ESMO 2014 Congress Scientific Meeting Report – Breast Cancer Extract

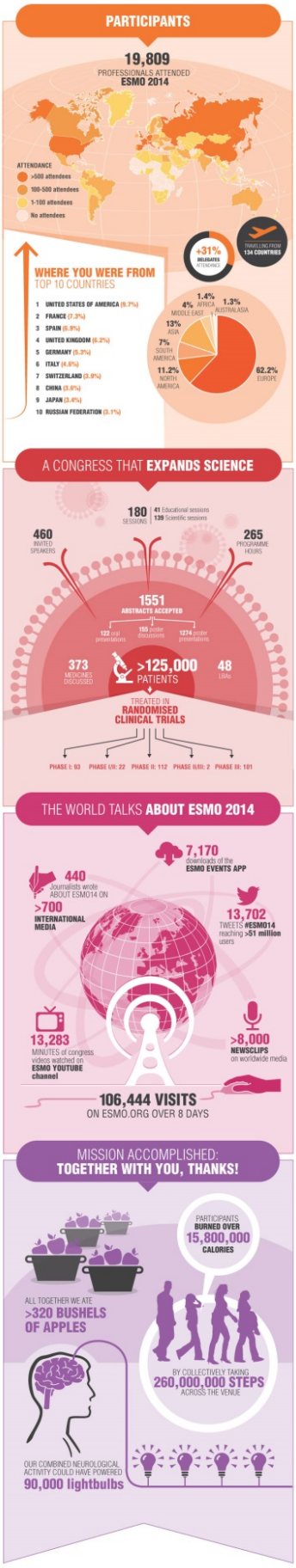
26-30 September 2014

Madrid, Spain

Summary

The European Society for Medical Oncology (ESMO) Congress, held September 26 to 30 in Madrid, Spain, was a record-breaker on nearly all levels. It was resounding success and in a dedicated infographic you can find the congress statistics. A primary emphasis in the scientific programme was placed on precision medicine and how it will change the future treatment landscape in oncology. In addition, a number of scientific presentations were dedicated to cancer immunology and immunotherapy across multiple tumour types. 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 2014 scientific programme, as well as advances in oncology.

Infographic (right): ESMO 2014 record breaking Congress



Contents

Breast Cancer

Randomised phase II, three armed, EORTC study of neoadjuvant treatment with docetaxel plus lapatinib/trastuzumab/or both, followed by an anthracycline based chemotherapy in HER2-positive breast cancer

Prof. Herve Bonnefoi of the Institute Bergonié, Bordeaux, France, presented results of a phase II study that demonstrated a numerically higher pathological complete response (pCR) rate with double anti-HER2 blockade (lapatinib-trastuzumab) plus chemotherapy, but the use of docetaxel rather than paclitaxel may not reduce toxicity. From a clinical perspective the modest increase in pCR comes with additional toxicity.

Neoadjuvant trials with a double HER2-blockade with lapatinib and trastuzumab, combined with different paclitaxel-containing chemotherapy regimens, have shown high pCR rates, but at the cost of important toxicity. The European Organisation for Researche and Treatments of Cancer (EORTC) researchers hypothesised that this toxicity might be due to a specific interaction between paclitaxel and lapatinib.

Patients with stage IIA to IIIC HER2-positive breast cancer received 6 cycles of chemotherapy every 3 weeks (3 cycles of docetaxel followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide. They were randomised to receive, during the first 3 cycles, either lapatinib in arm A, trastuzumab in arm B, or trastuzumab and lapatinib in arm C. The primary endpoint was pCR rate in the breast (ductal carcinoma in situ was allowed). Secondary endpoints included safety and toxicity, response rate, rate of breast conserving surgery and translational research. Exploratory analysis allowed pCR rates assessment in the breast and lymph nodes and its assessment by hormone receptors status.

For a null hypothesis of a 40% pCR rate and an alternative hypothesis of a 60% pCR rate, 50 eligible patients needed to be treated in each arm to have a 92.5% power. An experimental arm was deemed interesting for further research if at least 25 pCR out of 50 treated eligible patients are observed. This decision rule corresponded to rejecting the null hypothesis.

In June 2012, arm A was closed for futility based on the results from other studies. When the lapatinib monotherapy arm was closed prematurely, the statistical plan was not altered for the 2 remaining arms.

From October 2010 to January 2013, 128 patients were included in 14 centres, 6 patients were ineligible. The pCR rate in breast in arm A was 45.5%, 51.9% in arm B, and 60.4% in the C. The pCR rate in breast and lymph nodes in arm A was 36.4%, 51.9% in arm B, and 56.3% in arm C. The pCR rate in breast and lymph nodes in hormone receptor positive tumours was 51.9% in arm B and 47.8% in arm C. In hormone receptor negative tumours, it was 52% in arm B and 64% in arm C. Lapatinib group results were not presented since the numbers are small.

Frequency of most frequent grade 3-4 toxicities in arms A/B/C were: febrile neutropaenia 23/15/10%; diarrhoea 9/2/18%; other infection 9/4/8%; and liver enzyme alteration 0/4/10%. A dose reduction for any of the neoadjuvant drugs was required in 36/13/48% of patients.

Prof. Bonnefoi concluded that using the definition of pCR in both, breast and lymph nodes, the pCR rates for the lapatinib, trastuzumab and combination groups respectively are similar in the EORTC trial and in the 3 trials with a “pragmatic” design reported (CHERLOB, LPT, NSABP-B41). A meta-analysis of neoadjuvant trials with double HER2 blockade may be useful to better take into consideration the heterogeneity of HER2 positive breast cancer and to understand the differences in pCR rates between treatment groups and long-term outcomes.

Prof. Joseph Gligorov of the Tenon University Hospital, Paris, France, who discussed the study results, said that lapatinib-trastuzumab combination increases the pCR rate in neoadjuvant setting compared to lapatinib or trastuzumab alone. The study is not strictly comparable with other according to tumour characteristics (N0; hormone receptors status, chemotherapy partner). The comparison to other anti-HER2 doublet strategies is important because of toxicity and treatment discontinuation concerns. If pCR is the endpoint in the neoadjuvant strategies, then anti-HER2 doublets with chemotherapy do better. In metastatic setting, the best anti-HER2 doublet is actually pertuzumab-trastuzumab. However, Dr Gligorov questioned if there are new interesting doublets, could we better select the population to be treated with treatments according to pCR endpoint, and is pCR relevant from a clinical point of view in early stage HER2 positive breast cancers.

The sponsor of the study was EORTC. GlaxoSmithKline was the study collaborator.

Reference

253O: Neoadjuvant treatment with docetaxel plus lapatinib (L), trastuzumab (T), or both followed by an anthracycline based chemotherapy in HER2-positive breast cancer: Results of the randomised phase II EORTC 10054 study

Activity of neoadjuvant lapatinib plus trastuzumab for early breast cancer according to PIK3CA mutations: pCR rate in the CherLOB study and pooled analysis of randomised trials

Prof. Valentina Guarneri of the Oncology Institute, University of Padova, Padova, Italy reported that increased activity of the dual anti-HER2 blockade with trastuzumab plus lapatinib in the neoadjuvant breast cancer setting seems to be limited to tumours not harbouring PIK3CA mutations.

PIK3CA mutations are common in breast cancer. PIK3CA is mutated in 20 to 25% of HER2-positive breast cancer. Preclinical data have shown mutated PIK3CA to be assocated with resistance to lapatinib and trastuzumab. PIK3CA mutations are associated with poor prognosis in advanced HER2-positive breast cancer patients treated with chemotherapy and trastuzumab +/- pertuzumab or chemotherapy +/- lapatinib.

The aim of this study was to evaluate the correlation of PIK3CA mutational status with pCR in patients with HER2-positive early breast cancer treated with neoadjuvant chemotherapy plus trastuzumab, lapatinib or combined trastuzumab and lapatinib.

PIK3CA mutations were evaluated in 121 patients randomised to neoadjuvant anthracyclines/taxane-based chemotherapy plus trastuzumab, lapatinib, or both. Exon 9 and exon 20 PIK3CA mutations were evaluated on formalin-fixed, paraffin-embedded core biopsies by

pyrosequencing. An event-based pooled analysis of trials reporting pCR events according to PI3KCA mutation status was performed.

PIK3CA status was available for 108 of the 121 patients: 22 presented a PIK3CA mutation. In the whole population, pCR rates are similar in PIK3CA wild type and PIK3CA mutated patients (33.7% vs. 22.7%; p = 0.32). However, for 41 patients receiving trastuzumab plus lapatinib the probability of achieving a pCR is higher in case of PIK3CA wild type (48.4% vs. 12.5%; p = 0.06).

An event-based pooled analysis was accomplished by extracting activity events (pCR as reported by trialists) and deriving 95% CIs. Inclusion criteria considered trials in which HER2-positive breast cancer patients who where candidates for neoadjuvant chemotherapy were assigned to receive chemotherapy plus trastuzumab, lapatinib or the combination. The pCR was reported according to PIK3CA status (mutated and wild-type). In addition, a cumulative Odds Ratio of single versus dual HER2 inhibition was conducted (for randomised trials only), with a random effect model considering the known heterogeneity. Interaction according to PIK3CA status (mutated vs. wild-type) was calculated as well.

The accumulated data, including those deriving from the NeoALTTO and GeparSixto trials, in 702 patients. The pCR rates in PIK3CA mutated patients receiving lapatinib is 16.2%, 22.2% in those who received trastuzumab, and 21.4% in those who received lapatinib plus trastuzumab. In PIK3CA wild type patients who received lapatinib, the pCR was 21.3%, 26.9% in those who received trastuzumab, and 43.6% in those who received lapatinib plus trastuzumab.

The non-overlapping 95% CIs, between pCR in patients receiving lapatinib plus trasuzumab and those undergoing trastuzumab or lapatinib may suggest a higher activity of the dual HER2 inhibition in patients without PI3KCA mutation. Conversely, no difference in pCR according to PIK3CA status seems to emerge among patients treated with single anti-HER2 agents.

The strengths were that PIK3CA analysis was prospectively planned in all trials, effective sample collection and analysis (78%-89% of patients), consistent results regardless of the adopted technique, and similar effects across studies. The limitations are relatively limited sample size, too few studies for definitive conclusions, unknown surrogacy of pCR in PIK3CA wild type vs. mutated tumours, potential imbalance of HR status in wild-type vs. mutated tumours, no uniform pCR definition across studies, and chemotherapy as a confounder.

The authors concluded that PIK3CA wild-type status is related to a higher pCR rate following chemotherapy plus dual HER2 blockade with trastuzumab and lapatinib. PIK3CA mutational status does not predict any differential sensitivity to chemotherapy plus either trastuzumab or lapatinib. These data warrant further prospective validation testing of the interaction according to the PIK3CA mutation in the adjuvant setting. If confirmed, the wild-type PIK3CA status might be a marker to select patients to be treated with trastuzumab and lapatinib.

Prof. Joseph Gligorov of the Tenon University Hospital, Paris, France, who discussed the study results, said that PIK3CA mutation is a bad prognostic factor in early stage HER2 positive disease treated with trastuzumab. It is still not known clearly if all the mutations have the same value. Prognostic and predictive value of PIK3CA status might be confounding factors. Better pCR might not be clearly correlated with better disease-free survival (DFS) or overall survival (OS) in the adjuvant setting particularly if the patient receives trastuzumab. Until now, there is no even clinical

argument that PIK3CA mutated populations are more sensitive to PI3K inhibitors. PIK3CA mutation might be stratification factor for further studies, but not yet a decision factor for choosing optimal treatment.

The study was sponsored by GlaxoSmithKline.

Reference

254O: Activity of neoadjuvant lapatinib (L) plus trastuzumab (T) for early breast cancer (EBC) according to PIK3CA mutations: Pathological complete response (pCR) rate in the CherLOB study and pooled analysis of randomized trials

Dual blockade with afatinib and trastuzumab as neoadjuvant treatment for patients with locally advanced or operable breast cancer receiving taxane-anthracycline containing chemotherapy

Dr Claus Hanusch of the Rotkreuzklinikum, Munich, Germany presented results from the efficacy and safety analysis of the (DAFNE)-GBG70 study. Despite a tolerable safety profile of the dual blockade with afatinib, the pCR was lower than the challenging 70% expected rate. A subsequent phase III study therefore cannot be supported.

Neoadjuvant chemotherapy of anthracycline/taxane based combinations of at least 18 weeks is considered a standard treatment. Concurrent administration of trastuzumab in HER2-positive disease achieves a pCR rate of approximately 40%. Dual anti-HER2 blockade can increase the rate by another 20%.

The DAFNE is a multicenter, prospective, open-label phase II study evaluating efficacy and safety of afatinib, an irreversible ErbB-family inhibitor in combination with weekly paclitaxel plus trastuzumab, followed by epirubicin/cyclophosphamide/trastuzumab (ECH) as neoadjuvant therapy in untreated, centrally assessed HER2-positive, operable or locally-advanced breast cancer patients.

All patients were treated for 30 weeks: 6 weeks with afatinib and trastuzumab; 12 weeks with additional weekly paclitaxel; and 12 weeks with ECH. Afatinib was given every other day for the first 2 weeks to reduce the risk of diarrhoea and skin toxicities. Primary prophylaxis with loperamide was mandatory for the first 4 weeks of afatinib/trastuzumab and the first 2 weeks of paclitaxel.

Primary objective was pCR rate (ypT0/is ypN0). Secondary objectives were efficacy using other pCR definitions (ypT0 ypN0, ypT0 ypN0/+, ypTany ypN0), clinical response rates, rate and type of surgery, compliance and toxicity, correlation of skin toxicity and diarrhoea and pre-specified molecular markers with pCR. Assuming a pCR rate of 70%, a sample size of 65 patients was needed to exclude a pCR of ≤ 55%.

In total 74 patients were recruited from May 2012 to July 2013 in 11 German centers, with 65 intent-to-treat (ITT) patients. Median age was 50 years. cT2 had 76.6% of patients, 51.6% had cN0 disease, 89.2% ductal invasive, 60% grade 3 and 70.8% hormone receptors positive tumours.

Of the 22 serious adverse events in 16 patients, 27.3% were GI, 18.2% haematologic, 13.6% infections and 9.1% related to the nervous system. Afatinib and trastuzumab in combination with anthracycline-taxane-based chemotherapy as given in the DAFNE study showed no new safety signals.

The study didn't meet the primary objective with a pCR (ypT0/is ypN0) rate of 49.2%.

The pCR by other definitions was 33.9% for ypT0, ypN0; 55.4% for ypT0/is, ypN0/+; 83.1% for ypTany, ypN0. The pCR ypT0/is, ypN0 was 43.5% in patients with oestrogen receptor positive and 63.2% in those with oestrogen receptor negative tumours.

The pCR according to PIK3CA status was 54.2% in wild-type tumours and 38.5% in those with PIK3CA mutated tumours. The pCR according to lymphocyte predominant breast cancer (LPBC) status was 26.8% in those without LPBC and 77.8% in those with LPBC (p=0.0053). The authors stated that their results provide further support for the predictive value of LPBC and PIK3CA mutations in this treatment setting. There was no association between the pCR and skin toxicity or diarrhoea.

Clinical objective response rate at surgery was 96.3%. Complete/partial response after 6 weeks of dual HER2 blockade was 5.3 and 36.8%. Clinical signs of tumour progression after 6 weeks of dual HER2 blockade was recorded in 14% of evaluable patients. Breast-conserving surgery rate was 60%.

Prof. Joseph Gligorov of the Tenon University Hospital, Paris, France, who discussed the study results, said that dual HER2 blockade, afatinib-trastuzumab did not meet the primary endpoint, and the regimen is too toxic. However, the results of ExteNET trial, not yet presented, demonstrate that one year treatment with neratinib after one year treatment with trastuzumab result in 33% improvement in DFS vs. placebo (HR 0.67; p = 0.0046), suggesting that maybe independently of the drug difference, neoadjuvant and adjuvant situation are different for drug evaluation.

The study was organised by the German Breast Group. The study was supported by Boehringer Ingelheim.

Reference

255O: Dual blockade with afatinib and trastuzumab as neoadjuvant treatment for patients with locally advanced or operable breast cancer receiving taxane-anthracycline containing chemotherapy (DAFNE)-GBG70 - efficacy and safety analysis

Final OS analysis from the CLEOPATRA study in patients with HER2-positive metastatic breast cancer

In the CLEOPATRA study, first-line treatment with pertuzumab/trastuzumab/docetaxel significantly improved OS for patients with HER2-positive metastatic breast cancer compared with placebo/trastuzumab/docetaxel, providing a 15.7 month increase in the median values. The median OS of 56.5 months is unprecedented in first-line and this substantial improvement confirms the pertuzumab containing regimen as standard of care in this setting, reported Prof. Sandra Swain of the Medstar Washington Hospital Center, Washington Cancer Institute, Washington, USA.

In the CLEOPATRA study, 808 patients from 25 countries with HER2-positive metastatic breast cancer were randomised to receive first-line placebo/trastuzumab/docetaxel or pertuzumab/trastuzumab/docetaxel. Randomisation was stratified by geographic region and neo/adjuvant chemotherapy.

The patients were eligible for the study if they had HER2-positive (centrally confirmed), metastatic, locally recurrent, or unresectable breast cancer, measurable or non-measurable disease; had received ≤ 1 hormonal regimen for metastatic breast cancer prior to randomisation, disease-free interval at least 12 months since prior neo/adjuvant treatment, and left ventricular ejection rate (LVEF) ≥ 50% at baseline.

The study primary endpoint was progression-free survival (PFS) independently assessed. Secondary endpoints included investigator-assessed PFS, objective response rate (ORR), safety, and OS. Final analysis was planned at 385 deaths, with two interim analyses at 165 and 267 deaths.

At the primary analysis in May 2011, pertuzumab was shown to increase PFS significantly, with a strong trend to OS benefit. At a second interim analysis in May 2012, the OS was improved to a degree which was both statistically significant and clinically meaningful with hazard ratio (HR) 0.66 (p = 0.0008), but the median OS in patients who received pertizumab was not reached.

In July 2012, the patients still on placebo were offered crossover to pertuzumab.

At ESMO 2014 the CLEOPATRA researchers reported results of a final prespecified OS analysis (February 2014). This OS analysis was planned when ≥385 deaths were reported. The log-rank test, stratified by prior treatment status and geographic region, was used to compare OS between the arms, applying the threshold of p ≤ 0.0456. Subgroup analyses of OS were performed for stratification factors and other key baseline characteristics.

At median follow-up of 50 months (range 0 to 70 months), the statistically significant improvement in OS in favour of the pertuzumab/trastuzumab/docetaxel arm was maintained (HR = 0.68, p = 0.0002). Median OS was 40.8 months in the placebo arm and 56.5 months in the pertuzumab arm, with difference of 15.7 months.

The OS benefit in predefined subgroups was consistent with previous observations. It is to be noted that following the previous report of OS benefit, 48 patients in the placebo arm crossed over to the pertuzumab arm.

The PFS in the pertuzumab arm was 18.7 vs. 12.4 months in the placebo arm, HR 0.68 (p < 0.0001).

Median time on study treatment was 17.4 months in the pertuzumab arm vs. 11.4 months in the placebo group.

The safety profile of pertuzumab/trastuzumab/docetaxel in the overall population and in patients who crossed over to the pertuzumab arm was consistent with the known safety profile of pertuzumab with more pronounced diarrhoea, rash, mucosal inflammation, pruritus, dry skin, and muscle spasm. No new safety concerns were seen with longer follow-up. There was no evidence of cumulative or late toxicity. The long-term cardiac safety profile was maintained.

Dr Luca Gianni of the IRCCS San Raffaele Hospital, Milan, Italy, who discussed the study results, said that CLEOPATRA is an unquestionable therapeutic success with an unquestionable clinical implication: docetaxel/trastuzumab/pertuzumab is the new standard, not an option for first-line treatment of HER2-positive metastatic breast cancer. However, adjuvant trastuzumab was administered in only 10% of the study population. Dr Gianni said that the therapeutic role and wide applicability of dual HER2-blockade with monoclonal antibodies is established but new therapeutic

approaches to improve the overall results of CLEOPATRA should address the different biology and different drug sensitivity of subsets of HER2-positive tumours.

Improvements can be expected by addressing key features of HER2-positive breast cancer linked to different sensitivity in term of hormone receptor status (positive vs. negative), PIK3CA status (wild type vs. mutant), and immune environment.

The CLEOPATRA study did not allow endocrine therapy of patients with ER-positive tumours. Dual blockade of HER2 with pertuzumab/trastuzumab and concomitant endocrine therapy is feasible as shown by APHINITY study in the adjuvant setting. Dr Gianni wondered if the addition of endocrine therapy after the end of chemotherapy would increase the already large benefit observed in women with HER2-positive/ER-positive metastatic breast cancer patients enrolled in the CLEOPATRA study.

The PIK3CA status can be easily assessed on tumour biopsies or liquid biopsies. Many PI3K inhibitors are available and being tested in combination with standard HER2-directed therapy. T-DM1 is effective in HER2-positive breast cancer regardless of whether or not the tumours carry a mutation in the PIK3CA. Therapies tailored according to PIK3CA mutational status of HER2-positive metastatic breast cancer should be tested.

Immune mechanisms and tumour lymphocyte infiltration are involved in the probability of pCR in HER2-positive breast cancer. There is a high expression of PDL1 and CTLA4 linked to residual disease in ER-negative tumours. Dr Gianni concluded that tests should be carried out to see if blocking of CTLA4 and/or PD1/PDL1 will be useful for some patients treated per the CLEOPATRA protocol.

The CLEOPATRA study was sponsored by F.Hoffmann-La Roche

Reference

350O_PR: Final overall survival (OS) analysis from the CLEOPATRA study of first-line (1L) pertuzumab (Ptz), trastuzumab (T), and docetaxel (D) in patients (pts) with HER2-positive metastatic breast cancer (MBC)

IMELDA: Efficacy and safety of maintenance bevacizumab with or without capecitabine after initial first-line bevacizumab plus docetaxel

In IMELDA study, adding capecitabine to maintenance bevacizumab provided statistically significant and clinically meaningful improvements in PFS and OS. The rationale for the study was observation that prolonging first-line chemotherapy results with maintenance treatment may influence OS.

In HER2-negative patients with locally recurrent/metastatic breast cancer, combining bevacizumab with first-line chemotherapy significantly improves PFS. Bevacizumab benefit is most pronounced when combined with a taxane. Cumulative toxicity prevents taxane continuation until disease progression. Until regulatory withdrawal of bevacizumab/docetaxel in 2011, this combination was considered as a valid first-line option for HER2-negative metastaic breast cancer based on results of a phase III trial. The PFS and response rate (RR) with maximum 9 cycles of first-line docetaxel were significantly improved by adding bevacizumab continued until disease progression.

The open-label randomised phase III IMELDA trial tested whether switching to a more tolerable chemotherapy with a different mechanism of action while continuing VEGF inhibition may be more

effective. It was meant that by adding capecitabine to maintenance bevacizumab was continued until disease progression after initial bevacizumab/docetaxel which improved PFS. The study findings were presented by Prof. Joseph Gligorov of the Tenon University Hospital, Paris, France.

Patients with HER2-negative measurable metastatic breast cancer, ECOG performance status (PS) <2 and no prior chemotherapy were eligible for study inclusion.

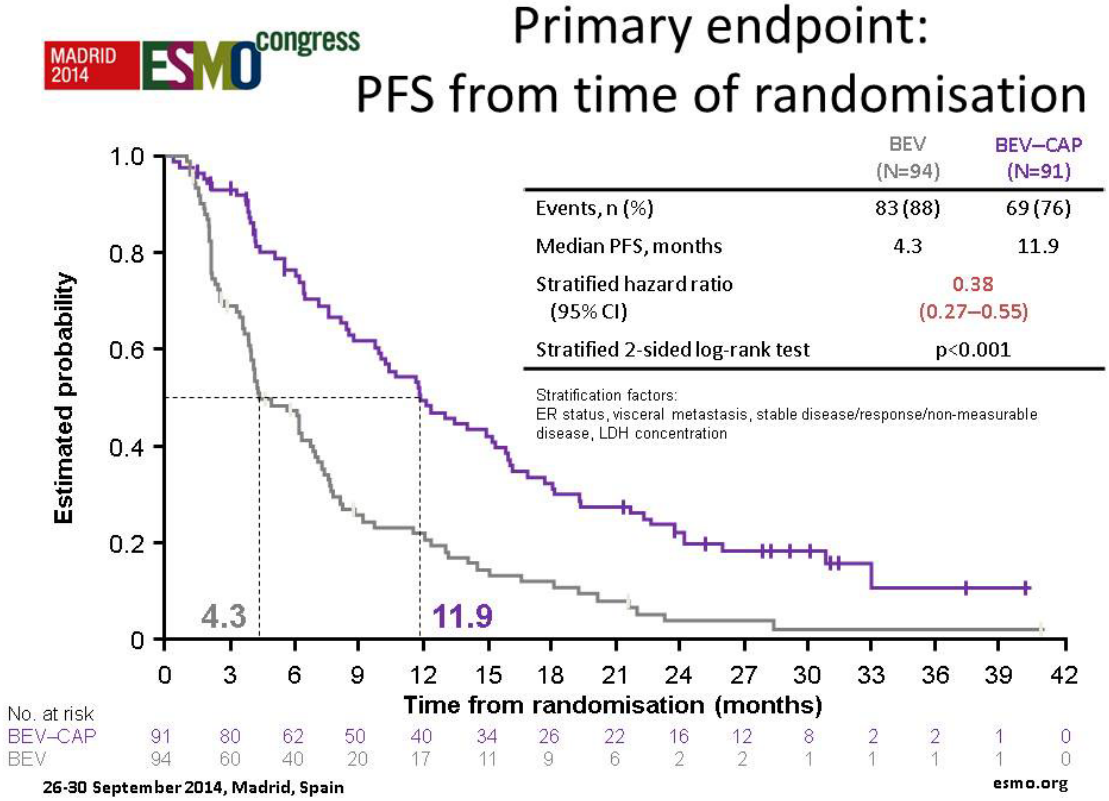
After 3–6 cycles of bevacizumab/docetaxel, patients without disease progression were randomised to bevacizumab alone or bevacizumab/capecitabine until disease progression. Stratification factors were oestrogen receptor (ER) status, presence of visceral metastases, response status and LDH concentration.

The primary endpoint was PFS from randomisation to progression/death; secondary endpoints included RR, clinical benefit rate, time to disease progression, OS from randomisation, safety and quality of life (QoL). The sample size was calculated based on a PFS HR of 0.70 with median PFS improvement from 5.8 to 8.3 months. In total 360 enrolled patients were required for 290 randomised patients. It was planned that 244 PFS events provide 80% power at 5% 2-sided α. The study was not designed for formal OS comparison.

Between June 2009 and March 2011 when enrolment was prematurely terminated, 287 patients were enrolled and 284 of them treated with 185 (65%) who completed initial treatment and subsequently randomised to maintenance treatment. The protocol was amended to continue follow-up for 2 years after last randomisation.

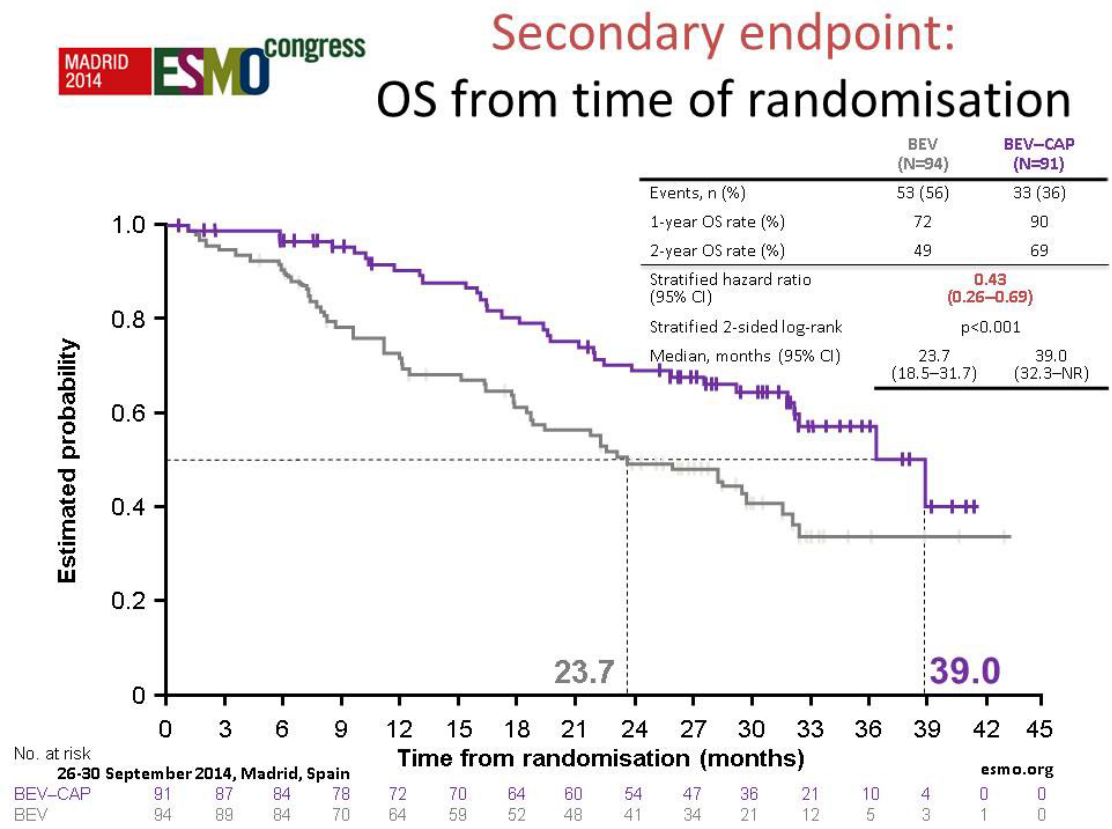
Median age in the bevacizumab arm was 54 years and 49 years in the bevacizumab/capecitabine arm. Triple-negative disease was recorded in 22% of patients included in the bevacizumab arm and 27% of patients in the bevacizumab/capecitabine arm. Visceral metastases were nearly identical in both group (69% vs. 68%), however their presence in ≥3 organs was higher in bevacizumab arm at enrolment to the initial phase (57% vs. 47%).

In the maintenance arm, median treatment duration was longer in bevacizumab/capecitabine group (8.3 vs. 3.5 months). Adding capecitabine to maintenance bevacizumab provided statistically significant and clinically meaningful improvements in PFS from time of randomisation (HR 0.38, p<0.001; median 11.9 vs. 4.3 months) and exploratory analysis (PFS from start of first-line therapy), as well as improvement in median OS from time of randomisation (HR 0.42, p<0.001; 39 vs. 23.3 months), despite the smaller than planned sample size because of early termination of accrual.



Caption: PFS from time of randomisation. © Joseph Gligorov

However, at the time of report there was insufficient duration of OS follow-up with the low event rate.



Caption: OS from time of randomisation. © Joseph Gligorov

There was a manageable increase in adverse events mainly due to hand-foot syndrome experienced in 33% of patients in bevacizumab/capecitabine arm. Hypertension was recorded in 9% of patients in the combined arm and 3% of patients in the bevacizumab only arm. The rate of proteinuria was same (4%) in both groups. Gastroenteritis occured in 3 patients in the bevacizumab single agent arm.

Prof. Gligorov concluded that in patients benefiting from first-line bevacizumab-containing therapy, continued bevacizuamb with capecitabine improves efficacy. Ongoing evaluation considers collection of data on anti-cancer treatment after study therapy and patient-reported outcomes.

Dr Hope Rugo of the UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, USA, who discussed the study results, said that the IMELDA trial tried to answer the question: does continuing bevacizumab post progression have an impact on outcome? Dr Rugo questioned if bevacizumab is an adequate maintenance therapy after response to first-line chemotherapy. In the study, there was a longer duration of treatment with capecitabine/bevacizumab vs. bevacizumab (twice the number of cycles), markedly longer PFS, and the PFS from start of first-line was doubled, OS was significantly longer, but there were also almost double the grade > 3 toxicity (mainly hand-foot syndrome, hypertension, but also thromboembolism). Hand-foot syndrome resulted in discontinuation of capecitabine in 10% of patients.

Upon the presentation at ESMO 2014, the study results were published in the Lancet Oncology.

The study was sponsored by F. Hoffmann-La Roche.

Reference

352O: Efficacy and safety of maintenance bevacizumab (BEV) with or without capecitabine (CAP) after initial first-line BEV plus docetaxel (DOC) for HER2-negative metastatic breast cancer (mBC): IMELDA randomised phase III trial

TANIA: Efficacy and safety of continued or reintroduced bevacizumab after first-line bevacizumab for HER2-negative locally recurrent/metastatic breast cancer

The primary objective of open-label randomised phase III TANIA study was met, showing statistically significantly improvement in PFS with bevacizumab after progression on first-line bevacizumab-containing therapy in bevacizumab-pretreated patients with HER2-negative locally recurrent/metastatic breast cancer. The study results were presented by Gunther von Minckwitz, Managing Director of the German Breast Group and University Women's Hospital, Neu-Isenburg, Germany.

Combining bevacizumab with first- or second-line chemotherapy in randomised phase III trials showed significantly improved PFS in HER2-negative locally recurrent/metastatic breast cancer. Sustained VEGF blockade may be important for long-term disease control. Patients with HER2-negative locally recurrent/metastatic breast cancer who had progressed during/after ≥12 weeks of first-line bevacizumab plus chemotherapy were randomised 1:1 to second-line single-agent chemotherapy either alone or with bevacizumab (15 mg/kg q3w or 10 mg/kg q2w).

Stratification factors were: hormone receptor status; time to first-line progression (<6 vs. ≥6 months); chemotherapy choice (taxane vs. non-taxane vs. vinorelbine); and LDH concentration (≤1.5 vs. >1.5 × upper normal limit).

Second-line therapy was continued until disease progression, unacceptable toxicity or consent withdrawal. At disease progression, patients in the chemotherapy arm received thirrd-line chemotherapy without bevacizumab (no crossover); patients initially randomised to chemotherapy plus bevacizumab received third-line chemotherapy plus bevacizumab.

Chemotherapy options were based on investigator's choice, but doublets were not allowed: paclitaxel, nab-paclitaxel, docetaxel, capecitabine, gemcitabine, pegylated liposomal doxorubicin, non-pegylated liposomal doxorubicin, doxorubicin, epirubicin, vinorelbine, cyclophosphamide, ixabepilone and in third line only eribulin.

The primary endpoint was PFS from randomisation to second disease progression/death. Additional endpoints included second-line PFS in prespecified subgroups, second- and third-line PFS calculated from randomisation to third disease progression/death, second-line ORR, OS, safety, QoL and biomarkers.

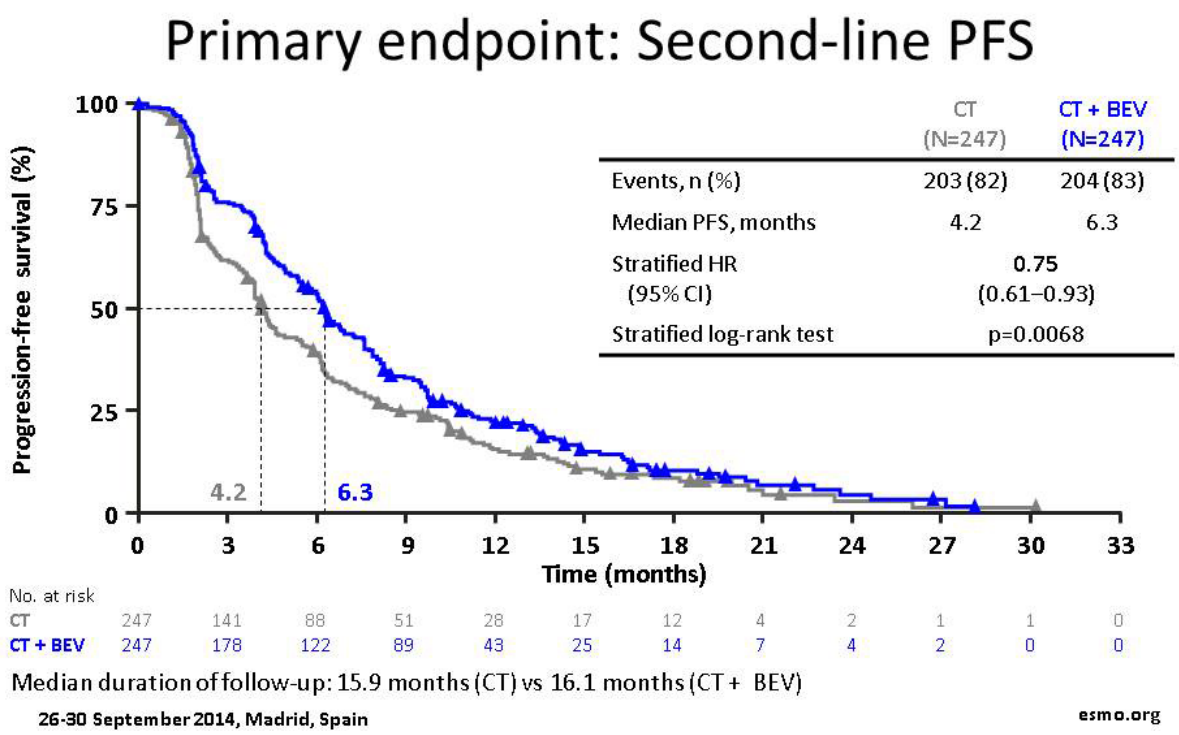
Sample size was calculated based on assuming prolonging median PFS from 7 to 9.3 months and a HR of 0.75. PFS events were required in 384 of 488 patients for 80% power at 2-sided α=0.05.

At ESMO 2014, the investigators presented the mature pre-specified second-line PFS analysis. Endpoints relating to third-line therapy will be presented at the final analysis.

From January 2011 to April 2013, 494 patients were enrolled (247 in chemotherapy arm and 247 in chemotherapy plus bevacizumab arm). Baseline characteristics were similar in chemotherapy vs. chemotherapy plus bevacizumab groups: median age 54 vs. 56 years; triple negative disease 23.1% vs. 19.8%; disease-free interval ≤12 months 9.7% vs. 7.3%.

The most frequently chosen second-line chemotherapy was capecitabine, 59.7% in chemotherapy group and 60.4% in the chemotherapy plus bevacizumab group.

Median follow-up was similar in both groups. At data cut-off on 20 December 2013, median second-line PFS was 4.2 months in chemotherapy vs. 6.3 months in chemotherapy/bevacizumab groups (stratified HR 0.75, p = 0.0068). Subgroup analysis for PFS by stratification factor was also more favourable for the bevacizumab/chemotherapy grooup.



Caption: Primary endpoint – Second-line PFS. © Gunter von Minckwitz

The best ORR was not statistically different in two groups (16.8% vs. 20.9%). However, the stable disease (SD) was recorded in 33.5% patients in the chemotherapy arm and 48.9% in the bevacizumab/chemotherapy arm.

Median duration of response (DoR) was 10.6 vs. 8.3 months for chemotherapy and bevacizumab/chemotherapy paients.

The rate of side effects was slighlty higher in the chemotherapy/bevacizumab arm: hypertension (7.1% vs. 13.5%), proteinuria (0.4% vs. 6.9%), venous thromboembolic event (2.1% vs. 3.3%), febrile neutropaenia (1.7% vs. 3.3%), congestive heart failure (0.4% vs. 2.0%), bleeding (1.7% vs. 0.4%), arterial thromboembolic event (1.3% vs. 0%), wound-healing complication (0% vs. 0.8%), GI perforation (0% vs. 0.4%), and fistula/abscess (0% in both groups).

The authors concluded that the primary objective of the study was met, showing statistically significantly improved PFS with bevacizumab after disease progression on first-line bevacizumab-containing therapy. Second-line safety results were as expected from previous bevacizumab trials in locally recurrent/metastatic breast cancer. Final OS, PFS from randomisation to third-line progression/death and third-line safety results are anticipated in mid 2015.

Dr Hope Rugo of the UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, USA, who discussed the results from this study as well, said that the TANIA trial tried to see the impact of chemotherapy vs. targeted therapy alone as maintenance therapy after response. Almost 85% of patients received first-line taxane (73% paclitaxel). There was an unusually long PFS in first-line. Almost 60% received second-line capecitabine. The PFS increased with continued bevacizumab; there was an increase in SD but not ORR and, as in prior studies, the

greater benefit was in triple-negative breast cancer. Furthermore, there was more toxicity with bevacizumab (hypertension, proteinuria, neutropenia).

Maintenance chemotherapy improves PFS and OS after response to first-line chemotherapy. Unclear additional benefit from bevacizumab must be balanced against cost and toxicity. Bevacizumab alone should not be used as maintenance therapy in this setting. Almost 75% had hormone receptor-positive disease and there might be a role of maintenance hormone therapy.

Dr Rugo concluded that at present the role of bevacizumab is unclear in breast cancer.

Upon the presentation at ESMO 2014, the study results were published in the Lancet Oncology.

The study was sponsored by F. Hoffmann-La Roche.

Reference

353O: Efficacy and safety in TANIA, a randomised phase III trial of continued or reintroduced bevacizumab (BEV) after 1st-line BEV for HER2-negative locally recurrent/metastatic breast cancer (LR/mBC)

RELATED INFORMATION

Click here to access the Conference abstracts.

Click here to access the meeting webcast page.

Save the date

European Cancer Congress 2015 (ECC 2015), Vienna, Austria, 25-29 September 2015.

Affiliations and Disclosure

Affiliation

Dr Svetlana Jezdic, ESMO Head Office

Disclosure

No conflicts of interest to disclose.

Acknowledgment

ESMO would like to thank Drs Gligorov, von Minckwitz, Zhu, Kang, Lenz, Stintzing, Konecny, Krishnansu, Goss, Robert, McArthur, Weber, and Blay for giving their permission to publish images from the studies presented during the ESMO 2014 Congress in the ESMO Scientific report.