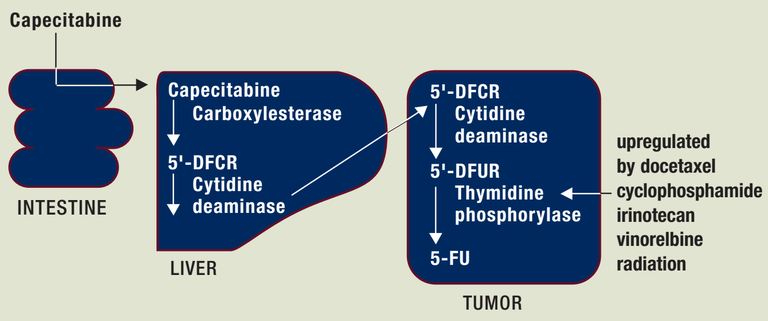
Capecitabine/Docetaxel: A Rationally Derived Combination

Systemic treatment for metastatic breast cancer is palliative, and a primary goal of therapy is maintenance and improvement in quality of life. In recent years, there has been a shift in medical oncology practice toward the use of less intensive chemotherapy in the metastatic setting, including the use of sequential single agents rather than combinations. The background of this trend is the lack of evidence that combination regimens improve survival. However, in December 2000, O'Shaughnessy et al. reported an improvement in the response rate and survival for women treated with the combination of capecitabine and docetaxel compared to docetaxel alone. A strong scientific rationale for this combination exists; namely, docetaxel upregulates thymidine phosphorylase, the final enzyme that activates capecitabine to 5-fluorouracil. New trials in the adjuvant and neoadjuvant settings are evaluating this regimen, which is also commonly utilized in women with rapidly progressing metastases.

ENZYMATIC CONVERSION OF CAPECITABINE TO 5-FLUOROURACIL



PHASE III TRIAL OF DOCETAXEL/CAPECITABINE (XT) COMBINATION THERAPY VS DOCETAXEL MONOTHERAPY (T) IN METASTATIC BREAST CANCER — Closed Protocol

Eligibility	**Metastatic breast cancer patients resistant to or relapsing after anthracycline-based therapy**
ARM 1	**Capecitabine 2500 mg/m² po in 2 daily divided doses days 1-14 + docetaxel 75 mg/m² IV q 3 weeks**
ARM 2	**Docetaxel 100 mg/m² IV q 3 weeks**

EFFICACY OF XT VS T IN PATIENTS WITH ANTHRACYCLINE-PRETREATED METASTATIC BREAST CANCER

	Capecitabine/Docetaxel (XT) n=255	Docetaxel (T) n=256	P value
Median time to progression	6.1 months [5.4-6.5]	4.2 months [3.4-4.5]	log rank p=0.0001
Objective tumor reponse	42% [36-48]	30% [24-36]	p=0.006
Stable disease	38% [32-44]	44% [38-50]	
Median survival	14.5 months [12.3-16.3]	11.5 months [9.8-12.7]	log rank p=0.0126

DERIVED FROM: O'Shaughnessy J et al. **Superior survival with capecitabine and docetaxel combination chemotherapy in anthracycline-pretreated patients with advanced breast cancer.** *J Clin Oncol* 2002;20:2812–2823.

XT VERSUS T: POST-STUDY CHEMOTHERAPY AFTER PROGRESSION

	XT	T
% receiving postrandomization chemotherapy	70%	63%
Agent received*		
capecitabine	3%	17%
5-FU	20%	23%
vinorelbine	31%	26%
anthracyclines	10%	11%
docetaxel	20%	7%

*** Reflects combination and single-agent chemotherapy regimens.**

- **Capecitabine versus all other chemotherapies resulted in a 50% decreased risk of death (HR=0.5, p<0.005).**
- **Vinorelbine-containing chemotherapy versus all other chemotherapy agents did not provide benefit (HR=1.0, p=0.94).**
- **Median survival was 21.0 months for single-agent capecitabine, versus 13.5 months for vinorelbine, versus 12.5 months for patients receiving any other chemotherapy regimen.**

DERIVED FROM: O'Shaughnessy J et al. *J Clin Oncol* 2002;20:2812-2823.

SELECT PUBLICATIONS

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CAPECITABINE/DOCETAXEL VERSUS DOCETAXEL

There were several reasons to combine docetaxel with capecitabine. First, they are both very active agents in treating metastatic breast cancer. Second, they have largely nonoverlapping toxicities. Third and very importantly, the two agents exhibit a rare example of biochemical synergism. Docetaxel quite profoundly upregulates the expression of thymidine phosphorylase, the pivotal and last enzyme in the metabolism of capecitabine to 5-FU at the tumor site. Thymidine phosphorylase is overexpressed in a majority of human breast cancers as well as in a number of other cancers. When you put docetaxel and capecitabine together, there is clear, synergistic tumor-cell killing. So, the trial was attempting to see whether this could translate into something of real importance to women with metastatic breast cancer.

—Joyce O'Shaughnessy, MD

QUALITY OF LIFE WITH CAPECITABINE/DOCETAXEL

Quality of life is a critical issue in treating advanced disease. If we prolong duration of response without a reasonable quality of life, we are kidding ourselves. The docetaxel/capecitabine study was one of the few clinical trials where quality of life was a primary endpoint. A rigorous quality-of-life measurement was used before and during the study, showing that patients receiving combination docetaxel/capecitabine had equal or better quality of life than patients receiving full-dose docetaxel alone. Although this may seem paradoxical, my interpretation is that if a patient has a response — and for example, her fungating tumor is gone and she can get out of bed, walk around and go to work — then obviously there's a quality-of-life benefit.

—Daniel R Budman, MD

SEQUENTIAL VERSUS COMBINATION THERAPY

In the docetaxel/capecitabine trial, concurrent use of docetaxel and capecitabine was better than single-agent docetaxel, and this surprised some people. The trial has been criticized, because not every patient who received docetaxel went on to receive second-line capecitabine. For the purist trying to answer the question of sequential versus concurrent therapy, this trial doesn't give us the exact answer. However, it is dramatic that there was a survival advantage to the combination.

—Edith A Perez, MD

The crucial question is whether combination therapy is better than sequential therapy. Since the progression-free and overall survival curves separated very early, many are hesitant not to use the combination of capecitabine and docetaxel in women with a good performance status. You potentially risk losing the advantage of the combination if these agents are not used together. In women who may not tolerate the combination because of toxicity, it may be reasonable to use sequential rather than combination therapy. Until we have a trial comparing sequential to combination therapy, we will not know the degree of benefit derived from combination therapy.

—David W Miles, MD

"… Whether combination capecitabine/docetaxel will provide superior benefit compared with sequential administration of the same agents (docetaxel followed by capecitabine or capecitabine followed by docetaxel) in the treatment of metastatic breast cancer is not known and was not addressed in this trial. However, it is a question of significant scientific interest. Until such data become available, capecitabine/docetaxel combination therapy is a valuable strategy based on the superior efficacy seen in the present trial. … The significantly superior survival, including a 3-month improvement in median survival, achieved with combined docetaxel plus capecitabine and the manageable toxicity should establish this regimen as an important treatment option for patients with anthracycline-pretreated metastatic breast cancer."

—O'Shaughnessy J, et al. J Clin Oncol 2002;20:2812-2823