21 November 2013
EMA/CHMP/627629/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Abraxane

International non-proprietary name: **PACLITAXEL**

Procedure No. EMEA/H/C/000778/II/0055

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AEoI	adverse event of interest
BSA	body surface area
CA19-9	carbohydrate antigen 19-9
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CR	complete response
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CW	class waiver
CrEL	cremophor EL (polyoxyethylated castor oil)
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DoR	duration of response
EC	European Commission
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FOLFIRINOX	folinic acid, 5-fluorouracil, irinotecan, oxaliplatin
5-FU	5-fluorouracil
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
Hb	haemoglobin
HIV	human immunodeficiency virus
HR	hazard ratio
HUVEC	human umbilical vein endothelial cells
IRR	independent radiological review
IV	intravenous
KPS	Karnofsky Performance Score
MAA	marketing authorisation application
MAH	marketing authorisation holder
MBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NOAEL	no observed adverse effect level
ORR	overall response rate
OS	overall survival
PD	progressive disease
PDAC	pancreatic ductal adenocarcinoma
PET	positron-emission tomography
PFS	progression-free survival
PR	partial response
PRAC	Pharmacovigilance and Risk Assessment Committee
PTX	paclitaxel

RECIST	Response Criteria in Solid Tumors
RMP	Risk Management Plan
SAE	serious adverse event
SD	stable disease
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SPARC	secreted protein acidic and rich in cysteine
STDEV	standard deviation
TEAEs	treatment-emergent adverse events
TTF	time to treatment failure
ULN	upper limit of normal
US	United States (of America)

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Celgene Europe Limited submitted to the European Medicines Agency on 8 April 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Abraxane	PACLITAXEL	See Annex A

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II	I, II, IIIA and IIIB

The MAH applied for a new indication for the first-line treatment of adult patients with locally advanced unresectable or metastatic adenocarcinoma of the pancreas in combination with gemcitabine. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC. The Package Leaflet was proposed to be updated in accordance. In addition, the MAH proposed a minor editorial amendment to section 2 of the SmPC.

The variation proposed amendments to the SmPC and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

Additional data protection / marketing exclusivity

The applicant requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Pieter de Graeff Co-Rapporteur: Ingunn Hagen Westgaard

Submission date:	8 April 2013
Start of procedure:	26 April 2013
Rapporteur's preliminary assessment report circulated on:	25 June 2013
CoRapporteur's preliminary assessment report circulated on:	17 June 2013
PRAC RMP advice and assessment overview adopted by PRAC on:	11 July 2013
Joint Rapporteurs' updated assessment report circulated on:	22 July 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 July 2013
MAH's responses submitted to the CHMP on:	22 August 2013
Joint Rapporteurs' assessment report on the MAH's responses circulated on:	7 October 2013
PRAC RMP advice and assessment overview adopted by PRAC	11 October 2013
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	24 October 2013
MAH's responses submitted to the CHMP on:	30 October 2013
Joint Rapporteurs' assessment report on the MAH's responses circulated on:	8 November 2013
CHMP opinion:	21 November 2013

2. Scientific discussion

2.1. Introduction

Problem statement

In Europe, pancreatic cancer is the fifth leading cause of cancer-related death with approximately 95,200 deaths each year and over 99% of affected patients dying of their disease. The incidence of pancreatic cancer is higher in men than women and increases with age, with 90% of pancreatic cancer presenting in patients over the age of 55 years and more than 70% presenting over the age of 65 years. The incidence varies from 0.5-3.6 per 100.000 for persons below the age of 50 years to 55.9-89.2 per 100.000 for persons above the age of 75 years. Risk factors for development of pancreatic cancer include a family history of pancreatic cancer, cigarette smoking, obesity and chronic pancreatitis.

Exocrine tumours are by far the most common type of pancreatic cancer, with adenocarcinoma accounting for about 95% of cancers of the exocrine pancreas. Initial staging classifies pancreatic cancers as resectable, borderline resectable, locally advanced and metastatic. In the case of resectable disease, the entire tumour can be surgically removed whereas for both locally advanced and metastatic disease, the tumour cannot be completely removed, and surgery would only be conducted to relieve symptoms.

For all stages of pancreatic cancer combined, the 5-year overall survival (OS) rate in the EU is about 5% (Sant *et al*, 2009). For patients with localised disease and small cancers (<2 cm) with no lymph node metastases and no extension beyond the capsule of the pancreas, complete surgical resection is associated with an actuarial 5-year survival rate of 18% to 24%. Median survival for patients with locally advanced unresectable disease is 8 to 12 months and only three to six months for those who present with metastases. In patients with metastatic disease, the 5-year OS rate is 1.6%.

Surgical resection is the only potentially curative treatment. The highest cure rate occurs if the tumour is truly localised to the pancreas; however, this stage of disease account for less than 20% of cases and only 15 to 20% of patients are candidates for pancreatectomy. Most patients (80 to 85%) have unresectable disease at the time of diagnosis.

For patients with metastatic pancreatic cancer, single agent systemic chemotherapy has been the mainstay of treatment. However, among active single agents, none has been consistently associated with objective response rates above 10% or median survival durations above 6 to 7 months. Gemcitabine has been the standard chemotherapy for first line treatment of pancreatic adenocarcinoma. A phase II study comparing gemcitabine to 5-fluorouracil (5-FU) suggested that patients who lacked an objective response to treatment often had improvement in symptoms (i.e., pain, weight loss) and performance status (Rothenber *et al*, 1996). The percentage of patients who derived clinical benefit from therapy was almost three-fold higher than the fraction that had an objective antitumor response (11% vs 27%). In another phase II trial, a significantly better overall survival (5.6 vs 4.4 months) was demonstrated for gemcitabine in comparison to 5-FU (Burris *et al*, 1997).

Although gemcitabine monotherapy is generally well tolerated, median OS remains less than 6 months in metastatic pancreatic cancer patients. In several clinical trials, gemcitabine activity in combination with other active cytotoxic agents including 5-FU, cisplatin, docetaxel, oxaliplatin and irinotecan has been studied. In general, other chemotherapy combinations failed to achieve improvement in OS over

three weeks or were accompanied by increased toxicity, limiting the number of patients that can actually use these therapy regimens.

The superiority of short-term infusional 5-FU, leucovorin, oxaliplatin and irinotecan (FOLFIRINOX) over gemcitabine monotherapy was initially suggested in a randomised phase II study conducted in 176 patients with previously untreated metastatic pancreatic cancer. FOLFIRINOX was associated with a high objective response rate (39% vs 11% with gemcitabine alone; Ychou *et al*, 2007). The study was expanded to a phase III trial (the Accord 11 trial) in which a total of 342 patients with chemotherapy-naïve, metastatic pancreatic cancer, were randomly assigned to gemcitabine alone versus FOLFIRINOX. The trial was stopped after enrolling only 250 patients at a pre-planned interim analysis showing a significantly higher objective response rate with FOLFIRINOX (31.6% versus 9.4%), longer median PFS (6.4 vs 3.3 months) and overall survival (11.1 vs 6.8 months). The increased efficacy of FOLFIRINOX compared to gemcitabine was accompanied with significantly higher treatment related toxicity with FOLFIRINOX (Conroy *et al*, 2011).

Finally, gemcitabine combined with erlotinib has been approved for the treatment of metastatic pancreatic cancer (Moore *et al*, 2007), but due to the very limited improvement in OS and the observed add-on toxicity, the combination gemcitabine-erlotinib is not frequently used in clinical practice.

About the product

Abraxane contains paclitaxel as the active substance formulated as albumin-bound nanoparticles. Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation, so that the normal dynamic reorganisation of the microtubule network, essential for vital cellular functions, is inhibited. The albumin-bound paclitaxel is expected to be more water-soluble, to achieve higher delivery of paclitaxel to the tumour and to cause less frequent hypersensitivity reactions compared to conventional solvent-based paclitaxel formulations due to the absence of Cremophor-EL (polyoxyethylated castor oil), a solvent present in standard paclitaxel formulations that has been associated with acute infusion-related hypersensitivity reactions.

Abraxane monotherapy is indicated for the treatment of metastatic breast cancer (MBC) in adult patients who have failed first-line treatment for metastatic disease and for whom standard anthracycline-containing therapy is not indicated. The recommended dose of Abraxane is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks.

With this variation application for addition of a new therapeutic indication, the MAH proposed the use of Abraxane in combination with gemcitabine in the first line treatment of adult patients with locally advanced unresectable or metastatic adenocarcinoma of the pancreas.

The clinical development of Abraxane for the treatment of advanced adenocarcinoma of the pancreas included a phase I/II study CA040 to determine the MTD, DLTs and initial antitumour activity of Abraxane followed by gemcitabine and a randomised, pivotal phase III Study CA046.

Orphan drug designation was granted to nanoparticle albumin-bound paclitaxel for the treatment of pancreatic cancer in the EU on 26 November 2010 (EU orphan designation number EU/3/10/809). The designation was withdrawn prior to the submission of this variation.

2.2. Non-clinical aspects

2.2.1. Introduction

The pharmacology of the active substance paclitaxel is well-known and in the initial Marketing Authorisation application (MAA) of Abraxane, several in vitro studies were submitted to compare the effect of solvent and albumin nanoparticles as carriers of paclitaxel on trans-endothelial transport and cellular uptake. Based on these studies it was suggested that Abraxane may result in higher tumour concentrations because of a) decreased bioavailability of paclitaxel due to sequestration in the plasma by Cremophor micelles, b) increased trans-endothelial transport that is mediated by the gp-60 albumin receptor and c) increased accumulation in the area of tumour due to the albumin-binding protein SPARC (secreted protein acidic rich in cysteine).

At the time of the MAA, a set of pharmacokinetic and tissue distribution studies were conducted with Abraxane with a goal of understanding the dispositional differences, if any, between Abraxane and the solvent-based paclitaxel formulation Taxol (CrEL:ethanol vehicle). Extensive studies to determine the metabolic pathways were not submitted in this application (see discussion on non-clinical aspects). Information derived from the literature was provided as supportive information for plasma protein binding, placental transfer, hepatic metabolism of paclitaxel and interaction with transporters.

Regarding toxicology, the nonclinical toxicology development program in the original MAA was focused on evaluating the safety or efficacy of paclitaxel in Abraxane compared to the Cremophor-EL-based comparator, Taxol.

2.2.2. Pharmacology

Primary pharmacodynamic studies

With this variation application, several nonclinical studies investigated the anti-tumour activity of Abraxane as a single agent and in combination with gemcitabine in different pancreatic tumour models (see Table 1).

A further in vitro study was submitted (XP-001) to compare the transport of paclitaxel across endothelial cells and uptake of paclitaxel in endothelial and cancer cells (PC-3 prostate cancer and HT-29 colon cancer) treated with Abraxane and Cremophor-based paclitaxel. The results indicated that CrEL significantly decreased paclitaxel transport across endothelial cells and interrupted paclitaxel uptake in both endothelial and tumour cells in a concentration-dependent manner (data not shown).

Table 1: Overview of new studies on anti- pancreatic tumour activity of Abraxane

Reference	tumour model	treatment	results
Von Hoff (2011)	athymic nude mice with 11 different patient-derived pancreatic tumor xenografts	- control - gem.[a] (100 mg/kg, 2/week, 4 weeks ip) - Abraxane (30 mg/kg/d, IV 5 days) - Gem + Abraxane	Increased frequency of regression (gem: 2/11, Abraxane: 4/11, gem+Abraxane: 7/11)
Frese (2012)	KPC mice[b]	- control - gem (100 mg/kg, q4dx3 ip) - Abraxane (120 mg/kg, q4dx3 IV)	Abraxane, Abraxane+gem[c]: ↓ tumour growth, ↑ survival, ↓ metastasis

		- gem + Abraxane	
Report S672	In vitro proliferation of PDAC cell lines[d] and fibroblast and endothelial cell line	72 hr various concentrations Abraxane, docetaxel, gemcitabine, bevacizumab, sunitinib,	IC50 values between ~0.2-5 µM, additive effects of gem, doc, sun (not all cell lines) bevac (some cell lines)
	Athymic nude mice with AsPC-1 xenograft sc, or NOD/SCID mice with AsPC-1 xenograft ip	- control - doc (4 mg/kg, biw) - gem (100 mg/kg, biw) - Abraxane (10 mg/kg, biw) - sun (20 mg/kg 5qw - bevac (10 µg, biw)	Antitumour activity Abraxane, increased by co-treatment with gem, bevac, or sun

a: gem: gemcitabine, PDAC: pancreatic ductal adenocarcinoma, doc: docetaxel, biw: biweekly, sun: sunitinib, bevac: bevacizumab, q4dx3: every 4 days for 3 treatments, 5qw: 5 times weekly.
b: genetically engineered mouse model of pancreatic ductal adenocarcinoma expressing endogenous mutant Kras and Trp53 alleles
c: Antitumour effect was more prominent in the combination gemcitabine + Abraxane
d: PDAC cell lines were AsPC-1, BxPC-3, MIA PaCa-2 and Panc-1, human fibroblast cell line was WI-38, and endothelial cells were human umbilical vein endothelial cells (HUVECs).

2.2.3. Pharmacokinetics

New data on pharmacokinetics were collected in toxicology studies SNBL.119.11 and 08AC21. Furthermore a drug-drug interaction study between Abraxane and gemcitabine was submitted (ABI PK 01005).

Study 08AC21 evaluated the repeat-dose toxicity potential of intermittent administration of Abraxane (0, 10, 20 and 30 mg/kg, every 5 days for 6 doses) given to Crl:CD(SD) rats; paclitaxel (PTX) at 10 mg/kg was also given as comparative control article. Toxicokinetics showed that Cmax and AUC_{0-24h} increased dose-dependently and there were no remarkable gender differences on each dosing day in the Abraxane groups. In the PTX group, Cmax and AUC_{0-24h} were higher than those in the Abraxane 10 mg/kg group for both sexes. Cmax and AUC_{0-24h} increased in all dosing groups at the final dosing in comparison to the first dosing.

Study SNBL.119.11 evaluated the pharmacokinetic and toxicological interaction between nab 17-AAG (geldanamycin (17-AAG) compounded with human serum albumin nanoparticles, 9 mg/kg), Abraxane (9 mg/kg), and Herceptin (12.4 mg/kg) in cynomolgus monkeys following once weekly intravenous administration for three weeks. This study included an Abraxane-only arm (9 mg/kg). In the Abraxane single agent treatment group, the mean paclitaxel Cmax and AUC appeared slightly higher in females than males and this difference was increased when Abraxane was combined with nab 17-AAG. Furthermore, nab 17-AAG appeared to cause accumulation of paclitaxel.

The drug-drug interaction study in rat (ABI-PK-01005) between Abraxane and gemcitabine was performed as data indicated that Abraxane-derived paclitaxel modulated intracellular disposition of gemcitabine (Frese *et al*, 2012). However, the study did not reveal any statistically significant differences in plasma paclitaxel and gemcitabine pharmacokinetics (Cmax and AUClast) when administered concurrently vs as single agents following a single intravenous dose (paclitaxel 21 mg/kg, gemcitabine 167 mg/kg), but the exposure to the inactive metabolite of gemcitabine dFdU was 2-fold increased in presence of paclitaxel. However, such an increase was not observed in clinical studies using a different paclitaxel formulation (paclitaxel 100-175 mg/m2, gemcitabine 1000-2000 mg/m2) and different schedules (Fogli *et al*, 2001,; Fogli *et al*, 2002; Kroep *et al*, 1999; Kroep *et al*, 2006).

A recent publication on transplacental transport of paclitaxel in baboons (Calsteren *et* al, 2010) confirmed previous mouse data that paclitaxel crosses the placental barrier, albeit to a limited extent.

2.2.4. Toxicology

Repeat dose toxicity

Study 08CA21 was a GLP repeat-dose toxicity study in rats of Abraxane at 0, 10, 20, and 30 mg/kg, and paclitaxel (PTX) at 10 mg/kg, intravenously a total of 6 times every 5 days over a 30-day period. Mortality occurred in 1/32, 4/32, and 23/32 rats in Abraxane 10, 20, and 30 mg/kg groups, respectively. All animals in the 10 mg/kg paclitaxel group survived throughout the study. The observed toxicity consisted mainly of clinical signs (alopecia, scab formation, oedema, gait effects, weight loss, food consumption), atrophic changes in the lymphatic/haematopoietic tissues, male reproductive organs, and skin and degenerative changes in the nervous system and eyes. The toxicological characteristics of Abraxane were similar to those of PTX. The changes in the reproductive organs, nervous system, or eye in the Abraxane and paclitaxel groups were not (fully) reversible within the 4 week recovery period.

Study SNBL.119.11 was a GLP-compliant weekly toxicology study evaluating the pharmacokinetic and toxicological profile of nab 17-AAG (17-AAG compounded with human serum albumin nanoparticles) when administered in conjunction with Abraxane and Herceptin. This study included an Abraxane-only arm, in which 9 mg/kg Abraxane (108 mg/m2) was administered by intravenous infusion to 3 males and 3 females on a weekly schedule for three weeks. Other treatment arms were nab 17-AAG alone, nab 17-AAG with Abraxane, nab 17-AAG + Abraxane and Herceptin, and vehicle control.

Administration of Abraxane alone resulted in adverse clinical observations (inappetence, hunched posture, liquid/soft/dry/mucous/bloody/black faeces, and/or emesis), decreased food consumption (in females) and body weights (in females), and changes in urinalysis (red colour, glucose, and nitrite), haematology (decreases in white blood cell count, red cell mass, and reticulocytes and increased red cell distribution width), and serum chemistry (decreased albumin) parameters. Post-mortem changes resulting from Abraxane administration included gross lesions (decreased thymic size), organ weight changes (increases in spleen weights and decreases in thymus, pituitary, testes, liver, and thyroid/parathyroid weights), and histopathologic lesions (decreased thymic cellularity in all animals, myocardial karyomegaly, seminiferous tubule degeneration in all males and hepatic leukocytosis and centrilobular vacuolation). A NOAEL was not established in this study.

2.2.5. Ecotoxicity / environmental risk assessment

The applicant submitted an ERA based on the EMEA/CHMP/SWP/4447/00 guideline (EMEA, 2006).

An Fpen default value of 0.01 (1%) is proposed in the guideline. However, published prevalence data indicate the number of patients with MBC in the EU5 (France, Germany, Italy, Spain, UK) to be 171,655 (CancerMpact© data, Kantar Health (Kantar Health Epi Database ®, October 2011.)). Extrapolating to the EU27 estimated population of 502,489,143, this would be a number of 272,920 which can be divided by the population of the EU27 to give a prevalence of 0.00055 (0.05%) for MBC.

Similarly, data indicate the prevalence of adenocarcinoma of the pancreas in the EU5 to be 37,380 (CancerMpact© data, Kantar Health), which can be extrapolated to 59,382 in the EU27, giving a prevalence of 59,382/502,489,143 or 0.0001 (0.01%).

The maximum daily dose for MBC is 260 mg/m2/day (442 mg/inh/day assuming 1.7m2 average body surface per patient) with a maximum of 18 cycles per year. The maximum daily dose for pancreatic

adenocarcinoma is 125 mg/m2 (225 mg/inh/day assuming 1.8m2 average body surface per patient) on day 1, 8, 15 of a 28 day cycle (a maximum of 12 cycles per year). Thus, the Fpen is further modified as follows:

Fpen = Pregion x (ttreatment x ntreatment, p/Nd)

Thus Fpen (MBC) = 0.00055 x (1 day x 18 cycles/365 days) = 0.0000271 and

Fpen (AP) = 0.0001 x (3 days x 12 cycles/365 days) = 0.0000099

Using the formula

$$PEC_{SW} = \frac{DOSEai \cdot F_{pen}}{WASTEW_{inhab} \cdot DILUTION}$$

with the following parameter values for MBC and AP:

*DOSE*ai =	442 (MBC) / 225 (AP)	(mg patient^{-1} d^{-1})
F_{pen} =	0.0000271 (MBC)/ 0.0000099 (AP)	(patient inh^{-1})
*WASTEW*inhab =	200	(L inh^{-1} d^{-1})
DILUTION =	10	(–)

the combined PEC amounts to 0.007 µg/L, which is below the trigger of 0.10 µg/L.

No specific study was conducted to determine the partition coefficient (logKow) of paclitaxel. Estimates of partition coefficient values for paclitaxel were available from published literature and from public domain websites (data not shown).

2.2.6. Discussion on non-clinical aspects

During the Marketing Authorisation application for Abraxane in the (second line) treatment of metastatic breast cancer, the strategy of the nonclinical development had been to conduct specific studies in vitro or in animal models to address the likely alterations in systemic exposure, efficacy and any change in safety assessment due to the change in formulation from Cremophor-EL-based to nanoparticulate, albumin-bound.

It was previously suggested that albumin binding proteins, such as SPARC, may play a role in the uptake and distribution of Abraxane. In the clinic it has been noted that high expression levels of SPARC in the stroma of patients with advanced pancreatic cancer were correlated with improved survival (Von Hoff *et al*, 2011; clinical study CA040 below). Yet it currently remains unclear to what extent SPARC expression in pancreatic tumours may contribute to the antitumour activity of Abraxane.

Both Von Hoff *et al* (2011) and Frese *et al* (2012) reported that the intra-tumour concentration of gemcitabine was increased by Abraxane co-treatment. Overall, non-clinical pharmacology data support the rationale for the use of Abraxane in pancreatic adenocarcinoma, alone or combined with gemcitabine. As the predictive value of nonclinical models in oncology is relatively limited, further evidence should be obtained clinically.

Several recent nonclinical studies by the MAH or in the literature (Desai *et al*, 2008; Volk *et al*, 2008; Volk *et al*, 2011; Report BTC-X8009; Report BTC-X8010) have suggested the antitumour activity of Abraxane alone or in combination with e.g. bevacizumab in other tumour models.

It was concluded that the primary pharmacology experiments with Abraxane have thus shown that this nanoparticle albumin-bound paclitaxel formulation retains the desired antitumour activity against various cancer cell types in vivo, both as a single agent and in combination with bevacizumab.

The metabolism of paclitaxel is well described in the literature and it is not expected to change based on the differences in the formulation, therefore lack of extensive studies to determine the metabolic pathways in this application is justified. Information derived from the literature was provided as supportive information for plasma protein binding, placental transfer, hepatic metabolism of paclitaxel and interaction with transporters.

The difference in exposure between Abraxane and paclitaxel has been noted in previous studies.

In study 08AC21, exposures were higher at the end of study when compared to first day treatment. This suggests that some accumulation may occur, although the increase in exposure was maximally 2-fold. As kinetics in patients was linear, no accumulation is expected in the clinic.

Studies SNBL.119.11 and ABI-PK-01005 suggested that there is no/limited pharmacokinetic interaction of Abraxane with gemcitabine or Herceptin; however, an interaction with albumin bound geldanamycin (nab 17-AAG) may not be excluded. Studies reported in the literature (Fogli *et al*, 2001,; Fogli *et al*, 2002; Kroep *et al*, 1999; Kroep *et al*, 2006) indicated that paclitaxel and gemcitabine did not affect each other's pharmacokinetics to a significant extent. Therefore, the absence of pharmacokinetic data regarding the interaction between paclitaxel and gemcitabine is considered acceptable. Relevant information has been included in section 4.5 of the SmPC.

No unexpected effects of Abraxane treatment were seen in the two newly submitted repeat-dose toxicity studies.

In study SNBL.119.11, deaths were noted in two groups, both receiving Abraxane in combination with other substances. It was concluded that treatment with Abraxane resulted in the earlier onset and more significant toxicity when compared to the other two substances (nab 17-AAG or Herceptin).

Regarding the ERA, the MAH considered that based on the overall consistency of the reported logKow values, it is reasonable to utilise these and not determine the logKow experimentally. Based on these data, the logKow ≥ 4.5 trigger value for further Persistence, Bioaccumulation and Toxicity testing is not exceeded and therefore supports the conclusion in the Environmental Risk Assessment that no further assessment is necessary. However, the CHMP considered that the logKow for paclitaxel has not been determined adequately to date and requested that this is determined experimentally after approval of the variation application. It should be noted that the expected log P of paclitaxel exceeds 4 (ClogP estimate is 4.73) which is out of range of the shake flask method. Log P values > 4 can only be reliably determined using the slow stirring method (OECD TG 123).

On the other hand, the PECsw was 0.007 µg/L, which is below the action limit of 0.01 µg/L. A further risk assessment was not deemed necessary.

2.2.7. Conclusion on the non-clinical aspects

Overall non-clinical data support the rationale for the use of Abraxane in pancreatic adenocarcinoma, alone or combined with gemcitabine.

The environmental risk assessment cannot be finalised as the PBT assessment cannot be concluded. The logKow study needs to be evaluated. Considering the above data, paclitaxel formulated as albumin bound nanoparticles is not expected to pose a risk to the environment.

Nevertheless, in the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed:

- The logKow needs to be evaluated, if necessary via a dedicated relevant study.

2.3. Clinical aspects

2.3.1. Introduction

The application for the extension of the Abraxane therapeutic indication to the treatment of pancreatic adenocarcinoma was based on a pivotal phase III study (CA046, N=861) and a supportive phase I/II study (CA040, N=67).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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.

- Tabular overview of clinical studies

Table 2: Overview and key design features of the pivotal and supportive studies of Abraxane in metastatic adenocarcinoma of the pancreas

Study Design Feature	Pivotal Study CA046 (N = 861)	Supportive Study CA040 (N = 67)
Design	Multicenter, Phase 3, randomized, international, controlled, open label	Multicenter, Phase 1/2, dose level escalation, MTD
Planned and actual Enrollment	Planned: 842 (randomized 1:1; 421 patients per arm) Actual: 861 (randomized 431 patients to Abraxane/gemcitabine arm and 430 patients to gemcitabine arm)	Planned: N = 66 (Phase 1 [n = 24], Phase 2 [n = 42]); Actual: N = 67 (Phase 1 [n = 30], Phase 2 [n = 37])
Treatment Regimen	Abraxane 125_ mg/m^2 IV followed by gemcitabine 1000 mg/m^2 IV were administered on Days 1, 8, 15 and 29, 36, 43 of a 56-day cycle in Cycle 1 only (ie, weekly for 3 weeks with a 1-week rest x 2) and subsequently administered on Days 1, 8, and 15 of a 28-day cycle in Cycle 2 and onwards **or,** Gemcitabine 1000 mg/m^2 was administered on Days 1, 8, 15, 22, 29, 36, 43 of a 56-day cycle in Cycle 1 (ie, weekly for 7 weeks and a 1-week rest period) and subsequently administered on Days 1, 8, and 15 of a 28-day cycle in Cycle 2 and onwards	Abraxane 100, 125, or 150 mg/m^2 IV followed by gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 of a 28-day cycle
Primary Efficacy Endpoint(s)	• OS	• ORRa
Secondary Efficacy Endpoints	• PFS by IRR • ORR by IRR	• Disease control rate, duration of response, PFS, OS

2.3.2. Pharmacokinetics

No new pharmacokinetic data were submitted, but reference was made to published clinical studies (Walle *et al*, 1995; Plunkett *et al*, 1995) investigating potential interactions between Abraxane and gemcitabine.

2.3.3. Pharmacodynamics

No new data regarding pharmacodynamics were submitted.

2.3.4. PK/PD modelling

No data regarding PK/PD modelling were submitted.

2.3.5. Discussion on clinical pharmacology

No new pharmacokinetics data have been submitted for the combination of 125 mg/m2 Abraxane with 1000 mg/m2 gemcitabine. The Abraxane dose of 125 mg/m2 is within the dose range of 80 to 300 mg/m2 that has demonstrated dose linear pharmacokinetics of paclitaxel.

Paclitaxel and gemcitabine do not share a common metabolic pathway. Paclitaxel clearance is primarily determined by cytochrome P450 2C8 and 3A4 mediated metabolism followed by biliary excretion, while gemcitabine is inactivated by cytidine deaminase followed by urinary excretion (Walle *et al*, 1995; Plunkett *et al*, 1995).

Nonclinical data and clinical data have shown there is no pharmacokinetic (PK) drug-drug interaction between paclitaxel and gemcitabine. Of note, the combination of gemcitabine and paclitaxel is approved for the first line treatment of non-resectable, locally recurrent or metastatic breast cancer following adjuvant/neo-adjuvant anthracycline-containing chemotherapy. Analysis of data from metastatic breast cancer patients showed that, on average, gemcitabine has little or no effect on the pharmacokinetics (clearance and half-life) of paclitaxel and paclitaxel has little or no effect on the pharmacokinetics of gemcitabine (Gemzar SmPC). As no significant impact on the pharmacokinetic profiles of paclitaxel and gemcitabine was observed in non-clinical study ABI-PK-01005 (discussed in the non-clinical section), there was no need to collect PK data for the combination of Abraxane and gemcitabine in pancreatic cancer patients.

2.3.6. Conclusions on clinical pharmacology

There were no clinical pharmacology concerns related to the combination of Abraxane with gemcitabine for the treatment of patients with pancreatic cancer.

2.4. Clinical efficacy

2.4.1. Dose response study

Study CA040 was a phase I/II, single-arm, dose escalation study designed to determine the MTD and DLTs of Abraxane/gemcitabine in patients with metastatic pancreatic cancer. Three dose level of Abraxane were evaluated: 100, 125 and 150 mg/m2. Patients received study treatment on Days 1, 8 and 15 of a 28 day cycle. The initial dose of Abraxane 100 mg/m^2 was based on safety and efficacy data collected for Abraxane-refractory advanced solid tumours or metastatic breast cancer and in taxane-refractory metastatic breast cancer.

Three patients were enrolled at each dose level starting with a dose of Abraxane 100 mg/m2 followed by gemcitabine 100 mg/m2. If 1 of up to 3 patients developed a DLT, up to 6 patients were enrolled at that dose level. If 2 of the 6 patients experienced a DLT, the next dose below the DLT-dose was defined as the MTD. During the study, the protocol was amended to enrol additional patients at the 100 mg/m2 and 125 mg/m2 dose level. Once the MTD was established, additional patients were enrolled during the Phase 2 portion of the study to include at least 42 patients at the MTD.

Overall, 22 patients (33%; 95% CI: 21.6, 44.1) had a confirmed overall response (all PRs). For patients in the Abraxane 125 mg/m2 cohort, 17 patients (39%; 95% CI: 24.2, 53.0) had confirmed overall response.

Table 3: Independent Radiological Reviewer Assessment of Overall Response Rate (study CA040, Treated Population)

Multivariate Analyses	$HR_{A+G/G}$ (Treatment Effect)	95% CI	P-value
Multivariate Analysis with Stratification Factors as Covariates	0.69	(0.585, 0.825)	< 0.0001
Multivariate Analysis Using Step-wise Procedure	0.66	(0.544, 0.796)	< 0.0001
Multivariate Analysis with Factors Selected From Step-wise Procedure and CA19-9	0.66	(0.549, 0.791)	< 0.0001

CI = confidence interval; $HR_{A+G/G}$ = hazard ratio of ABI-007 followed by gemcitabine / gemcitabine alone.

The disease control rate (ie, SD for ≥16 weeks, or complete or partial overall response) was 54% for all patients and 55% for patients in the Abraxane 125 mg/m^2 cohort.

A total of 37 (55%) patients had independently-determined PFS events, the median PFS was 6.1 months (95% CI: 5.4, 9.2). In the Abraxane 125 mg/m^2 cohort, 25 (57%) patients had independently determined PFS events; the median PFS was 6.9 months (95% CI: 4.8, 9.2).

Table 4: Independent Radiological Reviewer Assessed Progression-free Survival (Study CA040, Treated Population)

Variable	ABI-007/Gemcitabine 1000 mg/m^2			
	100 mg/m^2 (N = 20)	125 mg/m^2 (N = 44)	150 mg/m^2 (N = 3)	All Patients (N = 67)
Patients with independently determined PFS events	9 (45%)	25 (57%)	3 (100%)	37 (55%)
Median PFS (months)	6.1	6.9	1.6	6.1
95% Confidence Interval	3.7, --	4.8, 9.2	0.5, 10.0	5.4, 9.2

PFS = progression-free survival.

Note: Progression-free survival was defined as the time from the first dose of study drug to the start of progression or patient death (whichever occurred first). Patients who did not have progression or had not died were censored at the last known time the patient was progression-free. Patients who initiated other anticancer therapy prior to progression were censored at the time when the new anticancer therapy was initiated.

The patients who did not have progression or had not died were censored at the last known time that they were progression-free. Patients who initiated other anticancer therapy before disease progression were censored at the time when the new anticancer therapy was initiated. A total of 30 (45%) patients and 19 (43%) in the Abraxane 125 mg/m^2 cohort were censored. The most common reasons for censoring in all patients and patients in the Abraxane 125 mg/m^2 cohort were missing assessment followed by PFS even (31% and 30%, respectively), and new anticancer therapy (9% and 11%, respectively. The median follow-up time for censored patients was 4.5 and 4.8 months, respectively.

Patients were followed for survival for a median of 13 months. Overall 58 (87%) patients died, and the median OS was 10.3 months (955 CI: 8.4, 13,6). For patients in the Abraxane 124 mg/m^2 cohort, 38 (86%) patients died by the data cutoff; the median OS was 12.2 months (95% CI: 8.9, 17.9).

Table 5: Overall Survival (Study CA040, Treated Population)

Variable	ABI-007/Gemcitabine 1000 mg/m^2			
	ABI-007 100 mg/m^2 (N = 20)	ABI-007 125 mg/m^2 (N = 44)	ABI-007 150 mg/m^2 (N = 3)	All Patients (N = 67)
Patient Deaths, n (%)	17 (85%)	38 (86%)	3 (100%)	58 (87%)
Median Survival (months)	9.3	12.2	6.1	10.3
95% Confidence Interval	6.6, 11.9	8.9, 17.9	0.5, 17.9	8.4, 13.6

Note: Patients who did not die were censored at the last known time that the patient was alive.

2.4.2. Main study

CA046

Methods

Study CA046 was a multicentre, international, randomised, controlled, open-label study of Abraxane in combination with gemcitabine versus gemcitabine alone.

Study participants

The key inclusion and exclusion criteria are presented in the following Table 6.

Table 6: Key inclusion and exclusion criteria, study CA046

Inclusion criteria	Exclusion criteria
Histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas (diagnosis ≤ 6 weeks prior to randomisation)	Brain metastases, unless treated and controlled for at least 3 months
	Only locally advanced disease.
One or more metastatic lesions measurable by CT or MRI scan	≥ 10% decrease in KPS between baseline visit and within 72 hours prior to randomisation
Male or non-pregnant and non-lactating female, and ≥ 18 years of age	History of malignancy in the last 5 years, except for in situ cancer or basal or squamous cell skin cancer. Patients with other malignancies (except for chronic leukemias) were eligible if cured by surgery alone or surgery plus radiotherapy, and if continuously disease-free for at least 5 years
No previous surgery, radio-, chemo- or investigational therapy for treatment of metastatic disease, although prior treatment with 5-FU or gemcitabine adjuvant to radiotherapy >6 months prior to randomisation was allowed.	
Adequate biological parameters (neutrophil, platelet, Hb), blood chemistry levels (hepatic and renal function) and acceptable coagulation studies	Active uncontrolled infections requiring systemic therapy, as well as HIV, hep B or C
	Major surgery < 4 weeks prior to start
	High cardiovascular risk
Karnofsky performance status (KPS) ≥ 70	History of interstitial lung disease, slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies.
	History of chronic leukaemias.

Treatments

Patients were treated with Abraxane in combination with gemcitabine or gemcitabine alone. The cycle length in both arms was 56 days during Cycle 1 and 28 days from Cycle 2 onward. Treatment with study drug continued until one or more of the following:

- Progressive disease
- Development of toxicity (treatment-related AE) unacceptable in the opinion of the investigator
- Patient declined to continue therapy
- If, following the second dose reduction, there was a recurrence of Grade 4 neutropenia, or any other Grade 3 or 4 hematologic AE, or non-myelosuppressive AE, unless, there was evidence of continuing benefit to the patient that outweighed the risk of recurrent toxicity, and after consultation with the sponsor
- Initiation of other anticancer therapy

Patients in the Abraxane/gemcitabine arm received Abraxane at 125 mg/m^2 given IV over approximately 30 minutes (maximum infusion time not to exceed 40 minutes) followed by gemcitabine given at 1000 mg/m2 IV over 30 minutes.

Patients in the gemcitabine arm received gemcitabine at 1000 mg/m^2 (unless modification was required) given IV over approximately 30 minutes. The dosing of gemcitabine was chosen based on a standard dosing regimen in patients with locally advanced or metastatic adenocarcinoma of pancreas.

Patients did not require premedication prior to Abraxane administration as severe hypersensitivity reactions were not expected. Antiemetic prophylaxis was recommended due to the administration of gemcitabine following Abraxane treatment.

Erythropoietin and Granulocyte colony-stimulating factors were administered at the discretion of the investigator, consistent with institutional guidelines. Ciprofloxacin (or the alternative antibiotic) was distributed to patients with instructions to begin treatment immediately if they experienced a febrile episode. Long-term prophylactic ciprofloxacin administration to prevent recurrences in patients who had experienced a first febrile episode was allowed at the discretion of the treating physician. Prophylactic administration of antibiotics to patients with biliary stents but no complications was allowed.

Objectives

The primary objective of study CA046 was to evaluate the efficacy of the combination of Abraxane and gemcitabine versus gemcitabine alone in improving OS in patients with metastatic adenocarcinoma of the pancreas.

Outcomes/endpoints

- Primary efficacy endpoint: Overall Survival which was defined as the time from the date of randomisation to the date of death (from any cause).
- Secondary efficacy endpoints:
    - Progression-free survival
    - Overall response rate based on CT or MRI scans

Interpretation of radiological response for use in the PFS and ORR endpoints was completed by independent radiological review of CT (or MRI) scans at the centralised facility with radiologic reviewers who were blinded to treatment assignment (2 reviewers with a third reviewer for adjudication).

- Other secondary (exploratory) efficacy endpoints were:
    - Time to response and response duration (duration of response [DOR]) according to RECIST, v1.0
    - Disease control rate (ie, SD for ≥16 weeks or confirmed CR or PR)
    - Time to treatment failure (TTF)
    - Changes in serum CA19-9
    - Tumour response based on PET scans evaluated according to EORTC criteria
    - Determine whether a correlation exists between ORR based on CT or MRI scans and tumour response based on PET scans
    - Changes in plasma SPARC levels
    - Determine whether a correlation exists between ORR by CT or MRI scan, tumour response by PET scan, changes in serum CA 19-9 and OS
    - Determine whether correlations exist between ORR by CT or MRI scan, tumour response by PET, PFS, OS and expression of tumour markers (eg, SPARC; nucleoside transporters)
- Safety/tolerability Endpoints:
    - Incidence of treatment-emergent AEs (TEAEs) in Medical Dictionary for Regulatory Activities (MedDRA) V15.0 terms categorised and graded according to NCI CTCAE V3.0.
    - Incidence of dose reductions and interruptions, and incidence of treatment discontinuation and reason for discontinuation.

Sample size

The planned sample size was 842 patients, approximately 421 patients randomised in each treatment arm. With at least 608 events, this provided 90% power with two-sided Type I error of 0.049 to reject the primary efficacy null hypothesis that the Abraxane in combination with gemcitabine/gemcitabine hazard ratio (HR) for OS was equal to 1.0. This sample size calculation assumed that Abraxane in combination with gemcitabine would lead to a 30% improvement in OS compared with gemcitabine alone (HR=0.769).

Randomisation

Patients were randomised in a 1:1 ratio. The randomisation was stratified to: georgraphic region (Australia versus Eastern Europe versus Western Europe versus North America), Karnofsky Performance Status (70 to 80 versus 90 to 100), presence of liver metastases (yes versus no).

Blinding (masking)

This was an open-label study.

Statistical methods

Analysis populations included the Intention-to-Treat population (ITT, all randomised patients), the Treated population (assignment according to drug actually received) and Per-Protocol population (PP, eligibility criteria met, same treatment as randomised).

Interim analysis for futility (i.e. no stopping for efficacy) was planned when at least 200 patients had at least 6 months follow-up (total sample size planned 841). An alpha spending function was implemented using 0.001 for the interim and 0.049 for the final OS analysis.

Multiplicity for primary and key secondary endpoints was accounted for at 0.05 (two-sided) by a fixed sequence procedure (OS -> PFS -> ORR).

Time to event endpoints were described by Kaplan-Meier curves and analysed using stratified log-rank tests. Median and 95% CI would be provided.

For OS and PFS, multivariate Cox regression analyses were performed to assess the influence of several potential prognostic factors (1. all simultaneously, 2. stepwise selection), and a non-stratified log-rank test was performed. For OS, an analysis censoring for start new anticancer treatment was performed.

PFS censoring rules were as follows:

1. Patients who did not have disease progression or had not died were censored at the date of last tumour assessment, on or prior to the clinical cut-off, that the patient was progression free.

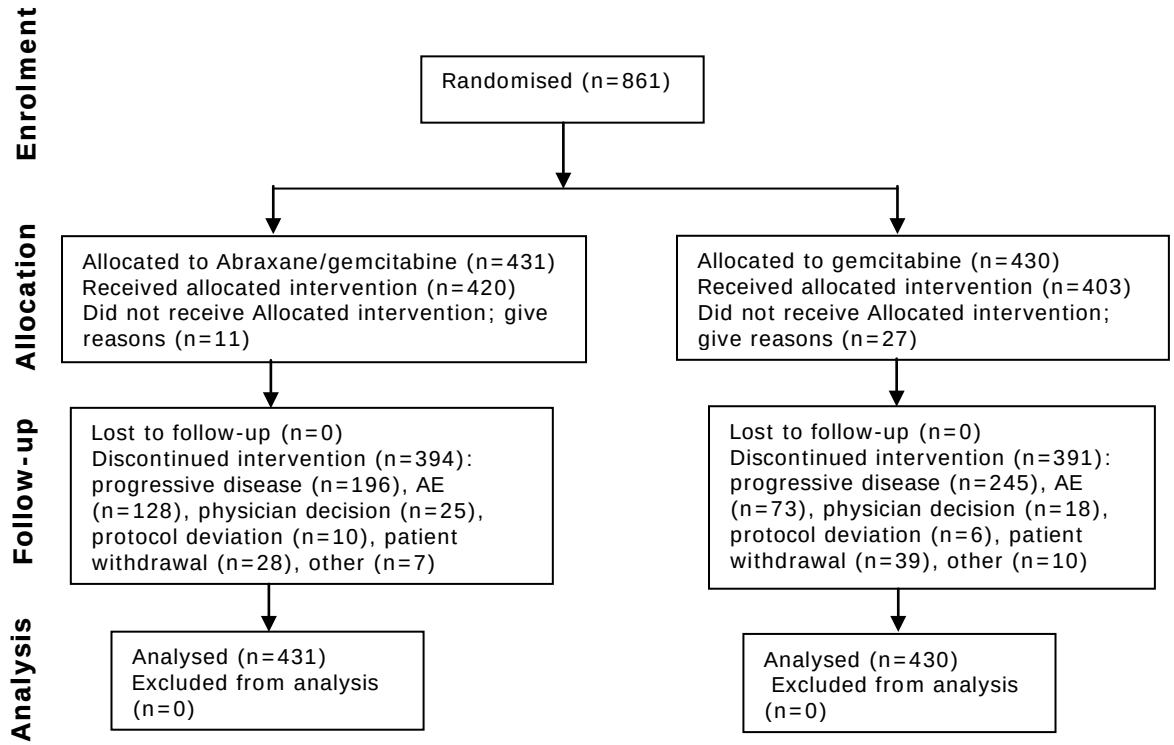
2. Patients who dropped out early without any post baseline tumour assessment and/or died more than 120 days after the randomisation were censored on the date of randomisation.

3. If a patient began a new anti-cancer chemotherapy prior to documented disease progression (or death), the patient was censored at the date of last assessment when the patient was documented as progression free prior to the intervention.

4. Patients with two or more consecutive missing response assessments prior to a visit with documented progression (or death) were censored at the last date of tumour assessment when the patient was documented to be progression free.

Results

Participant flow



Recruitment

Overall, 861 patients were randomised from 8 May 2009 until 17 April 2012. The study was conducted in 11 countries and patients were randomised at a total of 151 sites. The clinical cut-off date was 17 September 2012.

Conduct of the study

The original study protocol was dated 12 Nov 2008 and was subsequently amended 6 times. The major changes were as follows:

Protocol amendment 1 (20 Mar 2009): Added changes in serum CA19-9 and plasma SPARC levels as secondary endpoints; Clarified inclusion/exclusion criteria regarding measurable disease, pain symptoms, patients with only locally advanced disease; Added an interim analysis to evaluate futility; Clarified the primary efficacy endpoint hypothesis and modified the CI of OS HR to account for the interim analysis.

Protocol amendment 2 (17 Nov 2009): Limited the requirement for PET scans to the first 200 enrolled patients; Added and clarified inclusion/ exclusion criteria: a.o. Coumadin use was excluded; Modified the statistical procedure for testing the secondary endpoints (PFS and ORR) to a sequential step procedure, where PFS was tested first and ORR only if PFS was statistically significant; Clarified dose guidelines, the use of CT and MRI to determine disease progression (not PET or CA19-9) and analysis population for tumour response by PET scan.

Protocol amendment 3 (19 Apr 2010): Modified text to allow for additional patients with PET scans to be included beyond 200; Clarified inclusion criteria, specifically timeframe for initial diagnosis of metastatic disease; Clarified pulmonary embolism discontinuation guidelines to require treatment discontinuation for patient with moderate to severe pulmonary embolism.

Protocol amendment 4 (30 Sep 2010): Added safety findings related to 8 events of sepsis with or without neutropenia and 2 events of febrile neutropenia, including fatal outcome in a total of 4 patients with neutropenia; (A directive letter was sent to the investigators on measures to be taken in order to prevent and/or minimize the reoccurrence of septic events); Modified the patient sample size (increased required number of deaths to at least 608, and enrolled patients to 842) and related statistical considerations of the study to allow for an increase in statistical power from 80% to 90% to reject the null hypothesis that there is no difference between the two treatment arms, Abraxane in combination with gemcitabine and gemcitabine alone, for the primary endpoint of OS; Collection of additional PET scans ceased.

Protocol amendment 5 (12 Jan 2011): Modified maximum dose delay based upon recommendations from the DMC meeting of 15 Nov 2010 regarding dose modification in response to toxicity; Defined stratification by geographic region (Australia, Eastern Europe, North American, or Western Europe).

Protocol amendment 6 (12 Dec 2012): Added the pneumonitis directive measures intended to limit the incidence of interstitial pneumonitis through guidance regarding careful pre-study screening, continuous on-study monitoring for signs and symptoms of pneumonitis and, if observed, timely institution of appropriate management, as recommended by the DMC. A copy of the directive letter was sent to the investigators; Modified optional distribution to mandatory distribution of ciprofloxacin (or the alternative antibiotic) immediately to patients with instructions to begin treatment if they experienced a febrile episode.

In the Abraxane/gemcitabine arm, 17% of patients had protocol violations, vs. 12% in the gemcitabine arm. The most common violation was the inclusion of patients who did not meet all inclusion and

exclusion criteria, which occurred in 7% in both arms. The remainder were dosing errors. The greatest difference between the arms was that a larger percentage of patients in the Abraxane/gemcitabine arm did not reduce the treatment dose in the setting of AEs/toxicity, and had subsequent Grade 3 to 4 AEs (8% versus 3% in the gemcitabine arm). In both groups, dosing continued in 1% of patients following disease progression.

Baseline data

Baseline demographic and disease characteristics are summarised in Tables 7 and 8.

Table 7: Baseline demographic characteristics, study CA046, ITT population

Variable Category/Statistic	Abraxane/ Gemcitabine (N = 431)	Gemcitabine (N = 430)
Age (years)		
Median (Minimum, Maximum)	62.0 (27, 86)	63.0 (32, 88)
< 65 years, n (%)	254 (59%)	242 (56%)
≥ 65 years, n (%)	177 (41%)	188 (44%)
≥ 75 years, n (%)	41 (10%)	49 (11%)
Gender, n (%)		
Female	186 (43%)	173 (40%)
Male	245 (57%)	257 (60%)
Race/Ethnicity, n (%)		
Asian, Not Hispanic or Latino	8 (2%)	9 (2%)
Black, of African Heritage, Not Hispanic or Latino	16 (4%)	16 (4%)
Native Hawaiian or Other Pacific Islander, Not Hispanic or Latino	1 (<1%)	0
North American Indian or Alaska Native	0	0
White, Hispanic or Latino	25 (6%)	26 (6%)
White, Not Hispanic or Latino	378 (88%)	375 (87%)
Other, Unknown	3 (1%)	4 (1%)
Region, n (%)		
Australia	61 (14%)	59 (14%)
Eastern Europe	64 (15%)	62 (14%)
North America	268 (62%)	271 (63%)
Western Europe	38 (9%)	38 (9%)
Median BSA (m2) (Minimum, Maximum)	1.88 (1.2, 2.7)	1.85 (1.1, 2.6)
Karnofsky Performance Status		
100	69 (16%)	69 (16%)
90	179 (42%)	199 (46%)
80	149 (35%)	128 (30%)
70	30 (7%)	33 (8%)
60	2 (<1%)	0

BSA = body surface area.

[a] Karnofsky Performance Status was missing for 2 patients in the Abraxane/gemcitabine arm and 1 patient in the gemcitabine arm; percents are based on intent-to-treat population.

Table 8: Baseline disease characteristics, study CA046, ITT population

Variable Category / Statistic	Abraxane / Gemcitabine (N = 431)	Gemcitabine (N = 430)
Time from Primary Diagnosis to Randomization (Months)		
Median (Minimum, Maximum)	0.85 (0.1, 41.0)	0.92 (0.1, 109.4)
Time from Primary Diagnosis to First Documented Metastasis (Months)[a]		
Median (Minimum, Maximum)	0.03 (-1.6, 40.3)	0.03 (-2.4, 108.6)
Time from First Documented Metastasis to Randomization (Months)		
Median (Minimum, Maximum)	0.76 (0.0, 15.6)	0.82 (0.1, 14.6)
Stage at Primary Diagnosis, n (%)		
I	10 (2%)	9 (2%)
II	28 (6%)	16 (4%)
III	25 (6%)	18 (4%)
IV	336 (78%)	354 (82%)
Unknown	32 (7%)	33 (8%)
Stage at Current Diagnosis, n (%)		
I, II, or III	0	0
IV	431 (100%)	429 (>99%)
Unknown	0	1 (<1%)
Primary Location of Pancreatic Lesion, n (%)[b]		
Head	191 (44%)	180 (42%)
Body	132 (31%)	136 (32%)
Tail	105 (24%)	110 (26%)
Unknown	3 (1%)	1 (<1%)
CA19-9 Level, n (%)c		
Patients with Normal CA19-9	60 (14%)	56 (13%)
Patients with CA19-9 > ULN but < 59 x ULN	122 (28%)	120 (28%)
Patients with CA19-9 ≥ 59 x ULN	197 (46%)	195 (45%)
Unknown	52 (12%)	59 (14%)

CA19-9 = carbohydrate antigen 19-9, CNS = central nervous system, ULN = upper limit of normal

[a] The range for this interval can be negative as a metastatic site may be diagnosed before the primary anatomic site is identified.

[b] Patients can be in multiple current sites of metastasis categories.

[c] A total of 379 and 371 patients in the Abraxane/gemcitabine and gemcitabine arms had CA19-9 levels obtained; percentages are based on intent-to-treat population.

Numbers analysed

The analysis populations and their definitions are summarised in the following Table 9.

Table 9: Analysis populations, study CA046

Population	ABI-007/ Gemcitabine	Gemcitabine	All Patients
Intent-to-treat Population[a]	431	430	861
Treated Population[b]	421 (98%)	402 (93%)	823 (96%)
Treated as Randomized	420 (97%)	402 (93%)	822 (95%)
Treated Not as Randomized	1 (<1%)	0	1 (<1%)
Per-protocol Population[c]	394 (91%)	377 (88%)	771 (90%)

[a] Intent-to-treat population included all randomized patients.
[b] Treated population included all randomized patients who received at least one dose of study drug analyzed as treated.
[c] Per-protocol population included all patients who were treated as randomized and met all eligibility criteria.

Outcomes and estimation

A summary of results for the primary endpoint and the key secondary endpoints is provided in Table 10 and Figures 1 and 2.

Table 10: Summary of primary and secondary efficacy results, study CA046, ITT population

Efficacy Endpoint Statistic	Abraxane / Gemcitabine (N = 431)	Gemcitabine (N = 430)
Overall Survival		
Number of deaths, n (%)	333 (77%)	359 (83%)
Median Overall Survival (months)	**8.5**	**6.7**
95% CI	7.89, 9.53	6.01, 7.23
$HR_{A+G/G}$ (95% CI) [a]	0.72 (0.617, 0.835)	
P-value[b]	**<0.0001**	
Survival Rate, % (95% CI) at:		
1 Year	35% (29.7, 39.5)	22% (18.1, 26.7)
2 Years	9% (6.2, 13.1)	4% (2.3, 7.2)
75th Percentile Overall Survival (months)	14.8	11.4
Progression-free Survival[c]		
Death or progression, n (%)	277 (64%)	265 (62%)
Median Progression-free Survival (months)	**5.5**	**3.7**
95% CI	4.47, 5.95	3.61, 4.04
$HR_{A+G/G}$ (95% CI) [a]	0.69 (0.581, 0.821)	
P-value[b]	**<0.0001**	

Efficacy Endpoint Statistic	Abraxane / Gemcitabine (N = 431)	Gemcitabine (N = 430)
Overall Response Rate[c]		
Confirmed complete or partial overall response, n (%)	99 (**23%**)	31 (**7%**)
95% CI	19.1, 27.2	5.0, 10.1
p_{A+G}/p_G (95% CI)	3.19 (2.178, 4.662)	
P-value[d]	**<0.0001**	

CI = confidence interval, $HR_{A+G/G}$ = hazard ratio of Abraxane followed by gemcitabine / gemcitabine alone, $p_{A+G}/p_{G\,=}$ response ratio of Abraxane followed by gemcitabine / gemcitabine alone.

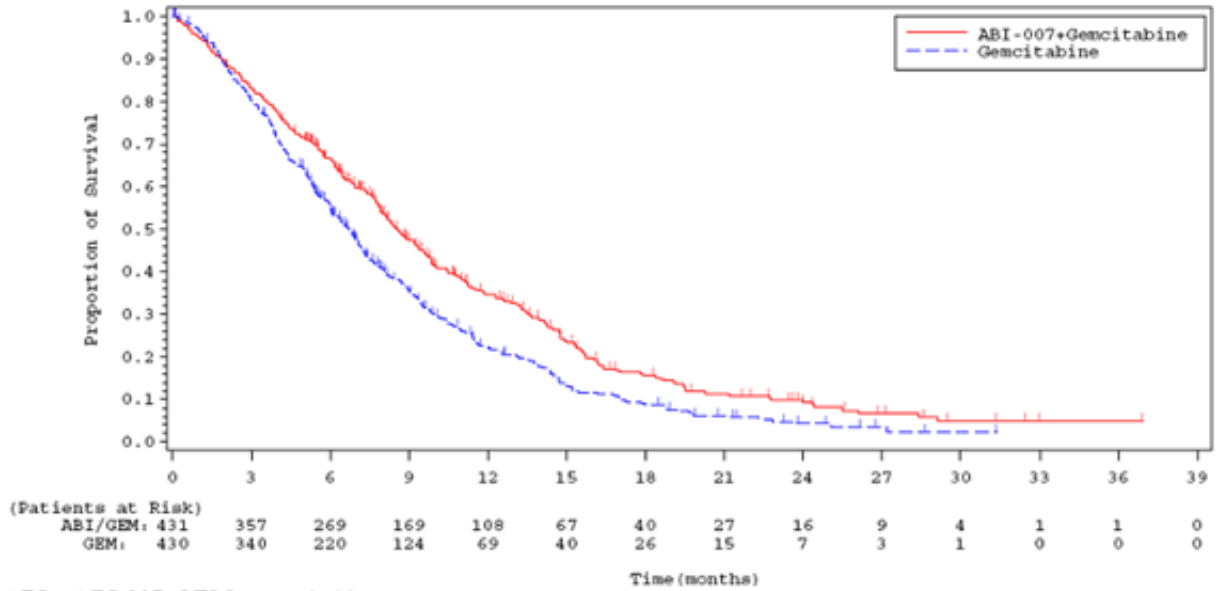
[a] The associated hazard ratio and two-sided 95% CI were estimated using a stratified Cox proportional hazard model.

[b] P-value was based on a stratified log-rank test stratified by randomisation strata of geographic region (North America versus Others), Karnofsky performance score (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no).

[c] Based on Independent Radiological Review.

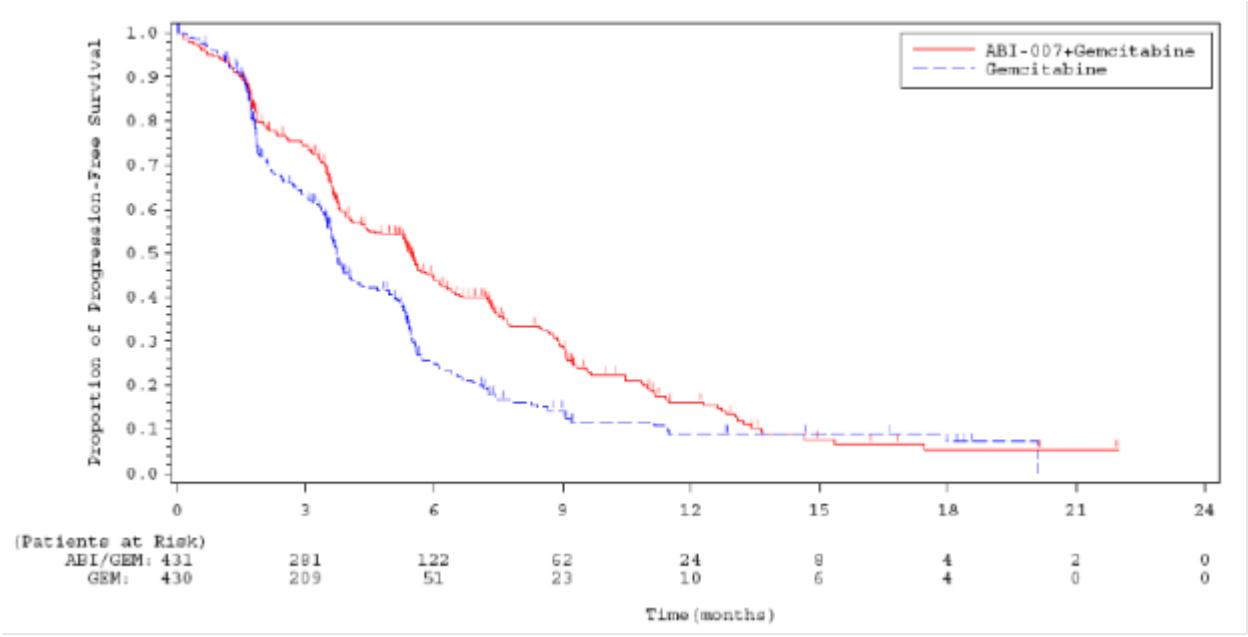
[d] P-value was based on a chi-square test.

Figure 1: Kaplan Meier Curve of Overall Survival, study CA046, ITT population



ABI = ABI-007; GEM = gemcitabine

Figure 2: Kaplan-Meier Curve of Progression-free Survival by Independent Radiological Review, study CA046, ITT population



In terms of other secondary endpoints, the median duration of response was similar in the two treatment arms: 11.1 months (95% CI 9.23, 13.11) in the Abraxane/gemcitabine arm compared with 11.4 months (95% CI 9.03, not estimable [NE]) in the gemcitabine arm. The duration of response was also calculated from the onset date of CR/PR to the date of PD. Of the patients who had a response, 39/99 patients (39%) in the Abraxane/gemcitabine arm and 8/31 (26%) patients in the gemcitabine arm subsequently had PD based on IRR. The median DOR in this analysis was 8.5 months (95% CI 7.43, 11.83) in the Abraxane/gemcitabine arm compared with 7.9 months (95% CI = 4.67, NE) in the gemcitabine arm.

Overall, 89% of patients in the Abraxane/gemcitabine arm and 94% of patients in the gemcitabine arm experienced treatment failure (i.e. patient had PD by IRR, died, or started subsequent anticancer therapy). The estimated median time to treatment failure was longer with Abraxane/gemcitabine: 5.1 months vs. 3.6 months in the gemcitabine arm ($HR_{A+G/G}$ = 0.70 [95% CI 0.60, 0.80]; p <0.0001).

The disease control rate (percentage of patients with confirmed CR, PR, or SD for ≥16 weeks) was higher in the Abraxane/gemcitabine arm: 48% compared to the gemcitabine arm: 33%, p < 0.0001.

A total of 130 patients from the Abraxane/gemcitabine arm and 127 patients from the gemcitabine arm were assessed by PET imaging at baseline and follow-up time-points. The PET scan response rate by IRR was significantly higher in the Abraxane/gemcitabine arm (63%) compared with the gemcitabine arm (38%), p < 0.0001. In patients who had a response per PET scan, the median time to response was 1.92 months in the Abraxane/gemcitabine arm compared with 1.87 months in the gemcitabine arm.

The median time of OS for responders by PET scan (patients with confirmed CR or PR by PET scan) was 13.1 months (95% CI = 10.51, 14.26) compared with 6.9 months (95% CI = 6.05, 8.15) in non-responders (patients with SD, PD, or was not-evaluable), p<0.0001. The median time of PFS for responders by PET scan was 7.4 month (95% CI = 6.05, 9.23) compared with 3.8 months (95% CI = 3.65, 4.96) in non-responders, p<0.0001. The concordance rate between CT scan-based response and PET scan-based response was 55% in Abraxane/gemcitabine arm and 67% in gemcitabine arm.

A total of 281 patients from the Abraxane/gemcitabine arm and 231 patients from the gemcitabine arm were evaluable for CA19-9 assessment (i.e. these patients had a baseline and at least one post-baseline CA19-9 assessment). A decrease in CA19-9 value post baseline was observed in 85% of patients in the Abraxane/gemcitabine arm compared with 77% of patients in the gemcitabine arm. The differences between the two treatment groups were larger for subgroups with a higher maximum absolute percent decrease from baseline. The largest difference was observed in patients with maximum decreases from baseline of ≥90%: this was observed in 42% of patients from the Abraxane/gemcitabine arm and 22% of patients from the gemcitabine arm, $p < 0.0001$.

The correlation of OS and maximum decrease of CA19-9 levels from baseline was evaluated using cut-offs of maximum decrease at 20%, 50%, 70%, and 90% (pooled across treatment arms). There was a clear correlation between OS and decrease in CA19-9 levels from baseline. At each cut-off point, patients with a greater decrease in CA19-9 values had longer median survival. Across all cut-off points, the reduction in the risk of death was consistently observed with HRs ranging from 0.46 to 0.53, all $p<0.0001$. Significant correlations were also observed using a CA19-9 level of 2000 U/mL (corresponds to 59x ULN) or an overall baseline median level of 2469.75 U/mL as cut-off points, although the HRs were lower. Similar to the correlation with OS, there was a significant correlation between PFS and decrease in CA19-9 levels from baseline using cut-offs of maximum decrease at 20%, 50%, 70%, and 90%. In contrary to OS, no correlation was observed for PFS using a CA19-9 level of 2000 U/mL or an overall baseline median level of CA19-9.

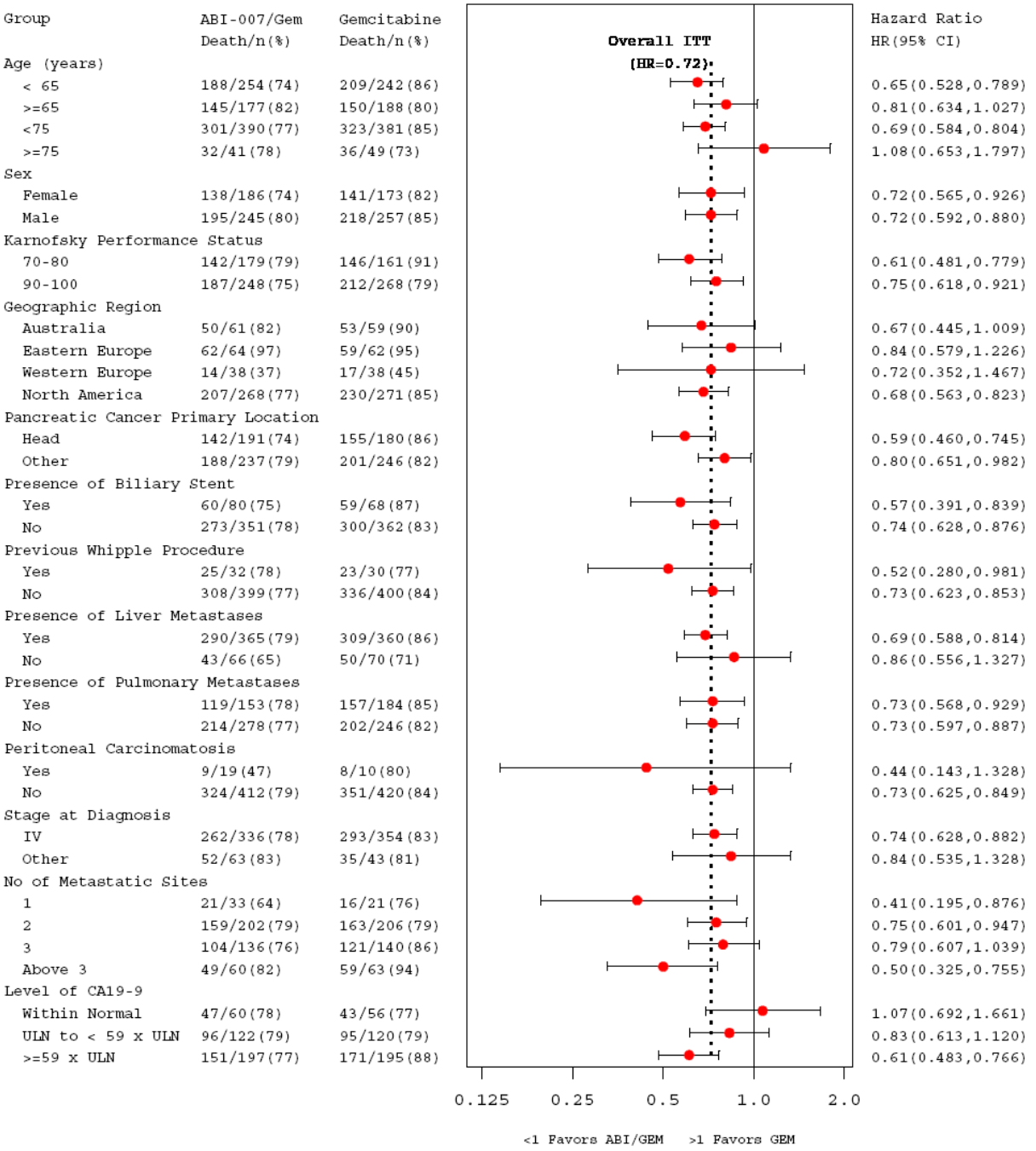
Tissue and plasma samples for analysis of tissue secreted protein acidic and rich in cysteine (SPARC, or osteonectin) were collected in the pivotal study. The plasma samples were collected on day 1 of each cycle. Results from the biomarker/pharmacodynamic portion of the study, including the correlation of SPARC with OS and PFS, are not yet available and will be reported in a separate stand-alone report.

Although quality of life (OoL) data were not collected, the pattern of shift in Karnofsky Performance Status (KPS) from baseline score to worst post-baseline score was similar between the two treatment arms. There was no indication of decrement in performance status in the Abraxane/gemcitabine arm compared with the gemcitabine arm.

Ancillary analyses

Subgroup analyses for Overall Survival are summarised in the following Figure 3.

Figure 3: Forest plot of overall survival, study CA046, ITT population



The results of a multivariate analysis on OS using a Cox proportional hazard model to evaluate the treatment effect adjusted for the stratification factors are presented in the following Table 11.

Table 11: Cox regression of overall survival-stepwise procedure, study CA046, ITT population

Covariates	Hazard Ratio	95% CI	P-value
Treatment Group (Abraxane/Gemcitabine versus Gemcitabine)	0.72	(0.605, 0.849)	0.0001
Geographic Region (Eastern Europe versus North America)	1.22	(0.979, 1.516)	0.0765
Age (< 65 years versus ≥ 65 years)	0.81	(0.686, 0.967)	0.0190
Karnofsky Performance Score (70 to 80 versus 90 to 100)	1.60	(1.346, 1.895)	< 0.0001
Presence of Liver Metastases (Yes versus No)	1.81	(1.404, 2.332)	< 0.0001
Number of Metastatic Sites (Continuous)	1.08	(0.988, 1.191)	0.0864

CI = confidence interval; CA19-9 = carbohydrate antigen 19-9; IV = intravenous.
Note: A stepwise selection with significance level for entry of 0.20 and significance level for stay of 0.10 was used to identify potential prognostic factors.
Note: The Cox proportional hazards model included the following explanatory covariates: treatment groups, age (< 65 years versus ≥ 65 years), sex, Karnofsky performance status (70 to 80 versus 90 to 100), geographic region (North America was used as the reference), pancreatic cancer primary location (head versus other), presence of biliary stent, previous Whipple procedure, presence of liver metastases, presence of pulmonary metastases, peritoneal carcinomatosis, stage of diagnosis (IV versus other), number of metastatic sites, level of CA19-9.

OS analyses were also performed for the Per-protocol and Treated populations, as well as further sensitivity analyses, like a non-stratified analysis. These sensitivity analyses were all consistent with the primary analysis and showed a statistically significant improvement in OS with a 26% to 32% reduction in the risk of death for the Abraxane/gemcitabine arm (data not shown).

As subsequent anticancer therapy may have an impact on OS, a review was conducted of the use of subsequent therapies and a sensitivity analysis was conducted. Overall, the proportion of patients who received subsequent anticancer therapy was balanced between the treatment arms: 38% in the Abraxane/gemcitabine arm and 42% in the gemcitabine arm: 26% and 30% of patients in the ABI 007/gemcitabine arm and gemcitabine arms, respectively, received other 5-FU/capecitabine based therapies (excluding FOLFIRINOX); and 4% and 6%, respectively, received modified or unmodified FOLFIRINOX. After completing gemcitabine therapy, 25 (7%) patients in the gemcitabine arm crossed over to receive ABI 007-containing combination therapy. The sensitivity analysis, which censored patients at the initiation of subsequent anticancer therapy, was consistent with the primary analysis with a $HR_{A+G/G}$ of 0.68 and $p < 0.0001$ indicating that the survival benefit seen in the primary analysis was independent of subsequent anticancer therapy (data not shown).

Similar to OS, the treatment effect on PFS consistently favored the Abraxane/gemcitabine arm across the majority of patient subgroups. The only exception was in patients ≥75 years of age, where PFS was equivalent between the two treatment arms. Compared with OS data the HR in patients with CA19-9 levels within normal range was lower, although the CI crossed 1 (HR 0.80, CI 0.48-1.36 treatment effect on PFS; HR 1.07, CI 0.69-1.66 treatment effect on OS).

Finally, the results of multivariate analysis of PFS with adjustment for potential prognostic factors, showed a consistent statistically significant treatment effect in the reduction of the risk of PD or death for the Abraxane/gemcitabine arm with HRs in the range of 0.66-0.69.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12: Summary of Efficacy for trial CA046

Title: randomised phase III study of weekly Abraxane plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas			
Study identifier	CA046, NCT00844649, 2009-011305-17		
Design	open-label, randomised, multicentre, phase III study of Abraxane plus gemcitabine versus gemcitabine alone as first line treatment of patients with metastatic adenocarcinoma of the pancreas		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Until disease progression 56 days not applicable
Hypothesis	Superiority		
Treatments groups	Abraxane		Abraxane 125 mg/m^2 on Days 1, 8, 15, 29, 36 and 43 (run-in phase) and on Days 1, 8 and 15 in subsequent cycles. Gemcitabine 1000 mg/m^2 on Days 1, 8, 15, 22, 29, 36 and 43 (run-in phase) and on Days 1, 8 and 15 in subsequent cycles
	Control		Gemcitabine 1000 mg/m^2 on Days 1, 8, 15, 22, 29, 36 and 43 (run-in phase) and on Days 1, 8 and 15 in subsequent cycles
Endpoints and definitions	Primary endpoint	Overall Survival (OS)	time from the date of randomisation to the date of patient death (from any cause)
	Secondary endpoint	Progression Free Survival (PFS)	time from the date of randomisation to the date of disease progression or death (any cause). Progression was assessed based on blinded independent radiological review of CT or MRI response using RECIST guidelines, v1.0
	Secondary endpoint	Overall Response Rate (ORR)	number and percentage of patients who achieved a confirmed CR or PR based on independent radiological review of CT or MRI scans
Database lock	17 September 2012		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat 17 September 2012		
Descriptive statistics and estimate variability	Treatment group	Abraxane	Control
	Number of patients	431	430
	OS (median, months)	8.5	6.7
	95% CI	(7.89, 9.53)	(6.01, 7.23)

	PFS (median, months)	5.5	3.7
	95% CI	(4.47, 5.95)	(3.61, 4.04)
	ORR (number of patients (%))	99 (23%)	31 (7%)
	95% CI	(19.1, 27.2)	(5.0, 10.1)
Effect estimate per comparison	Primary endpoint (OS)	Comparison groups	Abraxane vs Control
		Hazard Ratio (HR)	0.72
		95% CI	(0.617, 0.835)
		P-value	<0.0001
	Secondary endpoint (PFS)	Comparison groups	Abraxane vs Control
		Hazard Ratio (HR)	0.69
		95% CI	(0.581, 0.821)
		P-value	<0.0001
	Secondary endpoint (ORR)	Comparison groups	Abraxane vs Control
		Response Rate ratio	3.19
		95% CI	(2.178, 4.662)
		P-value	<0.0001
Notes	OS and PFS HR and 95% CI were estimated using a stratified Cox proportional hazards model. OS and PFS p-value was based on a stratified log-rank test. ORR p-value was based on a chi-squared test		

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

A comparison of OS, PFS and ORR data from the pivotal CA046 and the supportive, dose-response CA040 study is presented in the following Table 13.

Table 13: Comparison of OS, PFS and ORR data from studies in patients with metastatic adenocarcinoma of the pancreas

Efficacy Endpoint Statistic	**Abraxane / Gemcitabine (N = 431)**	**Gemcitabine (N = 430)**	**Abraxane / Gemcitabine (N = 44)**
Overall Survival			
Number of deaths, n (%)	333 (77%)	359 (83%)	38 (86%)
Number Censored, n (%)	98 (23%)	71 (17%)	6 (14%)
Median Overall Survival (months)	**8.5**	**6.7**	**12.2**
95% CI	7.89, 9.53	6.01, 7.23	8,9, 17.9
Progression-free Survival			
Death or progression, n (%)	277 (64%)	265 (62%)	25 (57%)
Number Censored, n (%)	154 (36%)	165 (38%)	19 (43%0
Median Progression-free Survival (months)	**5.5**	**3.7**	**6.9**
95% CI	4.47, 5.95	3.61, 4.04	4.8, 9.2

Efficacy Endpoint Statistic	Abraxane/ Gemcitabine (N = 431)	Gemcitabine (N = 430)	Abraxane/ Gemcitabine (N = 44)
Overall Response Rate			
Confirmed complete or partial overall response, n (%)	99 (**23%**)	31 (**7%**)	17 (**39**%)
95% CI	19.1, 27.2	5.0, 10.1	24.2, 53.0
Complete Response	1 (<1%)	0	0
Partial Response	98 (23%)	31 (7%)	17 (39%)

Clinical studies in special populations

In the pivotal study, 42% of patients were 65 years or older and less than 10% was ≥75 years of age. No improvement in OS or PFS was observed for Abraxane/gemcitabine in the patient group ≥75 years of age, and there was a higher incidence of serious adverse reactions and adverse reactions that lead to study discontinuation. The observed OS HR may have been impacted by confounding factors. The small sample size (41 patients ≥75 years of age received Abraxane/gemcitabine, and 49 gemcitabine) and high rate of early withdrawal prior to treatment in the gemcitabine arm (10% vs. 0%) may have contributed to a lack of precision around the estimate of OS in the gemcitabine arm. Additionally, imbalances in baseline characteristics were observed across the treatment arms in this patient group, including a number of prognostic factors identified to be predictors of poorer survival. Patients in the Abraxane/gemcitabine arm were more likely to have a worse performance status (KPS score of 70-80), more extensive disease burden and a higher incidence of liver metastases.

No separate clinical studies in patients with hepatic or renal impairment were submitted and no data are available in children or adolescents under 18 years, and pregnant or lactating women.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The analysis of the efficacy of Abraxane in combination with gemcitabine for the first-line treatment of adult patients with locally advanced unresectable or metastatic adenocarcinoma of the pancreas was based on a single pivotal trial, study CA046 and an uncontrolled, phase I/II dose finding study CA040. The pivotal study investigated whether abraxane in combination with gemcitabine improved overall survival (OS) compared with gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas.

The eligibility criteria were standard for advanced pancreatic cancer trials. The study included elderly patients with no age restriction, and patients with a Karnofsky Performance Status (KPS) score of ≥70.

The trial was designed to demonstrate superiority in OS for Abraxane/gemcitabine over gemcitabine alone. Overall survival as the primary end-point is the preferred end-point in clinical phase 3 cancer trials. The main secondary endpoints were investigator assessed PFS, ORR, and DR, which was considered acceptable.

The main study was an open study. This open label design was chosen due to known toxicity differences between Abraxane and gemcitabine, and also due to differences in dosing regimens between arms. The open design could lead to increased bias; however, blinded independent review on statistical analyses by a data monitoring committee (DMC) and independent radiological review on progression was performed to reduce this risk.

The choice of gemcitabine as comparator was made on the basis that gemcitabine is a well-established treatment in this setting.

The overall design of the pivotal study, including the inclusion and exclusion criteria, was adequate. The distribution of demographics and baseline characteristics, and also other important factors like previous malignancy and disease history, were well balanced between arms. A predominance of men versus women, and white versus other races was observed. The total number of patients ≥75 years or KPS of ≤70 in the Abraxane/gemcitabine arm was low (n=41 and n=32, respectively).

Efficacy data and additional analyses

In the dose-finding study and for both PFS and OS, better results were obtained in the Abraxane 125 mg/m2 cohort compared to the 100 mg/m2 cohort, while the 150 mg/m2 was not tolerated. The difference between the Abraxane 100 mg/m2 cohort and the Abraxane 125 mg/m2 for PFS was small (6.1 vs 6.9 months respectively). However, the number of patients included in the 100 mg/m2cohort was very limited; therefore, no definitive conclusion regarding the efficacy of this Abraxane dose could be drawn. Nevertheless, the choice of 125 mg/m2Abraxane dose for the phase 3 study was supported.

In the pivotal study, a statistically significant improvement of 1.8 months (8.5 vs. 6.7 months) in overall survival (OS) was shown for patients in the Abraxane/gemcitabine arm (n=431) vs. gemcitabine alone (n=430) (HR=0.72, 95% CI 0.6, 0.8, p<0.001). Approximately 80% of the patients had died at time of the final analysis. OS data were supported by several subgroup analyses, although no improvement was observed in patients with normal tumour marker CA19-9 levels and patients over 75 years of age. Results in secondary endpoints supported the efficacy shown for the primary endpoint.

Although the phase I/II dose escalating study included only 44 patients at the proposed dose of 125 mg/m2 Abraxane, efficacy results supported the beneficial effects observed in the pivotal study.

The indication initially applied for concerned the treatment of patients with metastatic and patients with locally advanced unresectable adenocarcinoma of pancreas. However, patients with locally advanced unresectable tumours were excluded from both the CA046 and the CA040 study and the indication was subsequently restricted to the treatment of patients with metastatic disease only. Of note, in the registration trial of gemcitabine/erlotinib, no improvement in OS was observed for patients with locally advanced disease (n=67 in gemcitabine/erlotinib arm), and this regimen has only been approved for metastatic pancreatic cancer. On the other hand, gemcitabine monotherapy was approved for patients with locally advanced unresectable or metastatic adenocarcinoma based on a phase III study that also included patients with locally advanced disease (n=18).

In most subgroups the treatment effect favoured the Abraxane/gemcitabine arm, with the exceptions of patients ≥75 years of age and patients with normal baseline CA19-9 levels where the survival was equivalent for the Abraxane/gemcitabine and gemcitabine arms. The HR for the subgroup of patients ≥75 years of age was 1.08 and therefore negative for the Abraxane/gemcitabine treatment. Although these “older” patients accounted for less than 10% of the total patient population (n=41 and n=49 in the Abraxane/gemcitabine and gemcitabine arms respectively) and an imbalance in baseline characteristics was reported for this patient group, the benefit for the Abraxane/gemcitabine treatment in comparison to gemcitabine monotherapy was not demonstrated in this subgroup of patients. As the risk of toxicity is also greater in these older patients, a warning regarding the use of Abraxane/gemcitabine for the treatment of patients above the age of 75 years was included in the SmPC.

The $HR_{A+G/G}$, for patients with normal CA19-9 level at baseline was 1.07, thereby no benefit in terms of overall survival for this subgroup of patients was demonstrated. This result could not be explained by a clear imbalance in post study treatment or baseline characteristics between the study arms, which would adversely affect the Abraxane/gemcitabine arm. Although, only a limited number of patients with normal CA19-9 levels were included in the study, the lack of data indicating a clear benefit for Abraxane/gemcitabine treatment in terms of prolonged overall survival in patients with normal CA19-9 levels prior to treatment start was reflected in the SmPC.

Efficacy data for patients with renal and hepatic impairment are lacking, as they were excluded from the pivotal study. These data are considered important since patients with hepatic and renal impairment represent a relevant subgroup of the population treated in clinical practice. Lack of data in patients with renal or hepatic impairment was already reflected in the SmPC in the form of insufficient information to support relevant posology recommendations and relevant warnings against treating with Abraxane patients with severe hepatic impairment and treating with caution patients with mild or moderate hepatic impairment. Moreover, use in patients with hepatic impairment is considered an important potential risk and use in patients with renal impairment considered as missing information in the SmPC.

Some clustering of censoring occurred around the median for OS which could have affected the median OS and the PFS analysis has not yet shown to be robust for possibly informative censoring (22% or 26%). The impact of these censored patients on the OS and PFS has been explored by additional sensitivity analysis using the date of observed PD as much as possible (i.e. not censoring for >2 missed visits and for death after >120 day) and informative reasons for censoring consider as events. For OS, a sensitivity analysis was performed were patients were considered to have died if they satisfied the criterion of “having a last-known-to-be-alive date more than 1 month earlier than the clinical cut-off date”. Furthermore, a conservative analysis was performed were patients satisfying this criterion were only considered to have died if they were in the experimental arm. These additional analyses confirmed the primary PFS and OS analysis.

The percentage of patients in the Abraxane/gemcitabine that had at least one dose reduction or who had delayed doses was high in comparison to the number of patients with dose reduction and/or delay in the gemcitabine arm and in principle this may affect efficacy. Moreover, the percentage of patients with TEAEs that resulted in permanent discontinuation of study drug was greater in the Abraxane/gemcitabine arm (35% for Abraxane and 30% for gemcitabine) than in the gemcitabine arm (24%). The need for dose reduction or dose delays and treatment discontinuation could diminish the benefit of treatment in a high number of patients. However, additional analysis indicated that for the subgroup of patients who needed a dose delay or reduction, the median OS and PFS was longer (8 months) for Abraxane/gemcitabine treated patients than for patients treated with gemcitabine (6.7 months). Furthermore, the OS for patients of the Abraxane/gemcitabine arm who had dose reduction and/or delay seems to be comparable to the OS of the ITT population treated with Abraxane/gemcitabine (median OS of 8.5 months). These data suggest that for patients who needed a treatment modification due to AEs, dose reduction and/or delay is a reasonable option to allow continuation of Abraxane/gemcitabine treatment providing the opportunity to benefit further from Abraxane/gemcitabine.

On the other hand, there was a concern that patients in the gemcitabine alone arm underwent too early dose reduction (median time to first reduction 0.9 months vs 1.5 months in the combination arm) and too frequent treatment withdrawals (24% is considered higher than expected) by which a bias could be introduced, especially as the study CA046 was an open label study. However, additional analysis indicated that for the whole study population the moment of first dose reduction or interruption in the gemcitabine arm was later than for the Abraxane/gemcitabine arm. Consistently

with this and as expected, the toxicity profile of the combination was worse than that of gemcitabine alone (see discussion on clinical safety). As the OS, PFS and drug exposure data for patients treated with gemcitabine monotherapy in the CA046 study were reasonably comparable to results reported for earlier (historical) studies, overall there was no suggestion that the patients in the gemcitabine arm were undertreated.

2.4.4. Conclusions on the clinical efficacy

The increase of 1.8 months in OS and PFS for the Abraxane/gemcitabine combination therapy in comparison to gemcitabine alone in the CA046 study is considered clinically relevant for the treatment of patients with metastatic adenocarcinoma of the pancreas. The benefit of Abraxane/gemcitabine treatment for patients older than 75 years of age was also demonstrated: however, a warning regarding the treatment of patients 75 years and older with the combination treatment Abraxane/gemcitabine was included in the SmPC. Moreover, the lack of data indicating a clear benefit for Abraxane/gemcitabine treatment in terms of prolonged overall survival in patients with normal CA19-9 levels prior to treatment start was also reflected in the SmPC.

The CHMP recommends that the following efficacy data should be submitted when made available:

- Data on the SPARC biomarker exploratory analysis

2.5. Clinical safety

2.5.1. Introduction

Based on experience in the existing Abraxane breast cancer indication the most common Adverse Drug Reactions (ADRs) of Abraxane include: bone marrow suppression (neutropenia, anaemia, leukopenia, thrombocytopenia, lymphopenia), neuropathy (peripheral neuropathy, hypoaesthesia, paraesthesia), anorexia and gastrointestinal toxicity (nausea, diarrhoea, vomiting, constipation, stomatitis), alopecia, rash, arthralgia, myalgia, fatigue, asthenia and pyrexia.

The safety and tolerability of Abraxane in combination with gemcitabine in patients with metastatic adenocarcinoma of the pancreas was assessed in two clinical studies (CA040 and CA046). For the phase 1/2 study CA040, 67 patients were treated with Abraxane/gemcitabine in the following Abraxane dose cohorts: 100 mg/m^2 (20 patients), 125 mg/m^2 (44 patients) and 150 mg/m^2 (3 patients). For Study 046, the safety data is derived from the treated population, i.e., all 823 patients who received at least one dose of study drug (abraxane/gemcitabine or gemcitabine alone).

Patient exposure

Time on study and treatment exposure are summarised in Table 14 and cumulative dose in Table 15.

Table 14: Number of cycles and study drug doses administered, treated population

Variables	Study CA046		Study CA040	Pooled[a]
	ABI-007 125 mg/m^2 / Gemcitabine (N=421)	Gemcitabine (N=402)	ABI-007 125 mg/m^2 / Gemcitabine (N=44)	ABI-007 125 mg/m^2 / Gemcitabine (N=465)
Time on Study (months)[b]				
n	421	402	44	465
Mean	9.0	7.4	13.9	9.5
STDEV	6.53	5.52	9.79	7.04
Median	7.7	6.1	10.3	7.9
Min, Max	0, 37	0, 31	0, 33	0, 37
Duration of Treatment (days)				
n	421	402	44	465
Mean	145.9	111.6	189.1	150.0
STDEV	107.81	92.97	150.08	113.0
Median	119.0	86.0	162.0	126.0
Min, Max	4, 666	2, 654	1, 694	1, 694
Number of Cycles Administered[c]				
n	421	402	44	465
Mean	4.4	3.3	7.1	4.7
STDEV	3.59	3.15	5.08	3.83
Median	3.0	2.0	6.0	4.0
Min, Max	1, 23	1, 23	1, 24	1, 24
Number of ABI-007 Doses Administered				
n	421	0	44	465
Mean	13.7	0	19.1	14.2
STDEV	10.27	0	14.27	10.81
Median	12.0	0	15.5	12.0
Min, Max	1, 71	0, 0	1, 71	1, 71
Number of Gemcitabine Doses Administered				
n	421	402	44	465
Mean	14.0	11.9	18.2	14.4
STDEV	10.39	9.72	12.60	10.67
Median	12.0	9.0	15.0	12.0
Min, Max	0, 71	1, 71	1, 50	0, 71

Max = maximum; Min = minimum; STDEV = standard deviation. [a] Includes patients treated with Abraxane 125 mg/m2/gemcitabine in studies CA040 and CA046. [b] Time on study was defined as the time from the randomization/registration date to the death date or the last follow-up date. [c] The pooled data for Cycle 1 includes a 56-day cycle in Study CA046 and a 28-day cycle in Study CA040.

Table 15: Cumulative dose, average dose intensity, and percentage of protocol dose administered, treated population

Variables	Study CA046		Study CA040	Pooled[a]
	ABI-007 125 mg/m^2 / Gemcitabine (N=421)	Gemcitabine (N=402)	ABI-007 125 mg/m^2 / Gemcitabine (N=44)	ABI-007 125 mg/m^2 / Gemcitabine (N=465)
Cumulative ABI-007 Dose (mg/m^2)				
n	421	0	44	465
Mean	1587.8	0	2230.1	1648.6
STDEV	1144.74	0	1479.66	1193.52
Median	1425.0	0	1875.0	1500.0
Min, Max	125, 7700	0	125, 5975	125, 7700
Cumulative Gemcitabine Dose (mg/m^2)				
n	420[c]	402	44	464[c]
Mean	12660.6	11238.8	17472.7	13116.9
STDEV	9168.65	9296.25	11711.82	9529.24
Median	11400.0	9000.0	14900.0	12000.0
Min, Max	1000, 70800	989, 67200	1000, 48600	1000, 70800

Max = maximum; Min = minimum; STDEV = standard deviation. [a] Includes patients treated with Abraxane 125 mg/m^2/gemcitabine in studies CA046 and CA040. [c] One patient in the Abraxane/gemcitabine arm in Study CA046 (Patient 1411-0001) did not receive gemcitabine; the patient only received Abraxane.

Adverse events

Treatment-emergent adverse events are summarised in the following Table 16.

Table 16: Summary of all treatment-emergent adverse events, treated population

Variables	Study CA046		Study CA040	Pooled[a]
	ABI-007 125 mg/m^2 / Gemcitabine (N=421)	Gemcitabine (N=402)	ABI-007 125 mg/m^2 / Gemcitabine (N=44)	ABI-007 125 mg/m^2 / Gemcitabine (N=465)
Patients with at Least 1 TEAE	417 (99%)	395 (98%)	44 (100%)	461 (99%)
Patients with at Least 1 Treatment-related AE	403 (96%)	371 (92%)	42 (95%)	445 (96%)
Patients with at Least 1 SAE	212 (50%)	172 (43%)	24 (55%)	236 (51%)
Patients with at Least 1 Treatment-related SAE	121 (29%)	53 (13%)	12 (27%)	133 (29%)
Patients with at Least 1 Grade 3 or Higher AE	374 (89%)	303 (75%)	42 (95%)	416 (89%)
Patients with at Least 1 Treatment-related Grade 3 or higher AE	325 (77%)	203 (50%)	38 (86%)	363 (78%)
Patients with at Least 1 TEAE Leading to Treatment Discontinuation	149 (35%)	95 (24%)	12 (27%)	161 (35%)
Patients with at Least 1 TEAE with Outcome of Death	18 (4%)	18 (4%)	1 (2%)	19 (4%)

AE=adverse event, TEAE=treatment-emergent adverse event, SAE=serious adverse event

In the Abraxane/gemcitabine arm of the treated population, the most frequently (≥40% of patient) reported TEAEs were fatigue, nausea, peripheral neuropathy SMQ, alopecia, peripheral oedema, diarrhoea, anaemia, neutropenia, and pyrexia. The TEAEs reported more often in the Abraxane/gemcitabine arm than in the gemcitabine arm (≥10% difference) in decreasing order were fatigue, alopecia, peripheral neuropathy SMQ, peripheral oedema, diarrhoea, neutropenia, pyrexia, decreased appetite, rash and dehydration.

The incidence of Grade 3 or higher TEAEs was greater in the Abraxane/gemcitabine arm than in the gemcitabine arm (89% vs 75%, respectively). The most frequently reported Grade 3 or higher TEAEs in the Abraxane/gemcitabine arm were neutropenia, fatigue, peripheral neuropathy SMQ, thrombocytopenia and anaemia. The Grade 3 or higher TEAES reported more often in the Abraxane/gemcitabine arm than in the gemcitabine arm (≥5%) in decreasing order were neutropenia, fatigue, peripheral neuropathy SMQ, thrombocytopenia, leukopenia, and diarrhoea.

Table 17: Treatment-emergent adverse events reported in at least 10% of patients MedDRA System Organ Class and Preferred Term (Treated Population)

System Organ Class Preferred Term	Study CA046		Study CA040	Pooled[a]
	ABI-007 125 mg/m^2 / Gemcitabine (N=421)	Gemcitabine (N=402)	ABI-007 125 mg/m^2 / Gemcitabine (N=44)	ABI-007 125 mg/m^2 / Gemcitabine (N=465)
Patients with at Least 1 AE	**417 (99%)**	**395 (98%)**	**44 (100%)**	**461 (99%)**
General Disorders and Administration Site Conditions	**361 (86%)**	**299 (74%)**	**43 (98%)**	**404 (87%)**
Fatigue	248 (59%)	183 (46%)	39 (89%)	287 (62%)
Oedema Peripheral	194 (46%)	123 (31%)	27 (61%)	221 (48%)
Pyrexia	171 (41%)	115 (29%)	23 (52%)	194 (42%)
Asthenia	79 (19%)	54 (13%)	7 (16%)	86 (18%)
Chills	49 (12%)	35 (9%)	10 (23%)	59 (13%)
Mucosal Inflammation	42 (10%)	16 (4%)	10 (23%)	52 (11%)
Gastrointestinal Disorders	**352 (84%)**	**315 (78%)**	**42 (95%)**	**394 (85%)**
Nausea	228 (54%)	192 (48%)	29 (66%)	257 (55%)
Diarrhoea	184 (44%)	95 (24%)	24 (55%)	208 (45%)
Vomiting	151 (36%)	113 (28%)	20 (45%)	171 (37%)
Constipation	126 (30%)	111 (28%)	21 (48%)	147 (32%)
Abdominal Pain	98 (23%)	91 (23%)	17 (39%)	115 (25%)
Abdominal Pain Upper	43 (10%)	28 (7%)	4 (9%)	47 (10%)
Skin and Subcutaneous Tissue Disorders	**294 (70%)**	**127 (32%)**	**42 (95%)**	**336 (72%)**
Alopecia	212 (50%)	21 (5%)	35 (80%)	247 (53%)
Rash	117 (28%)	39 (10%)	21 (48%)	138 (30%)

System Organ Class Preferred Term	Study CA046		Study CA040	Pooled[a]
	ABI-007 125 mg/m^2 / Gemcitabine (N=421)	Gemcitabine (N=402)	ABI-007 125 mg/m^2 / Gemcitabine (N=44)	ABI-007 125 mg/m^2 / Gemcitabine (N=465)
Blood and Lymphatic System Disorders	**280 (67%)**	**238 (59%)**	**37 (84%)**	**317 (68%)**
Anaemia	176 (42%)	133 (33%)	31 (70%)	207 (45%)
Neutropenia	175 (42%)	122 (30%)	26 (59%)	201 (43%)
Thrombocytopenia	128 (30%)	117 (29%)	27 (61%)	155 (33%)
Leukopenia	59 (14%)	39 (10%)	17 (39%)	76 (16%)
Nervous System Disorders	**277 (66%)**	**149 (37%)**	**38 (86%)**	**315 (68%)**
Peripheral Neuropathy SMQ[b]	227 (54%)	51 (13%)	33 (75%)	260 (56%)
Dysgeusia	68 (16%)	33 (8%)	16 (36%)	84 (18%)
Headache	60 (14%)	38 (9%)	9 (20%)	69 (15%)
Dizziness	48 (11%)	34 (8%)	13 (30%)	61 (13%)
Metabolism and Nutrition Disorders	**245 (58%)**	**182 (45%)**	**28 (64%)**	**273 (59%)**
Decreased Appetite	152 (36%)	104 (26%)	22 (50%)	174 (37%)
Dehydration	87 (21%)	45 (11%)	15 (34%)	102 (22%)
Hypokalaemia	52 (12%)	28 (7%)	12 (27%)	64 (14%)
Respiratory, Thoracic and Mediastinal Disorders	**212 (50%)**	**149 (37%)**	**33 (75%)**	**245 (53%)**
Cough[c]	72 (17%)	30 (7%)	13 (30%)	85 (18%)
Dyspnoea	72 (17%)	62 (15%)	12 (27%)	84 (18%)
Epistaxis	64 (15%)	14 (3%)	10 (23%)	74 (16%)
Infections and Infestations	**205 (49%)**	**129 (32%)**	**28 (64%)**	**233 (50%)**
Urinary Tract Infection	40 (10%)	15 (4%)	7 (16%)	47 (10%)
Investigations	**186 (44%)**	**172 (43%)**	**26 (59%)**	**212 (46%)**
Weight Decreased	57 (14%)	48 (12%)	8 (18%)	65 (14%)
Alanine Aminotransferase Increased	46 (11%)	36 (9%)	4 (9%)	50 (11%)
Musculoskeletal and Connective Tissue Disorders	**177 (42%)**	**107 (27%)**	**27 (61%)**	**204 (44%)**
Arthralgia	47 (11%)	13 (3%)	11 (25%)	58 (12%)
Pain In Extremity	48 (11%)	24 (6%)	9 (20%)	57 (12%)
Myalgia	44 (10%)	15 (4%)	10 (23%)	54 (12%)
Psychiatric Disorders	**151 (36%)**	**103 (26%)**	**25 (57%)**	**176 (38%)**
Insomnia	64 (15%)	46 (11%)	13 (30%)	77 (17%)
Depression	51 (12%)	24 (6%)	8 (18%)	59 (13%)
Anxiety	35 (8%)	45 (11%)	13 (30%)	48 (10%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query. a Includes patients treated with Abraxane 125 mg/m^2/gemcitabine in Studies CA046 and CA040. b Peripheral neuropathy evaluated using the MedDRA SMQ c Before rounding, the between-group difference in the incidence of cough in Study CA046 was 9.6%.

TEAEs grade 3 or higher for pivotal Study CA046, Study CA040 (Abraxane 125 mg/m^2/gemcitabine cohort) and the pooled analysis are summarised in Table 18.

Table 18: Grade 3 or higher adverse events by MedDRA System Organ Class and Preferred Term (at least 5% in pooled group), treated population

System Organ Class Preferred Term	Study CA046		Study CA040	Pooled[a]
	ABI-007 125 mg/m^2 / Gemcitabine (N=421)	Gemcitabine (N=402)	ABI-007 125 mg/m^2 / Gemcitabine (N=44)	ABI-007 125 mg/m^2 / Gemcitabine (N=465)
Patients with at Least 1 Grade 3 or Higher AE	**374 (89%)**	**303 (75%)**	**42 (95%)**	**416 (89%)**
Blood and Lymphatic System Disorders	**202 (48%)**	**128 (32%)**	**28 (64%)**	**230 (49%)**
Neutropenia	138 (33%)	85 (21%)	26 (59%)	164 (35%)
Thrombocytopenia	53 (13%)	33 (8%)	12 (27%)	65 (14%)
Anaemia	49 (12%)	32 (8%)	8 (18%)	57 (12%)
Leukopenia	39 (9%)	15 (4%)	11 (25%)	50 (11%)
General Disorders and Administration Site Conditions	**132 (31%)**	**76 (19%)**	**16 (36%)**	**148 (32%)**
Fatigue	77 (18%)	37 (9%)	14 (32%)	91 (20%)
Asthenia	29 (7%)	17 (4%)	2 (5%)	31 (7%)
Gastrointestinal Disorders	**114 (27%)**	**92 (23%)**	**17 (39%)**	**131 (28%)**
Abdominal Pain	27 (6%)	32 (8%)	6 (14%)	33 (7%)
Diarrhoea	26 (6%)	6 (1%)	2 (5%)	28 (6%)
Nausea	27 (6%)	14 (3%)	1 (2%)	28 (6%)
Vomiting	25 (6%)	15 (4%)	3 (7%)	28 (6%)
Nervous System Disorders	**82 (19%)**	**19 (5%)**	**12 (27%)**	**94 (20%)**
Peripheral Neuropathy SMQ[b]	70 (17%)	3 (1%)	10 (23%)	80 (17%)
Metabolism and Nutritional Disorders	**76 (18%)**	**48 (12%)**	**14 (32%)**	**90 (19%)**
Dehydration[c]	31 (7%)	10 (2%)	3 (7%)	34 (7%)
Decreased Appetite	23 (5%)	8 (2%)	3 (7%)	26 (6%)
Hypokalaemia	18 (4%)	6 (1%)	6 (14%)	24 (5%)
Investigations	**66 (16%)**	**61 (15%)**	**10 (23%)**	**76 (16%)**
Neutrophil Count Decreased	19 (5%)	15 (4%)	8 (18%)	27 (6%)
Vascular Disorders	**41 (10%)**	**39 (10%)**	**4 (9%)**	**45 (10%)**
Deep Vein Thrombosis	21 (5%)	22 (5%)	3 (7%)	24 (5%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query.
a Includes treated with Abraxane 125 mg/m^2/gemcitabine in Studies CA046 and CA040
b Peripheral neuropathy evaluated using the MedDRA SMQ
c Before rounding, the between-group difference in the incidence of dehydration in Study CA046 was 4.9%.

In the pivotal study, the most frequently (≥25% of patients) reported treatment-related AEs in the Abraxane/gemcitabine arm were fatigue, alopecia, nausea, neutropenia, anaemia, diarrhoea, peripheral oedema, vomiting, thrombocytopenia, pyrexia, decreased appetite, peripheral neuropathy, and peripheral sensory neuropathy.

In the same study, the treatment-related AEs reported more often (≥10% difference) in the Abraxane/gemcitabine arm than the gemcitabine arm were fatigue, alopecia, neutropenia, diarrhoea, peripheral oedema, vomiting, decreased appetite, peripheral neuropathy, and peripheral sensory neuropathy, and rash.

Finally, the incidence of Grade 3 or higher treatment-related TEAEs was 77% in the Abraxane/gemcitabine arm and 50% in the gemcitabine arm. The most frequent (≥10% of) Grade 3 or higher treatment-related TEAEs in the Abraxane/gemcitabine arm in decreasing order of frequency were neutropenia (33%), fatigue (17%), thrombocytopenia (12%) and anemia (10%). The Grade 3 or higher treatment-related TEAEs reported with a ≥5% difference in the Abraxane/gemcitabine arm than the gemcitabine arm were neutropenia (33% vs. 21%), fatigue (17% vs. 7%), leukopenia (9% vs. 4%), peripheral sensory neuropathy (8% vs. 0%), and peripheral neuropathy (8% vs. 0%).

Adverse events of interest (AEOI) were selected for further review because of their known association with Abraxane treatment in patients with other types of cancers, with gemcitabine, or with the underlying disease state.

Categories of AEs of interest included myelosuppression, sepsis, pneumonitis, peripheral neuropathy, gastrointestinal events, cardiotoxicity, hepatotoxicity, renal toxicity, myalgia and arthralgia, hypersensitivity reactions, injection site reactions/extravasation, cystoid macular oedema, Stevens-Johnson syndrome/toxic epidermal necrolysis, cranial nerve palsies and oedema.

Myelosuppression AEs were more common in the Abraxane/gemcitabine arm (66%) than in the gemcitabine arm (59%) of pivotal study CA046. The most frequent Preferred Terms (PT) reported were anaemia (42% vs. 33%), neutropenia (42% vs. 30%), thrombocytopenia (30% vs. 29%) and leukopenia (14% vs. 10%).

Incidence of bleeding events (all grades) was greater in the Abraxane/gemcitabine arm (23%) than in the gemcitabine arm (13%), primarily due to an increase in the incidences of epistaxis (15% vs. 3%). The frequencies of Grade 3 or higher bleeding events were identical in the 2 treatment arms (3% in each). Likewise, Grade 3/4 epistaxis was reported for 1 patient in each treatment arm.

Concomitant therapies to reduce the extent of myelosuppression were more common in the combination arm than in the gemcitabine arm of pivotal Study, i.e. WBC growth factors (26% vs. 15%), erythropoietins (16% vs. 11%), blood transfusions (12% vs. 7%) and blood products (4% vs. 3%).

87 MedDRA preferred terms related to sepsis, neutropenic sepsis and septic shock, as well as terms including bacteraemia with specific organisms, was used to identify sepsis AEs. In the following these terms are collectively referred to as sepsis.

Sepsis was more common in the Abraxane/gemcitabine arm (5%, n=22) than in the gemcitabine arm (2%, n=10). In almost half of the patients (n=11) in the Abraxane/gemcitabine arm complications of the underlying metastatic pancreatic cancer were a significant contributing factor, most commonly being abdominal infection due to cholangitis brought on by tumor compression of the common bile duct. No imbalance was found in demographics and cancer history (possible confounders for the risk of acquiring sepsis) for patients with sepsis in the two treatment arms. Nearly all cases of sepsis were considered to be SAEs, i.e. 5% (n=20) in the Abraxane/gemcitabine arm and 2% (n=9) in the gemcitabine arm. 5 patients (1%) in the Abraxane/gemcitabine arm died due to sepsis (2 patients had

sepsis and 1 patient each had bacterial sepsis, neutropenic sepsis, and septic shock) and 2 patients (<1%) in the gemcitabine arm died due to a sepsis AE of septic shock. In those who died of sepsis, neutropenia was observed in 3 of 5 cases in the Abraxane/gemcitabine arm and 0 of 2 cases in the gemcitabine arm.

Sepsis was also reported for 5 patients in Study CA040 (3 patients in Abraxane 125 mg/m^2/gemcitabine cohort, and 1 patient each in Abraxane 100 mg/m^2/gemcitabine cohort and Abraxane 150 mg/m^2/gemcitabine cohort). The subject in the Abraxane 150 mg/m^2/gemcitabine cohort died due to sepsis.

Of the 622 patients enrolled in CA046 up to September 19, 2011, 10 patients had developed interstitial pneumonitis, 9 in the Abraxane/gemcitabine arm (3.0%) of which 3 were fatal, and 1 in the gemcitabine arm (0.3%). The median time to onset of pneumonitis AEs was similar in the 2 treatment arms (86 days in the Abraxane/gemcitabine arm and 83 days in the gemcitabine arm).

The incidence of Grade 3 peripheral neuropathy increased with cumulative exposure to Abraxane. In the Abraxane/gemcitabine arm, patients received a median of 3 cycles of treatment. For patients treated for up to 3 cycles in the Abraxane/gemcitabine arm, the incidence of Grade 3 peripheral neuropathy was 7%. For patients treated for up to 6 cycles in the Abraxane/gemcitabine arm the incidence of Grade 3 peripheral neuropathy was 12%.

The median time to the first occurrence and improvement in Grade 3 peripheral neuropathy AE was longer in the Abraxane/gemcitabine arm (140 days) than in the gemcitabine arm (113 days). More patients in the Abraxane/gemcitabine arm than in the gemcitabine arm had an improvement by at least 1 grade (63% vs 33%), and the median time to improvement by at least 1 grade was shorter in the Abraxane/gemcitabine arm than in the gemcitabine arm (21 versus 29 days). Forty-three percent of patients with Grade 3 peripheral neuropathy in the Abraxane/gemcitabine arm had an improvement to Grade 1 or better, none of the 3 patents with Grade 3 peripheral neuropathy in the gemcitabine arm had an improvement to Grade 1 or better.

Gastrointestinal AEs were reported for 73% of patients in the Abraxane/gemcitabine arm and 62% in the gemcitabine arm in pivotal Study CA046. The most common events were nausea (54% vs. 48%), diarrhea (44% vs. 24%) and vomiting (36% vs. 28%). There was a greater incidence of Grade 3 or higher AEs in the Abraxane/gemcitabine arm than in the gemcitabine arm (15% vs. 7%). Likewise, SAE were more frequent in the Abraxane/gemcitabine arm (8%) than in the gemcitabine arm (4%) and dose reductions due to gastrointestinal AEs were more common in the Abraxane/gemcitabine arm (5% for Abraxane and 5% for gemcitabine) than in the gemcitabine arm (1%, see Table XXX).

Cardiotoxicity AEs were reported with a similar incidence in the Abraxane/gemcitabine and gemcitabine arm (5% and 4%, respectively). The most frequently reported cardiotoxicity AE in both treatment arms was tachycardia (4% in the Abraxane/gemcitabine arm and 2% in the gemcitabine arm). All other cardiotoxicity AEs were reported for ≤1 patient in each treatment arm. Grade 3 or higher cardiotoxicity AEs were reported for 2 patients in the Abraxane/gemcitabine arm (1 patient with intracardiac thrombus and 1 patient with tachycardia) and 2 patients in the gemcitabine arm (1 patient with unstable angina and 1 with cardiopulmonary failure). Cardiotoxicity SAEs were reported in 2 patients in the gemcitabine arm and no cases in the Abraxane/gemcitabine arm.

The incidence of hepatotoxicity AEs was similar in the 2 treatment arms (26% in both). The most frequently reported AEs in both treatment arms were alanine aminotransferase increased (11% in the Abraxane/gemcitabine arm and 9% in the gemcitabine arm) and aspartate aminotransferase (9% in both arms). Grade 3 or higher hepatotoxicity was reported with similar incidence in the Abraxane/gemcitabine arm and the gemcitabine arm (11% and 13%, respectively). The percentage of patients with hepatotoxicity considered to be a SAE was identical in the 2 treatment arms (4% each)

Renal toxicity, including haemolytic uraemic syndrome, is a known risk for gemcitabine. There was no difference between the Abraxane/gemcitabine and gemcitabine arm in the incidence of renal toxicity AEs (6% each). The most frequently reported renal toxicity AE in the Abraxane/gemcitabine was blood creatinine increased (reported for 3% of patients in each treatment arm). All other renal toxicity AEs were reported for ≤1% of patients in both treatment arms. The incidence of Grade 3 or higher renal toxicity AEs were similar in the 2 treatment arms (2% in the Abraxane/gemcitabine arm and 3% in the gemcitabine arm). The incidence of renal toxicity SAEs was also low and similar in the 2 treatment arms (1% and 2%, respectively).

Haemolytic uraemic syndrome, which is known for gemcitabine, was reported by 2 patients in the Abraxane gemcitabine arm and 1 patient in the gemcitabine arm. For all 3 patients with haemolytic uraemic syndrome, the event was Grade 3 or higher and was considered a SAE. Study drug (both Abraxane and gemcitabine) was discontinued for 1 patient in the Abraxane/gemcitabine arm due to haemolytic uraemic syndrome. There were no deaths due to haemolytic uraemic syndrome.

Myalgia and arthralgia AEs were reported more often in the Abraxane/gemcitabine arm than in the gemcitabine arm (18% versus 6%, respectively). The incidence of Grade 3 myalgia and arthralgia AEs was low in both treatment arms (1% versus <1%).

There were no reports of any hypersensitivity reactions.

Injection site reaction/extravasation AEs were reported with similar incidence in the Abraxane/gemcitabine and gemcitabine arm (3% and 2%, respectively). All injection site reaction/extravasation AEs were < Grade 3.

Cystoid macular edema was reported for 1 patient in the Abraxane/gemcitabine arm and no patients in the gemcitabine arm. The patient was discontinued from study drug (both Abraxane and gemcitabine) due to this event. As cystoid macular edema has been described for Abraxane monotherapy, it does not represent a new safety signal.

There were no instances of Stevens-Johnson syndrome or toxic epidermal necrolysis in any of the treatment arms.

Cranial nerve palsy AEs were reported for 2 patients (one Grade 1 facial nerve disorder and one Grade 2 VIIth nerve paralysis in the Abraxane/gemcitabine arm and no patient in the gemcitabine arm. The events did not result in study drug discontinuation.

There was a greater incidence of peripheral oedema in the Abraxane/gemcitabine arm (46%, 3% were grade 3) than in the gemcitabine arm (31%, 3% were grade 3).

Adverse drug reactions (treatment-related AEs) observed in the pivotal and the phase I/II study are summarised in the following Table 19.

Table 19: Incidence of treatment-related adverse events by preferred term (at least 5% in pooled group), treated population

	Study CA046		Study CA040			Pooled(a)
Preferred Term	ABI-007 125 mg/m^2 / Gemcitabine (N=421)	Gemcitabine (N=402)	ABI-007 100 mg/m^2 / Gemcitabine (N=20)	ABI-007 125 mg/m^2 / Gemcitabine (N=44)	ABI-007 150 mg/m^2 / Gemcitabine (N=3)	ABI-007 125 mg/m^2 / Gemcitabine (N=465)
Patients with at Least 1 Treatment-Related AE	403 (96%)	371 (92%)	18 (90%)	42 (95%)	3 (100%)	445 (96%)
Fatigue	226 (54%)	147 (37%)	14 (70%)	35 (80%)	2 (67%)	261 (56%)
Alopecia	211 (50%)	20 (5%)	15 (75%)	35 (80%)	1 (33%)	246 (53%)
Nausea	207 (49%)	165 (41%)	9 (45%)	22 (50%)	2 (67%)	229 (49%)
Neutropenia	175 (42%)	122 (30%)	10 (50%)	26 (59%)	2 (67%)	201 (43%)
Anaemia	161 (38%)	118 (29%)	11 (55%)	29 (66%)	2 (67%)	190 (41%)
Diarrhoea	156 (37%)	53 (13%)	5 (25%)	14 (32%)	1 (33%)	170 (37%)
Oedema Peripheral	141 (33%)	70 (17%)	6 (30%)	18 (41%)	0	159 (34%)
Thrombocytopenia	127 (30%)	116 (29%)	5 (25%)	26 (59%)	2 (67%)	153 (33%)
Vomiting	133 (32%)	83 (21%)	3 (15%)	15 (34%)	2 (67%)	148 (32%)
Neuropathy Peripheral	115 (27%)	3 (1%)	5 (25%)	29 (66%)	2 (67%)	144 (31%)
Pyrexia	122 (29%)	85 (21%)	5 (25%)	13 (30%)	1 (33%)	135 (29%)
Decreased Appetite	115 (27%)	57 (14%)	5 (25%)	13 (30%)	2 (67%)	128 (28%)
Rash	93 (22%)	31 (8%)	5 (25%)	19 (43%)	2 (67%)	112 (24%)
Peripheral Sensory Neuropathy	104 (25%)	11 (3%)	3 (15%)	3 (7%)	0	107 (23%)
Dysgeusia	65 (15%)	26 (6%)	3 (15%)	14 (32%)	2 (67%)	79 (17%)
Leukopenia	58 (14%)	39 (10%)	4 (20%)	17 (39%)	2 (67%)	75 (16%)
Asthenia	59 (14%)	38 (9%)	0	5 (11%)	1 (33%)	64 (14%)
Dehydration	52 (12%)	17 (4%)	1 (5%)	12 (27%)	1 (33%)	64 (14%)
Constipation	50 (12%)	37 (9%)	0	8 (18%)	0	58 (12%)
Mucosal Inflammation	39 (9%)	11 (3%)	1 (5%)	8 (18%)	1 (33%)	47 (10%)
Myalgia	40 (10%)	6 (1%)	0	6 (14%)	1 (33%)	46 (10%)
Epistaxis	39 (9%)	4 (1%)	1 (5%)	6 (14%)	0	45 (10%)
Haemoglobin Decreased	41 (10%)	26 (6%)	0	1 (2%)	0	42 (9%)
Chills	35 (8%)	22 (5%)	2 (10%)	4 (9%)	1 (33%)	39 (8%)
Alanine Aminotransferase Increased	36 (9%)	25 (6%)	2 (10%)	2 (5%)	0	38 (8%)
Arthralgia	32 (8%)	4 (1%)	0	5 (11%)	0	37 (8%)
Weight Decreased	31 (7%)	19 (5%)	0	5 (11%)	0	36 (8%)
Neutrophil Count Decreased	26 (6%)	19 (5%)	0	9 (20%)	0	35 (8%)
Platelet Count Decreased	33 (8%)	25 (6%)	1 (5%)	1 (2%)	1 (33%)	34 (7%)
Stomatitis	31 (7%)	13 (3%)	2 (10%)	1 (2%)	0	32 (7%)
Pain In Extremity	28 (7%)	7 (2%)	1 (5%)	3 (7%)	0	31 (7%)
Pruritus	24 (6%)	11 (3%)	1 (5%)	7 (16%)	0	31 (7%)
Aspartate Aminotransferase Increased	28 (7%)	22 (5%)	3 (15%)	1 (2%)	0	29 (6%)
Oral Candidiasis	27 (6%)	8 (2%)	0	1 (2%)	0	28 (6%)
Cough	26 (6%)	5 (1%)	0	1 (2%)	0	27 (6%)
Dyspnoea	26 (6%)	21 (5%)	0	1 (2%)	0	27 (6%)
Headache	24 (6%)	11 (3%)	1 (5%)	1 (2%)	0	25 (5%)
Abdominal Pain	21 (5%)	11 (3%)	0	3 (7%)	1 (33%)	24 (5%)

Serious adverse event / deaths / other significant events

Table 20: Serious adverse events by MedDRA System Organ Class and Preferred Term (at least 1% in pooled group), treated population

System Organ Class Preferred Term	Study CA046		Study CA040	Pooled[a]
	ABI-007 125 mg/m^2 / Gemcitabine (N=421)	Gemcitabine (N=402)	ABI-007 125 mg/m^2 / Gemcitabine (N=44)	ABI-007 125 mg/m^2 / Gemcitabine (N=465)
Patients with at Least 1 Serious AE	**212 (50%)**	**172 (43%)**	**24 (55%)**	**236 (51%)**
Gastrointestinal Disorders	**67 (16%)**	**45 (11%)**	**10 (23%)**	**77 (17%)**
Vomiting	18 (4%)	12 (3%)	0	18 (4%)
Abdominal Pain	11 (3%)	10 (2%)	0	11 (2%)
Nausea	11 (3%)	8 (2%)	0	11 (2%)
Diarrhoea	9 (2%)	3 (1%)	1 (2%)	10 (2%)
Small Intestinal Obstruction	4 (1%)	1 (<1%)	3 (7%)	7 (2%)
Ascites	4 (1%)	5 (1%)	1 (2%)	5 (1%)
Constipation	5 (1%)	6 (1%)	0	5 (1%)
Intestinal Obstruction	4 (1%)	1 (<1%)	1 (2%)	5 (1%)
Infections and Infestations	**66 (16%)**	**35 (9%)**	**9 (20%)**	**75 (16%)**
Pneumonia	17 (4%)	11 (3%)	2 (5%)	19 (4%)
Cellulitis	8 (2%)	5 (1%)	1 (2%)	9 (2%)
Urinary Tract Infection	6 (1%)	1 (<1%)	0	6 (1%)
Sepsis	5 (1%)	5 (1%)	0	5 (1%)
General Disorders and Administration Site Conditions	**42 (10%)**	**27 (7%)**	**4 (9%)**	**46 (10%)**
Pyrexia	27 (6%)	9 (2%)	3 (7%)	30 (6%)
Oedema Peripheral	6 (1%)	3 (1%)	0	6 (1%)
Blood and Lymphatic System Disorders	**32 (8%)**	**10 (2%)**	**5 (11%)**	**37 (8%)**
Febrile Neutropenia	11 (3%)	2 (<1%)	1 (2%)	12 (3%)
Anaemia	9 (2%)	2 (<1%)	1 (2%)	10 (2%)
Neutropenia	4 (1%)	1 (<1%)	1 (2%)	5 (1%)
Pancytopenia	3 (1%)	0	2 (5%)	5 (1%)
Respiratory, Thoracic and Mediastinal Disorders	**34 (8%)**	**32 (8%)**	**2 (5%)**	**36 (8%)**
Pulmonary Embolism	13 (3%)	20 (5%)	0	13 (3%)
Pleural Effusion	7 (2%)	5 (1%)	0	7 (2%)
Dyspnoea	5 (1%)	2 (<1%)	1 (2%)	6 (1%)

System Organ Class Preferred Term	Study CA046		Study CA040	Pooled[a]
	ABI-007 125 mg/m^2 / Gemcitabine (N=421)	Gemcitabine (N=402)	ABI-007 125 mg/m^2 / Gemcitabine (N=44)	ABI-007 125 mg/m^2 / Gemcitabine (N=465)
Metabolism and Nutrition Disorders	**29 (7%)**	**17 (4%)**	**3 (7%)**	**32 (7%)**
Dehydration[b]	20 (5%)	12 (3%)	3 (7%)	23 (5%)
Decreased Appetite	5 (1%)	0	0	5 (1%)
Hepatobiliary Disorders	**24 (6%)**	**16 (4%)**	**2 (5%)**	**26 (6%)**
Cholangitis	10 (2%)	5 (1%)	1 (2%)	11 (2%)
Bile Duct Obstruction	4 (1%)	3 (1%)	1 (2%)	5 (1%)
Vascular Disorders	**14 (3%)**	**21 (5%)**	**0**	**14 (3%)**
Deep Vein Thrombosis	9 (2%)	12 (3%)	0	9 (2%)
Pleural Effusion	7 (2%)	5 (1%)	0	7 (2%)
Dyspnoea	5 (1%)	2 (<1%)	1 (2%)	6 (1%)
Metabolism and Nutrition Disorders	**29 (7%)**	**17 (4%)**	**3 (7%)**	**32 (7%)**
Dehydration	20 (5%)	12 (3%)	3 (7%)	23 (5%)
Decreased Appetite	5 (1%)	0	0	5 (1%)
Hepatobiliary Disorders	**24 (6%)**	**16 (4%)**	**2 (5%)**	**26 (6%)**
Cholangitis	10 (2%)	5 (1%)	1 (2%)	11 (2%)
Bile Duct Obstruction	4 (1%)	3 (1%)	1 (2%)	5 (1%)
Vascular Disorders	**14 (3%)**	**21 (5%)**	**0**	**14 (3%)**
Deep Vein Thrombosis	9 (2%)	12 (3%)	0	9 (2%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
a Includes patients treated with Abraxane 125 mg/m^2/gemcitabine in Studies CA046 and CA040.
b Before rounding, the incidence of dehydration in the Abraxane/gemcitabine arm in Study CA046 was 4.8% and the between-group difference was 1.8%.

A summary of TEAEs with an outcome of death that occurred within 30 days of the last treatment dose are presented in Table 21. Twenty patients treated with Abraxane (any dose)/gemcitabine had a TEAE with an outcome of death, including 19 patients who received Abraxane 125 mg/m2/gemcitabine (18 patients in pivotal Study CA046 and one patient in Study CA040). In addition, one patient in the Abraxane 150 mg/m2/gemcitabine cohort of Study CA040 died due to sepsis (not shown in Table 21).

Table 21: Incidence of treatment-emergent adverse events with outcome of death, treated population

System Organ Class Preferred Term	Study CA046		Study CA040	Pooled[a]
	ABI-007 125 mg/m^2 / Gemcitabine (N=421)	Gemcitabine (N=402)	ABI-007 125 mg/m^2 / Gemcitabine (N=44)	ABI-007 125 mg/m^2 / Gemcitabine (N=465)
Patients with at Least 1 AE with Outcome of Death	**18 (4%)**	**18 (4%)**	**1 (2%)**	**19 (4%)**
Infections and Infestations	**7 (2%)**	**3 (1%)**	**0**	**7 (2%)**
Pneumonia	2 (<1%)	1 (<1%)	0	2 (<1%)
Sepsis	2 (<1%)	0	0	2 (<1%)
Bacterial Sepsis	1 (<1%)	0	0	1 (<1%)
Neutropenic Sepsis	1 (<1%)	0	0	1 (<1%)
Septic Shock	1 (<1%)	2 (<1%)	0	1 (<1%)
Respiratory, Thoracic and Mediastinal Disorders	**2 (<1%)**	**3 (1%)**	**1 (2%)**	**3 (1%)**
Acute Respiratory Distress Syndrome	1 (<1%)	0	0	1 (<1%)
Diffuse Alveolar Damage	1 (<1%)	0	0	1 (<1%)
Respiratory Failure	0	0	1 (2%)	1 (<1%)
Acute Respiratory Failure	0	1 (<1%)	0	0
Pulmonary Embolism	0	2 (<1%)	0	0
Cardiac Disorders	**2 (<1%)**	**3 (1%)**	**0**	**2 (<1%)**
Acute Coronary Syndrome	1 (<1%)	0	0	1 (<1%)
Cardiac Failure Congestive	1 (<1%)	0	0	1 (<1%)
Cardiac Arrest	0	2 (<1%)	0	0
Cardiopulmonary Failure	0	1 (<1%)	0	0
Gastrointestinal Disorders	**2 (<1%)**	**3 (1%)**	**0**	**2 (<1%)**
Intestinal Perforation	1 (<1%)	0	0	1 (<1%)
Upper Gastrointestinal Haemorrhage	1 (<1%)	0	0	1 (<1%)
Abdominal Pain	0	1 (<1%)	0	0
Gastrointestinal Haemorrhage	0	1 (<1%)	0	0
Large Intestine Perforation	0	1 (<1%)	0	0

System Organ Class Preferred Term	Study CA046		Study CA040	Pooled[a]
	ABI-007 125 mg/m^2 / Gemcitabine (N=421)	Gemcitabine (N=402)	ABI-007 125 mg/m^2 / Gemcitabine (N=44)	ABI-007 125 mg/m^2 / Gemcitabine (N=465)
General Disorders and Administration Site Conditions	**2 (<1%)**	**3 (1%)**	**0**	**2 (<1%)**
General Physical Health Deterioration	1 (<1%)	0	0	1 (<1%)
Multi-Organ Failure	1 (<1%)	1 (<1%)	0	1 (<1%)
Sudden Death	0	2 (<1%)	0	0
Hepatobiliary Disorders	**1 (<1%)**	**1 (<1%)**	**0**	**1 (<1%)**
Hepatic Function Abnormal	1 (<1%)	0	0	1 (<1%)
Hepatic Failure	0	1 (<1%)	0	0
Injury, Poisoning and Procedural Complications	**1 (<1%)**	**0**	**0**	**1 (<1%)**
Fall	1 (<1%)	0	0	1 (<1%)
Nervous System Disorders	**1 (<1%)**	**2 (<1%)**	**0**	**1 (<1%)**
Ischaemic Cerebral Infarction	1 (<1%)	0	0	1 (<1%)
Cerebrovascular Accident	0	1 (<1%)	0	0
Hypoglycaemic Coma	0	1 (<1%)	0	0
Renal and Urinary Disorders	1 (<1%)	1 (<1%)	0	1 (<1%)
Renal Failure	1 (<1%)	0	0	1 (<1%)
Renal Failure Acute	0	1 (<1%)	0	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**0**	**2 (<1%)**	**0**	**0**
Lymphangiosis Carcinomatosa	0	1 (<1%)	0	0
Pancreatic Carcinoma Metastatic	0	1 (<1%)	0	0
Vascular Disorders	**0**	**1 (<1%)**	**0**	**0**
Hypovolaemic Shock	0	1 (<1%)	0	0

AE = adverse event; Incl = including; MedDRA = Medical Dictionary for Regulatory Activities.
a Includes patients treated with Abraxane 125 mg/m^2/gemcitabine in Studies CA046 and CA040

Laboratory findings

Haematology and clinical chemistry were assessed at each treatment cycle and summarised using the NCI CTCAE Version 3.0 grades. The frequencies of patients experiencing grade 1-4 alterations in haematological parameters were higher in the Abraxane/gemcitabine arm than in the gemcitabine arm for neutropenia (73% vs. 58%) but comparable for anaemia (13% vs. 12%) and thrombocytopenia (13% vs. 9%). Concerning clinical chemistry for hepatic and renal functions, the frequencies of patients experiencing grade 1-4 alterations were comparable between the Abraxane/gemcitabine arm and gemcitabine arm, i.e. alkaline phosphatase (63% vs. 63%), ALT (41% vs. 50%), AST (41% vs.

48%), total bilirubin (6% vs. 14%) and creatinine (9% vs. 14%). Likewise, Grade 3/4 was also comparable, i.e. alkaline phosphatase (6% vs. 8%), ALT (1% vs. 2%), AST (2% vs. 1%), total bilirubin (2% vs. 3 %) and creatinine (0% vs. 0%).

Safety in special populations

There were 174 patients aged ≥65 years in the Abraxane/gemcitabine arm and 175 patients aged ≥65 years in the gemcitabine arm.

In general, the incidence and distribution of TEAEs is similar in patients <65 years and ≥65 years of age, and similar relationships are observed when comparing the Abraaxane/gemcitabine arm to the gemcitabine arm. In the Abraxane/gemcitabine arm, patients ≥65 years of age had a slightly greater incidence (≥10% difference) of diarrhoea (51% and 38%, respectively), decreased appetite (42% and 32%, respectively), dehydration (26% and 17%, respectively), and epistaxis (22% and 11%, respectively) compared with patients <65 years of age.

In the Abraxane/gemcitabine arm, patients ≥75 years of age had a greater incidence (≥10% difference) of diarrhoea (53% and 43%, respectively), dry mouth (13% and 2%, respectively), confusional state (13% and 3% respectively), and hypotension (205 and 8%, respectively) compared with patients <75 years of age. For other TEAEs, the rates were comparable or lower than those in patients <75 years of age.

Of the 40 patients in the Abraxane/gemcitabine arm who were ≥75 years of age, 5 patients had AE with an outcome of death. Of the 44 patients in the gemcitabine arm who were ≥75 years of age, 2 patients had AE with an outcome of death.

In the Abraxane/gemcitabine arm, more patients ≥75 years of age discontinued treatment due to TEAEs compared with the overall Treated population (43% discontinued Abraxane for patients ≥75 years versus 35% for overall; 38% discontinued gemcitabine versus 30%). In the Abraxane/gemcitabine arm, the incidence of Abraxane dose limiting toxicities of peripheral neuropathy and neutropenia were comparable among patients ≥75 years compared with the overall Treated population.

In general, the incidence and distribution of TEAEs is similar in male and female patients and similar relationships are observed when comparing the Abraxane/gemcitabine arm to the gemcitabine arm. The Abraxane/gemcitabine arm, TEAEs reported more often (≥10% difference) in female than male patients were neutropenia (49% and 36%, respectively) anaemia (49% and 36%, respectively), vomiting (44% and 29%, respectively) and urinary tract infection (17% and 4%, respectively). Cough was reported more often in males than females (22% and 11%, respectively).

The overall incidence of TEAEs was similar among patients enrolled at sites in the 4 geographic regions (North America, Western Europe, Eastern Europe and Australia).

Discontinuation due to adverse events

The percentage of patients with TEAEs that resulted in permanent discontinuation of study drug was greater in the Abraxane/gemcitabine arm (35% for Abraxane and 30% for gemcitabine) than in the gemcitabine arm (24%). In the Abraxane arm, the most commonly reported TEAEs resulting in abraxane discontinuation were peripheral neuropathy SMQ, fatigue, and thrombocytopenia.

Table 22: Treatment-emergent adverse events resulting in permanent discontinuation of Abraxane and/or gemcitabine and reported in at least 2% of patients in either treatment Arm (treated population)

System Organ Class Preferred Term	ABI-007/Gemcitabine (N=421)		Gemcitabine (N=402)
	ABI-007	Gemcitabine	
Patients with at Least 1 TEAE with Action of Study Drug Permanently Discontinued	**148 (35%)**	**126 (30%)**	**95 (24%)**
Nervous system disorders	**39 (9%)**	**21 (5%)**	**7 (2%)**
Peripheral neuropathy SMQ[a]	34 (8%)	16 (4%)	0
General disorders and administration site conditions	**30 (7%)**	**28 (7%)**	**18 (4%)**
Fatigue	16 (4%)	13 (3%)	2 (<1%)
Blood and lymphatic system disorders	**17 (4%)**	**15 (4%)**	**16 (4%)**
Thrombocytopenia	10 (2%)	8 (2%)	10 (2%)

MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event

[a] Peripheral neuropathy evaluated using the MedDRA SMQ; see Section 12.2.3.1.3.

Note: If a patient reported the same adverse event more than once, then that patient was only counted once for the summary of that adverse event, using the most severe intensity.

Post marketing experience

Abraxane was first authorised in the USA on 7 June 2005 for the treatment of breast cancer in adult patients after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated, In the EU, Abraxane was authorised on 11 January 2008 for the treatment of metastatic breast cancer (MBC) in adult patients who have failed first-line treatment for metastatic disease and for whom standard anthracycline-containing therapy is not indicated. As of 6 January 2013, Abraxane had been approved in 43 countries. An additional indication, for first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy, was approved in the USA on 12 October 2012.

2.5.2. Discussion on clinical safety

Safety evaluation is based on two studies - pivotal Study CA046 (n=421) performed with the Abraxane dose intended for marketing (125 mg/m2 Abraxane) and dose escalating Study CA040. Although the 125 mg/m2 Abraxane cohort of Study CA040 and the pivotal study used identical treatment regimens, the study populations were different rendering inter-study comparison less feasible. Consequently, safety assessment is mainly based on the pivotal study.

In the dose-escalating study, the low tolerance for the 150 mg/m2 Abraxane dose was illustrated by a high percentage (67%) of patients who received less than 70% of the protocol-directed dose of Abraxane and the high incidence of (serious) AEs.

The toxicity reported for the 125 mg/m2 Abraxane dose was consistently and substantially higher than that for the 100 mg/m2 dose. From the toxicity perspective, the 125 mg/m2 might not be optimal; however, the efficacy for the 125 mg/m2 was better than that for the 100 mg/m2. Moreover, the number of patients treated with 100 mg/m2 dose is very limited, therefore no definitive conclusions regarding the efficacy and toxicity of the 100 mg/m2 dose can be drawn.

The percentage of patients in the Abraxane/gemcitabine that had at least one dose reduction or who had delayed doses was high (38% for Abraxane and 44% for gemcitabine) in comparison to the

number of patients with dose reduction and/or delay in the gemcitabine arm (31%). Also the percentage of patients with an AE that resulted in permanent discontinuation of study drug was greater in the Abraxane/gemcitabine arm (35% Abraxane and 30% gemcitabine than in the gemcitabine arm (24%). On the other hand, in the pivotal study CA046 the mean duration of treatment was longer in the Abraxane/gemcitabine arm (145.9 days) than in the gemcitabine arm (111.6 days). Likewise, the mean number of cycles administered was higher in the Abraxane/gemcitabine arm (4.4 cycles) than in the gemcitabine arm (3.3 cycles). The unequal treatment durations may subsequently affect the level of TEAEs reported in the two treatment arms, which could bring uncertainties to the actual difference in safety profiles between the two treatments.

Most of the reported AE and SAE are already known AE of Abraxane and or gemcitabine, but they were reported at higher frequencies than would be expected. In the Abraxane/gemcitabine arm the most frequent reported AEs were fatigue, nausea, peripheral neuropathy, alopecia, peripheral oedema, diarrhoea, anaemia, neutropenia, and pyrexia. In patients treated with Abraxane followed by gemcitabine, more grade 3 or higher AE were reported, than in patients treated with gemcitabine alone (89% vs 75%, respectively). The most frequently reported Grade 3 or higher AEs in the Abraxane/gemcitabine arm were neutropenia, fatigue, peripheral neuropathy, thrombocytopenia and anaemia. Also the incidence of treatment related serious AEs was higher in the Abraxane/gemcitabine arm than in the gemcitabine arm (29% vs 13%). Serious AES that were reported more often in the Abraxane/gemcitabine arm than in the gemcitabine arm were pyrexia and febrile neutropenia, which are known AE of Abraxane treatment and the incidence reported in study CA046 was comparable with the previously reported incidence for Abraxane.

The myelotoxicity of Abraxane/gemcitabine was substantially higher in the Abraxane/gemcitabine arm than in the gemcitabine arm. Also in comparison to the myelotoxicity previously reported for single agent Abraxane an increase of haematologic AE was reported for Abraxane/gemcitabine. In comparison to the gemcitabine arm, more patients in the Abraxane/gemcitabine arm received G-CSF. Also erythropoietins, blood transfusion and blood products were more frequently used for patients treated with Abraxane/gemcitabine than for patients treated with gemcitabine. The time to start with G-CSF treatment was not significantly different for the two treatment arms (1.22 months in the Abraxane/gemcitabine arm and 0.95 months in the gemcitabine arm). Dose modifications for neutropenia and/or thrombocytopenia or other identified adverse reactions in the start of a cycle or within a cycle of treatment are described under section 4.2 in the SmPC.

The death incidence due to AEs was similar for both treatment groups (4% each). Fatal events that occurred more frequently in the Abraxane/gemcitabine arm than in the gemcitabine arm included sepsis and pneumonitis.

Pneumonitis was reported as SAEs for 3% in patients treated with Abraxane/gemcitabine and 1% in patients treated with gemcitabine. Two patients in the Abraxane/gemcitabine arm died due to pneumonitis. Hence, Protocol Amendment 6 (12 December 2011) was implemented which gave measures intended to limit the incidence of interstitial pneumonitis through guidance regarding careful pre-study screening, continuous on-study monitoring for signs and symptoms of pneumonitis and, if observed, timely institution of appropriate management. Also, patients with a history of slowly progressive dyspnoea and unproductive cough, or of conditions such as sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies was not to be enrolled into the study. No pneumonitis events were reported among the 53 patients (25 in the Abraxane/gemcitabine arm and 28 in the gemcitabine arm) enrolled after implementation of Amendment 6. Recommendations for careful screening, monitoring for signs and symptoms of pneumonitis and appropriate management information are included in section 4.4 of the SmPC.

Sepsis (all grade 3 or higher and reported as SAE) was reported for 5% of patients in the Abraxane/gemcitabine arm and 2% of patients in the gemcitabine arm. Five patients in the Abraxane/gemcitabine arm died due to sepsis. During the study additional guidance for monitoring for signs and symptoms of sepsis and appropriate management were provided. Also guidance regarding the early detection and management of sepsis are included in the SmPC.

The incidence of peripheral neuropathy was in accordance with the known occurrence of peripheral neuropathy due to Abraxane treatment. However, the frequency of Grade 3 peripheral neuropathy was considered high in comparison to which was previously reported. Guidance of management including treatment discontinuation is provided in the SmPC.

Generally the risk on AEs was similar for different subgroups (female/ male, geographic area). However, the risk on a fatal event was substantially higher for patients above the age of 75 years than for patients younger than 75 years. Moreover, the Abraxane/gemcitabine combination therapy was less well tolerated in this patients group. Especially the increased incidence of dehydration was a concern, because it was also associated with increased incidence of SAE, dose delays and dose reductions. According to the MAH the increased risk can be managed by monitoring the gastrointestinal loss, balancing fluid intake and fluid and electrolyte replacement as necessary. However, fluid replacements are less well tolerated by elderly. These measures are time- and labour-consuming especially in the last phase of life and must be balanced against the obtained benefit. Although, it is acknowledged that chronological age alone is not a suitable predictor of patients' ability to benefit from or tolerate chemotherapy, the use of Abraxane/gemcitabine for the treatment of patients ≥75 years of age, should be carefully considered having regard to the individual ability to tolerate Abraxane in combination with gemcitabine.

Lack of data in patients with renal or hepatic impairment was already reflected in the SmPC in the form of insufficient information to support relevant posology recommendations and relevant warnings against treating with Abraxane patients with severe hepatic impairment and treating with caution patients with mild or moderate hepatic impairment. Moreover, use in patients with hepatic impairment is considered an important potential risk and use in patients with renal impairment considered as missing information in the SmPC.

Regarding drug interactions, clinical and preclinical studies have sufficiently shown that paclitaxel and gemcitabine did not affect each other plasma pharmacokinetics to a significant extent and a clinical interaction study between Abraxane and gemcitabine was not considered necessary.

2.5.3. Conclusions on clinical safety

Combined treatment of Abraxane/gemcitabine induced mostly AEs known to be associated with gemcitabine and/or Abraxane monotherapy but at higher frequencies. Even though the higher rates of AEs are of concern in a palliative setting, the majority of the AEs may be considered manageable. Overall, all safety data indicated that the efficacy benefit of Abraxane/gemcitabine was accompanied with an increase toxicity profile in comparison to gemcitabine alone. Especially an increased myelotoxicity and incidence of sepsis, pneumonitis and pheripheral neuropathy was seen. For patients above the age of 75 years an additional the risk was reported. Dose modifications in case of neutropenia / thrombocytopenia, febrile neutropenia, peripheral neuropathy, cutaneous toxicity, gastrointestinal toxicity were included in the SmPC. A warning for the combined use of Abraxane and gemcitabine in patients ≥75 years of age was also included in the SmPC.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 6 January 2014.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

The RMP version 13.0 dated 16 August 2013 is acceptable. However, in the next RMP update the MAH should address some points as mentioned below.

No conditions or restrictions are required with regard to safety and efficacy for use of Abraxane in this additional indication once approved.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Table 23: Summary of safety concerns

Important Identified Risks:	– Myelosuppression (Neutropenia, anemia and thrombocytopenia) – Peripheral neuropathy – Cranial nerve palsies – Hypersensitivity reactions – Pneumonitis – Sepsis – Gastrointestinal events – Myalgia and arthralgia – Cardiotoxicity – Cystoid macular edema – Stevens-Johnson syndrome/toxic epidermal necrolysis – Infusion site reactions/extravasation – Safety in patients older than 75 years
Important Potential Risks:	– Hepatic toxicity (drug-induced liver injury) – Acute renal failure and hemolytic-uremic syndrome – Use in patients with hepatic impairment – Concomitant therapy and interactions requiring dose adjustments – Medication errors – Off-label use
Missing Information:	<u>Special Populations</u> – Patients with impaired renal function – Patients with central nervous system metastases – Children <u>Other Missing Information</u> – Reproductive toxicity – Genotoxicity long-term effect

Having considered the data in the safety specification, the PRAC considered that all relevant safety concerns are adequately addressed.

Pharmacovigilance plans

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product and to monitor the effectiveness of the risk minimisation measures. No studies as additional pharmacovigilance activities are considered necessary.

Risk minimisation measures

Table 24: Summary table of risk minimisation measures

Safety Concern	Proposed Routine Risk Minimization Measures	Proposed Additional Risk Minimization Measures
Identified Risks		
Myelosuppression	SmPC Sections 4.2 and 4.4 contain advice for dose reductions in the event of neutropenia for both ABRAXANE monotherapy and ABRAXANE in combination with gemcitabine. Neutropenia, anemia, thrombocytopenia and bone marrow suppression are labeled in Section 4.8.	None proposed
Peripheral Neuropathy	Dose delays and adjustments are recommended in the SmPC Sections 4.2 and 4.4 for patients experiencing neuropathy and neurotoxicity is labeled in Section 4.8.	None proposed
Cranial Nerve Palsies	Labeled in Section 4.8 of the SmPC	None proposed
Hypersensitivity Reactions	Hypersensitivity to the active substance or to any of the excipients is a contraindication (SmPC, Section 4.3) Labeled in Section 4.8 of the SmPC. Section 4.4 of the SmPC includes reference to fatal hypersensitivity reactions.	None proposed
Pneumonitis	A warning has been included in Section 4.4 of the SmPC to monitor for signs and symptoms of pneumonitis. Pneumonitis is currently labeled in Section 4.8 of the SmPC. This is a well-described toxicity in the literature seen when paclitaxel is combined with gemcitabine, and the rates seen in patients receiving ABRAXANE plus gemcitabine appear to be consistent with those described in the literature seen with paclitaxel and gemcitabine combination therapy.	None proposed
Sepsis	A warning has been included in Section 4.4 of the SmPC including instructions that if a patient becomes febrile, treatment with broad spectrum antibiotics should be initiated. Dosing advice in the case of febrile neutropenia is also provided. Sepsis is labeled in Section 4.8 of the SmPC.	None proposed
Gastrointestinal Events	Warning in Section 4.4 and labeled in Section 4.8 of the SmPC	None proposed
Myalgia and Arthralgia	Labeled in Section 4.8 of the SmPC	None proposed
Cardiotoxicity	Section 4.4 of the SmPC includes a warning of congestive heart failure and left ventricular dysfunction, and provides advice for monitoring for the occurrence of cardiac events.	None proposed
Cystoid Macular Edema	Labeled in Section 4.8 of the SmPC. Rare reports of reduced visual acuity due to CME and advice on diagnosis included in Section 4.8 of the SmPC.	None proposed
Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis	Labeled in Section 4.8 of the SmPC	None proposed
Infusion Site Reactions/ Extravasation	Labeled in Section 4.8 of the SmPC	None proposed
Safety in Patients	Dosing advice and warning in Section 4.2 and Section 4.4 of	None proposed

Sepsis	A warning has been included in Section 4.4 of the SmPC including instructions that if a patient becomes febrile, treatment with broad spectrum antibiotics should be initiated. Dosing advice in the case of febrile neutropenia is also provided. Sepsis is labeled in Section 4.8 of the SmPC.	None proposed
Gastrointestinal Events	Warning in Section 4.4 and labeled in Section 4.8 of the SmPC	None proposed
Myalgia and Arthralgia	Labeled in Section 4.8 of the SmPC	None proposed
Cardiotoxicity	Section 4.4 of the SmPC includes a warning of congestive heart failure and left ventricular dysfunction, and provides advice for monitoring for the occurrence of cardiac events.	None proposed
Cystoid Macular Edema	Labeled in Section 4.8 of the SmPC. Rare reports of reduced visual acuity due to CME and advice on diagnosis included in Section 4.8 of the SmPC.	None proposed
Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis	Labeled in Section 4.8 of the SmPC	None proposed
Infusion Site Reactions/ Extravasation	Labeled in Section 4.8 of the SmPC	None proposed
Safety in Patients Older Than 75 Years	Dosing advice and warning in Section 4.2 and Section 4.4 of the SmPC.	None proposed
Potential Risks		
Hepatic Toxicity (Drug-induced Liver Injury)	Increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma glutamyltransferase, increased blood alkaline phosphatase and increased bilirubin are labeled in Section 4.8 of the SmPC.	None proposed
Acute Renal Failure and Hemolytic-uremic Syndrome	Increased blood creatinine is labeled in Section 4.8 of the SmPC.	None proposed
Use in Patients with Hepatic Impairment	Section 4.2 of the SmPC advises that insufficient data are available to recommend dose modifications for patients with mild to moderate hepatic impairment and that patients with severe hepatic impairment should not be treated with paclitaxel. Sections 4.4 of the SmPC includes warnings that the toxicity of paclitaxel can be increased with hepatic impairment.	None proposed
Concomitant Therapy and Interactions Requiring Dose Adjustments	Section 4.5 of the SmPC provides details of potential interactions with other medicinal products.	None proposed
Medication Errors	The potential for medication errors is subject to routine risk minimization.	None proposed
Off-label Use	The potential for off-label use and concomitant therapy is subject to routine risk minimization.	None proposed
Missing Information		
Patients with Impaired Renal Function	The potential for use in patients with impaired renal function is subject to routine pharmacovigilance. Section 4.2 of the SmPC advises that insufficient data are available to recommend dose modifications for patients with renal impairment.	None proposed
Patients with Central Nervous System Metastases	The potential for use in patients with CNS metastases is subject to routine pharmacovigilance. Section 4.4 of the SmPC includes a warning that the efficacy and safety of ABRAXANE in patients with CNS metastases has not been established.	None proposed

Safety Concern	Proposed Routine Risk Minimization Measures	Proposed Additional Risk Minimization Measures
Missing Information		
Patients with Impaired Renal Function	The potential for use in patients with impaired renal function is subject to routine pharmacovigilance. Section 4.2 of the SmPC advises that insufficient data are available to recommend dose modifications for patients with renal impairment.	None proposed
Patients with Central Nervous System Metastases	The potential for use in patients with CNS metastases is subject to routine pharmacovigilance. Section 4.4 of the SmPC includes a warning that the efficacy and safety of ABRAXANE in patients with CNS metastases has not been established.	None proposed
Children	The potential for use in children is subject to routine pharmacovigilance. Section 4.2 of the SmPC advises that the safety and efficacy of ABRAXANE in children and adolescents aged 0-17 years has not yet been established.	None proposed
Reproductive Toxicity	Section 4.6 of the SmPC provides information on the reproductive toxicity of paclitaxel, and includes a warning on the use of ABRAXANE in pregnancy, breast-feeding, and in women of childbearing potential not using effective contraception, as well as the effect on male fertility.	None proposed
Genotoxicity Long-term Effect	Section 5.3 of the SmPC includes information on the carcinogenic and genotoxic potential of paclitaxel.	None proposed

No additional risk minimisation measures are considered necessary beyond the Product Information.

In the next RMP update the MAH should address the points as provided below:

- Table 43 of the currently submitted updated RMP (part II – Module SVII) needs to be updated. It currently includes information on the postmarketing cases reporting an adverse event of special interest (i.e. myeolosuppression, clinically severe infections (assessor NOS), dehydration) with a fatal outcome summarized by age group age < 65 years, versus age > 65 years versus age unknown. This postmarketing information lacks the requested distinction concerning age groups, i.e. < 75 years of age versus age > 75 years of age. Also the case reports with fatal outcome in the clinical trials that concern the elderly > 75 years of age versus case reports < 75 years of age with fatal outcome in the clinical trials with further specification on the administered therapy (abraxane monotherapy, abraxane in combination with gemcitabine, otherwise) are still missing.
- In part II – Module SVII of the updated RMP the MAH added detailed information on the dosing modifications at the identified risk 'Myeolosuppression' in line with MAH's currently SmPC-proposal. As of next RMP-update the MAH is requested to include a more general reference to the appropriate section of the SmPC valid at that date instead of a copy of the literal text of the SmPC to limit the number of RMP-updates in future in case of SmPC-updates.
- Part VI of the RMP (Summary for the public) should be amended to include the risks on anaemia and thrombocytopenia. Currently from the risk on bone marrow suppression only the risk on neutropenia and leukopenia is addressed.

In the next PSUR the MAH should address the following points:

- The MAH should ensure to closely monitor all reported adverse events in patients > 75 years of age and review and discuss these in PSURs, and not limit the review in the PSURs to the MedDRA terms as mentioned in this table 43 of the RMP version 13.0.
- The MAH should submit a detailed review and discussion on all reported cases of acute renal failure and haemolytic-uremic syndrome (HUS) received in the clinical trials of Abraxane monotherapy, as well as received post-marketing. If appropriate section 4.8 (undesirable effects) of the proposed SmPC should be amended to include acute renal failure and haemolytic-uremic syndrome (HUS) as an ADR of Abraxane *in general* instead of the current proposal to only include these ADRs applicable for the combination Abraxane/gemcitabine.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated. Specifically, the following indication was agreed:

Abraxane in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas,

i.e. the indication was restricted to patients with metastatic disease as discussion previously.

Moreover, posology recommendations and information on dose adjustments in patients with pancreatic adenocarcinoma were added to section 4.2. Information on patients 75 years and older was added to the same section, as well as a relevant warning in section 4.4 of the SmPC.

In the same section, warnings on neuropathy and pneumonitis were amended and, particularly, new warnings on sepsis, patients with normal CA19-9 at baseline and co-administration with erlotinib (as well as patients 75 years and older) were added.

Section 4.5 was amended to inform of the absence of expected or shown interactions between Abraxane and gemcitabine. Finally, sections 4.8 and 5.1 were amended to include information on adverse drug reactions expected from the combination of Abraxane and gemcitabine in pancreatic cancer patients and with information from the pivotal trial, respectively.

The Package Leaflet was amended accordingly.

In addition, the MAH took the opportunity to make minor editorial amendments to sections 2, 4.2, 4.3, 4.4, 4.8, 5.1, 5.2 and 7 of the SmPC, to the Annex II, Labelling and Package Leaflet.

No user consultation with target patient groups on the package leaflet has been performed on the following grounds:

- No significant changes to the design and layout from the approved package leaflet were

proposed;

- No significant changes to the key messages for safe use of the product are proposed.

The justification submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

Benefits

The median OS of patients treated with Abraxane/gemcitabine proved to be significantly longer than for patients treated with gemcitabine alone (8.5 months vs 6.7 months respectively, resulting in a HRA+G/G of 0.72 [95%CI 0.671, 0.835]). Also a prolongation of 1.8 months in median PFS was observed for Abraxane/gemcitabine treatment in comparison to gemcitabine alone (5.5 vs 3.7 months respectively, resulting in a HRA+G/G of 0.69 [95% CI 0.581, 0.821]). Furthermore, the percentage of ITT patients with a confirmed BOR (CR + PR) was significantly higher for the Abraxane/gemcitabine arm than for the gemcitabine arm (23% vs 7%, p<0.0001).

The results of most other secondary endpoints (such as change in target lesion diameter, disease control rate, time to treatment failure) were in line with the results of the primary endpoint. The remaining secondary endpoints at least exclude a diminished efficacy of Abraxane/gemcitabine in comparison to gemcitabine alone.

The increase of OS, PFS and response rate was consistently found in most of the pre-specified subgroup analyses.

Uncertainty in the knowledge about the beneficial effects

The increase of OS, PFS and response rate was consistently found in most of the pre-specified subgroups. Only for patients with an age of 75 years and older, the $HR_{A+G/G}$ was not in favour of the combination therapy (HR=1.08). Although an imbalance in baseline characteristics between the Abraxane/gemcitabine arm and the gemcitabine arm was reported for these patients, it was considered that a beneficial effect of combination treatment in comparison to gemcitabine monotherapy was not obviously demonstrated. This was reflected in the SmPC and caution before use in these patients was recommended.

Furthermore, the $HR_{A+G/G}$, for patients with normal CA19-9 level at baseline was 1.07, thereby no benefit in terms of overall survival for this subgroup of patients was demonstrated. This result could not be explained by a clear imbalance in post study treatment or baseline characteristics between the study arms, which would adversely affect the Abraxane/gemcitabine arm. Although only a limited number of patients with normal CA19-9 levels were included in the study, the lack of data indicating a clear benefit for Abraxane/gemcitabine treatment in terms of prolonged overall survival in patients with normal CA19-9 levels prior to treatment start was reflected in the SmPC.

Both in the primary OS and in the PFS analysis a large percentage of patients were censored for the Abraxane/gemcitabine arm (23% and 36%, respectively). Some clustering of censoring occured around the median for OS which could have affected the results. However, additional sensitivity and conservative analyses confirmed the positive results for the combination treatment seen in the primary analysis, thus addressing this concern.

Risks

Unfavourable effects

Combined treatment of Abraxane/gemcitabine induced AEs known to be associated with gemcitabine and/or Abraxane monotherapy, but at higher frequencies. The most common AEs in the combination arm of pivotal Study CA046 were fatigue (59%), nausea (54%), peripheral neuropathy SMQ (54 %) and alopecia (50%).

Grade 3 or higher TEAEs were frequent in both the Abraxane/gemcitabine arm (89 %) and the gemcitabine arm (75 %) of the pivotal study, the most frequent being neutropenia (33% vs. 21%), fatigue (18% vs. 9%), peripheral neuropathy SMQ (17 % vs. 1%), thrombocytopenia (13% vs. 8%) and anaemia (12% vs. 8%).

SAEs were more common in the Abraxane/gemcitabine arm (50%) than in the gemcitabine arm (43%) of pivotal Study CA046. The SAEs that occurred at ≥2% higher frequency in the Abraxane/gemcitabine arm than in the gemcitabine arm were pyrexia (6% vs. 2%) and febrile neutropenia (3% vs. <1%).

Several adverse events of interest (AEoI) in pivotal Study CA046 were observed at higher frequencies in the Abraxane/gemcitabine arm than in the gemcitabine arm; of particular importance were gastrointestinal AEs (73% vs. 62%), myelosuppression (66% vs. 59%), sepsis (5% vs. 2%), pneumonitis (4% vs. 1%) and peripheral neuropathy (54% vs. 13%). Other AEoI were reported at comparable levels, i.e. cardiotoxicity (5% vs.4%), hepatotoxicity (26% vs. 26%) and renal toxicity (6% vs. 6%), and hence, appeared not to represent additional safety concerns.

Death rates due to SAEs were similar in both treatment arms (4%). However, more subjects died due to treatment related SAE in the Abraxane/gemcitabine arm (n=7) than in the gemcitabine arm (n=2). In the Abraxane/gemcitabine arm 3/7 deaths were due to sepsis and 2/7 due to pneumonitis.

In the Abraxane/gemcitabine arm of pivotal Study CA046 a substantially higher frequency of SAEs was observed in patients ≥75 years (75%) than in those <75 years (48%). In contrary, in the gemcitabine arm SAEs were observed at comparable levels for patients ≥75 years (48%) and <75 years (42%).

Uncertainty in the knowledge about the unfavourable effects

Co-administration of Abraxane and gemcitabine induced more AEs than gemcitabine monotherapy. This was reflected in a higher frequency of dose reductions in the Abraxane/gemcitabine arm (38% for Abraxane and 44% for gemcitabine) than in the gemcitabine arm (31%). In addition, study drug discontinuation was more frequent in the Abraxane/gemcitabine arm (35% for Abraxane and 30% for gemcitabine) than in the gemcitabine arm (24%). On the other hand, in the pivotal Study CA046 the mean duration of treatment was longer in the Abraxane/gemcitabine arm (145.9 days) than in the gemcitabine arm (111.6 days). Likewise, the mean number of cycles administered was higher in the Abraxane/gemcitabine arm (4.4 cycles) than in the gemcitabine arm (3.3 cycles). The unequal treatment durations might have subsequently affected the level of TEAEs reported in the two treatment arms, which could bring uncertainties as to the actual difference in safety profiles between the two treatments. However, this uncertainty was not considered to significantly affect the safety results and the confidence in the conclusions made from them.

The safety profile of Abraxane/gemcitabine was of concern in older patients. Due to the higher frequencies of SAEs observed in patients ≥75 years receiving Abraxane/gemcitabine, the appropriateness of treatment in this subgroup is questionable. Moreover, only a small number of patients ≥75 years [Abraxane/gemcitabine arm (n=40), gemcitabine arm (n=44)] was included in the pivotal Study CA046, bringing additional uncertainty to the safety profile in this subgroup. Relevant posology recommendations and warnings have been included in sections 4.2 and 4.4 of the SmPC, respectively.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Single agent gemcitabine is the current standard of care, but the pivotal study CA046 indicated that the addition of Abraxane to gemcitabine can improve OS with 1.8 months in patients with metastatic pancreas carcinoma. This benefit was supported by several sensitivity analyses and secondary endpoints and it is considered clinically relevant.

Overall, all safety data indicated that the efficacy benefit of Abraxane/gemcitabine is accompanied with increased toxicity in comparison to gemcitabine alone. Particularly, increased myelotoxicity and incidence of sepsis, pneumonitis and peripheral neuropathy was seen, as is known to occur during treatment with Abraxane in other indications.

Benefit-risk balance

The benefit-risk balance of Abraxane in combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas is positive.

Discussion on the Benefit-Risk Balance

The prognosis for patients with advanced adenocarcinoma who are ineligible for surgery, including those with advanced or metastatic disease is poor, and the range of available treatment options is limited. Gemcitabine has been the standard drug therapy for first line treatment of pancreatic adenocarcinoma. Although gemcitabine was well tolerated, median OS remained less than 6 months in metastatic pancreatic cancer patients. Other chemotherapy combinations failed to achieve improvement in OS over three weeks or were accompanied by increased toxicity, limiting the number of patients that can actually use these therapy regimens. A new chemotherapy regimen showing substantial improvement in OS with acceptable toxicity would therefore be of benefit to patients with advanced adenocarcinoma of the pancreas.

The benefit of the Abraxane/gemcitabine treatment in comparison to the gemcitabine monotherapy in patients with metastatic pancreatic cancer is considered clinically relevant and of significant benefit to a patient population with generally very short OS and for whom only few treatment options are available.

As expected on the basis of its safety profile, the increase of toxicity by adding Abraxane to gemcitabine is substantial, by which treatment is only feasible for patients with a good performance status and good prognosis. However, the AEs including the serious AEs due to Abraxane/gemcitabine treatment were generally well manageable with dose reductions, delays, treatment discontinuation and/or supportive care.

Thus, in general the benefit/risk balance is considered positive but the use of Abraxane in metastatic pancreatic adenocarcinoma patients above the age of 75 should be carefully considered taken into account the individual patient characteristics and additional risk factors. Moreover, no clear benefit in terms of prolonged overall survival has been demonstrated in patients with normal CA19-9 levels prior to treatment start. These uncertainties and warnings were reflected in the SmPC.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of Indication to include new indication for Abraxane in combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas

As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated in order to: provide posology recommendations and dose adjustment information, add warnings on sepsis, co-administration with erlotinib, patients with normal CA19-9 at baseline and patients 75 years and older, amend existing warnings on neuropathy and pneumonitis, inform of the absence of expected or shown interactions between Abraxane and gemcitabine, include information on adverse drug reactions expected from the combination of Abraxane and gemcitabine in pancreatic cancer patients and include information from the pivotal trial to the SmPC. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to make minor editorial amendments throughout the Product Information.

The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Additional data exclusivity / market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

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