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**ESMO**

## Report

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### Introduction

New and exciting information was presented at the 33<sup>rd</sup> ESMO Congress, which was held in Stockholm on 12–16 September 2008 and which attracted more than 9000 delegates. Her Majesty Queen Silvia of Sweden officially opened the congress and emphasized the importance of comprehensive care for patients and families affected by cancer. ESMO's president, José Baselga, then made his opening speech, presenting the society's new strategic goals.

The conference comprised educational and scientific sections, both developed by international experts and presented in a way that encouraged delegates to fulfill their professional needs by participating as much as possible on specific topics. This report gives an overview of the important findings presented during the scientific program.

### Head and neck cancer

Several groups looked at prognostic and predictive markers in patients with head and neck cancer:

- $\beta$ -tubulin-II expression was determined in paraffin sections of pretreatment biopsy specimens of 265 patients randomized in the TAX 324 trial. Cytoplasmic staining intensity for  $\beta$ -tubulin-II was assessed by a semi-quantitative method and its expression was strongly correlated with an adverse outcome. For patients with low  $\beta$ -tubulin-II expression, the median overall survival (OS) was at least 58.6 months (95% confidence interval (CI) not reached). For patients with a high  $\beta$ -tubulin-II expression, median OS was significantly lower at 18.2 months (95% CI 13.11–30.06; hazard ratio (HR) 2.39; log-rank  $p < 0.0001$ ). The predictive value was higher in the docetaxel-cisplatin-5-Fluorouracil (5FU) arm (TPF) than in the cisplatin-5FU (PF) arm: in the TPF arm, median OS was not reached (95% CI 59 months not reached) versus 21 months (95% CI 8.5–40) for low versus high  $\beta$ -tubulin-II expression respectively, yielding a HR of 2.8 (log-rank  $p < 0.0001$ ); in the PF arm, median OS was not reached for low  $\beta$ -tubulin-II versus 18.3 months (95% CI 12.2–42.0) for high  $\beta$ -tubulin-II expression with a HR of 2.0 (log-rank  $p = 0.005$ ). This shows that expression of  $\beta$ -tubulin-II is strongly associated with adverse outcome in patients with a locally advanced squamous cell carcinoma of the head and neck. It was also shown that patients with a low  $\beta$ -tubulin-II expression showed the most benefit from induction TPF chemotherapy (1).
- Vermorken *et al.* assessed the association between skin rash, epidermal growth factor receptor (EGFR) expression and EGFR gene-copy numbers, and OS. Patients ( $n = 442$ ) were randomized to receive three-weekly cycles of cisplatin (100 mg/m<sup>2</sup> IV on day 1) or carboplatin (AUC 5, day 1) plus 5FU (1000 mg/m<sup>2</sup>/day continuous infusion during days 1–4) with or without cetuximab (initial dose 400 mg/m<sup>2</sup> then 250 mg/m<sup>2</sup> weekly). Skin reactions more than grade 1 developing up to a certain time were associated with a 23% reduction in the risk of death (HR 0.77; 95% CI 0.55–1.09;  $p = 0.14$ ), while there was no relation between EGFR expression and gene-copy number status and OS in patients treated with cetuximab (2).

Although these findings are promising, their value in predicting clinical outcomes for individual patients with specific treatments is limited and more research is needed before this information is of value in clinical practice.

### Chest tumors

#### Advanced disease

Two large phase III randomized trials of first-line treatment in advanced non-small cell lung cancer (NSCLC) were presented during the presidential symposium:

- Manegold *et al.* presented the updated results of the AVAIL study (a phase III randomized study of first-line bevacizumab combined with cis/gem) (3). Although progression-free survival (PFS), the primary endpoint, was slightly higher in the bevacizumab treatment arms (6.2 months placebo; 6.6 months bevacizumab 15 mg/kg; 6.8 months bevacizumab 7.5 mg/kg,  $p < 0.05$ ), there was no statistical difference in OS between the different arms.
- The study presented by Mok *et al.* (4) (PASS: a phase III, randomized, first-line study of gefitinib versus carboplatin/paclitaxel in selected advanced NSCLC patients) examined the question of upfront treatment with the tyrosine kinase inhibitor (TKI) gefitinib. Patients had no prior systemic therapy, had a diagnosis of adenocarcinoma, had never smoked or were light ex-smokers, and had measurable stage III B/IV NSCLC. It was planned as a non-inferiority trial and the primary endpoint was PFS. Other secondary endpoints were exploratory endpoints such as EGFR mutation, EGFR gene-copy number and EGFR protein expression. In this study, 609 patients were randomized to gefitinib and 608 to carboplatin/paclitaxel (CP). Gefitinib was superior to CP in terms of PFS (HR = 0.741;  $p < 0.0001$ ). The effect was irregular over time, initially favoring CP, and then favoring gefitinib. Preliminary OS was similar for both treatment arms. Overall EGFR+ mutation rate in this population was 60% (261 out of 437 patients). Patients with EGFR+ mutation had longer PFS with gefitinib compared with CP (HR = 0.48;  $p < 0.0001$ ).

Also in NSCLC, the quest for predictive biomarkers for targeted agents is of utmost importance in order to individualize treatment:

- Altorki *et al.* presented a multicenter phase II study of pazopanib given preoperatively to 26 patients with stage I–II disease (5). Pazopanib is an oral angiogenesis inhibitor that targets the vascular EGFR (VEGFR), the platelet-derived growth factor receptor (PDGFR), and the c-kit. The primary endpoint of this study was a change in tumor volume, measured by high resolution CT images performed before and after pazopanib treatment. Secondary endpoints included Response Evaluation Criteria in Solid Tumors (RECIST) response and safety, and analysis of pre- and post-treatment levels of 52 cytokines/angiogenic factors. In 87% of patients there was a reduction in tumor volume and three patients reached a partial

response. Grade 3 toxicities in three patients were: alanine transaminase (ALT) increase (two patients), hypertension (one), dyspnea (one), pneumonia (one), urinary tract infection (one), and lymphopenia (one). There was a significant correlation between baseline levels of plasma insulin-like growth factor-I receptor, interleukin (IL)-2R, IL-12, IL-16, tumor necrosis factor-related apoptosis-inducing ligand, stem-cell factor, IL-3, and thymus and activation-regulated chemokine, and tumor reduction. The team also observed a significant correlation between tumor reduction and changes in levels of sVEGFR-2 and VEGF.

- Gregorc *et al.* presented a study exploring the correlation of resistance to EGFR TKIs and serum proteomic profile in NSCLC patients (6). They evaluated the Veristat™ proteomic profile in 111 advanced NSCLC patients before and during gefitinib treatment. The team showed that the proteomic profile modified at progression, and concluded that this suggests a possible correlation between serum proteomic profile and resistance to gefitinib.
- In an exploratory analysis of tumor gene expression in erlotinib-treated NSCLC patients, Klughammer *et al.* (7) wanted to identify differentially expressed genes in 101 patients with and without clinical benefit, but were unable to identify such markers. However, they did identify molecular determinants of response comparing partial response (PR) patients with progressive disease (PD) patients (differences in expression levels of three genes: PSPH, RAPGEF5, EGFR – all located on chromosome 7).
- Smit *et al.* (8) presented a randomized phase II study of pemetrexed (pem) versus pemetrexed/carboplatin (pem/carbo) as a second-line treatment in patients with NSCLC progressing more than three months after primary treatment. In 236 patients that could be evaluated, the median PFS was 2.8 months for pem versus 4.2 months for carbo/pem (HR 0.67;  $p = 0.005$ ), and the median OS was 7.6 months for pem versus 8.0 months for carbo/pem (HR 0.85;  $p = \text{NS}$ ). The worst OS was observed in patients with squamous cell cancer histology treated with pem.

## Breast cancer

### Early disease

The place of taxanes in an adjuvant setting was addressed in two phase III studies presented by Cognetti *et al.* (9) in node-positive (N+) patients, and by Martin *et al.* (10) in node-negative (N-) patients.

- Cognetti's study compared the addition of docetaxel to epirubicin followed by cyclophosphamide-methotrexate-5FU (CMF) with epirubicin alone followed by CMF. The primary endpoint, disease-free

survival (DFS), was not reached (HR 0.82;  $p = 0.13$ ), but relapse-free survival (RFS) (excluding contralateral breast cancer and non-breast secondary cancer) was 0.75 ( $p = 0.04$ ) and the five-year OS was 90% in the arm with docetaxel and 85% in the standard arm (HR = 0.67;  $p = 0.017$ ). The benefit was gained at the expense of longer treatment duration and increased toxicity.

- In the study presented by Martin, TAC (docetaxel 75 mg/m<sup>2</sup>; doxorubicin 50 mg/m<sup>2</sup>; cyclophosphamide 500 mg/m<sup>2</sup> every three weeks) was compared with FAC (5FU 500 mg/m<sup>2</sup>, doxorubicin 50 mg/m<sup>2</sup>; cyclophosphamide 500 mg/m<sup>2</sup> every three weeks). The primary endpoint, DFS, was reached: the estimated five-year DFS was 91% for TAC and 86% for FAC (HR 0.66;  $p = 0.02$ ) while the estimated five-year OS was 97% for TAC and 95% for FAC (HR 0.72;  $p = 0.27$ ). TAC produced more hematological toxicity, although primary prophylaxis with granulocyte-colony stimulating factor (G-CSF) reduced neutropenic fever events. The study reported no toxic deaths.

The studies by Dang *et al.* (11) and Frasoldati *et al.* (12) addressed treatment optimization:

- The primary endpoint of the study by Dang was to determine the feasibility of dose-dense combined treatment (doxorubicin, cyclophosphamide with paclitaxel, lapatinib, trastuzumab (PTL)). The authors concluded that grade 3 diarrhea was excessive (26% overall) despite supportive treatment, and future and ongoing trials studying PTL should consider this toxicity in their designs. Pharmacogenomics might help to identify patients at high risk of toxicity. Congestive heart failure was seen in 2 of the 95 patients (2%).
- In the study by Frasoldati comparing immediate zoledronic acid (4 mg every six months) with delayed zoledronic acid (same dosing), the primary objective was the change in lumbar spine bone-mineral density at 12 months in patients receiving adjuvant letrozole. As a secondary endpoint, the study also assessed the time to disease recurrence. The results demonstrated that the use of zoledronic acid upfront prevents bone loss in women with early stage breast cancer receiving adjuvant letrozole. Zoledronic acid also showed an effect on disease recurrence (HR 0.573,  $p = 0.018$ ).

Goodwin *et al.* (13) and Ignatiadis *et al.* (14) addressed individualization of prognosis:

- In the study by Goodwin, disease outcome was evaluated in patients with familial BRCA1 and BRCA2 and non-familial (NF) breast cancer. Distant DFS and

OS did not differ significantly between BRCA1 carriers and NF patients in univariate or multivariate analyses (all HR < 1.43; all  $p > 0.11$ ). Distant DFS and OS were worse in BRCA2 carriers than in NF patients (HR 1.6;  $p = 0.04$  and HR 1.8;  $p = 0.01$ , respectively) in univariate analyses. These effects were lost after adjusting for age, T and N stage, grade, estrogen receptor (ER) status, and year of diagnosis (distant DFS HR 1.0,  $p = 0.98$ ; OS HR 1.13,  $p = 0.61$ ). In the small group who did not receive adjuvant chemotherapy, BRCA2 carriers had a significantly worse OS after adjusting for the above factors (HR 3.63,  $p = 0.005$ ). The authors concluded that BRCA1 and BRCA2 mutations are associated with adverse prognostic factors but do not independently impact distant DFS or OS.

- The aim of the study by Ignatiadis was to evaluate the prognostic value of circulating tumor cells (CTC) monitored with CK19 and HER2 before and after adjuvant chemotherapy. The results showed that persistent detection of CK19-positive/HER2-positive CTCs in early stage breast cancer patients before and after adjuvant chemotherapy predicts extremely poor clinical results (HR 3.940;  $p < 0.001$  for DFS and HR 3.862;  $p = 0.005$  for OS). The observation was similar in all subgroups (triple-negative, HER2-positive, and ER-positive/HER2-negative).

### Advanced disease

The interesting sessions on advanced breast cancer included presentations on treatments in trastuzumab-resistant disease, use of cytostatic agents, and treatment individualization.

The TBP phase III study (15) examined the efficacy of capecitabine versus capecitabine plus trastuzumab (CT) in patients progressing on trastuzumab. At a median follow-up of 15.6 months, the time to progression (TTP) for capecitabine was 5.6 months and 8.2 months for CT (HR 0.69;  $p = 0.04$ ); OS was 20.4 months for capecitabine and 25.5 months for CT (HR 0.77;  $p = 0.26$ ). There were no significant differences in grade III/IV toxicities.

There are no data supporting the superiority of any particular cytostatic regimen for treating metastatic breast-cancer patients. Polychemotherapy or agents used in sequence give similar results. Mavroudis *et al.* presented the role of anthracyclines in this setting and compared epirubicin plus docetaxel with capecitabine plus docetaxel in a phase III trial. There were no differences in TTP and OS (16).

Two papers on treatment individualization were presented in the oral session:

- The study by Ibrahim *et al.* (17) tested 20 variables to develop a multivariate model that could predict

brain metastases in patients with metastatic breast cancer. A nomogram was created that could be used for individual predictions. A prospective randomized study is in progress to confirm these results and test the effect of prophylactic treatment.

- Koh *et al.* (18) presented the correlation of early metabolic response and tumor biology using fluorodeoxy glucose (FDG)-positron emission tomography/computer tomography (PET/CT) before and after the first cycle of neo-adjuvant chemotherapy in patients with breast cancer. The authors concluded that early metabolic responses using FDG-PET/CT have a predictive value for assessing responses in patients with breast cancer after neo-adjuvant chemotherapy, and changes in maximum standard uptake values ( $SUV_{max}$ ) in PET after neo-adjuvant chemotherapy also reflects the subtype of breast cancer.

### Colorectal cancer

K-ras mutation status is a predictive biomarker for cetuximab benefit in the treatment of advanced colorectal cancer.

- This was shown in a randomized study (NCIC CTG co.17) comparing cetuximab with best supportive care (BSC) in patients with advanced colorectal cancer. Karapetis *et al.* (19) treated 394 patients, of whom the K-ras status was determined on primary tumor tissue. Direct gene sequencing detected activating mutations in exon 2 of the K-ras gene in tumor-derived genomic DNA; mutant K-ras was detected in 164 patients (42%). Within the mutant K-ras group, the median PFS was the same (1.8 months) for both groups (HR 0.99; 95% CI 0.73–1.35;  $p = 0.96$ ), and median OS was 4.6 months with cetuximab and 4.5 months with BSC (HR 0.98; 95% CI 0.70–1.37;  $p = 0.89$ ). In the 230 (58%) wild type (WT) patients, median PFS was 3.8 months for the cetuximab-treated group and 1.9 months with BSC (HR 0.40; 95% CI 0.30–0.54;  $p < 0.0001$ ). The survival of patients with WT K-ras was longer when they were treated with cetuximab, with a median OS of 9.5 months with cetuximab versus 4.8 months with BSC (HR 0.55; 95% CI 0.41–0.74;  $p < 0.0001$ ). The test for interaction between K-ras mutation status and cetuximab treatment demonstrates that the effect of cetuximab on OS ( $p = 0.01$ ) and PFS ( $p = 0.0001$ ) is significantly greater in the K-ras WT group than in the mutant group. The difference in the OS of patients with either WT or mutant K-ras in the BSC arm was not significant (HR 1.01; 95% CI 0.74–1.37;  $p = 0.97$ ). In the setting of pre-treated advanced colorectal cancer, there is an almost doubling of median OS and PFS in patients with WT K-ras tumors, while no significant benefit is observed in patients with mutant K-ras.

- The importance of K-ras mutation was also shown in early treatment for metastatic colorectal cancer. Samples were collected during the crystal study, in which patients received FOLFIRI as a first-line treatment, with or without cetuximab. Of 1198 randomized patients, 578 genomic DNA samples were available and K-ras mutation status were determined on codons 12/13 using a mutation-specific, quantitative polymerase chain reaction (PCR)-based assay. The relationship between K-ras mutation status and outcome was assessed in 540 patients who could be evaluated for K-ras. The team detected K-ras mutation in 192 patients (35.6%). A statistically significant difference in favor of cetuximab was seen in K-ras WT patients for the best overall response rate ( $p = 0.0025$ ) and PFS ( $p = 0.0167$ ). The improvement in OS from 21.0 to 24.9 months showed a strong trend in favor of cetuximab (20).

Determining K-ras mutation status should be considered a new standard of care when selecting patients for EGFR-targeted therapy.

Koopman *et al.* (21) reported that the number of CTCs in the blood of patients with advanced colorectal cancer is a valuable predictor of survival. Her group studied 467 patients who were being treated within a prospective clinical trial (CAIRO2 of the Dutch Colorectal Cancer Group) with chemotherapy plus bevacizumab, with or without the addition of cetuximab. In each patient they measured levels of CTCs before treatment and at different stages during treatment. The results showed that the median PFS time for patients with less than three CTCs in every 7.5 ml of blood was 10.5 months compared with 8.2 months for those with three or more. Furthermore, the median OS time for patients with less than three CTCs in every 7.5 ml of blood was 22.2 months, compared with 13.7 months for those with three or more.

### Conclusion

The 2008 ESMO Congress provided an interesting educational and scientific program, which can be found on the ESMO website [www.esmo.org](http://www.esmo.org). The site contains all abstracts, the educational book, and the opportunity to take part in a virtual consultation with all of the educational sessions.

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