European Medicines Agency
Evaluation of Medicines for Human Use

London, 23 April 2009
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WITHDRAWAL ASSESSMENT REPORT

FOR

Ixempra

International Nonproprietary Name: ixabepilone

Procedure No. EMEA/H/C/000930

CHMP Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" on the withdrawal of the application.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Bristol-Myers Squibb Pharma EEIG submitted on 5 October 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Ixempra, through the centralised procedure falling within the Article 3(1) and point 3of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 18-21 September 2006.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier:

Composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

The applicant applied for the following indication:

Treatment of locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy 1) in combination with capecitabine in patients failing prior therapy with a taxane and an anthracycline or for whom further anthracycline therapy is not indicated and 2) as monotherapy in patients failing prior therapy with taxanes, capecitabine and anthracyclines or for whom further anthracycline therapy is not indicated.

Scientific Advice
The applicant did not seek scientific advice at the CHMP.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Tomas P Salmonson** Co-Rapporteur: **Jens Ersbøll**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 5 October 2007.
- The procedure started on 25 October 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 January 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 January 2008. In accordance with Article 6(3) of Regulation (RC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 18-21 February 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 February 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 May 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 July 2008.

- During the CHMP meeting on 21-24 July, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- Preliminary written responses to list of outstanding issues from applicant in preparation of the SAG Oncology received on 21 August 2008.
- During a meeting of a SAG Oncology on 10 September 2008, experts were convened to address questions raised by the CHMP.
- Final written responses to list of outstanding issues from the applicant were received on 19 September 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 6 October 2008.
- During the CHMP meeting on 20-23 October 2008, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 17-20 November, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Breast cancer is a life-threatening disease affecting predominantly women, with an estimated incidence of 1.1 million new cases and some 400,000 related deaths reported worldwide annually[1]. In the European Union (EU), breast cancer is the most common malignancy in women and the leading cause of death in women between 35 and 55 years of age[2]. Deaths from breast cancer largely occur in the metastatic setting. Most patients with metastatic breast cancer (MBC) are initially diagnosed with early-stage disease but subsequently relapse following therapy.

Patients previously treated with anthracyclines and taxanes who are treated with capecitabine and progress currently have limited treatment options.

Ixabepilone is a semi-synthetic analogue of the natural product epothilone B and belongs to a class of antineoplastic agents called epothilones. The epothilones show some similarity to the taxanes, as they are tubulin-stabilising agents causing G2/M cell mitotic arrest and cell death.

Bristol Myers Squibb has applied for a marketing authorisation through the centralised procedure for ixabepilone in the treatment of locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy, either:

- in combination with capecitabine in patients failing prior therapy with a taxane and an anthracycline or for whom further anthracycline therapy is not indicated
or

- as monotherapy in patients failing prior therapy with taxanes, capecitabine and anthracyclines or for whom further anthracycline therapy is not indicated.

Following the scientific assessment, the CHMP had concerns about the benefit/risk in the monotherapy[p1] indication, particularly because the main efficacy data to support this indication were from a non-randomised Phase II trial. Subsequently, the applicant withdrew its claim in the monotherapy indication.

2.2 Quality aspects

[1] Kamangar F, Dores G, Anderson W. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006; 24:2137-2150.
[2] European Parliamentary Group on Breast Cancer Web site. Available at: http://www.epgbc.org. Accessed 05-Feb-2007.

Introduction

The medicinal product Ixempra contains the active substance ixabepilone as a single-use, sterile lyophilised powder for concentrate for solution. Two strengths 15 and 45 mg/vial have been developed. The medicinal product contains two vials; one for the powder and one for the constituting solvent. The lyophilised powder and the constituting solvent is packed separately in Type I flint moulded glass vials with grey butyl stoppers and aluminium flip-off seal. Both vials are co-packaged in a secondary container of paperboard folding carton. Prior to intravenous administration, the concentrate is further diluted with a suitable infusion fluid to a final ixabepilone concentration of 0.2 – 0.6 mg/ml.

Ixabepilone is a semi-synthetic analogue of the natural product epothilone B. The chemical name for ixabepilone is (1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(1*E*)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-17-oxa-4-azabicyclo[14.1.0] heptadecane-5,9-dione.

Ixabepilone appears as a white to off-white powder. It holds 7 chiral centres and is optically active. It is hydrophobic, soluble in methanol and ethanol, sparingly soluble in acetone, slightly soluble in acetonitrile and very slightly soluble in water. The solubility of ixabepilone is unaffected by pH changes (no ionizable groups).

The active ingredient has been fully characterised and the chemical structure of ixabepilone has been confirmed using analytical data by elemental analysis, IR absorption spectroscopy, UV absorption spectroscopy, 13C nuclear magnetic resonance spectroscopy, mass spectrometry and X-ray powder diffraction. All data are consistent with the proposed structure.

- Manufacture

Ixabepilone is manufactured from an intermediate (epothilone B) produced during fermentation of Sorangium cellulosum. After a purification step, epothilone B is chemically conversed into the active substance ixabepilone. The X-ray confirmed that the 7 chiral centres are formed during the fermentation and preserved during the subsequent chemical modifications. All manufacturing steps are adequately described. No component of animal origin is used in the manufacturing process and therefore, there is no TSE/BSE risk.

Appropriate specifications have been adopted for the starting materials, solvents, reagents and auxiliary materials

All relevant impurities and degradation products have been appropriately discussed and characterized. The levels of the impurities are supported by the results of toxicological studies and appropriate specifications have been set.

- Specification

Appropriate specifications for the active substance have been set. The specifications include appropriate tests for appearance, colour, identifications (HPLC and IR spectra), assay and impurity content (HPLC), residual solvents, heavy metals, water content and bacterial endotoxins. The analytical procedures have been satisfactorily described and validated in accordance with the ICH guidelines.

The impurity limits are acceptable and there is no concern in relation with safety or efficacy.

Batch analysis data for ixabepilone have been presented and all batches manufactured for commercial purposes have all parameters in compliance with the predefined active substance specification.

- Stability

The manufacturer has conducted the following stability studies on three batches during 36 months: a frozen study at -20°C, a long-term stability study at 5°C and an accelerated study at 25°C/60%RH. Furthermore, several stress studies have been performed, as well as an open-bag and photo stability study which have been performed on one batch. The parameters tested were appearance, colour, identification, assay, impurities, water and residual solvents. The data show that ixabepilone is very sensitive towards exposure of light, but remains stable when stored in the proposed containers and in a refrigerator (2 – 8ºC) and protected from light. A justified retest period has been defined and agreed.

- Pharmaceutical Development

Ixabepilone has low solubility and degrades rapidly in aqueous solution. A number of non-aqueous solvents and co-solvent systems can increase the solubility, but the stability was found to be insufficient for the formulation of a ready-to-use product. Therefore the applicant decided to develop a freeze-dried medicinal product with a special vehicle in a separate vial.

The pharmaceutical development of both the powder (the lyophilized active substance) and the solvent (a 50/50 (v/v) mixture of purified polyoxyethylated castor oil and anhydrous ethanol) was focussed on obtaining the greatest possible solubility and stability of ixabepilone in the reconstituted solution. The lyophilised powder contain only of the active substance without excipients. The reconstitution solvent is sterile and for single-use only, therefore no preservatives are added. Overfills are applied to ensure that the labelled potency can be withdrawn from the vials. Compatibility has been shown for the reconstituted solution with the four different solutions for infusion defined as suitable in the proposed SPC.

- Adventitious Agents

None of the excipients, nor the active substance, is considered to have a potential for transmission of BSE.

- Manufacture of the Product

The manufacturing process of the lyophilised powder involves dissolution of ixabepilone in a mixture of *tertiary*-butyl alcohol and water, aseptic filtration into vials and lyophilisation. The product can not be terminally sterilised due to the heat sensitivity of the active substance. The solvents are removed during lyophilisation and therefore, the final lyophilised powder only contains ixabepilone.

The manufacturing process of the constituting solvent involves mixing of polyoxyethylated castor oil and ethanol and aseptic filtration into vials. Terminal sterilisation can not be performed since it is a non-aqueous solvent and there are safety concerns regarding heating large quantities of ethanol.

Both manufacturing processes are satisfactorily described and validated, and the in-process controls applied are considered adequate.

The lyophilised powder and the constituting solvent is packed separately in Type I flint moulded glass vials with grey butyl stoppers and aluminium flip-off seal. The both vials are co-packaged in a secondary container of paperboard folding carton.

The manufacturing method is essentially the same for the two strengths of the powder and the same for the two pack sizes of the solvent.

All critical process parameters have been identified and controlled by appropriate in-process controls. The manufacturing process demonstrates to be reproducible and provides a finished product that complies with the in-process and finished product specifications.

- Product Specification

The proposed specifications for the powder vial include tests for appearance, identification, assay and impurity content, uniformity of dosage units, water content, constitution time, *t*-Butyl alcohol content, sterility and bacterial endotoxins. The specifications for the constituting solvent vial include tests for appearance, degree of coloration of the solution, clarity and degree of opalescence of solution, identification, ethanol content, pH, extractable volume, sterility and bacterial endotoxins. All tests included in the specification have been satisfactorily described and validated, according to the state of the art. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. Batch analysis results comply with the proposed specification and confirm consistency of the product.

- Stability of the Product

The medicinal product is a two vial system consisting of the lyophilised powder and the constituting solvent. Both components were placed on the stability studies initiated at the same time.

For the shelf-life specifications, the same parameters are tested as for the release specifications, with an additional test of pH and particulate matter. In all cases the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.

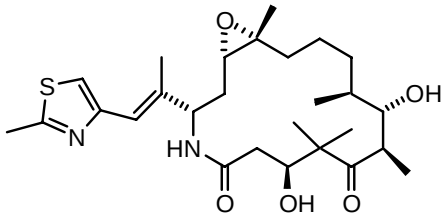
Discussion on chemical, pharmaceutical and biological aspects

The quality of Ixempra is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorisation. At the time of the Opinion no quality issues remained unresolved.

2.3 Non-clinical aspects

Introduction

The structure of the active substance, ixabepilone, is (1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[(*E*)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione.



Ixabepilone has the following characteristics:

Site of labelling (see structure)	Carbons 3, 5, 7, 11 and 15
Isomerism	7 stereogenic centres and a trans olefin
Molecular weight	506.7
Solubility in water	0.1 mg/ml
Solubility in other solvents	≥ 40 mg/ml in ethanol
Stability	sensitive to light and temperature

Pharmacology

- Primary pharmacodynamics and secondary pharmacodynamics

The pharmacological properties of ixabepilone *in vitro* and *in vivo* have been subject to extensive investigations, not only by the applicant but also by academic groups [REF]. *In vitro* ixabepilone anti-tumour activity was reflected as cytotoxicity with IC_{50} values ranging from 1.4 to 45 nM in human breast cancer cell lines (35 lines), IC_{50} values ranging from 4.7 to 42 nM in human colon tumour cell lines and IC_{50} values ranging from 2.3 to 19 nM in human lung carcinoma cell lines (23 lines).

Direct binding of ixabepilone to preformed microtubules was observed with a dissociation constant (K_D) of 220 nM. Ixabepilone, but not paclitaxel, suppressed dynamic instability of αβ-II microtubules as well as αβ-III microtubules. In non-clinical studies, ixabepilone demonstrated low susceptibility to multiple tumour resistance mechanisms including efflux transporters, such as MRP-1 and P-gp, which are involved in acquired and intrinsic drug resistance. The tubulin-binding mode of ixabepilone affects the microtubule dynamics of multiple β-tubulin isoforms, including βIII tubulin.

In vivo ixabepilone anti-tumour activity was shown against a broad spectrum of tumour types, including tumours that overexpress P-gp and are resistant to multiple agents including taxanes, anthracyclines and vinca alkaloids. In mouse human tumour xenograft models, ixabepilone appeared to show efficacy at doses higher than the lethal dose in a mouse neurotoxicity study.

- Safety pharmacology programme

The CNS, cardiovascular and respiratory system safety pharmacology of ixabepilone was evaluated *in vivo* as part of the pivotal single-dose, 5-day and 2-week toxicity studies (Table 1). Exposure to ixabepilone in these studies was approximately one tenth of the exposure in humans following a single administration of the therapeutic dose. Ixabepilone affected in a dose-dependent manner the peripheral nervous system causing slowing of sensory and motor maximal nerve conduction velocity and

reduction of sensory and motor compound response amplitudes. However, there was evidence of recovery at lower doses. Ixabepilone had no significant effect on cardiovascular parameters *in vitro* at concentrations of 30 µM (15.2 µg/ml).

Table 1 Safety pharmacology overview

Organ system	Species (#)	Dose/Duration	Major findings
Cardiovascular and respiratory	Rabbit, Purkinje fibers, *in vitro*	3, 10, 30 µM	No significant effect on action potential
Cardiovascular	Human embryonic kidney cells *in vitro*	10, 30 µM	Ixabepilone inhibited HERG/Ikr currents by 5.7 and 13.5%
Peripheral nervous system	Rat (Wistar) (6M+6F)	0, 0.1, 1, 2 mg/kg, i.v.	Dose-dependent slowing of sensory and motor maximal nerve conduction velocity and reduction of sensory and motor compound response amplitudes. At 2 mg/kg initial effects seen at 16/17 days in the distal digital nerve, at day 30/31 in the mixed caudal nerve, at 44/45 days in the tibial motor nerve. At 2 mg/kg effects at least as great as seen with 15 mg/kg of paclitaxel. Six weeks post dose effects still evident, at lower doses evidence of recovery

- Pharmacodynamic drug interactions

In studies using GEO human colon carcinoma, L2987 human lung carcinoma, KPL4 breast, A249 lung and Pat-26 pancreatic, synergism of ixabepilone with capecitabine and other anticancer agents were observed. The compounds were administered at their MTD.

Pharmacokinetics

Pharmacokinetics of ixabepilone was investigated in rat, mouse and dog, species used in toxicology studies and rabbit used in local tolerance. Reproduction toxicity studies were not included in the pharmacokinetic programme.

Absorption

The apparent volume of distribution of ixabepilone following i.v. administration was 6.3 l/kg in mice, 23 l/kg in rats and 25 l/kg in dogs and 21-26 l/kg in humans (based on a 70-kg person). These values are approximately 9- to 43–fold the volume of the total body water in the respective species indicating extra-vascular distribution of ixabepilone. The elimination of ixabepilone was at least biphasic with a relative fast initial phase and a very slow terminal phase in rats, dogs and humans. The terminal half-life ($t_{½}$) of ixabepilone was significantly longer in humans 35 hours (12 patients) and 52 hours (72 patients) as compared to the half-life in dogs (25 hours) in rats (10hours) and in mice (0.3-3).

The total plasma clearance of ixabepilone was in the order of the blood flow in the hepatic portal vein in mice (68 ml/min/kg), rats (56 ml/min/kg) and dogs (17 ml/min/kg). In humans, the total plasma clearance was approximately half the hepatic portal blood flow (616 ml/min).

The increase in exposure was generally more than proportional to the increase in dose. In the single-dose toxicity studies, the exposure measured as AUC and C_{max} was higher in female rats as compared to male rats (up to 14-fold). Conclusions in the dog were often hampered by a large inter-variability. No consistent gender differences in exposure were observed in the repeat-dose toxicity studies (in both the rat and dog). Daily but not weekly administrations of ixabepilone lead to an accumulation consisting with the half-life in the respective species, i.e., 99% is eliminated from the body during the first 3 days in the rat and 7 days in the dog. In humans, an accumulation following repeated administration would not be expected at the proposed dose regime (once every 3 weeks).

Distribution

Following a single i.v administration of ^{14}C ixabepilone in pigmented rats, tissue distribution was studied. Ixabepilone was widely distributed to tissues with no notable gender differences. Radioactivity reached maximum concentrations at 0.5 and 1 hour for all tissues except for the large intestine, eye lens, and thymus. The tissues with highest Cmax concentrations of radioactivity were lung, spleen, liver, kidney, gastrointestinal tract, the bone marrow and various glands

(thyroid/parathyroid, adrenal, pineal and pituitary). In general, the majority of the tissues with high affinity for ixabepilone had significantly slower tissue elimination as compared to plasma.

The concentrations of radioactivity for pigmented and non-pigmented skin were similar in males and females at all collection timepoints, suggesting that ixabepilone had no preferential binding to melanin-containing tissue. Low levels of radioactivity were observed in the cerebellum, spinal cord and testes, suggesting that the ixabepilone-derived radioactivity crossed the blood/brain and blood/testes barriers.

Tissue distribution studies in pregnant rats following intravenous doses showed wide distribution of drug-derived radioactivity in both foetal and maternal tissues. Highest levels were detected in liver, kidney, ovaries, lung and heart in maternal animals while foetal levels were highest in liver, kidney and carcass. Ixabepilone was distributed to the placenta (up to 13 times higher exposure than that in maternal plasma), amniotic fluid (up to 0.5 times) and foetuses (up to 0.6 times).

In the mouse and human, ixabepilone had no preferential binding to whole blood constituents indicating that plasma can be used for monitoring of ixabepilone. However, in the rat and dog, concentration-dependent distribution was observed leading to a distribution of ixabepilone into blood cells (blood/plasma ratio of 13 and 4, respectively) at low concentration (50 ng/ml). The blood/plasma ratios were between 0.75 and 1.10 in Long-Evans rats indicating no preferential binding of radioactivity to whole blood constituents. The concentration-time profile for radioactivity in rat blood and plasma was nearly identical.

The blood cell distribution was also investigated in the CD-1 mouse, SD rat and beagle dog. The blood to plasma ratio appeared to be dependent on concentration in all species but without any uniformity. The blood/plasma ratio of ixabepilone was 0.77 – 0.96 for the mouse, 1.3 – 1.47 for the rat and 0.75 – 0.76 for the dog and 0.65 – 0.85 for the human at concentrations in the range of 50 – 5000 ng/mL, respectively. Thus, the distribution of ixabepilone into blood cells appears to depend on the concentration of ixabepilone in the rat and dog, but not in mouse and humans.

Protein binding ranged from 44-82% in rats and 60-91% in dogs and 67-77% in humans. In mice, ixabepilone was highly bound to serum proteins (> 92%). The percent of free ixabepilone in serum increased as the concentration increased in rat, dog and human.

Metabolism

The biotransformation of ^{14}C-ixabepilone was investigated in rats, dogs and humans and in bile duct-cannulated (BDC) rats following i.v. administration. These biotransformation studies were conducted in male and female test animals or patients except the BDC rat study that was conducted only in male rats. In these studies, the metabolic profiles in plasma, urine, bile and faeces were determined by HPLC radio chromatography or HPLC-accelerator mass spectrometry (HPLC-AMS) (human samples only). There were 34 metabolites identified in rats, dogs and humans, all were oxidative metabolites. The metabolites were the product of mono-oxygenation, di-oxygenation and dehydrogenation of the parent molecule. No apparent species or sex difference in the metabolic profile of ixabepilone was detected. Ixabepilone was extensively metabolised in the rat, dog and human before excretion into bile/faeces and urine. Less than 6% of the dose administrated was recovered in urine and faeces (or bile) as unchanged ixabepilone. Unchanged ixabepilone was the major radioactive component in plasma in all species, accounting for 14-67% in the rat, 24-68% in the dog and 21-27% in humans (depending on the time of measuring).

Metabolism *in vitro* in microsomes from mouse, rat, dog, monkey and human was moderate to extensive. Twenty metabolites and one degradant was detected in all species. Metabolism appeared similar in human and animal preparations. The potential of the oxidative metabolites of ixabepilone to induce cytotoxicity seemed modest as determined in a clonogenic cell survival assay in the HCT116 human colon carcinoma cell line.

Results from studies in human hepatocytes and stability data were taken to indicate that chemical degradation rather than enzymatic degradation is the main clearance pathway *in vivo*.

The major enzymes involved in metabolism of ixabepilone were identified in studies using human cDNA expressed CYP enzymes. CYP3A4/5 was identified as the primary enzyme that metabolised

ixabepilone. Major metabolites identified were formed by CYP3A4, CYP3A5, CYP2D6 and CYP2C19 dependent pathways.

Elimination

The elimination of ixabepilone in humans is significantly longer ($t_{½}$ = 52 hours) than in the rat and dog ($t_{½}$ < 24 hours). The human samples consisted of urine (pooled 0-168 hours), faeces (pooled 0-168 hours) and plasma (pooled, from 8 patients separately for 4 and 8 hours) samples. Thus, the human faeces and urine samples should consist of approximately 90% of the administrated dose. This is partially confirmed by the excretion study (77% of the dose was recovered). It is reasonable to assume that plasma sampling at later time points in human plasma (> 8-hour post-dose) would have yielded higher amounts of each metabolite. Thus, some of the unidentified metabolites may be present in significant amount in human plasma at times later than 8-hour post-dose. Furthermore, extensive formation of these metabolites cannot be expected in the pivotal toxicity studies due to non-existing safety margins. To conclude, ixabepilone is extensively metabolised in all animal species with no major differences in either the *in vitro* or *in vivo* metabolic profile. Therefore, the investigation of the metabolic profile of ixabepilone is deemed adequate.

Excretion

The routes of excretion of radioactive ixabepilone have been determined in humans, dogs and two strains of rats. The majority of the administrated dose (> 78%) was recovered in faeces following i.v. administration indicating that the major route of excretion is via the bile. Urine excretion was significantly higher in humans (25%) as compared to the animal species (< 15%). In rats and dogs, the majority of the dose (80 and 55%, respectively) was excreted within the first 48 hours. In lactating rats, ixabepilone-derived radioactivity was excreted into milk with milk/plasma ratios ranged from 0.3 to 2.6.

Pharmacokinetic interactions

CYP3A4 and CYP3A5 are the major cytochrome isoforms responsible for the metabolism of ixabepilone. Co-administration of ixabepilone and drugs that inhibit or induce CYP3A4 may increase or decrease ixabepilone at clinically relevant concentrations. Ixabepilone is also metabolised by CYP2D6 and CYP2C19. However, no significantly pharmacokinetics interactions are expected at clinically relevant concentrations for these isoforms.

Ixabepilone inhibited human CYP3A4 with an IC_{50} value of 7.3 µM in an *in vitro* assay, but had no effect on the other CYP enzymes (IC_{50} > 200 µM). Using primary cultures of human hepatocytes it was found that ixabepilone did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1, but the compound inhibited CYP3A4/5 with an IC_{50} values of 15 µM. Therefore, it is not likely that ixabepilone will inhibit the major CYP isoforms responsible for the metabolism of other drugs at clinically relevant concentrations.

The applicant has not investigated the potential of ixabepilone to inhibit other enzymes involved in the metabolism of xenobiotics such as UGTs.

Toxicology

The toxicity of ixabepilone was characterised in extensive studies, primarily in rats and dogs, that also included investigations on impurities as well as mechanistic studies on neurotoxicity.

- Single dose toxicity

After single i.v. dose in rats a maximum non-lethal dose of ixabepilone of 15 mg/kg (90 mg/m2) was reported and an STD10 (severely toxic to 10% of rats) of 12.3 mg/kg was estimated. Toxicity was generally more severe in females than in males consistent with higher systemic exposure in females at equivalent doses. Single oral dose in rats from 20 to 100 mg/kg (AUC values of < x1 to up to x20 the expected clinical value) resulted in dose-dependent mortality.

After single i.v. administration in dogs, the observed maximum non-lethal dose was 0.5 mg/kg (10 mg/m^2). Single i.v. dose of 5 mg/kg in dog resulted in deaths. Given as single oral dose, ixabepilone was generally well tolerated at 0.5 mg/kg (10 mg/m^2).

Following administration of ixabepilone, toxicity was recorded in various organ: peripheral neuropathy, bone-marrow/lymphoid depletion, gastrointestinal lesions and testicular degeneration and

single-cell necrosis in cornea, tongue, skin, liver, spleen, adrenal gland and prostate. Mitotic activity in the uterus was increased. Axonal degeneration of peripheral nerves was a major toxicity and an expected microtubule stabilising agent-related effect. Severe toxicity and mortality occurred at 2.5 mg/kg (50 mg/m^2). Drug-related findings were reversible in dogs which included haematopoietic (bone marrow) and gastrointestinal toxicity. In addition, histamine like reactions were noted in dog, likely related to the vehicle (Cremophor).

Single i.v. and oral doses in rats and dogs were, thus, coupled to a range of toxic effects manifested as clinical signs (e.g., swelling muzzle, tongue, ataxia, chromodacryorrhea), serum chemistry changes (e.g., decreases in leukocytes, platelets, haemoglobin, reticulocytes, protein and increases in fibrinogen and urea nitrogen) and histopathological alterations in a multitude of organs and tissues. Overall severe toxicity, including deaths was evident at doses corresponding to systemic exposure levels lower or similar to clinical use.

- Repeat dose toxicity (with toxicokinetics)

Toxicity of repeated doses of ixabepilone was studied in rats and dogs using a consecutive dosing schedule of up to 2 weeks as well as intermittent dosing regimens of up to 6-month duration in rats and 9 months in dogs. In general systemic exposure multiples at the high doses were in the expected clinical range while based on C_{max}, multiples of 5 in dog and 25 in rat were achieved. In the 5-day dog study, plasma concentrations of ixabepilone were below quantifiable levels at 0.015 mg/kg (NOAEL), but systemic exposure was verified at a dose of 0.15 mg/kg. In dogs, as in rats, accumulation in exposure (1.8- to 4-fold) occurred with daily administration of ixabepilone for 5 or 14 days, but no accumulation was apparent using intermittent dosing regimens in the 1- and 9-month studies. No clear differences in exposure were noted between male and female dogs.

In rats, decreases in body weight and food intake were noted in most studies from doses of 0.3 mg/kg and higher. Deaths occurred at doses from 1 mg/kg and were coupled to gastrointestinal and haematopoietic lymphoid organ toxicity. Stool changes, swollen muzzle, alopecia, chromorhinorrhea and chromodacryorrhea were evident at doses from 0.12 mg/kg. Impaired rightning reflex and limb function was recorded from a dose of 3 mg/kg in the 6-month study. Haematological examinations showed decreases in haemoglobin, haematocrit from 1 mg/kg in the 1-month study and from 3 mg/kg in the 6 month study. Clinical chemistry changes included decreases in leukocytes, neutrophils, lymphocytes, reticulocytes and platelets at doses from 0.25 mg/kg. Protein and albumin were decreased in most studies while APTT, liver enzymes, fibrinogen and urea nitrogen were increased. Histopathological changes were seen in many organs and tissues:

- Single cell necrosis was recorded in seminal vesicle epithelium (from 0.05 mg/kg), bile duct (from 0.12 mg/kg), pancreas (from 0.12 mg/kg), mammary gland epithelium (from 0.12 mg/kg), liver (from 0.3 mg/kg), epididymidal duct (from 0.3 mg/kg, ocular accessory gland (from 0.3 mg/kg) and Brunner's gland epithelium (from 0.3 mg/kg)
- Lymphoid depletion was noted in lymph nodes (from 0.12 mg/kg) and spleen and thymus (from 0.3 mg/kg).
- Other changes included atrophy of epididimydes, seminal vesicles, thymus, testes and prostate, axonal degeneration of sciatic nerve (from 1 mg/kg) and loss of bony trabeculae on the diaphyseal surface of the growth plate in femur.

A NOEL of 0.05 mg/kg was identified in the 2-week intravenous study and corresponded to a cumulative dose of 0.7 mg/kg. Intermittent dosing of 2 mg/kg for 1 month resulting in a cumulative dose of 10 mg/kg was tolerated without mortality. Toxicities included haematopoietic, lymphoid, gastrointestinal and hepatic toxicities, peripheral neuropathy and delayed testicular toxicity. Intermittent dosing up to 6 months caused immunosuppression and or gastrointestinal toxicity resulting also in inflammation/septicaemia. The compound in solution appeared to have remarkable irritative, corrosive, ultimately painful characteristics leading to erosions, ulcers, self-mutilation of tail due to pain and sores, wounds were exacerbated by infections, inflammations likely due to immunosuppression.

In dog studies, histamine like reactions (swollen head, muzzle, forelimbs, erythema whole body, face, eyes, tremors and tonic convulsions) were noted in all studies, likely related to the Cremophor containing vehicle used. In many studies decreases in body weight and food intake and stool changes

were evident. Clinical chemistry and haematology analysis showed decreases in leukocytes, neutrophils, platelets, lymphocytes, reticulocytes, haemoglobin, haematocrit and increases in fibrinogen, bilirubin, liver enzymes and APTT from doses of 0.15 mg/kg (2-week study) and 0.75 mg/kg (1-month intermittent dosing study) and 0.5 mg/kg (9 month intermittent dosing study). Histopathological alterations were seen in many organs and tissues:

- Single cell necrosis in gallbladder mucosa, kidney tubule, liver, tests, skin, stomach mucosa, mammary gland epithelium, pancreas, and epididymal epithelium.
- Lymphoid depletion in thymus, spleen and lymph nodes was reported.
- At doses of 0.75 mg/kg in the 1-month study acute inflammation and abscesses in liver was recorded.
- Axonal/myelin degeneration of nerves at injection site was reported.

Overall, much lower doses than in rats were tolerated by dogs and major toxicities included, haematopoietic/lymphoid, gastrointestinal, renal, hepatic and testicular toxicity. Changes seemed to a large extent consistent with effects coupled to microtubule stabilising agents. An apparent higher renal excretion in human could indicate that the potential for renal toxicity is underestimated in non-clinical studies.

- Genotoxicity

Ixabepilone was tested for genotoxic potential in a gene mutation assay in bacteria, chromosomal aberrations *in vitro* and *in vivo* in rat.

Ixabepilone was not mutagenic in the Ames reverse bacterial mutagenicity assay as expected, since microtubules are not involved in bacterial cell division.

In the *in- vitro* chromosomal aberration assay, ixabepilone increased the incidence of polyploid lymphocytes in the absence of S-9 metabolic activity. A trend to increase the frequency of polyploidy was observed at low concentrations (>7 µg/mL). The response was bell-shaped as higher concentrations probably arrested cell division. However, no clastogenic effects were observed at concentrations up to 500 µg/mL and 2000 µg/mL in the absence and presence of S-9 metabolic activation, respectively.

In a chromosomal aberration *in-vivo* assay ixabepilone induced micro-nucleated erythrocytes after 3 daily dosages of 0.625 mg/kg/day i.v. and 1.25 mg/kg/day i.v.

In similarity with other microtubule stabilising anticancer agents ixabepilone was genotoxic *in vivo* in the rat micronucleus test, at systemic exposure levels lower than expected clinical.

- Carcinogenicity

No carcinogenicity studies have been conducted and this was justified by the applicant in view of the therapeutic indication.

- Reproduction Toxicity

Reproduction toxicity of ixabepilone was investigated using rats and rabbits. No effects on oestrus cycling, mating or fertility were evident in a rat study.

In rats, doses of 0.2 mg/kg during gestation Days 6 to 15 were coupled to increases in resorptions, increased pre-implantation loss and reduced number of corpora lutea. At maternally toxic doses, resorptions increased, litter sizes became smaller and foetal bodyweights decreased. Complete resorptions occurred at 0.3 mg/kg. Foetuses exhibited reduced ossification of caudal vertebrae, sternebrae and metacarpals.

In pregnant rabbits, no foetuses survived for evaluation at the high dose of 0.3 mg/kg and deaths occurred in maternal animals from doses of 0.15 mg/kg. Decreases in foetal weights were also evident at this dose and abortions were recorded. There is no metabolism data or general pharmacokinetic data available in rabbit and toxicokinetics showed wide inter-animal variability.

- Toxicokinetic data

See reproduction toxicity.

- Local tolerance

Local tolerance studies with the clinical formulation in rabbit showed acanthosis, single cell necrosis of epidermis, oedema and subacute inflammation at intravenous injection sites. Intra-arterial and paravenous administration also caused hyperkeratosis and mitotic activity in the epidermis increased after intra-arterial doses. At higher concentrations swelling and drooping of ear was evident and necrosis hyperkeratosis and increased mitotic activity was present.

- Other toxicity studies

Specific studies on impurities did not indicate any particularly toxic concerns with regards to impurities except an increased toxicity of a batch subsequently further processed to remove the majority of impurities and resulting in a batch to be used clinically. Systemic exposure to a diol degradation product of ixabepilone measured in the 5-day and 2-week studies in rat and dog was substantially lower than ixabepilone exposures.

Ixabepilone exhibited weak antigenicity in the active systemic anaphylaxis test following intravenous or subcutaneous sensitisation in guinea pigs. Ixabepilone-specific cytophilic antibodies were not detected in the passive cutaneous anaphylaxis test. The skin sensitising potential as assessed in a local lymph node assay in the mouse indicated a lack of sensitising potential...

Neurotoxicity was identified as a major clinical toxicity of ixabepilone and several specific studies were conducted to assess mechanism and potential for neurotoxicity. Data from these studies indicated a less severe sciatic nerve injury after an intravenous infusion compared with an intravenous bolus dose. Axonal degeneration was characterised by Wallerian-like degeneration, axonal swelling, secondary myelin fragmentation and demyelination. In neurotoxicity studies, no effects of a modulator/surrogate for glutathione, acetyl-L-carnitine or an inhibitor of p38 mitogen activated protein kinase were evident but a neutrotrophin enhancer (MCC-257) had a minimal protective effect but follow–up studies did not confirm the effect.

The UV spectrum of a solution of ixabepilone in acetonitrile was scanned from 190 to 400 nm. No absorption was observed at wavelengths higher than 290 nm. The UV spectrum of ixabepilone has not been obtained from 400-700 nm.

Ecotoxicity/environmental risk assessment

The environmental risk assessment submitted according to relevant guidelines was concluded in Phase I. The applicant calculated a $PEC_{surface\ water}$ value for ixabepilone which amounted to 0.00048 µg/L. Therefore, a phase II evaluation was not performed and ixabepilone was considered to represent a low risk to the environment. The $PEC_{surface\ water}$ calculation was based notably on a refined penetration factor.

Ixabepilone should not be disposed as normal waste.

Discussion on the non-clinical aspects

Non-clinical studies with ixabepilone have provided a sufficient characterisation of the pharmacology of this compound in in vitro and in vivo. Safety pharmacology studies showed that ixabepilone affected in a dose-dependent manner the peripheral nervous system and there was evidence of recovery at lower doses.

Pharmacokinetics of ixabepilone was investigated in rat, mouse and dog species and rabbit was used for local tolerance. Based on the results of distribution studies, an accumulation, however limited, following repeated administration in humans can be expected for the uterus and the cerebrum due to the long half-life in these tissues.

Chemical degradation might be more important in humans than indicated by the mass-balance data, but this has not been fully clarified. CYP3A4 apparently account for less than 50% of metabolism, but there might be other minor enzymatic pathways too. CYP3A4 and CYP3A5 are the major cytochrome iso-forms responsible for the metabolism of ixabepilone. Co-administration of ixabepilone and drugs that inhibit or induce CYP3A4 may increase or decrease ixabepilone at clinically relevant concentrations. Ixabepilone is also metabolised by CYP2D6 and CYP2C19.

The toxicity of ixabepilone following repeated dosing (once every three weeks) was severe leading to death in rats and dogs at exposure levels near and just below the exposure level in humans following administration of a single therapeutic dose of ixabepilone. In general, no NOAEL could be established. The toxicological findings were dose-related in incidence and severity.

In repeat dose toxicity studies in dog studies, the incidence and severity of the axonal/myelin degeneration and the testicular degeneration/atrophy was similar to that noted at the terminal necropsy indicating no resolution of these lesions in neither the rat nor the dog. These effects may not be reversible and are therefore safety concerns for patients treated with ixabepilone. However, the testicular degeneration is not per se a concern for the proposed indication.

In similarity with other microtubule stabilizing anticancer agents ixabepilone was genotoxic *in vivo* in the rat micronucleus test, at systemic exposure levels lower than expected clinical. There were no carcinogenicity studies that were conducted and this was acceptable.

Reproduction toxicity was evident in rat at doses of 0.2 mg/kg during gestation days 6 to 15 and coupled with increases in resorptions, increased preimplantation loss and reduced number of corpora lutea. In the study in pregnant rabbits no foetuses survived for evaluation at the high dose of 0.3 mg/kg and deaths occurred in maternal animals from doses of 0.15 mg/kg.

Neurotoxicity was identified as a major clinical toxicity of ixabepilone. Studies investigating neurotoxicity indicated a less severe sciatic nerve injury after an intravenous infusion compared with an intravenous bolus dose. Axonal degeneration was characterised by Wallerian-like degeneration, axonal swelling, secondary myelin fragmentation and demyelination.

Local tolerance studies with the clinical formulation in rabbit showed acanthosis, single cell necrosis of epidermis, oedema and subacute inflammation at intravenous injection sites.

The lack of phototoxicity is acceptable due to limited distribution of ixabepilone to the skin and the eyes (<10% of the administrated dose).

2.4 Clinical aspects

Introduction

Bristol-Myers Squibb Pharma EEIG applied through the centralised procedure for the marketing authorisation of a new medicinal product ixabepilone, a compound which belongs to the epothilones class of microtubule stabilizing agents. The marketing authorisation application is based on the:

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. In addition the applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The pharmacokinetics of ixabepilone was studied exclusively in the target population. A total of 384 patients with advanced cancer were treated in Phase I clinical pharmacology studies and all were evaluable for pharmacokinetic analyses. The principal pharmacokinetic parameters at the suggested clinical dosing regimen of 40 mg/m^2 administered as a 3-hour infusion are displayed in Table 2.

Table 2 Main pharmacokinetic parameters

	C_{max} (ng/ml)	$T_{1/2}$ (h)	AUC_{∞} ng.h/ml	CL/T (l/h)	V_{ss} (l)
N	73	72	72	72	72
Mean	285.6	52.2	2363.3	37.5	1844.1
SD	158.96	31.82	1127.01	16.31	1143.18
Geometric mean	251.9	46.2	2145.5	34.1	1542.5
CV	55.7	61.0	47.7	43.5	62.0

Analytical methods

Plasma and urine samples were assayed for ixabepilone and its chemical degradation products by validated liquid chromatography tandem mass spectrometry methods (LC/MS/MS).

Pharmacokinetic data analysis

Standard non-compartmental analysis has been used for pharmacokinetic analysis.

Statistical analysis

Standard descriptive and inferential statistics have been applied.

- Absorption

Not applicable

- Distribution

On the basis of *in vitro* studies at clinically relevant concentrations (50, 500 and 5,000 ng/ml), binding of ixabepilone to human serum proteins ranged from 67.1 to 76.6%.The protein binding of ixabepilone was not concentration dependent from 50 ng/ml to 5,000 ng/ml. At the same in vitro concentrations, ixabepilone distributes freely in human red blood cells; the blood to plasma concentration ratios in human blood ranged from 0.65 to 0.85. The mean volume of distribution at steady-state (V_{ss}) of ixabepilone in clinical studies at the proposed therapeutic dose of 40 mg/m^2 administered as a 3-hour infusion was 1,844 l. Compared with the human total body water (42 l), the V_{ss} in humans is approximately 44-fold greater than total body water, indicating that ixabepilone undergoes extensive extravascular distribution in humans.

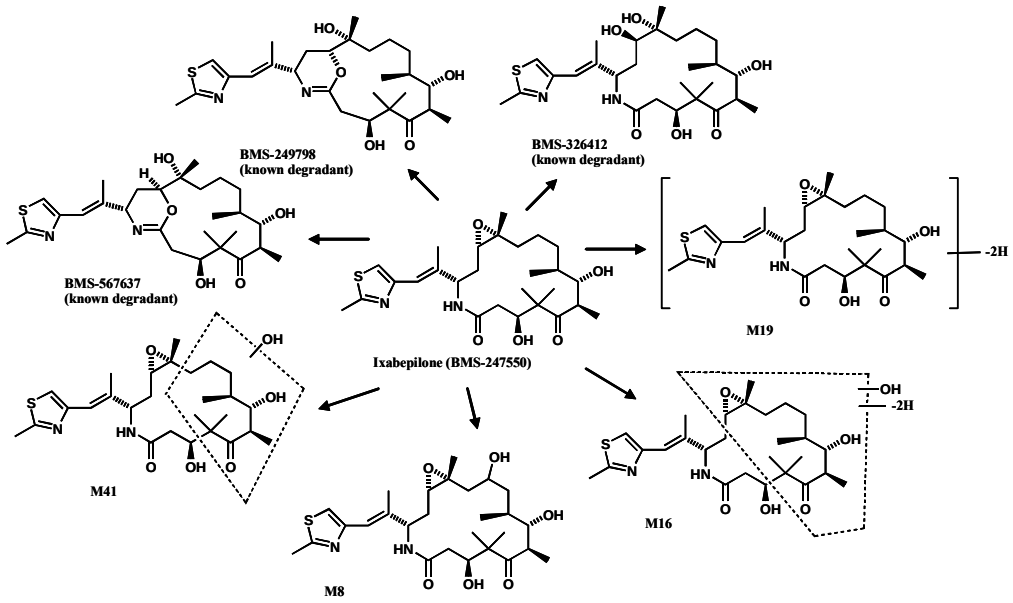
- Elimination

Following a single 70-mg i.v. dose of [^{14}C] ixabepilone to patients with advanced cancer, approximately 65 and 21% of the total dose of radioactivity was recovered in the faeces and urine, respectively. Ixabepilone accounted for approximately 1.6 and 5.5% of the administered dose in the faeces and urine, respectively. The $T_{1/2}$ of ixabepilone after 3-hour i.v. infusion of 40 mg/m^2 in patients with advanced cancer was approximately 52 hours.

Metabolite isolation and identification investigations were performed on human plasma, urine and faecal samples. The major radioactive component in plasma was unchanged ixabepilone which accounted for 26.8 and 20.6% of the total plasma radioactivity, respectively, in plasma collected at 4 and 8 hours, respectively. The known degradants of ixabepilone (BMS-249798 and BMS-326412) were also present in the plasma extracts in smaller amounts (2.7 and 8.6%). A prominent HPLC-radioactive peak was detected in the 8-hour plasma sample and it could not be determined whether this peak was an artefact or an oxygenated metabolite (its retention time was similar to the M+14 metabolite, M16). This peak accounted for about 13% of the total radioactivity of the 8-hour plasma sample and corresponded to < 5% of the maximum total plasma radioactivity at 3 hours. Therefore, even if the 8-hour plasma peak was a systemic metabolite, it was still a relatively minor component overall. There were numerous other minor radioactive components in the plasma extracts, each corresponding to < 5.4% of plasma radioactivity. The major radioactive component in urine was unchanged ixabepilone which accounted for 22.5% of radioactivity in the pooled urine (5.6% of the administered dose). The known degradants (BMS-249798 and BMS-326412) corresponded to 8.1 and < 5.4% of the total radioactivity in the pooled urine, respectively (2.0 and < 1.4% of the dose, respectively). Numerous other minor radioactive components were present, each corresponding to < 8.3% of the total radioactivity in the urine pool (< 2.1% of the administered dose). There were at least 29 drug related compounds, including known degradants of ixabepilone (BMS-249798, BMS-326412 and BMS-567637), in the faecal extract, each accounting for < 10.3% of the faecal radioactivity. Each of the drug related compounds in urine and faeces accounted for only a small amount of the administered dose, < 2.1 and < 5.4% of the dose, respectively. The identified metabolites in human plasma, urine or faeces were oxidised metabolites including M41 (M+16 metabolite), M8 (M+16 metabolite), M16 (M+14 metabolite) and M19 (M-2 metabolite).

The proposed biotransformation of ixabepilone in humans is presented in Figure 1.

Figure 1 Proposed biotransformation of ixabepilone in humans



Incubations of unlabeled ixabepilone were conducted at concentrations of 5 and 50 μM with human cDNA expressed CYP enzymes (CYP1A2, CYP2B6, CYP2D6, CYP2E1, CYP3A4, CYP3A5, CYP2C8, CYP2C9 and CYP2C19). Ixabepilone was metabolised by supersomes of CYP3A4 and CYP3A5 forming several M+16 metabolites (M2, M3, M8, M9, M10, M11) and two M-2 metabolites (M19 and M20). CYP3A4 and CYP3A5 also formed several M+14 metabolites (M4, M5, M14, M15, M16 and M17). Incubation of ixabepilone in human liver microsomes in the presence of inhibitors of specific CYP enzymes confirmed that CYP3A4 and CYP3A5 were the major CYP enzymes involved in the in vitro oxidative metabolism of ixabepilone. The findings from these studies indicate that ixabepilone is likely a CYP3A4 and CYP3A5 substrate *in vivo*.

The pharmacokinetics of the oxazine chemical degradant of ixabepilone, BMS-249798, was assessed in study CA163001. The exposure of patients with advanced cancer to BMS-249798 was less than 4% that of ixabepilone over the dose range of 7.4 to 50 mg/m^2. BMS-249798 is 174-fold less cytotoxic than ixabepilone against a human tumour cell line panel. The pharmacokinetic of the diol chemical degradant of ixabepilone, BMS-326412, was assessed in study CA163001. The exposure of patients with advanced cancer to BMS-326412 was less than 0.5% that of ixabepilone over the dose range of 7.4 to 50 mg/m^2 (BMS-326412 to ixabepilone ratio of AUC geometric means uncorrected for molecular weight difference). BMS-326412 is > 312-fold less cytotoxic than ixabepilone against a human tumour cell line panel.

- Dose proportionality and time dependencies

Dose proportionality

The dose proportionality and pharmacokinetic linearity for ixabepilone administration as a 1-hour infusion is described by data in studies CA163001 and CA163002. Across the 2 studies, dose levels of 15, 20, 25, 30, 50 and 57 mg/m^2 had pharmacokinetic parameters for at least 3 patients. For these dose levels increasing in a ratio of 1 : 1.3 : 1.7 : 2 : 3.3 : 3.8, the geometric mean AUC_∞ increased in the ratio of 1 : 1.9 : 1.8 : 1.8 : 3.3 : 4.6. Ixabepilone pharmacokinetics is linear based on this dose-related increase in AUC_∞. There is no specific evaluation of C_{max} or any specific statistical inference test to support dose-proportionality.

Time dependency

Summary data from study 163001 did not reveal changes in pharmacokinetics following 2 cycles of infusion with ixabepilone (Table 3).

Table 3 Summary of pharmacokinetic parameters

Appendix 1: Summary of Pharmacokinetic Parameters in Clinical Pharmacology Studies									
Study Protocol (Country)	Product Batch Number	Study Objective Study Design	Treated Patients (Males/ Females) Age (y): Median (min, max)	Treatment Dose [mg/m^2] (N=)	Pharmacokinetic Parameters				
					Geometric Mean (%CV)		Arithmetic Mean (SD)		
					Cmax (ng/mL)	AUC(INF) (ng•h/mL)	T-HALF (h)	CLT (L/h)	Vss (L)
CA163001 (US)	C99249 C99303 C00012 C00159 C00198 C01181 C00355	Maximum tolerated dose, maximum administered dose, dose limiting toxicity, and recommended Phase 2 dose of ixabepilone Plasma pharmacokinetics Safety and tolerability of ixabepilone Open-label, dose escalation	61 (32/29) 58 (18, 81)	1-hour infusion Cycle 1					
				7.4 (3)	182 (49)	553 (9)[a]	37 (19)[a]	21.6 (4.7)	830 (174)
				15 (3)	164 (63)	786 (42)	48 (9)	34.6 (10.5)	1969 (957)
				30 (3)	403 (80)	1383 (22)	37 (7)	36.1 (10.7)	1243 (456)
				50 (20)	674 (43)	2485 (42)	29(8)	41.5 (16.8)	1222 (459)
				57 (3)	1150 (18)	3481 (25)	32 (6)	34.8 (7.4)	810 (115)
				65 (2)	761 (45)	1861 (38)	25 (5)	75 (37.6)	1768 (1032)
				Cycle 2					
				7.4 (1)	178 (m)	d	d	d	d
				15 (3)	291 (47)	1113 (57)	34 (3)	25.2 (10)	908 (312)
				30 (3)	471 (39)	1516 (35)	43 (22)	32.5 (6.9)	1413 (655)
				40 (1)	349 (m)	1969 (m)	30 (m)	37.1 (m)	1365 (m)
				50 (18)	657 (47)	2145 (55)[c]	36 (14)[c]	50.9 (24.9)	1924 (1455)
				57 (1)	1132 (m)	4040 (m)	19 (m)	29.5 (m)	669 (m)
				3-hour infusion Cycle 1					
				40(14)	247 (72)	2406 (56)[b]	35 (12)[b]	35.3 (15.2)	1476 (836)
				50 (8)	281 (46)	2385 (47)	35 (11)	46 (22.8)	1511 (572)

Intra- and inter-individual variability

From the population pharmacokinetic study (see below), intra-individual variability was about 16% (CV) (for clearance) and interindividual variability was 49% (CV) for clearance of ixabepilone.

- Special populations

Population pharmacokinetics

The population pharmacokinetic analysis was performed on data collected in 2 Phase I monotherapy studies (studies CA163001 and CA163002) and the 10 disease specific Phase II studies. The final database consisted of 674 patients of whom 128 were from the Phase I studies and 546 were from the Phase II studies. The population pharmacokinetic analysis used data from approximately 75% of treated patients in the targeted Phase II studies.

The best final model was a 2-compartment model with zero order infusion and linear clearance. The final model estimated the population average CL of ixabepilone in patients with cancer to be 36.8 l/h with an inter-individual variability of 48.8%, consistent with previous non-compartmental analyses. The inter-occasion variability of ixabepilone was 16% in the 2 studies during which pharmacokinetics was evaluated in more than one cycle, (studies CA163001 and CA163080). Based on the analysis, chemotherapy-naive patients receiving ixabepilone for neoadjuvant treatment of breast cancer have a 25% higher clearance of ixabepilone than patients receiving ixabepilone for treatment of advanced metastatic cancer. No other covariates including body weight, body surface area, age, serum creatinine, AST, ALT, bilirubin, calculated creatinine clearance, gender or race were significant or contributed to inter-individual variability. However, since the levels of serum creatinine and bilirubin were restricted to < 1.5x ULN and the levels of AST and ALT were restricted to < 5x ULN in these studies, this evaluation of effect of AST, ALT, bilirubin, serum creatinine and creatinine clearance is limited to the normal range and mild abnormalities.

Impaired renal function

No specific clinical studies were conducted with ixabepilone in patients with impaired renal function. Based on the population pharmacokinetic analysis, creatinine clearance as a continuous covariate did not contribute to the inter-individual variability of pharmacokinetics. Since the levels of serum creatinine were restricted to < 1.5x ULN in these studies, this evaluation of creatinine clearance is

limited to the normal range and mild abnormalities. With only 5.5% of the administered dose is excreted as ixabepilone in the urine of patients with advanced cancer, the impact of renal impairment on ixabepilone elimination is expected to be minimal.

Impaired hepatic function

Study S0355 was an open-label, parallel group design evaluating the effect of varying levels of hepatic dysfunction on the tolerable dose and pharmacokinetics of ixabepilone in patients with advanced cancer. The primary objective was to define levels of hepatic dysfunction at which dose modifications of ixabepilone would be required based on dose-limiting toxicities (DLT) during Cycle 1 and a secondary objective was to characterise the effects of hepatic dysfunction on the plasma pharmacokinetics of ixabepilone. Dose adjustments (Table 4) for patients with hepatic impairment are based on the results from the hepatic dysfunction study S0355.

Table 4 Dose adjustments for ixabepilone as monotherapy in patients with hepatic impairment

Degree of hepatic impairment Transaminase levels		Bilirubin levels	Recommended dose[a] Ixabepilone
AST and ALT ≤ 2.5x ULN	and	≤ 1x ULN	40 mg/m^2
AST or ALT > 2.5x ULN - ≤ 10x ULN[b]	and	≤ 1x ULN	32 mg/m^2
AST and ALT ≤ 10x ULN	and	> 1x ULN - ≤ 1.5x ULN	32 mg/m^2
AST and ALT ≤ 10x ULN	and	> 1.5x ULN - ≤ 3x ULN	20 mg/m^2

[a] Dosage recommendations are for first course of therapy; further decreases in subsequent courses should be based on individual tolerance

[b] Both AST and ALT must be ≤ 10x ULN

- Pharmacokinetic interaction studies

In vitro

In human liver microsomes, ixabepilone did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 at concentrations up to 30 µM. Ixabepilone showed direct inhibition of CYP3A4/5 (as measured by midazolam 1'-hydroxylation activity) with an IC_{50} value of 15 µM. However, ixabepilone did not significantly inhibit testosterone 6β-hydroxylation, another marker of CYP3A4/5 activity. There was some evidence of time-dependent inhibition, as the inhibition of midazolam as well as testosterone increased upon pre-incubation. However, in the pre-incubation experiments there was no positive control. CYP3A4/5 inhibition by ixabepilone had a K_i of 7.5 µM and k_{inact} = 0.043 min^{-1} with midazolam as a probe substrate.

The inhibitory activity of ixabepilone on human cytochrome P450 was also evaluated using cDNA-derived P450 enzymes in microsomes prepared from baculovirus-infected insect cells. Ixabepilone did not inhibit the activity of CYP1A2, 2C9, 2C19 or 2D6 up to concentrations of 200 µM, while CYP3A4 was inhibited with IC50 of 7.3 µM.

In cultured human hepatocytes, ixabepilone at concentrations up to 20 µM did not cause statistically significant increases of the enzyme activity or the mRNA-expression of CYP1A2, CYP2B6, CYP2C9 or CYP3A4. The geometric mean C_{max} of 268 ng/ml (0.5 µM) for the 40-mg/m^2 infusion of ixabepilone over 3 hours in 77 patients with metastatic breast cancer was 1/40 of that concentration. Therefore, ixabepilone is not likely to be an inducer of these enzymes or cause drug-drug interactions via CYP induction with co-administered drugs that are metabolised by these CYP enzymes *in vivo*.

Whether ixabepilone is a P-gp substrate has been determined by its cytotoxic and cellular uptake in a P-gp-expressing, drug-resistant tumour cell line. The parent HCT116 (non-P-gp expressing) human colon carcinoma cell line and its P-gp-overexpressing, drug-resistant variant HCTVM46 were tested for sensitivity to paclitaxel and ixabepilone using a colony-formation assay. The P-gp (MDR1) overexpressing HCTVM46 was 25-fold more resistant to paclitaxel than its parent line HCT116. By contrast, HCTVM46 was only 2.2-fold more resistant to ixabepilone than the parental HCT116. Intracellular drug concentrations were assayed at intervals from 0 to 2.0 hours during incubation of paclitaxel and ixabepilone at the therapeutic concentration of 20 nM. Whereas both ixabepilone and

paclitaxel accumulated significantly in HCT116 cells, ixabepilone accumulated far more effectively in HCTVM46 than paclitaxel. The ratios of drug concentrations in HCT116 versus HCTVM46 cells at the end of the 2-hour incubation period were 48 and 4, respectively, for paclitaxel and ixabepilone, reflecting the decreased susceptibility of the latter compound to the efflux mechanism mediated by P-gp. P-gp expression in the HCTVM46 cell line was confirmed by flow cytometry, Western blot analysis and a functional Rhodamine 123 assay.

In vivo

Ketoconazole

As ixabepilone is primarily metabolised by CYP3A4/5, an *in vivo* interaction study with the CYP3A4 inhibitor ketoconazole was performed (Study CA163042). In Cycle 1, 27 cancer patients received 6 days of continuous daily dosing with 400 mg of ketoconazole from Day -1 to 5. A single dose of ixabepilone as 3-hour infusion was administered on Day 1 of Cycle 1, 2 hours after the ketoconazole dose. For safety reasons, the administration of ixabepilone with ketoconazole in Cycle 1 was conducted in a dose-escalation study, starting on 10 mg/m^2. In Cycle 2, patients received a single dose of 40-mg/m^2 ixabepilone without concomitant ketoconazole. Twenty-two patients had complete pharmacokinetic data from both cycles and were included in the statistical analysis.

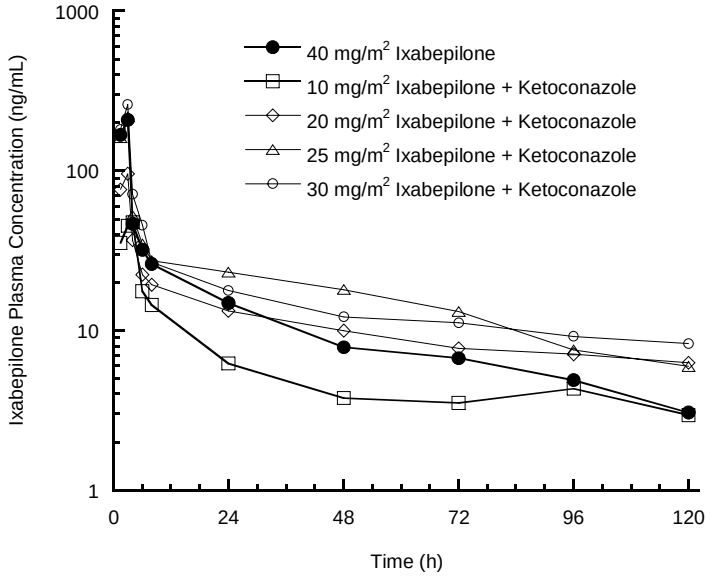
The MTD of ixabepilone administered as a 3-hour infusion with ketoconazole was 25 mg/m^2. The dose-adjusted mean C_{max} and AUC of ixabepilone were increased by 7 and 79%, respectively, by concomitant ketoconazole (Table 5).

Table 5 Study CA163042 – Results of ixabepilone dose/m^2-normalised C_{max} and AUC_∞ following administration of ixabepilone with or without ketoconazole

Pharmacokinetic parameter	Treatment	Adjusted geometric mean	Ratios of geometric means point estimate (90% CI)
C_{max} (ng/ml)	With ketoconazole	231.49	-
	Without ketoconazole	216.91	1.067 (0.931, 1.223)
AUC_∞ (ng•h/ml)	With ketoconazole	3457.19	-
	Without ketoconazole	1930.43	1.791 (1.547, 2.074)

The plasma concentration-time profile for 20 mg/m^2 ixabepilone + ketoconazole was similar to that of 40 mg/m^2 (normal dose) ixabepilone without ketoconazole (Figure 2).

Figure 2 Study CA163042 – Mean ixabepilone plasma concentration-time profiles, following administration of ixabepilone with or without ketoconazole



Capecitabine

A specific study was performed to evaluate the effect of capecitabine on ixabepilone pharmacokinetics and vice versa in 20 subjects. During Cycle 1, subjects were administered a single intravenous dose of ixabepilone 40 mg/m^2 over 3 hours on Day 1 and a single oral (p.o.) dose of capecitabine 1000 mg/m^2 on Day 15. During Cycle 2, subjects were administered a 3-hour i.v. infusion of ixabepilone 40 mg/m^2 on Day 1 and capecitabine 1000 mg/m^2 p.o. every 12 hours (q12h) on Days 1-5. One cycle was defined as 21 days. Ixabepilone pharmacokinetics was assessed on Day 1 of each cycle. Capecitabine and 5-FU pharmacokinetics were assessed on Day 15 of Cycle 1 and Day 1 of Cycle 2.

C_{max} and AUC decreased for both ixabepilone (19 and 6%, respectively) and capecitabine (27 and 5%, respectively), relative to the values when administered separately, whereas C_{max} and AUC increased for 5-FU (1 and 14%, respectively).

Other

Pharmacokinetics of ixabepilone and carboplatin, doxorubicin or irinotecan were determined in 3 dose-finding studies for the combination of ixabepilone with carboplatin, doxorubicin or irinotecan, respectively (data not shown).

- Pharmacokinetics using human biomaterials

Pharmacokinetics using human biomaterials were investigating plasma protein binding (see subsection on distribution), hepatic metabolism and drug interaction (see subsections on elimination and section on pharmacokinetic interaction studies).

Pharmacodynamics

- Mechanism of action

No clinical studies on the mechanism of action were submitted.

- Primary and Secondary pharmacology

No clinical primary and secondary pharmacodynamics studies were submitted.

Clinical efficacy

- Dose response study(ies)

Data from clinical studies in 3250 patients were included in the marketing authorisation application and contribute to the pharmacokinetic, efficacy, and safety data.

Initially, ixabepilone 50 mg/m^2 administered intravenously over 1 hour was proposed as the recommended Phase II dose and schedule was based on results from the Phase I dose escalation study (Study CA163001). Peripheral neuropathy was reported with this regimen during the initial part of Phase II studies in breast cancer (Grade 3/4 peripheral neuropathy was reported in 3 of 8 patients in Study CA163009 and in 8 of 19 patients in Study CA163010) as well as in other Phase II studies. Prolonging the infusion time to 3 hours but keeping the 50 mg/m^2 dose was associated with frequent serious gastrointestinal events. The dose was reduced to 40 mg/m^2. This regimen (40 mg/m^2 infused over 3 hours) was tolerable and active in the remainder of patients treated in Studies CA163009, CA163010 and CA163081, with an incidence of Grade 3/4 neuropathy of 16% of patients and of Grade 3/4 gastrointestinal disorders in 13%. The safety and efficacy of 40 mg/m^2 was confirmed in other Phase II studies in breast cancer (Studies CA163080 and CA163081) as well as in other tumour types. This dose and schedule was also reasonably tolerated in a Phase III study in breast cancer in which ixabepilone was administered in combination with capecitabine (Study CA163046).

The choice of 40 mg/m^2 for ixabepilone and 2000 mg/m^2 for capecitabine for the combination studies was based on results of a Phase I/II dose-escalation study (CA163031), which demonstrated that this combination was effective and had an acceptable safety profile. A pharmacokinetic study (CA163038) demonstrated that there were no significant interactions between these 2 compounds.

Based on these observations, the duration of infusion was extended to 3 hours. Subsequently, the dose was reduced to 40 mg/m^2 after the observation of frequent (4 of 8 patients) serious gastrointestinal events in Study CA163001.

- Main study(ies)

The main studies submitted in support of the combination therapy of ixabepilone and capecitabine were CA163046 and CA163048 (Table 6). The populations were anthracycline resistant or maximum cumulative dose and taxane resistant, or taxane and anthracycline pretreated, respectively. The primary endpoints were progression-free and overall survival, respectively. Both studies are randomised controlled, open-labeled studies.

Table 6 Summary of combination studies: Ixabepilone plus Capecitabine in MBC

Study No	Design	Enrolled	Treatment[a]	Population	Primary Efficacy Endpoint
CA163046	Phase 3, open-label, randomised multinational	752	Ixabepilone 40 mg/m2 on Day 1 + capecitabine oral 2000 mg/m2/day on Days 1-14, Q3 weeks v. capecitabine 2500 mg/m2/day on Days 1 - 14, Q3 weeks	Anthracycline resistant or minimum cumulative dose and Taxane resistant	PFS[c] (IRRC)
CA163048	Phase 3, open-label, randomised multinational	1221	Same as CA 163046	Taxane and anthracycline pretreated	OS
CA163031	Phase 1/2, open-label, multicenter, dose-escalation	62	Ixabepilone 40 mg/m2 Q3 weeks + capecitabine 2000 mg/m2/day Q3 weeks (Phase 2 expansion)	Taxane and anthracycline pretreated	ORR

PIVOTAL STUDY CA163046: IXABEPILONE IN COMBINATION WITH CAPECITABINE IN TREATMENT OF BREAST CANCER

METHODS

Study participants

Main eligibility criteria were:

- Women ≥ 18 years
- Metastatic or locally advanced breast cancer not curable by surgery or radiation
- At least 1 target lesion as defined by RECIST
- Anthracycline resistance or minimum cumulative dose: progression on treatment or within 3 months of last dose (6 months in the neoadjuvant/adjuvant settings); otherwise, must have received at least 240 mg/m^2 doxorubicin or 360 mg/m^2 epirubicin
- Taxane resistance: progression while on taxane or within 4 months of last dose (12 months in the neoadjuvant/adjuvant settings)
- Maximum of 3 prior chemotherapy regimens in any setting
- Adequate liver function: Grade < 2 total bilirubin and alanine aminotransferase (ALT) (Grade < 3 ALT with hepatic metastases)
- Adequate liver function: Grade < 2 aspartate aminotransferase, ALT or total bilirubin (regardless of hepatic metastases)
- Karnofsky Performance Status (KPS) of 70-100

Treatments

The eligible patients were allocated to one of the two treatment arms:

- Arm A:ixabepilone 40 mg/m^2 infused intravenously over 3 hours, in combination with capecitabine 1,000 mg/m^2 administered orally twice a day (BID) for 14 days, every 3 weeks.
- Arm B: capecitabine1 1,250 mg/m^2 administered orally twice a day (BID) for 14 days, every 3 weeks.

Patients were treated for a maximum of 18 cycles or until investigator determined PD or until patients met discontinuation criteria (although some patients remained on treatment longer than 18 cycles after consultation with the sponsor).

Patients in both treatment groups were assessed every 6 weeks while on treatment until investigators documented PD. Patients who discontinued treatment for reasons other than documented progression were assessed every 6 weeks until 24 weeks from randomisation and then every 3 months until investigators documented PD. After progression, patients were followed every 3 months until death.

Objectives

To demonstrate the activity of ixabepilone in combination with capecitabine in a heavily pre-treated patient population with breast cancer, previously exposed to anthracycline- and taxane- containing chemotherapy[p2].

Outcomes/endpoints

The primary endpoint was PFS assessed by an IRRC using modified RECIST. The IRRC, was blinded to treatment group, investigator selection of target and non target lesions and investigator response assessments.

Overall survival, ORR, time-to-response and response duration were secondary endpoint as well as safety.

Patients in both groups were assessed symmetrically every 6 weeks while on treatment until investigators documented progressive disease (PD). Patients who discontinued treatment for reasons other than documented progression were assessed every 6 weeks until 24 weeks from randomization,

and then every 3 months until investigators documented PD. After progression, patients were followed every 3 months until death.

Sample size

The number of events and power for the study were calculated assuming an exponential PFS distribution in each group. The PFS alpha level was adjusted for an interim analysis using the O'Brien-Fleming spending function. The final PFS analysis required 615 events; i.e., the number of events needed for a 2-sided log-rank test at the $\alpha = 0.05$ level, to have 90% power to show a statistically significant difference when the hazard ratio (HR) was 0.77 (i.e., when the median PFS in the ixabepilone plus capecitabine group was 30% greater assuming a median PFS of 3 months in the capecitabine group). The target accrual was to be 750 patients.

With a sample size of 750 randomised patients, there was at least 95% power to detect a significant difference in ORR of 32% in the ixabepilone plus capecitabine group, assuming an ORR of 20% in the capecitabine group. The alpha level for the log-rank test for PFS was not affected by the comparisons of ORR, as PFS was the only primary endpoint.

Randomisation

Patients were evenly randomised between the two treatment arms. The randomisation procedure was dynamically minimised the imbalance between treatment arms within the levels of each of the following stratification factors:

- presence of visceral metastases in liver and/or lung (yes/no)
- prior chemotherapy in the metastatic setting (yes/no)
- cumulative anthracycline dose of: 1) $\geq$ 240 mg/m^2 of doxorubicin or 2) $\geq$ 360 mg/m^2 of epirubicin and relapsed > 6 months in the adjuvant/neo-adjuvant setting provided this was the last setting in which they received drug (yes/no)
- study site.

Blinding (masking)

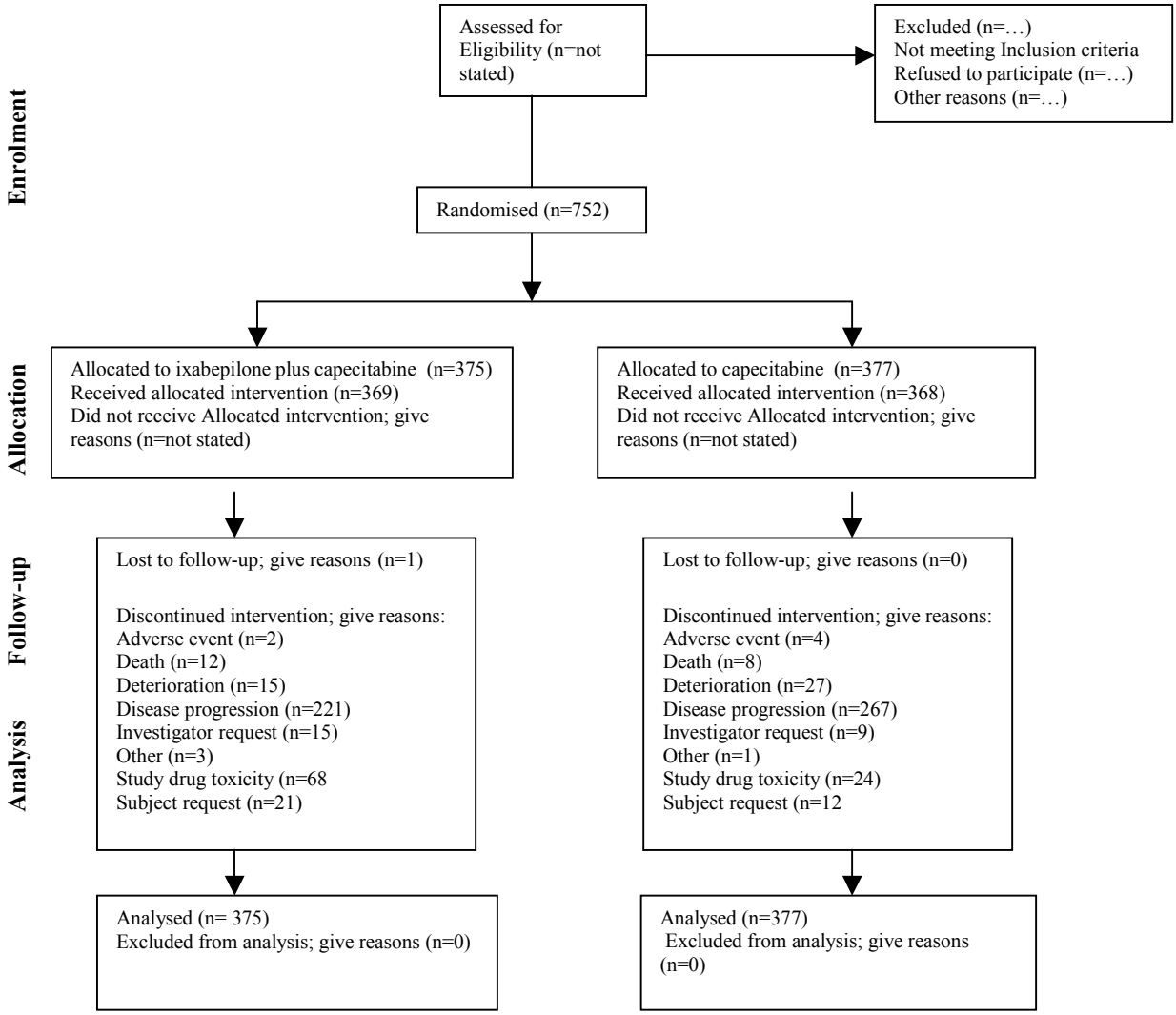
This was an open-label study.

Statistical methods

The primary analysis was a comparison of IRRC-assessed PFS between the 2 treatment groups using a log-rank test, stratified by the following factors assigned at randomisation: presence of visceral metastases in liver or lung; minimum of either doxorubicin 240 mg/m^2 or epirubicin 360 mg/m^2 and relapse > 6 months in adjuvant setting; prior chemotherapy for metastatic disease.

RESULTS

Participant flow



Recruitment

The enrolment period was from 04 September 2003 to 12 January 2006.

The study involved 160 investigational sites in 22 countries which enrolled at least 1 patient,. A total of 752 patients were randomised (ixabepilone plus capecitabine: 375 randomised, 369 treated and capecitabine: 377 randomised, 368 treated).

Conduct of the study

The study was modified 6 times by amendments. Amendment #1, dated 23 September 2003, specified that the DMC was to be conducted an interim analysis of both safety and efficacy, defined the criteria for CR for target lesions, measurable lesions as ≥ 20 mm in at least 1 diameter, modified the inclusion criteria related to at least 1 target lesion be radiographically measurable at baseline, specified that bone lesions followed as sites of non measurable disease be assessed by methods other than a bone scan (e.g., MRI, CT), capecitabine dose modifications not be required for alopecia, Grade 2/3 fatigue/asthenia and Grade 2 and transient Grade 3 arthralgia/myalgia and clarified additional methodological details

Amendment #4, dated 03 February 2005, revised the exclusion criteria to exclude patients with Grade ≥ 2 ALT or AST, the eligibility criteria of taxane resistance 1) in the adjuvant setting (recurrence period increased from 6 to 12 months) and 2) in the metastatic setting (progression period

increased from 3 to 4 months), the deletion of inclusion criteria requiring to have at least 1 prior metastatic chemotherapy regimen, the inclusion criteria to allow skin lesions with proper photographic evidence as measurable lesions and permitted a capecitabine dose reduction upon first occurrence of Grade 2 HFS or diarrhoea

Amendment #6, dated 11 August 2005, addressed the potential for interactions with strong inhibitors of CYP3A4 and added an exclusion criterion regarding the ongoing use of these drugs and defined the size of the filter to be used with ixabepilone infusions.

Twenty-four (6%) and 33 (9%), randomised patients in the combination and capecitabine alone, respectively, had significant eligibility deviations (non measurable disease, not taxane-resistant, not anthracycline-resistant or did not meet minimum cumulative dose, more than 3 prior chemotherapy regimens, no prior chemotherapy regimen, a male was randomised [but never treated] and patients were randomised following implementation of Amendment #4 with hepatic function tests (AST, ALT or bilirubin) Grade $\geq$ 2).

In addition, 23 (6%) and 13 (4%) patients in the combination and capecitabine alone, respectively, had significant on-treatment deviations (improper dose adjustment after Grade 3/4 neuropathy, no dose adjustment after Grade 3 HFS or Grade 3/4 diarrhoea, non study anticancer agents, improper treatment assignment, no premedication for HSR).

Baseline data

Baseline demographic and disease characteristics are presented in Table 7 and prior therapies in Table 8.

Table 7 Study CA163046 - Baseline demographic and disease characteristics

	Ixabepilone plus capecitabine n (%) N = 375	Capecitabine n (%) N = 377
Gender		
Male	-	0 1 (0.3)
Female	375 (100.0)	376 (99.7)
Race		
White	257 (68.5)	247 (65.5)
Black	11 (2.9)	11 (2.9) 22
Asian	83 (22.1)	87 (23.1)
American Indian	1 (0.3)	-
Other	23 (6.1)	32 (8.5)
Age (years)		
Median	53.0	52.0
Min–Max	25.0-76.0	25.0-79.0
< 65	336 (89.6)	322 (85.4)
≥ 65	39 (10.4)	54 (14.3)
< 50	135 (36.0)	145 (38.5)
≥ 50	240 (64.0)	231 (61.3)
Unknown		0 1 (0.3)
Karnofsky Performance Status		
100	108 (28.8)	105 (27.9)
90	145 (38.7)	132 (35.0)
80	86 (22.9)	102 (27.1)
70	33 (8.8)	34 (9.0)
< 70		0 1 (0.3)
Not reported	3 (0.8)	3 (0.8)
Menopausal status		
Pre-menopausal	54 (14.4)	51 (13.5)
Peri-menopausal	19 (5.1)	23 (6.1)
Post-menopausal	288 (76.8)	289 (76.7)
Not reported	14 (3.7)	14 (3.7)
HER2+[a]	59 (15.7)	53 (14.1)
ER+ or PR+	177 (47)	184 (49)
ER/PR/HER2-negative (triple negative)	91 (24.3)	96 (25.5)
Visceral disease (all lesions per IRRC)		
Visceral, liver and/or lung	316 (84)	315 (84)
Visceral, liver	245 (65)	228 (61)
Visceral, lung	180 (48)	174 (46)
Visceral, other	34 (9)	28 (7)
Disease sites (all lesions per IRRC)[b]		
1	39 (10)	34 (9)
2	85 (23)	98 (26)
3	110 (29)	121 (32)
4	79 (21)	69 (18)
≥ 5	58 (16)	53 (14)

[a] HER2 positive was defined as either any test result 3+ positive or Fluorescence In Situ Hybridization (FISH) positive

[b] The following types of lesions, regardless of location in the body, were grouped together by type and considered 1 disease site each: lymph node; bone; skin/soft tissue

Table 8 Study CA163046 - Prior Therapies in randomised patients

	Ixabepilone plus capecitabine n (%) N = 375	Capecitabine n (%) N = 377
Number of prior chemotherapy regimens[a]		
0 (never treated)	2 (1)	3 (1)
1	22 (6)	24 (6)
2	202 (54)	215 (57)
3	132 (35)	119 (32)
> 3	17 (5)	16 (4)
Number of prior metastatic regimens		
0[b]	27 (7)	33 (9)
1	179 (48)	184 (49)
2	152 (41)	138 (37)
3	13 (4)	21 (6)
> 3	4 (1)	1 (<1)
Prior taxane experience		
Prior taxane-containing regimens	373 (> 99)	374 (99)
Progression ≤ 12 months of last neoadjuvant/adjuvant chemotherapy	53 (14)	57 (15)
Progression ≤ 4 months of last metastatic chemotherapy	325 (87)	320 (85)
PD as best response to taxane	144 (38)	130 (35)
Discontinuation due to PD	270 (72)	269 (71)
Number of prior taxane regimens		
0	2 (1)	3 (1)
1	283 (76)	294 (78)
2	77 (21)	75 (20)
3	12 (3)	4 (1)
> 3	1 (< 1)	1 (< 1)
Prior docetaxel	165 (44)	178 (47)
Prior paclitaxel	157 (42)	142 (38)
Prior docetaxel and paclitaxel	51 (14)	54 (14)
Prior anthracycline experience		
Prior anthracycline-containing regimens	373 (> 99)	374 (99)
Progression ≤ 6 months of last neoadjuvant/adjuvant chemotherapy	54 (14)	65 (17)
Progression ≤ 3 months of last metastatic chemotherapy	115 (31)	103 (27)
PD as best response to anthracycline	51 (14)	36 (10)
Discontinuation due to PD	106 (28)	104 (28)
Number of prior anthracycline regimens		
0	2 (1)	3 (1)
1	285 (76)	302 (80)
2	85 (23)	68 (18)
3	2 (1)	4 (1)
> 3	1 (< 1)	0
Prior doxorubicin	216 (58)	218 (58)
Prior epirubicin	125 (33)	125 (33)
Prior doxorubicin and epirubicin	25 (7)	23 (6)
Selected other prior chemotherapy[c]		
Vinorelbine	43 (12)	47 (12)
Gemcitabine	35 (9)	36 (10)
Prior radiotherapy	251 (67)	268 (71)
Prior hormonal therapy	196 (52)	198 (53)
Prior trastuzumab	34 (9)	34 (9)

[a] Sequential neoadjuvant and adjuvant regimens counted as 1 regimen
[b] Recurrence within 12 months from adjuvant treatment
[c] Prior other chemotherapy received included cyclophosphamide, fluorouracil, methotrexate, carboplatin, liposomal doxorubicin and cisplatin

Numbers analysed

All randomised patients were included in the analyses. Three patient populations were analysed: All Randomised Patients dataset included 752 all patients randomised to receive study treatment, All

Treated Patients dataset included 737 patients who received at least 1 dose of study treatment and All Response-evaluable Patients dataset included 698 treated patients with measurable disease per IRRC (20 and 24 patients in the combination and capecitabine groups, respectively, had non measurable disease as per IRRC).

Outcomes and estimation

The efficacy results for studies CA163046 are presented in Table 9 and Figure 3 and 4. The results showed that PFS was 5.8 compared to 4.2 months [HR, 0.75; 95%CI, 0.64 - 0.88; P = 0.0003] in the combination arm compared to the capecitabine arm, respectively. In terms of overall survival, the effect was minimal with 12.9 months in the combination arm compared to 11.1 months [HR, 0.9; 95%CI, 0.77 – 1.05; P = 0.1936] in the capecitabine arm.

Table 9 Key Efficacy Results for CA163046 and CA163048 – PFS (IRRC assessment) and Overall Survival

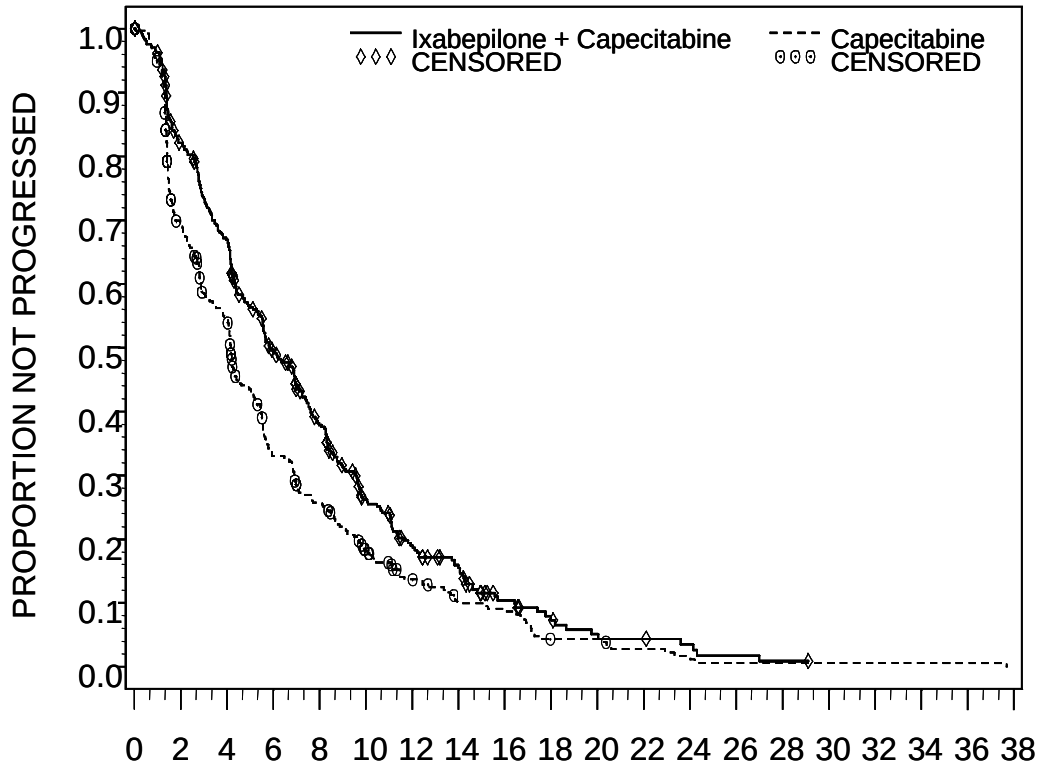
	CA163046			**CA163048**		
Parameter	**Ixabepilone + capecitabine**	**Capecitabine**	**Hazard Ratio (95% CI)**	**Ixabepilone + capecitabine**	**Capecitabine**	**Hazard Ratio (95% CI)**
PFS, Median, months (95% CI)	5.8 (5.5 - 7.0) (by IRRC)	4.2 (3.8 - 4.5) (by IRRC)	0.75 (0.64 - 0.88)	6.2 (5.6 - 6.8)	4.4 (4.1 - 5.4)	0.79 (0.69 - 0.90)
P value	0.0003			0.0005		
ORR, %	34.7% (by IRRC)	14.3% (by IRRC)		43.3%	28.8%	--
P value	< 0.0001			< 0.0001		
OS, Median, months (95% CI)	12.9 (11.5 - 14.2)	11.1 (10.0 - 12.5)	0.90 (0.77 - 1.05)	16.4 (15.0 - 17.9)	15.6 (13.9 - 17.0)	0.90 (0.78 - 1.03)
P value	0.1936			0.1162		
OS - Cox regression adjusted for prespecified baseline factors			0.87[a] (0.74 - 1.02)			0.85[b] (0.75 - 0.98)
P value			0.0803			0.0231

PFS = progression-free survival; ORR = objective response rate; OS = overall survival; HR = hazard ratio; IRRC = independent radiology review committee; CI = confidence interval

[a] As prespecified in the CA163046 protocol: adjusted for age, performance status, number of organ sites, estrogen receptor status, hepatic impairment, and time from diagnosis

[b] As prespecified in the CA163048 protocol: adjusted for age, performance status, number of organ sites, estrogen receptor status, hepatic impairment, visceral disease in liver or lung, and time from diagnosis

Figure 3 Study CA163046 – PFS curve of all randomised patients (IRRC assessment)

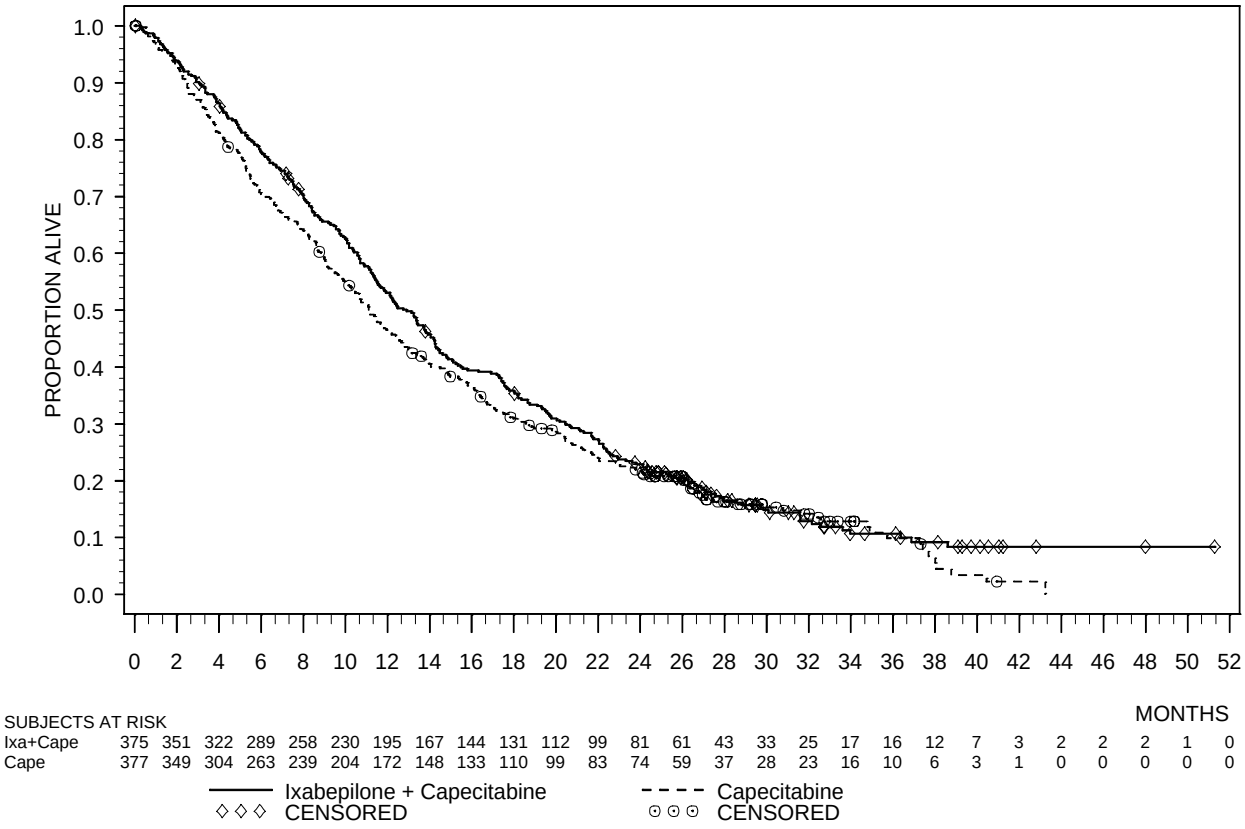


SUBJECTS AT RISK MONTHS

Ixa+Cape	375	299	242	170	122	75	51	37	18	12	7	6	4	2	1	0	0	0	0	0
Cape	377	250	192	110	83	53	35	23	21	9	9	5	3	1	1	1	1	1	1	0

GROUP	# PROGRESSED / # RANDOMIZED	MEDIAN (95% CI)
Ixabepilone + Capecitabine	310/375	5.8 (5.5 - 7.0)
Capecitabine	329/377	4.2 (3.8 - 4.5)

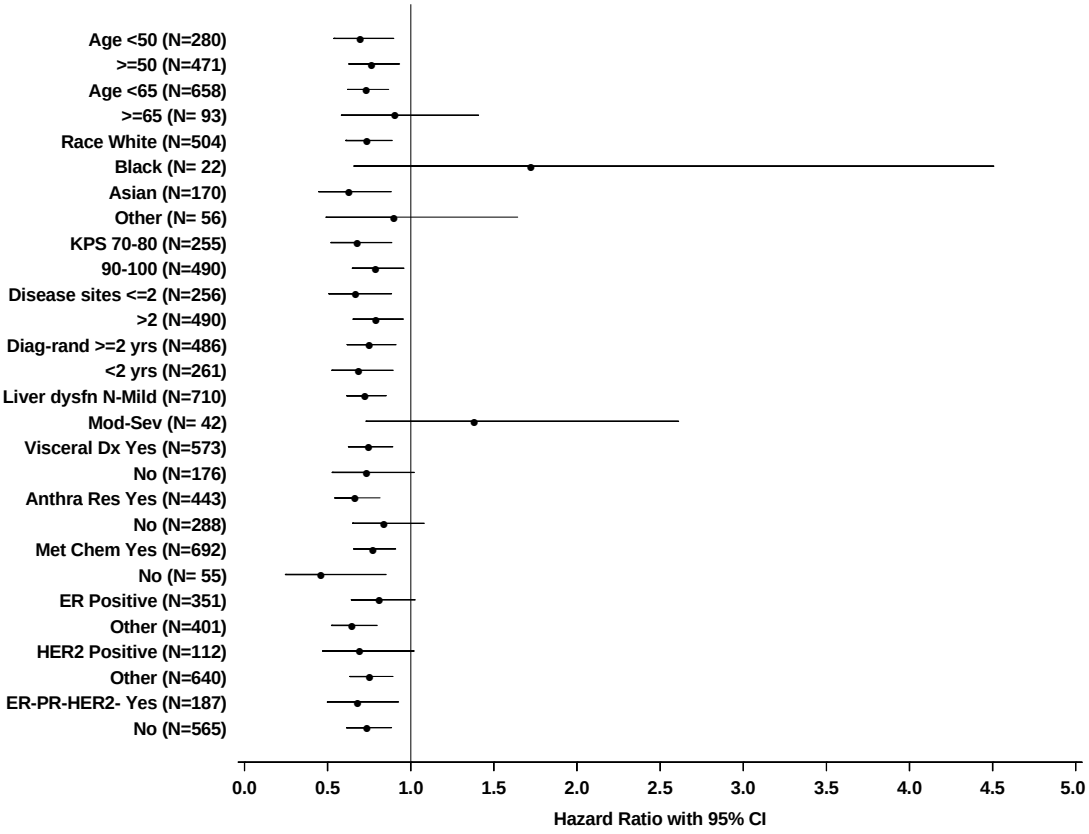
Figure 4 Study CA163046 – Overall Survival in Randomised Patients



Ancillary analyses

Several ancillary analyses were performed. Predefined subpopulation analyses of PFS across clinically and biologically diverse subpopulations in breast cancer were performed to evaluate the integrity of the primary result. Subpopulation analyses for ORR were performed using IRRC assessments. There was a larger proportion of responders in the ixabepilone plus capecitabine group in all subpopulation analyses, with the exception of the small subset of black race (ixabepilone plus capecitabine: 1/11 patients; capecitabine: 2/11 patients). Data from the PFS ancillary analyses are shown in Figure 5.

Figure 5 Study CA163046 – Subgroup analyses of randomised patients to the treatment arms (IRRC) for PFS



Note: an HR below 1.0 favoured the ixabepilone plus capecitabine group
Anthra Res: anthracycline resistant; Diag-rand: diagnosis to randomisation; Liver dysfn N-Mild: liver dysfunction normal/mild; Met Chem: metastatic chemotherapy; Mod-Sev: moderate/severe; Visceral Dx: visceral disease

CA163048: IXABEPILONE IN COMBINATION WITH CAPECITABINE IN THE TREATMENT OF BREAST CANCER

METHODS

Study participants

- Key Inclusion Criteria

1) Women ≥ 18 years of age with metastatic or locally advanced breast cancer who have previously been treated with an anthracycline and a taxane

2) Histologic or cytologic diagnosis of adenocarcinoma originating in the breast

3) Measurable disease or non-measurable disease, which could be assessed radiologically or by physical exam. Disease was to be assessed using RECIST criteria (Note: Target lesions were not be chosen from a previously irradiated area unless the lesion had appeared as a new lesion after completion of radiation therapy)

4) No more than 2 prior chemotherapy regimens including those administered in the neoadjuvant or adjuvant setting. Patients who had not received treatment for metastatic disease had to have relapsed within 1 year (Note: Sequential neoadjuvant or adjuvant regimens counted as a single regimen; hormonal anti-cancer agents and nontraditional cytotoxic agents such as trastuzumab were not counted as chemotherapy regimens when administered alone)

5) Karnofsky Performance status (KPS) of 70 to 100

6) Adequate recovery from prior systemic therapy.

- Key Exclusion Criteria

1) Any history of brain metastases and/or leptomeningeal metastases

2) CTC Grade 2 or greater neuropathy (motor or sensory) at enrollment

3) Hematologic function with absolute neutrophils ≤ 1,500/mm3 and/or platelets < 125,000/mm3

4) Hepatic function with serum bilirubin ≥ 1.5 the upper institutional limits of normal (ULN), ALT or AST ≥ 2.5 x ULN (for all patients, regardless of the presence of hepatic metastases)1

5) Concurrent treatment with trastuzumab (Herceptin), hormonal anticancer agents or other systemic treatment for cancer

6) Prior treatment with an epothilone and/or with capecitabine

Treatments

Patients received study treatment as a 21-day cycle as follows;

• Ixabepilone in combination with capecitabine: Ixabepilone 40 mg/m2 administered as a 3-hour intravenous (IV) infusion on Day 1 of each cycle only, plus oral capecitabine 1000 mg/m2 twice a day (BID) (2000 mg/m2 daily dose) x 14 days, followed by 1 week of rest

• Capecitabine alone: Capecitabine 1250 mg/m2 BID (2500 mg/m2 daily dose) x 14 days, followed by 1 week of rest

Patients could continue to receive additional cycles of therapy until progressive disease (PD) or intolerable toxicity. The protocol-defined maximum number of cycles was 18.

However, a patient could receive additional cycles of study treatment beyond cycle 18 at the investigator's discretion.

Treatment was repeated every 21 days for a maximum of 18 cycles for patients meeting the following retreatment criteria:

• Absolute neutrophil count (ANC) is > 1,500/mm3 and platelet count > 100,000/mm3

• Treatment-related non-hematologic toxicity including peripheral neuropathy must have resolved to baseline or ≤ Grade 1 (excluding Grade 2 alopecia and Grade 2 fatigue, for which resolution was not required)

1 After Amendment 3; before the amendment, only patients with bilirubin ≥ 1.5 x ULN or ALT ≥ 2.5x ULN (≥ 5x ULN in presence of hepatic metastasis) were excluded.

Study treatment doses were decreased based on tolerability and renal function.

Objectives

Primary objective: To compare OS for ixabepilone in combination with capecitabine versus capecitabine alone in patients with advanced breast cancer previously treated with an anthracycline and a taxane

Outcomes/endpoints

The primary endpoint was overall survival. Secondary endpoints included PFS, response rate (RR). Efficacy analyses of tumour response and progression were based on investigator assessment. Patients were assessed for toxicity at regular intervals during treatment. The doses and timing of treatment could be modified based on toxicity. Progression free survival, tumor response (using Response Evaluation Criteria in Solid Tumors [RECIST] criteria), and duration of response, were evaluated for all patients with measurable disease. Tumor response was evaluated on a scheduled basis every 6 weeks (± 3 working days) from randomization (regardless of the timing of treatment cycles) while on treatment until disease progression was documented. Patients with measurable disease who discontinued the protocol treatment for reasons other than disease progression had tumor assessments every 6 weeks until Week 24 (from time of randomization) and then every 3 months until documented disease progression by RECIST criteria. Patients with only non-measurable disease were assessed for progression no less frequently than every 12 weeks. Tumor assessments were not required for patients

with non-measurable disease after discontinuing study therapy regardless of the reason for discontinuation.

Sample size

The number of events and power for this study were calculated assuming an exponential survival distribution in each treatment group. This study required at least 846 events (deaths) to ensure the 2-sided, $\alpha = 0.05$ level, log-rank test to have 90% power to show a statistically significant difference in overall survival between treatment groups when the HR is 0.8 (ie, when the median survival in the combination group is 3.15 months greater than a median survival of 12.6 months1 in the capecitabine alone group).

The primary analysis on OS was prespecified to be conducted on the data set of all randomised patients on an intent-to-treat basis, using a two-sided, $\alpha = 0.05$ level log-rank test, stratified by taxane resistance (yes/no), anthracycline resistance (yes/no), prior chemotherapy for metastatic disease (yes/no) and measurable disease (yes/no) as assigned at the time of randomization.

Randomisation

Patients were randomised in a 1:1 ratio to receive ixabepilone in combination with capecitabine or capecitabine alone. Randomization was stratified according to taxane resistance (yes/no), measurable disease versus non-measurable disease, prior chemotherapy for metastatic disease (yes/no), anthracycline resistance (yes/no), and investigator site.

Blinding (masking)

This was an open-label study.

RESULTS

Participant flow/Recruitment/Conduct of the study

A total of 1221 patients were randomised at 199 study sites in 29 countries beginning on 11-Nov-03. The last patient last visit was on 01-Apr-08.

A total of 1198 patients were treated (ixabepilone in combination with capecitabine: 595; capecitabine alone: 601) (Table 5.1). Two patients were randomised to ixabepilone in combination with capecitabine but received capecitabine only. These patients are counted in the capecitabine alone group for dosing and safety analyses.

All but 3 randomised patients were off treatment as of the 04-Apr-2008 database lock. The most common reason for discontinuation was disease progression (by RECIST) in each group; the frequency of this outcome was lower in the combination group than the capecitabine alone group (45% vs 65%). In addition, 28 (5%) of patients in the combination group and 36 (6%) in the capecitabine alone group discontinued because of clinical disease progression. More patients in the combination group than in the capecitabine alone group discontinued all study treatment due to study drug toxicity (30% vs 11%). In the combination group, the median number of cycles to discontinuation due to study drug toxicity was 5.

Patients in the combination group received a median of 6 cycles, compared with 5 cycles in the capecitabine alone group (Table 10).

Table 10 Summary statistics of number of cycles per patient – treated patients

	Ixabepilone + Capecitabine N=595	**Capecitabine N=603**
Number of courses:		
N	595	603
Median	6.0	5.0
Min-Max	1.0 – 44.0	1.0 – 50.0

Disease progression was the primary reason for discontinuation in both treatment groups; it was less common for the combination group than for capecitabine alone (45% vs 65%). More patients in the combination group than the capecitabine alone group discontinued all study treatment because of study drug toxicity (30% vs 11%). In the combination group, the median number of cycles to discontinuation due to study drug toxicity was 5.

Patients in the combination group could discontinue 1 drug in the combination while remaining on the other. More patients discontinued ixabepilone and continued capecitabine than patients who discontinued capecitabine and continued ixabepilone (19% vs 7%). The most common reason for discontinuing ixabepilone was peripheral neuropathy and the most common reason for discontinuing capecitabine was nonhematological toxicity (HFS).

Ixabepilone in combination with capecitabine: a total of 48% of patients required at least 1 dose reduction of ixabepilone, either alone (14%) or along with capecitabine (34%). A total of 49% of patients required at least 1 dose reduction of capecitabine, either alone (15%) or along with ixabepilone (34%).

The most common reasons for a first dose reduction of ixabepilone were peripheral neuropathy (17%), hematological toxicity (16%), and nonhematologic toxicity (12%). The most common reasons for a first dose reduction of capecitabine were nonhematologic toxicity (42%), hematologic toxicity (3%), and unknown (3%).

Capecitabine alone: A total of 43% of patients in the capecitabine alone group required at least 1 dose reduction. The most common reason for a first dose reduction was nonhematologic toxicity (40%). Ixabepilone:

In the combination group, 49% of patients received at least 90% of the intended dose of ixabepilone; 89% of patients received at least 70% of the intended dose.

Capecitabine:

• In the combination group, 23% of patients received at least 90% of the intended dose of capecitabine; 62% of patients received at least 70% of the intended dose.

• In the capecitabine alone group, 44% of patients received at least 90% of the intended dose of capecitabine; 80% of patients received at least 70% of the intended dose.

Baseline data

Table 11 Pre-treatment patient characteristics – Randomised patients

	Number of Subjects (%)		
	Ixabepilone + Capecitabine N=609	**Capecitabine N=612**	**Total N=1221**
Gender			
Female	609 (100.0)	612 (100.0)	1221 (100.0)
Race			
White	480 (78.8)	502 (82.0)	982 (80.4)
Black/African American	25 (4.1)	21 (3.4)	46 (3.8)
Asian	90 (14.8)	69 (11.3)	159 (13.0)
American Indian	1 (0.2)	2 (0.3)	3 (0.2)
Other	13 (2.1)	18 (2.9)	31 (2.5)
Age (years)			
N	609	612	1221
Median	53.0	53.0	53.0
Min-Max	23.0 – 78.0	24.0 – 81.0	23.0 – 81.0
<65	532 (87.4)	531 (86.8)	1063 (87.1)
>=65	77 (12.6)	81 (13.2)	158 (12.9)
<50	225 (36.9)	235 (38.4)	460 (37.7)
>=50	384 (63.1)	377 (61.6)	761 (62.3)
Karnofsky Performance status			
100	219 (36.0)	265 (43.3)	484 (39.6)
90	187 (30.7)	188 (30.7)	375 (30.7)
80	151 (24.8)	130 (21.2)	281 (23.0)
70	44 (7.2)	26 (4.2)	70 (5.7)
<70	2 (0.3)	2 (0.3)	4 (0.3)
Not reported	6 (1.0)	1 (0.2)	7 (0.6)
Menopausal status			
Pre-menopausal	93 (15.3)	90 (14.7)	183 (15.0)
Peri-menopausal	32 (5.3)	32 (5.2)	64 (5.2)
Post-menopausal	475 (78.0)	481 (78.6)	956 (78.3)
Not reported	9 (1.5)	9 (1.5)	18 (1.5)

Approximately 77% (941/1221) of patients had measurable disease by RECIST criteria and 23% (280/1221) had only non-measurable disease. Of the 1221 randomised patients, 944 patients had at least 1 target lesion reported on the CRF by the investigator. Most of the patients had multiple target lesions, including at least 17% in each group with ≥ 5 targets.

Patients characteristics are presented in Table 11. Most patients (98%) had received up to 2 prior chemotherapy regimens as required by the protocol; approximately 91% received 1 and 9% received 2 prior anthracycline or taxane regimens; 26% (313/1221) of patients met protocol-defined criteria for anthracycline resistance (Supplemental Table S.3.34). Fifty-six percent of patients who were not anthracycline resistant received the minimum cumulative dose (at least 240 mg/m2 doxorubicin or at least 360 mg/m2 epirubicin). All but 2 patients (1119/1221) received prior anthracycline in any setting. Prior doxorubicin was received by 673/1221 (55%) patients and epirubicin was received by 564/1221 (46%) patients in any setting. The number of patients who received prior doxorubicin and epirubicin in any setting was balanced between the combination group and the capecitabine alone group (doxorubicin: 330 vs 343 patients, respectively and epirubicin: 281 vs 283 patients,

respectively). Sixty eight percent (826/1221) of patients received anthracycline in the neoadjuvant/adjuvant setting and 39% (476/1221) of patients received in the metastatic setting.

Forty-eight percent (585/1221) patients were taxane resistant at baseline. All 1221 patients received prior taxane in any setting. Prior docetaxel was received by 913/1221 (75%) patients and paclitaxel was received by 699/1221 (57%) patients in any setting. The number of patients who received prior docetaxel and paclitaxel in any setting was balanced between the combination group and the capecitabine alone group (docetaxel: 445 vs 468 patients, respectively and paclitaxel: 341 vs 358 patients, respectively). Thirty-two percent (387/1221) patients received taxane in the neoadjuvant/adjuvant setting and 76% (923/1221) of patients received taxane in the metastatic setting.

In the metastatic setting, 72 (5.9%) patients (39 [6%] in the combination group and 33 [5%] in the capecitabine group) received prior gemcitabine and 57 (4.7%) patients (30 [5%] in the combination group and 27 [4%] in the capecitabine group) received prior vinorelbine.

The number of patients who received hormonal interventions was similar between the treatment groups (67% vs 68%). Forty-eight (8%) patients in each group received trastuzumab.

Twenty-one percent (256/1221) patients were triple negative (ER-, PR-, and HER2-) and 15% (185/1221) were HER-2 positive.

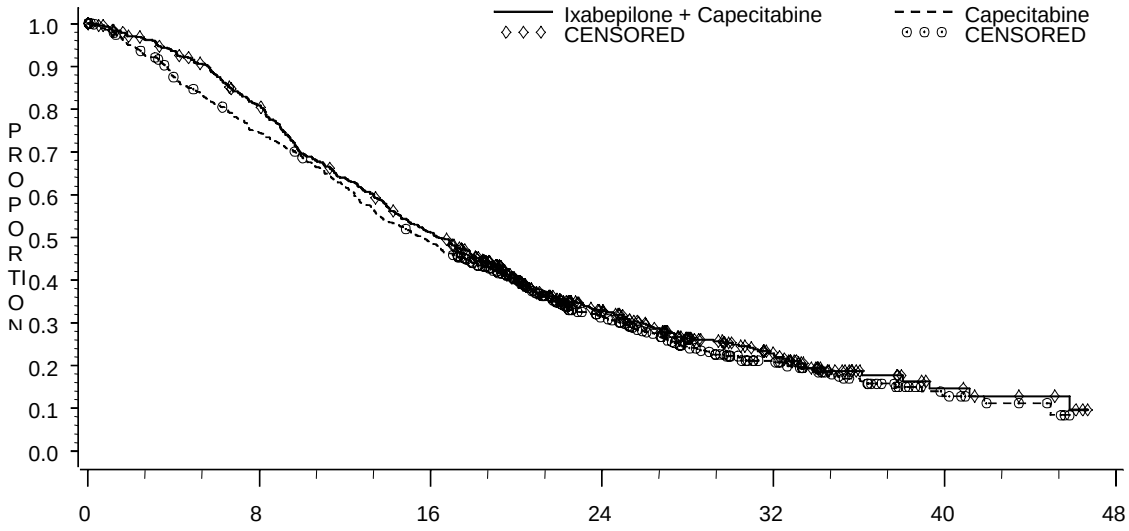
Most randomised patients had normal liver function (ALT, AST, ALP, and total bilirubin) at baseline; ≤ 1% patients reported Grade 3, and none had Grade 4 liver function abnormalities. A total of 9% (52/609) of randomised patients in the combination group and 6% (38/612) patients in the capecitabine alone group had moderate/severe hepatic impairment (AST/ALT: > 2.5 x ULN or total bilirubin > 1 x ULN) at baseline.

Numbers analysed

All randomised patients were included in the analyses.

Outcomes and estimation

Figure 6 Overall Survival by Treatment Group – Randomised Patients

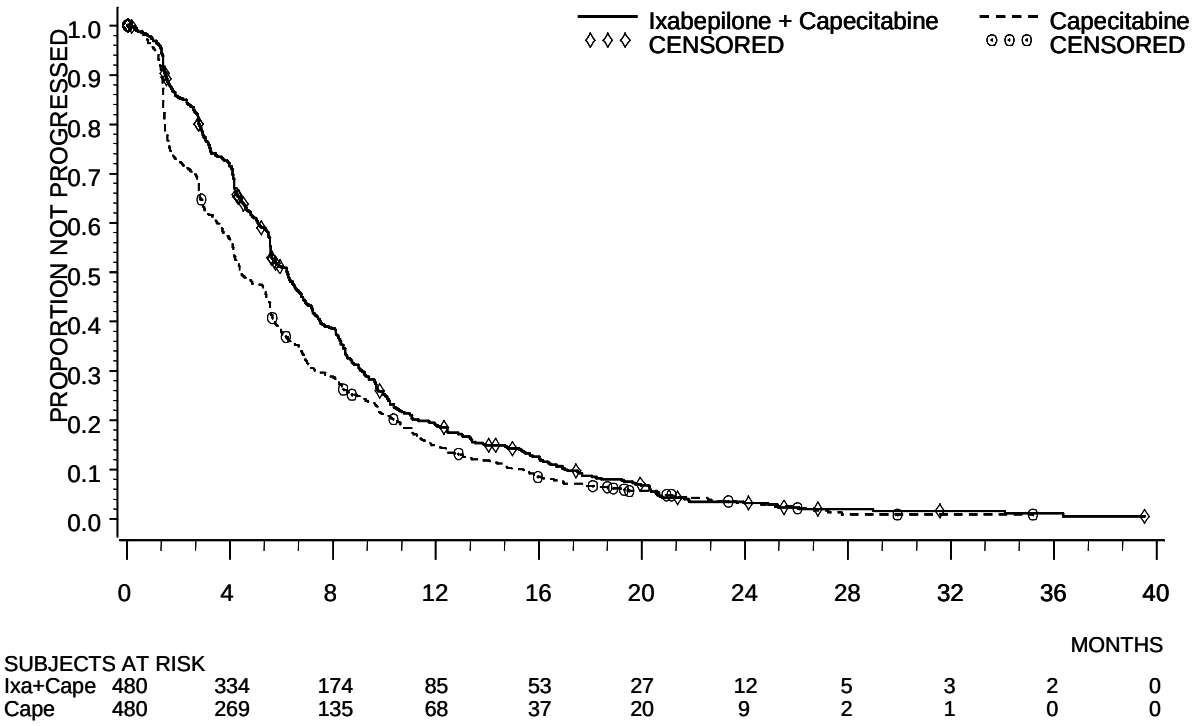


SUBJECTS AT RISK

Ixa+Cape	609	479	300	132	52	9	0
Cape	612	445	290	129	52	11	0

GROUP	# DIED / # RANDOMISED	MEDIAN (95% CI)
Ixabepilone + Capecitabine	430/609	16.4 (14.9 - 17.9)
Capecitabine	450/612	15.6 (13.9 - 17.0)

Figure 7 PFS by Treatment Arm – Patients Randomised to the Measurable Disease Stratum



GROUP	# PROGRESSED / # RANDOMISED	MEDIAN (95% CI)
Ixabepilone + Capecitabine	446/480	6.2 (5.6 - 6.8)
Capecitabine	457/480	4.4 (4.1 - 5.4)

The efficacy results for studies CA163048 are presented in Table 9, Figure 6 and 7. The results showed that PFS was 6.2 compared to 4.4 months [HR, 0.79, 95%CI, 0.69 – 0.90; P = 0.0005] in the combination arm compared to the capecitabine arm, respectively. In terms of overall survival, the effect was minimal with 16.4 months in the combination arm compared to 15.6 months [HR, 0.9; 95%CI, 0.78 – 1.03; P = 0.1162] in the capecitabine arm.

An additional analysis of OS using a Cox model adjusted for baseline factors was prespecified within the protocol. All baseline covariates were prespecified including KPS status which showed an imbalance between the 2 treatment groups at baseline (namely a higher proportion of patients with poor baseline KPS in the combination group (KPS of 70-80: 32% vs 25%) and a higher proportion of patients with good KPS in the capecitabine alone group (KPS of 100: 43% vs 36%); HR: 0.85 (95% CI: 0.75, 0.98), P=0.0231.

Table 12 Overall survival ratios and 95% CI for subset analysis – CA16048

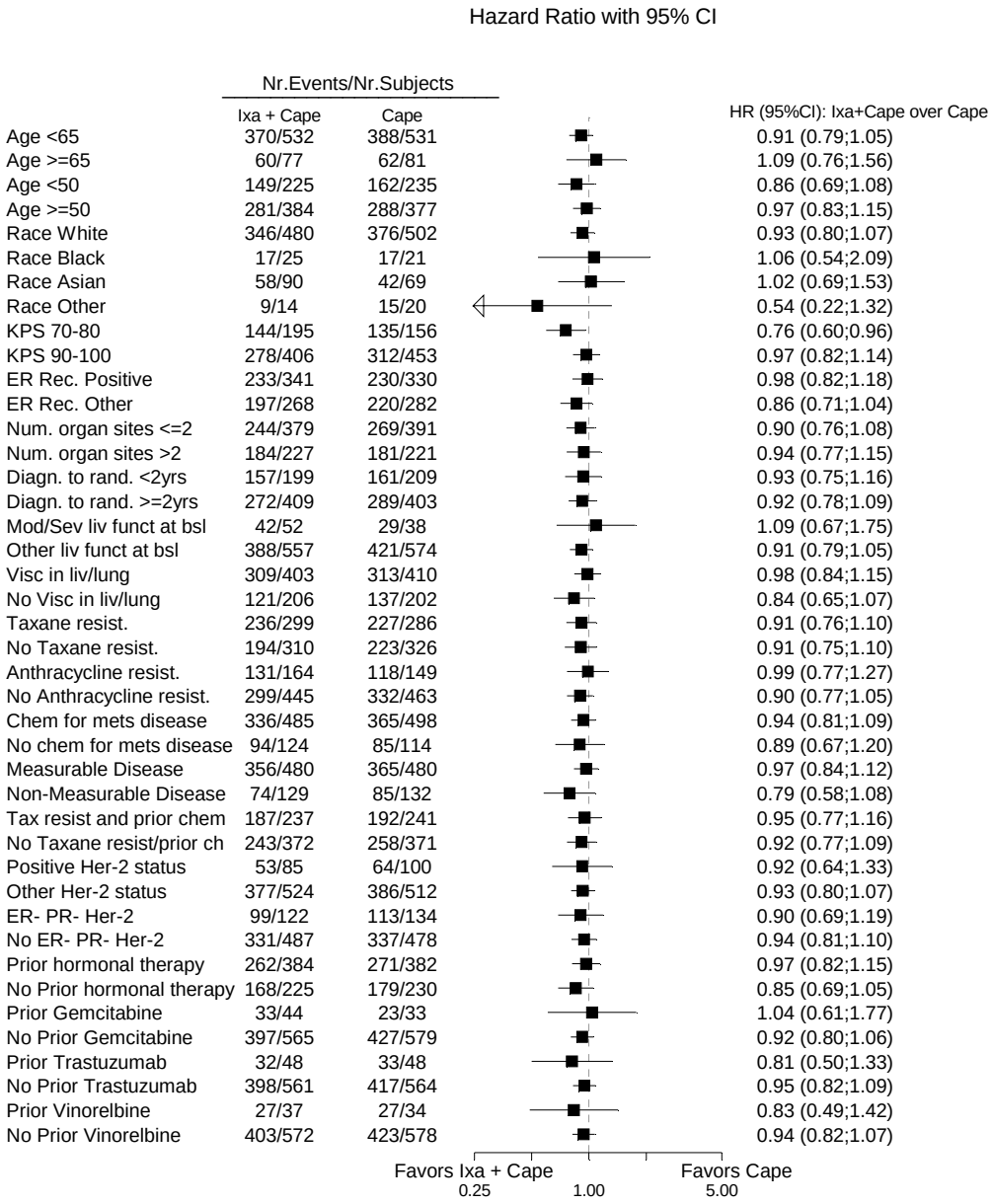


Table 12 describes the OS by subgroup analysis. No differences were observed in the different subgroups.

Analysis performed across trials (pooled analyses and meta-analysis)

No pooled analyses or meta-analyses were presented.

- Clinical studies in special populations

No clinical studies in special populations were presented.

- Supportive study

A number of supportive studies with ixabepilone monotherapy were presented to support the initial claim for monotherapy treatment. The programme with ixabepilone monotherapy consisted of four phase II studies, of which one (CA163081) was conducted in a population as described in the intended indication of anthracycline, taxane and capecitabine resistant patients with breast cancer (see summary table). Only data from the recommended dose (40 mg/m^2 infused over 3 hours) are presented (see Table 13 and 14).

Table 13 Summary of studies with Ixabepilone Monotherapy in Breast Cancer

Study No	Design	Setting/Population	Number (Enrolled/ Treated)	Response Criteria[a]	Efficacy Endpoints
CA163081	Phase 2, single-arm, multinational	Advanced breast cancer – anthracycline resistant or minimum cumulative dose, taxane-resistant, and capecitabine resistant	128/126	Tumour response evaluated by RECIST criteria every other cycle	**Primary**: ORR by IRRC **Secondary:** duration of overall response, time to response, duration of SD, month 6 SD rate, PFS, and OS
CA163009	Phase 2, open-label, multinational	Advanced breast cancer –taxane-resistant	49/49[b]	Tumour response evaluated by modified WHO criteria every other cycle	**Primary:** ORR **Secondary:** duration of overall response, PFS, and OS
CA163010	Phase 2, open-label, multinational	Advanced breast cancer – anthracycline pretreated in the adjuvant setting	65/65[b]	Tumour response evaluated by modified WHO criteria every other cycle	**Primary:** ORR **Secondary:** duration of overall response, PFS, and OS
CA163080	Phase 2, single-arm, multinational (Ixabepilone treatment was limited to 4 cycles)	Neoadjuvant therapy - T2-4, N0-3, M0 invasive breast adenocarcinoma ≥3 cm not amenable to breast conservation surgery	164/161	pCR using Sataloff criteria and ORR based on clinical, radiographic, and histopathologic evidence	**Primary:** pCR and ORR **Secondary:** none applicable to efficacy

ORR = objective response rate; IRRC = independent radiology review committee; SD = stable disease; PFS = progression-free survival; OS = overall survival; pCR = pathologic complete response; RECIST = Response Evaluation Criteria in Solid Tumours; WHO = World Health Organization

a Lesions are measured in 1 dimension using RECIST criteria or in 2 dimensions using WHO criteria

b Subset of patients treated with 40 mg/m2 ixabepilone

Table 14 Summary of Results with Ixabepilone Monotherapy in Breast Cancer

Results from CA163081	**Response-evaluable (IRRC) N = 113**
IRRC Best Response, n (%)	
PR	13 (12)
SD	57 (50)
PD	36 (32)
Unable to determine	7 (6)
IRRC ORR, % (95% CI)	11.5 (6.3 - 18.9)
Investigator Best Response, n (%)	
PR	21 (19)
SD	51 (45)
PD	33 (29)
Unable to determine	8 (7)
Investigator ORR, % (95% CI)	18.6 (11.9 - 27.0)
Duration of Response (months)	N = 13
Median (95% CI)	5.7 (4.4 - 7.3)
Time to Response (weeks)	N = 13
Median (Min - Max)	6.1 (5.0 - 19.0)
Duration of SD (months)	N = 57
Median (95% CI)	4.5 (3.7 - 6.0)
Month-6 SD Rate, % (95% CI	13.3 (7.6 - 20.9)
Progression-free Survival (months)	
Median (95% CI)	3.1 (2.7 - 4.2)
Survival (months)	8.6 (6.9 - 11.1)
Median (95% CI)	

For ixabepilone in combination with capecitabine, a dose finding single arm study has also been performed with the combination treatment (data not shown).

– Analysis of Quality of Life data

Both FACT-B and FBSI scale (a symptom measure based on FACT-B) were studied as secondary endpoints in the main trials (Figure 9, 10 and 11). According to the applicant, these data showed no clinically meaningful changes over time within each treatment arm: Individual sub-scales within FACT-B indicated that physical and functional sub-scales reflected the expected increased toxicity of the combination over capecitabine alone, and that social and emotional sub-scales reflected patient's overall perception of the impact of therapy. According to the applicant there were no differences between treatment arms. There was a greater drop-out in the capecitabine arm (Table 8). According to the applicant, all sensitivity analyses imputing for missing data showed no difference between arms. Overall, the applicant concluded that QoL was maintained during treatment with the combination.

Figure 8 **Cumulative Drop-Out by Study Week**

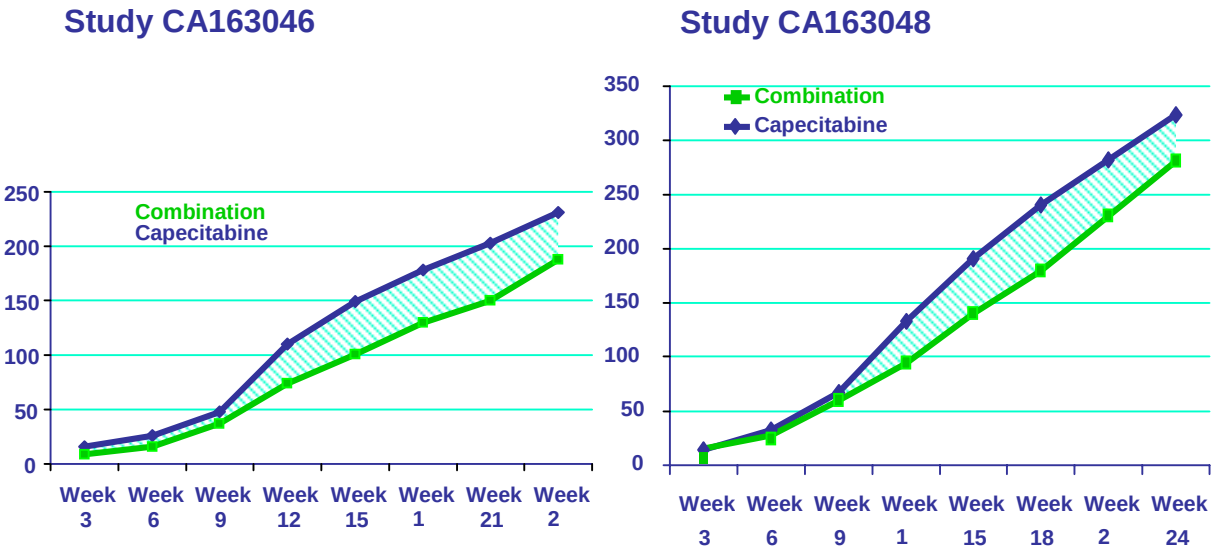


Figure 9 **Mean Change from Baseline (95% CI) in FBSI-8 (Imputing FBSI = 0 after PD or death)**

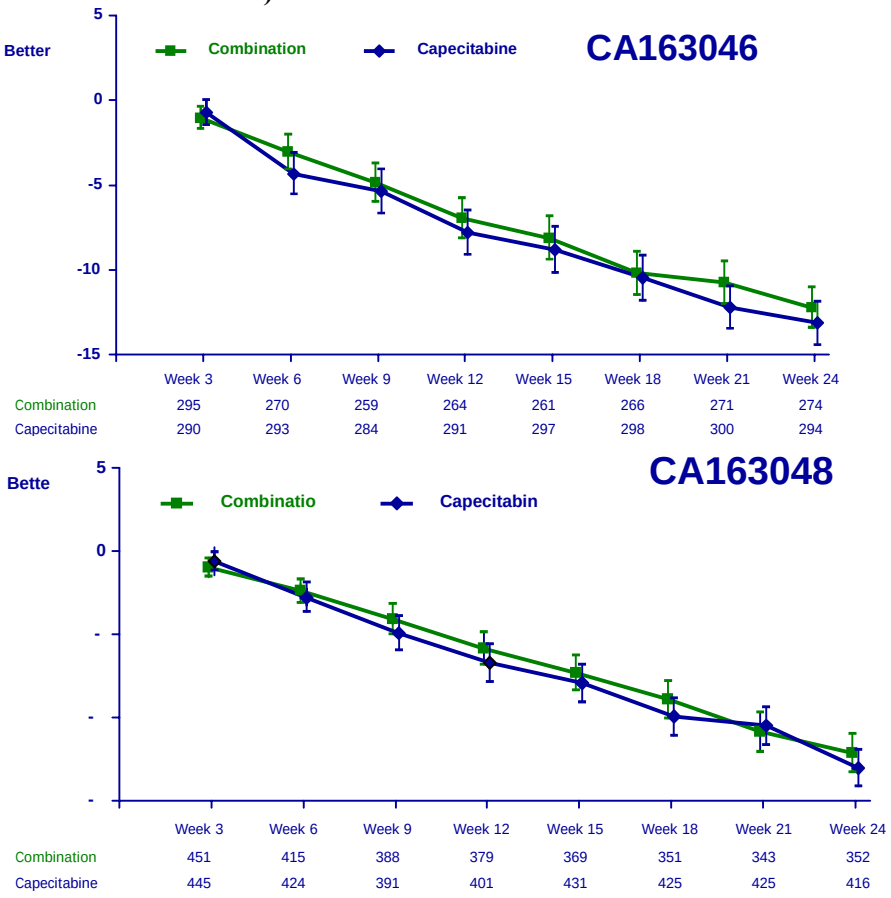


Figure 10 **FACT-B Physical + Functional Well-Being Subscales**

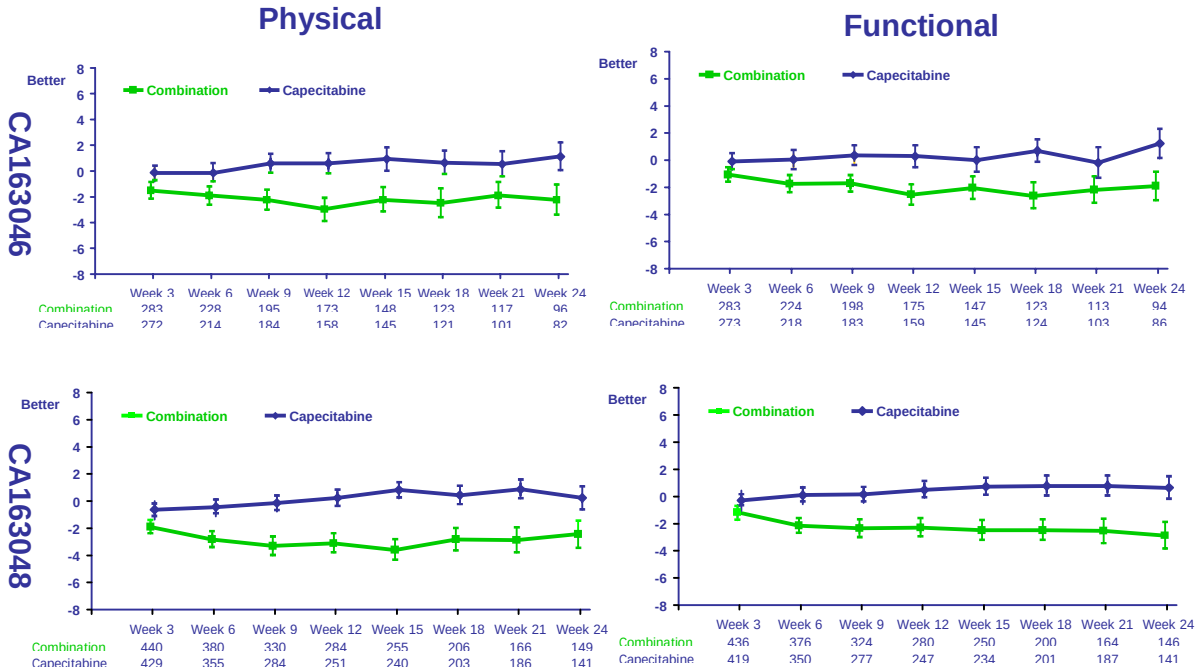
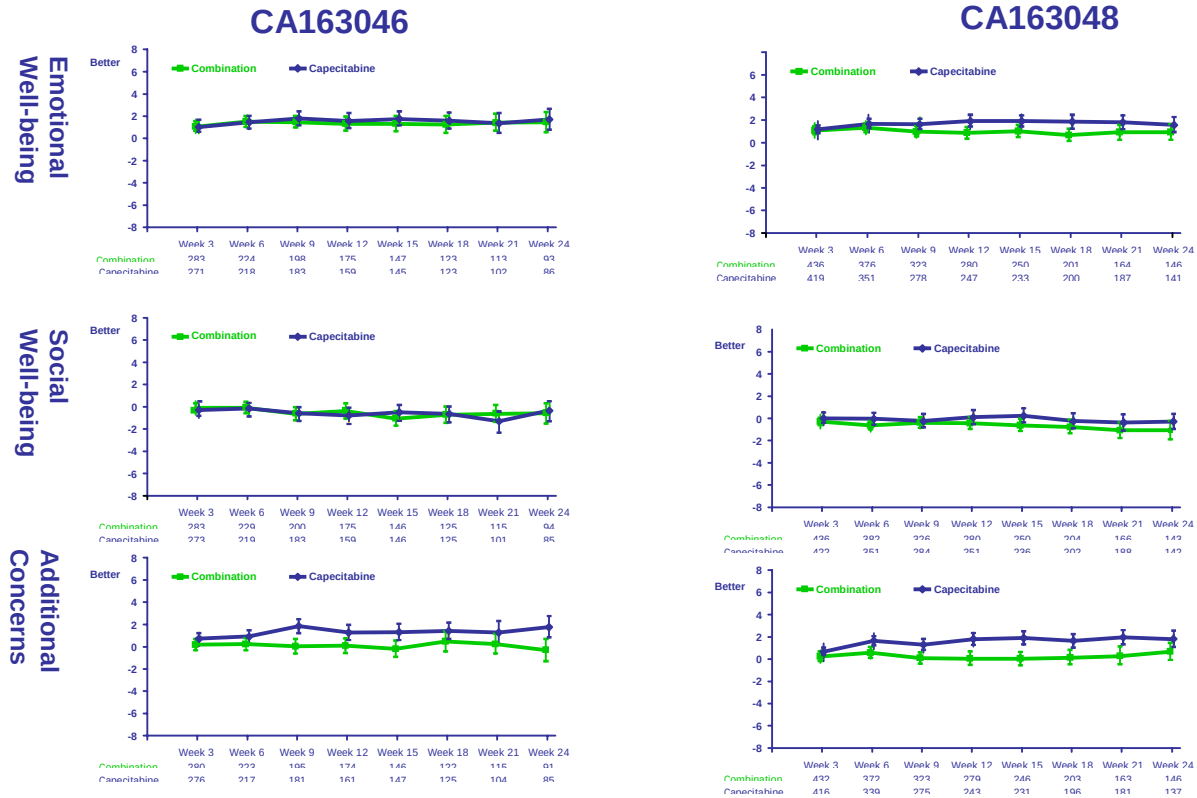


Figure 11 **FACT-B Emotional Well-Being, Social Well-Being and Additional Concerns Subscales**



- Discussion on clinical efficacy

Only single-arm studies with response as primary end-point have been conducted with ixabepilone monotherapy in breast cancer. The magnitude of the treatment effect is too small to prove patient benefit with reasonable certainty. The results could not be regarded as “dramatic” in any respect, and are therefore historical comparisons were not considered sufficient as sole support for licensing

ixabepilone as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumours are resistant or refractory to cytotoxic chemotherapy. For an approval as monotherapy in this target population, patients benefit should be demonstrated according to current standards, i.e. in a randomised trial vs. BSC or investigator's choice.

Concerning the combination, the main difference between the patient populations in the two studies is the grade of refractoriness, the population in CA 163046 was resistant and exposed to up to 3 lines of chemotherapy while the population in CA 163048 was pretreated and exposed to up to 2 lines of therapy before entering the study. The results were as expected with a better ORR of the reference treatment, capecitabine alone, 29 vs 14 % in the less refractory as compared to the more resistant group of patients. Both populations showed increased rates, 43 and 35 %, when ixabepilone was added to capecitabine.

An effect of combination therapy with ixabepilone and capecitabine in patients with MBC, previously exposed to anthracycline and taxane therapies, was observed in terms of prolongation of PFS of less than 2 months and hazard ratios of 0.75-0.79. This effect was considered as modest. Increased OS was also observed with median OS increased by approximately one month and a hazard ratio of 0.9 although these results were less convincing statistically.

The CHMP had concerns about the efficacy of ixabepilone combination treatment and convened a Scientific Advisory Group (SAG) meeting to provide advice on the list of questions raised by the CHMP. Regarding the combination indication, the CHMP asked the SAG if the effect on PFS (positive) and no negative effect on OS was adequate in demonstrating efficacy of ixabepilone in this indication. The SAG agreed that in general, PFS can be considered as a relevant clinical endpoint in this setting where delaying disease progression and prolonging survival constitute an important treatment goal. One can also expect that an effect in disease progression will correspond to a relevant effect on disease symptoms. To establish the efficacy, the effect observed in terms of PFS should be sufficiently large and ideally should be supported by an effect on symptoms control and health-related quality of life. For the combination of ixabepilone plus capecitabine, the effect in terms of PFS was statistically significant, but the estimated difference in median PFS was less than 2 months, so, the clinical impact may be considered to be of modest relevance. No detriment in OS has been observed compared to capecitabine alone (transient effect yielding to an overall hazard ratio=0.90). It has been claimed that a slight negative effect in terms of health related quality of life has been observed for the combination, which, however, might be of no clinical significance. If these claims are valid, the effect on PFS observed for the combination of ixabepilone plus capecitabine compared to capecitabine alone can be considered as a minimal difference to be of clinical importance, but still sufficiently large to establish the efficacy of the combination of ixabepilone plus capecitabine. Concerning the clinical relevance of the outcome in terms of PFS, the SAG agreed that the effect on PFS observed for the combination of ixabepilone plus capecitabine compared to capecitabine alone can be considered as a minimally clinically relevant difference. Concerning the observed effect on OS, the SAG agreed that based on exploratory analyses, including analyses adjusted for important prognostic factors, it is possible to rule out any important detriment in OS for the combination of ixabepilone plus capecitabine compared to capecitabine alone.

Concerning the QOL results presented by the applicant, the CHMP was of the opinion that it is unusual to find differences with statistical significance in QOL in patients with advanced cancers. The magnitude of the observed differences would indeed have been too small to support a claim had they been in a positive direction. However, when these differences are in the favor of the control arm, it cannot be concluded that the experimental arm is devoid of detrimental effects on the patients QOL. In contrast, it is probable that the safety profile of Ixempra is reflected by these results. This is important in a palliative treatment setting. Furthermore, the drop-out rate was problematic and the design of the QOL investigation was favoring the control arm as QOL was not determined after patients were progressing. Thus the negative impact of disease progression was not revealed and this favoured the control arm. However, the imputation technique proposed by the applicant (score=0 at radiological progression) not conservative and the lack of difference seen after this imputation should be interpreted with caution.

Clinical safety

The overall safety database for ixabepilone consists of 3,250 patients treated in applicant-sponsored completed and ongoing Phase I, II and III studies. The review of the safety of ixabepilone for the proposed indications is focused on the following groups:

- 431 patients with MBC treated with combination therapy in study CA163046 (n = 369) and study CA163031 (n = 62) at the recommended dose of 40 mg/m^2 ixabepilone on Day 1 and 2,000 mg/m^2/day capecitabine on Days 1-14 every 3 weeks. Also included for comparison are the 368 patients in study CA163046 who received capecitabine alone at a dose of 2,500 mg/m^2/day on Days 1-14 every 3 weeks.

- 240 patients with MBC treated with ixabepilone monotherapy in studies CA163081 (n = 126), CA163009 (n = 49) and CA163010 (n = 65) and neoadjuvant study in invasive breast cancer study CA163080 (n = 161) at the recommended dose of 40 mg/m^2 administered by i.v. infusion over 3 hours every 3 weeks.

Depending on relevance, the safety information for the combination and monotherapy indications is based on the patients in the primary efficacy and safety studies (i.e., study CA163046 for combination therapy and study CA163081 for monotherapy) or on the pooled datasets: combination (n = 431) and monotherapy (n = 240) studies.

- Patient exposure

Table 15 Summary of Patient exposure to ixabepilone in patients enrolled in monotherapy and combination therapy

	Patients enrolled	Patients exposed	Median number of treatment cycles (range)	Number of cycles administered at proposed dose level (40 mg/m^2)
Monotherapy				
CA163081	128	126	4 (1-16)	79.7%
CA163009	49	49	3 (1-15)	74.4%
CA163010	65	65	6 (1-14)	82.0%
Combination Therapy				
CA163046:				
Ixabepilone + Capecitabine	375	369	5 (1-37)	63.5%
Capecitabine	377	368	4 (1-33)	
CA163031:				
Ixabepilone + Capecitabine	64	62	4 (1-20)	64.3%

A summary table presents patient exposure to ixabepilone (Table 15). In study CA163081, patients received a median of 4 (range 1-16) cycles of therapy. 35 % of patients received ≥ 6 cycles, 25 % received ≥ 8 cycles. 80 % of cycles were administered at the planned dose, 20 % were administered at a reduced dose, most commonly due to peripheral neuropathy. 70 % of patients received ≥ 90 % of their relative dose intensity. The primary reason for discontinuation of the study was disease progression.

In study CA163046, the control arm capecitabine was given in a dose of 1250 mg/m^2 taken orally BID on Days 1 to 14 every 3 weeks. Patients in the experimental arm received a median of 5 cycles of study treatment (range 1-37), compared with 4 cycles in the control arm (range 1-33). On-treatment deviations were registered in 23 (6 %) in the experimental arm and 13 (4 %) in the control arm. In the experimental arm 51 % of patients had at least one dose reduction of ixabepilone and 45 % had at least one dose reduction of capecitabine. In the control arm 37 % had at least one dose reduction. 62 % of patients in the experimental arm and 45 % in the control arm required dose delays. In the experimental

arm 64 % of cycles were administered at the planned ixabepilone dose and 70 % at the planned capecitabine dose, in the control arm 64 % of cycles were at the planned capecitabine dose. In the experimental arm nearly half of treated patients received > 90 % of the relative dose intensity of ixabepilone, and 88 % received > 70 %. In the experimental arm nearly ¼ of patients received > 90 % of their relative dose intensity of capecitabine compared with nearly ½ in the control arm. In the experimental arm 62 % of patients received > 70 % of their relative dose intensity of capecitabine compared with 82 % in the control arm. In the experimental arm 18 % discontinued ixabepilone and continued on capecitabine, while 8 % discontinued capecitabine and continued on ixabepilone.

For studies 163009 and 163010), the median cumulative dose and median dose intensity was 159.6 mg/m^2 (range 0.6 to 626.3 mg/m^2) and 12.8 mg/m^2/week (range 0.2 to 14.2 mg/m^2/week, respectively. The median cumulative dose per patient was highest in CA163010 (206.5 mg/m^2) and lowest in CA163009 (120.0 mg/m^2). In CA163081, the median cumulative dose and median dose intensity was 156.9 mg/m^2 (range 0.6 to 626.3 mg/m^2) and 12.8 mg/m^2/week (range 0.2 to 14.2 mg/m^2/week), respectively. Across the 3 studies, about two thirds of patients received ≥ 90% of the planned dose intensity, ranging from 57% in CA163010 to 70% in CA163081.

For study CA163046, the median cumulative dose and median dose intensity of ixabepilone was 184.9 mg/m^2 and 11.8 mg/m^2/week, respectively. About half of patients (47%) received ≥ 90% of the protocol assigned dose of ixabepilone. Whereas for study CA163031, the median cumulative dose of ixabepilone was 161.1 mg/m^2. The relative dose intensity of ixabepilone was ≥ 90% for 53% of patients.

- Adverse events

Of the 240 patients in the monotherapy in the metastatic breast cancer setting studies, 231 (96%) patients reported at least 1 treatment-related AE. The majority of treatment-related AE were mild to moderate (Grade 1/2) in severity.

The most frequently reported (≥ 20%) treatment-related AE of any grade by composite categories included fatigue/asthenia (63%), peripheral sensory neuropathy (64%), alopecia (59%), arthralgia/myalgia (58%) and GI events including nausea (48%), stomatitis/mucositis (30%), vomiting (30%) and diarrhoea (26%).

The most frequently reported Grade 3/4 treatment-related AE are presented in table X211. The most frequently reported AE was peripheral sensory neuropathy, which was reported as Grade 3 in 37 (15%) patients and Grade 4 in 1 (< 1%) patient.

Table 16 Studies 163081, 163009, 163010 and 163080 – Grade 3/4 Treatment-related AEs Reported in ≥ 5% of Patients – Monotherapy

	Number (%) of Patients, 40 mg/m^2				
	CA163081	**CA163009**	**CA163010**	**CA163 081/009/010**	**CA163080**
Grade 3/4 Adverse Event[a]	**N = 126**	**N = 49**	**N = 65**	**N = 240**	**N = 161**
Peripheral sensory neuropathy	17 (13)	7 (14)[b]	14 (22)[b]	38 (16)	4 (2)
Fatigue/asthenia	16 (13)	13 (27)	4 (6)	33 (14)	3 (2)
Arthralgia/myalgia	10 (8)	5 (10)	7 (11)	22 (9)	3 (2)
Stomatitis/mucositis	8 (6)	2 (4)	3 (5)	13 (5)	3 (2)

[a] By composite categories (Appendix 2B).

[b] The CA163009 and CA163010 study reports used the CTC dictionary. The incidence of peripheral sensory neuropathy reported in these studies using CTC coding was 12% and 20%, respectively.

The safety profile of the combination therapy with ixabepilone plus capecitabine was consistent with that of the individual agents. In study CA163046, the frequency and severity of toxicities typically associated with capecitabine (e.g., hand and foot syndrome, diarrhoea and stomatitis) were similar between the 2 groups. As with ixabepilone monotherapy, the most common non haematologic toxicity for the combination was peripheral neuropathy. Nearly all patients (96%) of the 369 patient treated with ixabepilone plus capecitabine reported at least 1 treatment-related AE. The most frequently

reported (≥ 20%) treatment-related AE of any grade included peripheral sensory neuropathy (64%), hand and foot syndrome (MedDRA preferred term of palmar-plantar erythrodysaesthesia syndrome, 64%), fatigue/asthenia (60%), nausea (53%), diarrhoea (44%), vomiting (39%), arthralgia/myalgia (38%), anorexia (34%), stomatitis/mucositis (31%), alopecia (31%), abdominal pain (24%), nail disorder (24%), musculoskeletal pain (23%) and constipation (22%).

The most common (≥ 5%) Grade 3/4 treatment-related AE reported by patients receiving ixabepilone alone (Table 16) and ixabepilone plus capecitabine are presented in Table 17.

Table 17 Studies CA163046 and CA163031 – Grade 3/4 treatment-related AE reported in ≥ 5% of Patients, combination therapy

	CA163046		CA163031
	Ixabepilone + capecitabine N = 369	Capecitabine N = 368	Ixabepilone +capecitabine N = 62
Hand and foot syndrome[a]	67 (18)	62 (17)	21 (34)
Fatigue/asthenia	58 (16)	15 (4)	21 (34)
Arthralgia/myalgia	31 (8)	1 (<1)	15 (24)
Peripheral sensory neuropathy	78 (21)	0	12 (19)
Nausea	12 (3)	6 (2)	10 (16)
Diarrhoea	22 (6)	33 (9)	6 (10)
Vomiting	13 (4)	7 (2)	6 (10)
Constipation	0	1 (<1)	4 (6)

[a] Hand and foot syndrome was graded using Roche criteria in CA163046 and NCI criteria in CA163031

Myelosuppression

Myelosuppression was primarily manifested as neutropenia and leucopenia. Of the 240 patients in the 3 monotherapy studies, Grade 3 and 4 neutropenia was reported in 30 and 25% of patients, respectively. WBC growth factors were used in 13% of patients across the 3 studies. Time to nadir was typically 8 days after administration of ixabepilone and recovery usually occurred within the 21-day cycle. Neutropenia did not commonly lead to dose delays or dose reductions. In the 3 monotherapy studies, 26 (11%) patients had a cycle delayed because of neutropenia and 9 (4%) patients had a dose reduction because of neutropenia.

The incidence of infectious complications associated with febrile neutropenia and infection, was 4 and 5%, respectively. One patient with severe heart disease at baseline died of ixabepilone-related septic shock and neutropenia in Cycle 1. All other patients with febrile neutropenia or infection with neutropenia had resolution of their symptoms and most continued to receive additional cycles of ixabepilone, some at a reduced ixabepilone dose. Among the 240 patients in the monotherapy studies, 24 had baseline AST or ALT > 2.5x ULN or bilirubin > 1.5x ULN and none died of neutropenia-related causes.

Anaemia and thrombocytopenia occurred less frequently and were predominantly Grade 1 and 2. Anaemia was often present at baseline (34%) in this advanced, heavily pretreated population.

Neutropenia associated with the combination of ixabepilone plus capecitabine required white blood cell (WBC) growth factor support in 20% of patients. The frequency of Grade 3 and 4 neutropenia in study CA163046 was 32 and 36%, respectively. The frequency of febrile neutropenia and infection was 5 and 6%, respectively.

In study CA163046, there were 12 (3%) treatment-related neutropenic deaths in the ixabepilone plus capecitabine group compared with 2 (1%) in the capecitabine group. While the study was recruiting, initial reports of on-study deaths indicated that patients with Grade ≥2 ALT, AST or bilirubin at baseline were at higher risk of myelosuppression and of neutropenia-related death. As a result, the protocol was amended to exclude further recruitment of such patients. Excluding such patients, the incidence of on-study neutropenic deaths in patients with either normal liver function or mild hepatic impairment treated with the combination of ixabepilone plus capecitabine was 2% (7 of 353 patients). Of the 16 patients with Grade ≥2 ALT, AST or bilirubin, 5 died (31%). Combining data from both combination studies, studies CA163046 and CA163031, 8 (2%) neutropenic deaths occurred in the

414 ixabepilone plus capecitabine patients with normal or baseline Grade ≤ 1 ALT or AST or bilirubin.

Anaemia, which was often present at baseline in this heavily pretreated population, was predominantly Grade 1/2, with few patients (13%) requiring blood transfusions.

Nearly half of patients treated with the combination did not develop thrombocytopenia. When thrombocytopenia occurred, it was primarily Grade 1/2 in severity.

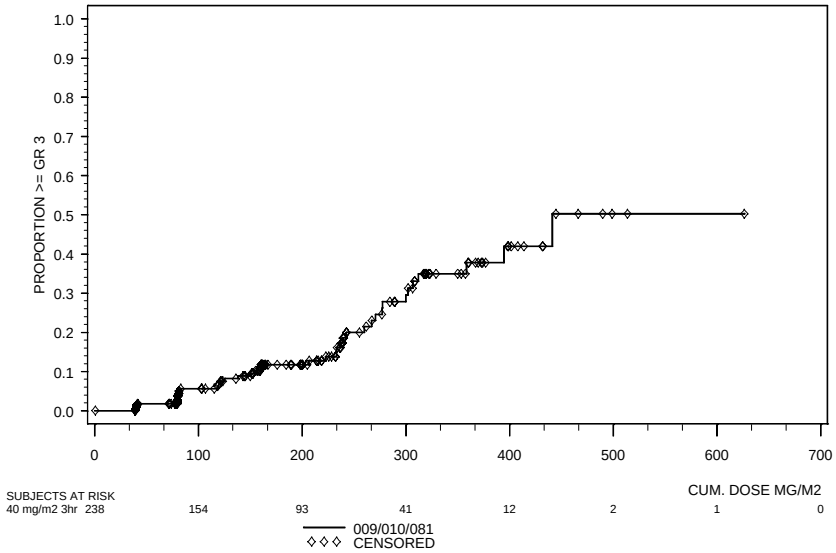
Peripheral neuropathy

Peripheral neuropathy is the main non-haematologic toxicity of ixabepilone. Peripheral neuropathy was reported in 67% of patients in study CA163046 and in 62% of patients in study CA163081 (64% across the 3 monotherapy studies). Painful neuropathies, as defined by the occurrence of neuropathic pain, dysaesthesia or neuralgia, were reported in 6% of patients in study CA163046 and in 6% of patients in the 3 monotherapy studies. Peripheral motor neuropathy was reported in 16% of patients in study CA163046 and in 7% of patients in the 3 monotherapy studies and usually occurred in patients with sensory neuropathy. Autonomic neuropathy was rare, occurring in 2% of patients in study CA163046 and in 1% of patients in the 3 monotherapy studies. The ixabepilone studies focused on patients who were resistant to prior therapies, including taxanes. As such, a proportion of patients had baseline peripheral sensory neuropathy (24 and 27% in studies CA163046 and CA163081, respectively), though patients with Grade 2 or higher peripheral neuropathy (sensory or motor) at study entry were excluded from studies with ixabepilone.

The risk of neuropathy was cumulative (Figure 12). Across studies, the highest rates of severe (Grade 3/4) peripheral neuropathy were reported in studies with the highest cumulative exposure to ixabepilone and the highest number of cycles on treatment. Severe peripheral neuropathy was reported more frequently with combination therapy than with monotherapy, consistent with the higher number of cycles of treatment prior to progression on the combination therapy compared with many of the monotherapy studies.

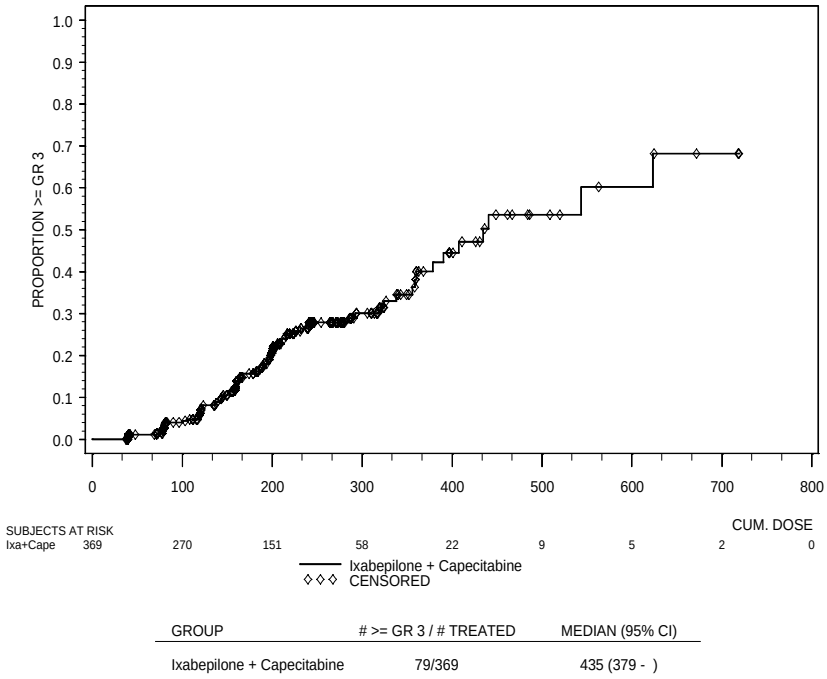
Figure 12 Studies CA163081 and CA163046 – Cumulative dose to onset of Grade 3 or higher for peripheral neuropathy

Study CA163081



GROUP	# >= GR 3 / # TREATED	MEDIAN (95% CI)
009/010/081	39/238	441 (395 -)

Study CA163046



GROUP	# >= GR 3 / # TREATED	MEDIAN (95% CI)
Ixabepilone + Capecitabine	79/369	435 (379 -)

In the primary combination therapy study CA163046 and the 3 monotherapy studies CA163081, CA163009 and CA163010, the incidence of Grade 3/4 peripheral (sensory and motor) neuropathy was 23 and 16%, respectively and the median cumulative dose to Grade 3/4 peripheral neuropathy was similar at 163 mg/m^2 and 160 mg/m^2, respectively. Given the cumulative nature of neuropathy, objective responses were first observed in most patients prior to the onset of severe neuropathy. A Cox analysis of risk factors to neuropathy with ixabepilone showed that diabetes was a risk factor, but prior neurotoxic therapy or presence of baseline neuropathy were not (as indicated earlier, patients with Grade > 1 neuropathy had been excluded from the studies). In study CA163046, Grade 3/4 sensory and motor neuropathy was reported in 21 and 5% of patients, respectively. The median time to resolution of Grade 3/4 peripheral neuropathy was 6.0 weeks from onset (Table 18 and Figure 13). Peripheral neuropathy was managed through dose reduction, which allowed most patients (67/84, 80%) to continue ixabepilone either with improvement or no worsening of their neuropathy.

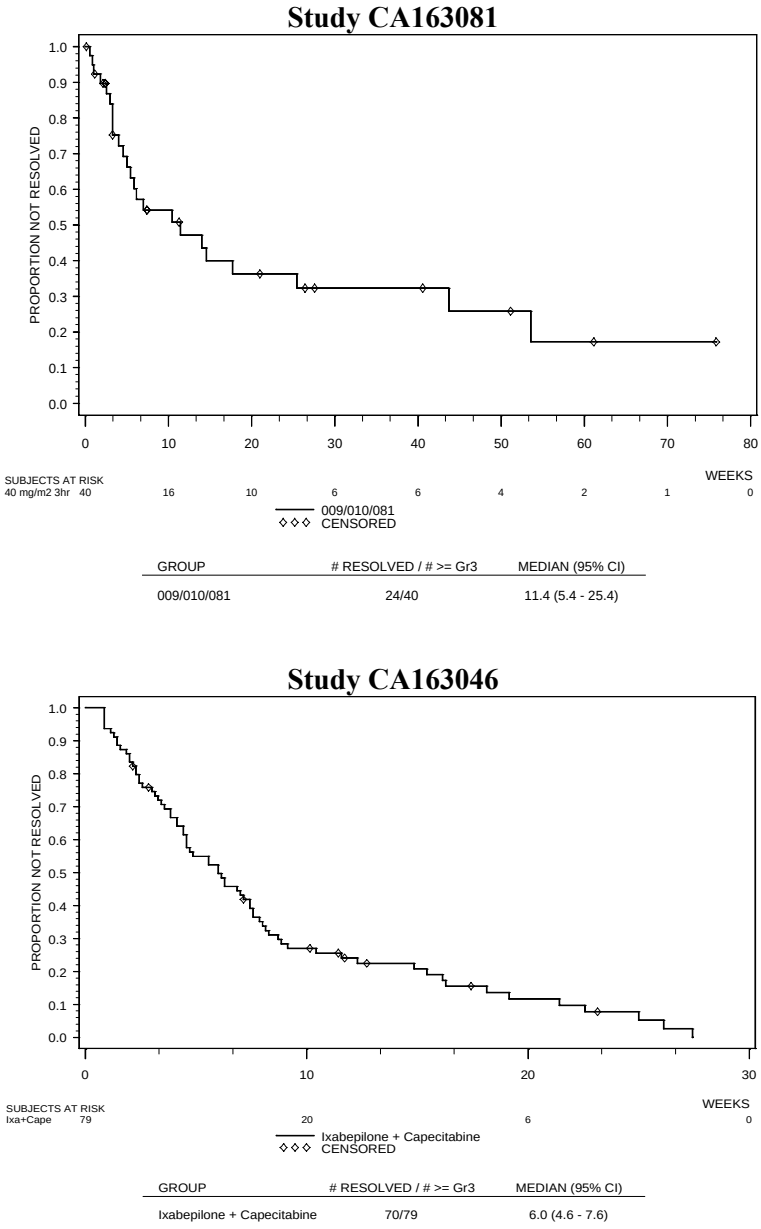
Peripheral neuropathy reported in the 3 monotherapy studies was primarily sensory and Grade 1/2 in severity, related to cumulative dose. Neuropathy was managed through dose reductions, which allowed most patients (37 of 42 patients, 88%) to continue ixabepilone either with improvement or at least no worsening of their neuropathy. The neuropathy associated with ixabepilone was generally reversible. In study CA163081, the median time to resolution of Grade 3/4 peripheral neuropathy was 5.4 weeks from onset (Table 18 and Figure 3).

Table 18 Studies CA163046 and CA163081 – Treatment-related peripheral neuropathy

	Study CA163046 Ixabepilone plus capecitabine	Study CA163081 Ixabepilone monotherapy
Peripheral neuropathy (All grades)	67%	62%
Grade 3/4 neuropathy	23%	13%
Baseline neuropathy (All grades)	24%	27%
Discontinuation due to neuropathy	21%	6%
Median cycles until discontinuation	6	8
Median number of cycles to onset of grade 3/4 neuropathy	4	4
Median time to improvement[a] of grade 3/4 neuropathy	4.1 weeks	4.6 weeks
Median time to resolution[b] of grade 3/4 neuropathy	6.0 weeks	5.4 weeks

[a] Improvement was defined as a decrease in symptoms by one grade
[b] Resolution was defined as a return of symptoms to baseline or Grade 1

Figure 13 Studies CA163081 and CA163046 – Time to resolution of Grade 3 or higher peripheral neuropathy



Cardiac events

A number of chemotherapeutic agents (anthracyclines, trastuzumab, paclitaxel and capecitabine) and chest wall radiography have been associated with cardiac events.

In non-clinical studies, ixabepilone had no effect on action potential parameters in isolated rabbit Purkinje-fibers and only weakly inhibited cardiac potassium currents at concentrations approximately 89-fold greater than the C_{max} in patients. There were no ixabepilone-related changes in cardiovascular function observed in studies conducted in dogs.

In study CA163046, the frequency of treatment-related cardiac events (e.g., myocardial ischemia and ventricular impairment) was higher with the combination of ixabepilone plus capecitabine (1.9%) than with capecitabine alone (0.3%). Two (0.2%) of 850 patients treated with ixabepilone as monotherapy had treatment-related myocardial ischemia (including one with known risk factors who developed a myocardial infarction). Confounding factors, including the presence of risk factors for cardiac disease and prior anthracycline exposure, were present in most of the patients who had cardiac events while

receiving ixabepilone alone or in combination with capecitabine and a number of cases could not be clinically substantiated.

The cardiac findings in the monotherapy and combination therapy do not raise safety concerns about ixabepilone. The clinical profile in these patients does not suggest an underlying effect on QT interval.

- Serious adverse event/deaths/other significant events

Deaths

In the monotherapy studies (studies CA163081, CA163009 and CA163010), 17 of 240 patients (7%) died on study. One patient in study CA163081 died of study drug toxicity, 10 died of disease progression and 6 of causes unrelated to study drug.

In the combination therapy, study CA163046 had 33 patients (9%) treated with ixabepilone plus capecitabine die on study (defined as deaths within 30 days of last dose) compared to 39 (11%) for capecitabine alone (Table 19). The majority of these deaths (16 out of 33 and 32 out of 39 in the combination and capecitabine groups, respectively) were related to disease progression. However, the combination group had more on-study deaths due to study drug toxicity than in the capecitabine group: 12 (3%) and 2 (1%), respectively. The higher on-study death rate in the combination group was detected while the study was recruiting and it became apparent that the deaths were primarily neutropenia related, with the highest rate in patients with moderate/severe hepatic impairment (defined as aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 2.5x ULN or bilirubin > 1.5x ULN). This was reported to the Data Monitoring Committee (DMC) and a protocol amendment was implemented to exclude further recruitment of such patients into the study. In study CA163031, 2 patients (3%) died on-study; one of disease progression and the other of study drug toxicity.

Table 19 Studies CA163046 and CA163031 – Deaths within 30 days of last dose

	CA163046		CA163031	CA163046/031
	Ixabepilone + capecitabine N = 369	Capecitabine N = 368	ixabepilone +capecitabine N = 62	ixabepilone +capecitabine N = 431
Deaths ≤ 30 days of last dose	33 (9)	39 (11)	2 (3)	35 (8)
Study Drug Toxicity	12 (3)[a]	2 (1)	1 (2)	13 (3)
PD	16 (4)	32 (9)	1 (2)	17 (4)
Other Causes	4 (1)	5 (1)	0	4 (1)
Unknown Causes	1 (<1)	0	0	1 (<1)

[a] 2 of these deaths were assessed as death due to "Disease" by the investigator but the applicant determined the deaths to possibly related to study medication after a review of the cases

Immunological events

Because ixabepilone is formulated in polyoxyethylated castor oil, all patients in the Phase II and III studies were required to receive H_1 and H_2 blockers (e.g., diphenhydramine and ranitidine) as premedication before each dose of ixabepilone. Steroids were not required as premedication, unless prior hypersensitivity reaction (HSR) had been reported. Patients with a prior history of HSR to polyoxyethylated castor oil were excluded from the studies.

Hypersensitivity reactions were reported in 79 (6%) of the 1323 patients who received any ixabepilone in the Phase II and III studies. Most HSR occurred in Cycles 1 (32/79; 41%) and 2 (36/79; 46%). Grade 3/4 hypersensitivity reactions, including anaphylaxis, were rare and were reported in 9 (1%) patients (all but 1 in the first 2 cycles), 3 of whom subsequently received additional cycles of ixabepilone. HSRs rarely led to discontinuation (< 1% of patients). There were no deaths due to hypersensitivity reactions.

- Laboratory findings

Haematologic laboratory tests

In studies CA16308, CA163009 and CA163010 hematologic toxicity consisted mostly of neutropenia and leukopenia. Neutropenia was Grade 3 in 30% and Grade 4 in 25% of patients. Anemia was often present at baseline (34%) and predominantly Grade 1/2 during treatment. Most patients had normal

platelet values at baseline and during treatment with ixabepilone. When thrombocytopenia occurred, it was predominantly Grade 1/2 in severity.

The use of WBC growth factors was reported for 13% of all treated patients in the 3 studies. ANC nadirs occurred at a median of 8 days after administration of ixabepilone (median ANC was 0.9 x 10^3 c/μL for all cycles. Neutropenia was not cumulative in nature, as Grade 3/4 neutropenia was reported in Cycle 1 for many patients. Recovery from neutropenia usually occurred within the 21-day cycle. Of the 240 patients, 26 (11%) had a dose delay because of neutropenia and 9 (4%) had a dose reduction because of neutropenia.

In study CA163046, hematologic toxicity with ixabepilone plus capecitabine consisted primarily of neutropenia and leukopenia. In the ixabepilone plus capecitabine group, neutropenia was Grade 3 in 32% and Grade 4 in 36% of patients. The rate of Grade 4 neutropenia is higher than the rate with monotherapy ixabepilone, which was 25%. The rate of Grade 4 neutropenia in the capecitabine only group was 2%. Anemia was often present at baseline in both groups and was predominantly Grade 1/2. Nearly half (46%) of patients treated with ixabepilone plus capecitabine had normal platelet values during treatment.

WBC growth factor support, most frequently filgrastim, was reported for 20% of patients in the ixabepilone plus capecitabine group**.** In the ixabepilone plus capecitabine group, the median time to ANC nadir was 9 days after administration of ixabepilone (median ANC was 0.7 x 10^3 c/μL for all cycles). The neutropenia with ixabepilone plus capecitabine was not cumulative in nature. Recovery from neutropenia usually occurred within the 21-day cycle; of the 369 patients, 21% had a dose delay because of neutropenia and 14% had a dose reduction because of neutropenia.

In study CA163031, the rates of Grade 3/4 neutropenia (69% vs 68%), thrombocytopenia (8% vs 8%) and anemia (7% vs 10%) were similar between CA163031 and CA163046.

Hepatic function tests

In studies CA163081, CA163009 and CA163010, baseline abnormalities in LFTs (i.e., AST, ALT, ALP and total bilirubin) were common (e.g., AST, 30%; ALT, 20%) 6265

and primarily Grade 1/2 in severity. On-treatment LFT abnormalities were primarily Grade 1/2; Grade 3/4 abnormalities for each LFT were reported in ≤ 5% of patients. Across all 240 patients, there were no reported Grade 4 bilirubin or transaminase (AST or ALT) elevations. Maximum transaminase values across all patients were < 550 U/l for both parameters. Nearly all Grade 3/4 LFT abnormalities were reported in patients who had similar abnormalities at baseline and/or metastatic disease in the liver. Each of these patients discontinued ixabepilone because of PD, many with progression in the liver and in many cases the abnormality coincided with this progression.

In study CA163046, there were fewer Grade 3/4 LFT abnormalities and AE related to hepatic function abnormalities in the ixabepilone plus capecitabine group than in the capecitabine group. AE related to hepatic function abnormalities considered at least possibly related to study medication were reported in 3% of patients in each group. In study CA163031, there were no reported AE related to hepatic function abnormalities.

In study CA163046, baseline abnormalities in AST, ALT, ALP and total bilirubin were common (e.g., AST and ALT abnormalities were ≥ 20% in both groups) and primarily Grade 1/2 in severity. On-treatment LFT abnormalities were primarily Grade 1/2 in both groups. The frequency of Grade 3/4 LFT abnormalities was higher in the capecitabine group than in the ixabepilone plus capecitabine group. One (< 1%) patient in each group had a Grade 4 transaminase elevation (the 1 patient in the ixabepilone plus capecitabine group [CA163046-5-705] had Grade 4 elevations in both AST and ALT).

On-treatment Grade 3/4 abnormalities in ALP, ALT and AST were primarily reported in patients who had similar abnormalities at baseline. In the ixabepilone plus capecitabine group, this included 3 of 4 patients with Grade 3/4 ALP, 1 of 3 patients with Grade 3/4 ALT and 4 of 7 patients with Grade 3/4 AST. Similar results were observed in the capecitabine group (16 of 18 patients with Grade 3/4 ALP, 6 of 8 patients with Grade 3/4 ALT and 8 of 11 patients with Grade 3/4 AST). Consistent with the potential for capecitabine to induce hyperbilirubinemia, patients in both groups experienced hyperbilirubinemia and most patients with Grade 3/4 bilirubin abnormalities had a normal bilirubin

level at baseline (6 of 9 in the ixabepilone plus capecitabine group and 13 of 18 in the capecitabine group).

Kidney function tests

In study CA163081, CA163009 and CA163010, most patients had normal renal function at baseline and during treatment. Thirteen (6%) patients had on-treatment Grade 1 or 2 creatinine abnormalities; 3 of the 13 patients had Grade 1/2 creatinine abnormalities at baseline. There were no on treatment Grade 3/4 creatinine laboratory abnormalities. Among the 240 patients, renal events were reported in 1 (< 1%) patient. There were no renal events considered related to ixabepilone, no SAEs, and no discontinuations related to renal function abnormalities.

In study CA163046, most patients in both treatment groups had normal renal function at baseline and during treatment. Nearly all on-treatment creatinine abnormalities were Grade 1/2 in both groups; there were no Grade 3/4 creatinine abnormalities in the ixabepilone plus capecitabine group and 2 (1%) in the capecitabine group. In the ixabepilone plus capecitabine group, 3 (1%) patients had AEs related to renal function abnormalities. Two (1%) of these patients had events considered related to study medication (both events were Grade 3, 1 of the 2 was reported as an SAE).

- Safety in special populations

Age

The frequency of treatment-related Grade 3/4 AE and SAE was higher in patients ≥ 65 years of age compared with those < 65 years of age in both ixabepilone plus capecitabine and capecitabine alone groups. In the ixabepilone plus capecitabine group, the rate of toxicity-related deaths was 6.7% (3/45) in patients ≥ 65 years of age compared with 2.6% (10/386) in patients < 65 years of age. Among the 45 patients ≥ 65 years of age, 43 had normal hepatic function or mild impairment at baseline; the rate of toxic death among these patients was 4.7% (2/43). In the capecitabine only group, the rate of toxicity-related deaths in patients who were ≥ 65 years of age was 1.9% (1/53).

In the ixabepilone plus capecitabine group, the rate of toxicity-related deaths was 4.4% (12/270) in patients ≥ 50 years of age compared with 0.6% (1/161) in patients < 50 years of age. In the capecitabine only group, the rate of toxicity-related deaths in patients ≥ 50 years of age was 0.4% (1/228).

Patients with hepatic impairment

In the combination study, an association of greater toxicity in patients with baseline elevated ALT or AST levels was observed during the conduct of the study and brought to the attention of the DMC and discussed at an ad hoc DMC meeting. The DMC recommended that the protocol be amended (Amendment #4, dated 03 February 2005) to exclude patients with baseline AST, ALT or total bilirubin levels Grade ≥ 2, regardless of the presence of liver metastases. This amendment effectively created 2 subsets of patients: those with abnormal liver function (as defined in the amendment) and those without.

Table 20 summarises on-study deaths in the stratum of patients with AST, ALT or bilirubin Grade ≥ 2 vs. all others (normal or Grade 1 abnormal in all 3 liver function test [LFTs]).

Table 20 Studies CA163046 and CA163031 – Deaths within 30 days of last dose by baseline liver function

	Study CA163046 Ixabepilone +capecitabine		**Study CA163031 ixabepilone +capecitabine**		**Pooled data of ixabepilone +capecitabine**	
	Grade ≥ 2 N =16	**N/Gr 1 N = 353**	**Grade ≥ 2 N = 1**	**N/Gr 1 N = 61**	**Grade ≥ 2 N = 17**	**N/Gr 1 N = 414**
≤ 30 days of last dose	5 (31)	28 (8)	0	2 (3)	5 (29)	30 (7)
Study Drug Toxicity	5 (31)[a]	7 (2)[a]	0	1 (2)	5 (29)	8 (2)
PD	0	16 (5)	0	1 (2)	0	17 (4)
Other causes	0	4 (1)	0	0	0	4 (1)
Unknown causes	0	1 (<1)	0	0	0	1 (<1)

Grade ≥ 2 = AST or ALT > 2.5x ULN or bilirubin > 1.5x ULN, N/Gr1 = AST and ALT ≤ 2.5x ULN and bilirubin ≤ 1.5x ULN

[a] 1 of these deaths was assessed as death due to "Disease" but the applicant determined the death to possibly related to study medication after a review of the case

In the monotherapy studies, patients with AST or ALT > 2.5x ULN and normal bilirubin reported higher toxicity in terms of febrile neutropenia and treatment-related serious adverse events. The pharmacokinetics data from the study in patients with hepatic impairment (study S0355) indicate that exposure to ixabepilone is increased by 22% in patients with mild hepatic impairment (AST > ULN/bilirubin ≤ ULN or any AST and bilirubin between 1.0 and 1.5x ULN), 30% in patients with moderate hepatic impairment (any AST and bilirubin between 1.5 to 3x ULN) and 81% in patients with severe hepatic impairment (any AST and bilirubin > 3x ULN). Assessing both clinical and pharmacokinetic data, the recommended dosage adjustments are shown in Table 21.

In both combination therapy and monotherapy studies, there were no clinically relevant differences in safety profiles between patients with AST/ALT up to 2.5x ULN with normal bilirubin. For this patient group, no dosage adjustment is required and 40 mg/m^2 every 3 weeks of ixabepilone is recommended either as monotherapy or in combination with capecitabine.

Table 21 Dose adjustments for ixabepilone as monotherapy in patients with hepatic impairment

Degree of hepatic impairment			Recommended dose[a]
Transaminase levels		**Bilirubin levels**	**of ixabepilone (mg/m^2)**
AST and ALT ≤ 2.5x ULN	and	≤ 1x ULN	40 mg/m^2
AST or ALT > 2.5x ULN - ≤ 10x ULN[b]	and	≤ 1x ULN	32 mg/m^2
AST and ALT ≤ 10x ULN	and	>1x ULN - ≤ 1.5x ULN	32 mg/m^2
AST and ALT ≤ 10x ULN	and	>1.5x ULN - ≤ 3x ULN	20 mg/m^2

[a] Dosage recommendations are for first course of therapy; further decreases in subsequent courses should be based on individual tolerance

[b] Both AST and ALT must be ≤ 10x ULN

In addition to the increased exposure to ixabepilone with hepatic impairment, exposure to capecitabine is increased by 60% in patients with hepatic impairment. In study CA163046, patients with AST/ALT > 2.5x ULN or any raised bilirubin above ULN were at excessive risk of neutropenic deaths and, together with pharmacokinetic data indicating increased exposure to each drug, it is recommended such patients should not be treated with this combination (Table 22).

Table 22 Dose adjustments for ixabepilone as combination with capecitabine in patients with hepatic impairment

Degree of hepatic impairment			Recommended dose[c]
Transaminase levels		**Bilirubin levels**	**of ixabepilone (mg/m^2)**
AST and ALT ≤ 2.5x ULN	and	≤ 1x ULN	40
AST or ALT > 2.5x ULN	or	> 1x ULN	Contraindicated

[a] Dosage recommendations are for first course of therapy; further decreases in subsequent courses should be based on individual tolerance

- Safety related to drug-drug interactions and other interactions

Ixabepilone does not inhibit cytochrome P450 (CYP) 3A4 at relevant clinical concentrations and is not expected to alter the plasma concentrations of other drugs.

Substances that inhibit CYP3A4 activity may decrease the metabolism and increase plasma concentrations of ixabepilone. The effect of ketoconazole, a strong CYP3A4 inhibitor, on the pharmacokinetic of ixabepilone was studied in patients with advanced cancer (study CA163042). The most frequently reported Grade 4 AE were neutropenia, mucosal inflammation and acute renal failure. Treatment-related AE leading to discontinuation of study therapy were fatigue, hyperkalaemia and renal failure. Based on the data from this study, ketoconazole, a strong CYP3A4 inhibitor, increases

exposure to ixabepilone Therefore, the dose of ixabepilone must be reduced when coadministered with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine or voriconazole). The effect of mild or moderate inhibitors on exposure to ixabepilone has not been studied.

- Discontinuation due to adverse events

In the combination therapy studies, drug toxicity led to discontinuation in the ixabepilone plus capecitabine arm in 37% of patients in study CA163046 and 27% of patients in study CA163031. The most common reasons for discontinuation because of study drug toxicity were peripheral sensory neuropathy (attributable to ixabepilone) and hand and foot syndrome (attributable to capecitabine).

- Discussion on clinical safety

The most common acute toxicity associated with ixabepilone was myelosuppression, in particular neutropenia. The neutropenia was dose dependent and manageable with dose reductions. Febrile neutropenia occurred in 5.1 compared to 0.5 % of the patients treated with ixabepilone plus capecitabine and capecitabine alone, respectively. The rate of infections doubled in the combination arm.

There were 12 (3%) treatment related neutropenic deaths in the ixabepilone plus capecitabine group, and 2 (1%) in the capecitabine group. Patients with moderate to severe liver impairment (defined as AST or ALT >2.5 ULN or bilirubin >1.5 ULN) treated with the combination of ixabepilone plus capecitabine are at excessive risk of neutropenic death and should not be treated with this combination.

The main non-hematologic toxicity associated with ixabepilone is peripheral neuropathy which occurred in 64-67% of the patients across studies. Grade 3-4 events were reported in 23 and 13% in combination (CA163046) and monotherapy (CA163081) studies, respectively. The neuropathy was displayed primarily as sensory, cumulative and generally reversible. The median time to resolution was 5 to 6 weeks from onset. Dose modification and treatment delays made peripheral neuropathy more manageable, and therefore, most patients were able to continue treatment without worsening of their neuropathy. A baseline risk factor identified for severe peripheral neuropathy with ixabepilone was the presence of diabetes. Patients with > Grade 1 neuropathy were excluded from the clinical studies of ixabepilone.

Other common AEs associated with ixabepilone (eg, arthralgias/myalgias, alopecia, stomatitis, fatigue) were manageable and reversible. In the combination therapy of ixabepilone plus capecitabine, the most common AEs were peripheral neuropathy, hand-foot-syndrome, fatigue, nausea, diarrhea, vomiting, arthralgia, anorexia, stomatitis and other GI-disturbances. The most common Grade 3 and 4 AEs were hand-foot-syndrome, fatigue, arthralgia and peripheral, sensory neuropathy.

The frequency of treatment-related Grade 3/4 AEs and SAEs was higher in patients ≥ 65 years of age compared with those <65 years of age in the combination therapy as well as the monotherapy. In the ixabepilone plus capecitabine group, the rate of toxicity-related deaths was 6.7% (3/45) in patients ≥ 65 years of age compared with 2.6% (10/386) in patients < 65 years of age.

The safety profile was consistent with the sum of events related to the individual agents. However, increased toxicity is suspected in some subsets of patients, e.g. elderly patients. The drug toxicity caused treatment discontinuation rates in the combination studies (CA163046 and CA163031) and in the monotherapy study CA163010 of 37, 27 and 34 %, respectively. These are considered high discontinuation values when compared with 7% treatment discontinuations due to drug toxicity with capecitabine alone.

Overall, the CHMP had concerns about the safety of ixabepilone and asked how the SAG viewed the safety profile in relation to the efficacy documentation for the combination therapy indication. Concerning the combination of ixabepilone plus capecitabine compared to capecitabine alone, the SAG agreed that the increased toxicity was significant and was an important concern, particularly in terms of peripheral neuropathy (grade 3-4: crude proportion 23% vs 1%, and median time to occurrence = 12 weeks). It had been claimed that this was primarily sensory, and generally reversible in ±6 weeks. It had also been claimed that no clinical significant detriment in quality of life had been observed, using the Functional Breast Symptom Index (44-item questionnaire). If these claims were

valid then the majority of the SAG members agreed that the toxicity of the combination was significant but did not outweigh the minimally clinically relevant effect observed. The SAG noted, however, that the studies presented only assessed peripheral neuropathies using clinical examination by the participating physicians. The SAG considered that it was possible that this might have led to underreporting of the severity and duration of toxicity. Furthermore, according to the SAG the toxicity would be expected to be of longer duration based on the assumed pathogenetic mechanism of axonal degeneration. Although from a clinical perspective the available data were considered compatible with a minimally positive benefit-risk balance, the SAG agreed that further studies should be conducted, to assess the incidence, severity and duration of peripheral neuropathy based on sensitive measurements, and further studies should be conducted to study the pathogenetic mechanisms involved, aiming to minimise the risks associated with the combination of ixabepilone plus capecitabine.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product was considered to be acceptable when used in accordance with the conditions defined in the proposed SPC. Physicochemical aspects relevant to the uniform clinical performance of the product had been investigated and were controlled in a satisfactory way. There were no unresolved quality issues, which had a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

The non-clinical studies with ixabepilone provided a good description and characterisation of the pharmacology and toxicology using *in vitro* and *in vivo* models. The main excretion pathway for ixabepilone and its metabolites was via the faeces. Co-administration of ixabepilone and drugs that inhibit or induce CYP3A4 may increase or decrease ixabepilone at clinically relevant concentrations.

Neurotoxicity was identified as a major clinical toxicity of ixabepilone. Axonal/myelin degeneration and the testicular degeneration/atrophy was observed. These effects may not be reversible. In general, no NOAEL could be established. The toxicological findings were dose-related in incidence and severity.

Ixabepilone was genotoxic *in vivo* in the rat micronucleus test. There were no carcinogenicity studies that were conducted. Ixabepilone was also found to affect reproduction toxicity in pregnant rat and rabbit.

Efficacy

The efficacy of combination therapy with ixabepilone and capecitabine in patients previously exposed to an anthracycline and a taxane was investigated in the two pivotal Phase III trials CA163046 and CA163048, open-labeled, randomised, controlled studies. The results showed that PFS was 5.8 compared to 4.2 months [HR, 0.75; 95%CI, 0.64 - 0.88; P = 0.0003] in the combination arm compared to the capecitabine arm, respectively in study CA163046 and 6.2 compared to 4.4 months [HR, 0.79, 95%CI, 0.69 – 0.90; P = 0.0005] in the study CA1630048 in the combination arm as compared to the capecitabine arm, respectively. In terms of overall survival, the effect was minimal with 12.9 months in the combination arm compared to 11.1 months [HR, 0.9; 95%CI, 0.77 – 1.05; P = 0.1936] in the capecitabine arm in study CA163046 and 16.4 months in the combination arm compared to 15.6 months [HR, 0.9; 95%CI, 0.78 – 1.03; P = 0.1162] in the capecitabine arm in study CA163048.

Safety

The most common acute toxicity associated with ixabepilone was hematologic toxicity , in particular neutropenia. In study CA163046, the frequency of Grade 3-4 neutropenia was 68% in the combination arm of study compared to 11% in the capecitabine alone arm. There were 12 (3%) treatment related neutropenic deaths in the ixabepilone plus capecitabine group, and 2 (1%) in the capecitabine group. Liver impairment was identified as a risk factor for neutropenic death and a specific dose recommendation for the use of ixabepilone was proposed based on the level of hepatic impairment of the patient.

The main non-hematologic toxicity associated with ixabepilone was peripheral neuropathy, which occurred in 64-67% of the patients across studies. Grade 3-4 events were reported in 23 and 13% in combination (CA163046) and monotherapy (CA163081) studies, respectively. In most cases, the neuropathy was sensory, cumulative and generally reversible. The median time to resolution was 5 to 6 weeks from onset. With dose modification and treatment delays, most patients were able to continue treatment without worsening of their neuropathy. A baseline risk factor identified for severe peripheral neuropathy with ixabepilone was the presence of diabetes. Patients with a baseline of Grade 1 or higher neuropathy were excluded from the clinical studies of ixabepilone.

Other common AEs associated with ixabepilone (eg, arthralgias/myalgias, alopecia, stomatitis, fatigue) were manageable and reversible. In the combination therapy of ixabepilone plus capecitabine, the most common AEs were peripheral neuropathy, hand-foot-syndrome, fatigue, nausea, diarrhea, vomiting, arthralgia, anorexia, stomatitis and other GI-disturbances. The most common Grade 3 and 4 AEs were hand-foot-syndrome, fatigue, arthralgia and peripheral, sensory neuropathy.

- User consultation

User testing of the PL was performed in English. The user testing of the PL was judged as acceptable.

Risk-benefit assessment

An effect of combination therapy with ixabepilone and capecitabine in patients with MBC, previously exposed to anthracycline and taxane therapies, was observed compared with capecitabine alone in two large phase III studies. However, the prolongation of median PFS of less than 2 months and hazard ratios of 0.75-0.79 was considered as modest by the CHMP. An effect on OS was observed, but the results were not statistically significant in the primary efficacy analysis. Treatment associated toxicity caused high treatment discontinuation rates and a high frequency of Grade 3-4 neutropenia was observed. Febrile neutropenia occurred in 5.1% and 7% of the patients treated with ixabepilone and capecitabine in the combination arm of the phase III studies. In monotherapy studies febrile neutropenia occurred in 1-5% of the patients. Peripheral neuropathy was the main non-hematologic toxicity associated with ixabepilone, occurring in 64-67% of the patients across studies. Grade 3-4 events, i.e. neuropathy interfering with daily activities, were reported in 23/ 24% in combination studies (CA163046/ CA163048) and 13% in the pivotal monotherapy (CA163081) study. The neuropathy was primarily sensory, cumulative and generally reversible. However, the CHMP had concerns about the benefit-risk profile of ixabepilone combination treatment and convened a Scientific Advisory Group meeting to provide advice on the list of questions raised by the CHMP.

The applicant attended an oral explanation at the CHMP. In its presentation, the applicant presented a number of arguments about the benefit risk of the combination of ixabepilone and capecitabine in the applied indication. The applicant argued that relevant and consistent efficacy had been shown in large randomised trials, that the safety profile was predictable and similar to other chemotherapeutic regimens. Concerning the peripheral neuropathy, despite pre-existing neuropathies, according to the applicant the rate of neuropathy was similar to that of other chemotherapeutic regimens and that the studies presented consistently demonstrated rapid resolution of drug-induced neuropathy (~ 6 weeks). According to the applicant, no clinically meaningful changes quality of life (QoL) occurred over time within each treatment arm, and that QoL was maintained during treatment with the combination. The applicant also submitted a further analysis to highlight the large unmet medical need in patients with estrogen receptor negative, progesterone receptor negative, and HER2-negative tumours, which represented 20% of the studied population, and highlighted the convincing efficacy results of the analyses in these subpopulations, whilst the neuropathy was considered to be sensory, manageable, and reversible as for the whole studied population.

Following the recommendations of the scientific advisory group and the oral explanation from the applicant, and the additional argumentation submitted by the applicant, the CHMP maintained the view that the modest benefit demonstrated in terms of prolonged progression-free survival and trends towards improved overall survival was not of sufficient magnitude to outweigh documented toxicity.

A minority of CHMP members disagreed. Their minority view was that significant improvement in PFS and ORR with the addition of ixabepilone to capecitabine, and trend in the direction of an improvement in OS, indicated significant benefit in these heavily pretreated patients. Some of the responses were long-lasting. According to this view, neurotoxicity is not an uncommon toxicity in the metastatic solid tumour setting and is adequately managed for a number of agents through rules for treatment discontinuation, dose reductions etc. when encountering these symptoms. The applicant conducted a very thorough assessment of the neurotoxicity and established that the neurotoxicity observed for the combination of ixabepilone and capecitabine was manageable and reversible and that it had no clinically significant impact on QoL. According to this minority view, the data presented indicated a positive benefit-risk profile in the proposed indication.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Ixempra in the treatment of locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy in combination with capecitabine in patients failing prior therapy with a taxane and an anthracycline or for whom further anthracycline therapy is not indicated, was unfavourable and therefore did not recommend the granting of the marketing authorisation.

GROUNDS FOR REFUSAL

- The CHMP considered that the effect in terms of PFS as demonstrated in the two pivotal studies did not outweigh the safety concerns, which primarily related to the frequency and magnitude of neuropathy.