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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

# ESMO Breast Cancer 2019

## 2-4 May 2019

## Berlin, Germany

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## Summary

The first European Society for Medical Oncology (ESMO) Breast Cancer showed great promise of becoming a highly anticipated annual event in the oncology community. It was held from 2 to 4 May 2019 in Berlin, Germany, and demonstrated ESMO's commitment to advancing breast cancer research and integrating research results into the clinic to ensure better care for patients. Oncology professionals assembled to hear a comprehensive overview of practice-changing new data, to discuss current issues, and to take part in the networking opportunities. A total of 1'646 participants attended this new event, which welcomed delegates from 94 countries. Information, communication, education, and expertise coalesced during the first ESMO Breast Cancer to create a unique experience that will be annually repeated in the upcoming years. A brief summary of some of the advances in breast cancer research and treatment that were presented at the ESMO Breast Cancer 2019 follows.

## Introduction

The first European Society for Medical Oncology (ESMO) Breast Cancer showed great promise of becoming a highly anticipated annual event in the oncology community. It was held from 2 to 4 May 2019 in Berlin, Germany, and demonstrated ESMO's commitment to advancing breast cancer research and integrating research results into the clinic to ensure better care for patients.

Oncology professionals assembled to hear a comprehensive overview of practice-changing new data, to discuss current issues, and to take part in the networking opportunities. A total of 1'646 participants attended this new event, which included 1'334 delegates, 86 faculty, 192 industry exhibitors, and 34 members of the press. The event welcomed delegates from 94 countries in Europe, the Middle East, Asia, Africa, Australia and the Pacific region, as well as North, Central, and South America. Germany, the host country, provided the most delegates (13.9%), followed by the United States of America (7.9%), and Italy (6.5%). The United Kingdom and Spain each contributed to 5.6% of the delegate population, while Switzerland, the Netherlands, Belgium, Greece, and Austria were represented by 4.4% to 2.6% of delegates. The average delegate age was 44 years, while 95.7% of delegates were in the 26 to 65 year age range. Women constituted the majority (56.7%) of delegates.

Most (77.9%) of the delegates were clinicians, basic scientists (12.7%), or pharmacists (5.7%), but medical students, patient advocates, nurses, statisticians and undergraduate science students also participated. Medical oncologist was the primary profession for 49.49% of the delegates with the remainder being comprised of clinical and surgical oncologists, scientists, clinical researchers, gynaecologists, oncology nurses, and many other occupations relevant to the oncology community.

The ESMO Breast Cancer 2019 provided a forum for original unpublished data and sharing ideas about innovation, as well as for disseminating evidence-based knowledge of clinical relevance. The primary areas of interest covered a broad range. Those most often expressed by the delegates were breast cancer (82.8%) and gynaecological malignancies (24.2%).

The participants expressed interest in topics across the spectrum of oncology. Delegates commented that the topics they most wanted to hear about included clinical research (47.3%), anticancer agents (41.3%), and cancer biology (39.7%). Translational research was cited by 28.6% of respondents as the topic of interest that drew them to the event, immunotherapy by 27.2%, and approximately 26% of delegates said that both, tumour immunology and pathology brought them to the ESMO Breast Cancer 2019.

This fledgling event attracted 368 scientific submissions. Of the 218 accepted abstracts, most (86%) were presented as posters and 30 (14%) abstracts were delivered as oral or mini-oral presentations. India provided the most abstract submissions (14.1%) while 6.5% came from Italy, 5.7% each came from China and Germany, 5.4% from the United Kingdom,

and 5.2% of abstracts came from Belgium. The Netherlands, United States of America, the Russian Federation, and Spain contributed 4.1% to 3.0%% of submissions.

Communication activity was apparent with the event providing 7 press releases that resulted in 124 news clips that were detected in many European countries and the United States. Thirty-eight accredited media representatives of 30 publications in 10 countries assembled at the event. Nearly 2000 Tweets were made by 493 participants.

The ESMO Events App proved to be a useful accessory to the online programme that was downloaded by 749 participants; on the peak day, the app was referred to by 631 users. The ESMO website traffic saw 119,623 visits on the ESMO Breast Cancer web page. The most viewed programme sessions were on early HER2-positive breast cancer with 1286 viewers, which was followed closely by early triple negative breast cancer with 1280 viewers. Immune oncology had 1195 views, early HER2-negative/hormone receptor-positive breast cancer had 1163 views, and 999 interested parties accessed the metastatic triple negative breast cancer programme session.

Information, communication, education, and expertise coalesced during the first ESMO Breast Cancer to create a unique experience that will be annually repeated in the upcoming years. A brief summary of some of the advances in breast cancer research and treatment that were presented at the ESMO Breast Cancer 2019 follows.

# BIOMARKERS, TRANSLATIONAL RESEARCH AND PRECISION MEDICINE

## Specific miRNAs are upregulated in BRCA-positive breast cancers lacking a clear second hit

Mattias Van Heetvelde, Biomolecular Medicine, Ghent University, Ghent, Belgium explained that a significant percentage of BRCA1-associated breast cancers do not display a clear second hit, such as loss of heterozygosity, methylation, or inactivating mutation. Professor Van Heetvelde and colleagues postulated that microRNAs could potentially be used to inhibit the remaining functional allele in patients with germline BRCA1 defects, thereby contributing to oncogenesis in a way similar to more conventional second hits. Therefore, overexpression of oncogenic microRNAs may play a role in downregulating the expression of the retained wild type BRCA1 allele, at least on a subclonal level.

The investigators used genome-wide microRNA expression profiling to determine the expression of microRNAs in 51 BRCA1-associated breast cancers. They evaluated the association between molecular subtype and histopathological features, and also the association with the presence of a residual functional BRCA1 allele using differential expression analyses. The expression of the BRCA1 protein in tumours was studied using immunohistochemistry. BRCA1 had been thoroughly investigated at the (epi-)genetic level in all of the tumours.

A total of 14 microRNAs were found to be upregulated in tumours that retained the BRCA1 wild type allele in >50% of tumour cells. Data from the differential expression analysis that was based on histopathological features of breast tumours was highly similar to publically available data from two prior independent studies. Several tumours had intratumoral heterogeneity for BRCA1 protein expression, but this but did not associated with the observed amount of retained BRCA1 wild type allele. Van Heetvelde *et al.* Abstract LBA1

### Practice point and future research opportunities

This study identified several microRNAs that are potentially active in BRCA1-associated breast tumourigenesis. These findings support the authors' hypothesis that miRNAs upregulated in tumours having a functional BRCA1 allele, but lacking BRCA1 protein expression may be involved in BRCA1 regulation. microRNAs involved in BRCA1 regulation, which may be direct or indirect, may have the potential to sensitise tumours to PARP inhibitors or platinum-based therapies.

## Double PIK3CA mutations in cis on the same allele enhance PI3Kα oncogene activation and sensitivity to PI3Kα inhibitors in breast cancer

Neil Vasan, Memorial Sloan Kettering Cancer Center in New York, USA discussed how activating mutations in *PIK3CA*, which codes for the catalytic subunit (p110α) of

phosphoinositide-3-kinase (PI3K), are the most frequent oncogenic alterations observed in oestrogen receptor (ER)-positive breast cancer and are also prevalent in other tumour types. PI3Kα inhibitors have recently been shown to be clinically active in ER-positive breast cancers harbouring PIK3CA mutations. Among these patients, there was a population that displayed deep and prolonged clinical benefit; Dr. Vassan and colleagues genomically characterised the tumours in this population. They detected the presence of double *PIK3CA* mutations in all metastatic sites and at different times over the course of tumour evolution.[1] This finding taken together with anecdotal observations of recurrent double *PIK3CA* mutations in a number of breast cancer genomes, prompted the investigators to perform a comprehensive analysis of the prevalence of these mutations and to investigate their potential biological relevance and the association with sensitivity to PI3Kα inhibitors.

Double PIK3CA mutations were detected in 12% to 15% of breast cancer and other tumour types. These double PIK3CA mutations were clonal, located in cis on the same allele, and were composed of a single hotspot mutation combined with a recurrent second-site mutation. According to the investigators, these double PIK3CA mutations in cis result in increased PI3K activity and downstream signalling together with enhanced cell proliferation and tumour growth compared to single hotspot mutations. They explained the biochemical mechanisms underlying this increased oncogenicity include increased disruption of p110α binding to the inhibitory subunit p85α, which relieves its catalytic inhibition, and increased membrane lipid binding. Double *PIK3CA* mutations are predictive of increased sensitivity to *PI3Kα* inhibitors and may served as a biomarker for improved outcome following therapy with a PI3Kα inhibitors, as compared to tumours with single hotspot mutations observed in experimental models and in patients with breast cancer. Vasan *et al.* Abstract 1O

Citation:

1. Juric D, *et al. Nature* 2015; 518(7538):240–244.

### Practice point and future research opportunities

These findings implicate double *PIK3CA* mutations in cis as a hypermorphic oncogene relative to single hotspot mutations, providing a rationale for development of PI3Kα inhibitors for the treatment of patients with double PIK3CA mutated breast cancer.

## EndoPredict accurately informs risk of ten-year disease recurrence in patients with invasive lobular or ductal carcinoma

Ivana Sestak, Queen Mary University, London, UK presented gene expression data that was evaluated according to clinical outcome from the largest cohort of patients with invasive lobular carcinoma (ILC) receiving adjuvant endocrine therapy without chemotherapy. The analysis included pooled data from 2630 breast cancer patients with oestrogen receptor (ER)-positive, HER2-negative disease participating in two large phase III randomised, controlled studies (ABCSG-6/8 and TransATAC). The EndoPredict (EPclin) test, a

2nd generation genomic test for women with newly diagnosed early-stage, ER-positive, HER2-negative breast cancer that combines a 12-Gene Molecular Score with tumour size and lymph node involvement, was used to determine the 10-year disease recurrence (DR) risk.The primary objective was the determination of the prognostic value of EPclin for DR within 0-10 years in women with ILC, and secondary objectives included subgroup analysis and comparison of the prognostic value of EPclin in ILC compared to invasive ductal carcinoma (IDC).

The EPclin cohort consisted of 470 (17.9%) patients with ILC, 1944 (73.9%) with IDC, and 215 (8.2%) patients with other histological types. EPclin was highly prognostic in women with ILC, hazard ratio (HR 3.32; $p < 0.0001$). The prognostic value with EPclin was greater than clinicopathological parameters alone (HR 2.17; $p < 0.0001$; added value: $\Delta LR\text{-}\chi^2=17.6$). It was determined that 298 (63.4%) patients with ILC could be categorised as low EPclin risk; these patients had a risk of 10-year DR of 4.8% compared to 172 (36.6%) high risk patients who had a 10-year DR risk of 26.6%; for the comparison of low versus high risk (HR 6.33; $p < 0.0001$).

EPclin also provided highly prognostic information for 326 women with lymph node negative disease (HR 2.56) and 144 patients with LN-positive disease (HR 3.70). Regarding patients with IDC, EPclin was also highly effective in categorising 59.1% of women into a low risk group and 40.9% into a high-risk group (HR 5.04). It was determined that 17% fewer women in the ILC cohort were at high risk according to EPclin than patients with IDC. The results suggest that histological subtyping is not indicated when interpreting EndoPredict, the authors concluded. Sestak *et al.* Abstract 2O

### Practice point and future research opportunities

Gene expression data acquired using the EPclin method from patients with ILC receiving adjuvant endocrine therapy without chemotherapy accurately categorised women according to high and low risk of 10-year DR. The high and low risk subgrouping was confirmed by a comparison to clinical outcome. Investigators were also able to determine the 10-year DR risk groups in patients with IDC and to determine that 17% more women with ILC were at low risk compared to women with IDC.

In this analysis, EPclin provided highly significant prognostic value and significant risk stratification for women with ILC. The 10-year DR risk in the EPclin low risk groups were similar between ILC and IDC, suggesting that chemotherapy in these low risk groups may not be indicated, irrespective of tumour type.

## Comprehensive evaluation of methodology to assess abundance of immune infiltrates in breast cancer

The need for systematic comparison of methods used to evaluate the amount and composition of tumour immune infiltrates was discussed by Iris Nederlof of the Molecular

Pathology, Netherlands Cancer Institute/Antoni van Leeuwenhoek hospital in Amsterdam, Netherlands. Together with investigators from the Netherlands, she characterised stromal and intra-tumoural tumour infiltrating lymphocytes (TILs) and 6 immune cell-types ($CD3^+$, $CD4^+$, $CD8^+$, $CD20^+$, $CD68^+$, $FOXP3^+$) using immunohistochemistry in the 560 genome cohort described in the International Cancer Genomics Consortium.[1] The same traits were computed using deconvolution methods (CIBERSORT, methylCIBERSORT, quanTIseq, EPIC), as well as published transcriptomic or methylation-based immune signatures. They began by studying the associations of immune cells as continuous variables. Then further categorised tumours as hot (stromal TIL ≥60%) or cold (stromal TIL ≤10%).

The immune infiltrate was reproducibly assessed by pathologists for all cell types. The concordance correlation coefficients ranged from 0.63 for stromal CD4 to 0.84 for stromal TIL. The correlations between all methods to assess global immune infiltration were extremely variable, ranging from 0.08 to 0.95. The correlations between methylation or transcriptomic estimates and histopathology were weak to moderate and did not exceed 0.56. Several transcriptomic estimates were strongly correlated with each other (>0.85). ROC analyses showed that most methods more accurately identify hot as compared to cold tumours. Comparison regarding the specific immune cell types further highlighted heterogeneity between the different methods. Nederlof *et al.* Abstract 3O

Citation:

1. Nik-Zainal S, *et al. Nature* 2016;534(7605):47-54.

### Practice point and future research opportunities

This study highlights important differences between the currently existing methods used to assess global immune infiltration in breast cancer and underscores the need for employing extreme caution when using immune infiltrate assessments in the clinical context.

## Levels of stromal tumour infiltrating lymphocytes signal response to neoadjuvant pembrolizumab plus chemotherapy in triple negative breast cancer

Sherene Loi, Peter MacCallum Cancer Centre, Melbourne, Australia noted that higher levels of stromal tumour infiltrating lymphocytes (sTILs) have been associated with higher pathologic complete response (pCR) rates with chemotherapy in early-stage triple negative breast cancer (TNBC), which prompted Dr. Loi and colleagues to evaluate the association between sTILs and PD-L1 expression with response to pembrolizumab plus chemotherapy as neoadjuvant treatment for TNBC. Using data from patients participating in the KEYNOTE-173 trial, the investigators quantified the levels of pre-treatment and on-treatment sTILs during first 3 weeks of pembrolizumab monotherapy. PD-L1 expression was determined during pre-treatment and reported as a combined positive score (CPS). The

study endpoints were pCR rates, including absence of cancer in breast tissue and lymph nodes (ypT0 ypN0), absence of cancer in breast tissue and lymph nodes regardless of the presence of ductal carcinoma (ypT0/is ypN0), and the objective response rate (ORR) after the first 4 cycles of neoadjuvant chemotherapy comprising a taxane with or without carboplatin plus pembrolizumab. The association of PD-L1 and sTILs was assessed by Spearman's rank correlation coefficient.

The level of sTILs were evaluated in the tumours of 53 pre-treatment and 50 on-treatment patients; of the pre-treatment tumours, 52 could also be evaluated for PD-L1 CPS, and 51 samples were evaluated for both sTILs and CPS. The ORR with treatment was 78.3%. There was a significant correlation higher levels of pre-treatment sTILs and PD-L1 CPS ($p < 0.001$) and between levels of pre-treatment sTILs and on-treatment sTILs ($p < 0.001$). The overall pCR rates for both endpoints were 56.7% (ypT0 ypN0 pCR rate) and 60% (ypT0/Tis ypN0 pCR rate).

Higher levels of sTILs were significantly associated with response: higher levels of pre-treatment sTIL and ypT0 ypN0 pCR response ($p = 0.033$), ypT0/Tis ypN0 pCR response ($p = 0.02$), and the ORR ($p = 0.028$). Regarding the on-treatment levels, higher sTIL significantly associated with ypT0 ypN0 ($p = 0.01$), ypT0/Tis ypN0 ($p = 0.008$), and ORR ($p = 0.005$). Pre-treatment PD-L1 CPS was significantly associated with response: ypT0 ypN0 pCR ($p = 0.073$), ypT0/is ypN0 ($p = 0.030$), and ORR ($p = 0.021$).

Pre-treatment median sTIL levels were higher in responders than non-responders: High TILs were observed in 40% of responders versus 10% of non-responders regarding the ypT0 ypN0 pCR endpoint, and 42.5% versus 10% for the ypT0/Tis ypN0 pCR rate. Median sTIL levels were 20% compared to 10% for the ORR. On-treatment median sTIL levels were also higher at 65% in responders compared to 22.5% in non-responders (ypT0 ypN0 pCR rate), and 65% versus 22.5% (ypT0/Tis ypN0 pCR rate), respectively. Regarding the ORR, median sTIL levels were higher in 60% of responders compared to 10% of non-responders.

However, likelihood ratio tests demonstrated that pre-treatment PD-L1 CPS and pre-treatment sTILs did not significantly add value to that of on-treatment sTILs when predicting pCR for both pCR endpoints; for the comparison of PD-L1 CPS for both endpoints ($p = 0.936$ and $p = 0.492$) and in comparing pre-treatment sTILs to response according to both endpoints ($p = 0.746$ and $p = 0.715$). NCT02622074. Loi *et al.* Abstract 4O

## Practice point and future research opportunities

Patients with higher levels of sTILs were more likely to achieve pCR following pembrolizumab plus chemotherapy as neoadjuvant treatment in TNBC. Higher quantities of pre-treatment sTILs and PD-L1 CPS and on-treatment sTILs were significantly associated with higher pCR rates and ORR in primary TNBC after treatment with pembrolizumab and neoadjuvant chemotherapy. Findings from this study suggest that sTIL levels may predict the response to this combination treatment in women with TNBC.

## High levels of tumour infiltrating lymphocytes point to poorer outcome in ER-positive/HER2-negative breast cancer

Carmen Criscitiello, New Drugs and Early Drug Development for Innovative Therapies Division, IEO, European Institute of Oncology IRCCS, Milan, Italy discussed findings from an investigation of the association of tumour infiltrating lymphocyte (TIL) levels and clinico-pathological features with distant disease-free survival (DDFS) in a large series of patients with oestrogen receptor (ER)-positive/HER2-negative breast cancer. The investigators constructed a case-cohort by randomly selecting 17% of the 3986 patients undergoing surgery at the IEO from 1998-2002; of these, 680 patients also had long-term follow-up data and 307 more patients with an event were added to this cohort, which totalled 987 cases. TILs were assessed on centralised haemotoxylin and eosin slides both as continuous variables, and according to categories of low (<5%) and high (≥5%) sets. The DDFS was calculated from the date of surgery to the date of any first event or the date of last contact with the patient. The log-rank test was used to determine differences between breast cancer subtypes and univariable and multivariable Cox proportional hazards regression with inverse sub-cohort sampling probability weighting were used to evaluate the risk across groups using SAS software version 9.4.

The median follow-up was 7.5 years (range, 0.1 to 10 years). The median TILs level was 2%. A positive association was determined between higher TIL levels and lymph node metastasis (pN; $p = 0.003$), grade ($p < 0.0001$), peritumoural vascular invasion ($p = 0.003$), Ki-67 ($p = 0.0001$), luminal B subtype ($p < 0.0001$), and chemotherapy ($p < 0.0001$). Higher TIL levels were inversely associated with ER ($p < 0.0001$) and age ($p = 0.02$). In multivariable regression analysis, only Ki-67 expression retained significant association with TILs, whereas age and ER showed a trend towards negative association with TILs. In univariate Cox regression, higher versus lower TIL expression (≥5% vs. <5%) was not associated with DDFS (hazard ratio 1.08; $p = 0.62$).

Stratified cox exploratory analyses showed an association between high TILs and lower risk in very young women ($p = 0.03$) and grade 3 tumours ($p = 0.047$). Furthermore, high TILs were associated with worse outcome in patients with grade 1 tumours ($p = 0.05$). TILs did not show an association with DDFS in patients not receiving chemotherapy. On the contrary, improved DDFS was associated with patients treated with chemotherapy and having high TIL levels ($p = 0.006$). This association also held for patients with Ki67 ≥20% ($p = 0.01$). Criscitiello *et al.* Abstract 5O

### Practice point and future research opportunities

In patients with ER-positive/HER2-negative breast cancer, high TIL levels significantly associated with several clinico-pathological measures of poorer outcome. It may be that this subgroup is more immunogenic, and the exploration of immunotherapy approaches may be beneficial to this subgroup.

## Circulating tumour DNA dynamics may serve as a surrogate for progression-free survival in patients with metastatic breast cancer participating in the BEECH trial

Sarah Hrebien, Breast Cancer Research, Institute of Cancer Research, London, UK presented the results on behalf of colleagues of an analysis of circulating tumour DNA (ctDNA) levels as a surrogate for progression-free survival (PFS) and as an early predictor of drug efficacy. They used samples from the phase I/II randomised BEECH trial, which randomly assigned patients with oestrogen receptor (ER)-positive metastatic breast cancer to paclitaxel plus placebo or to paclitaxel plus the AKT inhibitor, capivasertib. Patients in the development and validation cohorts provided plasma samples for ctDNA analysis at baseline and at multiple time points during treatment. ctDNA sequencing of baseline plasma samples identified mutations for longitudinal analysis, and the change in ctDNA allele fraction between baseline and 872 on-treatment samples were assessed by mutation specific digital droplet PCR assays. Early suppression of ctDNA assessment was used to define criteria in the development cohort that were independently evaluated in the validation cohort. Suppression of ctDNA was evident after 8 days of treatment in the development cohort ($p = 0.014$). The investigators determined that cycle 2 day 1, or 4 weeks of treatment, was the optimal timepoint to predict PFS from early ctDNA dynamics.

Regarding the validation cohort, median PFS was 11.1 months in patients showing suppressed ctDNA at 4 weeks compared to 6.4 months in patients with high ctDNA (hazard ratio [HR] 0.20; $p < 0.0001$). No differences were observed in the level of ctDNA suppression in patients randomised to capivasertib or to placebo in the overall population ($p = 0.904$) or in the PIK3CA mutated subpopulation ($p = 0.071$). Clonal haematopoiesis of indeterminate potential (CHIP) was evident in 30% of baseline samples and did not have effect on tolerance to chemotherapy or PFS. NCT01625286. Hrebien *et al.* Abstract 6O

### Practice point and future research opportunities

In the BEECH trial, on-treatment ctDNA dynamics evaluated in samples taken early during treatment were indicators of PFS. Dynamic ctDNA assessment shows potential for substantially enhancing early drug development.

## The prognostic model PAM50MET indicates survival following treatment for metastatic HR-positive/HER2-negative breast cancer

Recognising the clinical value of predicting the outcome following treatment in metastatic hormone receptor (HR)-positive, HER2-negative disease, Aleix Prat, Medical Oncology, Hospital Clínic y Provincial de Barcelona, Barcelona, Spain and colleagues developed and validated a prognostic biomarker in 765 patients participating in two phase III trials evaluating endocrine-based therapies. They reviewed PAM50 and clinical data from 821 patients treated with first-line letrozole plus placebo or lapatinib in the EGF3008 trial and selected 484 patients with HER2-negative disease who received no prior endocrine therapy

and did not relapse ≥6 months following tamoxifen discontinuation. They evaluated PAM50 subtypes, signatures and genes, ECOG performance status, the presence of visceral disease, the number of metastases, biopsy-type, and age as variables to determine a prognostic model. The prognostic cox model for progression-free survival (PFS) was evaluated in 2 out of 3 patients using Elastic Net (Monte Carlo CV). The concordance (C-index) of each model was estimated in one out of 3 patients. The final model was tested in 261 patients receiving exemestane plus placebo or everolimus in the BOLERO2 trial. PAM50 was performed in FFPE tumours of which approximately 80% were primary.

Using data from the EGF3008 study, prognostic models that integrated PAM50 and clinical variables yielded superior C-index values compared to models with PAM50-only or clinical variables-only. The final model, PAM50MET, comprised 21 variables that included 2 PAM50 subtypes, the Basal signature, 14 genes, and 4 clinical variables. Evaluation of this model with EGF3008 trial data showed that the optimised cut point was significantly associated with PFS (hazard ratio [HR] 0.41; $p < 0.0001$) and overall survival (OS; HR 0.41; $p < 0.0001$). Using BOLERO2 data, the PAM50MET score also was significantly associated with PFS ($p = 0.004$) and OS ($p < 0.0001$). At the same cut point, the investigators found that a PAM50MET-low score was associated with better PFS (HR 0.72; $p = 0.028$) and OS (HR 0.51; $p < 0.0001$). In the median PAM50MET-low set, median PFS was 6.9 months and median OS was 36.5 months compared to median PFS of 5.2 and median OS of 23.4 months in PAM50MET-high set. NCT00073528; NCT00863655. Prat *et al.* Abstract 7O

### Practice point and future research opportunities

PAM50MET scores may enable the identification of patients with HR-positive/HER2-negative metastatic disease that will benefit from endocrine therapy-only or endocrine therapy plus a CDK4/6 inhibitor or other treatment strategies, especially in the first-line setting. PAM50MET warrants further validation in pivotal clinical trials that have evaluated endocrine-based therapies.

## The mutational profile of inflammatory breast cancer demonstrates a higher mutational burden, deficiency of homologous recombination, and activation of NOTCH signalling

Steven J. Van Laere, CORE, University of Antwerp, Antwerp, Belgium referred to the gene expression profile developed together with colleagues that characterises inflammatory breast cancer (IBC), an aggressive form of breast cancer with elevated metastatic potential. Previous findings using the profile suggest that IBC has a specific molecular biology, prompting further investigation of genomic alterations underlying IBC. They assembled mutation and copy number variation (CNV) profiles for 756 genes in 2'920 primary tumour samples (subtype distribution: 63% hormone receptor (HR)-positive, 18% HER2-positive, and 19% triple negative breast cancer). One hundred and one profiles were in samples obtained from patients with IBC before therapy and 468 profiles were constructed using metastatic breast cancer samples. Differences in the frequency of genomic aberrations

between patients with and without IBC stratified per subtype, were investigated. Genomic perturbation differences for pathways and mutational signature (MS) profiles were also compared between patients with and without IBC.

Samples from patients with IBC showed evidence of extensive genomic alterations in 76 genes, as compared to samples from patients without IBC (i.e. false discovery rate <10%), whereas only 3 genes revealed the opposite pattern. The 10 top scoring genes according to the odds ratio include: *MYC, CYP2D6, VEGFA, CCND1, GNAQ, ZNF703, PTPN11, MCL1, CDK4*, and *CCDC6.* Analysis of the MS profiles revealed differences for signature 2, -11, -20, -23 and -24. As compared to metastatic breast cancer samples, mutations in genes involved in homologous recombination and in the NOTCH pathway were more prevalent in IBC samples. The analysis of MS profiles identifies 3 mutational processes in IBC that are associated with transcriptional strand-bias for mutations involving a cytosine, such as C>T and C>A, which is indicative for transcription coupled nucleotide excision repair and suggests that mutations involve the complementary guanine base. Van Laere *et al.* Abstract 8O

### Practice point and future research opportunities

Findings from this study suggest that IBC, as compared to metastatic breast cancer, is characterised by a more extensive mutational burden that results in the activation of NOTCH signaling and deficient homologous recombination, as well as activation of other signalling pathways.

## Expression of VEGFA metagene signature is identified by single-cell profiling in para-necrotic cells

Thomas Karn, Department of Gynaecology and Obstetrics, Breast Unit, Johann Wolfgang Goethe University, Frankfurt Am Main, Germany discussed the VEGFA metagene in triple negative breast cancer (TNBC) that he and colleagues had previously identified. The metagene abrogates the good prognostic effect of tumour infiltrating lymphocytes (TILs) and is associated with a poor prognosis.[1] He noted that high values of this signature prior to treatment were indicative of pathologic complete response (pCR) in the neoadjuvant GeparQuinto trial (odds ratio [OR] 2.40; p = 0.006) and showed an interaction with bevacizumab treatment (p = 0.020). The main cellular sources of the transcripts that comprise the *VEGFA* metagene remain undefined, since mRNA profiling of bulk biopsies contains signals from different cell types. Expression of the individual genes in endothelial cells, fibroblasts, and epithelial cancer cells has been reported.

The investigators analysed single-cell sequencing RNA-sequence (sc-RNA-Seq) data of 772 single cells from TNBC samples and 52,698 single cells from lung cancer tumours and non-malignant lung samples to identify the cellular source of the metagene expression. They established and validated single marker immunohistochemistry (IHC) assays for the *VEGFA* metagene and applied them to tissue micro arrays (TMA).

Analysis of the sc-RNA-Seq from TNBC revealed co-expression of *NDRG1, VEGFA, and DDIT4,* which are core genes of the *VEGFA* metagene in different cell types; the highest expression was found in basal-like cancer cells. Strong co-expression in a subset of carcinoma cells was also seen in lung cancer sc-RNA-Seq, as compared to limited expression in endothelial cells. IHC revealed strong para-necrotic expression in accord with functions in cellular stress and hypoxia. Whole-slide-IHC showed good correlation to mRNA expression even in core biopsies (Kappa=0.864, $p < 0.001$). However, comparison of whole-slide and TMA demonstrated high specificity but a profound loss of sensitivity, which was mainly due to heterogeneity in expression and the small sized TMA cores from pre-treatment biopsies. Nevertheless, a predictive value for pCR was detected in the TMA dataset ($p = 0.025$). Kam *et al.* Abstract 9O

Citation:

1. Karn T, *et al*. *Cancer Research* 2019; 79(4 Supplement):P3-10-01.

### Practice point and future research opportunities

These data indicate that the cellular source of the *VEGFA* metagene are peri-necrotic carcinoma cells. Thus, necrosis detection may help in response prediction and as stratification factor in trials. Since the signature indicates an immunosuppressive environment it should also be further studied in the context of combination therapies of anti-angiogenic and immune treatments.

## Comparisons of patient populations with different PD-L1 assays are mostly consistent in triple-negative breast cancer

Marietta Scott, Precision Medicine Laboratories, Precision Medicine and Genomics, AstraZeneca, Cambridge, UK and colleagues evaluated the degree of concordance among PD-L1 assays in triple-negative breast cancer (TNBC). Immunohistochemistry (IHC) was performed in 196 TNBC case samples using the VENTANA PD-L1 (SP263), VENTANA PD-L1 (SP142), Dako PD-L1 IHC 28-8 pharmDx, and Dako PD-L1 IHC 22C3 pharmDx assays. All slides were scored by a single pathologist for the proportions of membrane staining tumour cells (TC), staining immune cells (IC), the proportion of tumour occupied by staining immune cells ($IC_{TA}$), and the Combined Positive Score (CPS) was derived. Concordance between assays was evaluated using the Spearman coefficient ρ. Concordance in patient status was assessed using overall, positive and negative percent agreement at matched algorithms and cut-offs.

Regarding tumour cell PD-L1 staining, the SP263, 22C3, and 28-8 assays showed good analytical correlation ($\rho = 0.84–0.89$), whereas staining was lower for SP142 (0.44-0.46). All of the assays showed good correlation for $IC_{TA}$ (0.77-0.96) and CPS (0.78-0.95). Overall positive agreement (OPA) ranged from 58%–97% at matched algorithms. Specifically, the OPA with the Ventana SP263 and other assays for TC≥1%, $IC_{TA}$≥1%, and CPS≥1 was 91%,

96%, 92% for 22C3, 88%, 97%, 95% for 28-8, and 58%, 78%, 71% for SP143, respectively. Prevalence with the Ventana SP263 and other assays for TC≥1%, $IC_{TA}$≥1%, and CPS≥1 was 50%, 51%, 60% for 22C3, 46%, 52%, 61% for 28-8, and 11%, 32%, 35% for SP142, respectively. Prevalence for SP142 $IC_{TA}$≥1% and 22C3 CPS≥1 was in-line with the IMPassion 130 and KEYNOTE-086 clinical trials, respectively. Scott *et al.* Abstract 10O

## Practice point and future research opportunities

While the analytical performance is similar between SP263, 22C3 and 28-8, the SP142 assay provides less staining of both tumour and immune cells. In TNBC, tumour cell scores are lower and immune cell scores are higher, in contrast to other cancer types. Care should be taken when interchanging PD-L1 assays and interpreting efficacy data derived with different algorithms in TNBC; whereas SP263 would identify largely the same PD-L1 patient population as in KEYNOTE-086, it could potentially identify 22% additional cases as PD-L1 high than in IMPassion 130.

# EARLY BREAST CANCER: ADJUVANT THERAPY

## Long-term results show dose-dense adjuvant chemotherapy has similar efficacy in early breast cancer

Eva Blondeaux, Department of Medical Oncology U.O. Oncologia Medica 2, Ospedale Policlinico San Martino, Genova, Italy, pointed out that dose dense adjuvant chemotherapy is the preferred treatment option in patients with high-risk early breast cancer while presenting updated results after a median 15.8 years of follow-up of the MIG-1 study. MIG-1 compared the efficacy of fluorouracil, epirubicin and cyclophosphamide (FEC) regimen administered every 3 (FEC21) versus every 2 (FEC14) weeks in patients with early breast cancer patients. From November 1992 to June 1997, this open-label, multicentre phase III trial randomly assigned 1214 patients with node positive and high-risk node negative disease to receive 6 cycles of FEC21 (n=604) or FEC14 (n=610); both treatments included support with a granulocyte colony-stimulating factor. The primary endpoint was overall survival (OS) and secondary end-point was event-free survival (EFS).

Regarding the study endpoints, no statistically significant difference was observed between the regimens. The 15-year OS rate was 68% in the FEC21 group compared to 71% in the FEC14 group (hazard ratio [HR] HR=1.13; p = 0.25). The 15-year EFS was 43% versus 47% in the respective treatment arms (HR 1.13; p = 0.19).

A pre-planned subgroup analysis of patients with hormone receptor negative tumours revealed 15-year OS was 65% with FEC21 compared to 70% with FEC14 treatment (HR 1.34; p = 0.11; $p_{interaction}$ = 0.25). However, the 15-year EFS rate did favour the FEC 14 arm; 15-year EFS was 43% compared to 58% with the respective treatments (HR 1.47; p = 0.016; $p_{interaction}$ = 0.02). No differences between the two regimes was observed in patients with hormone receptor positive tumours. Blondeax *et al.* Abstract 86O

### Practice point and future research opportunities

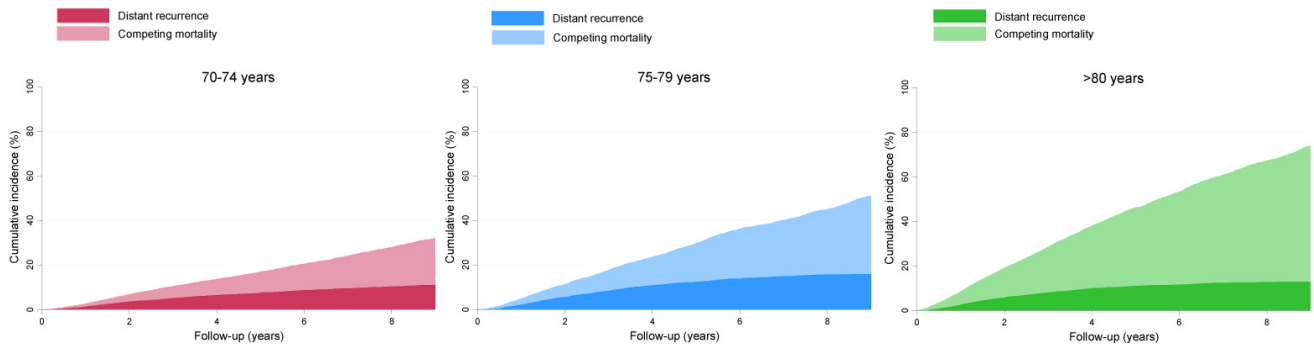
Updated results after 15 years of follow-up from the MIG1 study did not show a significant OS benefit with the use of dose-dense FEC (FEC14) chemotherapy in patients with early breast cancer However, EFS was prolonged with the use of dose-dense chemotherapy in a subgroup of patients with hormone receptor negative disease.

## In patients aged more than 70 years with early stage breast cancer, those aged 75 to 79 years have higher risk of distant recurrence than patients aged 70 to 74 years despite higher competing mortality

Anna Z. de Boer, Department of Surgery, Leiden University Medical Centre, Leiden, Netherlands and colleagues investigated the risk of recurrence and competing mortality in older patients with breast cancer. For the overall study population, they identified patients in the Netherlands Cancer Registry aged 70 years and older who were diagnosed with early

stage breast cancer and underwent surgery from 2003 to 2009. The investigators calculated the cumulative incidence of locoregional and distant recurrence according to age categories using the Cumulative Incidence Competing Risks (CIRC) method. In addition, the Fine and Gray model was used to estimate the effect of age on recurrence, which was expressed as subdistribution hazard ratio (sHR).

The analysis included 18,419 patients who were stratified according to age: 70-74 years (reference group), 75-79 years, and ≥80 years. The 9-year cumulative incidences of locoregional recurrence were 2.5%, 3.1%, and 2.9% in patients aged 70-74, 75-79, and ≥80 years, and 10.9%, 15.9%, and 12.7% for distant recurrence. In univariate analysis, the two higher age groups (age 75-79 years and ≥80 years) were associated with a higher risk of locoregional and distant recurrence compared to the reference age group of 70-74 years. According to the multivariable analysis, which adjusted for tumour and treatment characteristics, the risk of distant recurrence remained significantly higher for patients aged 75-79 (sHR 1.25; $p < 0.001$).




Stacked cumulative incidences of distant recurrence and competing mortality by age group.

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This large population-based study showed that patients aged 75 to 79 years were at increased risk of distant recurrence compared to the reference group of patients aged 70 to 74 years despite the higher competing mortality risk, possibly due to decreased treatment effectiveness with age and under treatment. However, this increased risk was not observed for patients aged ≥80 years (sHR 1.03; $p = 0.606$). No significant association between age and locoregional recurrence risk was found in the multivariable analysis. de Boer *et al.* Abstract 87O

## Practice point and future research opportunities

This large study found patients aged 75 to 79 were at higher risk for distant recurrence than patients aged 70 to 74 years following successful surgery for early breast cancer, which may be explained by suboptimal treatment selection and different treatment response in older patients compared to younger patients. Prediction tools that take competing mortality into account by including comorbidity or other geriatric parameters could play an important

role in improving breast cancer management in older patients.

## American Joint Committee on Cancer new prognostic stage groups for HER2-positive breast cancer patients is validated using ShortHER trial data

Maria V. Dieci, Department of Surgery, Oncology and Gastroenterology, University of Padova, Istituto Oncologico Veneto IRCCS, Padova, Italy and colleagues conducted a study to validate the American Joint Committee on Cancer (AJCC) 8th edition staging system, which introduced prognostic stage groups based on anatomic stage combined with biologic factors. They used the AJCC system to evaluate the data of 1253 patients with HER2-positive breast cancer participating in the prospective ShortHER trial. The patients in this trial were randomly assigned to receive 9 weeks or one year of trastuzumab in combination with anthracycline and taxane chemotherapy. Patients were classified according to the classic AJCC anatomic groups and the AJCC prognostic groups (8th edition). Distant disease-free survival (DDFS) was calculated as the time from randomisation to relapse at a distant site or death. The Harrell's C-index was used to compare the prognostic performance of the two staging systems.

Of the randomised patients, 1244 had complete clinicopathological data for both AJCC anatomic and AJCC prognostic stage classifications. Compared with the anatomic AJCC, the prognostic AJCC classified 517 (41.6%) patients to a more favourable stage category. Forty (100%) patients classified as IB according to the anatomic system were re-classified to IA, 246 (61.6%) patients with IIA were restaged as IB or IA, 94 (63.0%) staged as IIB were re-classified as IB or IA, 71 (58.7%) patients with IIIA were moved to IIA or IB, and 66 (100%) of patients staged as IIIC were re-classified into IIIB or IIIA categories.

The 5-year DDFS rates according to both systems were similar, although slightly lower in the prognostic system. By the anatomic system, in stages IA, IB, IIA, IIB, IIIA, IIIB, IIIC the 5-year DDFS was 96.6%, 94.1%, 92.4%, 87.3%, 81.3%, not estimable (NE; no patients with stage IIIB), and 70.5%. According to the prognostic system, 5-year DDFS rates were 95.7%, 91.4%, 86.9%, 85.9%, 77.6%, 67.7%, and NE (no patients with IIIC) (log rank $p < 0.001$ for all comparisons). The c-index was similar at 0.69209 for anatomic stage and 0.69249 for prognostic stage ($p = 0.975$). EUDRACT number: 2007-004326-25; NCT00629278. Dieci *et al.* Abstract 88O

### Practice point and future research opportunities

This evaluation of the two staging systems using data from the ShortHER trial showed that the AJCC prognostic system resulted in 41.6% of HER2-positive patients being reclassified to a more favourable stage category, while maintaining a similar prognostic performance as compared to the classic anatomic stage. With the AJCC prognostic staging, 59% of patients were classified as IA and showed an excellent prognosis after adjuvant treatment.

## Delayed adjuvant chemotherapy decreases survival in patients with triple negative breast cancer

According to lead author Alicia F.C. Okines, Department of Medicine, The Royal Marsden (RMH) NHS Foundation Trust, London, UK, the optimal time to deliver adjuvant chemotherapy has not been defined, despite reports that pre-menopausal women with oestrogen receptor (ER)-negative cancers derived more benefit when chemotherapy was administered within 20 days of surgery, and that overall survival (OS) decreased with delays of 60 days in chemotherapy administration (SEER database).

These reports prompted this retrospective study of all patients who received adjuvant anthracycline and/or taxane-based chemotherapy at RMH from 1993 to 2010. The investigators collected data for clinico-pathological features, surgery, radiotherapy, and chemotherapy regimens. The primary endpoint was 5-year disease-free survival (DFS) in patients commencing chemotherapy less than 31 days after surgery (early chemotherapy cohort) compared to 31 or more days (delayed chemotherapy). Secondary endpoints included 5-year OS by early compared to delayed chemotherapy, and outcomes in subgroups of patients defined by age, nodal status and ER and HER2 receptor status. Of the 2003 eligible patients, 99.5% were female with a median age of 50 years. Ductal carcinoma was diagnosed in 82.7% of patients, 57% were grade 3, 57.1% had involved lymph nodes (median 1 node), 68% of patients were ER-positive, 15.7% were HER2-positive, and 24.6% had HER2 unknown status. The median tumour size was 2.2cm.

No difference in 5-year DFS rates was observed in patients in both cohorts at a median follow-up of 115 months. The 5-year DFS in patients treated with early compared to delayed chemotherapy was 81% compared to 82%, respectively (hazard ratio [HR] 1.13; p = 0.324). The DFS analysis did not identify a sub-group that was significantly affected by delaying chemotherapy. The results of the 5-year OS analysis were similar; patients receiving early or delayed chemotherapy had 5-year OS rates of 90% compared to 91%, respectively (HR 1.16; p = 0.321).

However, mortality was doubled in 250 patients with triple negative breast cancer (TNBC) receiving delayed adjuvant chemotherapy compared to those receiving chemotherapy within 31 days of surgery (HR 2.18; p = 0.02). In this subgroup, the 5-year OS rate was 77% in TNBC patients who received late chemotherapy versus 89% in those receiving early chemotherapy. Okines *et al.* Abstract 89O

### Practice point and future research opportunities

Although delayed adjuvant chemotherapy did not affect DFS in patients with most types of breast cancer, this study showed that patients with TNBC who received adjuvant chemotherapy delayed beyond 30 days had significantly reduced 5-year OS, as compared to patients with TNBC receiving adjuvant chemotherapy within 30 days. In patients with

TNBC, delays in administering adjuvant chemotherapy post surgery should be avoided when possible.

## Dose-dense adjuvant chemotherapy has limited effects in patients with HER2-positive early breast cancer also treated with trastuzumab

Matteo Lambertini, Medical Oncology, IRCCS AOU San Martino - IST-Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy and colleagues investigated whether dose dense adjuvant chemotherapy, which is the standard of care in patients with high-risk early breast cancer, would also benefit patients with HER2-positive breast cancer, particularly when trastuzumab is also administered. They performed an exploratory analysis evaluating the efficacy of dose dense chemotherapy with and without trastuzumab in the subgroup of patients with HER2-positive breast cancer in the GIM2 trial.[1] The GIM2 trial randomised patients with node-positive early breast cancer to receive a dose dense regimen comprising 4 cycles of (fluorouracil)epirubicin/cyclophosphamide ([F]FEC) every 2 weeks, or to the standard interval regimen of the same chemotherapy given every 3 weeks followed by 4 cycles of dose dense or standard interval paclitaxel.

Patients in both arms received 4 cycles of each interval-based treatment at the same dose (FEC 600/90/600 mg/m2, paclitaxel 175 mg/m2). In addition, patients with HER2-positive breast cancer also received trastuzumab for one year following chemotherapy completion. Disease-free survival (DFS) and overall survival (OS) were compared between HER2-positive patients with or without subsequent trastuzumab and patients with HER2-negative or HER2-unknown status. Of the 2,003 patients in the GIM2 study, 452 (22.6%) patients had HER2-positive status, 1,243 (62.0%) were HER2-negative and HER2-unknown status was observed in 308 (15.4%) patients. Trastuzumab had been administered to 132 (29.2%) of the 452 patients with HER2-positive disease.

At a median follow-up of 8.1 years (interquartile range: 7.0-9.3), no significant interaction was found between trastuzumab therapy and the effect of dose dense chemotherapy on survival ($p_{interaction}$ = 0.603 for DFS and $p_{interaction}$ = 0.776 for OS). However, the effect of dose dense chemotherapy appeared to be decreased in patients treated with trastuzumab; (hazard ratio [HR] 1.08; p = 0.62). In patients not receiving subsequent trastuzumab the 7-year DFS rates were 67.0% with standard interval versus 72.1% with dose dense chemotherapy (HR 0.84) compared to 72.3% versus 70.4% in patients receiving trastuzumab, respectively (HR 0.80). NCT00433420. Lambertini *et al.* Abstract 90O

Citation:

1. Del Mastro L, *et al. Lancet* 2015; 385(9980):1863-1872.

### Practice point and future research opportunities

The results of this analysis suggest that dose dense chemotherapy is effective in patients with HER2-positive early breast cancer who do not receive trastuzumab subsequent to chemotherapy, but has diminished efficacy in the subgroup of patients receiving trastuzumab.

## Circulating tumour DNA and disease recurrence data in early stage breast cancer

Serena Di Cosimo, Department of Applied Research and Technological Development, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milano, Italy noted the need for biomarkers that are able to detect minimal residual disease (MRD) after breast cancer surgery. Together with colleagues, she investigated the feasibility of using circulating tumour DNA (ctDNA) for early detection of MRD in plasma samples collected during the follow-up of patients with early breast cancer. This 1:3 case-control study included 40 patients who underwent surgery with curative intent and regular follow-up for a minimum of 13 years. The investigators had established that heparinase I digestion does not affect the quality of DNA extracted from heparin-collected blood and that pre-amplification overcomes limitations due to small (<0.5 ml) plasma aliquots. They performed mutational analysis of archival breast cancer tissues by Ion AmpliSeq™ targeted sequencing and the identified Single Nucleotide Variations (SNV) were validated and tracked in plasma by digital Polymerase Chain Reaction.

One or more circulating SNVs were identified in 27 of the 40 cases prior to surgery. During follow-up (range, 80 to 200 months), 6 patients experienced local relapse, 4 had relapse at distant sites, and 17 patients remained disease-free. In 16 of the 17 disease-free patients, ctDNA was undetectable; however, ctDNA was detected in 9 of the 10 patients with recurrence that anticipated overt metastases/loco-regional recurrences with a median lead time of 20 (range, 10 to 47) months.

These results formed the basis for a prospective study of ctDNA tracking in patients with triple negative breast cancer (TNBC). This ongoing longitudinal study has enrolled 67 patents with early stage TNBC with follow up of 10 to 74 months. Prior to surgery, ctDNA was detectable in 64% of cases and its clearance was associated with disease-free status. ctDNA was analysed prior and during neoadjuvant chemotherapy in an additional 12 patients; ctDNA was detectable in 81% of the cases at baseline, and its dynamics during and after neo-adjuvant chemotherapy reflected tumour response, and anticipated overt metastases with a lead time up to 13 months. Cosimo *et al.* Abstract 91O

### Practice point and future research opportunities

Post-surgical ctDNA can anticipate the diagnosis of new disease manifestations, including loco-regional recurrences, which are amenable to treatment with a curative intent. Additional results on the ongoing longitudinal trial in TNBC are anticipated.

## Validation of the CTS5 algorithm using the IDEAL study cohort

Iris Noordhoek, Department of Surgical Oncology, Leids Universitair Medisch Centrum (LUMC), Leiden, Netherlands explained that the Clinical Treatment Score post-5 years (CTS5) was designed to predict disease recurrence after 5 years of endocrine therapy, prompting this evaluation of the CTS5 using the IDEAL study cohort. The CTS5 categorises patients remaining disease free for 5 years, into low (<5%), intermediate (5-10%) and high (>10%) risk groups for developing recurrence within 5 and 10 years after diagnosis.

The IDEAL cohort included 1591 patients remaining disease free after 5 years of standard adjuvant endocrine therapy who were randomised during 2.5 or 5 years of extended therapy with letrozole. IDEAL patients tended to be younger, had more lymph node involvement, higher grade tumours, and received more chemotherapy than patients in the ATAC and BIG 1-98 trial cohorts, which used to train and test the CTS5. Therefore, more patients were allocated to the high-risk group than in the training and testing cohorts. Regarding the prognostic value of the CTS5 score, significantly more disease recurrence between 5 and 10 years after diagnosis occurred in the high-risk group (hazard ratio [HR] 4.9) and the intermediate-risk group (HR 2.2) as compared to the low-risk group (log-rank $p < 0.001$). According to the CTS5 scores the expected risk scores for the low, intermediate, and high-risk groups were 3.6%, 7.2%, and 19.4% in the respective risk categories. Late disease recurrence by Kaplan-Meyer curves was 1.4%, 5.6%, and 10.6% for the low, intermediate and high-risk groups, respectively. The investigators found that the CTS5 risk score systematically overestimated the risk of late disease recurrence; therefore, since the algorithm could not be validated, it was not deemed relevant to examine its predictive abilities for extended endocrine therapy within the risk groups. BOOG 2006-05. Noordhoek *et al.* Abstract 92O

### Practice point and future research opportunities

According to findings from this analysis of patients in the IDEAL study, the CTS5 reliably categorises patients into three different risk categories. However, since the calibration could not be validated, the CTS5 should not be used as prognostic tool for distant breast cancer recurrence.

## No link observed between tamoxifen serum concentration and tamoxifen-related side effects among premenopausal patients with early breast cancer

Arlindo R. Ferreira, INSERM UMR 981, Gustave Roussy, Villejuif Cedex, France and a team of French researchers investigated the effects of the serum concentration of tamoxifen on the side effects that impact the quality of life and adherence to treatment in patients with breast cancer in the CANTO COMPLETE study. To date, serum biomarkers predicting tamoxifen side effects have not been elaborated, prompting the team to evaluate whether serum levels may be associated with side effects, and may be used to identify patients at risk for side effects who would benefit from tailored supportive interventions. They used data from 12'000 women in the CANTO French multicentre prospective longitudinal study characterising the long-term toxicities of breast cancer treatment. All of the participants had stages I-III breast cancer. CANTO COMPLETE was a pre-defined sub-study of adherence to endocrine therapy that assessed the serum concentrations of tamoxifen in premenopausal patients, including the association between continuous tamoxifen serum levels and side effects. The analysis was done after one year of tamoxifen initiation in patients with serum defined adherence to tamoxifen of >60 ng/mL. Tamoxifen levels were determined by liquid chromatography tandem mass spectrometry in 200 µL of serum. Selected tamoxifen related toxicities were assessed by increase in body weight ≥5%, CTCAE v4.0, patient reported outcomes using the EORTC C30 and the hospital anxiety and depression scale.

CANTO COMPLETE comprised 989 patients with serum defined adherence to tamoxifen; the patients' median age at diagnosis was 45 (range, 22 to 57) years, 43.7% were stage I, 64.6% of patients had received (neo)adjuvant chemotherapy, and 89.4% had a Charlson score of 0. The body mass index was ≥25 kg/m$^2$ in 33.8% of patients, 20.9% were active smokers, and the majority (52.4%) had a college education or higher. The median serum tamoxifen level was 119 ng/ml (P25-P75 96-152).

According to univariate and multivariate analyses, tamoxifen levels levels did not associate with worse side effects. Specifically, tamoxifen levels were not associated with weight gain, gynaecological, musculoskeletal, or neurologic toxicities, cognitive difficulties, fatigue or insomnia, and anxiety or depression. The authors plan to determine the association of tamoxifen metabolites and side effects next. NCT01993498. Ferreira *et al.* Abstract 93O

### Practice point and future research opportunities

In premenopausal women adherent to adjuvant tamoxifen, the serum levels of tamoxifen were not associated with tamoxifen-related side effects at one year following treatment initiation.

# EARLY BREAST CANCER: NEOADJUVANT THERAPY

## Factors predicting relapse in early breast cancer patients with a pathological complete response after neoadjuvant therapy

Jens Huober of the University Hospital Ulm, Ulm, Germany presented findings on behalf of colleagues from an analysis of patient characteristics that allow better identification of patients with an increased risk of relapse after achieving pathological complete response (pCR) who may benefit from additional post-neoadjuvant treatment strategies. The analysis cohort comprised 2188 patients who achieved pCR in one of 5 trials of neoadjuvant therapy in women with early breast cancer (GeparTrio, GeparQuattro, GeparQuinto, GeparSixto and GeparSepto). pCR was defined as absence of cancer in breast tissue and lymph nodes regardless of the presence of ductal carcinoma (ypT0/ypTis ypN0). Disease-free survival (DFS) served as the primary endpoint and secondary endpoints included distant DFS (DDFS) and overall survival (OS). Covariates in multivariate Cox regression models included potential risk factors, biological subtype, histological tumour type, grading, clinical cT and cN status, Ki-67, age, body mass index, planned number of cycles of chemotherapy, menopausal status, and clinical response after 2 to 4 cycles, as well as study identification. The two-sided significance level was set to $\alpha = 0.05$ and the multivariate analysis included data from 1217 patients.

All 5 trials had a median follow-up of 59 months. During follow-up 290 DFS, 197 DDFS, and 130 OS events were observed among the 2188 evaluable patients. The location of first relapse was locoregional in 129 patients, distant in 134, and both in 23 patients. On multivariate analysis, the stage of the tumour impacted OS, which was significantly worse in women treated for later stage cT3/4 tumours; for the comparison of cT3/4 versus cT1 (hazard ratio [HR] 2.48; $p = 0.030$). Histological tumour type also indicated poorer OS, with lobular tumour type posing the highest risk; for the comparison of lobular versus other tumour types, (HR 2.85; $p = 0.026$). Nodal involvement at diagnosis demonstrated a trend for worse OS; clinically node positive (cN+) compared to clinically node negative (cN0) disease (HR 1.67 $p = 0.067$).

In parallel to OS, DFS was also significantly shorter according to the cN status; for the comparison of cN+ versus cN0, (HR 1.70; $p = 0.002$). Lobular tumour type also signalled a trend for worse DFS; lobular versus other tumour types (HR 1.91; $p = 0.076$). A trend for poorer DFS was observed with later stage disease at diagnosis; cT3/4 compared to cT1 (HR 1.61; $p = 0.064$). The DDFS results demonstrated that DDFS was affected similarly by the same factors. Huober *et al.* Abstract 108O

## Practice point and future research opportunities

This study demonstrated that the initial tumour load consisting of the tumour size, nodal status, and histological tumour type are prognostic factors of long-term outcome in early breast cancer even when a pCR was achieved stage with treatment. These factors at diagnosis identified women who may benefit from additional post-neoadjuvant therapy to prevent disease recurrence and improve survival.

# EARLY BREAST CANCER: SURGERY AND RADIOTHERAPY

## Variation in radiotherapy between hospitals after breast conserving surgery in patients aged 75 years or older is not reflected in the locoregional recurrence risk

Anna Z. de Boer, Surgery, Leiden University Medical Centre, Leiden, Netherlands explained that there is variation in the proportion of older patients receiving radiotherapy after breast conserving surgery (BCS) due to uncertainty about the absolute benefit of radiotherapy in these patients. This study assessed the degree of variation between hospitals in the Netherlands of surgery provided to patients aged 75 years or older and described the impact on locoregional recurrence risk. The Netherlands Cancer Registry was reviewed to identify patients diagnosed from 2003 to 2009. The impact of omission of radiotherapy on locoregional recurrence risk was assessed using individual patient data with hospital as instrumental variable to avoid possible bias. Therefore, hospitals were sorted according to the proportion of radiotherapy given and the cohort was divided subsequently into three equally sized groups of radiotherapy high, middle and low, which were analysed using Fine and Gray regression models. This procedure was repeated according to stratification by age and comorbidity.

The analysis included 2390 patients and found that 86% of patients in the radiotherapy high group were treated with radiotherapy compared to 88.0% in the radiotherapy middle group, and 72.2% in the radiotherapy low group. No significant difference in locoregional recurrence risk was observed for either the radiotherapy middle group (adjusted hazard ratio [HR] 1.58; p = 0.240) or the radiotherapy low compared to the radiotherapy high group (adjusted sHR 1.76; p = 0.150). Although variation in the proportion of patients undergoing radiotherapy increased with increasing age and comorbidity, no significant difference in locoregional recurrence risk was seen between the constructed radiotherapy groups stratified by age and comorbidity. De Boer *et al.* Abstract 123O

### Practice point and future research opportunities

This study shows that omission of radiotherapy after breast conserving surgery in patients aged 75 years or older is not uncommon in the Netherlands, but the risk of locoregional recurrence did not associate with the observed variation in the proportion of patients receiving radiotherapy between hospitals.

# METASTATIC BREAST CANCER

## De-escalation of commonly used bone-targeting agents is a reasonable treatment option for patients with bone metastases from breast cancer

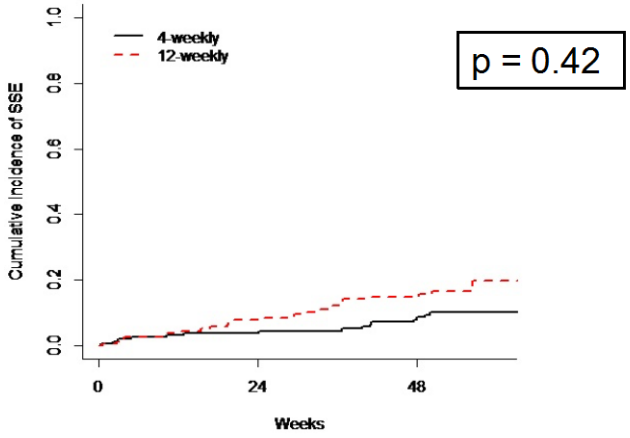
Mark Clemons, Department of Medicine, Division of Medical Oncology, The Ottawa Hospital Regional Cancer Centre, Ottawa, Canada discussed findings from the breast cancer cohort of the REaCT-BTA randomised trial comparing the non-inferiority of 12-weekly versus 4-weekly bone-targeting agents (BTAs) such as denosumab, zoledronate and pamidronate in patients with breast and prostate cancer. Women with breast cancer were elegible if they were BTA-naïve or already being treated with denosumab, zoledronate, or pamidronate. The 160 patients were randomly assigned 1:1 to receive their chosen BTA on a 12-week or 4-week schedule for one year. The primary endpoint was Health Related Quality of Life (HRQoL), as assessed using the EORTC Quality of Life Questionnaire (QLQ)-C30 Functional Domain-Physical Subdomain. Secondary endpoints included: pain, according to the EORTC-QLQ-BM22-pain domain, Global Health Status by the EORTC-QLQ-C30 and symptomatic skeletal event (SSE) rates, which was calculated as the cumulative incidence of SSEs, accounting for death as a competing risk. Adverse events and toxicity were also compared between the two regimens.

The cohort consisted of 160 patients of whom 64 (40%) patients were BTA-naïve. The 12-week treatment group comprised 79 (49.4%) patients, and 81 (50.6%) patients received a BTA on a 4-weekly basis; 60 (37.5%) patients were treated with denosumab, 48 (30%) received zoledronate, and 52 (32.5%) patients received pamidronate.

With the 12- and 4-weekly regimens, the reported outcomes showed no significant difference in change from baseline regarding HRQoL, pain, or Global Health Status. The change in HRQoL-physical domain median scores was 0 (range, -87 to 20) in the 12-weekly arm compared to 0 (range, -60 to 60) in the 4-weekly arm, and the median QLQ-BM-pain scores were 0 (range, -80 to 33) compared to 0 (range, -27 to 20), respectively. The median change in Global Health Status scores were also the same in the respective treatment arms; the median QLQ-C30 was 0 (range, -67 to 50) versus 0 (range, -50 to 50) in the 12- and 4-weekly treatment arms, respectively.

The SSEs rates at 48 weeks occurred in 9 (11%) of patients on the 12–week schedule and 7 (9%) patients receiving BTAs every 4 weeks ($p = 0.42$).

## CUMULATIVE INCIDENCE OF SSE




*SSE rate is cumulative incidence of SSE, accounting for death as a competing risk

ESMO BREAST CANCER

Presented by Mark Clemons (mclemons@toh.ca)

Cumulative incidence of symptomatic skeletal events.



Changes in dosing schedules occurred less often in the 12-week versus the 4-week arm; 17% of patients versus 31% of patients in the respective arms had dosing changes. The results were also similar for subgroup analyses across the BTA naïve and pre-treated groups, as well as for patients receiving denosumab, zoledronate, or pamidronate. NCT02721433. Clemons *et al.* Abstract LBA3

### Practice point and future research opportunities

The overall results of the REaCT-BTA trial are pending; findings from the breast cancer cohort are consistent with those previously reported for de-escalating zoledronate, although this trial also included patients receiving de-escalated denosumab and pamidronate. The data presented suggest that de-escalation of commonly used BTAs is a reasonable treatment option in patients with breast cancer.

## Adding everolimus to maintenance hormonal therapy boosts progression-free survival after first-line chemotherapy for HR-positive/HER2-negative metastatic breast cancer

Valentina Guarneri, University of Padua and the Istituto Oncologico Veneto, Padua, Italy reported results from a study that aimed to evaluate whether maintenance everolimus, an mTOR inhibitor, combined with aromatase inhibitors (AIs) could prolong progression-free survival (PFS) and disease control over AI alone in patients with advanced hormone receptor (HR)-positive/HER2-negative metastatic breast cancer after first-line chemotherapy. The investigator driven, randomised phase III Main-A trial enrolled postmenopausal women achieving disease control, which was defined as stable disease, partial response, or complete response after first-line chemotherapy. Following randomisation, 52 patients were treated with oral everolimus at 10 mg daily plus standard AI and 58 patients received AI alone. The primary aim was PFS. The patients' median age was 58 years, and exactly half (50%) had liver metastases. The median interval from the time of primary diagnosis to first metastasis in the overall population was 11.2 months.

After a total of 88 PFS events were recorded, 40 had occurred in the everolimus plus AI arm compared to 48 in the AI arm. These high-risk patients with metastatic breast cancer demonstrated prolonged PFS of 2.7 months following maintenance therapy with everolimus plus an AI. Although not statistically significant, median PFS was improved to 9.9 months with everolimus plus AI compared to 7.2 months with AI only (hazard ratio 0.764).

Everolimus raised no new safety signals. Treatment-related adverse events (AEs) were reported for 45 (87%) patients receiving everolimus compared to 15 (26%) patients on AI. The most commonly reported grade ≥2 AEs in the everolimus arm were stomatitis (19.2%), neutropenia (9.6%), interstitial pneumonia (7.7%) and skin toxicity (7.7%). Dose reductions of everolimus were reported for 28 patients and 16 patients discontinued everolimus due to an AE or non-compliance compared to just one patient who discontinued AI therapy due to an AE. Eudract: 2013-004153-24. Guarneri *et al.* Abstract LBA2

### Practice point and future research opportunities

This is the first randomised trial of maintenance endocrine therapy after chemotherapy for HR-positive/HER2-negative metastatic breast cancer. Although the findings did not reach statistical significance, the study demonstrated that everolimus plus AIs administered as maintenance treatment after chemotherapy provided nearly three months of additional PFS for patients with difficult to treat HR-positive/HER2-negative metastatic breast cancer.

## Outcome and mutational landscape of patients with PIK3CA-mutated metastatic breast cancer

Fernanda M. Mosele, Department of Medical Oncology, Gustave Roussy - Cancer Campus, Villejuif, France discussed the recently reported improved outcomes observed in patients with PIK3CA-mutated, hormone receptor (HR)-positive/HER2-negative metastatic breast cancer receiving an α-selective PI3K inhibitor. Dr Mosele and colleagues investigated the natural history of PIK3CA mutated breast cancer in 649 patients participating in the SAFIR02 trial. Patients having an available mutational profile and clinical data were selected for the outcome analysis. PIK3CA mutations were prospectively determined by next generation sequencing in metastatic samples as were the mutations enriched in PIK3CA in 629 metastatic breast cancer samples using whole exome sequencing.

In the overall cohort, the tumour samples of 143 (22%) patients harboured PIK3CA mutation; of these, PIK3CA mutations were found in 104 (29%) of HR-positive/HER2-negative tumours and in 27 (10%) of triple negative breast cancer (TNBC) tumours ($p < 0.001$).

Patients with HR-positive/HER2-negative, PIK3CA mutated tumours demonstrated less sensitivity to chemotherapy (odds ratio multivariate 0.40; $p = 0.002$). The median overall survival (OS) for patients with PIK3CA mutated, HR-positive/HER2-negative metastatic breast cancer was 19.6 months compared to 23.5 months for PIK3CA wild type patients ($p = 0.048$) (hazard ratio [HR] multivariate: 1.44; $p = 0.039$).

PIK3CA mutated, HR-positive/HER2-negative tumour samples were enriched in MAP3K1 mutation (17% versus 5%; $p = 0.0002$), whereas PIK3CA wild type tumours were enriched in GATA3 (25% versus 14%, $p = 0.022$) or AKT1 mutations (11% versus 3%; $p = 0.008$). Patients with HR-positive/HER2-negative, PIK3CA mutated tumours who also harboured MAP3K1 mutation had a 24-month OS of 14.7% compared to 45.5% for wild type patients ($p = 0.0059$; HR multivariate 1.84; $p = 0.02$). Median OS in patients with TNBC plus PIK3CA mutated tumours was 24.2 months compared to 14 months in patients with PIK3CA wild type tumours ($p = 0.028$).

Evaluation of PIK3CA mutation in metastatic TNBC, according to hormone receptor expression on the primary tumour revealed that 6% of patients with TNBC had a PIK3CA mutation both in the primary tumour and metastasis, whereas 39% of patients had a mutation in the metastasis. Fourteen patients who were HR-positive on the primary tumour had PIK3CA mutation. NCT02299999. Mosele *et al.* Abstract 149O

### Practice point and future research opportunities

The results of this analysis indicate that patients with PIK3CA mutated, HR-positive/HER2-negative metastatic breast cancer are less sensitive to chemotherapy and have a poorer outcome. MAP3K1 mutations are more frequent in these patients and are associated with shorter survival whereas patients with PIK3CA mutated TNBC have better survival. This

could be explained by an enrichment of PIK3CA mutations in patients with luminal breast cancer who lost expression of the hormone receptor in the metastatic setting.

Jens Huober, University Hospital Ulm, Ulm, Germany, and colleagues reasoned that a dual blockade of using pertuzumab plus trastuzumab followed by T-DM1 at progression might have efficacy similar to chemotherapy but less toxicity in patients with HER2-positive metastatic breast cancer. Therefore, they evaluated overall survival (OS) and Quality of Life (QoL) according to hormone receptor (HR) status in the phase II PERNETTA trial.

## Pertuzumab plus trastuzumab or chemotherapy followed by T-DM1 in case of progression provides similar 2-year overall survival in HER2-positive metastatic breast cancer

The study enrolled 210 patients with centrally confirmed HER2-positive metastatic breast cancer who were randomised equally to receive either pertuzumab plus trastuzumab alone or pertuzumab plus trastuzumab combined with weekly paclitaxel or vinorelbine, followed by maintenance treatment with pertuzumab plus trastuzumab until progression. At progression, patients in both arms were treated with second-line T-DM1. The primary endpoint was 24-month OS and the secondary endpoints included progression-free survival (PFS). QoL was assessed during first-line treatment every 3 months up to 24 months according to the NFBSI-16 and expressed as the summary score and subscale scores for disease-related symptoms, treatment side-effects, and function/well-being. Two single items assessed treatment burden and coping. The patients were enrolled from May 2013 until January 2016. Their median age was 58 years, 63% of patients had lung or liver metastases, and 36% of tumours were HR- negative. Paclitaxel/vinorelbine was administered to 46 of 59 patients.

Two-year OS was the same with both treatments; the median 2-year OS rates were 76.2% with the combination compared to 76.2% with chemotherapy. Receptor expression did not affect OS; in patients with oestrogen receptor (ER)-positive and/or progesterone receptor (PgR)-positive tumours, median 2-year OS was 75.0% versus 74.2% with the respective treatments. However, more patients negative for hormone receptor expression achieved OS at 2 years; median 2-year OS rates in the ER-negative and PgR-negative subgroup was 81.1% versus 79.5%.

The PFS during the duration of first-line therapy was shortened by more than a half in the pertuzumab plus trastuzumab arm compared to the chemotherapy combination arm: median PFS in the overall population was 8.4 months versus 23.3 months respectively. The same pattern of PFS was observed according to hormone receptor expression; in patients positive for receptors, median PFS was 8.3 months versus 23.7 months with the respective treatments. Median PFS in the ER-negative and PgR-negative cohort was 8.8 months versus 22.2 months, respectively.

Changes from baseline showed small improvements in QoL NFBSI-16 summary scores with pertuzumab plus trastuzumab, whereas the QoL scores remained stable with chemotherapy. Patients receiving chemotherapy also reported more treatment burden during the first 6 months and both arms demonstrated clinically relevant improved coping scores. Huober *et al.* Abstract 150O

### Practice point and future research opportunities

Although PFS was shorter during first-line pertuzumab plus trastuzumab compared to chemotherapy, the 2-year OS rates were similar for pertuzumab/trastuzumab followed by T-DM1 compared to chemotherapy. The QoL was also similar during first-line in both arms, but side-effects occurred less frequently in the chemotherapy-free arm.

## Novel U3-1402, a HER3-targeting antibody-drug conjugate, shows anti-tumour activity in HER3-overexpressing metastatic breast cancer

Kan Yonemori, Department of Breast and Medical Oncology, National Cancer Centre Hospital, Tokyo, Japan discussed the ongoing phase I/II study of U3-1402, a HER3-targeted antibody drug conjugate with a novel peptide-based cleavable linker and a potent topoisomerase I inhibitor payload. The study is evaluating the safety, tolerability, and efficacy of U3-1402 in patients with HER3-overexpressing metastatic breast cancer. Professor Yonemori presented updated results from the dose escalation and dose finding phase. During dose escalation, the U3-1402 dose was escalated from 1.6 to 8.0 mg/kg based on dose-limiting toxicity (DLT) data and guided by the modified Continuous Reassessment Method. During dose finding, patients received one of 2 doses at 4.8 or 6.4 mg/kg. The 42 enrolled patients had a median age of 54.5 years, and they had received a median of 6 prior anticancer regimens. The primary objectives were to determine the maximum tolerated dose (MTD), the recommended dose for expansion and safety/tolerability. Efficacy was described as investigator-assessed objective response rate (ORR) and disease control rate (DCR) per RECIST v1.1. Pharmacokinetics and anti-drug antibodies were also assessed.

As of 6 November 2018, U3-1402 was administered to 34 patients during dose escalation and 8 patients in the dose finding phase. Of these, 21 patients have discontinued treatment. In the overall population of 42 patients, the ORR was 42.9% and the DCR was 90.5%.

During a median 7.6-month exposure, 33.3% of patients had serious treatment-emergent adverse events (TEAEs) regardless of causality and 16.7% of patients had a drug-related AE. Grade ≥3 TEAEs occurred in ≥15% of patients regardless of causality that included thrombocytopenia (35.7%), neutropenia (28.6%), leukopenia (21.4%), and anaemia (16.7%). The MTD was not reached. The DLTs included events of decreased platelet count and increases in AST or ALT. One patient discontinued treatment due to a TEAE. No TEAEs leading to death were observed. NCT02980341.Yonemori *et al.* Abstract 151O

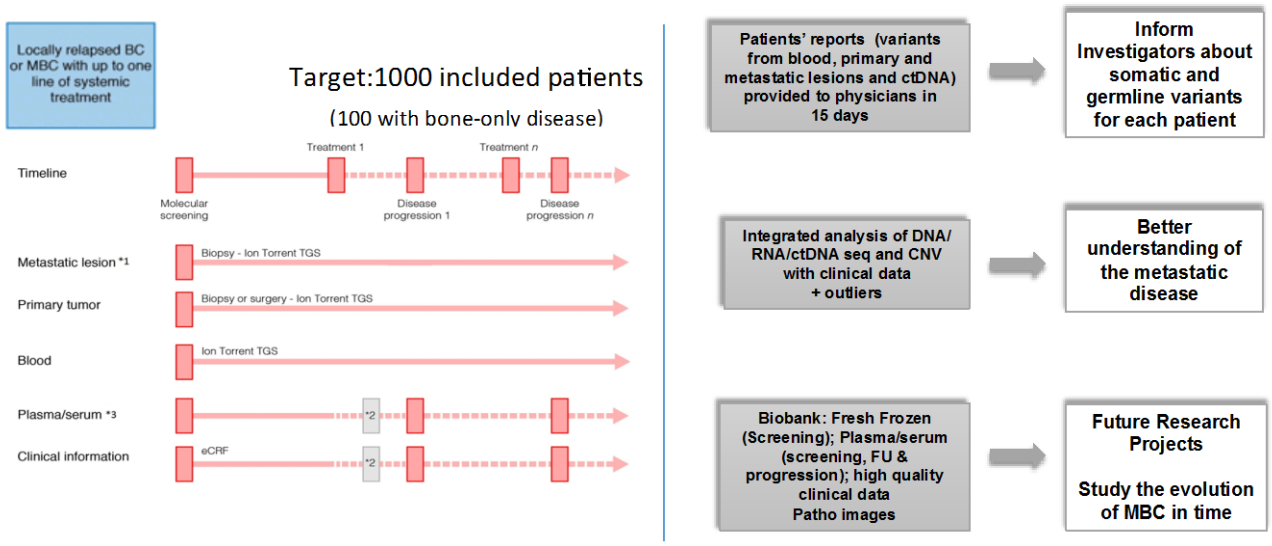
### Practice point and future research opportunities

Findings from this preliminary analysis of the ongoing phase I/II clinical trial of U3-1402 demonstrated that U3-1402 provided anti-tumour activity in heavily pre-treated patients with HER3-expressing metastatic breast cancer together with a manageable safety profile.

## Comprehensive molecular analysis of samples from the AURORA programme is underway

Philippe Aftimos, Clinical Trials Development Leader at Institut Jules Bordet, Brussels, Belgium, the co-principal investigator of the AURORA programme, which is a large pan-European molecular screening programme sponsored by the Breast International Group that aims to portray the comprehensive longitudinal molecular disease evolution in metastatic breast cancer. The programme includes patients presenting with metastatic breast cancer at first diagnosis or after receiving one line of therapy for metastatic disease. The investigators performed targeted gene sequencing (TGS) real-time in a central lab on DNA that was extracted from the primary tumour, from a metastatic biopsy, from whole blood, and on circulating tumour DNA (ctDNA) that was extracted from baseline plasma. RNA sequencing and copy number variations (CNVs) analyses were performed in batches. All samples including fresh frozen biopsies and sequential plasma and serum samples in the ongoing study are being biobanked for future research.

The ongoing analysis is designed to include a total of 1000 patients and up to 100 patients with bone-only disease. Pathology, clinical baseline and follow-up data are collected, and pathology slides are scanned at high resolution. In patients with assessable data, a report with the TGS data was annotated by a molecular advisory board and provided to the treating physician.




AURORA study design.

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Dr Aftimos presented the results that were available for the first 381 patients that had been included by November 2017. The pathological subtype distribution included 228 hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, 71 triple-negative breast cancer (TNBC) and 51 HER2-positive tumours; for 31 cases the information was not available. In total, 292 (77%) patients were treatment naïve in the metastatic setting including 76 patients (20%) with de novo metastatic disease. The analysis focused on patients with paired samples (primary and metastases) and showed a global increase in the number of mutations in metastatic samples.

The TGS and CNV analyses data identified molecular alterations enriched in the metastatic samples such as ESR1, PTEN, KAT6A, MYC, MDM4 and AKT3. Copy number losses were more prevalent in metastatic samples and included RB1 and ARID1A. RNA sequencing showed some subtype switching between the primary tumour and subsequent metastasis as well as a lower expression of immune signatures in the metastatic samples. TGS of ctDNA extracted from the baseline plasma samples proved to be complementary in certain cases by identifying potentially actionable molecular alterations that would have been missed otherwise.

While applying the new ESMO Scale for Clinical Actionability of molecular Targets (ESCAT), the investigators found that as much as 52% (42% when excluding HER2 amplification) of included metastatic breast cancer patients had at least one Tier I or Tier II alteration.

## Molecular screening of MBC: ready for daily practice?

| | Readiness of use in clinical practice | ESCAT for alterations in breast cancer | Prevalence in the AURORA population |
|---|---|---|---|
| **Tier I (I-A, I-B, I-C)** | Targets ready for implementation in routine clinical decisions | **ERBB2 amplification** (IA), **germline BRCA1/2 mutations** (IA), **PIK3CA mutations** (IA), MSI (IC), TRK fusions (IC) | **149 (39.4%)** |
| **Tier II (II-A, IIB)** | Investigational targets likely to define patients who benefit from a targeted drug, but additional data needed | **PTEN loss** (IIA), **ESR1 mutations** (IIA), **AKT1 mutations** (IIB), **ERBB2 mutations** (IIB) | **66 (17.5%)** |
| **Tier III (III-A, III-B)** | Clinical benefit previously demonstrated in other tumour type or for similar molecular targets | **Somatic BRCA1/2 mutations (IIIA), MDM2 amplification (IIIA), ERBB3 mutations (IIIB)** | 13 (3.4%) |
| **Tier IV (IV-A, IV-B)** | Preclinical evidence of actionability | ARID1A/B, **ATM/ATR/PALB2**, **CDH1**, **IGF1R**, INPP4B loss, **MAP2K4/MAP3K1**, MT4, **MYC, NF1**, **PIK3R1**, RUNXB1/CBFB, SF3B1, **TP53** (IVA) | 169 (44.7%) |
| **Tier V** | Evidence supporting co-targeting approaches | | |
| **Tier X** | Lack of evidence of actionability | **CCND1 amplification, FGFR1 amplification** | 15 (4%) |

**At least 1 alteration identified in 52% of patients**

In bold, Iterations tested using targeted gene sequencing real-time.

Mateo J et al. Ann Oncol 2018.
Condorelli R et al. Ann Oncol 2019.

ESCAT application in the AURORA programme.

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These integrated molecular analyses shed light on alterations that correlated with disease progression and therapeutic resistance in metastatic breast cancer. While the evidence supports molecular evolution of the disease during its life cycle, there are few molecular profiling studies that provide comprehensive longitudinal molecular and clinical data. NCT02102165. Aftimos *et al.* Abstract 152O

### Practice point and future research opportunities

This analysis of data from the AURORA programme sheds light on the molecular makeup of several clinically-relevant categories of metastatic breast cancer. The integrated molecular analyses include DNA-TGS, RNAseq, and CNV analyses from the AURORA programme that highlight molecular alterations enriched in metastatic breast cancer and correlated with disease progression and therapeutic resistance. The prevalence of Tier I and Tier II molecular alterations per ESCAT shows promise for routine molecular profiling in metastatic breast cancer. The biobank and curated clinical database within AURORA will

empower future research for metastatic breast cancer, which remains an incurable disease and the second cause of cancer mortality for women worldwide.

## Response rates in patients with HR-positive/HER2-negative advanced breast cancer according to geographic region are generally consistent with overall results of the SOLAR-1 trial

Sibylle Loibl of the Department of Medicine and Research, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany explained that approximately 40% of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor-2 (HER2)–negative advanced breast cancer have tumours that exhibit PIK3CA mutations, resulting in phosphatidylinositol 3-kinase (PI3K) pathway hyperactivation. Previously reported findings from the phase III, randomised, double-blind SOLAR-1 trial demonstrated that alpelisib, an oral α-specific PI3K inhibitor, plus fulvestrant therapy significantly improved progression-free survival (PFS) in patients with advanced breast cancer and a PIK3CA mutation (hazard ratio [HR] 0.65; $p < 0.01$). The SOLAR-1 enrolled men and postmenopausal women with HR-positive/HER2-negative advanced breast cancer that progressed on or after aromatase inhibitor treatment. The SOLAR-1 randomised 572 patients to alpelisib at 300 mg once daily or placebo plus fulvestrant at 500 mg every 28 days cycle 1, day 15. In total, 341 patients had a PIK3CA mutation.

Professor Loibl presented findings from the SOLAR-1 according to geographical region. The PIK3CA-mutated cohort comprised patients enrolled in Europe (n=173), North America (n=43), Asia (n=34), and Latin America (n=31); data for Japan will be presented separately.

Regarding the European arm, patients treated with alpelisib had median PFS of 11.0 months versus 3.6 months with placebo (HR 0.56); the overall response rate (ORR) was 27.9% compared to 11.5%, respectively. In North American patients, median PFS was 15.2 months versus 3.6 months (HR 0.41) and the ORR was 21.1% versus 16.7% with the respective treatments. Patients in the Asian cohort receiving alpelisib versus placebo/fulvestrant demonstrated median PFS of 14.5 versus 9.0 months (HR 0.55) and an ORR of 46.7% versus 10.5%, respectively. However, patients in Latin America demonstrated a different response with median PFS of 9.4 versus 12.9 months (HR 1.43) and an ORR of 21.4% versus 17.6%, with the respective treatments.

Among patients with mutated and non-mutated PIK3CA in the alpesilib arm, the median exposure in Europe, North America, Asia, Latin America, and overall was 5.5, 5.5, 7.6, 6.0, and 5.5 months, respectively. Median average daily alpesilib dose was 283.3, 294.0, 298.1, 260.2, and 286.1 mg/day.

Most common all-grade adverse events were hyperglycaemia in 63% of European, 75% of Asian, and 65% of Latin American patients whereas nausea most often occurred in 66% of North American patients. Diarrhoea occurred in European, North American, and Latin

American patients at rates of 61%, 66%, and 53% whereas decreased appetite was reported in 58% of patients in Asia. NCT02437318. Loibl *et al.* Abstract 153O

### Practice point and future research opportunities

The results of the SOLAR-1 trial according to geographical region were consistent with those reported for the overall population of the PIK3CA-mutated cohort; PFS was generally improved with alpesilib plus fulvestrant versus placebo and fulvestrant across most geographical regions. However, conclusions may be limited by a low number of PFS events and patient numbers in some regions.

## Achieving objective response improved patient-reported outcomes in patients with advanced breast cancer and a germline BRCA1/2 mutation in the EMBRACA study

Peter A. Fasching, Department of Gynaecology and Obstetrics, Universitätsklinik Erlangen, Erlangen, Germany discussed EMBRACA, a randomised phase III open-label study wherein patients with advanced breast cancer and a germline *BRCA*1/2 (gBRCA) mutation who were treated with talazoparib demonstrated a statistically significant higher objective response rate (ORR) compared to the treatment with physician's choice of chemotherapy (ORR 62.6% versus 27.2%; odds ratio [OR] 5.0; $p < 0.001$).

Professor Fasching and colleagues conducted this post hoc analyses among patients who achieved a response compared to those who did not to evaluate the effects of response on patient reported outcome (PRO). The evaluation was done on both treatments combined as well as for each treatment separately. PROs were assessed at baseline on day 1 at the start of each 3-week treatment cycle, and at the end of treatment using the EORTC Quality of Life Questionnaire (QLQ)-C30 and the breast cancer module QLQ-BR23. Higher scores indicated better global health status/quality of life (GHS/QoL). Stratification by ORR status (with response versus without response) within each treatment arm was done in 219 patients who received talazoparib and 114 patients who received chemotherapy in the trial. Repeated measures mixed-effects analyses were performed to compare the overall change from baseline scores while controlling for baseline. The time to definitive clinically meaningful deterioration (TDD) was defined as a decrease of ≥ 10 points in GHS/QoL and was compared between patients who had a response compared to those who did not using stratified log-rank test and Cox proportional hazards model.

In the combined arms, the overall change from baseline in GHS/QoL favoured patients achieving response versus those who did not respond (OR 3.9). Similarly, the overall change from baseline favoured patients with response versus those without response; in the talazoparib arm (OR 2.1) and in the chemotherapy arm (OR 3.4). When the two treatment arms were evaluated together, a greater delay in TTD in GHS/QoL was observed in patients with a response versus those without response (HR 0.67). This delayed TTD was also observed in patients in each separate arm; for responding versus non-responding

patients on talazoparib (HR 0.78) and on chemotherapy (HR 0.85). Fasching *et al.* Abstract 154O

## Practice point and future research opportunities

An overall change from baseline in QoL scores and greater delay in TTD in GHS/QoL were observed that favoured patients achieving a response with either talazoparib or chemotherapy treatment compared to those who did not achieve response. These results suggest that higher response rates may lead to better overall improvement in QoL from baseline in patients with advanced breast cancer and a gBRCA mutation.

# SUPPORTIVE CARE AND SURVIVORSHIP

## Long-term cardiac outcomes with trastuzumab plus lapatinib comparable to trastuzumab alone in patients with HER2-positive early breast cancer

Daniel Eiger, Academic Promoting Team, Institute Jules Bordet, Brussels, Belgium and a team of investigators evaluated the cardiotoxicity of a dual HER2 blockade using trastuzumab and lapatinib, which has been approved for patients with trastuzumab-resistant HER2-positive metastatic breast cancer. He reported cardiac data for 4,190 patients who received one year of adjuvant trastuzumab or concomitant trastuzumab/lapatinib in the ALTTO trial. ALTTO randomised 8,381 patients with early HER2-positive breast cancer into 4 arms to investigate the benefit of lapatinib and trastuzumab. The dataset for this analysis comprised patients randomised to the trastuzumab monotherapy arm and the combination trastuzumab plus lapatinib arm. Patients were required to have had a baseline left ventricular ejection fraction (LVEF) ≥50%, no serious cardiac illness, and cumulative doses of doxorubicin ≤360mg/m$^2$ or epirubicin ≤720mg/m$^2$. Signs and symptoms of heart failure and LVEF were assessed every 3 months during treatment, every 6 months until year 2, and yearly thereafter until year 10. Cardiac events were defined as symptomatic heart failure NYHA class II, III and IV associated with a significant LVEF drop, or an asymptomatic cardiac event described by a significant drop in LVEF without symptoms, and/or cardiac death. Acute recovery was defined as ≥2 consecutive LVEF assessments of ≥50% after a cardiac event. The distribution of cardiac events and endpoints are described by arm. A logistic regression model by arm was used to assess the odds of and risk factors for occurrence of a cardiac event.

Patient characteristics were balanced between the arms, except for diabetes, which was observed more often in the trastuzumab arm ($p = 0.024$). At median follow-up of 6.5 years (range, 5.6 to 7.1 years), fewer cardiac events were observed in the combination arm; 197 (9.3%) cardiac events occurred with trastuzumab and 166 (7.9%) occurred with trastuzumab/lapatinib. Median time to develop a cardiac event was also shorter with trastuzumab monotherapy; 6.4 months (range, 3.6 to 11.7 months) in the trastuzumab arm versus 7.1 months (range, 2.9 to 16.6 months) in the trastuzumab/lapatinib arm.

Most (73.2%) of the cardiac events occurred during treatment and 74% were asymptomatic. Acute recovery was reached in 83.6% and 84.1% of patients in the trastuzumab and trastuzumab/lapatinib arms, respectively. The time to recover from symptomatic cardiac events was 5.6 months with trastuzumab compared to 4.2 months with the combination, which was was longer than that observed for asymptomatic cardiac events of 3.1 months versus 2.9 months, respectively. Overall, 29.9% of patients recovering from a cardiac event also experienced a second LVEF drop to less than 50%.

The treatment completion rates were 84% with trastuzumab and 82% with trastuzumab/lapatinib; in the combination arm, 68% of patients completed lapatinib therapy.

Sixty percent of the patients discontinuing lapatinib cited safety as the cause, especially non-cardiac safety in 82% of these patients.

The investigators identified 5 risk factors for a cardiac event; of these the strongest association was seen between the occurrence of a LVEF 50-54% (versus >64%) prior to anti-HER2 treatment (multivariate OR 3.10; p = 0.002). The other risk factors with a strong association with a cardiac event included receipt of an epirubicin dose ≥480mg/m$^2$ (multivariate OR 2.33; p < 0.001), body mass index >30kg/m$^2$ as compared to <25kg/m$^2$ (multivariate OR 2.21; p < 0.001), and the presence of diabetes mellitus (multivariate OR 1.85; p = 0.002). NCT00490139; EudraCT Number: 2006-000562-36. Eiger *et al.* Abstract 199O

## Practice point and future research opportunities

Although one year of treatment comprising dual HER2 blockade with trastuzumab and lapatinib does not increase the rate of cardiotoxicity compared to trastuzumab monotherapy, identification of risk factors prior to start of therapy and close collaboration with cardiologists is essential to ensure proper treatment management and continuity.

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# Affiliations and Disclosure

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## Disclosure

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