

Table 27. Patient Disposition

Table 8.1: Patient Disposition - Enrolled Patients - 40 mg/m² 3 hours

	Number of Patients (%) N = 49
Enrolled	49 (100.0)
Treated	49 (100.0)
Discontinued	49 (100.0)
Disease Progression or Relapse	36 (73.5)
Study Drug Toxicity	8 (16.3)
Patient Request	2 (4.1)
Death	2 (4.1)
Lost to Follow-up	0
Clinical Deterioration	0
Physician's decision	1 (2.0)
Other	0
Still On-Study	0
Never Treated	0

Source: Supplemental Table S.8.3

Most patients (~74%) discontinued from the study because of progressive disease. About 16% of patients discontinued because of study drug toxicity.

6.2.4.6.6 Demographics of study patients are shown in Table 28 (Sponsor's Table 8.1). These data sets were not examined by the Reviewer. The patients are similar in age distribution, gender, race, ethnic background, PS and estrogen receptor status to those in the pivotal study. Pre-menopausal and post-menopausal patients are evenly balanced in this study than in the pivotal study. About 37% had ER+ tumors and 55%, ER-; 35% had PR+ and 51%, PR-; 39% had HER2- tumors and 26%, HER2+.

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Table 28. Demographic Characteristics

**Table 8.3: Demographic Characteristics - Treated Patients - 40 mg/m²
 3 hours**

	Number of Patients (%) N = 49
Time from Diagnosis (Months)	
N	49
Median	48
Min-Max	3-241
Age (years)	
N	49
Median	54
Min-Max	30-81
< 65	42 (86)
≥ 65	7 (14)
Gender	
Female	49 (100)
Race	
White	42 (86)
Black	3 (6)
Asian/Pacific Islanders	3 (6)
Hispanic/Latino	1 (2)
Performance Status (ECOG)	
0	10 (20)
1	38 (78)
2	1 (2)
Menopausal Status	
Pre-Menopausal	23 (47)
Post-Menopausal	25 (51)
Unknown	1 (2)
Estrogen Receptor^a	
Positive	18 (37)
Negative	27 (55)

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6.2.4.6.7 Extent of Disease: Imaging studies were generally used to measure target and non-target lesions at baseline and during assessments. Most of the patients had ≥ 2 metastatic disease sites at baseline (data in Sponsor's Table 8.4.1A, not shown). Forty-one patients (84%) had visceral-bone-skin/soft tissue disease, 3 had bone-soft tissue disease, and 5 had skin/soft-tissue disease.

6.2.4.6.8 Prior Chemotherapy:

All (100%) patients had received at least one prior taxane-containing regimen, 98% (48/49) for metastatic disease and 2% (1/49) in adjuvant setting only (data in Sponsor's Table S9.57, not shown). About 31% (15/49) received 2 or more taxane-containing regimens (metastatic and metastatic plus adjuvant or neoadjuvant). All but one had received a taxane-containing regimen as their most recent chemotherapy.

In addition, nearly all (48/49, 98%) patients had received at least one prior anthracycline-based chemotherapy regimen. Of these, 23/49 (45%) received anthracyclines for metastatic disease or for metastatic disease following prior neoadjuvant or adjuvant therapy; 20/49 (41%) received

anthracyclines only in adjuvant therapy and 5/49 (10%) only in neoadjuvant therapy (data in Sponsor's Table S9.57, not shown).

Thus, this population has strong similarities to the population in the pivotal study. The main differences are that only about half of the patients received anthracyclines only the metastatic setting and patients had fewer other chemotherapy regimens than in the pivotal study.

6.2.4.6.9 Extent of Exposure: Table 29 (data from Sponsor's Table S9.3) shows the numbers of patients and the dose levels for 8 of the 15 courses of treatment. The percentages of patients receiving the full 40 mg/m² doses started decreasing after the first course. About 77% of patients received the full doses during the 5th course and 50% during the 6th course. After the 8th course, all remaining patients received reduced doses. About 65% of patients (32/49) received all cycles at their starting dose level.

The table above does not show the percent decreases of the number of patients during the course of the study. Table 29 shows this decrease for the first 8 cycles. Since assessments were carried out after each 2 cycles, patient number decreases after cycles 2, 4, 6, and 8 are mainly due the results of assessment showing PD.

Table 29. Decreases of the Number of Patients Receiving Study Drug

Cycle Number	No. of Patients	% of Patients at the Start
1	49	100%
2	46	94%
3	30	61%
4	23	47%
5	17	35%
6	16	33%
7	9	18%
8	7	14%

6.2.4.6.10 Discontinuation of Study Therapy: Most patients discontinued study therapy because of PD (36/49, 73%). Ixabepilone toxicity resulted in discontinuation of the drug by 8 patients (16%); 5 because of neurotoxicity, and 1 each of pneumonia, febrile neutropenia/thrombocytopenia, and skin toxicity. Two patients (4%) died, 2 discontinued ixabepilone after Grade 1 AEs, and 1 was withdrawn by the investigator.

6.2.4.6.11 Dose Modifications: A total of 17 patients (35%) required dose reductions, the most common reason (in 12/17 patients) being Grade 2/3 sensory neuropathy. The first dose reduction because of sensory neuropathy occurred at a median of 4.5 cycles. Only 3 of 12 patients discontinued ixabepilone because of continuing sensory neuropathy. Dose delays occurred in 22% of courses (36/166 courses) for a variety of reasons.

6.2.4.6.12 Efficacy Results:

Primary efficacy endpoint: Six of 49 patients (12.2% [95% CI: 4.7, 26.5%]) had a PR according to modified WHO criteria (Table 30). These results do not include the two patients with PR (of

17 treated), who were treated with the 50 mg/m² dose. These results are similar in magnitude to the results in the pivotal study, although the response criteria were different in the two studies.

Table 30. Primary Efficacy Endpoint—ORR Assessed by the Sponsors’ Team

Response	All Treated Patients (40 mg/m ² over 3 hours every 21 days) N = 49
Complete	0
Partial	6 (12% [95% CI: 4.7, 26.5%])
Total	6 (12% [95% CI: 4.7, 26.5%])

The decreases in target lesions in responders were evident at the first assessment after the first 2 cycles and criteria for PR were achieved after a median of 4 cycles of therapy (individual patients achieved PR after 2, 3, 4, 4, 5, and 15 cycles). All of the responders had extensive disease, including visceral metastatic disease, and failed prior treatment with taxanes, 5/6 had also been treated with anthracyclines. The 6 patients with PR received a median of 10.5 cycles (range, 5.0 – 15.0 cycles) of ixabepilone therapy.

Reviewer’s Note: Among the 8 patients treated with ixabepilone at 50 mg/m² IV infused over 1-hour, there were 2 PRs. There were no PRs among the 9 patients treated with ixabepilone 50 mg/m² IV infused over 3 hours.

Secondary efficacy endpoints:

- Duration of response: median duration of response was 10.4 months (95% CI, 6.3 – 22.0).
- Median time to progression was 2.2 months (95% CI, 1.4 – 3.2).
- Median survival was 7.9 months (95% CI, 6.1 -14.5).

6.2.4.7 Supportive Study CA163010: A Phase 2 Study of Epothilone B Analog BMS-247550 in Patients with Metastatic Breast Cancer Previously Treated with An Anthracycline.

6.2.4.7.1 Study Design: This was a single-arm, multicenter (12 study centers in the U.S., France, Italy and Canada), open-label study that was carried out between February 15, 2001 (first patient enrolled) and July 22, 2003 (last patient completed follow-up). Please see CA163009 for reasons that led to decreasing the initial dose of ixabepilone from 50 mg/m² administered over 1 hour every 21 days (19 patients) to the same dose administered over 3 hours (9 patients) to 40 mg/m² administered over 3 hours. The two trials -009 and -010 were similar in design and were carried out at approximately the same time.

6.2.4.7.2 Objectives:

Primary: To assess the clinical activity of ixabepilone as measured by tumor response rate in patients with metastatic breast adenocarcinoma, previously treated with an anthracycline in the adjuvant setting.

Secondary: To evaluate safety, response duration, time to progression and survival in this population.

6.2.4.7.3 Study Population:

Main eligibility criteria were

- Women with histological or cytological diagnosis of metastatic breast cancer,
- At least one bi-dimensionally measurable lesion. Bony lesions were not measurable by definition. Primary breast lesions were not considered measurable by physical examination.
- Prior anthracycline-based regimen as adjuvant therapy (patients may have received a taxane as part of an adjuvant regimen provided that 1 year or more has elapsed since the completion of treatment).

6.2.4.7.4 Criteria for Evaluation: As in the CA163009 study.

6.2.4.7.5 Subject Disposition is shown in Table 31 (Sponsor’s Table 8.1. in CA163010 Study Report). The percentage of patients who discontinued treatment because of disease progression is smaller in this study (52%) than in studies CA163081 (74%) and CA163009 (74%). The percentage of patients who discontinued treatment in this study because of study drug toxicity was higher (34%) than in studies CA163081 (10%) and CA163009 (16%).

Table 31. Patient Disposition – All Enrolled and Treated Patients – 40 mg/m² Infused Over 3 Hours

Table 8.1: Patient Disposition - Enrolled Patients - 40 mg/m² 3 hours

	Number of Patients (%) N = 65
Enrolled	65 (100.0)
Treated	65 (100.0)
Discontinued	65 (100.0)
Completed Treatment	0
Disease Progression or Relapse	34 (52.3)
Study Drug Toxicity	22 (33.8)
Patient Request	1 (1.5)
Death	0
Lost to Follow-up	0
Never treated with study drug	0
Subject Non-compliance	0
Pregnancy	0
Clinical Deterioration	1 (1.5)
Physician's decision	5 (7.7)
Administrative Decision	1 (1.5)
No Improvement	1 (1.5)
Other	0
Still On-Study	0
Never Treated	0

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Source: Supplemental Table S.8.3

6.2.4.7.6 **Demographic Characteristics** of patients in this study are almost identical to those of patients in the -009 study and are shown in Reviewer’s Table 32 (Sponsor’s Table 8.3). Median (and range) time from diagnosis, median age, age ranges, gender, and racial and ethnic distribution were similar in both studies. The percentage of patients with PS 0 is greater in this study than in the -009 study (49% vs. 20%), a greater percentage were pre-menopausal (65% vs. 47%), and a greater percentage had ER+ tumors (65% vs. 37%).

Table 32. Demographic Characteristics – Study CA163010

Table 8.3: Demographic Characteristics - Treated Patients - 40 mg/m² 3 hours

	Number of Patients (%) N = 65
Time from Diagnosis (Months)	
N	65
Median	44
Min - Max	6 - 301
Age (years)	
N	65
Median	52
Min - Max	33 - 80
< 65	58 (89)
≥ 65	7 (11)
Gender	
Female	65 (100)
Race	
White	61 (94)
Black	1 (2)
Hispanic/Latino	1 (2)
Other	2 (3)
Performance Status (ECOG)	
0	32 (49)
1	32 (49)
2	1 (2)
Menopausal Status	
Pre-Menopausal	42 (65)
Post-Menopausal	23 (35)
Estrogen Receptor^a	
Positive	41 (63)
Negative	20 (31)
Borderline	1 (2)
Progesterone Receptor^a	
Positive	31 (48)
Negative	30 (46)
Borderline	1 (2)

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Source: Supplemental Tables S.8.6, S.8.12, and S.8.15

^a Three patients did not have estrogen and progesterone receptor assays performed at the time of their disease diagnosis.

6.2.4.7.7 **Extent of Disease:** 23% of patients had one involved site, 45% had 2 involved sites, 23% had 3 involved sites, 8% had 4 involved sites, and 1% had more than 5.

6.2.4.7.8 **Prior Chemotherapy:** Patients in this study had received prior chemotherapy in adjuvant and/or neoadjuvant setting. All patients (100%) had received one or two prior anthracycline containing regimens, 92% had received one regimen and 8%, two. About 66% of patients received anthracycline containing regimen(s) in adjuvant setting, 29% in neo-adjuvant, and 5% in both adjuvant and neo-adjuvant.

Eleven (17%) patients had received one taxane-based regimen in either adjuvant or neo-adjuvant setting.

About 86% of patients developed evidence of metastatic disease more than 6 months after last chemotherapy; only 5% of patients developed metastatic disease in less than 6 months after last chemotherapy.

Most of the patients (78.5%) developed metastatic disease more than 6 months following the last dose of anthracycline-containing chemotherapy; only 4.6% developed in less than 6 months (data from Sponsor's Table S.8.90).

6.2.4.7.9 Extent of Exposure: Table 33 (data condensed from Sponsor's Table 9.1) shows the numbers of patients for 8 of the 14 cycles of treatment. The percentages of patients receiving ixabepilone and receiving it in full 40 mg/m² doses decreased after the first cycle.

Table 33. Decreases of the Number of Patients Receiving Study Drug

Course Number	No. of Patients	% of Patients at the Start
1	65	100%
2	64	98%
3	52	80%
4	50	77%
5	40	62%
6	34	52%
7	16	25%
8	13	20%

6.2.4.7.9 Discontinuation of Study Therapy: The most common reason for discontinuation was disease progression or relapse (34/65 or 52% of patients). The second was study drug toxicity (22/65 or 34% of patients); 19 patients had developed drug-related neurotoxicity, 1 had fatigue accompanied by nausea/vomiting, 1 had myalgia and vomiting, and 1, gastroparesis.

6.2.4.7.10 Dose Modifications: Eighteen patients (28%) required dose reduction, primarily because of neuropathy (10 patients) and this occurred after the patient had received at least 4 or 5 cycles of ixabepilone. Four patients discontinued ixabepilone because of neuropathy. About 80% of therapy cycles were administered within 3 days of the scheduled day.

6.2.4.7.11 Efficacy Results:

Primary Efficacy Endpoint: The ORR is shown in Table 34 (data Sponsor's Table 10 from the -010 Study Report). Twenty-seven (27) of 65 of patients (41.5%, CI 29.4-54.4) achieved a PR according to modified WHO criteria. This is a far higher response rate than in -009 and in -081 studies, presumably because in this study ixabepilone was administered as first-line treatment in patients with metastatic disease.

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Table 34. Primary Efficacy Endpoint—ORR assessed by the Sponsor's team.

Response	All Treated Patients (40 mg/m ² over 3 hours every 21 days) N = 65
Complete	0
Partial	27 (41.5%, CI 29.4-54.4)
Total	27 (41.5%, CI 29.4-54.4)

Reviewer's Note: The response rate 58% (11/19 patients, all PRs) among patients treated with 50 mg/m² ixabepilone infused IV over one hour. Two (2/9) patients who were treated with 50 mg/m² ixabepilone infused over 3 hours had a PR.

The median time to PR was 6 weeks (2 cycles) (range, 5 – 17 weeks). About 74% of responders had achieved the response after 2 cycles, 19% after 4 cycles, and the remaining 7% after 6 cycles.

About 52% (14/27) of responders had 2 or more target lesions; 8 had 4 or more target lesions. Most responders had visceral metastatic disease involving the liver and lung.

Secondary Efficacy Endpoints:

Median duration of response was 8.2 months (95% CI, 5.7 -10.2 months). Six of 27 (22%) responders were without PD for 12 months or more.

Median time to progression: 4.8 months (95% CI, 4.2 – 7.6 months).

Median survival: 22.0 months (95% CI, 15.6 – 27.0 months).

6.3 Clinical Microbiology

Not applicable to an anti-neoplastic

6.4 Efficacy Conclusions

6.4.1 Combination Therapy

The pivotal efficacy trial is trial CA163046 (Study 046) which is an open label randomized trial that compared combination therapy to capecitabine alone in patients with advanced breast cancer. The primary endpoint of this trial was PFS, defined as radiological or quantifiable clinical progression or death from any cause. Trial CA163031 (Study 031) was a dose-finding trial that compared single day administration at a dose of 40 mg/m² to daily for three days administration at 8 mg/m² of ixabepilone, both in combination with capecitabine. Study 031 is supportive of Study 046.

The primary endpoint of PFS has been used previously in approval of drugs for advanced breast cancer. The clinical endpoint of PFS is not of certain clinical benefit, as it may not be in and of itself of benefit, and may not be a surrogate for a benefit in overall survival (OS), which is of clear clinical benefit. PFS is also subject to bias, particularly in unblinded trials, as the

assessment of radiological progression is essentially a judgment call. The sponsor in this case has attempted to minimize the effect of bias on determination of PFS. The definition of PFS was appropriate, and radiological progression was determined by independent review that was blinded to the treatment arm. In this patient population analysis of Study 046 as performed allows PFS to support approval for marketing.

In this multinational, multicenter study, patients were adult women with metastatic or locally advanced breast cancer who had previously received therapy with an anthracycline and a taxane, and whose disease was resistant to such therapy. Study arms were balanced with respect to race, age, extent of disease, previous therapies, hormone receptor status and HER2 expression. The study was conducted well, the patient population was clearly defined and clinically relevant, and the results are statistically significant. Patients in the capecitabine arm received a median of four cycles of chemotherapy, while those in the combination arm received a median of five cycles. Using the intent to treat population and data from the independent radiologic review, patients in the capecitabine alone arm had a median PFS point estimate of 4.17 months while for the combination arm it was 5.85 months with a hazard ratio of 0.75 (95.17% CI: 0.64, 0.88) and stratified log-ranked p-value of 0.0003 (Sponsor's analysis). Multiple sensitivity analyses, including an analysis of patients as treated and censoring patients with unevaluable disease yielded similar, statistically significant results. Similarly, PFS analysis using data generated by the investigators yielded a median PFS point estimate of 3.81 and 5.26 months for capecitabine and combination respectively, with a HR of 0.78 (95.17% CI: 0.67, 0.91) and a stratified log-ranked p-value of 0.0011.

Analysis of the secondary endpoint of overall survival (OS) is premature. Interim requested analysis by the data monitoring committee did not necessitate study cessation. The final OS analysis will be conducted when 631 patients have died. Four hundred eighty-three patients had died as of database lock. The objective response rate (ORR) for capecitabine was 14.3% (95% CI: 10.9, 18.3) and for combination therapy it was 34.7% (95% CI: 29.9, 39.7) as determined by the IRCC. The median time to response was similar in both groups at approximately twelve weeks, and the duration of response was 5.6 and 6.4 months for capecitabine and combination respectively. This difference was not statistically significant. Analyses using the investigators' assessments were similar.

Based on these findings, ixabepilone in combination with capecitabine has clinical utility in treating patients with advanced breast cancer in whom an anthracycline and a taxane have failed.

6.4.2 Monotherapy

The tumor response rate in the principal monotherapy trial of ixabepilone in treatment of anthracycline-, taxane- and capecitabine-resistant MBC patients was at least 12% (95% CI, 6.8 – 18.9), as assessed by IRRC, and as high as 18% (95% CI, 11.9 – 26.1), as assessed by the investigators. The reasons why the response rate may be higher than 12% include lesions that were evaluated by physical diagnosis, radiographic evaluations that were available to the investigators but were not submitted to IRRC or selection of target lesions by IRRC that were not evaluated at regular intervals, and differences in selection of target lesions.

Tumors in responders decreased by the time of the first assessment, after 2 cycles of therapy, and the extent of decreases reached > 30%, the criterion for a PR, within 6 cycles in all but one responder. The median time to response was 2 cycles of therapy (6.1 weeks).

The median duration of response was 6.3 months. Median PFS was 3.2 months and median overall survival was 9.0 months. In absence of a comparator arm, it is difficult to evaluate these data. Presumably, these PFS and OS values would be superior to placebo in these extensively treated patients.

Although the numbers in each subset are limited, analysis of responders by subsets showed ixabepilone activity in ER+ and ER- patients, in HER+ and HER- patients and in triple negative (ER-, PR-, and HER- patients) in patients < 65 years and in ≥ 65 years of age, probably in patients of all races (the number of Black patients was small), in patients with visceral metastases to liver and/or lung, PS of 70-100%), in patients with ≥ 2 disease sites, in patients whose time from cancer diagnosis was < 2 years or ≥ 2 years, and in patients ≥ 2 chemotherapy regimens for metastatic cancer. There were no responders among 14 patients without metastases to the liver and/or lung and among 14 patients with fewer than 2 prior chemotherapy regimens for metastatic cancer. Probably ixabepilone is active in all of the above subgroups.

The results of the monotherapy pivotal study are supported by results in smaller studies. The response rate in these trials were assessed by different (and more stringent) modified WHO criteria rather than RECIST criteria. The assessments were performed by the sponsor's internal team. The response of taxane-resistant MBC patients was 12% and the median duration of response was 10.4 months. The response in MBC patients who had been treated with an anthracycline in adjuvant setting and in whom ixabepilone was first-line therapy was 41.5% and the median duration of response was 8.2 months.

The data from the monotherapy trials support the proposed indication. The major limitation is the absence of a comparator drug, which would allow an assessment of the relative effectiveness of ixabepilone.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Under each heading, findings from monotherapy studies and combination therapy with capecitabine studies will be presented. For combination therapy, the primary analysis will be based on Study 046 which has the largest database and provides a direct comparison to adverse reactions expected with capecitabine alone. When appropriate, data from the single arm Study 031 (using only the same dose and schedule of ixabepilone as in 046) will be included. The analysis will rely on the sponsor's study report, as well as independent analysis of the provided

datasets as indicated. For monotherapy, the primary study will be Study 081, with supportive data from Study 009 and 010.

7.1.1 Deaths

Study 046

A total of 231 subjects in the combination arm and 243 subjects in the capecitabine arm had died as of the date of database lock. The majority of deaths were attributed to disease progression. A descriptive analysis will be performed of the deaths occurring within 30 days of the date of last dose of study drug for Study 046 comparing therapy with capecitabine plus ixabepilone to capecitabine alone. It is presumed that deaths occurring later than 30 days after last dose are unlikely to be related to study drugs..

The analysis presented by the sponsor divides the safety cohort into two groups: those with normal hepatic function or mild dysfunction (Grade 1 elevation in AST, ALT or total bilirubin) and those with moderate to severe hepatic dysfunction (Grade 2 or greater elevations in AST, ALT or total bilirubin). This dichotomy is dictated in part by Protocol Amendment 4 which excluded patients with Grade 2 or greater elevations in hepatic enzymes and bilirubin, regardless of the presence or absence of hepatic metastases. This change in the protocol was made in response to concerns of the DMC that patients with moderate to severe hepatic dysfunction who received combination therapy had a disproportionate number of febrile neutropenic events. We accept the separate analysis for normal function/mild dysfunction and moderate/severe dysfunction, and note that the majority of patients fell into the former category.

There were a total of 39 patients in the capecitabine arm and 33 in the combination arm who died within 30 days of last dose. A total of 12 patients in the combination arm who died within 30 days were determined to have died due to study drug administration. Two patients in the capecitabine arm dies due to drug toxicity. Those narratives are not presented.

Deaths within 30 days attributed to study drug

Patients with severe hepatic dysfunction (Combination therapy only)

Five of sixteen subjects (31.3%) in the combination arm, and five of twenty-six (19.2%) in the capecitabine arm with moderate/severe hepatic dysfunction died within 30 days of last dose. Four deaths in the combination arm were attributed to study drug by the investigator, and an additional death was attributed to study drug by the sponsor. Synopses of these deaths follow.

CA163046-42-11

65 y/o woman previously treated with epirubicin and paclitaxel developed fever and cough cycle 3, treated with azithromycin and steroids, then — hospitalized with neutropenia and respiratory infection. ANC 400/mm³. Neutrophils recovered, but patient developed cough and respiratory arrest on —. Investigator ascribed death to infection and neutropenia, asserted to be ongoing at time of death. Of note the patient did not have regular hematological assessment as

required by protocol. The patient had grade 2 hyperbilirubinemia at baseline. This case is likely related to neutropenia and infection, although it is poorly documented. In the absence of compelling evidence to the contrary, it is reasonable to conclude that the study drug was responsible for the neutropenia which led to pulmonary infection and death.

CA163046-58-193

61 y/o treated with CMF, CAF paclitaxel and radiotherapy, she had grade 3 elevation in AST at baseline. Between _____ the patient was diagnosed with DIC based on vague symptoms and laboratory abnormalities. The patient was hospitalized, developed neutropenia and *E. coli* septicemia along with pulmonary infiltrates, and died on _____. The neutropenia and resultant septicemia were considered probably related to study medication. This reviewer agrees with that assessment.

CA163046-60-371

A 55 y/o woman previously treated with CMF, CAF, paclitaxel and radiotherapy had grade 2 AST and grade 1 ALT elevations at baseline. The patient was admitted to the hospital on _____, for tumor pain, received study drug on _____, and had diarrhea leading to dehydration, hypotension, CV collapse, intubation and dobutamine on _____, with resolution of hypotension (but apparently not intubation) by _____. On _____ the patient developed neutropenia with fever, and suffered cardiac arrest on _____. Cultures were negative. The investigator considered respiratory failure leading to death as possibly related, and the dehydration probably related. According to this reviewer, diarrhea is likely related, but the proximate cause of death is neutropenic bacteremia, related to study medication.

CA163046-69-83

This patient is a 56 y/o woman previously treated with FAC, paclitaxel and gemcitabine who had baseline grade 1 elevation in ALT and grade 2 elevation in AST. She developed febrile neutropenia on _____ and subsequently expired despite appropriate care. The patient experienced neutropenia during cycle 2. The dose of ixabepilone was not changed for Cycle 2. This death is considered related to study medication.

CA163046-95-99

This is a 43 y/o woman with previous therapy of CAF, docetaxel, carboplatin, vinorelbine, ifosfamide and XRT and hormonal therapy who develop progressive hyperbilirubinemia during Cycle 1. The patient had extensive liver disease and baseline grade 3 elevation in AST, and grade 1 elevations in ALT and bilirubin. She received Cycle 1 and on Day 7 developed fatigue and nausea, with diarrhea on Day 8 which was treated with loperamide. She then developed dehydration and was admitted on _____ when she expired 2 hours after admission. There was a marked elevation in bilirubin as well as neutropenia and thrombocytopenia. The investigator claimed the death was due to disease progression, but the sponsor flagged the case as possibly related to study drug. It is unclear what the exact cause of death is, but it appears that there was a sudden cardiovascular collapse, which could be related to undocumented infection or direct cardiac toxicity.

Reviewer's Comment: All five of these deaths were likely caused by infection related to neutropenia. Diarrhea may have been contributory in at least two cases. Subject 95-99 likely died from infection related to neutropenia, but it is possible that a direct or indirect cardiac cause is responsible. There is a lack of details in the information from the investigator.

Because of the increased incidence of deaths in patients with hepatic insufficiency treated with ixabepilone and capecitabine, the DMC recommended that the study protocol be amended so that patients with moderate or severe hepatic insufficiency were excluded from the study. This was an appropriate recommendation. Based on the analysis of deaths in these patients, the risk-benefit ratio with combination therapy does not warrant treatment with patients with moderate or severe hepatic insufficiency as described above. This is reflected in the labeling proposed by the sponsor.

Patients with normal hepatic function (Combination therapy only)

Twenty-eight of 353 patients (7.9%) in the combination arm and 34 of 342 patients (9.9%) in the capecitabine arm who had normal hepatic function or mild dysfunction (\leq Grade 1 elevation in AST, ALT or total bilirubin) died within 30 days of the last dose of study drug. Of these, six deaths were deemed attributable to study drug by the investigators and an additional death was determined related to study drug by the sponsor. Synopses of these deaths are presented below.

CA163046-5-705

A 52 y/o woman with previous doxorubicin (540 mg/m²), paclitaxel, tamoxifen and radiation therapy, with grade 3 pain during cycle 1 leading to dose reduction for Cycle 2. ——— patient had grade 1 AST and ALT elevation. The patient's course then becomes complicated. — the patient was hospitalized for dehydration. She had previously experienced vomiting and other constitutional symptoms for which she self-administered multiple medications, including apap/hydcod(?), fluconazole and prochlorperazine. On admission, the patients LFTs were markedly elevated and she developed a fever. CXR showed an infiltrate and cardiomegaly. The dehydration resolved as did the fever with fluids and antibiotic therapy. The patient developed a neutropenia, a pulmonary effusion and poor oxygenation, and an echocardiogram revealed an ejection fraction below 15%. The patient was transferred in and out of the intensive care unit, developed a non-STEMI diagnosed by elevated troponin levels and expired on ———. Blood cultures were persistently negative. The investigator cause of death was cardiomyopathy deemed related to study drug. It is likely that the cardiomyopathy in this case was secondary to either disease progression, infection or possibly study drug. It does not appear that cardiac dysfunction was the underlying cause for admission, but if the patient had underlying occult cardiovascular disease, exacerbated by dehydration and sepsis this could lead to progressive cardiac dysfunction. The lack of positive blood cultures does not rule out a bacterial infection, which could have been fatal in the setting of neutropenia despite appropriate antibiotic coverage.

CA163046-24-351

A 59 y/o woman previously treated with doxorubicin, paclitaxel, docetaxel, vinorelbine and CMF presented with mental status changes on ———, along with ANC of 420/mm³. The patient

was started on empiric antibiotics. Blood cultures grew *S. aureus*, appropriate antibiotics were started, but the patient failed to respond and expired on _____. ANC _____ was 0/mm³. The proximate cause of death was ruled progressive disease by the investigator. This is clearly a case of neutropenic sepsis, and should be considered related to ixabepilone therapy. The sponsor has flagged this case as possibly related to study drug despite the investigator's assertion that the cause of death was disease progression.

CA163046-67-31

The subject is a 60 y/o woman who had received CEF, paclitaxel, hormonal therapy and radiotherapy. She had received 4 cycles of study drugs. She received only ixabepilone in cycle 5 due to hand-foot syndrome attributed to capecitabine. The patient experienced grade 2 diarrhea _____, treated with oral antibiotics and loperamide on _____. Patient developed neutropenia _____ with continued diarrhea. She developed hypovolemic shock on _____ and died shortly afterward. The investigator attributed her death to diarrhea and hypovolemic shock, possibly related to study medication. Her neutropenia which was certainly related was likely contributory or causative.

CA163046-75-149

This 57 y/o who had previously received CAF and docetaxel died on _____ of sepsis despite antibiotic therapy following the development of febrile neutropenia. She had not experienced neutropenia in cycles 1 or 2, but developed fever, Grade 4 neutropenia and a chest infiltrate in cycle 3. There were no baseline LFT abnormalities. This case is related to study drug.

CA163046-200-506

This is a 50 y/o woman previously treated with CAF, docetaxel, vinorelbine and XRT who received 2 cycles of study drug with no serious adverse events. On _____ patient was hospitalized for diarrhea, neutropenia and fever, and was treated with broad spectrum antibiotics, growth factor and supportive care. The next day the patient had a GI bleed (source unspecified) and on _____ experienced worsening oxygenation for which she was admitted to the ICU and eventually placed on mechanical ventilation. The patient expired on _____ from septic shock. Cultures were negative. This case is related to study drug as determined by the investigator. The reviewer concurs.

CA163046-212-375

A 72 y/o woman with previous CAF, paclitaxel and tamoxifen experienced grade 3 mucositis and pneumonitis with _____. Dose was not reduced for _____ in violation of protocol. She developed fever and dyspnea on _____ which required hospitalization on _____. She was neutropenic on presentation. The patient died 12 hours after hospitalization. Blood cultures were positive for *Enterobacter* species. The neutropenia leading to infection and death are determined to be related to study drug.

CA163046-254-633

This subject is a 72 y/o woman with previous CMF, docetaxel, irinotecan, epirubicin tamoxifen and XRT. The patient was hospitalized on _____ with fever, diarrhea and neutropenia. The

patient was treated with antibiotics and growth factors but died three days later. The investigator regarded the neutropenia leading to infection and death as probably drug related.

Reviewer's Comment: All but one of these deaths (Subject 5-705) is clearly related to infection with neutropenia, three of which were also associated with diarrhea. Subject 5-705, who also demonstrated neutropenia may have had an underlying hepatic and/or cardiac toxicity that is contributory. Diarrhea may be contributory to the development of infection, but it is unclear whether this is due to ixabepilone or capecitabine or both.

Deaths within 30 days not attributed by the investigator to study drug

These deaths are described here because they occurred within 30 days of the last dose of study drug and because a relationship to study drug could not definitively be ruled out.

Cardiac Events

CA163046-19-389

A 49 y/o woman with multiple cardiac risk factors—hypertension, angina, previous cardiac surgery—had a myocardial infarction on _____. No other details are available. The relationship of this death to study drug is indeterminate.

CA163046-89-443

A 57 y/o woman with prior history of hypertension taking metoprolol, was hospitalized on _____ with fatigue and hypokalemia. Electrolyte replacement did not relieve fatigue, and bronchoscopy showed inflamed mucosae and hemorrhage. Cardiac workup was either not performed or not reported. The patient died 22 days after the last dose of study drug due to “cardiorespiratory arrest”.

CA163046-94-214

A 64 y/o woman with history of tachycardia taking metoprolol. The patient had extensive lung disease. On _____ the patient developed fatigue, and died at home three days later. Death was attributed to cardio-respiratory failure secondary to extensive lung disease.

CA163046-215-605

A 69 y/o woman with a previous history of LVH and LBBB taking enalapril, experienced sudden onset dyspnea and tachycardia on _____, and was dead on arrival at the hospital. Death was attributed to sudden death, unrelated to study drug.

Other

The remaining narratives for deaths in the combination arm occurring within 30 days of the last dose of study drug were reviewed. All of these deaths can reasonably be attributed to disease progression. No further analysis of these deaths will be performed.

Reviewer's Comments: The five deaths attributed to cardiopulmonary collapse may be related to study drug administration. Two of these patients, numbers 19-389 and 215-605, died within ten days of administration of study drug of an acute cardiac event. The actual cause of cardiopulmonary collapse in the other patients is less clear, and may have other contributory causes. No acute cardiac events were reported in the capecitabine arm. Cardiac events resulting in AEs other than death will be reviewed below. The remaining deaths within 30 days not described in this review may be reasonably attributed to disease progression.

Study 031

Study 031, a Phase 1/2 study in a similar patient population with identical dosing of study drugs enrolled 62 patients. Two patients died within 30 days of the last dose of study drug, one from progressive disease and one from sepsis associated with neutropenia.

CA163081

There were 12 deaths during the course of the study and within 30 days of the last dose of ixabepilone (~ 10% of the all treated population).

CA163081-18-98. One death considered by the investigator to be related to ixabepilone (patient CA163081-18-98). This patient had Grade 4 CHF at baseline and her entry into the study was a protocol violation. The investigator thought her CHF was related to anthracycline cardiomyopathy. She had received cumulative doses of 600 mg/m² of epirubicin and 450 mg/m² of doxorubicin. On Day 4 of Cycle 1 she was hospitalized with CHF. On Day 6 of Cycle 1 the patient developed Grade 4 neutropenia, anemia and thrombocytopenia. Despite treatment with antibiotics and G-CSF, patient developed septic shock, multi-organ failure and died. An autopsy was not performed.

The other deaths were not considered to be related to ixabepilone. Patient -18-102 died from septic shock, but without neutropenia. The patient had intermittent fever and septicemia. Her ANC were 3,300 – 5,460/μL. An autopsy was not performed. Patients -48-10, -48-122, and -54-127 died from cardiomyopathy, CHF and heart attacks. An autopsy on patient -48-10 confirmed myocardial hypertrophy, dilatation of ventricles, and moderate sclerosis of coronary arteries. Autopsies were not performed on the other two patients with suspected cardiomyopathy.

Seven patients died of progressive disease.

Subsequent to the study period and the 30-day period after the last dose of ixabepilone, 4 patients died from causes unrelated to ixabepilone (one from respiratory failure, 40 days after the last dose of ixabepilone; one from multi-organ failure 171 days after the last dose; one from cardiopulmonary arrest 250 days after the last dose; and one from respiratory failure 419 days after the last dose). By the time of the December 15, 2006 database lock, one year after the original study report database lock, there were a total of 96 deaths (76% of the all treated patients), (Clinical Study Report Addendum 02, Appendix 12.15). All but 9 patients, described above, died from disease progression. At least some if not most of the cardiac cases had cardiomyopathy due to previous anthracycline therapy.

Table 35 lists all deaths that were not due to progressive disease.

Table 35. Deaths NOT Attributed to Progressive Disease While On-Study, Within 30 Days of the Last Dose and on Follow-up

Patient ID	Age	Total Cycles	Days Since Last Ixabepilone Dose	Cause of Death
CA163081-				
-48-10	63	1	1	Cardiomyopathy, CHF, MI
-18-98*	44	1	6	Cardiomyopathy, CHF, neutropenia, septic shock, multi-organ failure
-54-127	64	1	8	Cardiomyopathy, CHF, ARDS
-18-102	61	3	10	Septic shock w/o neutropenia
-48-122	71	4	11	Cardiomyopathy, CHF, MI
-82-100	62	1	40	Respiratory arrest
-54-55	57	4	171	Multiorgan failure
-80-126	49	5	250	Cardiac arrest
-82-74	53	2	419	Respiratory failure

*Ixabepilone-related.

Studies 009 and 010

There were 5 deaths during the 009 study and during the 30-day period after the last dose of ixabepilone. One of the deaths, which occurred 26 days after the last dose of ixabepilone, was due to febrile neutropenia and thrombocytopenia. It was thought to be unrelated to ixabepilone by the investigator. *(The Reviewer considers this death ixabepilone-related, unless there are other causes of neutropenia and thrombocytopenia.)* There was one death during the 010 study and the follow-up period. It was due to progressive disease.

Appears This Way
 On Original

7.1.2 Other Serious Adverse Events

Study 046

Serious AEs were defined as AEs resulting in death, hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, overdose, drug dependency or were life-threatening, a cancer or birth defect.

Of 369 patients treated with combination therapy, 151 (41%) reported a serious adverse event. Of these, 91 (25%) reported at least one treatment-related serious adverse event. For the capecitabine alone arm, there were a total of 127 SAEs from 368 treated patients. Of these, 31 (8%) reported at least one treatment-related SAE. The majority of SAEs in both arms were attributed to disease progression. Review of the case report forms for all SAEs on the combination arm demonstrates that events were faithfully captured and reported in sponsor Appendix 12.5 with only minor exceptions.

Study 031

Of 62 patients treated with ixabepilone and capecitabine in combination, 15 reported SAEs, and 9 of these were treatment related. CRFs for these events were not reviewed.

Reviewer Table 36 shows the major treatment related SAEs by System Organ Class for each study. Only those treatment related SAEs that occurred in more than 1% of patients in any study are shown. Data are from Table 2.1.3B from the Summary of Clinical Safety.

Table 36. Treatment related SAEs for combination therapy

System Organ Class	046 Combination n (%)	046 Capecitabine n (%)	031 Combination n (%)
Blood and lymphatic System disorders	43 (11.7)	31 (8.4)	3 (4.8)
Any	91 (24.7)	31 (8.4)	9 (14.5)
Cardiac Disorders	6 (1.6)	1 (0.3)	0
GI Disorders	6 (1.6)	1 (0.3)	0
General Disorders and Administration Site Conditions	17 (4.6)	6 (1.6)	2 (3.2)
Infections and Infestations	16 (4.3)	2 (0.5)	2 (3.2)
Metabolism and Nutrition Disorders	10 (2.7)	2 (0.5)	2 (3.2)
Investigations	4 (1.1)	2 (0.5)	0
Musculoskeletal and Connective Tissue Disorders	6 (1.6)	0	0
Nervous System Disorders	11 (3.0)	1 (0.3)	0
Respiratory Thoracic and Mediastinal Disorders	5 (1.4)	2 (0.5)	1 (1.6)

System Organ Class	046 Combination n (%)	046 Capecitabine n (%)	031 Combination n (%)
Skin and Subcutaneous Tissue Disorders	6 (1.6)	1 (0.3)	1 (1.6)
Vascular Disorders	6 (1.6)	0	0

Reviewer's Comments: The SAEs in general reflect the most common AEs (see below). There are more SAEs in the combination arm in most categories. SAEs leading to discontinuation are discussed in detail below.

Study 081

Table 37 of SAEs together with the CTC grade is derived from data in Sponsor's Table S.12.6. A total of 41 patients (41/126 = 32.5%) had an SAE. Most of the SAEs were Grade 3 and 4. There were 12 deaths (Grade 5), one death was treatment-related and is described above.

According to the Sponsor, of the 41 patients with SAEs, 21 (16.7%) had at least one treatment-related SAE. The most common treatment-related SAE was stomatitis (5 patients); two of these patients were discontinued from the study.

The most notable differences between the lists of all SAEs and of Treatment-Related SAEs were: 1) 12 deaths vs. 1, 2) 14 vs. 8 gastrointestinal disorders, 3) 9 vs. 5 general disorders, 4) 6 vs. 3 infections, 5) 4 vs. 1 dehydration events, 6) 1 vs. 0 musculoskeletal, 7) all 9 neoplastic events, 8) 2 MIs, 9) 2 vascular events, 10) 10 vs. 1 respiratory events, and 11) single renal and reproductive events. Both lists are notable for the absence of neuropathic events.

There were no new SAEs reported in the 120-day Safety Update.

Table 37. SAEs in all treated patients—Study 081

System and Organ AE Preferred Term	Grade 3	Grade 4	Total (%)
Patients with Any Treatment-Related SAE	19 Grade 3 4 Grade 2	7 Grade 4 12 Grade 5	41/126 (32.5%)
Blood & Lymphatic Systems	4	3	7 (5.6%)
---Febrile neutropenia	3	0	3
---Neutropenia	1	2	3
---Leukopenia	0	2	2
---Pancytopenia	0	1	1
Cardiac		[2] Grade 5	2 (1.6%)
---Myocardial infarction		2 Grade 5	
GI Disorders	11	2	14 (11.1%)
---Stomatitis	4	1	
---Diarrhea	2		
---Abdominal pain	2	1	
---GI pain	1		
---Nausea	2		

System and Organ AE Preferred Term	Grade 3	Grade 4	Total (%)
---Vomiting	1		
---Constipation	1		
---Rectal prolapse	1 (Grade 2)		
General disorders	5 (plus [2] Gr. 1 and [2] Gr. 2)	0	9 (7.1%)
---Asthenia	[1] Gr. 2 + 1		4
---Pyrexia	[1] Gr. 1 + 1		2
---Fatigue	1		1
---Pain	2		2
Hepatobiliary (hyperbilirubinemia)	1	0	1 (0.8%)
Immune (hypersensitivity reactions)	(1 Grade 2)	0	1 (0.8%)
Infections & Infestations	2 (plus [2] Gr. 2)	2 Grade 5	6 (4.8%)
---Catheter-related	1		
---Lung infection	1 (Gr. 2)		
---Pneumonia	1 (Gr. 2)		
---Sepsis	1		
Dehydration	4	0	4 (3.2%)
Laboratory Investigations		2	2 (1.6%)
---Platelet count decreased	1		
---Platelet count		2	
---Neutrophil count		1	
Metabolism (Dehydration)	1	0	1 (0.8%)
Musculoskeletal	0	1	1 (0.8%)
---Chest wall pain		1	
Neoplastic	1	2 + [6] Gr. 5	9 (7.1%)
---Progression of disease		[5] Grade 5	
---Pleural effusion	[1] Grade 2	0	
---Cancer pain		1	
---Lymphangiosis carcinomatosis		[1] Grade 5	
---Pleural mesothelioma		1	
Renal	1	0	1 (0.8%)
---Oliguria			
Reproductive	1	0	1 (0.8%)
---Cervical dysplasia			
Respiratory	7	[3] Grade 5	10 (%)
---Dyspnea	3	[2] Grade 5	
---Hypoxia	1		
---Pleural effusion	1 + [1] Gr. 2	[1] Grade 5	
---Pneumothorax	[1] Grade 2		
Skin	1 (plus [1] Gr.2)	0	2 (1.6%)
---Rash	1		
---Skin reaction	1		
Vascular	0	2	2 (1.6%)
---Lymphedema		1	
---Peripheral ischemia		1	

7.1.3 Dropouts and Other Significant Adverse Events

Combination Therapy

Overall profile of dropouts

Most patients discontinued therapy for disease progression. There were no signals to suggest a particular patient population was susceptible to dropouts from toxicity.

Adverse events associated with dropouts

In Study 046 patients were allowed to continue on only one treatment if an adverse event was determined to be due to the other drug. Of the 369 patients treated in the combination arm, 163 (44%) discontinued one or both medications due to adverse events. Of these, 136 were deemed to be treatment related. Seventy-nine (21%) patients discontinued for treatment related neuropathy after a median of 6 cycles. Forty-four of these patients continued on capecitabine for at least one cycle.

Database AESAE.xpt was analyzed to determine the most common AEs related to dropouts. Patients who discontinued therapy because of an AE considered possibly, likely or certainly related to a study drug were classified according to AE. The results of this analysis, with listings by System Organ Class and MedDRA Preferred Term, are shown below in Table 38. Note that a single patient may have more than one AE associated with discontinuation of study drug. No attempt was made to determine which AE was the causative factor in these cases. This analysis largely agrees with the sponsor's analysis, although there are minor differences in the frequency of Gastrointestinal and Skin disorders. These do not raise a significant additional concern.

Table 38. Reviewer analysis of patients who discontinued study medication because of an adverse event—Study 046.

System Organ Class	Preferred Term	Combination		Capecitabine	
		n	%	n	%
BLOOD AND LYMPHATIC SYSTEM DISORDERS		7	1.9	5	1.4
	ANAEMIA	0	0.0	1	0.3
	COAGULOPATHY	0	0.0	1	0.3
	FEBRILE NEUTROPENIA	3	0.8	2	0.5
	NEUTROPENIA	4	1.1	0	0.0
	THROMBOCYTOPENIA	0	0.0	1	0.3
CARDIAC DISORDERS		5	1.4	1	0.3
	ANGINA PECTORIS	1	0.3	0	0.0
	CARDIOMYOPATHY	1	0.3	0	0.0
	MYOCARDIAL ISCHAEMIA	1	0.3	1	0.3
	SINUS ARRHYTHMIA	1	0.3	0	0.0
	VENTRICULAR DYSFUNCTION	1	0.3	0	0.0

Clinical Review
Edvardas Kaminskas, Robert Lechleider
NDA 22-065
Ixempra, ixabepilone

System Organ Class	Preferred Term	Combination		Capecitabine	
		n	%	n	%
GASTROINTESTINAL DISORDERS		10	2.7	12	3.3
	ABDOMINAL PAIN	0	0.0	1	0.3
	ABDOMINAL PAIN UPPER	1	0.3	0	0.0
	ANAL ULCER	0	0.0	1	0.3
	COLITIS	0	0.0	1	0.3
	CONSTIPATION	0	0.0	1	0.3
	DIARRHOEA	3	0.8	4	1.1
	NAUSEA	1	0.3	2	0.5
	STOMATITIS	0	0.0	1	0.3
	VOMITING	5	1.4	1	0.3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		7	1.9	3	0.8
	ASTHENIA	2	0.5	0	0.0
	FATIGUE	2	0.5	1	0.3
	MUCOSAL INFLAMMATION	0	0.0	2	0.5
	PAIN	2	0.5	0	0.0
	PYREXIA	1	0.3	0	0.0
HEPATOBIILIARY DISORDERS		0	0.0	1	0.3
	HYPERBILIRUBINAEMIA	0	0.0	1	0.3
IMMUNE SYSTEM DISORDERS		1	0.3	0	0.0
	HYPERSENSITIVITY	1	0.3	0	0.0
INFECTIONS AND INFESTATIONS		5	1.7	1	0.3
	PNEUMONIA	2	0.5	1	0.3
	SEPSIS	3	0.8	0	0.0
INVESTIGATIONS		4	1.1	3	0.8
	ASPARTATE AMINOTRANSFERASE INCREASED	1	0.3	0	0.0
	HAEMOGLOBIN DECREASED	0	0.0	1	0.3
	NEUTROPHIL COUNT DECREASED	1	0.3	0	0.0
	PLATELET COUNT DECREASED	1	0.3	2	0.5
	WHITE BLOOD CELL COUNT DECREASED	1	0.3	0	0.0
METABOLISM AND NUTRITION DISORDERS		4	1.1	1	0.3
	ANOREXIA	1	0.3	1	0.3
	DEHYDRATION	1	0.3	0	0.0
	HYPOKALAEMIA	1	0.3	0	0.0
	HYPONATRAEMIA	1	0.3	0	0.0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		7	1.9	0	0.0
	ARTHRALGIA	1	0.3	0	0.0

System Organ Class	Preferred Term	Combination		Capecitabine	
		n	%	n	%
	MUSCULOSKELETAL CHEST PAIN	1	0.3	0	0.0
	MUSCULOSKELETAL PAIN	1	0.3	0	0.0
	MYALGIA	4	1.1	0	0.0
NERVOUS SYSTEM DISORDERS		107	29.0	2	0.5
	COORDINATION ABNORMAL	1	0.3	0	0.0
	DIZZINESS	1	0.3	0	0.0
	DYSAESTHESIA	2	0.5	1	0.3
	HYPOAESTHESIA	1	0.3	0	0.0
	LETHARGY	1	0.3	0	0.0
	NERVOUS SYSTEM DISORDER	3	0.8	0	0.0
	NEURALGIA	3	0.8	0	0.0
	NEUROPATHY	4	1.1	0	0.0
	NEUROPATHY PERIPHERAL	9	2.4	0	0.0
	NEUROTOXICITY	1	0.3	0	0.0
	PARAESTHESIA	16	4.3	1	0.3
	PERIPHERAL MOTOR NEUROPATHY	18	4.9	0	0.0
	PERIPHERAL SENSORY NEUROPATHY	45	12.2	0	0.0
	POLYNEUROPATHY	1	0.3	0	0.0
	SENSORY LOSS	1	0.3	0	0.0
RENAL AND URINARY DISORDERS		0	0.0	1	0.3
	RENAL FAILURE	0	0.0	1	0.3
	RENAL FAILURE ACUTE	0	0.0	1	0.3
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		3	0.8	0	0.0
	ACUTE PULMONARY OEDEMA	1	0.3	0	0.0
	DYSPNOEA	1	0.3	0	0.0
	RESPIRATORY FAILURE	1	0.3	0	0.0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		32	8.7	15	4.1
	DRY SKIN	0	0.0	1	0.3
	ERYTHEMA MULTIFORME	1	0.3	0	0.0
	EXFOLIATIVE RASH	1	0.3	0	0.0
	NAIL DISORDER	4	1.1	1	0.3
	ONYCHOCCLASIS	1	0.3	0	0.0
	PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	24	6.5	11	3.0
	RASH	0	0.0	1	0.3
	SKIN FISSURES	0	0.0	1	0.3
	TOXIC SKIN ERUPTION	1	0.3	0	0.0
VASCULAR DISORDERS		1	0.3		0.0
	HYPOTENSION	1	0.3	0	0.0

The most common drug-related cause for discontinuation was neuropathy. This is discussed in more detail on Section 7.1.3.3.1 below. Second most common was hand-foot syndrome, but this is overwhelmingly related to capecitabine therapy. Gastrointestinal disorders caused about three percent of patients to discontinue study drug, but this is not an excessive number.

Monotherapy

Study 081

Table 39 lists the AEs that led to the discontinuation of study therapy by MEDRA v. 8.1 preferred term and including the severity of AE by NCI CTC criteria. One patient is now reported as having Grade 3 neuropathy (instead of “no corresponding AE”) and one patient with “necrosis” is now reported with “CNS necrosis”. In addition, under the category “Investigator Request”, one patient discontinued study treatment because of “progressive pain” and under the subject discontinued because of “Grade 3 thoracic pain”. These two patients should be included under patients who discontinued study drug because of AE. So should 2 patients with MIs.

The sponsor states in the Safety Update that the number of patients who discontinued because of study drug-related adverse events is now 15 (11.9%). The number of patients with any AE leading to discontinuation is larger, 25 (19.8%). With the 2 cardiac deaths this number increases to 27 (21.4%). A total of 32 AEs is listed as leading to discontinuation of ixabepilone.

Table 39. Adverse events leading to discontinuation of ixabepilone—All treated patients study 081

AE Preferred Term	CTC Grade	Total (%)
Number of Patients with Any AE Leading to Discontinuation of Ixabepilone		27/126 (21.4%)
Blood		
---Pancytopenia	Grade 4	1 (0.8%)
Cardiac		
---Myocardial infarction	Grade 5	2 (1.6%)
Eye		
---Blurred Vision	Grade 3	1 (0.8%)
GI Disorders		4 (3.2%)
---Abdominal pain	Grade 3, Grade 4	2
---Stomatitis	Grade 3 (2)	2
General disorders		3 (2.4%)
---Asthenia	Grade 3	1
---Edema	Grade 3	1
---Pain	Grade 2	1
Hepatobiliary		
---hyperbilirubinemia	Grade 3	1 (0.8%)
Immune		
---hypersensitivity reactions	Grade 1	1 (0.8%)
Infections & Infestations		4 (3.2%)
---Septic shock	Grade 5 (2)	

---Sepsis	Grade 3	
---Skin Infection	Grade 3	
Dehydration	Grade 3	1 (0.8%)
Musculoskeletal (pain in extremity)	Grade 2	1 (0.8%)
Neoplastic		4 (3.2%)
---Progression of disease	Grade 5 (3)	
---CNS metastasis	Grade 2	
---CNS necrosis	Grade 2	
Nervous System		8 (6.3%)
---Peripheral sensory neuropathy	Grade 2 (4), Grade 3(2)	
---Hypoesthesia	Grade 3	
---Neuropathy, peripheral	Grade 3	
Respiratory		2 (1.6%)
---Dyspnea	Grade 4	
---Pleural effusion	Grade 4	
Vascular		1 (0.8%)
---Lymphedema	Grade 2	

Reviewer's Comments on probably or possibly ixabepilone treatment-related AEs that led to discontinuation of study therapy:

- Treatment-related peripheral neuropathy in 8 patients (6.3%). The CTC severity grade was 2 in four cases and 3 in the other four cases. Treatment discontinuations occurred after a median of 7 cycles (range, 3 to 9 cycles). All eight instances of neuropathy resolved. The median time to resolution was 13.2 weeks (range, 4.6 to 38.4 weeks). The median times to resolution were about the same for Grade 2 and Grade 3 neuropathies.
- Severe abdominal pain, stomatitis, and sepsis were other noteworthy AEs leading to discontinuation from the study. Most of the AEs led to discontinuations in one or two patients. Grade 4 pancytopenia and Grade 3 hyperbilirubinemia were two outstanding laboratory abnormalities leading to ixabepilone discontinuation.

Other significant adverse events

7.1.3.3.1 Neuropathy

Trial 046

Peripheral neuropathy was a significant finding in the combination trial. Patients with a baseline peripheral neuropathy from any cause of grade 2 or greater were excluded from this study. The rate of neuropathy in treated patients is summarized in Table 40 below. These rates were derived from the dataset AESAE.xpt for study 046. For Sensory Neuropathy the following patient level terms were used: areflexia, dysaesthesia, hyperaesthesia, hypoaesthesia, hyporeflexia, nervous system disorder, neuralgia, neuropathy, neuropathy peripheral, neurotoxicity, pallanaesthesia, paraesthesia, peripheral sensory neuropathy, polyneuropathy, sensory loss. For Motor Neuropathy the following terms were used: multifocal motor neuropathy, peripheral motor neuropathy, sensorimotor disorder. Some patients had both sensory and motor neuropathies. The total reflects patients who had either one or both neuropathies.

Table 40. Treatment emergent peripheral neuropathy in Study 046-Reviewer Analysis

	Capecitabine plus Ixabepilone, n=369 N (%)		Capecitabine, n=368 N (%)	
	Total	Grade 3-4	Total	Grade 3-4
All Neuropathies	259 (70)	94 (25)	83 (22)	5 (1) ^a
Motor Neuropathies	71 (19)	24 (7) ^a	13 (4)	4 (1)
Sensory Neuropathies	251 (68)	84 (23)	74 (20)	1 (<1)

^aNo grade 4 events

Neuropathy considered to be related to study drug (according to investigator assessment of possibly, probably or certainly) is shown in Table 41.

Table 41. Drug-related peripheral neuropathy in Study 046-Reviewer analysis

	Capecitabine plus Ixabepilone, n=369 N (%)		Capecitabine, n=368 N (%)	
	Total	Grade 3-4	Total	Grade 3-4
All Neuropathies	250 (68)	87 (24)	61 (17)	0 (0)
Motor Neuropathies	59 (16)	18 (5) ^a	2 (<1)	0 (0)
Sensory Neuropathies	243 (66)	80 (22)	60 (16)	0 (0)

^aNo grade 4 reactions

The above two tables were derived from the AESAE.xpt dataset for Study 046 using JMP 7.0.

Reviewer's Comments: The findings from these two analyses are essentially concordant. There are slightly fewer events when investigator attribution is used, especially for the capecitabine arm. This is not surprising, as neurotoxicity is not a prominent effect of capecitabine, and investigators might be unwilling to ascribe an emergent neurotoxicity to capecitabine therapy. The predominant effect is sensory, although a sizable percentage of patients (14%) had both motor and sensory neuropathies. Motor neuropathies were less severe than were sensory neuropathies when graded on the NCI CTCAE scale.

The sponsor's analysis differs slightly (by 1-2%) from the reviewer's. This is likely due to differences in the terms used to capture neuropathy. It is not felt that this difference results in any differences in conclusions about the overall safety of ixabepilone in this population for this indication.

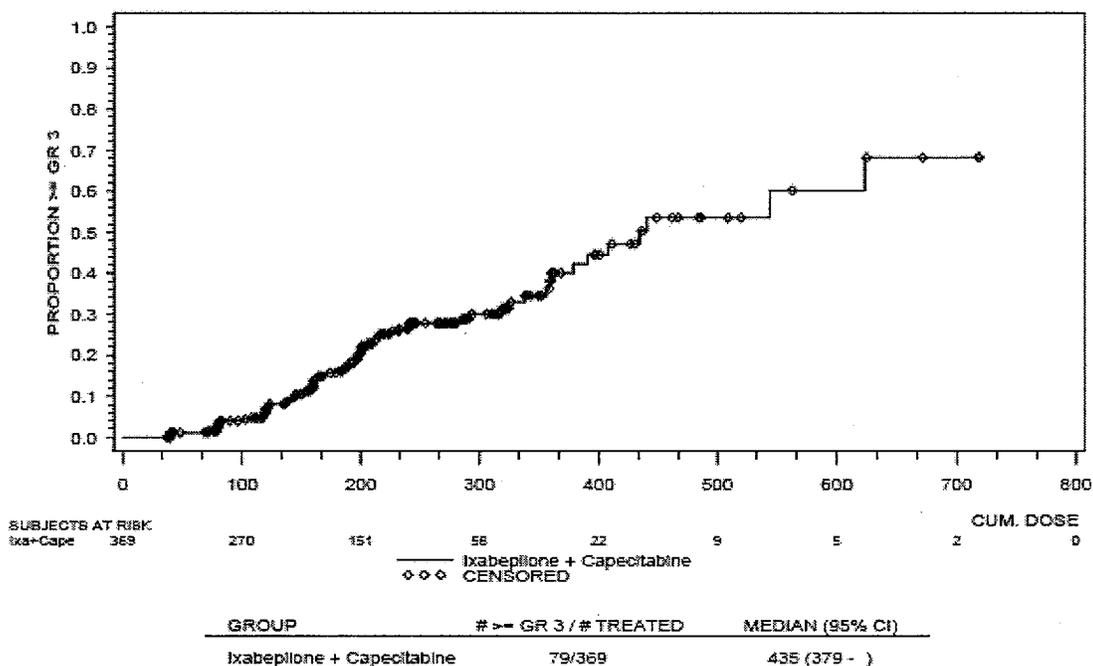
The sponsor presented several analyses to define the quality of the observed neuropathy. These results are summarized below. Painful neuropathy was found in 6% of patients. The incidence of peripheral neuropathy was slightly higher in study 046 than in studies where ixabepilone was used as monotherapy. This is likely related to higher total dose of ixabepilone administered when used in combination therapy due to an increase in the median number of cycles administered.

The median number of cycles to onset of grade 3 motor neuropathy was 5. Autonomic neuropathy may have been observed in 7 patients receiving ixabepilone in Study 046. Two patients reported orthostatic hypotension and 5 reported ileus, but it is not certain that these were due to autonomic dysfunction. In all cases symptoms resolved.

The median time to onset of grade 3/4 neuropathy was 2.9 months, and most patients had experienced grade 1 or 2 neuropathy previously, but those with grade 2 or greater were excluded from the trial. Figure 5 (Sponsor's Figure 2.1.5.2.2B) shows the relationship between cumulative dose and development of grade 3 or greater neuropathy.

Figure 5.

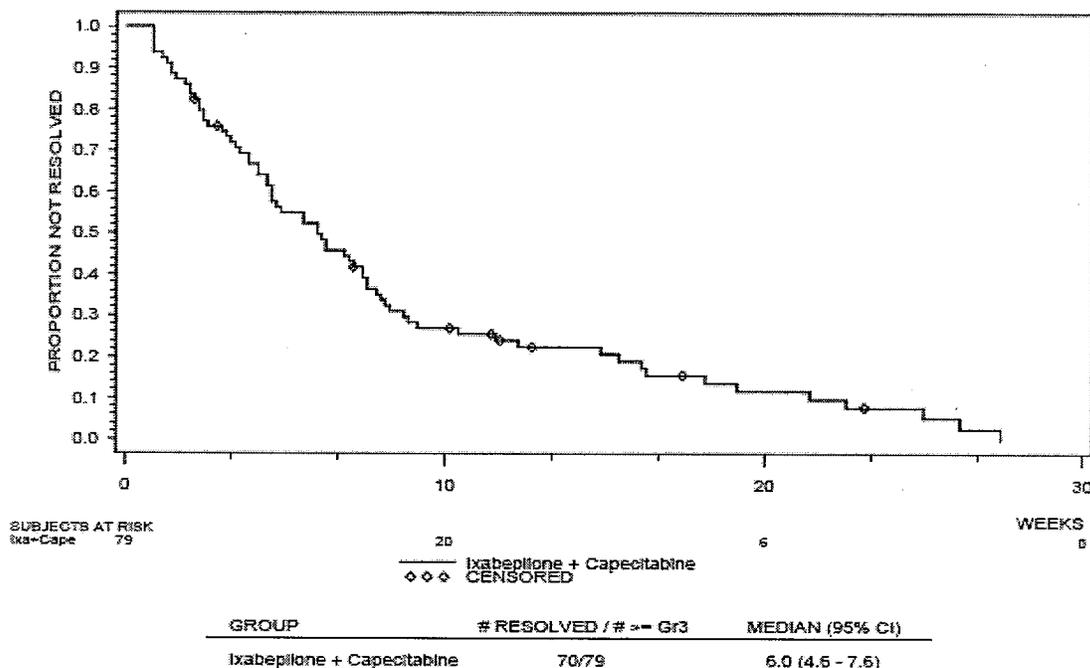
Figure 2.1.5.2.2B: Cumulative Dose to Onset of Grade 3 or Higher Peripheral Neuropathy - CA163046 Combination Therapy (Treated Patients).



Peripheral neuropathy led to discontinuation of ixabepilone therapy in 79 (21%) patients in study 046, and in 11% of patients in study 031 administered the same dose and schedule. Forty-four of the 79 patients continued on capecitabine for at least one more cycle. The 79 patients experiencing grade 3 or 4 peripheral neuropathy were evaluated for resolution of their symptoms. Eighty-nine percent of patients reported resolution of their symptoms with a median time of 6 weeks. Nine patients did not have resolution of their symptoms; four had subsequent neurotoxic therapy, two died shortly after development of neuropathy, two were lost to follow-up and one continued on therapy. The sponsor's analysis of time to resolution is shown in Figure 6 below.

Figure 6.

Figure 2.1.5.2.5E: Time to Resolution of Grade 3 or Higher Peripheral Neuropathy - CA163046 Combination Therapy



In order to determine what baseline risk factors exposed patients to greater risk for grade 3 or 4 neuropathy, the sponsor performed univariate and multivariate analyses of patients treated with ixabepilone at varying doses. Included were studies at different doses and in disease settings other than breast cancer. Data from 943 patients (473 in combination with capecitabine) were analyzed. Prior neurotoxic therapy, including taxanes was associated with lower risk, perhaps because patients with grade 2 or greater were excluded from trials with ixabepilone. Diabetes increased risk of severe neuropathy. Age and the presence of baseline neuropathy did not increase the risk of severe neuropathy.

Reviewer Comment: These analyses were not replicated by the reviewer. The slight differences seen in the incidence of neuropathy between the sponsor and reviewer assessment are unlikely to greatly influence the sponsor's analysis. The definitions used for resolution (improvement to \leq grade 1 or baseline) and the censoring rules are reasonable. The results across studies are also consistent, and generally consistent with data from the monotherapy studies.

Monotherapy Study 081

At baseline, 92 patients (73%) had no neuropathy, 32 (25%) had Grade 1 neuropathy, and 2 (1.6%) had Grade 2 neuropathy. During treatment approximately 64% of patients developed a first occurrence of neuropathy or a worsening of pre-existing neuropathy. Reviewer's Table 42 shows the number of patients with or without neuropathy at baseline and the number of patients who developed neuropathy or had a worsening of neuropathy during treatment by worst grade (data from Sponsor's Tables S.12.11.1, S.12.11.2, and S.12.11.3).

Table 42. Peripheral neuropathy at baseline and worst grade during study

Grade at baseline and N	Grades of neuropathy developed during treatment				Total
	1	2	3	4	
Grade 0, N=92	18 (19.6%)	27 (29.3%)	12 (13.0%)	0	57 (62.0%)
Grade 1, N=32	1 (3.1%)	17 (51.5%)	4 (12.1%)	1 (3.1%)	23 (69.7%)
Grade 2, N=2	1 (50%)	0	0	0	1 (50%)
Total, N=126	20 (15.8%)	44 (34.9%)	17 (13.4%)	1 (0.8%)	81 (64.3%)

Peripheral neuropathy was mainly sensory (in 79/126 or 62.7% of patients); motor neuropathy occurred in 12 (9.5%). Subjects could have more than one type of neuropathy.

Neuropathy developed in a slightly higher percentage of patients with pre-existing neuropathy as in patients without baseline neuropathy (69.7% vs. 62.0%). Grade 3 or 4 neuropathy was also slightly more frequent in patients with pre-existing neuropathy than without (15.2% vs. 13.0%).

New development or worsening of peripheral neuropathy occurred early in the course of treatment. It occurred in 21%, 11%, 16%, and 6% of all treated patients during the 1st, 2nd, 3rd and 4th cycles, respectively (i.e. in about 54% of 64% of patients who developed peripheral neuropathy). Only 9% of all neuropathies first occurred after the fourth cycle (in 1 or 2 patients during cycles 5-17). The median number of cycles to the onset or worsening of any grade of neuropathy was 2. Grade ≥ 3 neuropathy developed more gradually. Ten (10) of 17 patients (54%) developed Grade ≥ 3 neuropathy during the first four cycles. The median number of cycles to the onset of Grade ≥ 3 neuropathy was 4.

Dose reductions due to neuropathy. Grade ≥ 2 peripheral neuropathy was the most common cause of dose reductions (first dose reduction in 26/39 patients and second dose reduction in 5/9 patients). The reduced doses were administered for a median of 3 cycles (range, 1 – 10 cycles). In 20 patients neuropathy improved or did not worsen. (See below for Drug Discontinuation). Ten patients continued to be treated with ixabepilone without a dose reduction.

Dose delays due to toxicity. Peripheral neuropathy was the most common reason for dose delays (14% of all treated patients accounting for 5% of all treatment cycles).

Drug discontinuation. Peripheral neuropathy was the most common reason for drug discontinuation because of drug toxicity (8/126 or 6.3% of all treated patients).

Resolution of neuropathy. Peripheral neuropathy, Grades 2 and 3, resolved to baseline or Grade 1 in 88% of patients (54/61). (Resolution of Grade 1 neuropathy in 20 patients is not discussed in the submission.) In 33 patients neuropathy resolved while treatment was continued (at full or reduced doses); in 21 patients neuropathy resolved when treatment was discontinued. Seven patients are listed as having neuropathy not resolve. Three had died, three had subsequent neurotoxic therapy, and one was lost to follow-up 75 weeks after the last ixabepilone dose. The median time to resolution of Grade ≥ 2 neuropathy to baseline or Grade 1 was 4.3 weeks (95% CI, 3.0 – 5.4). The median time to resolution was about the same in patients with Grade 3 neuropathy (4.6 weeks). The 12-week rate of resolution of Grade 3 neuropathy was 79.2% (95% CI, 58.4 – 100%).

Peripheral neuropathy is a serious adverse reaction to therapy with ixabepilone both as monotherapy and in combination with capecitabine. There do not appear to be predictive factors other than cumulative dose and diabetes that predict which patients will develop grade 3 or 4 neuropathy. In general, neuropathy improves with cessation of ixabepilone therapy. In the capecitabine alone arm of study 046, there was a 22% incidence of treatment emergent neuropathy, although the severity of neuropathy was less. Compared to ixabepilone monotherapy, there does not appear to be a difference in either the incidence or severity of neuropathy when ixabepilone is combined with capecitabine.

7.1.3.3.2 Myelosuppression

Therapy with ixabepilone is associated with significant myelosuppression.

Study 046-Combination therapy

Frequencies of treatment-emergent neutropenia in trial 046 are shown in Table 43 below. Patients were required to have an absolute neutrophil count of 1500 or greater before therapy.

Table 43. Treatment emergent neutropenia by arm and grade.

Treatment Arm	Total n (%)	Grade 3-4 n (%)
Capecitabine	171 (46)	44 (12)
Combination	326 (88)	251 (68)

Febrile neutropenia was also higher in the combination arm, as would be expected. Table 44 and Table 45 below show treatment emergent and treatment related (by investigator determination) frequencies of febrile neutropenia in study 046. These tables were generated by searching the lower level term febrile neutropenia, the preferred term febrile neutropenia and neutropenic fever and the investigator term febrile neutropenia and neutropenic fever in database AESAE.xpt and then identifying the highest grade for each individual patient using JMP 7.0. For treatment related events, only those with a designation of possible, probable or certain were included.

Table 44. Treatment emergent febrile neutropenia

Treatment Arm	Total n (%)	Grade 3-4 n (%)	Deaths
Capecitabine	5 (1)	5 (1)	0 (0)
Combination	20 (5)	17 (5)	3 (1)

Table 45. Treatment related febrile neutropenia

Treatment Arm	Total n (%)	Grade 3-4 n (%)	Deaths
Capecitabine	2 (1)	2 (1) ^a	0 (0)
Combination	19 (5)	6 (4)	3 (1)

^aNo grade 4 reactions.

Note that the three deaths in the table above were described in Section 7.1.N. Other deaths related to febrile neutropenia were not captured as such in database AESAE, and thus the incidence of febrile neutropenia, especially in the combination arm, may in fact be slightly higher. Note also that there is no grade 1 or 2 febrile neutropenia in CTCAE v 3.0. Infections with lower grade of neutropenia are categorized, but these were not captured by the above analysis. Approximately 20% of patients used growth factor support, most commonly GCSF. Most patients experienced recovery of neutrophils within the 21 day treatment cycle.

The sponsor performed an analysis of infection with neutropenia and febrile neutropenia. Terms related to infection were used to search the AE database and those infections present with neutropenia were isolated. Results of this search for studies 046 and 031, as well as the sponsor's analysis of treatment-related febrile neutropenia are shown below in Table 46.

Table 46.

Table 2.1.5.1.2B: Febrile neutropenia and Infection with Neutropenia - Combination Therapy (Treated Patients)

Adverse Event	Number (%) of Patients, 40/2000 mg/m ²		
	CA163046		CA163031 ixabepilone + capecitabine
	Ixabepilone + capecitabine	Capecitabine	
	N = 369	N = 368	N = 62
Any infectious complication associated with neutropenia	37 (10)	4 (2)	4 (6)
Febrile neutropenia ^a	19 (5) ^b	2 (1)	1 (2) ^c
Infection with neutropenia ^d	21 (6) ^b	2 (1)	4 (6) ^c

Source: Appendices 2.1BL, 2.3B1, and 2.30BL

^a MedDRA preferred term; treatment-related

^b 3 patients had events reported as both febrile neutropenia and infection (CA163046-153-37, CA163046-210-241, and CA163046-240-377)

^c 1 patient had both febrile neutropenia and infection AEs reported in the same cycle (CA163031-6-58)

^d Defined in the methods at the beginning of this section.

In total, twelve patients in the combination group died in association with neutropenia. (Nine of these are captured in either the febrile neutropenia or infection with neutropenia groups above. Three were not captured by these search methods.) Five of these were patients with moderate or severe hepatic dysfunction. All other patients recovered and only one discontinued therapy because of neutropenia or a complication associated with neutropenia. In the capecitabine group, two patients had febrile neutropenia and two had infection with neutropenia. One patient died from septic shock, but the death was considered unrelated to study therapy.

Reviewer Comment: These results concur with the sponsor's analysis for total number of cases of febrile neutropenia. In the proposed labeling, sponsor lists the frequency of grade 3-4 febrile neutropenia as four percent. While this is technically true, the remaining cases are deaths. This clarification will be reflected in the proposed label.

Thrombocytopenia was a common adverse reaction to treatment with ixabepilone in combination with capecitabine as seen in Table N below derived from the LABRES01, LABRES02 and LABRES03 databases using JMP 7.0.

Table 47. Thrombocytopenia in Study 046

Treatment Arm	Total n (%)	Grade 3-4 n (%)
Capecitabine	129 (35.1)	18 (4.9)
Combination	203 (55.0)	34 (9.2)

There did not appear to be any bleeding events clearly associated with thrombocytopenia, using the search terms bleeding and hemorrhage in the AESAE database. Therapy was interrupted or discontinued for thrombocytopenia eight times in the combination arm and three times in the capecitabine arm. Thrombocytopenia with ixabepilone in combination with capecitabine, while significant, does not appear to have a significant impact on the ability to administer therapy or patient safety.

An independent analysis of anemia was not performed by the reviewer. From the sponsor:

Anemia was often present at baseline in both groups (38%, ixabepilone plus capecitabine; 41%, capecitabine alone). Anemia occurring during treatment was predominantly Grade 1/2. Grade 2 or higher anemia was more common with ixabepilone plus capecitabine compared with capecitabine alone (52% vs. 21%). Twenty-six of the 34 patients who developed Grade 3/4 anemia in the ixabepilone plus capecitabine group had anemia at baseline. Transfusions were reported for 13% of patients in the ixabepilone plus capecitabine group and 6% of patients in the capecitabine group.

Monotherapy Study 081

Severe neutropenia and leukopenia were the most noteworthy evidence of myelosuppression; they were far more frequent than thrombocytopenia and anemia. Reviewer's Table 48 shows the incidence of Grade 3 and 4 hematologic abnormalities during the study (data from Sponsor's Table 12.5.1A in Clinical Study Report).

Table 48. Worst On-Study Grade – Hematological Toxicity

CTC Toxicity	Grade 3	Grade 4	Grades 3 + 4
Leukopenia	36.3 %	12.9%	49.2%
Neutropenia	30.6%	23.4%	54.0%
Thrombocytopenia	5.6%	1.6%	7.3%
Hemoglobin	5.6%	1.6%	8.1%

There were 3 cases of infection in neutropenic patients. One patient died from sepsis. One withdrew from the study. In one case the infection (ear) resolved and the patient continued on study. Febrile neutropenia was reported in 4 (3%) of patients; all instances resolved during the same treatment cycle.

In general, recovery from neutropenia occurred within one cycle. However,

- 3.5% of treatment courses (17/488) were delayed because of delayed hematologic recovery (Table S.9.13 in CSR Addendum 02)
- 5.4% of patients (6/112) had a dose reduction because of hematologic toxicity (of the total of 40 patients (35.7%) who had at least one dose reduction).
- Only one patient (0.8% of 126) discontinued the study (out of a total of 24 who discontinued because of adverse events). The reason was pancytopenia.

It should be noted that at baseline 87% of patients had normal WBC and 95% had normal neutrophil count. Only 12% had Grade 1 leukopenia, 1.6% Grade 2 leukopenia and none had leukopenia greater than Grade 2. There were only 5% of patients with Grade 2 neutropenia and none with higher grade.

The effect of ixabepilone on the bone marrow is significant. There is a high rate of neutropenia and lower rate of thrombocytopenia. As noted in Section 7.1.1 there was an increase in deaths due to febrile neutropenia in patients with impaired hepatic function with combination therapy with capecitabine. It is clear that patients with impaired hepatic function should not receive ixabepilone in combination with capecitabine because of increased deaths due to toxicity. Twenty percent of patients receiving combination ixabepilone and capecitabine in Study.046 received growth factor support, and the use of growth factor support (GM-CSF or GCSF) in accordance with product labeling is probably warranted when treating patient with ixabepilone combination therapy, and perhaps with monotherapy. Thrombocytopenia does not appear to cause significant

morbidity despite its frequency. The rate of anemia is consistent with that seen with other cytotoxic chemotherapies.

7.1.3.3.3 Palmar-plantar Erythrodysesthesia (Hand-foot) syndrome.

Combination Therapy

Hand-foot syndrome is a well-known adverse reaction associated with capecitabine. In study 046, 64% of patients in the combination arm and 62% in the capecitabine arm experienced hand-foot syndrome with grade 3-4 rates of 18 and 17 percent respectively. Thus, there does not appear to be an increase in either the incidence or severity of hand-foot syndrome with the administration of ixabepilone in combination with capecitabine compared to capecitabine alone.

Hypersensitivity Reactions (HSR).

Monotherapy

In spite of pre-medication (H1-blocker + H2-blocker +/- corticosteroids) of all patients before each cycle (with one exception), one patient experienced a Grade 3 HSR, three patients Grade 2 HSR and three patients Grade 1 HSR. One patient, whose infusion was interrupted because of HSR, had a second HSR upon re-challenge 2 days later. She discontinued ixabepilone treatment. The other patients were medicated for HSR and were able to continue receiving ixabepilone until disease progression (2 additional cycles).

Combination Therapy

A composite examination of the 1323 patients treated both with monotherapy and combination therapy (n=475) identified 79 (6%) hypersensitivity reactions. Forty-one percent of these occurred in cycle 1 and 46% in cycle 2. Nine patients (0.7%) reported Grade 3 or 4 reactions. All reactions resolved.

7.1.3.3.4 Gastrointestinal events

Combination Therapy

There is a slightly higher incidence of gastrointestinal adverse reactions in the combination therapy arm. This is not surprising considering the cytotoxic nature of the therapy. The vast majority of these events were grade 1 or 2 and did not require cessation of therapy. The types of gastrointestinal events associated with ixabepilone therapy are common to cytotoxic oncology drugs, and physicians treating patients with these drugs are familiar with the supportive measures needed.

Monotherapy

The incidence of GI events in the monotherapy trial was high, about 65% of patients reported them. About 55% were CTC Grades 1 or 2, but 10% were CTC Grades 3 or 4.

7.1.3.3.5 Cardiac events

The AESAE database was searched with the terms myocardial infarction, arrhythmia, ventricular arrhythmia, myocardial ischemia, sudden death and ischaemic coronary artery disorders. The system organ class term cardiac disorders was also searched. The following Preferred Terms were used to describe cardiac related adverse reactions with association with study drug: angina pectoris, atrial fibrillation, atrial flutter, cardiomyopathy, cardio-respiratory arrest, myocardial infarction, myocardial ischaemia, palpitations, sinus arrhythmia, sinus tachycardia, tachycardia, ventricular dysfunction and ventricular tachycardia. A total of twenty adverse reactions with these terms were reported, two in the capecitabine arm and eighteen in the combination. Supraventricular arrhythmias (at least possibly attributed to study drug) occurred in 2.2% of patients in the combination arm, and 0.3% in the capecitabine alone arm.

The following discussion will only address the combination arm. There were eight grade 3 or 4 events and 2 deaths. Sinus arrhythmia and ventricular dysfunction were each listed twice as grade 3 events. Angina pectoris and myocardial ischaemia had one grade 3 event each. Atrial flutter and myocardial infarction had one grade 4 event each. The two deaths were due to cardio-respiratory arrest and cardiomyopathy.

It is possible that there is selection bias in this analysis, as investigators may be more likely to label events in the experimental arm as more likely related to study drug. To analyze this, all events, regardless of attribution were identified. This analysis is presented in Table 49 below.

Table 49. Frequency of events under SOC term Cardiac disorders without attribution

MedDRA Preferred Term	Capecitabine		Combination		
	Total (n)	Grade 3-4 (n)	Total (n)	Grade 3-4 (n)	Grade 5
ACUTE MYOCARDIAL INFARCTION	0	0	1	1	0
ANGINA PECTORIS	0	0	2	1	0
ARRHYTHMIA	1	0	1	0	0
ARRHYTHMIA SUPRAVENTRICULAR	0	0	1	1	0
ATRIAL FIBRILLATION	1	0	3	2	0
ATRIAL FLUTTER	0	0	1	1	0
CARDIAC ARREST	0	0	1	0	1
CARDIAC FAILURE	0	0	1	0	1
CARDIOMYOPATHY	0	0	1	0	1
CARDIOPULMONARY FAILURE	0	0	1	0	1
CARDIO-RESPIRATORY ARREST	2	2	1	0	1
MYOCARDIAL INFARCTION	0	0	1	1	0
MYOCARDIAL ISCHAEMIA	1	1	1	1	0
PALPITATIONS	6	0	4	0	0
PERICARDIAL EFFUSION	5	1	1	1	0
SINUS ARRHYTHMIA	0	0	2	2	0
SINUS TACHYCARDIA	4	0	8	0	0
SUPRAVENTRICULAR TACHYCARDIA	0	0	2	1	0
TACHYARRHYTHMIA	1	0	0	0	0
TACHYCARDIA	4	0	4	0	0
VENTRICULAR DYSFUNCTION	0	0	3	3	0
VENTRICULAR TACHYCARDIA	0	0	1	0	0

Using this analysis, the total number of cardiac events in the capecitabine arm was 25, and in the combination arm 41, including 5 deaths. There were no deaths in the capecitabine arm.

There is concern that an infrequently manifest cardiac toxicity is induced with ixabepilone therapy. Most events were mild and included usually benign findings such as palpitations or atrial flutter. However, this patient population has previously received cardiotoxic drugs (anthracycline, and for patients with HER2 positive tumors, possibly trastuzumab) and thus may be susceptible to further cardiac damage. The numbers of patients studied here are too few to make any firm conclusions, but further analysis is warranted. Patients with underlying cardiac disease or significant risk factors may be at risk for cardiac toxicity, including arrhythmias and myocardial ischemia. Further data collection, including data from ongoing study CA163048 will help to clarify this risk. The use of ixabepilone in patients with underlying cardiac disease should currently be evaluated on an individual basis.

7.1.4 Other Search Strategies

See Section 7.1.3.3 above

7.1.5 Common Adverse Events

Eliciting adverse events data in the development program

In trial 046 patients were evaluated at every visit for adverse events. Patients were evaluated prior to each cycle, and additionally at week 1 and week 2 of the first four cycles. Trial 031 was similar. Adverse events were recorded on the CRF. A checklist was used for evaluation of the neurological exam.

Appropriateness of adverse event categorization and preferred terms

Adverse events were coded to the Preferred Term in the MedDRA library. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v 2.0 for Study 031 and v 3.0 for Study 046. Mapping was generally appropriate.

Incidence of common adverse events

Common adverse events (those occurring with a frequency greater than 5% in the combination arm) are listed by MedDRA Preferred Term in Table 50 below.

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On Original**

Table 50. Treatment emergent adverse events Study 046

Adverse Event (MedDRA Preferred Term)	Combination				Capecitabine			
	All grades		Grade 3-4		All grades		Grades 3-4	
	n	%	n	%	n	%	n	%
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	237	64.2	68	18.4	229	62.2	63	17.1
NAUSEA	210	56.9	13	3.5	170	46.2	6	1.6
DIARRHOEA	183	49.6	26	7.0	151	41.0	35	9.5
FATIGUE	167	45.3	38	10.3	99	26.9	16	4.3
VOMITING	165	44.7	18	4.9	108	29.3	12	3.3
PERIPHERAL SENSORY NEUROPATHY	144	39.0	45	12.2	36	9.8	0	0.0
MYALGIA	132	35.8	29	7.9	25	6.8	2	0.5
ANOREXIA	129	35.0	11	3.0	76	20.7	6	1.6
ALOPECIA	129	35.0	0	0.0	27	7.3	0	0.0
CONSTIPATION	125	33.9	3	0.8	61	16.6	3	0.8
ASTHENIA	102	27.6	29	7.9	62	16.8	5	1.4
WEIGHT DECREASED	90	24.4	7	1.9	44	12.0	3	0.8
ARTHRALGIA	89	24.1	11	3.0	29	7.9	2	0.5
COUGH	84	22.8	3	0.8	72	19.6	3	0.8
NAIL DISORDER	83	22.5	5	1.4	38	10.3	0	0.0
PARAESTHESIA	76	20.6	15	4.1	28	7.6	0	0.0
PAIN IN EXTREMITY	74	20.1	6	1.6	32	8.7	3	0.8
DYSPNOEA	74	20.1	20	5.4	77	20.9	28	7.6
ABDOMINAL PAIN	71	19.2	8	2.2	56	15.2	7	1.9
PERIPHERAL MOTOR NEUROPATHY	68	18.4	22	6.0	10	2.7	2	0.5
NEUTROPENIA	67	18.2	59	16.0	9	2.4	5	1.4
PYREXIA	65	17.6	3	0.8	48	13.0	2	0.5
STOMATITIS	64	17.3	7	1.9	40	10.9	5	1.4
HEADACHE	64	17.3	6	1.6	41	11.1	4	1.1
MUCOSAL INFLAMMATION	63	17.1	11	3.0	41	11.1	7	1.9
INSOMNIA	61	16.5	1	0.3	27	7.3	0	0.0
DIZZINESS	53	14.4	4	1.1	37	10.1	4	1.1
OEDEMA PERIPHERAL	51	13.8	2	0.5	48	13.0	4	1.1
BACK PAIN	49	13.3	4	1.1	62	16.8	4	1.1
RASH	49	13.3	3	0.8	29	7.9	0	0.0
ABDOMINAL PAIN UPPER	48	13.0	2	0.5	34	9.2	4	1.1
MUSCULOSKELETAL PAIN	47	12.7	3	0.8	20	5.4	2	0.5
DYSGEUSIA	43	11.7	0	0.0	14	3.8	0	0.0
SKIN HYPERPIGMENTATION	43	11.7	0	0.0	53	14.4	0	0.0
DYSPEPSIA	36	9.8	2	0.5	35	9.5	0	0.0
ANAEMIA	31	8.4	8	2.2	14	3.8	3	0.8
CHEST PAIN	31	8.4	3	0.8	20	5.4	2	0.5
BONE PAIN	31	8.4	1	0.3	27	7.3	5	1.4
HYPOAESTHESIA	31	8.4	4	1.1	13	3.5	0	0.0
NEUROPATHY PERIPHERAL	31	8.4	6	1.6	6	1.6	0	0.0
PAIN	28	7.6	5	1.4	9	2.4	0	0.0
NEUTROPHIL COUNT DECREASED	28	7.6	20	5.4	6	1.6	2	0.5
LEUKOPENIA	27	7.3	21	5.7	1	0.3	1	0.3

Adverse Event (MedDRA Preferred Term)	Combination				Capecitabine			
	All grades		Grade 3-4		All grades		Grades 3-4	
	n	%	n	%	n	%	n	%
ERYTHEMA	27	7.3	0	0.0	19	5.2	1	0.3
UPPER RESPIRATORY TRACT INFECTION	26	7.0	0	0.0	17	4.6	0	0.0
MUSCULOSKELETAL CHEST PAIN	25	6.8	3	0.8	24	6.5	2	0.5
WHITE BLOOD CELL COUNT DECREASED	24	6.5	17	4.6	3	0.8	0	0.0
DRY SKIN	23	6.2	0	0.0	25	6.8	0	0.0
PRURITUS	23	6.2	0	0.0	16	4.3	0	0.0
LACRIMATION INCREASED	22	6.0	0	0.0	21	5.7	1	0.3
HAEMOGLOBIN DECREASED	22	6.0	3	0.8	5	1.4	1	0.3
DECREASED APPETITE	22	6.0	0	0.0	9	2.4	0	0.0
DEHYDRATION	21	5.7	10	2.7	13	3.5	6	1.6
PNEUMONIA	20	5.4	12	3.3	9	2.4	3	0.8
ABDOMINAL DISTENSION	19	5.1	3	0.8	14	3.8	1	0.3
PLATELET COUNT DECREASED	19	5.1	9	2.4	7	1.9	2	0.5
ANXIETY	19	5.1	1	0.3	15	4.1	2	0.5

These frequencies were derived from the AESAE.xpt dataset for Study 046 with JMP 7.0, using the MedDRA Preferred Terms. Some caution must be used in interpreting this table for subjective events as this was an open label study.

Adverse events with a frequency of greater than 5% reported during the course of single arm trial 031 at the same dosing and schedule as in trial 046 are reported in Reviewer Table 51 below.

Table 51. Treatment emergent adverse events in Study 031

Adverse Event (MedDRA Preferred Terms)	All		Grade 3-4	
	n	%	n	%
FATIGUE	57	91.9	23	37.1
NAUSEA	51	82.3	10	16.1
ALOPECIA	49	79.0	0	0.0
MYALGIA	42	67.7	14	22.6
PARAESTHESIA	39	62.9	8	12.9
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	39	62.9	21	33.9
CONSTIPATION	35	56.5	4	6.5
DIARRHOEA	34	54.8	6	9.7
VOMITING	33	53.2	6	9.7
STOMATITIS	28	45.2	3	4.8
LACRIMATION INCREASED	21	33.9	0	0.0
PYREXIA	20	32.3	1	1.6
RASH	19	30.6	1	1.6
DYSPNOEA	18	29.0	3	4.8
ARTHRALGIA	17	27.4	1	1.6
NAIL DISORDER	12	19.4	0	0.0

Adverse Event (MedDRA Preferred Terms)	All		Grade 3-4	
	n	%	n	%
HEADACHE	10	16.1	1	1.6
NEUROPATHY PERIPHERAL	10	16.1	2	3.2
INSOMNIA	9	14.5	0	0.0
PERIPHERAL SENSORY NEUROPATHY	8	12.9	1	1.6
COUGH	8	12.9	0	0.0
ABDOMINAL PAIN	7	11.3	2	3.2
ANOREXIA	7	11.3	2	3.2
DEHYDRATION	7	11.3	3	4.8
LYMPHOEDEMA	7	11.3	0	0.0
NEUROPATHIC PAIN	6	9.7	2	3.2
UPPER RESPIRATORY TRACT INFECTION	5	8.1	0	0.0
WEIGHT DECREASED	5	8.1	0	0.0
DECREASED APPETITE	5	8.1	0	0.0
BONE PAIN	5	8.1	2	3.2
CHEST WALL PAIN	5	8.1	0	0.0
NEUTROPENIA	4	6.5	4	6.5
NON-CARDIAC CHEST PAIN	4	6.5	2	3.2
OEDEMA	4	6.5	0	0.0
HYPERSENSITIVITY	4	6.5	0	0.0
ORAL CANDIDIASIS	4	6.5	0	0.0
BACK PAIN	4	6.5	0	0.0
PAIN IN EXTREMITY	4	6.5	1	1.6
CANCER PAIN	4	6.5	1	1.6
DIZZINESS	4	6.5	0	0.0
HYPOAESTHESIA	4	6.5	0	0.0
PHARYNGOLARYNGEAL PAIN	4	6.5	0	0.0

These frequencies were derived from dataset AESAE.xpt for trial 031 using JMP 7.0.

The frequency of most adverse events related to combination therapy in the two trials was similar.

Study 081

All 100% of study subjects (N=126) reported at least one adverse event. Table 52 shows the severity of adverse events by CTC grade. Approximately 48% of patients experienced Grades 3 or 4 events; approximately 43%, Grades 1 or 2 events.

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Table 52. Adverse events in all treated patients and their severity—Study 081

Worst CTC Grade	Subjects with Any Adverse Event, N = 126, (%)
1	7 (5.6%)
2	47 (37.3%)
3	49 (38.9%)
4	11 (8.7%)
5	12 (9.5%)

Common adverse event table for the CA163081 monotherapy study are presented in Table 53. The data were checked against Supplementary tables in the submission and, in some cases, in CRFs. Approximately 94% of patients reported drug-related AEs. Most common were AEs involved the nervous system (peripheral neuropathy), gastrointestinal system, fatigue and asthenia, musculoskeletal system and skin.

Table 53. Common adverse reactions in Study 081

Table 12.1.1: Treatment-related Adverse Events Reported in At Least 5% of Patients - Treated Patients

SYSTEM ORGAN CLASS (%) PREFERRED TERM (%)	Number of Patients (%) (N=126)			
	DMC 1-2	Worst CTC Grade 3-4	5	Total
Patients with Any Drug Related Adverse Event	69 (54.0)	49 (39.9)	1 (0.8)	118 (93.7)
GASTROINTESTINAL DISORDERS				
Nausea	69 (54.9)	13 (10.3)	0	92 (65.1)
Stomatitis	51 (40.5)	2 (1.6)	0	53 (42.1)
Vomiting	29 (23.0)	8 (6.3)	0	37 (29.4)
Diarrhea	25 (27.9)	1 (0.8)	0	36 (28.6)
Constipation	27 (21.4)	1 (0.8)	0	28 (22.2)
Abdominal Pain	19 (14.3)	2 (1.6)	0	20 (15.9)
Pain	10 (7.9)	2 (1.6)	0	12 (9.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue	61 (48.4)	22 (17.5)	0	93 (65.9)
Asthenia	39 (26.2)	13 (10.3)	0	46 (36.5)
Edema	31 (24.6)	3 (2.4)	0	34 (27.0)
Pain	9 (7.1)	1 (0.8)	0	10 (7.9)
Pain	4 (3.2)	4 (3.2)	0	8 (6.3)
INVESTIGATIONS				
Weight Decreased	7 (5.6)	2 (1.6)	0	9 (7.1)
Weight Decreased	7 (5.6)	0	0	7 (5.6)
METABOLISM AND NUTRITION DISORDERS				
Anorexia	23 (18.3)	3 (2.4)	0	26 (20.6)
Anorexia	21 (16.7)	2 (1.6)	0	23 (18.3)

Drug related adverse events are events with relationship to study therapy of certain, probable, possible or missing
 Patients may have more than one event within a class
 Only events with at least 5% overall incidence rate will be reported.
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Table 12.1.1: Treatment-related Adverse Events Reported in At Least 5% of Patients - Treated Patients

SYSTEM ORGAN CLASS (%) REFERRED TERM (%)	Number of Patients (%) (N=126)			Total
	URK, 1-2	Worst CTC Grade 3-4	5	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
MYALGIA	64 (50.8)	14 (11.1)	0	78 (61.9)
ARTHRALGIA	44 (34.9)	9 (7.1)	0	53 (42.1)
PAIN IN EXTREMITY	35 (27.8)	2 (1.6)	0	37 (29.4)
MUSCULOSKELETAL PAIN	10 (7.9)	2 (1.6)	0	12 (9.5)
	5 (4.8)	2 (1.6)	0	8 (6.3)
NERVOUS SYSTEM DISORDERS				
PERIPHERAL SENSORY NEUROPATHY	57 (53.2)	18 (14.3)	0	75 (67.5)
PAROSMIA	34 (27.0)	7 (5.6)	0	41 (32.5)
HYPERAESTHESIA	24 (19.0)	5 (4.8)	0	30 (23.8)
HEADACHE	14 (11.1)	0	0	14 (11.1)
NEUROPATHY PERIPHERAL	10 (7.9)	3 (2.4)	0	13 (10.3)
PERIPHERAL MOTOR NEUROPATHY	11 (8.7)	1 (0.8)	0	12 (9.5)
DIZZINESS	9 (7.1)	0	0	9 (7.1)
DYSGEUSTIA	8 (6.3)	0	0	8 (6.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
DYSNOEA	19 (15.1)	2 (1.6)	0	21 (16.7)
	9 (7.1)	1 (0.8)	0	10 (7.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
ALOPECIA	71 (56.3)	3 (2.4)	0	74 (68.7)
ONCHOCYTES	60 (47.6)	0	0	60 (47.6)
HAIR DISORDER	10 (7.9)	0	0	10 (7.9)
ERYTHEMA	8 (6.3)	2 (1.6)	0	10 (7.9)
ERYTHEMA TOXICUM	9 (6.3)	1 (0.8)	0	9 (7.1)
ERYTHEMA	7 (5.6)	1 (0.8)	0	8 (6.3)

Drug related adverse events are events with relationship to study therapy of certain, probable, possible or missing
 Patients may have more than one event within a class
 Only events with at least 5% overall incidence rate will be reported.
 MedDRA Version: 9.1

Worst CTC grade per subject hematology laboratory values are shown in Table 54. The infrequency of Grade 3/4 thrombocytopenia and anemia contrasts sharply with > 50% of patients experiencing Grade 3/4 neutropenia and leukopenia.

Table 54.

Table S.12.1: On-Study Hematology - Worst CTC Grade per Subject - Treated Subjects

CTC Grade	Number of Subjects (%) N = 126
WBC	N = 124
Grade 0	13 (10.5)
Grade 1	22 (17.7)
Grade 2	28 (22.6)
Grade 3	45 (36.3)
Grade 4	16 (12.9)
Grade 1-4	111 (89.5)
Grade 3-4	61 (49.2)
Absolute Neutrophil Count	N = 124
Grade 0	26 (21.0)
Grade 1	10 (8.1)
Grade 2	21 (16.9)
Grade 3	38 (30.6)
Grade 4	29 (23.4)
Grade 1-4	98 (79.0)
Grade 3-4	67 (54.0)

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Table S.12.1:
 On-Study Hematology - Worst CTC Grade per Subject - Treated Subjects

CTC Grade	Number of Subjects (%) N = 126
Platelet Count	
	N = 124
Grade 0	69 (55.6)
Grade 1	41 (33.1)
Grade 2	5 (4.0)
Grade 3	7 (5.6)
Grade 4	2 (1.6)
Grade 1-4	55 (44.4)
Grade 3-4	9 (7.3)
Hemoglobin	
	N = 124
Grade 0	20 (16.1)
Grade 1	62 (50.0)
Grade 2	32 (25.8)
Grade 3	7 (5.6)
Grade 4	3 (2.4)
Grade 1-4	104 (83.9)
Grade 3-4	10 (8.1)

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Common adverse event tables

See Section 7.1.5.3

Identifying common and drug-related adverse events

The database AESAE was used to identify common adverse reactions related to study drugs. Only those events listed in the database as having a relationship to study drug as possible, probable or certain were included. All adverse reactions with three or more events by MedDRA preferred term in the combination arm are listed in decreasing frequency (Table 55).

Table 55. Adverse reactions occurring in 3 or more patients—Study 046

MedDRA Preferred Term	Combination				Capecitabine			
	Total n	%	Grade 3-4 n	%	Total n	%	Grade 3-4 n	%
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	237	64.2	67	18.2	228	62.0	62	16.8
NAUSEA	194	52.6	12	3.3	149	40.5	6	1.6
DIARRHOEA	161	43.6	21	5.7	142	38.6	33	9.0
FATIGUE	149	40.4	33	8.9	74	20.1	12	3.3
VOMITING	144	39.0	13	3.5	88	23.9	7	1.9
PERIPHERAL SENSORY NEUROPATHY	138	37.4	42	11.4	27	7.3	0	0.0
MYALGIA	123	33.3	29	7.9	14	3.8	1	0.3
ALOPECIA	118	32.0	0	0.0	11	3.0	0	0.0
ANOREXIA	116	31.4	11	3.0	53	14.4	4	1.1
ASTHENIA	87	23.6	27	7.3	37	10.1	3	0.8
CONSTIPATION	83	22.5	0	0.0	22	6.0	1	0.3
NAIL DISORDER	77	20.9	5	1.4	31	8.4	0	0.0

MedDRA Preferred Term	Combination				Capecitabine			
	Total n	%	Grade 3-4 n	%	Total n	%	Grade 3-4 n	%
ARTHRALGIA	72	19.5	10	2.7	9	2.4	0	0.0
PARAESTHESIA	68	18.4	15	4.1	18	4.9	0	0.0
NEUTROPENIA	65	17.6	57	15.4	9	2.4	5	1.4
STOMATITIS	61	16.5	6	1.6	38	10.3	4	1.1
MUCOSAL INFLAMMATION	61	16.5	10	2.7	40	10.9	7	1.9
PERIPHERAL MOTOR NEUROPATHY	59	16.0	18	4.9	2	0.5	0	0.0
ABDOMINAL PAIN	55	14.9	6	1.6	34	9.2	3	0.8
PAIN IN EXTREMITY	48	13.0	1	0.3	10	2.7	0	0.0
DYSGEUSIA	42	11.4	0	0.0	14	3.8	0	0.0
WEIGHT DECREASED	40	10.8	3	0.8	12	3.3	0	0.0
SKIN HYPERPIGMENTATION	40	10.8	0	0.0	48	13.0	0	0.0
PYREXIA	39	10.6	2	0.5	14	3.8	0	0.0
RASH	39	10.6	3	0.8	15	4.1	0	0.0
ABDOMINAL PAIN UPPER	35	9.5	2	0.5	19	5.2	1	0.3
INSOMNIA	32	8.7	1	0.3	9	2.4	0	0.0
DIZZINESS	31	8.4	2	0.5	17	4.6	2	0.5
NEUROPATHY PERIPHERAL	30	8.1	6	1.6	5	1.4	0	0.0
ANAEMIA	29	7.9	8	2.2	11	3.0	3	0.8
HEADACHE	29	7.9	1	0.3	12	3.3	0	0.0
NEUTROPHIL COUNT DECREASED	28	7.6	20	5.4	6	1.6	2	0.5
LEUKOPENIA	26	7.0	21	5.7	1	0.3	1	0.3
HYPOAESTHESIA	26	7.0	4	1.1	8	2.2	0	0.0
DYSPNOEA	25	6.8	5	1.4	17	4.6	4	1.1
DYSPEPSIA	24	6.5	2	0.5	26	7.1	0	0.0
PAIN	24	6.5	3	0.8	2	0.5	0	0.0
WHITE BLOOD CELL COUNT DECREASED	24	6.5	17	4.6	3	0.8	0	0.0
MUSCULOSKELETAL PAIN	24	6.5	2	0.5	3	0.8	0	0.0
COUGH	22	6.0	0	0.0	6	1.6	0	0.0
OEDEMA PERIPHERAL	21	5.7	0	0.0	16	4.3	0	0.0
HAEMOGLOBIN DECREASED	21	5.7	3	0.8	3	0.8	1	0.3
BACK PAIN	21	5.7	1	0.3	6	1.6	0	0.0
PLATELET COUNT DECREASED	19	5.1	9	2.4	7	1.9	2	0.5
DRY SKIN	19	5.1	0	0.0	21	5.7	0	0.0
ERYTHEMA	18	4.9	0	0.0	8	2.2	0	0.0
PRURITUS	18	4.9	0	0.0	7	1.9	0	0.0
LACRIMATION INCREASED	17	4.6	0	0.0	15	4.1	1	0.3
FEBRILE NEUTROPENIA	16	4.3	16	4.3	2	0.5	2	0.5
DRY MOUTH	16	4.3	0	0.0	8	2.2	0	0.0
DECREASED APPETITE	16	4.3	0	0.0	7	1.9	0	0.0
DEHYDRATION	16	4.3	6	1.6	6	1.6	1	0.3
BONE PAIN	16	4.3	1	0.3	2	0.5	0	0.0
SKIN EXFOLIATION	15	4.1	1	0.3	10	2.7	0	0.0

MedDRA Preferred Term	Combination				Capecitabine			
	Total n	%	Grade 3-4 n	%	Total n	%	Grade 3-4 n	%
ABDOMINAL DISTENSION	14	3.8	2	0.5	7	1.9	0	0.0
CHEST PAIN	13	3.5	2	0.5	1	0.3	0	0.0
NEUROPATHY	13	3.5	6	1.6	0	0.0	0	0.0
HOT FLUSH	12	3.3	0	0.0	6	1.6	0	0.0
THROMBOCYTOPENIA	11	3.0	6	1.6	1	0.3	1	0.3
DYSAESTHESIA	11	3.0	2	0.5	2	0.5	0	0.0
HYPOREFLEXIA	11	3.0	0	0.0	2	0.5	0	0.0
NEURALGIA	11	3.0	4	1.1	0	0.0	0	0.0
MALAISE	10	2.7	1	0.3	0	0.0	0	0.0
HYPOTENSION	10	2.7	1	0.3	3	0.8	1	0.3
MUSCULAR WEAKNESS	9	2.4	1	0.3	1	0.3	0	0.0
PHARYNGOLARYNGEAL PAIN	9	2.4	1	0.3	3	0.8	0	0.0
GASTRITIS	8	2.2	0	0.0	5	1.4	1	0.3
PNEUMONIA	8	2.2	5	1.4	2	0.5	1	0.3
MUSCULOSKELETAL CHEST PAIN	8	2.2	2	0.5	3	0.8	0	0.0
NASOPHARYNGITIS	7	1.9	0	0.0	2	0.5	0	0.0
NEUROTOXICITY	7	1.9	3	0.8	1	0.3	0	0.0
ONYCHOLYSIS	7	1.9	1	0.3	1	0.3	0	0.0
CHILLS	6	1.6	0	0.0	2	0.5	0	0.0
HYPERSENSITIVITY	6	1.6	2	0.5	0	0.0	0	0.0
ORAL CANDIDIASIS	6	1.6	0	0.0	4	1.1	0	0.0
UPPER RESPIRATORY TRACT INFECTION	6	1.6	0	0.0	4	1.1	0	0.0
ALANINE AMINOTRANSFERASE INCREASED	6	1.6	0	0.0	4	1.1	1	0.3
ASPARTATE AMINOTRANSFERASE INCREASED	6	1.6	0	0.0	5	1.4	0	0.0
MUSCLE SPASMS	6	1.6	1	0.3	3	0.8	0	0.0
LETHARGY	6	1.6	2	0.5	3	0.8	0	0.0
EPISTAXIS	6	1.6	0	0.0	0	0.0	0	0.0
NAIL DISCOLOURATION	6	1.6	0	0.0	1	0.3	0	0.0
FLUSHING	6	1.6	0	0.0	1	0.3	0	0.0
DRY EYE	5	1.4	0	0.0	2	0.5	0	0.0
VISION BLURRED	5	1.4	0	0.0	3	0.8	0	0.0
ABDOMINAL DISCOMFORT	5	1.4	0	0.0	2	0.5	0	0.0
MOUTH ULCERATION	5	1.4	0	0.0	0	0.0	0	0.0
PARAESTHESIA ORAL	5	1.4	0	0.0	0	0.0	0	0.0
INFLUENZA LIKE ILLNESS	5	1.4	0	0.0	1	0.3	0	0.0
INJECTION SITE REACTION	5	1.4	0	0.0	0	0.0	0	0.0
NAIL INFECTION	5	1.4	0	0.0	1	0.3	0	0.0
HYPONATRAEMIA	5	1.4	3	0.8	0	0.0	0	0.0
SYNCOPE	5	1.4	5	1.4	0	0.0	0	0.0
BREAST PAIN	5	1.4	1	0.3	1	0.3	0	0.0
DYSPHONIA	5	1.4	1	0.3	2	0.5	0	0.0

MedDRA Preferred Term	Combination				Capecitabine			
	Total n	%	Grade 3-4 n	%	Total n	%	Grade 3-4 n	%
PHLEBITIS	5	1.4	0	0.0	1	0.3	0	0.0
GINGIVAL BLEEDING	4	1.1	0	0.0	0	0.0	0	0.0
INFUSION SITE PAIN	4	1.1	0	0.0	0	0.0	0	0.0
OEDEMA	4	1.1	0	0.0	0	0.0	0	0.0
HYPOKALAEMIA	4	1.1	2	0.5	3	0.8	2	0.5
SENSORY LOSS	4	1.1	0	0.0	0	0.0	0	0.0
ANXIETY	4	1.1	0	0.0	3	0.8	0	0.0
HYPERHIDROSIS	4	1.1	0	0.0	2	0.5	0	0.0
PAIN OF SKIN	4	1.1	0	0.0	0	0.0	0	0.0
PIGMENTATION DISORDER	4	1.1	0	0.0	2	0.5	0	0.0
HYPERTENSION	4	1.1	0	0.0	0	0.0	0	0.0
CONJUNCTIVITIS	3	0.8	0	0.0	2	0.5	0	0.0
DYSPHAGIA	3	0.8	0	0.0	3	0.8	0	0.0
FLATULENCE	3	0.8	0	0.0	4	1.1	0	0.0
GASTRIC DISORDER	3	0.8	0	0.0	0	0.0	0	0.0
GLOSSODYNIA	3	0.8	0	0.0	1	0.3	0	0.0
ILEUS	3	0.8	3	0.8	1	0.3	0	0.0
OESOPHAGITIS	3	0.8	2	0.5	1	0.3	0	0.0
TOOTHACHE	3	0.8	0	0.0	0	0.0	0	0.0
AXILLARY PAIN	3	0.8	1	0.3	0	0.0	0	0.0
EXTRAVASATION	3	0.8	0	0.0	0	0.0	0	0.0
PARONYCHIA	3	0.8	0	0.0	1	0.3	0	0.0
SEPSIS	3	0.8	3	0.8	0	0.0	0	0.0
PROCEDURAL PAIN	3	0.8	0	0.0	0	0.0	0	0.0
AGEUSIA	3	0.8	0	0.0	0	0.0	0	0.0
AREFLEXIA	3	0.8	0	0.0	2	0.5	0	0.0
CRANIAL NEUROPATHY	3	0.8	2	0.5	0	0.0	0	0.0
NERVOUS SYSTEM DISORDER	3	0.8	2	0.5	0	0.0	0	0.0
RESTLESS LEGS SYNDROME	3	0.8	0	0.0	0	0.0	0	0.0
TREMOR	3	0.8	0	0.0	1	0.3	0	0.0
DEPRESSED MOOD	3	0.8	0	0.0	0	0.0	0	0.0
VAGINAL INFLAMMATION	3	0.8	1	0.3	0	0.0	0	0.0
DYSPNOEA EXERTIONAL	3	0.8	0	0.0	0	0.0	0	0.0
ACNE	3	0.8	0	0.0	0	0.0	0	0.0
ECZEMA	3	0.8	0	0.0	0	0.0	0	0.0
RASH MACULAR	3	0.8	0	0.0	1	0.3	0	0.0
LYMPHOEDEMA	3	0.8	0	0.0	3	0.8	0	0.0

It is difficult to determine if there are any additional serious adverse events that will be better defined with further study of ixabepilone therapy. Most events not discussed in detail elsewhere in this review were mild and should not lead to major morbidity. Further analysis when more patients are treated with combination therapy, particularly when study CA163048 is complete and analyzed will be beneficial.

Monotherapy Study 081

Approximately 94% of patients in Study CA163081 were thought to experience drug-related adverse events (Sponsor's Table S.12.7). The following classes of adverse events appear to be the most important in evaluating the safety of ixabepilone:

- Peripheral neuropathy, both sensory and motor,
- Neutropenia, leukopenia and febrile neutropenia
- Fatigue/asthenia
- Myalgias, arthralgias, and musculoskeletal pain
- Hypersensitivity reactions
- Anorexia, nausea, vomiting, stomatitis, diarrhea, constipation, and abdominal pain
- Alopecia, rash, and nail disorder, and
- Dehydration, weight loss, and peripheral edema.

Additional analyses and explorations

None performed except as described above.

7.1.6 Less Common Adverse Events

Please see above analyses.

7.1.7 Laboratory Findings

Combination Therapy

The most significant laboratory abnormality, myelosuppression, is discussed in detail in Section 7.1.3.3, Significant Adverse Events. Other laboratory abnormalities were identified through a search of the LABRES.xpt databases for each trial as indicated. All laboratory abnormalities of any CTC grade were identified. For Trial 046 comparison is made between the combination arm and the capecitabine arm. Single arm trial data for study 031 at the same dose as used in trial 046 is also presented.

Overview of laboratory testing in the development program

Combination Therapy

Serum chemistries and CBC with differential were evaluated prior to each cycle in study 046. For cycles 1-4, a CBC with differential was also obtained weekly. Urinalysis was not performed. Coagulation studies were obtained at baseline and then as indicated. In study 031, patients were evaluated weekly with a CBC with differential, and before the start of each cycle for serum chemistries. Coagulation studies and urinalysis were performed as clinically indicated.

Selection of studies and analyses for drug-control comparisons of laboratory values

The randomized study of combination therapy versus capecitabine (Study 046) provides the database for the primary analysis of laboratory safety data. Study 031, a trial of various doses of ixabepilone in the same patient population is also analyzed. Only the arm of the trial corresponding to the dose used in study 046 is analyzed, as other arms had differences in capecitabine, ixabepilone or both, and comparison is difficult.

For monotherapy, only the Study 081 was used, since the populations in Studies 009 and 010 differ from the population in Study 081.

Standard analyses and explorations of laboratory data

Laboratory Values were analyzed using JMP 7.0 to identify abnormalities of all grades. Datasets LABRES01.xpt, LABRES02.xpt and LABRES03.xpt, containing data from all patients enrolled in trial 046 were analyzed. Hematological laboratory abnormalities with a frequency of greater than 5% are presented in Table 56 below.

Table 56. Hematological laboratory abnormalities-Study 046 Reviewer analysis

Laboratory Term	Capecitabine				Combination			
	All		Grade 3-4		All		Grade 3-4	
	n	%	n	%	n	%	n	%
Hemoglobin	275	74.7	16	4.3	339	91.9	40	10.8
Leukocytes	212	57.6	25	6.8	333	90.2	210	56.9
GRANULOCYTES	171	46.5	43	11.7	326	88.3	251	68.0
Lymphocytes (relative)	195	53.0	31	8.4	232	62.9	89	24.1
Neutrophils (relative)	94	25.5	26	7.1	204	55.3	150	40.7
Platelet Count	129	35.1	18	4.9	203	55.0	34	9.2
Lymphocytes (absolute)	160	43.5	29	7.9	170	46.1	56	15.2
Neutrophils (absolute)	79	21.5	19	5.2	149	40.4	112	30.4
Prothrombin Time (PT)	38	10.3	5	1.4	37	10.0	8	2.2
Partial Thromboplastin Time (PTT)	23	6.3	6	1.6	35	9.5	8	2.2
Hemoglobin	275	74.7	16	4.3	339	91.9	40	10.8

Non-hematological laboratory abnormalities are presented in table 57 below.

Table 57. Non-hematological laboratory abnormalities, Study 046 Reviewer Analysis

Laboratory Term	Capecitabine				Combination			
	All		Grade 3-4		All		Grade 3-4	
	n	%	n	%	n	%	n	%
Aspartate Aminotransferase (AST)	224	60.9	18	4.9	200	54.2	16	4.3
Alkaline Phosphatase (ALP)	223	60.6	23	6.3	187	50.7	12	3.3
Calcium, Total	151	41.0	25	6.8	164	44.4	26	7.0
Sodium, Serum	129	35.1	16	4.3	162	43.9	30	8.1

Laboratory Term	Capecitabine				Combination			
	All		Grade 3-4		All		Grade 3-4	
Alanine Aminotransferase (ALT)	179	48.6	11	3.0	161	43.6	4	1.1
Albumin	150	40.8	4	1.1	148	40.1	5	1.4
Potassium, Serum	148	40.2	19	5.2	145	39.3	26	7.0
Magnesium, Serum	111	30.2	17	4.6	113	30.6	13	3.5
Glucose, Fasting Serum	96	26.1	10	2.7	96	26.0	14	3.8
Bilirubin, Total	123	33.4	20	5.4	80	21.7	12	3.3
Phosphorus, Inorganic	53	14.4	9	2.4	57	15.4	20	5.4
Creatinine	35	9.5	2	0.5	31	8.4	1	0.3

Patients in Study 046 with baseline LFTs of AST or ALT ≥ 2.5 X ULN or bilirubin ≥ 1.5 X ULN were excluded from the study. Prior to amendment 4 patients with higher limits and the presence of liver metastases were allowed.

Of note, aside from hematological abnormalities, there do not appear to be significant differences between the combination and capecitabine arms.

Laboratory abnormalities were also evaluated in trial 031. Only the arm with the same dosing and schedule as that used in Study 046 were analyzed. Database AESAE.xpt for trial 031 was used for this analysis. The results of this analysis are presented in Tables 58 and 59 below.

Table 58. Hematological Laboratory Abnormalities in Study 031

Laboratory Value	All Grades		Grade 3-4	
	n	%	N	%
Hemoglobin	60	96.8	4	6.5
Leukocytes	57	91.9	33	53.2
Lymphocytes (relative)	57	91.9	30	48.4
GRANULOCYTES	55	88.7	43	69.4
Neutrophils (relative)	48	77.4	35	56.5
Platelet Count	38	61.3	5	8.1
Prothrombin Time (PT)	16	25.8	1	1.6
Partial Thromboplastin Time (PTT)	13	21.0	2	3.2
Lymphocytes (absolute)	11	17.7	6	9.7
Neutrophils (absolute)	11	17.7	9	14.5
Intl Normalized Ratio	5	8.1	1	1.6

Table 59. Laboratory abnormalities in Study 031

Laboratory Value	All Grades		Grade 3-4	
	n	%		n
Albumin	47	75.8	1	1.6
Alkaline Phosphatase (ALP)	36	58.1	0	0.0
Potassium, Serum	27	43.5	5	8.1
Sodium, Serum	27	43.5	2	3.2
Alanine Aminotransferase (ALT)	26	41.9	0	0.0
Calcium, Total	24	38.7	1	1.6
Magnesium, Serum	18	29.0	3	4.8
Bicarbonate	16	25.8	0	0.0
Phosphorus, Inorganic	16	25.8	6	9.7
Bilirubin, Total	9	14.5	0	0.0
Aspartate Aminotransferase (AST)	5	8.1	1	1.6
Creatinine	5	8.1	0	0.0

Study 031 had similar frequencies of laboratory abnormalities related to ixabepilone.

Monotherapy

Liver Function Test (LFT) Abnormalities. Changes in LFT abnormalities during treatment are difficult to interpret because of the presence of LFT abnormalities at baseline and the high prevalence of metastatic foci in the liver. Reviewer's Table 60 presents the number of subjects with LFT abnormalities at baseline and worst on-study (data from Sponsor's Tables S.8.20 and S.12.2). (Note: Eligibility criteria excluded patients with Grade 2 bilirubin values [$> 1.5 \times \text{ULN}$] and Grade 2 ALT [$\geq 2.5 \times \text{ULN}$] or Grade 3 [$\geq 5 \times \text{ULN}$] if documented hepatic metastases were present).

Table 60. Liver Function Abnormalities at Baseline and On-Study

LFT Abnormality	CTC Grade at Baseline	Worst CTC Grade On-Study
Alkaline phosphatase		
---Grade 1	30.2%	38.7%
---Grade 2	4.0%	9.2%
---Grade 3	2.4%	3.4%
---Grade 4	0	0.8%

LFT Abnormality	CTC Grade at Baseline	Worst CTC Grade On-Study
Total bilirubin		
---Grade 1	4.0%	3.3%
---Grade 2	1.6%	2.5%
---Grade 3	0	2.5%
---Grade 4	0	0
ALT		
---Grade 1	16.7%	20.0%
---Grade 2	3.2%	7.5%
---Grade 3	0.8%	3.3%
---Grade 4	0	0
AST		
---Grade 1	16.7%	26.1%
---Grade 2	7.1%	7.6%
---Grade 3	2.4%	5.0%
---Grade 4	0	0

The Sponsor performed a correlation between baseline abnormality grades and worst on-study grades in individual patients (Table S.12.25). In general, most patients retained the baseline abnormality grade through the study, but approximately 15 – 20% of patients experienced an advance to the next grade of abnormality (abnormalities were grouped in 0, 1-2, and 3-4 grades).

It is uncertain to what extent, if any, ixabepilone treatment contributed to worsening of LFTs. One patient with Grade 3 hyperbilirubinemia had it attributed to the drug by the investigator; however, further work-up demonstrated obstruction of hepatic ducts by the tumor.

Renal Function. At baseline, 96% of patients had normal creatinine clearance. There were 2 patients with Grade 1 renal impairment. During the study 5 patients experienced Grade 1 impairment and one patient Grade 2; 95% of patients had normal renal function.

7.1.8 Vital Signs

Overview of vital signs testing in the development program

Vital signs including weight were determined at every visit prior to administration of therapy, and every 30 minutes during ixabepilone infusions. These records were reviewed by the sponsor and by the reviewers in part. Most of the patients had normal heart rates and blood pressures during drug administration. Some patients had transient borderline hypertension during the infusion. The reviewers agree with the sponsor's conclusion that "most patients had vital sign parameters within or near normal range that generally remained stable throughout treatment."

Selection of studies and analyses for overall drug-control comparisons

Study 046 provides the primary comparison for vital sign analysis.

Standard analyses and explorations of vital signs data

The database AESAE was searched for the terms hypotension, low blood pressure, blood pressure low, hypertension, high blood pressure and blood pressure high. Results are presented in Table 61 below. Those events felt to be related to study drug are shown in Table 62.

Table 61. Treatment emergent changes in blood pressure.

	Capecitabine		Combination	
	Total n (%)	Grade 3-4 n (%)	Total n (%)	Grade 3-4 n (%)
Hypertension	10 (2.7)	1 (0.3) ^a	12 (3.3)	2 (0.5) ^a
Hypotension	10 (2.7)	5 (1.4)	18 (4.9)	2 (0.5) ^a

^a No grade 4 events.

Table 62. Treatment related changes in blood pressure

	Capecitabine		Combination	
	Total n (%)	Grade 3-4 n (%)	Total n (%)	Grade 3-4 n (%)
Hypertension	0 (0)	0 (0) ^a	4 (3.3)	0 (0)
Hypotension	3 (0.8)	1 (0.3) ^a	10 (2.7)	3 (0.8) ^a

^a No grade 4 events.

In one case of grade 3 hypotension on combination therapy a patient was discontinued from therapy.

Changes in weight are captured in common adverse events.

There were two cases of tachycardia (terms tachycardia, heart rate fast) in combination therapy and one in capecitabine that were attributed to study drug. All were grade 1.

There does not appear to be a major effect of ixabepilone therapy on vital signs, particularly blood pressure and heart rate. Weight changes are captured in common adverse events above.

7.1.9 Electrocardiograms (ECGs)

Overview of ECG testing in the development program, including brief review of preclinical results

ECG was routinely performed in studies 046 and 081 at study entry, and then when deemed appropriate. Routine ECG testing during on-study period was not performed, nor was an analysis of the effect of ixabepilone on QT prolongation performed as part of this protocol.

A post-marketing commitment to study the effect of ixabepilone on QT length was proposed by the Clinical Pharmacology review team.

Selection of studies and analyses for overall drug-control comparisons

Standard analyses and explorations of ECG data

Database ECGJN.xpt was analyzed for recognized abnormalities of ECGs obtained during treatment. Fourteen patients had ECG abnormalities recognized after the baseline visit. Two patients treated with capecitabine had sinus tachycardia and one had ventricular premature beats. In the combination arm, three patients had sinus tachycardia, one had ventricular tachycardia, one had left atrial hypertrophy, one had 1st degree AV block, four had non-specific ST-T wave abnormalities and one patient had an unidentified abnormal ECG.

There is no evidence by this analysis that ixabepilone in combination with capecitabine causes electrocardiographic abnormalities to a significant degree. However see Section 7.1.3.3.5 for a discussion of cardiac toxicity related to ixabepilone therapy.

Additional analyses and explorations

7.1.10 Immunogenicity

Ixabepilone is a small molecule with minimal immunogenic potential. No evidence was presented to suggest development of immunogenicity. The major immunogenic component of Ixabepilone for infusion is the Diluent, which consists of a 50/50 (v/v) mixture of purified polyoxyethylated castor oil (Cremaphor) and dehydrated alcohol. Cremaphor is associated with hypersensitivity reactions.

7.1.11 Human Carcinogenicity

No formal studies have been undertaken.

7.1.12 Special Safety Studies

None were performed during the development program.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is unlikely to be any abuse potential for ixabepilone as it is not a psychoactive drug. No withdrawal phenomenon have been reported.

7.1.14 Human Reproduction and Pregnancy Data

No data is available.

7.1.15 Assessment of Effect on Growth

No pediatric patients were treated in any of the studies performed.

7.1.16 Overdose Experience

One case of overdose of ixabepilone has been reported. The patient mistakenly received 100 mg/m² (total dose 185 mg) and was admitted to the hospital for observation. The patient experienced myalgia (grade 1) and fatigue (grade 1) one day after infusion and was treated with a centrally acting analgesic. The patient recovered and was discharged without incident.

Please see the Pharmacology/Toxicology review for information from animal studies regarding drug overdose.

7.1.17 Postmarketing Experience

None

7.2 Adequacy of Patient Exposure and Safety Assessment

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The two primary studies to analyze exposure in combination therapy are studies 046 and 031. These are described in more detail in Section 6.1. The pivotal monotherapy Study 081 is described in 6.2.

Study type and design/patient enumeration

Please see Sections 6.1 and 6.2.

Demographics

Please see Sections 6.1 and 6.2.

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Extent of exposure (dose/duration)

Combination Therapy

From the sponsor's Summary of Clinical Safety:

The 431 treated patients [receiving combination therapy with ixabepilone and capecitabine] received a total of 2306 cycles of ixabepilone, the majority (64%) of which were administered at the starting dose level of 40 mg/m².

CA163046: In the ixabepilone plus capecitabine group, the 369 treated patients received a total of 2001 cycles of ixabepilone (median: 5 cycles, range 1 to 21 cycles); nearly half (43%) the patients in this group received ≥ 6 cycles of ixabepilone. In the combination group, capecitabine was administered in 2309 cycles (median; 5 cycles, range 1 to 37 cycles). The median number of cycles of capecitabine was higher in these patients than in the capecitabine only group (N = 368 patients, median; 4 cycles of capecitabine, range 1 to 33 cycles). The majority (64%) of cycles of ixabepilone were administered at the planned dose level of 40 mg/m². Following a dose reduction, ixabepilone was administered at 32 mg/m² in 523 (26%) cycles and at 25 mg/m² in 202 (10%) cycles. The remaining 2 (< 1%) cycles were administered at a dose of < 25 mg/m².

CA163031: The 62 treated patients received a total of 305 cycles of ixabepilone (median: 4 cycles, range 1 to 20 cycles); 40% of patients received at least 6 cycles of ixabepilone. Capecitabine was administered in 296 of the 305 cycles. The majority (64%) of cycles of ixabepilone were administered at the planned dose level of 40 mg/m². Following a dose reduction, ixabepilone was administered at 32 mg/m² in 94 (31%) cycles and at 25 mg/m² in 15 (5%) cycles.

Monotherapy

The number of cycles administered at each dose level and the number (and percentage) of patients who received ixabepilone therapy in the pivotal monotherapy trial (081) are shown in Tables 63 and 64. These findings are discussed by the reviewer below.

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Table 63. Number of Cycles of Ixabepilone Administered at Each Dose Level

Table 9.1A: Number of Cycles Administered at Each Dose Level for Ixabepilone - Treated Patients

Ixabepilone Dose Level (a)	Number of Cycles (%) N = 605
<25 mg/m ²	2 (0.3)
25 mg/m ²	24 (4.0)
32 mg/m ²	97 (16.0)
40 mg/m ²	482 (79.7)

(a) Calculated dose level

Source: Supplemental Table S.9.2

Table 64. Ixabepilone Therapy Administered per Cycle

Table 9.1B: Study Therapy Administered Per Cycle - Treated Patients

Cycle	Number of Patients (%) N = 126
Cycle 1	126 (100.0)
Cycle 2	111 (88.1)
Cycle 3	81 (64.3)
Cycle 4	74 (58.7)
Cycle 5	49 (38.1)
Cycle 6	44 (34.9)
Cycle 7	33 (26.2)
Cycle 8	32 (25.4)
Cycle 9	22 (17.5)
Cycle 10	16 (12.7)
Cycle 11	7 (5.6)
Cycle 12	6 (4.8)
Cycle 13	2 (1.6)
Cycle 14	1 (0.8)
Cycle 15	1 (0.8)
Cycle 16	1 (0.8)

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Source: Supplemental Table S.9.3

Reviewer's comments regarding the above Tables:

- Ixabepilone was administered at the planned dose of 40 mg/m² in about 80% of cycles. The most common reason for administration of study drug at reduced doses (mainly 32 mg/m²) was peripheral neuropathy.
- There were 2 patients who received < 25 mg/m². In one patient the infusion was stopped when it was discovered that the patient had an elevated bilirubin. The patient received less than 1 mg of ixabepilone; she was removed from the study because she no longer met the eligibility criteria. Infusion was stopped in the second patient because of restlessness, anxiety and hypertension during Cycle 6. The patient was discontinued from the study 6 days later when CNS metastases were discovered. A third patient received < 1 mg/m² in cycle 2 because infusion was interrupted due to a hypersensitivity reaction (HSR). The dose was recorded as 0, and ixabepilone was never resumed.

- Almost 90% (88.1%) of patients received 2 cycles of therapy; almost 60% (58.7%), 4 cycles; about 35%, 6 cycles; and about 25%, 8 cycles. The median number of cycles received was 4. At the time of database lock (December 21, 2005) all but 2 of 126 patients were off treatment. The most common reason for discontinuation of ixabepilone therapy was disease progression (PD) (in 74% of patients, see above Sponsor's Table 8.1). Since tumor assessments were carried out per protocol every 2 cycles, PD was generally detected after cycles 2, 4, 6, 8, etc., resulting in stepwise decrease in the numbers of treated patients. However, tumor assessments were also carried out in addition at other than specified intervals, e.g. after odd-numbered cycles.
- About 35% (39/126) of patients required at least one dose reduction. The most common reason (in 26 of 39 patients) was peripheral neuropathy. The reductions due to neuropathy generally occurred after 3 cycles of 40 mg/m² doses. Neutropenia was the cause of dose reduction in 6 patients; pain plus fatigue, myalgia, stomatitis, mucositis, leg pain, tinnitus, neuropathy plus hematologic toxicity resulted in dose reductions in single patients.
- Nine patients (11%) required two dose reductions; the most common reason was, again, peripheral neuropathy (5/9) patients. Single patients had dose reductions for neutropenia and stomatitis.
- Dose interruption occurred in 13 (10%) patients; the most common reason was HSR. In all but 3 patients, the infusion was restarted and the patients received their full ixabepilone dose.
- Dose delays occurred in 54 (43%) patients. About one-half of the delays (10% of cycles, 34/54 patients) were due to toxicities (peripheral neuropathy, delayed hematologic recovery, and delayed non-hematologic recovery); the other one-half of the delays were for administrative reasons (holidays, scheduling, patient requests).
-

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

None used.

7.2.3 Adequacy of Overall Clinical Experience

- The pivotal trials in metastatic or locally advanced breast cancer patients were multicenter, multinational trials that were able to accrue relatively large numbers of patients in whom therapy with an anthracycline and a taxane, or an anthracycline, a taxane and capecitabine had failed. They were sufficiently large to draw conclusions regarding efficacy and safety.
- The majority of patients were White. The numbers of American Indian, Native Alaskan, Black and Asian patients are not sufficient to assess efficacy and safety findings for monotherapy in these populations. The number of Asian patients enrolled in Study 046 was sufficient to conclude that no major differences in either safety or efficacy of

combination therapy are present in this population compared to White patients. Conclusions about other races and combination therapy cannot be determined.

- The percentage of patients less than 65 years of age was about 85-90% in these studies. This age distribution is appropriate for this patient population.
- The doses and durations were adequate to assess the experience with ixabepilone. The main reason for patient withdrawal from the studies was disease progression.
- The design of the randomized study permitted a comparison with capecitabine as monotherapy. There was no adequate comparator drug for the monotherapy trial.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Ixabepilone was tested extensively in rodents, lagomorphs and canines. The major clinical toxicities, peripheral neuropathy, gastrointestinal toxicities and myelosuppression, were predicted by the nonclinical toxicology in one or more of these species. Cardiac toxicities were not predicted by nonclinical models, and *in vitro* and *in vivo* tests did not reveal abnormalities in cardiac conduction. The nonclinical testing program was adequate.

7.2.5 Adequacy of Routine Clinical Testing

In studies 046 and 081 patients were evaluated prior to each cycle (every three weeks) and at end of study. Hematology labs were evaluated weekly during the first four cycles. A directed history and physical exam were performed at each study visit. Comprehensive hematological and serum chemistry laboratory tests were performed. Patients were not evaluated by ECG except at study entry or unless clinically indicated.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please see Section 5. Clinical Pharmacology.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor addressed the main safety concerns regarding the use of ixabepilone. In particular, peripheral neuropathy, myelosuppression, gastrointestinal toxicity and cardiac toxicity were analyzed. Additionally, the sponsor recognizes the potential for hypersensitivity reactions with the use of the diluent during drug administration. The incidence of peripheral neuropathy as determined by the reviewer differs from that of the sponsor, but both analyses are of the same magnitude.

7.2.8 Assessment of Quality and Completeness of Data

The data submitted for studies 046 and 031 were adequate for review. Investigator terms were appropriately matched to MedDRA preferred terms. In study 046 18,661 Adverse Events were

listed. All but two had appropriate mapping to a MedDRA Preferred Term. The sponsor's grouping of terms, especially for peripheral neuropathy and neutropenia with infection was appropriate except where noted in the review.

The data submitted for studies 081, 009 and 010 were adequate for review.

7.2.9 Additional Submissions, Including Safety Update

A safety update was received August 7, 2007. There were changes in efficacy findings and safety updates which did not result in new conclusions.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Ixabepilone in combination with capecitabine

- Ixabepilone in combination with capecitabine was evaluated in Study 046, a randomized trial comparing combination therapy to capecitabine alone, and study 031, which evaluated multiple doses of combination therapy, including the final recommended dose. The studies were conducted well and collected adequate safety data. The data was evaluable and easily accessed. The primary analysis was conducted primarily with study 046 as it allowed for a comparison with capecitabine monotherapy.
- There is limited exposure data. The median number of cycles received in the combination arm was 5, however 43% of patients received 6 or more cycles. Most patients discontinued therapy for disease progression. This limits the ability to identify adverse reactions that may only be found with prolonged therapy.
- Twelve patients receiving combination therapy in Study 046 died from a toxicity related to study drug. The comparable number for capecitabine therapy is two. Five of these twelve patients had moderate or severe hepatic insufficiency. The rate of death in patients with moderate or severe hepatic insufficiency (5 of 17 patients) is significantly higher than in patients with normal hepatic function or mild insufficiency. (Section 7.1.1)
- All but one of the drug-related deaths can be attributed to complications from neutropenia. One of the deaths may also be related to neutropenia, but hepatic and/or cardiac insufficiency may have contributed.
- Two deaths occurred from cardiac causes within ten days of administration of ixabepilone.
- The most frequent non-hematological adverse events associated with combination therapy are peripheral neuropathy, hand-foot syndrome, fatigue/asthenia,

myalgias/arthralgias and gastrointestinal disturbances including pain, constipation, nausea and vomiting (Section 7.1.2).

- The most frequent grade 3 or 4 adverse reactions associated with ixabepilone combination therapy were neutropenia, palmar-plantar erythrodysesthesia, fatigue and peripheral neuropathy.
- Of the 369 patients treated in the combination arm in Study 046, 163 (44%) discontinued one or both medications due to adverse events. Of these, 136 were deemed to be treatment related. Seventy-nine (21%) discontinued for treatment related neuropathy after a median of 6 cycles. Forty-four of these patients continued on capecitabine for at least one cycle. Thus neuropathy was the biggest cause of discontinuation due to drug toxicity.
- Peripheral neuropathy was the major non-hematological toxicity related to ixabepilone. Seventy percent of patients had a treatment-emergent neuropathy, and 68% treatment related. Analysis by the sponsor demonstrated that dose and diabetes were the only factors related to development of neuropathy. The majority of patients with severe (Grade 3 or 4) neuropathy had resolution of their symptoms to Grade 1 or better following cessation of ixabepilone therapy.
- Myelosuppression was a major hematological toxicity. Sixty-eight percent of patients receiving combination therapy experienced Grade 3 or 4 neutropenia, and 5% had febrile neutropenia. Thrombocytopenia was also common, with 55% of patients experiencing thrombocytopenia that was generally mild. Bleeding was not a noticeable consequence of thrombocytopenia. Anemia was common but not debilitating.
- Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) was common in the combination and capecitabine arms. There is a slightly higher (two percent) increase in the combination arm, but this is unlikely to be significant. No dose reduction for hand-foot syndrome is necessary for ixabepilone.
- Cardiac toxicities were rare, but appeared to be increased with combination therapy. These included myocardial infarction, ischemia and ventricular dysfunction. Arrhythmias were also more common. Further study is required to determine the precise relationship between ixabepilone and cardiac toxicity.
- Other toxicities were common, as would be expected with a cytotoxic drug. These include gastrointestinal toxicities, myalgias and arthralgias, fatigue and asthenia. Hepatic toxicity does not appear to be a concern with ixabepilone combination therapy. The majority of adverse reactions were Grade 1 or 2 and easily managed.

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Ixabepilone as monotherapy

- There are two major limitations of the monotherapy data. One is the limitation of exposure due to the decrease in at-risk population, mainly as a result of disease progression. The median number of cycles received by patients was 4. Almost 60% of patients received 4 cycles, about 35% received 6 cycles, and about 25% 8 cycles. The numbers of patients who received more than 10 cycles is in the single digits. The second limitation of data is due to the lack of a comparator treatment arm. This limitation is not important for the evaluation of the main toxicities, as patients in large numbers are not likely to spontaneously develop peripheral neuropathy or severe neutropenia, but it impedes the evaluation of less common toxicities and prevents the development of an adequate safety profile.
- Drug-related adverse events were reported by virtually all (94%) patients treated with ixabepilone in the monotherapy study. Severity of AEs was CTC Grade 5 in 1% of patients, Grade 4 in 5%, Grade 3 in 34%, Grade 2 in 44% and Grade 1 in 11%. Thus, 40% of patients experienced drug-related adverse events of Grades ≥ 3 , a relatively high percentage experiencing moderate or severe toxicity.
- SAEs occurred in 33% of patients. Most common were gastrointestinal events, respiratory events, complications of metastatic breast cancer, infections, and hematologic events.
- Discontinuation of ixabepilone due to drug toxicity (in 21% of patients) was due to a variety of causes. The most common were peripheral neuropathy, progression and complications of metastatic breast cancer, infections, gastrointestinal disorders, and asthenia/edema/pain.
- There was one drug-related death (a Grade 5 event) due to Grade 4 neutropenia and septic shock.
- The most outstanding adverse events related to ixabepilone therapy were peripheral neuropathy and neutropenia, because of their prevalence, severity and as causes of dose modifications and treatment discontinuation.
- Peripheral neuropathy affected approximately 64% of patients. It was Grade 4 in 1% of patients, Grade 3 in 13%, Grade 2 in 35%, and Grade 1 in 16%. At baseline, 73% of patients had no neuropathy, 25% had Grade 1 neuropathy, and 2% had Grade 2 neuropathy. During ixabepilone treatment, patients with neuropathy at baseline developed neuropathy slightly more frequently (71% of patients) than patients without neuropathy at baseline (62% of patients). Development of Grade ≥ 3 neuropathy occurred in about the same percentage of patients with neuropathy at baseline (15%) as in patients without neuropathy at baseline (13%). Peripheral neuropathy was sensory in 63% of patients and motor in 10%. Some patients had more than one type of neuropathy.

- Onset of neuropathy. New development or worsening of neuropathy started early in the course treatment. Twenty-one (21%) of all treated patients developed a neuropathy in the first cycle of treatment, 11% in the second, 16% in the third and 6% in the fourth. Only 9% of all neuropathies first occurred after the fourth cycle (in 1 or 2 patients during cycles 5-17). The median number of cycles to the onset or worsening of any grade of neuropathy was 2. Grade ≥ 3 neuropathy developed more gradually. The median number of cycles to the onset of Grade ≥ 3 neuropathy was 4 (range, 1 – 11).
- Dose reductions due to neuropathy. Grade ≥ 2 peripheral neuropathy was the most common cause of dose reductions (first dose reduction in 26/39 patients and second dose reduction in 5/9 patients). The reduced doses were administered for a median of 3 cycles (range, 1 – 10 cycles). In 20 patients neuropathy improved or did not worsen. Ten patients continued to be treated with ixabepilone without a dose reduction.
- Dose delays due to neuropathy. Peripheral neuropathy was the most common reason for dose delays (14% of all treated patients accounting for 5% of all treatment cycles).
- Drug discontinuation due to neuropathy. Peripheral neuropathy was the most common reason for drug discontinuation because of toxicity (8/126 or 6.3% of all treated patients).
- Resolution of neuropathy. Grades 2 and 3 neuropathy resolved to baseline or Grade 1 in 88% of patients (54/61). (Resolution of Grade 1 neuropathy in 20 patients is not discussed in the submission.) In 33 patients neuropathy resolved while treatment was continued (at full or reduced doses); in 21 patients neuropathy resolved when treatment was discontinued. Neuropathy did not resolve in seven patients. The median time to resolution of Grade ≥ 2 neuropathy to baseline or Grade 1 was 4.3 weeks (95% CI, 3.0 – 5.4). The median time to resolution was about the same in patients with Grade 3 neuropathy (4.6 weeks). The 12-week rate of resolution of Grade 3 neuropathy was 79.2% (95% CI, 58.4 – 100%).
- Neutropenia. The second most important toxicity was Grade 3 and 4 neutropenia and leukopenia occurring in about 50% of patients. Platelets and RBC were much less affected by therapy. Only 7 - 8% of patients experienced Grade 3 or 4 thrombocytopenia and anemia. At baseline, 87% of patients had normal WBCs, 95% had normal ANCs, 95% had normal platelet counts, and 67% had normal hemoglobin values .
- Complications of neutropenia. Three neutropenic patients (2%) had infections. One of them died, the others recovered. Four patients (3%) had febrile neutropenia, which subsided in the same treatment cycle. Neutropenia was a minor cause of dose reductions (6/126 patients = 5%), dose delays (3.5% of treatment courses), and discontinuations from the study (1 patient with pancytopenia, 1%). In general, recovery from neutropenia occurred within one cycle.

- Hypersensitivity reactions (HSR) occurred in 7 patients (6%) in spite of pre-medication. One patient discontinued treatment because of a repeat HSR on re-challenge. The other 6 patients continued with appropriate pre-medication.
- Liver function abnormalities. Changes in LFT abnormalities during treatment are difficult to interpret because of the presence of LFT abnormalities at baseline and the high prevalence of metastatic disease in the liver. Most patients (about 85%) retained the baseline abnormality grade throughout the study, but approximately 15 – 20% of patients experienced an advance to the next higher grade of abnormality. To what extent, if any, ixabepilone contributed to LFT abnormalities is uncertain. One Grade 3 hyperbilirubinemia initially attributed to ixabepilone treatment was later shown to be due to hepatic duct obstruction.
- Gastrointestinal disorders, anorexia, asthenia, fatigue, myalgias, arthralgias, and alopecia were common during treatment. They were mostly of Grades 1-2 severity, but they contributed to 19% discontinuations from the study.
- The ixabepilone safety profile in Study 009 is basically similar to the profile in pivotal study 081. Peripheral neuropathy occurred in 65% of patients (Grade 3 in 12% of patients) and was the cause of discontinuation from the study in 10% of patients. Neutropenia was Grade 4 in 20% of patients and Grade 3 in 33%. Febrile neutropenia and infection in the presence of neutropenia each occurred in 4% of patients. Grade 4 anemia (in 4%) and thrombocytopenia (in 4%) were uncommon. Fatigue (in 27%), myalgia (in 10%), nausea (in 6%) and vomiting (in 6%) were the other most common Grade 3/4 AEs. Treatment-related AEs resulted in discontinuation of 16% of patients from the study. There were no deaths related to ixabepilone therapy.
- In Study 010, peripheral neuropathy occurred in 78% of patients (Grade 3 in 25% of patients) and was the cause of discontinuation from the study in 28% of patients. Neutropenia was Grade 4 in 31% of patients and Grade 3 in 27% of patients. Febrile neutropenia and infection in the presence of neutropenia occurred in 5% and 6% of patients, respectively. There were no cases of Grade 4 anemia or thrombocytopenia. Other Grade 3/4 AEs were myalgia (in 8%), fatigue (in 6%), vomiting (in 6%), and neuropathic pain, arthralgia, stomatitis/pharyngitis in 5% each. Treatment-related AEs resulted in discontinuation of 37% of patients from the study. There were no deaths related to ixabepilone therapy.
- In summary, ixabepilone therapy was associated with a high incidence of drug-related adverse events and with risk of death and disability posed by severe neutropenia/leukopenia and peripheral neuropathy. The decision to use it in the treatment of refractory metastatic or locally advanced breast cancer needs to take into account the potential benefit and the attendant discomforts and risks.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

In general, data are presented from individual studies except as noted. In the case of the randomized trial Study 046 this allows for direct comparison to another therapy. For the monotherapy studies, there was insufficient conformity in the patient populations and study designs to pool data and obtain an accurate indication of adverse reaction frequencies. Data from study 046 and the same dose and schedule of single arm Study 031 are pooled where indicated and appropriate.

7.4.2 Explorations for Predictive Factors

Age

Patients above the age of 65 had a higher incidence of adverse reactions with ixabepilone therapy when used in combination with capecitabine. The incidence of Grade 3 and 4 toxicities with capecitabine alone is also higher in this population. Deaths were also more frequent in patients above the age of 65. Three of 45 patients (6.7%) 65 or older died from drug toxicity on combination therapy compared to 10 of 386 (2.6%) below 65. For capecitabine alone the rate of toxicity associated death was 1 in 53 (1.9%) for patients 65 or older. Older patients also had a higher incidence of adverse reactions leading to study drug discontinuation (40% vs. 35%), and drug-related SAEs (40% vs. 21%). Together, these data suggest caution in the use of ixabepilone in combination with capecitabine in patients older than 65.

See section 7.1.3.3.1 for a discussion of factors related to peripheral neuropathy.

7.4.3 Causality Determination

Causality was generally determined by the investigator. Where indicated, all treatment-emergent adverse events are shown or tabulated. Future analysis with a greater safety database may give a more accurate indication of adverse reaction frequencies without dependency on determination of attribution by the investigator.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended dose of ixabepilone when used in combination with capecitabine is 40 mg/m² IV over three hours once every three weeks. Capecitabine is to be administered at a dose of 2000

mg/m²/day orally in two divided doses every day for the first 14 days of each 21 day cycle. This dose was used in Study 046. The primary dose finding study that established this dose was Study 031, which explored multiple dosing regimens. In addition, data from monotherapy studies that evaluated various doses and schedules were used. In Study 031, 2 of 30 patients experienced a DLT at the above dose. Data from monotherapy studies suggested that 40 mg/m² had clinical activity. Based on these data, and the findings from study 046, the dose appears to be appropriate.

Dose-response relationships were more fully explored in monotherapy studies. The suggested dose appears to be efficacious and has demonstrated a benefit for PFS compared to capecitabine alone. Higher doses of ixabepilone (50 mg/m²) were associated with significant increases in toxicity, particularly peripheral neuropathy.

The sponsor recommends that ixabepilone in combination with capecitabine not be administered to patients with moderate to severe hepatic insufficiency, as determined by AST or ALT >2.5 x ULN or bilirubin > 1 x ULN. There is no need for dose modification in other populations.

8.2 Drug-Drug Interactions

The use of concomitant strong CYP3A4 inhibitors should be avoided.

8.3 Special Populations

Combination Therapy

- There is no modification suggested for age. Patients above the age of 65 had a higher incidence of adverse reactions, grade 3-4 adverse reactions, serious adverse reactions and deaths, in both arms of Study 046. Patients above the age of 65 did not demonstrate a difference in efficacy of ixabepilone.
- Ixabepilone has not been tested in male patients with breast cancer. Male breast cancer is a rare disease.
- Ixabepilone should not be used in combination with capecitabine in patients with moderate or severe hepatic insufficiency.
- The safety of ixabepilone during pregnancy and lactation has not been tested.

These findings are based on review of Study 046 and Study 031 and the sponsor's reports from these studies.

Monotherapy

The same conclusions can be made for ixabepilone monotherapy. Treatment-related adverse event data in patients aged less than 50 (N = 103) and 50 and older (N = 137) show similar

percentages of patients with all drug-related AEs, Grades 3 and 4 AEs, SAEs, AEs leading to discontinuation, and on-study deaths (Sponsor's Table 5.5.1B).

8.4 Pediatrics

Ixabepilone has not been tested in a pediatric population. Breast cancer does not occur in this population.

8.5 Advisory Committee Meeting

An Oncology Drug Advisory Committee (ODAC) Meeting was not held in regards to this application.

Dr. Joanne Mortimer, a standing member of the ODAC was consulted after conflict of interest clearance about the findings from the two pivotal trials. The FDA asked specifically about the utility of the PFS endpoint in Study 046 and the incidence of myelosuppression and peripheral neuropathy.

Dr. Mortimer expressed the view that, in general, combination therapy has not been shown to be beneficial compared to sequential monotherapy in breast cancer treatment. She noted that combination therapy with trastuzumab is a known exception to this finding. She expressed concern that the difference in PFS as demonstrated in Study 046 might not be a surrogate for an improvement in OS. She agreed that ixabepilone clearly demonstrated activity against breast cancer as demonstrated in Study 081. Dr. Mortimer further expressed concern about the degree of neurotoxicity and myelosuppression reported in the two pivotal trials. She agreed that further clinical studies as proposed in the Phase 4 commitments were warranted.

8.6 Literature Review

A formal literature review was not performed.

8.7 Postmarketing Risk Management Plan

A risk management plan was not requested and was not submitted.

8.8 Other Relevant Materials

The Division of Drug Marketing, Advertising and Communication have made suggestions for changes in proposed labeling and are reviewing the proposed proprietary name of Ixempra.

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9 OVERALL ASSESSMENT

9.1 Conclusions

The trials reviewed in this submission were designed to test the activity of an NME, ixabepilone, in women with metastatic or locally advanced breast cancer for whom the mainstays of therapy have failed and who have limited therapeutic options.

Ixabepilone was shown to be an active agent in combination with capecitabine in MBC patients in whom therapy with an anthracycline and a taxane have failed. In a multicenter, multinational, two-arm, randomized trial, 377 patients randomized to treatment with ixabepilone and capecitabine had a significantly longer PFS, the primary efficacy endpoint, than 375 patients randomized to treatment with capecitabine alone (5.85 months vs. 4.17 months, HR=0.75 [95% CI: 0.64, 0.88], p=0.0003). The ORR was 34.7% (95% CI: 29.9, 39.7) in patients treated with ixabepilone plus capecitabine as compared to 14.3% (95% CI: 10.9, 18.3) in capecitabine-treated patients. Response durations were 6.4 months (95% CI: 5.6, 7.1) in the combination treatment arm and 5.6 months (95% CI: 4.2, 7.5) in the capecitabine arm. Overall survival data are not available at the time of this review; an interim analysis did not result in a recommendation to stop the study.

Ixabepilone was also shown to be an active agent in women with metastatic or locally advanced breast cancer, when therapy with an anthracycline, a taxane and capecitabine has failed. In a multicenter, multinational, single-arm study of 126 women, the ORR by RECIST criteria as assessed by an independent radiological review, the primary efficacy endpoint, was 12%. All were partial responses, with median duration of 6.3 months. The ORR by RECIST criteria as assessed by investigators was 18%. A number of reasons account for the differences in the two response rates. The median PFS was 3.2 months and the median survival was 9.0. In the absence of a comparator arm, it is difficult to evaluate these PFS and OS estimates. Two smaller single-arm monotherapy studies supported the results of the main monotherapy trial. The ORR in 49 taxane-resistant MBC patients was 12.2% (95% CI: 4.7, 26.5%) and the response duration was 10.4 months (95% CI: 6.3, 22.0). The ORR in 65 patients whose tumor recurred after anthracycline treatment in the adjuvant setting was 41.5% (95% CI: 29.4, 54.4) and the response duration was 8.2 months (95% CI: 5.7, 10.2).

Ixabepilone therapy is accompanied by substantial toxicity. Patients treated with ixabepilone plus capecitabine had a higher death rate from drug toxicity than patients treated with capecitabine alone. All but one of the deaths can be attributed to complications of neutropenia. Approximately 25% of the patients with moderate or severe hepatic insufficiency treated with ixabepilone in combination with capecitabine died from febrile neutropenia. As a result, the ixabepilone label carries a Black Box warning stating that ixabepilone in combination with capecitabine must not be given to patients with hepatic impairment. The single drug-related death in the ixabepilone monotherapy trials was also related to complications of neutropenia.

Moderate and severe (CTC grades 3 and 4) neutropenia (in as many as 68% of patients) and leukopenia were the most common hematological toxicities in both the combination and the monotherapy trials. The major non-hematological toxicities were peripheral neuropathy (in about 65% of patients), fatigue/asthenia, gastrointestinal disturbances, hand-foot syndrome, myalgias/arthralgias, and alopecia. Cardiac toxicities in the combination trial, manifested as myocardial infarction, ischemia, ventricular dysfunction and arrhythmias, were rare, but require further investigation. Prevention of hypersensitivity reactions requires pre-medication and careful monitoring.

Peripheral neuropathy was the most common reason for discontinuing treatment in both the combination and the monotherapy studies. It was also the most common reason for dose reductions and dose delays. Most cases (about 88%) of neuropathy improved or resolved; the remainder remained unimproved.

In summary, ixabepilone is an active agent in MBC patients who are refractory to currently most effective drugs, but ixabepilone therapy is associated with a high incidence of drug-related adverse events including death. The decision to use it needs to take into account the potential benefit and the attendant discomforts and risks.

9.2 Recommendation on Regulatory Action

The clinical reviewers conclude that ixabepilone should be granted regular approval for the following indications:

Indication 1

In combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane-resistant and for whom further anthracycline therapy is contraindicated. Anthracycline resistance is defined as progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting. Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting.

Indication 2

As monotherapy for the treatment of metastatic or locally advanced breast cancer patients whose tumors are resistant or refractory to an anthracycline, a taxane, and capecitabine.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The Sponsor should provide periodic safety reporting and continue post-marketing surveillance activities.

9.3.2 Required Phase 4 Commitments

The following Phase 4 commitments are required:

By the Clinical Review Team:

- To submit the complete study report and datasets for the ongoing clinical study CA163048 “A Phase 3 Trial of Novel Etoposide BMS-247550 plus Capecitabine versus Capecitabine Alone in Patients with Advanced Breast Cancer Patients Previously Treated with An Anthracycline and a Taxane” with a primary endpoint of overall survival following the collection of data for a prespecified number of events (deaths), or earlier if recommended by the independent data monitoring committee.
- To submit the final study report and datasets for the study CA163046 “A Phase III Trial of Novel Etoposide BMS-247550 Plus Capecitabine Versus Capecitabine Alone in Patients With Advanced Breast Cancer Previously Treated With or Resistant To an Anthracycline and Who are Taxane Resistant” after collection of overall survival data following the prespecified number of deaths for a mature analysis.

The following commitments were requested by the Clinical Pharmacology review team:

- To submit the completed report for the rifampin drug-drug interaction evaluation and datasets for study CA163102.
- To perform an *in vitro* assessment to determine if ixabepilone is a P-glycoprotein substrate or inhibitor.
- To design, conduct and submit the completed study report and datasets for a study to assess the potential for ixabepilone to prolong the QT interval in patients.

9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

Changes were proposed to the following sections of the label based on clinical review:

Indications:

The proposed indications are:

Indication 1: Ixabepilone in combination with capecitabine is indicated for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane.

Indication 2: Ixabepilone as monotherapy is indicated for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine.

The proposed revised indications are:

Ixabepilone is indicated in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated. Anthracycline resistance is defined as progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting. Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting.

Ixabepilone is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine.

The changes were proposed to more accurately reflect the study populations in which the drug was evaluated.

Dosage and Administration

The Dose Adjustment table should be modified to reflect the practice in Study 046. Dose modifications for capecitabine, where they differ from the capecitabine label, should be included.

Warnings and Precautions

Adverse Reactions

Changes should be made to more accurately reflect the extent of adverse reactions when ixabepilone is used in combination with capecitabine.

Clinical Studies

For combination therapy, only data from the IRRC should be presented. Response data only should include ORR rate and duration of response. No investigator data should be included.

Clinical Review
Edvardas Kaminskas, Robert Lechleider
NDA 22-065
Ixempra, ixabepilone

9.5 Comments to Applicant

None.

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10 APPENDICES

10.1 Review of Individual Study Reports

Please see the main review.

10.2 Line-by-Line Labeling Review

In process.

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Robert J Lechleider
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MEDICAL OFFICER

Ramzi Dagher
10/3/2007 07:49:42 AM
MEDICAL OFFICER