ASCO 2020

Rupert Bartsch^a Veronique Dieras^b Javier Cortes^c Volkmar Müller^d
Thomas Ruhstaller^e

^aDepartment of Medicine 1, Division of Oncology, Medical University of Vienna, Vienna, Austria;

^bCentre Eugène-Marquis, Rennes, France; ^cIOB Institute of Oncology, Quiron Group, Madrid & Barcelona, Spain;

^dDepartment of Obstetrics and Gynecology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;

^eBreast Center Eastern Switzerland, St. Gallen, Switzerland

Question 1: What Is the Role of Local Therapy Such as Surgical Resection of the Primary Tumor in Stage IV Disease in Your Practice? Will There Be Any Change after ASCO 2020?

Dieras: Local therapy for de novo metastatic breast cancer is still debated. Two randomized trials published conflicting results with some caveats in the design (lack of standard treatment in one and time to randomization in another one). The French ESME database demonstrated a positive impact of local therapy on overall survival for patients with ER+ or HER2+ metastatic breast cancer. However, we acknowledge the bias of retrospective studies as only patients with a better prognosis are offered such treatment. The ECOG-ACRIN Research Group (E2108) presented the results of a phase III randomized study addressing the impact of local therapy after 4–8 months of systemic therapy with overall survival as the primary endpoint. They didn't observe a significant difference between the two arms (median: 54 months in the two arms) but there were fewer local relapses in the locoregional treatment. For triple-negative MBC, there was a trend of a deleterious effect of local treatment with the limits of a small size.

In my opinion, local treatment should be discussed on a case-by-case basis with the patient but probably there is a positive impact in oligometastatic disease with the option of local treatment of metastatic sites with surgery and/or radiotherapy. In this population we may even expect a cure for the disease. The negative impact for TNBC, also observed in the ESME database, may be explained by

the dismal prognosis of this population and the fact that during local treatment the systemic treatment is discontinued.

Müller: For me this presentation of Khan et al. (abstract LBA 2) was one of the highlights of ASCO 2020. Patients with metastatic disease at diagnosis of breast cancer often ask for surgery of their primary tumor. Having seen two studies from India and Turkey with, at least for me, confusing results, Khan et al. evaluated a treatment setting with adequate systemic therapy. Patients received systemic therapy and were randomized to systemic therapy alone or additional surgery of the primary tumor. The results are clear: no advantage for the primary endpoint OS with additional surgery of the primary tumor – moreover, no improvement in QOL. These results help us to counsel our patients in this clinical setting. Nevertheless, I think that patients should have the option to choose surgery in individual cases after learning about these findings.

Ruhstaller: We learned from ASCO 2020 that surgical resection is not changing the overall survival, progression-free survival, or quality of life of the patients and should not be offered in general to patients with systemic metastases.

On an individualized basis, for example for a patient with well-controlled systemic disease and locally progressive disease, it can be considered.

The research should now focus more on oligo-metastatic patients with biologically well-targetable disease to combine systemic and local therapy with the intention of hopefully curing such patients in the future. In such a

highly selected patient population, the distinction between curative and palliative situations is becoming less sharp than in the past.

Question 2: The First Results of the Phase III KEYNOTE-355 Trial Have Been Presented at This Year's ASCO Annual Meeting. How Do These Data Compare with IMpassion 130? What Developments Do You Expect in the Near Future?

Dieras: KEYNOTE-355 is the second phase III trial addressing the value of adding immunotherapy to chemotherapy as first-line therapy for triple-negative metastatic breast cancer. This trial differs from IMpassion130 in the inclusion criteria (free interval >6 months), the statistical design, the cytotoxic partner (taxane or gemcitabine-carboplatin), and the selection of CPS instead of PD-L1 expression on immune cells (IC). The trial demonstrates a statistically significant improvement of progression-free survival in patients with CPS ≥ 10 . So this is the second positive trial with immunotherapy in triple-negative breast cancer but clearly only approximately 40% of patients are candidates for this option.

There are still many questions to be answered:

- What is the impact on overall survival? The data are eagerly awaited.
- How to better select patients: PD-L1 (IC) or CPS? In clinical practice it would be useful to select one and we should suggest the same work as for IMpassion130 to compare the different antibodies and CPS in order to select the companion test for IO in clinical practice.
- Which chemotherapy is the best partner? The trial doesn't give a definitive answer but it suggests, if patients have received prior cytotoxic chemotherapy in an early setting, giving another regimen.
- The best sequencing: we observed a low efficacy of immunotherapy after first line. The SAFIR-02 trial may suggest a role for maintenance therapy.

We also have to consider, if immunotherapy with a longer follow-up of the neoadjuvant study demonstrates a clear benefit in overall survival, which place it should have in a metastatic setting (rechallenge? another combination?).

Cortes: I think it is great data. Of course, we need to see OS, but in the meantime, the HR for PDL1 CPS 10 or higher is very good (HR = 0.65), with significant improvement in the median PFS (from 5.6 to 9.7 months). Also, the opportunity of being combined with different chemo agents is important in clinical practice. HR is very similar to IMpassion130 in PDL1+ patients, although the median PFS improvement was slightly better with pembro. Both drugs are very important to treat these patients. Let's see OS data in both studies.

Müller: Also for me these are importing findings. The abstract that was presented by Cortes et al. adds two new treatment perspectives to the setting of the IMpassion130 trial as first-line therapy for triple-negative patients with PDL-1 expression besides using another checkpoint inhibitor: (1) patients were also allowed to receive a nontaxane combo with carbo/gemcitabine, and (2) inclusion was also allowed for patients with recurrence between 6 and 12 months. Therefore, I am also anxiously waiting for the OS results. One challenge that should be kept in mind is standardization of testing as the European approvals usually do not define the test method. For pembrolizumab in the trial, the CPS score was used with a defined antibody and I hope that it will be possible to set up comparable testing conditions with other tests.

Ruhstaller: The expression of PD-L1 also determines the effect of pembrolizumab. Consistent with IMpassion130 no benefit was seen in TNBC without PD-L1 expression (CPS <1), but so far we have only positive PFS data for pembrolizumab. In the IMpassion130 study with atezolizumab also an impressive overall survival benefit was shown. However, in the Keynote-355 different chemotherapies were concomitantly used instead of only nab-paclitaxel as in the IMpassion130 trial; that is opening new options for us in daily practice also regarding toxicity like hair loss. The best cut-off for PD-L1 expression remains unclear.

Question 3: How Much De-Escalation Is Already Possible in HER2-Positive Early-Stage Breast Cancer? Do You Believe that Anthracyclines Are Still Required?

Dieras: The TRAIN study compares an anthracycline taxane-based regimen versus carboplatin-paclitaxel with dual blockade in the two arms for HER2+ stage II–III breast cancer. It is important to note that it was a high-risk population (64% N+, 33% stage III, and 42% HR–). The pCR rates were similar and high in the two arms (respectively, 68 and 67%) as the event-free survival. As expected, there was less of a decrease in LVEF in the carboplatin arm.

Clearly these results are interesting:

- The duration of chemotherapy is less than that of the “standard regimen” (4 cycles of anthracycline and 12 of paclitaxel trastuzumab). A dual blockade may thus decrease the duration of chemotherapy.
- For patients with a high risk of cardiac toxicity (age and a prior history of HTA), carboplatin-paclitaxel with dual blockade is a good option.
- However, for the others we would like to have predictive biomarkers for the response to anthracyclines. In France, the NEOTOP study evaluates the pCR according to topoisomerase II amplification in a randomized

study with two arms anthracycline-based and carboplatin with dual blockade.

It is also important to note that the KAITLIN study addressing the role of T-DM1 in the adjuvant setting was negative on the primary endpoint, but we should point out that the iDFS was 94% at 3 years in the control arm. Clearly we should stop these large adjuvant trials focusing on the neoadjuvant setting in order to select better candidates for de-escalation or escalation approaches.

Cortes: How much de-escalation is already possible in HER2-positive early-stage breast cancer? Do you believe that anthracyclines are still required?

I am not sure that TRAIN-2 is enough to de-escalate anthracyclines. Non-taxane-based cycles are not a standard of care, so their clinical use should be restricted to clinical trials. In my opinion, strategy-based studies such as PHERGAIN might help to de-escalate chemotherapy in the future

Müller: I share the view of Prof. Cortes and also think we should consider strategies to de-escalate the taxane part of the chemo regimes in the long term as we tend to neglect the relevant impact of neurotoxicity in our patients. For me, the trial setting would be to shorten chemo before surgery and use additional compounds in those patients without a pathologic complete response. This was in part already examined in trials of the WSG, although treatment after surgery was not randomized. In this context the PHERGAIN trial is also of great relevance.

Ruhstaller: Regarding efficacy the Dutch trial confirms that we can de-escalate the chemotherapy in HER2-positive disease in the neoadjuvant setting and abandon the anthracyclines, even if taking into account higher-risk patients with cN2/cN3 disease.

Regarding safety, the arm without anthracyclines showed less cardiotoxicity and less secondary malignancies, particularly acute leukemia, as seen in previous trials. The rate of neuropathy was not increased in a relevant way according to the presentation.

Question 4: Have There Been Any Data on Prognostic or Predictive Biomarkers that May Find Their Way into the Clinical Practice in the Near Future? Do You Believe that the Role of PARP Inhibitors May Expand beyond the Group of Patients with Germline BRCA Mutations?

Dieras: The presentation biomarkers in MONALEESA studies from Fabrice André are of great interest, generating hypotheses and new drug developments but with no clinical impact on the selection of patients.

The TBCRC 048 phase II study addressed the potential role of PARP inhibitors in patients with germline muta-

tions other than BRCA (cohort 1) or with a somatic mutation (cohort 2). The results are very interesting for the PALB2 germline mutation, with a response rate of 33% and a median duration of 9 months. For cohort 2, the response rate was 50% only in patients with somatic BRCA mutations. It is important to note that the responses were observed in all molecular subtypes (luminal, triple negative or HER2+), addressing the question of genomic sequencing in all patients. The number of patients screened for this study was not presented.

Müller: The presentation of Tung et al. (abstract 1002) was one of my highlights. It is difficult to imagine that PARP inhibitors work only on patients with germline BRCA mutations. In this context, the small study with only 54 patients has examined two cohorts: one with germline mutations apart from BRCA 1 and 2 that are potentially involved in DNA damage repair and one with patients with somatic (tumor) mutations of BRCA 1 or 2. For the first cohort with germline mutations, a response was only observed in patients with PALB2, with 9 out of 11 patients showing a response. An encouraging response was also seen in patients with somatic mutations in the tumor, with 38.5% response. Although these results could only be considered as hypothesis generating, I believe that especially the evidence for germline PALB2 is extremely encouraging.

Ruhstaller: For a long time, I thought that BRCAness was not an optimal target for PARP inhibition in breast cancer – this in contrast to ovarian cancer. However, some proof-of-principle studies showed that we have to differentiate more between “BRCAness,” germline PALB2 mutation, and somatic BRCA mutation predicted response to olaparib, others like CHEK2 or ATM mutations not. We will learn a lot more in the near future.

Participants

Dr. Veronique Dieras
Centre Eugène-Marquis
Avenue Bataille Flandres-Dunkerque
35042 Rennes, France
v.dieras@rennes.unicancer.fr

Dr. Javier Cortes
Head, Breast Cancer Program
IOB Institute of Oncology, Madrid & Barcelona
Plaça d'Alfonso Comín, 5
08023 Barcelona, Spain
jacortes@vhio.net

Prof. Volkmar Müller
Department of Obstetrics and Gynecology
University Medical Center Hamburg-Eppendorf
Martinistrasse 52
20246 Hamburg, Germany
v.mueller@uke.de

Prof. Thomas Ruhstaller
Breast Center Eastern Switzerland
Schuppisstrasse 10
9016 St.Gallen, Switzerland
Thomas.Ruhstaller@bz-ost.ch

Conflict of Interest Statement

Rupert Bartsch: advisory role in Astra-Zeneca, Celgene, Daiichi, Eisai, Eli-Lilly, MSD, Novartis, Pfizer, Pierre-Fabre, Puma, Roche, and Samsung; lecture honoraria from Accord, AstraZeneca, BMS, Celgene, Eli-Lilly, Novartis, Pfizer, Pierre-Fabre, Roche, and Sandoz; and research support from Daiichi, MSD, Novartis, and Roche.

Veronique Dieras: consultant/advisory board for Roche/Genentech, Novartis, Lilly, Pfizer, AstraZeneca, Eisai, AbbVie, MSD, Daiichi Sankyo, and Seattle Genetics.

Javier Cortes: consulting/advisor for Roche, Celgene, Cellestia, AstraZeneca, Biothera Pharmaceutical, Merus, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Servier, Merck Sharp&Dohme, GSK, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, and Kyowa Kirin; honoraria from Roche, Novartis, Celgene, Eisai, Pfizer, SamsungBioepis, Lilly, Merck Sharp&Dohme, and Daiichi Sankyo; research funding to the institution from Roche, Ariad Pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer Healthcare, Eisai, F. Hoffmann-La Roche, Guardanth Health, Merck Sharp & Dohme, Pfizer, Piquar Therapeutics, Puma C, and Queen Mary University of London; and stock, patents, and intellectual property from MedSIR.

Volkmar Müller: consultant for Genomic Health, Hexal, Roche, Pierre Fabre, Amgen, ClinSol, Novartis, MSD, Daiichi-Sankyo, Eisai, Lilly, Tesaro, and Seattle Genetics and Nektar; and institutional research support from Novartis, Roche, Seattle Genetics, and Genentech.

Thomas Ruhstaller: consultant/advisory boards for Roche/Genentech, Novartis, Lilly, and AstraZeneca.