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Gemcitabine, epirubicin and docetaxel as primary systemic therapy in patients with early breast cancer: results of a multicentre phase I/II study☆

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Abstract

Developing primary systemic chemotherapy (PST) regimens that induce higher pathological complete response (pCR) rates remains a challenge in operable breast cancer. We recruited 77 eligible patients into a multicentre phase I/II study to evaluate the maximum tolerated dose (MTD), toxicity and efficacy of preoperative gemcitabine day 1 and 8 (800 mg/m^2 fixed dose), epirubicin and docetaxel on day 1 (doses escalated from 60 mg/m^2) (GEDoc), repeated 3-weekly for 6 cycles with filgrastim support. MTD for epirubicin was 90 mg/m^2 and for docetaxel 75 mg/m^2. Dose-limiting toxicities (DLTs) included febrile neutropenia and grade 3 diarrhoea. Clinical response rate was 92%, pCR rate was 26%. 79% of patients had breast-conserving surgery. Grade 3/4 leucopenia was the main toxicity, occurring in 55 (87%) of 63 patients treated at the MTD. Non-haematological toxicity caused no serious clinical problems. In conclusion, GEDoc is highly active as PST. Efficacy and toxicity compare favourably with other effective combinations.

Keywords: Breast cancer; Chemotherapy; Docetaxel; Epirubicin; Gemcitabine; Neoadjuvant therapy

1. Introduction

Preoperative (primary systemic) and postoperative (adjuvant) chemotherapy are equally effective in terms of disease-free and overall survival in early breast cancer (BC) [1]. However, primary systemic treatment (PST), allows for more breast-conserving surgeries, and tumour response to PST may be a surrogate for evaluating the effect of chemotherapy on micrometastases [2]. Patients with pathological complete response (pCR) following PST show significantly improved survival compared with patients with a persistent invasive tumour [3], and an increase in pCR rate is likely to lead to improved survival [4]. Randomised trials have shown that several strategies may be useful in increasing pCR rate. These include the dose-dense sequential administration of an anthracycline

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and paclitaxel [5], extending the duration by adding more treatment cycles [6], or adding sequential docetaxel [7,8]. In patients responding to 4 cycles of an anthracycline-containing regimen, the change to docetaxel nearly doubled the rate of pCR compared with continuation of anthracycline-containing therapy [9].

Gemcitabine has single-agent activity in metastatic breast cancer [10]. As a consequence of its favourable toxicity profile and lack of complete cross-resistance — particularly with anthracyclines and taxanes — it has been combined in several regimens for the treatment of advanced BC [11,12]. Docetaxel/gemcitabine, in particular, has demonstrated high activity in phase II studies in anthracycline- and taxane-pretreated metastatic disease [13,14]. Furthermore, triplet gemcitabine, anthracycline and paclitaxel achieved overall response rates of 92% and 83%, with 31% and 44% of patients achieving a complete response [15,16]. Despite possible patient selection bias, few studies of conventional chemotherapy regimens in advanced BC have reported comparable complete and overall response rates.

Thus, evidence suggests that an intensive chemotherapy regimen comprising gemcitabine, epirubicin and docetaxel as PST for an extended period of time may achieve a remarkable pCR rate and, eventually, survival for patients with metastatic breast cancer. We performed this multicentre phase I/II study to establish the safety profile, maximum tolerated dose (MTD) and efficacy of this triplet.

2. Patients and methods

2.1. Eligibility criteria

Women with newly diagnosed non-metastatic breast cancer presenting at the Universities of Heidelberg or Tuebingen or the community hospital of Weinheim were invited to participate in this study if they met the following eligibility criteria: histologically-confirmed, unilateral large ($\geqslant$ 2.5 cm in diameter in postmenopausal or $\geqslant$ 2.1 cm in premenopausal women) or inflammatory BC; no evidence of distant metastatic disease as assessed by physical examination, chest X-ray, liver ultrasound, bone scan, and full blood count; Eastern Cooperative Oncology Group (ECOG) performance status of $\leqslant 2$; adequate bone marrow function (absolute neutrophil count (ANC) $\geqslant 1.5 \times 10^9$ cells/L, platelet count $> 100 \times 10^9$ cells/L); adequate cardiac, renal and hepatic function; and a negative pregnancy test. A diagnosis of invasive BC was made using clinical examination, mammography, ultrasonography and core biopsy. The study protocol was approved by the Joint Ethical Committee of the Universities of Heidelberg and Tuebingen. All patients provided informed written consent and their characteristics are listed in Table 1.

Table 1
Baseline patient characteristics

Characteristic	Median (range)	*n*	(%)
No. of patients		77	(100)
Age (years)	48 (30–65)		
Histology			
Ductal		63	(82)
Lobular		10	(13)
Tubular		4	(5)
Tumour size (by ultrasound) (cm)	3.0 (2.1–12.0)		
Clinical node status			
N0		32	(42)
N+		41	(53)
NA		4	(5)
Histological grade			
1		2	(3)
2		37	(48)
3		30	(39)
Unknown		8	(10)
Hormone receptor status			
ER-positive		51	(66)
PgR-positive		48	(62)
ER- or PgR-positive		55	(71)
ER- and PgR-negative		20	(26)
ER- and PgR-unknown		2	(3)
HER2/neu expression			
0 or 1+ or 2+ and FISH-negative		49	(64)
3+ or 2+ and FISH-positive		26	(34)
Unknown		2	(3)
Ki-67 expression			
$\leqslant$ 50% positive nuclei		48	(62)
> 50% positive nuclei		10	(13)
Unknown		19	(25)
p53 expression			
$\leqslant$ 50% positive nuclei		46	(60)
> 50% positive nuclei		13	(17)
Unknown		18	(23)
Bcl-2 expression			
0–1+		37	(48)
2–3+		22	(29)
Unknown		18	(23)

ER, oestrogen receptor; FISH, fluorescence *in situ* hybridisation; PgR, progesterone receptor; NA, not available.

2.2. Treatment, assessment of toxicity and dose modifications

Chemotherapy consisted of increasing doses of epirubicin and docetaxel in combination with fixed doses of gemcitabine (800 mg/m^2). The doses of epirubicin and docetaxel were both 60 mg/m^2 at dose level 1, 60 and 75 mg/m^2 at level 2, respectively, both 75 mg/m^2 at level 3, and 90 and 75 mg/m^2 at level 4, respectively. All drugs were sequentially administered on day 1, another dose of gemcitabine 800 mg/m^2 was given on day 8. Cycles were repeated every 21 days for up to 6 cycles. Prophylactic filgrastim 5 μg/kg body weight was administered

subcutaneously (s.c.) from day 2 to day 6, and day 9 until neutrophil recovery. Patients developing anaemia greater than grade 1 could receive erythropoietin alpha 10 000 IU 3 times weekly. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) from 1990 [17]. The MTD was defined as the dose level at which one of three or two of six patients experienced a dose-limiting toxicity (DLT). DLT was evaluated for each patient during the first cycle of treatment and was defined as one of the following: (i) febrile neutropenia, (ii) grade 4 thrombocytopenia or (iii) the occurrence of any grade 3 or 4 non-haematological toxicity other than alopecia or nausea/vomiting. Three to six patients were treated at each dose level. If a DLT occurred in none of three patients or no more than one of six patients at the preceding dose level, patients were moved to the next higher dose level. Once the MTD was defined, the following patients started treatment at this dose level in phase II of the study (Table 2). Restarting treatment was delayed until platelet count recovered to $>100 \times 10^9$ cells/L and leucocyte count was $\geqslant 3.0 \times 10^9$ cells/L on day 1 or $\geqslant 1.5 \times 10^9$ cells/L on day 8.

2.3. Assessment of clinical response

Clinical tumour response was assessed after every 6 weeks of treatment. Before the first cycle of chemotherapy and at each reassessment, the size of the greatest tumour diameter was measured by palpation, breast ultrasound and, if indicated, magnetic resonance imaging (MRI). Tumour size was assessed by mammography before the first and after the last cycle of chemotherapy. Clinical tumour response was graded according to Response Evaluation Criteria in Solid Tumors (RECIST) [18], with the size of the tumour at baseline (before administration of the first pulse of chemotherapy) serving as the reference.

2.4. Surgery, radiotherapy and assessment of pathological response

Patients proceeded to surgery within 4 weeks after receiving the last dose of chemotherapy. If breast-conserving surgery was not possible, a modified radical mastectomy was recommended. If the tumour size allowed breast-conserving surgery, the following guidelines were observed: (1) surgical margins were free of invasive or non-invasive breast cancer and, if required, repeat excision was performed; (2) an adequate cosmetic result was anticipated; and (3) if cosmetically acceptable, the whole previously involved area was excised. In patients with a clinically complete response or an unfavourable ratio of tumour to breast size, a biopsy specimen of adequate size was taken from a representative area. All patients undergoing a breast-conserving procedure received standard radiotherapy to the remaining breast. Radiotherapy to the chest wall or regional lymph nodes was performed according to the standards of each participating centre.

2.5. Immunohistochemistry

Tumour tissue from core biopsy was embedded in paraffin and the tissue cut into sections (≈ 2 μm). Sections were stained using an automated immunohistochemical technique (BioTek TechMate™, BioTek Solutions, Newport Beach, CA, USA) with strict adherence to the staining protocol. The following primary antibodies were used (clones in brackets): HER2/neu (A0485), Ki-67 (MIB-1), p53 (DO7), Bcl-2 (124), oestrogen receptor (ER) (1D5), and progesterone receptor (PgR) (PR88) (all reagents from DakoCytomation Ltd., Ely, UK). Antibody staining was recorded as the percentage of positive tumour nuclei for Ki-67 and p53. Bcl-2 and HER2/neu immunoreaction was scored from 0 to 3, only with respect to cell membrane staining. In the case of a HER2/neu score 2+, fluorescent *in situ* hybridisation (FISH) was performed. Receptor positivity was assumed when the semiquantitative score was 3 points or more (out of a maximum of 12 points).

2.6. Calculation of SDIP

Dose intensity was expressed as the summation dose intensity product (SDIP) [19,20]. SDIP was calculated from the unit dose intensity (UDI), defined as the dose (mg/m^2/week) of a specific single agent that produces a 30% overall response rate in first-line therapy for metastatic breast cancer for epirubicin (UDI 25 mg/m^2/week) [19], docetaxel (UDI 17 mg/m^2/week) [19] and gemcitabine (UDI 1000 mg/m^2/week) (W Hryniuk, data not shown, written communication, Barabra Ann Karmanos Cancer Institute, Detroit, MI, USA, May 2002) [20]. Planned dose intensities for all treatments (mg/m^2/week) were then divided by their specific UDI and the resulting decimal fractions added to give the summation dose intensity (SDI). Multiplying SDI by scheduled cycle length (weeks) and number of cycles gives the scheduled SDIP. Relative SDIP was calculated as the percentage of that actually administered versus scheduled SDIP.

2.7. Statistical analysis

Descriptive statistics were used to report relative SDIP of chemotherapy, toxicities, and clinical and pathological response rates. Multiple baseline patient and disease characteristics of patients treated at MTD were dichotomised and analysed for their possible effect on the pCR rate using the χ^2 test. Variables included age ($\leqslant 50$ versus > 50 years), histology (ductal invasive

versus non-ductal invasive), largest tumour diameter as measured by ultrasound (⩽ 5 versus > 5 cm), clinical nodal status (N0 versus N1-2), grade (1–2 versus 3), ER and PgR status (positive versus negative), HER2/neu expression (positive (defined as score 3+ or score 2+ plus FISH positivity) versus negative), Ki-67 (⩽ 50% versus > 50% positive nuclei), p53 (⩽ 50% versus > 50% positive nuclei), Bcl-2 (0–1+ versus 2–3+), and achievement of partial response (PR) after 2 cycles (yes versus no). Analyses were performed on an intent-to-treat basis, but patients with missing values for these factors were excluded. Statistical tests were performed using SYSTAT® software (Version 7.0; SYSTAT, Witzenhausen, Germany).

3. Results

3.1. Patient and tumour characteristics

A total of 80 patients were recruited between January 2002 and March 2003. Three patients were considered ineligible due to a pre-existing, uncontrolled psychiatric disorder (1 patient), primary bone metastases (1 patient), and chronic infectious disease (1 patient). Baseline characteristics of the 77 eligible patients are summarised in Table 1. Eligible patients received a total of 445 chemotherapy cycles (median 6 and range 4–6). All cycles were assessable for toxicity and all eligible patients were assessable for response.

3.2. Dose escalation and dose-limiting toxicity

The dose escalation scheme and dose-limiting toxicities are shown in Table 2. Dose escalation was stopped when one of three and two of six patients experienced a DLT at dose level 4; one patient had grade 3 diarrhoea, the other developed febrile neutropenia. An additional three patients were enrolled at dose level 4 to confirm MTD and one patient experienced dose-limiting diarrhoea. Dose level 4 was therefore considered the MTD (epirubicin 90 mg/m^2 day 1, followed by docetaxel 75 mg/m^2 day 1 and gemcitabine 800 mg/m^2 days 1 and 8, supported by filgrastim). During the subsequent phase II portion of the study, another 54 patients were treated at the MTD.

Table 2
Dose escalation and dose-limiting toxicities

	Level 1	Level 2	Level 3	Level 4 (MTD)
Epirubicin (mg/m^2) day 1	60	60	75	90
Docetaxel (mg/m^2) day 1	60	75	75	75
Gemcitabine (mg/m^2) day 1 and 8	800	800	800	800
n	3	4	7	9
DLT	0	0	0	3[a]

DLT, dose limiting toxicities; MTD, maximum tolerated dose.
[a] Febrile neutropenia (1 patient), diarrhoea grade 3 (2 patients).

3.3. Toxicity

Toxicities for all patients treated at MTD are summarised in Table 3. Of the 63 patients who received the MTD, the main haematological toxicity was grade 3 or 4 leucopenia, which occurred in 56% and 32% of patients, respectively. No other grade 4 haematological toxicities were observed. There were 8 episodes of febrile neutropenia (2% of cycles and 13% of patients). The incidence of severe anaemia was low; patients who developed at least grade two anaemia ($n = 35$) received prophylactic treatment with erythropoietin (10 000 IU s.c. 3 times weekly). Severe, clinically relevant non-haematological toxicities equivalent to DLT consisted mainly of fatigue (grade 3 30% of patients, grade 4 5% of patients) and stomatitis (grade 3 27% of patients).

3.4. Received dose and dose intensity

Fifty six (89%) of all 63 patients who received MTD as their starting dose completed the planned treatment course of 6 cycles. Treatment was discontinued after 5 cycles in 5 patients (due to toxicity in 4, one refused further chemotherapy) and after 4 cycles in 2 patients (due to toxicity). Dose reductions were required in 30 patients. The administered dose intensity of chemotherapy expressed as the mean SDIP ± standard deviation (SD) was 54 ± 5 units (median 58 units and range 38–58), corresponding with 93% (mean) or 97% (median) of the planned SDIP.

3.5. Response

Clinical and pathological efficacy results are shown in Table 4. 17 patients [22%; 95% Confidence Interval (CI), 13–31%] achieved cCR and 54 patients (70%; 95% CI, 60–80%) achieved cPR, as assessed by ultrasound scanning, resulting in an overall clinical response rate of 92% (95% CI, 86–98%). No patient progressed during preoperative chemotherapy. For the 63 patients who received the MTD, the results are nearly identical (cCR rate 21% and overall clinical response rate 92%). No cCRs occurred at dose levels 1 or 2. All 77 patients were evaluable for pathological response. No viable tumour cells were detected in the breast tissue removed from 10 patients (pCR breast 13%; 95% CI, 5–20%; 1/7 patients treated at level 3, 9/63 patients at MTD). Another 10 patients had only residual carcinoma *in situ* (pCR_{INV} breast 13%; 95% CI, 5–20%; 1/4 patients at level 2, 2/7 patients

Table 3
Toxicity at the maximum tolerated dose ($n = 63$; worst episode per patient was counted)

	NCI-CTC grade							
	1		2		3		4	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Haematological toxicity								
Leucopenia	1	(2)	5	(8)	35	(56)	20	(32)
Thrombocytopenia	37	(59)	10	(16)	5	(8)	0	(0)
Anaemia	24	(38)	30	(48)	5	(8)	0	(0)
Febrile neutropenia	0	(0)	0	(0)	8	(13)	0	(0)
Non-haematological toxicity								
Nausea/vomiting	26	(41)	20	(32)	5	(8)	0	(0)
Diarrhoea	21	(33)	24	(38)	7	(11)	0	(0)
Constipation	32	(51)	15	(24)	2	(3)	0	(0)
Stomatitis	15	(24)	29	(46)	17	(27)	0	(0)
Infection	15	(24)	18	(29)	5	(8)	0	(0)
Fatigue	8	(13)	33	(52)	19	(30)	3	(5)
Skin	27	(43)	3	(5)	4	(6)	0	(0)
Kidney	12	(19)	1	(2)	0	(0)	0	(0)
Liver	28	(44)	16	(25)	1	(2)	0	(0)
Lung	19	(30)	10	(16)	10	(16)	0	(0)
Heart	11	(18)	13	(21)	2	(3)	0	(0)
Neuropathy	36	(57)	8	(13)	1	(2)	0	(0)
Nail changes	22	(35)	4	(6)	0	(0)	0	(0)
Pain	28	(44)	22	(35)	4	(6)	0	(0)
Hypersensitivity	6	(10)	1	(2)	1	(2)	0	(0)
Fluid retention	43	(68)	8	(13)	2	(3)	0	(0)
Alopecia	0	(0)	0	(0)	63	(100)	0	(0)

NCI-CTC, National Cancer Institute Common Toxicity Criteria.

at level 3, 7/63 patients at MTD) yielding an overall pCR rate (pCR breast + pCR_{INV} breast) of 26% (95% CI, 16–36%). A pathological node-negative status was found in 55 patients (71%; 95% CI, 61–82%). No invasive tumour residuals in breast and axilla (pCR breast and axilla + pCR_{INV} breast) could be detected in 25% (95% CI, 15–34%) of patients. All patients proceeded to surgery and breast conservation was possible in 61 patients (79%); of these, nine had repeat excision to remove all viable tumour tissue.

Table 4
Clinical and pathological efficacy

Efficacy variable	Level 1 ($n = 3$)	Level 2 ($n = 4$)	Level 3 ($n = 7$)	Level 4 (MTD) + Phase II ($n = 63$)	Total ($n = 77$)	
	n	*n*	*n*	*n*	*n*	(%)
Clinical response[a]						
cCR	0	0	4	13	17	(22)
cPR	2	4	3	45	54	(70)
cCR + cPR	2	4	7	58	71	(92)
NC	1	0	0	5	6	(8)
Pathological response						
pT0	0	0	1	9	10	(13)
pTis	0	1	2	7	10	(13)
pN0	2	1	5	47	55	(71)
pCR + pCR_{INV} breast (pT0 + pTis)	0	1	3	16	20	(26)
pCR + pCR_{INV} breast + axilla [(pT0 or pTis) and pN0]	0	1	3	15	19	(25)
Breast-conserving surgery (with/without repeat excision)	2 (1/1)	2 (0/2)	5 (1/4)	52 (7/45)	61	(79)

cCR, clinical complete response; cPR, clinical partial response; NC, no change; pCR, pathological complete response, pCR_{INV}, pCR with only residual carinoma *in situ*.

[a] By ultrasound according to Response Evaluation Criteria in Solid Tumours (RECIST).

3.6. Predictors of pCR

Considering the 63 patients treated at MTD, the pCR rate was significantly higher in patients with ductal invasive carcinoma (30% versus 7% for non-ductal invasive carcinoma; $P < 0.001$), with overexpression of Ki-67 (71% versus 10% for patients without overexpression; $P < 0.001$) and HER2/neu (66% versus 7% for HER2/neu-negative tumours; $P < 0.001$), and low expression of Bcl-2 (29% versus 0% for patients with high expression; $P < 0.001$). The pCR rate was also higher in patients with ER-negative tumours (56% versus 12% for ER-positive tumours; $P < 0.001$), PgR-negative tumours (55% versus 10% for PgR-positive tumours; $P < 0.001$) and ER/PgR-negative tumours (63% versus 11% for ER/PgR-positive tumours; $P < 0.001$). Patients who had a PR after 2 cycles of GEDoc were significantly more likely to achieve pCR than those who did not (38% versus 5%, respectively; $P < 0.001$). Age, tumour size, clinical nodal status, grade and p53 expression were not found to be significant predictors of pCR.

4. Discussion

Several clinical trials strongly suggest pCR in the breast and axilla after preoperative chemotherapy for early breast cancer is associated with an excellent long-term prognosis [3]. Furthermore, it is apparent from several phase II studies that gemcitabine enhances the activity of taxanes and/or anthracyclines in the preoperative or palliative setting when given in two- or three-drug combinations. Overall clinical response rates consistently exceeded 90% in studies of preoperative gemcitabine/epirubicin [21] or gemcitabine/epirubicin/paclitaxel (GEPac) [22], and pCR rates were 17% (doublets) and 23% (triplets), respectively.

We demonstrate that epirubicin and docetaxel can be safely combined at doses of up to 90 and 75 mg/m^2, respectively, with a fixed dose of gemcitabine 800 mg/m^2 on days 1 and 8 of 3-week cycles given with filgrastim support. The overall clinical response rate was 92%, as assessed by ultrasound, breast-conserving surgery was possible in 79% of patients and the pCR rate across all dose levels was 26%. This pCR rate of GEDoc compares favourably with the best results reported from big trials evaluating new, highly active sequential anthracycline-taxane chemotherapy regimens in this setting.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial compared 4 cycles of doxorubicin/cyclophosphamide (AC) with 4 cycles AC followed by 4 cycles docetaxel (Doc) [8]. The pCR rate for the more active sequential regimen was 26%. Similarly, the pCR rate in the Geparduo trial ($4 \times AC \rightarrow 4 \times Doc$) was 22% for breast and 14% for breast and axilla [23]. The pCR rate for a regimen consisting of 3 cycles of epirubicin followed by 3 cycles of paclitaxel was 18% [5].

Most patients in this study tolerated the planned 6 cycles of GEDoc (88% of all patients and 89% of those treated at the MTD). Dose intensity, as measured by SDIP, ranged from 66–100% at MTD, with a median of 97% of the target SDIP value of 58 units. Contrasting with conventional measures, SDIP accounts not only for dose intensity, but for the cumulative dose of each drug in combination chemotherapy and for differences in drug activity. By comparison, conventional FAC chemotherapy 5-fluorouracil (5-FU 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2) given on day 1 3-weekly for 6 cycles is equivalent to 33 SDIP units. The high SDIP of 58 units achieved in this study with the GEDoc regimen over a relatively short treatment period of 18 weeks may therefore explain the superior pCR rate compared with traditional chemotherapy regimens used before the taxane era.

The high received dose intensity also results from the favourable toxicity profile of the GEDoc regimen. Toxicity was mainly haematological. Although leucopenia grade 3 and 4 occurred in one-half and one-third of patients, respectively, there were only 8 episodes of febrile neutropenia and five grade 3 infections. Anaemia, while relatively common, rarely exceeded grade 2, which may be attributed to our policy of offering erythropoietin to any patient as soon as anaemia worsened to grade 2. The most common severe non-haematological toxicities were alopecia (all patients) and fatigue, which reached grade 4 in three patients. No other grade 4 non-haematological toxicities were observed. Grade 3 adverse events other than fatigue and alopecia occurring in more than 10% of patients included stomatitis (27%), cough and/or dyspnoea (16%) and diarrhoea (11%). This toxicity profile is similar to that reported in other trials involving anthracycline-taxane containing regimens.

The identification of clinical and molecular predictors of pCR may help to tailor preoperative chemotherapy in early breast cancer. High nuclear or histological grade is consistently associated with a favourable response [24], while other reported associations for biomarkers vary across studies [25]. Achieving a pCR in this study was significantly associated with multiple patient and tumour characteristics including histology, hormone receptor status, the biological markers HER2, Ki-67 and Bcl-2, and the achievement of PR after 2 cycles of GEDoc. Unexpectedly, large tumour size, extensive nodal involvement and low grade were not significantly associated with a poor pCR rate. Although conceivably, some associations weaken with increasing activity of chemotherapy or are valid only for specific regimens or agents, it is more likely that the patient sample used in this study was too small to allow a reliable evaluation of predictive factors.

Considering the high pCR rate achieved with the GE-Doc regimen in this study, it seems worthwhile exploring new strategies to further increase the activity of this promising combination. As a dose-dense administration of chemotherapy in the adjuvant setting was associated with significantly improved relapse-free and overall survival compared with 3-weekly treatment [26], a subsequent phase I/II study has been initiated to evaluate the feasibility, MTD and activity of a dose-dense neoadjuvant protocol with gemcitabine, epirubicin and docetaxel.

Conflict of Interest Statement

A. Schneeweiss, J. Huober, D. Wallwiener and G. Bastert have spoken at meetings sponsored by pharmaceutical companies, including Eli Lilly and Aventis. Their departments have received research grants from pharmaceutical companies, including Eli Lilly and Aventis.

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