in vivo *28*: 235-242 (2014)

Neoadjuvant Chemotherapy for Breast Cancer with Weekly *Nab*-paclitaxel Followed by Epirubicin and Cyclophosphamide – Results of a Case Series

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Abstract. *Background/Aim: To substitute paclitaxel in neoadjuvant chemotherapy of breast cancer by nab-paclitaxel due to its improved efficacy and safety profile. Patients and Methods: Sixteen patients with primary breast cancer received neoadjuvant chemotherapy with 4 cycles of nab-paclitaxel at 150 mg/m^2 (d1, 8, 15, every 28 days followed by 4 cycles of epirubicin at 90 mg/m^2 d1, every 21 days and cyclophophosphamide at 600 mg/m^2 (d1, every 21 days plus, if human epidermal growth factor receptor 2 (HER2)-positive, trastuzumab, and in 2 cases trastuzumab and lapatinib. End-points were the rate of pathological complete response (pCR) and safety. Results: All patients responded after two cycles. Overall, 11/16 patients had pathological complete response: 5/6 with HER2-positive, 3/4 with triple-negative and 3/6 with HER2-negative, hormone receptor-positive disease. Adverse events of grade 3 or more occurred in 4 patients. There were no grade 4 or 5 toxicities. The most frequent side-effects (all grades) were peripheral polyneuropathy (n=11, n=4 grade 2), fatigue (n=9) and hand-foot syndrome (n=8). Overall, side-effects were easily managed. Conclusion: Neoadjuvant chemotherapy with nab-paclitaxel is a good alternative to paclitaxel-based regimens.*

Neoadjuvant chemotherapy has become an established therapeutic option for patients with primary breast cancer. It can improve operability and the rate of breast-conserving surgery. Furthermore, neoadjuvant chemotherapy allows real-time evaluation of a patient's individual response to a specific regimen and facilitates individualization of therapy if no response occurs (1, 2). Several randomized trials suggest that neoadjuvant and adjuvant chemotherapy results in comparable progression-free and overall survival (1).

A pathological complete response (pCR) is the optimal outcome of neoadjuvant chemotherapy. According to the most conservative definition of pCR, no residual invasive or residual non-invasive disease in breast and axillary lymph nodes must be detectable. PCR is regarded as a predictive marker for a more favorable long-term prognosis (3). A meta-analysis of seven neoadjuvant trials showed that this does not apply to all intrinsic subtypes. There was a significant association between pCR and improved disease-free and overall survival for those with hormone receptor-negative, human epidermal growth factor receptor-2 (HER2)-negative and HER2-positive tumors (*i.e.* triple-negative and non-luminal HER2-positive subtype) and hormone receptor-positive poorly-differentiated tumors (*i.e.* luminal B/HER2-negative subtype) (3).

Clinical practice guidelines recommend taxane-based neoadjuvant chemotherapy, which is usually a sequence of 4 to 6 cycles of an anthracyline-based regimen followed by 4 cycles of a taxane-based regimen (4). However, there are also data for the reverse sequence. Neoadjuvant weekly paclitaxel followed by an anthracyline-based regimen resulted in a pCR rate of 28.2% (5). For HER2-positive tumors, the combination of trastuzumab and chemotherapy is the standard of care. Dual HER2-inhibition with lapatinib and trastuzumab can be indicated in individual cases (4).

The efficacy of taxanes is undisputed. However, the use of conventional taxanes is also limited by relevant side-effects that are caused by the solvents necessary due to their hydrophobicity (6-8).

Nab-paclitaxel is a solvent-free colloidal suspension of paclitaxel and human serum albumin. The *nab* platform binds hydrophobic drugs to albumin, thus eliminating the

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Key Words: Breast cancer, neoadjuvant chemotherapy, nab-paclitaxel.

need for toxic solvents. *Nab*-paclitaxel does not require for corticosteroid pre-medication and can be given as a short infusion over 30 min (9, 10). *Nab*-paclitaxel probably exploits the natural feature of albumin as a carrier protein and binds to the albumin-binding glycoprotein secreted protein rich in cysteine which is expressed on the surface of tumor cells and in the tumor stroma. A specific transport mechanism leads to a rapid uptake and to an increased accumulation of paclitaxel in tumor tissue (11-13).

Treatment of metastatic breast cancer with *nab*-paclitaxel (260 mg/m^2, d1 every three weeks) resulted in a significantly higher overall response rate and longer time-to-progression as compared to conventional solvent-based paclitaxel (175 mg/m^2, d1 every three weeks). Patients who received *nab*-paclitaxel as a second-line or further treatment had a significant overall survival benefit (9). As a first-line therapy, *nab*-paclitaxel (150 mg/m^2 d1, d8, d15, every four weeks) led to a higher overall response rate and a significantly longer progression-free survival compared to docetaxel (100 mg/m^2, d1 every three weeks) (14, 15). Overall, *nab*-paclitaxel was well-tolerated and led to a significantly lower incidence of neutropenia compared to paclitaxel and docetaxel. Sensory neuropathy grade 3 was more common with *nab*-paclitaxel compared to conventional paclitaxel (10% *vs*. 2%, respectively). However, it improved within a significantly shorter time with *nab*-paclitaxel compared to paclitaxel (22 *vs*. 79 days, respectively). There is also evidence from several phase II trials of *nab*-paclitaxel as a neoadjuvant therapy in various combinations (16-23).

Hence, due to its improved efficacy and safety profile for metastatic breast cancer, we decided to treat patients with *nab*-paclitaxel-based neoadjuvant chemotherapy. Here we report our experience with this regimen in 16 patients treated under our clinical practice since July 2011.

Patients and Methods

Patients. Patients were required to have histologically-confirmed primary breast cancer and an indication for chemotherapy. Each case was discussed at the multi-disciplinary tumor board of our Institution. Patients gave their informed consent regarding chemotherapy with *nab*-paclitaxel and documentation of their data.

Treatment. Patients received four cycles of *nab*-paclitaxel at a dose of 150 mg/m^2 on days 1, 8, 15 every 28 days followed by four cycles of epirubicin at a dose of 90 mg/m^2 and cyclophophosphamide at a dose of 600 mg/m^2 on day 1 every 21 days. Regarding the sequence of taxane, epirubicin and cyclophosphamide (EC), our regimen followed the experimental arm of the German GeparSepto trial (24).

One patient with a triple-negative tumor and an initial Ki-67 level of 90% received 5-fluorouracil in addition to EC as the presence of a *c-myc* amplicification was considered likely according to data recently published (25). Patients with a HER2-positive tumor received trastuzumab starting with the first dose of *nab*-paclitaxel. Trastuzumab was given at a starting dose of 4 mg/kg and at a dose of 2 mg/kg at subsequent weekly administrations during chemotherapy with *nab*-paclitaxel and every three weeks at a dose of 6 mg/kg during chemotherapy with EC. After surgery, trastuzumab was continued for a total treatment duration of 12 months. Two very young patients with HER2-positive, hormone receptor-negative and highly proliferative disease received dual HER2 inhibition with trastuzumab and lapatinib. Lapatinib was dosed at 750 to 1000 mg per day depending on the patients' tolerance.

Assessments. Following recently published data (26), a sentinel lymph node biopsy (SNB) was performed if there were no augmented lymph nodes, as assessed by palpation or ultrasound before the start of neoadjuvant chemotherapy. After every cycle of neoadjuvant chemotherapy with *nab*-paclitaxel and every two cycles of EC or at the end of chemotherapy, response was assessed by ultrasound. Patients underwent surgery after completion of neoadjuvant chemotherapy. Breast-conserving surgery with the objective of complete resection of the tumor and a cosmetically-satisfactory result was performed whenever possible. Response was defined as pCR if no residual tumor cells were detected in the breast and in the axillary lymph nodes. Side-effects were classified accordinto the common terminology criteria for adverse events (CTCAE) version 4.0 of the U.S. National Institutes of Health and National Cancer Institute.

Results

From July 2011 to October 2013, 16 patients with histologically-confirmed primary breast cancer completed neoadjuvant treatment and surgery. The median age at diagnosis was 47 (range=30-71) years. Tumor sizes ranged from 1.3 cm to 10.0 cm in diameter. A detailed overview of patient and tumor characteristics is given in Table I.

Neoadjuvant therapy. One patient received *nab*-paclitaxel at a dose of 100 mg/m^2 which she had requested in order to reduce the risk of sensory neuropathy. All other patients were treated at the planned dose of 150 mg/m^2 of *nab*-paclitaxel. There were no dose reductions for *nab*-paclitaxel. One patient with pre-existing disease of both eyes had an impairment of visual acuity after chemotherapy with *nab*-paclitaxel was completed. It was decided to omit further chemotherapy with EC and proceed to surgery instead.

In both patients receiving trastuzumab and lapatinib, the dose of lapatinib was reduced to 500 mg per day during the course of treatment due to continuing and treatment-related cutaneous side-effects. This dose was tolerated without further side-effects. Both patients had a clinical complete response after 4 cycles of *nab*-paclitaxel.

Response. After two cycles of *nab*-paclitaxel all patients showed a response which continued throughout neoadjuvant chemotherapy. An overview of outcome for each individual patient is given in Table I. 14 patients underwent breast-conserving surgery which was not feasible in two patients. Overall, 11 patients had pCR. pCR was seen in five out of six

Table I. *Patient and tumor characteristics, treatment administered and clinical outcome.*

Age (years)	TNM stage at baseline	Baseline immunohisto-chemistry	Neoadjuvant therapy	Clinical response after 4 cycles of *nab*-P	Surgery	TNM stage post-surgery	Response
HER2-positive subtype							
35	cT3, cN1, M0, G2-3	ER 20%, PRG 20%, HER2+, Ki67 30%	4 × *nab*-P, 4 × EC, plus T	PR	Mastectomy axillary dissection	ypT1mic, pTis (DCIS, 95%), pN0 (0/15), M0, G3, R0,	PR
43	cT1c, cN1, M0, G2	ER 10%, PRG 50%, HER2+, Ki67 50%	4 × *nab*-P, 4 × EC, plus T	CR	SNB*, BCT, axillary dissection	ypT0, ypN0 (1/12), M0, L0	pCR
33	cT2, cN0, M0, G2-3	ER 30%, PRG 20%, HER2+, Ki67 60%	4 × *nab*-P, 4 × EC, plus T and Lap	CR	SNB*, BCT, axillary dissection	ypT0, ypN0 (0/20), M0, L0, V0, R0	pCR
30	cT1c, cN1, M0, G3	ER 0%, PRG 0%, HER2+, Ki67 60%	4 × *nab*-P, 4 × EC, plus T and Lap	CR (confirmed by MRT)	BCT, axillary dissection	ypT0, ypN0 (0/9), M0, L0, V0	pCR
30	cT3, cN2, G3	ER 10%, PRG 5%, HER2+, Ki67 60%	4 ×*nab*-P, 4 × EC, plus T	PR	Mastectomy axillary dissection	ypT0, ypN0 (0/12), M0, V0, L0, R0	pCR
64	cT2, cN1, M0, G3	ER 5%, PRG 1%, HER2+, Ki67 60%	4 × *nab*-P (100 mg/m^2), 4 × EC, plus T	CR	BCT, SNB (Patient refused axillary dissection)	ypT0, ypN0 (0/1 sn), M0, G3, R0	pCR
Triple-negative subtype							
63	cT2, cN0, M0, G1, L1	ER 0%, PRG 0%, HER2–, Ki67 15%	4 × *nab*-P, 4 × EC	PR	SNB*, BCT	ypT1b, pN0 (0/2 sn), M0, G2, L0, V0, R0	PR
48	cT3, cN2, M0, G3	ER 0%, PRG 0%, HER2–, Ki67 30%	4 × *nab*-P, 4 × EC	PR	BCT, axillary dissection	ypT0, ypN0 (0/13), M0, L0, V0	pCR
44	cT2, cN0, M0, G3	ER 0%, PRG 0%, HER2–, Ki67 90%	4 × *nab*-P, 4 × FEC	PR	SNB*, BCT	ypT0, pN0 (0/10), M0, L0, V0, R0	pCR
32	cT2, cN1, M0, G3	ER 0%, PRG 0%, HER2–, Ki67 90%	4 × *nab*-P, 4 × FEC	CR	BCT, axillary dissection	ypT0, ypN0 (0/16), M0, L0, V0	pCR
HER2-negative subtype							
33	cT1c, cN0, M0, G2	ER 90%, PRG 10%, HER2–, Ki67 20%	4 × *nab*-P, 4 × EC	SD	SNB*, BCT,	ypT1a, pN0 (0/2 sn), M0, G2, L0, V0, R0	PR
58	cT2, cN0, M0, G3	ER 95%, PRG 95%, HER2–, Ki67 25%	4 × *nab*-P, no further CHT due to impairment in visual acuity	CR	SNB*, BCT	ypT1a, pN0 (0/11), M0, G3, L0, V0. R0	PR
71	cT2, cNx, M0, G2	ER 0%, PRG 5%, HER2–, Ki67 30%	4 × nab-P, 4 × EC	PR	SNB*, BCT, axillary dissection	ypT2, ypN0 (0/11), M0, G3, V0, L1, R0	PR
65	cT2, cN1a, M0, G2-3	ER 5%, PRG 15%, HER2–, Ki67 40%	4 × nab-P, 4 × EC	PR	BCT, axillary dissection	ypT0, ypN0 (0/10), M0, L0, V0	pCR
37	cT2, cN1, M1 (liver), G2-3	ER 70%, PRG 80%, HER2–, Ki67 60%	4 × nab-P, 4 × EC	PR	BCT, axillary dissection	ypT0, ypN0 (0/12), Mx (hepatic lesions no longer detectable), V0, L0	pCR
71	cT2, cN0, M0, G2-3	ER 5%, PRG 0%, HER2–, Ki67 80%	4 × nab-P, 4 × EC	PR	SNB*, BCT	ypT0, pN0 (0/6 sn), M0, L0, V0	pCR

Nab-P: Nab-paclitaxel, E: epirubicin, C: cyclophosphamide, T: trastuzumab, Lap: lapatinib, CR: complete response, CHT: chemotherapy, PR: partial response, pCR: pathological complete response, SNB: sentinel lymph node biopsy, *SNB: before neoadjuvant chemotherapy, BCT: breast conserving therapy, ER: estrogen receptor expression, PRG: progesteron receptor expression.

patients with HER2-positive disease, in three out of four patients with a triple-negative tumor, and in three out of six patients with HER2-negative, hormone receptor-positive disease.

There was more than a 50% decrease in the size of the breast tumor and no detectable residual tumor cells in axillary lymph nodes in all five patients who did not have pCR. This included the patient where chemotherapy with EC was omitted. In four out of the five cases the Ki-67 levels clearly decreased.

One patient with an initially triple-negative tumor of 26 mm showed an unexpected poor response which resulted in a residual tumor of 9 mm in size. Immunohistochemistry of the first biopsy was not carried out in our pathology. The examination of the surgically-removed tissue showed a highly hormone receptor-positive and HER2-negative tumor, which seems to explain the poor response.

Side-effects. Overall, the side-effects of neoadjuvant chemotherapy were easy to manage. Table II provides an overview of the incidence of all adverse events.

The most frequent adverse events of all grades were hand-foot-syndrome (8/16), fatigue (9/16) and peripheral neuropathy (11/16). There were no grade 4 or 5 toxicities. Grade 3 adverse events were documented for 4 patients. The earliest cases of fatigue were seen in the late second cycle but in most cases fatigue occurred during the third cycle with *nab*-paclitaxel and improved subsequently during chemotherapy with EC.

Overall, 11 out of 16 patients experienced sensory polyneuropathy until the end of chemotherapy with *nab*-paclitaxel. In seven patients polyneuropathy was of grade 1 and presented as a slight numbness of the fingertips. In four patients the maximum intensity of polyneuropathy was of grade 2. There was no polyneuropathy of grade 3 or higher. In all cases, polyneuropathy improved until the end of chemotherapy with EC and was no longer present after surgery except for one patient. This patient had been pre-treated with six cycles of solvent-based paclitaxel and carboplatin a few years earlier due to a diagnosis of ovarian cancer.

Two patients developed hyperopia during therapy with *nab*-paclitaxel which resolved completely after the end of treatment.

Hematotoxicity under neoadjuvant chemotherapy with *nab*-paclitaxel and EC was mild. Leukopenia occurred in 13/16 and was predominantly grade 1. Leukopenia grade 2 occurred in 6/16. The administration of growth factors was not clinically indicated. There was no hematotoxicity of grade 3 or more.

Table II. *Adverse events experienced during neoadjuvant therapy. Adverse events are reported per patient. The highest grade observed in a patient is given.*

Adverse event	All grades N (%)	Grade 3 N (%)	Grade 4 N (%)
Non-hematological			
Sensory polyneuropathy	11 (69%): 7 (44%) Grade 1, 4 (25%) Grade 2	0 (0%)	0 (0%)
Fatigue	9 (56%)	4 (25%)	0 (0%)
Hand-foot syndrome	8 (50%)	0 (0%)	0 (0%)
Nausea	12 (75%)	0 (0%)	0 (0%)
Mucositis	6 (38%)	0 (0%)	0 (0%)
Hematological			
Leukopenia	13 (81%)	0 (0%)	0 (0%)
Anemia	4 (25%)	0 (0%)	0 (0%)

Discussion

In our series of 16 cases, neoadjuvant chemotherapy with 4 cycles of *nab*-paclitaxel followed by 4 cycles of EC in combination with HER2-targeted treatment for HER2-positive disease proved to be an effective and manageable therapeutic option.

The clinical results achieved with our neoadjuvant therapy are comparable to those reported for neoadjuvant standard regimens in the literature, although we do admit that comparisons between experiences from individual cases and data from controlled clinical studies have limitations. Overall, the pCR rate in our patients was 11/16, 5/6 in patients with HER2-positive disease and 3/6 in those with HER2-negative, hormone receptor-positive disease. These pCR rates are similar to those achieved with neoadjuvant standard regimens including docetaxel or weekly paclitaxel (1). PCR rates of 40% have been published for conventional neoadjuvant chemotherapy in hormone receptor-negative disease. For HER2-positive disease, pCR rates of up to 65% have been reported for neoadjuvant chemotherapies in combination with HER2-targeted therapies (1). According to a meta-analysis of 30 neoadjuvant studies with a total of 11,695 patients, neoadjuvant therapy results in pCR in 8.3% of patients with HER2-negative hormone receptor-positive disease, in 18.7% of HER2-positive hormone receptor-positive, in 38.9% of HER2-positive hormone receptor-negative, and in 31.1% of those with triple-negative disease (27).

In a phase II study conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), 66 patients with locally advanced breast cancer were treated with neoadjuvant *nab*-paclitaxel at a dose of 100 mg/m^2 once a week for 12 weeks followed by 4 cycles of 5-fluorouracil, epirubicin and cyclophosphamide (FEC). A total of 17 out of 19 patients with HER2-positive disease received trastuzumab in addition. Overall, treatment resulted in pCR in 29% of patients and in 58% of patients in the HER2-positive sub-group (23).

If breast-conserving surgery or a better cosmetic result are the treatment objectives, neoadjuvant chemotherapy can be indicated in luminal low-risk and luminal high-risk subtypes despite reported low pCR rates and no proven correlation of

pCR and overall survival for patients with luminal low-risk tumors. In our series, three out of the six patients with HER2-negative hormone receptor-positive carcinoma had a pCR. These patients had the lowest expression of hormone receptors and the highest Ki-67 levels. Breast-conserving surgery was possible for all of 6 patients.

Overall, side-effects were easily managed. They rarely resulted in a delay of therapy. Fatigue was the side-effect that mostly limited the quality of life of those affected. Hematotoxicity was mild. Leukopenia occurred in 13 patients, yet none was of grade 3 or more. Moreover, we saw no febrile neutropenia. In the NSABP study cited, neoadjuvant *nab*-paclitaxel was associated with incidences of grade 2 neutropenia of 6%, of grade 3 neutropenia of 5% and grade 3 febrile neutropenia of 2%. Under neoadjuvant FEC, incidences of grade 2, 3 and 4 neutropenia were 8%, 15% and 16%, respectively, and incidences of grade 3 and grade 4 febrile neutropenia were 2% and 5%, respectively (23).

Neuropathy that occurred in our case series with 4 neoadjuvant cycles of *nab*-paclitaxel was of lower severity than neuropathy that has been reported with *nab*-paclitaxel in the treatment of metastatic breast cancer. This correlates with the pathophysiology of sensory polyneuropathy as a toxicity occurring more frequently and with a higher intensity with cumulative doses. In the study of *nab*-paclitaxel in metastatic breast cancer reported by Gradishar *et al*. the dose administered was 150 mg/m^2 once a week in three out of four weeks and the median number of cycles was ten. Grade 3 neuropathy occurred in 22% of patients (14). In the neoadjuvant study reported by the NSABP patients received 12 weekly administrations of *nab*-paclitaxel at 100 mg/m^2. The incidences of grade 2 and grade 3 neuropathy were 11% and 5%, respectively (23).

Vision disorders have been reported for *nab*-paclitaxel in the literature. However, these were associated with cystoid macular edema (28, 29). It is unclear if this caused the temporary changes in visual acuity presenting as hyperopia in two of our patients.

Following recently published evidence (30) we treated two young patients with HER2-positive disease and high Ki-67 levels at baseline with dual HER2 inhibition. The additional therapy with lapatinib was managed clinically. However, cutaneous side-effects prompted a dose reduction to 500 mg per day. This was also the reason why we decided to stop lapatinib treatment when clinical complete response had been detected.

Due to the small patient number, we cannot draw any conclusion as to what extent lapatinib contributed to the clinical outcome. Yet the results of studies in the neoaodjuvant and the first-line setting seem to confirm the clinical benefit of dual HER2 inhibition (31-33).

The handling of *nab*-paclitaxel is much easier than that of conventional solvent-based paclitaxel. *Nab*-paclitaxel does not require for any corticosteroid medication and can be given as a short infusion over 30 min. In our case series, *nab*-paclitaxel was very effective and well-tolerated. Based on our experience, we regard neoadjuvant chemotherapy with *nab*-paclitaxel as a valuable alternative for regimens based on conventional solvent-based paclitaxel. The ongoing German GeparSepto trial with an expected total of ~1,200 patients to be enrolled compares 12 weekly *nab*-paclitaxel to 12 weekly paclitaxel administrations both followed by 4 cycles of EC. It will provide randomized evidence on the more appropriate taxane to be used in neoadjuvant chemotherapy. First results are expected in 2014 (24).

Disclosure

The Authors received editorial support in the preparation of this manuscript from Dr. Susanne Hell, funded by Celgene Corporation. The Authors are fully-responsible for all content and editorial decisions for this manuscript.

References

1 Huober J and von Minckwitz G: Neoadjuvant therapy – What have we achieved in the last 20 years. Breast Care *6*: 419-426, 2011.

2 Von Minckwitz G, Untch M and Loibl S: Update on neoadjuvant/preoperative therapy of breast cancer: experiences from the German Breast Group. Curr Opin Obstet Gynecol *25*: 66-73, 2013.

3 Von Minckwitz G, Untch M, Blohmer JU, Cost SD, Eidtmann H, Fasching PA, Gerber B, Eiermann W, Hilfrich J, Huober J, Jackisch C, Kaufmann M, Konecny GE, Denkert C, Nekliudova V, Mehta K and Loibl S: Definition and impact of pathological complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes, J Clin Oncol *30*: 1796-1804, 2012.

4 Arbeitsgemeinschaft Gynäkologische Onkologie (AGO), Guidelines Breast, version 2013.1, available at http://www.ago-online.de/index.php?lang=de&site=mamma_guide_topical&topic=mamma_guide, last accessed on January 27th 2014

5 Green MC, Buzdar AU, Smith T, Ibrahim NK, Valero V, Rosales MF, Cristofanilli M, Booser DJ, Pusztai L, Rivera E, Theriault RL, Carter C, Frye D, Hunt KK, Symmans WF, Strom EA, Sahin AA, Sikov W and Hortobagyi GN: Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every three weeks. J Clin Oncol *23*: 5983-5992, 2005.

6 Authier N, Gillet JP, Fialip J, Eschalier A and Coudore F: Assessment of neurotoxicity following repeated cremophor/ethanol injections in rats. Neurotox *3*: 563-564, 2001.

7 Ten Tije AJ, Verweij J, Loos WJ and Sparreboom A: Pharmacological effects of formulation vehicles: Implications for cancer chemotherapy. Clinical Pharmacokinetics *42*: 665-668, 2003.

8 Alex Sparreboom,1 Lia van Zuylen, Eric Brouwer, Walter J. Loos, Peter de Bruijn, Hans Gelderblom, Marrimuthoo Pillay, Kees Nooter, Gerrit Stoter, and Jaap Verweij: Cremophor EL-mediated alteration of paclitaxel distribution in human blood: Clinical pharmacokinetic implications. Cancer Res *59*: 1454-1457, 1999.

9 Nyman DW, Campbell KJ, Hersh E, Long K, Richardson K, Trieu V, Desai N, Hawkins MJ and von Hoff DD: Phase I and pharmacokinetics trial of ABI-007, a novel nanoparticle formulation of paclitaxel in patients with advanced nonhematologic malignancies. J Clin Oncol *23*: 7785-7793, 2005.

10 Gradishar W, Tjulandin S, Davidson N, Ahaw H, Desai N, Bhar P, Hawkins M, and O'Shaughnessy J: Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol *23*: 7794-7803, 2005.

11 Desai N, Trieu V, Yao Z, Louie L, Ci S, Yang A, Tao C, De T, Beals B, Dykes D, Noker P, Yao R, Labao E, Hawkins M and Soon-Shiong P: Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. Clin Cancer Res *12*: 1317-1324, 2006.

12 Vogel SM, Minshall RD, Pilipovic M, Tiruppathi C and Malik AB: Albumin uptake and transcytosis in endothelial cells in vivo induced by albumin-binding protein. Am J Physiol Lung Cell Mol Physiol *281*: L1512-L1522, 2001.

13 Trieu V, Frankel T, Labao E, Soon-Shiong P and Desai N: SPARC expression in breast tumors may correlate to increased tumor distribution of paclitaxel albumin nanoparticles (ABI-007) *vs*. taxol, Proc Amer Assoc Cancer Res *46*: abstract 5584, 2005.

14 Gradishar W, Krasnojon D, Ceporpv S, Makhson AN, Manikhas GM, Clawson A and Bhar P: Significantly longer progression-free survival with *nab*-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. J Clin Oncol *27*: 3611-3619, 2009.

15 Gradishar WJ, Krasnojon D, Cheporov S, Makhson AN, Manikhas GM, Clawson A, Bhar P, McGuire JR and Iglesias J: Phase II trial of *nab*-paclitaxel compared with docetaxel as first-line chemotherapy in patients with metastatic breast cancer: Final analysis of overall survival. Clin Breast Cancer *12*: 313-321, 2012.

16 Yardley DA, Raefsky E, Castillo R, Lahiry A, LoCicero R, Thompson D, Shastry M, Trieu V, Knauer D and Desai N: Results of a multicenter pilot study of weekly *nab*-paclitaxel, carboplatin with bevacizumab, and trastuzumab as neoadjuvant therapy in HER2+ locally advanced breast cancer with SPARC correlatives. J Clin Oncol *27*: 15s (suppl.) abstract 527, 2009.

17 Yardley DA, Daniel BR, Inhorn RC, Vazquez ER, Trieu VN, Motamed K, Hwang L, Rugo HS and Desai N: SPARC microenvironment signature (SMS) analysis of a phase II trial of neoadjuvant gemcitabine (G), epirubicin (E), and *nab*-paclitaxel (nab-P) in locally advanced breast cancer (LABC). J Clin Oncol *28*: 15s (suppl.) abstract 10574, 2010.

18 Yardley DA, Raefsky E, Castillo R, Lahiry A, LoCicero R, Thompson D, Shastry M, Burris HA 3rd and Hainsworth JD: Phase II study of neoadjuvant weekly *nab*-paclitaxel and carboplatin, with bevacizumab and trastuzumab, as treatment for women with locally advanced HER2+ breast cancer. Clin Breast Cancer *11*: 297-305, 2011.

19 Snider JN, Allen JW, Young R, Schwartzberg L, Javed Y, Jahanzeb M and Sachdev JC: Neoadjuvant bevacizumab with weekly nanoparticel albumin bound (nab)-paclitaxel plus carboplatin followed by doxorubicin plus cyclophosphamide (AC) for triple-negative breast cancer, Cancer Research *72(24 Suppl)*: Abstract OT3-3-07, 2012

20 Sinclair NF, Abu-Khalaf MM, Rizack T, Rosati K, Chung G, Legare RD, DiGiovanna M, Fenton MA, Bossuyt V, Strenger R, Sakr BJ, Lannin DR, Gass JS, Harris L, and Sikov WM: Neoadjuvant weekly *nab*-paclitaxel (wA), carboplatin (Cb) plus bevacizumab (B) with or without dose-dense doxorubicin-cyclophosphamide (ddAC) plus B in ER+/HER2-negative (HR+) and triple-negative (TN) breast cancer (BrCa): A BrUOG study. J Clin Oncol *30(suppl)*: Abstract 1045, 2012.

21 Shinde AM, Yim JH, Kruper L, Vito C, Chen SL, Paz IB, Luu TH, Tagawa T, Yu KW, Wilczynski S, Shaw S, Vora L, Park JM and Somlo G: Pathologic complete response rates observed in women with locally advanced and inflammatory breast cancer receiving neoadjuvant carboplatin and paclitaxel. J Clin Oncol *30(Suppl)*: Abstract 1035, 2012.

22 Kaklamani VG, Siziopikou K, Scholtens D, Lacouture M, Gordon J, Uthe R, Meservey C, Hansen, Khan SA, Jeruss JS, Bethke K, Cianfrocca M, Rosen S, Von Roenn J, Wayne J, Parimi V, Jovanovic B and Gradishar W: Pilot neoadjuvant trial in HER2 positive breast cancer with combination of *nab*-paclitaxel and lapatinib. Breast Cancer Res Treat *132*: 833-842, 2012.

23 Robidoux A, Buzdar AU, Quinaux E, Jacobs S, Rastogi P, Fourchotte V, Younan RJ, Pajon ER, Shalaby IA, Desai AM, Fehrenbacher L, Geyer CE Jr., Mamounas EP and Wolmark N: A phase II neoadjuvant trial of sequential nanoparticle albumin-bound paclitaxel followed by 5-fluorouracil/epirubicin/cyclophosphamide in locally advanced breast cancer. Clin Breast Cancer *10*: 81-86, 2010.

24 Untch M, Jackisch C, Blohmer JU, Costa SD, Denkert C, Eidtmann H, Gerber B, Hanusch C, Hilfrich J, Huober J, Kuemmel S, Schneeweiss A, Paepke S, Loibl S, Nekljudova V and von Minckwitz G: A randomized phase III trial comparing nanoparticle-based paclitaxel with solvent-based paclitaxel as part of neoadjuvant chemotherapy for patients with early breast cancer (GeparSepto) GBG 69, Cancer Res *72(24 Suppl)*: abstract OT3-3-11, 2012.

25 Rakha E, El-Sayed ME, Green AR, Lee AHS, Robertson JS and Ellis I: Prognostic markers in triple-negative breast cancer, Cancer *109*: 25-32, 2007.

26 Kuehn T, Bauerfeind IGP, Fehm T, Fleige B, Helms G, Lebeau A, Liedtke C,von Minckwitz G, Nekljudova V, Schrenk P, Staebler A and Untch M: Sentinel lymph node biopsy before or after neoadjuvant chemotherapy – Final results from the prospective German, multiinstitutional SENTINA trial, Cancer Research *72(24 Suppl)*: Abstract S2-2, 2012

27 Houssami N, Macaskill P, von Minckwitz G, Marinovich ML and Mamounas E: Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy, Eur J Cancer *48*: 3342-3354, 2012.

28 European Medicines Agency (EMA), Abraxane: EPAR - product information, last updated January 2013, available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000778/WC500020435.pdf, last accessed on January 27th, 2014

29 Tanaka Y, Bando H, Hara H, Ito Y and Okamoto Y: Cystoid macular edema induced by *nab*-paclitaxel. Breast Cancer 2012 May 17, epub ahead of print.

30 Baselga J, Bradbury I, Eidtmann H, Di Cosimo S, de Azambuja E, Aura C, Gómez H, Dinh P, Fauria K, van Dooren V, Aktan G, Goldhirsch A, Chang TW, Horváth, Coccia-Portugal M, Domont

J, Tseng LM, Kunz G, Sohn JH, Semiglazov V, Lerzo G, Palacova M, Probachai V, Pusztai L, Untch M, Gelber RD, Piccart-Gebhart M, on behalf of the NeoALTTO Study Team, Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase III trial. Lancet *379*: 633-640, 2012.

31 Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, Lluch A, Staroslawska E, de la Haba-Rodriguez J, Im SA, Pedrini JL, Poirier B, Morandi P, Semiglazov V, Srimuninnimit V, Bianchi G, Szado T, Ratnayake J, Ross G and Valagussa P: Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase II trial, Lancet Oncol *13*: 25-32, 2012.

32 Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, Roman L, Pedrini JL, Pienkowski T, Knott A, Clark E, Benyunes MC, Ross G and Swain SM, for the CLEOPATRA Study Group, Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med *366*: 109-119, 2012.

33 O'Regan R, Ozguroglu M, Andre F, Toi M, Jerusalem GHM, Wilks S, Isaacs C, Xu B, Masuda N, Arena FP, Yardley DA, Yap YS, Mukhopadhyay P, Douma S, El-Hashimy M, Taran T, Sahmoud T, Lebwohl DE and Gianni L, Phase III, randomized, double-blind, placebo-controlled multicenter trial of daily everolimus plus weekly trastuzumab and vinorelbine in trastuzumab-resistant, advanced breast cancer (BOLERO-3). J Clin Oncol *31(suppl)*: Abstract 505, 2013.

Received November 8, 2013
Revised January 30, 2014
Accepted February 3, 2014