Phase II Trial of Combination of Pegylated Liposomal Doxorubicin, Cisplatin, and Infusional 5-Fluorouracil (CCF) Plus Trastuzumab as Preoperative Treatment for Locally Advanced and Inflammatory Breast Cancer

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Abstract

Background: Pegylated liposomal doxorubicin (PLD) was shown as active but less toxic compared to doxorubicin in advanced breast cancer. Given its low cardiotoxicity, the combination of PLD and trastuzumab appears most attractive in the treatment of human epidermal factor receptor 2 (HER2)-positive breast cancer. **Patients and Methods:** We investigated the activity of 8 courses of PLD in combination with cisplatin and infusional 5-fluorouracil (CCF) plus 3-week trastuzumab in patients with primary or recurrent cT2-T4 a-d, N0-3, M0 any estrogen receptor (ER), HER2-positive breast cancer. Patients with ER and/or progesterone receptor (PgR) ≥ 10% tumors received also letrozole (plus triptorelin if premenopausal). The principal endpoint was clinical response rate; secondary endpoints were the pathologic complete response rate (pCR) and the cardiac safety of the combination. **Results:** Thirty-two patients were enrolled in the study and all are evaluable for response and toxicity. Fifteen patients (47%) had ER-positive tumors, 15 patients and 2 patients had ER absent and ER poor tumors, respectively. Thirteen patients (41%) had inflammatory breast cancer (IBC) and 84% of patients had clinically positive nodes. A clinical response rate of 94% (95% CI, 79%-99%) and a pCR rate of 41% (95% CI, 24%-59%) were observed. Fifty-four percent of patients with IBC obtained a pCR. Eleven patients discontinued treatment before completing 8 courses as planned. No patient developed relevant cardiac toxicity. **Conclusion:** In this series of very locally advanced breast cancer, the combination of CCF and trastuzumab was very active obtaining an impressive rate of pCR, particularly in IBC, which merits further investigation in larger series.

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Introduction

Anthracyclines represent a key drug in the treatment of breast cancer at any stage.[1] However, the use of these agents is burdened by several acute side effects, most importantly, the risk of cardiac toxicity.[2] Because cardiac toxicity is dose dependent, it is recommended that the cumulative lifetime dose of conventional doxorubicin should not exceed 450 mg/m^2.[2,3] Pegylated liposomal doxorubicin (PLD, Caelyx®) is a formulation of doxorubicin in polyethylene glycol-coated liposomes with a prolonged circulation time and unique profile.[4] Pegylated liposomal doxorubicin's long circulation time seems to prevent the high peak concentration of anthracyclines, which has been associated with the increased risk of cardiotoxicity.[5] Pegylated liposomal doxorubicin was shown to have a much lower toxicity as compared to doxorubicin, in terms of cardiotoxicity, vesicant effects, nausea, vomiting, and alopecia.[6] In a phase III study, no significant difference in terms of response rate, disease-free survival (DFS),

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and overall survival (OS) was observed between PLD and doxorubicin as first-line therapy in patients with advanced breast cancer.[6] Anthracyclines represent the key drug for HER2-positive tumors,[7] but the concomitant administration of doxorubicin and trastuzumab was burdened by an unacceptable high rate of congestive heart failure (CHF) in advanced breast cancer.[8] Recent data have shown that the combination of anthracyclines and trastuzumab is feasible and highly active in locally advanced breast cancer[9] but data on long-term cardiac outcome are still lacking and the search for trastuzumab-containing regimens including drugs with a reduced cardiac risk is pursued. From a theoretical point of view, PLD represents an ideal drug maintaining the high clinical activity of an anthracycline while minimizing risk of cardiotoxicity.

In the current study, we investigated the activity of the combination of PLD with cisplatin and infusional 5-fluorouracil (CCF) as preoperative treatment in a population of patients with locally advanced (including inflammatory) primary and recurrent HER2-positive breast cancer. The rationale for investigating this regimen was based on a number of studies showing substantial activity for the combination of epirubicin, cisplatin, and infusional 5-fluoruracil (ECF) in the treatment of locally advanced operable and inoperable and metastatic breast cancer.[10-13] In addition, the combination of PLD and trastuzumab was proven active and safe in HER2-positive advanced breast cancer patients.[14-16] According to combination studies of PLD with gemcitabine, we chose a PLD dose of 25 mg/m^2 every 3 weeks.[17] No phase I trial was judged necessary before conducting a phase II trial.

Concomitant endocrine therapy with letrozole was administered to patients with ER and/or PgR ≥ 10% tumors. Although the combination of preoperative chemotherapy and endocrine therapy is not routinely used because of inconclusive results of previous studies,[18-21] some evidence of increased activity on proliferative rate observed in other studies suggests that an endocrine maneuver may be useful in estrogen receptor (ER)-positive tumors.[19,21] Premenopausal patients received letrozole in combination with a gonadotropin-releasing hormone (GnRH) analogue, according to our previous results showing the activity of this combination as preoperative therapy in premenopausal patients with ER-positive tumors.[22]

Patients and Methods

Patients with histologically confirmed primary T2-T4d N0-N3c M0 or M1 to the chest wall HER2 positive (IHC 3 + or HER2 amplification at FISH) any ER and PgR breast cancer and patients with locoregional recurrent rT1-T4a-d rN1-3, M0 or M1 to the chest wall HER2 positive any ER and PgR breast cancer consecutively admitted to the Department of Medicine were enrolled in the study. Either primary or recurrent breast cancer should be candidates to radical locoregional treatment to be eligible.

A Tru-cut biopsy was performed for diagnosis and for assessment of tumor biologic characteristics. Investigations (chest x-ray, abdomen ultrasound, bone scan, and/or fluorine-18 fluorodeoxyglucose positron emission tomography [FDG-PET]) were performed to exclude distant metastasis and blood tests were performed to assess bone marrow, renal, and hepatic function. Cardiac function was assessed at baseline by electrocardiogram and echocardiography. A left ventricular ejection fraction (LVEF) ≥ 55% and no impairment of ventricular kinesis were required for study enrollment.

Eligibility criteria also included Eastern Cooperative Oncology Group (ECOG) performance status 0-2, measurable lesions, patients' age between 18 and 75 years, white blood cells ≥ 3000/mm^3, platelets ≥ 100,000/mm^3, aspartate aminotransferase, alanine aminotransferase, ≤ 2.5 × upper limit of normal and bilirubin ≤ 1.5 mg/100 mL.

Written informed consent was obtained from all patients and the protocol was approved by the Ethical Committee.

Treatment

The CCF regimen containing PLD 25 mg/m^2 intravenous (I.V.) on day 1, cisplatin 60 mg/m^2 I.V. on day 1, and 5-fluorouracil 200 mg/m^2 as a continuous infusion from day 1 through day 21 to be repeated every 21 days for 8 courses plus trastuzumab (Herceptin®) at the loading dose of 8 mg/kg at the first administrations and 6 mg/kg for all of the following courses as I.V. infusion on day 2. Trastuzumab was provided at no cost by Roche Diagnostics International AG (Basel, Switzerland).

A central venous catheter (CVC) in the subclavian or in the jugular vein contralateral to the site of the tumor was implanted in all patients before starting chemotherapy.

Patients with ER and/or PgR ≥ 10% tumor received also endocrine therapy with letrozole 2.5 mg/day in combination with triptorelin in premenopausal patients. Letrozole started concomitantly with the first course of chemotherapy in postmenopausal patients. In premenopausal patients the GnRH analogue (triptorelin 3.75 mg 1 intramuscular every 28 days) started concomitantly with chemotherapy and letrozole was added when estradiol levels were in the postmenopausal range according to the European Institute of Oncology (EIO) laboratory reference values.

Sentinel node biopsy was offered to patients with clinically negative nodes (either by FDG- PET and/or ultrasound) at the end of chemotherapy irrespective of nodal status at diagnosis.

Radiation therapy was indicated in patients undergoing breast-conserving surgery and in patients with T4 tumors. Patients with recurrent tumors previously treated with radiation therapy on the breast were offered radiation therapy on supraclavicular nodes.

Response Criteria

Tumor was evaluated at baseline by physical measurement with caliper of the 2 largest diameters and by means of mammography and ultrasound. After 4 and 8 cycles, patients also had mammography and ultrasound breast examination to assess response. Clinical responses were evaluated according to both radiologic (breast ultrasound and/or mammography) and clinical evaluation, by measuring the largest diameters of the tumor, and were graded according to standard Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[23] In case of inflammatory breast tumors without a palpable mass, changes in clinically evaluable skin criteria (erythema, edema, peau d'orange) other than breast enlargement and tenderness were considered as response criteria.

Patients with stable disease, partial remission, or complete remission after 4 courses were candidates to receive 4 more courses of therapy.

Pathology

All patients had pathologic evaluation performed at diagnostic core biopsy and at final surgery at the EIO. Surgical specimens

were extensively sampled for the evaluation of residual tumor after primary chemotherapy. In cases where there was a lack of gross evidence of tumor, the quadrantectomy specimens were entirely blocked in paraffin and examined histologically, as were the tumor-bearing quadrants of the mastectomies. In the latter cases, the other quadrants were also thoroughly evaluated with the examination of at least 3 tissue blocks.

Pathologic complete remissions (pCR) were evaluated according to Kuerer et al. A pCR was defined as a total disappearance of invasive tumor either in the breast or in the axilla: the presence of intraductal carcinoma qualified for pCR.[24]

Estrogen receptor and PgR status, assessment of the proliferative activity (percent of Ki-67 stained cells) and overexpression of HER2 were determined on core biopsies obtained for diagnosis, as previously published.[25] The results were recorded as the percentage of immunoreactive cells over at least 2000 neoplastic cells. Steroid hormone receptors status was classified as negative, poor (ER, 1%-9% of the cells), or positive (ER and PgR, ≥ 10% of the cells). The value of Ki-67 labeling index was used as a cut-off in distinguishing tumors with low (< 20%) and high (≥ 20%) proliferative fraction. The value of 20% was selected based on previous data from our group indicating that this threshold significantly correlated with higher response rate to preoperative chemotherapy.[25] HER2 status was defined at immunohistochemistry (IHC) as negative (absent or faint and partial staining in > 10% of cells = 1+); and equivocal (faint and complete staining in > 10% of cells = 2+). In the latter cases, fluorescence in situ hybridization (FISH) was performed to assess the amplification of the *HER2* gene.

Criteria for Dose Modification

Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria for Adverse Events v3.0 (NCI-CTCAE 3). Cardiac toxicity was defined as the occurrence of symptomatic cardiac heart failure (CHF) associated with LVEF < 50% irrespective of decline from baseline LVEF; and decrease ≥ 20% from baseline LVEF value in asymptomatic patients.

Hematologic toxicity requiring a dose modification was defined as grade 4 neutropenia lasting > 7 days; febrile neutropenia; anemia and/or thrombocytopenia grade ≥ 3; grade 3 neutropenia; and grade 2 leukopenia at day 21.

In case of hematologic toxicity, the dosage of all chemotherapeutics was reduced by 25%. For subsequent cycles: any grade 3 or grade 4 hematologic toxicity noted during the course of treatment should be managed by a 25% dose reduction in the total amount of drug administered in each cycle after hematologic recovery.

For grade 2 nonhematologic drug-related toxicities, chemotherapy administration was delayed by 1 week and/or the responsible drug was reduced by 25%. In case of persistent grade ≥ 2 toxicity after drug reduction, treatment discontinuation was considered if surgery was feasible.

Statistical Considerations

The main objective of the study was to evaluate the rate of clinical response (partial and complete remission) after primary therapy with CCF plus trastuzumab. Secondary objectives were the rate of pCR and the safety of the combination.

Previous data on preoperative use of trastuzumab in combination with chemotherapy, have reported a response rate ranging from 50% to 95%.[26]

Considering a Simon's two-stage optimal design with a significance level of $\alpha = 0.10$ and $(1 - \beta) = 0.80$, using a two-sided χ^2 test, a total sample size of 31 patients was required in order to test the hypothesis of a maximum response rate of 60% for a poor treatment versus a minimum response rate of 80% for a good treatment.

Disease-free survival was defined as the length of time from the date of surgery to any relapse (including ipsilateral breast recurrence), the appearance of a second primary cancer (including contralateral breast cancer), or death. All analyses were performed with the SAS software version 8.02 (SAS, Cary, NC).

Results

From July 2007 to October 2008, 32 patients entered the study. All patients were evaluable for clinical response and toxicity. Table 1 summarizes the baseline patient and clinical characteristics.

Fifteen patients diagnosed with T4 breast cancer, 13 with T4d and 2 with T4b, were included in the study. In addition 84% of patients had clinically positive nodes. Almost half of the patients (47%) had ER-positive tumors and another 47% had ER absent tumors. Results are reported in Table 2.

Breast-conserving surgery and sentinel node biopsy were performed overall in 9 and 8 patients, respectively. However, breast conserving surgery was feasible in 56% of patients who had no T4 or recurrent tumors who were candidates to mastectomy irrespective of clinical response.

Overall, 4 patients (13%) and 26 patients (81%) obtained a complete and a partial response, respectively, with an overall clinical response rate of 94% (95% CI, 79%-99%); no patient progressed. Thirteen patients (41%, 95% CI, 24%-59%) obtained a pCR; in addition, 1 patient had only isolated tumor cells and 2 patients had pT1a residual tumor. The pCR rate was 33% and 47% in patients with HR-positive and HR-negative tumors, respectively. Seventy-four percent (95% CI, 59%-90%) of patients had negative nodes at surgery, although there were 84% who had clinical positive nodes before treatment.

Among the 13 T4d cancers, 7 patients obtained a pCR (54%, 95% CI, 27%-81%). In particular, 2 out of 6 HR-positive (33%), 4 out of 6 HR-negative (66%) and 1 out of 1 HR poor T4d tumors achieved a pCR (Table 3).

At a median follow-up of 24.5 months (range, 15-33 months) only 2 patients had experienced a disease recurrence. The 2-year DFS was 94% (95% CI, 77%-98%). Treatment was completed in 21 patients, 11 patients discontinued treatment before completion of 8 cycles, although only 7 grade > 2 nonhematologic toxicities were observed, 3 of them in the same patient (diarrhea, hand-foot syndrome, and deep venous thrombosis [DVT], all grade 3). Reasons for treatment discontinuation were: patient refusal (1 patient), port-a-cath–related complications (2 patients had deep vein thrombosis and 1 patient had malfunction of the device), chemotherapy related toxicity (grade 2 neurologic toxicity in 1 patient, hand-foot syndrome grade 2 in 1 patient, gastroenteric grade 2 toxicity in 1 patient, blood marrow toxicity in 3 patients), gastroenteric infection 1 patient (no documented *Clostridium difficilis* at biopsy).

Table 1 Patient and Tumor Characteristics at Baseline

Characteristic, n (%)	Value, CCF + T
Total Enrolled/Evaluable	32/32
Age, Years	
Median	47
Range	(28-69)
Menopausal Status	
Premenopausal	20
Postmenopausal	12
Type of Tumor	
Primary	31
Recurrent	1
Clinical Tumor Size	
T2	11 (34)
T3	6 (19)
T4b	2 (6)
T4d	13 (41)
Clinical Nodal Status	
Nx	
N0	5 (16)
N1	21 (66)
N2	3 (9)
N3	3 (9)
ER Status	
ER absent	16 (47)
ER 1%-9%	2 (6)
ER ≥ 10%	14 (47)
PgR Status	
PgR absent	21 (63)
PgR 1-9%	3 (9)
PgR ≥ 10%	8 (28)
Ki-67	
< 20%	0
≥ 20%	32
HER2 Status	
+ + +	31 (97)
+ +	1 (3)[a]
+	–
Negative	–

[a]FISH was positive for HER2/neu amplification.
Abbreviations: CCF = cisplatin, pegylated liposomal doxorubicin (Caelyx®) and infusional fluorouracil; ER = estrogen receptor; FISH = fluorescence in situ hybridization; HER2 = human epidermal factor receptor 2; PgR = progesterone receptor; T = trastuzumab

Table 2 Results

Efficacy Measure, n (%)	CCF + T
Evaluable Patients	32
Pathologic Complete Response	13 (41)
Clinical Response	
Complete	4 (13)
Partial	26 (81)
Stable disease	2 (6)
Progression	0
Type of Surgery	
Breast conserving surgery	9 (29)
Mastectomy	22 (71)

Abbreviations: CCF = cisplatin, pegylated liposomal doxorubicin (Caelyx®) and infusional fluorouracil; T = trastuzumab

Table 3 Pathologic and Clinical Response in Patients With T4d Tumor

Response	ER ≥ 10% (n = 6)	ER 1%-9% (n = 1)	ER Negative (n = 6)
pCR	2	1	4
OR	6	1	6
SD	0	0	0
PD	0	0	0

Abbreviations: ER = estrogen receptor; OR = objective response; pCR = pathologic complete response; PD = progressive disease; SD = stable disease

Among these patients, only 2 received 4 cycles or less because of the occurrence of DVT, 7 patients completed 6 cycles and 2 patients omitted only the last cycle. Among these 11 patients, we observed 3 pCR (1 in the patient who stopped treatment after 4 cycles), 1 patient with only isolated tumor cells in the breast and negative nodes, 1 patient with unmeasurable foci of invasive carcinoma within extensive fibrosis, 1 patient with pCR in the breast but residual node involvement, 3 patients with clinically positive nodes before therapy with residual tumor in the breast but negative lymph nodes and 2 patients with residual tumor both in the breast and in the axilla. The main grade ≥ 2 toxicities and grade 1 reported in ≥ 5% of patients are summarized in Table 4.

Cardiac function was evaluated by means of LVEF calculated with echocardiography at baseline and was monitored after 4 cycles and at the end of treatment or at any time in case of occurrence of cardiac symptoms.

Twenty-six patients had available measurement of LVEF at the end of trastuzumab. In 2 patients a LVEF decline ≥ 20% was observed but with an LVEF absolute value ≥ 50% and associated with no symptoms of CHF.

Discussion

Although the overall benefit of anthracyclines has been recently questioned, a number of studies and pooled analysis clearly show that the administration of anthracyclines containing chemotherapy is superior to CMF-like regimens in HER2-positive breast cancer.[27] However, in these patients, a concern is represented by the inclusion since early stages of disease of additional agents with potential cardiotoxicity as trastuzumab.[27]

The addition of trastuzumab to standard chemotherapeutic agents as preoperative treatment of HER2-positive breast cancer has yielded

a high rate of clinical and pathologic responses.[28] Recently, a large randomized trial has reported that the combination of anthracycline, taxanes, and trastuzumab impressively increased pathologic response rate and also improved event-free survival without significant cardiac toxicity.[9] Other studies with large numbers of patients have confirmed the feasibility of this combination in terms of short-term cardiac tolerability.[28-30] However, caveats on the concurrent administration of trastuzumab and doxorubicin raised by the high rate of cardiac toxicity observed in advanced disease (up to 27%) are not completely banished. Observations on long-term cardiac safety emerging from large adjuvant trials are still lacking and the combination is not still routinely recommended in clinical practice.

On the other hand, PLD, characterized by a low cardiotoxicity profile raises less concern when used in combination with trastuzumab.

The combination of PLD and trastuzumab has been investigated in small series of patients with advanced breast cancer showing substantial activity and no relevant cardiac effects.[14-16] As far as we are aware, the current study is the first report demonstrating high activity of the combination of PLD and trastuzumab in the neoadjuvant treatment of patients with locally advanced primary and recurrent HER2-positive breast cancer. We observed 94% of clinical responses and a pCR rate of 41%, which are similar to those reported with the combination of trastuzumab and conventional anthracyclines and taxanes.[9,28,29] In the largest randomized trial of preoperative trastuzumab, the NOAH (Neoadjuvant Herceptin®) trial, a longer treatment schedule including the concurrent administration of doxorubicin and paclitaxel, followed by paclitaxel and by CMF with or without trastuzumab yielded a pCR rate of 38%.[9]

It is worth of note that the large proportion of patients with inflammatory breast cancer included in the current study (13 of 32; 41%). Inflammatory breast cancer (IBC) represents a relatively infrequent subset of breast tumors (1%-6%) characterized by an hominis prognosis.[31] Although the prevalence of HER2-positive tumors are higher among inflammatory tumors (40%) than among other breast tumors, only small phase II studies and limited subsets of IBC within larger population of locally advanced tumors are available, preventing the definition of a standard preoperative approach for this subset of tumors.[31,32]

In our study, all patients with IBC achieved a clinical response and 53% had a pCR. Interestingly, these figures were comparable or even better than those observed in non-inflammatory locally advanced breast cancer. Although these results arise from a limited number of patients, they favorably compare in terms of clinical activity and of sample size with literature data available on HER2-positive IBC.[31] The only available data on a larger number of HER2-positive IBC derive from the NOAH study which included 62 patients with HER2-positive IBC. In the 31 patients receiving trastuzumab in addition to chemotherapy, a pCR rate of 55% was obtained.[33]

The unique pharmacokinetic profile of PLD may contribute to this finding.[4] Because of their small size (circa 100 nm) and long half-life in circulation, pegylated liposomes are able to penetrate the altered tumor vasculature, resulting in an enhanced delivery in the tumor site.[4] In Kaposi sarcoma PLD selectively accumulates in skin lesions 10- to 15-fold higher than in circulation.[34] Because increased angiogenesis has been documented in IBC,[35] we may thus speculate that in this subset of breast cancers the presence of dermal lymphatic involvement leading to a greater damage of vasculature may translate in an enhanced extravasation of liposomes other than a selective accumulation in the skin.

Table 4 Main Toxicities

Toxicity	CCF + T		
	Grade 1	Grade 2	Grade 3
Anemia	10 (31)	9 (28)	1 (3)
Leukopenia	7 (22)	10 (31)	3 (9)
Neutropenia	3 (9)	10 (31)	8 (25)
Nausea	12 (38)	16 (50)	1 (3)
Vomiting	8 (25)	11 (34)	1 (3)
Diarrhea	3 (9)	5 (16)	2 (6)
Sepsis	7 (22)	4 (13)	0
Mucositis	12 (38)	15 (47)	0
Hand-Foot Syndrome	7 (22)	20 (63)	2 (6)
Skin (Other) Folliculitis	0	1 (3)	0
Rash	0	3 (9)	0
Asthenia	12 (38)	7 (22)	1 (3)
Epigastralgia	3 (9)	6 (19)	0
Hypertension	0	1 (3)	0
DVT	0	0	2 (6)
Neurologic	7 (22)	3 (9)	0
Infection	0	2 (6)	0
Alopecia	6 (19)	0	0
Transaminitis	2 (6)	0	0
Hot Flashes	3 (9)	1 (3)	0
Arthralgia	8 (25)	0	0

No grade 4 toxicity was observed.
Abbreviations: CCF = cisplatin, pegylated liposomal doxorubicin (Caelyx®) and infusional fluorouracil; DVT = deep vein thrombosis; T = trastuzumab

Because either clinical response and pCR have been shown to be surrogate markers of outcome also for IBC, the striking clinical and pathologic response rate we observed may represent an encouraging step forward in the attempt to improve the hominous long-term prognosis for this tumor subset.[36] The result of a 2-year DFS of 94%, albeit encouraging considering the high risk of relapse of our study population, is too preliminary to draw conclusions on the long-term efficacy of our regimen. Importantly, no grade 4 toxicity was observed. Eleven patients did not complete the 8 cycles planned. Five patients discontinued treatment because of chemotherapy-related events whereas the majority of patients completed treatment as planned, although dose reduction was applied mostly in absence of a grade 3 toxicity because of poor patient compliance. The only frequent toxicity was palmar-plantar erythrodysesthesia. We observed a high rate of grade 2 (up to 63%) but only a 6% of G3 hand-foot syndrome, which is lower than that reported in other studies, and it was always reversible after treatment discontinuation.[5,6] The combination with infusional 5-fluorouracil may explain the high incidence of grade 1-2 cutaneous toxicity. No grade 2 alopecia was observed.

Most importantly no relevant cardiac toxicity was reported. Among the 26 patients with available LVEF at the end of trastuzumab, only 2 patients experienced a LVEF decline ≥ 20% but in both cases associated with LVEF absolute value ≥ 50% and with non symptoms of CHF. Both patients recovered rapidly after surgery and received postoperative trastuzumab without developing cardiac events. Different definitions of cardiac events among studies including the combination of PLD and trastuzumab prevent a comparison with our results, which are encouraging as compared to those obtained with conventional anthracyclines.[9,14-16]

Conclusion

The combination of CCF and trastuzumab was very active yielding similar results as the combination of standard anthracyclines/taxanes and trastuzumab in terms of either clinical responses or pCR in a population of very locally-advanced breast cancer and should be further evaluated in the preoperative treatment of HER2-positive breast cancer. The impressive rate of pCR observed in women with inflammatory breast cancers supports a peculiar role for this regimen in this tumor subset and merits further investigations in larger series of IBC.

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