# SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 21 March 2002. For scientific information on procedures after this date please refer to module 8B.

## 1. Introduction

Myocet is a liposome formulation of a clinically well-established drug, doxorubicin hydrochloride (HCl), and an anthracycline cytotoxic agent. Myocet, in combination with cyclophosphamide, is indicated for the first line treatment of metastatic breast cancer in women. The product is presented as a three-vial system; Myocet doxorubicin HCl, Myocet liposomes and Myocet buffer. At constitution, the doxorubicin HCl is dissolved in 20 ml 0.9% sodium chloride for injection and heated before a mixture of the liposomes and the buffer is added to form a liposome-encapsulated doxorubicin-citrate complex. The resulting reconstituted preparation of Myocet contains 50 mg of doxorubicin HCl/25 ml of concentrate for liposomal dispersion for infusion (2 mg/ml). The recommended initial dose is 60-75 $mg/m^2$ every 3 weeks in combination with cyclophosphamide (600 $mg/m^2$). Myocet should be constituted and diluted prior to administration and should be administered by intravenous (i.v.) infusion over a period of one hour.

**Anthracyclines**

Anthracyclines still belong to the most commonly used cytotoxic agents against haematological as well as solid tumours. Since their introduction in cancer treatment in the late 1960's, anthracyclines have been associated with cardiotoxicity.

Anthracycline-induced cardiomyopathy appears to result from free radical damage to the myocardium. Free radicals, in turn, cause damage to multiple intracellular sites including the cell membrane, mitochondria, sarcoplasmic reticulum, and DNA. In the presence of iron, a $Fe^{3+}$ -doxorubicin chelate complex forms. This complex accelerates the reaction leading to increased production of free radicals with increased myocardial damage.

In solid tumours, doxorubicin has been the dominating anthracycline but has increasingly been substituted in Europe by the analogue epirubicin. Doxorubicin may exert its antitumour and toxic effects by a number of mechanisms including inhibition of topoisomerase II, intercalation with DNA and RNA polymerases, free radical formation and membrane binding.

Several analogues of doxorubicin and other anthracyclines have been studied aiming at lessened cardiac toxicity. Epirubicin (4'-epidoxorubicin) demonstrates a small but statistically significant decrease in cardiac toxicity, compared with doxorubicin given by rapid infusion. Preliminary data concerning pirarubicin suggest this analogue of doxorubicin may have significant less cardiotoxicity than doxorubicin given standard infusion schedules. Idarubicin (demethoxy daunorubicin), when given in amounts of equivalent myelotoxicity to daunorubicin, has cardiotoxicity similar to this drug. Anyway, cardiotoxicity from these agents is cumulative and crossing over from one agent to another does not offer protection.

Encapsulation of doxorubicin within liposomes has been another way of trying to reduce cardiac toxicity. Preclinical studies have shown that liposomes reduce the peak distribution of doxorubicin, apparently linked to cardiac toxicity, while favouring the distribution of encapsulated drug to reticulo-endothelial organs and to areas of inflammation or of fenestrated endothelium as in tumour tissue.

**Metastatic breast cancer (MBC)**

In breast cancer, anthracycline based combination chemotherapy has been found superior to previously used regimens without anthracyclines, both in the adjuvant and in the metastatic setting. Although the use of newly introduced taxanes is increasing, anthracycline-based combinations could still be considered standard of care in chemotherapy of breast cancer (BC). Doxorubicin is usually used in combination with one or two cytotoxic drugs of other classes to improve the benefit/risk balance.

The risk of irreversible cardiomyopathy is the most important treatment-limiting factor in the long-term. The clinical presentation of anthracycline-induced cardiomyopathy is congestive heart failure (CHF). At a cumulative doxorubicin dose of 500 mg/m$^2$ the risk for CHF is approximately 5% and thereafter it increases exponentially. It may lead to CHF in 1-10% of the patients at a cumulative dose of >550 mg/m$^2$. Although acute myopericarditis may occur following doxorubicin administration, the later occurring cardiomyopathy is of greater concern. The late presentation of anthracycline cardiomyopathy has been described to occur up to several years after completion of the treatment. It is observed in patients who had recovered from subacute cardiac symptoms or in patients with no previous symptoms.

There is considerable individual difference in sensitivity to doxorubicin-induced cardiomyopathy, which sometimes occurs after a very low cumulated dose. Combination of doxorubicin with 5-FU and cyclophosphamide in the CAF regimen seems to increase the risk for CHF many fold.

The current standard strategy to decrease the risk for doxorubicin induced CHF is to limit the cumulative dose to approximately 550 mg/m$^2$ and/or to pursue therapy under regular cardiac monitoring until a significant decrease in LVEF is observed.

Endomyocardial biopsy is the gold standard for assessment of anthracycline-induced cardiomyopathy. Histopathology correlates reasonably well to multigated radionuclide angiography (MUGA) scan based measurement of left ventricular ejection fraction (LVEF) which could be considered a routine standard for the assessment of anthracycline induced cardiac effects. LVEF measurement based on echocardiography is generally considered to be less accurate.

Doxorubicin has so far been administered as i.v. bolus injection or as short 30 min to 1 h i.v. infusion. Prolonged infusion over up to 96 h has been described to decrease the risk for doxorubicin induced CHF, seemingly without compromising the antitumour activity. However, despite the promising results prolonged infusion of doxorubicin is not in routine use in the treatment of BC.

Among many compounds that have been studied to evaluate possible protection from anthracycline-associated cardiomyopathy, dexrazoxane, a bisdiketopiperazine, is the most interesting. This drug demonstrated significant cardioprotection in a trial where patients where randomised to receive doxorubicin and cyclophosphamide with or without dexrazoxane and in subsequent trials. However, experimental data concerning a putative decrease of anti-tumour activity of doxorubicin when given with dexrazoxane are still equivocal.

## 2. Chemical, pharmaceutical and biological aspects

### Composition

Myocet is presented as a three-vial system; Myocet doxorubicin HCl, Myocet liposomes and Myocet buffer. In addition a small amount of 0.9% sodium chloride for injection is needed, which is not provided in the package. The constituted product is a liposome-encapsulated doxorubicin-citrate complex.

The formulation contains doxorubicin HCl, lactose and methyl parahydroxybenzoate (methylparaben). The constituted liposomes are stable pluri-lamellar liposomes composed of egg phosphatidylcholine (EPC) and cholesterol and with an aqueous core. It is important to follow the avian encephalitis (AE) situation in countries used for EPC production and report changes to the CPMP and national authorities. A protocol on how this is accomplished should be submitted.

Doxorubicin HCl is provided in 50 ml type I (Ph. Eur.) glass vials sealed with butyl rubber stoppers and aluminium flip-off seals. The liposomes are filled in 2 ml type I flint glass tubing vial with grey stoppers siliconised with dimethicone and a flip-off seal. The buffer is filled in 5 ml type I moulded glass vials with grey stoppers siliconised with dimeticone and a flip-off seal. After constitution the finished product is in the vial, which originally contained the doxorubicin HCl powder.

### Active substance

Doxorubicin HCl is an antineoplastic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* var. *caesius*. It is described in Ph. Eur. During the manufacture, Daunorubicin HCl is

converted into 14-bromodaunorubicin and the next step yields doxorubicin HCl. The following main related substances are identified in an HPLC method: doxorubicinone, 11-deoxydoxorubicin HCl, 13-dihydrodaunorubicin HCl, 13-dihydrocarminomycin HCl, daunorubicin HCl. Typically, batches contain between 0.14% and 0.30% total related substances.

The active ingredient manufacturer controls doxorubicin HCl according Ph. Eur. with the TLC method for related substances replaced by the HPLC-method used for assay. This is acceptable. Individual impurities are controlled in the active substance specifications of Pharmacia & Upjohn. However, as individual impurities are not included in their release specifications for the lyophilised doxorubicin, there is no need for the applicant to include individual impurities in their release specifications. Doxorubicin HCl complies with the main pharmacopoeias including Ph. Eur. and USP. Results of 4 batches have been presented. All batches meet the specifications.

Stability data of three batches in amber glass bottles with a polypropylene closure and a polyethylene inner stopper over 6 months at 25 °C/60% RH and 6 months at 40 °C/70% RH are presented. The results support a retest period of one year.

**Other ingredients**

Myocet liposomes: Citric acid, nitrogen, sodium hydroxide and water for injections are controlled according to Ph. Eur. Cholesterol is controlled according to Ph. Eur. and NF with an additional test for purity of not less than 95.0% by HPLC. EPC is obtained by purifying egg yolk through extractions and chromatography. In view of a potential for contamination of the phosphatidylcholine with aflatoxins, suitable upper limits for aflatoxins need to be included in the specification. Therefore, the applicant agreed to submit a variation addressing aflatoxin control during the manufacturing process The remaining lipids other than phosphatidylcholine are sphingomyelin and lysophosphatidylcholine.

Myocet buffer: Sodium carbonate and water for injections are controlled according to Ph. Eur.

**Product development and finished product**

***Product development***

The objective of the development program was to obtain an effective but less cardiotoxic parenteral dosage form of doxorubicin using liposome technology.

The constituted liposomes are stable pluri-lamellar liposomes, with an aqueous core, comprised of EPC and cholesterol. The drug is entrapped into the liposomes during the constitution of the ready to use liposomal formulation. During constitution, doxorubicin is driven across the liposome membrane by a pH gradient. A pH of 4-5 is maintained inside the liposomes by citric acid and outside the liposomes a pH of 7-8 is obtained by adding sodium carbonate buffer. Dissolved doxorubicin HCl is added and the membrane-permeable neutral form (in excess at pH 7.5) crosses the liposome bilayer into the aqueous core where it is protonated and, as such, forms a complex with citric acid. The complex is in the form of flexible fibres comprised of stacked doxorubicin molecules cross-linked into bundles by the citrate anions. The complexing with citrate aids the retention of the doxorubicin molecules within the liposome.

The loading efficiency as well as the biological activity of liposomal doxorubicin was used to establish the optimal lipid/drug ratio, EPC/cholesterol ratio, liposome size and concentration of the citrate buffer. Larger liposomes had less acute toxicity while smaller liposomes had a higher anti-tumour efficacy. Taken together, the mean survival time in a murine leukemia model increased with smaller liposomes. Based on these studies it was decided to have a mean diameter of 100-230 nm. In the same study the drug to lipid ratio was investigated. It was found that a higher drug to lipid ratio was less toxic than a lower drug to lipid ratio. This is suggested to result from a more stable complex between doxorubicin and citrate at the higher drug to lipid ratio, resulting in a slower deaggregation and subsequent release of doxorubicin from the liposomes. The highest drug to lipid ratio studied was 0.28:1. This ratio showed the lowest acute toxicity and was selected for the final composition.

The development studies are thoroughly performed and described, and are considered to support the chosen formulation. The clinical trial formulation was identical to the formulation to be used for the market.

***Manufacturing process***

Myocet doxorubicin HCl: the applicant purchases Doxorubicin HCl as a finished product. The vials are relabelled. During manufacture the product is sterilised using a 0.22 µm filter.

Myocet liposomes: The citric acid buffer is prepared, the pH adjusted with sodium hydroxide solution, and filtered through a 0.2 µm nominal filter into a reactor.

The liposomes are clarified by filtration and subsequently filtered through a 0.22 µm filter (sterilisation process) and stored under nitrogen pressure at 2-8°C before filling. The vials are sterilised using dry heat and the stoppers are autoclaved. The particle size distribution is measured as an important part of the in-process controls.

Myocet buffer: Sodium carbonate is added to water for injections, the solution is mixed and filtered through a 0.22 µm filter into sterile tank and stored at room temperature prior to filling.

***Validation***

The validation results for Myocet liposomes are satisfactory.

Myocet buffer: Twelve stability and clinical batches produced during the last 8 years with different batch sizes and equipment gave products within specifications. The buffer is sterilised by filtration since autoclaving the high pH solution results in the formation of glass related particles in the solution.

Constitution: Several validation studies were conducted on the constitution procedure and all constituted products were found to be acceptable supporting the ruggedness of the procedure. *GMP*

The product is being manufactured in a facility that holds the necessary Manufacturing Authorisation (see Annex II of the Opinion).

***Specifications***

The finished product specifications for the constituted liposomal doxorubicin include tests for appearance, pH, particle size, 'entrapment', i.e. the percentage of active substance encapsulated in the liposome interior which is also an indicator of 'free' doxorubicin, and assay.

***Batch analysis***

Batch analysis results of 2 batches were presented. Both batches comply with the specifications.

***Stability of the product***

The results of stability studies indicate that a shelf life of 18 months for the finished product, when stored at 2-8 °C, is acceptable. Protection from light is not necessary. The constituted drug product was shown to be chemically and physically stable when stored at 2-8°C for 8 days and for 24 hours at room temperature. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at $2^{o}$C - $8^{o}$C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

## 3. Toxico-pharmacological aspects

### Introduction

The pharmacology and toxicology of doxorubicin (Dox) are well established and, thus, the preclinical file for Myocet aimed mainly at comparing liposome-encapsulated Dox with conventional Dox with respect to efficacy, toxicity and pharmacokinetics.

### Pharmacodynamics

***In vitro and in vivo studies***

Antitumour activity of liposomal and conventional Dox *in vivo* was compared in murine tumour models using a range of murine and human xenograft tumour types. The drug formulations were administered via the i.v. route. At similar doses, liposomal Dox appeared to be as effective as conventional Dox in these models, possibly with the exception of the melanoma model, and was better

tolerated. Survival was recorded until day 60. Therapeutic response was based on the median day of death and expressed as the percent increased life span compared with untreated controls. The change in viable tumour cell population was also assessed. The results indicate that the liposome formulation permitted delivery of higher Dox doses and the more intensive treatment resulted in apparent cures that were not achieved with the conventional Dox. Clear dose-response relationships were seen for both formulations, up to the optimal dose (the highest dose without drug-induced deaths). Although direct comparisons at similar doses were not made, no apparent decrease in efficacy of liposomal Dox compared with conventional Dox was observed.

No antitumour activity studies using BC models were performed. However, there is a long-term clinical experience of Dox in this disease and it would not be expected that liposome-encapsulation of the drug affects possible disease-specificity that is due to mechanism of cytotoxic action. Thus, the results from other tumour types, indicating that liposomal Dox is at least as effective as conventional Dox, may most likely be extrapolated also to BC models.

No preclinical studies were performed to evaluate efficacy of liposomal Dox in cytotoxic drug combinations. Liposomal Dox did not increase the drug sensitivity of Dox-resistant cancer cell lines, neither *in vitro* nor *in vivo*.

The equal or improved survival of animals receiving Myocet compared with conventional Dox may indicate that liposome-encapsulation of Dox does not decrease its activity against metastases. However, from these data it is difficult to assess the long-term protection against micrometastases because of lack of long-term follow-up of survivors (the animals were observed for 60 days). This issue is not considered critical in the palliative setting of MBC. However, further investigations would be needed in order to clarify the issue with respect to the adjuvant setting (see SPC 4.4, *Special warnings and special precautions for use*).

***Interaction studies***

The effect of liposomal Dox or free Dox formulations on the single dose toxicity (lethality) of cyclophosphamide (CPA), 5-FU or CPA + 5-FU was compared showing similar toxicological profiles when combined with each of the drugs individually or with both.

***General and safety pharmacology programme***

The effects of liposomal Dox on CNS, cardiovascular and reproductive system have not been investigated in pharmacology studies. This is considered acceptable, due to the vast clinical experience with Dox, and since results in the toxicology studies indicate qualitatively similar toxicity of free and liposome-encapsulated Dox. The distribution study in dogs indicates that liposome-encapsulation of Dox does not increase the uptake of drug into CNS. In a temperature response study in rabbit, liposomal Dox induced temperature increases of 1.0 to 2.1 ºC at 5 to 9 hr post-dose while no temperature increases were seen in animals treated with conventional Dox.

**Pharmacokinetics**

In dogs, at the same dose (1.5 mg/kg) the liposomal formulation resulted in higher plasma concentrations and >80 times higher exposure (AUC) for total Dox (encapsulated+free) than did conventional Dox. The liposomal formulation gave somewhat lower $C_{max}$ but higher systemic exposures of free (unencapsulated) Dox than did conventional Dox. However, there are doubts on the validity of the assay to measure free Dox, due to methodological difficulties.

Administration of liposomal $^{14}$C-doxorubicin to dogs resulted in lower concentrations of Dox-related radioactivity in the myocardium and gastrointestinal tissues, but higher concentrations in the liver, spleen and bone marrow, compared with conventional $^{14}$C-doxorubicin. This is in agreement with the observed reduction in cardiomyopathy and increased bone marrow toxicity for liposomal Dox.

In mice with subcutaneously growing human breast carcinoma cells, the Dox-related fluorescence in tumour tissue seemed to be higher after administration of liposomal Dox than after administration of conventional Dox. Taken together with clinical efficacy data, the results indicate that liposome-encapsulated Dox is distributed to and effective against BC cells to at least a similar extent as conventional Dox.

The metabolism of Dox from liposomal formulations was not investigated. The main metabolite of Dox is doxorubicinol. Metabolism in man is reported to be similar to rabbit and mouse.

**Toxicology**

***Single dose toxicity***

Single dose toxicity of liposomal Dox, conventional Dox and empty liposomes was evaluated in mouse and dog. In acute toxicity studies in mice and dog, liposomal Dox and conventional Dox induced similar toxicity profiles, but toxicity was less severe or occurred at higher doses for the liposome-encapsulated drug. Female mice appeared less susceptible than males to liposomal Dox. This sex difference was not seen for other species.

Single dose toxicity of conventional Dox or liposomal Dox in combination with 5-FU or CPA in mice was evaluated indicating that also in combination the acute toxicity of liposomal Dox is lower than that of conventional Dox.

The potential for liposomal Dox to induce thrombi was studied in rabbits. There were no signs of thrombi or emboli in rabbits receiving a high single dose of liposomal Dox.

***Repeat dose toxicity***

In chronic toxicity studies, where dogs were administered 1.5 mg/kg Dox once every three weeks for 8-12 cycles, the toxicity profiles were qualitatively similar between the two preparations. Liposomal Dox appeared better tolerated, inducing less severe gastrointestinal toxicity and fewer unscheduled deaths compared with conventional Dox, although histopathological data indicated more severe bone marrow atrophy in liposomal Dox treated dogs.

The only effect specific for liposomal Dox but not seen with conventional Dox in the toxicology studies was an increase in body temperature in dogs, generally occurring around 24 hr post-dose, whereas no temperature increases were seen in animals treated with conventional Dox. Although it is not possible to draw definite conclusions, one possible explanation for the Myocet-induced temperature increase is that liposome-encapsulation of Dox results in a greater uptake of Dox by the phagocytic cells of the reticulo-endothelial system (RES), and thus, mediators of inflammation become responsible for the observed temperature increase.

A blood compatibility test of liposomal Dox and empty liposomes was performed as part of the two acute toxicity studies. The results from the two studies were similar and indicated a low haemolytic potential of the liposome formulations.

***Cardiotoxicity***

Apparently, liposome-encapsulation of Dox did not prevent cardiac toxicity but delayed it. In one study, histopathological evidence of cardiac toxicity was noted in all dogs that received eight doses of conventional Dox at 1.5 mg/kg but in none of the dogs treated with the same dose of liposomal Dox. In a second study, all dogs receiving 8-10 cycles of conventional Dox had lesions consistent with myocardial toxicity and heart failure, and none of these animals survived more than 10 doses. After 8 doses, cardiac lesions were also seen in liposomal Dox-treated animals, but were graded less severe than in the conventional-Dox group. In the animals receiving 12 doses of liposomal Dox there were signs of cardiotoxicity in most animals, at a similar grade of severity as in the conventional Dox-treated animals after 8 doses. The more severe toxicity observed in preclinical studies after administration of conventional Dox may partly have been due to very high peak concentrations of free drug that would not have been obtained if the treatment had been given as slow infusion. Nevertheless, the difference between the infusion time used in preclinical studies and that recommended for the clinical administration is probably not of concern regarding relevance for the myocardial effect.

***Genotoxicity, Carcinogenicity***

Studies to evaluate genotoxicity and carcinogenicity of liposomal Dox were not performed and are not considered necessary, due to the known mutagenic and carcinogenic potential of Dox.

***Reproduction toxicity***

Dox *per se* is known to be teratogenic in animals and humans and to induce abortions (rabbits).

***Local tolerance***

Local macroscopic reactions in rabbit after a single perivascular or subcutaneous bolus injection of liposomal Dox and conventional Dox were similar but were graded slightly less severe in the liposomal Dox-treated animals. No ulceration was observed in the liposomal Dox-treated animals.

***Ecotoxicity/Environmental risk assessment***

Based on the pattern of use and disposal of Myocet coupled to the predicted annual usage and low estimates for concentrations in the environment it has been considered that no immediate risk for the environment is associated to the therapeutic use of Myocet.

**Discussion on toxico-pharmacological aspects**

The antitumour activity of Myocet has been investigated in several murine tumour models and compared with that of free Dox. Myocet allowed the administration of higher (or at least similar) doses of Dox without increased toxicity. Myocet seemed to display a different pharmacokinetic profile compared to the free Dox formulation. Some increased therapeutic benefit expressed by increased life span was shown by the liposomal formulation in most (but not all) studies performed.

The claimed reduction of toxicity on the formulation has been shown in some studies, in relation to cardiotoxicity (dog) after repeated administration, but on the other side increased bone marrow suppression was observed when compared to the free Dox one.

From the preclinical data it is difficult to assess the long-term protection against micrometastases due to the lack of long-term follow-up. This issue is not considered critical in the metastatic setting but further investigations would be needed in order to evaluate this possible effect with respect to less advanced stages of the disease (see SPC section 4.4 *Special warnings and special precautions for use*).

## 4. Clinical aspects

Myocet, in combination with cyclophosphamide (CPA), is indicated for the first line treatment of MBC in women. The clinical database comprises data from 3 pivotal phase III trials (studies 1-3), 4 supportive phase II trials in MBC (studies 4-7) and 11 phase I/II trials (8-18) in solid tumours, non small-cell lung cancer (NSCLC), acute nonlymphocytic leukaemia (ANLL), AIDS-related Kaposi's sarcoma (AIDS-KS) and brain metastases (Table 1).

**Table 1. Summary of clinical trials**

| | | | | Patients | | Treatment(s) | |
|---|---|---|---|---|---|---|---|
| **Study No.** | **Protocol Description** | **Site(s)** | **Design** | **Gender (Age in years)** | **No. of patients** | **Starting dosage (mg/m$^2$/day)** | **Schedule** |
| 1 | Phase III MBC | United States, India, Canada | R, C, CT, MC | 297 F (25-88) | 142<br>155 | Myocet + CPA<br>Myocet: 60 mg/m$^2$, 60-min inf.<br>CPA: 600 mg/m$^2$, 15-min inf.<br>Dox + CPA<br>Dox: 60 mg/m$^2$, 60-min inf.<br>CPA: 600 mg/m$^2$, 15-min inf. | q3w |
| 2 | Phase III MBC | United States, Canada | R, C, MC | 224 F (26-85) | 108<br>116 | Myocet: 75 mg/m$^2$, 60-min inf.<br>Dox: 75 mg/m$^2$, 60-min inf. | q3w |
| 3 | Phase III MBC | Europe | OL, R, C, CT, MC | 160 F (19-82) | 80<br>80 | Myocet + CPA<br>Myocet: 75 mg/m$^2$, 60-min inf.<br>CPA: 600 mg/m$^2$, 1-to 2-min inf.<br>Epi + CPA<br>Epi: 75 mg/m$^2$, 60-min inf.<br>CPA: 600 mg/m$^2$, 1-to 2-min inf. | q3w, max 8 cycles |
| 4 | Phase II MBC | Canada | | 32 F (44-77) | 32 | Myocet: 75 mg/m$^2$, 60-min inf. | q3w |
| 5 | Phase II MBC | United States | MC | 28 F (28-78) | 28 | Myocet: 60 or 75 mg/m$^2$, 60-min inf. | q3w |
| 6 | Phase II MBC | United States | CT | 41 F (38-76) | 41 | Myocet + 5-FU + CPA<br>Myocet: 60 mg/m$^2$, 60-min inf.<br>5-FU: 500 mg/m$^2$, 30-min inf.<br>CPA: 500 mg/m$^2$, 60-min inf. | q3w |
| 7 | Phase II MBC | United States | MC | 52 F (35-82) | 52 | Myocet: 135 mg/m$^2$, 60-min inf. | q3w |

| | | | | Patients | | Treatment(s) | |
|---|---|---|---|---|---|---|---|
| **Study No.** | **Protocol Description** | **Site(s)** | **Design** | **Gender (Age in years)** | **No. of patients** | **Starting dosage (mg/m²/day)** | **Schedule** |
| | | | | | | | |
| 8 | Phase I Solid Tumours | United States | DE | 12 F, 26 M (33-76) | 38 | Myocet: 20 mg/m², 60-min inf. q3w or daily for 3 consecutive days | q3w, 2 cycles |
| 9 | Phase I Solid Tumours | United States | DE | 13 F, 17 M (27-67) | 30 | Myocet: 90 mg/m² 60-min inf. | q3w |
| 10 | Phase I Solid Tumours | Canada | DE | 3 F, 7 M (35-67) | 10 | Myocet: 60 mg/m² (decreased to 20 mg/m² for patients 2-10) | q3w, 3 cycles |
| 11 | Phase I Solid Tumours | Japan | MC, DE | 9F, 4 M (34-73) | 13 | Myocet: 30 mg/m², 30-min inf. | q3w |
| 12 | Phase I Solid Tumours | France | R, C, DE | 30F, 9M 22-68 | 38 27* | Myocet: 75 mg/m², 60-min inf. Dox: 75 mg/m² * one dose of Dox as first or second dose | q3w |
| 13 | Phase I/II NSCLC | Canada | DE | 4 F, 12 M 46-76 | 16 | Myocet: 60 mg/m² | q3w |
| 14 | Phase II NSCLC | Belgium | | 2 F, 4 M (48-62) | 6 | Myocet: 135 mg/m², 60-min inf. | q3w, max 12 month |
| 15 | Phase I/II ANLL | United States | DE | 1 F, 4 M (22-60) | 5 | Myocet: 25 mg/m², 60-min inf. daily x 3 days | q2w |
| 15 | Phase I/II ANLL | United States | MC, DE | 2 F, 3 M (21-79) | 5 | Myocet: 40 mg/m², 60-min inf. daily x 3 days | q2w |
| 16 | Phase II AIDS-KS | United States | R, MC | 40 M (26-47) | 19 21 | Myocet: 10 mg/m², 60-min inf. Myocet: 20 mg/m², 60-min inf. | q2w, max 6 cycles |
| 17 | Phase II AIDS-KS | France | DE, MC | 24 M (22-59) | 24 | Myocet: 30 mg/m², 4-hour inf. | q2w |
| 18 | Phase I/II Brain Metastases | France | R, C | 3 F, 11 M (34-71) | 10 4 | Myocet: 75 mg/m², 60-min inf. Dox: 75 mg/m², 60-min inf. | Single dose |

Abbreviations: Design (R, randomised; C, comparative; CT, combination therapy; MC, multicentre; DE, dose escalation); F: female; M: male; Dox: doxorubicin; Epi: epirubicin; CPA: cyclophosphamide; UNK: unknown; 5-FU: 5-fluorouracil; q3w, every three weeks; inf., infusion.

**Clinical pharmacology**

Six single dose studies were conducted. One was conducted as a pharmacokinetic substudy of a phase III study (study 1), in which both Myocet and conventional Dox were administered in combination with CPA. Three single-arm studies (8, 9 and 13) with Myocet were conducted and two other studies (12 and 18) compared Myocet with conventional Dox. In studies 12 and 9, attempt was made to separate free Dox from encapsulated substance. The main metabolite doxorubicinol was measured in studies 1 and 12.

***Pharmacodynamics***

Dox is a well-known cytotoxic agent, with a very broad spectrum of clinical anticancer activity and is one of the most frequently prescribed anti-neoplastic agents. Against BC, Dox presents curative potential when it is included in multimodality regimens, and has an established value in palliative treatment of patients with advanced tumors.

Cardiomyopathy is limiting with respect to cumulative dose and this liposomal formulation was developed having in view the reduction in the risk of cardiotoxicity.

The choice of using the same dose of Myocet as of conventional Dox in phase III trials is justified by the results of preclinical studies and the phase I and phase II trials (see *Dose-response studies*) where comparable efficacy and reduced cardiac and gastrointestinal toxicity were apparent.

***Pharmacokinetics***

As long as Dox is associated with its carrier, the pharmacokinetics of the drug is determined by the pharmacokinetics of the liposome. Liposomes of the size of Myocet are generally cleared from blood by uptake by the RES-cells. There is a gradual release of drug from the liposome, dependent on factors such as drug properties, liposome composition, pH or osmotic gradients and the liposome environment. Since released Dox displays the same elimination pathway as conventional Dox, the pharmacokinetic behaviour of Myocet is a mixture of the behaviour of encapsulated and free Dox.

The variability in all pharmacokinetic parameters is markedly higher for liposomal drug compared with conventional dosing. This may to some extent be due to the poor performance of the assay procedure so that kinetic data should be interpreted with caution.

The clearance of total doxorubicin was 5.1±4.8 l/h and the volume of distribution at steady state ($V_d$) was 56.6 l, while after conventional doxorubicin, clearance and $V_d$ were 46.7±9.6 l/h and 1,451±258 l, respectively. With Myocet given over 1 hour, the total Dox peak plasma level is very high (~ 9-fold greater than that seen with conventional Dox) but since most of the drug is encapsulated, the peak level of free drug is likely to be very low, mimicking a continuous infusion. The AUC of total Dox in patients receiving Myocet is also very high (~ 20 fold greater than that in patients receiving the same dose of conventional Dox) but, again, most of the circulating drug is encapsulated. The precise plasma AUC of released Dox in patients receiving Myocet is unknown due to analytical difficulties, however, the exposure to free Dox after administration of Myocet appears similar to the exposure to Dox after administration of the same dose of conventional drug.

When Dox is given as a continuous infusion, the peak plasma levels are much reduced compared with the usual slow bolus administration while the plasma AUC is the same. Clinical trial data from the literature support the hypothesis that chronic cardiotoxicity is related primarily to peak drug concentration, whereas anti-tumour effect is more dependent on the total drug exposure (AUC). Mucositis and the potential for extravasation injury are however increased with prolonged infusions of conventional Dox. A similarity between the formulations as regards the general toxicity profile (excluding cardiac toxicity) and the antitumour activity suggest the concept that liposome-encapsulation provides an "intravenous slow-release formulation". However, based on an observed difference in incidence and severity of mucositis and diarrhoea it is possible to speculate that Myocet does not merely mimic infusional Dox.

For conventional Dox a relationship between AUC and dose-limiting granulocytopenia is observed. Preclinical studies in dogs have shown that bone marrow atrophy was somewhat more pronounced after treatment with liposome-encapsulated compared with conventional Dox. However, no differences between Myocet and conventional Dox regarding haematological parameters (neutropenia, anaemia, thrombocytopenia) were observed either in the preclinical or clinical studies. No definite conclusion regarding the relationship between AUC and myelotoxicity can be drawn from available data. As dose adjustment for Myocet is not based on AUC levels but on haematological monitoring, the issue is not considered critical.

The pharmacokinetics of one of the metabolites, doxorubicinol, is similar after liposomal and conventional Dox, with the exception of a slower formation rate after liposomal Dox. Doxorubicinol is formed in the liver via aldo-keto-reductase enzymes. It appears in the plasma later with Myocet than with conventional Dox.

No pharmacokinetic studies were performed with respect to age, impaired renal or hepatic function. The available data from patients with impaired liver function is too limited to be a basis for a dose recommendation in these patients. Therefore, the Marketing Authorisation Holder agreed to perform further post-marketing investigations on the pharmacokinetics and safety of Myocet in patients with impaired liver function. Until these further data become available, conservative dose reduction recommendations are necessary (see SPC 4.2, *Posology and method of administration*).

Clinically significant drug interactions between Dox and cytochrome 3A4 substrates have been described for agents, which also interact with P-glycoprotein (PgP), e.g., cyclosporin and paclitaxel. It appears as if PgP-inhibitors increase the exposure to both Dox and its metabolite. No formal interaction studies were performed for Myocet. However, the interaction potential for Myocet might be even higher due to a more pronounced distribution to the liver compared to conventional Dox. A warning considering concomitant treatment with PgP-inhibitors has been included in the SPC. Also, concomitant treatment with other substances reported to be cardiotoxic or with cardiologically active substances (e.g. calcium antagonists) may increase the risk for cardiotoxicity. Concomitant therapy with other liposomal or lipid-complexed drugs or i.v. fat emulsions could change the pharmacokinetic profile of Myocet (see SPC 4.5, *Interactions with other medicaments and other forms of interactions*).

Myocet should be used in combination with CPA. CPA is metabolised mainly by CYP2B6. No formal interaction studies were conducted with CPA and Dox. However, no changes in Dox or CPA

pharmacokinetics were evident when compared with other studies, although the variability was very high.

In conclusion, the pharmacokinetic profile of liposomal Dox in plasma have been characterised in cancer patients, confirming the expected behaviour of a liposomal formulation. From the pharmacokinetic documentation it is not possible to draw any conclusions regarding specific liposomal tumour targeting. Liposomal Dox and conventional Dox essentially show similar efficacy and, except for the cardiac toxicity, also similar toxicity profiles. This might be explained by the exposure to free Dox after liposomal compared to conventional dosing of Dox being of the same range but with different time characteristics.

**Clinical efficacy**

Pivotal data on the efficacy and safety of Myocet derive from 3 phase III trials, studies 1, 2 and 3. Supportive data in MBC were obtained from 4 phase II trials, studies 4 – 7.

***Dose-response studies***

Results from 11 phase I/II clinical trials in 242 patients with a diverse range of tumours were reported. The results showed that the dose-limiting toxicity was neutropenia. In dose-ranging studies, the MTD was 75 - 90 mg/m$^2$ without G-CSF support. With G-CSF, a subsequent phase II trial showed that a dose of 135 mg/m$^2$ was associated with unacceptable toxicity. With the exception of cardiac toxicity, the adverse events seen in the phase I/II studies of Myocet were similar in type to those seen with conventional Dox. Although the numbers of patients at the various dose levels are relatively small, there is a rough correlation with the dose of Myocet and frequency of adverse events commonly seen with Dox.

Bolus administration of Myocet was associated with an acute syndrome of infusion-related side effects and there is very limited experience from other schedules for administration of Myocet. For monotherapy trials, a dose of 75 mg/m$^2$ administered every three weeks was selected.

The recommended dose of Myocet is 60-75 mg/m$^2$ in combination with CPA (600 mg/m$^2$), every three weeks. The administration is by i.v. infusion over a period of one hour.

***Main studies***

Three pivotal trials with similar designs were performed. All studies were randomised multicentre, parallel group, open-label studies. Treatment was assigned using blocked randomisation (block size of 2 for studies 1 and 2, size unknown to the investigators), which was stratified according to centre and in studies 1 and 2 also according to prior adjuvant Dox.

Study 1 compared Myocet, 60 mg/m$^2$, in combination with CPA, *versus* Dox, 60 mg/m$^2$, in combination with CPA. Study 2 compared Myocet, 75 mg/m$^2$ (with dose escalation up to 105 mg/m$^2$), monotherapy, *versus* Dox, 75 mg/m$^2$, monotherapy and study 3 compared Myocet, 75 mg/m$^2$, in combination with CPA *versus* epirubicin (Epi) 75 mg/m$^2$ in combination with CPA. Regimens were administered every three weeks and in all combination regimens, CPA, 600 mg/m$^2$ was given as i.v. bolus injections or short infusions prior to Myocet or Dox.

The main selection criteria were histologically or cytologically proven MBC, adequate bone marrow, liver and renal function and resting LVEF ≥ 50%. Prior radiotherapy (RT) to the mediastinum >35 Gy was an exclusion criterion. In studies 1 and 3, G-CSF was permitted in the case of pronounced myelotoxicity whereas in study 2, and later in study 1, it was started routinely 48 h after Myocet was administered. Dexrazoxane was permitted, at the discretion of the physician in trials 1 and 2 in patients with a lifetime cumulative dose of Dox of >300 mg/m$^2$ but never came to use in any patient.

*Endpoints*

*Efficacy endpoints*

Response rate according to WHO criteria with confirmation after 6 weeks was the primary efficacy endpoint in all three studies. An independent blinded response review of radiology imaging was not carried out. Although an independent blinded review of all tumour imaging would have been optimal, a procedure involving a “blinded” core radiologist in each site was used in trials 1 and 2 and this is

considered to be acceptable from a data quality point of view. In general, progression-free-survival (PFS) and overall survival (OS) are considered more clinically relevant endpoints in advanced BC. However, it is possible that in direct comparison between two Dox formulations response rate could be a sensitive endpoint for detection of a difference. Furthermore, provided reliable results in other relevant endpoints are obtained, it seems reasonable to give relative weight to various endpoints based on scientific reasoning. Thus, response rate can be considered as an adequate endpoint as long as findings are supported by reliable data on PFS and OS, which were also interpreted in the light of any subsequent treatments administered.

*Safety endpoints*

Reduction of cardiotoxicity was an additional primary objective in studies 1 and 2. Independent/blinded evaluation of CHF was not required in any protocol but was used for the final establishment of CHF. LVEF assessment was blinded in all trials. A cardiac toxicity event was defined as the occurrence of one or more of the following conditions:

- Type I: decrease in resting LVEF of ≥20 points from baseline, to a final value ≥50%;
- Type II: decrease in resting LVEF of ≥10 points to a final value <50%;
- Clinical evidence of CHF.

Patients experiencing a cardiotoxicity event were discontinued from study treatment. Additional criteria for study treatment discontinuation were patient refusal, SAE, surgical removal of target lesions, RT to target lesions, progressive disease and, subject to the discretion of the investigator, stable disease after 4 courses.

Cardiac evaluation was performed by ECG and by MUGA scans (study 1 and 2) or by echocardiography (study 3). Irrespective of method, evaluation was to be performed:

- at baseline;
- prior to the next cycle after reaching a lifetime cumulative Dox or Epi dose of 300 mg/m$^2$ and 400 mg/m$^2$;
- prior to each subsequent cycle after reaching a lifetime cumulative Dox or Epi dose of 500 mg/m$^2$;
- three months after the last dose of study medication (post study discontinuation);
- at the end of treatment visit, if a patient had received a lifetime cumulative Dox or Epi dose of ≥300 mg/m$^2$ and a MUGA scan had not been performed within the previous 3 weeks;
- any other time clinically indicated.

For cardiotoxicity, a significant decrease, as defined in the protocols, in LVEF blindly and prospectively assessed by MUGA scans seems to be an established surrogate endpoint of clinical relevance for the later occurrence of CHF. Evaluation by echocardiography is considered less accurate but is considered acceptable because evaluation was blinded. CHF is not considered to be a reliable measure due to the fact that only those cases selected by the unblinded investigator were reviewed independently. Thus, for cardiotoxicity the main outcome measure is suggested to be changes in LVEF.

Secondary endpoints were time to progression, overall survival, change in performance status and disease related symptoms and, in studies 1 and 3, quality of life (QoL) assessed using the EORTC QLQ-C30 (BR23) questionnaire.

*Statistical design*

With respect to response rate, all trials were designed to show non-inferiority. Non-inferiority was defined so as to rule out a reduction in response rate for Myocet of 15% or more (Δ=15%). The antitumour efficacy data are presented according ITT (all randomised patients according to randomised treatment). Confirmatory analyses were carried out on the per protocol population (PPP). With respect to cardiotoxicity, treatment arms were compared using the logrank test stratified by adjuvant doxorubicin, with a two-sided type I error of 0.05. The patient population for the

cardiotoxicity endpoint was all randomised patients who started treatment, according to treatment actually received.

*Results*

Demographic and clinical characteristics of patients included in the main efficacy analysis as well as the primary analyses for antitumour efficacy are reported in the following sections whereas patient exposure and primary analyses for cardiotoxicity are reported under *Clinical Safety*.

*Patient Population*

The most notable differences in baseline characteristics (Table 2) were a higher proportion of patients in the Myocet group with visceral involvement in study 1 (72% *versus* 60%), and a significantly higher proportion of patients receiving Myocet with negative progesterone-receptor status in study 2 (43% *versus* 29%). Study-drug exposure was comparable between treatment groups within each study. The median number of cycles per patient was six for both combination-regimen studies (studies 1 and 3), and four for the single-agent study. Study 3 was planned for 300 patients but was terminated prematurely due to cost and rate of enrolment.

Study-drug exposure was comparable between treatment groups within each study. The median number of cycles per patient was six for both combination-regimen studies (studies 1 and 3), and four for the single-agent study as detailed in table 3.

The main reasons for study treatment discontinuation for study 1 were (Myocet/CPA *versus* Dox/CPA): progressive disease (31 *versus* 25%), maximum response achieved (25 *versus* 27%), institutional practice (11 *versus* 10%), refusal (8 *versus* 5%), cardiotoxicity (5 *versus* 10%), adverse event (5 *versus* 8%), risk of cardiotoxicity (1 *versus* 5%) and death (5 *versus* 1%). For study 2 these were (Myocet *versus* Dox): progressive disease (52 *versus* 28%), maximum response achieved (12 *versus* 14%), refusal (9 *versus* 7%), cardiotoxicity (10 *versus* 25%), adverse event (3 *versus* 7%), risk of cardiotoxicity (2 *versus* 8%) and death (0 *versus* 2%). For study 3 these were (Myocet/CPA *versus* Epi/CPA): progressive disease (18 *versus* 24%), maximum response achieved (9 *versus* 4%), refusal (9 *versus* 12%), cardiotoxicity (4 *versus* 5%), adverse event (4 *versus* 7%), risk of cardiotoxicity (1 *versus* 0%) and death (4 *versus* 5%).

**Table 2. Patient baseline characteristics**

| | Study 1 | | Study 2 | | Study 3 | |
|---|---|---|---|---|---|---|
| | **Myocet + CPA** | **Dox + CPA** | **Myocet** | **Dox** | **Myocet + CPA** | **Epi + CPA** |
| Starting dose (mg/m$^2$) | 60/600 | 60/600 | 75 | 75 | 75/600 | 75/600 |
| No. of patients[a] | 142 | 155 | 108 | 116 | 80 | 80 |
| Median age, years (range) | 55 (30-80) | 54 (25-88) | 58 (26-85) | 58 (29-82) | 54 (19-78) | 53 (26-82) |
| ECOG performance status 0 | 37% | 42% | 47% | 42% | 44% | 44% |
| 1 | 49% | 45% | 44% | 43% | 45% | 49% |
| 2 | 13% | 13% | 6% | 11% | 10% | 8% |
| Visceral involvement[b] | 72% | 60% | 72% | 72% | 61% | 60% |
| Estrogen-receptor status +ve | 38% | 40% | 43% | 49% | 20% | 24% |
| –ve | 26% | 22% | 34% | 29% | 23% | 19% |
| Unknown | 36% | 39% | 23% | 22% | 58% | 58% |
| Progesterone-receptor status | | | | | | |
| +ve | 31% | 33% | 33% | 50% | 12% | 9% |
| –ve | 30% | 26% | 43% | 29% | 15% | 20% |
| Unknown | 39% | 41% | 24% | 21% | 74% | 71% |
| Prior radiation | 33% | 38% | 45% | 46% | 58% | 66% |
| Prior hormonal therapy | 45% | 51% | 53% | 56% | 39% | 46% |
| Prior adjuvant chemotherapy | 32% | 39% | 40% | 41% | 40% | 41% |
| Prior doxorubicin | 10% | 10% | 17% | 18% | — | — |

| | | | | | | |
|---|---|---|---|---|---|---|
| Prior lifetime cumulative doxorubicin (median mg/m$^2$) (min, max) | 240 (50-294) | 240 (63-270) | 240 (167-300) | 240 (70-360) | — | — |
| LVEF at baseline (median %) (min, max) | 65 (50-83) | 63 (50-80) | 64 (50-79) | 63 (45-78) | MUGA not done[c] | |

[a]Based on randomised group. [b]Includes sites of metastases in lung, liver, pleural effusion, ascites, or abdomen/pelvis. [c]Echocardiograms performed instead

**Table 3. Drug exposure in the pivotal trials**

| | Study 1 | | | Study 2 | | | Study 3 | |
|---|---|---|---|---|---|---|---|---|
| | Myocet /CPA | Dox/CPA | | Myocet | Dox | | Myocet /CPA | Epi/CPA |
| Starting dose (mg/m$^2$) | 60/600 | 60 /600 | | 75 | 75 | | 75/600 | 75/600 |
| No. of patients[a] | 142 | 154 | | 105 | 118 | | 76 | 78 |
| Median no. of cycles per patient (min, max) | 6 (1, 25) | 6 (1, 12) | | 4 (1, 14) | 4 (1, 11) | | 6 (1, 8) | 6 (1, 8) |
| Median duration of treatment (wks) (min, max) | 19 (3, 78) | 18 (3, 39) | | 13 (3, 44) | 15 (3, 38) | | 19 (3, 33) | 18 (3, 29) |
| Median cumulative dose of study drug (mg/m$^2$) (min, max) | 360 (60, 1500) | 350 (60, 660) | | 360 (75, 1110) | 390 (75, 840) | | 443 (75, 600) | 450 (75, 600) |
| Median dose intensity (mg/m$^2$/wk) (min, max)[b] | 19 (12, 20) | 19 (13, 21) | | 26 (12, 35) | 27 (16, 33) | | 23 (15, 25) | 24 (17, 26) |

[a]Based on actual treatment received.

[b]Dose escalation was allowed only in study 2 (single-agent).

*Antitumour efficacy*

According to the predefined criterion, Myocet in combination with CPA showed non-inferiority in response rate compared to Dox (Table 4). Generally, the predefined Δ of 15% for response rate would be considered to be too large, nevertheless the results shown in terms of confidence intervals allows to rule out smaller differences. Particularly, Myocet in combination with CPA showed non-inferiority with respect to an *a posteriori* defined Δ of 10%. In all three studies the majority of patients were assessed using objective imaging techniques (75 – 91%). The results of the analyses performed in the PPP (data not shown) were consistent with those performed in the ITT population. Response rate in patients with prior adjuvant Dox treatment was 50 *versus* 20% (combination) and 17 *versus* 5% (monotherapy), for Myocet and Dox respectively. In patients with no prior Dox treatment response rate was 42 *versus* 45% (combination) and 28 *versus* 31% (monotherapy), for Myocet and Dox respectively.

The observed response rate in the monotherapy study was low in both arms, compared to what has been seen in trials with single-agent Dox. Nevertheless, the difficulties of comparisons between studies, particularly with respect to response rates, make the similar relative efficacy of the treatment arms more relevant. In addition, the monotherapy study by itself is of limited value in assessing the role of Myocet in combination with CPA.

Outcome with respect to PFS and OS are summarised in Table 5. The data are considered reasonably mature. For study 1, in a 24-month period, 108 of 142 patients (76%) in the Myocet arm progressed (median PFS 5.1 months) compared to 126 of 154 patients (82%) on the Dox arm (median PFS 5.5 months).

In study 2, Myocet was found to have worse OS although the difference was not statistically significant at the 5% level (logrank *p*-value=0.076). A multiple regression analysis for response rate, PFS and OS exploring the importance of baseline covariates was performed for study 2. Adjustment for baseline prognostic factors did not result in any important changes in response rate, PFS or OS. Based on the response rate and all other efficacy data from the 3 pivotal trials and taking into account

that study 2 was a single-agent study, the observed tendency for worse survival for Myocet compared with Dox seems of limited concern. The survival difference in favour of Dox is likely to be related to events after treatment or to differences in unknown prognostic factors. Furthermore, although comparison with historical data is hazardous, it might be concluded that survival for the Myocet arm was not significantly compromised.

**Table 4. Objective response rates**

| | Combination | | | | Single-Agent | |
|---|---|---|---|---|---|---|
| | Study 1 | | Study 3 | | Study 2 | |
| | Myocet /CPA (n=142) | Dox/CPA (n=155) | Myocet /CPA (n=80) | Epi/CPA (n=80) | Myocet (n=108) | Dox (n=116) |
| Difference in Response Rate | 0% | | 7% | | 0% | |
| Two-sided 95% CI | (-10%, 12%) | | (-8%, 23%) | | (-9%, 13%) | |
| One-sided *p*-value (Δ=15%)[a] | 0.003 | | 0.002 | | 0.0012 | |
| One-sided *p*-value (Δ=10%)[b] | 0.03 | | 0.012 | | 0.0165 | |
| Response Rate | 43% | 43% | 46% | 39% | 26% | 26% |
| 95% CI | (35-52%) | (35-51%) | (35-58%) | (28-50%) | | |
| Risk Ratio (95% CI) | 1.01 (0.78-1.31) | | 1.19 (0.83-1.72) | | 1.00 (0.64-1.56) | |
| Complete response | 5% | 6% | 11% | 11% | 0% | 2% |
| Partial response | 38% | 37% | 35% | 28% | 26% | 24% |
| Stable disease | 29% | 25% | 31% | 33% | 34% | 39% |
| Progressive disease | 20% | 24% | 15% | 21% | 32% | 27% |
| Not evaluable | 8% | 9% | 8% | 8% | 7% | 9% |

[a]One-sided test to rule out 15% difference in response rate (prespecified test for non-inferiority).

[b]One-sided test to rule out 10% difference in response rate.

Abbreviations: CI, confidence interval; OR, odds ratio for objective response (control taken as reference).

**Table 5. Progression-free and overall survival**

| | Combination | | | | Single-Agent | |
|---|---|---|---|---|---|---|
| | Study 1 | | Study 3 | | Study 2 | |
| | Myocet /CPA (n=142) | Dox/CPA (n=155) | Myocet /CPA (n=80) | Epi/CPA (n=80) | Myocet (n=108) | Dox (n=116) |
| **Progression-free survival** | | | | | | |
| Median (months) | 5.1 | 5.5 | 7.7 | 5.6 | 2.9 | 3.2 |
| 95% CI | 4.3-6.4 | 4.2-6.8 | 5.4-8.9 | 4.4-6.4 | | |
| logrank *p*-value[a] | 0.821 | | 0.022 | | .352 | |
| Rel. risk (Dox or Epi:Myocet) | 1.03 | | 1.52 | | 0.87 | |
| Two-sided 95% CI[b] | 0.80–1.34 | | 1.06-2.20-- | | .66-1.16 | |
| **Overall survival** | | | | | | |
| Median (months) | 18.6 | 16.4 | 18.3 | 16.0 | 15.7 | 21.2 |
| 95% CI | 14.3-30.3 | 14.6-20.7 | 14.9-23.8 | 12.8-18.3 | | |

| | | | |
|---|---|---|---|
| logrank *p*-value[a] | 0.793 | 0.504 | .076 |
| Rel. risk (Dox or Epi:Myocet) | 1.042 | 1.147 | .755 |
| One-sided lower 95% CI[b] | 0.804 | -- | 0.581 |

[a] Log-rank *p*-value (two-sided test). [b] not applicable to study 3.
Abbreviations: see Table 4.

With respect to changes in performance status, body weight, pain and other symptoms in study 1 there were no differences between the treatment groups. There were minor changes to the advantage of Myocet in patient-reported symptoms at cycles 2, 3 and 4 but not when comparing changes throughout the study. Mean changes for most QoL parameters were similar between treatment groups. Minor differences in a few parameters to the advantage of either arm were observed. In study 2, no differences in weight, pain or other symptoms were observed. The Dox group improved slightly, but significantly more than the Myocet arm in performance status.

***Supportive studies***

The supportive phase II trials (study 4, 5, 6 and 7) do not provide any critical data for this assessment but rather confirm the feasibility of Myocet administration with respect to efficacy and safety.

Study 6-combined Myocet with CPA and 5-FU, resulting in a high response rate without obviously increased cardiotoxicity but with a tendency for more pronounced other toxicity. Study 7 (single-agent Myocet with a starting dose of 135 mg/m$^2$ as a 1 h infusion every three weeks, with G-CSF), on the other hand, confirmed the fairly modest advantage from Myocet since the high dose used clearly produced unacceptable cardiotoxicity.

***Discussion on clinical efficacy***

The choice of treatment in the control and the experimental groups in trials 1 is considered relevant. Dox/CPA is still regarded as a clinically relevant combination although the inclusion also of 5-FU (CAF regimen) is more commonly used. Single-agent Dox at conventional doses is probably mostly not accepted as a clinical standard but for the purpose of elucidating differences in the therapeutic ratios for Myocet and Dox, the comparison is relevant.

The Myocet *versus* Epi comparison at identical doses in study 3 is more problematic with respect to antitumour efficacy due to the comparison at identical doses with Epi, which might have a better therapeutic index than Dox. Based on prior experience Epi seems to be less cardiotoxic, with an incidence of CHF at 900 mg/m$^2$ approximately similar to that of 550 mg/m$^2$ Dox. Although equivalent antitumour efficacy is suggested from randomised comparisons using identical doses, this is not yet fully accepted. Currently, many clinicians would probably suggest that 75 mg/m$^2$ of Epi correlates to approximately 60 mg/m$^2$ of Dox with respect to toxicity and efficacy.

Unfortunately, very precise data on the effect of chemotherapy on OS in MBC are missing but retrospective cohort data indicate a survival benefit from non-anthracycline chemotherapy *versus* no treatment in the range 6 – 9 months. A somewhat better effect might be expected from anthracycline-based treatment. Against this background, a non-inferiority requirement for the lower bound 95% confidence interval for the hazard ratio for PFS and OS in the range 0.7 – 0.8 was considered relevant.

With respect to antitumour efficacy, some of the data presented are not fully satisfactory, notably the survival data from study 2 as well as choice of tumour response rate as primary endpoint in the phase III trials. However, it seems reasonable to conclude that the survival difference in study 2 is unlikely to be due to different antitumour activity of Myocet *versus* Dox. Based on a global assessment of all efficacy data from the phase III trials, it seems reasonable to conclude that Myocet is non-inferior to Dox and, thus, an active drug for the treatment of MBC.

**Clinical safety**

Adverse events were graded according to NCI CTC criteria. Safety data were presented according to treatment actually received.

***Patient exposure***

Three hundred and twenty-three patients were actually exposed to Myocet in studies 1 – 3. Fourteen and 13% of Myocet and Dox cycles, respectively, were delayed in study 1 and the corresponding figures for study 2 were 16 and 14% and 17 and 15% for study 3. The fraction of cycles with dose reductions was 4 and 9% for Myocet and Dox, respectively, in study 1, 28 and 25% in study 2 and 11 and 4% in study 3. The main reason for dose delays/reductions was myelosuppression. G-CSF use between treatment arms was 38 and 45% of cycles for Myocet and Dox, respectively in study 1, with corresponding figures of 56 and 68% in study 2 and 39 and 29% in study 3.

***Adverse events, serious adverse events and deaths***

In study 1, there were 10 patients on the Myocet/CPA arm who died within 30 days of study treatment administration. Four of these deaths occurred after one cycle of therapy; 3 were considered to be due to progressive disease and 1 death was due to sepsis in the setting of grade 4 neutropenia. Four Myocet/CPA patients died after their second cycle of study therapy; 3 died of progressive disease and 1 of the four died of complications related to coronary artery disease. One patient died due to a pre-existing radiation-induced constrictive pericarditis and the tenth Myocet/CPA death was observed after six cycles due to grade 4 neutropenic sepsis. Two Dox/CPA patients died within 30 days of their last dose of study therapy, one of unknown causality after one cycle. The second patient died after two cycles, due to progressive disease. In study 2, two Dox patients died while on the study, both due to progressive disease. There were no deaths on the Myocet arm. In study 3, 3 Myocet/CPA and 4 Epi/CPA patients died within 30 days of study treatment administration. All cases were considered to be due to progressive disease.

The observed SAEs in studies 1 and 3 did not present any unexpected findings with respect to incidence or type of SAEs, nor in the comparisons across treatment arms. In study 2, SAEs other than deaths were reported for 41 and 40% of patients in the Myocet and Dox arms, respectively. Eighty-nine and 94%, respectively, of these SAEs were of grade 3 or 4 and are partly also covered in the adverse events section below. The overall incidence of grade 3 – 4 SAEs according to organ system was fairly balanced (including types of events).

**Cardiotoxicity**

Cardiotoxicity results for studies 1 and 2 in which MUGA scans were used, are summarised in Table 6. A total of 9 *versus* 32 cardiotoxic events were observed in the Myocet and Dox arms, respectively, in study 1. The corresponding figures for study 2 were 18 and 44. The 5 confirmed cases of CHF in study 1 had lifetime Dox exposures in the range 360 – 480 mg/m$^2$ with 1 patient having received a cumulative dose of adjuvant Dox of 240 mg/m$^2$. The 2 patients with CHF in the Myocet arm in study 2 had life-time Dox exposure of 1100 and 785 mg/m$^2$ (290 mg/m$^2$ adjuvant), respectively. The 9 patients with CHF in the Dox arm had lifetime Dox exposure in the range 525 – 765 mg/m$^2$ with 2 patients having a cumulative dose of adjuvant Dox of 195 and 300 mg/m$^2$, respectively.

In study 2, cardiac biopsies were performed in the initial phase of the study, for patients with lifetime Dox exposure of >400 mg/m$^2$. Thirty-six patients (19 Myocet and 17 Dox) had biopsies that were blindly evaluated and scored according to Billingham. None of the patients in the Myocet arm compared with 7 in the Dox arm showed the highest score, *i.e.*, 3.0, whereas 5 patients in each arm had a score of 2.5. Nevertheless, although an important selection bias is unlikely, the data for the 36 patients with a biopsy need to be assessed with caution.

Cardiotoxicity was not a primary endpoint in study 3 and a less reproducible method for LVEF monitoring, *i.e.*, echocardiography, was used. The maximal cumulative dose of Myocet and Epi was 600 mg/m$^2$. Nine patients (12%; 5 type I and 4 type II) in the Myocet arm and 8 patients (10%; 5 type I and 3 type II) in the Epi arm developed reductions on LVEF. There were no cases of CHF.

Three hundred and seventy-nine anthracycline-naive patients with solid tumours treated with Myocet at starting doses of <100 mg/m$^2$ in all clinical studies were included in the assessment of risk of CHF. Two patients (0.5%) developed CHF. The cumulative risk of developing CHF was 3% at 650 mg/m$^2$ and 9% at 750 mg/m$^2$. Exploratory analyses indicated that the cardiotoxicity advantage of Myocet over Dox was observed in subgroups seemingly at higher risk for cardiotoxicity (by age, prior Dox and radiation to the chest) as well as in remaining lower-risk subgroup.

Follow-up with respect to LVEF changes was similar between treatment arms and generally most events occurred within the study periods. With respect to CHF, 6 of the 16 total cases were reported >3 months after the last study treatment administration. Thus, the majority of CHF cases were reported close to the trials, which increase the reliability of these data. However, CHF might occur very late after therapy and there is probably a risk for underreporting since events might be attributed to 2nd line or other therapy, part of natural ageing, *etc*. Thus, with respect to CHF there remains uncertainty about the quality of the data due the procedure for data collection, *i.e.*, spontaneous reporting from the investigators.

**Table 6. Cardiotoxicity in studies 1 and 2**

| | **Combination** | | | **Single-Agent** | |
|---|---|---|---|---|---|
| | **Study 1** | | | **Study 2** | |
| | **Myocet /CPA (n=142)** | **Dox/CPA (n=154)** | | **Myocet (n=105)** | **Dox (n=118)** |
| No. of patients with LVEF change (Type I, II) | 9 | 32 | | 13 | 32 |
| No. of patients with cardiac biopsy grade ≥2.5 | -- | -- | | 5/19 | 12/17 |
| No. of patients with CHF | 0 | 5 | | 2 | 9 |
| Median lifetime cumul. dose (mg/m$^2$) to cardiac event | >1260 | 480 | | 785 | 533 |
| Log-rank *p*-value[b] | 0.0001 | | | 0.0001 | |
| Median months since first dose of study drug[a] | >15.2 | 9.8 | | 9.8 | 6.9 |
| Log-rank *p*-value[b] | 0.0005 | | | 0.0007 | |
| CHF by lifetime cumul. dose (mg/m$^2$) of Dox | >1920 | >660 | | 1110 | 690 |
| Log-rank *p*-value[b] | 0.0206 | | | 0.0001 | |

[a] Two-sided test to reject null hypothesis of no difference

### *Clinical adverse events and laboratory findings*

In study 2 the median duration of thrombocytopenia was 6 and 5 days for Myocet and Dox, respectively. In study 3 the median duration of thrombocytopenia was 9 and 5 days for Myocet and Epi. In study 3 median duration of neutropenia was 7 and 10 days for Myocet and Epi, respectively. Otherwise there were no differences in the duration or degree of thrombocytopenia or neutropenia.

There was generally little skin toxicity. With respect to palmar-plantar erythrodysesthesia, 1 Dox/CPA patient developed a grade 1 reaction whereas in study 2, there were 2 grade 2 cases in the Dox arm and 1 grade 2 cases in the Myocet arm. This toxicity was not detailed for study 3. Pronounced alopecia was observed in approximately 80 – 90% of patients in both arms in all studies. Injection site reactions were more common in the Dox arm but significantly so only in study 3. Experience of 9 cases of extravasation of Myocet was reported. Ulcerative lesions or necrosis were not observed.

There were no apparent differences between the treatment arms in events considered less relevant for chemotherapy or with incidences <5%. Table 7 summarises the non-cardiac clinical and haematological adverse events considered to be relevant for chemotherapy and with a frequency of >5% in either arm.

**Table 7. Adverse events occurring in >5% of patients (% of patients)**

| | Study 1 | | | Study 2 | | | Study 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Dose (mg/m$^2$)** | **Myocet 60 CPA 600 (n=142)** | **Dox 60 CPA 600 (n=154)** | | **Myocet 75 (n=105)** | **Dox 75 (n=118)** | | **Myocet 75 CPA 600 (n=76)** | **Epi 75 CPA 600 (n=78)** | |
| Haematological Toxicity | | | | | | | | | |
| Neutropaenia All grades | 96 | 97 | | 87 | 92 | | 100 | 99 | |
| Grade 4 | 61 | 75 | | 50 | 58 | | 87 | 67 | |
| Neutropenic Fever | 10 | 15 | | 14 | 10 | | 8 | 1 | |
| Anaemia All Grades | 88 | 92 | | 85 | 96 | | 96 | 78 | |
| Hgb <8 gm/dl | 23 | 27 | | 22 | 26 | | 25 | 14 | |
| Thrombocytopaenia All grades | 51 | 47 | | 83 | 75 | | 54 | 27 | |
| <20,000 cells/µl | 4 | 5 | | 13 | 10 | | 4 | 3 | |
| Infection | | | | | | | | | |
| Infection All grades | 53 | 53 | | 36 | 58 | | 22 | 15 | |
| Grade ≥ 3 | 11 | 8 | | 5 | 12 | | 7 | 1 | |
| Gastro-intestinal Toxicities | | | | | | | | | |
| Diarrhoea | | | | | | | | | |
| All grades | 28 | 38 | | 26 | 42 | | 21 | 19 | |
| Grade ≥ 3 | 3 | 8 | | 1 | 4 | | 1 | 1 | |
| Nausea / Vomiting All grades | 80 | 84 | | 90 | 90 | | 84 | 81 | |
| Grade ≥ 3 | 13 | 16 | | 13 | 24 | | 21 | 19 | |
| Stomatitis / Mucositis All grades | 40 | 56 | | 56 | 69 | | 36 | 12 | |
| Grade ≥ 3 | 4 | 6 | | 9 | 14 | | 7 | 0 | |
| Skin | | | | | | | | | |
| Cutaneous All grades | 11 | 12 | | 16 | 9 | | 4 | 10 | |
| Grade ≥ 3 | 0 | 1 | | 1 | 1 | | 0 | 1 | |
| Injection Site All grades | 5 | 8 | | 15 | 18 | | 1 | 10 | |
| Grade ≥ 3 | 1 | 1 | | 0 | 2 | | 0 | 1 | |
| Flue-Like Symptoms | | | | | | | | | |
| Asthenia All grades | 42 | 47 | | 70 | 73 | | 33 | 31 | |
| Grade ≥ 3 | 6 | 5 | | 14 | 19 | | 0 | 1 | |

Definitions: Neutropenia Grade 4, <500 cells/µl; Neutropenic fever, ANC <500, fever >38ºC; Asthenia, includes Fatigue / Malaise

There was no indication of apparent different safety profiles in patients below and above 65 years of age. There is no experience reported on the safety profile in patients with impaired renal or liver function.

Drug-related grade 3 or 4 adverse events reported for the Myocet but not for the Dox arm in study 1 included bronchospasm, emotional lability, pain, pneumonia and supraventricular tachycardia (1 patient each). Corresponding observations for study 2 were folliculitis, glossitis, pericardial effusion and pruritus (1 patient each) and for study 3 stomatitis (5 patients), gastric ulcer (2 patients), somnolence (2 patients), bronchitis, haemorrhagic cystitis, dizziness, dysphonia, abnormal gait,

gingivitis, herpes zoster, melena, muscle weakness, palpitation and supraventricular tachycardia (1 patient each).

Other laboratory parameters measured included transaminases, alkaline phosphatase, bilirubin, sodium, potassium, urea, creatinine, albumin, urate, calcium, phosphate, glucose, chloride in blood and renal toxicity was also investigated by dipsticks/microscopy for erythrocytes, leukocytes, protein, glucose and casts. There were essentially no differences between the treatment groups in these parameters.

Twenty and 18% of Myocet and Dox patients, respectively, in study 1 had at least one grade 3 toxicity. The corresponding figures for study 2 were 18 and 11% and for study 3, 5 and 10%.

Grade 3 and 4 hepatic laboratory abnormalities ranged 0 – 4% and 0 – 1%, respectively, in trials 1 – 3, with no apparent differences between treatment arms. There was 1 patient in each arm of trial 1 with creatinine elevation of grade 3 and a few cases in both arms of grades 3 – 4 electrolyte and mineral abnormalities in trials 1 and 3. In study 3, there were 4 patients in each arm with serum urea elevation of grade 3.

***Discussion on clinical safety***

With respect to cardiotoxicity, Myocet compared to Dox (studies 1 and 2) clearly reduced the risk for a significant decrease in LVEF although the absolute differences were small. There was also a difference in the incidence in CHF although this observation is less convincing given the unblinded procedures for reporting this event. Differences in LVEF changes or incidence of CHF did not appear to be due to differences in post-study therapy. Based on the seemingly acceptable surrogate value of a decreased LVEF for the future development of CHF it is concluded that the cardiac safety profile for Myocet is better than that of Dox.

Myocet by no means completely relieves the risk of significant cardiotoxicity from Dox based chemotherapy. Thus, LVEF changes were observed also in the Myocet groups and seemed to be dose-dependent, as evidenced by comparing studies 1 and 2. In both trials the relative Myocet/Dox dose to produce similar frequencies of LVEF changes approximately ranged 1.2 – 1.5/1. This is a modest but clinically relevant achievement that might improve cardiac safety and/or the possibility to prolong a putatively beneficial treatment in MBC patients.

Most observed cases of CHF occurred quite early after treatment and there remains a risk for underreporting of very late occurring events. It seems unlikely that poor or biased reporting of late CHF would change the overall conclusion regarding cardiac safety of Myocet compared to Dox. Nevertheless, late onset cardiotoxicity is known to occur with anthracyclines and the comparison of cardiotoxic events after long-term follow-up needs to be considered. Thus, it will be necessary to perform future surveillance in order to assess the long-term cardiotoxicity for patients who have received Myocet.

The profiles for Myocet and Dox were similar with a trend for Myocet to be less myelotoxic and to produce less stomatitis. Particularly, Myocet was associated with less frequent anaemia (85% *versus* 96% in study 2), infection (36% *versus* 58% in study 2), and stomatitis / mucositis (40% *versus* 56%, in study 1). It should be noted, however, that these differences concern all grades of those events, while statistically significant differences are not attained for the higher intensities of the same manifestations. Furthermore, the assessment of myelotoxicity is obscured by the frequent use of G-CSF.

Compared to Epi, Myocet was associated with significantly more frequent haematological adverse events and mucositis but, as Epi was probably underdosed, evidence of definitive inferiority of the safety profile of Myocet cannot be retained. In study 3, cardiotoxicity was not a primary endpoint and was less accurately assessed. Cardiotoxicity seemed to be similar between the treatment groups. Tentatively, and based on the experience of lower cardiotoxicity of Epi compared with Dox at identical doses, this would also suggest a favourable cardiac safety profile for Myocet. The favourable cardiotoxic profile of Myocet also seemed to hold for patients at increased risk for cardiotoxicity.

## 5. Overall conclusion and benefit/risk assessment

### Quality

The quality of Myocet is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Aflatoxin control, the risk assessment of virological inactivation and validation of use of a dry heat block in the preparation of the final constituted product will be addressed as a Follow-up Measures.

### Preclinical pharmacology and toxicology

The antitumour activity of Myocet has been investigated in animal models and compared with that of free Dox. Myocet allowed the administration of higher doses of Dox, which seemed to display a different pharmacokinetic profile compared to the free Dox formulation.

The equal or improved survival that was observed in short-term animal studies of Myocet *versus* conventional Dox allows speculating that Myocet might maintain its activity also against the development of metastases. However, the actual long-term protection against the effect of micrometastases cannot be determined from the data. This issue is not considered critical in the palliative setting of MBC whereas it would need further investigations in earlier stages of the disease.

In summary, the preclinical data for Myocet are satisfactory.

### Efficacy

Although pharmacokinetic data may be somewhat unreliable, it appears that liposome-encapsulation of Dox results in lower peak plasma concentrations (thus mimicking continuous infusion) while the AUC for free drug may be approximately similar for the two treatments. This could explain why the efficacy and toxicity profiles are similar for Myocet and conventional Dox, whereas cardiotoxicity is somewhat reduced for Myocet.

The pharmacokinetics and safety in patients with impaired liver function will be addressed as a follow-up measure.

The choice of the combination Dox/CPA in the control and the experimental groups in one pivotal trial is considered relevant although the CAF regimen is more commonly used. Single-agent Dox at conventional doses, as was used in the second pivotal trial, although generally not accepted as a clinical standard, is considered relevant for the purpose of elucidating differences in the therapeutic ratios for Myocet and Dox.

In general, PFS and OS are considered more clinically relevant endpoints than response rate in advanced BC. However, in direct comparison between two Dox formulations, response rate was considered to be a sensitive endpoint for detection of a difference, if adequately supported by reliable PFS and OS data.

The pivotal trials show that Myocet is non-inferior to Dox on a mg per mg basis with respect to antitumour efficacy. It is acknowledged that there are some efficacy concerns, notably the inferior survival data observed for Myocet in study 2. However, it appears reasonable to conclude that the survival difference in study 2 is unlikely to be due to different antitumour activity of Myocet *versus* Dox. In addition, this study is less relevant for the approved indication.

Based on the assessment of all efficacy data from the pivotal trials it seems reasonable to conclude that Myocet is an active drug for the treatment of MBC and that its activity is non-inferior to that of Dox. Concerns were raised about the real added value of the liposomal formulation compared to conventional Dox.

It should be noted that demonstrated differences in pharmacokinetics between Myocet and Dox might be of importance for the eradication of micrometastasis. Myocet should therefore not be used in the adjuvant treatment of BC.

### Safety

With respect to cardiotoxicity, both in combination or single-agent studies, Myocet reduced the risk of a decrease in LVEF compared to Dox although the absolute differences were small. The observed

difference in the incidence in CHF in favour of Myocet is less convincing given the unblinded reporting of cases. Based on the acceptable surrogate value of a decrease in LVEF for the development of CHF it is concluded that the cardiac safety profile for Myocet is better than for Dox.

Most observed cases of CHF occurred quite early after treatment and there remains a risk for underreporting of very late occurring events. Late onset cardiotoxicity is known to occur with anthracyclines and the comparison of cardiotoxic events after long-term follow-up needs to be considered.

Excluding cardiotoxicity, the combination and single-agent trials of Myocet/CPM *versus* Dox/CPM and Myocet *versus* Dox showed comparable toxicity profiles. Experimental safety data are insufficient to allow a comparison of Myocet with Epi.

Myocet does not completely relieve the risk for significant cardiotoxicity. LVEF changes were observed also with Myocet and seemed to be dose-intensity dependent. The relative Myocet/Dox dose to produce similar frequencies of LVEF changes was approximately 1.2 to 1.5 times that of Dox. For MBC patients, this is a modest but still clinically relevant achievement that might provide an improved cardiac safety and/or the possibility to prolong treatment.

The evaluation of left ventricular function is considered mandatory before each additional administration of Myocet once a patient exceeds a lifetime cumulative anthracycline dose of 550 $mg/m^2$ or whenever cardiomyopathy is suspected (see SPC 4.4, *Special warnings and special precautions for use*).

It will be necessary to monitor the long-term cardiotoxicity for patients who have received Myocet.

**Benefit/risk assessment**

Overall it has been demonstrated that Myocet lowers the risk of cardiotoxicity compared with conventional Dox in dosages clinically equipotent with respect to antitumour activity. The absolute benefit from this, however, appears modest in patients with MBC. With respect to other aspects of toxicity, the safety profiles of Myocet and Dox are clinically similar.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by majority decision that the benefit/risk profile of Myocet, in combination with cyclophosphamide, in the first line treatment of metastatic breast cancer in women was favourable.