EPICS

EPICS ASCO CONFERENCE COVERAGE: BREAST CANCER

Virtual meeting, June, 2020

EXECUTIVE SUMMARY
On June 3, 2020, Aptitude Health brought together a group of scientists and clinical investigators with expertise in breast cancer to attend an expert panel. The goal of the expert panel was to discuss the latest therapeutic developments and translational research in breast cancer treatment, apply these advances to dynamic and oftentimes individualized clinical decision-making, and explore how emerging data will affect ongoing research, development of new compounds, and future treatment paradigms.
FACULTY

> Adam Brufsky, MD, PhD (chair)
  - UPMC Hillman Cancer Center-University of Pittsburgh MC
  - Pittsburgh, PA

> Pierfranco Conte, MD
  - University of Padova, Veneto Oncological Institute
  - Padova, Italy

> William Gradishar, MD
  - Northwestern University Feinberg School of Medicine
  - Chicago, IL

> Nadia Harbeck, MD, PhD
  - University of Munich
  - Munich, Germany

> Christian Jackisch, MD, PhD
  - Sana Klinikum Offenbach
  - Offenbach, Germany

> Joyce O’Shaughnessy, MD
  - Baylor-Sammons Cancer Center
  - Dallas, TX

> Mark Pegram, MD
  - Stanford University
  - Stanford, CA
# AGENDA

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<td><strong>Insights Into Immune-Based and Chemotherapy for Breast Cancer</strong></td>
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“TNBC is becoming a really heterogeneous group of breast cancer patients; we will have very soon multiple therapeutic options.”
Unfortunately, you don’t get a registration based on equivalent efficacy and better quality of life.

– Nadia Harbeck, MD, PhD

Enthusiasm for using tucatinib is going to be much greater in people with CNS disease.

– William Gradishar, MD

We need a smart GPS system to run breast cancer treatment based on the various traffic jams we are going to see in all signaling pathways.

– Christian Jackisch, MD, PhD
Advances in Triple-Negative Breast Cancer

PIERFRANCO CONTE, MD
Background

1000: KEYNOTE-355 is a phase III trial of pembrolizumab plus chemotherapy vs placebo plus chemotherapy for previously untreated, locally recurrent, inoperable or metastatic triple-negative breast cancer. First author: Javier Cortes

Patients were randomized 2:1 to either arm. Chemotherapy included nab-paclitaxel; paclitaxel; or gemcitabine-carboplatin. Pembrolizumab or placebo were given until progressive disease or intolerable toxicity, up to 35 administrations.

Dual primary endpoints were progression-free survival (PFS; Response Evaluation Criteria In Solid Tumors v1.1, blinded independent central review) and overall survival (OS) by tumor programmed cell death protein 1 ligand 1 (PD-L1) expression (combined positive score [CPS] ≥10 and ≥1) and in all patients.

Results

There was a numeric, nonsignificant difference in PFS for the intent-to-treat population favoring pembrolizumab (7.5 mo vs 5.6 mo) and for patients with CPS ≥1 (7.6 vs 5.6 mo), representing 75% of the patient population.

Statistically significant PFS benefit with pembrolizumab was observed for patients with CPS ≥10 (9.7 vs 5.6 mo; hazard ratio 0.65), which included 38% of the patient population.

Grade 3–5 treatment-related adverse event (AE) rates were 68.1% with pembro plus chemo (2 deaths) vs 66.9% with chemo (0 deaths).
Background

A subgroup analysis of the KEYNOTE-119 trial was presented. This phase III randomized study compared pembrolizumab to investigator's choice chemotherapy in pretreated metastatic (m)TNBC patients. The primary endpoint was OS. The trial endpoint was not met. A trend in OS benefit with pembrolizumab (14.9 mo vs 12.5 mo; hazard ratio 0.58) was observed, with increasing PD-L1 enrichment in patients with CPS >20, representing 17.5% of patients. By applying the TMB score, available for 40% of patients, there was a trend for increase in objective response rate (ORR) and OS for patients with high TMB (≥10 mutations/mb; n = 26).
1001: RESULTS OF A PHASE II RANDOMIZED TRIAL OF CISPLATIN +/- VELIPARIB IN METASTATIC TRIPLE-NEGATIVE BREAST CANCER (TNBC) AND/OR GERMLINE BRCA-ASSOCIATED BREAST CANCER (SWOG S1416). FIRST AUTHOR: PRIYANKA SHARMA

Background

SWOG S1416 is a phase II randomized trial of cisplatin plus veliparib vs cisplatin plus placebo in patients with metastatic TNBC and/or germline BRCA-associated breast cancer. The trial aimed to evaluate the combination of cisplatin and veliparib in patients with BRCA1/2 mutations and/or BRCA1 methylation.

Results

The primary endpoint was progression-free survival (PFS) in the 3 predefined subgroups. PFS favoring veliparib is not significantly different in the germline BRCA-positive (+) group (hazard ratio 0.66) at 62% of the projected accrual. In the BRCA-like subgroup, median PFS is 5.9 vs 4.2 months, and the hazard ratio favoring veliparib is 0.53, which is statistically significant (P = .006). There is also a trend for better overall survival (OS) with veliparib (hazard ratio 0.64) that is not statistically significant.

Increased toxicity in terms of neutropenia, anemia, and thrombocytopenia in the veliparib plus cisplatin arm has been observed.
Background

This was a phase II trial in mBC pts with germline or somatic mutations in DDR genes. Most of the patients (75%) had hormone receptor-positive BC in both subgroups; only 19% of the patients had TNBC.

Cohort 1: patients with germline mutations in non-BRCA1/2 DDR pathway genes

Cohort 2: somatic mutations in non-BRCA1/2 DDR pathway genes or in BRCA1/2

Patients received maximum 1 line of chemotherapy for metastatic disease; no prior poly(ADP-ribose) polymerase (PARP) inhibitors or prior platinum were allowed.

Primary endpoint was ORR.

Results

Primary objective was achieved in both cohorts - ORR in cohort 1 was 29%; all responders had PALB2 mutation. ORR in cohort 2 was 31%; all responders had BRCA mutation.
TPS1109: A PHASE III TRIAL OF CAPIVASERTIB AND PACLITAXEL IN FIRST-LINE TREATMENT OF PATIENTS WITH METASTATIC TRIPLE-NEGATIVE BREAST CANCER (CAPitello290). FIRST AUTHOR: PETER SCHMID

Background

CAPitello290 is an ongoing phase III trial in which TNBC patients are randomized to paclitaxel plus capivasertib (protein kinase B [AKT] inhibitor) or paclitaxel plus placebo. 800 patients will be enrolled in the trial.

Earlier results

There are two phase II randomized trials exploring the value of AKT inhibitors in TNBC. In the PAKT trial (Schmid P, et al. J Clin Oncol. 2020;38:426-433) with capivasertib plus paclitaxel vs paclitaxel plus placebo, there was a trend for better PFS favoring capivasertib (median PFS 5.9 vs 4.2 mo; hazard ratio 0.74), and OS improvement with capivasertib (median OS 19.1 vs 12.6 mo; hazard ratio 0.61). The LOTUS study (Dent R, et al. ESMO Breast Cancer Virtual 2020, Abstract 1390) comparing paclitaxel plus ipatasertib vs paclitaxel plus placebo showed similar data to the PAKT trial, favoring ipatasertib vs placebo (median PFS 5.9 vs 4.2 mo; hazard ratio 0.60; median OS 25.8 vs 16.9 mo; hazard ratio 0.8). The phase III IPATunity130 trial with ipatasertib is ongoing (NCT03337724).
The KEYNOTE-355 trial, a phase III study of pembrolizumab plus chemotherapy vs placebo plus chemotherapy vs chemo alone, showed a statistically significant and clinically meaningful improvement in PFS for patients with PD-L1 expression of CPS ≥10. PFS benefit was 9.7 vs 5.6 mo, hazard ratio 0.65 (95% CI: 0.49–0.86); P = .0012. These patients were previously untreated and had locally recurrent inoperable or mTNBC.

KEYNOTE-355 showed very similar data to the IMpassion130 trial (Schmid P, et al. N Engl J Med. 2018;379:2108–2121), where atezolizumab plus nab-paclitaxel demonstrated median PFS of 7.2 vs 5.5 mo with placebo plus nab-paclitaxel (hazard ratio 0.80; 95% CI: 0.69–0.92; P = .002).

The subgroup of pembrolizumab plus gemcitabine-carboplatin showed little benefit. The explanation may be that many TNBC patients received carboplatin in the neoadjuvant setting (in Europe). Subgroup analysis from this trial, which has not yet met its primary endpoint, should be interpreted with caution.

Pembrolizumab trials in TNBC (KEYNOTE-119, 355, and 522) have different patient subsets; this must be taken into consideration when interpreting data.

Pembro plus chemo was generally well tolerated, with no new safety concerns.

PD-L1 testing is still a challenge, due to the use of different antibodies/platforms, different scoring systems, primary tumor vs metastases, expression in different metastatic sites (low liver, high lung), and increased expression after chemotherapy or radiotherapy.

The same patient can show very low PD-L1 expression in liver metastasis and much higher in lung metastasis. Also, the expression of PD-L1 can be increased in the same patient after chemotherapy.

There is PD-L1 enrichment in patients responding to immune checkpoint inhibitors in the metastatic setting. Further translational research is necessary to understand whether (high-level) intratumoral immunogenicity is required for the activity of immunotherapies in TNBC. More effort is required to define the role of PD-L1 as a predictive test for selected patients.
DISCUSSION – PARP INHIBITORS IN TNBC

Trials with PARP inhibitors (PARPi’s) showed clear benefit in TNBC patients with gBRCA mutations. Single-agent olaparib provides PFS benefit in gBRCA+ advanced BC. Combination of veliparib plus cisplatin provides PFS benefit in gBRCA+ and BRCA- like TNBC patients. Patients with gPALB2+ and sBRCA+tumors may also benefit from PARPi, but to a lesser extent. Hazard ratios seem to be greater when single-agent PARPi is compared with single-agent chemotherapy, and when PARPi is added to platinum-based chemotherapy. Apart from gBRCA1 or BRCA2 mutation, BRCA- like phenotypes are also predictive of PARPi efficacy. gPALB2+ and sBRCA+tumors may also benefit from PARPi’s.

Tolerability of PARPi plus chemotherapy for an extended period of time can be an issue. The advisors agreed that PARPi maintenance strategy can be a reasonable approach, as it is used in other indications (eg, ovarian cancer, prostate cancer). In the BROCADE trial (Dieras VS, et al. ESMO 2019. Abstract 2520), veliparib plus chemo vs placebo plus chemo was followed by veliparib or placebo maintenance in gBRCA-mutant ABC, and the veliparib combination and maintenance showed benefit to gBRCA-mutant patients.
At present, there is no optimal treatment sequence for patients with co-expression of multiple biomarkers.

Determining BRCA status quickly at diagnosis can be a challenge. In most cases, PD-L1 status is requested after the initiation of first-line treatment.

The advisors discussed in BRCA-mutant patients the need for DNA-damaging agents early in the treatment, as these patients have a good chance to remain progression-free for a long time. Use of long-term chemotherapy is limited by tolerability issues.

Platinum-based chemotherapy with PARPi could be used in frontline and could be followed by PARPi maintenance (as per BROCADE-3 trial, Dieras VS, et al. ESMO 2019. Abstract LBA9). PARPi monotherapy can be used first if the patient is against receiving chemotherapy.

Immune checkpoint inhibitor could be used in the second line in BRCA-wildtype and PD-L1+ TNBC.

Immune checkpoint inhibitor in combination with chemotherapy could be used in frontline, chemotherapy in second line, and sacituzumab govitecan in later line, when available in BRCA-mutant and PD-L1-negative (–) TNBC.

PARPi upfront as a single agent, on the basis of OS results of the OlympiAD trial (Tung N, et al. Ann Oncol. 2019;30:558-566) with olaparib in frontline, with better tolerability and quality of life.

Chemotherapy in second line...
TNBC is becoming a heterogeneous group of BC patients. Around 80% are Trop-2+ and about 40% are PD-L1+ or have CPS ≥10. Around 30% have phosphoinositide 3-kinase (PI3K)/AKT/phosphatase and tensin homolog (PTEN) dysregulation. About 15–30% have BRCA mutation. New drugs are actively moving to the TNBC arena and showing promising activity (e.g., capivasertib, sacituzumab govitecan), in mTNBC as well as in earlier stages of treatment. Immune checkpoint inhibitors in (neo)adjuvant treatments. PARPi's in post-(neo)adjuvant treatments. AKT inhibitors are under investigation in unselected TNBC and other indications (advanced ovarian, endometrial, or breast cancer). Clarity is needed on whether the activity of AKT inhibitors is observed only in PI3K/AKT/mechanistic target of rapamycin (mTOR) pathway-dysregulated tumors. There is a need for better biomarkers for TNBC patient selection.
Sacituzumab govitecan is a promising new agent in the TNBC treatment landscape. It has recently been approved in the US, but not yet in the EU. Sacituzumab govitecan is a Trop-2–directed antibody-drug conjugate (ADC) with a high drug:antibody ratio of 7.6 molecules of payload for every molecule of antibody. The payload is SN-38, an active metabolite of irinotecan (Topoisomerase-1 inhibitor).

In the phase I/II trial in TNBC, sacituzumab govitecan achieved a 33.3% ORR, with a median PFS of 5.5 months and a median OS of 13 months (Bardia A, et al. *N Engl J Med*. 2019;380:741-751).

There was an ongoing randomized trial comparing sacituzumab govitecan to chemotherapy. The trial, named ASCENT, was stopped for compelling efficacy in favor of sacituzumab govitecan.

Phase II data show activity of AKT inhibitors in TNBC; phase III trials are ongoing. AKT inhibitors are not easy to combine with chemotherapy due to their tolerability profile. Benefit can be limited to patients with the PI3K/AKT/PTEN pathway dysregulation.

Aurora kinase A (AURKA) inhibitors are promising new agents in TNBC (Faruki FA, et al. ASCO 2020. Abstract e13106) with a manageable safety profile.
Evolving Therapies for Hormone Receptor-Positive Breast Cancer

NADIA HARBEEK, MD, PHD
505: LETROZOLE + RIBOCICLIB VERSUS LETROZOLE + PLACEBO AS NEOADJUVANT THERAPY FOR ER+ BREAST CANCER (FELINE TRIAL). FIRST AUTHOR: QAMAR J. KHAN

Background

The FELINE trial is a randomized, 3-arm adjuvant trial with 6 cycles of letrozole plus intermittent-dose ribociclib or letrozole plus continuous doses of ribociclib or letrozole plus placebo. Patients had small, nonproliferating tumors.

The primary objective was 20% increase in achieving preoperative endocrine prognostic index (PEPI) score 0 at surgery between letrozole plus ribociclib (combined dosage) vs letrozole plus placebo.

Results

Addition of ribociclib to letrozole as neoadjuvant endocrine therapy did not result in more women with a PEPI score of 0 (25.8% vs 25.4%; \( P = \) not significant).

At day 14 cycle 1, twice as many women on letrozole plus ribociclib had complete cell cycle arrest (CCCA) compared with letrozole plus placebo (92% vs 52%). However, significantly more women on letrozole plus ribociclib had increased proliferation (by Ki67 expression) between day 14 cycle 1 and surgery, resulting in similar CCCA at surgery.
601: ADAPTCYCLE: ADJUVANT DYNAMIC MARKER-ADJUSTED PERSONALIZED THERAPY (ADAPT) COMPARING ENDOCRINE THERAPY PLUS RIBOCICLIB VERSUS CHEMOTHERAPY IN INTERMEDIATE-RISK HR+/HER2- EARLY BREAST CANCER (EBC). FIRST AUTHOR: NADIA HARBECK

Background

The ADAPTcycle trial, a phase III prospective study, is ongoing with adjuvant cyclin-dependent kinase 4/6 (CDK4/6i) plus endocrine therapy vs chemotherapy plus endocrine therapy in early BC patients. The objective is to evaluate whether enhancing endocrine therapy with CDK4/6i is superior to chemotherapy for early BC patients who may be undertreated with endocrine therapy alone, on the basis of their endocrine responsiveness or high tumor burden.
531: PHASE II STUDY OF ADJUVANT ENDOCRINE THERAPY WITH CDK 4/6 INHIBITOR, RIBOCICLIB, FOR LOCALIZED ER+/HER2- BREAST CANCER (LEADER). FIRST AUTHOR: LAURA SPRING

Background

> The LEADER trial is an adjuvant study using endocrine therapy with ribociclib for localized BC with 2 different
1007: PARSIFAL: A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE II TRIAL TO EVALUATE PALBOCICLIB IN COMBINATION WITH FULVESTRANT OR LETROZOLE IN ENDOCRINE-SENSITIVE PATIENTS WITH ESTROGEN RECEPTOR (ER)[+] / HER2[-] METASTATIC BREAST CANCER. FIRST AUTHOR: ANTONIO LLOMBART-CUSSAC

Background

The phase II PARSIFAL trial is investigating palbociclib plus letrozole or palbociclib plus fulvestrant in the first-line setting of metastatic disease.

Primary objective is PFS

Results

Efficacy did not show significant difference at 256 PFS events, with median follow-up of 32 months.

There was no subgroup where one endocrine partner was favored over the other.

Safety profiles of the study arms were similar.
HR+ BC ABSTRACTS

1006: ALPELISIB (ALP) + FULVESTRANT (FUL) IN PATIENTS (PTS) WITH PIK3CA-MUTATED (MUT) HORMONE RECEPTOR-POSITIVE (HR+), HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2-NEGATIVE (HER2–) ADVANCED BREAST CANCER (ABC) PREVIOUSLY TREATED WITH CYCLIN-DEPENDENT KINASE 4/6 INHIBITOR (CDKI) + AROMATASE INHIBITOR (AI): BYLIEVE STUDY RESULTS. FIRST AUTHOR: HOPE S. RUGO

Background
>
> BYLieve is a noncomparable cohort study with alpelisib plus fulvestrant in patients who previously received

...
The following abstracts were summarized and discussed:

1. **A phase Ib study to evaluate the oral selective estrogen receptor degrader GDC-9545 alone or combined with palbociclib in metastatic ER-positive HER2-negative breast cancer.** First author: Elgene Lim

2. **A phase I dose escalation and expansion study of the next generation oral SERD AZD9833 in women with ER-positive, HER2-negative advanced breast cancer.** First author: Erika P. Hamilton

3. **Phase I/II study of SAR439859, an oral selective estrogen receptor degrader (SERD), in estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-)/metastatic breast cancer (mBC).** First author: Mario Campone

4. **SERENA-2: A randomized, open-label, parallel-group, multicenter phase II study comparing the efficacy and safety of oral AZD9833 versus fulvestrant in women with advanced ER-positive HER2-negative breast cancer.** First author: Mafalda Oliveira
Background

Efficacy of fulvestrant, the only approved SERD, may be limited by poor bioavailability. Oral SERDs may achieve higher exposures and have better activity. These agents are in early development: phase I and phase II data are available, but as yet there are no randomized trials.

Results

The phase Ib trial evaluated GDC-9545 in 2 cohorts; greater efficacy was shown when combined with palbociclib.

In the phase I dose-escalation trial with AZD9833, there are some patients who have derived long benefit, as the trial has been going for about a year. There will be a phase II study (SERENA-2) that compares AZD9833 to fulvestrant (NCT04214288).

The phase I/II trial with SAR439859 is looking at very heavily pretreated patients who received SERD, mTOR inhibitor, CDK4/6i, or chemotherapy, and shows promising stabilization rates.

There is some consistency in side effects with nausea, diarrhea, and vomiting. Some drugs show neutropenia. One agent, RAD1901, produced visual disturbances, and GDC-9545 in combination with palbociclib showed some cardiac toxicity (discussed by Komal Jhaveri at ASCO 2020).
HR+ BC ABSTRACTS

1038: ADDITION OF ENDOCRINE THERAPY TO DUAL ANTI-HER2 TARGETED THERAPY IN INITIAL TREATMENT OF HER2+/HR+ METASTATIC BREAST CANCER. FIRST AUTHOR: MATTHEW LOFT

Background

A nonrandomized meta-analysis from an Australian database that examined dual targeted therapy plus...
Several presented trials evaluated the role of CDK4/6i in early stages of HR+ BC (FELINE: neoadjuvant letrozole plus ribociclib; LEADER: adjuvant CDK4/6i; ADAPTcycle: adjuvant CDK4/6i vs chemotherapy). Addition of ribociclib to letrozole as neoadjuvant endocrine therapy did not result in more women with a PEPI score of 0. An important issue with CDK4/6i in the adjuvant setting is adherence to treatment. The LEADER trial demonstrated that even though serious AEs with 1 year of adjuvant ribociclib are few, a number of patients discontinued adjuvant CDK4/6i. The NeoPal study (Cottu P, et al. Ann Oncol. 2018;29:2334-2340) compared letrozole and palbociclib vs chemotherapy in the neoadjuvant setting and found similar clinical activity between the CDK4/6i regimen and chemotherapy. ADAPTcycle, started in 2019, seeks to evaluate whether endocrine-based therapy with a CDK4/6i is superior to chemotherapy followed by endocrine therapy in patients with luminal early BC who may be undertreated with endocrine therapy alone (on the basis of either lack of endocrine responsiveness or high tumor burden). Translational research from this study aims to assess potential mechanisms of resistance to endocrine therapy and/or CDK4/6i or chemotherapy. PARSIFAL shows no efficacy difference between endocrine therapy partners for ribociclib in mBC, with a similar safety profile.
PALLAS, a phase III study of early stage HR+, HER2– BC with palbociclib in the adjuvant setting, is unlikely to show a statistically significant improvement in the primary endpoint of invasive disease-free survival. The data were not released. The advisors considered the effect of patient selection and compliance as reasons this trial was not successful, rather than any issue with the drug. Patients with early stage disease may not show events during the follow-up period, and may not take the medication.

The advisors noted that there is ongoing research in another patient population that can benefit from palbociclib in this setting. The phase III PENELOPE-B study (NCT01864746) is evaluating palbociclib plus endocrine therapy after neoadjuvant chemotherapy in high-risk HR+, HER2– disease.

The phase III monarchE trial (NCT03155997) is ongoing with abemaciclib added to standard endocrine therapy vs standard endocrine therapy in the neoadjuvant setting in high-risk, node-positive patients. This population is very different from the PALLAS trial.

Subgroup analysis and longer follow-up of the PALLAS trial data will provide more information. For example, the early evaluation of the APHINITY trial was hardly positive, and a recent update at SABCS 2019 (Piccart M, et al. SABCS 2019. Abstract GS1-04) after 6-year follow-up showed benefit of the pertuzumab-based triplet in early HER2+, node-positive BC.

Dr Fatima Cardoso presented an update of the MINDACT trial (Cardoso F, et al. ASCO 2020. Abstract 506). MammaPrint can identify high-genomic-risk patients who do poorly on available therapies. These patients would benefit from earlier usage of new agents that are available in the metastatic setting.
CDKi’s are established first-line treatment of HR+, HER2– advanced BC
Second-line treatment

> The advisors would not rechallenge with CDKi in case of true progression due to class effect. In case of treatment failure due to safety, they would switch to another, better CDKi with a different toxicity profile.
DISCUSSION – NOVEL AGENTS IN HR+ ADVANCED BC

> Oral SERDs are promising new agents
  - Some oral SERDs are active in patients who received multiple prior therapies. Advisors are interested in

...
DISCUSSION – TRIPLE-POSITIVE BC

Dual anti-HER2–targeted therapy with chemotherapy for triple-positive BC patients is in clinical practice. Preclinical synergy between HER2 pathway and antiestrogens (Pietras JR, et al. Oncogene. 1995;10:2435-244) has been confirmed by a variety of trials:

New Therapeutic Approaches for Early Stage and Metastatic HER2+ Breast Cancer

MARK PEGRAM, MD
501: THREE-YEAR FOLLOW-UP OF NEOADJUVANT CHEMOTHERAPY WITH OR WITHOUT ANTHRACYCLINES IN THE PRESENCE OF DUAL HER2-BLOCKADE FOR HER2-POSITIVE BREAST CANCER (TRAIN-2): A RANDOMIZED PHASE III TRIAL. FIRST AUTHOR: ANNA VAN DER VOORT

Background

> The TRAIN-2 study was designed to obstruct the use of anthracyclines in the neoadjuvant setting of HER2+

Results

> At 3 years of follow up, there was no difference in pCR observed (67% with anthracycline vs 68% without anthracycline)

> Event-free survival was not different (3-year EFS rate 92.7% vs 93.5%, with vs without anthracycline)

> There was no benefit for anthracyclines for any of the subgroups including high-risk subgroups (cN2/3; HR = 0.75 with trend favoring non-anthracycline)

> The results were irrespective of hormone receptor and nodal status

> There were 2 leukemias reported in the anthracycline arm and none in the control arm
500: PRIMARY ANALYSIS OF KAITLIN: A PHASE III STUDY OF TRASTUZUMAB EMTANSINE (T-DM1) + PERTUZUMAB VERSUS TRASTUZUMAB + PERTUZUMAB + TAXANE, AFTER ANTHRACYCLINES AS ADJUVANT THERAPY FOR HIGH-RISK HER2-POSITIVE EARLY BREAST CANCER (EBC). FIRST AUTHOR: NADIA HARBECK

Background

The KAITLIN trial was a large (n = 1846) phase III adjuvant trial in high-risk HER2+ early BC patients using T-DM1 plus pertuzumab vs dual HER2 blockade plus taxane following anthracyclines. The primary endpoint was IDFS in the ITT population.

Results

At the primary analysis, the combination of T-DM1 plus pertuzumab did not show superiority to the control arm. Three-year IDFS was 93.1% in the T-DM1 arm vs 94.2% in the control arm. The patient number was changed from 2500 to 1846, based on the Kaplan-Meier analyses, having more patients would not have made a difference. T-DM1 plus pertuzumab is a suitable treatment for selected patients, who might be intolerant of taxanes or intolerant of co-medications (eg, steroids).
508: PRIMARY RESULTS OF NRG ONCOLOGY / NSABP B-43: PHASE III TRIAL COMPARING CONCURRENT TRASTUZUMAB (T) AND RADIATION THERAPY (RT) WITH RT ALONE FOR WOMEN WITH HER2-POSITIVE DUCTAL CARCINOMA IN SITU (DCIS) AFTER LUMPECTOMY. FIRST AUTHOR: MELODY A. COBLEIGH

Background

A prospective phase III adjuvant trial (n = 2014) with the addition of trastuzumab to radiation therapy vs
1005: TUCATINIB VERSUS PLACEBO ADDED TO TRASTUZUMAB AND CAPECITABINE FOR PATIENTS WITH PREVIOUSLY TREATED HER2+ METASTATIC BREAST CANCER WITH BRAIN METASTASES (HER2CLIMB). FIRST AUTHOR: NANCY U. LIN

Background

In the phase III HER2CLIMB trial, tucatinib in combination with trastuzumab and capecitabine resulted in better PFS and OS outcomes in heavily pretreated HER2+ MBC patients when compared with trastuzumab and capecitabine (Murthy RK, et al. N Engl J Med. 2020; 382:597-609).

HER2CLIMB included 291 patients with brain metastasis and the subgroup analysis of these patients were presented at ASCO 2020.

Results

The analysis of patients with CNS metastasis showed that tucatinib provided statistically significant PFS benefit vs control arm (9.9 months vs 4.2 months). Duration of intracranial response was also higher in the tucatinib arm (6.8 month vs 3.0 months) for these patients.

ORR - IC was higher in the tucatinib arm (47.3%; 95% CI: 33.7, 61.2) vs the control arm (20.0%; 95% CI: 5.7, 43.7). Median DOR - IC was 6.8 mo (95% CI: 5.5, 16.4) vs 3.0 mo (95% CI: 3.0, 10.3).

Median OS for the CNS metastasis group was 18.1 months in the tucatinib arm and 12 months in the control arm. The risk of CNS progression or death was reduced by 68% in the tucatinib arm in patients with CNS metastasis.
1040: SOPHIA ANALYSIS BY CHEMOTHERAPY (CTX) CHOICE: A PHASE III (P3) STUDY OF MARGETUXIMAB (M) + CTX VERSUS TRASTUZUMAB (T) + CTX IN PATIENTS (PTS) WITH PRETREATED HER2+ METASTATIC (MET) BREAST CANCER (MBC). FIRST AUTHOR: SANTIAGO ESCRIVÁ

Background

In the phase III SOPHIA trial, margetuximab plus chemotherapy led to significant improvements in PFS and clinical benefit compared with trastuzumab chemotherapy in heavily pretreated HER2+ MBC patients (Rugo H, et al. SABCS 2019. Abstract 1000). A subset analysis by chemotherapy assignment was presented at ASCO 2020:

- mPFS was 8.28 vs 5.52 months with margetuximab plus capecitabine vs trastuzumab plus capecitabine
- mPFS was 5.39 vs 3.52 months with margetuximab plus gemcitabine vs trastuzumab plus gemcitabine
- mPFS was 5.95 vs 4.17 months with margetuximab plus eribulin vs trastuzumab plus eribulin
- mPFS was 5.62 vs 5.13 months with margetuximab plus vinorelbine vs trastuzumab plus vinorelbine

Results

Median PFS was very similar when margetuximab was combined with gemcitabine or eribulin or vinorelbine chemotherapy. The margetuximab plus capecitabine combination showed a little longer PFS; those patients probably had less disease burden. There was no PFS difference between margetuximab plus vinorelbine vs trastuzumab plus vinorelbine.
Background

The WSG-TP-II study compared a de-escalated chemotherapy plus pertuzumab plus trastuzumab vs
Background

> The PHERGAIN study is a chemotherapy de-escalation trial with TCHP in Arm A and endocrine therapy plus dual HER2 blockade in Arm B.
Background

In the phase II DESTINY-Breast01 trial, trastuzumab deruxtecan showed durable antitumor activity (ORR was 60.9% and DOR was 14.8 mo). In addition to nausea and myelosuppression, interstitial lung disease was observed in 13.6% of patients and required attention to pulmonary symptoms and careful monitoring. (Modi S, et al. N Engl J Med. 2020; 382:610-621)

Results presented at ASCO 2020

An overall subgroup analysis of the DESTINY-Breast01 trial was presented at ASCO. There were clinical variables associated with better objective response rates, duration of response, or median PFS in a multivariate analysis—HER2/3+, as opposed to lower levels of HER2 expression in a central reference lab confirmation—Prior pertuzumab in the first or second line was a favorable predictive factor for response to trastuzumab deruxtecan—Fewer numbers of prior regimens as well as normal hepatic and renal function were predictive for higher respond rates.

Results presented at ESMO Breast Cancer 2020

A subgroup analysis of patients with brain metastasis was presented at ESMO Breast Cancer. Trastuzumab deruxtecan demonstrated efficacy in patients who had stable, treated brain metastases with efficacy similar to the overall population (ORR was 58.3% and DOR was 16.9 mo). Progression in the brain was noted in only 8% of patients. The safety profile of trastuzumab deruxtecan was consistent with the overall population.
Neoadjuvant therapy of BC in TRAIN-2 clearly shows that anthracyclines do not improve efficacy, and are associated with increased febrile neutropenia and cardiotoxicity. A neoadjuvant carboplatin-taxane-based regimen with dual HER2-blockade can be considered in all stage II–III breast cancer patients, regardless of hormone receptor and nodal status. There are still some patients who can benefit from anthracyclines, but there is a need for optimal chemotherapy in the neoadjuvant setting. Further de-escalation of chemotherapy needs to be pursued. The use of anthracyclines is an ongoing debate in the neoadjuvant setting. The TRAIN-2 trial confirmed that the use of anthracyclines does not give benefit to CTHP therapy in the neoadjuvant setting. Criticism of the TRAIN-2 trial may include patient number (n = 438), 3 weeks of FEC-T treatment, and epirubicin dose of 90 mg/m² (instead of 100 or 120 mg/m²). The experts have used TCHP without anthracyclines in the US since the TRYPHENA trial (Schneeweiss A, et al. Ann Oncol. 2013;24(9):2278-2284). At the Stanford group, 50% of the physicians use anthracyclines without compelling clinical evidence. In Europe, there is no available alternative to anthracyclines; carboplatin is not approved in the adjuvant setting. In Italy, anthracyclines have been used for 30 years.
KAITLIN did not meet its co-primary endpoints. Replacing adjuvant taxane and trastuzumab with ado-
trastuzumab emtansine (T-DM1) did not result in significantly improved efficacy or overall safety. However, in
this high-risk population, a favorable iDFS outcome was achieved in both study arms. This confirms that
pertuzumab plus trastuzumab plus chemotherapy remains the standard of care for patients with high
risk HER2+ early BC.

Superiority design for the KAITLIN trial with T-DM1 in the adjuvant setting was probably too optimistic given the
outcomes of previous T-DM1 trials in the adjuvant setting, eg

• KRISTINE trial (Hurwitz SA, et al. ASCO 2019. Abstract 500)
• ATEMPT trial (Tolaney SM, et al. SABCS 2019. Abstract GS1-05)

Patients who did not receive previous taxane treatment showed less neuropathy with T-DM1 than was reported in the

T-DM1 was probably developed as an escalation drug. There are other ADCs arriving to the neoadjuvant setting that
might have a chance to be developed as a de-
escalation drug.

T-DM1 is a suitable treatment for selected patients, who showed hypersensitivity to taxane-based treatment or
are intolerant of co-
medications used to manage these reactions (eg, steroids)
DISCUSSION – HER2+ DCIS BC

> The idea that trastuzumab can increase radiotherapy effectiveness was only partially supported by
In the WSG-TP-II de-escalation study dual HER2+ blockade plus paclitaxel showed promising results, and was very safe over a relatively short course of 12 weeks. The PHERGain trial also confirmed that chemotherapy de-escalation is feasible and effective, as nearly 40% of patients who started dual HER2 blockade and were PET responders achieved complete response. Also important is that the strategy was less toxic and did not jeopardize breast surgery. The advisors highlighted that the chemotherapy-free regimen (dual HER2 blockade with endocrine therapy) allowed for breast-conserving surgery to the rate similar to chemotherapy (dual HER2 blockade with chemotherapy) and that omission of chemotherapy is associated with more favorable toxicity. For elderly/frail patients, ET plus dual HER2 blockade is a reasonable chemo-free option. Overall conclusions from these trials and the consolidated opinion of the experts is that de-escalation is a valid option and should continue to be investigated and brought to clinical practice.
DISCUSSION – R/R HER2+, HR+ MBC (1/2)

The advisors found the CNS data very impressive from the HER2CLIMB trial with tucatinib in HER2+
advanced BC and would like to see tucatinib in earlier lines of therapy to prevent brain metastases.

HER2CLIMB included a heavily pretreated patient population. Almost half of the patients in this trial had brain metastasis (n = 291); a large proportion had active brain metastasis (n = 174) and there were patients with untreated brain metastasis (n = 66) who benefited from tucatinib.

The powerful message in this dataset is that even patients with progressing brain metastasis have clinical benefit with tucatinib that is translated into OS benefit. In patients with isolated brain progression who completed study therapy after local treatment, the risk of second progression or death was reduced greatly by 67% in the tucatinib arm.

The EMA approval process is currently ongoing.

The CNS subgroup analysis (ESMO Breast Cancer 2020) of the DESTINY-Breast01 trial with trastuzumab deruxtecan are encouraging, however, the preferred choice in patients with CNS metastasis is clearly tucatinib.

The payload can be highly effective in brain metastases, but the results are hard to interpret.

Some antibody-drug conjugates (ADCs) could have benefit in patients with brain metastases.

The subgroup analysis of DESTINY-Breast01 (ASCO 2020) showed the ERBB2 plasma copy number in circulating tumor DNA might become a more convenient way of monitoring response in the future, which correlated with objective response probability in this trial.

PIK3CA and HER2 kinase domain mutations have no impact on DM1 response.

The advisors are waiting for further details of the gene alterations observed in the study.
The multivariate analysis of the SOPHIA trial showed favorable interactions between margetuximab and chemotherapies in heavily pretreated patients. The cohort assignments were done by the treating physicians in a non-randomized fashion. The reason for the lack of difference in the vinorelbine subset with or without margetuximab could be that the control arm showed similar benefit or that this retrospective analysis included relatively small subgroups. Similarly, in the RIBBON-2 trial (Brufsky AM, et al. J Clin Oncol. 2011;29(32):4286-4293) there was no benefit observed in the bevacizumab plus vinorelbine arm vs vinorelbine only.

Dr Brufsky described a theoretical patient who relapsed after receiving available therapies before the metastatic setting. First, the patient received TCHP, but after surgery there was residual disease. In the post-neoadjuvant setting, the patient received T-DM1 for 1 year, and later they had a relapse within 8 months.

The advisors agreed that in this rare case, they would consider the possibility of using tucatinib or trastuzumab deruxtecan in the first line of metastatic BC, however, these drugs are not approved in this setting.

For patients who showed very early relapse, which is suggestive of resistance to HER2-directed therapies, trastuzumab deruxtecan showed very promising results in HER2-refractory disease. If relapse occurs years later, and is not due to HER2 therapy resistance, dual HER2 blockade would be possible to repeat in combination with taxane as first-line treatment.
Insights Into Immune-Based and Chemotherapy for Breast Cancer

JOYCE O’SHAUGHNESSY, MD
1014: RESULTS OF ENCORE 602 (TRIO025), A PHASE II, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLINDDED, MULTICENTER STUDY OF ATEZOLIZUMAB WITH OR WITHOUT ENTINOSTAT IN PATIENTS WITH ADVANCED TRIPLE-NEGATIVE BREAST CANCER (ATNBC). FIRST AUTHOR: JOYCE O'SHAUGHNESSY

Background
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The ENCORE trial is a randomized phase II trial of atezolizumab with or without the HDAC inhibitor entinostat in patients with TNBC. Patients received 1 or 2 prior lines of systemic therapy.

The trial enrolled 81 patients; the primary endpoint was PFS based on RECIST 1.1.

Results
>

The trial was negative; there was no difference between atezolizumab plus entinostat vs atezolizumab plus placebo in PFS (1.68 mos vs 1.51). The OS was 12.25 mos vs 11.20 and the ORR was 12.5% vs 2.4%.

There was more fatigue and GI toxicities reported in the entinostat arm. Also, there were 4 deaths in the entinostat arm and 2 deaths in the placebo arm, but these were unrelated to the treatment.
Background

The A-BRAVE trial is an ongoing adjuvant avelumab trial in high-risk, primary TNBC patients, who have
IMMUNE-BASED AND CHEMOTHERAPY FOR BC ABSTRACTS

TPS596: KEYLYNK-009: A PHASE II/III, OPEN-LABEL, RANDOMIZED STUDY OF PEMBROLIZUMAB (PEMBRO) PLUS OLAPARIB VS PEMBRO PLUS CHEMOTHERAPY AFTER INDUCTION WITH FIRST-LINE PEMBRO PLUS CHEMOTHERAPY IN PATIENTS WITH LOCALLY RECURRENT INOPERABLE OR METASTATIC TRIPLE-NEGATIVE BREAST CANCER (TNBC). FIRST AUTHOR: HOPE S. RUGO

Background

[Text regarding the background of the study]

Results

[Text regarding the results of the study]
Background

- The GLORIA trial is ongoing with adagloxad simolenin, an anti-Globo H vaccine, as maintenance therapy in patients who had benefit from chemotherapy in early stage TNBC. In the trial, high-risk TNBC patients will be randomized to 2 years of adagloxad simolenin vs standard of care after they received chemotherapy and tested positive for Globo-H. They are then randomized to 2 years of vaccine, subcutaneous therapy.

- The trial is planned to enroll 668 patients; the primary endpoint is IDFS.

- Eligible patients received anthracyclines and taxanes, and concurrent capecitabine, platinum, and/or radiation therapy.
TPS1105: A PHASE II TRIAL OF NIVOLUMAB (NIVO) + ABEMACICLIB (ABE) OR PALBOCICLIB (PAL) + ANASTROZOLE (ANA) IN POSTMENOPAUSAL WOMEN AND MEN WITH ESTROGEN RECEPTOR (ER)+/HUMAN EPIDERMAL GROWTH FACTOR 2 (HER2)- PRIMARY BREAST CANCER (BC): CHECKMATE 7A8. FIRST AUTHOR: SARA M. TOLANEY

Background

CheckMate 7A8 is a phase II presurgery trial of nivolumab plus palbociclib plus anastrozole in postmenopausal...
ENCORE 602 (TRIO025) failed to show a statistically significant increase in PFS with the addition of entinostat to atezolizumab in patients with previously treated advanced TNBC.

HDAC inhibitors positively influence antitumor immune responses by increasing homologous recombination deficiency, activating the STING pathway, and upregulating PD-L1. They can downregulate immune suppressive cells such as regulatory T cells.

Atezolizumab shows very modest objective response rates in second and third line; this confirms that IO agents and these combination strategies need to be used much earlier in the course of the disease.

In the KEYNOTE-355 trial, pembrolizumab combined with several chemotherapeutic partners showed a statistically significant and clinically meaningful improvement.

The advisors highlighted the importance of the safety profile of the nivolumab plus palbociclib plus anastrozole triplet. At AACR 2020, Hope Rugo presented data on the combination of abemaciclib plus AI plus pembrolizumab in first line, where the safety of the triplet proved inadequate. 46% of the patients experienced grade 3 transaminase elevation, 4 patients had interstitial lung disease, and 2 of them died.
Immunotherapy has not arrived in breast cancer yet, and there are many open questions to be answered regarding testing optimal treatment and patient selection. Guidance for immunotherapy usage needs to be developed in the coming years.

How does immunotherapy work in BC? How it can be combined?

Where can it be used most effectively?

How can drugs be added to enhance the effectiveness of IO?

Several trials with immunotherapy drugs were reported as ongoing (nivolumab, pembrolizumab, avelumab, etc). The following trials were specifically mentioned by the advisors:

- Advisors are waiting for further iDFS analysis of the KEYNOTE-522 trial, which could be practice changing.
- The SWOG 1418 trial (NCT02954874) with pembrolizumab vs observation in the post-neoadjuvant setting of TNBC is ongoing, with the sample size of 1000 patients.
- In the I-SPY 2 trial (Pusztai L, et al. AACR 2020) high-risk patients showed remarkable pCR benefit with preoperative avelumab with chemotherapy in ER+ patients.
DISCUSSION – NOVEL THERAPIES IN BC

There is increasing interest in ADCs; T-DM1 and trastuzumab deruxtecan are available in BC. The bystander effect is not always clear from the clinical view; the mode of action regarding toxic effects of T-DM1 and trastuzumab deruxtecan needs more clarification. Better ADCs are needed that will allow for targeting multiple antigens, to address disease heterogeneity. There are ADCs directed to new signaling pathways (eg, HER3) under development that will bring new treatment options to different BC subtypes.

Regarding the KEYLYNK-009 trial, the advisors expressed their interest in the olaparib maintenance approach to prolong the therapy without the cumulative myelosuppression of gemcitabine carboplatin that leads to treatment failure, instead of disease progression. PARP inhibitors can increase PD-L1 expression and there is some immune basis to the response to gemcitabine/carboplatin/pembrolizumab even though these patients may be PD-L1 negative.

Multiple hypotheses are under investigation with Globo-H vaccine combinations for high-risk TNBC patients in the post or preoperative setting, with immune checkpoint inhibitors and chemotherapies. Earlier, adagloxad simolenin has shown a clinical activity in metastatic BC in patients who benefited from previous chemotherapy (Huang CS, et al. ASCO 2016. Abstract 1003). Patients who showed an IgM and IgG humoral response to this vaccine showed improvement in PFS and OS, but those who did not show humoral activity did not have benefit.
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