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R. I. Lalisang, F. L. G. Erdkamp, C. J. Rodenburg, C. T. A. M.

Knibbeler-van Rossum, J. W. R. Nortier, A. Bochove, P. H. Th. J. Slee, E. E.

Voest, J. A. Wils, J. Wals, et al.

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Epirubicin and paclitaxel with G-CSF support in first line metastatic breast cancer: A randomized phase II study of dose-dense and dose-escalated chemotherapy

*R.I. Lalisang<sup>1</sup>, F.L.G. Erdkamp<sup>2</sup>, C.J. Rodenburg<sup>3</sup>, C.T.A.M. Knibbeler-van Rossum<sup>4#</sup>, J.W.R. Nortier<sup>5\*</sup>, A. van Bochove<sup>6</sup>, P.H.TH.J. Slee<sup>7</sup>, E.E. Voest<sup>8</sup>, J.A. Wils<sup>9</sup>, J. Wals<sup>10</sup>, O.J.L. Loosveld<sup>11</sup>, A.E.M. Smals<sup>12</sup>, G. H. Blijham<sup>8</sup>, V.C.G. Tjan-Heijnen<sup>1</sup> and H.C. Schouten<sup>1</sup>*

<sup>1</sup>Maastricht Universitair Medisch Centrum, GROW-School of Oncology and Developmental Biology, Maastricht; <sup>2</sup>Orbis Medisch Centrum, Sittard; <sup>3</sup>Meander Medisch Centrum, Amersfoort; <sup>4</sup>St. Elisabeth Ziekenhuis, Tilburg; <sup>5</sup>Diaconessenhuis, Utrecht; <sup>6</sup>Zaans Medisch Centrum, Zaandam; <sup>7</sup>St. Antonius Ziekenhuis, Nieuwegein; <sup>8</sup>Universitair Medisch Centrum Utrecht, Utrecht; <sup>9</sup>Laurentius Ziekenhuis, Roermond; <sup>10</sup>Atrium Medisch Centrum, Heerlen; <sup>11</sup>Amphia Ziekenhuis, Breda; <sup>12</sup>St. Anna Ziekenhuis, Geldrop; momentarily <sup>#</sup>Jeroen Bosch Ziekenhuis, Den Bosch and <sup>\*</sup>Leids Universitair Medisch Centrum, Leiden all in the Netherlands.

Corresponding author:

Roy Lalisang, MD PhD

Division of Medical Oncology

Department of Internal Medicine

Maastricht Universitair Medisch Centrum

P.O. Box 5800

6202 AZ Maastricht

The Netherlands

Tel: +31 43 3877025

Fax: +31 43 3875006

E-mail address: roy.lalisang@mumc.nl

## Introduction

In advanced breast cancer anthracycline non-taxane combination regimens as first-line systemic therapy results in a 30-50% overall response rate, a complete response rate of 5-10%, and a median progression-free survival of 4-8 months [1, 2]. The combination of paclitaxel and doxorubicin showed promising response rates of 83-95% in clinical phase I and II studies, but at the cost of considerable increase in treatment related toxicity, mainly febrile neutropenia, infections and cardiac toxicity [3,4].

Epirubicin is a synthetic doxorubicin analogue, with a similar activity but decreased toxicity profile, in particular less cardiotoxicity [5]. The addition of G-CSF may reduce the incidence of febrile neutropenia, but also increases the dose-intensity of cytotoxic agents. This can be accomplished by reducing the interval between the administrations of “standard doses” of chemotherapy or by increasing the dose with a “standard inter-cyclic interval”. These two approaches of dose-intensification have also been called “dose-densification” and “dose-escalation”, respectively. However, the biological effect and clinical relevance of these approaches may be quite different. Dose-densification of chemotherapy may be important to kill chemo sensitive tumor cells, by preventing early regrowth of dormant cells. The major effect of dose-escalation may be a more effective eradication of resistant tumor cells and the dose size may also be the most important factor in reducing the risk of developing resistant cells [6,7].

Our group initially investigated both approaches with epirubicin/cyclophosphamide combination chemotherapy supported by G-CSF, in the treatment of advanced breast cancer. We concluded that dose-densification allowed a higher dose-intensity than dose-escalation [8]. Based on these results we next determined the maximal dose-intensity of the epirubicin/paclitaxel combination supported with G-CSF. In the dose-dense approach the inter-cyclic interval of epirubicin 75 mg/m<sup>2</sup> and paclitaxel 135 mg/m<sup>2</sup> could be reduced to 10 days. In this 10 days interval it was feasible to increase the paclitaxel dose up to 175 mg/m<sup>2</sup>, enabling a dose intensity of 52 mg/m<sup>2</sup>/week for epirubicin and 122 mg/m<sup>2</sup>/week for paclitaxel, respectively [9]. In the dose-escalation approach the maximal tolerated doses of a 3-weekly schedule was 110 mg/m<sup>2</sup> for epirubicin and 240 mg/m<sup>2</sup> for paclitaxel (unpublished data). The dose-intensity of this latter schedule is 37 and 80 mg/m<sup>2</sup>/week, respectively.

The current randomized phase II study evaluates the efficacy and tolerability of the two dose-intensified chemotherapy regimens consisting of epirubicin and paclitaxel, supported with G-CSF. The main objective of the study was to test whether a high response rate (overall response rate ≥80%) could be achieved. Secondary objectives were to assess the progression-free interval, and evaluate the safety profiles and cardiotoxicity.

## Materials and methods

### Patient selection

The inclusion criteria for women with advanced breast cancer were: measurable and histological proven breast cancer; age 18 to 70 years; performance status 0 to 2 (Eastern Cooperative Oncology Group [ECOG] scale); adequate hematological, hepatic and renal function; no prior chemotherapy for metastatic disease; prior adjuvant (non-taxane containing) chemotherapy was allowed, if interval after last chemotherapy cycle ≥1 year and at entry cumulative dose of doxorubicin ≤300 mg/m<sup>2</sup> or epirubicin ≤450 mg/m<sup>2</sup>; normal left ventricular ejection fraction (LVEF) assessed using multigated acquisition (MUGA) scan and without symptomatic cardiovascular disease. Exclusion criteria were central nervous system involvement, history of other malignancy, active infectious disease and pre-existing neuropathy. During the study period the HER2 tumor status was not performed routinely.

### Study design

This open-label multi-centre randomized phase II trial was approved by the institutional review boards of the 12 participating hospitals, and the procedures followed were in accordance with the Helsinki Declaration 1996 of the World Medical Association. Randomization was independently centrally performed, and patients were stratified according to participating centre and prior adjuvant anthracycline containing chemotherapy (yes/no).

Pre-study evaluation included history, physical and blood examination, chest x-ray, liver ultrasound, skeletal scintigraphy, ECG and cardiac MUGA-scan. Suspected lesions were assessed by the best

evaluable and reproducible (radiological) technique. Full blood count was weekly repeated and routine biochemistry was assessed before each cycle. Assessment of LVEF was scheduled at baseline, after treatment cycles three and six, before each additional treatment cycle after a cumulative dose of 800 mg/m<sup>2</sup> epirubicin, in case of clinical signs of cardiac failure, if patients went off study, and three months after the last chemotherapy cycle.

In this study the epirubicin (Pfizer Inc., New York, NY) was given as a short intravenous infusion, followed by paclitaxel (Taxol®, Bristol-Myers Squibb, New York, NY) as a three-hour infusion. A routine premedication regime was adopted to prevent hypersensitivity reactions and nausea/vomiting. Concomitant endocrine, erythropoietin or prophylactic antibiotic therapy was not allowed. Patients were transfused when necessary to maintain a platelet count of  $\geq 15,000/\mu\text{l}$  and hemoglobin level  $\geq 8.0$  g/dl. Dose-intensity is defined as the chemotherapy dose per unit time and was expressed as mg/m<sup>2</sup>/week. The cumulative dose is the product of dose per cycle and number of cycles of chemotherapy.

In the dose-escalated arm initially epirubicin 110 mg/m<sup>2</sup> and paclitaxel 240 mg/m<sup>2</sup> was given both on day 1, q 21 days, with R-metHuG-CSF (Filgrastim®, Amgen Inc. Thousands Oaks, CA) 5  $\mu\text{gr}/\text{kg}$  subcutaneously on days 2 - 14, for six cycles. However due to an excess of serious adverse events in four out of the first nine patients, the paclitaxel dose was reduced to 200 mg/m<sup>2</sup> (see results). The new scheduled cumulative doses for epirubicin were 660 mg/m<sup>2</sup> and for paclitaxel 1200 mg/m<sup>2</sup>, and the dose-intensity was 37 and 67 mg/m<sup>2</sup>/week, respectively.

The dose-dense schedule consisted of epirubicin 75 mg/m<sup>2</sup> and paclitaxel 175 mg/m<sup>2</sup> both on day 1 with a 10 days interval, with G-CSF support on days 2 - 10, for six cycles. The scheduled cumulative doses were for epirubicin 450 mg/m<sup>2</sup> and paclitaxel 1050 mg/m<sup>2</sup>. The scheduled dose-intensity was 52 mg/m<sup>2</sup>/week and 122 mg/m<sup>2</sup>/week. (Figure 1)

In both study arms no further chemotherapy was given beyond six cycles of scheduled study treatment, until the time of progression, because of the cumulative dose of epirubicine.

### **Dose modifications and Toxicity evaluation**

Toxicity was assessed after each course according to National Cancer Institute Common Toxicity Criteria version 1.0. A 20% dose reduction of epirubicin and paclitaxel was recommended in case of nadir thrombocytopenia grade 4, neutropenia grade 4 for a period of more than seven days, febrile neutropenia and any non-hematological toxicity grade  $\geq 3$  in the previous cycle. The neutrophil ( $\geq 2,000/\mu\text{l}$ ) and platelet ( $\geq 100,000/\mu\text{l}$ ) counts had to be recovered on the day of scheduled chemotherapy. In case of incomplete hematological recovery or persistence of non-hematological toxicity grade  $\geq 2$  (excluding alopecia and anticipatory nausea and vomiting), treatment was delayed for a maximum period of two weeks. If a longer recovery period is needed the patient went off study.

Cardiotoxicity was defined as the development of either symptomatic cardiotoxicity characterized by clinical cardiac failure in combination with a decreased LVEF or asymptomatic cardiotoxicity characterized by an absolute decrease in LVEF either  $\geq 20\%$  (EF absolute units) from baseline to a value above 50% or  $\geq 10\%$  to a value below 50%. In the case of cardiotoxicity study treatment had to be ceased.

### **Study end points**

Tumor response evaluation of all known metastases was scheduled after cycle 3 and 6 by the same pre-study techniques. In addition, extra assessments had to be performed if there was clinical suspicion of progression. Standard UICC response criteria were applied [10].

### **Statistical considerations**

The main objective of the study was to test whether a high response rate (overall response rate  $\geq 80\%$ , with  $\geq 15\%$  complete remission) could be achieved with either dose-intensified schedules. A response rate of 60% or lower is also feasible with non-taxane combination chemotherapy, and considered not interesting for further investigation. Using a 90% power and a significance level of 5% in a Simon two-stage phase II design for  $P_1 - P_0 = .20$ , at least 45 for response evaluable patients in each arm were needed. Secondary objectives were to assess the progression-free interval, and evaluate the safety profiles and cardiac toxicity of these two approaches separately.

If a patient continued or restarted with other antitumor therapy without objective progressive disease, the patient was censored on this date for progression-free survival.

## Results

### Patient characteristics

In total, 123 patients were entered and randomized in this study during November 1998 till May 2003. After inclusion of the first 18 patients (nine in both arms), an interim safety analysis was warranted due to an unexpected high number of dose-limiting toxicities in the dose-escalated arm. In contrast with our experiences in the phase I study, where only one out of 12 patients developed peripheral neurotoxicity during the first three cycles, in this study three out nine patients in the dose-escalated arm developed grade 2 - 3 neurotoxicity. These side-effects were debilitating for the patients and prevented the patients to undergo scheduled treatment. The dose of paclitaxel in this arm was therefore reduced to 200 mg/m<sup>2</sup>, a dose-level that was considered to be effective but presumably resulting in less peripheral neurotoxicity. In the dose-escalated arm a new cohort of patients was entered at this new dose level up to a total of 50 patients. Patients in the dose-dense arm continued to be entered at the original dose level. The randomization procedure was adapted temporarily to a 2:1 design in favor of the dose-escalated arm until the disappearance in imbalance of the number of patients.

So, 114 patients were randomized, excluding the first nine patients in the dose-escalated arm. Of these, eight patients were shown not to be eligible because of; central nervous system tumor involvement (n=3), too high prior adjuvant cumulative anthracycline dose (n=2), other antitumor treatment started immediately after randomization but prior to scheduled chemotherapy (radiotherapy, n=2) and early withdrawal of consent (n=1). All 106 eligible patients were evaluable for the safety analysis, 51 in the dose-escalated and 55 patients in the dose-dense arm. The patient characteristics in both study arms were well balanced (Table 1). Ten and eleven patients in each arm presented with primary metastatic disease and about half of the patients had undergone prior systemic adjuvant therapy and palliative endocrine therapy. In both arms there were a high number of patients with osseous, hepatic and/or lymph node metastases. About 40% of the patients had metastases in three or more organ systems.

### Treatment summary

In both arms, a median number of six cycles was delivered. Forty-two (82%) patients completed all six treatment cycles in the dose-escalated arm, with 84% of the cycles delivered at  $\geq 90\%$  of scheduled dose-intensity. In the dose-dense arm, forty-three (78%) patients completed all six treatment cycles, with 85% of the cycles delivered at  $\geq 90\%$  scheduled dose-intensity.

The median delivered cumulative doses and dose-intensities are displayed in Table 2.

### Efficacy

Tumor response was assessable in 48 patients of the dose-escalated arm and 53 patients of the dose-dense arm (Table 3). The best overall response rate was 75% in the dose-escalated arm and 70% in the dose-dense arm. Last follow-up and retrieval of patient data was performed in April 2009. All patients ultimately developed progressive disease. The median progression-free survival was 6 months (95% CI 5.1 – 6.9) and 7 months (95% CI 5.6 – 8.4) for the dose-escalated arm and dose-dense arm, respectively. The median overall survival was 16 months (95% CI 12.1 – 20.0) and 14 months (95% CI 9.6 – 18.4), respectively.

### Toxicity

Acute treatment related dose-limiting toxicities during scheduled 6 cycles of chemotherapy are displayed in Table 4. In the dose-escalated arm, twenty-nine (57%) patients encountered an initial dose-limiting toxicity at the starting dose-level. Sixteen (31%) patients had a grade  $\geq 3$  toxicity, ten (20%) patients had a delayed recovery at the time of the next scheduled cycle (partly overlapping reasons for dose-modifications), and four (8%) patients developed an asymptomatic cardiotoxicity. After a first treatment modification due to the initial toxicity, a second/later dose-limiting toxicity occurred in 12 (24%)

patients. Of the grade  $\geq 3$  toxicities, febrile neutropenia, thrombocytopenia and neurotoxicity were most frequently seen. Febrile neutropenic episodes all occurred during the first cycle (n=6, 12%); one patient died in a septic shock. Grade 3 neurotoxicity was observed in three (6%) patients after the 3<sup>rd</sup>, 4<sup>th</sup> and 5<sup>th</sup> cycle, respectively. Four additional patients developed an asymptomatic cardiotoxicity, so in this arm in total we have eight patients with an asymptomatic cardiotoxicity (median fall in LVEF 17% [range 15 – 37%]). Only one of these eight had received prior anthracycline-based chemotherapy in the adjuvant setting. The onset of cardiotoxicity occurred at a median total cumulative dose of epirubicin of 657 mg/m<sup>2</sup> (range 556 – 778). One patient ultimately developed symptoms of cardiac failure nine months after stopping study treatment.

In the dose-dense arm, 27 (49%) patients had an initial dose-limiting toxicity at the starting dose-level. Fourteen (25%) patients with a grade  $\geq 3$  toxicity, two (4%) patients with an asymptomatic cardiotoxicity and 11 (20%) patients with a delayed recovery precluding the next scheduled cycle. After treatment-modification, 11 (20%) patients encountered a second/late dose-limiting toxicity which necessitated a further treatment-modification. Febrile neutropenia was observed in four (7%) patients, of whom one with a fatal outcome after the 6<sup>th</sup> cycle. One patient with active thromboembolic disease developed a cerebrovascular accident and pulmonary infection after the first cycle and died after the second cycle. Autopsy revealed extensive thromboembolic disease in lungs, liver and kidneys. Peripheral neurotoxicity grade  $\geq 3$  was observed in five (9%) patients. In total four patients developed an asymptomatic cardiotoxicity, with a median fall in LVEF of 22% (range 13-25%). Three of these four had received anthracycline combination chemotherapy in the adjuvant setting. In these patients the median total cumulative dose of epirubicin, 798 mg/m<sup>2</sup> (range 420 – 850), was considerably higher than the subgroup without a fall in LVEF, 450 mg/m<sup>2</sup> (range 144 – 902). One of these patients ultimately developed symptoms of cardiac failure three months later.

## Discussion

In this randomized phase II study two different approaches of dose-intensification of an anthracycline/taxane combination were tested for their outcome on response rate, progression-free survival and safety profile as first-line chemotherapy in patients with advanced breast cancer. Both arms appeared to be very effective with response rates of 70% and more. Response evaluation was done by the UICC response criteria, and although this is currently not the standard way of assessment, this probably has influenced the results of both arms in a similar way. Of note, we aimed for an objective response rate of at least 80% with a complete remission rate of at least 15%. In fact, these rates appeared too optimistic. Although, in our study a response rate of more than 70% overall, and already after three cycles of chemotherapy the response rates were 51% for the dose-dense regime (after one month of treatment) and 55% for the dose-escalated regime (after two months of treatment), still seems a worthwhile result. In more recent phase III chemotherapy studies it is confirmed that first-line response rates in metastatic breast cancer are generally in the range of 55-70% [11-15]. In our study, despite the almost halved treatment duration in the dose-dense arm, the progression-free survival seemed to be quite comparable for both treatment arms. Or, in other words, with a much shorter treatment period and a lower cumulative chemotherapy dose, patients remained longer off-treatment. For the dose-dense regime the treatment-free period was five months, whereas for the dose-escalated regime this was only two months. Obviously, apart from the benefit for the patient also from an economic viewpoint this may be an interesting observation.

Also, different toxicity frequencies were observed, with a better overall profile for the dose-dense regime. In the dose-escalated arm there was a higher incidence of hematological toxicity showing more febrile neutropenia (14% vs. 7%), despite the use of primary G-CSF prophylaxis, and more grade four thrombocytopenia (14% vs. 7%). A higher incidence of mainly asymptomatic cardiotoxicity was also observed in the dose-escalated arm (16% vs. 8%), likely associated with the higher cumulative dose of epirubicin in this arm, but also the interaction between epirubicin and paclitaxel may have played a role. Others have reported that the combination of doxorubicin and paclitaxel was associated with the development of heart failure at cumulative doxorubicin doses much lower than usual [3]. Grade 3 or higher peripheral neurotoxicity was observed in 6% and 13% of the patients with the dose-escalated and dose-dense regime, respectively. In the CALGB 9840 trial it was shown that weekly paclitaxel was indeed associated with significantly more grade 3 neuropathy than the every three-week therapy [16]. However, as weekly paclitaxel was superior to every-three-weeks administration in terms of response, median time to progression and overall survival, it is now generally appreciated that if there is an indication for paclitaxel in advanced breast cancer, it should be used in a weekly dense schedule. The

superiority of the weekly paclitaxel schedule over a 3-weekly schedule, after four cycles of doxorubicin and cyclophosphamide, was also confirmed in the adjuvant setting (ECOG 1199) [17]. A limitation of the study could have been the introduction of an ascertainment bias, due to more frequent assessments of toxicity and efficacy in the dose-densified treatment arm as compared to the dose-escalated treatment arm. However, as hematological toxicity was the most frequently occurring toxicity and blood counts were weekly monitored in both treatment arms it is unlikely that a bias by ascertainment had occurred. And, as progressive disease was hardly seen while on treatment, the earlier tumor response evaluation in the densified arm seems not to have confounded the comparison between the two arms. The introduction of G-CSF permitted the administration of myelosuppressive chemotherapy in intervals shorter than the conventional three weeks. However, although post-chemotherapy G-CSF reduces neutropenia, G-CSF shortly before chemotherapy may increase myelotoxicity. Timmer-Bonte et al. showed that during dose-densified chemotherapy daily G-CSF until two days before the next cycle compared to G-CSF until five days before the next chemotherapy cycle significantly worsened the degree of thrombocytopenia of that next cycle [18]. Timely withdrawal of G-CSF during dose-densified chemotherapy was advised, to reduce chemotherapy-related thrombocytopenia without jeopardizing neutrophil recovery. In the present study, we administered G-CSF on days 2 – 10 in the dose-dense arm and on days 2 - 14 in the dose-escalated arm. Nevertheless, the incidence of grade 4 thrombocytopenia was not increased but seemed to be even lower in the dose-dense arm when compared with the dose-escalated arm.

Cytotoxic therapy generally induces tumor regression with repeated cycles. Smaller tumors theoretically experience greater log kill (cell kill on a logarithmic scale) when chemotherapy is applied, because they are growing more rapidly than larger tumors of the same kinetics. However there is always re-growth between treatment cycles. The Norton-Simon hypothesis model suggests that chemotherapy is more effective by giving pulses of chemotherapy at a greater dose rate [6,7]. By minimizing the regrowth of cancer between cycles of treatment, the cumulative cell kill might be enhanced and thereby achieving a greater therapeutic effect. The CALGB 9741 trial in node positive early breast cancer tested in a 2 x 2 factorial design the role of sequential versus concurrent chemotherapy and conventional three-weekly intervals versus “dose dense” 2-weekly intervals [19]. Although the cumulative doses of doxorubicin, cyclophosphamide and paclitaxel were equal in the four arms, the dose intensities were quite different. The dose-dense approach resulted in a reduced annual odd for disease-recurrence of 26%. Interestingly, the dose-dense arms were also associated with less severe neutropenia and neutropenic fever, compared with the conventional treatment arms. In that respect, it may be very interesting to investigate our dose densification scheme in the (neo-) adjuvant setting.

Also in advanced ovarian cancer densification of chemotherapy has been investigated by a Japanese study group in a randomized phase 3 study. As first line treatment six cycles of either paclitaxel (180 mg/m<sup>2</sup>; 3-h intravenous infusion) plus carboplatin AUC 6 mg/mL per min, given on day 1 of a 21-day cycle was compared with dose-dense paclitaxel (80 mg/m<sup>2</sup>; 1-h intravenous infusion) given on days 1, 8, and 15 plus carboplatin given on day 1 of a 21-day cycle. In comparison with the conventional treatment group the dose-dense treatment group showed a statistically significant improved median progression free survival (28.0 vs. 17.2 months) and 3 years overall survival (72.1% vs. 65.1%) However the dose dense treatment resulted in more frequent hematological toxicity, mainly neutropenia and anaemia [20].

When discussing dose density, it is also important to take the issue of combination versus sequential administration of cytotoxic drugs into account. With sequential schedules, one can aim at higher dose intensity per drug, but it ignores the concept of ‘non-overlapping’ resistance mechanisms which may be better addressed by combination chemotherapy. There are several randomized trials that have directly compared the combination versus sequence of anthracyclines and taxanes in the advanced breast cancer setting [21-23]. None of these showed a survival benefit, although a higher response rate and longer time to treatment failure with the combination was observed in one trial [21]. However, the concept of maximizing the dose intensity in the sequence using single-agents was not tested. Further of note, the impact of densification may be different for a drug like paclitaxel than for an anthracycline [16,24]. At present, in the absence of specific predictive factors to select a subgroup of responsive patients, combination chemotherapy may be preferentially reserved for patients with rapidly progressing visceral metastatic disease, or in the emergency situations in which a rapid response is warranted [25].

In conclusion, we observed that dose-dense and dose-escalated chemotherapy of the combination epirubicin and paclitaxel was quite effective. The dose-dense regime seemed to be the preferred schedule, because of fewer side effects. Dose-densification also seemed to be more attractive as the treatment was administered over only 60 days compared to almost 130 days in the three-weekly dose-escalated schedule. With a comparable time-to-progression this shorter treatment schedule resulted in a substantial

longer off-treatment period. We feel that in breast cancer the concept of dose-density warrants further testing.

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**Conflict of interest statement** The authors declare that they have no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within that could inappropriately influence (bias) their work.



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**Table 1. Patient characteristics**

Characteristics	Dose-escalated epirubicin/paclitaxel N=51		Dose-dense epirubicin/paclitaxel N=55	
	N	(%)	N	(%)
Median age, years	51 (range 31 - 72)		53 (range 29 - 69)	
ECOG performance status				
0	23	(45)	30	(55)
1	24	(47)	24	(44)
2	4	(8)	1	(2)
Hormone receptor status				
ER positive	28	(55)	34	(62)
PR positive	26	(51)	31	(56)
Prior adjuvant systemic therapy	20	(40)	26	(47)
Endocrine	10	(20)	17	(31)
Chemotherapy, anthracyclines	11	(22)	10	(18)
Chemotherapy, non-anthracyclines	4	(8)	6	(11)
Median disease-free interval (months)	28 (range 0 - 143 )		31 (range 0 - 360 )	
Median MBC interval (months)	2 (range 0 - 76)		3 (range 0 - 104)	
Primary metastatic	10	(20)	11	(20)
Prior palliative endocrine therapy	23	(45)	30	(55)
Metastatic sites				
Osseous	29	(57)	33	(60)
Hepatic	22	(43)	30	(55)
Pulmonary	17	(33)	10	(18)
Lymph nodes / Soft tissue	27/14	(53/27)	27/8	(49/15)
≥ 3 organ system localisations	21	(41)	22	(40)

**Legend table 1:**

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor; DFS Disease Free Survival time interval between primary diagnosis of breast cancer and diagnosis of metastatic disease; MBC interval time interval between diagnosis of metastatic breast cancer and date of randomization.

**Table 2. Delivered treatment of epirubicin and paclitaxel**

	Dose-escalated epirubicin / paclitaxel			Dose-dense epirubicin / paclitaxel		
	No of patients	median DI mg/m <sup>2</sup> /wk epirubicin	median DI mg/m <sup>2</sup> /wk paclitaxel	No of patients	median DI mg/m <sup>2</sup> /wk epirubicin	median DI mg/m <sup>2</sup> /wk paclitaxel
Cycle 1	51	37	67	55	53	123
Cycle 2	49	37	67	55	53	123
Cycle 3	49	37	67	53	53	123
Cycle 4	45	37	67	52	48	112
Cycle 5	44	37	67	49	52	122
Cycle 6	42	37	67	43	52	122
<b>Overall</b>		<b>36</b>	<b>67</b>		<b>51</b>	<b>120</b>
<b>Median Cumulative dose epirubicin paclitaxel</b>	656 mg/m <sup>2</sup> 1194 mg/m <sup>2</sup>	(range 109 - 694) (range 199 – 1400))		448 mg/m <sup>2</sup> 1045 mg/m <sup>2</sup>	(range 144 – 494) (range 349 - 1165)	
<b>Median cumulative total dose epirubicin<sup>&amp;</sup></b>	659 mg/m <sup>2</sup>	(range 109 – 1117)		450 mg/m <sup>2</sup>	(144 - 902)	
<b>Median treatment duration (days)</b>		126 (range 21 - 212)			61 (range 20 - 102)	

**Legend table 2:**

<sup>&</sup> Median total cumulative dose Epirubicin; the eventually adjuvant total epirubicin given previously is added to the median cumulative dose epirubicin given during this study.

**Table 3. Efficacy of epirubicin and paclitaxel, dose-escalated and dose-dense regimens**

	<b>Dose-escalated epirubicin / paclitaxel</b>		<b>Dose-dense epirubicin / paclitaxel</b>	
<b>No. receiving treatment</b>	51	(%)	55	(%)
<b>Assessable for response</b>	48		53	
Overall	36	(75)	37	(70)
Complete remission	3	(6)	3	(6)
Partial remission	33	(69)	34	(64)
Stable disease	9	(19)	14	(26)
Progressive disease	3	(6)	2	(4)
<b>Progression</b>	51	(100)	55	(100)
<b>Death</b>	48	(94)	54	(98)
<b>Median PFS</b> (months, 95%CI)	6	(5.1 – 6.9)	7	(5.6 – 8.4)
<b>Median OS</b> (months, 95% CI)	16	(12.1 – 20.0)	14	(9.6 – 18.4)
<b>Total MBC OS</b> (months, 95% CI)	24	(17.8 – 30.2)	26	(15.6 – 36.4)

**Legend table 3:**

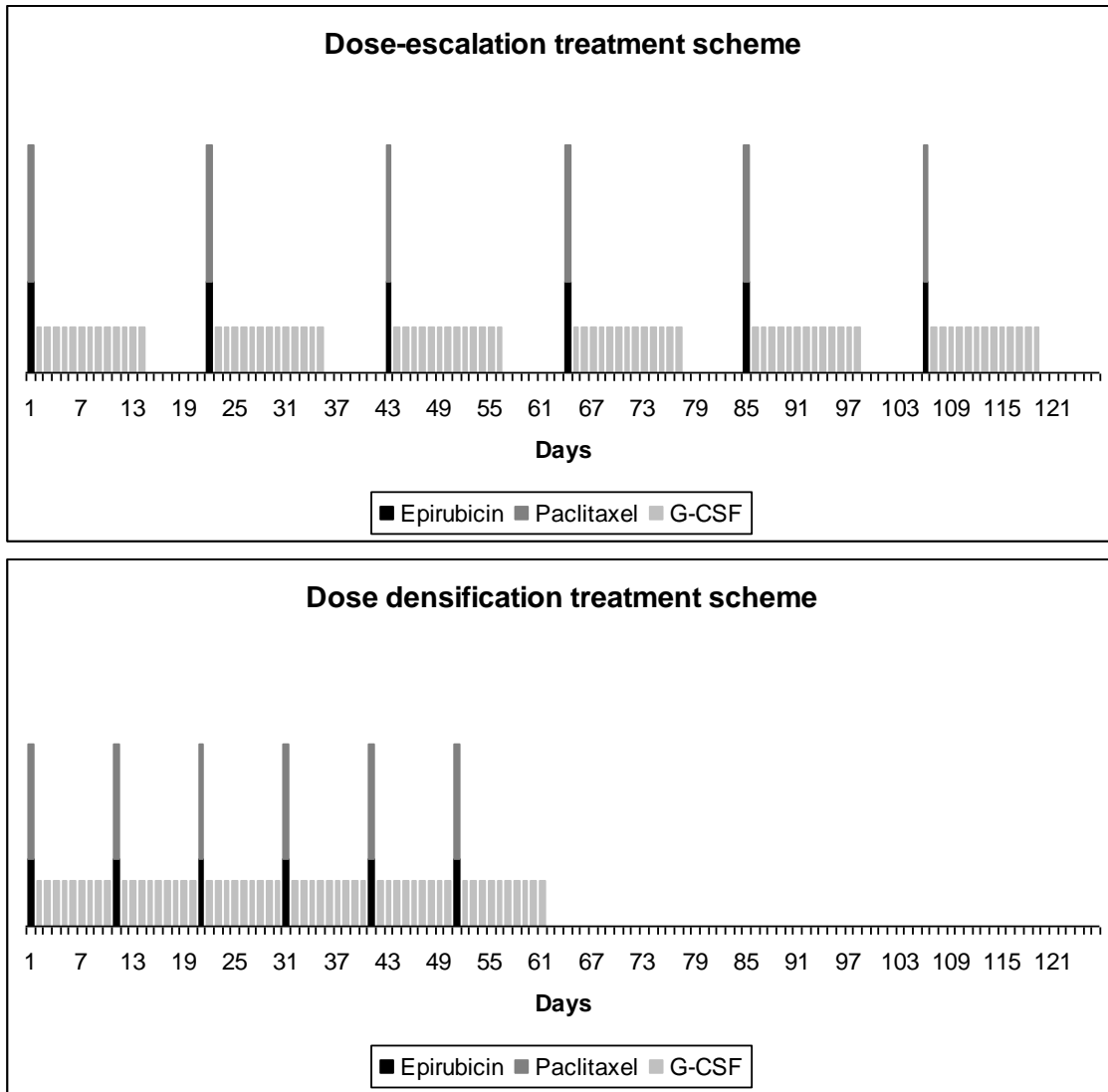
PFS, progression-free survival; OS, overall survival; MBC, metastatic breast cancer

**Table 4. Initial and second/later acute treatment related dose limiting toxicities during the 6 cycles of study treatment**

Toxicities	Dose-escalated N=51				Dose-dense N=55			
	Initial toxicity N (%)		Second/later toxicity N (%)		Initial toxicity N (%)		Second/later toxicity N (%)	
<b>No. Patients</b>	29	(57)	12	(24)	27	(49)	11	(20)
<b>NCI-CTC <math>\geq</math>grade 3</b>	16	(31)	4	(8)	14	(25)	4	(7)
Neutropenic fever	6	(12)	1	(2)	4	(7)		
Platelets, grade IV	5	(10)	2	(4)	3	(5)	1	(2)
Neurotoxicity	3	(6)			5	(9)	2	(4)
Infection	2	(4)	1	(2)	1	(2)		
Gastro-intestinal	1	(2)			4	(7)	1	(2)
Skin							1	(2)
<b>Cardiotoxicity</b>	4	(8)	4	(8)	2	(4)	2	(4)
Symptomatic								
Asymptomatic	4	(8)	4	(8)	2	(4)	2	(4)
<b>Delayed recovery</b>	10	(20)	4	(8)	11	(20)	5	(9)
Neutrophils	1	(2)			2	(4)	1	(2)
Platelets	3	(6)	3	(6)	1	(2)	2	(4)
Neurotoxicity	1	(2)	1	(2)	2	(4)	2	(4)
Infection	3	(6)			5	(9)		
Miscellaneous	3	(6)			2	(4)		

**Legend table 4:** The initial dose-limiting toxicity is the first occurrence of a dose-limiting toxicity during 6 cycles of scheduled treatment, at the starting dose and interval level. According to the study protocol a dose modification and/or delay of next scheduled is applied. If a patient again encounters a next dose-limiting toxicity, this is considered as a second/later dose-limiting toxicity.

**Figure 1. Study design: dose-escalated and dose-dense epirubicin and paclitaxel**



**Legend figure 1:**

Dose-escalation (upper): epirubicin  $110 \text{ mg/m}^2$  + paclitaxel  $200 \text{ mg/m}^2$  day 1 and G-CSF day 2-14, q 21 days x 6 cycles

Dose-densification (lower): epirubicin  $75 \text{ mg/m}^2$  + paclitaxel  $175 \text{ mg/m}^2$  day 1 and G-CSF day 2-10, q 10 days x 6 cycles

(black: epirubicin; grey: paclitaxel; light grey: G-CSF)