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

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Background

- Retrospective analyses suggest that in patients with HER2-negative disease, benefit from anthracyclines may not outweigh acute and long term toxicities[1].
- The Recurrence score (RS) provides an estimate of 10 year risk of recurrence and is predictive of chemotherapy (CHT) benefit in hormone receptor positive, HER2-negative early BC[2-4].
- Plan B trial has two goals:
  - spare chemotherapy to pN0-1 patients identified to be at low risk by integrating RS (**see oral presentation S4-3**)
  - Spare anthracyclines in HER2-neg BC (EC→Doc vs TC)
- Toxicity data for the comparison of EC x4 → Doc x4 vs TC x6 are presented here.

Objectives

- **Primary objective**: disease-free survival of the two CHT arms
- **Secondary objectives**: overall survival, toxicity, evaluation of survival in patients spared from CHT, evaluation of prognostic/predictive factors

Materials & Methods

- **Study design:** prospective, randomized phase III study. The statistical design assumes n=2448 randomized to CHT (non inferiority design).
- **Inclusion criteria (cht):** female patients, 18-75 years
- M0 unilateral primary invasive HER2-negative BC
- Operable pT1-4 , pN+, high-risk pN0 (>2cm; HR -; high uPA/PAI-1; age <35; G2/3)
- HR+ and pN0-1 and RS> 11
- adequate organ function (leukocytes ≥3.5 G/l, platelets ≥100 G/l, hemoglobin ≥10 g/dL, total bilirubin ≤ 1 ULN, sGOT/sGPT ≤2.5 ULN, creatinine ≤2 mg/dL, LVEF and ECG within normal limits)
- written informed consent
- Patients with HR+ and pN0-1 and RS≤ 11 can participate (patient´s decision) , but should receive endocrine treatment (ET) alone
- **Main exclusion criteria**: known polyneuropathy ≥ grade 2, relevant comorbidity, prior malignancy (except basalioma of the skin, pTis cervix uteri, ipsilateral pTis BC), time since axillary dissection >42 days, concurrent pregnancy and breast feeding.
- **Treatment:** TC: 6 x docetaxel (75 mg/m²) + cyclophosphamide (600 mg/m²), q3w
  EC-DOC: 4 x epirubicin (90 mg/m²) + cyclophosphamide (600 mg/m²) followed by 4 x docetaxel (100 mg/m²), q3w
  ET and radiation is recommended according to national standard.
  Primary G-CSF prophylaxis is recommended according to current ASCO guidelines.
  ET and radiotherapy according to national standards

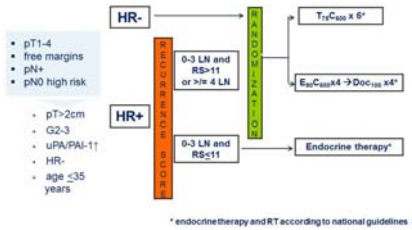

Fig. 1: Study Design

Results

- From April 2009 to October 2011, 3193 patients have been recruited and 2444 (TC:1225 /EC-Doc: 1219) patients randomized (Fig. 2).
- Among the patients randomized to CHT, 1930 were <65 years old (TC/EC-Doc: 961/969) and 514 ≥65 years old (TC/EC-Doc: 258/256).

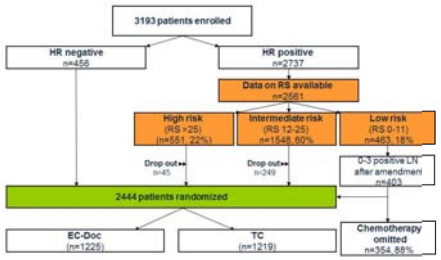

Fig. 2: Disposition of patients

- RS distribution in HR+ disease (n=2561) : RS ≤11: 18 %; RS 12-25: 60% and RS> 25: 22%
- RS ≤ 11 - low risk: 88 % of patients (including those who withdrew consent) decided not to have CHT within the protocol .
- RS 12-25 - intermediate risk: 16% drop outs before randomization have been reported.
- Randomized to CHT: 116 drop outs in patients reported until end of treatment (6.5% of all fully documented and monitored patients, n=1780).
- 13,868 cycles of CHT have been documented so far.
- **Therapy stops**: In 1897 documented and/or monitored patients significantly less toxicity-related therapy stops have been reported in the TC arm (4%) compared to the EC-Doc arm (7.2%; p<0.001).
- **Dose reductions:** Toxicity related dose reductions occurred significantly fewer in the TC arm (5.3%) than in the EC-Doc arm (15.6%; p<0.001).
- **Treatment-postponement:** Incidence of treatment-postponement due to adverse events was significantly lower for TC (1.9% vs. 3.1% of all documented given CHT cycles; p<0.001).
- **G-CSF:** Primary prophylaxis (overall 10.8%) was given significantly more frequently in the TC arm (13.6%) of all documented CHT cycles than in the EC-Doc arm (8.6%, p=0.007). Secondary prophylaxis with G-CSF was applied in 17.8% of all documented cycles and did not differ in both arms (TC: 18% vs. EC-Doc: 17.6%; n.s.).
- **SUSARs:** So far, 6 SUSARs have been reported (TC: psychosis, memory disturbance, amnesia, acute pancreatitis; EC-Doc: confusion, ataxia).
- **Adverse events/CTC toxicity grades:** Data on 13,868 courses in 1,644 patients (TC: 826; EC-Doc: 818) for CTC toxicity grades are available: haematotoxicity, nausea/vomiting, mucositis, stomatitis, diarrhea, pain, skin/nail toxicity, hepatic and cardiovascular disorders, infections, and neurotoxicity. Highest CTC toxicity grades in each category per patient are evaluated.
  - Significantly less grade 3/4 toxicities are reported in the TC arm (n =787) vs. EC-Doc arm (n= 900; p<0.001).
  - Grade 3/4 toxicity is mostly restricted to hematotoxicity and infections. The difference favoring TC arm is due to lower rates of anemia, stomatitis, nausea, pain, cardiovascular disorders, vomiting, and neurotoxicity (see figure 3).
  - Significantly more G3-5 infections were reported in the TC arm (6.1% vs. 3.9%, p=0.014; Fig. 3).

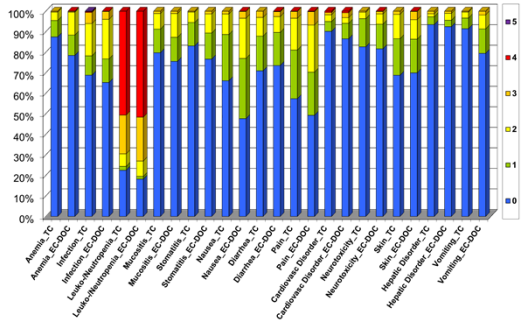

Fig. 3: highest toxicity grade reported per patient per treatment arm

- **SAEs:** 755 serious adverse events have been reported (TC/EC-Doc: 358/397, Tab. 1). There are significantly more infections (p<0.001) reported in the TC arm. Significantly more cardiovascular events were reported in older patients ≥65 years (p=0.012) treated with EC-Doc.
- **Therapy related deaths:** There were 6 therapy related deaths (TC: 5 (0.4%) / EC-Doc: 1 (0.08%); p=0.1): 5 due to sepsis, 1 due to pulmonary embolism. 3 deaths are reported in patients <65 years old (TC/EC-Doc: 2/1 and 3 in patients >65 years old (all in the TC arm)

	Patients < 65 years				Patients ≥ 65 years			
	Arm A - TC	%	Arm B - EC-Doc	%	Arm A - TC	%	Arm B - EC-Doc	%
Infection	53	5.5	34	3.5	22	8.5	17	6.6
leukopenia/neutropenia	26	2.7	38	3.9	19	7.4	25	9.8
febrile neutropenia	30	3.1	30	3.1	13	5.0	10	3.9
Mucositis/Nausea/Diarrhea	38	4.0	49	5.1	17	6.6	21	8.2
FUO	15	1.6	13	1.3	1	0.4	5	1.9
Pain	9	0.9	18	1.9	4	1.6	5	1.9
Heart/Vascular Disease/Thrombosis	32	3.3	32	3.3	10	3.9	21	8.2
Lung dysfunction	5	0.5	4	0.4	4	1.6	3	1.2
Neurology (not vascular caused)	9	0.9	4	0.4	1	0.4	4	1.6
Skin	10	1.0	5	0.5	2	0.8	5	2.0
Local recurrence/second neoplasia	0	0.0	0	0.0	0	0.0	0	0.0
Death	3	0.3	0	0.0	2	0.8	1	0.4
Others	19	2.0	39	4.0	14	5.4	14	5.5
total	249		266		109		131	

Tab. 1: SAEs per age and treatment arm

Summary & Discussion

- The majority (88%) of HR+/HER2- patients in planB trial with RS ≤ 11 opted against CHT. Highest drop out rates before CHT-randomization are reported in the intermediate risk group, RS 12-25 (16%).
- CHT administered within the study was generally well tolerated. CHT-related mortality was 6/2444 (0.002%). Clinically predominant grade 3-4 toxicities were hematotoxicity and infections followed by pain and nausea.
- Regarding more severe toxicities, TC was significantly less toxic than EC→Doc in terms of anemia, stomatitis, nausea/vomiting, pain, cardiovascular disorders, and neurotoxicity
- These effects are even more pronounced in the population ≥65 yrs
- TC caused significantly more severe infections despite more frequent use of G-CSF in this arm.
- TC caused (non significantly) more therapy related deaths (5:1) due to infections/septicemia.
- Long term toxicity remains to be evaluated

References

1. Gennari et al. JNCI J Natl Cancer Inst. 2008;100(1):14-20.
2. Albain et al. Lancet Oncol. 2010;11(1):55-65.
3. Paik et al NEJM. 2004; 30;351(27):2817-26
4. Paik et al JCO 2006. 24(23):3726-34