XELODA® (capecitabine) in the Treatment of Metastatic Breast Cancer

Epidemiology of breast cancer

Breast cancer is the most common malignancy affecting women in the United States.[57] The incidence of breast cancer is 110.6 cases per 100,000 women, and the National Cancer Institute estimates that 1 in 8 women in the United States (12.6%) will develop breast cancer during her lifetime.[85,86] The projected annual cancer mortality rate for women is 40,000 due to breast cancer, second only to lung cancer.[86,88] Metastatic breast cancer remains the leading cause of death in women between the ages of 40 and 55 years. However, from 1990 to 1997, the death rate associated with breast cancer declined by 13.8%, reflecting advances in early detection and treatment.[89,90]

Characteristics of metastatic breast cancer

Despite an increase in the diagnosis of stage 1 breast cancer, 5% of patients with breast cancer are first diagnosed with metastatic (stage IV) breast cancer.[89,91] Metastatic cancer can also occur due to relapse from a lower stage disease. The most common sites of metastatic involvement include the skin and soft tissues of the cell wall, axilla or supraclavicular area; bone; lung; and liver. While the 5-year survival for patients presenting with stage I or II breast cancer is as high as 96.5%, it is only 21.4% in those first diagnosed with metastatic disease.[89] In patients with metastases to the liver, median survival is less than 12 months.[92-94] Ultimately, more than one-third of women with breast cancer will die of metastatic disease.[89]

Treatment of metastatic breast cancer

The aims of chemotherapy in metastatic breast cancer are to relieve tumor-related symptoms by inducing remission or halting progression, while maintaining or improving the patient's quality

of life, and prolonging survival. Systemic cytotoxic chemotherapy is the treatment of choice for patients who are hormone resistant, hormone-receptor negative, or have rapidly growing visceral tumors.[97]

Chemotherapy-naïve patients

In patients who have not received adjuvant anthracyclines, first-line treatment usually includes an anthracycline-containing combination regimen, such as AC/EC (doxorubicin/epirubicin plus cyclophosphamide) or CAF/CEF (cyclophosphamide, doxorubicin/epirubicin, 5-FU).[92]

Anthracycline-pretreated patients

Until recently, treatment options following disease progression with anthracycline-based therapy have been limited. In the past, docetaxel monotherapy was considered the standard of care for anthracycline-pretreated breast cancer. Although response rates of 29%–54% have been reported, the median time to disease progression was approximately 4 months, and the median overall survival with this regimen was approximately 11 months.[98] Nevertheless, docetaxel monotherapy demonstrated superior survival compared with mitomycin C/vinblastine (11.4 vs 8.7 months).[100]

Paclitaxel monotherapy is also used as treatment for anthracycline-pretreated metastatic breast cancer.[101] In phase II studies, paclitaxel produced response rates in the range of 6%–42%, and a median time to disease progression of approximately 3–4 months when administered by 3-hour infusion.[102] Overall survival in anthracycline-pretreated patients is typically less than 1 year with paclitaxel monotherapy.

Based on a study conducted by O'Shaughnessy et al.,[114] the current standard for the treatment of metastatic breast cancer in anthracycline-pretreated patients is the Xeloda plus docetaxel (XT) regimen. The results of this international, phase III trial demonstrated that the highly-active

regimen of Xeloda/docetaxel results in significant improvements over docetaxel alone in antineoplastic activity, including better response rates, time to disease progression, and overall survival. This was the first study to demonstrate a significant survival benefit with a cytotoxic combination regimen over a standard cytotoxic monotherapy in metastatic breast cancer patients pretreated with anthracyclines.

Taxane-pretreated patients

Another challenge facing oncologists is the growing number of patients with metastatic disease refractory to both anthracyclines and taxanes. The development of refractory disease is due in part to the increased use of paclitaxel or docetaxel earlier in the disease, or as adjuvant treatment in high-risk patients.[101,105] Efficacy data for several agents studied in taxane-pretreated metastatic breast cancer are summarized in Table 10.

Table 10. Investigational treatment approaches for taxane-pretreated metastatic breast cancer

Therapy	Response rate (%)	Median time to Disease progression (months)	Median overall survival (months)
Standard-dose vinorelbine (n=14)[107]	0	N/A	N/A
Weekly vinorelbine (n=40)[111]	25	N/A	6
High-dose vinorelbine + G-CSF (n=40)[108]	25	3.0	7.6
3-weekly docetaxel (n=46)[106]	12	2.3	10.5
96-hour paclitaxel infusion (n=26)[112]	27	N/A	N/A
Continuous infusion 5-FU (n=18)[109]	17	N/A	N/A
Pemetrexed (n=31)[113]	26	N/A	N/A
Gemcitabine (n=23)[110]	0	1.9	7.8
Pegylated liposomal doxorubicin (n=151)[Keller]	N/A	2.9	10.4

N/A = not available

Sequential versus combination therapy

Until recently, sequential administration of antitumor agents was considered the optimal approach to the treatment of metastatic breast cancer, due to the unfavorable risk/benefit ratio of

combination regimens of cytotoxic agents. However, recent reports of improved outcomes with combination cytotoxic regimens show that combined administration also may be an optimal approach in appropriate patients.[Miles,2002]

Since treatment in the metastatic setting is palliative, patient tolerability and quality of life are major concerns. In elderly or frail patients with poor performance status, a sequential regimen may be the appropriate treatment approach. However, a rationally designed combination regimen may be appropriate in more hardy patients, especially those with a large or rapidly progressing tumor burden.

The XT regimen (Xeloda/docetaxel) is one example of a rationally designed combination regimen. There is preclinical evidence of antineoplastic synergy with the combination of Xeloda and taxanes such as docetaxel, and clinical evidence of non-overlapping toxicities.[Miles,2002] In the phase III trial conducted by O'Shaughnessy et al, the combination regimen of Xeloda/docetaxel resulted in significant improvements over docetaxel alone in overall survival, response rates, and time to disease progression.[114] As important, this was achieved without compromising the patient's quality of life.[114] Although the objectives of this trial did not include a comparison of combination versus sequential administration, a portion of the patients in the docetaxel monotherapy arm were subsequently treated with Xeloda monotherapy. The outcomes in this subgroup suggest that sequential administration of the XT regimen may confer a survival benefit in patients unable to tolerate the combination XT regimen.

Xeloda treatment of metastatic breast cancer: combination regimens

An oral agent suitable for chronic outpatient treatment, Xeloda was designed to mimic continuous infusion 5-FU without the inconvenience or complications associated with i.v.-

administered agents. In addition, the unique enzymatic activation of Xeloda results in the generation of 5-FU preferentially at the tumor site, potentially sparing the exposure of healthy tissue to 5-FU.

Phase II trial: Xeloda plus paclitaxel as first- or second-line therapy

A multicenter phase II study evaluated the response rate and safety profile of Xeloda combined with paclitaxel, mainly as first-line treatment of women with metastatic breast cancer.[Meza] The combination regimen was administered in 3-week cycles as follows:

- Xeloda 825 mg/m^2 twice daily on days 1–14
- Paclitaxel 175 mg/m^2 on day 1

Efficacy outcomes for the 47 evaluable patients are summarized in Table 11.

Table 11. Summary of efficacy of Xeloda plus paclitaxel[Meza]

Parameter	Outcome (N=47)
Overall response rate	51.1%
Complete response	12.7%
Median time to disease progression	10.5 months
Overall survival	>22 months

The toxicities were manageable. Xeloda in combination with paclitaxel demonstrated promising efficacy with an acceptable safety profile in the first-line treatment of metastatic breast cancer.

Phase III trial: Xeloda plus docetaxel (XT) in anthracycline-pretreated patients

The combination of Xeloda with docetaxel was shown by O'Shaughnessy in a phase III trial to significantly improve the survival of patients with anthracycline-pretreated breast cancer compared with docetaxel alone.[114] This was the first cytotoxic combination regimen to significantly surpass the survival time achieved with standard monotherapy. Xeloda, the only agent indicated for the treatment of patients with metastatic breast cancer after the failure of anthracyclines and paclitaxel, is now considered the standard of care in this setting.

Study design

The randomized phase III trial was conducted in 511 patients whose disease had progressed during or following prior anthracycline-based chemotherapy.[114] Patients were stratified according to previous exposure to paclitaxel, and randomized to either Xeloda/docetaxel combination therapy or docetaxel monotherapy, in the following 3-weekly cycle regimens:

- Xeloda 1250 mg/m^2 twice daily, days 1–14, in combination with docetaxel 75 mg/m^2 on day 1

OR

- Docetaxel 100 mg/m^2 on day 1

The primary objective of this study was to compare the time to disease progression (defined as time to disease progression or death in patients without documented disease progression) with the combination regimen versus the docetaxel monotherapy regimen. Secondary objectives included comparison of additional efficacy parameters, safety profiles, and medical resource use

in the two treatment arms. Quality of life was assessed using the EORTC QLQ-C30 Global Health Score and the breast cancer module BR-23.

Patient population

The baseline demographics and clinical characteristics of the treatment groups were well balanced (Table 12). The most common metastatic sites were lymph nodes, liver, bone, and lung.

Table 12. Baseline characteristics

	Xeloda/Docetaxel (n=255)	Docetaxel (n=256)
Age (years)		
Median	52	51
Range	26-79	25-75
Karnofsky Performance Scale (median)	90	90
Metastatic sites (%)		
Lymph nodes	47%	49%
Liver	45%	48%
Bone	42%	46%
Lung	37%	39%
Skin	29%	29%

The two groups also were well balanced with regard to history of prior chemotherapy. As defined by the protocol, all patients had received previous anthracycline-based chemotherapy, with approximately two-thirds receiving anthracyclines in the metastatic setting (60% in the combination regimen arm, 64% in the monotherapy arm) (Table 13).

Table 13. Treatment histories

Prior therapy	Xeloda/Docetaxel (n=255)	Docetaxel (n=256)
Anthracyclines*	100%	100%
Alkylating agents	93%	92%
5-FU	77%	74%
Paclitaxel	10%	9%

*Anthracyclines were administered in both the neo-adjuvant and adjuvant settings in 6% and 5% of the combination and monotherapy arms, respectively.

Approximately one-third of the patients in each treatment group received prior endocrine therapy in the adjuvant setting, and one-half received endocrine therapy for metastatic disease. The treatment setting for study therapy in each group is shown in Table 14.

Table 14. Treatment setting for study therapy

	Xeloda/Docetaxel (n=255)	Docetaxel (n=256)
First-line therapy	35%	31%
Second-line therapy	48%	53%
Third-line therapy	17%	16%*

*Two patients received study therapy as fourth-line treatment.

Efficacy

Xeloda in combination with docetaxel resulted in statistically significant improvement in time to disease progression, overall survival and objective response rate over monotherapy with docetaxel (Table 15). All efficacy data are reported using analyses of the randomized (intent-to-

treat) population, with a minimum follow-up of 15 months in all patients.

Table 15. Efficacy of Xeloda/docetaxel versus docetaxel

	Xeloda/docetaxel (n=255)	Docetaxel (n=256)	
Response rate (%)			
Investigator	42%	30%	*P*=.006
IRC	32%	22%	*P*=.009
Median time to disease progression			
Months	6.1	4.2	*P*=.001*; HR=.643
Days	186	128	
Median overall survival			
Months	14.5	11.5	*P*=.013*; HR=.775
Days	442	352	

*Long-rank test

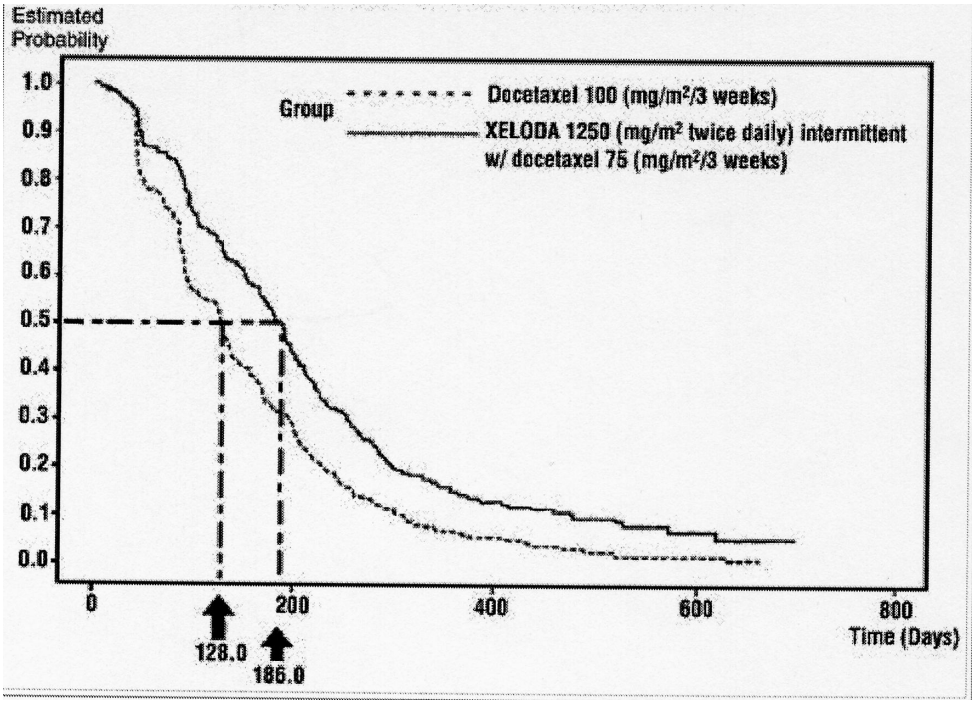
IRC = Independent Review Committee

HR = hazard ratio over the entire curve

The objective tumor response rate was significantly superior in the Xeloda/docetaxel group than in the docetaxel group, 42% vs 30% according to investigator assessment, and 32% vs 22% according to assessment by the Independent Review Committee (*P*=.006; *P*=.009).[114] The primary endpoint, the time to disease progression, also was significantly superior in the Xeloda/docetaxel group than in the docetaxel group (log-rank *P*=.001) (Figure 11). Median time to disease progression was 6.1 months (95% CI: 5.4-6.5 months) in the Xeloda/docetaxel group and 4.2 months (95% CI: 3.4-4.5 months) in the docetaxel group (log-rank *P*=.001). The hazard ratio of 0.643 indicates a 36% reduction in risk of disease progression in patients receiving

combination therapy compared with those treated with docetaxel monotherapy.

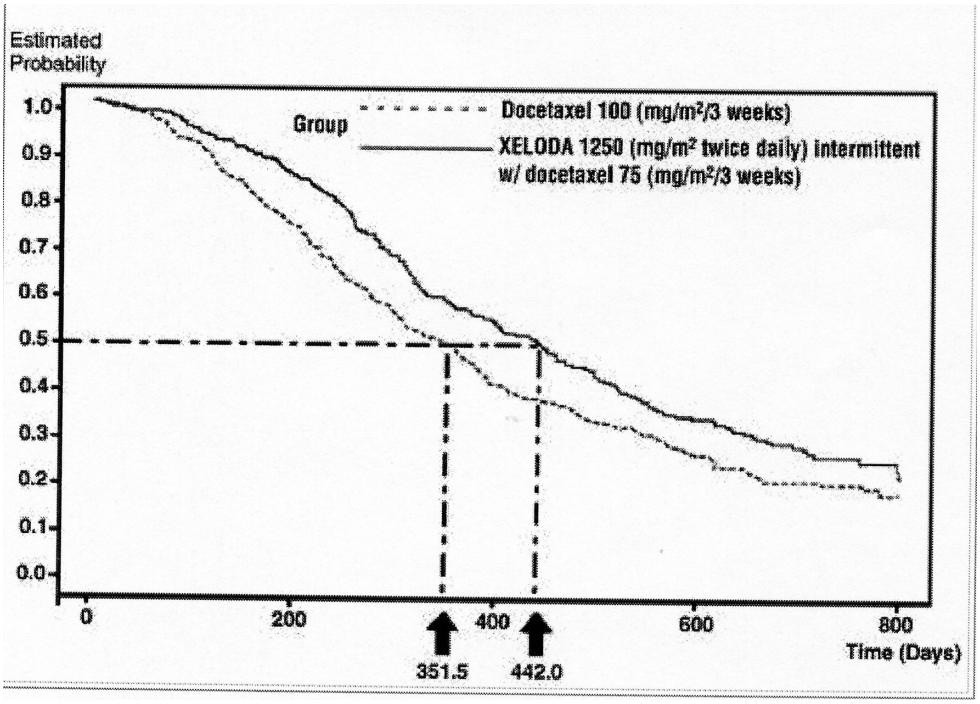
Figure 11. Time to disease progression



The ultimate aim of therapy is to prolong survival, a benefit especially difficult to achieve with metastatic breast cancer. This trial demonstrated that the addition of Xeloda to docetaxel significantly improves overall survival (log-rank *P*=.013, hazard ratio=0.775) (Figure 12). The hazard ratio indicates a 22.5% lower risk of death in the combination group than in the monotherapy group. This translated into a 3-month survival benefit with Xeloda/docetaxel; the median survival was 14.5 months (95% CI: 12.3-16.3 months) in the combination group and 11.5 months (95% CI: 9.8-12.7 months) in the monotherapy group. The 1-year survival rate was 57% (95% CI: 51%-63%) with Xeloda/docetaxel and 47% (95% CI: 41%-53%) with docetaxel. As with the time to disease progression curves in Figure 11, the survival curves in Figure 12 separate very early and remain separated, indicating that most patients derived these benefits

from Xeloda/docetaxel therapy.

Figure 12. Kaplan-Meier estimates of survival

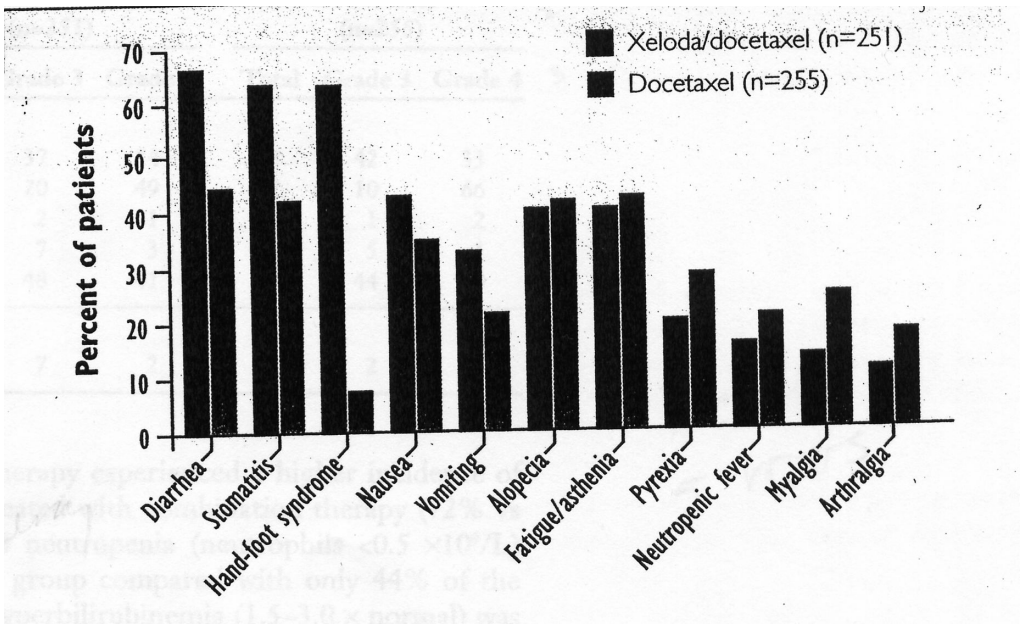


Safety

Adverse events

The safety population included all patients who received at least one dose of study drug (n=251 in the combination arm, n=255 in the monotherapy arm). The toxicity of the Xeloda/docetaxel combination regimen was generally manageable by dose reduction. The most common treatment-related adverse events in the combination arm were diarrhea, stomatitis, and hand-foot syndrome. In the docetaxel monotherapy arm, they were diarrhea, stomatitis, fatigue/asthenia, and alopecia (Figure 13).

Figure 13. Most common treatment-related adverse events

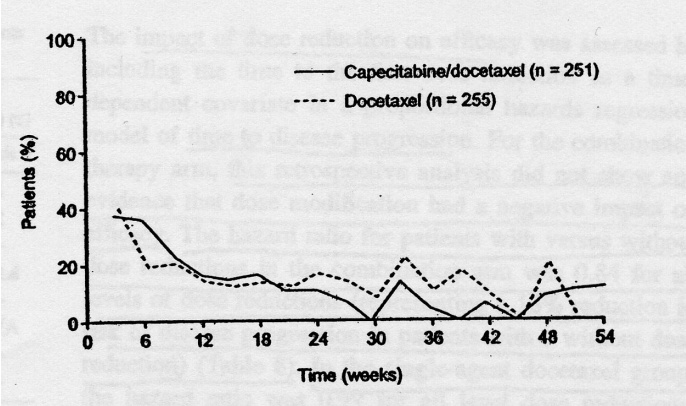


Presumably because of the higher dose of docetaxel administered in the monotherapy regimen (100 mg/m^2) compared with the docetaxel dose in the combination regimen (75 mg/m^2), patients in the monotherapy arm reported more neutropenic fever, myalgia, arthralgia, and pyrexia. Patients receiving the combination regimen experienced more gastrointestinal and cutaneous adverse effects.

In both treatment arms the profile of grade 3 and 4 adverse events was similar to the profile described for all grades. Primarily due to the occurrence of hand-foot syndrome, the incidence of grade 3/4 adverse events was higher in the combination arm than in the monotherapy arm (71% vs 49%). However, the incidence of grade 4 adverse events was higher in the monotherapy arm than in the combination arm (31% vs 25%), because of the higher incidence of neutropenic fever. Except for the impact of grade 3 hand-foot syndrome in the combination arm during the second cycle, the incidence of grade 3/4 treatment-related adverse events was similar in both treatment

arms (Figure 14).

Figure 14. Incidence of grade 3/4 adverse events over time[114]



Dose reduction was effective in reducing the recurrence of grade 3/4 treatment-related adverse events (Figure 15). However, a retrospective analysis comparing hazard ratios of patients with full dose versus reduced dose found that dose modification did not have a negative effect on efficacy. In patients in the combination arm, time to disease progression and overall survival were similar in those receiving a second-cycle reduced dose of Xeloda (approximately 75% of first cycle dose) compared to those who received a full dose of Xeloda (Figure 16).

Figure 15. Reduced vs full dose of Xeloda and docetaxel in the combination arm[114]

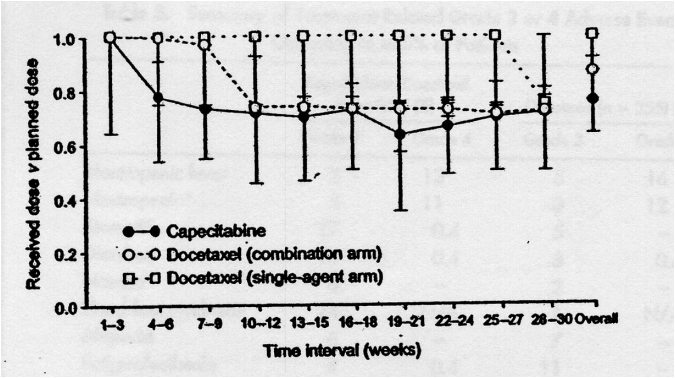
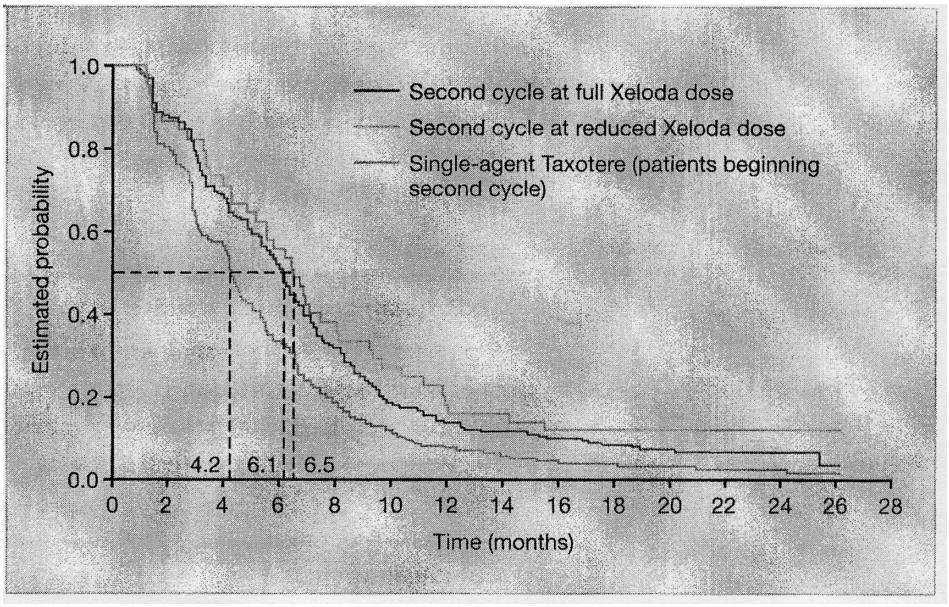


Figure 16. Impact of Xeloda dose reduction on time to disease progression[114]



The number of treatment-related hospitalizations was similar in the two groups: 95 patients in the combination arm versus 91 patients in the monotherapy arm. Neutropenia and neutropenic fever were the most frequent causes of hospitalization and occurred at similar rates in both groups.

Laboratory abnormalities

Laboratory abnormalities were also similar in both groups with the exception of grade 3 hyperbilirubinemia (1.5–3.0 X normal), which was more common with the combination regimen (6.8% vs 1.6%, respectively). The incidence of grade 4 bilirubin elevations (>3.0 X normal) was similar in the two treatment groups (2.0% vs 1.6% in the combination and monotherapy arms, respectively).

Table 16. Incidence of laboratory abnormalities related/unrelated to treatment

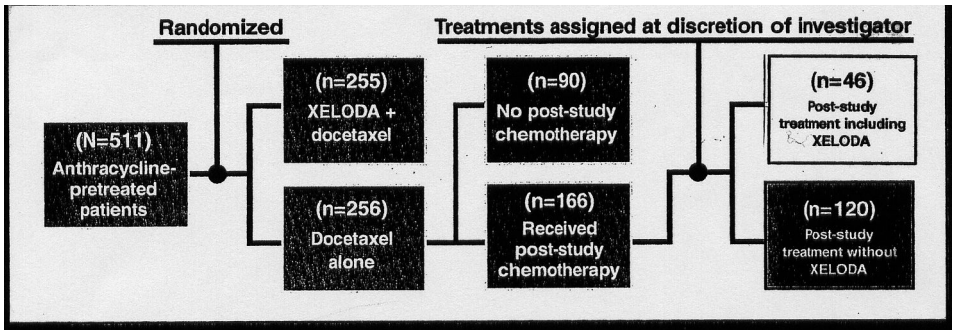
Body System Adverse Event	Percent (%) of Patients					
	Xeloda + Docetaxel (n=251)			Docetaxel (n=255)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
Hematologic						
Leukopenia	91	37	24	88	42	33
Neutropenia/ Granulocytopenia	86	20	49	87	10	66
Thrombocytopenia	41	2	1	23	1	2
Anemia	80	7	3	83	5	<1
Lymphocytopenia	99	48	41	98	44	40
Hepatobiliary						
Hyperbilirubinemia	20	7	2	6	2	2

Post-study analyses

A retrospective analysis of treatments and outcomes following this phase III trial was presented at the San Antonio Breast Cancer Symposium, 2001. [Vukelja,Miles 2001] Among study patients who discontinued study therapy for any reason, a similar proportion in both treatment groups received further chemotherapy, assigned at the discretion of the investigator (Figure 17). Patients who had been randomized to the combination XT arm who discontinued docetaxel treatment prior to disease progression were considered to have remained on study therapy (Xeloda/docetaxel therapy → Xeloda monotherapy). However, patients who had been randomized to the combination arm who discontinued Xeloda treatment prior to disease progression were

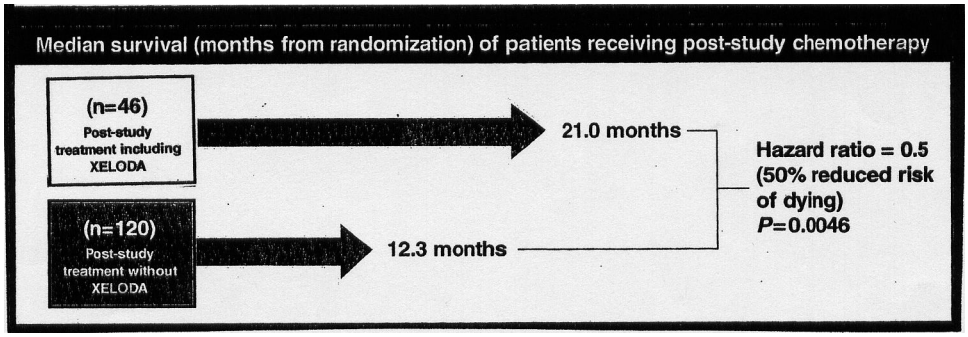
considered to be receiving docetaxel monotherapy as post-study therapy (Xeloda/docetaxel therapy → docetaxel monotherapy).

Figure 17. Post-study disposition of phase III study population



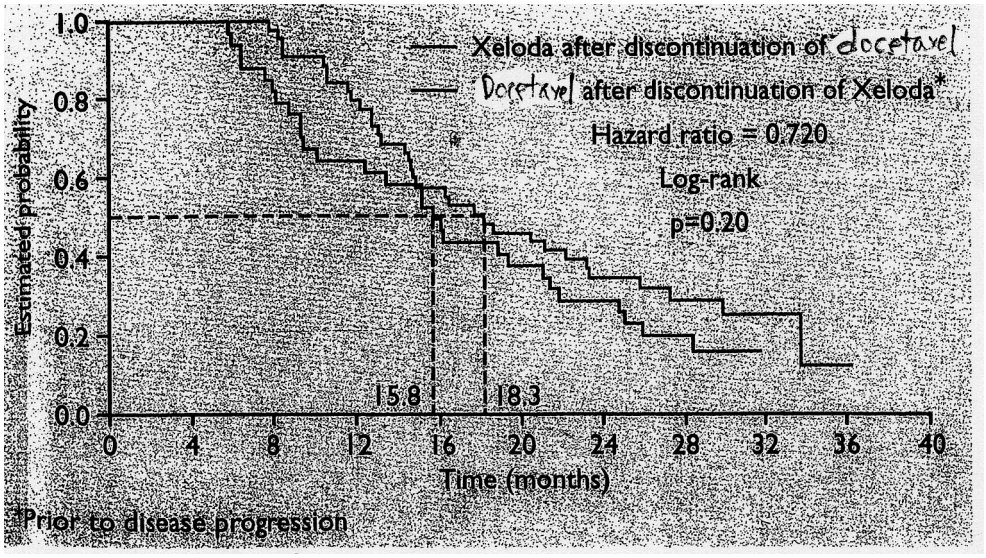
After a minimum follow-up of 23 months, patients who received Xeloda monotherapy post-study (docetaxel monotherapy→Xeloda monotherapy) survived longer than those who received any other chemotherapy post-study.[Miles,2001] The median survival of these patients receiving Xeloda monotherapy (n=46) was 21.0 months (95% CI: 15.6-27.6 months) compared with 12.3 months (95% CI: 10.5-14.0 months) in those who received any other chemotherapy post-study (*P*=.005).[Miles,2001] The hazard ratio was 0.5, indicating a 50% reduction in the risk of death when treated with Xeloda monotherapy post-study (Figure 18). [Miles,2001]

Figure 18. Median survival with vs without Xeloda post-study



The separation of survival curves that was seen for the two treatment arms during the phase III trial continued post-study for those who received Xeloda monotherapy versus those who received docetaxel monotherapy. This survival advantage remained statistically highly significant (log-rank *P*=.02, hazard ratio = 0.72) (Figure 19).[Miles,2001?]

Figure 19. Kaplan-Meier survival with Xeloda vs docetaxel post-study



Based on these retrospective post-study analyses, it appears that Xeloda monotherapy is the most appropriate therapy for patients who discontinue Xeloda/docetaxel or docetaxel monotherapy for any reason. However, until a trial is conducted that compares a combination regimen of Xeloda and docetaxel with a sequential administration of the two agents, this combination regimen should be considered the therapy of choice for patients with anthracycline-pretreated breast cancer.

Xeloda treatment of metastatic breast cancer: Xeloda monotherapy

Xeloda monotherapy is the only agent indicated for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen

or resistant to paclitaxel and for whom further anthracycline therapy is not indicated, e.g., patients who have received cumulative doses of 400 mg/m^2 of doxorubicin or doxorubicin equivalents. Resistance is defined as progressive disease while on treatment, with or without an initial response, or relapse within 6 months of completing treatment with an anthracycline containing adjuvant regimen.

Approval of Xeloda in anthracycline- and paclitaxel-pretreated metastatic breast cancer was based on data from a large, multicenter, single-arm, phase II study. Xeloda demonstrated an impressive response rate and overall survival in this heavily pretreated patient population, with a favorable safety profile. The findings of this study are described here.

Study design

This open-label phase II trial included women with metastatic disease that had progressed on paclitaxel therapy.[115] The primary objective of this study was to determine the tumor response rate to Xeloda monotherapy administered in an intermittent schedule, expected to be approximately 20%. Other objectives included evaluation of the safety and tolerability of Xeloda, secondary efficacy parameters, and the effect of Xeloda on clinical benefit.

Treatment schedule

Xeloda was administered in the outpatient setting and given orally at a dose of 1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period, repeated in 3-week cycles. Xeloda was taken with water 30 minutes postprandial (breakfast and evening meal, approximately 12 hours apart). If a grade 2, 3, or 4 adverse event was observed, the dose modification schedule shown in Table 3 was applied.[79]

Assessment of response

Tumor response was assessed by investigators based on WHO criteria. The effect of Xeloda on tumor-associated symptoms was assessed using the Clinical Benefit Response (CBR) score. This was determined through measurement of pain intensity, analgesic consumption, and performance status. These parameters are particularly important in metastatic breast cancer because of the palliative nature of treatment in these patients. Pain intensity (measured using the Visual Analogue Memorial Pain Assessment Card) and analgesic consumption were recorded daily in a patient diary. Patients also kept a weekly record of their performance status using the KPS scale. In addition, a 3-weekly KPS assessment was performed by the investigator. A positive CBR was recorded if a patient had a major improvement lasting for 4 or more consecutive weeks in at least one of the parameters, and was at least stable in the other two measures (Table 17).

Table 17. Definitions of a positive Clinical Benefit Response

Parameter	**Outcome**
Pain intensity	≥50% reduction in patients with baseline pain ≥20 mm*
Analgesic consumption	≥50% reduction in patients with baseline analgesic consumption ≥70 morphine equivalents/week
Karnofsky Performance Status	Improvement of ≥20 points

*Maintained for at least 4 weeks

Patient population

Of the 163 patients who entered the study, 162 received Xeloda and were included in the analyses. A total of 135 patients presented with measurable disease and 27 had evaluable disease. The median time from initial diagnosis to this recurrence was 2.5 years. The median age was 56 years (range 26-78 years) and the median KPS was 90% (range 70%-100%). The study population consisted of a homogeneous group of heavily pretreated patients:

- All patients had received prior paclitaxel therapy (median cumulative dose 835 mg/m^2); 77% were paclitaxel resistant and 23% had failed paclitaxel
- 91% were pretreated with anthracycline therapy
- 82% were pretreated with a 5-FU containing regimen

The mean numbers of previous therapies were:

- Chemotherapeutic regimens 2.5
- Chemotherapeutic agents 4.7
- Hormonal therapies 1.3

The distribution and number of metastatic sites indicated that the study population represented a very poor prognostic group. Visceral metastases were the predominant site in 68% of patients, and 64% of patients had more than two metastatic sites at baseline.

Efficacy

The overall objective response rate with Xeloda was 20% (95% CI: 14%-28%). Efficacy results are summarized in Table 18.

Table 18. Response rates in paclitaxel-pretreated patients

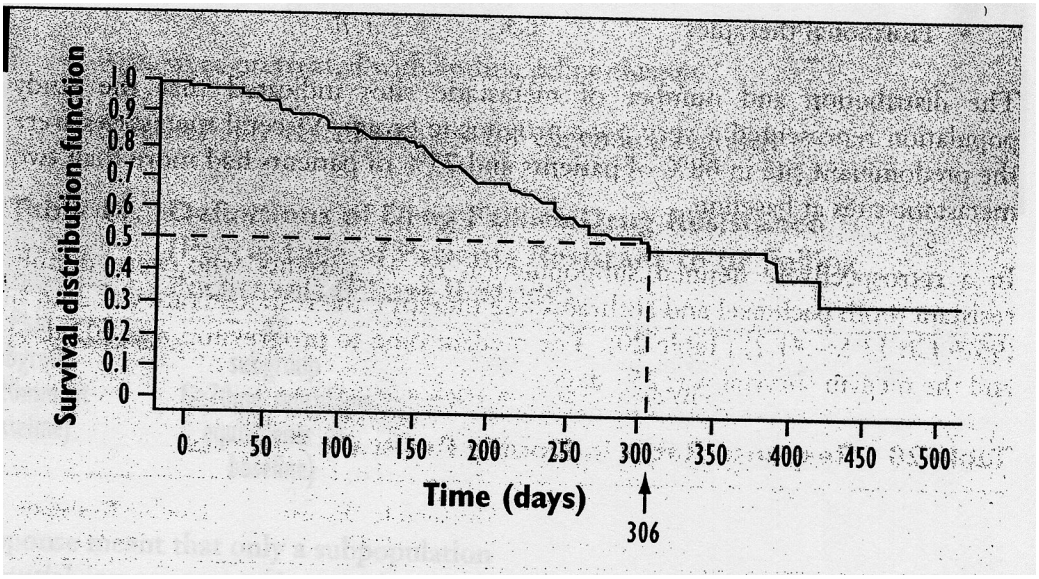
	Overall (N=162)	Measurable disease (n=135)	Evaluable disease (n=27)
Objective response	20%	20%	19%
Complete response	2%	2%	0%
Partial response	18%	18%	19%
Stable disease	43%	40%	60%
Disease control	63%	60%	79%

The response rates in patients with visceral metastases or those with soft tissue metastases as the predominant metastatic site were 19% and 23%, respectively. In a retrospectively defined subpopulation of 43 patients who were unequivocally resistant to both paclitaxel and doxorubicin therapy, the response rate was an impressive 25.6% (95% CI: 13.5%-41.2%). These results emphasize the high activity of Xeloda in taxane-refractory patients, a group for whom there was previously no established treatment options.

The median duration of response with Xeloda in patients with measurable disease was 7.9 months, median time to disease progression was 3.0 months, and median survival was 10.2 months (Figure 20). Median survival for the entire population was 12.6 months. This survival time compares favorably with prior outcomes reported in the literature, where paclitaxel or docetaxel therapy in a less heavily pretreated population with anthracycline-refractory breast cancer demonstrated median survival times of 9.5 months and 10.0-11.4 months,

respectively.[100,116,117]

Figure 20. Median survival of patients with measurable disease



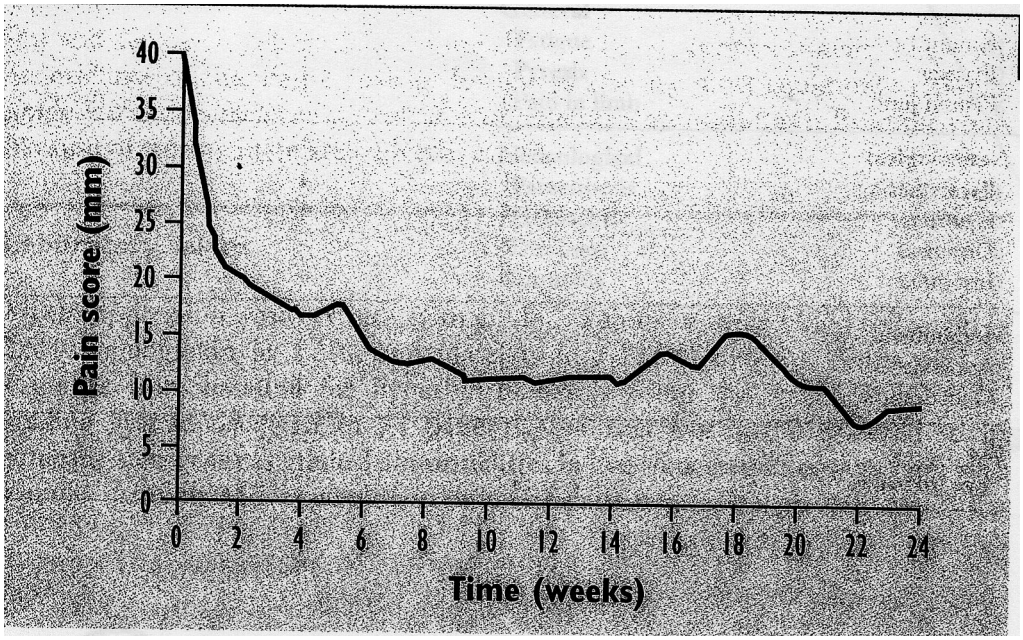
Clinical Benefit Response

In this patient population the palliative effect of treatment is especially important since the primary aim is to relieve tumor-related symptoms, with a minimum incidence of toxicity. Secondary aims include enhancing or maintaining performance status and, ultimately, prolonging survival. Among the 147 patients evaluable for CBR, the overall score was positive in 29 patients (20%) and stable in 45 patients (31%).

The strict definition of CBR meant that only a subpopulation of patients was able to achieve the substantial improvements in pain intensity, analgesic consumption, and KPS. However, 47% of the 51 patients with significant pain at baseline (≥20 mm) experienced a durable ≥50% decrease in pain intensity. The curve for mean pain over time in pain responders is shown in Figure 21. In addition, in patients with analgesic consumption of ≥70 morphine equivalents at baseline, 30%

reported a positive CBR response. These data provide evidence that Xeloda reduces tumor-related symptoms in patients with metastatic breast cancer.

Figure 21. Mean pain over time in pain responders



Safety

Adverse events

The safety of Xeloda was evaluated in all 162 patients who received at least one dose of study drug. Xeloda was well tolerated in this heavily pretreated patent population: grade 3 or 4 adverse events were infrequent and myelosuppression was rare. Alopecia was not observed and hair growth occurred in some patients with alopecia at baseline. The safety profile of oral Xeloda was otherwise typical of infused fluoropyrimidines. The most frequent treatment-related adverse events with Xeloda were cutaneous effects (hand-foot syndrome [57%]), gastrointestinal effects (diarrhea [57%], nausea [53%], and vomiting [37%]), and fatigue (41%).

The majority of treatment-related adverse events were graded as mild to moderate in intensity. The only treatment-related grade 3 or 4 adverse events occurring in more than 5% of patients were diarrhea (14%), hand-foot syndrome (10%), and fatigue (7%). Grade 4 adverse events occurred in only four patients (diarrhea in three patients and asymptomatic coagulation disorder in one patient receiving warfarin). The incidence of grade 3 or 4 adverse events per treatment cycle was low and decreased substantially during the first 18 weeks of treatment. There was no evidence of cumulative toxicity for any of the five most commonly reported grade 3 or 4 adverse events. Only 8% of patients were withdrawn from the study because of treatment-related adverse events.

Laboratory values

Myelosuppression was very rare, with few patients experiencing grade 3/4 shifts in leukocytes (2.5%), hemoglobin (1.2%), and platelets (3.1%). Shifts of 3 or 4 grades from baseline for hyperbilirubinemia using the strict NCIC CTC grading system (≥1.5 x upper limit of normal) occurred in 22 patients, but this was not considered to be clinically significant. Grade 3 abnormalities in liver function tests were rare, with a grade 3 shift in ALT occurring in only one patient.

Impact of dose modification on efficacy

As with the Xeloda clinical trials described previously, treatment was modified according to an established schedule (Table 3) in the event of grade 2 or greater toxicities. Fifty-four patients (33%) required a dose reduction due to an adverse event after a median of 1.5 months (range 1.0-2.3 months). The most frequent adverse events leading to dose reduction, alone or in combination, were hand-foot syndrome (27% of patients), diarrhea (18%), nausea (9%), and

vomiting (8%). Dose reduction was effective in reducing the recurrence of side effects or the development of more severe adverse events, as shown in Table 19.

Table 19. Impact of dose reduction on safety profile

	Improved	Stable	Worsened
Diarrhea			
Grade 2 (n=12)	83%	17%	0%
Grade 3 (n=12)	92%	8%	0%
Grade 4 (n=4)	100%	0%	0%
Hand-foot syndrome			
Grade 2 (n=24)	88%	8%	4%
Grade 3 (n=10)	100%	0%	0%
Stomatitis			
Grade 2 (n=3)	100%	0%	0%
Grade 3 (n=7)	100%	0%	0%

The impact of the dose modification scheme on efficacy was analyzed using a time-dependent Cox regression analysis, which confirmed that the risk of disease progression or death was not increased in patients requiring Xeloda dose reduction (to either 75% or 50% of the baseline dose) for adverse events compared with patients who did not require dose reduction (hazard ratio = 1.02, Wald test $p = 0.935$).[118]

Implication for a lower starting dose

In a retrospective review of pharmacy records and clinical data, an analysis of post-marketing use of Xeloda chemotherapy for metastatic breast cancer supported anecdotes of dose reductions improving tolerability without compromising efficacy.[Michaud] Patients were grouped by starting dose level (DL): DLA was 2375-2625 mg/m^2/day; DLB was 2101-2374 mg/m^2/day; and DLC was ≤2100 mg/m^2/day.

Table 20. Outcomes with lower starting dose of Xeloda in metastatic breast cancer [Michaud]

	DLA (n=49)	DLB (n=15)	DLC (n=41)	All patients (n=106)
Improved disease	18%	20%	24%	22%
Stable disease*	35%	47%	37%	37%
Progressive disease	47%	33%	39%	41%
Time to progression (weeks)	11.9	19.9	15.1	13.9

*Stable ≥6 weeks

DL = starting dose level

DLA was 2375-2625 mg/m^2/day; DLB was 2101-2374 mg/m^2/day; and DLC was ≤2100 mg/m^2/day

While efficacy outcomes in this small analysis were slightly improved in those receiving a lower starting dose, the incidence of toxicities was markedly reduced in the lowest dose level, especially for hand-foot syndrome, stomatitis and diarrhea.[Michaud] The resulting improved therapeutic index in the DLC group suggests a starting dose of 2000 mg/m^2/day may be acceptable in some patients.

Additional phase II studies in patients previously treated with taxanes

A number of confirmatory studies have evaluated Xeloda in patients whose disease has progressed with either paclitaxel or docetaxel therapy. In all studies, Xeloda was administered at a dose of 1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period.

Efficacy

All studies[119-122] have confirmed the results of the pivotal paclitaxel-failure study described above.[115] The results available to date for all trials of Xeloda in taxane-pretreated metastatic breast cancer are summarized in Table 21, providing data on more than 500 patients.

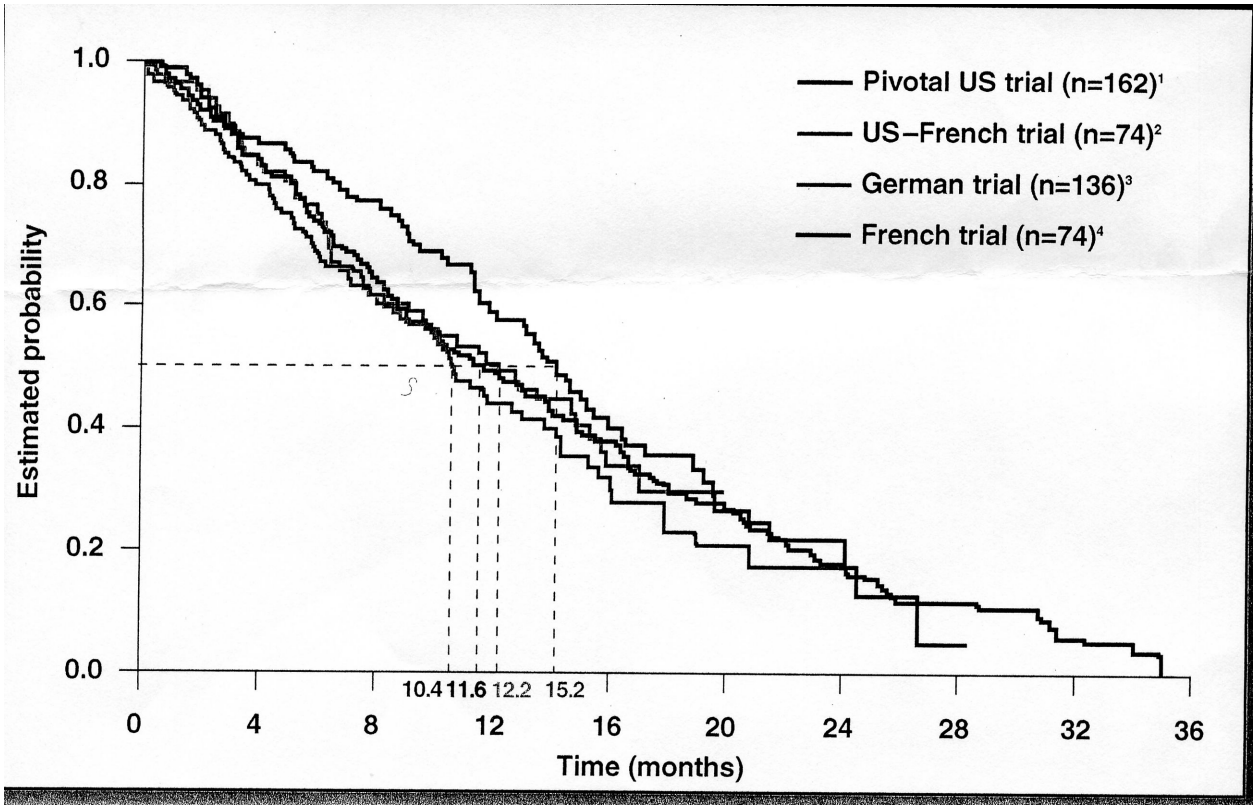
Table 21. Summary of efficacy in taxane-pretreated metastatic breast cancer

No. of patients treated	Overall response rate (%)	Stable disease rate (%)	Disease control rate (%)	Median time to disease progression or death (months)	Median overall survival (months)
162[115]	20%	43%	63%	3.0	11.6
74[119]	26%	31%	57%	3.2	12.2
136[120]	15%	46%	61%	3.3	10.4
126[Fumoleau]	29%	32%	61%	4.6	15.2
32[121]	44%	19%	63%	4.0	11.9

The reproducibility of the efficacy results of the trial in paclitaxel-resistant patients and the confirmatory studies in taxane-pretreated patients provide strong support for the use of Xeloda in patients with metastatic breast cancer that has progressed with taxane therapy (Figure 22). Furthermore, as discussed previously, the survival benefit compares very favorably with the reported literature for patients who have been pretreated with taxanes (Table 10). Kaplan-Meier

estimates of median survival for participants in these phase II studies range from 10.4 months to 15.2 months.[119-122]

Figure 22. Survival curves in 4 phase II studies of Xeloda monotherapy



Safety

The safety profile of Xeloda in all of these studies was similar to that observed in the pivotal phase II trial in paclitaxel-pretreated patients, described above.[115] In particular, myelosuppression and alopecia were rare and the adverse events associated with Xeloda treatment were predictable and manageable. Hand-foot syndrome was typically the predominant adverse event, most frequently of grade 1 or grade 2 severity.

Conclusion

The phase II clinical trials described above provide clear evidence of the efficacy and safety of Xeloda in patients with heavily pretreated metastatic breast cancer. Xeloda was found to produce an impressive response rate of 15%–44% and survival duration of approximately 1 year, which compares favorably to the outcomes with other agents. Side effects were manageable, with minimal myelosuppression or alopecia. Based on its proven efficacy and favorable safety profile, Xeloda has become the standard of care for taxane-pretreated metastatic breast cancer.

Phase III study of Xeloda monotherapy

Xeloda is also being used as a reference agent in studies of investigational drugs. A randomized phase III study compared Xeloda monotherapy with Xeloda plus bevacizumab in anthracycline- and taxane-pretreated metastatic breast cancer.[Miller] Bevacizumab is a humanized monoclonal antibody directed against VEGF, a potent stimulator of angiogenesis. According to investigator analysis, the overall response rate was 19.1% in the Xeloda monotherapy arm (n=230) and 30.2% in the Xeloda/bevacizumab arm (n=232). However, the duration of response was not significantly different. The investigator-reported median duration of response was 6.7 months with Xeloda monotherapy, versus 4.96 months with Xeloda/bevacizumab. This response rate with Xeloda monotherapy falls within the range of response rates reported by phase II studies of Xeloda monotherapy reported above.

Summary

- A phase III trial in anthracycline-pretreated patients demonstrated that Xeloda in combination with docetaxel resulted in:

- — Significantly superior overall survival (23% reduction in risk of death, with a median 3-month survival advantage)
- — Significantly superior time to disease progression (36% reduction in risk of progression)
- — Significantly superior response rates (32% vs 22% for docetaxel monotherapy)
- — Adverse events that developed could be managed by symptomatic treatment, dose interruptions, or adjustment of Xeloda dose.
- — Post-study treatment with Xeloda monotherapy following discontinuation of docetaxel (in Xeloda/docetaxel or docetaxel monotherapy arms) for any reason had a significant positive influence on survival.

- Monotherapy Xeloda demonstrated high antitumor activity in heavily pretreated patients with metastatic disease refractory to taxanes
- Consistent response rates and survival times with Xeloda monotherapy have been shown in phase II and phase III trials conducted in over 700 patients with taxane-pretreated metastatic breast cancer

References Newly Cited in This Chapter

Fumoleau P, Largilier R, Trillet-Lenoir V, et al. Phase II study of capecitabine (Xeloda®) in patients with advanced breast cancer (ABC) previously treated with anthracyclines and taxanes. Breast Cancer Res Treat. 2001;69:285. Abstract 435.

Keller AM, Mennel RG, Nabholtz JM, et al. Phase III trial of pegylated liposomal doxorubicin (Caelyx/Doxil) for the treatment of patients with advanced breast cancer who have failed a prior taxane-containing chemotherapy regimen. Proc Am Soc Clin Oncol 2001;20:30a. Abstract 115.

Meza LA, Amin B, Hill T, et al. Capecitabine plus paclitaxel ass first- or second-line therapy; a multicenter phase II study in metastatic breast cancer. Breast Cancer Res Treat. 2001;69:271. Abstract 358.

Michaud LB, Gauthier MA, Wojdylo JR, et al. Improved therapeutic index with lower dose capecitabine in metastatic breast cancer (MBC) patients (Pts). Breast Cancer Res Treat. 2001;69. Abstract 402.

Miles D, Ayoub J-PM, O'Shaughnessy JA, et al. Survival benefit with Xeloda (capecitabine)/docetaxel vs docetaxel: analysis of post-study therapy. Breast Cancer Res Treat 2001;69:287. Abstract 442.

Miles D, von Minckwitz G, Seidman AD. Combination versus sequential single-agent therapy in metastatic breast cancer. Oncologist. 2002;7(suppl 6):13-19.

Miller KD, Rugo HS, Cobleigh M, et al. Phase III trial of capecitabine plus bevacizumab versus capecitabine alone in women with previously treated metastatic breast cancer. Poster presented at the 25th Annual Breast Cancer Symposium, San Antonio, TX, 2002.

Vukelja SJ, Moiseyenko V, Leonard R, et al. Xeloda (capecitabine) plus docetaxel combination therapy in locally advanced/metastatic breast cancer: latest results. Breast Cancer Res Treat 2001;69:269. Abstract 352.