ESMO Congress 2016: Three of the most important studies in the field of breast cancer

ABSTRACT
The 2016 European Society for Medical Oncology (ESMO) annual congress highlighted the latest discoveries in different types of cancer research, including breast cancer. Immunotherapy and targeted therapies are the most rapidly evolving. This year’s meeting featured studies on targeted therapy (CDK4/6 inhibitor) plus endocrine therapy for advanced/metastatic breast cancer, a new approach in endocrine treatment, or possibility of using molecular/biological features in specific groups of patients to identify those for whom sentinel lymph node biopsy might be avoided. In this paper three selected studies dedicated to breast cancer patients, presented during the meeting, will be discussed.

Key words: ESMO, congress, breast cancer, CDK4/6 inhibitor, endocrine therapy

Introduction
The largest oncology meeting in Europe — The European Society for Medical Oncology (ESMO) 2016 Congress was held on October 7–11 in Copenhagen, Denmark. It provided a unique opportunity for experts from all over the world to meet and network. The participants were from over 130 countries [1]. Many studies were reported at the meeting, including practice-changing clinical trials results. It is well known that this year new discoveries in immunotherapy dominated many sessions. A number of scientific presentations were dedicated to immuno-oncology across multiple tumour types [1]. Despite that, the subject of breast cancer is always fascinating for oncologists, and dedicated sessions always meet with unflagging interest. In this paper the results of three selected studies will be discussed, which are predicted to have an impact on clinical practice in the field of breast cancer.

The MONALEESA-2 Study
Currently, there is one CDK4/6 inhibitor that is approved by the Food and Drug Administration (FDA), palbociclib [2]. Also, ribociclib and abemaciclib are in development [3].

Interim results from the randomised double-blind, phase III, placebo-controlled study of LEE011 (ribociclib) in combination with letrozole for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer, who received no prior therapy for advanced disease, were presented during the annual ESMO meeting [1, 3–5]. Ribociclib is a selective cyclin-dependent kinase inhibitor drug that helps to slow the progression of cancer by inhibiting two proteins called cyclin D-cyclin-dependent kinase (CDK) 4 and 6 (CDK4/6). Targeting CDK4/6 blocks the phosphorylation of retinoblastoma protein, resulting in G1 cell cycle arrest in vitro [6, 7].

In the Mammary ONcology Assessment of LEE011’s Efficacy and Safety (MONALEESA-2) study 668 patients underwent randomisation and were assigned into either a ribociclib group or a placebo group [1, 4, 5]. They received either ribociclib (600 mg per day for three weeks, every 28 days) plus letrozole 2.5 mg per day or placebo plus letrozole.

Results from the study show that combination treatment significantly prolonged progression-free survival.
(PFS) compared to letrozole alone [1, 4, 5]. The median PFS for the ribociclib group was not reached (but it is expected to exceed 20–24 months [8]) versus 14.7 months in the placebo group (hazard ratio, 0.56; 95% CI, 0.43–0.72; \( P = 3.29 \times 10^{-6} \) for superiority) [4]. After 18 months, the PFS rate was 63.0% and 42.2% in the ribociclib group and in the placebo group, respectively [4]. By adding CDK4/6 inhibitor to letrozole a 44% lower relative risk of progression was noted [1, 4]. The overall response rate was 40.7% in the ribociclib group in the intention-to-treat population [4]. Further studies should focus on finding cancer biomarkers to identify patients who are in the group of potential responders to combination treatment [1].

The most common adverse events in the ribociclib group were neutropenia (74.3%), nausea, infections (mainly urinary and upper respiratory tract infections), fatigue, and diarrhoea [4]. The most common grade 3/4 adverse events were neutropenia (59.3% in the ribociclib group and 0.9% in the placebo group) and leukopenia (21% and 0.6%, respectively) [4]. Other grade 3/4 adverse events in the ribociclib plus letrozole arm were hypertension, increased alanine aminotransferase level, lymphopenia, and increased aspartate aminotransferase level [4]. Interruptions or ribociclib dose reductions were noted in 76.9% and 53.9%, respectively, and allowed most patients to remain on treatment [4].

During the Congress the results of this trial were widely commented on. The CDK4/6 inhibitors are changing the breast cancer treatment landscape. Studies with a third CDK4/6 inhibitor, abemaciclib, are ongoing. For instance, the phase II trials neoMONARCH, MONARCH 1, next-MONARCH 1, and ABC-POP are underway [3].

The FALCON Study

The results of a randomised, double-blind, multi-centre, phase III study to compare the efficacy and tolerability of fulvestrant with anastrozole as hormonal treatment for postmenopausal women with hormone receptor-positive, locally advanced, or metastatic breast cancer, who have not previously been treated with any hormonal therapy (FALCON) were also presented [1, 3, 9]. Patients could receive only one line of cytotoxic chemotherapy for breast cancer prior to randomisation [3].

Patients treated with fulvestrant had a significant 21% improvement in PFS compared to those treated with anastrozole: 16.6 months and 13.8 months, respectively (\( P = 0.048 \)) [1, 9]. However, for patients whose disease had not spread to the liver or lungs at baseline, the PFS was as much as 22.3 months [1, 9]. A greater duration of response to treatment in the fulvestrant group was also observed [1, 9]. Researchers concluded that these results confirm the superior efficacy of fulvestrant over anastrozole [1, 9].

The health-related quality of life was similar for patients receiving either fulvestrant or anastrozole, and the most common adverse events were arthralgia (16.7% vs. 10.3%) and hot flushes (11.4% vs. 10.3%), respectively [1, 9].

Because of good efficacy and low toxicity, this approach could be especially useful for older patients, with low volume disease, and with non-visceral disease.

Taken together, the MONALEESA-2 and the FALCON study results, it seems that an even more satisfying outcome should be reached by combining ribociclib with fulvestrant (MONALEESA-3) [3]. This phase III study is ongoing [3]. Also, data from the MONALEESA-7 study of efficacy and safety in premenopausal women with hormone receptor positive, HER2-negative advanced breast cancer are awaited [3].

The role of Ki67

The authors of the third study that is worth mentioning investigated the relationship between Ki67, tumour size, and age with axillary lymph node metastases in early breast cancer patients [10]. The Ki67 protein was originally identified by Gerdes et al. in the 1980s and is known as a good marker of proliferation [11, 12].

Researchers analysed over 1700 patients treated for breast cancer (T1-2 N0-1). They found that higher tumour size was associated with higher Ki67 values in patients aged 50 years or older, regardless of hormone receptor or HER2 status [10]. This group had an increased possibility of axillary lymph node metastases [1]. The likelihood of lymph nodes involvement was also greater according to tumour size in all types of breast cancer with the exception of triple negative [1].

Despite its mono-institutional and retrospective nature, the results of this study could have an influence on clinical practice in the future. Of course, first the results have to be confirmed in clinical trials (CTs) evaluating the potential to eliminate axillary surgery and sentinel node biopsy. Based on this study, breast cancer patients, for example, aged over 50 with small tumours and low Ki67 seem to be the best candidates when looking for an answer to whether they really could be spared from some procedures by use of stratification based on the mentioned features [1, 10]. It is interesting that the results of future studies may indicate the group of patients for whom sentinel lymph node biopsy might be avoided.

Conclusions

This Congress provided an opportunity for attendees to meet top oncological experts and gain updated knowledge in the breast cancer field. As we could predict the studies that evaluated endocrine treatment with or
without targeted therapies (such as a CDK4/6 inhibitor) dominated sessions as the most important reports. Still, we have a lot of work to do for our patients with breast cancer and I am sure that new breakthrough therapies will be discovered soon.

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