

First interim toxicity analysis of the randomized phase III WSG Plan B trial comparing 4xEC-4xDoc versus 6xTC in breast cancer patients with HER2 negative BC

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Background: Anthracycline-taxane based adjuvant chemotherapy is considered as a standard in treatment of node-positive and high risk node negative disease. However retrospective analyses suggest that in a large subgroup of patients with HER2 negative disease a benefit from anthracyclines may not outweigh acute and long term toxicities. Recurrence score (RS) identifies a subgroup of patients who are not candidates for chemotherapy on the basis of their low risk of recurrence. The WSG Plan B trial investigates the effect of anthracycline-free chemotherapy in HER2 negative BC and is the first trial in Europe prospectively incorporating RS for decision making regarding adjuvant chemotherapy in both node-negative and positive disease.

Methods:

Plan B trial randomizes HER2 negative BC patients with either high risk N0 (at least one of the following factors:  $\geq pT2$ ; negative HR status; G2-3; age  $\leq 35$  years old; high uPA/PAI-1) or N+ disease to 6xTC (Docetaxel<sub>75</sub>Cyclophosphomide<sub>600</sub>) vs. 4xEC (Epirubicin<sub>90</sub>Cyclophosphomide<sub>600</sub>)-4xDoc (Docetaxel<sub>100</sub>). Primary G-CSF prophylaxis is recommended according to current ASCO guidelines. The statistical design previews n=2,448 randomized to chemotherapy. Patients with HR positive disease, N0-3 and a RS  $\leq 11$  receive endocrine therapy only.

Results:

From April 2009 to June 2011, 3037 patients have been recruited and 2296 (TC/EC-Doc: 1146/1150) randomized. From the patients with HR+ disease (n=2368) 18% had a RS 0-11, 61% a RS 12-25 and 21% a RS  $\geq 25$ . In patients with 0-3 positive LN and RS of 0-11 (n=329) who opted for no chemotherapy 257 are in the observational arm. In the group with an intermediate risk (RS 12-25) 14% drop outs before start of chemotherapy have been reported. Among the patients randomized to cht, 1811 were <65 years old (TC/EC-Doc:900/911) and 485  $\geq 65$  years old (TC/EC-Doc:246/239)

In 1172 fully monitored patients 22 toxicity-related therapy stops have been reported in the TC arm and 34 in the EC-Doc arm (p=0.12)

SAEs: 614 serious adverse events (SAE) have been reported (299 TC+ vs. 315 EC-Doc-). There is no difference in patients <65 years old (TC vs. EC-Doc: 218/218), but slightly more SAE's in patients  $\geq 65$  years old treated by EC-Doc (97 vs. 81, p=0.13). The most frequent SAEs were: leucopenia, febrile neutropenia (TC 37 (3.3%) vs. EC-Doc 31 (2.7%), n.s.), infections and heart/vascular events (TC: 29; EC-Doc 40, n.s.). In patients  $\geq 65$  years old, there is a trend towards more febrile neutropenia associated with TC treatment (13 vs. 5 under EC-Doc; p=0.06), and more severe mucositis/diarrhea/nausea (3 vs. 15, p=0.007) and heart/vascular events (5 vs. 14, p=0.06) in the EC-Doc arm

Therapy related deaths: there were 5 therapy related deaths (TC 5 (0.4%)/EC-Doc 0, p=0.03). There are 5 therapy-related deaths (3 in patients <65 years old, 2 in patients  $\geq 65$  years old: 4 due to sepsis, 1 due to cardiac failure.

Detailed data on impact of RS on patient decision, toxicity analysis, use of G-CSF support will be updated for the SABCS meeting.

Conclusions: The Plan-B trial is one of the largest randomized phase III trials currently evaluating anthracycline-free adjuvant chemotherapy in HER2 negative BC. The chemotherapy administered within the study was generally well tolerated, but higher number of treatment-related deaths has been observed within the TC arm. The short term toxicity profile seems be different between both study arms, particularly in patients  $\geq 65$  years old. On the basis of prognosis as determined by RS a substantial group of patients decided not to undergo chemotherapy.