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REVIEW

Neoadjuvant *nab*-paclitaxel in the treatment of breast cancer

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Abstract Neoadjuvant chemotherapy has the advantage of converting unresectable breast tumors to resectable tumors and allowing more conservative surgery in some mastectomy candidates. Chemotherapy agents, including taxanes, which are recommended in the adjuvant setting, are also considered in the neoadjuvant setting. Here, we review studies of *nab*-paclitaxel as a neoadjuvant treatment for patients with breast cancer. PubMed and conference or congress proceedings were searched for clinical studies of *nab*-paclitaxel in the neoadjuvant treatment of breast cancer. We also searched ClinicalTrials.gov for ongoing trials of *nab*-paclitaxel as a neoadjuvant agent in breast cancer. Twenty studies of *nab*-paclitaxel in the neoadjuvant setting were identified. In addition to reviewing key efficacy and safety data, we discuss how each trial assessed response, focusing on pathologic complete response and residual cancer burden scoring. Safety profiles are also reviewed. *nab*-Paclitaxel demonstrated antitumor activity and an acceptable safety profile in the neoadjuvant treatment of breast cancer. Ongoing and future trials will further evaluate preoperative *nab*-paclitaxel in breast cancer, including in combination with many novel immunological targeted therapies.

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Background

Introduction to neoadjuvant therapy

Breast cancer remains one of the most commonly diagnosed cancers in the United States, representing 29 % of annual cancer diagnoses in women [1]. More than 200,000 new cases of invasive breast cancer, with approximately 40,000 related deaths, were expected in 2015 [1]. The 5-year survival rate for all stages of breast cancer combined is 89 % [1]. However, patients with localized breast cancer have a higher 5-year survival rate of 99 % compared with those with regional disease in the axillary lymph nodes, which confers a 5-year survival rate of 85 % [1]. Metastatic dissemination further reduces 5-year survival rates to 25 % [1].

Surgery with the goal of removing the primary tumor and achieving negative tumor margins is the primary therapeutic approach for minimizing risk of recurrence and increasing survival of patients with early-stage breast cancer. Chemotherapy before surgery, or neoadjuvant chemotherapy, helps convert large, unresectable tumors to resectable tumors [2, 3]. In addition, neoadjuvant therapies can shrink operable tumors, allowing breast-conserving surgery to be performed instead of mastectomy [2, 3]. Regional disease may also be decreased with the use of sentinel lymph node biopsy, potentially reducing the need for axillary lymph node dissection [4].

In addition to treatment benefits, neoadjuvant studies provide valuable tissue samples for biomarker evaluation. Because loco-regional responses to neoadjuvant therapies

correlate with long-term outcomes, neoadjuvant therapies also offer unique opportunities for early prediction of responses and individualization of treatment.

Using pathologic complete response (pCR) and residual cancer burden (RCB) as endpoints in neoadjuvant studies

The US Food and Drug Administration (FDA) supports pCR as an endpoint for evaluating new neoadjuvant agents for high-risk, early-stage breast cancer [5, 6]. pCR is defined by the FDA as the "absence of residual invasive cancer in the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0/Tis ypN0 in the current AJCC staging system)" or "absence of the residual invasive and in situ cancers in the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0ypN0)" [6]. In a large FDA-led meta-analysis, pCR defined as ypT0/isypN0 or ypT0ypN0 was more closely associated with improved survival compared with ypT0/is (defined as absence of invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement) [3, 5]. It is important to note that, according to the FDA, "high risk" specifically refers to "patients with early-stage breast cancer who have a high risk of distant disease recurrence and death despite use of optimal modern local and systemic adjuvant therapy" [6]. Inclusion of patients with low-grade, hormone receptor (HR)-positive tumors in neoadjuvant breast cancer trials using pCR as an endpoint is not recommended by the FDA; these patients generally have better long-term outcomes compared with patients with high-risk disease.

RCB also measures response to neoadjuvant agents [7]. RCB was initially devised to address the oversimplified dichotomized pCR data and is derived from the dimensions of the primary tumor, cellularity of the tumor bed, and axillary node burden. Although RCB is not routinely assessed in clinical trials, this measurement was used in some of the studies reviewed here.

Chemotherapy in the neoadjuvant setting

Neoadjuvant versus adjuvant treatment with doxorubicin and cyclophosphamide (AC) was first compared in operable breast cancer in NSABP B-18 [8]. No significant differences in overall survival (OS; 55 % for both groups; $P = 0.90$) or disease-free survival (DFS; 42 vs 39 %; $P = 0.27$) were found after 16 years of follow-up. However, neoadjuvant AC reduced node-positive disease, with a significantly increased percentage of negative axillary nodes (58 vs 42 %; $P < 0.0001$) and increased frequency of breast-conserving surgery (68 vs 60 %; $P = 0.001$) [8]. EORTC trial 10902 also found no differences in 10-year OS (64 vs 66 %; hazard ratio [HR] = 1.09; 95 % CI 0.83–1.42; $P = 0.54$) or DFS (48 vs 50 %; HR = 1.12; 95 % CI 0.90–1.39; $P = 0.30$) after preoperative vs postoperative chemotherapy (fluorouracil, epirubicin, and cyclophosphamide [FEC]) [9]. However, as reported by the phase III European Cooperative Trial in Operable Breast Cancer (ECTO), neoadjuvant vs adjuvant paclitaxelplus doxorubicin, followed by cyclophosphamide, methotrexate, and fluorouracil (AT → CMF) significantly increased the incidence of lumpectomy (63 vs 34 %; $P < 0.001$) despite no change in OS (HR = 1.10; $P = 0.60$) [10].

pCR was significantly correlated with DFS in the NSABP B-18 trial (HR = 0.47; $P < 0.0001$) or OS (HR = 0.32; $P < 0.0001$) [8], suggesting that pCR after neoadjuvant treatment may predict favorable long-term outcome. A meta-analysis conducted by the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC), which included approximately 12,000 patients in 12 randomized trials, confirmed better long-term outcomes in patients who achieved pCR (HR = 0.36; 95 % CI 0.31–0.42) [3]. In addition, the TECHNO trial of neoadjuvant trastuzumab plus chemotherapy for human epidermal growth factor receptor 2 (HER2)-positive (+) breast cancer showed a correlation between pCR and improved DFS (HR = 2.5; 95 % CI 1.2–5.1; $P = 0.013$) [11].

Role of neoadjuvant paclitaxel in breast cancer

Multiple clinical trials support paclitaxel in the neoadjuvant treatment of breast cancer. ECTO established an in-breast pCR of 23 % and breast-plus-node pCR of 20 % after neoadjuvant AT followed by CMF [12]. The NOAH trial showed similar results, with an in-breast pCR of 17 % and breast-plus-node pCR of 16 % in HER2-negative patients treated with neoadjuvant AT followed by paclitaxel and CMF [13]. In patients with HER2+positive disease treated with neoadjuvant chemotherapy plus neoadjuvant and adjuvant trastuzumab, pCR rates were 43 % in breast and 38 % in breast-plus axilla [13].

SWOG 0012 compared 21-day AC followed by paclitaxel versus weekly AC with granulocyte colony-stimulating factor (G-CSF) support followed by paclitaxel [14]. Although pCR was slightly higher after weekly AC plus paclitaxel (24.3 vs 20.7 %; $P = 0.45$), a significantly higher pCR was achieved in patients with stage IIIB disease who received weekly AC versus 21-day AC (25.8 vs 9.3 %; $P = 0.0057$). Subsequently, phase III Neo-tAnGo found that paclitaxel followed by anthracyclines significantly improved pCR compared with anthracyclines followed by paclitaxel (20 vs 15 %; $P = 0.03$) [15].

CALGB 40603 evaluated neoadjuvant weekly paclitaxel followed by dose-dense AC ± bevacizumab and/or carboplatin for triple-negative breast cancer (TNBC) [16]. Carboplatin significantly increased breast pCR (60 vs 46 %; $P = 0.0018$) and breast-plus-axilla pCR (54 vs 41 %; $P = 0.0029$), whereas bevacizumab increased only breast pCR (59 vs 48 %; $P = 0.0089$).

Neoadjuvant lapatinib plus trastuzumab followed by neoadjuvant lapatinib plus trastuzumab plus paclitaxel significantly improved pCR vs neoadjuvant trastuzumab alone followed by neoadjuvant trastuzumab plus paclitaxel (51.3 vs 29.5 %; $P = 0.0001$) in patients with HER2+ breast cancer in the NeoALTTO study [17]. Similarly, NSABP B-41 reported higher pCR when neoadjuvant AC followed by trastuzumab plus lapatinib plus paclitaxel was compared with AC followed by trastuzumab plus paclitaxel (62 vs 52.5 %; $P = 0.095$) [18]. CALGB 40601 also demonstrated numerically increased pCR after weekly paclitaxel plus trastuzumab plus lapatinib versus weekly paclitaxel plus trastuzumab (51 vs 40 %; $P = 0.11$) [19].

These trials collectively support the efficacy of neoadjuvant paclitaxel in all subtypes of breast cancer. As a result, many National Comprehensive Cancer Network-preferred neoadjuvant regimens now include taxanes [20].

Development of *nab*-paclitaxel

Paclitaxel is formulated with Kolliphor EL (formerly Cremophor EL), which can elicit hypersensitivity reactions and peripheral neuropathy [21]. Nanoparticle albumin-bound paclitaxel (*nab*®-paclitaxel, Celgene Corporation, Summit, NJ) minimizes these toxicities and obviates prophylactic antihistamine and steroid treatment [21, 22]. Compared with paclitaxel, *nab*-paclitaxel yields a 10-fold higher mean maximal concentration of free paclitaxel [23]. In addition, *nab*-paclitaxel is transported more rapidly across endothelial cell layers and exhibits greater tissue penetration and slower elimination of paclitaxel [24, 25]. According to preclinical models, increased intratumoral delivery and retention result in 33 % higher intratumoral drug concentrations [24].

A significantly improved overall response rate (ORR) (33 vs 19 %; $P = 0.001$) and time to tumor progression (23.0 vs 16.9 weeks; HR= 0.75; $P = 0.006$) were reported for *nab*-paclitaxel in a phase III trial of *nab*-paclitaxel (260 mg/m^2 every 3 weeks [q3w]) vs paclitaxel (175 mg/m^2 q3w) in metastatic breast cancer (MBC) [26]. *nab*-Paclitaxel was associated with a lower incidence of grade 4 neutropenia (9 vs 22 %; $P < 0.001$) and higher incidence of grade 3 sensory neuropathy (10 vs 2 %; $P < 0.001$). In a subsequent phase II trial of first-line *nab*-paclitaxel vs docetaxel for MBC, *nab*-paclitaxel 150 mg/m^2 the first 3 of 4 weeks (qw 3/4) significantly prolonged PFS by independent (12.9 vs 7.5 months; $P = 0.0065$) and investigator (14.6 vs 7.8 months; $P = 0.012$) review vs docetaxel [22]. In addition, *nab*-paclitaxel improved ORR, although the difference was not significant. Grade 3 fatigue and grade 4 neutropenia were lower with *nab*-paclitaxel, whereas the incidence of grade 3/4 sensory neuropathy was similar. These trials support the overall efficacy and safety of *nab*-paclitaxel in MBC.

Methods

The search terms "*nab*-paclitaxel" or "nanoparticle paclitaxel" and "breast cancer" and "neoadjuvant" and "clinical trial" were applied to retrieve publications from PubMed and presentations from conferences and congresses, including American Society of Cancer Oncology annual meetings, Breast Cancer Symposium, and the San Antonio Breast Cancer Symposium. Results were evaluated for study design and key efficacy and safety data with a focus on TNBC.

Results

Twenty studies of neoadjuvant *nab*-paclitaxel in breast cancer were retrieved (Table 1). Most reported the results of phase II trials. Disease subtype varied among studies, as did treatment dose and schedule. Study design, including doses and sequencing of agents, and key results are summarized (Table 1). In addition, key safety data are provided (Table 2).

Unselected disease

nab-Paclitaxel (260 mg/m^2 q3w) plus capecitabine was evaluated for previously untreated locally advanced breast cancer (LABC) in a phase II study ($N = 14$) [27]. The study was terminated early due to a low response rate. Grade 3/4 toxicities included hand-foot syndrome, neutropenia or neutropenic fever, syncope, and hypertension.

In another phase II trial, gemcitabine and epirubicin were combined with neoadjuvant *nab*-paclitaxel (175 mg/m^2 every 2 weeks [q2w]) for LABC ($N = 123$) [28]. Pegfilgrastim was also administered. pCR occurred in 20 % of patients, and 3-year PFS and OS were 48 and 86 %, respectively. Among 44 patients with TNBC, 12 (27 %) had pCR. The most common grade 3/4 toxicity, occurring in 11 % of patients, was neutropenia. Grade 3 sensory neuropathy occurred in 3 (2 %) patients, with no grade 4 sensory neuropathy. Non-hematologic toxicities were uncommon.

nab-Paclitaxel (100 mg/m^2 once weekly [qw]) followed by FEC was evaluated for previously untreated LABC in a phase II trial ($N = 66$) [29]. Patients with HER2+ disease

Table 1 pCR rates in breast and nodes in neoadjuvant studies of *nab*-paclitaxel

Author and year of study	Regimen			Phase	ER/PR status	HER2 status	Stage	ITT		pCR rate in populations of interest	Definition of pCR
	Sequence	*nab*-P	Concurrent agents					*n*	pCR (%)		
Veerapaneni 2008 [27]	*nab*-P + cape	260 mg/m^2 q3w (21-day cycle)	Cape 825 mg/m^2 BID days 1–14 (21-day cycle)	II	Unselected	Unselected	II–IIIB	14	7	NR	No residual invasive carcinoma
Yardley 2010 [28]	*nab*-P + gem + E + peg	175 mg/m^2 q2w × 6 cycles	Gem 2000 mg/m^2 q2w + E 50 mg/m^2 q2w + peg 6 mg q2w × 6 cycles	II	Unselected	Unselected	I–IIIC	123	20	TNBC ($n = 44$), 27 %	ypT0 ypN0
Robidoux 2010 [29]	*nab*-P → 4 cycles FEC (+ trastuzumab for HER2+)	100 mg/m^2 qw × 12 cycles	None	II	Unselected	Unselected	IIB-IIIB	66	In-breast: 29; breast-plus-node: 26	pCR in breast only: TNBC ($n = 18$), 28 % HR+/HER2+ ($n = 9$), 44 % HR-/HER2+ ($n = 10$), 70 %	In-breast ypT0 and breast-plus-node ypT0 ypN0 assessed
Yardley 2011 [52]	*nab*-P + carbo + trastuzumab + bevacizumab	100 mg/m^2 qw 3/4 (28-day cycles) × 6 cycles	Carbo AUC = 6 q3w + trastuzumab 2 mg/kg qw after 4 mg/kg in first week + bev 5 mg/kg qw (28-day cycles) × 6 cycles	II	Unselected	HER2+	IIA–IIIC	30	54	ER+, 43 %; ER−, 66 %	ypT0 ypN0
Khong 2011 [68]	*nab*-P + AC + peg	100 mg/m^2 qw 2/3 × 6 cycles	A 50 mg/m^2 q3w + C 500 mg/m^2 q3w + peg q3w × 6 cycles	I	Unselected	HER2−	II–III	16	NR	TNBC ($n = 4$), 100 %	ND
Li 2012 [69]	Docetaxel + AC	NA	NA	II	Unselected	Unselected	II–III	18	17	Treatment arms combined: Basal-like ($n = 12$), 25 % Luminal ($n = 26$), 8 % HER2+ ($n = 15$), 53 %	RCB 0
	AC → *nab*-P + carbo	100 mg/m^2 qw 3/4 × 3 cycles	Carbo AUC = 2 qw 3/4 × 3 cycles					26	8		
	AC + trastuzumab → *nab*-P + carbo + trastuzumab	100 mg/m^2 qw 3/4 × 3 cycles	Carbo AUC = 2 qw 3/4 × 3 cycles					28	46		
Kaklamani 2012 [31]	*nab*-P + lapatinib	260 mg/m^2 q3w (28-day cycles) × 4 cycles	Lapatinib 1000 mg qd × 12 weeks	Pilot	Unselected	HER2+	I–III	30	ypT0 ypN0: 18; RCB 0: 21.7	NR	ypT0 ypN0 and RCB 0

Table 1 continued

Author and year of study	Regimen			Phase	ER/PR status	HER2 status	Stage	ITT		pCR rate in populations of interest	Definition of pCR
	Sequence	*nab*-P	Concurrent agents					*n*	pCR (%)		
Sinclair 2012 [34]	Cohort 1: *nab*-P → *nab*-P + bevacizumab + carbo	100 mg/m^2 qw × 2 weeks → 100 mg/m^2 qw × 12 weeks	Bevacizumab 15 mg/m^2 q3w × 3 cycles + carbo AUC = 6 q3w × 4 cycles	II	Unselected	HER2−	IIA–IIIC	31	ypT0 ypN0/is: 11; RCB 0 + 1: 37	TNBC (n = 11): ypT0 ypN0/is, 27 %; RCB 0 + 1, 55 %	ypT0 ypN0/is and RCB 0 + 1
	Cohort 2: bevacizumab → *nab*-P + bevacizumab + carbo → AC + bevacizumab	100 mg/m^2 qw × 12 weeks	Bevacizumab 15 mg/m^2 q3w × 4 cycles + carbo AUC = 6 q3w × 4 cycles					29	ypT0 ypN0/is: 54; RCB 0 + 1: 64	TNBC (n = 16): ypT0 ypN0/is, 81 %; RCB 0 + 1, 100 %	
Snider 2013 [70]	*nab*-P + carbo + bevacizumab → AC + bevacizumab	100 mg/m^2 qw 3/4 (28-day cycle) × 4 cycles	Carbo AUC = 6 q4w + bevacizumab 10 mg/kg q2w (28-day cycle) × 4 cycles	NR	ER− PR−	HER2−	I–III	41	ypT0, 61; ypT0 ypN0, 53	NA	ypT0 and ypT0 ypN0 assessed
Masumoto 2014 [71]	*nab*-P q3w + carbo → FEC	NR	NR	II	Unselected	Unselected	Operable; stage not reported	55	36.5	HER2+ ,59 %; TNBC, 57 %; ER+ HER2−, 4 %	ypT0 ypN0
Martin 2014 [37]	*nab*-P qw 3/4	150 mg/m^2 qw 3/4 × 4 cycles	NA	II	ER+ PR unselected	HER2−	I–III	83	24.1 %	RCB 0 + 1 24.7 % of treated population (20/81)	RCB 0 + 1
Nahleh (S0800) 2014 [35]	Bevacizumab + *nab*-P → AC + peg-G *nab*-P → AC + peg-G AC + peg-G → *nab*-P	100 mg/m^2 qw × 12 weeks	Bevacizumab 10 mg/kg q2w × 12 weeks	II	Unselected	HER2−	IIB–IIIC	215	No bevacizumab, 21; bevacizumab, 36 (P = 0.021)	HR−: no bevacizumab, 28 % versus bevacizumab, 59 % (P = 0.014) HR+: no bevacizumab, 18 % versus bevacizumab, 25 % (P = 0.41)	ypT0 ypN0
Untch 2016 [39]	*nab*-P → EC	125 mg/m^2 qw[a]	–	III	Unselected	Unselected	Operable or inoperable; cT2-cT4a-d; cT1c and cN+ or pNSLN+	606	ypT0 ypN0, 38; ypT0/is ypN0, 43; ypT0/is ypN0/+, 49	HER2+: *nab*-P, 62 %; P, 54 % (P = 0.13) TNBC: *nab*-P, 48 %; P, 26 % (P < 0.001)	Primary: ypT0 ypN0; secondary endpoints included ypT0/is ypN0 and ypT0/is ypN0/+, and ypN0
	Paclitaxel → EC	NA						600	ypT0 ypN0, 29; ypT0/is ypN0, 35; ypT0/is ypN0/+, 40		

Table 1 continued

Author and year of study	Regimen			Phase	ER/PR status	HER2 status	Stage	ITT		pCR rate in populations of interest	Definition of pCR
	Sequence	*nab*-P	Concurrent agents					*n*	pCR (%)		
Mrozek 2010 [36]	*nab*-P + carbo + bevacizumab	100 mg/m^2 qw 3/4 × 6 cycles	Carbo AUC = 2 qw 3/4 + bevacizumab 10 mg/kg q2w × 6 cycles (no bevacizumab in 6th cycle)	II	Unselected	HER2−	II–III	33	21	TNBC, 55 %	ypT0 ypN0
Zelnak 2012 [32]	*nab*-P → vin + trastuzumab	260 mg/m^2 q2w × 4 cycles	–	II	Unselected	HER2+	I–III	27	48.1	ER+/PR+, 18.1 %; ER−/PR−, 68.8 %	ypT0 ypN0
Connolly 2015 [72]	*nab*-P + carbo + placebo	100 mg/m^2 qw × 12 weeks	Carbo AUC = 2 qw + placebo 3 times per week × 12 weeks	II	Unselected	HER2−	Operable; T1cN1-3 or T2-4, any *N*, all M0	31	29	TNBC: placebo, 58.3 % versus vorinostat, 41.7 %	ypT0 ypN0
	nab-P + carbo + vorinostat	100 mg/m^2 qw × 12 weeks	Carbo AUC = 2 qw + vorinostat 400 mg 3 times per week × 12 weeks					31	25.8		
Huang 2015 [30]	*nab*-P + carbo	125 mg/m^2 qw × 4 cycles	Carbo AUC = 2 qw × 4 cycles	II	Unselected	Unselected	II–III	30	26.7	HER2+, 43.6 % versus 39.6 % for *nab*-P versus P ($P = 0.769$)	ypT0/is ypN0
	paclitaxel + carbo	NA	Paclitaxel 80 mg/m^2 qw + carbo AUC = 2 qw × 4 cycles					90	25.6		
Shimada 2015 [40]	*nab*-P → EC	260 mg/m^2 q3w × 4 cycles	–	NA	Unselected	HER2−	II–III	53	5.7	NR	ypT0/is, ypNany
Tanaka 2015 [33]	EC or FEC → *nab*-P + trastuzumab	260 mg/m^2 q3w	–	II	Unselected	HER2+	I–IIIA	46	49	ER+, 36 %; ER−, 71 %	ypT0/is ypN0
Gluz 2015 [41]	*nab*-P + gem	125 mg/m^2 qw 2/3	gem 1000 mg/m^2 qw 2/3	II	ER-	HER2−	I-IV	182	28.7	NA	ypT0/is ypN0
	nab-P + carbo	125 mg/m^2 qw 2/3	Carbo AUC 2 day 1, 8 q3w		PR-			154	45.9	NA	

AC doxorubicin/cyclophosphamide, *AUC* area under the curve, *bev* bevacizumab, *BID* twice daily, *carbo* carboplatin, *E* epirubicin, *EC* epirubicin/cyclophosphamide, *ER* estrogen receptor, *FEC* fluorouracil/epirubicin/cyclophosphamide, *gem* gemcitabine, *HER2* human epidermal growth factor receptor 2, *ITT* intent to treat, *NA* not applicable, *nab-P nab*-paclitaxel, *NSLN* non-sentinel lymph node, *ND* not defined, *NR* not reported, *peg* pegfilgrastim, *pCR* pathologic complete response, *PR* progesterone receptor, *q3w* every 3 weeks, *qd* once daily, *qw* once weekly, *qw 3/4* for the first 3 of 4 weeks, *RCB* residual cancer burden, *TNBC* triple-negative breast cancer, *vin* vinorelbine, *ypT0 ypN0* absence of invasive cancer and in situ cancer in the breast and axillary nodes, *ypT0/is ypN0* absence of invasive cancer in the breast and axillary nodes, irrespective of ductal carcinoma in situ, *ypT0/is* absence of invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement

[a] Dose reduced from 150 mg/m^2 qw ($n = 229$) to 125 mg/m^2 qw ($n = 377$) after study amendment

Table 2 Adverse events (all grade) by schedule in neoadjuvant studies of *nab*-paclitaxel

Trial	*nab*-P schedule and dose	Neutropenia (%)	Peripheral neuropathy (%)	Fatigue (%)
Veerapaneni [27]	q3w 260 mg/m^2	NR	NR	NR
Kaklamani [31]	q3w 260 mg/m^2	NR	0[a]	7[a]
Masumoto [71]	q3w	NR	NR	NR
Shimada [40]	q3w 260 mg/m^2	37.7	1.9	NR
Tanaka [33]	q3w 260 mg/m^2	36	84[b]	64
Yardley [28]	q2w 175 mg/m^2	11	2[b]	7
Zelnak [32]	q2w 260 mg/m^2	38	88	73
Robidoux [29]	qw 100 mg/m^2	3[a]	5[a]	6[a]
Sinclair [34]	qw 100 mg/m^2	75	0[c]	13
Sinclair [73]	qw 100 mg/m^2	71[a]	7[a,c]	7[a]
Nahleh [35]	qw 100 mg/m^2	NR	NR	NR
Untch [39]	qw 125 mg/m^{2d}	60.8[a]	10.4[a]	5[a]
Connolly [72]	qw 100 mg/m^2	NR	NR	NR
Huang [30]	qw 125 mg/m^2	100	43[e]	NR
Mrozek [36]	qw 3/4 100 mg/m^2	58[a]	NR	NR
Yardley [52]	qw 3/4 100 mg/m^2	39[a]	0[a]	NR
Khong [68]	qw 2/3 100 mg/m^2	NR	NR	NR
Li [69]	NR	NR	NR	NR
Snider [70]	qw 3/4 100 mg/m^2	78[a]	NR	5
Martin [37]	qw 3/4 150 mg/m^2	16[a]	2.5[a]	3.7[a]

NR not reported, *q3w* every 3 weeks, *qw* once weekly, *q2w every 2 weeks, qw 2/3 the first 2 of 3 weeks, qw 3/4* for the first 3 of 4 weeks

[a] Grade 3/4

[b] Reported as sensory neuropathy

[c] Reported as neurosensory

[d] Dose reduced from 150 mg/m^2 qw (n = 229) to 125 mg/m^2 qw (n = 377) after study amendment

[e] Reported as peripheral neurotoxicity

also received trastuzumab. An in-breast pCR of 29 % and breast-plus-node pCR of 26 % were reported. Analysis by molecular subtype showed pCR in 28 % of TNBC, 70 % of HR-/HER2+, and 44 % of HR+/HER2+ patients. PFS and OS were 81 and 95 %, respectively, for the intent-to-treat (ITT) population. The regimen was tolerable, with no grade 4 toxicities due to *nab*-paclitaxel treatment. Grade 3/4 febrile neutropenia due to FEC occurred in 7 % of patients.

nab-Paclitaxel (125 mg/m^2 qw; $n = 30$) and paclitaxel (80 mg/m^2 qw; $n = 90$) were recently compared in combination with carboplatin in a phase II trial for LABC [30]. Trastuzumab was added for HER2+ disease. pCR rates were similar (26.7 vs 25.6 % with *nab*-paclitaxel vs paclitaxel, respectively; $P = 0.904$), and no differences were found with trastuzumab (43.6 vs 39.6 %; $P = 0.769$). One of two patients with TNBC achieved pCR with *nab*-paclitaxel. Interestingly, *nab*-paclitaxel showed benefit in patients with stage II disease, with a pCR of 36.8 versus 15.8 % with paclitaxel ($P = 0.051$). No grade 3/4 peripheral neurotoxicity was reported in either arm. However, grade 4 neutropenia increased with *nab*-paclitaxel (56.7 vs 21.1 %; $P < 0.001$).

nab-Paclitaxel with HER2-targeted therapies

Several studies examined *nab*-paclitaxel for HER2-overexpressing breast cancer. *nab*-Paclitaxel (260 mg/m^2 q3w) plus lapatinib was investigated in a phase I study for early-stage, HER2+ breast cancer ($N = 30$) [31]. A pCR of 17.9 % (95 % CI 3.7–32.1 %) was reported, with fatigue and diarrhea being the most common grade 3 toxicities. No grade 4 toxicities were reported.

A recent phase II study of preoperative *nab*-paclitaxel (260 mg/m^2 q2w) followed by vinorelbine plus trastuzumab in HER2-overexpressing breast cancer ($N = 27$) reported a pCR of 48 % [32]. Sub-analysis by HR status showed a pCR of 18 % in patients with estrogen receptor (ER)+/progesterone receptor (PR)+ disease and 69 % in patients with ER−/PR− disease. Six patients had grade 2/3 neuropathy, with no grade 4 neuropathy reported. Similarly, another

phase II trial of neoadjuvant anthracycline followed by *nab*-paclitaxel (260 mg/m^2 q3w) plus trastuzumab reported 49 % pCR in the ITT group for operable HER2+ breast cancer ($N = 46$) [33]. A pCR of 71 % was achieved in cases with ER− disease compared with 36 % in ER+ disease. Hematologic toxicities were the most common cause of treatment delays or dose reductions, with one case of peripheral neuropathy requiring dose reduction.

In general, compared with patients with HER2+/HR+ disease, those with HR−/HER2+ cancer had higher pCR rates. Response rates to lapatinib plus *nab*-paclitaxel were low.

nab-Paclitaxel with bevacizumab

Neoadjuvant *nab*-paclitaxel plus bevacizumab has also been evaluated as a potential treatment for breast cancer. In a study of weekly *nab*-paclitaxel (100 mg/m^2), carboplatin, and bevacizumab with ($n = 31$) or without ($n = 29$) dose-dense AC, pCR was 11 and 27 % in the ITT group and TNBC subset, respectively [34]. Addition of dose-dense AC increased pCR to 54 %, with a pCR of 81 % in the TNBC subpopulation. Grade 3/4 toxicities included neutropenia, thrombocytopenia, and anemia, with no grade 3/4 neurosensory toxicities.

Weekly neoadjuvant *nab*-paclitaxel (100 mg/m^2) ± bevacizumab followed by dose-dense AC was evaluated for HER2− LABC in phase II SWOG S0800 ($N = 215$) [35]. The overall pCR was 28 %, but a significantly higher pCR was achieved with bevacizumab (36 vs 21 %; $P = 0.021$). In HR+ patients, the difference was not significant (bevacizumab vs no bevacizumab, 25 vs 18 %; $P = 0.41$). However, HR- patients had significantly improved pCR with bevacizumab (59 vs 28 %; $P = 0.014$). Grade 3/4 toxicities were common and not significantly different between arms. In another phase II study, *nab*-paclitaxel (100 mg/m^2 qw 3/4), carboplatin, and bevacizumab achieved a pCR of 21 % in the ITT group ($N = 33$), with a pCR of 55 % in TNBC patients [36]. Neutropenia and thrombocytopenia were the main toxicities.

These trials demonstrated efficacy of *nab*-paclitaxel with bevacizumab in combination with carboplatin or dose-dense AC for TNBC. However, hematologic toxicities were common and should be monitored with this treatment combination.

Recent trials

GEICAM (ITT $N = 83$; phase II) investigated neoadjuvant *nab*-paclitaxel (150 mg/m^2 qw 3/4) in HER2− breast cancer and reported an ORR of 76.5 % [37]. RCB 0 + I was reported in 24.7 % of the treated population. In addition, 40 % of patients received breast-conserving surgery after *nab*-paclitaxel. Ki-67 > 20 % and high stromal Cav1 correlated with low RCB (RCB 0 + I), suggesting predictive roles for these markers. Grade 3/4 neutropenia (16 %), leukopenia (3.7 %), fatigue (3.7 %), and neuropathy (2.5 %) were the most common toxicities [38].

The phase III GeparSepto trial compared neoadjuvant paclitaxel 80 mg/m^2 qw ($n = 600$) vs *nab*-paclitaxel ($n = 606$; dose reduced from 150 mg/m^2 qw [$n = 229$] to 125 mg/m^2 qw [$n = 377$] after study amendment) followed by epirubicin and cyclophosphamide (EC) as part of a neoadjuvant regimen for early-stage breast cancer [39]. Patients with HER2+ disease were also treated with trastuzumab plus pertuzumab. *nab*-Paclitaxel achieved significantly higher pCR vs paclitaxel, regardless of the pCR definition (ypT0 ypN0, 38 vs 29 %, $P = 0.00065$; ypT0/is ypN0, 43 vs 35 %, $P = 0.004$; ypT0/is ypN0/+, 49 vs 40 %, $P = 0.002$). The largest difference was in the TNBC subgroup in which *nab*-paclitaxel achieved a pCR of 48 versus 26 % with paclitaxel ($P < 0.001$). GeparSepto originally used 150 mg/m^2 weekly *nab*-paclitaxel, which caused more peripheral neuropathy and more frequent discontinuations than paclitaxel. Thus, after recruitment of 464 patients, the study protocol was amended to use 125 mg/m^2 weekly *nab*-paclitaxel. For patients who were randomized and started treatment before the amendment, pCR occurred in 34 versus 23 % ($P = 0.022$) of the patients in the *nab*-paclitaxel vs paclitaxel group. In patients randomized on or after study amendment and who started treatment, the pCR was 41 % in the *nab*-paclitaxel group and 32 % in the paclitaxel group ($P = 0.013$). In a subsequent study ($N = 53$), sequential *nab*-paclitaxel (260 mg/m^2 q3w) and EC achieved pCR in 3 (5.7 %) and near-pCR in 7 (13.2 %) patients with stage II/III HER2− breast cancer [40]. Grade 3 toxicities were rare and included one case of peripheral neuropathy.

The randomized phase II Adjuvant Dynamic marker-Adjusted Personalized Therapy (ADAPT) Triple Negative trial of neoadjuvant *nab*-paclitaxel (125 mg/m^2 qw 2/3) plus carboplatin ($N = 154$) or gemcitabine ($N = 182$) reported an overall pCR of 36 % with significant differences between arms (carboplatin, 45.9 % vs gemcitabine, 28.7 %; $P < 0.001$) [41]. Early response ($P < 0.001$) was predictive of pCR regardless of treatment arm.

Toxicities

Most neoadjuvant *nab*-paclitaxel trials in breast cancer demonstrated acceptable tolerability profiles (Table 2). A few studies compared *nab*-paclitaxel vs paclitaxel in the preoperative setting in patients with breast cancer. In the GeparSepto study, *nab*-paclitaxel (150 or 125 mg/m^2 qw) followed by EC was associated with significantly improved pCR rates and comparable grade 3/4 adverse events vs paclitaxel followed by EC (neutropenia, 60.8 vs 61.7 %;

febrile neutropenia, 4.6 vs 4.0 %; fatigue, 5 vs 4 %) [39]. However, in patients treated with either *nab*-paclitaxel 150 or 125 mg/m^2 qw, grade 3/4 peripheral sensory neuropathy was significantly higher in the *nab*-paclitaxel arm vs paclitaxel arm (10.4 vs 3 %, $P < 0.0001$) [39]. In another phase II study comparing *nab*-paclitaxel with carboplatin vs paclitaxel with carboplatin as neoadjuvant therapy in patients with LABC, the *nab*-paclitaxel arm had less grade 3/4 neutropenia (30 vs 52 %) and leukopenia (23 vs 35 %), but slightly more thrombocytopenia (8 vs 0 %) and anemia (5 vs 3 %) [30]. Overall, *nab*-paclitaxel appears to be a promising neoadjuvant agent for breast cancer with an acceptable safety profile; however, toxicities, including peripheral neuropathy, should be monitored.

Discussion

Clinical trials of neoadjuvant *nab*-paclitaxel for breast cancer have yielded highly encouraging results. Most trials evaluated weekly or q3w *nab*-paclitaxel in combination with anthracyclines, carboplatin, or cyclophosphamide, or with targeted agents, such as bevacizumab or trastuzumab. pCR rates ranged from 7 to 54 %, with the TNBC subpopulation demonstrating particularly strong responses, ranging from 25.7 to 81 %. In general, pCR rates in TNBC were significantly higher than those observed in other breast cancer subtypes. Overall, neoadjuvant *nab*-paclitaxel was safe, although hematologic toxicities were reported in some studies. Results from the recent GeparSepto and ADAPT TNBC trials were especially promising, with significantly increased pCR rates after *nab*-paclitaxel followed by EC, or carboplatin in patients with TNBC. Additional ongoing trials will further examine the efficacy of *nab*-paclitaxel-based regimens in TNBC. In addition, the long-term effects of *nab*-paclitaxel need to be compared with those of paclitaxel.

While data in the neoadjuvant setting are limited, some clinical and economic data from model-based and retrospective analyses support the cost-effectiveness of *nab*-paclitaxel in MBC [42, 43]. An economic analysis of a phase II trial in MBC assessed the average cost of *nab*-paclitaxel and docetaxel use from a United Kingdom National Health Service perspective. Accounting for cost components, including chemotherapy, drug delivery, and hospitalization due to toxicity, the average costs of *nab*-paclitaxel 100 and 300 mg/m^2 q3w were comparable to the cost of docetaxel 100 mg/m^2 q3w (approximately £15,000 per patient for each *nab*-paclitaxel dose vs £12,000 per patient for docetaxel) [42]. Furthermore, a meta-analysis of randomized clinical trials in MBC found that *nab*-paclitaxel was associated with a lower incidence of grade 3/4 toxicities compared with paclitaxel and docetaxel and that this translated to lower overall costs with respect to managing these events [44].

Predictive biomarkers of response

Identification of predictive biomarkers continues to advance individualized treatment of cancer patients. The GeparSixto trial found a significant correlation between the percentage of stromal tumor-infiltrating lymphocytes and pCR after neoadjuvant carboplatin, anthracycline, and taxane [45]. An unmet need exists in identifying patients who are most likely to respond to *nab*-paclitaxel neoadjuvant therapy by establishing biomarkers of response. Secreted protein acidic and rich in cysteine (SPARC) interacts with albumin and is localized in tumor stroma. Thus, it was hypothesized that SPARC expression may affect the antitumor activity of *nab*-paclitaxel [46–48].The exact role of SPARC in tumor progression is unclear, as some studies suggest a pro-tumorigenic and angiogenic role, whereas others support an anti-tumorigenic role [48]. However, in an exploratory analysis from a large phase III trial of patients with metastatic pancreatic cancer, SPARC expression was neither predictive nor prognostic of OS [49]. Future neoadjuvant *nab*-paclitaxel-based trials that prospectively evaluate the predictive value of potential molecular and biological markers are warranted.

Ongoing trials

Based on encouraging results with sequential neoadjuvant *nab*-paclitaxel and FEC, the phase III Evaluating Treatment with Neoadjuvant Abraxane (ETNA) trial has been initiated. (Table 3) [29, 50]. Sequential neoadjuvant *nab*-paclitaxel and EC are also being evaluated in early-stage breast cancer in a phase II trial [51]. Based on the efficacy of carboplatin with *nab*-paclitaxel, particularly in TNBC, an ongoing phase II study is examining this combination in LABC or inflammatory TNBC [30, 34, 36, 41, 52, 53]. Neoadjuvant *nab*-paclitaxel will also be tested with carboplatin, AC, and bevacizumab with pegfilgrastim support for locally invasive TNBC [54]. *nab*-Paclitaxel plus carboplatin will be combined with trastuzumab for early HER2+ disease or with bevacizumab for HER2− cancers [55]. In addition, based on data showing increased expression of epidermal growth factor receptor (EGFR) in half of inflammatory breast cancers, the EGFR monoclonal antibody panitumumab will be combined with carboplatin, FEC, and *nab*-paclitaxel for HER2− IBC [56, 57]. The results of these ongoing neoadjuvant *nab*-paclitaxel-based trials may yield improved treatment options for patients with breast cancer.

Table 3 Future/ongoing neoadjuvant studies of *nab*-paclitaxel

Trial #, PI, institution	Phase	Planned *N*	Patient population	Stage	Regimen	*nab*-P treatment
ETNA (NCT01822314), Luca Gianni, San Raffaele Hospital, Italy	III	632	High-risk HER2−	Operable T2N0-1, T3N0 and locally advanced T3N1, T4, any N2-3	*nab*-P or P → AC or EC or FEC	125 mg/m^2 qw 3/4 × 4 cycles
NCT00397761, Anita Aggarwal, Washington Hospital Center	II/III	33	Unselected	II–IIIB	*nab*-P + capecitabine	NA
NCT01525966, George Somlo, City of Hope Medical Center	II	49	TNBC	II–IIIC	*nab*-P + carbo	Dose not given; qw every 28 days for 4 courses
NCT00944047, Qamar Khan, University of Kansas Medical Center Cancer Center	II	30	Low HER2	II–III	*nab*-P + trastuzumab → ddAC	100 mg/m^2 qw × 12 weeks
NCT01036087, Naoto Ueno, MD Anderson Cancer Center	II	40	HER2− IBC	NR	Panitumumab → panitumumab + *nab*-P + carbo → FEC	100 mg/m^2 qw × 12 weeks
NCT00856492, Zeina Nahleh, Barbara Ann Karmanos Cancer Institute	II	200	HER2− IBC or LABC	IIB–IIIC	*nab*-P ± bevacizumab before or after AC + peg	Dose not given; qw × 12 weeks
NCT00618657, Rita Mehta, Chao Family Comprehensive Cancer Center, UC Irvine	II	120	HER2+ or HER2−	IA-IIIC	*nab*-P + carbo + trastuzumab (HER2+) *nab*-P + carbo + bevacizumab (HER2−)	qw × 12 (HER2+) q2w × 5 (HER2−)
NCT00617942, William Sikov, Brown University	II	60	HER2+	IIA–IIIB	*nab*-P + trastuzumab qw + carbo q3w	100 mg/m^2 qw
NCT00777673, Jasgit Sachdev, University of Tennessee Cancer Institute	II	60	TNBC	NA	*nab*-P + carbo + bevacizumab → AC + bevacizumab	Dose not given; qw 3/4 × 4 cycles
NCT01830244, Mustafa Khasraw, Barwan Health, Australia	II	60	Unselected	T2-4, N0-2	*nab*-P + EC	125 mg/m^2 qw × 12 weeks
NCT02530489, Jennifer Litton, MD Anderson Cancer Center	II	37	TNBC	NA	*nab*-P + atezolizumab followed by surgery and then adjuvant atezolizumab	100 mg/m^2 qw × 12 weeks
NCT02598310, Mitsuhiko Iwamoto, Osaka Medical College, Japan	II	30	ER−/ HER2+	Operable (tumor size ≤ 3 cm, N0)	*nab*-P + trastuzumab	260 mg/m^2 q3w
NCT01625429, Zhimin Shao, Fudan University, China	II	30	Unselected	II–III	*nab*-P + carbo (+trastuzumab for HER2+)	125 mg/m^2 qw 3/4
NCT02489448, Lajos Pusztai, Yale University	I/II	61	TNBC	I–III	*nab*-P + durvalumab followed by ddAC	100 mg/m^2 qw × 12 weeks

AC doxorubicin/cyclophosphamide, *carbo* carboplatin, *dd* dose-dense, *EC* epirubicin/cyclophosphamide, *ER* estrogen receptor, *FEC* fluorouracil/epirubicin/cyclophosphamide, *HER2* human epidermal growth factor receptor 2, *IBC* inflammatory breast cancer, *LABC* locally advanced breast cancer, *NA* not available, *nab-P nab*-paclitaxel, *peg* pegfilgrastim, *PI* principal investigator, *q2w* every 2 weeks, *q3w* every 3 weeks, *qd* once daily, *qw* once weekly, *qw 3/4* for the first 3 of 4 weeks, *P* paclitaxel, *TNBC* triple-negative breast cancer

Future directions: *nab*-paclitaxel and immune therapy

Upon exposure to chemotherapeutic agents, dying tumor cells induce immune responses and promote the release of tumor antigens [58, 59]. Preclinical data suggest synergistic activity between chemotherapy and checkpoint inhibitors [60]. In mouse models of pancreatic cancer resistant to immune checkpoint inhibition alone, addition of *nab*-paclitaxel to immune checkpoint inhibitors improved response and survival [61]. *nab*-Paclitaxel also demonstrated clinical benefit when combined with checkpoint inhibitors in multiple types of solid tumors. A phase Ib study of atezolizumab, a PD-L1 inhibitor, combined with *nab*-paclitaxel demonstrated activity in 5 evaluable patients with metastatic TNBC (4 partial responses, 1 stable disease) and tolerability [62]. First-line treatment of locally advanced or metastatic non-small cell lung cancer (N = 58) with atezolizumab plus *nab*-paclitaxel and carboplatin resulted in 25 % complete response and 31.25 % partial response rate, with an ORR of 56 % (95 % CI 30–80 %) [63]. Atezolizumab in combination with *nab*-paclitaxel vs placebo plus *nab*-paclitaxel as first-line treatment for metastatic TNBC is currently being evaluated in the phase III IMpassion130 trial (planned $N = 350$; NCT02425891) [64]. The combination of atezolizumab and *nab*-paclitaxel is also being evaluated as a neoadjuvant regimen in an ongoing phase II trial in early-stage TNBC [65]. Similarly, the combination of the PD-L1 inhibitor durvalumab plus *nab*-paclitaxel is being examined as neoadjuvant therapy for early-stage TNBC in an ongoing phase I/II trial [66]. An ongoing trial will also examine nivolumab, a PD-1 inhibitor, in combination with *nab*-paclitaxel for recurrent, HER2− MBC [67]. Results from these trials may provide further rationale for combining *nab*-paclitaxel with immune therapies as an exciting new treatment approach for early-stage breast cancer.

Conclusions

In summary, *nab*-paclitaxel appears to be an effective and well-tolerated neoadjuvant therapy for breast cancer. Ongoing and future trials will further evaluate *nab*-paclitaxel in all subtypes of breast cancer, including TNBC, which exhibits a particularly high sensitivity to this treatment strategy. Future studies should examine the long-term benefits of *nab*-paclitaxel vs paclitaxel and should explore combining *nab*-paclitaxel with novel immunological therapies. The inclusion of molecular or biological/immunological analyses in future trials should help identify predictive markers of response, which can be used to guide patient selection and ultimately improve response rates to neoadjuvant *nab*-paclitaxel-based regimens.

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Compliance with ethical standards

Conflict of interest Naoto T. Ueno: clinical trial support of panitumumab—Celgene. Eleftherios P. Mamounas: consultant (advisory board)—Celgene, Pfizer, Novartis, Genomic Health Inc; speakers bureau—Genentech/Roche, Genomic Health Inc.

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