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Review Article

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Asco annual meeting 2021 Some news to use in our oncological practice

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Every year, ASCO Annual Meeting provides new options for the treatment of our patients

What are the news this year about breast cancer?
I would initially highlight the presentation made in the plenary, results that modify our decisions in daily practice.

PLENARY SESSION

OlympiA: A phase III, multicenter, randomized placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline BRCA1/2 mutations and high-risk HER2-negative early breast cancer.

Olympia is a clinical study to evaluate if adding 1 year of oral olaparib treatment, after surgery and chemotherapy ,reduce the risk of breast cancer returning in people who had an inherited mutation in their BRCA1 1or BRCA 2 genes Olaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular functions, such as DNA transcription and DNA repair. In vitro studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes, resulting in DNA damage and cancer cell death.

Preliminary studies has shown efficacy in metastatic breast cancer. OlympiAD (NCT02000622) was an open-label study in which patients with gBRCAm HER2- negative metastatic breast cancer were randomized 2:1 to receive Olaparib 300 mg tablets or healthcare provider's choice of chemotherapy (capecitabine, eribulin, or vinorelbine, at standard doses) until progression or unacceptable toxicity. Olaparib monotherapy provided a significant benefit over standard therapy; median progression-free survival was 2.8 months longer and the risk of disease progression or death was 42% lower with olaparib monotherapy than with standard therapy.
How was the Olympia study carried out?

Adults treated for early breast cancer with BRCA1 or BRCA2 germline pathogenic or likely pathogenic variants and high-risk clinicopathological factors who had received local treatment and neoadjuvant or adjuvant chemotherapy. Patients were randomly assigned (in a 1:1 ratio) to 1 year of oral olaparib or placebo. The primary endpoint was invasive disease–free survival.

Design :Study population in neoadjuvant group was TNBC non pCR or Hormone receptor -positive non-pCR and CPS +EG score ≥3 , received ≥ 6 cycles neoadjuvant chemotherapy
In the adjuvant group , TNBC ≥ pt2 or ≥ pN1 or Hormone receptor positive : ≥ 4 positive lymph nodes , who were treated with surgery , ≥ 6 cycles of adjuvant chemotherapy . Both groups did surgery and radiotherapy , if indicated.

Patients were randomly assigned in a 1:1 ratio to receive olaparib (300 mg) or matching placebo tablets taken orally twice daily for 52 weeks. Patients were stratified according to hormone-receptor status (positive or negative), timing of previous chemotherapy (neoadjuvant or adjuvant), and use of platinum chemotherapy for current breast cancer (yes or no)

A total of 1836 patients underwent randomization. At a prespecified event-driven interim analysis with a median follow-up of 2.5 years, the 3-year invasive disease–free survival was 85.9% in the olaparib group and 77.1% in the placebo group (difference, 8.8 percentage points; 95% confidence interval [CI], 4.5 to 13.0; hazard ratio for invasive disease or death, 0.58; 99.5% CI, 0.41 to 0.82; P<0.001). The 3-year distant disease–free survival was 87.5% in the olaparib group and 80.4% in the placebo group (difference, 7.1 percentage points; 95% CI, 3.0 to 11.1; hazard ratio for distant disease or death, 0.57; 99.5% CI, 0.39 to 0.83; P<0.001). Olaparib was associated with fewer deaths than placebo (59 and 86, respectively) (hazard ratio, 0.68; 99% CI, 0.44 to 1.05; P=0.02); however, the between-group difference was not significant at an interim-analysis boundary of a P value of less than 0.01.

The safety profile of olaparib was consistent with that previously reported; adverse events with olaparib treatment were largely of grade 1 or 2. The only grade 3 toxic effect that occurred in more than 5% of the patients was anemia (8.7%), which infrequently led to transfusion. Dose interruptions and reductions appear to have been effective management strategies. Serious adverse events were not more frequent with olaparib than with placebo. Although PARP inhibitors are DNA-interacting drugs and have the potential to induce mutation in DNA and hematologic malignant conditions,32 the frequency of MDS or AML was not increased by olaparib, and further blinded follow-up is continuing.

Conclusions

Among patients with high-risk, HER2-negative early breast cancer and germline BRCA1 or BRCA2 pathogenic or likely pathogenic variants, adjuvant olaparib after completion of local treatment and neoadjuvant or adjuvant chemotherapy was associated with significantly longer survival free of invasive or distant disease than was placebo. Olaparib had limited effects on global patient-reported quality of life.

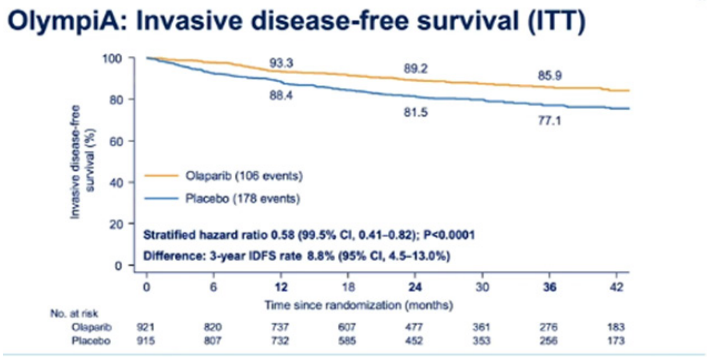
Take Home Points

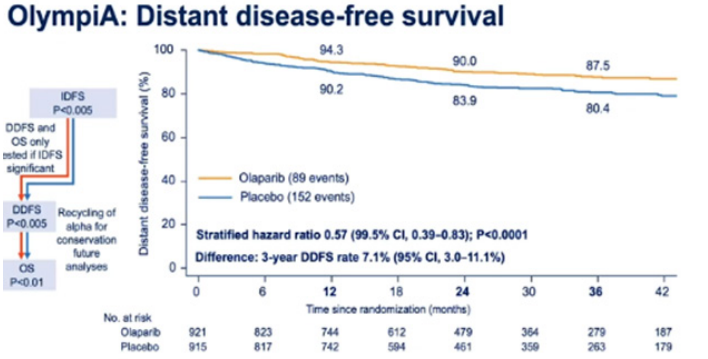
Germline BRCA 1 and BRCA2 sequencing is an important biomarker in early cancer

Addition of Olaárib to standard therapy improved 3y iDFS and DDFS for gBRCA 1/2m carriers with Her 2neg breast cancer and

- TNBC (> 2 cm or node positive and RH positive > 4 nodes positives
- Non pCR after NAC and higher tumor burden HRpositive/ Her2 negative

Results are Practice Changing





Abstracts session:

Metastatic breast cáncer

Overall survival with palbociclib + fulvestrant in women with hormone receptor–positive ,human epidermal growth factor receptor 2–negative advanced breast cancer : Updated analyses from PALOMA-3.

Updated overall survival results from the phase III MONALEESA-3 trial of postmenopausal patients with HR+/HER2- advanced breast cancer treated with fulvestrant ± ribociclib

Overall survival (OS) with palbociclib (PAL) + fulvestrant (FUL) in women with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC): Updated analyses from PALOMA-3.

In PALOMA-3, a randomized, double-blind, placebo-controlled, phase 3 study, PAL+FUL significantly prolonged progression-free survival (PFS) compared with placebo (PBO) + FUL (1-sided P<0.0001). The final protocol-specified OS analysis, which was conducted with a median follow-up of 44.8 months (mo), showed improved OS with PAL+FUL vs PBO+FUL (median OS, 34.9 vs 28.0 mo; hazard ratio, 0.814 [95% CI, 0.644–1.029]; 1-sided P=0.0429). Here, we report the results from an OS analysis with a longer median follow-up of 73.3 mo.

A total of 521 patients (pts) with HR+/HER2– ABC who had progressed on prior endocrine therapy were randomized 2:1 to PAL (125 mg/d orally, 3/1 week schedule) + FUL (500 mg intramuscular injection) or PBO+FUL. Investigator-assessed PFS was the primary endpoint; OS was a key secondary endpoint. An ad hoc OS analysis was performed when 393 events (75% of the total population) were observed. Circulating tumor DNA (ctDNA) analysis was conducted among pts who consented for this study.

Results

Improvement in OS continues to be observed with longer follow-up, with a hazard ratio of 0.806 (95% CI, 0.654–0.994; 1-sided nominal P=0.0221). The 5-year OS rate was 23.3% (95% CI, 18.7–28.2) with PAL+FUL and 16.8% (95% CI, 11.2–23.3) with PBO+FUL. Favorable OS with PAL+FUL vs PBO+FUL was observed in most subgroups except among pts who were endocrine resistant or had prior chemotherapy for ABC. No new safety signals were identified. Eighteen pts remain on study treatment, including 15 (4.3%) on PAL+FUL and 3 (1.7%) on PBO+FUL. A post-study cyclin-dependent kinase 4/6 inhibitor was received by 20 pts (7.5%) in the PAL+FUL arm and 32 pts (22.2%) in the PBO+FUL arm. ctDNA analyses of tumor mutation profiles (ie, ESR1, PIK3CA, RB1) at the end of treatment and their effect on OS will also be presented.

Conclusions

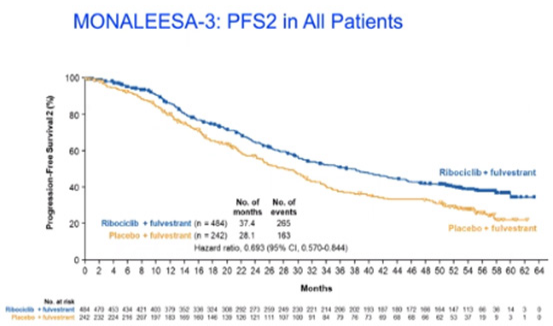
The clinically meaningful improvement in OS with PAL+FUL was maintained with >6 years of median follow-up in pts with HR+/HER2– ABC who had progressed on prior endocrine treatment.

Updated overall survival (OS) results from the phase III MONALEESA-3 trial of postmenopausal patients (pts) with HR+/

HER2- advanced breast cancer (ABC) treated with fulvestrant (FUL) ± ribociclib (RIB)

The Phase III MONALEESA-3 trial (NCT02422615) previously demonstrated a statistically significant improvement in OS with RIB, a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i), plus FUL compared with placebo (PBO) plus FUL as first-line (1L) or second-line (2L) treatment in postmenopausal pts with HR+/HER2− ABC (median, not reached vs 40.0 mo; hazard ratio [HR], 0.72; 95% CI, 0.57-0.92, P =.00455). This analysis was final per the protocol; following the unblinding of the study, pts still on study treatment in the PBO arm were allowed to cross over to the RIB arm. We report an exploratory analysis of OS after an additional median 16.9 mo of follow-up, allowing for further characterization of long-term survival benefits of RIB.

The previously demonstrated robust and clinically meaningful OS benefit with RIB + FUL compared with PBO + FUL was maintained after almost 5 years of follow-up in postmenopausal pts with HR+/HER2− ABC. The OS benefit of RIB was observed in the 1L and 2L subgroups, which further supports the use of RIB in these populations. The results also demonstrated a significant delay in the use of subsequent CT with RIB vs PBO. Clinical trial information NCT02422615.



Dalpiciclib versus placebo plus fulvestrant in HR+/HER2- advanced breast cancer that relapsed or progressed on previous endocrine therapy (DAWNA-1): A multicenter, randomized, phase 3 study.

In this randomized, double-blind, phase 3 trial, patients (pts) with HR+/HER2− locally advanced or metastatic breast cancer who had relapsed or progressed on previous endocrine therapy were enrolled. Eligible pts were randomized 2:1 to receive dalpiciclib (dalp; 150 mg po qd, d1-21, q4w) or placebo (PBO) with fulvestrant (fulv; 500 mg im, cycle 1 d1, d15, then d1 q4w). The primary endpoint was investigator (INV)-assessed PFS. As of Nov. 15, 2020, 162 (71.4% of total projected) events of disease progression or death had occurred and a preplanned interim analysis was done. The corresponding superiority boundary was 1-sided P = 0.0080 (Lan-DeMets [O'Brien-Fleming] boundary)

Result

Overall, 361 pts were randomized to receive dalp-fulv (n = 241) or PBO-fulv (n = 120). With a median follow-up of 10.5 mo, dalp-fulv significantly improved INV-assessed PFS versus PBO-fulv (median, 15.7 [95% CI 11.1-NR] vs 7.2 [95% CI 5.6-9.2] mo; HR, 0.42 [95% CI 0.31-0.58]; P < 0.0001). PFS per IRC were consistent with INV assessment (Table). The benefit of dalpiciclib extended beyond initial study treatment based on time to first subsequent chemotherapy (TFSCT; HR, 0.47 [95% CI 0.32-0.69]; P < 0.0001). OS data were not mature with a total of 25 deaths documented. Median duration of exposure was 9.4 (IQR, 4.3-11.4) mo with dalpiciclib and 9.9 (4.7-11.9) mo with fulvestrant in the dalp-fulv group and was 6.1 (3.7-11.0) mo with fulvestrant in the PBO-fulv group. The most common (incidence ≥3%) grade 3 or 4 AEs with dalp-fulv were neutropenia (84.2%; vs 0% with PBO-fulv) and leukopenia (62.1%; vs 0%). Treatment discontinuation due to AE was reported for 2.5% of pts with dalp-fulv vs 3.3% with PBO-fulv. The incidence of SAE was 5.8% with dalp-fulv vs 6.7% with PBO-fulv

Conclusión: The study met its primary endpoint, demonstrating that dalpiciclib plus fulvestrant significantly improved PFS versus placebo plus fulvestrant, with a manageable safety profile. Our findings support dalpiciclib plus fulvestrant as a new treatment option in pts with HR+/HER2- ABC who relapsed or progressed on endocrine therapy. Clinical trial information: NCT03927456.

Trastuzumab plus endocrine therapy or chemotherapy as first-line treatment for metastatic breast cancer with hormone receptor-positive and HER2-positive: The sysucc-002 randomized clinical trial. For metastatic breast cancer with hormone receptor-positive and HER2-positive, no evidence showed that which first-line regimens were preferred, either anti-HER2 therapy plus endocrine therapy or anti-HER2 therapy plus chemotherapy. This study aimed to determine whether trastuzumab plus endocrine therapy is as efficacious as trastuzumab plus chemotherapy and with decreased toxic effects.

Methods

We conducted an open-label, non-inferiority, phase 3, randomized, controlled trial at nine hospitals in China. Patients with hormone receptor-positive and HER2-positive histologically confirmed advanced breast cancer were randomly assigned (1:1) to receive trastuzumab plus chemotherapy (CT group) or endocrine therapy (ET group). The primary endpoint was progression-free survival with a non-inferiority upper margin of 1.35 for the hazard ratio (HR). This trial is registered with ClinicalTrials.gov, number NCT01950182.

Between Sep 16, 2013, and Dec 28, 2019, 392 patients were enrolled and randomly assigned to receive trastuzumab plus endocrine therapy (n = 196) or trastuzumab plus chemotherapy (n = 196). In the intention-to-treat population, the median PFS was 14.8 months (95% CI 12.8-16.8) in the CT group and 19.2 months (95% CI 16.7-21.7) in the ET group (HR 0.88, 95% CI 0.71-1.09; Non-inferiority< 0.0001). Significantly higher frequency of toxicities were observed in CT group compared with ET group, including: leucopenia (98 [50%] vs 13 [6.6%]), nausea (93 [47%] vs 24 [12%]), fatigue (47 [24%] vs 31 [16%]), vomiting (45 [23%] vs 12 [6%]), headache (65 [33%] vs 24 [12%]) and alopecia (125 [64%] vs 8 [4%]). No patients died from treatment-related causes.

Conclusions

Trastuzumab plus endocrine therapy was non-inferior to and had decreased toxicities to trastuzumab plus chemotherapy in patients with metastatic breast cancer with hormone receptor-positive and

HER2-positive. Trastuzumab plus endocrine therapy could provide more convenient treatment and allow better treatment tolerance. Clinical trial information: NCT01950182.

Results from VERONICA: A randomized, phase II study of second-/third-line venetoclax (VEN) + fulvestrant (F) versus F alone in estrogen receptor (ER)-positive, HER2-negative, locally advanced, or metastatic breast cancer (LA/MBC).
For patients (pts) with ER-positive, HER2-negative MBC, CDK4/6 inhibitors + endocrine therapy (ET) is standard first-line treatment, with single-agent ET considered for second-line. Nevertheless, most pts progress. A novel therapeutic target is the antiapoptotic protein BCL2, which is overexpressed in ~85% of primary ER-positive breast cancers. VEN is a potent, selective BCL2 inhibitor that has shown promising clinical activity in pts with ER-positive and BCL2-positive MBC who have received prior ET. We report the prespecified primary and updated (for overall survival [OS]) analysis of VERONICA (NCT03584009),

A phase II study of VFrom the primary analysis, VERONICA did not show an improved CBR or PFS with VEN + F, vs F alone, in pts with endocrine- and CDK4/6 inhibitor-refractory LA/MBC. Biomarker analysis is ongoing.EN + F vs F in ER-positive, HER2-negative LA/MBC
Treatment-related side effects and views about dosage assessment to sustain quality of life: Results of an advocate-led survey of patients with metastatic breast cancer (MBC).
1,221 patients with MBC completed the survey within 15 days. The median number of lines of MBC therapy was 2.5 (range 1 - ≥5) and 46% (n = 564) of patients received their MBC diagnosis within two years of taking the survey. 86% (n = 1,051) reported experiencing at least one significant treatment-related side effect, and of these, 20% (n = 213) visited the Emergency Room/hospital and 43% (n = 454) missed at least one treatment. 98% (n = 1,026) of patients with side effects discussed them with their doctors and 82% (n = 838) were helped by their physicians. The most common (non-exclusive) mitigation strategies were dosage reductions (66%, n = 556) and prescription medications (59%, n = 494). Of the 556 patients given a dosage reduction, 83% (n = 459) reported feeling better. Notably, 92% (n = 1,127) of patients expressed willingness to discuss alternative dosing options with their physicians based upon their personal characteristics and individual preferences.

Conclusions
Given that 86% of patients with MBC experienced at least one significant treatment-related side effect and 83% improved after dosage reduction, innovative dosage-related strategies are warranted to sustain Quality of Life. Patient-physician discussions in which the patient's physical attributes and circumstances are periodically assessed may determine the right dose for the patient upon treatment initiation and afterwards, and the vast majority of patients would be receptive to such discussions.

The tumor microenvironment (TME) and atezolizumab + nab-paclitaxel (A+nP) activity in metastatic triple-negative breast cancer (mTNBC): IMpassion130.
IMpassion130 was the first randomized phase 3 study to show clinical benefit of cancer immunotherapy (CIT) in untreated PD-L1+ mTNBC. Enhanced A + nP efficacy vs placebo (P) + nP was seen in pts with a richer immune TME but was confined to PD-L1 IC+ pts (PD-L1–expressing immune cells on ≥1% of tumor area; Emens JNCI 2021). While TNBC molecular subtyping and CD8 localization are prognostic in early TNBC, it is unknown whether these features are associated with CIT benefit in mTNBC. This exploratory analysis aimed to identify TME components associated with A + nP efficacy in IMpassion130.

Conclusions
PD-L1 IC+ immune-inflamed tumors and PD-L1 IC+ BLIA tumors show highest CIT sensitivity, and LAR tumors may be resistant to CIT. These data warrant further study and validation. Clinical trial information: NCT02425891.

Combination of famitinib with camrelizumab plus nab-paclitaxel as first-line treatment for patients with immunomodulatory advanced triple-negative breast cancer (FUTURE-C-PLUS): A prospective, single-arm, phase 2 study

Camrelizumab (anti-PD-1 antibody) and nab-paclitaxel (nab-P) have demonstrated promising anti-tumour activity in patients with immunomodulatory (IM) subtype metastatic triple negative breast cancer (TNBC), with 52.6% of ORR observed in heavily pretreated patients in our previous umbrella trial (FUTURE). As antiangiogenic agents were known to enhance the response to immune checkpoint inhibitors, we assessed the efficacy and safety of novel triplet combination of famitinib (tyrosine kinase inhibitor targeting VEGFR-2, PDGFR and c-kit), camrelizumab and nab-paclitaxel in patients with IM subtype advanced TNBC.

Conclusions
Addition of famitinib to camrelizumab and nab-paclitaxel showed promising antitumour activity as first-line therapy with manageable toxicity profile for IM subtype advanced TNBC patients. Results from ongoing randomized controlled trial FUTURE-SUPER (NCT 04395989) are eagerly awaited.

Randomized multicenter trial of 3 weekly cabazitaxel versus weekly paclitaxel chemotherapy in the first-line treatment of HER2 negative metastatic breast cancer (MBC)
Paclitaxel is commonly used as first line chemotherapy for HER2 negative MBC. However, with response rates of 21.5-53.7% and a significant risk of peripheral neuropathy there is a need for more effective and better tolerated chemotherapy (CCT). 3 weekly cabazitaxel as first line chemotherapy in HER2 negative MBC does not significantly improve PFS compared to weekly paclitaxel, though it has a lower risk of peripheral neuropathy with better patient reported overall health outcomes. Cabazitaxel is safe and well tolerated for MBC and requires fewer hospital visits, an important consideration in the COVID pandemic and beyond.

Take Home Points
- Improvement in OS with PAL+FUL was maintained with >6 years of median follow-up in pts with HR+/HER2– ABC who had progressed on prior endocrine treatment.
- OS benefit with RIB + FUL compared with PBO + FUL was maintained after almost 5 years of follow-up in postmenopausal pts with HR+/HER2− ABC. The OS benefit of RIB was observed in the 1L and 2L subgroups,
- Dalpiciclib plus fulvestrant significantly improved PFS ver-

sus placebo plus fulvestrant, with a manageable safety profile. Dalpiciclib plus fulvestrant as a new treatment option in pts with HR+/HER2- ABC who relapsed or progressed on endocrine therapy.

Trastuzumab plus endocrine therapy was non-inferior to and had decreased toxicities to trastuzumab plus chemotherapy in patients with metastatic breast cancer with hormone receptor-positive and HER2-positive.

Abstracts

EARLY BREAST CANCER AND NEO/ ADJUVANT TREATMENT

Outcome of patients with an ultralow risk 70-gene signature in the MINDACT trial
Breast Cancer Index (BCI) and prediction of benefit from extended aromatase inhibitor (AI) therapy (tx) in HR+ breast cancer: NRG oncology/NSABP B-42.
Utility of the 70-gene MammaPrint assay for prediction of benefit from extended letrozole therapy (ELT) in the NRG Oncology/ NSABP B-42 trial.
De-escalated neoadjuvant pertuzumab+trastuzumab with or without paclitaxel weekly in HR-/HER2+ early breast cancer: ADAPT-HR-/HER2+ biomarker and survival results.
Prognostic impact of recurrence score, endocrine response and clinical-pathological factors in high-risk luminal breast cancer: Results from the WSG-ADAPT HR+/HER2- chemotherapy trial.
Neoadjuvant talazoparib in patients with germline BRCA1/2 (gBRCA1/2) mutation-positive, early HER2-negative breast cancer (BC): Results of a phase 2 study.
Durvalumab improves long-term outcome in TNBC: results from the phase II randomized GeparNUEVO study investigating neodjuvant durvalumab in addition to an anthracycline/taxane based neoadjuvant chemotherapy in early triple-negative breast cancer
Evaluation of intra-tumoral (IT) SD-101 and pembrolizumab (Pb) in combination with paclitaxel (P) followed by AC in high-risk HER2-negative (HER2-) stage II/III breast cancer: Results from the I-SPY 2 trial.
A randomized phase III post-operative trial of platinum-based chemotherapy (P) versus capecitabine (C) in patients (pts) with residual triple-negative breast cancer (TNBC) following neoadjuvant chemotherapy (NAC): ECOG-ACRIN EA113

Outcome of patients with an ultralow risk 70-gene signature in the MINDACT trial

Gene signatures have proven successful in identifying patients with a low risk of distant recurrence who could forego chemotherapy (CT) and are currently included in international treatment guidelines for breast cancer. For the 70-gene signature (MammaPrint) an additional threshold was established within the low risk category to identify patients with an ultralow risk of distant recurrence. In independent cohorts, these patients had excellent breast cancer specific survival at 15 years, suggesting that ultralow risk cancers represent indolent disease (Esserman, JAMA Oncol 2017, Delahaye, BC Res Treat 2017). Here we evaluate survival of patients with an ultralow risk 70-gene signature who participated in the randomized phase 3 MINDACT trial (Piccart, Lancet Oncol 2021). Assessed 5- and 8-year distant metastasis free interval (DMFI) and breast cancer specific survival (BCSS) in patients stratified by 70-gene signature result (high, low, ultralow),In this prospective study,

Breast Cancer Index (BCI) and prediction of benefit from extended aromatase inhibitor (AI) therapy (tx) in HR+ breast cancer: NRG oncology/NSABP B-42.

The BCI HOXB13/IL17BR ratio (BCI-H/I) has been shown to predict endocrine tx (ET) and extended ET (EET) benefit. We examined the effect of BCI-H/I for EET benefit prediction in NSABP B-42, evaluating extended letrozole tx (ELT) in HR+ breast cancer patients (pts) who completed 5 yrs of ET.

Utility of the 70-gene MammaPrint assay for prediction of benefit from extended letrozole therapy (ELT) in the NRG Oncology/NSABP B-42 trial.

The 70-gene MammaPrint (MP) assay predicts risk of distant recurrence (DR) in hormone-receptor positive early-stage breast cancer and classifies cancers as Low Risk or High Risk. NSABP B-42 evaluated ELT in patients (pts) who had completed 5 yrs of adjuvant endocrine therapy (tx). The primary objective was to determine the utility of MP to identify pts enrolled in NSABP B-42 who are likely to benefit from ELT.

Conclusions

Statistically significant ELT benefit was observed for MP-L, but not MP-H. The treatment by risk group interaction was not statistically significant for DR, but it was for DFS and BCFI. The benefit appears to be stronger in MP-LNUL than in MP-UL. NCT: 00382070. Support: U10CA180868, -180822, U24CA196067;

De-escalated neoadjuvant pertuzumab+trastuzumab with or without paclitaxel weekly in HR-/HER2+ early breast cancer: ADAPT-HR-/HER2+ biomarker and survival results.

Optimal use of de-escalated, particularly chemotherapy(CT)-free, neoadjuvant regimens in HER2+ early breast cancer (EBC) is currently unclear as there are limited survival data so far. In ADAPT-HR-/HER2+, we previously showed an excellent pCR rate of 90% after 12-week neoadjuvant paclitaxel (Pac) +pertuzumab (P) +trastuzumab (T) and a substantial and clinically meaningful pCR rate of 34% after P+T alone in HR-/HER2+ EBC. Here, we present first survival data.

Low HER2 expression and/or no early response was strongly associated with worse dDFS (p =.029) and iDFS (p =.068).

Conclusions

For the first time, we have shown both excellent pCR and survival in patients treated by de-escalated neoadjuvant CT+P+T irrespective of further CT use in a prospective multicenter study. Investigation of CT-free regimens may need to be focussed on selected patients only (e.g. with high HER2 expression/non-basal-like tumors). In ADAPT HR-/HER2+, early pCR after only 12 weeks of neoadjuvant P+T+pac was strongly associated with improved

outcome and may thus serve as a predictive clinical marker for further treatment (de)-escalation

Prognostic impact of recurrence score, endocrine response and clinical-pathological factors in high-risk luminal breast cancer: Results from the WSG-ADAPT HR+/HER2- chemotherapy trial.

In HR+/HER2- N0-1 early BC, postmenopausal patients (pts) with RS™> 25 and a substantial proportion of premenopausal pts seem to benefit from addition of adjuvant chemotherapy (CT) to endocrine therapy (ET). However, the magnitude of absolute benefit from this treatment intensification seems to depend on clinical-pathological and biological prognostic factors. For the first time, we present outcome from the CT part of the prospective phase III WSG-ADAPT HR+/HER- trial combining both static (RS in baseline core biopsy (CB) and dynamic (Ki67 response) biomarkers to optimize adjuvant therapy in luminal EBC.

5625 pts were screened and 4621 (ITT) entered the trial. After 4.9y median follow-up, higher baseline and post-endocrine Ki-67 levels were associated with poorer iDFS (both $p < 0.001$). In the CT cohort (n = 2331), higher RS, nodal status, and tumor size were generally associated with poorer iDFS. However, iDFS differed between N1 and N0 status only among younger pts (<50 years).

In pts with >4 positive LN (n = 390), lower RS was associated with improved iDFS (RS0-11 vs RS > 25: plog-rank= 0.016, 5y-iDFS 90% vs. 64%).

In pts with RS > 25 (n = 965), low Ki67postendocrine, N0 status, and c/pT1 status were associated with improved iDFS.

In particular, ET-responders had higher 5y-iDFS (84%) than ET-non-responders (77%; plog-rank= 0.040). Younger patients (<50 years old) with N0-1 RS 12-25/ ET-non-responders treated by CT had non-significantly poorer 5-year iDFS (89%) compared to those with ET-response treated by ET only (92%) (plog-rank= 0.249).

Conclusions

First results from the prospective high risk cohort from a large prospective phase III ADAPT trial provide evidence for good prognosis in some pts with >4 positive LN and e.g. low RS. Moreover, combination of lower post-endocrine Ki-67 and limited tumor burden may be a promising criterion for CT de-escalation strategies even in patients with high RS.

Neoadjuvant talazoparib in patients with germline BRCA1/2 (gBRCA1/2) mutation-positive, early HER2-negative breast cancer (BC): Results of a phase 2 study.

Talazoparib (TALA) is a poly(ADP-ribose) polymerase inhibitor approved as monotherapy for treating adult patients (pts) with gBRCA1/2-mutated HER2-negative locally advanced or metastatic BC.

This phase 2, non-randomized, single-arm, open-label study (NCT03499353) evaluated the efficacy and safety of TALA in the neoadjuvant setting for pts with early gBRCA1/2-mutated HER2− BC. Primary endpoint was evaluation of pathologic complete response (pCR) as assessed by Independent Central Review (ICR) after completing 24 weeks of neoadjuvant TALA monotherapy 1 mg QD (0.75 mg for moderate renal impairment) followed by surgery. Secondary endpoints included pCR by investigator (INV) and residual cancer burden (RCB) by ICR (RCB: 0 [pCR], I [minimal], II [moderate], III [extensive]). The evaluable population included pts who received at least 80% of the TALA dose prescribed at treatment start and underwent breast surgery and pCR assessment, plus those who progressed before pCR could be assessed. The intent-to-treat (ITT) population included all pts who received at least 1 dose of TALA.

Conclusions

TALA monotherapy in the neoadjuvant setting was active and showed pCR rates comparable to those observed with combination anthracycline and taxane-based chemotherapy regimens and was generally well tolerated.

Durvalumab improves long-term outcome in TNBC: results from the phase II randomized GeparNUEVO study investigating neodjuvant durvalumab in addition to an anthracycline/ taxane based neoadjuvant chemotherapy in early triple-negative breast cancer (TNBC).

The GeparNuevo trial investigated the addition of durvalumab, an anti-PD-L1 checkpoint inhibitor (CPI), to standard neoadjuvant chemotherapy (NACT) in patients with early TNBC. Durvalumab increased the pathological complete response (pCR) rate particularly in patients treated with durvalumab alone before start of chemotherapy (Loibl et al. Ann Oncol 2019).

GeparNuevo randomized patients with cT1b-cT4a-d tumors and centrally confirmed TNBC to durvalumab (D) 1.5 g i.v. or placebo every 4 weeks. D/placebo monotherapy (0.75 g i.v.) was given for the first 2 weeks (window phase), followed by D/placebo plus nab-paclitaxel 125 mg/m² weekly for 12 weeks, followed by D/placebo plus epirubicin/cyclophosphamide (EC) q2 weeks for 4 cycles. Randomization was stratified by stromal tumor infiltrating lymphocytes (sTILs) (low (≤10%), intermediate (11-59%), high (≥60%)). The primary objective was pCR (ypT0 ypN0). Secondary time-to-event endpoints included invasive disease-free survival (iDFS), distant disease-free survival (DDFS) and overall survival
A total of 174 patients were enrolled between June 2016 and September 2017. The pCR rate with durvalumab was 53.4% versus placebo 44.2%

Conclusions

Durvalumab added to neoadjuvant chemotherapy in TNBC significantly improved long-term outcome despite a small pCR increase and no continuation after surgery. It needs to be questioned whether adjuvant therapy with CPI is needed at all

Evaluation of intra-tumoral (IT) SD-101 and pembrolizumab (Pb) in combination with paclitaxel (P) followed by AC in high-risk HER2-negative (HER2-) stage II/III breast cancer: Results from the I-SPY 2 trial.

I-SPY 2 is a multicenter, phase 2 trial using response-adaptive randomization within molecular subtypes defined by receptor status and MammaPrint (MP) risk to evaluate novel agents as neoadjuvant therapy for women with high-risk breast cancer. SD-101 is an investigational Toll-like receptor 9 (TLR9) agonist CpG-C class

oligodeoxynucleotide that stimulates the production of IFN-α and interleukin (IL)-12, functional maturation of plasmacytoid dendritic cells, and production of cytotoxic antibodies. IT SD-101 was combined with systemic anti-PD-1 antibody Pb to investigate the antitumor and immunologic activity of this novel immunotherapeutic strategy.

Women with tumors ≥ 2.5cm were eligible for screening. Only pts (pts) with HER2- disease were eligible for this treatment. Treatment included weekly P x 12 in combination with IT SD-101 2 mg/ml (1 ml for T2 tumors, 2 ml for >T3 tumors) weekly x 4, then q3 weeks x 2, and IV Pb q3 weeks x 4, followed by doxorubicin/cyclophosphamide (AC) q2-3 weeks x 4 (SD-101+Pembro 4). Pts in the control arm received weekly P x 12 followed by AC q2-3 weeks x 4.

Conclusions

SD-101+Pembro 4 regimen was active but did not meet the pre-specified threshold for graduation in I-SPY 2. pCR/RCB 1 analysis suggests improved response in the HR+/HER-negative signature compared to control. The clinical significance of these findings needs to be weighed against the potential risk of immune-related toxicities.

A randomized phase III post-operative trial of platinum-based chemotherapy (P) versus capecitabine (C) in patients (pts) with residual triple-negative breast cancer (TNBC) following neoadjuvant chemotherapy (NAC): ECOG-ACRIN EA1131

Pts with TNBC who have residual invasive disease (RD) after completion of NAC have a very high risk for recurrence, which is reduced by adjuvant capecitabine (C). Pre-clinical models support the use of platinum agents (P) in the TNBC basal subtype. EA1131 tested the hypothesis that invasive disease-free survival (iDFS) would not be inferior but improved in pts with basal subtype TNBC after NAC with the adjuvant use of a P instead of C (primary objective).

pts with clinical stage II/III TNBC post neoadjuvant taxane +/- anthracycline-based chemotherapy with at least 1 cm RD in the surgical specimen were randomized (1:1) to receive P (carboplatin or cisplatin once every 3 weeks for 4 cycles) or C (14/7d every 3 weeks for 6 cycles Non-inferiority was tested first. If non-inferiority was shown, a formal test for superiority of P compared to C would be conducted.

Conclusions

Participants with TNBC with RD after NAC had a lower than expected 3-year iDFS regardless of study treatment. Available data show that it is very unlikely that the study would be able to establish non-inferiority of P to C. In addition, severe toxicities were more common with P. In pts with TNBC, particularly basal subtype, with at least 1 cm RD after NAC and high-risk of recurrence, adjuvant P use does not improve outcomes.

Take Home Points

- Patients with an ultralow risk 70-gene signature MINDACT have an excellent prognosis with 8-year BCSS above 99% regardless of clinical risk status, and with an 8-year DMFI of 95-98%
- Statistically significant extended letrozole therapy benefit was observed for Mammaprint -L, but not Mammaprint-H.
- Phase III ADAPT trial provides evidence Patients with higher RS, nodal status, and tumor size were generally associated with poorer iDFS. However, iDFS differed between N1 and N0 status only among younger pts (<50 years).
- In pts with >4 positive LN (n = 390), lower RS was associated with improved iDFS .Low Ki67 Post Endocrine, N0 status, and c/pT1 status were associated with improved iDFS.Moreover, combination of lower post-endocrine Ki-67 and limited tumor burden may be a promising criterion for CT de-escalation strategies even in patients with high RS.
- Talazoparib monotherapy in the neoadjuvant setting was active and showed pCR rates comparable to those observed with combination anthracycline and taxane-based chemotherapy regimens and was generally well tolerated.
- Durvalumab added to neoadjuvant chemotherapy in TNBC significantly improved long-term outcome despite a small pCR increase and no continuation after surgery.
- Participants with TNBC with Residual Disease after NAC had a lower than expected 3-year iDFS regardless of study treatment. In pts with TNBC, particularly basal subtype, with at least 1 cm RD after NAC and high-risk of recurrence, adjuvant Platinum use does not improve outcomes.

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