Taxanes in the Metastatic Setting

The role of taxanes in patients with metastatic breast cancer is evolving. A recent Phase III trial demonstrated that every three-week regimen of docetaxel has better efficacy than every three-week paclitaxel. A Phase III trial found paclitaxel with greater efficacy when administered weekly rather than every three weeks, and 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. A recently conducted meta-analysis concluded there was no overall survival advantage due to the use of taxanes alone or combined with anthracyclines in the first-line treatment of patients with metastatic breast cancer. 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
Grade III/IV hematologic adverse events	**Docetaxel (n = 222)**	**Paclitaxel (n = 222)**	***p*-value**
Neutropenia	93.3%	54.5%	<0.0001
Febrile neutropenia	14.9%	1.8%	<0.001
Anemia	10.4%	7.3%	0.24
Thrombocytopenia	4.6%	2.8%	0.31

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

PHASE II TRIALS OF WEEKLY VERSUS EVERY THREE-WEEK DOCETAXEL

Grecea et al[1]

ARM 1	Docetaxel 35 mg/m^2 qwk x 8-12 weeks (median = 10 weeks)
ARM 2	Docetaxel 100 mg/m^2 q3wk x 6 cycles

Tabernero et al[2]

ARM 1	Docetaxel 40 mg/m^2 qwk x 6 weeks, then two weeks off*
ARM 2	Docetaxel 100 mg/m^2 q3wk*

Trial	Grecea et al[1]		Tabernero et al[2]	
Parameter	**Weekly (n = 25)**	**3-weekly (n = 35)**	**Weekly (n = 41)**	**3-weekly (n = 42)**
Intent-to-treat overall response rate	36%	42%	34%	33%
Median time to progression (months)	5.2	5.8	5.7	5.3
Incidence of Grade III/IV adverse events	30	64	44	96
Number of patients experiencing Grade III/IV adverse events	12	23	20	31

* Treatment continued until disease progression or unacceptable toxicity.

SOURCES: [1] Grecea D et al. *Proc ASCO* 2005;Abstract 736.
[2] Tabernero J et al. *Ann Oncol* 2004;15(9):1358-65.

CALGB-9840: PHASE III STUDY COMPARING WEEKLY VERSUS THREE-WEEKLY PACLITAXEL (N = 738)

Efficacy end point	Weekly paclitaxel	3-weekly paclitaxel	HR	*p*-value
Tumor response rate	40%	28%	NR	0.017
Time to progression (months)	9	5	1.45	0.0008
Overall survival (months)	24	16	1.19	0.17
Grade III/IV toxicity	**Weekly paclitaxel**	**3-weekly paclitaxel**	**HR**	***p*-value**
Sensory neuropathy	23%	12%	NR	0.001
Motor neuropathy	8%	4%	NR	0.04
Granulocytopenia	5%	15%	NR	0.013

HR = hazard ratio; NR = not reported

SOURCE: Seidman AD et al. Presentation. ASCO 2004;Abstract 512.

META-ANALYSIS OF TRIALS OF TAXANES (T) ALONE OR COMBINED WITH ANTHRACYCLINES (A) IN FIRST-LINE TREATMENT

Single-agent trials, T vs A	
Overall response with taxanes	33%
Overall response with anthracyclines	38%
	T vs A, $p = 0.08$
PFS, T vs A	HR = 1.19, $p = 0.01$
OS, T vs A	HR = 1.01, $p = 0.90$
Combination trials, T-based vs A-based	
Overall response in T-based	56%
Overall response in A-based	45%
	T-based vs A-based, $p < 0.001$
PFS, T-based combination vs A-based	HR = 0.93, $p = 0.06$
OS, T-based combination vs A-based	HR = 0.95, $p = 0.23$

HR = hazard ratio

SOURCE: Piccart MJ et al. *Proc San Antonio Breast Cancer Symposium* 2005; Abstract 6086.

ERASME 3: PHASE III TRIAL OF DOXORUBICIN/ DOCETAXEL VERSUS DOXORUBICIN/PACLITAXEL IN PATIENTS WITH METASTATIC BREAST CANCER

Efficacy parameter	Doxorubicin + docetaxel (n = 107)	Doxorubicin + paclitaxel (n = 103)	*p*-value
Overall response rate	39.6%	41.8%	NS
Median disease-free survival	8.7 months	8.0 months	0.977
Overall survival	21.4 months	27.3 months	0.099

NS = not significant

SOURCE: Cassier PA et al. Poster. San Antonio Breast Cancer Symposium 2005;Abstract 6087.

SELECT PUBLICATIONS

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

Cassier PA et al. **A phase III randomized trial of doxorubicin (A) and docetaxel (D) versus doxorubicin and paclitaxel (P) in metastatic breast cancer preliminary results of the Erasme 3 study.** Poster. San Antonio Breast Cancer Symposium 2005;Abstract 6087.

Eniu A et al. **Weekly administration of docetaxel and paclitaxel in metastatic or advanced breast cancer.** *The Oncologist* 2005;10:665-85.

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

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.

Piccart MJ et al. **Effects of taxanes alone or in combination with anthracyclines on tumor response, progression-free survival and overall survival in first-line chemotherapy of patients with metastatic breast cancer: An analysis of 4,256 patients randomized in 12 trials.** *Proc San Antonio Breast Cancer Symposium* 2005;Abstract 6086.

Seidman AD et al. **Phase III study of weekly paclitaxel via 1-hr infusion vs standard 3-hr infusion every third week in the treatment of metastatic breast cancer, with trastuzumab for HER2 positive MBC and randomized for trastuzumab in HER2 normal MBC.** *Proc ASCO* 2004;Abstract 512.

Tabernero J et al. **A multicentre, randomised phase II study of weekly or 3-weekly docetaxel in patients with metastatic breast cancer.** *Ann Oncol* 2004;15(9):1358-65.

PHASE III TRIAL OF DOCETAXEL VERSUS 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.

DOSE AND SCHEDULE OF TAXANE THERAPY

Optimizing the dose and schedule of taxane therapy to maximize antitumor activity while maintaining a favorable toxicity profile remains an important goal in MBC. Weekly, rather than the standard every-3-weeks, dosing of docetaxel and paclitaxel at lower doses is one way to provide an efficacious method of drug delivery while maintaining a favorable toxicity profile. Various studies support weekly taxane dosing as an active regimen in MBC, even in heavily pretreated, refractory disease and in elderly patients or those with poor performance status. Importantly, this regimen is associated with a low incidence of severe hematologic toxicities and acute nonhematologic toxicities.

— Alexandru Eniu, MD.* The Oncologist *2005;10:665-85.

META-ANALYSIS OF TRIALS OF TAXANES WITH OR WITHOUT ANTHRACYCLINES

Single agent A [anthracyclines, doxorubicin or epirubicin] was significantly better than single agent T [taxanes, paclitaxel or docetaxel] in terms of PFS [progression-free survival], marginally better in terms of response rate but not different in terms of OS [overall survival]. T-based combinations were significantly better than A-based combinations in terms of response rates, marginally better in terms of PFS but not different in terms of OS.

— Martine J Piccart-Gebhart, MD, PhD et al.* Proc San Antonio Breast Cancer Symposium *2005;Abstract 6086.

DOXORUBICIN/DOCETAXEL VERSUS DOXORUBICIN/PACLITAXEL

In this study paclitaxel and docetaxel in combination with doxorubicin were equivalent in terms of overall quality of life scores and efficacy. Significant differences in toxicity profile did not result in significant differences in QOL.

— PA Cassier et al.* Poster. San Antonio Breast Cancer Symposium *2005;Abstract 6087.

WEEKLY VERSUS EVERY THREE-WEEK DOCETAXEL

The present study was conducted to assess the tolerability and activity of weekly and 3-weekly docetaxel in patients with anthracycline-resistant metastatic breast cancer. Weekly docetaxel 40 mg/m^2 and 3-weekly docetaxel 100 mg/m^2 produced overall response rates of 34% and 33%, respectively. The mean cumulative dose of docetaxel was similar for both treatment groups (620 and 614 mg/m^2 for the weekly and 3-weekly schedules, respectively). Although both schedules were well tolerated, the weekly regimen appears to have a more favourable toxicity profile than 3-weekly docetaxel with respect to grade 3–4 neutropenia, neurotoxicity, febrile neutropenia and stomatitis.

— Josep Tabernero et al.* Ann Oncol *2004;15(9):1358-65.

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.

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