22 January 2015
EMA/76768/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Abraxane

International non-proprietary name: PACLITAXEL

Procedure No. EMEA/H/C/000778/II/0067

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

AE	Adverse event
ALK	Anaplastic large-cell lymphoma kinase
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
AUCinf	Area under the curve extrapolated to infinite time
β-hCG	β-subunit of human chorionic gonadotropin
BSA	Body surface area
Cav-1	Caveolin-1
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance
Cmax	Maximum plasma concentration of drug
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DEHP	Di(2-ethylhexyl) phthalate
DLT	Dose-limiting toxicity DMC Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EML4	Echinoderm microtubule-associated protein-like 4
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End-of-study
ERα	Estrogen receptor alpha
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
GalNAc-T	Alpha-N-acetylgalactosaminyltransferase
G-CSF	Granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
Ha	Alternative hypothesis
HER-2	Human epidermal growth factor receptor-2
Hgb	Hemoglobin
Ho	Null hypothesis
HR	Hazard ratio
HRA/T	Hazard ratio of Abraxane/carboplatin to Taxol/carboplatin
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board

ITT	Intent-to-treat
IV	Intravenous
IVR	Interactive voice response
KM	Kaplan-Meier
K-ras	Kirsten rat sarcoma
LD	Longest diameter
LLN	Lower limit of normal
MAGE-A3	Melanoma-associated antigen 3
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NA	Not applicable
NCI	National Cancer Institute
ND	Not done
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
pA	Abraxane/carboplatin response rate
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
pT	Taxol/carboplatin response rate
RARβ2	Retinoic acid receptor beta 2
RECIST	Response Evaluation Criteria in Solid Tumors
RI	Reconstruction interval
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SEM	Standard error of the mean
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SLD	Sum of the longest diameter
SMQ	Standardized MedDRA query
SPARC	Secreted protein, acidic and rich in cysteine
t1/2	Half-life
TEAE	Treatment-emergent adverse event
TTP	Time to tumour progression
UE	Unable to evaluate
ULN	Upper limit of normal
USP	United States Pharmacopeia
Vz	Volume of distribution
WBC	White blood cell (count)
WHO Drug	World Health Organization Drug

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 6 June 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product: **For presentations: See Annex A**	**International non-proprietary name:**
Abraxane	PACLITAXEL

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	Type II	I and IIIB

Extension of Indication to add a new indication for Abraxane in combination with carboplatin for the first-line treatment of non-small cell lung cancer (NSCLC) in adult patients who are not candidates for potentially curative surgery and/or radiation therapy. Consequently the MAH proposed to update sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC and to update the Package Leaflet accordingly. Further, an updated RMP version 14.0 was provided as part of the application.

The variation proposed amendments to the Summary of Product Characteristics 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.

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

Timetable	
Submission date	06 June 2014
Start of procedure:	27 June 2014
CHMP CoRapporteur Assessment Report	18 August 2014
CHMP Rapporteur Assessment Report	19 August 2014
PRAC Rapporteur Assessment Report	21 August 2014
Committees comments on PRAC Rapp Advice	01 September 2014
PRAC Rapporteur Updated Assessment Report	05 September 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	11 September 2014
CHMP comments	15 September 2014
Rapporteur Revised Assessment Report	19 September 2014
Request for supplementary information (RSI)	25 September 2014
CHMP Rapporteur joint response Assessment Report	22 December 2014
CHMP Rapporteur amended joint response Assessment Report	24 December 2014
PRAC Rapporteur response Assessment Report	15 December 2014
Committees comments on PRAC Rapp Advice	05 January 2015
PRAC Rapporteur Updated Assessment Report	N/A
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	09 January 2015
CHMP comments	12 January 2015
CHMP Rapporteur updated joint response Assessment Report	15 January 2015
CHMP Rapporteur updated joint response Assessment Report	19 January 2015
Opinion	22 January 2015

2. Scientific discussion

2.1. Introduction

Problem statement

Lung cancer is the leading cause of cancer-related deaths (men and women) worldwide, with 1.8 million new case diagnosed each year (World Health Organization, 2012[1]). Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 80% to 85% of all new cases, which account for about 1.6 million deaths worldwide, each year. The most important risk factor for lung cancer is tobacco use.

The majority of patients are not diagnosed until the tumour has progressed beyond the primary site. Despite recent advances in identifying optimal chemotherapy regimens, patients with advanced NSCLC continue to have a poor prognosis. Only 10% to 15% of those treated are still alive 2 years after diagnosis.

Treatment of patients with lung cancer depends upon the subtype (NSCLC versus small cell lung cancer), histology (adenocarcinoma vs squamous cell carcinoma), tumour stage, molecular characteristics (e.g. mutation status of EGFR, ALK, RAS1 etc.), and an assessment of the patients' overall medical condition. Patients with stage I, II, or III [according to the Union for International Cancer Control, Version 7 (UICC 7)] NSCLC are generally treated with curative intent using surgery, chemotherapy, radiation therapy, or a combined modality approach. Systemic chemotherapy is generally indicated for patients who present metastatic (stage IV) disease. Palliative systemic chemotherapy is also used for patients who have relapsed with advanced disease following prior definitive treatment.

In the EU, the standard first line chemotherapy is a platinum-based doublet chemotherapy. Third generation regimens including gemcitabine and taxanes could be used. Pemetrexed is also a treatment of choice in first line non-squamous NSCLC[2].

About the product

Abraxane (ABI-007) nanoparticle albumin-bound contains paclitaxel as active cytotoxic substance, and is indicated as a single agent, 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 and in the adjuvant setting. The approved dosing is 260 mg/m^2 given intravenously over 30 minutes every 3 weeks. At the end 2013 the indication of Abraxane was extended in combination with gemcitabine for first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. The approved dosage for this indication is 125 mg/m^2 administered intravenously over 30 minutes on days 1, 8 and 15 of each 28-day cycle.

Abraxane was developed to improve the therapeutic index of paclitaxel by providing an alternative formulation free of ethanol and of the toxic solvent Cremophor-EL, two substances associated with severe hypersensitivity reactions.

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. This stability results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

[1] World Health Organization. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012.
[2] Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol (2014) 25 (suppl 3): iii27-iii39.

Pharmacological classification (ATC-code): L01CD01

The first marketing authorization for paclitaxel albumin was granted on 7 January 2005 in the USA. The initial European Union (EU) marketing authorization (EU/1/07/428/001-002) for Abraxane was granted on 11 January 2008.

This application concerns a type II variation (C.I.6) for the following extension of the indication: "*Abraxane in combination with carboplatin is indicated for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy".*

2.2. Non-clinical aspects

2.2.1. Ecotoxicity / environmental risk assessment

The applicant has submitted an updated ERA summarised in the table below.

Table 1 Summary of main study results

Substance (INN / Invented Name): paclitaxel / Abraxane			
CAS-number: 33069-62-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.31	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.31	not B
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.011	µg/L	> 0.01 threshold (Y)

As the total $PEC_{SURFACEWATER}$ is above the action limit of 0.01 µg/L, a Phase II environmental fate and effects analysis is triggered and has been initiated by the MAH.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of paclitaxel to the environment.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation:

- Conduct a phase II assessment including a refinement of Fpen.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

- Tabular overview of clinical studies

Study ID	No. of study centres /locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary efficacy Endpoint
CA031	102 sites: 29 Russia, 25 US, 21 Japan, 16 Ukraine 6 Canada And 5 Australia	Phase 3 multicentre, controlled randomized open-label, superiority study, included optional space PK study. Randomization is stratified by disease stage, age, gender histology geographic region	Treatment Arm A (Abraxane/carboplatin): 100 mg/m^2 Abraxane given IV once per week. carboplatin was administered after Abraxane on day 1 only of each cycle repeated every 3 weeks. Treatment Arm B (Taxol/carboplatin): Taxol 200 mg/m^2 given IV with standard premedication followed by carboplatin. Cycles were repeated every 3 weeks with both drugs given on day 1 of each cycle.	Compare ORR in Abraxane/carboplatin versus Taxol/carboplatin as first line therapy in patients with advanced NSCLC. Main secondary objective was to compare the toxicity.	arm A Abraxane/carboplatin n= 521 arm B Taxol/carboplatin n=531	Treatment was continued in absence of disease progression, development of an unacceptable toxicity, or withdrawal of consent	75% M/ 25% F 60 yrs (24-84 yrs) 81% White; 2% Black: 15% Asian: 2% other	Histologically/cytologically confirmed NSCLC stage IIIb/IV disease Patients with active brain metastases were ineligible (prior evidence of metastasis was permitted only if it was treated and stable ≥ 1 months after treatment.	ORR Main secondary endpoints: PFS and OS
CA028	13 sites Russia	Phase 2 open-label dose-escalating study	Weekly or every 3 weeks Abraxane + carboplatin on day 1 of a 3 weeks cycle Dosing Abraxane every 3 weeks: 250 mg/m^2-340mg/m^2 Weekly: 100 mg/m^2-140 mg/m^2	Obtain preliminary data on the anitumour activity and AEs of the Abraxane/carboplatin combination	Planned: Cohort 1 to 7 N=25/cohort Cohort 8 N=75 Actual entered N=254 Treated N=251	Continued in absence of PD and unacceptable toxicity	80% M/ 20% F 60 yrs (34-81 yrs) 100% White	Histologically/cytologically confirmed NSCLC stage IIb with pleural effusion or evidence of inoperable local recurrence or metastasis (Stage IV); with no prior therapy for metastatic disease	ORR
CA015	1 site USA	Phase 1-2 open-label dose escalating study	Abraxane 3 consecutive weeks followed by one week of rest Dose 100-175 mg/m^2 Phase 2: weekly Abraxane Dose at MTD 125 mg/m^2	Determine MTD and DLT of weekly Abraxane	Planned: Phase 1 N=15 to 24 (3 to 6/dose level) Phase 2 N=65	Continued in absence of PD and unacceptable toxicity	IV over 30 mins: 52% M/ 48% F 69.5 yrs (41-84 yrs) 76% White 14% Black 8%	Histologically/cytologically confirmed advanced (Stage IV) NSCLC; evidence of inoperable local recurrence or metastasis	ORR

					Actual: Entered: N=77 Treated: N=75		Hispanic/Latino 2% Other IV over 2 hours 44% M/ 56% F 66.0 yrs 49-83 yrs) 88% white 8% Black 4% Hispanic/Latino		
CA018	7 sites Russia	Phase 2 open-label	Abraxane 260 mg/m^2 every 3 weeks	Determine antitumor activity and evaluation safety/tolerability o Abraxane in patients with metastatic NSCLC	Entered N=43 Treated N=43	Continued in absence of PD and unacceptable toxicity	77% M/ 23% F 58 yrs 43-75 yrs) 100% white	Histologically/cytologicall y confirmed NSCLC: evidence of inoperable local recurrence or metastasis and no other malignancy	ORR
J-0100	1 site Japan	Investigation of PK in a phase 1 open-label	Abraxane 175 mg/m2, 200 mg/m2, 260 mg/m2, 300 mg/m2	Calculate PK parameters and investigate linearity with administered doses	12 subjects	The PK data were analysed after the first dose	N/A	Patients with solid tumour	PK
J-0101	1 site Japan	Investigation of PK in a phase 1 open-label	Abraxane 175 mg/m2, 200 mg/m2, 260 mg/m2, 300 mg/m2	To quantify the concentrations of the unchanged form of paclitaxel in blood and plasma and investigate linearity with administered doses	15 subjects	The PK data were analysed after the first dose	N/A	Patients with solid tumour	PK

2.3.2. Pharmacokinetics

A number of clinical studies have been conducted in order to investigate the PK of Abraxane (also known as ABI-007) in the applied indication.

Report Number (Study Code)	Description of PK Analysis	ABI-007 Dose	Study Population (Race)	Number of Patients (M/F)	Sponsor
BIO-VT-5 (CA031 sub-study)	Single-dose sparse PK, in combination with carboplatin	100 mg/m^2 Cycle 1 Day 1	NSCLC (White/Black[a])	15 (10/5)	Celgene Europe Ltd.
08DA33 (J-0103) (CA031 sub-study)	Single and multiple-dose PK Drug-drug interaction between ABI-007 and carboplatin	100 mg/m^2 Cycle 1 Days 1, 8, 15	NSCLC (Japanese)	12 (9/3)	Taiho Pharmaceutical Co., Ltd.[b]
05DA11 (J-0101)	Single ascending dose PK	80-125 mg/m^2 Cycle 1 Day 1	Advanced solid tumor (Japanese)	15 (6/9)	Taiho Pharmaceutical Co., Ltd.[b]
05DA13 (J-0100)	Single ascending dose PK	200-300 mg/m^2 Cycle 1 Day 1	Advanced solid tumor (Japanese)	12 (10/2)	Taiho Pharmaceutical Co., Ltd.[b]

F = female; M = male; NSCLC = non-small cell lung cancer; PK = pharmacokinetics.
[a] Of the 15 patients, the race categories included 14 White (Non-Hispanic) patients and 1 Black patient.
[b] Taiho Pharmaceutical Co., Ltd. is the Marketing Authorization Holder and Distributor of ABI-007 in Japan.
Source: Summary of Clinical Pharmacology

2.3.2.1. BIO-VT-5 (CA031 substudy)

The sparse PK profile of paclitaxel in European/US NSCLC patients who received the ABI-007/carboplatin combination therapy was presented in Report BIO-VT-5, the PK sub-study of study CA031.

Methods

Only those patients randomized to receive ABI-007/carboplatin treatment in Canada, Russia, Ukraine, and US had the option to participate in this PK sub-study.

ABI-007 was administered to these patients by IV infusion over 30 minutes at a dose of 100 mg/m^2. carboplatin was administered by IV infusion over 60 minutes at a dose of AUC = 6 min•mg/mL after the completion of ABI-007 infusion on Day 1. Blood samples for PK analysis were collected on Day 1 of Cycle 1 at 0.75, 4, and 24.5 hours after the start of ABI-007 infusion (i.e., at 0.25, 3.5, and 24 hours after the end of the infusion). The concentration of paclitaxel in plasma was determined by a validated liquid chromatography atmospheric pressure ionization tandem mass spectrometry method.

Results

Of the 15 NSCLC patients who provided sparse PK samples, 14 patients were White (Non- Hispanic) and one patient was Black. There were 10 males and 5 females. The mean age of these patients was 54.8 years (range: 39 to 68 years old) and mean weight was 79.4 kg (range: 53 to 125 kg).

Due to the small sample size (N = 15), the population PK analysis was not conducted; however, the non-compartmental PK analysis was attempted for each patient. Because of the limited number of sampling time points available for the non-compartmental PK analysis, the estimates of PK parameters

are considered to be unreliable (Report BIO-VT-5). Therefore, only the concentration data are summarized and reported (Table 2).

Table 2: Mean (SD) Plasma Concentration of paclitaxel in European/US NSCLC Patients Receiving ABI-007 and carboplatin

Time after the Start of ABI-007 Infusion (hour)	Plasma Paclitaxel Concentration (ng/mL)
0.75	966 (699)
4.0	96.3 (44.5)
24.5	22.6 (8.5)

SD = standard deviation.
Source: Bioanalytical Report ABRCA01A-15, Table 2.

The mean concentrations observed at 0.75 and 4 hours after the start of the infusion in European/US NSCLC patients (966 and 96.3 ng/mL, respectively) were comparable with the historical data observed in White patients with solid tumours (1117 and 91.7 ng/mL, respectively) who received the same dose of ABI-007 without concomitant carboplatin (CA005-0). The mean concentration at 4 hours was also consistent with that observed in Japanese NSCLC patients (89.1 ng/mL) who received the same ABI-007/carboplatin combination therapy (Report 08DA33).

2.3.2.2. 08DA33 (CA031 substudy)

Taiho Pharmaceutical Co., Ltd. (Taiho) was the local Sponsor of study CA031 in Japan. In a PK sub-study of study CA031, Taiho also investigated the full PK profile of paclitaxel when given to NSCLC patients as ABI-007 in the absence and presence of carboplatin. In addition, Taiho assessed the PK of plasma total and free platinum after administration of carboplatin to the patients pre-infused with ABI-007. The results obtained from this PK sub-study were presented in Report 08DA33.

Methods

This was an open-label, multicentre, single-sequence, within patient comparison, PK sub-study. ABI-007 was administered to these patients once a week (on Days 1, 8, and 15 of Cycle 1) by IV infusion over 30 minutes at a dose of 100 mg/m^2. carboplatin was administered by IV infusion over 60 minutes on Day 1 after the completion of ABI-007 infusion. The dose of carboplatin was calculated according to the Calvert formula: carboplatin dose (mg) = (Target AUC) • (GFR + 25), where GFR was the glomerular filtration rate and AUC was for the free carboplatin in plasma. In this study, GFR was replaced with the creatinine clearance estimated by the Cockcroft-Gault formula. The carboplatin dose was chosen to achieve an AUC of 6 min•mg/mL for the free carboplatin in plasma.

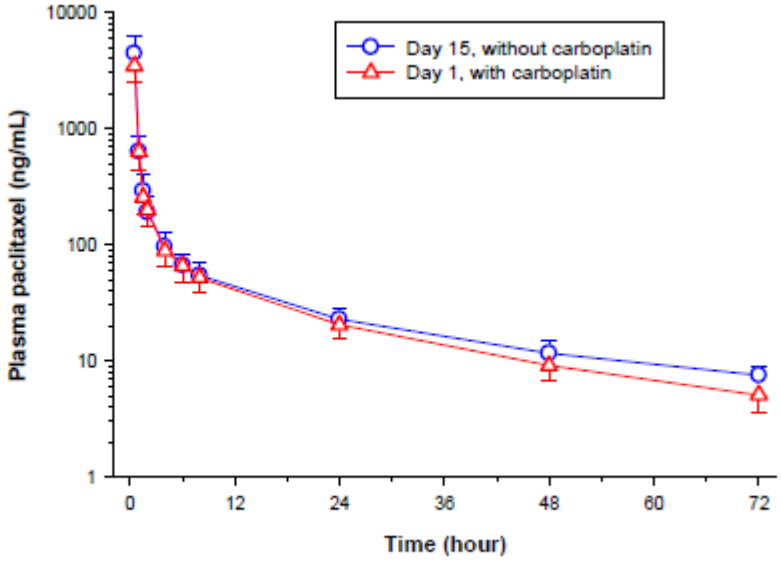
Serial sampling of blood for the determination of paclitaxel concentrations in plasma was performed for 72 hours after the start of ABI-007 infusion on Days 1 and 15. Serial sampling of blood for the determination of platinum concentration in plasma was performed for 23.5 hours after the start of carboplatin infusion on Day 1.

Results

A total of 12 Japanese NSCLC patients who met the eligibility criteria of study CA031 participated in the study. The maximum concentration (Cmax) for paclitaxel was observed immediately after the infusion, and the mean concentration subsequently declined in a multiphasic manner (Figure 1). The mean paclitaxel concentration in plasma dropped by greater than 80% within 30 minutes after cessation of the ABI-007 infusion, followed by a terminal half-life ($t_{1/2}$) of 24.2 to 29.5 hours. There was no obvious

difference in the mean concentration-time profile for plasma paclitaxel between Day 1 (first ABI-007 dose and in the presence of carboplatin) and Day 15 (third ABI-007 dose and in the absence of carboplatin) (Figure 1).

Table 3 compares the plasma paclitaxel PK parameters between Day 1 and Day 15. The mean total clearance (CL) values (21 to 25.9 L/h/m^2) on both days were within the range observed in Japanese or White patients with solid tumours (17.9 to 30.6 L/h/m^2) (05DA11 and CA005-0). The exposure levels (C_{max} and AUC) on both days were also comparable with those observed in Japanese or White patients who received the same dose of ABI-007 alone.



Source: Report 08DA33, Figure 1.1.

Figure 1: Mean (SD) Plasma Concentration of paclitaxel in Japanese NSCLC Patients Receiving ABI-007 with or without Subsequent carboplatin

Table 3: Plasma Pharmacokinetic Parameters of paclitaxel in Japanese NSCLC Patients Receiving ABI-007 with or without Subsequent carboplatin

Paclitaxel PK parameter	Day 1 ABI-007 100 mg/m^2 followed by carboplatin (AUC=6 min•mg/mL) (N = 12)	Day 15 ABI-007 100 mg/m^2 alone (N = 10)
AUC_t (h•ng/mL)	3893 (897)	4565 (1346)
AUC_∞ (h•ng/mL)	4073 (929)	5060 (1325)[a]
C_{max} (ng/mL)	3460 (905)	4443 (1827)
$t_{1/2}$ (h)	24.2 (3.02)	29.5 (3.18)[a]
CL (L/h/m^2)	25.9 (6.61)	21.0 (5.51)[a]
V_{ss} (L/m^2)	324 (108)	330 (173)[a]

AUC = area under the concentration versus time curve; AUC_t = AUC from time zero to the time for the last quantifiable concentration; AUC_∞ = AUC from time zero extrapolated to infinity; CL = total clearance; C_{max} = maximum concentration; $t_{1/2}$ = terminal half-life; V_{ss} = volume of distribution at the steady state; PK = pharmacokinetic.
Mean (SD) data are presented for all parameters.
[a] N = 9
Source: Report 08DA33, Table 4.1 and Table 4.2.

There was a statistically significant difference for AUC from time zero extrapolated to infinity (AUC∞) between the two days (Day 1 to Day 15 ratio of geometric means = 0.85, 90% confidence interval [CI] = 0.76 to 0.95, p = 0.031). However, the difference was not clinically meaningful (15% difference in geometric means for AUC∞) and the sample size was too small to exclude an artificial effect. Table 4 summarizes plasma carboplatin PK parameters derived from the plasma concentration time curve for total platinum (protein-bound plus unbound) and free platinum (protein-unbound) on the basis of a carboplatin/platinum molar ratio of 1.903. The observed mean AUC∞ for free carboplatin in plasma was 7.41 min•mg/mL, approximately 24% higher than the targeted value (6 min•mg/mL). However, the mean $t_{1/2}$ and CL for total and free carboplatin were consistent with those reported in the absence of paclitaxel (Obasaju, 1996), thereby excluding the possibility of pharmacokinetic drug-drug interactions.

Table 4: Plasma Pharmacokinetic Parameters of carboplatin in Japanese NSCLC Patients Receiving the ABI-007/carboplatin Combination Therapy

Carboplatin PK parameter	Total carboplatin (in plasma) (N = 12)	Free carboplatin (in ultrafiltered plasma) (N = 12)
AUC_∞ (min•mg/mL)[a]	10.68 (1.23)	7.41 (0.68)
$t_{1/2}$ (h)	12 (1.42)	3.97 (0.21)
CL (mL/min)	62.7 (9.77)	93.4 (16.2)

AUC = area under the concentration versus time curve; AUC_∞ = AUC from time zero extrapolated to infinity; CL = total clearance; $t_{1/2}$ = terminal half-life; PK = pharmacokinetic.
[a] The carboplatin AUC_∞ values were converted from platinum AUC_∞ values with a conversion factor of 1.903 (molecular weight of carboplatin/atomic weight of platinum = 371.25/195.08).
Mean (SD) data are presented for all parameters.
Source: Report 08DA33 Table 5.1 and Table 5.2.

2.3.2.3. 05DA11 (J-0101): Single-dose PK in Japanese Patients with Solid Tumours

Methods

A Phase 1, open label, single-centre, parallel group, dose-escalation study was conducted by Taiho in Japan to investigate the safety, tolerability, and PK after the administration of ABI-007 once a week to patients with advanced solid tumours. ABI-007 was administered at 80, 100, or 125 mg/m^2 by IV infusion over 30 minutes. Serial sampling of blood was performed for up to 72 hours after dosing on Day 1. The concentration of paclitaxel in blood and plasma was determined by a validated LC-MS/MS method.

Results

The PK of paclitaxel was determined in 15 patients after the first ABI-007 dose (Day 1).

Table 5 summarizes paclitaxel PK parameters in plasma at various dose levels of ABI-007. Mean C_{max} and AUC of paclitaxel increased as the dose of ABI-007 increased. Because of the narrow dose range, it was difficult to evaluate the dose proportionality of the systemic exposure for paclitaxel within this study. However, there was no apparent dose dependence in the mean value for $t_{1/2}$, CL, and V_{ss}, which was consistent with the linear PK. Similar results were observed for paclitaxel PK parameters in whole blood (data not shown).

Table 5: Plasma Pharmacokinetic Parameters of paclitaxel after a Single Dose of ABI-007 in Japanese Patients with Solid Tumours (80 to 125 mg/m^2)

Paclitaxel PK Parameter	Dose of ABI-007		
	80 mg/m^2 (N = 3)	100 mg/m^2 (N = 6)	125 mg/m^2 (N =6)
AUC_t (h•ng/mL)	3822 (1277)	3937 (516)	5246 (1628)
AUC_∞ (h•ng/mL)	4006 (1300)	4141 (538)	5483 (1722)
C_{max} (ng/mL)	4217 (594)	4253 (518)	5397 (1008)
$t_{1/2}$ (h)	25.2 (2.29)	26.1 (7.33)	24.6 (4.30)
CL (L/h/m^2)	21.3 (5.97)	24.5 (3.15)	24.8 (8.10)
V_{ss} (L/m^2)	267 (94.3)	311 (58.3)	280 (91.5)

AUC = area under the concentration versus time curve; AUC_t = AUC from time zero to the time for the last quantifiable concentration; AUC_∞ = AUC from time zero extrapolated to infinity; CL = total clearance; C_{max} = maximum concentration; $t_{1/2}$ = terminal half-life; V_{ss} = volume of distribution at the steady state; PK = pharmacokinetic.
Mean (SD) data are presented for all parameters.
Source: Report 05DA11, Table 8.2

2.3.2.4. 05DA13 (J-0100): Single-dose PK in Japanese Patients with Solid Tumours

Methods

A Phase 1, open-label, multicentre, parallel group, dose-escalation study was conducted by Taiho in Japan to investigate the safety, tolerability, and PK after the administration of ABI-007 to patients with advanced solid tumours once every 3 weeks. The PK of paclitaxel was determined in 12 patients after the first ABI-007 dose (Day 1). ABI-007 was administered at 200, 260, or 300 mg/m^2 by IV infusion over 30 minutes. Serial sampling of blood was performed for up to 72 hours after dosing on Day 1.

Results

Table 6 summarizes paclitaxel PK parameters in plasma at various dose levels of ABI-007. Mean C_{max} and AUC of paclitaxel increased as the dose increased. Because of the narrow dose range, it was difficult to evaluate the dose proportionality of the systemic exposure for paclitaxel within this study. Mean $t_{1/2}$ and CL appeared to decrease slightly with an increase of the ABI-007 dose from 200 to 300 mg/m^2. Similar results were observed for paclitaxel PK parameters in whole blood.

Table 6: Pharmacokinetic Parameters of paclitaxel in Plasma after a Single Dose of ABI-007 in Japanese Patients with Solid Tumours (200 to 300 mg/m^2)

Paclitaxel PK Parameter	Dose of ABI-007		
	200 mg/m^2 (N = 3)	260 mg/m^2 (N = 6)	300 mg/m^2 (N =3)
AUC_t (h•ng/mL)	8738 (2502)	13030 (2768)	15941 (1695)
AUC_∞ (h•ng/mL)	9146 (2708)	13330 (2763)	16271 (1822)
C_{max} (ng/mL)	9040 (3077)	12000 (2111)	12700 (2600)
$t_{1/2}$ (h)	29.0 (5.13)	20.8 (4.06)	19.8 (1.93)
CL (L/h/m^2)	23.1 (6.08)	20.2 (4.35)	18.6 (1.97)
V_{ss} (L/m^2)	240 (41.1)	172 (51.5)	144 (14.5)

AUC = area under the concentration versus time curve; AUC_t = AUC from time zero to the time for the last quantifiable concentration; AUC_∞ = AUC from time zero extrapolated to infinity; CL = total clearance; C_{max} = maximum concentration; $t_{1/2}$ = terminal half-life; Vss = volume of distribution at the steady state; PK = pharmacokinetic.
Mean (SD) data are presented for all parameters.
Source: Report 05DA13, Table 8.2.

2.3.2.5. Potential of Drug-Drug Interactions with carboplatin

Paclitaxel is highly bound to serum proteins (89%-98%). It is metabolized primarily in liver by cytochrome P450 (CYP) 2C8 and CYP 3A4 (Taxol prescribing information [PI]; Abraxane PI). Urinary excretion of the unchanged drug only accounted for approximately 4% of the dose (260 mg/m^2) while urinary excretion of the two metabolites, 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel, was less than 0.2% of the dose (CA012-0). In contrast, carboplatin is not bound to plasma proteins. The major route of elimination of carboplatin is renal excretion of the unchanged drug, with approximately 71% of the dose excreted in urine within 24 hours (Paraplatin PI). In addition, there have been no reports indicating that carboplatin is an inhibitor or inducer of any CYP enzymes. Thus, paclitaxel and carboplatin are not expected to interact with each other via competing for protein binding or affecting the same clearance pathways.

The pharmacokinetic drug-drug interactions between solvent-based paclitaxel (Taxol) and carboplatin were previously investigated in clinical studies (Obasaju, 1996; Belani, 1999). These studies concluded that there were no pharmacokinetic drug-drug interactions between the two compounds. Further, alteration of the infusion sequence for solvent-based paclitaxel and carboplatin did not affect the exposure of paclitaxel or the degree of neutropenia in NSCLC patients (Huizing, 1997).

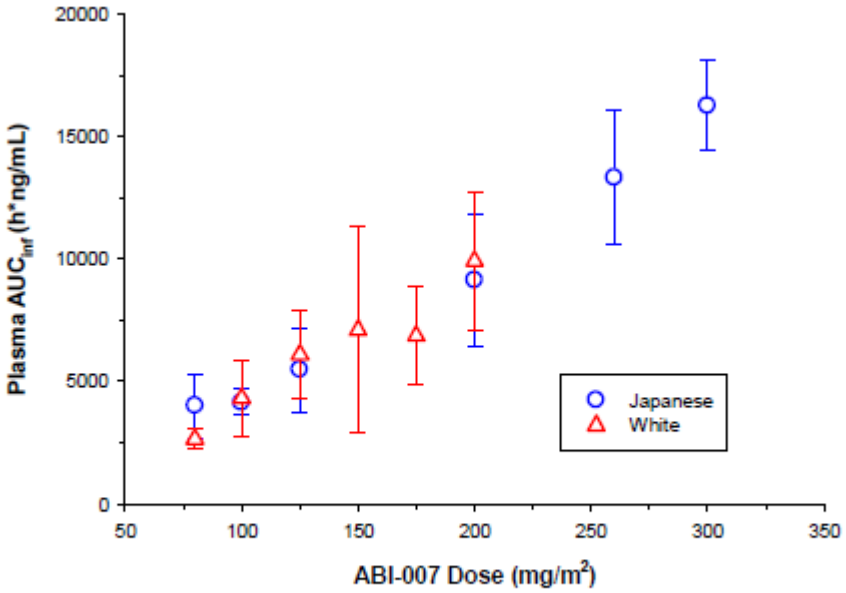
Consistent with the previously mentioned findings, pharmacokinetic drug-drug interactions were not observed between paclitaxel and carboplatin in Japanese NSCLC patients who received the ABI-007/carboplatin combination therapy (study 08DA33). In addition, alteration of the infusion sequence between ABI-007 and carboplatin did not affect the PK of paclitaxel and the nadir of the absolute neutrophil counts in US patients with solid tumours (Stinchcombe, 2007).

2.3.2.6. Relationship Between ABI-007 Dose and Plasma paclitaxel Exposure

The dose proportionality from 80 to 300 mg/m^2 in Japanese patients was explored by using the ABI-007 dose and mean plasma AUC∞ data combined from Report 05DA11 and Report 05DA13 (see Table 5 and Table 6) according to the following equation:

Ln(AUC∞) = a + b•Ln(Dose), where a = intercept and b = slope of the regression line.

The slope of Ln(AUC∞) versus Ln(Dose) was close to 1 (1.11) and the 90% CI for the slope contained 1 (0.94 to 1.28). This result indicated that an increase in ABI-007 dose resulted in approximately a proportional increase in plasma exposure from 80 to 300 mg/m^2. Similarly, plasma paclitaxel AUC∞ was approximately proportional to the dose of ABI-007 from 80 to 200 mg/m^2 in White patients (Figure 2). The plasma data at higher doses of ABI-007 (> 200 mg/m^2) were lacking in White patients. Since there was no racial difference in the PK of paclitaxel, doses of ABI-007 up to 300 mg/m^2 in White patients are not expected to depart considerably from the dose proportionality observed in Japanese patients.



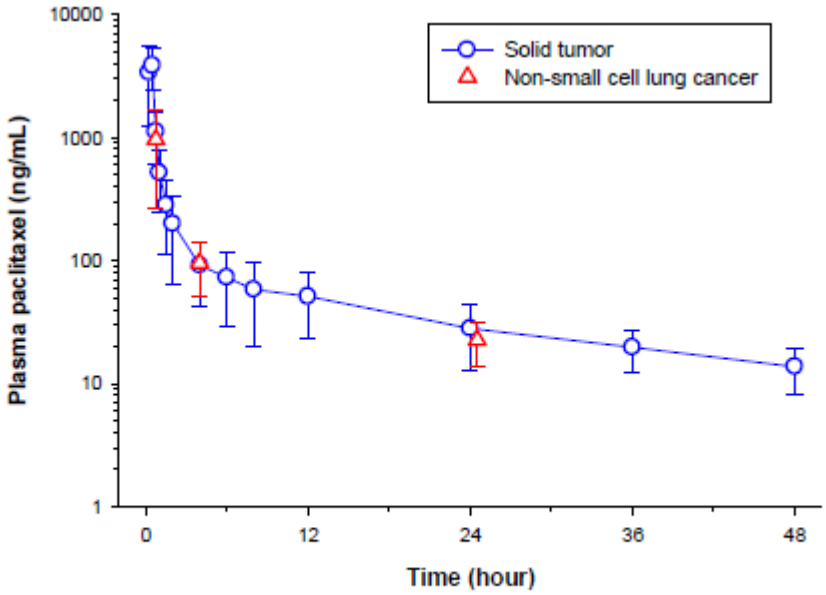
Data are from Reports 05DA11, 05DA13, DM97-123, and CA005-0. The AUC at 200 mg/m^2 for White patients is the mean of the data pooled from DM97-123 and CA005-0.

Figure 2: Relationship between Plasma paclitaxel Exposure and Dose of ABI-007

2.3.2.7. Comparison of PK between patients with solid tumours and NSCLC

Since coadministration of ABI-007 and carboplatin is not likely to result in pharmacokinetic drug-drug interactions (Section 2.3.2.5), the impact of the type of tumours on PK of paclitaxel was explored by comparing the single-dose PK data between the NSCLC studies (ABI-007/carboplatin combination) and the solid tumour studies (ABI-007 alone).

As shown in Figure 3, the mean plasma concentrations of paclitaxel at 0.75, 4, and 24.5 hours after dosing from European/US NSCLC patients who received the combination therapy of ABI-007/carboplatin (Report BIO-VT-5) were superimposed with the mean concentration-time profile from White patients with solid tumours who received the same dose of ABI-007 (100 mg/m^2) without concomitant carboplatin (CA005-0). According to this similarity, tumour type is not expected to have a significant effect on the PK parameters of paclitaxel after ABI-007 administration. The single-dose PK parameters of paclitaxel observed in Japanese NSCLC patients receiving ABI-007 in combination with carboplatin were almost identical to those in the historical data observed in Japanese solid tumour patients receiving ABI-007 alone (Table 3).



Data are from CSR CA005-0 (100 mg cohort) and Bioanalytical Report ABRCA01A-15. Except for 1 patient (Black), all patients were White.

Figure 3: Mean (SD) Plasma Concentration of paclitaxel between White Patients with Non–small Cell Lung Cancer and Solid Tumours (Cycle 1, Day 1)

2.3.2.8. Comparison of PK between Japanese and white patients

Table 7 compares the demographic data and the PK of paclitaxel between Japanese and White patients who received a single dose of ABI-007 at 100 mg/m^2. Mean plasma exposure (Cmax and AUC∞) was comparable between Japanese and White patients with solid tumours. The mean CL was almost identical between the two ethnic groups. Mean t1/2 appeared shorter in White patients with solid tumours compared with the corresponding Japanese patients (18.2 vs 26.1 hours). This difference can be explained by the different PK sampling duration between the two studies (48 vs 72 hours). Overall, these data suggested that there was no race/ethnicity-associated difference in the PK of paclitaxel after ABI-007 administration between Japanese and White patients with solid tumours.

Table 7: Comparison of single-dose PK parameters of paclitaxel in plasma between Japanese and white patients receiving ABI-007

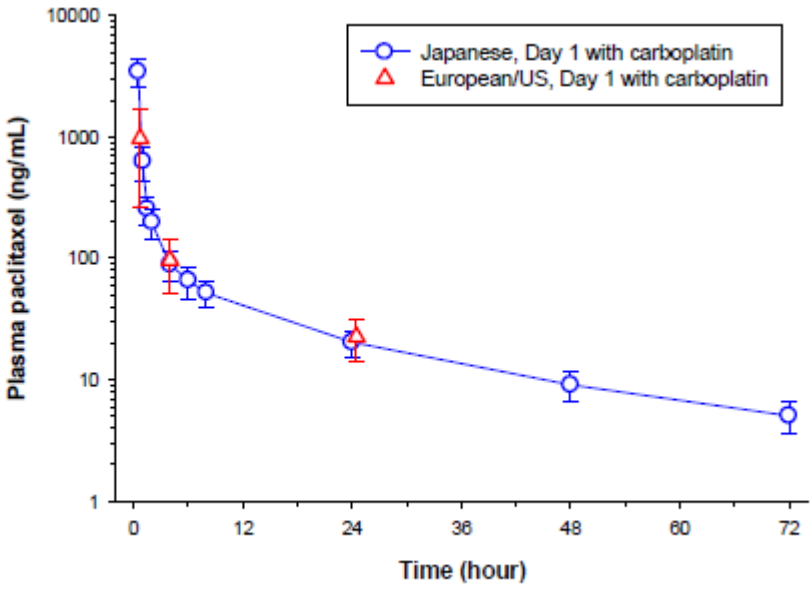
Paclitaxel PK parameter	ABI-007 100 mg/m^2, Cycle 1 Day 1		
	White Patients Solid Tumors ABI-007 Alone [CSR CA005-0][a]	Japanese Patients Solid Tumors ABI-007 Alone [Report 05DA11]	Japanese Patients NSCLC ABI-007 + Carboplatin [Report 08DA33]
N	6	6	12
Age (year)	57 (38-74)	59 (49-73)	63 (37-72)
Body Surface Area (m^2)	1.90 (1.60-2.14)	1.64 (1.55-1.75)	1.61 (1.41-1.83)
Weight (kg)	80.4 (58.9-101.7)	60.7 (54.7-68.0)	58.9 (49.2-71.7)
AUC_∞ (h•ng/mL)	4311 (1557)	4141 (538)	4073 (929)
C_{max} (ng/mL)	4513 (2002)	4253 (518)	3460 (905)
CL (L/h/m^2)	25.7 (8.3)	24.5 (3.15)	25.9 (6.61)
$t_{1/2}$ (h)[b]	18.2 (3.04)	26.1 (7.33)	24.2 (3.02)
V_{ss} (L/m^2)	Not done	311 (58.3)	324 (108)

AUC = area under the concentration versus time curve; AUC_∞ = AUC from time zero extrapolated to infinity; CL = total clearance; C_{max} = maximum concentration; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; $t_{1/2}$ = terminal half-life; V_{ss} = volume of distribution at the steady state.

[a] Excludes 1 patient who had severe obstructive liver disease.

[b] Estimated based on 48-hour sampling duration in CA005-0 and 72-hour sampling duration in Report 05DA11 and Report 08DA33.

Mean (SD) data are presented for PK parameters while mean (range) data are present for demographic parameters.



Source: Report 08DA33 and Bioanalytical Report ABRCA01A-15.

Figure 4: Mean (SD) Plasma Concentration of paclitaxel between Japanese and European/US Non-small Cell Lung Cancer Patients (Cycle 1, Day 1)

2.3.3. Discussion on clinical pharmacology

To support the combination of Abraxane with carboplatin for the first-line treatment of non-small cell lung cancer (NSCLC), pharmacokinetic data of paclitaxel in combination with carboplatin were collected in two sub-studies of the pivotal study CA031. In addition, data from studies J-0100 and J-0101 in Japanese patients were used in across-study comparisons to evaluate the dose dependency of ABI-007 and effect of race (Japanese) on the PK of paclitaxel after ABI-007 administration. The pharmacokinetic data were in agreement with the pharmacokinetics submitted in the initial MAA for breast cancer.

The key clinical PK evaluations for ABI-007 to support this application for the first-line treatment of NSCLC are:

- The PK profile of paclitaxel in NSCLC patients who received combination therapy with ABI-007/carboplatin at the recommended dosing regimens (100 mg/m^2 for ABI-007 and AUC = 6 for carboplatin) was similar to that observed in patients with solid tumours who received the same dose of ABI-007 alone (study CA031).

- No pharmacokinetic drug-drug interactions were observed between paclitaxel and carboplatin in Japanese NSCLC patients who received the ABI-007/carboplatin combination therapy (study CA031).

- Plasma paclitaxel exposure increased linearly with ABI-007 dose over dose range of 80 to 300 mg/m^2 (studies J-0100 and J-0101).

- Although the full PK profile of paclitaxel from White NSCLC patients receiving ABI-007, was not available, the limited concentration data obtained from the European/US NSCLC patients (Report BIO-VT-5) allowed a comparison of the concentration profile of plasma paclitaxel between Japanese and European/US NSCLC patients who received the same ABI-007 (100 mg/m2)/carboplatin (AUC = 6 min•mg/mL) combination therapy on Day 1 of Cycle 1. There was no difference in the PK of paclitaxel after ABI-007 administration between Japanese and White patients (studies CA031, J-0100 and J-0101).

2.3.4. Conclusions on clinical pharmacology

The pharmacokinetics of paclitaxel to support the dosing regimen of Abraxane 100 mg/m^2 qd with carboplatin AUC = 6 mg•min/mL on Day 1 only of each 21-day cycle, have been sufficiently investigated and are supportive for the use as first-line treatment of NSCLC in adult patients who are not candidates for potentially curative surgery and/or radiation therapy. In addition, based on the evidence presented, co-administration of Abraxane and carboplatin is not likely to result in pharmacokinetic drug-drug interactions.

2.4. Clinical efficacy

2.4.1. Dose response studies

The posology of Abraxane used in the pivotal CA031 study was supported by results from the Phase 1 and Phase 2 studies CA015 and CA028.

CA015

Study CA015 was an open-label, Phase I/II trial in which Abraxane as single agent was administered weekly to chemotherapy naïve patients with advanced NSCLC. The study was designed to determine the maximum tolerated dose (MTD) and Dose limiting toxicity (DLT) of weekly Abraxane and to evaluate the safety/tolerability and anti-tumour effect of Abraxane at the MTD.

This study had two phases. In the first phase the MTD and DLT was determined using protocol-specified criteria. Once the weekly MTD was determined, the patients in the second phase of the study were treated at the MTD to further characterize the safety/tolerability of Abraxane and to evaluate the potential anti-tumour activity. In the Phase II portion of the study, patient response was evaluated by the investigator. It was planned to enrol 3-6 patients per dose level (between 15 to 24 patients) for Phase 1 MTD portion plus an additional 65 patients for the Phase II portion of the study.

Four dose levels were planned for the MTD Phase I portion of the study; 100 mg/m^2, 125 mg/m^2, 150 mg/m^2 and 175 mg/m^2. Because DLTs were observed in the 150 mg/m^2 dose, escalation to 175 mg/m^2 dose was not initiated. For the phase II portion of the study, patients were administered 125 mg/m^2 over 30 minutes or 2 hours. The 2 hour dosing window was selected to determine if a longer duration of dosing would mitigate reports of peripheral neuropathy.

Efficacy

In total of 77 patients were enrolled in study CA015. In the Phase II portion of the study, an objective overall response (confirmed CR or PR) was observed in 18 patients. One patient had a CR and the remaining 17 patients were PRs.

Overall response rates ranged from 14.3% to 33.3% (in 150 mg/m^2 dose and 100 mg/m^2 dose groups respectively). For all doses over 30 minutes, the average response rate was 28%. For patients in the 100 mg/m^2 dose group, the response date was 33.3% (1 of 3 patients). For the 125 mg/m^2 dose over 30 minutes, the response rate was 30% (12 of 40 patients). For the 150 mg/m^2 dose, the response rate was 14.2% (1 of 7 patients). The ORR for patients who received Abraxane at the 125 mg/m^2 over 2 hours was 16% (4 of 25 patients).

Safety

For the phase I portion the DLTs that were identified included febrile neutropenia (grade 3) sensory neuropathy (grade 3) and motor neuropathy (grade 3). The MTD was determined to be 125 mg/m^2.

All 75 patients who participated in study CA015 reported at least 1 AE. The most commonly reported non-haematological toxicity was fatigue, which occurred in 83% of the patients dosed with any dose of Abraxane over 30 minutes.

Grade 3 and grade 4 treatment-related toxicities were reported among all patients who received 100 mg/m^2, 125 mg/m^2 or 150 mg/m^2 in the 30 minute dose duration. Among the patients who received 125 mg/m^2 over 2 hours, 14 treatment-related grade 3 and 1 treatment-related grade 4 events were reported. The most severe event for any patient administered 100 mg/m^2 was a grade 3 event of constipation. Among the events experienced by the patients who received 125 mg/m^2 over 30 minutes, the most severe were two grade 4 events of neutropenia. Among the events reported by the patients who received 150 mg/m^2, the most severe were six grade 3 events. Toxicities including sensory neuropathy, were similar across all dose levels and both dose durations.

Over the course of the study, 3 patients experienced AEs that resulted in death. None of the deaths were considered by the Investigator to be related to study drug.

In an exploratory manner, Abraxane was evaluated at the MTD over 30 minutes and 2 hours to determine if duration of dosing would mitigate reports of peripheral neuropathy. Length of dosing duration and presumed reduction of peak drug levels (due to long dosing) did not on average impact the Investigator rating of patient perception of peripheral neuropathy. However, the number of grade 2 and Grade 3 incidence of peripheral neuropathy and neutropenia were reduced in the longer dosing group.

For monotherapy Abraxane a DLT was observed at a weekly dose of the 150 mg/m^2, therefore from a safety perspective, the use of this dose in combination therapy is ruled out. At all tested dosages (100 mg/m^2, 125 mg/m^2 and 150 mg/m^2) anti-tumour responses were reported, with no clear dose response correlation. The number of patients treated with each dose was too limited to draw any conclusion regarding the optimal dose of Abraxane monotherapy regarding to efficacy.

Limited data suggest that the Grade 2 and 3 neuropathy and neutropenia was slightly reduced by prolongation of the infusion time from 30 minutes to 2 hours, however response rate for the long infusion time was lower.

CA028

Study CA028 was a multi-centre, open-label, Phase II Trial of increasing doses of Abraxane and carboplatin in patients with advanced NSCLC.

The primary objectives of this study were to obtain preliminary data on the anti tumor activity and adverse events (AEs) of Abraxane in combination with carboplatin. The secondary objectives were to evaluate the percentage of patients with stable disease (SD) for ≥ 16 weeks, or complete or partial overall response (i.e., total response); PFS, duration of response and patient survival.

Patients were treated with Abraxane doses plus carboplatin in 7 cohorts of 25 patients. The first 4 cohorts of this have examined increasing q3w doses of Abraxane (225, 260, 300 and 340 mg/m^2) in combination with carboplatin. The 260 mg/m^2 dose corresponded to the dose of Abraxane that was compared to solvent-based paclitaxel 175 mg/m^2 in women with breast cancer. The highest dose levels explored (300 and 340 mg/m^2 q3w) corresponded to approximately 50% increases of doses of solvent-based paclitaxel (200 to 225 mg/m^2) used in combination with carboplatin for the treatment of NSCLC patients.

The fifth cohort studied Abraxane 140 mg/m^2 given on days 1 and 8 every 3 weeks. Patients in the sixth cohort were treated with 100 mg/m^2 Abraxane administrated on days 1, 8 and 15 every 3 weeks. Finally the seventh cohort studied weekly administration of Abraxane at a dose of 125 mg/m^2, in an attempt to further increase the Abraxane dose intensity. Besides the patients included in the different cohorts of this study, an additional 75 patients were treated at a dose of 340 mg/m^2 q3w. In all treatment regimens, Abraxane was given IV over approximately 30 minutes without steroid premedication and without granulocyte colony-stimulating factor prophylaxis (unless supportive treatment was indicated based on AEs). All patients received carboplatin AUC=6 on Day 1 of the treatment cycle.

Efficacy

Results for objective response rate, SD≥ 16 weeks, and total response (objective response SD≥16 weeks) are presented by patient cohort in table 8.

Table 8: Response Rate and Stable Disease at ≥16 weeks by dose cohort

	225 mg/m² q3w (C1; n = 25)	260 mg/m² q3w (C2; n = 25)	300 mg/m² q3w (C3; n = 25)	340 mg/m² q3w (C4; n = 25)[a]	140 mg/m² q2/3w (C5; n = 25)	100 mg/m² weekly (C6; n = 25)	125 mg/m² weekly (C7; n = 25)	340 mg/m² q3w (C4 + C8; n = 101)[b]
Complete Response	0	1 (4%)	0	0	0	1 (4%)	1 (4%)	1 (<1%)
Partial Response	10 (40%)	5 (20%)	6 (24%)	8 (32%)	14 (56%)	11 (44%)	8 (32%)	32 (32%)
Patients with Confirmed Complete or Partial Overall Response	10 (40.0%)	6 (24.0%)	6 (24.0%)	8 (32.0%)	14 (56.0%)	12 (48.0%)	9 (36.0%)	33 (32.7%)
95% Confidence Interval	20.80 – 59.20	7.26 – 40.74	7.26 – 40.74	13.71 – 50.29	36.54 – 75.46	28.42 – 67.58	17.18 – 54.82	23.53 – 41.82
Stable Disease ≥ 16 Weeks	5 (20%)	8 (32%)	3 (12%)	0	2 (8%)	2 (8%)	3 (12%)	15 (15%)
Patients with Stable Disease for ≥ 16 Weeks or Confirmed Complete or Partial Overall Response	15 (60.0%)	14 (56.0%)	9 (36.0%)	8 (32.0%)	16 (64.0%)	14 (56.0%)	12 (48%)	48 (47.5%)
95% Confidence Interval	40.80 – 79.20	36.54 – 75.46	17.18 – 54.82	13.71 – 50.29	45.18 – 82.82	36.54 – 75.46	28.42 – 67.58	37.79 – 57.26

[a] Includes patients treated at 340 mg/m² q3w during dose escalation phase of the study.

[b] Includes all patients treated at 340 mg/m² q3w.

There was no apparent direct dose proportional relationship observed in objective response rate across the q3w or weekly cohorts in terms of Abraxane planned dose. In general, response rate was not lower for the weekly regimens and in fact, there was a tendency for improved response rate in the weekly cohorts.

Table 9: Progression-free survival by dose cohort

	225 mg/m² q3w (C1; n = 25)	260 mg/m² q3w (C2; n = 25)	300 mg/m² q3w (C3; n = 25)	340 mg/m² q3w (C4; n = 25)[a]	140 mg/m² q2/3w (C5; n = 25)	100 mg/m² weekly (C6; n = 25)	125 mg/m² weekly (C7; n = 25)	340 mg/m² q3w (C4 + C8; n = 101)[b]
Number of Patients who Died or had Progression	20 (80%)	19 (76%)	20 (80%)	20 (80%)	21 (84%)	18 (72%)	17 (68%)	73 (72%)
Median Progression-Free Survival (months)	6.9	6.5	5.3	4.8	5.6	6.2	6.4	6.2
95% Confidence Interval	4.2 – 9.6	4.3 – 9.1	2.2 – 8.5	3.9 – 7.8	3.9 – 7.7	4.2 – 9.7	4.2 – 7.9	5.1 – 7.8

[a] Includes patients treated at 340 mg/m² q3w during dose escalation phase of the study.

[b] Includes all patients treated at 340 mg/m² q3w.

There was no apparent direct dose proportional relationship observed in PFS across the q3w cohorts or the weekly cohorts in terms of Abraxane planned dose.

Other efficacy endpoints were Time to progression, duration of response, and OS. There was no clear difference between the cohorts in overall patient survival. There was a trend toward more consistent time to tumour progression (TTP) among the weekly cohorts compared to the q3w cohorts.

Safety

The most common non-hematologic treatment-related adverse event was peripheral neuropathy occurring in 184/251 (73%) of all treated patients. A total of 50 (20%) of all treated patients had Grade 3 treatment-related peripheral neuropathy. None of the patients had Grade 4 peripheral neuropathy. Treatment–related peripheral neuropathy was greater in the q3w groups (ranging from 64-92%) than in the weekly groups (48%-56%). Grade 3 treatment-related peripheral neuropathy ranged between 12-48% in the q3w groups, and between 8-16% in the weekly groups. A dose (mg/m²/week) relationship was observed in both the q3w and weekly cohorts in the incidence of both any peripheral neuropathy and Grade 3 neuropathy.

The most common hematologic adverse event was neutropenia, occurring in 210/251 (84%) of all treated patients. Neutropenia occurred in 82 (82%) patients in the initial four q3w cohorts, in 81 (80%) patients given Abraxane 340 mg/m^2 q3w, and in 66 (88%) of patients on weekly regimens of Abraxane. Grade 3 or higher treatment related neutropenia occurred in 55 (55%) patients in the initial four q3w cohorts, in 50 (50%) patients given Abraxane 340 mg/m^2 q3w and in 50 (67%) of patients on weekly regimens of Abraxane.

Table 10: Most Frequently-occurring Adverse Events of Grade 3 or Higher by NCI CTCAE Term (Reported in ≥10% for Patients in Any Cohort)

	225 mg/m^2 q3w (C1; n = 25)	260 mg/m^2 q3w (C2; n = 25)	300 mg/m^2 q3w (C3; n = 25)	340 mg/m^2 q3w (C4; n = 25)[a]	140 mg/m^2 q2/3w (C5; n = 25)	100 mg/m^2 weekly (C6; n = 25)	125 mg/m^2 weekly (C7; n = 25)	340 mg/m^2 q3w (C4 + C8; n = 101)[b]
Patients with at Least 1 Grade 3 or Greater Toxicity	24 (96%)	20 (80%)	19 (76%)	25 (100%)	20 (80%)	20 (80%)	23 (92%)	88 (87%)
Blood/Bone Marrow: Neutrophils[c]	16 (64%)	15 (60%)	12 (48%)	12 (48%)	19 (76%)	16 (64%)	15 (60%)	50 (50%)
Blood/Bone Marrow: Platelets[c]	10 (40%)	6 (24%)	7 (28%)	6 (24%)	8 (32%)	5 (20%)	9 (36%)	27 (27%)
Neurology: Neuropathy: Sensory	3 (12%)	5 (20%)	6 (24%)	12 (48%)	2 (8%)	2 (8%)	4 (16%)	29 (29%)
Blood/Bone Marrow: Hemoglobin[c]	5 (20%)	6 (24%)	4 (16%)	3 (12%)	5 (20%)	4 (16%)	11 (44%)	14 (14%)
Constitutional Symptoms: Fatigue	6 (24%)	4 (16%)	4 (16%)	6 (24%)	4 (16%)	2 (8%)	5 (20%)	17 (17%)
Blood/Bone Marrow: Leukocytes	3 (12%)	4 (16%)	5 (20%)	4 (16%)	7 (28%)	5 (20%)	5 (20%)	17 (17%)
Pain: Myalgia	0	1 (4%)	1 (4%)	6 (24%)	0	0	0	15 (15%)
Pain: Arthralgia	0	1 (4%)	1 (4%)	2 (8%)	0	0	0	11 (11%)

[a] Includes patients treated at 340 mg/m^2 q3w during dose escalation phase of the study.
[b] Includes all patients treated at 340 mg/m^2 q3w.
[c] Based on central laboratory data.

A total of 22 events resulted in death. Of those, 7 were considered treatment-related. Treatment related death was reported for the following treatment cohorts; one in the 225 mg/m^2 q3w, 3 in the 300 mg/m^2 q3w, 2 in the 340 mg/m^2 q3w and 1 in the weekly 100 mg/m^2 cohort. Reported fatal AEs included systolic dysfunction, haemorrhage bleeding, infection and ischemia. Serious adverse events were experienced by 28% of patients in the q3w cohorts, primarily due to thrombocytopenia (6%) and neutropenia (4%) and by 24% of patients in the weekly cohorts, primarily due to thrombocytopenia (11%).

The percentage of patients with at least 1 treatment-emergent toxicity leading to permanent discontinuation of study treatment ranged between 20% (260 mg/m^2 q3w) and 60% (340 mg/m^2 q3w) in the q3w cohorts and between 20% (100 mg/m^2 weekly) and 36% (125 mg/m^2 weekly) in the weekly cohorts. The most common toxicities that led to discontinuation were thrombocytopenia and peripheral neuropathy in the 3qw cohorts, and thrombocytopenia and neutropenia in the weekly cohorts.

For study CA028, in general, with comparable cumulative Abraxane exposure, the rate of adverse events was mostly lower with the weekly relative to the 3 weeks Abraxane schedules. In particular, the incidence of neuropathy seems to be lower with weekly administration of Abraxane, whereas the incidence of neutrophil toxicity was slightly higher for the weekly cohorts in comparison to the 3qw cohorts. Efficacy results for ORR were best for the weekly 100 mg/m^2 cohort and 140 mg/m^2 q2/3w cohort (48% and 56% respectively). ORR regarded only PR. No CR was documented.

In combination with carboplatin the toxicity of the weekly 125 mg/m^2 dose was substantially higher than the toxicity for the weekly 100 mg/m^2, whereas the median cumulative Abraxane exposure for the 125 mg/m^2 dose was lower than for the 100 mg/m^2 and the efficacy results was not clearly better. Also the toxicity in the 300 mg/m^2 and the 340 mg/m^2 q3w cohorts was high in relation to the 225 q3w, 260 q3w,

140 q2/3w and weekly 100 mg/m^2 cohorts, whereas the median PFS was shorter in the 300 and 340 mg/m^2 cohort than in the other cohorts.

The response rate reported for weekly Abraxane 100 mg/m^2 in combination with carboplatin was better than the response rate reported for Abraxane monotherapy at every dose tested in study CA015 (Abraxane 100 mg/m^2/carboplatin qd CR: 4 % and PR 44 % and Abraxane mono 125 mg/m^2 qd: ORR 30%).

2.4.2. Main studies

CA031 - A randomized, phase III trial of ABI-007 and carboplatin compared with Taxol and carboplatin as first-line therapy in patients with advanced non-small cell lung cancer (NSCLC)

Methods

Study CA031 was a controlled, randomized, multicentre, Phase 3 study evaluating the safety/tolerability and anti-tumour effect of intravenously (IV) administered Abraxane/carboplatin combination therapy compared with that of Taxol/carboplatin combination therapy as first-line treatment in patients with advanced NSCLC.

Study participants

For study CA031, patients with histologically or cytologically confirmed stage IIIb or IV NSCLC were included.

Patients with radiographically documented measurable disease (defined by the presence of ≥ 1 radiographically documented measurable lesion) were included.

Patients that were included had no prior chemotherapy for the treatment of metastatic disease. Adjuvant chemotherapy was permitted providing cytotoxic chemotherapy was completed 12 months prior to starting the study.

Patients with pre-existing neuropathy of grade 2, 3 or 4, or serious medical risk factors involving any of the major organ systems were excluded from the study. In addition, patients were excluded if they received radiotherapy in the preceding 4 weeks, except if to a non-target lesion only. Prior radiation to a target lesion was permitted only if there had been clear progression of the lesion since radiation was completed.

Treatments

Abraxane

The Abraxane dose used in this study was 100 mg/m^2 given weekly (i.e. on Days 1, 8 and 15 of each 21-day cycle) in combination with carboplatin (AUC=6 mg•min/mL) every 3 weeks (i.e. on Day 1 only of each 21-day cycle beginning immediately after the end of Abraxane administration). Abraxane was administered IV over approximately 30 minutes without steroid premedication and without G-CSF prophylaxis.

Taxol

The used Taxol dose was 200 mg/m^2 administered once every 3 weeks as an intravenous infusion over 3 hours with standard premedication, immediately followed by carboplatin administered intravenously at AUC = 6 mg•min/mL. Each drug was administered on Day 1 of each 21-day cycle.

In both study arms treatment was administered until disease progression or development of an unacceptable toxicity. Patients received a median of 6 cycles of treatment in both study arms.

Dose modification

A maximum of two dose reductions were allowed from the original dose on the basis of AEs encountered during study performance.

Table 11: Dose reductions for haematologic toxicities in patients with non-small cell lung cancer

Haematologic Toxicity	Occurrence	Dose of Abraxane (mg/m^2)	Dose of carboplatin (AUC mg•min/mL)
Nadir ANC <500/mm^3 with neutropenic fever > 38°C OR Delay of next cycle due to persistent neutropenia[1] (Nadir ANC <1500/mm^3) OR Nadir ANC <500/mm^3 for > 1 week	First	75	4.5
	Second	50	3.0
	Third	Discontinue Treatment	
Nadir platelets <50,000/mm^3	First	75	4.5
	Second	Discontinue Treatment	

[2]Maximum of 7 days post scheduled Day 1 dose of next cycle.

Table 12: Dose reductions for non-haematologic toxicities in patients with non-small cell lung cancer

Non-haematologic Toxicity	Occurrence	Dose of Abraxane (mg/m^2)	Dose of carboplatin (AUC mg•min/mL)
Grade 2 or 3 cutaneous toxicity Grade 3 diarrhoea Grade 3 mucositis ≥ Grade 3 peripheral neuropathy Any other Grade 3 or 4 non-haematologic toxicity	First	75	4.5
	Second	50	3.0
	Third	Discontinue Treatment	
Grade 4 cutaneous toxicity, diarrhoea, or mucositis	First	Discontinue Treatment	

Objectives

Primary objective

The primary objective of this study was to compare disease response (using Response Evaluation Criteria in Solid Tumour, version 1.0) of Abraxane/carboplatin versus Taxol/carboplatin as first line therapy in patients with advanced NSCLC. The null hypothesis of this study was that the Abraxane/carboplatin regimen response rate was non-inferior to that of the Taxol/carboplatin regimen.

Main Secondary Objectives

- Compare the frequency of toxicities grade using the Common Terminology Criteria for Adverse Events (CTCAE)
- Compare PFS
- Compare overall survival
- Compare duration of response in responding patients

Outcomes/endpoints

Primary efficacy endpoint

The primary efficacy endpoint was the percentage of patients who achieved an objective confirmed CR or PR based on the blinded radiological review using RECIST response guidelines (Version 1.0).

Secondary Efficacy Endpoints

- PFS defined as the time from the day of randomization to the start of disease progression or death (any cause), whichever occurred first, based on the blinded radiological review assessment of response.
- OS defined as the time from the day of randomization to patients death (any cause).
- Evaluation of PK parameters (C_{max}, AUC, AUC_{inf}, $T_{1/2}$, total body clearance and volume of distribution.
- Percentage of patients with stable disease for ≥16 weeks or confirmed CR or PR response (i.e., disease control rate)
- Duration of response in responding patients
- Correlation of SPARC and other molecular biomarker with efficacy outcomes

Sample size

Phase III data on Taxol plus carboplatin showed a response rate of 17% in patients previously untreated for advanced NSCLC (Schiller, 2002). The applicant assumed that Abraxane plus carboplatin would have a response rate of 24% (a relative improvement of approximately 40% over Taxol plus carboplatin). Based on this assumption, a sample size of 525 patients per arm in the ITT analysis would provide 80% power with a 2 sided type 1 error of 0.049 to reject the null hypothesis that the Abraxane/carboplatin response rate was equal to that of Taxol/carboplatin.

An interim analysis of response rate was performed after 200 patients per arm had completed the second response assessment. The purpose of this interim analysis was to evaluate the initial assumption of treatment difference in response rate (24% vs 17%). If the treatment difference at the interim analysis was lower than assumed, the sample size was to be increased accordingly.

Randomisation

The randomization schedule was generated by a randomization statistician from the sponsor. The randomization was implemented via ICON Interactive Voice Response (IVR) system. Patients were randomized in a 1:1 ratio and the randomization was stratified by the following strata:

- Disease stage (IIIb vs IV)
- Age (<70 years vs ≥70 years)
- Gender (male vs female)
- Histology (squamous cell carcinoma versus adenocarcinoma versus other histology)
- Geographic region (North America vs Australia/New Zealand vs Eastern Europe vs Asia/Pacific)

Blinding (masking)

This was an open-label study. Blinding was not feasible due the differences in study drug appearance, the frequency and duration of administration, and the required administration of premedication for Taxol.

Statistical methods

General remarks of the final statistical analysis plan:

- Data from all study centres were combined for analysis
- All statistical tests of the treatment effect preserved a significance level of 0.050 for 2 –side tests. Testing of interactions was performed at the 0.100 significance level

- The day of the first dose of any study drug was defined as Day 1; baseline was defined as the last value before the first study drug dose; and final evaluation was defined as the last on-treatment value.

Analysis of primary efficacy endpoint

The primary efficacy endpoint was the percentage of patients who achieved an objective confirmed CR or PR based on the blinded radiological review.

The null hypothesis was that the Abraxane/carboplatin regimen response rate was equal to that of Taxol/carboplatin regimen, hereby would the ratio of response for the Abraxane arm versus the Taxol arm (p_A/p_T) be 1. Superiority of Abraxane/carboplatin to Taxol/carboplatin was to be established if the lower bound of the 2-sided 95% CI of p_A/p_T is >1.

An interim analysis of response rate was to be performed after 200 patients per arm have completed the second treatment response assessment. An alpha spending function was to be utilized to preserve the overall Type 1 error at 0.050. This spending function allocate alpha of 0.001 and 0.049 at the interim and final analyses of response rate, respectively (Haybittle, 1971; Peto, 1977).

Treatment regimen comparison of response rates was tested using the chi-square test.

Exploratory analyses were performed to assess the potential influence of the following prognostic factors on the primary efficacy endpoint of objective response: Region, Gender, Race, Age, Smoking Status, Baseline ECOG, Time from date of primary diagnosis to date of study entry, Stage at Primary Diagnosis, Histology at Primary Diagnosis, Time from date of first documented metastasis/relapse to date of study entry, Stage at current Diagnosis, Number of Lesion.

For each prognostic factor, its effect on objective response was tested using a logistic regression model with effects for treatment regimen, prognostic factor and treatment regimen by prognostic factor interaction. If the interaction was significant, then the nature of the interaction was evaluated.

Analysis of key secondary efficacy endpoints

Secondary efficacy endpoints were to be analysed only if the primary efficacy endpoint displayed superiority of Abraxane/carboplatin over Taxol/carboplatin. To control the overall family-wise Type I error rate at 2-sided alpha=0.050 for the 2 key secondary efficacy endpoints PFS was tested first at alpha=0.050; OS was tested at alpha=0.050 only if PFS showed significant improvement.

Progression-free survival was analysed using Kaplan-Meier (KM) methods. The final analysis for PFS was to be conducted once 70% of patients had an event of disease progression or death (any cause).

Overall survival (OS) was analysed in a similar manner to PFS. The final analysis for OS was conducted once 70% of patients had died.

An addendum to the Statistical analysis Plan was finalized on 11 April 2011. The addendum was prepared prior to the final database lock and prior to the PFS and OS analyses. The following issues were addressed by the addendum:

- Progression-free survival per European Medicines Agency (EMA) methodological considerations for PFS endpoint
- Non-inferiority analysis consistent with recommendations of EMA guidelines
- Supportive analysis of non-inferiority based on OS

Non-inferiority of Abraxane/carboplatin compared with Taxol/carboplatin for PFS and OS was assessed based on the upper bound of the 95% CI of the HR ($HR_{A/T}$). If the upper bound is less than 1.176, the non-inferiority was considered met.

As the upper bound of the 95.1% CI is larger than the upper bound of the 95% CI, by convention, non-inferiority also was established if the upper bound of the 95.1% CI was <1.176. For OS, recalculation of the 95% CI was done only if the 95.1% CI was not sufficient to meet this criterion.

PFS was chosen as the primary endpoint of these non-inferiority analyses. For the non-inferiority PFS analysis as well as supportive non-inferiority OS analysis, the non-inferiority margin was chosen as 15%, i.e., when the upper bound of the 95% CI of the HR ($HR_{A/T}$) was less than 1.176, then non-inferiority criterion was considered met.

The selection of this margin was based on regulatory precedence (i.e., Alimta, Xeloda) and an assessment of clinical benefit based on a meta-analysis of relevant historical studies.

To evaluate the impact of 15% non-inferiority margin, the relative efficacy of Abraxane/carboplatin over "Placebo" (i.e., Etoposide/cisplatin combination in this case) was projected when Abraxane/carboplatin sits at the margin.

Results

Participant flow

At the time of the final analysis of study CA031, based on the data cut-off of 31 January 2011, of the 1038 treated patients, 1035 patients had discontinued study treatment and 3 patients were still on therapy. These 3 patients had discontinued from the study by 21 December 2012.

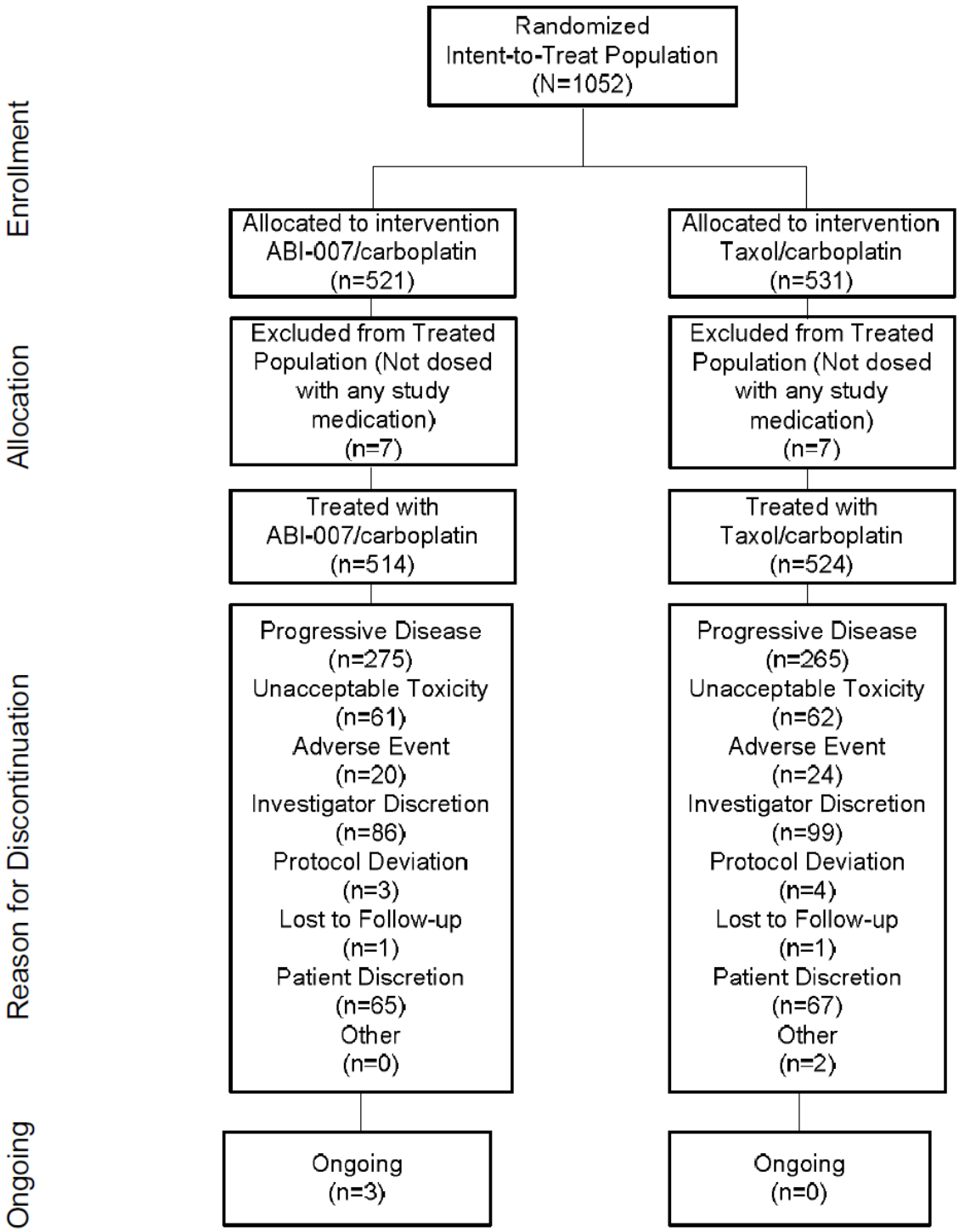


Figure 5: Patient Flow Chart

Recruitment

In total 1052 patients were enrolled for study CA031. First patient was enrolled on 14 December 2007, last patients completed study treatment at 21 December 2012. The data cut-off date for analysis of the primary efficacy endpoint of ORR was 12 October 2009 (the date at which the last randomized patient completed the second response assessment). The data cut-off date for the final analysis was 31 January 2011.

A total of 102 study sites enrolled patients including 29 sites in Russia, 25 sites in the US, 21 sites in Japan, 16 sites in Ukraine, 6 sites in Canada and 5 sites in Australia.

Conduct of the study

Fourteen patients were randomized but were not dosed; 7 due to investigator discretion, 3 due to adverse events, 3 due to protocol deviations and 1 due to withdrawal of consent.

The proportion of treated patients in the ITT population was the same for each treatment arm (99%).

As of the 31 January 2011 cut-off date, >99% of patients had discontinued study treatment. In both treatment arms, the most common reason for discontinuation was progressive disease (52% overall). The other reasons for discontinuation were similar for the 2 treatment arms (investigator discretion, patient discretion, and unacceptable toxicity). The group of patients who discontinued treatment due to investigator discretion included; “patient’s interest/benefit,” “6 cycles completed,” and “further treatment is no longer beneficial for the patient”. One patient was randomized twice. This patient was discontinued after the first randomization because the site had already reached the maximum enrolment allowed per site. The patient was re-randomized after the planned number of patients per site was increased. The patients was assigned at the second randomization but excluded from the analyses in order to maintain a true ITT population.

Baseline data

Table 13: Demographics (ITT population)

Variable	ABI-007/ carboplatin (N=521)	Taxol/ carboplatin (N=531)	All Patients (N=1052)	p-value [a]
Country, N	521	531	1052	0.801
Australia, n (%)	5 (<1%)	9 (2%)	14 (1%)	
Canada, n (%)	21 (4%)	23 (4%)	44 (4%)	
Japan, n (%)	74 (14%)	75 (14%)	149 (14%)	
Russia, n (%)	238 (46%)	231 (44%)	469 (45%)	
Ukraine, n (%)	120 (23%)	135 (25%)	255 (24%)	
United States, n (%)	63 (12%)	58 (11%)	121 (12%)	
Age (years), N	521	531	1052	0.625
Mean (SD)	59.5 (9.14)	59.7 (9.53)	59.6 (9.33)	
Median (Min, Max)	60.0 (28, 81)	60.0 (24, 84)	60.0 (24, 84)	
Age Category, N	521	531	1052	
< 65 Years, n (%)	360 (69%)	348 (66%)	708 (67%)	0.197
≥ 65 Years, n (%)	161 (31%)	183 (34%)	344 (33%)	
< 70 Years, n (%)	447 (86%)	449 (85%)	896 (85%)	0.539
≥ 70 Years, n (%)	74 (14%)	82 (15%)	156 (15%)	
< 75 Years, n (%)	503 (97%)	513 (97%)	1016 (97%)	0.971
≥ 75 Years, n (%)	18 (3%)	18 (3%)	36 (3%)	
Gender, N	521	531	1052	0.820
Male, n (%)	392 (75%)	397 (75%)	789 (75%)	
Female, n (%)	129 (25%)	134 (25%)	263 (25%)	
Race, N	521	531	1052	0.410
Asian, n (%)	79 (15%)	80 (15%)	159 (15%)	
Black, of African Heritage, n (%)	12 (2%)	8 (2%)	20 (2%)	
North American Indian or Alaska Native, n (%)	1 (<1%)	0	1 (<1%)	
White, Non-Hispanic and Non-Latino, n (%)	416 (80%)	433 (82%)	849 (81%)	
White, Hispanic or Latino, n (%)	11 (2%)	5 (<1%)	16 (2%)	
Other, n (%)	2 (<1%)	5 (<1%)	7 (<1%)	
Smoking Status, N	519	526	1045	0.280
Never Smoked, n (%)	137 (26%)	144 (27%)	281 (27%)	
Smoked and Quit Smoking, n (%)	168 (32%)	148 (28%)	316 (30%)	
Smoked and Currently Smokes, n (%)	214 (41%)	234 (44%)	448 (43%)	
ECOG Performance Status[b], N	521	531	1052	0.121
0 (Fully Active) , n (%)	133 (26%)	113 (21%)	246 (23%)	
1 (Restrictive but Ambulatory), n (%)	385 (74%)	416 (78%)	801 (76%)	
2 (Ambulatory but Unable to Work), n (%)	3 (<1%)	2 (<1%)	5 (<1%)	
Physician Assessment of Sensory Neuropathy, N	520	529	1049	0.578
0, n (%)	497 (96%)	502 (95%)	999 (95%)	
1, n (%)	22 (4%)	27 (5%)	49 (5%)	
2, n (%)	1 (<1%)	0	1 (<1%)	
Alkaline Phosphatase	517	527	1044	0.285
Below LLN	1 (<1%)	2 (<1%)	3 (<1%)	
Within Normal Limits	441 (85%)	436 (83%)	877 (84%)	
Above ULN	75 (15%)	89 (17%)	164 (16%)	
ALT (SGPT)	505	519	1024	0.075
Below LLN	0	0	0	
Within Normal Limits	472 (93%)	498 (96%)	970 (95%)	
Above ULN	33 (7%)	21 (4%)	54 (5%)	

Table 13: Demographics (ITT population) continued

Variable	ABI-007/ carboplatin (N=521)	Taxol/ carboplatin (N=531)	All Patients (N=1052)	p-value
AST (SGOT)	515	527	1042	0.028*[a]
Below LLN	0	0	0	
Within Normal Limits	481 (93%)	508 (96%)	989 (95%)	
Above ULN	34 (7%)	19 (4%)	53 (5%)	
Total Bilirubin	518	527	1045	0.363
Below LLN	84 (16%)	77 (15%)	161 (15%)	
Within Normal Limits	433 (84%)	449 (85%)	882 (84%)	
Above ULN	1 (<1%)	1 (<1%)	2 (<1%)	
Hemoglobin	517	527	1044	0.397
Below LLN	174 (34%)	163 (31%)	337 (32%)	
Within Normal Limits	338 (65%)	361 (69%)	699 (67%)	
Above ULN	5 (<1%)	3 (<1%)	8 (<1%)	
Creatinine	518	527	1045	0.368
Below LLN	47 (9%)	39 (7%)	86 (8%)	
Within Normal Limits	450 (87%)	466 (88%)	916 (88%)	
Above ULN	21 (4%)	22 (4%)	43 (4%)	

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; ECOG = Eastern Cooperative Oncology Group; Max = maximum; Min = minimum; SD = standard deviation; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

[a] P-values are based on a CMH test (general association) for country and region, a 2-way ANOVA model with effects for geographic region and treatment regimen for age, weight, number of years patient has/had smoked, and number of packs per day patient smokes/had smoked, a CMH test (general association) stratified by geographic region for gender, race, and smoking status, and a CMH test (modified ridit scores) stratified by geographic region for age category, ECOG performance status, physician assessment of sensory neuropathy, and baseline lab category. Significant P-values are marked with an asterisk.

[b] Five patients with ECOG score 2 at Cycle 1 Day 1. However at study screening, ECOG scores were 0 or 1 for these 5 patients.

Note: For each variable, a value of N less than the value in the ITT population reflects missing patient data.

Note: Baseline laboratory values were assessed by a central laboratory except for patients enrolled in Japan, where local laboratory assessments were used.

Source: Table 4.0.

The percentage of patients with a relative favourable prognosis, who never smoked seems to be high, but between treatment arms the percentage of "never smoked" patients is comparable (32% and 28%). Around the 50% of patients in both treatment arm were diagnosed with an adenocarcinoma.

In both arms, the majority of patients were randomized within one month of their lung cancer diagnosis, with a median time from primary diagnosis to enrolment of 0.7 months, and a median time from first documented metastasis/relapse to study entry of 0.5 months.

Prior chemotherapy was uncommon, reported in only 3% of enrolled patients.

Numbers analysed

All efficacy analyses were performed using the ITT population, which includes all randomized patients regardless of whether the patient received any study drug or had any efficacy assessments collected. There were 521 patients in the ITT population in the Abraxane/carboplatin arm and 531 patients in the ITT population in the Taxol/carboplatin arm (1052 patients in total).

Outcomes and estimation

ORR

The proportion of patients with a confirmed complete or partial overall response per the blinded radiology assessment was significantly higher for the Abraxane/carboplatin regimen relative to the Taxol/carboplatin regimen (33% versus 25%, p=0.005; response rate ratio $[p_z/p_T]=1.313$).

Table 14: Blinded Radiology Assessment of Overall Response Rate (ITT population) CA031

Variable Category/Statistic	ABI-007/ carboplatin (N=521)	Taxol/ carboplatin (N=531)	Response Rate Ratio (p_A/p_T)	P-value
Patients with Confirmed Complete or Partial Overall Response				
n (%)	170 (33%)	132 (25%)	1.313	0.005*
Confidence Interval (CI) [a]	28.6, 36.7	21.2, 28.5	1.082, 1.593	
Complete Response	0	1 (< 1%)		
Partial Response	170 (33%)	131 (25%)		

[a] 95% CI of response rate and 95.1% CI of response rate ratio.
Note: P-value is based on a chi-square test.
* Indicates p-value < 0.049

Blinded Radiological Assessment of Progression-free Survival (PFS)

For the Abraxane/carboplatin arm the median PFS was 6.3 months (95% CI=5.6, 7.0 months), while for the Taxol/carboplatin arm the median PFS was 5.8 months (95% CI=5.6, 6.7 months). The $HR_{A/T}$ was 0.92 (95.1% CI=0.767, 1.060). The PFS difference between the arms was not statistically significant (p=0.214).

Table 15: Progression-free Survival determined by Blinded Radiology Assessment (ITT Population) CA031

Variable Category/Statistic	ABI-007/ carboplatin (N=521)	Taxol/ carboplatin (N=531)	Hazard Ratio ($HR_A/_T$)	P-value
Number of Patients who Died or had Progression	297 (57%)	312 (59%)		
Median Progression-free Survival (months)	6.3	5.8	0.902	0.214
Confidence Interval[a]	5.6, 7.0	5.6, 6.7	0.767, 1.060	

[a] 95% confidence interval of median value and 95.1% confidence interval of hazard ratio.
P-value is based on a stratified log-rank test stratified by geographic region (North America/Australia, Eastern Europe, or Asia/Pacific) and histology of primary diagnosis (squamous cell carcinoma or non-squamous cell carcinoma).

The investigator assessed median PFS in the Abraxane/carboplatin arm was 5.5 months (95% CI=5.1, 5.7) and 5.4 months (95% CI=5.1, 5.6 months) in the Taxol/carboplatin arm. The difference was statistically non-significant (p=0.371), which is in line with the PFS results of the IRR.

The Figure below presents the Kaplan Meier curve for PFS for each treatment regimen. The KM estimated patients without an event (progression or death) at 6 months (52% versus 49%), 12 months (22% versus 19%) and 18 months (11% versus 9%) was numerically higher in the Abraxane/carboplatin arm versus the Taxol/carboplatin arm.

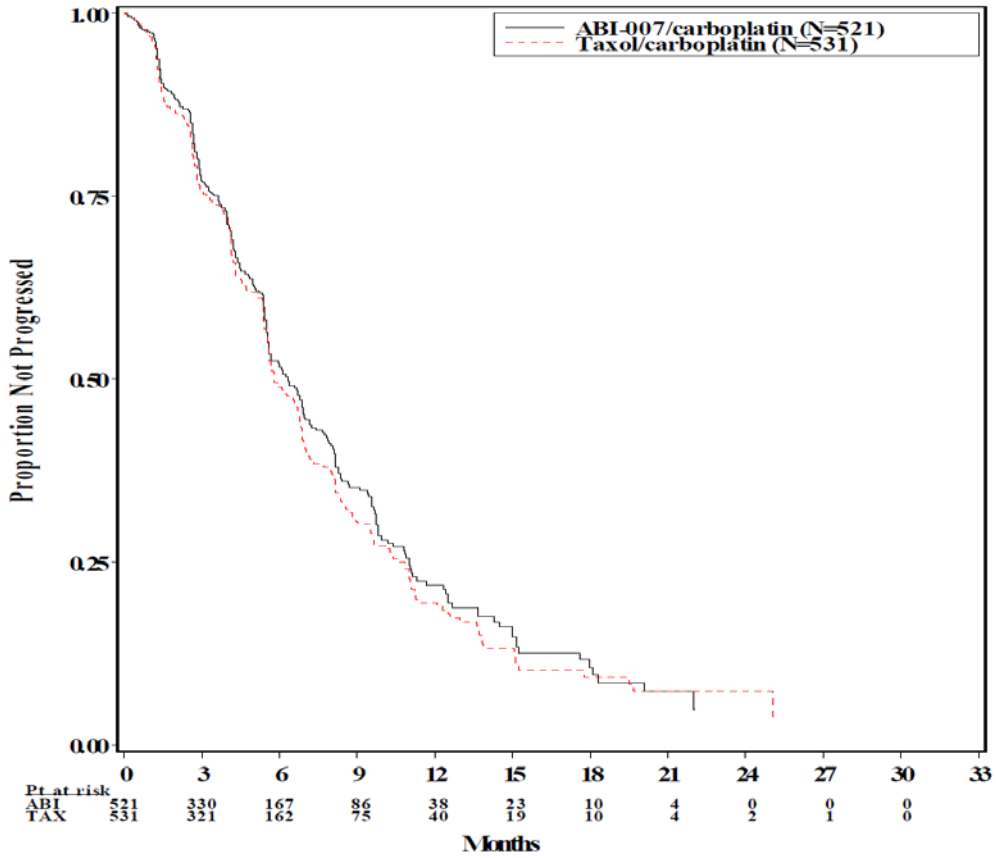


Figure 6: Kaplan-Meier curve of Progression-free Survival Determined by blinded Radiology Assessment (ITT population) CA031

Although the difference in PFS between treatment arms was not statistically significant, the point estimated median PFS for the Abraxane/carboplatin arm was higher than for the Taxol/carboplatin arm (6.3 versus 5.8 months respectively).

A high percentage (43% and 41% for the Abraxane/carboplatin arm and Taxol/carboplatin arm respectively) of patients in this PFS analysis were censored. The two most common reasons for censoring were discontinuation of scanning by the investigator for progressive disease (per protocol 28% and 25%, respectively) and onset of another anticancer therapy or lesion site surgery (8% for both arms).

Overall Survival (ITT Population)

Table 16: Overall Survival (ITT Population) CA031

Variable	ABI-007/ carboplatin (N=521)	Taxol/ carboplatin (N=531)	Hazard Ratio ($HR_{A/T}$)	P-value
Number of Patient Deaths	360 (69%)	384 (72%)		
Median Survival (months)	12.1	11.2	0.922	0.271
Confidence Interval[a]	10.8, 12.9	10.3, 12.6	0.797, 1.066	

[a] 95% confidence interval of median value and 95.1% confidence interval of hazard ratio.
Note: Patients that did not die were censored at the last known time the patient was alive.
Note: P-value is based on a stratified log-rank test stratified by geographic region (North America/Australia, Eastern Europe, or Asia/Pacific) and histology of primary diagnosis (Squamous cell carcinoma or Non-squamous cell carcinoma).

Figure 7 presents the KM curve for OS for each treatment arm. There was a non-significant trend towards improved survival for patients in Abraxane/carboplatin treatment arm (p=0.271 [stratified log-rank test]; $HR_{A/T}$=0.922).

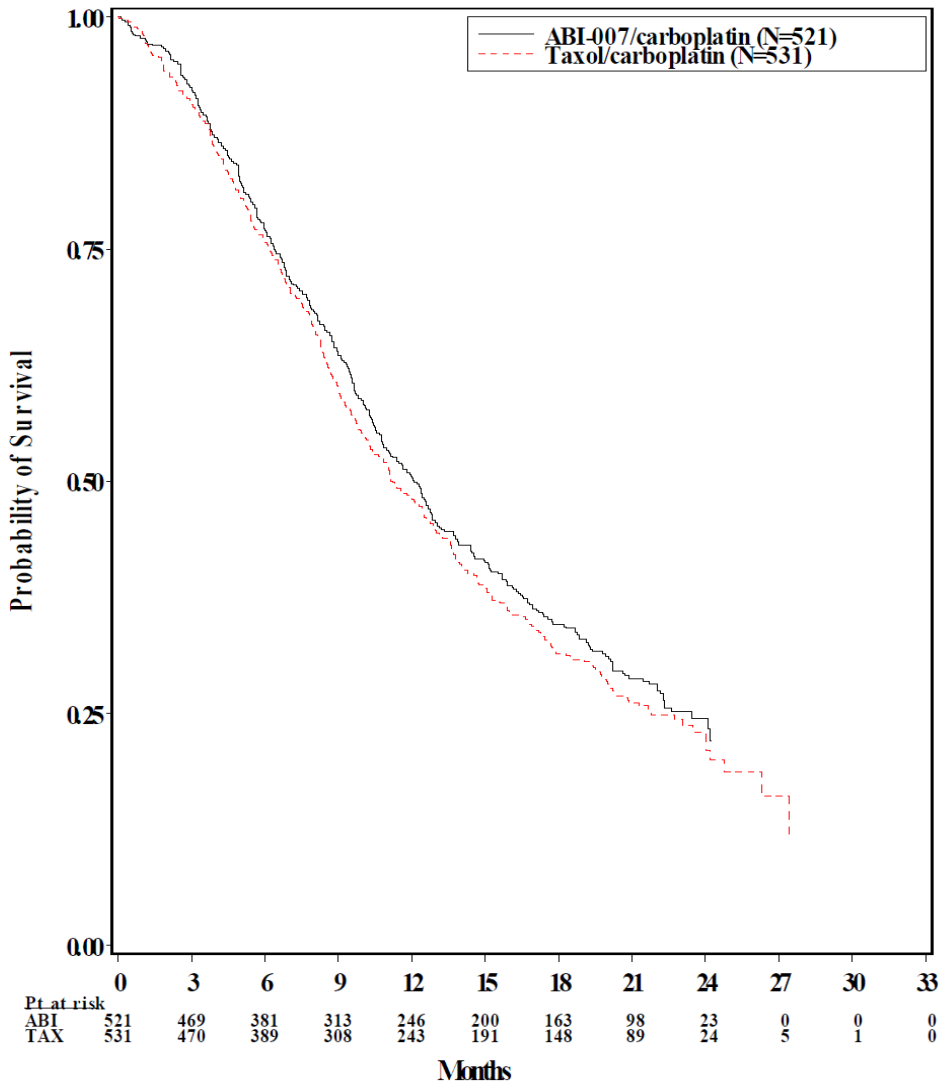


Figure 7: Kaplan-Meier Curve of Overall Survival (ITT Population) CA031

A total of 31% of Abraxane/carboplatin patients and 28% of Taxol/carboplatin patients were censored. The most common reasons for censoring were that the patients had completed 18 months of follow-up (13% and 12%, respectively) and that follow-up for survival was on-going (13% and 11%, respectively).

Other secondary endpoints:

Disease control rate

A summary of investigator based assessment of disease control, compared with independent radiological review is presented in Table 17.

Table 17: Blinded Radiology/Investigator Assessed Stable Disease for ≥ 16 Weeks or Confirmed Complete or Partial Overall Response (ITT Population)

	ABI-007/ carboplatin (N=521)	Taxol/ carboplatin (N=531)	Disease control rate ratio P_A/P_T	p-value
Blinded radiology assessment				
Number of Patients with Stable Disease for ≥ 16 weeks or Confirmed Complete or Partial Overall Response	274 (53%)	260 (49%)	1.074	0.239
95% CI	48.3, 56.9	44.7, 53.2	0.953, 1.210	
CR	0	1 (< 1%)		
PR	170 (33%)	131 (25%)		
Stable Disease for ≥ 16 weeks	104 (20%)	128 (24%)		
Investigator assessment				
Number of Patients with Stable Disease for ≥ 16 weeks or Confirmed Complete or Partial Overall Response	289 (55%)	276 (52%)	1.067	0.256
95% CI	51.2, 59.7	47.7, 56.2	0.954, 1.194	
CR	2 (< 1%)	4 (< 1%)		
PR	198 (38%)	156 (29%)		
Stable Disease for ≥ 16 weeks	89 (17%)	116 (22%)		

Abbreviations: CI = confidence interval; CR = complete response; ITT = intent-to-treat; PA = ABI-007/carboplatin disease control rate; PT = Taxol/carboplatin disease control rate; PA/PT = disease control rate ratio; PR = partial response.
Source: CSR CA031 Table 16.0, CSR CA031 Table 16.1

Duration of response

Table 18: Duration of Response - Progression-free Survival Determined by Blinded Radiology Assessment for Patients with a Confirmed Complete or Partial Overall Response (ITT Population)

Variable	ABI-007/ carboplatin (N=170)	Taxol/ carboplatin (N=132)	Hazard Ratio ($HR_{A/T}$)	P-value
Number of Patients who Died or had Progression	85 (50%)	78 (59%)		
Median Progression-free Survival (months)	9.6	9.5	0.901	0.551
95% Confidence Interval	8.3, 10.8	8.1, 11.0	0.652, 1.244	

Note: P-value is based on a stratified log-rank test stratified by geographic region (North America/Australia, Eastern Europe, or Asia/Pacific) and histology of primary diagnosis (Squamous cell carcinoma or Non-squamous cell carcinoma).
Source: Table 17.0.

Duration of response analyses without censoring events of PFS preceded by missing assessment or start of new anticancer therapy have been performed.

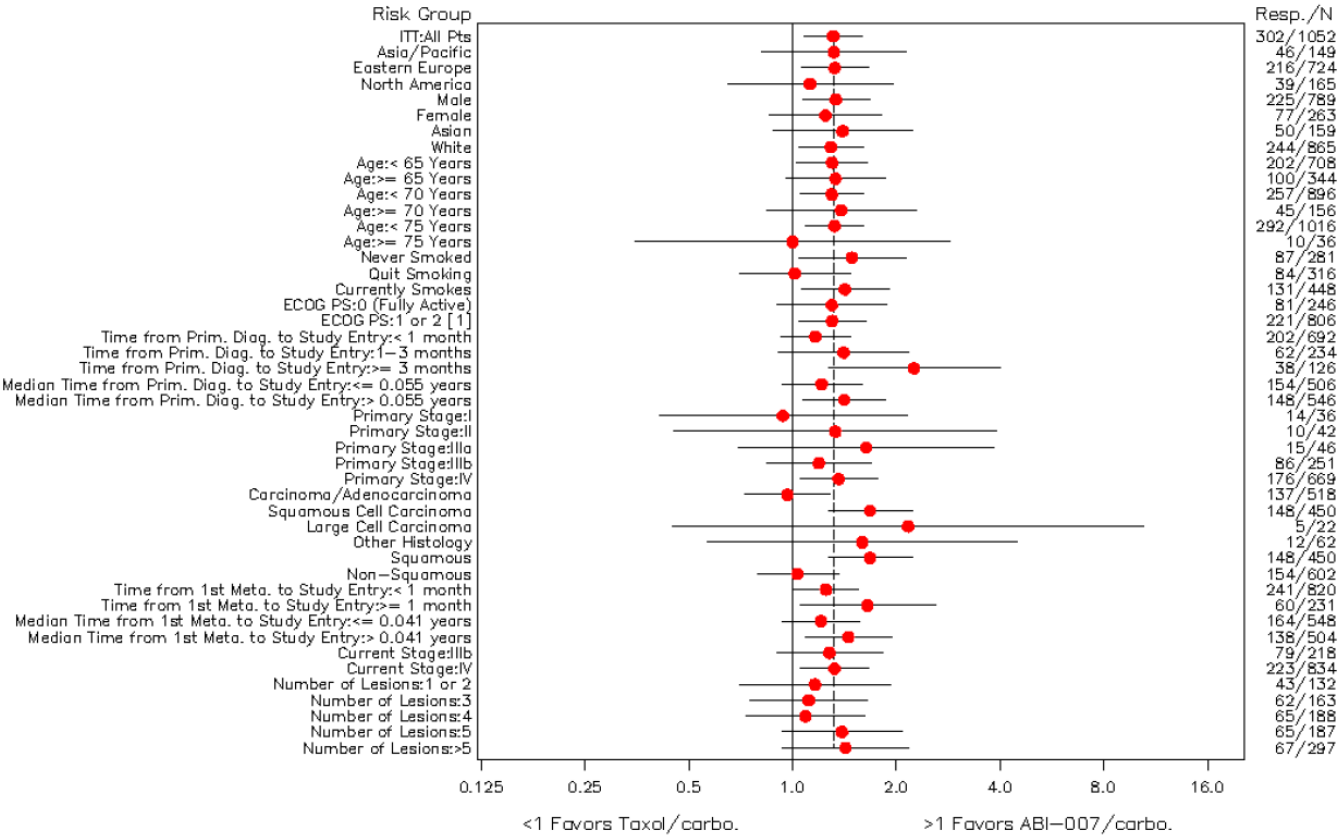
Results were consistent with the original analysis that censors PFS preceded by 2 or more missing assessments or start of new anticancer therapy for both blinded radiology and investigator assessments:

- Blinded radiology assessment: $HR_{A/T}$ of 0.980 (95% CI: 0.747, 1.287) versus 0.901 (95% CI = 0.652, 1.244)
- Investigator assessment: $HR_{A/T}$ of 0.925 (95% CI = 0.737, 1.161) versus 0.903 (95% CI = 0.706, 1.155).

Subgroups

ORR

Figure 8 hereafter displays the forest plot of all prognostic factors analysed for ORR based on the blinded radiological assessment.



Note: The horizontal axis uses a logarithmic scale.
Note: The Australia/New Zealand region (N = 14 patients) is not shown.
[1] ECOG PS: 1 (Restrictive but Ambulatory) or 2 (Ambulatory but Unable to Work)

Figure 8: Effect of Prognostic Factors on Blinded Radiology Assessed Confirmed Overall Response Rate Ratio (ITT Subgroups) CA031

Time from primary diagnosis

For the time from primary diagnosis to randomization, a treatment interaction was found on ORR and PFS, but not OS. In addition, while patients whose time from date of the first documented metastasis/relapse to date of study entry was < 1 month showed similar PFS in both treatment arms, patients in the Abraxane treatment arm whose time since documented metastasis/relapse was ≥1 month displayed improved PFS compared to Taxol treated patients (data not shown).

Histology

Results of exploratory analyses of ORR, PFS and OS according to histology are shown in Table 19.

Table 19: Blinded Radiology Assessment of ORR, PFS and OS by histology (ITT Subgroups)

Prognostic Factor Category/Statistic/N	ABI-007/ carboplatin	Taxol/ carboplatin	Response Rate/ Hazard Ratio (A/T)[a]	P-value
Patients with Confirmed Complete or Partial Overall Response				
Squamous cell carcinoma	94/229 (41%)	54/221 (24%)	1.680	< 0.001*
95% Confidence Interval			1.271, 2.221	
Non-squamous cell carcinoma	76/292 (26%)	78/310 (25%)	1.034	0.808
95% Confidence Interval			0.788, 1.358	
Progression-free Survival				
Squamous cell carcinoma	5.6	5.7	0.865	0.245
95% Confidence Interval	5.5, 6.7	5.4, 6.7	0.680, 1.101	
Non-squamous cell carcinoma	6.9	6.5	0.933	0.532
95% Confidence Interval	6.0, 8.1	5.6, 7.0	0.750, 1.159	
Overall Survival				
Squamous cell carcinoma	10.7	9.5	0.890	0.284
95% Confidence Interval	9.4, 12.5	8.6, 11.6	0.719, 1.101	
Non-squamous cell carcinoma	13.1	13.0	0.950	0.611
95% Confidence Interval	11.5, 16.1	11.1, 14.3	0.779, 1.158	

Additional analyses of PFS without censoring events of PFS preceded by 2 or more missing assessments or start of new anticancer therapy and by histology (squamous cell carcinoma and non-squamous cell carcinoma) for both the blinded radiology and investigator assessed PFS were performed (table 20).

Table 20: Blinded Radiology/Investigator Assessed PFS by EMA Methodology by Histology (ITT Population)

	ABI-007/ carboplatin	Taxol/ carboplatin	$HR_{A/T}$	p-value
Blinded radiology assessed PFS				
Squamous cell carcinoma	**N = 229**	**N = 221**		
Number of patients who died or had progression	194 (85%)	193 (87%)		
Median PFS (months)	5.9	5.9	0.893	0.271
95% CI	5.5, 7.7	5.6, 6.9	0.730, 1.091	
Non-squamous cell carcinoma	**N = 292**	**N = 310**		
Number of patients who died or had progression	235 (80%)	249 (80%)		
Median PFS (months)	7.0	6.7	0.998	0.988
95% CI	6.1, 8.3	5.6, 7.6	0.832, 1.197	
Investigator assessed PFS				
Squamous cell carcinoma	**N = 229**	**N = 221**		
Number of patients who died or had progression	210 (92%)	202 (91%)		
Median PFS (months)	5.5	5.4	0.918	0.387
95% CI	5.1, 5.7	4.3, 5.6	0.755, 1.115	
Non-squamous cell carcinoma	**N = 292**	**N = 310**		
Number of patients who died or had progression	265 (91%)	284 (92%)		
Median PFS (months)	5.7	5.6	0.951	0.559
95% CI	4.9, 6.8	5.3, 6.1	0.803, 1.126	

Abbreviations: CI = confidence interval; EMA = European Medicines Agency; HR = hazard ratio; ITT =- intent-to-treat; PFS = progression-free survival.
Source: Table EU_Q6_01a, Table EU_Q6_01b, Table EU_Q6_03a, Table EU_Q6_03b

Region/Age

When OS was analysed per region, a statistically significant difference between treatment arms was only found in the region of North-America.

Analysis of efficacy endpoints by age subgroup is presented in the below table.

Table 21: ORR, PFS, and OS by Age Subgroup

	Patients Aged < 70 (N=896)				Patients Aged ≥ 70 (N=156)			
	ABI-007/ Carbo	Taxol/ Carbo	RR/HR	P-value	ABI-007/ Carbo	Taxol/ Carbo	RR/HR	P-value
ORR	32%	25%	1.300	0.013*	34%	24%	1.385	0.196
Median PFS	6.0 mo	5.8 mo	0.903	0.256	8.0 mo	6.8 mo	0.687	0.134
OS	11.4 mo	11.3 mo	0.999	0.988	19.9	10.4	0.583	0.009*

Ancillary analyses

In order to investigate whether there is a benefit in treating patients for more than 6 cycles , analyses of PFS and OS were conducted in responders treated for ≤ 6 cycles and > 6 cycles.

Table 22: Blinded Radiology Assessed PFS for Responder Patients Receiving ≤ 6 Cycles or > 6 Cycles of Therapy (ITT Population)

	ABI-007/carboplatin		Taxol/carboplatin	
	≤ 6 cycles (N = 78)	> 6 cycles (N = 92)	≤ 6 cycles (N = 57)	> 6 cycles (N = 75)
Number of patients who died or had progression	36 (46%)	49 (53%)	37 (65%)	41 (55%)
Median PFS (months)	7.9	10.2	6.8	11.3
95% CI	6.8, 9.8	9.5, 11.3	5.7, 8.0	9.6, 13.8

Abbreviations: CI = confidence interval; ITT = intent-to-treat; PFS = progression-free survival.
Source: Table EU_Q10b_01a, Table EU_Q10b_01b

Table 23: Overall Survival for Responder Patients Receiving ≤ 6 Cycles or > 6 Cycles of Therapy (ITT Population)

	ABI-007/carboplatin		Taxol/carboplatin	
	≤ 6 cycles (N = 78)	> 6 cycles (N = 92)	≤ 6 cycles (N = 57)	> 6 cycles (N = 75)
Number of patients who died	46 (59%)	50 (54%)	34 (60%)	43 (57%)
Median OS (months)	16.2	19.3	17.6	21.7
95% CI	12.4, 22.3	16.7, --	13.8, --	18.6, 24.8

Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.
Note: Patients that did not die were censored at the last known time the patient was alive.
Source: Table EU_Q10b_02a, Table EU_Q10b_02b

Additional and sensitivity analysis were conducted including: sensitivity analysis regarding censored patients in the PFS analysis and regarding the impact of second-line therapy for the OS results. The results of the additional and sensitivity analysis were consistent with the primary analysis.

Based on the EMA methodological considerations for PFS, a subsequent non-inferiority analysis was conducted for PFS and OS, with a pre-specified non-inferiority margin of 15%. The non-inferiority criterion was met for both PFS and OS with the upper bound of the 95% confidence interval for the associated hazard ratios being less than 1.176 (Table 24).

Table 24: Non-inferiority analyses on progression-free survival and overall survival in randomized non-small cell lung cancer trial (intent-to-treat population)

Efficacy Parameter	Abraxane (100 mg/m²/week) + carboplatin (N=521)	Solvent-based paclitaxel (200 mg/m² every 3 weeks) + carboplatin (N=531)
Progression-free Survival[a] (independent review)		
Death or progression, n (%)	429 (82%)	442 (83%)
Median PFS (95% CI) (months)	6.8 (5.7, 7.7)	6.5 (5.7, 6.9)
$HR_{A/T}$ (95% CI)	0.949 (0.830, 1.086)	
Overall Survival		
Number of deaths, n (%)	360 (69%)	384 (72%)
Median OS (95% CI) (months)	12.1 (10.8, 12.9)	11.2 (10.3, 12.6)
$HR_{A/T}$ (95.1% CI)	0.922 (0.797, 1.066)	

CI = confidence interval; $HR_{A/T}$ = hazard ratio of Abraxane/carboplatin to solvent-based paclitaxel/carboplatin; p_A/p_T = response rate ratio of Abraxane/carboplatin to solvent-based paclitaxel/carboplatin.
[a] Per EMA methodological considerations for PFS endpoint, missing observations or initiation of subsequent new therapy were not used for censoring.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 25: Summary of Efficacy for trial CA031

Study identifier	CA031		
Design	Multi center randomized phase III study		
	First patient enrolled: Last patient discontinued study treatment:		14 December 2007 21 December 2012
Hypothesis	Non-inferiority: The null hypothesis was that the Abraxane/carboplatin regimen response rate was equal to that of Taxol/carboplatin regimen		
Treatments groups	Abraxane/carboplatin (A)		Abraxane 100 mg/m² given weekly carboplatin (AUC=6) every 3 weeks N=521
	Taxol/carboplatin (T)		Taxol 200 mg/m² every 3 weeks carboplatin (AUC=6) every 3 weeks
Endpoints and definitions	Primary-endpoint	ORR	percentage of patients who achieved an objective confirmed CR or PR based on the blinded radiological review using RECIST response guidelines
	Secondary endpoint	PFS	time from the day of randomization to the start of disease progression or death (any cause), whichever occurred first, based on the blinded radiological review assessment of response
	Secondary endpoint	OS	time from the day of randomization to patients death (any cause)
	Secondary endpoint	Disease control	percentage of patients with stable disease for ≥16 weeks or confirmed CR or PR response
	Secondary endpoint	Duration of response in responding patients	
Database cut-off	31 January 2011		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT n=1052, Treated population n=1038		
Descriptive statistics and estimate variability	Treatment group	Abraxane/carboplatin	Taxol/carboplatin
	Number of subject	N=521	N=531
	ORR	170 (33%)	132 (25%)
	Response Rate ratio (p_A/p_T) P=value	1.313 0.005	
	Median PFS by blinded Radiological Assessment (CI)	6.3 months (5.6, 7.0)	5.8 months (5.6, 6.7)
	$HR_{A/T}$ (CI) P-value	0.902 (0.767, 1.060) 0.214	
	Median PFS – non inferiority analysis based on EMA methodological considerations (95% CI)	6.8 months (5.7, 7.7)	6.5 months (5.7, 6.9)
	$HR_{A/T}$ (CI)	0.949 (0.830, 1.086)	
	Median OS (CI)	12.1 months (10.8,12.9)	11.2 months (10.3, 12.6)
	$HR_{A/T}$ (CI) P-value	0.922 (0.797, 1.066) 0.271	
	Disease Control Rate	53%	49%
	p_A/p_T (CI) p-value	1.074 (0.953, 1.210) 0.239	
	Duration of Response (CI)	9.6 months (8.3, 10.8)	9.5 months (8.1, 11.0)
	P-value	0.551	

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

The study results for the 4 submitted clinical studies (CA031, CA028, CA015 and CA018) were presented separately by the applicant and no pooled analyses across studies were performed.

Efficacy of Abraxane/carboplatin Compared with paclitaxel (175 mg/m^2)/cisplatin

The Applicant identified two published Phase 3, randomized, controlled, registration trials (Giaccone, 1998; Gatzemeier, 2000) and one other published Phase 3 trial (Smit, 2003) that evaluated the EU-approved combination of paclitaxel (175 mg/m^2) and cisplatin in advanced NSCLC patients.

- Giaccone et al[3] randomized 332 patients with advanced NSCLC to receive either
    - cisplatin 80 mg/m^2 on Day 1 and teniposide 100 mg/m^2 on Days 1, 3 and 5 of each 3-week cycle,
    - cisplatin 80 mg/m^2 on Day 1 and paclitaxel 175 mg/m^2 by 3-hour infusion on Day 1 of each 3-week cycle.
- The second study, conducted by Gatzemeier et al[4], randomized 414 patients with Stage IIIb/IV NSCLC to compare
    - high dose cisplatin 100 mg/m^2 on Day 1 of each 3-week cycle versus
    - cisplatin 80 mg/m^2 on Day 1 and paclitaxel 175 mg/m^2 by 3-hour infusion on Day 1 of each 3-week cycle.
- A third study, conducted by Smit et al[5], randomized 480 chemotherapy-naïve patients with advanced NSCLC to receive 1 of 3 treatment regimens:
    - paclitaxel 175 mg/m^2 by 3-hour infusion on Day 1 combined with cisplatin 80 mg/m^2 on Day 1 of each 3-week cycle,
    - gemcitabine 1250 mg/m^2 on Day 1 and Day 8 combined with cisplatin 80 mg/m^2 on Day 1 of each 3-week cycle,
    - paclitaxel 175 mg/m^2 by 3-hour infusion on Day 1 combined with gemcitabine 1250 mg/m^2 on Day 1 and Day 8 of each 3-week cycle.

The table below provides a side-by-side comparison of the key efficacy endpoints (ORR, PFS, and OS) for Abraxane/carboplatin with the approved combination of paclitaxel (175 mg/m^2)/cisplatin.

Table 26: Efficacy from study CA031 (Abraxane/carboplatin and paclitaxel [200 mg/m^2]/carboplatin arms) and paclitaxel (175 mg/m^2)/cisplatin studies

Study (N)	Platinum Doublet (n)	ORR (%)	PFS (Median, months)	OS (Median, months)
Study CA031 (N = 1052)	Abraxane/carboplatin (n = 521)	33% by RECIST	6.3	12.1
Giaccone, 1998 (N = 332)	Paclitaxel/cisplatin (n = 155)	41% by WHO	5.4	9.7
Gatzemeier, 2000 (N = 414)	Paclitaxel/cisplatin (n = 190)	26% by WHO	4.1[a]	8.1
Smit, 2003 (N = 480)	Paclitaxel/cisplatin (n = 151)	32% by WHO	4.2	8.1
Study CA031 (N = 1052)	Paclitaxel/carboplatin (n = 531)	25% by RECIST	5.8	11.2

Abbreviations: CSR = clinical study report; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization.
[a] Time to progression, PFS not assessed in this study.

Supportive study

CA018

CA018 was multi centre, an open-label, Phase II Trial of Abraxane in patients with NSCLC. The primary objectives of this study were to determine the antitumor activity of Abraxane (monotherapy) as first line

[3] Giaccone, 1998; Study Protocol CA 139-103 in Food and Drug Administration [FDA] Taxol Medical Review, 1998
[4] Gatzemeier, 2000; Study Protocol CA 139-208 in FDA Taxol Medical Review,1998
[5] Smit EF, van Meerbeeck JP, Lianes P et al. Three-arm randomized study of two cisplatin-based regimens and paclitaxel plus gemcitabine in advanced non-small-cell lung cancer: A phase III trial of the European Organization for Research and Treatment of Cancer Lung Cancer Group—EORTC 08975. J Clin Oncol 2003; 21: 3909 –3917.

therapy in patients with metastatic NSCLC and to evaluate the safety/tolerability of Abraxane in this study population. The primary efficacy endpoint was the proportion of patients in the treated population who achieved an objective confirmed complete or partial response. Secondary objectives were to evaluate disease control rate (proportion of patients with SC ≥ 16 weeks, or a confirmed complete or partial overall response), TTP, duration of response and OS.

Eligible patients were ≥ 18 years of age with histologically or cytologically confirmed NSCLC, with evidence of inoperable local recurrence or metastasis and no other malignancy. Patients had to have at least one measurable lesion, adequate hematologic levels and hepatic/renal function, baseline ECOG PS of 0 or 1, and expected survival of > 12 weeks. No prior therapy for metastatic disease was permitted. Patients were excluded if they had active brain metastasis; prior brain metastasis was permitted if the patient was in complete remission for ≥ 1 month after treatment. First patient was enrolled on 01 March 2004 and the study was completed on 10 June 2005.

Abraxane was used at a dose of 260 mg/m^2 administered IV over 30 minutes every 3 weeks without steroid premedication. Patients were allowed to continue treatment in the absence of disease progression or unacceptable toxicity.

Patients were evaluated for response on Day 15 of every third cycle per the RECIST guidelines. Patients who achieved a response or had SD for ≥ 16 weeks were re-evaluated 4 weeks later to confirm their clinical response. Survival was assessed on a monthly basis for 6 months after study completion and every 3 months thereafter for 18 months (total of 2 years).

Results

The investigator-determined ORR (proportion of patients with confirmed complete or partial overall response) in study CA018 was 16% (95% CI=5.2, 27.3).

Median PFS was 5.7 months (95% CI=3.9, 6.5 months) and median OS was 11.1 months (95% CI=9.5 months, upper bound not reached). Median TTP was 6.0 months and the probability of surviving 1 year was 42%. The proportion of patients who achieved controlled disease was 49% (95% CI=33.9, 63.8).

Table 27: Efficacy results CA018

Study CA018	
Efficacy Parameter	**ABI-007 260 mg/m^2 Every 3 Weeks (N = 43)**
Investigator Assessment of ORR	
Confirmed complete or partial overall response, n (%)	7 (16%)
95% CI	5.2, 27.3
Investigator Assessment of PFS	
Death or progression, n (%)	33 (77%)
Median PFS (months)	5.7
95% CI	3.9, 6.5
Overall Survival	
Number of deaths, n (%)	18 (42%)
Median OS (months)	11.1
95% CI	9.5, --
Investigator Assessment of Disease Control Rate	
SD ≥ 16 weeks, CR or PR, n (%)	21 (49%)
95% CI	33.9, 63.8

CI = confidence interval; CR = complete response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; SD = stable disease.

2.4.3. Discussion on clinical efficacy

The indication applied for concerns use of Abraxane in combination with carboplatin for first-line treatment of patients with non-small cell lung cancer who are not candidates for potentially curative surgery and/or radiation therapy. This variation was supported by one pivotal study CA031 and three supportive Phase II trials.

Design and conduct of clinical studies

The dose-finding study CA028 investigated the efficacy and safety of different dose levels and administration regimens of Abraxane. The study indicated that a weekly regimen of Abraxane 100 mg/m^2 seemed appropriate when taking both the efficacy and safety data from the study into consideration. However, study CA028 did not investigate dosing regimens and schedules of Taxol and Abraxane which would result in comparable levels of biological active paclitaxel in the tumour, taking into account the expected mechanistic differences in paclitaxel uptake due to formulation. Thus, it cannot be excluded that the reported better ORR with Abraxane (see efficacy data and additional analysis below) is caused by differences in dosing schedule and not differences in formulation of paclitaxel.

In the comparator arm of study CA031, Taxol was given once every 3 weeks at a dose of 200 mg/m^2 which is higher than the 175 mg/m^2 dose once every 3 weeks used in combination with cisplatin, which is the recommended treatment regimen for Taxol in the treatment of NSCLC. In addition, Taxol was combined with carboplatin instead of cisplatin, which is the recommended combination for NSCLC treatment in Europe. However, this dose has been used in some countries already in the EU and in various clinical trials and can be considered acceptable as a reference dose.

In response to a CHMP request to further discuss the efficacy and safety of the comparator versus the Taxol/cisplatin regimen as used in the EU, the MAH compared the efficacy of Abraxane/carboplatin with historical data of paclitaxel (175 mg/m^2)/cisplatin. The efficacy results of 3 published studies in which paclitaxel/cisplatin was used for the treatment of advanced NSCLC were submitted. Despite the limitations of the differences between the methods for assessing radiological response, all studies reported meaningful ORR outcomes in the intent-to-treat population. The PFS and OS for Abraxane/carboplatin in Study CA031 were numerically better compared with paclitaxel (175 mg/m2)/cisplatin in the other three studies.

Although no firm conclusion can be drawn from cross study comparisons, the comparison with historical data suggests that the efficacy of the Abraxane/carboplatin combination is comparable with the efficacy results for the paclitaxel/cisplatin combination.

In general the baseline characteristics are reasonably balanced between the treatment groups.

The eligibility for study CA031 was not restricted to a specific histologic subtype or to specific molecular characteristics of the tumour. The study was initiated in 2005. At that time treatment was not based on histology or molecular targets.

As the study was open-label, the sample size re-assessment was unblinded, which is discouraged (reflection paper on adaptive design, CHMP/EWP/2459/02) because an increase of the sample size would give information of the magnitude treatment effect at time of the interim analysis. This knowledge could have biased end-of-trial results (e.g. because investigators alter their recruitment based on knowledge of the interim analysis treatment effect). However, it appears that the patient enrolment had been completed before the interim analysis. Therefore, it is not expected that the results of the interim analysis have introduced a bias regarding patient selection. The provided baseline characteristics of the cohorts of patients that were included in the interim analysis (n=404) and not (n=648) [data not shown], showed that in general, the baseline characteristic and cancer history, were similar between both cohorts of patients.

OS or alternatively PFS are preferred as primary endpoint for oncologic agents instead of ORR. However, as this is a study with paclitaxel, - of which its activity in treatment of patients with NSCLC is an acknowledged option- the ORR as primary endpoint can be accepted when results of PFS and OS as important secondary endpoints, are in line with the ORR results.

The efficacy endpoints the ORR, PFS and OS, showed comparable improvements between the two cohorts of patients.

Overall, the efficacy analysis showed similar results between the cohorts. Therefore, it seems plausible that no selection or information bias has been introduced by the interim analysis.

Efficacy data and additional analyses

The proportion of patients with a confirmed complete or partial overall response per blinded radiology assessment, was significantly higher for the Abraxane/carboplatin regimen relative to the Taxol/carboplatin regime (33% versus 25%, p=0,005; response rate ration [p_A/p_T]=1.313).

In general the treatment effect in the Abraxane/carboplatin on ORR was consistent. With the exception of patients aged ≥ 75 years or patients with primary Stage I tumours or adenocarcinomas, all subgroups response rate ratios were in favour of Abraxane/carboplatin.

For the Abraxane/carboplatin arm the median PFS was 6.3 months (95% CI=5.6, 7.0 months), while for the Taxol/carboplatin arm the median PFS was 5.8 months (95% CI=5.6, 6.7 months). The $HR_{A/T}$= was 0.92 (95.1% CI=0.767, 1.060). The PFS difference between the arms was not statistical significant (p=0.214). The median OS for patients treated with Abraxane/carboplatin was 12.1 months and for Taxol/carboplatin 11.2 months. The $HR_{A/T}$= was 0.92 (95.1% CI=0.797, 1.066). The OS difference between the arms was not statistically significant (p=0.271).

The study was set up as superiority study for the ORR response, and effectively a switch from superiority to non-inferiority was made for PFS and OS and non-inferiority analyses were conducted. The non-inferiority margin was set after the interim analyses, but before the final analyses. Based on methodological and clinical grounds, the applicant considered that the 15% margin was justifiable for this study. However, the non-inferiority margin has external validity as these margins were also applied in previous procedures. It was concluded that for both PFS and OS, non-inferiority of Abraxane/carboplatin compared with Taxol/carboplatin was determined as the upper bounds of the 95% CIs of the $HR_{A/T}$ were <1.176. The point estimates for the medians for PFS and OS are higher in the experimental group than in the control arm, supporting non-inferiority. The PFS results following the non-inferiority analysis based on EMA methodological considerations for PFS were 6.8 months (95% CI=5.7, 7.7 months) for the Abraxane/carboplatin arm versus 6.5 months (95% CI=5.7, 6.9 months) for the Taxol/carboplatin arm. The $HR_{A/T}$= was 0.949 (95% CI=0.830, 1.086).

A high percentage (43% and 41% for the Abraxane/carboplatin arm and the Taxol/carboplatin arm, respectively) of patients in the PFS analysis of the blinded reviewer was censored. Most patients were censored due to scanning discontinuation per PD by Investigator. Also a high percentage of patients were censored for the OS analysis (31% and 28% of the Abraxane/carboplatin and Taxol/carboplatin arm, respectively). The percentage of patients who were censored due to completion of 18 months follow-up time is comparable for the two treatment arms and will not influence the median OS results.

The applicant has performed analyses of interaction of prognostic factors with treatment effect. For ORR (determined by the blinded radiology assessment) two prognostic factors showed a significant interaction (defined as $p \leq 0.10$ in the SAP) based on a logistic regression model: Time interval from primary diagnosis to randomization, and histology.

For patients with ≥3 months since primary diagnosis, the response rate was highest in the Abraxane arm. An exploratory PFS analysis showed that the results in both arms seem more favourable the longer the time since primary diagnosis, and seem most favourable in the Abraxane arm.

For patients with tumours of squamous histology the response rate was found to be higher in the Abraxane arm than in the Taxol arm, while for patients with adenocarcinoma there was no difference between treatment arms. In the investigator based analyses of ORR, although a significant difference was found between treatment arms for patients with squamous tumour histology, there was no obvious difference within treatment arms according to histology. The response rates were similar and the confidence intervals overlapped. The difference between treatment arms in response rates in patients with squamous tumour histology observed in the blinded review did not result in any significant difference between treatment arms in terms of PFS and OS. Further to the CHMP request, the applicant has performed analyses of the effect of prognostic factors on ORR (complete or partial response) in patients with squamous cell carcinoma by independent blinded radiology review and investigator assessment (data not shown). The findings were overall not indicative of any clustering of prognostic factors in either treatment arm.

Most of the patients that had a complete or partial response obtained this response during the first 6 cycles of treatment. Thus in terms of ORR, there seems to be little to gain by treating the patients for more than 6 cycles. However additional analyses of PFS and OS in responders treated for ≤ 6 cycles and > 6 cycles indicate that median PFS and OS are longer for patients receiving > 6 cycles of therapy of ABI-007/carboplatin. The same holds true for patients receiving therapy with Taxol/carboplatin. Since there were no indications of increased frequency of AEs of myelosuppression, peripheral neuropathy, and myalgia or arthralgia in patients receiving > 6 cycles of therapy compared to those receiving ≤ 6 cycles, or increased frequencies of Grade 3 or 4 AEs of the same categories (see clinical safety) it seems justified that treatment may continue beyond 6 cycles.

When OS was analysed per region, a statistically significant difference between treatment arms was only found in the region of North-America (data not shown). This could be driven by the larger number of patients ≥ 70 years from North-America. An interaction was also found for age. Results of exploratory analyses of ORR, PFS and OS according to age (≥70 or <70) revealed a tendency in patients ≥70 years of prolonged PFS in the Abraxane arm and an unusual long OS.

The results of the secondary endpoints (disease control rate, duration of response and chance in performance status) were comparable for both treatment arms (Abraxane/carboplatin and Taxol/carboplatin). In addition, the subgroup analysis for pre-specified categories were consistent with the primary analysis for all efficacy endpoints.

The issue of infusion lines flushing was raised during the last PSUR procedure (EMEA/H/C/000778/PSUV/0066 adopted by PRAC on 11 September 2014) further to a potential signal of medication error resulting in a lack of efficacy (substantial amount of product remaining in the infusion line). Given the small volume of Abraxane being administered, the potential impact of not flushing the infusion line on the administered dose was considered important. In a subsequent procedure (LEG 29 adopted by PRAC on 4 December 2014), the PRAC noted that the current wording in the Abraxane SmPC does not inform on flushing the line in order to ensure delivering of the full dose. Furthermore, the PRAC considered that additional information should be gathered from re-analysing data from registration studies, from the provision of stability data of Abraxane with commonly used diluents and calculations on the amounts of Abraxane lost if flushing is not performed. The MAH committed to submit this information in the next PSUR in order for the PRAC to better understand the extent and the exact nature of the issue.

The need to introduce a statement in the PI in relation to infusion lines flushing was discussed by CHMP in the context of the current procedure and it was considered important to include a statement in sections 4.2 and 6.6 of the SmPC to recommend the flushing of the injection line to ensure that the correct amount of product is administered to patients, acknowledging that this issue will be closely followed in the next PSURs.

2.4.4. Conclusions on the clinical efficacy

The currently provided efficacy data suggest a similar efficacy Abraxane/carboplatin combination therapy as for Taxol/carboplatin combination therapy for the treatment of NSCLC. Further to the review of all data submitted to support the dose of Abraxane and the use of Taxol/carboplatin in the comparator arm of the pivotal study CA031, the CHMP considers that Abraxane/carboplatin can be used as an alternative treatment to Taxol/cisplatin in the treatment of NSCLC, based on individual characteristic and preferences of patients.

2.5. Clinical safety

Introduction

The safety data for Abraxane in combination with carboplatin for the treatment of NSCLC are mainly obtained from study CA031. In study CA028 limited number (25) of patients were treated with the same dose of Abraxane/carboplatin as in the CA031 study. For the use of Abraxane monotherapy in the treatment of NSCLC patients, safety data was obtained from two clinical studies (CA015 and CA018).

Patient exposure

A total number of 765 patients received Abraxane/carboplatin therapy during the studies CA031 and CA028. Of these patients 589 received weekly Abraxane in combination with q3w carboplatin in the pivotal CA031 study and primary supportive study CA028 and 176 patients received Abraxane every 3 weeks/carboplatin in study CA028. The most common Abraxane dose administered during the Abraxane/carboplatin treatment was 100 mg/m^2 (N=539).

In study CA031, a median of 6.0 cycles was administered in each treatment arm. Duration of treatment was comparable between the treatment arms in Study CA031 and for combination therapy with Abraxane given weekly over every 3 weeks; i.e., approximately 75% of patients received 4 cycles; approximately 50% of patients received 6 cycles; approximately 10% of patients received 12 cycles.

The median cumulative taxane dose and median average taxane dose intensity were in Study CA031, higher with Abraxane/carboplatin (1325.0 mg/m^2 and 81.98 mg/m^2/week, respectively) relative to Taxol/carboplatin (1125.0 mg/m^2 and 65.12 mg/m^2/week, respectively). The median percentage of the protocol-specified dose administered and the proportion of patients receiving ≥90% of the protocol-specified taxane dose was lower with Abraxane/carboplatin (81.98% and 34%, respectively) relative to Taxol/carboplatin (97.67% and 73% respectively). The median percentage of protocol-specified carboplatin dose administered was comparable for the 2 treatment arms (99.77% and 100.00%, respectively).

Taxane dose reductions

In study CA031, the proportion of patients with treatment-related AEs resulting in taxane reduction was higher in the Abraxane/carboplatin (45%) arm relative to the Taxol/carboplatin arm (22%). Treatment-related AEs resulting in dose reduction in ≥5% of patients in either treatment arm were neutropenia (24%), thrombocytopenia (13%), and anaemia (5%) with Abraxane/carboplatin. In the Taxol/carboplatin arm AEs that resulted in taxane dose reduction were neutropenia (9%), thrombocytopenia (4%), and peripheral sensory neuropathy (5%). Despite the overall lower incidence of neutropenia in the Abraxane/carboplatin arm compared to the Taxol/carboplatin arm, neutropenia more commonly lead to dose reductions in the Abraxane/carboplatin arm.

There was a lower incidence of sensory neuropathy leading to dose reduction in the Abraxane/carboplatin arm compared to the Taxol/carboplatin arm (1% versus 6%), but a higher incidence of thrombocytopenia resulting in dose reductions in the Abraxane/carboplatin arm than in the Taxol/carboplatin arm.

Dose Interruptions/Delays

In study CA031, taxane dose delay due to treatment-related AEs were common in both treatment arms, and more frequent with Abraxane/carboplatin relative to Taxol/carboplatin (67% versus 35%). Results were comparable for carboplatin dose delays. Even though there was a lower incidence of neutropenia and grade ¾ neutropenia in the Abraxane/carboplatin arm, neutropenia resulted more commonly in dose interruptions or delays in that arm. The 3 treatment-related events most frequently resulting in taxane dose delay were neutropenia (41%), thrombocytopenia (30%), and anaemia (14%) with the

Abraxane/carboplatin arm. For the Taxol/carboplatin arm the AEs most frequently resulting in dose delay were neutropenia (12%), thrombocytopenia (12%) and peripheral sensory neuropathy (5%).

Adverse events

Table 28: Overview of Adverse Events during the NSCLC studies (Treated Populations: Non-small Cell Lung Cancer Studies; Abraxane combination and monotherapy)

Category	ABI-007/carboplatin Therapy					ABI-007 Monotherapy
	CA031		CA031, CA028			CA015, CA018
	ABI-007 100 mg/m^2/ Week + carboplatin (N =514) n (%)	Taxol 200 mg/m^2 Every 3 Weeks + carboplatin (N =524) n (%)	ABI-007 (All Doses) Weekly + carboplatin[a] (N = 589) n (%)	ABI-007 (All Doses) Every 3 Weeks + carboplatin[b] (N = 176) n (%)	ABI-007 + carboplatin Pooled[c] (N = 765) n (%)	Pooled[d] (N = 118) n (%)
Any TEAE	483 (94%)	504 (96%)	557 (95%)	174 (99%)	731 (96%)	117 (>99%)
Treatment-related AE	469 (91%)	481 (92%)	541 (92%)	172 (98%)	713 (93%)	115 (97%)
TEAE ≥ grade 3	360 (70%)	355 (68%)	423 (72%)	151 (86%)	574 (75%)	78 (66%)
Treatment-related AE ≥ grade 3	321 (62%)	315 (60%)	379 (64%)	138 (78%)	517 (68%)	53 (45%)
Fatal SAEs	18 (4%)	19 (4%)	23 (4%)	17 (10%)	40 (5%)	4 (3%)
Treatment-related fatal SAEs	1 (<1%)	1 (<1%)	2 (<1%)	6 (3%)	8 (1%)	0
SAEs (fatal and nonfatal)	93 (18%)	80 (15%)	111 (19%)	49 (28%)	160 (21%)	40 (34%)
Treatment-related SAEs (fatal and nonfatal)	37 (7%)	30 (6%)	49 (8%)	31 (18%)	80 (10%)	12 (10%)
AEs resulting in permanent taxane discontinuation	80 (16%)	84 (16%)	101 (17%)	58 (33%)	159 (21%)	45 (38%)
Treatment-related AEs resulting in permanent taxane discontinuation	60 (12%)	60 (11%)	75 (13%)	44 (25%)	119 (16%)	34 (29%)
AEs resulting in dose reduction	237 (46%)	120 (23%)	275 (47%)	78 (44%)	353 (46%)	12 (10%)
Treatment-related AEs resulting in dose reduction	233 (45%)	117 (22%)	270 (46%)	78 (44%)	348 (45%)	12 (10%)

Abbreviations: AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a] Includes Studies CA031 (N=514) and CA028 (N=75).
[b] Includes Study CA028 (N=176).
[c] Includes Studies CA031 (N=514) and CA028 (N=251).
[d] Includes Studies CA015 (N=75) and CA018 (N=43).

For study CA031 the incidence of treatment related AE, treatment related AE grade 3 or higher, treatment-related SAEs, fatal SAEs, treatment related AEs resulting in permanent taxane discontinuation, were comparable for patients treated with Abraxane/carboplatin and for patients treated with Taxol/carboplatin.

During Abraxane/carboplatin dosing (CA031 and CA028), the most frequently reported TEAEs were alopecia (54%), neutropenia (52%), and thrombocytopenia (41%) with Abraxane weekly combined with carboplatin. In study CA031 the treatment related events that were reported less often in the Abraxane/carboplatin arm relative to Taxol/carboplatin arm were peripheral sensory neuropathy, arthralgia, and myalgia. Treatment-related events that were reported more frequently in Abraxane/carboplatin arm than in the Taxol/carboplatin arm included thrombocytopenia, anaemia, haemoglobin decreased, peripheral oedema and epistaxis.

In study CA031, treatment-related, grade 3 or higher AEs were reported in approximately 61% of patients in both treatment arms. The most frequently reported events were all hematologic toxicities in both arms.; i.e., neutropenia (36% and 40%), anaemia (21%) and thrombocytopenia (17%) with Abraxane/carboplatin; and neutropenia (40%), neutrophil count decreased (10%), and leukopenia (8%) with Taxol/carboplatin. Grade 3 or higher peripheral sensory neuropathy and peripheral neuropathy were reported less often with Abraxane/carboplatin relative to Taxol/carboplatin. On the other hand, grade 3 or higher anaemia and thrombocytopenia were reported more often with Abraxane/carboplatin relative to Taxol/carboplatin. Grade 3 to 4 decreased Absolute neutrophil count (ANC) occurred less frequently with Abraxane/carboplatin relative to Taxol/carboplatin.

Table 29: Treatment-emergent Adverse Event Reported in at Least 10% of Patients in Either Treatment Arm (Treated Population: Pivotal Study CA031)

System Organ Class Preferred Term (MedDRA [Version 12.1])	ABI-007 100mg/m² Weekly +carboplatin (N = 514) n (%)	Taxol 200mg/m² Every 3 Weeks + carboplatin (N = 524) n (%)	p-value[a]
Patients with ≥ 1 TEAE	483 (94%)	504 (96%)	0.114
Blood and Lymphatic System Disorders	**388 (75%)**	**317 (60%)**	**< 0.001***
Neutropenia	260 (51%)	250 (48%)	0.385
Anaemia	226 (44%)	109 (21%)	< 0.001*
Thrombocytopenia	208 (40%)	123 (23%)	< 0.001*
Leukopenia	97 (19%)	91 (17%)	0.573
Skin and Subcutaneous Tissue Disorders	**314 (61%)**	**333 (64%)**	**0.442**
Alopecia	287 (56%)	312 (60%)	0.233
Rash	50 (10%)	43 (8%)	0.447
Nervous System Disorders	**276 (54%)**	**348 (66%)**	**< 0.001***
Peripheral sensory neuropathy	136 (26%)	209 (40%)	< 0.001*
Neuropathy peripheral	104 (20%)	118 (23%)	0.405
General Disorders and Administration Site Conditions	**262 (51%)**	**235 (45%)**	**0.054**
Fatigue	126 (25%)	120 (23%)	0.560
Asthenia	84 (16%)	76 (15%)	0.440
Oedema peripheral	53 (10%)	21 (4%)	< 0.001*
Gastrointestinal Disorders	**212 (41%)**	**201 (38%)**	**0.375**
Nausea	140 (27%)	130 (25%)	0.396
Constipation	84 (16%)	67 (13%)	0.113
Diarrhoea	75 (15%)	58 (11%)	0.095
Vomiting	64 (12%)	64 (12%)	0.925
Respiratory, Thoracic and Mediastinal Disorders	**172 (33%)**	**154 (29%)**	**0.161**
Dyspnoea	63 (12%)	64 (12%)	> 0.999
Investigations	**154 (30%)**	**151 (29%)**	**0.733**
White blood cell count decreased	60 (12%)	64 (12%)	0.848
Haemoglobin decreased	56 (11%)	34 (6%)	0.015*
Neutrophil count decreased	55 (11%)	58 (11%)	0.921
Musculoskeletal and Connective Tissue Disorders	**130 (25%)**	**207 (40%)**	**< 0.001***
Arthralgia	65 (13%)	129 (25%)	< 0.001*
Myalgia	50 (10%)	97 (19%)	< 0.001*
Metabolism and Nutrition Disorders	120 (23%)	118 (23%)	0.768
Decreased appetite	89 (17%)	96 (18%)	0.686

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
[a] P-values tested using Fisher's exact test.
* Indicates statistically significant treatment difference.

Peripheral Neuropathy

In study CA031, the incidence of peripheral neuropathy was lower after Abraxane/carboplatin treatment than after Taxol/carboplatin treatment (48% versus 64%, respectively). For Abraxane/carboplatin, the incidence of Grade 3 sensory neuropathy was 4%, while for Taxol/carboplatin it was 12%. All cases of treatment-related, grade 4 neuropathy were in the Taxol/carboplatin arm.

Events of peripheral neuropathy occurred earlier during treatment and generally took longer to resolve with Taxol/carboplatin in comparison to Abraxane/carboplatin. The time to resolution to grade 1 neuropathy, measured from the day grade 3 or higher neuropathy developed to the day it resolved to grade 1 or better, was 38 days with Abraxane/carboplatin and 104 days with Taxol/carboplatin.

Anaemia

In the analysis of anaemia reported as an AE (by the investigator), the term anaemia includes haemoglobin decrease, haematocrit decreased, and red blood cell count decreased. In study CA031, anaemia events occurred more frequently with Abraxane/carboplatin relative to Taxol/carboplatin (54% versus 28%, respectively). This finding was consistent for anaemia events rated as grade 3 or higher (28% versus 7%). Only 4% of the events in the Abraxane/carboplatin and <1% of the events in the Taxol/carboplatin arm were considered SAEs. Very few Abraxane/carboplatin patients discontinued treatment (<1%) and a minority of patients had their doses reduced (6%) or delayed (17%) due to anaemia.

In study CA031 more patients in the Abraxane/carboplatin arm relative to the Taxol/carboplatin required anti-anaemic medications (35% versus 20%) and transfusions. Similarly, more Abraxane/carboplatin-treated patients had a concomitant blood transfusion than Taxol/carboplatin-treated patients (16% versus 4%). Of the patients who received a concomitant blood transfusion, the majority received one transfusion (62% (Abraxane/carboplatin) and 79% (Taxol/carboplatin)). The median time to the first transfusion was 65 days, or at the beginning of Cycle 4 in both arms.

Thrombocytopenia

The reported term thrombocytopenia includes thrombocytopenia and platelet count decrease. In study CA031, thrombocytopenia AEs occurred more frequently in the Abraxane/carboplatin arm than in the Taxol/carboplatin arm (45% versus 27%). Also grade 3 or higher events were more frequent in the Abraxane/carboplatin arm than in the Taxol/carboplatin arm (18% versus 7%). A higher percentage of patients in the Abraxane/carboplatin arm relative to the Taxol/carboplatin arm experienced a dose delay due to thrombocytopenia (34 versus 14%). There were very few thrombocytopenia SAEs (<1% in each treatment arm) and a minority of thrombocytopenia events led to taxane dose reductions (13% and 4%, respectively) or taxane discontinuations (3% and <1%, respectively).

There was no increase in haemorrhagic AEs with Abraxane/carboplatin relative to Taxol/carboplatin (13% and 10%, respectively). The types of haemorrhagic events were similar between the arms and there were few haemorrhagic SAEs in either treatment arm. In addition, the incidence of haemorrhagic events occurring within 2 weeks of a thrombocytopenic event was low in both treatment arms (5 patients (Abraxane/carboplatin) versus 1 patient (Taxol/carboplatin).

The results of time-to-improvement by at least 1 grade of Grade 3 or 4 anaemia and thrombocytopenia are presented below.

Table 30: Time to Recovery of Grade 3 or 4 Anaemia and Thrombocytopenia by Treatment Arm (Treated Population)

	Grade 3 or 4 TEAE			Grade 3 or 4 Related TEAE		
	ABI-007/ carboplatin (N = 514)	Taxol/carboplatin (N = 524)	p-value[a]	ABI-007/ carboplatin (N = 514)	Taxol/carboplatin (N = 524)	p-value[a]
Anemia						
Number of patients with a Grade 3 or 4 TEAE of anemia[b]	145 (28%)	37 (7%)	< 0.001	125 (24%)	33 (6%)	< 0.001
Number of patients with improvement by at least 1 grade	127 (88%)	30 (81%)		111 (89%)	28 (85%)	
Median time to improvement (days)	15.0	15.0	0.354	15.0	15.0	0.586
95% CI	11.0, 15.0	8.0, 26.0		9.0, 15.0	8.0, 26.0	
Thrombocytopenia						
Number of patients with a Grade 3 or 4 TEAE of thrombocytopenia[c]	94 (18%)	35 (7%)	< 0.001	94 (18%)	35 (7%)	< 0.001
Number of patients with improvement by at least 1 grade	87 (93%)	29 (83%)		87 (93%)	29 (83%)	
Median time to improvement (days)	8.0	12.0	0.079	8.0	12.0	0.079
95% CI	8.0, 9.0	8.0, 15.0		8.0, 9.0	8.0, 15.0	

Abbreviations: CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse events.
a Fisher exact test to compare percentage of patients with grade 3 or 4 anaemia/thrombocytopenia; Log-rank test for median time comparison.
b Anaemia is an event of interest as defined by ad hoc grouping of preferred terms based on MedDRA v12.1.
c Thrombocytopenia is an event of interest as defined by ad hoc grouping of preferred terms based on MedDRA v12.1.
Note: Time to improvement was defined as the time from the first occurrence of Grade 3 or higher to improvement by at least 1 grade. Patients not experiencing improvement were censored at the last time the patient was evaluated for adverse events.

Gastrointestinal Disorders

The overall incidence of gastrointestinal AEs was comparable for the Abraxane/carboplatin and Taxol/carboplatin arms (41% and 38%, respectively) of study CA031. The most common events in both arms were nausea (27% and 25%, respectively), constipation (16% and 13%, respectively), diarrhoea (15% and 11%, respectively), vomiting (12% for both arms) and stomatitis (65 and 4%, respectively). The incidence of grade 3 or higher events was low (≤5%) for both arms. Approximately 1% of patients in each treatment arm experienced a Gastrointestinal disorder SAE and 1 patient in the Taxol/carboplatin arm discontinued due to a gastrointestinal haemorrhage. Dose modifications due to these events were low in both arms.

ADRs

The below table lists the adverse reactions associated with the administration of Abraxane in combination with carboplatin. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

Table 31: Adverse reactions reported with Abraxane in combination with carboplatin (N = 514)

Infections and infestations	*Common:* Pneumonia, bronchitis, upper respiratory tract infection, urinary tract infection *Uncommon:* Sepsis, oral candidiasis
Blood and lymphatic system disorders[1]	*Very Common:* Neutropenia[1], thrombocytopenia[1], anaemia[1], leukopenia[1] *Common:* Febrile neutropenia, lymphopenia *Uncommon:* Pancytopenia
Immune system disorders	*Uncommon:* Drug hypersensitivity, hypersensitivity
Metabolism and nutrition disorders	*Very Common:* Decreased appetite *Common:* Dehydration
Psychiatric disorders	*Common:* Insomnia
Nervous system disorders	*Very common:* Peripheral neuropathy[2] *Common:* Dysgeusia, headache, dizziness
Eye disorders	*Common:* Vision blurred
Vascular disorders	*Common:* Hypotension, hypertension *Uncommon:* Flushing
Respiratory thoracic and mediastinal disorders	*Very common:* Dyspnoea *Common:* Haemoptysis, epistaxis, cough *Uncommon:* Pneumonitis[3]
Gastrointestinal disorders	*Very common:* Diarrhoea, vomiting, nausea, constipation *Common:* Stomatitis, dyspepsia, abdominal pain, dysphagia
Hepatobiliary disorders	*Common:* Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	*Very common:* Rash, alopecia *Common:* Pruritus, nail disorder *Uncommon:* Skin exfoliation, dermatitis allergic, urticaria
Musculoskeletal and connective tissue disorders	*Very common:* Arthralgia, myalgia *Common:* Back pain, pain in extremity, musculoskeletal pain
General disorders and administration site conditions	*Very common:* Fatigue, asthenia, oedema peripheral *Common*: Pyrexia, chest pain *Uncommon:* Mucosal inflammation, infusion site extravasation, infusion site inflammation, infusion site rash
Investigations	*Common:* Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, weight decreased

MedDRA = Medical Dictionary for Regulatory Activities: SMQ = Standardized MedDRA Query
[1] Based on laboratory assessments: maximal degree of myelosuppression (treated population)
[2] Peripheral neuropathy is evaluated using the SMQ neuropathy (broad scope)
[3] Pneumonitis is evaluated using the SMQ interstitial lung disease (broad scope)

Serious adverse event / deaths / other significant events

In the CA031 study the incidence and type of SAEs was comparable between the two trial arms; 93 (18%) patients in the Abraxane/carboplatin arm and 80 (15%) patients in the Taxol/carboplatin arm. Anaemia was reported as an SAE more often with Abraxane/carboplatin relative to Taxol/carboplatin (45 versus <1%). The incidence of all other SAEs was comparable between the 2 treatment arms. Febrile neutropenia was infrequently reported in both treatment arms (<1%).

Table 32: Treatment-emergent Serious Adverse Events (Fatal and Nonfatal) Reported in At least 1% of Patients in Either treatment Arms (Treated Population: Pivotal NSCLC study CA031)

System Organ Class Preferred Term	ABI-007 100mg/m^2 Weekly/ carboplatin (N = 514) n (%)	Taxol 200mg/m^2 Every 3 weeks/ carboplatin (N = 524) n (%)
Patients with ≥ 1 SAE	93 (18%)	80 (15%)
Blood and Lymphatic System Disorders	**26 (5%)**	**12 (2%)**
Anaemia	19 (4%)	3 (< 1%)
Infections and Infestations	**21 (4%)**	**16 (3%)**
Pneumonia	14 (3%)	11 (2%)
Respiratory, Thoracic and Mediastinal Disorders	**18 (4%)**	**26 (5%)**
Dyspnoea	4 (< 1%)	6 (1%)
Pulmonary embolism	4 (< 1%)	8 (2%)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse events.

Deaths

SAEs with outcome of death were reported in 18 (4%) patients in the Abraxane/carboplatin arm and 19 (4%) patients in the Taxol/carboplatin arm. Events with outcome of death is more than 1 patient in Abraxane/carboplatin arm were pulmonary embolism, pulmonary haemorrhage, and cardiac arrest. Such events reported in more than 1 patient in the Taxol/carboplatin arm were pulmonary embolism and pulmonary haemorrhage.

Laboratory findings

In study CA031 there were no significant differences in the incidence of clinically significant chemistry values between the Abraxane/carboplatin and Taxol/carboplatin treatment arms. With the exception of glucose level changes, clinically significant chemistry values mostly occurred as isolated events and resolved to normal values.

Clinical laboratory parameter reported as SAEs were uncommon; 1 SAE for increased AST was reported in the Abraxane/carboplatin arm and 1 SAE for increased ALT was reported in the Taxol/carboplatin arm. There were no positive correlating between the liver enzyme SAEs and liver metastases. For each parameter, less than 1% of patients permanently discontinued treatment or had their dose reduced due to a chemistry value change in either treatment arm. In addition, ≤4% of patients in either treatment arm experienced a dose delay due to a chemistry laboratory value shift.

Safety in special populations

Elderly

In both treatment arms myelosuppression, neuropathy events and arthralgia were more common in patients ≥ 65 compared with those < 65 years. Grade ≥ 3 TEAEs were more common in patients ≥65 years (80%) than <65 years (65%), and treatment emergent SAEs (39% vs. 17%) and TEAEs leading to death (6% vs. 3%) was higher in patients above 75 years than under 75 years. In addition, similar to what was observed in the overall population, elderly patients in the Abraxane/carboplatin arm had higher

incidences of grade 3 or higher anaemia and thrombocytopenia, and lower incidences or grade 3 or higher peripheral neuropathy and peripheral sensory neuropathy relative to the Taxol/carboplatin arm.

Key safety parameters from study CA031 are summarized in the below tables.

Table 33: Overall Summary of Treatment-Emergent Adverse Events by Age Group (<65 Years, >=65 Years) – Treated Population

	ABI-007/Carboplatinr		Taxol/Carboplatin	
Summary of Adverse Events	<65 Years Old (N=356)	>=65 Years Old (N=158)	<65 Years Old (N=343)	>=65 Years Old (N=181)
Patients with at Least 1 Treatment-Emergent AE	330 (93%)	153 (97%)	326 (95%)	178 (98%)
Patients with at Least 1 Treatment Related Treatment-Emergent AE	320 (90%)	149 (94%)	308 (90%)	173 (96%)
Patients with at Least 1 SAE	61 (17%)	32 (20%)	46 (13%)	34 (19%)
Patients with at Least 1 Treatment Related Treatment-Emergent Serious AE	24 (7%)	13 (8%)	18 (5%)	12 (7%)
Patients with at Least 1 Grade 3 or higher Treatment-Emergent AE	233 (65%)	127 (80%)	212 (62%)	143 (79%)
Patients with at Least 1 Treatment Related Grade 3 or higher Treatment-Emergent AE	202 (57%)	119 (75%)	187 (55%)	128 (71%)
Patients with at Least 1 Treatment-Emergent AE Leading to Treatment Discontinuation	52 (15%)	31 (20%)	46 (13%)	42 (23%)
Patients with at Least 1 Treatment-Emergent AE Leading to Death	14 (4%)	4 (3%)	11 (3%)	8 (4%)
Patients with at Least 1 Treatment-Emergent AE Leading to Dose Reduction of ABI-007 or Carboplatin	156 (44%)	83 (53%)	72 (21%)	49 (27%)
Patients with at Least 1 Treatment-Emergent AE Leading to Dose Interruption of ABI-007 or Carboplatin	1 (<1%)	0	6 (2%)	2 (1%)
Patients with at Least 1 Treatment-Emergent AE Leading to Dose Delay of ABI-007 or Carboplatin	242 (68%)	123 (78%)	136 (40%)	79 (44%)

Table 34: Overall Summary of Treatment-Emergent Adverse Events by Age Group (<70 Years, >=70 Years) – Treated Population

	ABI-007/Carboplatinr		Taxol/Carboplatin	
Summary of Adverse Events	<70 Years Old (N=441)	>=70 Years Old (N=73)	<70 Years Old (N=443)	>=70 Years Old (N=81)
Patients with at Least 1 Treatment-Emergent AE	412 (93%)	71 (97%)	426 (96%)	78 (96%)
Patients with at Least 1 Treatment Related Treatment-Emergent AE	400 (91%)	69 (95%)	406 (92%)	75 (93%)
Patients with at Least 1 SAE	79 (18%)	14 (19%)	65 (15%)	15 (19%)
Patients with at Least 1 Treatment Related Treatment-Emergent Serious AE	32 (7%)	5 (7%)	24 (5%)	6 (7%)
Patients with at Least 1 Grade 3 or higher Treatment-Emergent AE	302 (68%)	58 (79%)	288 (65%)	67 (83%)
Patients with at Least 1 Treatment Related Grade 3 or higher Treatment-Emergent AE	266 (60%)	55 (75%)	253 (57%)	62 (77%)
Patients with at Least 1 Treatment-Emergent AE Leading to Treatment Discontinuation	67 (15%)	16 (22%)	69 (16%)	19 (23%)
Patients with at Least 1 Treatment-Emergent AE Leading to Death	17 (4%)	1 (1%)	16 (4%)	3 (4%)
Patients with at Least 1 Treatment-Emergent AE Leading to Dose Reduction of ABI-007 or Carboplatin	199 (45%)	40 (55%)	91 (21%)	30 (37%)
Patients with at Least 1 Treatment-Emergent AE Leading to Dose Interruption of ABI-007 or Carboplatin	1 (<1%)	0	8 (2%)	0
Patients with at Least 1 Treatment-Emergent AE Leading to Dose Delay of ABI-007 or Carboplatin	309 (70%)	56 (77%)	175 (40%)	40 (49%)

Table 35: Overall Summary of Treatment-Emergent Adverse Events by Age Group (<75 Years, >=75 Years) – Treated Population

	ABI-007/Carboplatinr		Taxol/Carboplatin	
Summary of Adverse Events	<75 Years Old (N=496)	>=75 Years Old (N=18)	<75 Years Old (N=507)	>=75 Years Old (N=17)
Patients with at Least 1 Treatment-Emergent AE	465 (94%)	18 (100%)	487 (96%)	17 (100%)
Patients with at Least 1 Treatment Related Treatment-Emergent AE	452 (91%)	17 (94%)	464 (92%)	17 (100%)
Patients with at Least 1 SAE	86 (17%)	7 (39%)	75 (15%)	5 (29%)
Patients with at Least 1 Treatment Related Treatment-Emergent Serious AE	35 (7%)	2 (11%)	28 (6%)	2 (12%)
Patients with at Least 1 Grade 3 or higher Treatment-Emergent AE	345 (70%)	15 (83%)	338 (67%)	17 (100%)
Patients with at Least 1 Treatment Related Grade 3 or higher Treatment-Emergent AE	309 (62%)	12 (67%)	299 (59%)	16 (94%)
Patients with at Least 1 Treatment-Emergent AE Leading to Treatment Discontinuation	77 (16%)	6 (33%)	83 (16%)	5 (29%)
Patients with at Least 1 Treatment-Emergent AE Leading to Death	17 (3%)	1 (6%)	18 (4%)	1 (6%)
Patients with at Least 1 Treatment-Emergent AE Leading to Dose Reduction of ABI-007 or Carboplatin	227 (46%)	12 (67%)	113 (22%)	8 (47%)
Patients with at Least 1 Treatment-Emergent AE Leading to Dose Interruption of ABI-007 or Carboplatin	1 (<1%)	0	8 (2%)	0
Patients with at Least 1 Treatment-Emergent AE Leading to Dose Delay of ABI-007 or Carboplatin	349 (70%)	16 (89%)	207 (41%)	8 (47%)

Gender

Women compared with men experienced higher rates of gastrointestinal TEAEs in the Abraxane/carboplatin arm, including nausea, vomiting, constipation, and diarrhoea. Trends were similar in the Taxol/carboplatin arm with nausea, constipation, and vomiting. Women compared with men in the Abraxane/carboplatin arm experienced higher rates of laboratory abnormalities, in particular decreased WBC, haemoglobin, and ANC, and increase ALT. Trends were similar in the Taxol/carboplatin arm. Women overall had a higher incidence of grade 3 or higher leukopenia than men, and women in the Taxol/carboplatin arm had higher rates of grade 3 or higher neutropenia than women in the Abraxane/carboplatin arm. The difference in neutropenia rates between the treatment arms was most prominent in women.

Discontinuation due to adverse events

Taxane discontinuation

In study CA031, TEAEs resulting in permanent taxane discontinuation were reported in 16% of patients in each arm; and most of these events were treatment-related with both Abraxane/carboplatin (12%) and Taxol/carboplatin (11%). In the Abraxane/carboplatin arm AEs resulting in permanent taxane discontinuation included neutropenia (3%), thrombocytopenia (3%), and peripheral sensory neuropathy (1%). In the Taxol/carboplatin arm AEs resulting in discontinuation of taxane treatment included peripheral sensory neuropathy (4%), peripheral neuropathy 2%), and neutropenia (2%).

Additional safety analyses

The applicant submitted cross-trial comparison of Abraxane/carboplatin and paclitaxel [200 mg/m^2]/carboplatin) Compared with EU-Approved paclitaxel (175 mg/m^2)/cisplatin (see Analysis performed across trials (pooled analyses and meta-analysis)).

The incidences of peripheral neuropathy, anaemia, and thrombocytopenia with Abraxane/carboplatin in Study CA031 are compared with paclitaxel (175 mg/m^2)/cisplatin in the below table.

Table 36: peripheral neuropathy, anaemia, and thrombocytopenia: study CA031 (Abraxane/carboplatin and paclitaxel [200 mg/m2]/carboplatin arms) and paclitaxel (175 mg/m2)/cisplatin studies

PT/SMQ[a] Grade	Abraxane/ carboplatin (Study CA031) (N=514)	Paclitaxel/ cisplatin (Giaccone, 1998) (N=152)	Paclitaxel/ cisplatin (Gatzemeier, 2000) (N=202)	Paclitaxel/ cisplatin (Smit, 2003) (N=159)	Paclitaxel/ carboplatin (Study CA031) (N=524)
Peripheral Neuropathy					
All Grades	48%	68%[b]	54%	--	64%
Grade 3/4	4%	9%[b,c]	4%[c]	--	12%
Anemia					
All Grades	54%	77%[b]	67%	--	28%
Grade 3/4	28%	10%	10%	3%	7%
Thrombocytopenia					
All Grades	45%	--	11%	--	27%
Grade 3/4	18%	3%	1%	1%	7%

Abbreviations: FDA = Food and Drug Administration; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SMQ = Standardized MedDRA Query.

[a] All AEs in Study CA031 were coded using MedDRA v12.1. Peripheral neuropathy was defined by SMQ peripheral neuropathy (broad scope). Anemia and thrombocytopenia were defined using ad hoc grouping of preferred terms. The terms for peripheral neuropathy, anemia and thrombocytopenia in the Giaccone, Gatzemeier and Smit studies may be defined by preferred terms and adverse event coding dictionary and/or version different from those used in Study CA031.

[b] Percentages from FDA Taxol Medical Review, 1998, were not reported in Giaccone, 1998 and Gatzemeier, 2000.

[c] Grade 3 only.

Risk of Anaemia with Abraxane/carboplatin Compared with paclitaxel (175 mg/m^2)/cisplatin

In Study CA031, the term anaemia includes the MedDRA v12.1 preferred terms anaemia, haemoglobin decreased, haematocrit decreased, and red blood cell count decreased.

In Study CA031, 4% of the anaemia events were serious TEAEs. Very few Abraxane/carboplatin-treated patients who experienced anaemia discontinued treatment (<1%), while 6% had dose reduction, and 17% had dose delayed due to anaemia. In the Giaccone study, no patient discontinued treatment due to anaemia; although 7% of patients had dose reductions, and 9% had treatment delays due to hematologic toxicity. No details on dose reductions or treatment delays associated specifically with anaemia were reported. In the Gatzemeier study, no details on dose reductions or treatment delays associated specifically with anaemia were reported; 5% (10/202) of patients had a first dose reduction due to hematologic toxicity and treatment delays due to hematologic toxicity occurred in 16% of courses.

The rate of blood transfusions was similar for Abraxane/carboplatin in Study CA031 and the paclitaxel 175 mg/m^2/cisplatin arms in the Giaccone and Gatzemeier studies (16%, 13%, and 15%, respectively; CSR CA031 in-text Table 50; Giaccone, 1998; Gatzemeier, 2000), and higher in the Smit study (24%; Smit, 2003).

Risk of Thrombocytopenia with Abraxane/carboplatin Compared with paclitaxel (175 mg/m^2)/cisplatin

In Study CA031, thrombocytopenia includes the MedDRA v12.1 preferred terms thrombocytopenia and platelet count decreased. The incidence of Grade 4 thrombocytopenia (potentially to be at risk for bleeding) was 4% in Study CA031, 1% in the Giaccone study, and < 1% in the Gatzemeier study. However, the incidence of Grade 4 thrombocytopenia across these studies must be interpreted with caution as Study CA031 utilized Common Toxicity Criteria Adverse Event (CTCAE) v3, while the prior studies likely utilized CTCAE v2. The change between versions moved the cut off from < 10.0 x10^9/L to < 25.0 x 10^9/L, which may have increased the reporting of Grade 4 events in Study CA031 compared with the earlier paclitaxel (175 mg/m^2)/cisplatin studies.
Of the patients treated with Abraxane/carboplatin in Study CA031 who experienced thrombocytopenia, 30% had their doses delayed, 13% had their doses reduced and 3% discontinued treatment due to thrombocytopenia.
In the Giaccone study, only one patient discontinued treatment because of unspecified hematotoxicity; One patient died of haemorrhage during an episode of severe thrombocytopenia after Cycle 3. Although 7% of patients had dose reductions and 9% had treatment delays due to hematologic toxicity, no reported dose reductions were due to thrombocytopenia. No details were reported regarding treatment delays associated with thrombocytopenia.
None of the patients in the Gatzemier study discontinued because of hematotoxicity. No further details on dose reductions or treatment delays associated specifically with thrombocytopenia were reported.
In Study CA031, among the patients in the Abraxane/carboplatin arm who experienced Grade 3/4 thrombocytopenia, 7% received platelet transfusions during the course of the study. In the Giaccone study, 13% of patients in the paclitaxel (175 mg/m^2)/cisplatin arm received blood transfusions for "hematologic toxicity"; no further information is available.

Other Adverse Events of Special Interest for Abraxane/carboplatin Compared with paclitaxel (175 mg/m^2)/cisplatin

The incidence of of nausea/vomiting, arthralgia/myalgia, renal toxicity and hypersensitivity reactions were all lower in the Abraxane/carboplatin arm in study CA031 when compared to historical safety data for the paclitaxel/cisplatin combination.

2.5.1. Discussion on clinical safety

As could be expected, the safety profile for Abraxane combination therapy was worse than for Abraxane monotherapy, however the increased toxicity seen with Abraxane/carboplatin did not result in an increased number of patients for whom paclitaxel treatment was permanently discontinued, compared to monotherapy.

In study CA031, both Abraxane and Taxol were combined with carboplatin, although in EU paclitaxel is approved in combination with cisplatin for the treatment of NSCLC.

Further to the CHMP request to discuss the benefit compared with the Taxol/cisplatin combination, the MAH submitted historical data showing that the toxicity profile of the Abraxane/carboplatin combination is different from the toxicity profile of paclitaxel/cisplatin. This comparison indicated a higher incidence of anaemia and thrombocytopenia for Abraxane/carboplatin, but a lower incidence of neuropathy, nauseas/vomiting, arthralgia/myalgia, renal toxicity and hypersensitivity reactions.

Most of the reported AEs and SAEs are already known AEs of Abraxane and/or carboplatin. For the treatment with Abraxane/carboplatin the most frequently reported TEAEs were alopecia, neutropenia, and thrombocytopenia.

In study CA031 the incidence of SAEs was comparable between both treatment arms (18% in the Abraxane/carboplatin arm and 15% in the Taxol/carboplatin arm). Most frequently reported SAE in both arms included anaemia, pneumonia, dyspnoea and pulmonary embolism.

For patients treated with Abraxane/carboplatin the incidence of peripheral sensory neuropathy and grade 3 sensory neuropathy was lower than for patients treated with Taxol/carboplatin. Events of peripheral neuropathy occurred earlier during treatment and generally took longer to resolve with Taxol/carboplatin in comparison to Abraxane/carboplatin. If Grade 3 or higher peripheral neuropathy develops, treatment should be withheld until improvement to Grade 0 or 1 followed by a dose reduction for all subsequent courses of Abraxane and carboplatin (see sections 4.2 and 4.4).

The decreased incidence of neuropathy, including a lower incidence of Grade 3/4 neuropathy, and a lower percentage of patients who discontinued treatment due to peripheral neuropathy, is considered an advantage of the Abraxane/carboplatin combination.

Treatment-related events that were reported more frequently for patients treated with Abraxane/carboplatin than for patients treated with Taxol/carboplatin included thrombocytopenia, anaemia, haemoglobin decreased, peripheral oedema and epistaxis. In particular the incidence of anaemia and thrombocytopenia was substantially higher in the Abraxane/carboplatin arm than in the Taxol/carboplatin arm (54% versus 28% and 45% versus 27%, respectively). Also, grade 3 or higher anaemia and thrombocytopenia was reported more frequently for patients treated with Abraxane/carboplatin than for Taxol/carboplatin (28% versus 7% and 18% versus 7% respectively). However, the haematological AEs are mostly manageable with dose modification (see SmPC section 4.2).

Despite the overall lower incidence of neutropenia in the Abraxane/carboplatin arm compared to the Taxol/carboplatin arm, neutropenia more commonly lead to dose reductions in the Abraxane/carboplatin arm. According to the applicant this is attributable to the weekly administration schedule of Abraxane/carboplatin arm, providing more opportunities for protocol-specified dose reductions due to paclitaxel-induced myelosuppression.

The overall incidence of gastrointestinal AEs was comparable for the Abraxane/carboplatin and Taxol/carboplatin arms of study CA031 (41% versus 38%, respectively).

In the Abraxane/carboplatin arm, arthralgia (13% versus 25%) and myalgia (10% versus 19%) were reported less frequently. The average age at which lung cancer is diagnosed is 71 years. The median age in the pivotal studies was 60 years, which is considerably younger. In study CA031, Grade ≥3 TEAEs were more common in patients ≥65 years (80%) than <65 years (65%), and treatment emergent SAEs (39% vs. 17%) and TEAEs leading to death (6% vs. 3%) was higher in patients above 75 years than under 75 years. As mentioned above, the incidence of myalgia and arthralgia reported for the whole study population was lower in the Abraxane/carboplatin arm than in the Taxol/carboplatin arm. In contrast, for patients of the age of 75 years and above, these AEs were reported less frequently in the Taxol/carboplatin arm than in the Abraxane/carboplatin arm. Further to the CHMP request, the applicant provided additional analyses to demonstrate that the reduced incidence of myalgia/arthralgia was not related to the relatively young patient population (60 years) [data not shown]. These analyses showed that although the incidence of myalgia and arthralgia reported for the whole study population was lower in the Abraxane/carboplatin arm than in the Taxol/carboplatin arm, these events were reported less frequently in the Taxol/carboplatin arm than in the Abraxane/carboplatin arm for patients of the age of 75 years and above. The CHMP agrees with the applicant that the number of elderly (≥ 75 years of age) patients was very limited and no definitive conclusions can be drawn. However, the provided data do not support a specific benefit for the Abraxane/carboplatin combination in comparison to the Taxol/carboplatin combination. The limited experience for Abraxane/carboplatin use in the very elderly

(18/514 patients were ≥75 years of age) has therefore been included in section 4.2 of SmPC. The safety profile based on age group appears to be as anticipated.

For Grade 2 or 3 cutaneous toxicity, Grade 3 diarrhoea, or Grade 3 mucositis, treatment should be interrupted until the toxicity improves to ≤ Grade 1, then treatment should be restarted at a lower dose (see section 4.2 of the SmPC). For any other Grade 3 or 4 non-haematologic toxicity, the treatment should be interrupted until the toxicity improves to ≤ Grade 2, then treatment should be restarted at a lower dose (see section 4.2).

In study CA031 more patients treated with Abraxane/carboplatin than with Taxol/carboplatin had a treatment related AE resulting in taxane reduction (45% versus 22%, respectively). Also dose delay was reported more frequently for patients treated with Abraxane/carboplatin than for patients treated with Taxol/carboplatin (67% versus 35%). Further to the CHMP request to discuss the impact of the frequently reported dose modifications in case of AEs on the efficacy of the Abraxane/carboplatin treatment, the Applicant performed analyses (data not shown) indicating a better OS for patients who did have a dose modification than for the patients who did not have a dose modification. However, as also stated by the applicant, these 2 groups were non-randomized. Therefore, the groups are possibly not comparable at baseline. Nevertheless, the data provide no indication of a decreased efficacy of Abraxane due to dose modification.

For both treatment arms in study CA031 4% of patients had a SAE with outcome of death. Events with outcome deaths reported in more than 1 patient included pulmonary embolism, pulmonary haemorrhage and cardiac arrest. The proportion of patients with a AEs resulting in permanent taxane discontinuation was similar for both treatment arms in study CA031 (16% for both the Abraxane/carboplatin and Taxol/carboplatin arms).

Treatment related fatal events occurred at equally low frequencies in both the Abraxane arm (1/514) and in the Taxol arm (1/524) of pivotal Study CA031. Higher frequency of treatment related fatal events was observed in phase II Study CA028 than in the Abraxane arm of pivotal Study CA031. The applicant indicated that the 6 of the 7 treatment-related deaths observed in Study CA028 received 3 weeks dosing regimens using a single dose of Abraxane between 225 mg/m^2 and 340 mg/m^2 in combination with carboplatin and only 1 death occurred in the weekly cohort at the recommended therapeutic dose of 100 mg/m^2 in combination with carboplatin. Administration of higher doses every three weeks is more toxic and likely to explain the higher frequency of treatment related deaths in Study CA028 than in pivotal Study CA031. Risk factors for fatal events were also investigated by the Applicant (e.g. treatment arm, age, sex, stage at primary diagnosis, etc…) however none of the explored risk factors that could potentially impact the chance of death by an AE appeared to be prognostic for fatal events.

2.5.2. Conclusions on clinical safety

Overall, the neurotoxicity for the Abraxane/carboplatin combination was lower than for the Taxol/carboplatin combination. On the other hand, the hematologic toxicity was higher for the Abraxane/carboplatin combination than for the Taxol/carboplatin combination. A decreased incidence of peripheral sensory neuropathy could be an important safety advantage for the Abraxane/carboplatin combination above the Taxol/carboplatin combination.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 14.0 is acceptable.

In addition, a number of issues will be reviewed in the next PSUR as detailed in the attached PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The PRAC Advice is based on the following content of the RMP.

Safety concerns

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	Special Populations – Patients with impaired renal function – Patients with central nervous system metastases – Children Other Missing Information – Reproductive toxicity – Genotoxicity long-term effect

Pharmacovigilance Plan

Routine pharmacovigilance measures are proposed in order to identify and characterise the risks of the product.

Risk minimisation measures

Summary of Risk Minimization Measures

Safety Concern	Proposed Routine Risk Minimization Measures	Proposed Additional Risk Minimization Measures
Identified Risks		
Myelosuppression (Neutropenia, Anemia and Thrombocytopenia)	SmPC Sections 4.2 and 4.4 contain advice for dose reductions in the event of neutropenia and/or thrombocytopenia for ABRAXANE in combination with carboplatin or gemcitabine and ABRAXANE monotherapy. Neutropenia, anemia, thrombocytopenia and bone marrow suppression are labeled in Section 4.8.	None proposed
Peripheral Neuropathy	Dose adjustments are recommended in the SmPC Sections 4.2 and 4.4 for patients experiencing sensory 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. For febrile neutropenia, withhold ABRAXANE and gemcitabine until fever resolves and ANC ≥ 1500, then resume treatment at reduced dose levels. Sepsis is labeled in Section 4.8 of the SmPC.	None proposed
Gastrointestinal Events	Dose modifications for ABRAXANE in combination with carboplatin or gemcitabine are recommended in the SmPC Section 4.2 for patients experiencing gastrointestinal toxicity. 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	Dose modifications for ABRAXANE in combination with carboplatin or gemcitabine are recommended in the SmPC Section 4.2 for patients experiencing cutaneous toxicity. 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 patients with severe hepatic impairment should not be treated with paclitaxel. Section 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 pharmacovigilance.	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

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

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, 5.1 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Please refer to Attachment 1 for the final agreed product information adopted by the CHMP on 22 January 2015.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In study CA031, the proportion of patients with a confirmed complete or partial overall response according to the blinded radiology assessment, was statistically significantly higher in the Abraxane/carboplatin arm compared to the Taxol/carboplatin arm (33% and 25% respectively; p=0.005).

The reported median PFS for the Abraxane/carboplatin was 6.3 months, while for the Taxol/carboplatin arm the median PFS was 5.8 months. The $HR_{A/T}$ for PFS was 0.92 (95.1% CI=0.77, 1.060).

The PFS results following the non-inferiority analysis based on EMA methodological considerations for PFS were 6.8 months (95% CI=5.7, 7.7 months) for the Abraxane/carboplatin arm versus 6.5 months (95% CI=5.7, 6.9 months). The HRA/T= was 0.949 (95% CI=0.830, 1.086).

The median OS for patients treated with Abraxane/carboplatin was 12.1 months and for Taxol/carboplatin 11.2 months. The $HR_{A/T}$ for OS was 0.92 (95.1% CI=0.797, 1.066).

The results of the other secondary endpoints (disease control rate, duration of response and change in performance status) were comparable for both treatment arms. The results of ORR, OS and PFS were consistent for most of the pre-specified subgroups.

Uncertainty in the knowledge about the beneficial effects

The dose finding study CA028 did not investigate which dosing regimen of Taxol and Abraxane would result in comparable levels of biological active paclitaxel in the tumour. Based on the data from study CA028 it cannot be firmly concluded that the weekly regimen of Abraxane 100 mg/m^2 is the optimal regimen for comparison with Taxol 200 mg/m^2 q3w in the phase III study CA031, and thus it cannot be

excluded that the reported better ORR with Abraxane is caused by differences in dosing schedule and not differences in formulation of paclitaxel.
The treatment dosage used in the comparator arm is approved in the US however in Europe, a lower dose of Taxol 175 mg/m^2 is approved and combined with cisplatin. The efficacy of Abraxane/carboplatin compared with historical data of paclitaxel (175 mg/m^2)/cisplatin do not suggest a clear or consistent diminished efficacy of treatment for the Abraxane/carboplatin in comparison with the paclitaxel/cisplatin combination, although, it is acknowledged that no firm conclusion should be drawn by comparison of efficacy results obtained from different studies.

Although a significant difference in the investigator based analyses of ORR was found in the Abraxane/carboplatin arm compared to the control arm for patients with squamous tumour histology, the results of the PFS subgroup analysis did not provide support for a higher efficacy of Abraxane/carboplatin in the squamous cell carcinoma over non-squamous cell carcinoma compared to Taxol/carboplatin (see SmPC section 5.1).
The pivotal CA031 study was set up as superiority study for the ORR response, and effectively a switch from superiority to non-inferiority for PFS and OS was made. The non-inferiority margin was set after the interim analyses, but before the final analyses. The same non-inferiority margins were applied as in previous procedures for other products (Alimta, Xeloda). The rationale for the non-inferiority margin is considered to be sufficiently non-data-driven and the non-inferiority margin has external validity as these margins were also applied in previous procedures. After analyses of PFS and OS, it can be concluded that the Abraxane/carboplatin combination was non-inferior to the Taxol/carboplatin combination.

Risks

Unfavourable effects

For the treatment with Abraxane/carboplatin the most frequently reported TEAEs were alopecia, neutropenia and thrombocytopenia.

For patients treated with Abraxane/carboplatin peripheral sensory neuropathy, arthralgia and myalgia were reported less frequently than for patients treated with Taxol/carboplatin. Events of peripheral neuropathy occurred earlier during treatment and generally took longer to resolve with Taxol/carboplatin in comparison to Abraxane/carboplatin. The time to resolution to grade 1 neuropathy was shorter with Abraxane/carboplatin than with Taxol/carboplatin.

Treatment related events that were reported more frequently for patients treated with Abraxane/carboplatin than for patients treated with Taxol/carboplatin included thrombocytopenia, anaemia, haemoglobin decreased, peripheral oedema and epistaxis. For patients with Grade 3/4 anaemia (TEAEs) median time to improvement by at least one grade was similar in both the Abraxane/carboplatin arm and in the Taxol/carboplatin arm. Concerning thrombocytopenia, Grade 3/4 (TEAEs) median time to improvement by at least one grade was shorter in the Abraxane/carboplatin arm than in the Taxol/carboplatin arm.

In study CA031 the incidence of SAEs was comparable between both treatment arms (18% in the Abraxane/carboplatin arm and 15% in the Taxol/carboplatin arm). Most frequently reported SAEs in both arms included anaemia, pneumonia, dyspnoea and pulmonary embolism.

In study CA031 more patients treated with Abraxane/carboplatin had a treatment related AE resulting in taxane reduction than with Taxol/carboplatin. Also dose delay was reported more frequently for patients treated with Abraxane/carboplatin than for patients treated with Taxol/carboplatin.

Uncertainty in the knowledge about the unfavourable effects

Both Abraxane and Taxol were combined with carboplatin, whereas in the EU, paclitaxel/cisplatin is the approved combination for the treatment of NSCLC. The use of cisplatin is associated with less haematological site effects hampering the comparison. The same applies to the dose of Taxol of 200 mg/m^2 used as comparator. This may have favourably influenced the comparison with Abraxane in terms of myelosuppression and neuropathy as in Europe, a lower dose of paclitaxel is approved (175 mg/m^2). The comparison of the safety results obtained in study CA031 with the safety profile of paclitaxel (175 mg/m^2)/cisplatin as published in three different clinical trials showed that the safety profile of the Abraxane/carboplatin combination and paclitaxel/cisplatin are different, with a higher incidence of anaemia and thrombocytopenia but a lower incidence of neuropathy, nausea/vomiting, arthralgia/myalgia, renal toxicity and hypersensitivity reactions in the Abraxane/carboplatin combination.

Higher frequency of treatment-related fatal events was observed in phase II Study CA028 than in the Abraxane arm of the pivotal Study CA031. However patients in study CA028 received higher doses of Abraxane, which likely explains the higher frequency of treatment related deaths in this study.

The incidence of myalgia and arthralgia reported for the whole study population was lower in the Abraxane/carboplatin arm than in the Taxol/carboplatin arm, these events were reported less frequently in the Taxol/carboplatin arm than in the Abraxane/carboplatin arm for patients of the age of 75 years and above. Since the number of elderly (≥ 75 years of age) patients was very limited, no definitive conclusions can be drawn. In general, the safety profile based on age groups appears to be as anticipated with no particular findings. However the limited experience for Abraxane/carboplatin use in the very elderly (≥75 years of age) has therefore been included in section 4.2 of SmPC.

Benefit-risk balance

Importance of favourable and unfavourable effects

The efficacy results of study CA031 suggest a similar efficacy for the Abraxane/carboplatin combination as for the Taxol/carboplatin combination in patients with NSCLC. The comparator arm is not an approved therapy in Europe where a lower dose of Taxol (paclitaxel, 175 mg/m^2 instead of 200 mg/m^2) with cisplatin is approved. However, this dose has been used in some countries already in the EU and in various clinical trials and can be considered acceptable as a reference dose.

The relevance of improved ORR with Abraxane compared to Taxol without significantly improved PFS and OS is unclear, but there is no indication that the Abraxane/carboplatin regimen is less effective in terms of PFS and OS compared to the Taxol/carboplatin regimen used in study CA031. Carboplatin is a frequently used alternative to cisplatin in combination with paclitaxel as first-line treatment of NSCLC. Abraxane in combination with carboplatin may therefore be an alternative to the combination of Taxol/ carboplatin that has been used in some countries already in the EU and in various clinical trials .

The safety profile seen in study CA031 for the Abraxane/carboplatin combination was different from that of the Taxol/carboplatin combination, with a decreased neurotoxicity and increased haematologic toxicity for the Abraxane/carboplatin. A reduced incidence of peripheral sensory neuropathy in particular grade 3 or higher could be an advantage for the Abraxane/carboplatin combination compared to the Taxol/carboplatin combination.

The reported increased haematologic toxicity for the Abraxane/carboplatin combination in comparison to Taxol/carboplatin, can be easily managed with dose reductions and supportive care when the bone marrow status during treatment is closely monitored (see SmPC sections 4.2 and 4.4).

Benefit-risk balance

In terms of efficacy, the Abraxane/carboplatin regimen appears to be a valuable alternative to the Taxol/carboplatin regimen that is considered an acceptable comparator. Abraxane and Taxol have different toxicity profiles which may be considered to favour Abraxane. Although the patient has to be treated on a weekly basis with Abraxane, it has the advantage of shorter infusion time and less need for pre-medication. The benefit-risk balance is therefore considered positive.

Discussion on the benefit-risk balance

Study CA031 demonstrated a statistically significant improvement in the Abraxane arm for the primary endpoint of ORR based on blinded radiological review, but this is not supported by statistically significant improvements in PFS and OS. Switching from superiority to non-inferiority was not prospectively included in the study design and the delta margin was defined after inspection of the interim data for PFS and OS.

The approach taken by the applicant to show non-inferiority is thus considered disputable, and the strength of the evidence of non-inferiority may be questioned. However, even without considering the questionable non-inferiority results there is no evidence in terms of PFS and OS that Abraxane 100 mg/m^2 administered weekly is less effective than Taxol administered every 3 weeks. Compared to the primary analysis of PFS, the non-inferiority analysis indicated even smaller differences between the treatment arms with fewer patients censored in this analysis (based on censoring rules from the EMA guideline). From a regulatory point of view the non-inferiority analysis seems to be the most robust analysis of PFS.

The toxicity profile of the Abraxane/carboplatin is different from the toxicity profile of the Taxol/carboplatin or Taxol/cisplatin. However the levels of AEs were equal, indicating that patients in the Abraxane arm did not experience more toxicity. The approval of the Abraxane/carboplatin combination represents an additional treatment option for first line treatment of patients with NSCLC who are not candidates for potentially curative surgery and/or radiation therapy.

4. Recommendations

Final Outcome

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

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

Extension of Indication to add a new indication for Abraxane in combination with carboplatin for the first-line treatment of non-small cell lung cancer (NSCLC) in adult patients who are not candidates for potentially curative surgery and/or radiation therapy. Consequently sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated. Further, sections 4.2 and 6.6 of the SmPC have been updated with a recommendation to flush the intravenous line with sodium chloride to ensure administration of the complete dose. The Package Leaflet has been updated accordingly. Further, an updated RMP version 14.0 was agreed during the procedure.

The requested variation proposed amendments to the SmPC and Package Leaflet.