ESMO 2016 Congress

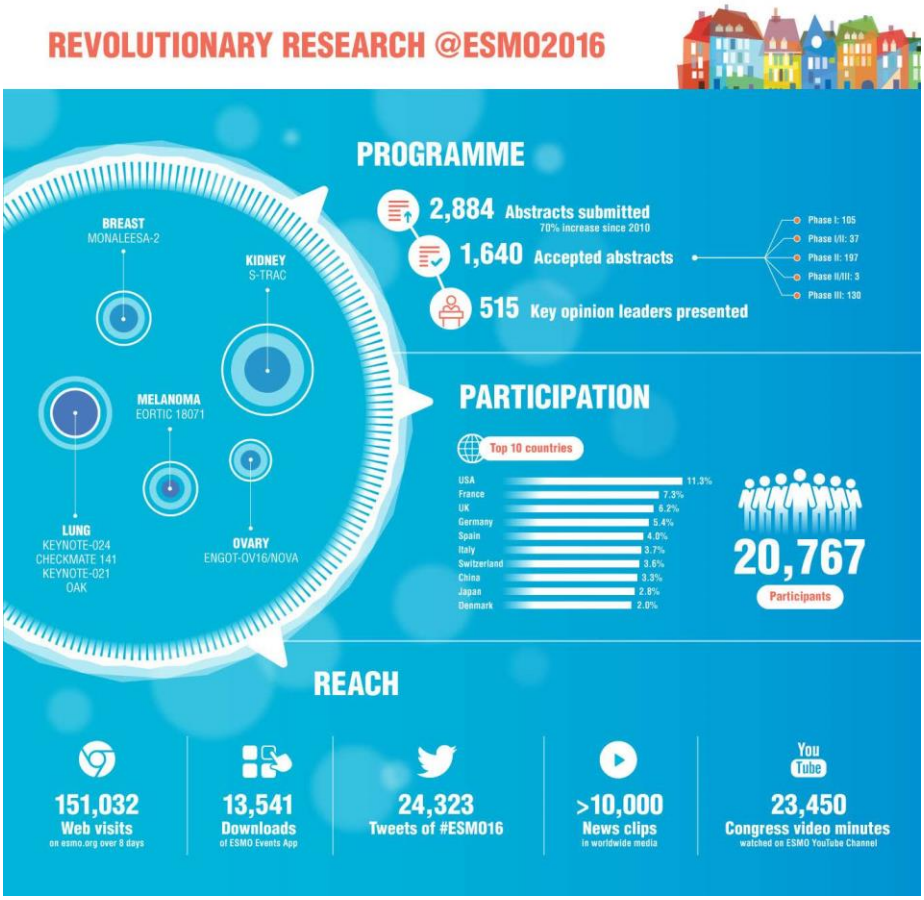
7-11 October, 2016

Copenhagen, Denmark

Table of Contents

Summary

The European Society for Medical Oncology (ESMO) 2016 Congress, held October 7 to 11 in Copenhagen, Denmark, was a record-breaker on all levels. It was resounding success and in a dedicated infographic you can find the congress programme statistics. A primary emphasis in the scientific programme was placed on two areas: precision medicine and immunology and immunotherapy across multiple tumour types and how these advances change the treatment landscape in oncology. This report is an overview of key scientific presentations made during the Congress by leading international investigators. It attempts to represent the diversity and depth of the ESMO 2016 scientific programme, as well as advances in oncology.



ESMO 2016 record breaking Congress

BREAST CANCER - Locally Advanced and Metastatic

Phase III results show first-line ribociclib and letrozole significantly improves PFS over letrozole monotherapy in HR-positive, HER2-negative, advanced breast cancer

Lead author Gabriel Hortobagyi from the University of Texas MD Anderson Cancer Center in Houston, USA presented the first preplanned interim analysis from the double-blind phase III MONALEESA2 trial that tested whether first-line ribociclib plus letrozole could improve progression-free survival (PFS) and delay or overcome the development of resistance to endocrine therapy in hormone receptor (HR) positive advanced breast cancer. MONALEESA2 enrolled 668 postmenopausal women who had not received prior systemic treatment for HR-positive, HER2-negative advanced breast cancer who were randomised to ribociclib at 600 mg/day, for 3 weeks on, one week off plus continuous letrozole at 2.5 mg/day, or to letrozole plus placebo.

The trial's primary objective, PFS, was met; patients in the ribociclib arm demonstrated a highly significant 44% improvement in PFS compared to the placebo arm, hazard ratio [HR] 0.556 (p = 0.00000329). At data cut-off, median PFS had not been reached with ribociclib versus 14.7 months in the placebo/letrozole arm. A significantly improved objective response rate of 53% with ribociclib plus letrozole was also seen compared to 37% with placebo/letrozole (p = 0.00028). The clinical benefit rate was 80% with ribociclib/letrozole compared with 72% with placebo/letrozole (p = 0.02). Overall survival data, a key secondary endpoint, were not yet mature.

The incidence of adverse events (AEs) was higher in the ribociclib arm; neutropenia occurred in 59% versus 1%, leukopenia 21% versus 1%, and lymphopenia occurred in 7% versus 1% of patients in the ribociclib/letrozole versus placebo/letrozolem respectively. A higher incidence of elevated alanine aminotransferase and elevated aspartate aminotransferase was also observed with ribociclib. Serious AEs occurred in less than 5% of patients in both arms. These results were published simultaneously online in *The New England Journal of Medicine (NEJM)*. NCT01958021. Hortobagyi *et al.* Abstract LBA1_PR; *NEJM* 2016; 375:1738-1748.

Practice point and future research opportunities

Endocrine therapy is an established first-line treatment for advanced breast cancer; however, resistance to endocrine therapy eventually develops in the majority of patients, leading to disease progression. CDK 4/6 inhibition with ribociclib is a valid treatment strategy to delay resistance development in for HR-positive advanced breast cancer. The interim results from the MONALEESA2 trial definitively demonstrate that adding ribociclib to letrozole therapy significantly improves PFS. These results represent a compelling proof of principle, and suggest a paradigm shift in metastatic, HR-positive, HER-negative breast cancer. They also suggest that

testing combinations of ribociclib with other inhibitors of various signalling pathways might lead to additional progress in the management of several subtypes of breast cancer.

Biomarker analyses from the PALOMA-2 trial of palbociclib plus letrozole in postmenopausal women with ER-positive/HER2–negative advanced breast cancer

Lead investigator Richard Finn, MD, from the Jonsson Comprehensive Cancer Center at UCLA, presented results of a biomarker analysis conducted on samples from 568 (85%) patients participating in the phase II PALOMA-2 trial. Of these, 566 samples were evaluable. PALOMA-2 compared the combination of palbociclib and letrozole to letrozole alone as a frontline treatment for postmenopausal women with ER-positive, HER2-negative advanced breast cancer. The combination nearly doubled the median progression-free survival (PFS) over letrozole; median PFS was 24.8 versus 14.5 months, hazard ratio [HR], 0.58 ($p < 0.001$) with combination versus monotherapy, respectively.

The biomarker analyses reported at ESMO 2016 was done to identify potential markers of clinical response and used tumour tissues from either the original diagnostic or the metastatic specimen, which were required from all patients. The investigators performed a central blinded analysis using immunohistochemistry (H-score ≥1 defined positivity) for determination of oestrogen receptor expression (ER-positive), retinoblastoma (Rb), p16, cyclin D1, and Ki-67 (proliferative indices based on 15%, 20%, and 40% cutpoints). Central review confirmed that 89% of samples were ER-positive. In the palbociclib plus letrozole cohort, the ER median (interquartile range) H-score was 120 (range: 45 to 170) versus 110 (range: 38 to 158) with placebo plus letrozole. By H-scores, PFS improvement with palbociclib/letrozole was observed across all ER quartiles. In Rb positive patients, which represented more than 90% of the intent-to-treat (ITT) population, median PFS was 24.2 versus 13.7 months, HR 0.53 ($p < 0.0001$). Patients that were p16-positive represented 85% of the ITT population and showed median PFS of 24.8 versus 13.8 months, HR 0.52 ($p < 0.0001$).

A trend was noted in the 56 patients that were p16 negative towards a benefit with palbociclib plus letrozole but no conclusion could be drawn for 29 Rb negative patients. Cyclin D1 was expressed in 97% of tumour samples but the benefit did not vary with H-score and Ki-67 index values did not identify a cohort that had better or worse PFS with combination treatment over letrozole alone. NCT01740427. Finn *et al.* Abstract LBA15

Practice point and future research opportunities

Palbociclib inhibits CDK4/6 thereby preventing DNA replication by blocking progression from G1 to S phase during cell division and tumour cell proliferation through control of the cell cycle. The rationale for the combination of an aromatase inhibitor with palbociclib stemmed from early preclinical evidence suggesting that CDK4/6 is more active in patients with ER-positive breast cancer, as a result of an intact Rb-pathway. This is consistent with results from this biomarker analysis showing a benefit from adding a CDK4/6 inhibitor in ER-positive patients. However, no additional markers for benefit from palbociclib/letrozole emerged from this analysis.

Improved PFS with fulvestrant over anastrozole in HR-positive advanced breast cancer

Matthew Ellis, Lester and Sue Smith Breast Center, Baylor College of Medicine in Houston, Texas, USA presented findings that showed progression-free survival (PFS) was significantly increased with fulvestrant in women with hormone receptor (HR)-positive advanced breast cancer. Fulvestrant is a selective oestrogen receptor (ER) degrader that targets the HR without affecting oestrogen levels. Dr. Ellis and colleagues conducted a double-blind, multi-centre phase III trial that enrolled 462 women with inoperable locally-advanced or metastatic ER-positive, HER2-negative breast cancer. The women, who had not received prior hormone therapy, were randomised to 500 mg intramuscular injections of fulvestrant on days 0, 14, 28, and then every 28 days (n=230), or to 1 mg of anastrozole daily (n=232). All patients were also allowed one line of chemotherapy.

Median PFS by RESIST 1.1 (primary endpoint) after a median follow-up of 25 months was 16.6 months in patients receiving fulvestrant compared with 13.8 months in patients receiving anastrozole; patients in the fulvestrant arm had a statistically significant 21% improvement in PFS (p = 0.048). The results with fulvestrant were particularly impressive in patients with less aggressive lower-volume disease where PFS was 22.3 versus 13.8 months in patients receiving fulvestrant over those on anastrozole in patients with non-visceral disease who did not show liver or lung involvement at baseline. The objective response rate was 46.1 with fulvestrant and 44.9% with anastrozole, odds ratio 1.07; 95 % confidence interval [CI] 0.72, 2.61 (p = 0.729), and the median duration of response was 20 versus 13.2 months in the respective groups. Death occurred in 29.1% of fulvestrant versus 32.3% of anastrozole patients, hazard ratio 0.88; 95% CI 0.63, 1.22 (p = 0.428)

Both treatment arms showed a similar health-related quality of life. The most commonly reported adverse events (AEs) were arthralgia, which occurred in 16.7% versus 10.3%, and hot flushes in 11.4% versus 10.3% of patients receiving fulvestrant and anastrozole, respectively. NCT01602380. Ellis *et al.* Abstract LBA14_PR

Practice point and future research opportunities

These phase III trial results represent an important advance in the treatment of the most common form of breast cancer, and suggest a potential benefit for using fulvestrant earlier in a patient's treatment. These results confirm the superior efficacy of fulvestrant over anastrozole in postmenopausal women with hormone receptor (HR)-positive locally advanced or metastatic breast cancer who have not received prior hormonal therapy. Physicians would typically choose endocrine therapy as a first approach in patients with non-visceral disease; these findings suggest that fulvestrant could be a new standard of care compared to anastrozole, since the two treatments are tolerated similarly well.

However, since the design of the study, the standard of care for women with this type of disease

has moved on to the CDK4/6 inhibitor, palbociclib, in combination with an aromatase inhibitor, for this group of patients. Fulvestrant may be a preferred option for women with non-visceral breast cancer, where particularly strong results were seen with fulvestrant, or for older patients who require a treatment with low toxicity.

Safety and efficacy findings from the Heritage phase III trial of the proposed trastuzumab biosimilar Myl-1401O

Trastuzumab markedly improves survival in women with HER2-positive breast cancer, but the high cost makes it unavailable to many women. Hope S. Rugo, University of California San Francisco Comprehensive Cancer Center and colleagues evaluated the biosimilar, MYL-1401O, for equivalence to the reference drug, trastuzumab, with the goal that introduction of a biosimilar will expand patient access to this effective drug. The investigators conducted the Heritage randomised, double-blind, phase III trial in 500 treatment-naive women with metastatic, HER2-positive breast cancer at 95 sites across Asia, Latin America, and Europe. The women were randomised to first-line treatment with a taxane (docetaxel or paclitaxel, per investigator's choice) plus MYL-1401O or to a taxane plus trastuzumab for at least eight cycles. Patients with stable disease after 8 cycles continued their assigned treatment.

The regulatory requirements for a biosimilar include demonstration of structural and functional similarity to the reference product, similar pharmacokinetics and pharmacodynamics, and confirmed similar safety, efficacy, and immunogenicity. After 24 weeks of treatment, data from 458 women were evaluable which revealed that the biosimilar demonstrated comparable efficacy, safety, and immunogenicity to the reference product, meeting the primary endpoint. The primary endpoint, objective response rate (ORR) by RESIST1.1 was met; ORR was 69.6% for MYL-1401O compared to 64% for branded trastuzumab. The difference in ORR was 5.5%, which fell within the equivalency range. The ratio of ORR was 1.09; confidence intervals [CI] at 2 limits were both within the pre-defined equivalence margin (90% CI 0.974, 1.211) and (95% CI 0.954, 1.237). Median progression-free survival was assessed with a minimum follow up of 48 weeks and was not statistically different at 11.1 months in both arms, hazard ratio [HR] 0.96 (95% CI 0.730, 1.261; log rank p = 0.764). Median overall survival (OS) had not been reached in either arm; however, 48 week-OS rates were 89.1% and 85.1% for MYL-1401O and trastuzumab, respectively.

Immunogenicity and safety were comparable between treatment arms. The rate of serious adverse events was 39.3% in the biosimilar arm versus 37.0% in the trastuzumab arm. Neutropenia was the most common serious adverse event in both arms. Six and 4 fatal events occurred in the MYL-1401O and trastuzumab arms, respectively. EudraCT No: 2011-001965-42. Rugo *et al.* Abstract LBA16

Practice point and future research opportunities

For regulatory approval, the FDA requires the primary endpoint to be ORR ratio, whereas the European Medicines Agency (EMA) requires it to be the difference in ORR. The trastuzumab biosimilar is not yet FDA-approved, but it appears that 24-week results met FDA requirements

of ORR ratio and Myl-1401O appears to be equivalent to trastuzumab when given in combination with a taxane as first line therapy for metastatic breast cancer. Safety, immunogenicity and pharmacokinetic data were also comparable between the biosimilar and reference product.

Just one oncology biosimilar has been FDA-approved thus far, filgrastim-sndz which is marketed for about 15% less than the reference product in the United States. The EMA approved pegfilgrastim biosimilar costs about 25% less than the reference product.

These results of this study show potential ists to broaden access to a lifesaving agent.

Phase I trial results show trastuzumab biosimilar candidate BCD-022 is equivalent to trastuzumab in patients with HER2+ metastatic breast cancer

Maria Shustova, Medical Department, JSC "BIOCAD", St. Petersburg, Russian Federation, and colleagues conducted a trial of BCD-022, a trastuzumab biosimilar, which has already demonstrated equivalence to trastuzumab in a comprehensive comparability physicochemical, non-clinical pharmacokinetic (PK) and pharmacodynamic studies. Dr. Shustova presented findings from an international multicentre randomised double blind PK clinical study that was carried out in patients with HER2-positive metastatic breast cancer. The phase I study randomised 126 patients in a 1:1 ratio to receive either BCD-022 or trastuzumab at a loading dose of 8 mg/kg followed by a maintenance dose of 6 mg/kg in combination with paclitaxel at 175 mg/m^2 every 3 weeks for up to 6 cycles of therapy or until progression or unbearable toxicity.

The objective response rate (ORR), the trial's primary endpoint, was similar in the treatment arms; ORR was 53.57% (95% confidence interval [CI] 40.70%, 65.98%) in the BCD-022 group compared to 53.70% (95% CI 40.60%, 66.31%) with trastuzumab. On the lower end of the spectrum, BCD-022 statistically showed that it was not inferior to trastuzumab since the lower limit of the 95% CI for the difference in ORR between the groups (-19.83%) did not exceed the non-inferiority margin.

No differences between the groups were observed for all other efficacy parameters. Complete response was achieved by 5.36 versus 3.70%, partial response by 48.21% versus 50.00%, and stable disease was reported for SD 25.00% versus 25.93% of patients in the BCD.022 versus trastuzumab arms, respectively. In all, 21.43% of patients receiving BCD-022 compared to 20.37% of trastuzumab patients experienced disease progression.

The adverse event (AE) profiles of BCD-022 and trastuzumab were equivalent; no statistically significant difference was observed between the treatment arms in the rate of all observed AEs, including severe AEs. The investigators determined that the majority of AEs were chemotherapy-associated; the most commonly reported AEs that occurred in 40% or more in either group included neutropenia (73.02% versus 73.77%), anaemia (82.54% versus 77.05%), leukopenia (73.02% versus 68.85%), lymphopenia (69.84% versus 65.57%), hyperglycaemia (57.14% versus 70.49%), ALP increase (38.68% versus 42.62%), AST increase (42.86% versus 42.62%),

and increased ALT (33.33% versus 40.98%), Trastuzumab-specific cardiovascular events included tachycardia (34.92% versus 19.67%), and arterial hypertension (20.63% versus 18.03%), which occurred in BCD-022 versus trastuzumab, respectively. Other trastuzumab-specific cardiovascular events that occurred only in the trastuzumab arm were atrial fibrillation at 3.28%, and extrasystoles at 1.64%) whereas CAD grade 1 occurred at 1.59%, and aggravated myocardiodystrophy occurred at 1.59% only with BCD-022. Binding antibodies with neutralizing activity were detected in just one patient in each group, indicating the low immunogenic potential of both drugs. Shustova *et al.* Abstract 224PD

Practice point and future research opportunities

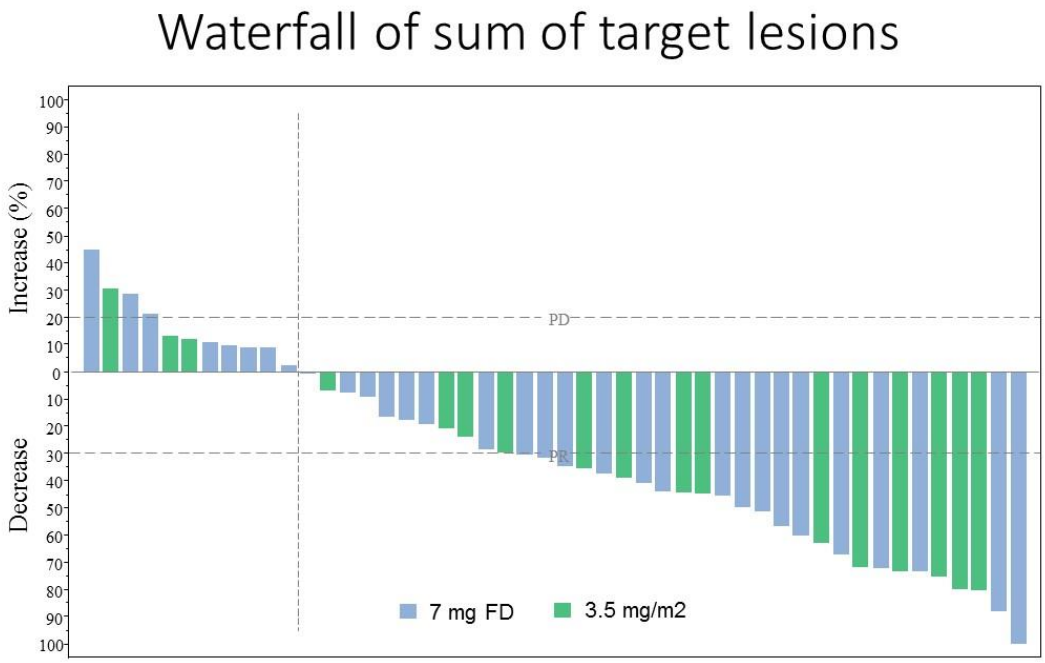
Trastuzumab is an important drug for treating HER2-positive metastatic breast cancer and biosimilars could cost less and make treatment available to far more women. In this phase I study, BCD-022 showed non-inferiority to trastuzumab in ORR rate and other efficacy parameters also were equivalent between the agents. Both medications demonstrated comparable safety and immunogenicity findings. The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have guidelines for obtaining marketing authorisation of biosimilars. An agent is considered a biosimilar if it is proven to be highly similar to an already approved biologic therapy, based upon analytical, animal, and clinical studies assessing immunogenicity, pharmacokinetics or pharmacodynamics. Thus biosimilars could be considered interchangeable if they demonstrate similar clinical outcomes compared with the reference product in a larger clinical trial, such as a phase III study. Results from the next step in testing BCD-022 are anticipated.

Lurbinectedin demonstrates clinical benefit in patients with BRCA mutation positive metastatic breast cancer and proceeds to phase III trial evaluation

Lead investigator Judith Balmaña, Department of Medical Oncology, Hospital Vall d'Hebron and Vall d'Hebron Institute of Oncology in Barcelona, Spain, presented findings from a phase II trial of lurbinectedin in 54 patients with BRCA mutation positive measurable metastatic breast cancer per RECIST v1.1. BRCA1 mutations were documented in 30 patients and 31 patients had triple negative breast cancer. The patients' median age was 43 years. The patients had performance status ≤ 1, and 30 patients were performance status 0. More than 2 metastatic sites were identified in 33 patients. The patients had a median of one prior chemotherapy treatment for advanced disease; additionally, 45 patients had received prior anthracyclines, 47 received taxanes, 27 received platinum, and 9 had been treated with PARP inhibitors. Lurbinectedin was initially to be administered to all patients at 7 mg fixed dose by i.v. every 3 weeks but the dose was changed by protocol amendment to 3.5 mg/m^2 for improved safety. In all, 35 patients received 7 mg of lurbinectedin and 19 patients were treated with 3.5 mg/m^2.

Lurbinectedin (PM01183) blocks trans-activated transcription by binding to the minor groove of DNA. Activity has been demonstrated in patients with diverse tumour types, and in those that are resistant to platinum-based chemotherapy. Observations that lurbinectedin was active against homologous-recombination-deficient cell lines led investigators to test it in patients with metastatic breast cancer having deleterious germline BRCA mutations.

Lurbinectedin had been administered to 54 patients as of May 2016, with patients receiving a median of 6 (range: 1 to 24) treatment cycles. The trial met the primary endpoint of confirmed overall response rate (ORR) by RECIST v1.1 Of 54 patients with evaluable data, the ORR was 39% (95% CI 26, 54) in patients receiving the fixed dose, and 44% in patients dosed at 3.5 mg/m^2, with an overall response rate of 40.7% (95% CI 27, 55). The best overall response with lurbinectedin included complete response in one (2%) patient, partial response in 21 (39%) patients, and stable disease in 23 (43%) patients. Just 9 (17%) patients with advanced metastatic breast cancer experienced progressive disease. The median duration of response was 6.7 months (95% CI 3.0, 11.3) and progression-free survival was 4.1+ months (95% CI 2.8, 5.9). Platinum pre-treated patients demonstrated an ORR of 26% (95% CI 11, 26).



Waterfall of sum of target lesions.

© Judith Balmaña.

The most commonly reported grades 3/4 adverse events (AEs) in the subgroup receiving lurbinectedin at the 7 mg fixed dose included neutropenia in 71% of patients and grade 4 neutropenia, which was seen in 51%. Febrile neutropenia occurred in 29%, thrombocytopenia, and transaminase increase were each seen in 26% of patients. Grade 4 thrombocytopenia, and transaminase increase occurred in 20%, and 3% of patients respectively. Grade 3 fatigue and nausea occurred in 17% and 9% of patients, respectively. At the reduced dose, AEs included neutropenia in 50% of patients, febrile neutropenia and thrombocytopenia in 6% each, transaminase increase occurred in 11%, and grade 3 fatigue and nausea occurred in 17% and

6%, respectively. Grade 4 neutropenia was seen in 5% of patients but no other grade 4 AEs occurred in this cohort. Based on these results, a phase III trial of lurbinectedin is planned. Balmaña *et al.* Abstract 223O

Practice point and future research opportunities

Findings from this phase II trial demonstrate that lurbinectedin (PM01183) has activity in BRCA mutation positive metastatic breast cancer regardless of prior platinum treatment. Lurbinectedin blocks trans-activated transcription and activity has been also demonstrated in patients with diverse tumour types, and in those showing resistance to platinum-based chemotherapy.

Tolerance to lurbinectedin improved at the lower 3.5 mg/m^2 dose without compromising efficacy; indeed, the primary endpoint of ORR was met at both dose levels and was highest in the cohort receiving the reduced dose. Based on these results and on predefined criteria of 17 or more confirmed responses in the cohort of evaluable patients, further development of lurbinectedin in patients with BRCA mutation and metastatic breast cancer is warranted and lurbinectedin is being taken forward to a phase III trial in this indication.

Evaluation of the CTC count as a basis for clinical choice of first-line hormone therapy or chemotherapy for HR-positive, HER2-negative metastatic breast cancer

Francois-Clement Bidard, Medical Oncology, Institut Curie, Paris, France, explored the clinical applications of the circulating tumour cell (CTC) count in patients with hormone receptor (HR)-positive, HER2-negative metastatic breast cancer and its utility in clinical decisions. Prognostic factors are generally used in choosing between front-line hormone therapy, the preferred option, or chemotherapy; however, recent reports indicate that the CTC count better informs this decision. Professor Biddard and colleagues compared these strategies in the STIC CTC trial, a large multicentre phase III randomised trial. The investigators evaluated whether the front-line treatment type was best chosen according to clinician decision or by CTC levels.

This analysis was performed on 530 patients whose clinical and pathological characteristics were registered at the time of study inclusion, together with the *a priori* treatment of hormone therapy or chemotherapy that was preferred by clinicians in each patient according to these demographics. CTC count was done using CellSearch® and patients were randomised to receive *a priori* treatment or CTC-driven treatment comprised of hormone therapy when CTC levels were <5 CTC/7.5ml or chemotherapy if CTC counts were higher. In addition to standard statistical tests, multiple correspondence analysis (MCA) was also used to detect and represent underlying structures in the dataset. Many patients had adverse prognostic factors; 7% of patients had performance status 2 or 3, 34% had 3 or more metastatic sites, 39% had lymphocytopenia, and metastasis to the liver or pleuropulmonary region were identified in 20% and 37% of patients, respectively. Hormone therapy was the *a priori* treatment for 371 (70%) and chemotherapy was decided for 159 (30%) patients.

Patient characteristics that independently associated with the *a priori* choice included age ($p = 0.01$), treatment centre ($p < 0.001$), prior (neo)adjuvant chemotherapy (hazard ratio [HR] 0.47

favouring chemotherapy; p = 0.02), elevated SGOT (HR 0.41; p < 0.001), liver metastasis (HR 0.45; p = 0.005) and bone-only metastasis (HR 3.16 favouring hormone therapy; p < 0.001), and a disease-free interval more than 10 years (HR 3.45; p = 0.003).

In MCA, the first 2 axes were CTC count and the receipt of prior chemotherapy for early breast cancer, and the other clinical and pathological factors were distributed accordingly. Elevated CTC counts (≥5 CTC/7.5ml) were detected in 205 (39%) patients. Among the 263 patients randomised to the CTC-driven decision arm, *a priori* hormone therapy was decided for 186 (71%) patients that was confirmed in 122 (68%) patients and later switched to chemotherapy in 58 (32%) patients. The decision for *a priori* chemotherapy was made for 77 (29%) that was confirmed in 35 (49%) patients and then switched to hormone therapy in 37 (51%) patients. Bidard *et al.* Abstract 226PD

Practice point and future research opportunities

In the absence of any predictive factor, treatment decision is influenced by numerous prognostic factors and CTC can provide different and complementary data. Patient follow-up is ongoing to compare the outcome of patients with HR-positive, HER2-negative metastatic breast cancer whose treatment was CTC-driven compared to treatment based on the *a priori* clinical decision.

BRAF genomic alterations in metastatic breast cancer

Joan Albanell, Cancer Research Program, Institut Hospital del Mar d'Investigacions Mèdiques in Barcelona, Spain, investigated whether defining BRAF genomic alterations in metastatic breast cancer could identify druggable targets. The genomic alterations included base substitutions, indels, copy number alterations (CNA) and fusions/rearrangements. Dr. Albanell and colleagues extracted DNA from 40 microns of FFPE sections obtained from 7850 tumours to perform comprehensive genomic profiling (CGP) on hybridization-captured, adaptor ligation based libraries to a mean coverage depth of 579X for up to 315 cancer-related genes plus 37 introns from 14 genes frequently rearranged in cancer. The investigators identified 83 (1.1%) patients with BRAF-altered breast cancer, with a mean age of 57 years (range: 32 to 84 years). There were 39 ductal, one inflammatory, 3 metaplastic, 2 lobular, and 38 NOS tumours. The primary tumour could be used for CGP in 29 (34.9%) cases and tumours from metastatic sites including lymph nodes, liver, bone, lung, brain adrenal, and soft tissue was used in 54 (65.1%) cases.

CGP revealed BRAF genomic alterations that could possibly lead to aberrant MAPK signalling; 51.8% of cases contained BRAF amplifications, 15.7% had base substitutions in V600E, 3.6% had K601E base substitutions, 21.6% of cases had other missense base substitutions, and 6.0% of cases harboured fusions (6.0%). Three (3.6%) additional mutations were identified that are uncharacterised for their effect on BRAF signalling activity. Of the fusions identified, 2 were KIAA1549-BRAF, one each of AGK-BRAF, FCHSD2-BRAF, and KLHDC10-BRAF was found.

Tumours harbouring a BRAF amplification or base substitution genomic alteration also showed a statistically significant reduction in ERBB2 mutations.

Targetable genes that were more commonly amplified in tumours with BRAF genomic alteration compared to BRAF wild-type breast cancer, include CDK6 ($p = 0.001$), HGF ($p < 0.001$), and MET ($p < 0.001$). Although BRAF genomic alterations are uncommon in breast cancer and have been identified in 1.1% of cases, targetable base substitutions and rare fusions were identified. BRAF genomic alterations in metastatic breast cancer more commonly occur in HER2-negative and triple negative breast cancer. Alban ell, *et al.* Abstract 228PD

Practice point and future research opportunities

This study found that BRAF genomic alterations were rarely present in metastatic breast cancer but did identify alterations that were potentially targetable with currently available drugs, particularly in triple negative breast cancer. Continued study of BRAF alterations in breast cancer is warranted.

Comprehensive genomic profiling reveals therapeutically targetable molecular subtypes of breast carcinomas

Lead Jeffrey S. Ross, Pathology, Albany Medical Center in Albany, USA, and colleague evaluated whether comprehensive genomic profiling (CGP) could be used to reveal targetable genomic alterations, and also redefine breast carcinoma classification into therapeutically relevant subtypes as an alternative to the hormone receptor (HR) expression-based classifications of basal, luminal A, luminal B, and HER2 overexpressed. Clinically relevant genomic alterations (CRGA) are those linked to drugs on the market or under evaluation in clinical trials. DNA was extracted from 40 µm of FFPE sections obtained from 8654 consecutive breast cancer patients. CGP was performed on hybridization-captured, adaptor ligation-based libraries (mean coverage >500X) for up to 315 cancer-related genes. Total mutational burden (TMB) was determined on 1.2 Mbp of sequenced DNA.

CGP revealed 6959 (80.4%) tumours harboured a genomic alteration in at least one pathway, and 2697 (31.2%) breast cancer tumours harboured alterations in just one pathway. The investigators found that several distinct pathways are altered in breast cancer, making them potentially targetable with therapies that are already FDA approved for oncology indications. The ERBB pathway was altered in 1294 cases, suggesting that trastuzumab, pertuzumab, afatinib, lapatinib, and neratinib could have activity against tumours with these alterations. Alterations in the PI3K/AKT/mTOR pathway occurred in 4375 cases, making them potentially targetable with everolimus and temsirolimus, whereas palbociclib could be active against alteration in the CDK pathway that were detected in 2685 cases. A total of 2650 case showed alterations in the FGFR pathway, making these tumours potentially susceptible to pazopanib or ponatinib. Mutations in other targetable kinases such as RET, ROS1, and RAF were found in 424 cases, meaning they could be sensitive to sorafenib, regorafenib, dabrafenib, vemurafenib, crizotinib, cabozantinib, or sunitinib. Fulvestrant and tamoxifen may be putative agents targeting the 792 cases harbouring ESR1 mutations, which confer hormone therapy resistance in breast cancer.

Olaparib could have activity in the1266 cases that were identified as homologous recombination deficient. Immunotherapy sensitivity, defined as TMB >20 mut/Mbp or mutation of specific DNA repair pathways was identified in 419 cases that could make these tumours druggable with pembrolizumab, nivolumab, atezolizumab, or ipilimumab. In addition, homologous recombination deficiency, defined as mutation of the BRCA genes, other genes in the FANC complex, or DNA repair genes, have all been shown to confer sensitivity to PARP inhibitors.

To underscore the utility of CGP, the investigators pointed out that only 9.8% of breast cancer tumours would be HER2-positive by immunohistochemistry. Ross *et al.* Abstract 229PD

Practice point and future research opportunities

Comprehensive genomic profiling was successfully used to identify clinically relevant genomic alterations allowing for stratification of tumours according to predicted sensitivity to a variety of therapies. The majority (80%) of breast cancer tumours harbour targetable genomic alterations, many of which would not be identified by immunohistochemistry or hotspot testing, but are detectable by next-generation sequencing. Comprehensive genomic profiling is a powerful tool to guide treatment across therapeutically distinct, but targetable, pathways. More trials wherein patients with breast cancer are stratified and treated according to comprehensive genomic profiling results are anticipated.

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ESMO 2017 Congress, Madrid, Spain, 8-12 September 2017.

Affiliations and Disclosure

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Disclosure

No conflicts of interest to disclose.

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