Taxanes in the Metastatic Setting

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In patients with metastatic breast cancer, the roles of the taxanes — docetaxel, paclitaxel and *nab* paclitaxel — are evolving. Recent Phase III trials have demonstrated that every three-week regimens of docetaxel or *nab* paclitaxel have better efficacy than every three-week paclitaxel. *Nab* paclitaxel presents the advantage of not requiring premedication, which avoids side effects, particularly of steroid premedication. Another advantage of *nab* paclitaxel is that it can be administered over 30 minutes. *Nab* paclitaxel has also been evaluated in two Phase II trials on a weekly schedule, which seems to retain efficacy with less toxicity. A Phase II trial found weekly docetaxel comparable to every three-week docetaxel in terms of efficacy, but weekly docetaxel appeared to have a more favorable toxicity profile. Clinical trials will continue to delineate the role of the taxanes in the metastatic setting.

PHASE III TRIAL COMPARING DOCETAXEL VERSUS PACLITAXEL IN PATIENTS WHO HAD PROGRESSED AFTER AN ANTHRACYCLINE-CONTAINING REGIMEN

Response to treatment (intention-to-treat population)	Docetaxel q3wk (n = 225)	Paclitaxel q3wk (n = 224)	*p*-value
Overall response rate	32.0% (95% CI 25.9-38.1)	25.0% (95% CI 19.3-30.7)	0.10
Time to tumor progression	5.7 months	3.6 months	<0.0001
Duration of response	7.5 months (95% CI 5.8-9.1)	4.6 months (95% CI 3.9-6.0)	0.01
Overall survival	15.4 months	12.7 months	0.03
Hematologic adverse events	**Docetaxel (n = 222)**	**Paclitaxel (n = 222)**	***p*-value**
Grade III/IV neutropenia	93.3%	54.5%	<0.0001
Febrile neutropenia	14.9%	1.8%	<0.001
Grade III/IV anemia	10.4%	7.3%	0.24
Grade III/IV thrombocytopenia	4.6%	2.8%	0.31

SOURCE: Jones SE et al. *J Clin Oncol* 2005;23(24):5542-51.

PHASE III TRIAL COMPARING *NAB* PACLITAXEL VERSUS STANDARD PACLITAXEL

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			
Grade IV neutropenia	9%	22%	<0.001
Grade III sensory neuropathy	10%	2%	<0.001
Growth factors used	3%	6%	NR

* *Nab* paclitaxel = 260 mg/m^2 IV every three weeks without premedication.
† Standard paclitaxel = 175 mg/m^2 IV every three weeks with premedication.
NR = not reported

SOURCE: Gradishar WJ et al. *J Clin Oncol* 2005;23(31);[Epub ahead of print].

PHASE II STUDY OF WEEKLY VERSUS EVERY THREE-WEEK DOCETAXEL

Accrual: 60 (Closed)

Eligibility	Metastatic breast cancer
ARM 1	Docetaxel 35 mg/m^2 qwk x 8 – 12 cycles
ARM 2	Docetaxel 100 mg/m^2 q3wk x 6 cycles

Proportion of patients receiving docetaxel as: first-line treatment, 83.3%; second-line treatment, 16.6%

EFFICACY DATA

Parameter	Weekly docetaxel (n = 25)	3-weekly docetaxel (n = 35)
Intent to treat overall response rate	36%	42%
Median time to progression	5.2 months	5.8 months
Toxicity data		
Incidence of Grade III/IV adverse events	30	64
Number of patients experiencing Grade III/IV adverse events	12	23

Conclusions: "Weekly docetaxel is an active regimen in metastatic breast cancer with comparable efficacy to 3-weekly docetaxel. Both schedules were well tolerated, weekly docetaxel appears to have a more favourable toxicity profile, providing an attractive strategy for palliative treatment of metastatic breast cancer."

SOURCE: Grecea D et al. *Proc ASCO* 2005;Abstract 736.

ANTHRACYCLINES WITH OR WITHOUT TAXANES AS FIRST-LINE CHEMOTHERAPY: POOLED META-ANALYSIS OF 2,805 PATIENTS

Parameter	Risk ratio*	95% CI	*p*-value
Time to progression	1.10	1.00-1.21	0.05
Overall response rate	1.21	1.10-1.32	<0.001
Complete response rate	2.04	1.41-2.94	<0.001
Overall survival	1.05	0.90-1.23	0.58
Neutropenia	1.19	1.11-1.29	<0.001
Febrile neutropenia	2.82	1.39-5.69	<0.001

"All Phase III peer-reviewed published or presented trials were considered eligible. A pooled analysis (Method A) and a literature-based meta-analysis (Method B) were accomplished, and event-based relative risk ratios (RR_{A-B}) with 95% confidence intervals were derived. Both analyses were performed to examine for significant differences in time to disease progression (TTP), overall response rate (ORR), overall survival (OS), complete response rate (CR), neutropenia, and febrile neutropenia (FN).

"The adjunction of taxanes to anthracyclines in first-line chemotherapy for metastatic breast carcinoma yielded a significant benefit in activity (ORR, CR), a slight advantage in TTP, and a trend in OS, although with a significant cost in hematologic toxicity."

* Risk ratio of anthracycline + taxane vs anthracycline + nontaxane

SOURCE: Bria E et al. *Cancer* 2005;103(4):672-9.

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.

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. **Superior efficacy of albumin-bound paclitaxel, ABI-007, compared with polyethylated castor oil-based paclitaxel in women with metastatic breast cancer: Results of a phase III trial.** *J Clin Oncol* 2005;23(31);[Epub ahead of print].

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.

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.

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

Nyman DW et al. **A phase I trial of ABI-007, nanoparticle paclitaxel, administered to patients with advanced nonhematologic malignancies.** *J Clin Oncol* 2004;22(14 Suppl);Abstract 2027.

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.

PHASE III TRIAL OF DOCETAXEL VS PACLITAXEL

This is the first clinical trial to compare directly the taxanes docetaxel and paclitaxel as monotherapy for patients with advanced breast cancer. Using US Food and Drug Administration-approved doses and schedules for each agent, this phase III study has demonstrated that docetaxel is superior to paclitaxel in TTP (5.7 *v* 3.6 months; $p < .0001$), response duration (7.5 *v* 4.6 months; $p = .01$), and OS (15.4 *v* 12.7 months; $p = .03$). The overall response rate was also greater with docetaxel (32% *v* 25%; $p = .10$). The survival advantage for docetaxel was observed despite the increased incidence of toxicities leading to dose reductions and treatment withdrawal, and the slightly greater use of salvage treatment in patients randomly assigned to paclitaxel. The results of this study are consistent with those reported for previous phase III studies of single-agent docetaxel and paclitaxel...

— Stephen E Jones, MD et al.* J Clin Oncol *2005;23(24):5542-51.

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):[Epub ahead of print].

NANOPARTICLE PACLITAXEL COMPARED TO OTHER TAXANES

I believe nanoparticle paclitaxel is more active than paclitaxel based on the randomized trials. 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, whether given weekly or every three weeks, 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)

CHOICE OF TAXANES IN THE METASTATIC SETTING

A weekly regimen of the original paclitaxel formulation would have been my choice in the past. Now that we have data with *nab* paclitaxel, I think that's a reasonable option also. From the data, *nab* paclitaxel may be preferable. It outperformed the original paclitaxel formulation when administered every three weeks. A weekly regimen also seems to outperform an every three-week regimen of the original paclitaxel formulation, and I'm left wondering which is the best drug to use. For patients who prefer an every three-week schedule, I believe *nab* paclitaxel is the way to go. Otherwise, it's a toss-up between every three-week *nab* paclitaxel and a weekly regimen of the original paclitaxel formulation. I don't believe there's a way to compare the two. CALGB is planning to conduct a head-to-head trial comparing weekly regimens of *nab* paclitaxel and the original paclitaxel formulation.

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