6 inhibitor ribociclib to endocrine therapy versus endocrine therapy alone and led to a significant prolonged PFS [4–6]. A retro-

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spective exploratory analysis found that the intrinsic subtype of their tumors was associated with the prognosis of these patients. In all, 1160 patient samples across the three trials were pooled and analyzed by prediction analysis of microarray 50 (PAM 50) aiming to compare the main intrinsic subtypes of HR-positive, HER2-negative breast cancer: luminal A (47%), luminal B (24%), HER2-enriched (13%), normal-like (14%) and basal-like (3%). Patients with luminal A tumors had a median PFS of 19.48 (95% CI 15.61–24.80) months in the placebo arm and 29.8 (23.03–not available [NA]) months in the ribociclib arm. In the luminal B group the median PFS was increased from 12.85 (95% CI 10.84–14.82) months in the placebo arm to 22.21 (95% CI 18.79–NA) months in the ribociclib arm. The greatest effect in relative risk reduction was achieved in patients with HER2-enriched tumors: the median PFS in the placebo arm was 5.52 (95% CI 3.12–9.17) months and 16.39 (95% CI 12.71–26.6) months in the ribociclib arm. Remarkably, patients with basal-like tumors had a poor prognosis with a median PFS of 3.58 (1.87–NA) in the placebo group and 3.71 (1.91–13.0) in the experimental group and therefore did not have a benefit from additional ribociclib. Given the fact that this is a retrospective exploratory analysis further studies are needed to confirm the clinical utility of the intrinsic subtypes in this setting [7].

Abstract 3: Circulating tumor cells as a monitoring tool in metastatic breast cancer

Another retrospective pooled analysis was presented on the predictive role of detection of circulating tumor cells (CTCs) in patients undergoing treatment for metastatic breast cancer. CTC assessment was done at baseline and after a median follow-up of 29 days in 4079 patients. The median overall survival (OS) in patients without CTCs at baseline was 43.04 months, in patients with 1–4 CTCs 30.55 months, 24.16 months in patients with 5–25 CTCs and 15.44 months in patients who had more than 25 CTCs at baseline. There were also significant differences regarding the change of CTCs: patients who were persistently negative for CTCs had a median OS of 47.05 months, whereas patients who remained CTC-positive during their treatment showed a survival rate with a median OS of 17.87 months. Those patients who were positive at baseline and negative for CTCs at follow-up had an increased survival with a median OS of 32.20 months [8]. Although these results seem to be encouraging a potential role for clinical routine is questionable: in the SWOG S0500 trial early switching to an alternative treatment due to persistently positive CTCs in patients with metastatic breast cancer did not influence survival [9].

Take home message

New treatment options for patients with metastatic HR-positive, HER2-negative breast cancer are imminent. Acquired endocrine resistance is very common in this patient population and remains a challenging field, especially after progression to CDK 4/6 inhibitor treatment.

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