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Adapting In Vivo Chemosensitivity for Further Evaluation of Preoperative Chemotherapy in Patients with Operable Primary Breast Cancer. Interim Analysis of the GEPAR-*TRIO* Trial

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ABSTRACT*

Background: As previously demonstrated, evaluation of early response of at least 2 cycles of preoperative chemotherapy might enhance the likelihood for a pathologic complete remission (pCR) in patients (P) with operable primary breast cancer (OPBC) up to 4-fold (von Minckwitz G, SABCS 2000). We prospectively address this observation in the GEPAR-*TRIO* trial where chemotherapy is randomly allocated according to early tumor response.

Patients and methods: P with OPBC (T ≥2 cm by palpation) or locally advanced breast cancer are treated with 2 cycles TAC (docetaxel 75 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m² Day 1, q21). In case of significant tumor reduction (cCR or ≥50% reduction), P are randomized to receive either 4 or 6 additional cycles TAC. Nonresponders are randomized to either additional 4 cycles TAC or 4 cycles NX (vinorelbine 25 mg/m² Day 1 + 8, capecitabine 2000 mg/m² Day 1–14, q21) (TAC–NX). Primary endpoint is pCR rate. Secondary objectives are clinical response at surgery, toxicity, compliance, and the rate of cCR/cPR after 2 cycles TAC.

Results: 1105 P (983 operable and 122 inoperable) of 2259 planned P with a median clinical tumor size of 4.0 cm have been recruited since Oct 2001. 75% of operable and 68% of inoperable patients obtained a cCR/cPR after 2 cycles of TAC. Due to toxicity treatment was discontinued in 16 P (15 x TAC, 1 x NX), on patient's request in 14 P (11 x TAC, 3 x NX) and tumor progression in 6 P (5 x TAC, 1 x NX). Grade III/IV neutropenia is the most frequently reported toxicity and serious adverse events have been documented in 328 cases for TAC and in 10 cases for NX.

Conclusions: TAC is a highly effective preoperative treatment in breast cancer. NX seems to be associated with a better toxicity profile compared to TAC. Response after 2 cycles can identify P with a high or minimal chance of achieving a pCR and might be considered as an in vivo chemosensitivity test.

*The poster contains updated data, which may differ from the abstract.

INTRODUCTION

The main objectives of preoperative (neoadjuvant) chemotherapy for breast cancer are downstaging of the primary tumor prior to surgical resection – thus increasing the likelihood of breast conservation – and arrest of the systemic spread of micrometastatic disease. Docetaxel (Taxotere®) is one of the most active agents in breast cancer and clinical studies have shown that it is highly effective in the neoadjuvant setting, either as monotherapy or in combination with other agents.[1–4] In one Phase II study, weekly neoadjuvant docetaxel monotherapy resulted in an overall response rate (ORR) of 68% and a pathologic complete response (pCR) rate of 16%.[1] Preoperative docetaxel plus doxorubicin (Adriamycin®) gave an ORR of 93% and significantly reduced primary tumor size by approximately 50% in one study[2] and gave an ORR of 81%, a pCR rate of 10%, and a breast conservation rate of 69% in another study[3] (with or without simultaneous tamoxifen). Furthermore, interim data from the randomized GEPAR-DUO Phase III trial showed that both a neoadjuvant dose-dense schedule of docetaxel–doxorubicin (once every 2 weeks) and a neoadjuvant sequential schedule of doxorubicin–cyclophosphamide followed by docetaxel are effective approaches.

The prognosis of patients with breast cancer who do not respond to the first 2–3 cycles of neoadjuvant chemotherapy remains poor. The present prospective, randomized, multicenter, Phase II–III study comprised an in vivo chemosensitivity test (to initial treatment with 2 cycles of neoadjuvant docetaxel–doxorubicin–cyclophosphamide [TAC]) and explored the effectiveness of a neoadjuvant salvage regimen (vinorelbine–capecitabine [NX]). Toxicity data from an interim analysis of the GEPAR-*TRIO* trial are presented in this poster.

OBJECTIVES

Primary objective

- pCR rate of (i) 4 cycles of TAC and (ii) 4 cycles of NX as neoadjuvant salvage therapy for patients who did not respond to 2 cycles of neoadjuvant TAC.

Secondary objectives

- Toxicity and compliance with TAC–NX
- Clinical response rate for the initial 2 cycles of TAC
- pCR rate of 6 cycles of TAC in responding patients
- Disease-free survival and survival in each arm.

Other objectives

- pCR rate in the subgroup of *HER-2*-positive and -negative patients (detected centrally by fluorescence in situ hybridisation [FISH])

METHODS

Main inclusion criteria

- Histologically confirmed (by core or Tru-Cut biopsy) unilateral or bilateral breast cancer
- Previously untreated operable (T2–3 N0–2 M0) or locally advanced (T4a–T4d N0–3 M0) breast cancer
- At least one bidimensionally measurable breast tumor (by palpation, mammography, ultrasonography, or magnetic resonance imaging); the largest lesion was measured in patients with multifocal or multicentric disease
- Age ≥18 years
- Karnofsky performance status ≥80%
- Normal cardiac function as evidenced by left ventricular ejection fraction (LVEF)
- Adequate hematologic, hepatic, and renal function
- Complete staging work-up within 3 months prior to study registration
- Written informed consent.

Study design and treatment

- The first 286 patients fulfilling all the inclusion criteria were enrolled and treated in the GEPAR-*TRIO* (pilot study) up to July 2002 as shown in Figure 1a (for details, see poster 236).
- From July 2002, the Phase II–III component of the study was initiated and a further 819 patients were enrolled. Patients initially responding (clinical complete response [cCR] or clinical partial response [cPR]) to 2 cycles of TAC were randomized to receive an additional 4 or 6 cycles of TAC, as shown in Figure 1b.
- In the event of disease progression during the initial 2 cycles of TAC, patients were not randomized to further TAC or NX but were treated at the investigator's discretion.
- Prophylactic supportive therapy comprised:
  - dexamethasone 20 mg iv immediately before each docetaxel infusion and 4 mg po twice daily on Days 2 and 3 and once daily on Day 4 after chemotherapy
  - antiemetic (5-HT_3 antagonists) and antibiotic (ciprofloxacin or a suitable alternative) treatment for all patients.
- Prophylactic granulocyte colony-stimulating factor (G-CSF) was not permitted for the first treatment cycle but was allowed as curative treatment in the event of febrile neutropenia or infection and as prophylactic treatment for subsequent cycles (if there was a case of febrile neutropenia in a prior cycle).

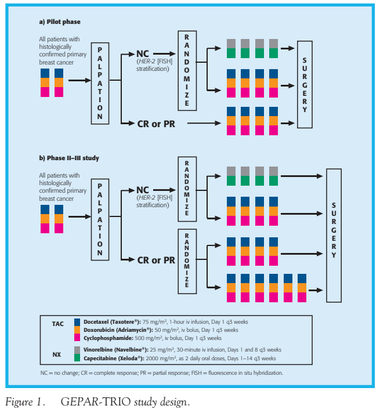

Figure 1. GEPAR-TRIO study design.

RESULTS: GEPAR-*TRIO* (PHASE II–III STUDY)

Patients

- A total of 1105 (983 operable and 122 inoperable) of 2259 planned patients have been enrolled in the ongoing GEPAR-*TRIO* trial since Oct 2001:
  - 286 patients previously enrolled in the GEPAR-*TRIO* trial (pilot phase)
  - 819 patients enrolled in the GEPAR-*TRIO* trial (Phase II–III study)
- Accrual into the GEPAR-*TRIO* trial is shown in Figure 2.

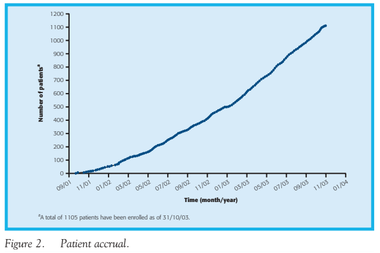

Figure 2. Patient accrual.

- Baseline patient and tumor characteristics are summarized in Table 1.
- Median clinical tumor size before treatment was 4 cm.

CHARACTERISTIC	VALUE
Median age [range], years	50 [25–76]
Disease stage, n (%)	
Operable (T2–3 N0–2 M0)	983
Inoperable (T4a–T4d N0–3 M0)	122
Karnofsky performance status, n (%)	
100%	901 (81.5)
95%	2 (0.2)
90%	173 (15.7)
80%	10 (0.9)
Missing data	19 (1.7)
Tumor grade, n (%)	
1	51 (4.7)
2	554 (50.1)
3	307 (27.8)
Missing data	193 (17.5)
Tumor size, n (%)	
T1	14 (1.3)
T2	762 (68.9)
T3	164 (14.8)
T4	120 (10.9)
Missing data	45 (4.1)
Nodal status, n (%)	
N0	555 (50.2)
N1	409 (37.0)
N2	42 (3.8)
Missing data	99 (9.0)
Histologic type, n (%)	
Ductal invasive	833 (75.3)
Lobular invasive	161 (14.6)
Other	91 (8.3)
Missing	20 (1.8)
Hormone receptor status, n (%)	
ER and PR negative	250 (22.6)
ER and/or PR positive	588 (53.2)
Missing data	267 (24.2)
***HER-2* (FISH) status, n (%)**	
Negative	367 (33.2)
Positive	178 (16.1)
Missing data	560 (50.7)

ER = estrogen receptor; PR = progesterone receptor; FISH = fluorescence in situ hybridization.

Table 1. Baseline patient and tumor characteristics (n=1105)

Treatment and response data

- In total, 75% of operable and 68% of inoperable patients with histologically confirmed invasive breast cancer obtained a cCR or cPR after the first 2 cycles of TAC.
- On the basis of the response data for the first 2 cycles of TAC:
  - 178 nonresponders were randomized to either 4 cycles of NX (n=77) or 4 cycles of TAC (n=101)
  - 533 responders were randomized to either 4 cycles of TAC (n=276) or 6 cycles of TAC (n=257)
  - 108 patients were not randomized owing to missing data or not having completed 2 cycles of TAC at the time of randomization.
- Patient flow through the GEPAR-*TRIO* trial (pilot phase) and GEPAR-*TRIO* trial (Phase II–III study) is summarized in Figures 3a and b, respectively.

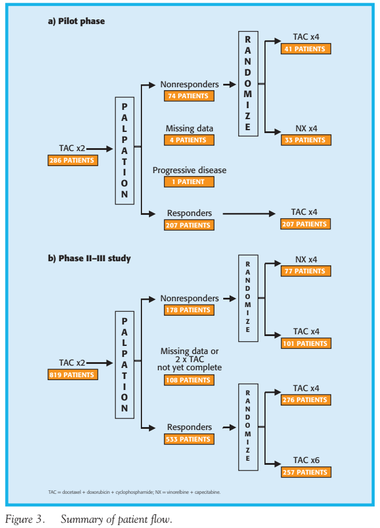

Figure 3. Summary of patient flow.

Safety and tolerability

- A total of 36 patients discontinued treatment due to:
  - toxicity (TAC: n=15; NX: n=1)
  - tumor progression (TAC: n=5; NX: n=1)
  - patient request (TAC: n=11; NX: n=3)
- Treatment discontinuation is summarized in Table 2.

	NUMBER OF PATIENTS (%)		
	DUE TO TOXICITY	DUE TO TUMOR PROGRESSION	DUE TO PATIENT REQUEST
All patients			
TAC x2 (n=819)	4 (0.5)	4 (0.5)	5 (0.6)
Responder			
TAC x4 (n=276)	7 (2.5)	1 (0.4)	4 (1.4)
TAC x6 (n=257)	3 (1.2)	0 (0)	2 (0.8)
Nonresponder			
TAC x4 (n=101)	1 (1.0)	0 (0)	0 (0)
NX x4 (n=77)	1 (1.3)	1 (1.3)	3 (3.9)

Table 2. Summary of treatment discontinuations

Toxicity

- Grade III–IV neutropenia was the most frequently reported toxicity.
- A total of 328 serious adverse events (in 269/1105 patients) were reported for the TAC group and 10 serious adverse events (in 9/110 patients) for the NX group (Table 3).

	NUMBER OF PATIENTS (%)	
TOXICITY	TAC (n=1105)	NX (n=110)
Hematologic		
Neutropenia/leukopenia	95 (8.6)	1 (0.9)
Febrile neutropenia	49 (4.4)	0 (0)
Anemia	3 (0.3)	0 (0)
Thrombocytopenia	1 (0.1)	0 (0)
Nonhematologic		
Infection	17 (1.5)	2 (1.8)
Nausea/vomiting	10 (0.9)	0 (0)
Fever	12 (1.1)	0 (0)
Diarrhea	9 (0.8)	2 (1.8)
Hypotension	8 (0.7)	0 (0)
Allergic reaction	6 (0.5)	0 (0)
Cardiac	6 (0.5)	0 (0)
Dyspnea	5 (0.5)	0 (0)
Gastritis	5 (0.5)	0 (0)
Pneumonia	5 (0.5)	0 (0)
Pain	4 (0.4)	0 (0)
Septic shock	3 (0.3)	0 (0)
Thrombosis	3 (0.3)	0 (0)
Abdominal pain	2 (0.2)	0 (0)
Hand–foot syndrome	2 (0.2)	0 (0)
Acute psychosis	1 (0.1)	1 (0.9)
Apoplexia	1 (0.1)	0 (0)
Bone fracture	1 (0.1)	1 (0.9)
Embolism	1 (0.1)	1 (0.9)
Other	20 (1.8)	1 (0.9)

Table 3. Serious adverse events (grade III or IV)

CONCLUSIONS

- **All neoadjuvant schedules investigated in the GEPAR-*TRIO* trial (TAC x2 → NX x4, TAC x6, and TAC x8) are feasible preoperative treatments for breast cancer and show moderate toxicity.**
- **The rationale for this ongoing study is well accepted, as demonstrated by the high recruitment rate.**

References

1. Estevez LG, Cuevas JM, Anton A, et al. Weekly docetaxel as neoadjuvant chemotherapy for stage II and III breast cancer: efficacy and correlation with biological markers in a phase II, multicentre study. Clin Cancer Res 2003;9:686–692.
2. Von Minckwitz G, Costa SD, Eiermann W, et al. Maximized reduction of primary breast tumour size using preoperative chemotherapy with doxorubicin and docetaxel. J Clin Oncol 1999;17:1999–2005.
3. Von Minckwitz G, Costa SD, Raab G, et al. Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: a randomised, controlled, open phase IIb study. J Clin Oncol 2001;19:3506–3015.
4. Jackisch C, von Minckwitz G, Eidtmann H, et al. Dose-dense biweekly doxorubicin/docetaxel versus sequential neoadjuvant chemotherapy with doxorubicin/cyclophosphamide/docetaxel in operable breast cancer: second interim analysis. Clin Breast Cancer 2002;3:276–280.
5. Von Minckwitz G, Raab G, Blohmer JU, et al. Primary chemotherapy adapted on in-vivo-chemosensitivity in patients with primary breast cancer. The pilot GEPARTRIO -study. Proc Am Soc Clin Oncol 2003;22:22 [Abstract 85].