GLOBAL PERSPECTIVES: CURRENT AND FUTURE MANAGEMENT OF BREAST CANCER

Virtual meeting on October 5 and 14, 2020

FULL REPORT
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Current and Emerging Approaches in Triple-Negative Breast Cancer

ANDREAS SCHNEEWEISS, MD
Background

On the basis of findings from IMpassion130, international guidelines now recommend atezolizumab (A) + nab-paclitaxel (nP) for patients (pts) with locally advanced or metastatic triple-negative breast cancer (mTNBC) whose tumors express programmed cell death protein 1 ligand 1 (PD-L1) on tumor-infiltrating immune cells (IC). The authors reported prespecified final overall survival (OS) and long-term safety results.

Results

Clinically meaningful OS benefit was observed in PD-L1–positive pts (7.5-month median OS improvement). A + nP remained safe and tolerable with longer follow-up. Results from this final and mature OS analysis are consistent with prior interim analyses.

Background

> Tumor mutational burden (TMB), a surrogate for neoantigen load, is associated with improved outcomes following
ESMO LBA15: Primary results from IMpassion131, a double-blind placebo-controlled randomised phase 3 trial of first-line paclitaxel (PAC) +/- atezolizumab (atezo) for unresectable locally advanced/metastatic triple-negative breast cancer (mTNBC). D.W. Miles, et al

Background

Impassion131 (NCT03125902) evaluated atezo + solvent-based PAC as first-line treatment for mTNBC
ESMO LBA11: IMpassion031: results from a Ph 3 study of neoadjuvant (neoadj) atezolizumab + chemotherapy in early triple-negative breast cancer (TNBC). N. Harbeck, et al

Background

IMpassion031 is a global phase III, multicenter, double-blind, randomized, PBO-controlled study in pts with high-risk primary invasive early stage TNBC evaluating the efficacy and safety of neoadj A or PBO with nP followed by A or PBO with dose-dense doxorubicin + cyclophosphamide. Authors reported the primary analysis of IMpassion031

Results

Conclusion

In pts with early stage TNBC, A + neoadj chemotherapy significantly improved pathologic complete response (pCR) rates regardless of PD-L1 status, with an acceptable safety profile.

FN, febrile neutropenia; SAE, serious adverse event.
ESMO LBA13: Tumor infiltrating lymphocytes (TILs), PD-L1 expression and their dynamics in the NeoTRIPaPDL1 trial. G. Bianchini, et al

Background
> NeoTRIP randomized 280 pts to 8 cycles of nab-paclitaxel–carbo (CT) or with atezolizumab (CT-A); 260 pts were evaluable
ESMO LBA17: ASCENT: A randomized phase 3 study of sacituzumab govitecan (SG) vs treatment of physician’s choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC). A. Bardia, et al

Background

- SG (TRODELVY™) is a first-in-class antibody-drug conjugate (ADC) composed of an anti–Trop-2 antibody coupled to the active metabolite of irinotecan, SN-38, via a unique hydrolyzable linker that allows for SN-38 release intracellularly and in the tumor microenvironment (bystander effect). In the phase I/II IMMU-132-01 study, SG demonstrated 33% overall response rate (ORR) and a median PFS of 5.5 mo in pts with mTNBC with manageable safety, leading to accelerated US Food and Drug Administration (FDA) approval of SG. The randomized phase III ASCENT study was initiated to confirm those results.

Results

Conclusion

ASCENT is the first phase III study of an ADC with significant PFS and OS improvement over standard-of-care chemotherapy in pretreated mTNBC, confirming the clinical activity and safety profile of SG monotherapy.

- SG was well tolerated, with a manageable safety profile
  - AEs leading to treatment discontinuation: 4.7%
  - No severe cardiotoxicity
  - No grade >2 neuropathy
  - No grade >3 interstitial lung disease (ILD)
ESMO 348P: First findings from SYNERGY, a phase I/II trial testing the addition of the anti-CD73 Oleclumab (O) to the anti-PD-L1 Durvalumab (D) and Chemotherapy (ChT) as 1st line therapy for patients (pts) with metastatic triple-negative breast cancer (mTNBC). D. Eiger, et al

Background

The adenosine pathway has demonstrated ability to limit antitumor activity in TNBC, making CD73, the adenosine-generating enzyme, an attractive target to enhance the efficacy of immunotherapy in this disease.

Results

Besides neutropenia, the safety profile appears favorable. Carboplatin was reduced from area under the concentration-time curve (AUC) 2 to AUC 1.5.

Recommended phase II dose of oleclumab in this combination is 3000 mg.

There were preliminary signs of activity with long-lasting responses in some pts in phase I. Final efficacy results are expected in 2023.

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Early TNBC

At ESMO 2020, some potentially practice-changing data with immune checkpoint inhibitors in the early TNBC setting were presented. The IMpassion031 study and the KEYNOTE-522 study showed good concordance—Both trials showed substantial pCR improvement, and both illustrate the predictive impact of PD-L1 status with regard to chemotherapy efficacy, but not with regard to immunotherapy efficacy. It would be interesting to understand the role of TILs and the tumor microenvironment.

In Germany, it is a challenge to treat pts with immunotherapy in the early TNBC setting, as the drugs have not yet been submitted for registration for this indication. It is important to tell pts of the “lifelong-lasting side effects.” Due to the trials’ design, it remains to be seen whether an increase in pCR rate translates into a clinically meaningful improvement in disease-free survival (DFS). The chemotherapy backbone plays an important role in deriving benefit from checkpoint inhibitor treatment. Nab-paclitaxel is a good partner; however, it is not approved in early TNBC in Europe, and therefore cannot be used outside clinical trials. Importantly as well, in the adjuvant setting there is a need to further understand the role of chemotherapies in deriving clinical benefit, as a carboplatin-based regimen and dose-dense chemotherapy both increase pCR rates.
Immunotherapy has arrived in the treatment of mTNBC pts. However, it is important to understand which pts derive benefit.

In mTNBC, baseline PD-L1 status is predictive for additional benefits from checkpoint inhibitors in the first-line setting, and TMB showed correlation with clinical benefit.

Experts would like to see further work on predictive biomarkers, such as BRCA mutation, microsatellite instability, and NTRK fusion genes in TNBC.

Further translational work is needed to examine the tumor microenvironment and other immune biomarkers beyond PD-L1.

The final analysis of the IMpassion130 trial provided compelling data with the combination of atezolizumab + nab-paclitaxel in PD-L1-positive pts. There was a difference in OS vs PBO + nab-paclitaxel that was maintained over long-term follow-up.

Data from IMpassion131 showed the importance of careful chemotherapy partner selection for atezolizumab, as paclitaxel + atezolizumab combination did not demonstrate survival benefit.

It is unclear why no survival benefit was observed with atezolizumab + paclitaxel in IMpassion131. One difference noted that could offer an explanation is that there were more de novo pts in IMpassion130.
mTNBC

There is some uncertainty whether pembrolizumab could be more flexible in partnering compared with atezolizumab, as seen in the KEYNOTE-355 study, where pembrolizumab was combined with nab-paclitaxel, paclitaxel, or gemcitabine-carboplatin. There was a difference in pt selection between IMpassion130 and KEYNOTE-355 that adds further complexity to interpretation of these trials. Pts who relapsed very quickly responded well to pembrolizumab in the KEYNOTE-355 trial, where pts with disease-free interval (DFI) ≥6 months were included; however, early relapse pts were not included in the IMpassion130 study, where DFI was ≥12 months. It would be interesting to see a posthoc analysis to better understand similarities and differences between these trials.

PD-L1–positive antibody testing coupled with atezolizumab usage is not as standardized as for pembrolizumab, and in addition to its more restrictive chemo backbone choice, it was postulated that pembrolizumab may be a preferred anti–PD-L1 regimen. . . it is going to change clinical practice, because the instinct is going to be to give nab-paclitaxel rather than ordinary paclitaxel, based on the data.

Pt selection . . . we are not capturing the right patients with the biomarkers, and we have a lot of patients that are absolutely not benefiting from the combination with introduction of the PD-L1 regimen. So, I think that we are still far from having something consistent enough to be considered or shown to be a standard of care.

Gene expression signatures in mTNBC . . . as long as we have not shown that a higher pCR rate achieved with checkpoint inhibition really translates into better survival, we should not use this tool outside of clinical trials.
A third player in the metastatic setting is bevacizumab, which, in Europe, is extensively used in combination with paclitaxel.

SG is an effective treatment option in heavily pretreated pts in mTNBC, with manageable toxicity.

Oleclumab in addition to paclitaxel carboplatin + durvalumab is an interesting combination that should further be explored.

"We have optimized the use in the metastatic setting, and we all know how to deal with the toxicities as well as the combination.

"I think the nab-paclitaxel and saci data really are compelling. It's a regimen I've been using. I find it overall well tolerated in our patient population."
New Standards in HER2+ Early Breast Cancer

PETER A. KAUFMAN, MD
ESMO 165MO: Patient (pt) preference for the pertuzumab-trastuzumab fixed-dose combination for subcutaneous use (PH FDC SC) in HER2-positive early breast cancer (EBC): Primary analysis of the open-label, randomised crossover PHranceSCa study. J. O'Shaughnessy, et al

Background

Background

Results

Conclusion

PHranceSCa clearly showed that the majority of pts preferred PH FDC SC over PH IV. PH FDC SC was generally well tolerated with no new safety signals. PH FDC SC offers a quicker alternative to PH IV and reduces pts' time in the tx room.
ESMO 166MO: A phase III trial to compare the efficacy, safety, pharmacokinetics and immunogenicity of HD201 to trastuzumab in HER2+ early breast cancer patients (TROIKA).

P. Xavier, et al

Background

- HD201 is a candidate biosimilar to trastuzumab. TROIKA is a randomized, double-blind, parallel-group, equivalence study designed to compare the efficacy, safety, pharmacokinetics (PK), and immunogenicity of HD201 vs trastuzumab in pts with human epidermal growth factor receptor 2 (HER2)-positive EBC.

Results

- Equivalence in efficacy, safety, PK, and immunogenicity profiles was demonstrated between HD201 and Herceptin. TROIKA is currently in its follow-up phase. Complete safety, immunogenicity, and survival data are to follow.
ESMO 223P: Safety and tolerability of subcutaneous trastuzumab (H Sc) self-administered at home via single-use injection device (SID) in patients (pts) with HER2-positive early breast cancer (EBC): Primary and final analysis of the open-label, phase IIIB HOMERUS study. Albert J. Ten Tije, et al

Background

HOMERUS (NCT02040935) assessed safety and tolerability of H Sc monotherapy self-administered at home by trained healthcare professionals (or the trained pt under supervision, if the pt was deemed competent) via SID, in pts with HER2-positive EBC.

Results

Conclusion

H Sc administered by SID in the hospital followed by home administration was well tolerated, with findings in line with the known H safety profile. No new safety signals or problems with multiple home administrations were identified, and most pts chose continued home administration. H exposure was comparable in each setting.
Discussion
The TRAIN-2 trial, presented at the American Society of Clinical Oncology 2020 Annual Meeting, provided practice-changing results. The usage of anthracyclines may decline, as this study showed they do not improve treatment efficacy in the neoadjuvant setting and are associated with clinically relevant toxicity. However, their usage is important for high-risk HER2-positive pts, who have very poor responses to HER2-positive targeted therapy. It would be interesting to pursue translational studies on biopsies, to identify a subgroup of pts who may benefit more (eg, TOPO2 amplification).

All experts agreed that the data presented at ESMO 2020 on the fixed-dose subcutaneous (SC) formulation of pertuzumab-trastuzumab are compelling, particularly in COVID-19 times. There are major differences between healthcare systems and reimbursement policies that are important drivers of IV vs SC treatment decisions. Although SC is the preferred choice (easier, more pt friendly, time saving) it is more expensive, and this is often the main driver preventing its use in clinical practice. In the US, administration of trastuzumab SC is popular in outpatient clinics, whereas home administration is challenging and rarely utilized. In community hospitals and private practices, though, IV formulation is used more often, due to cost. Use of SC trastuzumab has dramatically dropped in some European countries (eg, Spain, UK, France) after the introduction of IV trastuzumab biosimilars. Trastuzumab biosimilars show convincing efficacy, and the possibility of SC fixed-dose formulations of trastuzumab and pertuzumab biosimilars is very appealing (although availability may be constrained by the patent formulations of the reference product).
QUOTES – NEW STANDARDS IN HER2+ EARLY BREAST CANCER

Then came the biosimilars... the price of the biosimilar and the reduction of the pricing by 70% means that you have come back for 100% of the patients to IV formulation.

...so it’s different everywhere in the world, and even regionally in the countries, so I think that Roche needs to approach this with a clever strategy if they want to get the drug into the market... it’s the reimbursement, it’s not the doctors or the patients that don’t want to do it.

I think clearly nobody disputes the fact that the biosimilars are here to stay.
Current and New Treatments in HER2+ mBC

ANTONIO LLOMBART-CUSSAC, MD, PHD
ESMO 288P: Final results from PERUSE, a global study of pertuzumab (P), trastuzumab (H) and investigator’s chosen taxane as first-line therapy for HER2-positive locally recurrent/metastatic breast cancer (LR/mBC). D.W. Miles, et al

Background

- P + H + docetaxel (DOC) is the standard first-line therapy for HER2-positive LR/mBC, on the basis of results from the phase III CLEOPATRA trial. The single-arm PERUSE study (NCT01572038) assessed the safety and efficacy of P + H with investigator-selected taxane in HER2-positive LR/mBC. Preliminary results by taxane have been reported [Bachelot T, et al. Ann Oncol. 2019;30:766-773]; authors presented final safety and efficacy results

Results

- Final results from PERUSE are consistent with CLEOPATRA, support first-line P + H + taxane therapy for HER2-positive LR/mBC, and suggest that paclitaxel is a valid alternative to DOC as backbone chemotherapy

- 26% of pts remain long-term progression-free survivors
- A Plato on relapses is observed beyond 4 years of treatment
- Median PFS: 20.7 months (95% CI, 18.9–23.1 months)
- Median OS: 65.3 months (95% CI, 60.9–70.9 months)

Background

Trastuzumab emtansine (T-DM1) is indicated for the treatment of metastatic HER2-positive BC after progression on prior trastuzumab and taxane (TT) combination. There are few data on its efficacy after pertuzumab, trastuzumab, and taxane (PTT). The present study is a regional multicenter retrospective evaluation of the activity of T-DM1 after frontline pertuzumab-based therapy.

Results

Conclusion

T-DM1 was an effective and well-tolerated treatment in routine clinical practice in pts with HER2-positive mBC after PTT. ORR, PFS, and OS were similar to pivotal studies after only the TT combination. A toxicity profile similar to TT studies was observed.
Background

- Pts with HER2-positive mBC, particularly pts with brain mets, have limited tx options and increased likelihood to report deterioration in HRQOL. In the HER2CLIMB study, tucatinib (TUC) + trastuzumab (T) + capecitabine (C) demonstrated statistically significant improvement in PFS and OS over T + C alone. In HER2+ mBC pts with and without BM, TUC + T + C had a manageable safety profile similar to T + C alone. Authors reported the impact of TUC on HRQOL, a secondary objective in HER2CLIMB.

Results

Conclusion

QOL in pts treated with TUC + T + C was maintained throughout the tx period, which was longer compared with pts receiving only T + C.
ESMO 293P: Impact of Tucatinib on Progression Free Survival in Patients with HER2+ Metastatic Breast Cancer and Stable or Active Brain Metastases. T. Bachelot, et al

Background

> Up to 50% of HER2+ mBC pts will have brain mets, for which effective treatments are needed. In the HER2CLIMB (NCT02614794) double-blind trial, TUC added to T and C resulted in statistically significant improvements in PFS and OS in HER2-positive mBC pts with and without brain mets. Risk of disease progression or death in brain mets pts was 52% lower in the TUC arm vs the control arm ($P < .001$). Authors presented exploratory analyses of PFS by type of brain mets in HER2CLIMB.

Conclusion

Addition of TUC to T and C significantly improved PFS regardless of brain mets type, indicating delay of progression not only in the body, but also in the brain. Pts with active brain mets (typically excluded from HER2-positive mBC trials) had substantially longer PFS with TUC treatment.
Background

Trastuzumab deruxtecan (T-DXd: DS-8201) is a HER2-targeted ADC with demonstrated antitumor activity and a manageable safety profile in HER2-expressing/mutated solid tumors. ILD is an important identified risk for pts treated with T-DXd. Authors reported incidence of independently adjudicated drug-related ILD events and explored potential risk factors.

Results

In this population, higher incidence of ILD related to T-DXd treatment was observed among pts from Japan and those with BC. However, these results should be interpreted with caution, given that the majority of pts in the analysis had BC.
ESMO 347P: Results of the phase 1b dose escalation study of MEN1611, a PI3K Inhibitor, combined with trastuzumab (T) ± fulvestrant (F) for HER2+/PIK3CA mutant (mut) advanced or metastatic (a/m) breast cancer (BC). M. Piccart, et al

Background

- MEN1611 is an oral phosphoinositide 3-kinase (PI3K) inhibitor active on the p110α mutant and wild-type β and γ isoforms, while sparing the δ.

Results

- Tolerability of MEN + T ± F is acceptable; most treatment-related AEs were reversible and manageable by supportive care.

Conclusion

- Promising antitumor activity in heavily pretreated pts, together with prolonged disease control, provide the rationale for cohort expansion at the recommended phase II dose in pts with HER2-positive/PIK3CA-mutant a/m BC.

Grade 3–4 AEs were not dose dependent:
- 2 hyperglycemia (grade 3)
- 1 pneumonitis (grade 4)
- 1 generalized edema (grade 3)

No dose-limiting toxicities were observed in any dose cohort.

48 mg was selected as the recommended dose for phase II studies.
Discussion

EPICS
Use of the trastuzumab-pertuzumab combination as standard treatment in the frontline setting has greatly improved survival outcomes of HER2-positive mBC in recent years. The PERUSE trial effectively built on this combination, with the addition of taxanes leading to OS >5 years.

New agents tucatinib and T-DM1 are changing the treatment landscape. The experts recognize a shift in the pattern of mBC treatment.

Tucatinib, neratinib, and T-DM1 are approved and available in the US.

- **Sequencing of agents**
  - **First line**
    - The experts keep the standard pertuzumab-trastuzumab-docetaxel combination.
  - **Second line**
    - T-DM1 is used.
    - T-DM1 is very well tolerated, and the head-to-head trial data with T-DXd are needed to assess its activity.
    - In the US, experts will consider use of the tucatinib triplet before T-DM1 for pts with brain mets.

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Sequencing of agents (cont.)

- Beyond second line
  - Choice of the novel agents in later lines is based on whether the pt has brain mets
  - If a pt has brain mets
    - Experts will use tucatinib triplet to control the disease. In pts who present with multiple brain mets, who will unlikely receive benefit from radiotherapy, surgery, or stereotactic surgery, tucatinib is a very valid option
    - The possibility of using tucatinib to prevent development of brain mets is viewed with interest, although this has not yet been adopted in clinical practice
    - Neratinib has the same half maximal inhibitory concentration as tucatinib and can be used in the same population of pts; however, management of diarrhea is more challenging with neratinib. Additionally, neratinib may be preferred in later lines to avoid potential cross-resistance with oral tyrosine kinase inhibitors (TKIs), as neratinib has an epidermal growth factor receptor effect not observed with tucatinib
  - It is important to distinguish between pts with brain mets who have been pretreated. In pretreated pts, the blood-brain barrier has been disrupted and the efficacy of a TKI or an ADC may be the same
  - In some European countries, early access programs make novel drugs available. The EU experts are more impressed with the activity and toxicity profile of tucatinib than T-DXd for pts with brain mets, and speculate that usage of novel drugs will likely be similar to that in the US
CURRENT AND NEW TREATMENTS IN HER2+ mBC (3/4)

> Sequencing of agents (cont.)

- Beyond second line
  - If a pt does not present with brain mets – T-DXd would be the preferred choice
  - ILD associated with T-DXd remains a challenge, as it is not known which pts will get it, but management of this side effect continues to improve with the ongoing trials
  - Additionally, ILD is associated with checkpoint inhibitors, and experience in close monitoring and early identification will help establish the usage of T-DXd

- Leptomeningeal disease (LMD) in HER2-positive BC
  - Pts with LMD are excluded from clinical trials, as they have very poor prognosis, but there is still much to learn on how to best manage their treatment
  - There are some ongoing clinical trials administering intrathecal trastuzumab, intrathecal immunotherapy, or the triplet with tucatinib
  - Pts who present with LMD at diagnosis or shortly thereafter are more likely to respond better to treatment than pts with very rapidly progressing LMD

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Novel HER2-positive agents

Margetuximab is an interesting drug that may be relevant to pretreated HER2+ mBC pts with low-affinity CD16A genotypes (as shown in the SOPHIA trial; an exploratory endpoint).

Immunotherapy

The KATE2 trial was mentioned (T-DM1 + atezolizumab vs T-DM1); however, experts are not impressed by the data.
In clinical practice, dual HER2 blockade + taxane chemotherapies + endocrine therapy (ET) are used in the treatment of hormone receptor (HR)-positive, HER2-positive pts. Many of these pts are overtreated, and there is a lack of data on best treatment strategies for them. In the future, it may be possible to eliminate chemotherapy usage for some of these pts. It is important to understand which pts will require chemotherapy to increase immunogenicity, and which pts can be treated effectively without chemotherapy.

There may be a role for cyclin-dependent kinase (CDK)4/6 inhibitors + HER2 agent in heavily pretreated pts (monarcHER trial), and their role in the first-line setting requires further exploration.

The ongoing PATINA trial evaluates palbociclib + dual HER2-targeted therapy + ET vs dual HER2-targeted therapy + ET after induction treatment in HR-positive, HER2-positive disease.

The DETECT V trial will assess ribociclib + dual HER2-targeted therapy + ET vs dual HER2-targeted therapy + chemo in HR-positive, HER2-positive pts.
I think around the world neratinib is already a little bit ahead of tucatinib in terms of negotiating with all the payors from country to country. So it's likely going to be around before tucatinib gets there... but I think that tucatinib, trastuzumab, capecitabine is clearly better in terms of survival benefit.

For practical terms, the diarrhea is much easier to manage with tucatinib, so it's going to be the de facto drug, there's no doubt about it.

I think that this may be some sort of new paradigm that we're coming into, more of a brain met prevention paradigm where we use TKIs earlier.

Until I see the data of the head-to-head from trastuzumab deruxtecan against T-DM1, that's going to be my standard go-to regimen.

But I think the IO [immunotherapy] story doesn't feel right for the HER2 group at the moment, for whatever reason.
EPICS

New Standards in HR+, HER2–Early Breast Cancer

JOSEPH GLIGOROV, MD, PHD
EBCC ORAL-018: Recommendations from the European Commission Initiative on Breast Cancer on multigene tests to guide the use of adjuvant chemotherapy in patients who have hormone receptor positive, HER-2 negative, lymph node negative or up to 3 lymph nodes positive invasive breast cancer. P.G. Rossi, et al

Background

The European Commission Initiative on Breast Cancer (ECIBC) Guidelines Development Group (GDG) prioritized the following question for the European Guidelines on Breast Cancer Screening and Diagnosis: “Should multigene tests be used in pts who have HR-positive, HER2-negative, lymph node-negative or up to 3 lymph nodes positive invasive BC, to guide the use of adjuvant chemotherapy?”

Conclusion

For women with HR-positive, HER2-negative, lymph node-negative invasive BC, the ECIBC’s GDG suggests the use of 21-gene recurrence score (RS) to guide use of chemotherapy (conditional recommendation; very low certainty of the evidence).

The GDG suggests use of the 70-gene signature (GS) for women at high clinical risk who have HR-positive, HER2-negative, lymph node-negative or up to 3 lymph nodes positive invasive BC (conditional recommendation; low certainty of evidence).

Results: Evidence to decision framework
EBCC ORAL-007: Clinical utility of MammaPrint testing in invasive lobular carcinoma (ILC): results from the MINDACT phase III trial. O. Metzger, et al

**Background**

> Chemotherapy treatment decision for pts diagnosed with ILC remains controversial. The authors investigated the clinical utility of

Background

- Invasive lobular breast cancer is the second most common BC subtype. Clinicopathologic parameters associated with lobular BC

Results

- Lobular BC is associated with low/intermediate RS, although 5-year DFS is similar to non-lobular BC

Conclusion

- The prognostic impact of RS in the lobular subtype appears to be distinct from that in non-lobular BC. For risk assessment, RS thus needs to be complemented by clinicopathologic parameters for therapy decision.

CONTACT US TO OBTAIN A COPY OF THE FULL REPORT
Background
>
Superior treatment options are needed to prevent early recurrence and development of metastases for pts with HR-positive.

Background

> Palbociclib (P) added to ET improves PFS in HR-positive, HER2-negative mBC. The global PALLAS trial (NCT02513394) was designed to determine if the addition of 2 years of P to adjuvant ET improves IDFS over ET alone in pts with HR-positive, HER2-negative early stage BC.

Results

Conclusion

Within the PALLAS trial, at the second interim analysis, 2 years of adjuvant palbociclib with ET did not improve IDFS compared with ET alone. Ongoing long-term follow-up and additional clinical and translational analyses will explore the effect of P in this pt population.
PENELLOPE-B trial of palbociclib in early breast cancer did not meet its primary endpoint. 
Press release on October 9, 2020

Background

The phase II GeparOLA study randomized pts with homologous recombination deficient (HRD), HER2-negative EBC to receive neoadjuvant treatment with paclitaxel 80 mg/m² IV weekly + olaparib tablets 100 mg orally (PO) twice daily for 12 weeks or paclitaxel + carboplatin AUC 2 IV (PCb) weekly for 12 weeks (PCb) prior to epirubicin-cyclophosphamide. Authors determined pCR (ypT0/is ypN0) according to treatment arm and germline mutation status

Results

Conclusion

Even in pts with HRD tumors, germline BRCA1/2 mutation status predicts therapy outcome. For pts without BRCA1/2 mutations, higher pCR rates were observed in the PO arm vs the PCb arm. Results should be interpreted with caution due to limited sample size, but may guide future clinical trials.

CONTACT US TO OBTAIN A COPY OF THE FULL REPORT
Discussion
NEW STANDARDS IN HR+, HER2– EARLY BREAST CANCER (1/2)

CDK4/6 inhibitors in the adjuvant setting

Data presented at ESMO for the monarchE (ET±abemaciclib) showed a 25.3% reduction in the risk of invasive disease at 2 years. Although experts agreed on the importance of collecting long-term data (4–5 years), the results of monarchE are impressive, and if the data hold with time and abemaciclib receives a label extension, it will be practice changing in high-risk pts.

In contrast, the PALLAS trial (ET±palbociclib) showed no significant difference in IDFS at 3 years. Experts believe there may be a variety of reasons for the differences observed in PALLAS and monarchE—Risk factors: pts in the PALLAS study were a lower-risk group who may relapse late compared with pts in the monarchE study, who were high-risk and may relapse earlier. In the low-risk pts in PALLAS, relapse may be observed after 3 years, whereas the trial was set up to analyze IDFS at 2 years.

Given the good response of pts with metastatic disease to frontline CDK4/6 inhibitors, it was hypothesized that the response to abemaciclib in the monarchE trial already observed at the 16-month follow-up may have been due to some high-risk pts having metastatic disease, not detected by staging at the time of inclusion.

Pts who recur early are primary ET resistant, and there may be a difference in how pts respond to palbociclib and abemaciclib in this pt population.

Differences in PK and exposure to the drugs (requirement for continuous dosing with abemaciclib)

There was a comment that the PALLAS trial was stopped too early, and given that there were no safety concerns, the trial should have continued, as the effects of palbociclib may have appeared later.
NEW STANDARDS IN HR+, HER2– EARLY BREAST CANCER (2/2)

Optimizing the use of CDK4/6 inhibitors

Although abemaciclib and palbociclib are both CDK4/6 inhibitors and have similar efficacy profiles in the metastatic setting, their pharmacologically distinct CDK inhibitory profiles may influence the differential efficacy effect observed in the adjuvant setting. On the basis of trial data thus far, experts will not use palbociclib in the adjuvant setting. Importantly, the toxicity profile of abemaciclib should not be ignored, especially thromboembolic events. Experts agreed the adjuvant data may, in due time, influence the choice of CDK4/6 inhibitors in the metastatic setting (palbociclib, abemaciclib, and ribociclib), also in the context of endocrine-sensitive vs endocrine-resistant pts or pts who have received prior chemotherapy (as shown in PALOMA-3, EBCC ORAL-009). It was noted that in Italy, on the basis of trial data from the metastatic and adjuvant settings, more physicians would now consider abemaciclib in place of palbociclib in metastatic disease. An important consideration for these adjuvant regimens is what happens after pts are taken off the drug, and the concern for a “rebound” effect after treatment with CDK4/6 inhibitors.
KEY QUOTES – CDK4/6 INHIBITORS IN THE ADJUVANT SETTING

“...PALLAS and PENELOPE weren’t positive...and palbociclib will never be used in the adjuvant setting.”

“So abemaciclib has got that space in the high-risk women, but it’s not an easy drug to use.”

“[PALLAS and monarchE trials]...we must collect long-term data.”

“[MONARCH trial] I think that really is the concern. It’s what happens when everybody’s off the drugs?”

“[Abemaciclib and palbociclib]...there may be some inherent different impact for the 2 molecules. Clearly, the side-effect profile is very different, demonstrating that their physiological effect is somewhat different as well.”

“I think that monarchE data is definitely practice changing and we’ll use that in clinical practice once the label extension is there.”

CONTACT US TO OBTAIN A COPY OF THE FULL REPORT
NEW STANDARDS IN HR+, HER2– EARLY BREAST CANCER (1/2)
Multigene tests for HR-positive EBC

Both MammaPrint and Oncotype DX® have reliable and robust data sets. Experts agreed the tests should not be performed in low-risk pts. The utility of the tests is to identify pts who qualify for de-escalation strategies. The tests could be used for high-risk non-classical lobular breast cancer. In this instance, the quality of the pathology report is very important, to ensure accurate distinction between classical and non-classical lobular BC. Additionally, it would be necessary to look at other clinical risk factors besides the results of the diagnostic test, before deciding on a de-escalation strategy for a pt with high-risk non-classical lobular BC.
NEW STANDARDS IN HR+, HER2– EARLY BREAST CANCER (2/2)

Poly(ADP-ribose) polymerase (PARP) inhibitors in HRD BRCA-mutated pts, in the neoadjuvant setting

Experts agreed that the results of the GeparOLA trial (paclitaxel + olaparib vs paclitaxel + carboplatin) show signals that should be followed up in the HR-negative vs the HR-positive population.

Although the study is small and it is still early to use PARP inhibitors in BRCA-mutated pts in the neoadjuvant setting, the signals are interesting to pursue in further trials. “. . . numbers are very small, they are hypothesis generating, it’s interesting, but it’s not for daily practice, so I would go with carboplatin, if I would have to escalate, and I would not use olaparib outside of studies.”
Recent Developments and Evolving Treatments in HR+, HER2– Metastatic Breast Cancer

ADAM BRUFSKY, MD, PHD
ESMO LBA18: Overall Survival (OS) Results From SOLAR-1, a Phase 3 Study of Alpelisib (ALP) + Fulvestrant (FUL) for Hormone Receptor-Positive (HR+), Human Epidermal Growth Factor Receptor 2-Negative (HER2–) Advanced Breast Cancer (ABC). F. André, et al

Background

> PI3K pathway hyperactivation due to *PIK3CA* mutations contributes to poor survival in pts with HR-positive, HER2-negative advanced BC. In the phase III SOLAR-1 trial of pts with progression on/after aromatase inhibitor (AI), the PI3Kα inhibitor ALP together with FUL significantly improved PFS in the *PIK3CA*-mutant cohort. At final PFS analysis, the first interim OS results were immature.

Results

Conclusion

Though not statistically significant, OS was prolonged by a clinically relevant ~8 mo with ALP when added to FUL in HR-positive, HER2-negative, *PIK3CA*-mutant advanced BC. Median time to chemotherapy was also prolonged with ALP + FUL vs PBO + FUL. Coupled with the statistically and clinically significant PFS, these data further support ALP + FUL in this poorer prognosis population of pts with *PIK3CA*-mutant advanced BC.
ESMO 273O: nextMONARCH: Final overall survival analysis of abemaciclib monotherapy or in combination with tamoxifen in patients with HR+, HER2- metastatic breast cancer. E.P. Hamilton, et al

Background

In the phase II nextMONARCH study, primary analysis of PFS and ORR confirmed the robust single-agent activity of abemaciclib in heavily pretreated HR+ positive, HER2-negative mBC with no significant improvement by addition of tamoxifen. Authors reported the final 24-month OS results.

Results

Addition of tamoxifen to abemaciclib provided a statistically significant median OS improvement compared with abemaciclib monotherapy in this heavily pretreated HR- positive, HER2- negative mBC pt population. PFS was consistent with the primary results of nextMONARCH, with no significant difference. No new safety findings were observed.
ESMO 277MO: SAR439859, an oral selective estrogen receptor (ER) degrader (SERD), in ER+/HER2- metastatic breast cancer (mBC): Biomarker analyses from a Phase 1/2 study.
S. Chandarlapaty, et al

Background

- SAR439859 has antitumor activity in pts with wild-type and mutated ESR1 mBC. Authors described tumor molecular features and
ESMO 278MO: cfDNA analysis from Phase 1/2 study of lerociclib (G1T38), a continuously dosed oral CDK4/6 inhibitor, with fulvestrant in HR+/HER2- advanced breast cancer patients. B. Krastev, et al

Background

Lerociclib, dosed twice-daily with no drug holiday in combination with fulvestrant, has a favorable safety profile with low rates of gastrointestinal AEs and grade 3/4 neutropenia, as well as encouraging antitumor activity in pts with HR- positive, HER2- negative advanced BC. Cell-free DNA (cfDNA) analysis in peripheral blood was conducted to characterize mechanisms of response and resistance in pts who received lerociclib and fulvestrant.

Results

Conclusion

The most common baseline mutations detected were PIK3CA and ESR1. Additional analyses, including cycle 1 day 15 change from baseline and correlation with clinical response, are anticipated, to help elucidate predictors of response and/or resistance to the combination of lerociclib and fulvestrant in pts with HR- positive advanced BC.
ESMO 283MO: Ipatasertib (IPAT) + paclitaxel (PAC) for PIK3CA/AKT1/PTEN-altered hormone receptor-positive (HR+) HER2-negative advanced breast cancer (aBC): Primary results from Cohort B of the IPATunity130 randomised phase 3 trial. N. Turner, et al

Background

> PI3K/protein kinase B (AKT) pathway alterations occur in ~50% of HR-positive BC. In a phase II trial in advanced TNBC. adding
ESMO 329P: Ribociclib (RIB) in patients (pts) with HR+/HER2− advanced breast cancer (ABC) and resistance to prior endocrine therapy (ET) in the MONALEESA (ML) -3 and -7 trials. S.A. Hurvitz, et al

Background

ET resistance is a challenge in the treatment of pts with advanced BC. RIB + ET demonstrated significant OS benefit vs PBO in postmenopausal and pre- and perimenopausal pts with HR-positive, HER2-negative advanced BC. Authors reported outcomes (including 6-mo PFS rate and OS) associated with RIB + ET in pts with ET-resistant disease in ML-3 and -7.

Results

Conclusion

Among pts with ET resistance in ML-3 and -7, RIB demonstrated a greater estimated 6-mo PFS rate than PBO. In both trials, the median PFS in pts with ET resistance treated with RIB was more than twice as long compared with PBO. In ML-3 and -7, RIB treatment led to a 30% and 41% respective relative reduction in risk of death in pts with ET resistance.

Background

The mechanistic target of rapamycin complex 1 inhibitor everolimus (EVE) in combination with the AI exemestane (EXE) is approved for treatment of HR-positive, HER2-negative advanced BC pts whose disease progressed on/after prior nonsteroidal AI therapy. However, the efficacy of EVE-EXE after tumor progression on CDK 4/6 inhibitors is unknown.

Results

Prior CDK 4/6 inhibitor-containing treatment is associated with poorer efficacy of EVE-EXE in HR-positive advanced BC pts. Pts treated with EVE-EXE as first-line therapy had the longest PFS. Prospective data are needed to define the role of EVE-EXE in the era of CDK 4/6 inhibitors.
ESMO 2740: Health-related quality of life (HRQoL) changes with veliparib in patients (pts) with metastatic or locally advanced breast cancer in the Phase 3 BROCADE 3 study. V. Dieras, et al

Background

Veliparib, a PARP1/2 inhibitor, was evaluated in the phase III BROCADE 3 study for efficacy and safety in combination with paclitaxel-carboplatin (VPC) in pts with HER2-negative metastatic or locally advanced unresectable germline (g) BRCA-associated BC, in which VPC significantly prolonged PFS. In this analysis, authors investigated the impact of veliparib on HRQOL.
276O: Pooled analysis of patient (pt)-reported quality of life (QOL) in the MONALEESA (ML)-2, -3, and -7 trials of ribociclib (RIB) plus endocrine therapy (ET) to treat hormone receptor–positive, HER2-negative (HR+/HER2−) advanced breast cancer (ABC). P.A. Fasching, et al

Background

Pt-reported QOL results have been presented separately for each phase III ML trial, which tested efficacy and safety of RIB with

Results

Conclusion

In pts receiving first-line ET across the ML trials, RIB delayed deterioration in QOL. Time to deterioration (TTD) for global health status (GHS), pain, and emotional functioning scores was longer with RIB vs PBO. Overall, this large, robust analysis demonstrated favorable QOL results with the addition of RIB to ET in pts with HR-positive, HER2-negative advanced BC

Background

> In PALOMA-3. ET-sensitive pts with HR-positive, HER2-negative advanced BC and disease progression on prior ET derived OS

CONTACT US TO OBTAIN A COPY OF THE FULL REPORT
Discussion
RECENT DEVELOPMENTS AND EVOLVING TREATMENTS IN HR+, HER2– METASTATIC BREAST CANCER

CDK4/6 inhibitors in the metastatic setting

- Ribociclib has shown promising efficacy results (PFS and OS) in MONALEESA-3 and -7 in the endocrine-resistant population, and in pts with liver metastases.
- If abemaciclib (monarchE data) receives regulatory approval in the adjuvant setting for high-risk pts, many of the pts who receive it will recur 1–2 years after treatment. How this will impact sequencing in the metastatic setting remains an open question.
- By then, other novel agents may be available, eg, oral selective estrogen receptor downregulators (SERDs; if trials are positive), AKT inhibitors; other CDK4/6 inhibitors may be used or abemaciclib reintroduced (as pts will have been off abemaciclib for 1–2 years already).
- Depending on their tolerability and efficacy, the question of rechallenge with CDK4/6 inhibitors may be relevant.
- In the metastatic setting, upon progression on abemaciclib, reintroduction of abemaciclib is not favored, as there will have been no treatment break. Switching to another CDK4/6 inhibitor may be an option, and the choice will be influenced by manageability of the drug. Nevertheless, usage of CDK4/6 inhibitors should remain in earlier lines in the metastatic setting, where they have greater efficacy.
- If the OS data for the ongoing pivotal first-line trials in the metastatic setting (MONARCH, MONALEESA) are positive, this will be compelling regarding rechallenging pts with CDK4/6 inhibitors.
"...many of them will recur a year or 2 after completion of their adjuvant abema, and until we have any data that really impacts on treatment in the metastatic setting, my usage will still not really change very much. I still tend to recommend a CDK4/6 inhibitor, particularly abema, as a metastatic therapy."

"If someone had never had abema or if they were progressing quite soon after it and I could get access to another CDK4, I would switch, just because it's easier to use a different drug."

"...in the metastatic setting, I'm still not convinced that the drugs are very different in efficacy, but they're clearly different in manageability. Palbo is the easiest to use, I would say."

[Regarding risk of thromboembolic events] "I don't see myself giving tamoxifen and abema in a hurry. I'll mix tamoxifen with most things, but probably not abema."

[CDK4/6 inhibitor data in adjuvant setting and influence in the metastatic setting] "My prediction is, in the US these data will start to lead to an increase in the use of abema vs palbo, but we'll see how that plays out."

"One thing we know for sure is that if you use CDK4/6 too late in the metastatic setting, it's not very helpful."

[MONALEESA-3 and -7] "...ribo is coming on as an agent that looks good in primary endocrine therapy refractory and in liver mets."
RECENT DEVELOPMENTS AND EVOLVING TREATMENTS IN HR+, HER2– METASTATIC BREAST CANCER (1/2)

> Alpelisib in the metastatic setting

- OS data (secondary endpoint) from SOLAR-1 presented at ESMO, although not statistically significant, showed encouraging signals for pts with PIK3CA mutation

- In a hypothetical situation, where a high-risk pt with PIK3CA mutation treated with abemaciclib in the adjuvant setting had relapsed, alpelisib frontline would be considered, if there are no safety concerns with the pt

- With alpelisib it will be important to better manage the toxicities and understand who will benefit

> “...I think most of us, if someone does have a PI3 kinase mutated tumor and the drug is available, they will get alpelisib + fulvestrant.”
RECENT DEVELOPMENTS AND EVOLVING TREATMENTS IN HR+, HER2– METASTATIC BREAST CANCER (2/2)

- The advent of new biomarkers in the metastatic setting calls for the need to rebiopsy pts and collect metastatic tissue.

- Oral SERDs in the metastatic setting

  - Compared with fulvestrant
    - Oral therapy is preferred by pts compared with fulvestrant injections (2 injections/month)
    - However, in the US, price of oral therapy remains an issue
  - The toxicity of these agents is a concern (bradycardia, ocular toxicities)
    - Experts agreed SAR439859 is among the oral SERDs with a manageable safety profile

- The predictive role of the choice of ET or SERDs + CDK4/6 inhibitor vs ET or SERDs alone is unclear in ESR1-mutated pts
  - There may be a role for single-agent SERDs in a subset of pts with ESR1 mutation

- The caveat to current SERDs trials is that they are in the frontline race with CDK4/6 inhibitors + AI. Fulvestrant, however, has shown activity in ESR1-mutated pts, and the opportunity to compare it with SERDs in ESR1-mutated pts in second line is being missed

- If SERDs demonstrate superior efficacy and safety (compared with AIs) in the metastatic setting, there could be an opportunity for them to move to the adjuvant or the neoadjuvant setting (the latter would be less of a risk if the drug fails, as follow-up times are shorter than in the adjuvant setting). The question remains whether this will be ± CDK4/6 inhibitor
  - As first-line data from metastatic trials will take a long time to read out, robust first-line single-agent data regarding safety and efficacy may suffice to move oral SERDs to an adjuvant or neoadjuvant trial.

CONTACT US TO OBTAIN A COPY OF THE FULL REPORT
KEY QUOTES – ORAL SERDS IN THE METASTATIC SETTING

"I think that the studies are looking at replacing fulvestrant, and that is likely where they will first go if they're superior to fulvestrant.

. . . if they're better than the current agents in the metastatic disease or at least as good, they might fly into the adjuvant setting or they'll end up in a nice little niche, perhaps for the clearly detected ESR1 mutations.

I'm a little bit confused about the positioning of the different companies on this setting, because they are really trying to look for the big price concerning the first-line, but not so much on the secondary options in the second-line for ESR1 mutation patients.

I'm not so convinced that we should go too fast to the adjuvant setting, because we will lose a lot of money and a lot of patients. So I really would be happy to see more data from the metastatic setting to do this step.

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RECENT DEVELOPMENTS AND EVOLVING TREATMENTS IN HR+, HER2– METASTATIC BREAST CANCER

- Oral taxanes in the metastatic setting

  Results of the CONTESSA trial (capecitabine ± tesetaxel) are very encouraging for the use of an oral taxane in the metastatic setting; however, with all the current and novel agents (eg, ADCs, selective androgen receptor modulators), chemotherapy will be moving to later lines.

  Another oral chemotherapy that will be coming to the mBC space is oral paclitaxel and encequidar (Athenex), expected to be approved by FDA in February 2021.

  “...this is really an advance for patients, but we've learned from the past trials that we will see chemotherapy later and later in the luminal metastatic breast cancer, and just because the taxane is not old doesn't mean that we have to give it earlier.”

  “There’s a whole bunch of things, the standard chemo is going to go to eighth line because we have so many other things to use in the setting, and our dilemma is going to be what to use. Is it going to benefit if one is given after the other? Expense, approval, that's where we're going in this setting.”