Chemotherapy for Metastatic Disease

Clinical trials of chemotherapeutic agents and regimens in the metastatic setting not only help better define clinical care but also provide important clues to future adjuvant therapy strategies. A series of recent studies have resulted in encouraging results with new combinations, including capecitabine/docetaxel, capecitabine/paclitaxel, and gemcitabine/paclitaxel. However, most breast cancer clinical research leaders support nonprotocol therapy with sequential single-agent chemotherapy in the metastatic setting, and the choice of agents is mainly based on prior adjuvant treatment and toxicity considerations.

PHASE III TRIALS COMPARING SINGLE-AGENT AND COMBINATION CHEMOTHERAPY FOR METASTATIC BREAST CANCER

	XT Trial[1]: Comparing docetaxel monotherapy and combination capecitabine/docetaxel		Intergroup Trial E1193[2]: Comparing doxorubicin, paclitaxel and combination doxorubicin/paclitaxel		
Treatment	**Docetaxel**	**Capecitabine/docetaxel**	**Doxorubicin**	**Paclitaxel**	**Doxorubicin/paclitaxel**
Objective response	30%	42%	36% (20% response to crossover)	34% (22% response to crossover)	47%
Median survival	11.5 months	14.5 months	18.9 months	22.2 months	22.0 months

SOURCES: [1] O'Shaughnessy J et al. *J Clin Oncol* 2002;20(12):2812-23.

[2] Sledge GW et al. *J Clin Oncol* 2003;21(4):588-92.

PHASE III TRIAL OF GEMCITABINE/PACLITAXEL VERSUS PACLITAXEL AS FIRST-LINE TREATMENT IN PATIENTS WITH ANTHRACYCLINE-PRETREATED METASTATIC BREAST CANCER: INTERIM SURVIVAL REPORT

Accrual: 529 (Closed)

Eligibility	**Locally recurrent or metastatic breast cancer Prior adjuvant anthracycline treatment No prior therapy for advanced disease**
ARM 1	**Gemcitabine + paclitaxel q3wk**
ARM 2	**Paclitaxel q3wk**

Endpoint	GT (n=267)	T (n=262)	*p*-value
Response rate (95% CI)	40.8% (34.9, 46.7)	22.1% (17.2, 27.2)	<0.0001
Median TTP (95% CI)	5.2 mo (4.2, 8.6)	2.9 mo (2.6, 3.7)	<0.0001
Median overall survival (95% CI)	18.5 mo (16.5, 21.2)	15.8 mo (14.4, 17.4)	0.018

TTP = time to progression

SOURCE: Albain KS. Presentation. ASCO, 2004;Abstract 510.

MULTICENTER PHASE II STUDY OF CAPECITABINE PLUS PACLITAXEL AS FIRST-LINE THERAPY (N=47)

Efficacy endpoints	No. of responders	Response rate
Overall response (90% CI)	24	51% (38, 64)
Complete response	7	15%
Partial response	17	36%
Stable disease ≥6 mo	9	19%
Clinical benefit (95% CI)	33	70% (55, 83)

Grade III/IV adverse events	No. of patients	Percent
Neutropenia	7	15
Alopecia	6	13
Hand-foot syndrome	5	11
Fatigue	4	9
Dyspnea	4	9
Paraesthesia	3	6
Peripheral neuropathy	3	6

Capecitabine = 825 mg/m^2 twice daily, days 1-14, every three weeks
Paclitaxel = 175 mg/m^2 day 1 every three weeks

source: Gradishar WJ et al. *J Clin Oncol* 2004;22(12):2321-7.

ACTIVE PHASE III TRIALS OF COMBINATION CHEMOTHERAPY REGIMENS IN METASTATIC BREAST CANCER

Protocol ID	Target accrual	Eligibility	Randomization
CA163-048	Not reported	Prior anthracycline and taxane; no more than two prior chemotherapy regimens	Ixabepilone (BMS-247550) + capecitabine Capecitabine
GSK-EGF100151	372	Progression in metastatic disease or relapse within six months after adjuvant taxane and anthracycline	Lapatinib (GW572016) + capecitabine Capecitabine
CA163-046	Not reported	Two or three prior chemotherapy regimens; one in the metastatic setting; taxane resistant and prior anthracycline	Ixabepilone (BMS-247550) + capecitabine Capecitabine
GSK-EGF30001	570	No prior chemotherapy for Stage IV HER2-negative or unknown	Paclitaxel + lapatinib (GW572016) Paclitaxel + placebo

SOURCE: NCI Physician Data Query, January 2005.

PHASE II TRIAL OF CAPECITABINE AND WEEKLY PACLITAXEL IN TAXANE-NAÏVE PATIENTS WITH METASTATIC BREAST CANCER: EFFICACY AND TOXICITY

Response*	Percent
Complete response	0
Partial response	50
Stable disease	30
Clinical benefit	65

* N = 54 evaluable patients

Grade III/IV adverse events (>5%)	No. of patients Grade III/IV	Percent Grade III/IV
Hand-foot syndrome	10/0	18.2
Neutropenia	3/4	12.7
Nausea	3/0	5.5
Leukopenia	1/2	5.5
Diarrhea	3/0	5.5

SOURCE: Blum JL. Poster 5053. San Antonio Breast Cancer Symposium, 2004.

SELECT PUBLICATIONS

Alba E et al; Spanish Breast Cancer Research Group. **Multicenter randomized trial comparing sequential with concomitant administration of doxorubicin and docetaxel as first-line treatment of metastatic breast cancer: A Spanish Breast Cancer Research Group (GEICAM-9903) phase III study.** *J Clin Oncol* 2004;22(13):2587-93.

Albain KS et al. **Global phase III study of gemcitabine plus paclitaxel (GT) vs paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival.** *Proc ASCO* 2004;Abstract 510.

Blum JL et al. **A Phase II trial of combination therapy with capecitabine and weekly paclitaxel for metastatic breast cancer (MBC): Preliminary results in taxane-naïve patients.** Poster 5053. San Antonio Breast Cancer Symposium, 2004.

Gradishar WJ et al. **Capecitabine plus paclitaxel as front-line combination therapy for metastatic breast cancer: A multicenter phase II study.** *J Clin Oncol* 2004;22(12):2321-7.

O'Shaughnessy J et al. **Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results.** *J Clin Oncol* 2002;20(12):2812-23.

Sledge GW et al. **Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: An Intergroup trial (E1193).** *J Clin Oncol* 2003;21(4):588-92.

CAPECITABINE/PACLITAXEL IN PATIENTS WITH TAXANE-NAÏVE METASTATIC BREAST CANCER

In our trial evaluating capecitabine plus weekly paclitaxel, patients could have undergone one prior chemotherapy regimen for metastatic breast cancer, which is in contrast to the front-line trial conducted by Bill Gradishar that evaluated a similar regimen but used paclitaxel 175 mg/m^2 every three weeks. Our response rate was very exciting, with 50 percent of patients achieving a partial response and an additional 30 percent of patients with stable disease for greater than six months, which is comparable to the 70 percent clinical benefit seen in Dr Gradishar's trial. The median progression-free survival is 12.1 months, and overall median survival has not yet been reached. The combination was remarkably well tolerated and the hand-foot syndrome that occurred in 18 percent of patients was easily managed with dose modification.

— Joanne L Blum, MD, PhD

FIRST-LINE CAPECITABINE/PACLITAXEL

"This phase II study supports the concept that the complementary mechanisms of action and non-overlapping major toxicities of capecitabine and taxanes create a highly effective and well-tolerated combination chemotherapy regimen for MBC. Both capecitabine and taxanes are effective when used as monotherapy, and preclinical studies in tumor xenograft models demonstrate synergistic antitumor activity when the drugs are used in combination. … The high clinical activity of capecitabine plus paclitaxel documented in this phase II study is consistent with that reported from the recent large international phase III trial of capecitabine combined with docetaxel, compared with docetaxel alone, in anthracycline-pretreated patients."

— Gradishar WJ et al. J Clin Oncol *2004;22(12):2321-7.*

COMBINATION VERSUS SEQUENTIAL DOXORUBICIN AND PACLITAXEL AS FIRST-LINE THERAPY

"Trial E1193 tested whether the combination of two active drugs, representing what are arguably the two most active classes of agents (anthracyclines and taxanes) used in breast cancer, might prove superior to sequential, single-agent therapy with the same agents. Combination therapy resulted both in a superior overall response rate and a superior TTF, two frequent measures of efficacy in metastatic chemotherapy trials. Despite this superiority, combination therapy failed to improve overall survival. Perhaps more importantly, given the usually fatal nature of the disease, combination therapy did not improve quality of life."

— Sledge GW et al. J Clin Oncol *2003;21(4):588-92.*

GEMCITABINE (G) PLUS PACLITAXEL (T) VERSUS PACLITAXEL AS FIRST-LINE THERAPY

"GT had phase II safety and efficacy in MBC after anthracyclines, so it was compared to T in a phase III study of frontline therapy. … GT provides significant OS advantage over T when both are given on a q3 week cycle, a result to be confirmed in the final planned analysis in late 2004. The TTP benefit predicted OS improvement with longer follow-up. GT should be considered a frontline regimen in MBC."

— Albain KS et al. Proc ASCO *2004;Abstract 510.*

CAPECITABINE/DOCETAXEL VERSUS DOCETAXEL IN PATIENTS WITH METASTATIC BREAST CANCER

"This phase III study demonstrates that capecitabine/docetaxel combination therapy is more effective than a current standard treatment, single-agent docetaxel, and is thus a significant development for patients with breast cancer whose disease has progressed after an anthracycline containing regimen. The addition of capecitabine to docetaxel 75 mg/m^2 resulted in a significant improvement in overall survival, time to disease progression, and response rate compared with docetaxel 100 mg/m^2 alone. The addition of capecitabine to docetaxel resulted in a 23% reduction in risk of death compared with docetaxel, with an increase in median survival of 3 months. The survival benefit with capecitabine/docetaxel combination therapy was seen early in the course of treatment and persisted throughout the study."

— O'Shaughnessy J et al. J Clin Oncol *2002;20(12):2812-23.*

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