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Expert Discussion

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News from the San Antonio Breast Cancer Symposium 2022

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The 45th San Antonio Breast Cancer Symposium, held December 6–10 in San Antonio, Texas is the largest breast cancer conference and this year saw the participation of nearly 10,000 clinicians, researchers, and patient advocates, in person. Scientists shared many important new findings that are going to change the clinical practice in the near future. Here, we will present the most important news with a group of Italian colleagues and we will discuss how these results will impact the management of breast cancer.

Question 1: Should patients with endocrine receptor positive breast cancer and aggressive distant disease receive first-line chemotherapy? Is there new evidence for this patient group?

Puglisi

The standard first-line treatment of hormone receptor (ER)-positive HER2-negative advanced breast cancer (ABC) is the combination of endocrine therapy (ET) with a cyclin-dependent kinase 4/6 inhibitor (CDK 4/6i). The scientific evidence supporting this approach derives from indirect evaluations since there are no studies that have compared head-to-head chemotherapy (CT) versus ET associated with CDK 4/6is. In the only phase III trial that compared the combination of Palbociclib plus ET versus capecitabine, the patient population with aromatase inhibitor resistant ABC, mostly (approximately 80%) was in ≥2nd line at study entry.

The literature on first-line treatment draws on the results of randomized clinical trials that evaluated the efficacy of the combination of ET and CDK 4/6is in different clinical settings (e.g., de novo vs. recurrent disease, endocrine-sensitive vs. endocrine-resistant disease, visceral vs. bone only disease) and included patient populations with different characteristics (i.e., pre-, peri-, post-menopausal patients with different exposure to neo/adjuvant treatment). In all these scenarios, the addition of a CDK 4/5i to ET produced a clinically and statistically significant benefit in terms of progression-free survival (PFS) and overall survival.

However, no prospective data had so far been produced regarding the efficacy and safety of CDK 4/6-associated ET in the treatment of patients with disease judged to be aggressive for any of the following characteristics: (1) symptomatic visceral disease; (2) rapidly progressing or imminent organ failure; (3) markedly symptomatic non-visceral disease. In such clinical context, the RIGHT Choice study, through a randomized

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phase II design, seeks to answer a clinical question in great demand by medical oncologists regarding the comparison of ET associated with CDK 4/6i versus a combination CT.

In total, the study enrolled 232 pre/perimenopausal patients (1:1 randomization) of which approximately 50% per arm were defined as having visceral crisis according to the judgment of the principal investigator and based on the ABC3 and NCCN criteria. Experimental arm with ET (i.e., letrozole or anastrozole in combination with goserelin) and CDK 4/6i (ribociclib 600 mg, 3 weeks on/1 week off) was compared to a combination CT of investigator's choice (docetaxel/capecitabine, paclitaxel/gemcitabine, capecitabine/vinorelbine). Of interest, the observed benefit with the ET/ribociclib combination in terms of PFS (24.0 vs. 12.3 months; HR: 0.54) and time-to-treatment failure (18.6 vs. 8.5 months; HR: 0.45) was confirmed. Equally noteworthy is the objective response rate, similar between the two treatment arms (65% vs. 60%). In addition, in terms of toxicity, combination CT was associated with higher rates of treatment-related adverse events. Therefore, considering the results of the RIGHT Choice trial, a piece of evidence has been added to support the use of ET associated with CDK 4/6i in the first-line treatment of patients with HR-positive HER2-negative ABC with an aggressive clinical presentation.

Question 2: The choice of second and subsequent lines of treatment in endocrine receptor positive metastatic breast cancer is a true challenge for the medical oncologist. This year, new interesting data have been presented. How are these going to modify the clinical practice? Do we need to design new sequence strategies?

Zambelli

The treatment of the endocrine-sensitive/HER2-metastatic breast cancer (mBC), after progression on first-line antiestrogen therapy plus cyclin-dependent kinase 4/6 inhibition (CDK 4/6i), is a rapidly evolving landscape with a current crowded pipeline, including the novel oral SERD elacestrant, camizestrant, and the AKT-inhibitor capivasertib in combination with fulvestrant, as presented at SABCS 2022. Moreover, growing data from antibody-drug-conjugates support the role of trastuzumab deruxtecan and sacituzumab govitecan in ER+/HER2-(low) mBC, failing prior ET and other treatments for advanced disease.

These novel options come in addition to those already available of fulvestrant, everolimus plus exemestane, alpelisib plus fulvestrant, as well as those of CDK 4/6i beyond progression, PARP-inhibitors, and conventional CT. Lacking a direct drug-sequences comparison, we are not fully informed on how to prioritize therapies for an optimal treatment strategy. The extensive search of molecular predictive biomarkers for anticancer drug selection eventually obtained a limited advantage in ER + mBC, except for alpelisib and PARP inhibitors, with a more convincing capacity to exclude rather than choose a specific treatment among the others.

Recently, elacestrant demonstrated a significant PFS improvement versus standard of care both in the overall population and in patients with ESR1 mutations, with greater effect in those patients with activating mutations. Conversely, the expected predictive role of AKT-pathway alterations has been questioned by data from CAPITELLO291 trial since the advantage of capivasertib has been reported regardless of the presence of targeted mutations.

With restricted clear-cut molecular clues able to shape the treatment sequencing, clinical judgment still prevails in defining the priority of the anticancer drug program. Indeed, in a context of competitive treatment choices, clinicians may take into account different factors, including (1) the global cancer burden, the site-specific and symptomatic disease, and the expected attrition rate of subsequent lines of therapy; (2) the treatment response to the previous therapy (TTF/PFS1), as it has been observed in the EMERALD trial: the longer stay with CDK 4/6i in first-line, the greater benefit with elacestrant in second-line; (3) the clinical patients' characteristics of age, performance status, comorbidity, and individual preferences. Finally, we have to recognize the increasing drug cost and the obstacles in drug access by regulatory constraints might impact the availability and sequencing of several treatments. In this context, a coherent assignment of the drug value, based on common and reproducible criteria for the ESMO-magnitude of clinical benefit scale (MCBS), should inform clinicians and stakeholders to promote the timely use of high-value anticancer therapy, to reduce patients' disparity and to maximize the entire cancer treatment program.

Question 3: There is a role for trastuzumab deruxtecan in HER2 low/ER positive early breast cancer? Is HER2 low overall a separate entity?

Curigliano

During the meeting, data on neoadjuvant trastuzumab deruxtecan have been presented (GS2-03: TRIO-US B-12 TALENT: neoadjuvant trastuzumab deruxtecan with or without anastrozole for HER2-low, HR+ early stage breast cancer). Investigators conducted the phase II TRIO-US B-12 TALENT clinical trial to assess the safety and efficacy of trastuzumab deruxtecan (T-DXd) when used as a neoadjuvant treatment, either alone or in combination with the

aromatase inhibitor anastrozole. At the time of first data cutoff (May 10, 2022), 17 patients had completed the planned eight cycles of T-DXd, and 16 patients had completed the planned six cycles of T-DXd plus anastrozole. According to Bardia, the primary endpoint for the study was a 5 percent pathologic complete response (pCR) rate, defined as complete tumor regression and no lymph node involvement at the time of surgery. At the time of first data cutoff, no patients had experienced a pCR in the combination treatment arm, and 1 out of 19 patients (5.3 percent) had experienced a pCR in the solo treatment arm. As of the data cutoff, 33 patients had completed neoadjuvant treatment and undergone surgery, 7 patients were awaiting surgery, and 13 patients were still undergoing T-DXd treatment. Among the response-evaluable population, in the solo treatment arm, the overall response rate was 75 percent, including 11 partial responses and one complete response. In the combination treatment arm, the overall response rate was 63 percent, including 10 partial responses and two complete responses. The most common treatment-related adverse events of grade 3 or higher were hypokalemia, diarrhea, neutropenia, fatigue, headache, vomiting, dehydration, and nausea, each of which occurred in fewer than 6 percent of patients. One patient developed grade 2 interstitial lung disease, which resolved after treatment discontinuation. The study demonstrated that T-DXd was relatively safe in HER2-low, hormone receptor-positive, localized breast cancer. It provides a translational framework for future studies, including combination regimens in the neoadjuvant setting to further improve clinical outcomes.

B). The confirmation of the HER2-low status had a major impact in breast oncology. This is a biomarker that may predict the activity of trastuzumab deruxtecan. About half of all breast cancers were HER2-low expression with immunohistochemical detection, which can be targeted with the anti-HER2 antibody-drug conjugate T-DXd, leading to a relevant progression free and survival benefit in the metastatic setting. Given this observation, treatment algorithms for both hormone receptor-positive and triple-negative breast cancer are expected to significantly evolve in the next future. Several challenges, however, remain in the interpretation of HER2-low expression related to its biological role, its pathologic diagnosis, and the definition itself of HER2-low. During the SABCS, new data have been presented on the results of the DESTINY Breast-04. Concordance between historical and central HER2 IHC results has been presented: for samples with historical and central HER2 results, 849/1,108 (77%) were centrally scored as HER2-low. Of the samples that were not centrally scored as HER2-low, 88% were scored as HER2 IHC 0. Efficacy of T-DXd versus TPC for patients in DESTINY-Breast-04 was consistent across all tumor sample characteristics (primary vs. metastatic, specimen type, archival vs. fresh, and tissue collection date). Many other abstract have been presented to let us understand if the HER2-low subgroup is or not a separate entity. Investigators retrieved clinical, pathological, and genomic data of BCs that were subjected to targeted sequencing using the FDA-cleared MSK-IMPACT assay from April 2014 to December 2021 in 3,608 samples. Among these, 1,460 (40%) and 2,148 (60%) were HER2-0 and HER2-low, respectively. Hormone receptor (HR) expression was significantly higher in HER2-low than HER2-0 tumors. In HR-positive BCs, HER2-0 BCs harbored higher frequency of TP53 (33% vs. 25%; odds ratio [OR]: 1.49, 95% confidence interval [CI]: 1.25–1.78, $q < 0.001$) and CDKN1A (1% vs. 0%; OR: 17.47, 95% CI: 2.48–756.37, $q = 0.02$) alterations than HER2-low BCs. Similar findings were observed in metastatic but not in primary HR-positive BCs. According to this analysis, HER2-low BCs seem not to represent a distinct pathologic subtype. At the genomic level, however, some differences were identified and these became more conspicuous upon subclassification of HER2 IHC expression into 1+ and 2+. Finally, among tumors with sufficient tumor purity for ERBB2 copy count analysis ($n = 374$ and 419 for HER2-low and HER2-0, respectively), HER2-low tumors had a significantly higher number of ERBB2 alleles as compared to HER2-0 (<2 copies, 15.0% vs. 30.9%, 2 copies 67.4% vs. 60.5%, and >2 copies, 17.6% vs. 8.6%; $p < 0.001$). These data further support the notion that HER2-low, as currently defined, is not a distinct molecular subtype of breast cancer.

Question 4: The monarchE trial showed that the use of adjuvant abemaciclib plus ET extended disease-free survival in high-risk ER+ early breast cancer. What about data with longer follow-up? Is now the role of adjuvant abemaciclib strengthened?

Guarneri

CDK4/6 inhibitors have substantially changed the management of patients with HR+/HER2 negative ABC, being nowadays standard of care in combination with hormonal therapy for the vast majority of patients. Given the impressive results achieved in this setting, these molecules have been evaluated in early disease. In particular, the monarchE phase III randomized trial evaluated 2 years abemaciclib in combination with standard ET in patients selected for being at high risk of relapse (e.g., >4 positive nodes, or 1–3 positive nodes and T size 5 cm, or grade 3 or ki67 >20% per central assessment). At the second pre-planned interim analysis for efficacy, which occurred at a median follow-up of 15.5 months, abemaciclib plus ET

demonstrated a statistically significant improvement in IDFS versus ET alone (HR: 0.75; 95% CI: 0.60–0.93), with 2-year IDFS rates of 92.2% versus 88.7% observed in the control arm. Subsequent updates at 18 and 27 months of median follow-up have confirmed the significant benefit of abemaciclib versus control. At SABCS 2022, the 4-year results from monarchE have been presented. The previously reported iDFS benefit was confirmed (HR: 0.664; 95% CI: 0.578 to 0.762), and the Kaplan-Meier curves continued to diverge: at 4 years, the absolute difference in invasive disease-free survival between the groups was 6.4. Similar results were observed *n* terms of distant-relapse-free survival. It is important to remind that, at this timepoint, all the patients have completed the 2-year treatment period. Interestingly, a post hoc analysis estimating yearly piecewise hazard ratios (HRs) for IDFS showed a decreased from 0.782 in year 0–1 to 0.618 in years 2–3, decreasing further to 0.602 at years 3 and more. These data suggest a potential carry-over effect of abemaciclib treatment. This further analysis with additional follow-up supports the use of abemaciclib in high-risk patients.

Question 5: Fertility preservation and the possibility of a pregnancy should be discussed with every young woman with endocrine sensitive early breast cancer. What is the evidence from the POSITIVE trial? Can adjuvant ET be safely interrupted to seek a pregnancy? How strong are these data?

Del Mastro

Nearly 50% of young breast cancer survivors desire pregnancy. Retrospective studies showed that pregnancy after breast cancer does not worsen outcomes. However, the standard 5–10 years of adjuvant ET does compromise conception in women with hormone receptor positive (HR+) disease. The safety of the interruption of ET to attempt pregnancy has not been studied prospectively. Positive was a prospective single-arm trial addressing the question: it is safe, in terms of breast cancer relapse, to temporarily interrupt ET to attempt pregnancy? In this study, 518 premenopausal HR+ breast cancer patients wishing to become pregnant and treated with adjuvant ET for at least 18 months were enrolled. The primary analysis of breast cancer outcomes was carried out using a cohort of 1,499 SOFT/TEXT patients as external control. The 3-year cumulative incidence of breast cancer free interval events was 8.9% in the positive trial as compared to 9.2% in the controls. 74% of the patients had at least one on trial pregnancy and 64% had at least one live birth (full-term or preterm). 62% of the patients who had a live birth reported breastfeeding. 76% of the patients resumed ET after the up to 3 years' break to allow conception, delivery + breastfeeding.

The required 3 months washout between treatment interruption and pregnancy attempt was reasonable, taking into account SERMs and AI median half-life, as well as the advice of the tamoxifen pharmaceutical company about informing women of the potential risks to the fetus should they become pregnant while taking tamoxifen or within 2 months of cessation of therapy.

In conclusion, the results of POSITIVE trial suggest that temporary interruption of ET to attempt pregnancy does not impact short-term disease outcomes. During the 2-year break from ET, 70% of women are able to have at least one pregnancy.

Conflict of Interest Statement

Alessandra Genna received advisory role from AstraZeneca, Daiichi, Eisai, Lilly, Novartis, Pfizer, Roche, Seagen, Gilead, Teva, and Gentili; lecture honoraria from Novartis, Pfizer, Gilead, Roche, Eisai, Seagen, Teva, and Gentili; and research support from Roche, Eisai, Gilead, and Pharmanutra. Giuseppe Curigliano received advisory role from BMS, Roche, Pfizer, Novartis, Lilly, Astra Zeneca, Daichii Sankyo, Merck, Seagen, Ellipsis, and Gilead and research support from Merck. Lucia Del Mastro received advisory role from AstraZeneca, Daiichi, Eisai, Eli Lilly, MSD, Novartis, Pfizer, Pierre-Fabre, Roche, Seagen, Gilead, GSK, Exact Sciences, and Agendia; lecture honoraria from Eli Lilly, Novartis, Pfizer, Roche, Seagen, and Gilead; and research support from Daiichi, Novartis, Roche, and Pfizer. Valentina Guarneri has no conflict of interest to declare. Fabio Puglisi received advisory role from AstraZeneca, Daichii Sankyo, Eisai, Eli Lilly, Gilead, Novartis, Roche, Seagen, and Viatris; lecture honoraria from AstraZeneca, Daichii Sankyo, Eisai, Eli Lilly, Exact Sciences, Gilead, Novartis, Roche, and Seagen; and research support from AstraZeneca, Eisai, and Roche. Alberto Zambelli received advisory role from Roche, Pfizer, Novartis, Lilly, AstraZeneca, Daichii Sankyo, Merck, Seagen, BMS, and Gilead and research support from Pfizer.

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