2015 EUROPEAN CANCER CONGRESS

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Vienna, Austria

SUMMARY

The European Cancer Congress (ECC 2015) combined the 40th European Society for Medical Oncology (ESMO) congress with the 18th congress of the European CanCer Organisation (ECCO) and was held 25 to 29 September, 2015. The meeting was organised in partnership with the European Society of Radiation and Oncology (ESTRO), the European Society of Surgical Oncology (ESSO), the European Academy for Cancer Research (EACR), the European Oncology Nursing Society (EONS), and International Society of Paediatric Oncology (SIOPE). The efforts of all partner organisations were united to continue advancing multidisciplinarity as the way forward to optimise the prevention, diagnosis, treatment, and care of cancer patients by encouraging participants to leverage knowledge, promote education and build awareness for patient-centred oncology.

Contents

BREAST CANCER

Study supports omitting a re-excision for a focally positive surgical margin after primary breast conserving surgery

Lead investigator Elvira Vos, Erasmus MC Cancer Institute, Rotterdam, The Netherlands reported on the ipsilateral breast tumour recurrence (IBTR) overall survival of patients with invasive breast cancer patients after primary breast conserving surgery (BCS) followed by re-excision compared with patients having primary BCS only. Dutch national guidelines in place since 2002 recommend reserving re-excision for invasive tumours showing a 'more than focally positive' margin, which was defined as the foci of tumour touching ink, but over a length of <4mm. Noting that Dutch re-excision indications are less stringent compared with Society of Surgical Oncology-American Society for Radiation Oncology guideline, the investigators conducted a retrospective analyses of data from a Dutch registry of 35,261 women, aged less than 75 years with unilateral invasive breast cancer, stage pT1–T3 but no prior malignancy, that were treated by BCS and radiotherapy between 1999 and 2012. Patients without information about margin status or incomplete follow-up were excluded.

Information on margin status and follow-up was available in 7,940 patients who were placed into cohorts based upon 'primary BCS only', 're-excision by BCS', and 're-excision by mastectomy'. Univariable and multivariable Cox regression analyses were performed that adjusted for clinicopathological characteristics, including age, histology, differentiation grade, tumour status, regional lymph node status, oestrogen-, progesterone-and HER2 receptor status, chemotherapy and hormonal therapy use. Median time of follow-up was 87 (interquartile range 65 to 120) months. Negative margins were found in 5,887 (74.1%) patients, 'focally positive' margins in 831 (10.5%), and 'more than focally positive' margins were found in 1222 (15.4%) patients. No association was found between margin status and the occurrence of IBTR, odds ratio (OR) 1.04; 95% CI 0.89, 1.20). IBTR was reported in 171 (2.9%) women with negative margins, and in 22 (2.6%) women with focally positive margins; 52 (4.3%) women with more than focally positive margins showed an elevated rate of IBTR that did not reach statistical significance (p = 0.034).

Importantly, in the cohort wherein treatment was carried out in 365 (43.9%) patients having a 'focally positive' margin per Dutch guidelines, specifically no re-excision, no significant association with IBTR was observed (unadjusted HR 1.40; 95%CI 0.61, 3.24; adjusted HR 1.54 95%CI 0.64, 3.74). This cohort also showed no association with disease-free survival (unadjusted HR 1.02; 95%CI 0.70, 1.50) or with overall survival (unadjusted HR 1.09; 95% CI 0.74, 1.61). The authors

concluded that omission of a re-excision for a focally positive surgical margin 87 months after primary BCS for invasive breast cancer does not seem to be associated with IBTR, disease-free survival, and overall survival. Vos et al. Abstract 1806.

Practice point and future research opportunities

These data, though limited in numbers, support the Dutch guideline that considers it to be a safe procedure to omit a re-excision in patients having a focally positive margin after breast conserving surgery. Additional analyses would be needed to inform a review of overall guidelines.

Predictors for pathological complete response with combined trastuzumab and lapatinib emerge from the NeoALTTO Trial

An analysis of gene signatures by RNA sequencing was conducted by Christos Sotiriou, Institut Jules Bordet, Brussels, Belgium and colleagues to identify the genes implicated in the response to combination trastuzumab/lapatinib plus weekly paclitaxel for HER2 positive early breast cancer. They used data from the phase III NeoALTTO trial, wherein the combination nearly doubled the rate of pathological complete response (pCR) over trastuzumab or lapatinib plus paclitaxel. The investigators identified clinically relevant genes in order to guide treatment. Of 455 patients enrolled in NeoALTTO, 254 patient baseline biopsies had RNA of sufficient quality and quantity. Random primed cDNA libraries were constructed and sequenced on the Illumina HiSeq 2000 platform in paired end mode. The gene sequences tested were related to proliferation, immune, stromal, AKT/mTOR and androgen receptor pathway activation. No significant differences in clinical parametres between the sequenced population and the main study population were observed. The relationship between pCR and the expression of several clinically and biologically relevant genes signatures (GS), as well as of the ERBB2 and ESR1 genes was assessed using logistic regressions.

The median sequencing depth was 54.7M read pairs. High ERBB2 expression associated the most strongly with pCR and was identified as the most significant predictor of pCR ($p = 1.9e-08$), followed by low levels of ESR1 ($p = 7.2e-05$), and expression of immune and proliferation-based signatures (GGI; $p = 0.0065$). Multivariate analysis of combination treatment versus sole trastuzumab or lapatinib showed the best model included ERBB2, ESR1 and an immune gene signature.

Analysis by treatment arm revealed that ERBB2 and ESR1 expression associated most strongly with pCR in the combination treatment arm but were also expressed in the monotherapy arms. The

immune signatures were significant only in the combination trastuzumab plus lapatinib arm, which was confirmed with an interaction test (p = 0.0029, OR 3.4). No other signatures or genes were found to be a significant predictor of pCR independently of ESR1, ERBB2 and an immune gene signature. Sortiriou et al. Abstract 1811.

Practice point and future research opportunities

NeoALTTO demonstrated that trastuzumab plus lapatinib was superior to either agent alone in achieving pCR in HER2 positive early breast cancer. RNA sequencing and multivariate analysis determined that high levels of ERBB2 and low levels of ESR1 associated with pCR in all treatment arms, but the association was strongest with combination treatment. High expression of immune genes associated with pCR only in the combination arm. These gene signatures may serve as predictors of pathological complete response and identify patients that are likely to benefit from combination trastuzumab plus lapatinib treatment.

Discordance found between the HER2-phenotype on circulating tumour cells and the primary tumour in women with HER2 negative metastatic breast cancer

Wolfgang Janni, University Hospital Ulm, Ulm, Germany, presented findings on behalf of the DETECT study group from an interim analysis of the DETECT study, which was designed to evaluate the prognostic and predictive value of HER2-status of circulating tumour cells (CTCs) in patients with metastatic breast cancer (MBC). The study first assessed the prevalence of HER2 positive CTCs in patients with HER2 negative MBC, and then determined the association of the CTCs to the primary tumour and patient characteristics. CTCs were quantitated using the FDA-cleared CellSearch® System and HER2 status was evaluated in 1123 (as of April 2015) women with HER2-negative MBC. Patients were defined as CTC positive if at least 1 CTC was detected in 7.5 ml of peripheral blood, and as having a positive HER2-status on CTCs if at least 1 CTC with a strong (+++) immunocytochemical HER2 staining intensity was found.

CTCs were detected in 711 (63.3%) screened patients, who showed a median 7 CTCs (range: 1 to 35078). Of these CTC-positive patients, 139 (19.5%) had one CTC, 184 (25.9%) had 2 to 5 CTCs, 90 (12.7%) had 6 to 10 CTCs, 175 (24.6%) had 11 to 50 CTCs, and 123 (17.3%) had more than 50 CTCs. The presence of CTCs significantly associated with a higher proportion of pN2/pN3 tumours (28.3% versus 19.9%; p = 0.008) and a higher proportion of lobular carcinomas (22.5% versus. 9.5%; p < 0.001). However, no association was found between CTCs and the grade (p = 0.326) or hormone receptor status (p = 0.103) of the primary tumour. In addition, the presence of CTCs was

not associated with patient age (p = 0.313), menopausal status at screening (p = 0.823), or the time interval between primary diagnosis and screening (p = 0.992).

At least one HER2-positive CTC was found in 134 (18.8%) of the patients with HER2-negative MBC and CTCs (median 2 HER2-positive CTCs; range: 1 to 80), indicating frequent HER2 status discordance between the primary tumour and CTCs. Of the patients with HER2-positive CTCs, 51 (38.1%) had one HER2-positive CTC, 48 (35.8%) had 2 to 5 HER2-positive CTCs, 15 (11.2%) had 6 to 10 HER2-positive CTCs, 16 (11.9%) had 11 to 50 HER2-positive CTCs, and 4 (3.0%) patients had more than 50 HER2-positive CTCs. The presence of HER2-positive CTCs was associated with hormone-receptor positive primary tumours, meaning that patients with triple-negative tumours were less likely to have HER2-positive CTCs than patients with HER2-negative but hormone-receptor positive tumours (6.1 versus 21.9%; p < 0.001), respectively. The investigators are evaluating the efficacy of individualised breast cancer treatment based on the HER2 phenotype of CTCs in the randomised DETECT III trial. Janni et al. Abstract 1805.

Practice point and future research opportunities

Findings from a large cohort of patients with HER2-negative MBC confirmed discordance in HER2 status between the primary tumour and CTCs in 18.8% of patients. Furthermore, the presence of HER2-positive CTCs was associated with hormone-receptor positive tumours. The results of the DETECT III trial should inform whether the phenotype of CTCs may be used to guide treatment in HER-2 negative breast cancer.

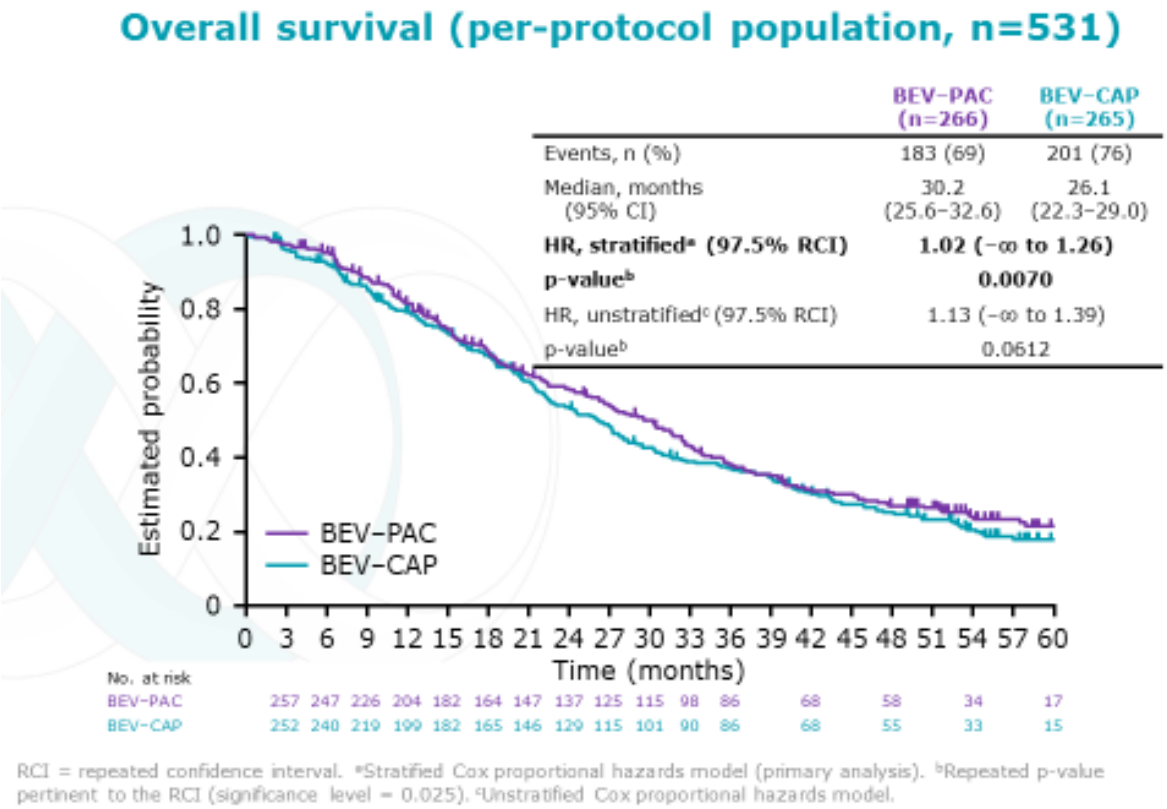
TURANDOT: Overall survival analysis shows first-line bevacizumab plus capecitabine non-inferior to bevacizumab plus paclitaxel in locally recurrent metastatic breast cancer

Thomas Brodowicz, Medical University Vienna in Vienna, Austria presented overall survival (OS) results from the open-label randomised phase III TURANDOT trial, which aimed to demonstrate non-inferior OS with first-line bevacizumab/capecitabine versus bevacizumab/paclitaxel in patients with locally recurrent/metastatic breast cancer (LR/MBC). Currently, bevacizumab/capecitabine and bevacizumab/paclitaxel regimens are approved by European regulatory authorities based on the superior progression-free survival (PFS) demonstrated with both of these regimens versus chemotherapy alone (Miller et al., NEJM 2007; Robert et al, JCO 2010). However, until now, the relative efficacy of these two regimens in terms of OS has remained unclear.

TURANDOT enrolled 564 patients from 51 centres in 12 countries. Eligible patients had HER2-negative LR/MBC and had received no prior chemotherapy for advanced disease. Patients were randomised to receive either bevacizumab/paclitaxel (intravenous (i.v.) bevacizumab at 10 mg/kg on days 1 and 15 plus i.v. paclitaxel at 90 mg/m2 on days 1, 8 and 15, repeated every 4 weeks; n=285) or bevacizumab/capecitabine (i.v. bevacizumab at 15 mg/kg on day 1 plus oral capecitabine at 1000 mg/m2 twice daily on days 1–14, repeated every 3 weeks; n=279) until disease progression or unacceptable toxic effects. The stratification factors were country, oestrogen/progesterone receptor status and menopausal status. The primary objective was to demonstrate non-inferior OS with first-line bevacizumab/capecitabine versus bevacizumab/paclitaxel by rejecting the null hypothesis of inferiority (HR ≥1.33) using a stratified Cox proportional hazard model. Sensitivity analyses were performed in the intent to treat (ITT) population and also using an unstratified Cox model in both populations. Subgroup analyses in clinically relevant populations were prespecified.

Whereas previously reported results of the interim analysis were inconclusive and non-inferior OS could not be demonstrated, the final results from TURANDOT demonstrated non-inferior OS in the bevacizumab/capecitabine arm compared with bevacizumab/paclitaxel in the primary stratified analysis in the per-protocol (PP) population, which was performed after 183 (69%) deaths occurred in 266 bevacizumab/paclitaxel patients and 201 (76%) in 265 patients in the bevacizumab/capecitabine arm. The stratified HR was 1.02 (97.5% repeated CI –∞ to 1.26; p = 0.007), meeting the criteria for non-inferiority and meeting the trial's primary objective. Median OS was 30.2 months in the bevacizumab/paclitaxel arm versus 26.1 months in the bevacizumab/capecitabine arm.

Results of the stratified ITT analysis were consistent with the PP results; however, results from stratified and unstratified analyses were inconsistent. The unstratified analysis in the PP population showed HR 1.13 (97.5% repeated CI –∞, 1.39). The PFS benefit with bevacizumab/paclitaxel over bevacizumab/capecitabine was supported by this final analysis, as was the superior objective response rate.



Caption: *Final results of the randomised phase III TURANDOT trial demonstrated non-inferior overall survival with bevacizumab plus capecitabine versus bevacizumab plus paclitaxel as first-line therapy for HER2-negative metastatic breast cancer in the primary analysis.*

Credit: Christoph Zielinski

Subgroup analyses according to hormone receptor status, ECOG performance status, age, presence of visceral metastases and prior anthracycline and/or taxane therapy, showed no difference in OS between the treatment arms. However, in the subgroups of premenopausal females and patients with a body surface area ≥1.8 m2, OS appeared to be more favourable with bevacizumab/paclitaxel than with bevacizumab/capecitabine. However, only 95 pre-menopausal patients were included in the subgroup, and the small sample size may have biased the data. The authors noted that, although the TURANDOT trial met its primary objective in the primary final OS analysis, there was inconsistency between the stratified and unstratified analyses and plan to explore this inconsistency, as well as the heterogeneity among subgroups. NCT00600340. Brodowicz et al. Abstract 1800.

Practice point and future research opportunities

The inconsistency between stratified and unstratified results is under examination. This study shows that paclitaxel is as good as capecitabine in HER-2 negative disease, strengthening the ABC Guidelines for first-line chemotherapy in patients with locally recurrent/metastatic breast cancer. Selection of a specific bevacizumab-containing regimen should be based on each patient's individual treatment priorities.

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AFFILIATION AND DISCLOSURE

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Disclosure

No conflicts of interest to disclose.

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