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CLINICAL TRIAL

A randomized phase III study comparing three anthracycline-free taxane-based regimens, as first line chemotherapy, in metastatic breast cancer

A Hellenic Cooperative Oncology Group study

G. Fountzilas · U. Dafni · M. A. Dimopoulos · A. Koutras · D. Skarlos · P. Papakostas · H. Gogas · D. Bafaloukos · A. Kalogera-Fountzila · E. Samantas · E. Briasoulis · D. Pectasides · N. Maniadakis · F. Matsiakou · G. Aravantinos · C. Papadimitriou · M. Karina · C. Christodoulou · P. Kosmidis · H. P. Kalofonos

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Abstract *Background* Effective anthracycline-free combinations need to be evaluated in metastatic breast cancer (MBC), due to the increased number of patients treated with anthracycline-based adjuvant chemotherapy. *Patients and methods* Patients with MBC were randomized to paclitaxel and carboplatin (PCb) every 3 weeks or docetaxel and gemcitabine (GDoc) every 3 weeks or weekly paclitaxel (Pw). Trastuzumab was given to patients with HER-2 overexpressing tumors. The primary endpoint of the study was survival. Quality of life (QoL) and cost were assessed. *Results* Totally, 416 eligible patients entered the study. Median survival times were 29.9 months for PCb, 26.9 for GDoc and 41.0 for Pw ($P = 0.037$). According to multivariate analysis, adjuvant chemotherapy, >1 metastatic sites, lack of maintenance hormonal therapy, and worse performance status (PS) were significant adverse prognostic factors for survival, while Pw when compared to GDoc improved survival ($P = 0.03$), as well as when compared to PCb in the subgroup of patients with PS = 1 ($P = 0.01$,

G. Fountzilas (✉) · M. Karina
Department of Medical Oncology, Papageorgiou Hospital, Aristotle University of Thessaloniki School of Medicine, Thessaloniki, Macedonia, Greece
e-mail: fountzil@med.auth.gr

U. Dafni
Laboratory of Biostatistics, University of Athens School of Nursing, Athens, Greece

M. A. Dimopoulos · C. Papadimitriou
Department of Clinical Therapeutics, Alexandra Hospital, University of Athens School of Medicine, Athens, Greece

A. Koutras · H. P. Kalofonos
Department of Medicine, Division of Oncology, University Hospital of Patras, Patras, Greece

D. Skarlos · C. Christodoulou
2nd Department of Medical Oncology, Henry Dunant Hospital, Athens, Greece

P. Papakostas · F. Matsiakou
Oncology Department, Ippokration Hospital, Athens, Greece

H. Gogas
Laikon Hospital, University of Athens School of Medicine, Athens, Greece

D. Bafaloukos
1st Department of Medical Oncology, Metropolitan Hospital, Athens, Greece

A. Kalogera-Fountzila
Department of Radiology, Ahepa Hospital, Aristotle University of Thessaloniki School of Medicine, Thessaloniki, Greece

E. Samantas · G. Aravantinos
3rd Department of Medical Oncology, Agii Anargiri Cancer Hospital, Athens, Greece

E. Briasoulis
Department of Medical Oncology, Ioannina University Hospital, Ioannina, Greece

D. Pectasides
2nd Department of Internal Medicine-Propaedeutic, Oncology Section, University General Hospital Attikon, Athens, Greece

N. Maniadakis
Department of Economics, University of Piraeus, Piraeus, Greece

P. Kosmidis
2nd Department of Medical Oncology, Hygeia Hospital, Athens, Greece

treatment by PS interaction $P = 0.03$). No significant differences in terms of time to progression were found. Severe myelotoxicity and mucositis were more frequent with GDoc, while severe neuropathy with PCb and Pw. QoL changes did not differ significantly between treatment groups, while cost analysis favored Pw. *Conclusions* Pw appears to be the most preferable choice among the 3 anthracycline-free taxanes-based regimens tested in the present study.

Keywords Breast cancer · Chemotherapy · Taxanes · Gemcitabine · Trastuzumab

Introduction

It is true that, although advances in breast cancer detection and treatment have improved the odds of long term survival, breast cancer remains the second most common cause of cancer related death in women, surpassed only by lung cancer [1]. Metastatic disease as an initial diagnosis accounts for approximately 1% to 5% of new breast cancer cases. However, it is estimated that 20% to 30% of the patients initially diagnosed with early-stage disease will eventually develop metastatic breast cancer (MBC) [2].

Anthracyclines, epirubicin and doxorubicin, are considered to be among the most active drugs in the treatment of breast cancer. For this reason they became an integral part of adjuvant chemotherapy, administered to most women with high-risk and certain groups of intermediate-risk operable breast cancer. However, their re-administration in relapsed patients is limited by the increased risk of irreversible cardiomyopathy. Moreover, many patients with MBC, especially those with old age or serious co-morbidity, are not capable of being treated with anthracyclines. Therefore, other active drugs and effective anthracycline-free combinations need to be evaluated in MBC, especially in patients pretreated with anthracyclines. The taxanes paclitaxel and docetaxel, platinum analogs, gemcitabine, and capecitabine belong to this category.

Our group and others have conducted several phase II studies with non-anthracycline containing regimens in MBC. Three of them, paclitaxel and carboplatin [3, 4], docetaxel and gemcitabine [5, 6] and weekly paclitaxel [7–9] have demonstrated significant activity and manageable toxicity. Furthermore, the first of these combinations was found to be effective in a phase III trial [10], when compared to the combination of paclitaxel and epirubicin, in terms of overall response rate (ORR), survival and quality of life (QoL).

Motivated by this information, we designed and conducted a phase III trial in patients with MBC comparing paclitaxel and carboplatin, docetaxel and gemcitabine and weekly paclitaxel. The primary endpoint of the study was survival. Secondary endpoints were time to disease progression (TTP), overall response rate (ORR), acute severe toxicities, and QoL.

Patients and methods

Eligibility criteria

To be eligible for the study, women had to have histologically proven MBC, life expectancy $\geq$12 weeks, age $\geq$18 years, performance status (PS) $\leq$2 on the Eastern Cooperative Oncology Group (ECOG) scale, and adequate bone marrow, hepatic and renal function.

Patients treated with adjuvant chemotherapy were allowed to enter the study, if the interval between completion of adjuvant chemotherapy and first relapse (RFI) was >1 year. Patients with osseous metastases as the only metastatic site and receptor-positive status were eligible only if they progressed after at least one hormonal manipulation. Exclusion criteria were symptomatic brain metastases, history of other malignancies (except curatively resected non-melanoma skin cancer or in situ cervical cancer), myocardial infarction within the last 6 months, or other serious illnesses that would impair the ability *o*f the patient to receive protocol treatment. Previous chemotherapy for advanced disease was not allowed.

However, patients pretreated with hormonal or radiation therapy either in the adjuvant setting or for metastatic disease were eligible, provided that such treatment was stopped at least two weeks before study entry.

The clinical protocol and collateral research studies were approved by the HeCOG Protocol Review Committee and the Institutional Review Board of AHEPA University Hospital, as well as, the Bioethics Committees of the Aristotle University of Thessaloniki School of Medicine and the University of Athens School of Medicine. Written informed consent was obtained from all patients prior to study entry.

Treatment plan

Stratified block randomization balanced by center was performed centrally at the HeCOG Data Office in Athens. Stratification factors included the history of previous adjuvant chemotherapy and risk category, in a modified version of that used by Cavalli et al. [11]. Risk categories were defined as follows: (a) interval from initial radical surgery to first recurrence >5 years with only osseous or locoregional metastases, (b) interval from initial radical surgery to first recurrence 1–5 years and absence of visceral metastases and (c) all others.

Patients randomized to the first group were treated with paclitaxel 175 mg/m^2 over 3 h followed by carboplatin at an AUC of 6, in 500 ml normal saline given as a 30 min

infusion immediately after the end of the paclitaxel infusion, q 3 weeks for 6 cycles (PCb). Creatinine clearance was calculated using the Jelliffe formula [12] and AUC using the Calvert formula [13].

Patients randomized to the second group were treated with gemcitabine 1000 mg/m^2 dissolved in 500 ml normal saline administered as a 30 min infusion on days 1 and 8 followed by docetaxel 75 mg/m^2 given as a 1 h infusion on day 8 only, q 3 weeks for 6 cycles (GDoc).

Finally, patients randomized to the third group received weekly paclitaxel 80 mg/m^2 over 1 h for 12 weeks (Pw). Patients with partial response (PR) could continue treatment at their physician's discretion.

Premedication for prophylaxis of possible hypersensitivity reactions was given to all patients 30 min before each treatment and consisted of dexamethasone 8 mg, dimethidene maleate 4 mg and cimetidine 150 mg intravenously. Patients in the GDoc group received methylprednisolone 16 mg bid orally for 2 days, starting the day before the gemcitabine treatment. Ondansetron was given as antiementic treatment to all patients.

Maintenance treatment

Tailoring hormonal therapy (HT) after the completion of chemotherapy for patients with ER/PgR positive status was left to the discretion of the treating physician. However, recommendations for the management of these patients were included in the clinical protocol. Accordingly, letrozole was preferably given to all postmenopausal patients with ER/PgR positive status after the completion of chemotherapy until disease progression. Furthermore, premenopausal patients underwent ovarian ablation with an LH–RH analog and letrozole after the completion of chemotherapy until disease progression. Patients with osseous metastases were allowed to receive bisphosphonates during the entire chemotherapy period and thereafter, at the discretion of the treating physician.

Importantly, in the initial version of the clinical protocol, patients with HER-2 over-expressing tumors (2+ or 3+ by immunohistochemistry or FISH positive) were treated, after the completion of chemotherapy (23 patients), with trastuzumab 4 mg/kg, as a loading dose, followed by 2 mg/kg weekly. In July 2003, the protocol was amended and trastuzumab was initiated at the first day of chemotherapy (80 of the 103 patients treated with trastuzumab = 78%). Of note, the policy of our group was to continue treatment with trastuzumab beyond disease progression in all patients with expected survival of over 3 months and no serious cardiac problems.

Dose modification

Biochemistry and complete blood count (CBC) were done on the day of treatment. CBC was repeated between cycles only in the case of fever, hemorrhagic manifestations or severe mucositis. In case of granulocytopenia or thrombocytopenia on the first day of the cycle, treatment was delayed until absolute neutrophil count (ANC) was $\geq$1,500/μl and platelets $\geq$100,000/μl, respectively. In case of severe toxicity the drug dosages of the three regimens were modified, as previously described [3, 5, 8]. Erythropoietin was recommended to all patients with a hemoglobin level of $\leq$11 g/dl.

Response evaluation and follow-up

Standard ECOG criteria were used to define measurable disease, evaluable disease, response, and toxicity [14]. Response was evaluated clinically (whenever applicable) in each cycle and by imaging techniques after the third and sixth cycle of chemotherapy in PCb and GDoc or after the twelfth cycle in Pw. However, since ORR was a secondary objective of the study, patients with non-measurable or non-evaluable disease were eligible for the study. After the completion of chemotherapy, all patients were followed with a physical examination, CBC and biochemistry every three months and with chest x-rays, bone scans and CT-scans every six months, unless otherwise indicated. Notably, central evaluation of imaging material pertinent to tumor response was not performed in this study.

QoL assessment

QoL was assessed by the EUROQOL EQ-5D Questionnaire [15], administered to the patients at 3 time points: prior to chemotherapy, at chemotherapy completion and at the 6-month follow-up point. The 5 dimensions of the EQ-5D correspond to the levels of mobility, self-care, usual activities, pain/discomfort and anxiety/depression as rated by the patient (no problem, moderate problem, inability/severe problem). The European value set was used to convert the health states to the single summary EQ-5D Index [16]. Higher values correspond to better health state levels. In addition, the patient's rating of her overall "Health State" is marked on the EQ VAS, a visual analog scale from 0 to 100, with 0 corresponding to "worst" and 100 to "best imaginable health state".

Economic evaluation

The economic evaluation has been carried out from the perspective of the National Health Service (NHS) in Greece and in this context only direct health care costs borne by the NHS are included. The time horizon was that of the trial. Total cost included costs related to chemotherapy, administration, other medications, hospitalization for any reason, as well as laboratory and imaging examinations. Unit costs were based on hospital prices for the

specific resources used and refer to year 2007. Bootstrapping of the original data set was used in order to deal with uncertainty and to test the significance of differences observed between treatment groups. Treatment cost and survival in each group is combined to estimate cost per life year saved with each treatment over its next best alternative. QoL scores obtained by the EQ-5D Index are used to estimate cost per quality adjusted life years.

Statistical analysis

The primary endpoint of the study was survival. Secondary endpoints included TTP, ORR, severe toxic effects and QoL. All endpoints except toxicity and treatment characteristics were analyzed according to the intent-to-treat (ITT) principle. Treatment characteristics and safety analyses were based on the actual treatment administered.

The pre-study hypothesis assumed a difference of ±20% in survival rate at the 2-year time point to a baseline rate of 40%, on any of the treatment arms. For 80% power and a two-sided test with a type I error rate of 1.67% for each of the three comparisons between groups (preserving an overall type I error rate of 5%), a total of 426 patients were needed. This accrual corresponded to maximum study duration of approximately 4 years for observing 192 events. Taking into consideration a 3% withdrawal rate, the total number of patients was increased to 439. An interim analysis based on the O'Brien Fleming boundary values was planned at the 50% information time. A first interim was performed on March 2005 resulting in no crossing of the boundaries and continuation of all three arms. A second interim with data updated up to July 2006 was performed and presented in September 2006 [17], while the final analysis is based on data updated in December 2006. EaSt was used for the sequential design and analysis of the study (EaSt 4.0, Cytel Software Corporation, Cambridge, MA).

Survival was calculated from the randomization date to the date of death or of last contact. TTP was defined as the time interval between randomization and disease progression, secondary neoplasm, death from the disease, or death from any other cause (in case of unknown date of disease progression). The median survival and the TTP time were estimated with the Kaplan–Meier method, whereas the log rank test was used to compare time to event distributions. Repeated Confidence Intervals (RCIs) and adjusted *P*-values for the primary endpoint produced by EaSt are presented in the results section.

Since PS at entry was not balanced between randomization groups, analysis adjusting for PS category was also performed. Cox proportional hazards regression models were used to assess the influence on survival and TTP outcome of treatment group (PCb vs GDoc vs Pw), age, PS (1 vs 0), adjuvant chemotherapy (yes vs no), osseous metastases at entry (yes vs no), visceral metastases at entry (yes vs no), number of metastatic sites at entry (≥3 vs 2 vs 1), maintenance HT for advanced disease (yes vs no), HER-2 overexpression (yes vs no), and treatment with trastuzumab (yes vs. no) and as a time-varying covariate (yes from initiation of treatment and beyond). A backward selection procedure with removal criterion $P > 0.10$ was used to select the predictors included in the final Cox model which was preplanned.

Mixed effect models were used to explore the effect of treatment on the time progression of QoL measures [18]. The models of the change from baseline with intercept as a random effect included treatment group (PCb vs GDoc vs Pw), time and the respective interactions as covariates.

For the economic evaluation, since treatment cost estimates from clinical trials are skewed, samples were bootstrapped 5,000 times to get unbiased estimates of mean treatment cost and confidence intervals (CIs), [19]. Mean survival corresponds to the mean time of follow-up, i.e., time up to date of death or of last contact. Incremental cost effectiveness ratios (ICERs), in the form of cost per life year saved, were used to evaluate the alternative treatment regimens and the bootstrapped results were used to estimate cost effectiveness acceptability curves. These indicate the probability an ICER holds true for different ranges.

Unplanned statistical analysis

In a multivariate Cox model including PS (1 vs 0), treatment group (Pw vs PCb, Pw vs GDoc) and the corresponding treatment by PS interaction, the survival difference between Pw and PCb for PS 0 and PS 1 was checked. Such data however, need to be viewed with caution, since subgroup analyses are usually underpowered and exploratory and are mainly hypothesis generating.

Results

Eligibility

Between January 2002 and January 2006, 437 patients entered the study. Twenty-one patients were found ineligible. Reasons for ineligibility were: RFI less than a year (9 patients), history of other cancer (2), no evidence of metastatic disease at study entry (4), PS = 3 (2), and history of previous chemotherapy for MBC (4). A total of 416 eligible patients were included in the analysis according to the ITT principle. Thirteen of them never started treatment and for 5 patients medical records were considered incomplete.

The progress of the patients through the various stages of the trial is shown in Fig. 1, according to the Consolidated Standards of Reporting Trials [20].

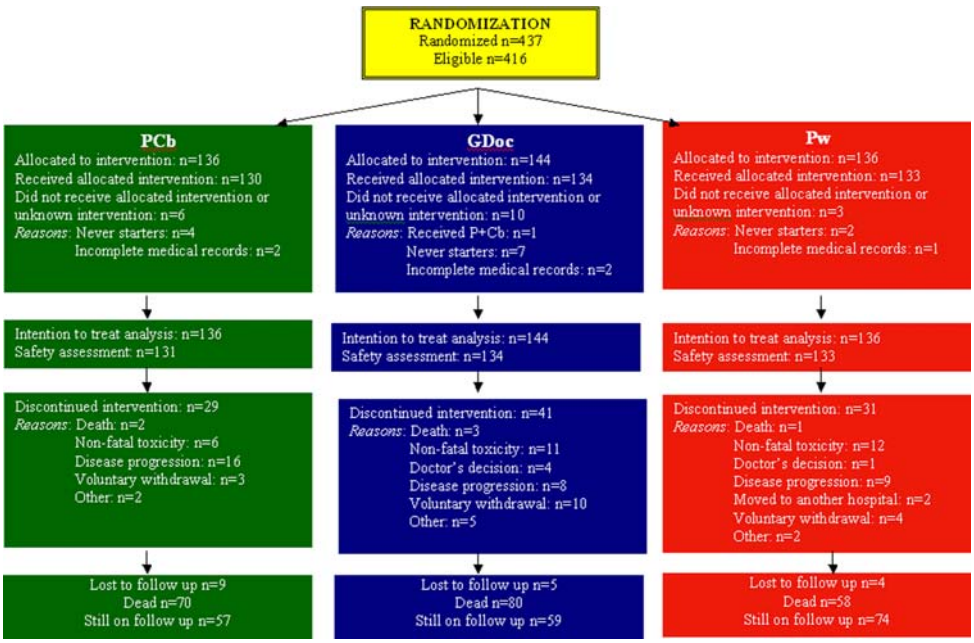


Fig. 1 Progress through the various stages of the trial. Survival status was updated in December 2006

Patient population

Important patient and tumor characteristics, shown in Tables 1 and 2, were found to be equally balanced between the three treatment groups, with the exception of PS ($P = 0.03$) and the incidence of osseous metastases at study entry ($P = 0.03$). One third of the patients had received anthracycline-containing adjuvant chemotherapy. In 30% of the patients the tumors over-expressed HER-2. Central review of the slides from patients with HER-2 over-expression was not performed in this study. Furthermore, it is worth noting that 73% of the patients had visceral metastases at the time of randomization.

Compliance to treatment and toxicity

Totally, 101 patients (24%) discontinued treatment. The main reasons for premature treatment discontinuation were tumor progression in 33 patients (PCb vs GDoc vs Pw) (16 vs 8 vs 9), non-fatal toxicity in 29 patients (6 vs 11 vs 12) and voluntary withdrawal in 17 patients (3 vs 10 vs 4). Six patients (2 vs 3 vs 1) died during chemotherapy treatment. Cause of death was the disease in four of them. One patient suffering from angina in the GDoc group died after the first day of the third cycle from gallbladder rupture and acute peritonitis. One toxic death was observed in the PCb group. According to the patient's medical records, she was hospitalized one week after the first cycle of chemotherapy for grade 3 diarrhea and grade 4 neutropenia. She succumbed three days later from sepsis. There were no other treatment-related deaths in the study.

Selected treatment characteristics are depicted in Table 3. The vast majority of chemotherapeutic cycles were given at full dose, resulting in a sufficient dose intensity of gemcitabine and taxanes. However, significantly more cycles in the GDoc group were administered in less than 90% of the dose defined by the protocol (PCb: 11%, GDoc: 24%, Pw: 10%, $P < 0.001$). Additionally, significantly more patients in PCb and GDoc experienced a treatment delay (more than two days) compared to Pw (PCb: 13%, GDoc: 25%, Pw: 8.5%, $P < 0.001$). The median number of cycles delivered in the three treatment arms, PCb vs GDoc vs Pw, were 6 vs 6 vs 12, respectively. A very limited number of patients (max 2–3) in each arm received extra cycles when PR was observed.

Among the 123 patients with HER-2 over-expression, 103 (84%) received trastuzumab during or following first line chemotherapy. The remaining 20 patients had not received trastuzumab, mainly because of delayed determination of HER-2 status (11 patients), cardiac problems (2), advanced age (1), patient refusal (1) and physician's decision (5). Additionally, 7 patients with HER-2 protein expression of 2+ received trastuzumab, bringing the number of patients treated with trastuzumab to 110 (38 vs 33 vs 39). Sixty-one (55%) of them continued to receive trastuzumab beyond disease progression. Notably, within the context of a collateral translational research study performed after the completion of the clinical trial, all the above cases with HER-2 protein expression of 2+ proved to be FISH-negative.

The incidence of grade 3 or 4 acute toxicities in the three groups of patients is shown in Table 4. Patients treated with gemcitabine and docetaxel experienced significantly more frequent severe neutropenia ($P < 0.001$), thrombocytopenia ($P = 0.001$), anemia ($P = 0.04$), and leukopenia ($P = 0.04$). On the other hand, patients treated with

Table 1 Selective patient characteristics

	PCb ($N = 136$)	GDoc ($N = 144$)	Pw ($N = 136$)
Age (years)			
Median	60	60	60.5
Range	31–84	28–80	27–80
	N (%)	*N* (%)	*N* (%)
Menopausal status			
Premenopausal	25 (18)	33 (23)	27 (20)
Postmenopausal	111 (82)	110 (76)	108 (79)
Unknown	0	1 (1)	1 (1)
Performance status[a]			
0	89 (65)	84 (58)	102 (75)
1	43 (32)	48 (33)	27 (20)
2	4 (3)	10 (7)	6 (4)
Unknown	0	2 (1)	1 (1)
Adjuvant CT			
No	65 (48)	62 (43)	63 (46)
Yes	71 (52)	80 (56)	72 (53)
Unknown	0	2 (1)	1 (1)
Anthracycline-containing	42 (59)	47 (59)	46 (64)
Adjuvant HT			
No	73 (54)	70 (49)	68 (50)
Yes	61 (45)	70 (49)	67 (49)
Unknown	2 (1.5)	4 (3)	1 (1)
Adjuvant RT			
No	78 (57)	91 (63)	79 (58)
Yes	56 (41)	49 (34)	56 (41)
Unknown	2 (1.5)	4 (3)	1 (1)

[a] At study entry; $P = 0.03$

CT, chemotherapy; HT, hormonal therapy; RT, radiation therapy

Values were rounded up

paclitaxel in the PCb and Pw groups developed severe sensory neuropathy more often ($P = 0.002$), as was expected. Finally, severe mucositis and alopecia were reported more often in patients from the GDoc group ($P = 0.02$) and the PCb group ($P < 0.001$). Febrile neutropenia occurred in 8 patients (3 vs 3 vs 2).

Response to chemotherapy, severe toxicity and survival were compared in an unplanned analysis according to age at randomization (≤65 vs >65 years). One hundred forty three patients (34%) were more than 65 years of age. No significant differences between the two age groups were found ($P > 0.05$ in all cases, with and without adjustment for treatment group). Furthermore, 56 patients (13%) presented with "triple negative" disease. No differences were observed between patients with "triple negative" disease vs the rest, in ORR (54% vs 47%, $P = 0.39$), TTP (10.7 months vs 10.9 months, $P = 0.94$) and survival (26.3 months vs 32.4 months, $P = 0.25$).

Table 2 Selective tumor characteristics

	PCb ($N = 136$) *N* (%)	GDoc ($N = 144$) *N* (%)	Pw ($N = 136$) *N* (%)
ER/PgR status			
Negative	34 (25)	33 (23)	31 (23)
Positive	89 (65)	95 (67)	97 (71)
Unknown	13 (10)	15 (10)	8 (6)
Triple negative disease	19 (14)	17 (12)	20 (15)
Grade			
I	3 (2)	8 (6)	1 (1)
II	49 (36)	46 (32)	51 (37.5)
III	60 (44)	63 (44)	63 (46)
Undifferentiated	0	0	1 (1)
Unknown	24 (18)	27 (19)	20 (15)
Site of metastases			
Locoregional			
Nodes	39 (29)	37 (26)	35 (26)
Skin	17 (12.5)	13 (9)	17 (12.5)
Residual breast	15 (11)	9 (6)	13 (10)
Distant			
Bones[a]	67 (49)	82 (57)	56 (41)
Visceral	97 (71)	102 (71)	104 (76.5)
Lung/Pleura	65 (48)	65 (45)	66 (48.5)
Soft tissue	26 (19)	37 (26)	36 (26.5)
Abdomen	2 (1.5)	0	0
Other breast	0	4 (3)	4 (3)
Unknown	1 (1)	2 (1)	1 (1)
Locoregional only	16 (12)	11 (8)	10 (7)
Locoregional and distant	36 (26.5)	36 (25)	40 (29)
Distant only	83 (61)	95 (66)	85 (62.5)
No of metastatic sites			
1	51 (37.5)	45 (31)	44 (32)
2	42 (31)	51 (35)	49 (36)
≥3	42 (31)	46 (32)	42 (31)
Unknown	1 (1)	2 (1)	1 (1)
HER-2 over-expression			
No	78 (57)	81 (56)	81 (60)
Yes	40 (29)	41 (28.5)	42 (31)
Unknown	18 (13)	22 (15)	13 (10)
Treatment with trastuzumab			
No	98 (72)	111 (77)	97 (71)
Yes	38 (28)	33 (23)	39 (29)

[a] $P = 0.03$, all other comparisons non-significant at 5% level

Values were rounded up

Supportive care is presented in Table 5. Use of bisphosphonates, G-CSF, antibiotics, and hospitalization was recorded more frequently in GDoc treated patients ($P = 0.02$, $P < 0.001$, $P = 0.001$, and $P < 0.001$, respectively).

Table 3 Selective treatment characteristics

	PCb ($N = 131$)		GDoc ($N = 134$)		Pw ($N = 133$)
Number of cycles delivered	747		704		1675
Median	6		6		12
Range	1–10		1–9		1–30
% of cycles at full dose[a]	89		76		90
% of cycles with a delay (>2 days)[b]	13		25		8.5
Median interval between cycles (days)	21		21		7
	P	Cb	G	Doc	Pw
Cumulative dose (mg/m^2)					
Planned	1050		12000	450	1080
Median delivered	1044	3350	11895	441	1078.5
DI					
Planned	58		667	25	90
Median delivered	56.5		569	23	83
Median relative DI	0.97		0.85	0.92	0.93

[a] Full dose: ≥90% of the dose defined in the protocol

DI: Dose intensity (mg/m^2/week)

[a, b] $P < 0.001$

Table 4 Incidence (%) of worst toxicities

	PCb ($N = 131$)		GDoc ($N = 134$)		Pw ($N = 133$)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Anemia[a]	1	0	3	1	0	0
Leukopenia[b]	4	2	10	4	5	1
Neutropenia[c]	7	6	20	10	6	5
Thrombocytopenia[d]	2	1	5	3	0	0
Nausea/Vomiting	0	0	3	0	2	0
Stomatitis	0	0	2	0	0	0
Diarrhea	1	0	3	0	0	0
Infection	2	0	5	0	0	0
Alopecia[e]	67	0	43	0	44	0
Fatigue	3	0	5	0	6	0
Peripheral neuropathy[f]	5	0	0	0	8	0
Hypersensitivity reactions	6	0	5	0	2	1
Dyspnea	0	0	0	0	1	0
Nail changes	0	0	1	0	1	0
Cardiotoxicity	0	0	0	0	2	0
Pain	1	0	0	0	1	0

[a] $P = 0.04$ (Severe anemia: 1% vs. 4% vs. 0%)

[b] $P = 0.04$ (Severe leukopenia: 6% vs. 14% vs. 6%)

[c] $P < 0.0001$ (Severe neutropenia: 13% vs. 30% vs. 11%)

[d] $P = 0.001$ (Severe thrombocytopenia: 3% vs. 8% vs. 0%)

[e] $P < 0.0001$ (Severe alopecia: 67% vs. 43% vs. 44%)

[f] $P = 0.002$ (Severe peripheral neuropathy: 5% vs. 0% vs. 8%)

Values were rounded-up

Table 5 Type of supportive care

	PCb ($N = 136$) N (%)	GDoc ($N = 144$) N (%)	Pw ($N = 136$) N (%)
Bisphosphonates[a]	38 (28)	62 (43)	41 (30)
Erythropoietin	41 (30)	52 (36)	39 (29)
G-CSF[b]	54 (40)	82 (57)	41 (30)
Antibiotics[c]	15 (11)	40 (28)	20 (15)
Hospitalizations[b]	15 (11)	43 (30)	26 (19)
RBC transfusions	7 (5)	2 (1)	1 (1)
PLT transfusions	1 (1)	0	0

[a] $P = 0.02$, [b] $P < 0.001$, [c] $P = 0.001$

G-CSF, granulocyte-colony stimulating factor; RBC, red blood cells; PLT, platelets

Response and survival

Overall response rates, as given by the investigators, in the three treatment arms are shown in Table 6. There were no significant differences between the three treatment groups ($P = 0.20$).

At a median follow-up of 34 months, 294 patients (71%) (68% vs 73% vs 71%) demonstrated disease progression and 208 (50%) (52% vs 56% vs 43%) died. Twenty-two patients died without documented progression and were considered as events for TTP estimation.

Among the patients showing tumor progression, 189 (64%) received some type of second line chemotherapy (PCb vs GDoc vs Pw) (59 vs 61 vs 69). Such chemotherapeutic regimens consisted mainly of capecitabine monotherapy (22%), a combination of capecitabine with other drugs (12%) or a combination of anthracyclines with other drugs (30%), while the number of patients receiving the various regimens was balanced across the three arms.

Table 6 Best response to treatment[a]

	PCb ($N = 136$) N (%)	GDoc ($N = 144$) N (%)	Pw ($N = 136$) N (%)
Response			
CR	15 (11)	7 (5)	25 (18)
PR	37 (27)	59 (41)	42 (31)
ORR	52 (38)	66 (46)	67 (49)
95% CI	30–47%	37.5–54%	41–58%
SD	46 (34)	37 (26)	36 (26.5)
PD	21 (15)	11 (8)	17 (12.5)
NE	13 (10)	27 (19)	14 (10)
Unknown	4 (3)	3 (2)	2 (1.5)

[a] Responses were determined by participating investigators

CR, complete response; PR, partial response; ORR, overall response rate; SD, stable disease; PD, progressive disease; NE, non-evaluable

The overall differences in survival between the three treatment groups were found to be significant (log-rank $P = 0.037$). Median survival times for PCb, GDoc and Pw were 29.9 months (range: 0.01–54.6+), 26.9 months (range: 0.01–51.4) and 41.0 months (range: 0.92–56.9+), respectively (Fig. 2). No significant differences in terms of TTP were found between the three groups (log-rank $P = 0.57$). Median TTP was 11.5 months (range: 0.01–54.6) for PCb, 10.4 (range: 0.01–51.4) for GDoc and 11.4 (range: 0.92–56.9+) for Pw.

Comparing survival pair wise between the three treatment groups, taking into account the sequential design and analysis of the trial, the corresponding adjusted P-values were 0.40, 0.10 and 0.01 for PCb vs GDoc, Pw vs PCb and Pw vs GDoc, respectively. The corresponding adjusted point estimates and $(1-\alpha)$% CI for the hazard ratio (HR) were 0.91 with 98.34% CI: 0.57 to 1.32 for PCb vs GDoc; 0.74 with 98.34% CI: 0.48 to 1.15 for Pw vs PCb; and 0.67 with 98.34% CI: 0.42 to 0.99 for Pw vs GDoc.

A Forest Plot depicts the pair wise survival comparisons between GDoc and Pw, and PCb and Pw, in the relevant subgroups according to candidate patient and tumor characteristics (Figs. 3a, b, respectively).

Multivariate models

PS was not balanced between the three groups (Table 1) and thus adjustment for PS was used in all subsequent analyses. All prognostic factor analyses excluded the PS 2

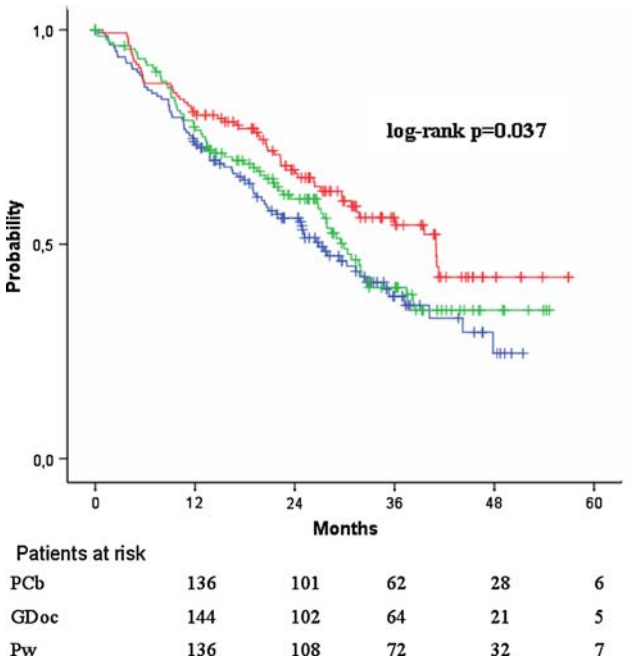
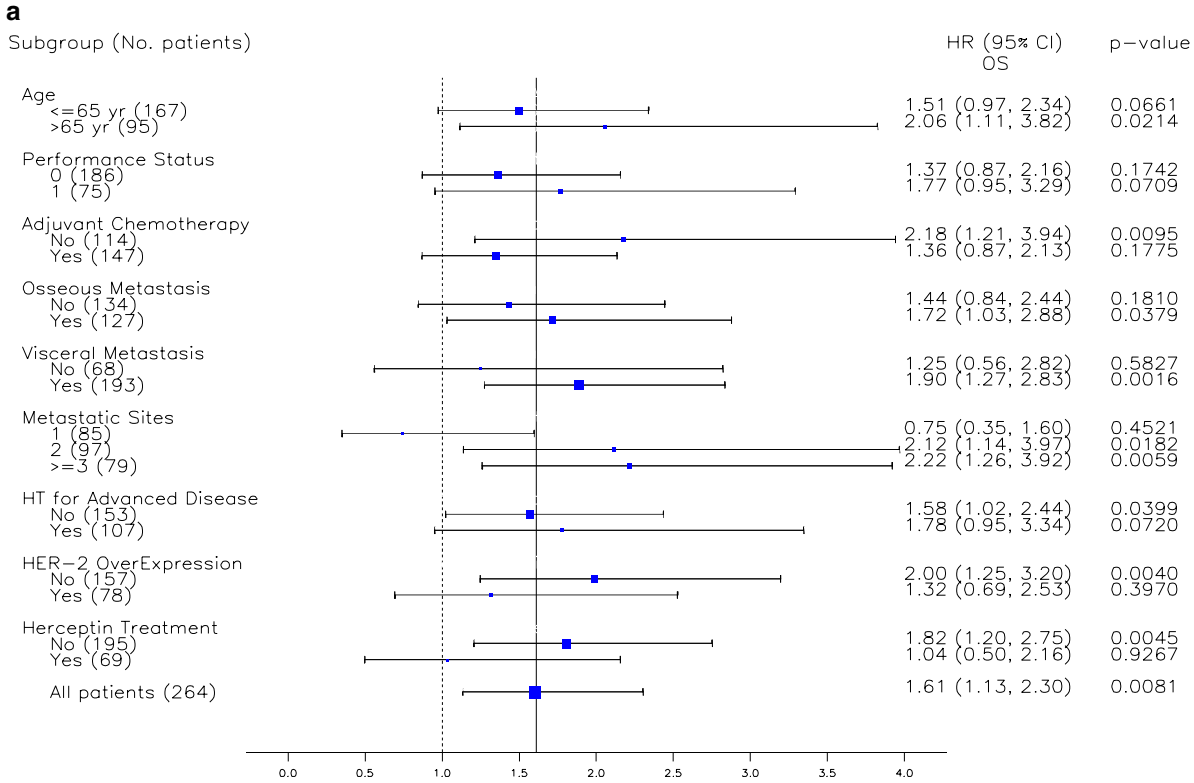


Fig. 2 Survival of patients treated with PCb (——), GDoc (——), or Pw (——) ($P = 0.037$)



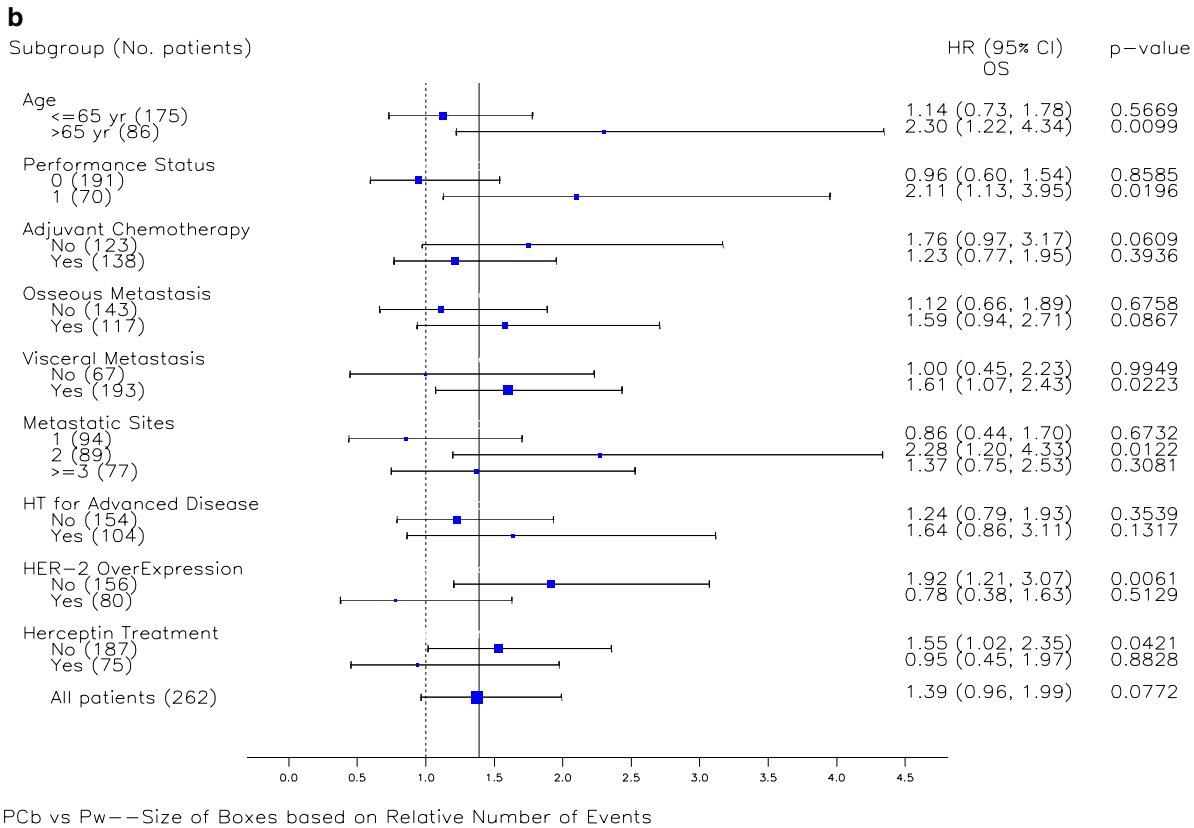


Fig. 3 (**a, b**) Hazard Ratios for pair wise survival comparisons according to patient and tumor characteristics

category, since robust results on outcome could not be drawn from such a small sample (20 patients, 16 deaths).

In a multivariate Cox model including PS (1 vs 0), treatment group (Pw vs PCb, Pw vs GDoc), and the corresponding treatment by PS interaction ($P = 0.029$), the survival difference between Pw and PCb for PS 1 was statistically significant in favor of Pw (HR = 0.50, $P = 0.007$), while it was not significant for PS 0 (HR = 0.99, $P = 0.96$). The survival difference between Pw and GDoc was statistically significant in favor of Pw (HR = 0.65, $P = 0.021$) and was not affected by PS category (Fig. 4).

According to the multivariate Cox regression model chosen by the backward selection procedure (Table 7), history of adjuvant chemotherapy (yes vs no: HR = 1.31, 95% CI 0.97–1.77, $P = 0.075$) and higher number of metastatic sites at study entry (2 vs 1: HR = 1.51, 95% CI 1.03–2.21, $P = 0.03$; ≥3 vs 1: HR = 2.47, 95% CI 1.68–3.63, $P < 0.001$), were significant adverse prognostic factors for survival.

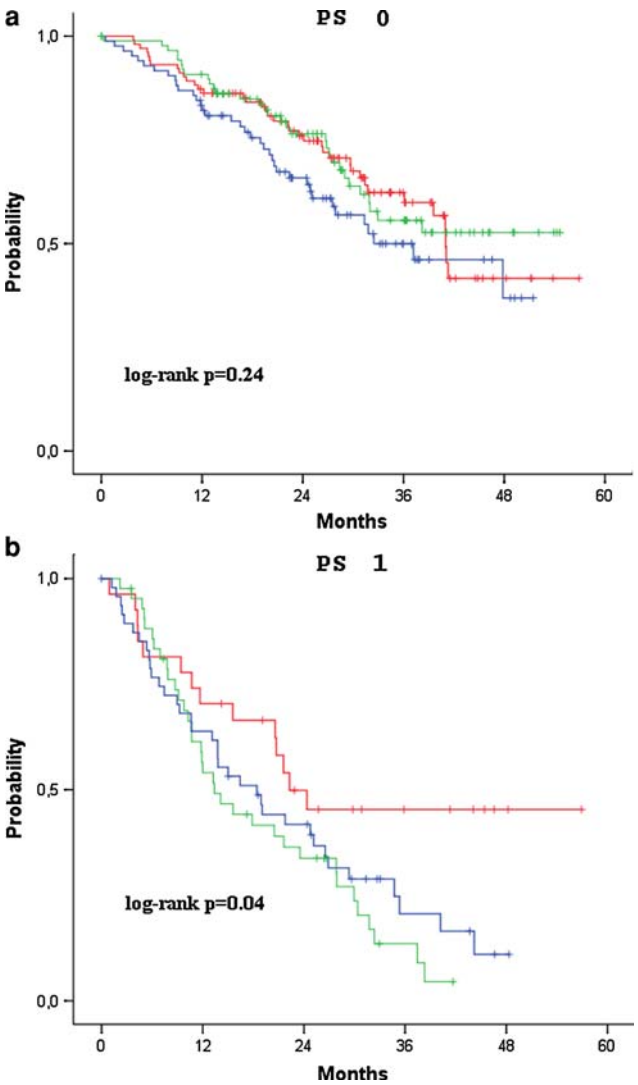


Fig. 4 Survival by randomization group stratified by PS (0–1), PCb (——), GDoc (——), or Pw (——)

Table 7 Estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for survival: results of the multivariate Cox model

	HR	95% CI	*P*-value
Survival			
Treatment group			
Pw	1		
PCb	1.90	1.14–3.16	0.01
GDoc	1.50	1.04–2.16	0.03
Adjuvant CT			
No	1		
Yes	1.31	0.97–1.77	0.075
PS			
1	1		
0	0.56	0.38–0.82	0.003
Number of metastatic sites at entry			
1		1	
2	1.51	1.03–2.21	0.03
≥3	2.47	1.68–3.63	<0.001
Maintenance HT			
No		1	
Yes	0.49	0.36–0.68	<0.001
PCb by PS interaction	0.51	0.27–0.94	0.03

CT, Chemotherapy; HT, Hormonal therapy; PS, Performance status

On the other hand, maintenance HT (HR = 0.49, 95% CI 0.36–0.68, $P < 0.001$) and better PS (0 vs 1: HR = 0.56, 95% CI 0.38–0.82, $P = 0.003$) significantly decreased the hazard of death.

Patients treated in the GDoc group had a significantly increased risk of death compared to Pw (HR = 1.50, 95% CI 1.04–2.16, $P = 0.03$). In addition, statistically significant evidence indicated that the treatment effect on the hazard of death for PCb compared to group Pw was different according to PS (interaction $P = 0.03$). More specifically, in patients with PS 1, the hazard of death was significantly higher for PCb compared to Pw (HR = 1.90, 95% CI 1.14–3.16, $P = 0.01$), while in patients with PS 0 no significant difference between the two treatment groups was found (HR = 0.96, 95% CI 0.60–1.54, $P = 0.87$). These results did not change when including treatment with trastuzumab as a time varying covariate in the Cox model.

Quality of life

A total of 325 patients (78% of eligible patients) completed at least once the EUROQOL questionnaire. Prior to chemotherapy, the overall percent of patients reporting at least some problems in any of the 5 dimensions of EQ-5 were:

Table 8 Quality of life results

Treatment group		EQ-5D index (×100)			EQ VAS Score		
		Time points			Time points		
		Pre	Post	6-months follow up	Pre	Post	6-months follow up
PCb	*N*	100	78	74	100	79	74
	Mean ± SD	62 ± 26	68 ± 22	70 ± 27	66 ± 21	70 ± 16	73 ± 19
	Median	69	70	78	70	70	75
GDoc	*N*	100	73	62	97	73	61
	Mean ± SD	59 ± 25	65 ± 21	69 ± 23	67 ± 20	70 ± 16	76 ± 17
	Median	66	69	76	70	70	80
Pw	*N*	102	83	72	101	82	72
	Mean ± SD	63 ± 24	66 ± 25	74 ± 22	72 ± 19	73 ± 18	81 ± 14
	Median	69	69	78	70	75	80

37%, 20%, 41%, 58%, and 76% for mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, respectively. At the 6-month follow-up point, these percentages were reduced to 31%, 17%, 33%, 40%, and 64%. The corresponding percent of patients with overall "Health State" below 80, as marked on the EQ VAS, was 62% at baseline and reduced to 41% at the 6-month follow-up point. The mean EQ-5 index at baseline was 0.62, 0.59 and 0.63 for groups PCb, GDoc and Pw, respectively, with corresponding mean EQ VAS Score of 66, 67 and 72 points (Table 8).

At the 6-month follow-up time point, a mean increase in EQ-5 index of 0.071 points [standard error (SE) = 0.024] was observed in PCb, with a corresponding increase of 0.049 points (SE = 0.025) and 0.066 points (SE = 0.247) observed in GDoc and Pw, respectively. Regarding the EQ VAS Score, a mean increase of 6.7 points (SE = 2.13) was observed in PCb, with a corresponding increase of 5.8 points (SE = 1.97) and 4.5 points (SE = 1.65) observed in groups GDoc and Pw, respectively. At chemotherapy completion, a smaller mean increase was apparent both in EQ-5 index and in EQ VAS Score in each of the 3 groups.

Based on the mixed effects model analysis, a significant improvement across time in the EQ-5 index and EQ VAS Score was detected for all treatment groups ($P < 0.001$). These changes across time did not differ significantly between groups.

Economic analysis

It was estimated that total treatment cost (in euros) in PCb was 20,498 [95% Uncertainty Interval (UI): 19,044–22,020, range: 17,647–23,258], in GDoc 19,343 (95% UI: 18,088–20,570, range: 16,743–21,535) and in Pw 20,578 (95% UI: 19,249–21,958, range: 18,126–23,058). As indicated in Fig. 5, chemotherapy accounted for about 59% of the total cost of treatment, the remaining medications for about 25% and the rest 16% of the cost involved hospitalizations and laboratory examinations. Next to chemotherapy, the second most costly item was imaging, followed by treatment with trastuzumab, bisphosphonates, erythropoietin, G-CSF, HT, hospitalization, and laboratory tests.

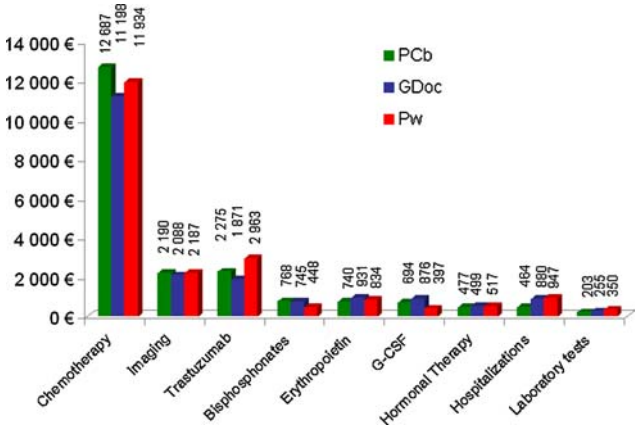


Fig. 5 Cost (in euros) components per treatment group

In terms of effectiveness, mean survival was 23.0 months (95% UI: 20.9–25.1, range: 19.7–28.5) in PCb, 21.4 months (95% UI: 19.4–23.4, range: 18.2–25.6) in GDoc, and 25.5 months (95% UI: 23.3–27.6, range: 22.1–29.8) in Pw. The first group was dominated by the other two. The cost per life year saved of Pw over GDoc was 3,660 (95% UI: dominance – 9,261, range: dominance – 14,664) and the incremental cost per quality adjusted life year saved was 3,596 (95% UI: dominance – 8,956, range: dominance – 15,154). Thus, the data support, in a robust manner, that monotherapy with weekly paclitaxel represents a cost-effective treatment option for patients with MBC in the Greek National Health Service.

Discussion

In the present phase III study, weekly administration of paclitaxel (Pw) resulted in significantly longer survival than the one observed with gemcitabine and docetaxel (GDoc) (HR = 0.65, $P = 0.021$). In addition, when PS category was taken into account, survival for patients with PS 1 was found to be significantly longer in Pw as compared to the paclitaxel followed by carboplatin group (PCb) (HR = 0.50, $P = 0.007$). The latter was a result of an unplanned analysis, while in the overall comparison of survival between Pw and PCb, survival was not significantly different. Nevertheless, the improvement in survival in Pw vs GDoc, and in Pw vs PCb for the subgroup of patients with PS 1, remained significant in the presence of all other prognostic factors in the multivariate models. The latter however, needs to be viewed with caution, since subgroup analyses are usually underpowered and exploratory and are mainly hypothesis generating.

Survival rates at two-years ranged from 56% for GDoc, 61% for PCb to 67% for Pw, higher than the observed survival rates in the previous randomized study by our group [10], in which the corresponding 2-year survival rates were 45% and 53% for the paclitaxel/epirubicin and PCb groups, respectively. This improvement in all treatment arms could probably be attributed to the wider use of trastuzumab and the availability of additional effective chemotherapy agents in subsequent lines of treatment such as capecitabine for patients in the current study. It should be noted that treatment duration was not the same in the three arms. How this asymmetry impacts outcome is unknown.

Weekly dosing of paclitaxel has been extensively studied, in an attempt to increase dose density and improve tolerability. Several phase II studies (reviewed in Ref. [21]) have evaluated weekly paclitaxel in patients with MBC. This regimen was generally well tolerated with main toxicities being neutropenia and peripheral neuropathy. Of note, in a sub-analysis of a large phase II study [22] according to the age of patients, there was no significant difference in ORR and the tolerability profiles were similar among older or younger than 65 years patients. Similarly, in our study no difference was found in ORR, acute severe toxicity or survival between these two groups of patients. These results suggest that weekly paclitaxel is a safe and convenient regimen for elderly patients with MBC.

In terms of effectiveness weekly paclitaxel probably constitutes the preferred schedule of administration in patients with MBC. Its superiority over the standard 3-weekly administration (175 mg/m^2 over 3-h infusion) was demonstrated in a randomized study [23], conducted by the Cancer and Leukemia Group B (CALGB). In that study, weekly paclitaxel was found to be superior to the 3-weekly regimen in terms of ORR (42% vs 29%, $P = 0.0004$) and TTP (9 months vs 5 months, $P = 0.0001$). It has to be mentioned that trastuzumab was administered to patients with HER-2 over-expressing tumors. Interestingly, in case the tumor was HER-2 negative, patients were further randomized to receive either trastuzumab or placebo. Weekly paclitaxel resulted in a significantly higher rate of grade 3 sensory neuropathy (24% vs 12%, $P = 0.0003$), but lower rate of severe neutropenia (9% vs 15%, $P = 0.017$). Trastuzumab did not improve response in patients with HER-2 negative status. The results of the CALGB study are similar to those reported in our study and strongly suggest that paclitaxel monotherapy is more effective and less toxic when given in a weekly schedule. In the Cox model, maintenance HT significantly reduced the hazard of death in our patients. However, no differences were observed in ORR or survival between the three regimens when trastuzumab was added, probably due to the small number of patients treated with trastuzumab in each arm of the study.

Notably, in a randomized study reported by Robert et al. [24], 196 women with HER-2 over-expressing MBC were treated with paclitaxel and carboplatin, as given in our study, or with paclitaxel alone. Both regimens were given every 3 weeks along with weekly trastuzumab. Improved clinical outcomes were observed with the combination compared to paclitaxel monotherapy, with an ORR of 57% vs 36% ($P = 0.03$) and corresponding median TTP of 13.8 vs 7.6 months ($P = 0.005$). The ORR and TTP observed with the paclitaxel/carboplatin arm in our study were both lower (38% and 10.7 months, respectively). This discrepancy in the results between the above study and ours may be attributed to several factors, such as schedule of paclitaxel monotherapy, patient selection and sample size, but mainly to the fact that our study included HER-2 negative patients that were not treated with trastuzumab.

Toxicity was manageable in our study. Severe side effects were infrequent. In general, the toxicity profile of the three regimens was similar to that shown in previously reported phase II studies with these regimens in patients with MBC [3–9]. The combination of gemcitabine and docetaxel was more myelotoxic than the other two regimens, while paclitaxel containing combinations were more neurotoxic. Febrile neutropenia occurred rarely in all three regimens.

At baseline, a substantial percentage of patients reported at least some problems in the 5 dimensions of EQ-5 and the median reported EQ VAS was around 70 for all three groups. An improvement across time was recorded to the reported health states both at the completion of chemotherapy and at the 6-month follow-up time point. This is consistent with findings from other prospective studies [25, 26], where even though deterioration in quality of life following administration of chemotherapy was reported, a

quick rebounding effect was observed. The improvement of reported health states observed in our study was not different between treatment arms.

Economic analysis indicated that the combination therapy of paclitaxel with carboplatin was dominated by the other two therapies. The GDoc combination was the least costly but also a less effective treatment option. Higher cost corresponding to higher effectiveness was associated with Pw. Its incremental cost-effectiveness ratio over the later therapy was quite low and very attractive. In this context it should be a preferred treatment option on the basis of the value for money gained from its use.

In conclusion, the present study indicates that Pw is a more effective treatment with respect to survival in patients with MBC, with the GDoc group fairing worse than Pw for all patients and the PCb group for the subgroup of patients with PS 1. In addition, Pw was found the most cost-effective treatment. No differences were detected with respect to secondary outcomes such as ORR, and TTP as well as quality of life.

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