Clinical Development of a Novel Taxane, Nanoparticle Albumin-bound Paclitaxel (ABI-007), in Metastatic Breast Cancer

The taxanes docetaxel and paclitaxel are efficacious agents in the metastatic setting. However, both are associated with toxicities that limit their duration of use and combination with other agents. Nanoparticle albumin-bound paclitaxel (*nab* paclitaxel, ABI-007) is a novel taxane that was developed in an attempt to increase the therapeutic index of paclitaxel while avoiding the toxicities associated with Cremophor® delivery and steroid premedication. Recent Phase II and III studies with *nab* paclitaxel on a weekly or every three-week schedule have demonstrated a retention of efficacy with a more favorable toxicity profile in comparison to standard paclitaxel. A Phase II clinical trial to assess the activity and adverse event profile of the combination regimen of *nab* paclitaxel and gemcitabine has recently opened to patient accrual.

PHASE III TRIAL OF NANOPARTICLE PACLITAXEL (ABI-007) VERSUS PACLITAXEL IN METASTATIC BREAST CANCER

Efficacy data	All treated patients		First-line patients	
Investigator response assessments	ABI-007 (n = 229)	Paclitaxel (n = 225)	ABI-007 (n = 97)	Paclitaxel (n = 89)
Overall response rate (CR + PR)	33% (95% CI: 27-39%)	19% (95% CI: 14-24%)	42% (95% CI: 32-52%)	27% (95% CI: 18-36%)
	$p < 0.001$		$p = 0.029$	
Efficacy data	**All treated patients**		**First-line patients**	
Independent radiology review	ABI-007 (n = 215)	Paclitaxel (n = 214)	ABI-007 (n = 97)	Paclitaxel (n = 89)
Overall response rate (CR + PR)	21% (95% CI: 16-27%)	10% (95% CI: 6-14%)	29% (95% CI: 20-38%)	14% (95% CI: 6-21%)
	$p = 0.002$		$p = 0.011$	
Time to tumor progression	ABI-007 21.9 weeks	Paclitaxel 16.1 weeks	*p*-value 0.029	

Toxicity data	ABI-007 (n = 229)		Paclitaxel (n = 225)		
Parameter	Grade III	Grade IV	Grade III	Grade IV	*p*-value
Neutropenia	25%	9%	31%	22%	<0.001
Sensory neuropathy	10%	0%	2%	0%	<0.001

CR = complete response; PR = partial response

SOURCE: O'Shaughnessy J et al. Presentation. San Antonio Breast Cancer Symposium, 2003;Abstract 44.

RESPONSE TO *NAB* PACLITAXEL IN PHASE II STUDIES OF TAXANE- AND ANTHRACYCLINE-REFRACTORY METASTATIC BREAST CANCER

Treatment: *Nab* paclitaxel 300 mg/m^2 q3wk without premedication

Efficacy data	
Overall response rate	48% (95% CI: 35.3%-60.0%)
Complete response	3%
Partial response	44%
Response by prior metastatic regimens	
0	64% (95% CI: 49.1%-79.2%)
1	20% (95% CI: 4.3%-48.1%)
>2	22% (95% CI: 2.8%-60.0%)
Response by prior anthracycline therapy	
Anthracycline naïve	58% (95% CI: 38.7%-76.7%)
Anthracycline exposed	41% (95% CI: 24.7%-56.4%)
Response by site of dominant lesion	
Visceral	40% (95% CI: 24.9%-54.2%)
Nonvisceral	68% (95% CI: 47.5%-89.3%)
Median time to progression	
All patients	26.6 weeks
Responding patients*	48.1 weeks
Median overall survival	63.6 weeks

* Confirmed complete or partial response.

SOURCE: Ibrahim NK et al. *J Clin Oncol* 2005;23(25):6019-26.

PHASE III TRIAL COMPARING *NAB* PACLITAXEL VERSUS STANDARD PACLITAXEL

Accrual: 460 (closed)

Eligibility	Measurable metastatic breast cancer, no prior paclitaxel or docetaxel for metastatic disease
ARM 1	*Nab* paclitaxel 260 mg/m^2 with no premedications q3wk
ARM 2	Standard paclitaxel 175 mg/m^2 with premedications q3wk

Efficacy data	*Nab* paclitaxel (n = 229)	Standard paclitaxel (n = 225)	*p*-value
Response rates All patients	33% (95% CI: 27.09-39.29)	19% (95% CI: 13.58-23.76)	0.001
First-line therapy	42% (95% CI: 32.44-52.10)	27% (95% CI: 17.75-36.19)	0.029
Second-line or greater	27% (95% CI: 18.98-34.05)	13% (95% CI: 7.54-18.93)	0.006
Prior anthracycline therapy	34% (95% CI: 27.09-41.09)	18% (95% CI: 12.56-24.01)	0.002
Time to tumor progression	23.0 weeks	16.9 weeks	0.006
Median survival All patients	65.0 weeks	55.7 weeks	0.374
Second-line or greater	56.4 weeks	46.7 weeks	0.024
Safety data	***Nab* paclitaxel (n = 229)**	**Standard paclitaxel (n = 225)**	***p*-value**
Grade IV neutropenia	9%	22%	<0.001
Grade III sensory neuropathy	10%	2%	<0.001
Hypersensitivity (any grade)	<1%	2%	NR
Growth factors used	3%	6%	NR

NR = not reported

SOURCE: Gradishar WJ et al. *J Clin Oncol* 2005;23(31):7794-803.

PHASE II STUDY OF ABI-007 AND GEMCITABINE IN WOMEN WITH METASTATIC BREAST CANCER

Protocol ID: NCCTG-N0531
Target accrual: 43 (open)

Eligibility	Metastatic breast cancer with measurable disease, no brain metastasis, no prior chemotherapy for metastatic disease
Protocol	(*Nab* paclitaxel, 125 mg/m^2 + gemcitabine 1,000 mg/m^2) d1, 8 q3wk

Treatment continues in the absence of disease progression or unacceptable toxicity.

SOURCES: NCI Physician Data Query, January 2006; Moreno-Aspitia A, Perez EA. *Clin Breast Cancer* 2005;6(4):361-4.

SELECT PUBLICATIONS

Blum JL et al. **ABI-007 nanoparticle paclitaxel: Demonstration of anti-tumor activity in taxane-refractory metastatic breast cancer.** Presentation. ASCO 2004;Abstract 543.

Blum JL et al. **ABI-007 nanoparticle paclitaxel: Demonstration of anti-tumor activity in taxane-refractory metastatic breast cancer.** *Proc ASCO* 2003;Abstract 64.

Bria E et al. **Taxanes with anthracyclines as first-line chemotherapy for metastatic breast carcinoma.** *Cancer* 2005;103(4):672-9.

Ghersi D et al. **A systematic review of taxane-containing regimens for metastatic breast cancer.** *Br J Cancer* 2005;93(3):293-301.

Gradishar WJ et al. **Phase III trial of nanoparticle albumin-based paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer.** *J Clin Oncol* 2005;23(31):7794-803.

Grecea D et al. **A phase II study of weekly or 3-weekly docetaxel in patients with metastatic breast cancer.** *Proc ASCO* 2005;Abstract 736.

Harries M et al. **Nanoparticle albumin-bound paclitaxel for metastatic breast cancer.** *J Clin Oncol* 2005;23(31):7768-71.

Ibrahim NK et al. **Multicenter phase II trial of ABI-007, an albumin-bound paclitaxel, in women with metastatic breast cancer.** *J Clin Oncol* 2005;23(25):6019-26.

Jones SE et al. **Randomized phase III Study of docetaxel compared with paclitaxel in metastatic breast cancer.** *J Clin Oncol* 2005;23(24):5542-51.

Moreno-Aspitia A, Perez EA. **North Central Cancer Treatment Group N0531: Phase II trial of weekly albumin-bound paclitaxel (ABI-007; Abraxane™) in combination with gemcitabine in patients with metastatic breast cancer.** *Clin Breast Cancer* 2005;6(4):361-4.

Nabholtz JM, Gligorov J. **The role of taxanes in the treatment of breast cancer.** *Expert Opin Pharmacother* 2005;6(7):1073-94.

O'Shaughnessy J et al. **ABI-007 (ABRAXANE™), a nanoparticle albumin-bound (*nab*) paclitaxel demonstrates superior efficacy vs taxol in MBC: A phase III trial.** Presentation. San Antonio Breast Cancer Symposium 2003;Abstract 44.

O'Shaughnessy JA et al. **Weekly nanoparticle albumin paclitaxel (Abraxane) results in long-term disease control in patients with taxane-refractory metastatic breast cancer.** *Breast Cancer Res Treat* 2004;88(Suppl 1);Abstract 1070.

NANOPARTICLE VERSUS STANDARD PACLITAXEL

The superior efficacy, favorable safety profile, and greater patient convenience of ABI-007 [nanoparticle paclitaxel] make this novel albumin-bound paclitaxel an important advance in the treatment of patients with MBC [metastatic breast cancer]. ABI-007 warrants further investigation, using additional dosing regimens (eg, weekly) and in combination with other treatment modalities, as front-line treatment of breast cancer and other solid tumors.

— William J Gradishar, MD et al.* J Clin Oncol *2005; 23(31):7794-803.

Compared with three-weekly polyoxyethylated castor oil-based paclitaxel, ABI-007 would seem to have several advantages. First, efficacy with respect to response and time to progression seems superior. Second, and arguably most importantly, this is a taxane that can be given three-weekly, in 30 minutes, and without premedication. For patients with a contraindication to steroids, this is a major advantage. In addition, the lower incidence of myelosuppression favors ABI-007, and although sensory neuropathy was more common, this was reversible and relatively short lived for the majority of patients.

— Mark Harries, MD et al.* J Clin Oncol *2005;23(31):7768-71.

The ability to deliver drugs more safely offers a real potential benefit. Even if the randomized trial, perhaps, didn't show a higher response rate or a modestly longer time to progression compared to paclitaxel (O'Shaughnessy 2003), simply not having to premedicate and not having to worry about serious allergic reactions, in my mind, would make *nab* paclitaxel the obvious choice.

— Andrew D Seidman, MD.* Breast Cancer Update *2005 (8)

An interesting observation, corroborated in the pivotal trial and in the weekly trial that Joanne Blum reported (Blum 2003), is that the behavior of the neuropathy appears to be slightly different than that seen with standard paclitaxel. Although we don't have sufficient data to be absolutely definitive, there is a suggestion that with *nab* paclitaxel the neuropathy is much shorter lived — on the order of 10 days to three weeks — and it tends to diminish to a point where you can re-treat the patients. That's something that warrants further evaluation.

— William J Gradishar, MD.* Breast Cancer Update *2005 (4)

NANOPARTICLE PACLITAXEL VERSUS OTHER TAXANES

In cross-study comparisons of nanoparticle paclitaxel versus docetaxel, each given every three weeks, the response rates were similar in the 30 percent range. However, docetaxel in the metastatic setting is toxic because of side effects like asthenia, fluid retention and neutropenia, and it's difficult to administer for long periods of time.

One can give docetaxel in the adjuvant setting where treatment is short term, but I believe nanoparticle paclitaxel is better tolerated. I don't use single-agent docetaxel in the metastatic setting, and I would use nanoparticle paclitaxel in lieu of weekly paclitaxel.

I would like to see more data on combinations with nanoparticle paclitaxel to learn more about the toxicity profiles before using it in a combination off protocol.

— Joanne L Blum, MD, PhD.* Breast Cancer Update *2005 (1)

The availability of *nab* paclitaxel is a welcome advance in drug delivery. Combining paclitaxel tightly with a nanoparticle allows it to dissolve without the use of Cremophor, which is one of the compounds in the original paclitaxel formulation that causes acute allergic reactions and necessitates the use of steroids. Evidence also exists from laboratory models that you may have better tumor penetration with *nab* paclitaxel.

What is happening in humans is hard to know, but in a head-to-head study, the clinical endpoints of response rate and time to progression were actually improved with *nab* paclitaxel compared to the original paclitaxel formulation. It was a difficult comparison because the doses weren't the same. It may be that *nab* paclitaxel was more tolerable and patients were able to receive a higher dose; therefore, they had a better response.

— Debu Tripathy, MD.* Breast Cancer Update *2005 (5)