



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for nanoparticle albumin-bound (nab) paclitaxel

Proprietary Product Name: Abraxane

Sponsor: Abraxis Bioscience Australia Pty Ltd

January 2014

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I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of Indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	6 August 2013
<i>Active ingredient:</i>	Nanoparticle albumin-bound (nab) paclitaxel
<i>Product name:</i>	Abraxane
<i>Sponsor's name and address:</i>	Abraxaxis Bioscience Australia Pty Ltd Level 1, 711 High Street Kew East VIC 3102
<i>Dose form:</i>	Powder for injection (suspension)
<i>Strength:</i>	100 mg
<i>Container:</i>	Vial
<i>Pack size:</i>	50 mL
<i>New approved therapeutic use:</i>	Metastatic Breast Cancer: Abraxane is indicated for the treatment of metastatic carcinoma of the breast after failure of anthracycline therapy. Non-small Cell Lung Cancer: Abraxane, in combination with carboplatin, is indicated for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation.
<i>Route of administration:</i>	Intravenous
<i>Dosage (abbreviated):</i>	100 mg/m ² as IV infusion over 30 minutes on Days 1, 8 and 15 of each 21 day cycle.
<i>ARTG number:</i>	133500

Product background

Abraxis Bioscience Australia Pty Ltd (the sponsor) proposed a new indication of non-small cell lung cancer (NSCLC) for Abraxane (paclitaxel) in combination with carboplatin, indicated for the first-line treatment of NSCLC in patients who are not candidates for potentially curative surgery and/or radiation therapy.

Paclitaxel is obtained from a natural product (*Taxus media*) with antitumour activity. The drug is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. This action results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions.

Abraxane was developed to improve the therapeutic index of paclitaxel by reducing the toxicities associated with Taxol® (paclitaxel) and generic paclitaxel that use the

Cremophor® EL and ethanol vehicle, while improving the chemotherapeutic effect of the drug by taking advantage of endogenous transport pathways to deliver higher doses of paclitaxel to the tumour.

Carboplatin (proposed in this application for use with Abraxane) has no formal NSCLC indication. There have also been no previous submissions for paclitaxel in combination with carboplatin for the treatment of NSCLC.

In Australia, Abraxane was first approved for registration on 29 September 2008 for the following indication:

Abraxane is indicated for the treatment of metastatic carcinoma of the breast after failure of anthracycline therapy.

On 30 May 2012 the sponsor applied to extend the current indication for Abraxane to include Non-Small Cell Lung Cancer (NSCLC) as follows:

Abraxane, in combination with carboplatin, is indicated for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation.

Regulatory status

The product Abraxane received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 17 October 2008.

To extend the indications of Abraxane to include the following: “*Abraxane in combination with carboplatin is indicated for the first line treatment of non-small cell lung cancer (NSCLC) in patients who are not candidates for potentially curative surgery and/or radiation therapy*”, dossiers have been, and are proposed to be, submitted in the countries and regions identified below:

Table 1: List of countries in which a similar application has been submitted

Countries or Regions	Date of or Proposed Date of Submission	Date of or Expected Date of Approval
USA	9 December 2011	October 2012
EU	Proposed June 2012	N/A
Canada	Not confirmed	
New Zealand	Proposed June 2012	Expected June 2013
Switzerland	Not confirmed	

The information provided is current at the time this application was considered.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

The sponsor's clinical rationale for the submission is based on the need for new therapeutic options for the treatment of NSCLC. The sponsor considers that Abraxane addresses this unmet need because, in combination with carboplatin, the drug provides evidence of increased effectiveness in the treatment of NSCLC compared with Taxol in combination with carboplatin, and significantly reduces taxane related severe peripheral neuropathy and solvent-based paclitaxel drug related hypersensitivity reactions.

Comment: It is accepted that there is an unmet need for new treatment options for NSCLC. In 2007, lung cancer was the fourth most commonly diagnosed cancer in Australia in both males and females, excluding basal and squamous cell carcinoma of the skin (Australian Institute of Health and Welfare (AIHW) and Cancer Australia 2011¹). In that year, a total of 5,948 lung cancers were diagnosed in males and 3,755 in females. The occurrence of lung cancer was strongly related to age, with 84% of new lung cancers in males and 80% in females diagnosed in patients aged 60 years and over. In 2007, 4,715 males and 2,911 females died from lung cancer in Australia making it the leading cause of death in both sexes (21% of all cancer deaths in males, and 17% of all cancer deaths in females). In Australia, between 1982 and 2007 the age-standardised mortality rate from lung cancer for males decreased by 41%, while the mortality rate for females increased by 56%. The prognosis for patients with lung cancer remains poor, and improved little over the 26 years from 1982 to 2007. The 5-year relative survival in 2000-2007 was 11% for males and 15% for females, which compares with 8% for males and 10% for females in 1982-1987.

Clinically, primary lung cancer is divided into small-cell lung cancer (SCLC) and NSCLC, and NSCLC accounts for about 80% of all lung cancers (Boyer MJ, 2003²). There are three main subtypes of NSCLC, squamous cell carcinoma (25%), adenocarcinoma (40%) and large cell carcinoma (10%) with the remainder consisting of other subtypes with low frequencies (National Cancer Institute (NCI), 2012). In patients with NSCLC, the possibility of cure depends mainly on their suitability for surgical resection (Carney D and Hansen H, 2000³). However, at the time of diagnosis only about 30% of patients with NSCLC are

¹ AIHW & Cancer Australia 2011. Lung cancer in Australia: an overview. Cancer series no. 64. Cat. no. CAN 58. Canberra: AIHW.

² Boyer MJ. Drug therapy for lung cancer. *Aust Prescr* 2003; 26: 103-105.

³ Carney DN, Hansen HH. Non-small cell lung cancer – stalemate or progress? *N Engl J Med* 2000; 343: 1261-1262.

candidates for surgery, while the remaining 70% have inoperable disease (30% with locally advanced inoperable disease and 40% with inoperable confirmed metastatic disease) (Carney D and Hansen H, 2000). Chemotherapy is the mainstay of treatment for patients with advanced NSCLC (TNM stage IIIB and stage IV) (Goldstraw P *et al.*, 2011⁴). The median duration of survival and 5-year survival rates are poor both in patients with NSCLC TNM stage III B (10 months and 7%), and TNM stage IV (6 months and 2%) (Goldstraw P *et al.*, 2007⁵).

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- Four clinical pharmacology studies, including four that provided pharmacokinetic data and one that provided PD data.
- One population PK analysis.
- One pivotal efficacy/safety study in patients with NSCLC.
- Three supportive efficacy/safety studies in patients with NSCLC.
- Four clinical studies relating to indications other than NSCLC.
- Documentation of Statistical Methods and Interim Analysis Plans for Safety and Efficacy, Statistical Tables and Figures (Safety and Efficacy).
- Post-marketing experience.
- Literature references.

Paediatric data

The submission did not include paediatric data. The sponsor indicated that there is currently no paediatric development program in place for Abraxane. The sponsor considered that *“because non-small cell lung cancer is an adult-related condition that may qualify Abraxane for a disease specific waiver, [it] believes ..[an]..application in the paediatric population is not feasible, and therefore additional evidence of impossibility or impracticality is not necessary”*. The sponsor has applied to the FDA for *“Waiver of Paediatric Assessment”*.

Comment: The sponsor’s decision not to include paediatric data is acceptable.

Good clinical practice

The submitted studies were conducted in accordance with the ethical principles of Good Clinical Practice.

⁴ Goldstraw P, Ball D, Jett JR *et al.* Non-small-cell lung cancer. *Lancet* 2011; 378; 1727-40.

⁵ Goldstraw P, Crowley JJ, Chansky K *et al.* The IASLC Lung Cancer Staging Project: proposals for revision of the stage groupings in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007; 2: 706-714.

Pharmacokinetics

Studies providing pharmacokinetic data

The submission included four completed pharmacokinetic (PK) studies (see Table 2, below). In the tables included in this AusPAR, Abraxane is referred to as ABI-007. The four studies have been evaluated and reviewed. The submission also included comparisons and analyses of the PK of Abraxane across studies and the results have been reviewed.

Two of the PK Studies BIO-VT-5 and 08DA33 were sub-studies of the pivotal Phase III clinical efficacy and safety Study CA031. Study 08DA33 was of interest as it provided PK interaction data for Abraxane/carboplatin in Japanese patients. Study BIO-VT-5 was planned as a population-PK analysis in a subgroup of patients from the pivotal efficacy and study but due to the small sample size (n=15) this analysis was not undertaken. Instead, Study BIO-VT-5 provided individual and mean Abraxane plasma PK parameters calculated using standard non-compartmental methods in White patients. However, these non-compartmental PK data were of limited value due to sparse sampling time points following administration of Abraxane. Studies 05DA11 and 05DA13 were single ascending dose PK studies in Japanese patients with advanced solid tumours providing both blood and plasma paclitaxel PK data and formally assessing dose linearity. In addition, both Studies 05DA11 and 05DA13 attempted to define a Maximum Tolerated Dose (MTD) for Abraxane over the dose range studied.

Table 2: Four completed PK studies.

Report No. (Study Code)	Description of PK Analysis	ABI-007 Dose	Study Population (Race)	No. 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 ^a)	15 (10/5)	Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation
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; No. = number; NSCLC = non-small cell lung cancer; PK = pharmacokinetics. Of the 15 patients, the race categories included 14 White (Non-Hispanic) patients and 1 Black patient and were referred to collectively as White patients for ease of discussion. Taiho Pharmaceutical Co., Ltd. is the Marketing Authorisation Holder and Distributor of ABI-007 in Japan.

Evaluator's overall conclusions on pharmacokinetics

The submission included a limited amount of new paclitaxel PK data in patients with NSCLC treated with Abraxane. The PK findings are summarised below.

- The data suggest that co-administration of Abraxane/carboplatin at the proposed dosages in patients with NSCLC are unlikely to significantly affect each other's PK when given alone. However, in Japanese patients mean exposure to free carboplatin (Area Under the plasma concentration time Curve from time zero to infinity (AUC_{inf})) was approximately 24% higher than the targeted mean value when Abraxane was co-administered with carboplatin (Study 08DA33). These results were inconsistent with

those from the published literature (Obasaju *et al.*, 1996⁶) which showed that exposure to free carboplatin (Area Under the plasma concentration time Curve over 24 hours (AUC_{24h})) was similar and consistent with the target value irrespective of whether carboplatin was administered with or without Taxol. The sponsor postulates that the differences between the results observed in Study 08DA33 and Obasaju *et al.*, 1996 were due to methodological differences used to calculate the carboplatin dose.

- The data from a cross-study comparison of the plasma PK of paclitaxel in Japanese patients with solid tumours administered Abraxane 100 mg/m² (Study 05AD11) were comparable with those in Japanese patients with NSCLC administered Abraxane 100 mg/m² in combination with carboplatin (AUC = 6 mg.min/mL, Study 08DA33).
- The data indicate that the PK of paclitaxel following Abraxane are linear in Japanese patients with NSCLC over the dose range 80 mg/m² to 300 mg/m² (combined data from Studies 05DA11 and 05DA13), and in White patients with solid tumours over the dose range 80 mg/m² to 200 mg/m² (Studies DM1723 and CA005-0).
- The data suggest that the PK of paclitaxel following Abraxane administered alone are similar in White and Japanese patients with solid tumours (Studies CA005-0 and 05DA11), and in White and Japanese patients with NSCLC treated with the same Abraxane/carboplatin regimen (Studies BIO-VT-5 and 08DA33).

Pharmacodynamics

Studies providing pharmacodynamic data

The submission included one pharmacodynamic (PD) report (SPARC Biomarker Report BIO-VT-6). This secreted protein acidic and rich in cysteine (SPARC) biomarker report was a sub-study of the pivotal Phase III efficacy and safety study in patients with advanced NSCLC (Study CA031). The objective of the report was to assess SPARC in tumour tissue and to determine the relationship between the biomarker and efficacy outcomes.

Comment: SPARC (also known as osteonectin and BM40) is an albumin-binding protein that is over expressed in NSCLC tumours and is associated with a poor prognosis in NSCLC patients (Koukourakis *et al.*, 2003⁷). In Koukourakis *et al.*, 2003, cancer cells from NSCLC tissue were found to be unreactive in 107 of 113 cases analysed (95%), whereas substantial production of SPARC by stromal fibroblasts was noted in 42 of 113 cases (37%). Stromal SPARC was significantly linked with tumour necrosis and survival analysis showed a significant association between stromal SPARC and poor prognosis. Due to its albumin binding ability, it has been hypothesised that SPARC expression in tumours results in increased concentration of albumin-bound drugs, such as Abraxane, and may be partly responsible for the greater activity of Abraxane when compared with conventional formulations (Hawkins, Soon-Shiong, Desain, 2008⁸).

⁶Obasaju CK, Johnson SW, Rogatko A, Kilpatrick D, Brennan JM, Hamilton TC, *et al.* Evaluation of carboplatin pharmacokinetics in the absence and presence of paclitaxel. *Clin Cancer Res.* 1996;2:549-552.

⁷Koukourakis MI, Giatromanolaki A, Brekken RA, *et al.* Enhanced Expression of SPARC/Osteonectin in the Tumor-associated Stroma of Non-Small Cell Lung Cancer Is Correlated with Markers of Hypoxia/Acidity and with Poor Prognosis of Patients. *Cancer Res.* 2003; 63: 5376-80.

⁸Hawkins MJ, Soon-Shiong P, and Desai N. Protein nanoparticles as drug carriers in clinical medicine. *Adv Drug Deliv Rev* 2008;60:876-885.

Overall conclusion on pharmacodynamics

The submission included one exploratory PD sub-study investigating the effect of SPARC status (high versus low) on efficacy outcomes of progression-free survival (PFS), overall survival (OS), and overall response rate (ORR) in a subset of patients (n=71) from the pivotal Phase III Study CA031. This exploratory sub-study showed that SPARC status had no significant effects on the clinical outcomes irrespective of how the data were analysed. However, the SPARC subset of patients appeared to be unrepresentative of the total patient population from which it was derived as the clinical outcomes (PFS, OS, and ORR) for patients in the subset were superior to those for the total population. The sponsor concludes that '*no definitive conclusions about the correlation between clinical outcomes and SPARC status can be drawn*' from the subgroup analysis due to the limitations arising from the small sample size. Other exploratory molecular biomarker analysis referred to in the protocol were not undertaken due to the low number of consenting patients with sufficient samples available for study.

Dosage selection for the pivotal studies

In the pivotal Phase III Study CA031, the Abraxane dose was 100 mg/m² given weekly. The sponsor stated that results from the Phase I/II Studies CA015, CA018 and CA028 suggested that a greater response rate could be anticipated in patients with NSCLC with a once weekly rather than once every three weeks regimen of Abraxane, and with an Abraxane/carboplatin combination rather than Abraxane alone. Based on the data from the Phase I/II Studies and the risk/benefit ratio for dose cohorts in Study CA028, the Abraxane regimen evaluated in the pivotal Phase III Study was 100 mg/m² given weekly in combination with carboplatin (AUC = 6 mg.min/mL) every three weeks as first-line treatment for patients with metastatic NSCLC.

In the pivotal Phase III Study, the Taxol dose was 200 mg/m² given once every three weeks. The sponsor stated that the 200 mg/m² dose was selected for two reasons:

1. the protocol Steering Committee strongly recommended that a Taxol dose of 225 mg/m² was not appropriate for the control arm due to toxicity associated with this dose; and
2. 200 mg/m² is the most commonly administered Taxol dose.

In addition, the sponsor stated that the dose of Taxol used in the pivotal Phase III Study in combination with carboplatin (AUC = 6 mg.min/mL) is the same as that used in the study of the doublet-combination of Taxol/carboplatin versus the triplet-combination of Taxol/carboplatin/bevacizumab that resulted in global approval of bevacizumab for the first-line treatment of advanced NSCLC (Sandler *et al.*, 2006⁹).

Furthermore, the sponsor stated that the recommended standard of care for first line treatment of NSCLC is Taxol within the range of 175 to 225 mg/m² in combination with carboplatin (AUC = 6 mg.min/mL) (Schiller *et al.*, 2002¹⁰).

⁹ Sandler, A, Gray, R, Perry, MC, *et al.* Paclitaxel-Carboplatin alone or with Bevacizumab for non-small-cell lung Cancer. *N Engl J Med* 2006; 355: 2542-50.

¹⁰ Schiller, JH, Harrington, D, Belani, CP, *et al.* Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002; 346(2): 92-98.

Efficacy

Studies providing efficacy data

The sponsor submitted four clinical efficacy and safety studies to support the submission to extend the indications of Abraxane to include the treatment of advanced NSCLC.

The Phase III Study CA031 was nominated by the sponsor as the pivotal study. This study included 1052 patients and randomised 521 to Abraxane/carboplatin at the proposed dosage regimen and 531 to the control of Taxol/carboplatin. This was a good quality study and the evaluator agreed that it should be considered to be pivotal.

The sponsor nominated the non-randomised, uncontrolled, open-label, dose-escalation Phase II Study CA0028 as the key supportive study. However, this study is considered to provide limited supportive data. The study included a cohort of only 25 patients treated with the proposed Abraxane/carboplatin dosage regimen, and the absence of a control arm makes the observed results in these patients difficult to interpret. The sponsor also nominated Studies CA015 (Phase I/II) and CA018 (Phase II) as supportive. However, it is considered that neither of these two studies can be considered to provide supportive data as neither included patients treated with the proposed dosage regime. In Study CA015, Abraxane 100 mg/m² was administered as a single-agent to three patients, and in Study CA018 Abraxane was administered as a single-agent at a dose of 260 mg/m² once every three weeks to 43 patients.

Evaluator's conclusions on clinical efficacy for advanced NSCLC

Pivotal Phase III Study CA031

In the pivotal Phase III Study CA031, the primary efficacy endpoint was the ORR including patients who achieved a confirmed Complete Response (CR) or Partial Response (PR) based on blinded radiological assessment using Response Evaluation Criteria In solid Tumours (RECIT) guidelines. In this study, all efficacy evaluations were based on the intent to treat (ITT) population (n=1052), including 521 patients in Abraxane arm and 531 patients in the Taxol/carboplatin arm. The ORR in patients with advanced NSCLC was statistically significantly higher in the Abraxane/carboplatin arm (33% [95% Confidence Interval (CI): 28.6, 36.7]) than in the Taxol/carboplatin arm (25% [95% CI: 21.2, 28.5]), p=0.005; Abraxane/carboplatin response rate/Taxol/carboplatin response rate (pA/pT) = 1.313 (95.1% CI: 1.082, 1.593). However, the clinical significance of the absolute difference between the two treatment arms of 8% in favour of Abraxane/carboplatin is unlikely to be clinically meaningful in the absence of statistically significant differences between the two arms in the clinical benefit outcomes of PFS and OS.

The primary superiority analysis of the first key secondary efficacy endpoint of PFS (blinded radiological assessment) showed that the difference between median PFS duration in the two treatment arms was not statistically significant: 6.3 months in the Abraxane/carboplatin arm and 5.8 months in the Taxol/carboplatin arm, p=0.214; Hazard Ratio of Abraxane/carboplatin to Taxol/carboplatin (HR_{A/T}) = 0.902 (95.1% CI: 0.767, 1.060). The primary superiority analysis of the second key secondary efficacy endpoint of OS also showed no statistically significant difference in median survival time between the two treatment arms: 12.1 months in the Abraxane/carboplatin arm and 11.2 months in the Taxol/carboplatin arm, p=0.271; HR_{A/T} = 0.922 (95.1% CI: 0.797, 1.066). However, this analysis is considered to be exploratory rather than confirmatory as the protocol specified that superiority testing of OS should proceed only if initial superiority testing of PFS had demonstrated a statistically significant result in favour of the Abraxane/carboplatin arm relative to the Taxol/carboplatin arm.

The non-inferiority analysis of PFS and OS showed that the Abraxane/carboplatin arm was non-inferior to the Taxol/carboplatin for both parameters. In the PFS (blinded radiological assessment) non-inferiority analysis, median PFS was 6.8 months in the Abraxane/carboplatin arm and 6.5 months in the Taxol/carboplatin arm; $HR_{A/T} = 0.949$ (95% CI: 0.830, 1.086). In the OS non-inferiority analysis, median OS was 12.1 months in the Abraxane/carboplatin arm and 11.2 months in the Taxol/carboplatin arm; $HR_{A/T} = 0.922$ (95% CI: 0.797, 1.066). In the non-inferiority analyses of both the PFS and the OS, the upper bound of the 95% CI of $HR_{A/T}$ was less than the pre-specified non-inferiority margin of 1.176 (that is, non-inferiority margin of 15%).

The results for the secondary efficacy endpoints of investigator assessed ORR and PFS were consistent with the primary analysis of these endpoint based on blinded assessment. In addition, there was no statistically significant difference between the two treatment arms as regards the secondary efficacy endpoints of disease control rate and duration of response.

The planned exploratory analysis of the effect of baseline stratification factors on the ORR (blinded radiological assessment) showed that the ORR was statistically significantly higher in the Abraxane/carboplatin arm compared with the Taxol/carboplatin arm in patients with squamous cell carcinoma (41% versus 24%, $p < 0.001$), patients with Stage IV disease (31% versus 23%, $p=0.015$), male patients (33% versus 24%, $p=0.011$), patients aged < 70 years (32% versus 25%, $p=0.013$), and patients from Eastern Europe (34% versus 27%, $p=0.014$). The planned exploratory analysis of the effect of baseline stratification factors on OS showed that median survival was longer in the Abraxane/carboplatin arm compared with the Taxol/carboplatin in North American patients (12.7 versus 9.8 months, $p=0.008$; $HR_{A/T} = 0.622$ [95% CI: 0.436, 0.866]), and patients aged ≥ 70 years (19.9 versus 10.4 months, $p=0.009$; $HR_{A/T} = 0.583$ [95% CI: 0.388, 0.975]). The planned exploratory analysis of the effect of baseline stratification factors on PFS (blinded radiological assessment) showed no statistically significant difference between the two treatment arms for any of the factors.

Overall, the exploratory analyses of the effect of baseline stratification factors (planned) and other baseline prognostic factors (unplanned) on ORR, PFS and OS showed consistent benefits for patients in the Abraxane/carboplatin arm compared with the Taxol/carboplatin arm.

Phase I/II studies nominated by the sponsor as supportive (CA028, CA015, CA018)

The sponsor nominated the Phase II Study CA028 as the “primary supportive” efficacy study. However, this preliminary, single-country (Russia), multi-site, non-randomised, open-label, single-arm, dose escalation study in patients with advanced NSCLC is considered to provide only limited supportive efficacy data. The study included one cohort of 25 patients treated with the proposed Abraxane/carboplatin treatment regimen. The key efficacy results for this regimen were ORR (investigator assessed Response Evaluation Criteria In Solid Tumours (RECIST)) 48.0% (95% CI: 28.4, 67.58), PFS (investigator assessed RECIST) 6.2 months (95% CI: 4.2, 9.7), and OS 11.3 months (95% CI: 7.8, > 20.1). The ORR (investigator assessed) in the supportive Phase II Study for the proposed Abraxane/carboplatin treatment regimen was greater than the comparable endpoint from the pivotal Phase III Study (48% versus 38%), while median PFS (investigator assessed) values for the two studies were 6.3 and 5.5 months, and median OS values were 11.3 and 12.1 months. However, in the absence of a comparator arm in the Phase II Study CA028, it is difficult to interpret the clinical relevance of the ORR, PFS and OS results from this study.

The sponsor nominated the Phase I/II Study CA015 as supportive. However, this single-site (USA), non-randomised, uncontrolled, open-label, dose-escalating study in patients with advanced NSCLC included only three patients treated with single-agent Abraxane 100

mg/m². Consequently, this study is considered to provide no meaningful clinical data on the Abraxane/carboplatin combination proposed for registration for the treatment of advanced NSCLC.

The sponsor nominated the Phase II Study CA018 as supportive. However, this single-country (Russia), multi-centre (seven sites), non-randomised, uncontrolled, open-label study in patients with advanced NSCLC did not investigate the Abraxane/carboplatin combination proposed for registration. The study investigated single-agent Abraxane 260 mg/m² administered once every three weeks to 43 treated patients. This regimen is markedly different from that being proposed. Consequently, this study is considered to provide no meaningful clinical data on the Abraxane/carboplatin combination proposed for registration for the treatment of advanced NSCLC.

Safety

Studies providing evaluable safety data

The submission included safety data from four studies in patients with advanced NSCLC, Studies CA031, CA028, CA015, and CA018. The number of patients exposed to Abraxane by dosing regimen, dose and study for the treatment of NSCLC is summarised below in Table 3.

Table 3: Summary of patients with NSCLC exposed to Abraxane.

Regimen	Number of Patients Exposed										
	ABI-007 Weekly (mg/m ²)					ABI-007 Every 3 Week (mg/m ²)					ABI-007 Weekly or Every 3 Weeks (mg/m ²)
Dose	100	125	140	150	All	225	260	300	340	All	All
ABI-007/carboplatin therapy											
Phase 3, CA031	514	-	-	-	514	-	-	-	-	-	514
Phase 2, CA028	25	25	25	-	75	25	25	25	101	176	251
Total	539	25	25	-	589	25	25	25	101	176	765
ABI-007 Monotherapy											
Phase 2, CA015	3	65	-	7	75	-	-	-	-	-	75
Phase 2, CA018	-	-	-	-	-	-	43	-	-	43	43
Total	3	65	-	7	75	0	43	-	-	43	118

The submission included a total of 539 patients exposed to Abraxane/carboplatin at the proposed dosage regimen (514 from the pivotal Study CA031 and 25 from the sponsor nominated key supportive Study CA028). The pivotal safety data is derived from Study CA031. This study includes safety data on 514 patients with advanced NSCLC treated with Abraxane/carboplatin at the proposed dosage regimen and 524 patients treated with Taxol/carboplatin. The evaluation of the safety data for the proposed combination focuses on the pivotal Phase III Study CA031.

Summary of patient/drug exposure

A total of 1038 patients received at least one dose of study drug and were included in the "treated population". The median number of treatment cycles was six in both treatment arms. The median number of Abraxane doses was 2.5 times higher than the median number of Taxol doses due to the different administration regimens for the taxanes (15 versus six doses), while the median number of carboplatin doses was the same in both treatment arms (six doses in both arms). Exposure in the two treatment arms is

summarised below in Table 4. All patients in both treatment arms received one cycle; four cycles were received by 75% of patients in the Abraxane/carboplatin arm and 73% of patients in the Taxol/carboplatin arm; and six cycles were received by 52% and 54% of patients in the two treatment arms.

Table 4: Study CA031 – Number of cycles and study drug administered; treated population.

Variable Category / Statistic	ABI-007/ carboplatin (N=514)	Taxol/ carboplatin (N=524)
Number of Cycles Administered		
Mean (SD)	6.3 (4.57)	6.1 (4.30)
Median (Min, Max)	6.0 (1, 31)	6.0 (1, 30)
Number of Taxane Doses Administered		
Mean (SD)	17.3 (13.03)	6.1 (4.30)
Median (Min, Max)	15.0 (1, 85)	6.0 (1, 30)
Number of Carboplatin Doses Administered		
Mean (SD)	6.2 (4.40)	6.1 (4.26)
Median (Min, Max)	6.0 (1, 28)	6.0 (1, 30)

Note: Patients with multiple dose modifications can be in more than one category.

Note: Cycle length is defined as time between Day 1 of two sequential cycles.

Table 5: Study CA031 – Overview of all treatment-emergent adverse events; treated population.

Category	ABI-007/ carboplatin (N=514)	Taxol/ carboplatin (N=524)
	n (%)	n (%)
Patients with at least 1 AE	483 (94%)	504 (96%)
Patients with at least 1 AE after 6 cycles of therapy	143 (28%)	143 (27%)
Patients with at least 1 grade 3 or higher AE	360 (70%)	355 (68%)
Patients with at least 1 treatment-related AE	469 (91%)	481 (92%)
Patients with at least 1 treatment-related grade 3 or higher AE	321 (62%)	315 (60%)
Patients with at least 1 serious AE	93 (18%)	80 (15%)
Patients with at least 1 treatment-related serious AE	37 (7%)	30 (6%)
Patients with at least 1 AE with action of taxane permanently discontinued	80 (16%)	84 (16%)
Patients with at least 1 AE with action of taxane dosage reduced	237 (46%)	120 (23%)
Patients with at least 1 AE with action of taxane interrupted	0	5 (<1%)
Patients with at least 1 AE with action of taxane delayed	365 (71%)	214 (41%)

Deaths and serious adverse events

Deaths

Treatment-emergent adverse events with an outcome of death within 30 days of the last treatment occurred in 18 (4%) patients in the Abraxane/carboplatin arm and 19 (4%) patients in the Taxol/carboplatin arm. No TEAE with an outcome of death was reported at the Preferred Term (PT) level for $\geq 1\%$ of patients in either treatment arm. Events with outcome of death in more than one patient in the Abraxane/carboplatin arm were pulmonary embolism (four patients), pulmonary haemorrhage (two patients), and cardiac arrest (two patients). Events with outcome of death in more than one patient in the Taxol/carboplatin arm were pulmonary embolism (four patients) and pulmonary haemorrhage (three patients). There were two treatment-related TEAEs with an outcome

of death; one in each arm (one multi-organ failure, Abraxane/carboplatin, and one gastrointestinal haemorrhage, Taxol/carboplatin).

In the pooled data from Studies CA031 and CA028, treatment-related serious adverse events (SAEs) occurred in eight (1%) of the 765 patients receiving Abraxane/carboplatin (one patient from Study CA031 referred to in the above paragraph and seven patients from Study CA028). The seven deaths in Study CA028 were due to pneumonia (two), cardiopulmonary failure (one), cerebrovascular accident (one), disease progression (one), endotoxic shock (one) and pulmonary haemorrhage (one). No treatment-related fatal SAEs occurred during Abraxane monotherapy (n=236).

Post-marketing data

The submission included a summary of the post-marketing experience of Abraxane from the International Birth Date of the drug (7 January 2005) to the most recent Periodic Safety Update Report cut-off date (6 July 2011). During this time interval, approximately 116,527 patients were exposed to commercial Abraxane, including 103,614 patients from the US and 12,913 patients from outside the US. The recommended dose of single-agent Abraxane for patients with metastatic breast cancer is 260 mg/mL² administered intravenously over 30 minutes every three weeks. The sponsor estimates that the number of vials per cycle over the assessed time interval for all patients is 4.4, and that the average number of treatment cycles per patient is 5.5.

The sponsor states that the major risks associated with the use of Abraxane for the treatment of patients with metastatic breast cancer reflect the known toxicities of paclitaxel. These risks include alopecia, haematologic toxicities (neutropenia and anaemia), peripheral sensory neuropathy, myalgia/arthralgia, fatigue/asthenia, hypersensitivity reactions, gastrointestinal events (nausea and diarrhoea), infections, elevated aspartate aminotransferase (AST), elevated alkaline phosphatase and abnormal electrocardiogram.

Overall, the post-marketing data for Abraxane administered for the treatment of lung cancer are insufficient to conclude that the safety profile of the drug for this condition is consistent with the safety of the drug for the treatment of metastatic breast cancer.

Evaluator's overall conclusions on clinical safety

Overall, the submission included safety data on Abraxane from a total of four studies in 883 patients with NSCLC treated with Abraxane administered weekly or once every three weeks combined with carboplatin (n=765) or as monotherapy (n=118), and one study in 32 patients with metastatic breast cancer treated with Abraxane/Herceptin¹¹ weekly combined with carboplatin administered once every three weeks. In general, the safety profile of Abraxane was consistent in the five submitted studies.

The pivotal safety data for Abraxane/carboplatin at the proposed dose for the proposed indication are derived from the pivotal Phase III efficacy and safety Study CA031. In this study, 514 patients were treated with Abraxane administered weekly at a dose of 100 mg/m² on Days 1, 8 and 15 of each 21-day cycle combined with carboplatin (Area under the plasma concentration time curve (AUC) = 6 mg.min/mL) administered on Day 1 of each 21-day cycle. The safety data from these 514 patients was compared with the safety data from 524 patients in the pivotal study treated with Taxol administered at a dose of 200 mg/m² combined with carboplatin (AUC = 6 mg.min/mL) on Day 1 of each 21-day cycle. The safety data summarised below refers to the data from the pivotal Phase III efficacy and safety Study CA031 unless otherwise stated.

¹¹ Herceptin (trastuzumab (rch)) is indicated for the treatment of patients with breast cancer, in association with chemotherapy.

Exposure to Abraxane/carboplatin and Taxol/carboplatin in Study CA031 is considered sufficient to adequately characterise the safety profile of the two treatment arms. In each treatment arm the median number of 21-day treatment cycles was 6.0. However, the median cumulative taxane dose was 17.8% higher with Abraxane administered weekly (1325 mg/m²) relative to Taxol administered every three weeks (1125 mg/m²). In addition, the median average taxane dose intensity per week was 25.9% higher with Abraxane weekly (81.98 mg/m²/week) relative to Taxol every three weeks (65.12 mg/m²/week).

Treatment-emergent adverse events (all Grades¹²) were reported in nearly all patients in both the Abraxane/carboplatin and Taxol/carboplatin arms (94% and 96%). The most commonly reported TEAEs (all Grades) occurring in ≥ 20% of patients in the Abraxane/carboplatin versus the Taxol/carboplatin arm were alopecia (56% versus 60%), neutropenia (51% versus 48%), anaemia (44% versus 21%), thrombocytopenia (40% versus 23%), nausea (27% versus 25%), peripheral sensory neuropathy (26% versus 40%), fatigue (25% versus 23%), and peripheral neuropathy (20% versus 23%).

Treatment-emergent adverse events (all Grades) reported statistically significantly more commonly in patients in the Abraxane/carboplatin compared with the Taxol/carboplatin arm were anaemia (44% versus 21%, p<0.001), thrombocytopenia (40% versus 23%, p<0.001), peripheral oedema (10% versus 4%, p<0.001), epistaxis (7% versus 2%, p<0.001), Haemoglobin (Hgb) decreased (11% versus 6%, p=0.015), upper abdominal pain (3% versus 1%, p=0.039), haemorrhoids (2% versus < 1%, p=0.020), and nail disorder (2% versus <1%, p=0.002). TEAEs (all grades) reported statistically significantly more commonly in patients in the Taxol/carboplatin arm compared with the Abraxane/carboplatin arm were peripheral sensory neuropathy (40% versus 26%, p<0.001), arthralgia (25% versus 13%, p<0.001), myalgia (19% versus 10%, p<0.001), and pruritus (4% versus 2%, p=0.050). The pattern of treatment-related AEs (all grades) in both treatment arms was consistent with that for TEAEs (all grades), and the majority of events were considered to be treatment-related.

Treatment-emergent adverse events (Grade 3 or higher) were reported in a similar proportion of patients in the Abraxane/carboplatin and Taxol/carboplatin arms (70% versus 68%). The most commonly reported TEAEs (all Grades) occurring in ≥ 20% of patients in the Abraxane/carboplatin versus the Taxol/carboplatin arm were neutropenia (36% versus 40%) and anaemia (25% versus 6%). TEAEs (Grade 3 or higher) reported statistically significantly more commonly in patients in the Abraxane/carboplatin arm compared with the Taxol/carboplatin arm were anaemia (25% versus 6%, p<0.001), thrombocytopenia (17% versus 6%, p<0.001), Hgb decreased (4% versus < 1%, p=0.006), Alanine aminotransferase (ALT) increased (2% versus < 1%, p=0.032), and platelet count decreased (2% versus < 1%, p=0.020). TEAEs (Grade 3 or higher) reported statistically significantly more commonly in patients in the Taxol/carboplatin arm compared with the Abraxane/carboplatin arm were peripheral neuropathy (5% versus 2%, p=0.018), peripheral sensory neuropathy (7% versus < 1%, p<0.001), arthralgia (2% versus < 1%, p=0.021), and myalgia (2% versus < 1%, p=0.011). The pattern of treatment-related AEs (Grade 3 or higher) in both treatment arms was consistent with that for TEAEs (all grades), and the majority of events were considered to be treatment-related.

¹² Common Terminology Criteria for Adverse Events v4.0 (CTCAE); Publish Date: May 28, 2009: Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily life (ADL). Grade 3 Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care ADL. Grade 4 Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to AE.

The study included specific analyses of a number of AEs of special interest. Anaemia (including preferred terms of anaemia, Hgb decreased, haematocrit decreased, and red blood cell count decreased) occurred in a greater proportion of patients in the Abraxane/carboplatin arm compared with the Taxol/carboplatin arm for all grades (54% versus 24%) and for Grade 3 or higher (28% versus 7%). The percentage of patients in the Abraxane/carboplatin arm who received a blood transfusion during the study was greater than in the Taxol/carboplatin arm (16% versus 4%), and the majority of transfused patients in both treatment arms required only one transfusion. In the Abraxane/carboplatin arm, greater percentages of patients discontinued, had dose reductions, or dose delays/dose not given due to anaemia than patients in the Taxol/carboplatin arm.

Most severe neutropenia (NCI Common Terminology Criteria for Adverse Events (CTCAE)) showed a statistically significant reduction in severity across all Grades ($p=0.007$) and for Grades 3-4 ($p<0.001$) in patients in the Abraxane/carboplatin arm relative to the Taxol/carboplatin arm ($p=0.007$). The analysis of neutropenia using combined Medical Dictionary for Regulatory Activities (MedDRA) PTs of neutropenia, granulocytopenia, neutrophil count decreased, and granulocyte count decreased showed that neutropenia (all Grades) occurred more commonly in patients in the Abraxane/carboplatin arm than in the Taxol/carboplatin arm (59% versus 56%), while Grade 3 or higher events occurred more commonly in patients in the Taxol/carboplatin arm than in the Abraxane/carboplatin arm (48% versus 42%). There were very few neutropenia SAEs ($<1\%$ for both arms), and the proportion of patients discontinuing taxane due to neutropenia (preferred term) was 3% in the Abraxane/carboplatin arm and 2% in the Taxol/carboplatin arm. Febrile neutropenia was reported in 1% and 2% of the Abraxane/carboplatin and Taxol/carboplatin arms. Infection and infestation (MedDRA System Order Classification (SOC)) treatment emergent SAEs occurred in a similar proportion of patients in the Abraxane/carboplatin and Taxol/carboplatin arms (4% versus 3%).

Thrombocytopenia (PTs thrombocytopenia and platelet count decreased) occurred in a greater proportion of patients in the Abraxane/carboplatin arm compared with the Taxol/carboplatin arm for all Grades (45% versus 27%) and for Grade 3 or higher (18% versus 7%). The majority of thrombocytopenic events resulted in taxane dose delays in both treatment arms, with a minority resulting in taxane dose reductions and small number in discontinuations of taxane.

Peripheral neuropathy (broad scope) occurred in a statistically significantly greater proportion of patients in the Taxol/carboplatin arm than in the Abraxane/carboplatin arm (64% versus 48%, $p<0.001$). The time to onset of treatment-related peripheral neuropathy (any grade) was statistically significantly shorter in the Taxol/carboplatin arm compared with the Abraxane/carboplatin arm (37.5 versus 49 days, $p<0.001$). The median time to improvement of Grade 3 or higher treatment-related peripheral neuropathy to Grade 1 was shorter in the Abraxane/carboplatin arm than in the Taxol/carboplatin arm (38 versus 104 days, $p=0.326$). In addition, both physician assessment of peripheral neuropathy at every visit and patient reported outcome using the Functional Assessment of Cancer Therapy (FACT)-Taxane assessment instrument significantly favoured patients in the Abraxane/carboplatin arm compared with the Taxol/carboplatin arm. Peripheral sensory neuropathy was the most common TEAE (preferred term) resulting in taxane discontinuation in the Taxol/carboplatin arm 4% (versus 1% in the Abraxane/carboplatin arm), followed by peripheral neuropathy (2%, Taxol/carboplatin versus $<1\%$, Abraxane/carboplatin) and neutropenia (2%, Taxol/carboplatin versus 3%, Abraxane/carboplatin).

Arthralgia was reported in a greater proportion of patients in the Taxol/carboplatin arm than in the Abraxane/carboplatin arm (25% versus 13%; $p<0.001$), as was myalgia (19%

versus 10%; $p < 0.001$). However, few patients in both treatment arms had treatment discontinued or doses reduced or delayed due to arthralgia or myalgia.

Skin and subcutaneous tissue disorders (MedDRA, SOC term) occurred frequently in both treatment arms and in a comparable proportion of patients (61%, Abraxane/carboplatin versus 64%, Taxol/carboplatin). The most common TEAEs reported in this SOC ($\geq 5\%$ of patients) in the Abraxane/carboplatin versus Taxol/carboplatin arms were alopecia (56% versus 60%) and rash (10% versus 8%). There were no reports of Stevens-Johnson syndrome or toxic epidermal necrolysis. Few patients in both treatment arms had treatment discontinued or doses reduced or delayed due to skin and subcutaneous tissue disorders.

Gastrointestinal disorders (MedDRA, SOC term) occurred in a comparable proportion of patients in both treatment arms (41%, Abraxane/carboplatin versus 38%, Taxol/carboplatin). Few patients in both treatment arms had treatment discontinued or doses reduced or delayed due to skin and subcutaneous tissue disorders.

Drug hypersensitivity and hypersensitivity occurred infrequently in both the Abraxane/carboplatin and Taxol/carboplatin arms, although these events were more common in the Taxol/carboplatin arm than in the Abraxane/carboplatin arm. Drug hypersensitivity and hypersensitivity were reported in two patients each ($< 1\%$) in the Abraxane/carboplatin arm, and in eight (2%) and six (1%) patients in the Taxol/carboplatin arm. The majority of cases of drug hypersensitivity/hypersensitivity in both treatment arms were related to the taxane component of the combinations with very small numbers of cases being related to carboplatin. Drug hypersensitivity/hypersensitivity Grade 3 or higher was not reported in the Abraxane/carboplatin arm, but was reported in four ($< 1\%$) patients in the Taxol/carboplatin arm. There were very few treatment discontinuations and dose interruptions due to drug hypersensitivity/hypersensitivity, with nearly all reported events occurring in the Taxol/carboplatin arm.

Treatment-emergent adverse events with an outcome of death within 30 days of the last treatment occurred in 18 (4%) patients in the Abraxane/carboplatin arm and 19 (4%) patients in the Taxol/carboplatin arm. No TEAE with an outcome of death was reported at the PT level for $\geq 1\%$ of patients in either treatment arm. Treatment-emergent SAEs (fatal and non-fatal) were reported in 18% of patients in the Abraxane/carboplatin arm and 15% of patients in Taxol/carboplatin arm. The main difference between the two treatment arms as regards treatment-emergent SAEs (fatal and non-fatal) was the higher percentage of patients with anaemia in the Abraxane/carboplatin arm (4%) compared with the Taxol/carboplatin arm ($< 1\%$).

The proportion of patients discontinuing the taxane component of the combination due to TEAEs was identical (16%) in both treatment arms, while the proportion of patients discontinuing carboplatin was similar in the Abraxane/carboplatin and Taxol/carboplatin arms (16% and 15%). The most common TEAEs resulting in taxane and carboplatin discontinuation in the Abraxane/carboplatin arm were neutropenia (3% for both) and thrombocytopenia (3% for both), and in the Taxol/carboplatin arm the most common event resulting in discontinuation was peripheral sensory neuropathy (4%, Taxol and 3%, carboplatin). All other TEAEs resulting in treatment discontinuation related to taxane and carboplatin were reported in $\leq 2\%$ of patients in either treatment arm.

The proportion of patients who had their taxane dose reduced was two-fold higher in the Abraxane/carboplatin arm compared with the Taxol/carboplatin arm (46% versus 23%). This difference was most likely due to the greater frequency of taxane dosing in the Abraxane/carboplatin arm (once weekly) than in the Taxol/carboplatin arm (once every three weeks), resulting in more opportunities for protocol-specified dose reductions due to taxane induced toxicities. In both treatment arms, nearly all taxane dose reductions were due to AEs/toxicities. In the Abraxane/carboplatin arm, taxane dose reductions

occurred notably more frequently ($\geq 2\%$ more patients) than in the Taxol/carboplatin arm for the TEAEs of neutropenia (24% versus 9%), thrombocytopenia (13% versus 4%), anaemia (6% versus $< 1\%$), and neutrophil count decreased (4% versus 1%). In the Taxol/carboplatin arm, taxane dose reductions occurred notably more frequently ($\geq 2\%$ more patients) than in the Abraxane/carboplatin arm for the TEAE of peripheral sensory neuropathy (5% versus $< 1\%$).

The proportion of patients with delayed/not given taxane doses was also higher in the Abraxane/carboplatin arm (82%) than in the Taxol/carboplatin arm (54%), as was delayed/not given carboplatin doses (72% versus 54%). In both treatment arms, the majority of delayed/not given taxane dose were due to AEs/toxicities. In the Abraxane/carboplatin arm, taxane dose delays occurred notably more frequently ($\geq 2\%$ more patients) than in the Taxol/carboplatin arm for the TEAEs of neutropenia (41% versus 12%), thrombocytopenia (30% versus 12%), anaemia (16% versus 1%), leucopenia (6% versus 1%), neutrophil count decreased (8% versus 2%), platelet count decreased (4% versus 2%), ALT increased (4% versus 2%), pneumonia (3% versus 1%), and fatigue (3% versus $< 1\%$). In the Taxol/carboplatin arm, taxane dose delays occurred notably more frequently ($\geq 2\%$ more patients) than in the Abraxane/carboplatin arm for the TEAE of peripheral sensory neuropathy (5% versus 1%). Dosing interruptions at the time of infusion of taxane or carboplatin were uncommon occurring in $< 1\%$ of patients and $< 1\%$ of cycles in both treatment arms.

Treatment-emergent adverse events (all Grades) reported or worsening after six treatment cycles occurred in a similar proportion of patients in the Abraxane/carboplatin arm (28%) and the Taxol/carboplatin arm (27%), and the proportion of patients with TEAEs (Grade 3 or higher) was higher in the Taxol/carboplatin arm (18%) compared with the Abraxane/carboplatin arm (14%). The general pattern of TEAEs reported or worsening after six treatment cycles was consistent with the overall pattern of TEAEs.

There were no marked differences between the two treatment arms as regards clinical laboratory assessment of hepatic or renal function. The study included no assessment of treatment on vital signs or ECG findings. There were a number of TEAEs associated with Abraxane/carboplatin that occurred more notably commonly in patients aged ≥ 65 years compared with patients aged < 65 years (particularly haematological toxicities), females compared with males, and Asians compared with Whites.

First round benefit-risk assessment

First round assessment of benefits

The pivotal Phase III Study CA031 showed that the benefits of Abraxane/carboplatin for the treatment of advanced NSCLC are comparable with those for Taxol/carboplatin. However, Taxol/carboplatin is not a TGA approved combination for the treatment of advanced NSCLC, although the combination is included in Australian clinical oncology guidelines as an accepted treatment for the condition.

In the pivotal Phase III Study, all efficacy evaluations were based on the ITT population (n=1052): 521 patients in Abraxane arm and 531 patients in the Taxol/carboplatin arm. The ORR in patients with advanced NSCLC was statistically significantly higher in the Abraxane/carboplatin arm (33%) than in the Taxol/carboplatin arm (25%), $p=0.005$; $pA/pT = 1.313$ (95.1% CI: 1.082, 1.593). However, the clinical significance of the absolute difference between the two treatment arms of 8% in favour of Abraxane/carboplatin is unlikely to be clinically meaningful in the absence of statistically significant differences between the two arms in PFS and OS. The primary superiority analysis of the PFS (blinded radiological assessment) showed that the difference between the median duration of PFS in the two treatment arms was not statistically significant. Consequently, the primary

analysis of OS (which also showed no statistically significant difference between the two treatment arms) was considered to be exploratory rather than confirmatory due to the pre-specified hierarchical statistical analysis (that is, superiority analysis of OS to proceed only if superiority of Abraxane/carboplatin over Taxol/carboplatin had been initially established).

The non-inferiority analysis of the PFS and OS (key secondary efficacy endpoints) showed that the Abraxane/carboplatin arm was non-inferior to the Taxol/carboplatin for both parameters. In the PFS (blinded radiological assessment) non-inferiority analysis, median PFS was 6.8 months in the Abraxane/carboplatin arm and 6.5 months in the Taxol/carboplatin arm; $HR_{A/T} = 0.949$ (95% CI: 0.830, 1.086). In the OS non-inferiority analysis, median OS was 12.1 months in the Abraxane/carboplatin arm and 11.2 months in the Taxol/carboplatin arm; $HR_{A/T} = 0.922$ (95% CI: 0.797, 1.066). In the non-inferiority analyses of both the PFS and the OS, the upper bound of the 95% CI of the $HR_{A/T}$ was less than the pre-specified non-inferiority margin of 1.176 (that is, non-inferiority margin of 15%).

The results for the secondary efficacy endpoints of investigator assessed ORR and PFS were consistent with the primary analysis of these endpoint based on blinded assessment. In addition, there was no statistically significant difference between the two treatment arms as regards the secondary efficacy endpoints of disease control rate (53% and 49% in the Abraxane/carboplatin and Taxol/carboplatin arms) and median duration of response (9.6 and 9.5 months in the Abraxane/carboplatin and Taxol/carboplatin arms).

The pre-specified exploratory analysis of the effect of baseline stratification factors on the ORR showed that ORR was statistically significantly higher in the Abraxane/carboplatin arm compared with the Taxol/carboplatin arm in patients with squamous cell carcinoma (41% versus 24%, $p < 0.001$), patients with Stage IV disease (31% versus 23%, $p=0.015$), male patients (33% versus 24%, $p=0.011$), patients aged < 70 years (32% versus 25%, $p=0.013$), and patients from Eastern Europe (34% versus 27%, $p=0.014$). The corresponding exploratory unplanned analysis for OS showed that median survival was longer in the Abraxane/carboplatin arm compared with the Taxol/carboplatin in North American patients (12.7 versus 9.8 months, $p=0.008$), and patients aged ≥ 70 years (19.9 versus 10.4 months, $p=0.009$). The corresponding exploratory unplanned analysis for PFS showed no statistically significant differences between the two treatment arms for any of the stratification factors. Overall, the exploratory analyses (planned and unplanned) of the effect of baseline stratification factors and other baseline prognostic factors on ORR, PFS and OS showed consistent benefits for patients in the Abraxane/carboplatin arm compared with the Taxol/carboplatin arm.

It is considered that limited support for the benefits of the proposed Abraxane/carboplatin combination for the treatment of advanced NSCLC is provided from Study CA028 in which 25 patients were treated with combination. However, no meaningful clinical data relating to the proposed Abraxane/carboplatin combination for the treatment of advanced NSCLC can be derived from Studies CA015 and CA018 nominated by the sponsor as supportive as in neither study were patients exposed to the proposed combination dose regimen.

First round assessment of risks

Overall, it is considered that the risks of treatment with Abraxane/carboplatin for advanced NSCLC are satisfactory and generally comparable with those of Taxol/carboplatin, although the risk profiles of the two treatment regimens differ. The sponsor (Clinical Overview) states that "*Abraxane/carboplatin is better tolerated than Taxol/carboplatin, with a marked reduction in Grade 3-4 peripheral neuropathy, neutropenia, arthralgia, and myalgia*". However, the sponsor's contention that

Abraxane/carboplatin is better tolerated than Taxol/carboplatin is unconvincing. Overall, it is considered that tolerability is comparable between the two treatment arms.

The pivotal Phase III Study showed that the major risks of treatment with Abraxane/carboplatin at the proposed dose for the proposed indication relate to anaemia, thrombocytopenia, neutropenia, and peripheral neuropathy. While both anaemia and thrombocytopenia occurred notably more commonly in patients in the Abraxane/carboplatin arm, peripheral neuropathy occurred notably more commonly in the Taxol/carboplatin arm as did severe neutropenia. Arthralgia and myalgia also occurred commonly in patients in the Abraxane/carboplatin arm, but both of these events were reported notably more frequently in patients in the Taxol/carboplatin arm. In the Abraxane/carboplatin arm, both taxane and carboplatin dose reductions and dose delays/doses not given occurred in a greater proportion of patients than in the Taxol/carboplatin arm. However, the proportion of patients discontinuing the taxane component of the combination due to AEs was identical in both treatments, while the proportion of patients discontinuing the carboplatin component was similar. SAEs (fatal and non-fatal) were reported marginally more frequently in patients in the Abraxane/carboplatin arm than in the Taxol/carboplatin arm, but AEs with a fatal outcome were reported in an identical proportion of patients in both treatment arms. A notably higher proportion of patients used concomitant pre-dosing medications of corticosteroids, antihistamines, drugs for acid-related disorders, and anti-emetics/anti-nauseants in the Taxol/carboplatin arm compared with the Abraxane/carboplatin arm.

The pivotal Phase III Study showed that the most commonly occurring risks ($\geq 20\%$ of patients) associated with treatment with Abraxane/carboplatin (versus Taxol/carboplatin) were alopecia (56% versus 60%), neutropenia (51% versus 48%), anaemia (44% versus 21%), thrombocytopenia (40% versus 23%), nausea (27% versus 25%), peripheral sensory neuropathy (26% versus 40%), fatigue (25% versus 23%), and peripheral neuropathy (20% versus 23%).

More TEAEs (all Grades) occurred statistically significantly more commonly in patients in the Abraxane/carboplatin arm than in the Taxol/carboplatin arm (8 versus 4 events). TEAEs (all Grades) reported statistically significantly ($p \leq 0.05$) more commonly in patients in the Abraxane/carboplatin arm compared with the Taxol/carboplatin arm were anaemia (44% versus 21%), thrombocytopenia (40% versus 23%), peripheral oedema (10% versus 4%), epistaxis (7% versus 2%), Hgb decreased (11% versus 6%), upper abdominal pain (3% versus 1%), haemorrhoids (2% versus $< 1\%$), and nail disorder (2% versus $< 1\%$). TEAEs (all grades) reported statistically significantly ($p \leq 0.05$) more commonly in patients in the Taxol/carboplatin arm compared with the Abraxane/carboplatin arm were peripheral sensory neuropathy (40% versus 26%), arthralgia (25% versus 13%), myalgia (19% versus 10%), and pruritus (4% versus 2%).

The most commonly reported TEAEs (Grade 3 or higher) occurring in $\geq 10\%$ of patients in the Abraxane/carboplatin arm versus the Taxol/carboplatin arm were neutropenia (36% versus 40%), anaemia (25% versus 6%), and thrombocytopenia (17% versus 6%). The number of statistically significant TEAEs (Grade 3 or higher) was similar in the Abraxane/carboplatin and Taxol/carboplatin arms (5 versus 4). TEAEs (Grade 3 or higher) reported statistically significantly ($p \leq 0.05$) more commonly in patients in the Abraxane/carboplatin arm compared with the Taxol/carboplatin arm were anaemia (25% versus 6%), thrombocytopenia (17% versus 6%), Hgb decreased (4% versus $< 1\%$), ALT increased (2% versus $< 1\%$), and platelet count decreased (2% versus $< 1\%$). TEAEs (Grade 3 or higher) reported statistically significantly ($p \leq 0.05$) more commonly in patients in the Taxol/carboplatin arm compared with the Abraxane/carboplatin arm were peripheral neuropathy (5% versus 2%), peripheral sensory neuropathy (7% versus $< 1\%$), arthralgia (2% versus $< 1\%$), and myalgia (2% versus $< 1\%$).

Anaemia (broadly defined to include anaemia, Hgb decreased, haematocrit decreased, and red blood cell count decreased), occurred more commonly in the Abraxane/carboplatin arm than in the Taxol/carboplatin arm for all Grade AEs (54% versus 24%) and for Grade 3 or higher adverse events (28% versus 7%). Anti-anaemic preparations were administered to a higher proportion of patients in the Abraxane/carboplatin arm (35%) than in the Taxol/carboplatin arm (20%). In both treatment arms, a minority of patients with anaemia required blood transfusion (16%, Abraxane versus 4%, Taxol/carboplatin). However, the majority of transfused patients in both treatment arms required only one transfusion. In the Abraxane/carboplatin arm, greater percentages of patients discontinued, had reductions in dose, or dose delay/dose not given due to anaemia (PT) than patients in the Taxol/carboplatin arm. The incidence of haemorrhagic AEs was similar in the Abraxane/carboplatin and the Taxol/carboplatin arms (13% versus 10%), suggesting that the observed anaemia in both treatment arms is due to a direct toxic effect on red blood cell formation.

Thrombocytopenia (including MedDRA PTs of thrombocytopenia and platelet count decreased) occurred more commonly in the Abraxane/carboplatin arm than in the Taxol/carboplatin arm for all Grade AEs (45% versus 27%) and for Grade 3 or higher AEs (18% versus 7%). The majority of thrombocytopenic events (PT) resulted in taxane dose delays in both treatment arms, with a minority resulting in taxane dose reductions and small number in taxane discontinuation. Thrombocytopenia did not result in platelet transfusions in either treatment arm. The increased risk of thrombocytopenia observed in patients in the Abraxane/carboplatin arm appeared to result in a small increased risk of haemorrhagic adverse events (13%, Abraxane/carboplatin versus 10%, Taxol/carboplatin), predominantly due to an increased risk of epistaxis in the Abraxane/carboplatin arm compared with the Taxol/carboplatin arm (7% versus 2%).

Neutropenia (NCI CTCAE) showed a statistically significant reduction in severity across all grades in patients in the Abraxane/carboplatin arm relative to the Taxol/carboplatin arm ($p=0.007$), as did Grade 3-4 neutropenia ($p < 0.001$). The incidence of neutropenia (NCI CTCAE Grades 1-4) including MedDRA PTs neutropenia, granulocytopenia, neutrophil count decreased, and granulocyte count decreased was higher in patients in the Abraxane/carboplatin arm compared with the Taxol/carboplatin arm (59% versus 56%), but neutropenia (NCI CTCAE) Grade 3 or higher occurred more frequently in patients in the Taxol/carboplatin arm compared with the Abraxane/carboplatin arm (48% versus 42%). Febrile neutropenia was reported in 1% and 2% of the Abraxane/carboplatin and Taxol/carboplatin arms. Infection and infestation (MedDRA SOC) treatment emergent SAEs occurred in a similar proportion of patients in the Abraxane/carboplatin and Taxol/carboplatin arms (4% versus 3%).

Peripheral neuropathy (broadly defined) occurred statistically significantly ($p \leq 0.05$) more commonly in patients in the Taxol/carboplatin arm than in the Abraxane (64% versus 48%), as did arthralgia (25% versus 13%) and myalgia (19% versus 10%).

Drug hypersensitivity/hypersensitivity events occurred infrequently in both the Abraxane/carboplatin and Taxol/carboplatin arms, although these events were more common in the Taxol/carboplatin arm than in the Abraxane/carboplatin arm.

There were no marked differences between the two treatment arms as regards gastrointestinal disorders or skin and subcutaneous tissue disorders (no cases of Stevens-Johnson syndrome or toxic epidermal necrolysis were reported). The Abraxane/carboplatin combination did not appear to notably impair renal, hepatic or cardiac function. However, patients were required to have adequate hepatic and renal function in order to be included in the study, and patients with clinically significant hepatic or renal function were excluded as were patients with any significant concurrent illness. No cranial nerve palsies were reported in the pivotal Phase III Study.

Cardiac disorders occurred in a similar proportion of patients in both treatment arms (6%, Abraxane/carboplatin versus 5%, Taxol/carboplatin). Hepatobiliary disorders also occurred in a similar proportion of patients in the Abraxane/carboplatin and Taxol/carboplatin arms (3% versus 2%) with the majority of TEAEs (PTs) in both arms being hyperbilirubinaemia (2% versus 1%). Similarly, renal and urinary disorders occurred in a similar proportion of patients in both the Abraxane/carboplatin and Taxol/carboplatin arms (3% versus 2%), with no TEAE (PT) occurring in more than 1% of patients in either treatment arm.

TEAEs with an outcome of death occurred in 4% of patients in both treatment arms, and SAEs (fatal or non-fatal) were reported in 18% of patients in the Abraxane/carboplatin arm and 16% of patients in the Taxol/carboplatin arm. The main difference between the two treatment arms as regards treatment-emergent SAEs (fatal and non-fatal) was the higher percentage of patients with anaemia in the Abraxane/carboplatin arm (4%) compared with the Taxol/carboplatin arm (<1%).

The risks of treatment with Abraxane/carboplatin were notably increased in patients aged ≥ 65 years compared with patients aged < 65 years (particularly haematological toxicities), and in Asian patients compared with White patients. In addition, females appear to be at an increased risk of experiencing AEs with the combination compared with males.

First round assessment of benefit-risk balance

The benefit-risk balance of Abraxane/carboplatin at the proposed dosage regimen for the proposed usage is considered to be favourable. In the pivotal Phase III Study, the clinical benefits relating to PFS and OS were similar for the Abraxane/carboplatin and Taxol/carboplatin arms, and tolerability of the two treatment arms was comparable although the risk profiles differed.

Clinical questions

There were no clinical questions.

First round recommendation regarding authorisation

It is recommended that Abraxane at a dose of 100 mg/m² administered IV over 30 minutes on Days 1, 8, and 15 of each 21-day cycle combined with carboplatin AUC = 6 mg.min/mL on Day 1 of each 21-day cycle be approved for the first-line treatment of non-small cell cancer in patients who are not candidates for potentially curative surgery or radiotherapy.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan identified as EU-RMP Version: 11.0, dated 5 April 2012, and Australian Specific Annex (ASA) Version: 2.0, dated 24 May 2012, which was reviewed by the TGA's Office of Product Review (OPR). The sponsor subsequently submitted an updated ASA Version: 2.1, dated 18 December 2012.

Safety specification

Subject to the evaluation of the clinical aspects of the Safety Specification (SS) by the TGA's Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows:

Table 6: Summary of Ongoing Safety Concerns

Important Identified Risks	
	Myelosuppression
	Neurotoxicity
	Gastrointestinal events
	Myalgia and arthralgia
	Hypersensitivity reactions
	Cranial nerve palsies
	Cardiotoxicity
	Stevens-Johnson syndrome/toxic epidermal necrolysis
	Pneumonitis
	Infusion site reactions/extravasation
Important Potential Risks	
	Use in patients with hepatic impairment
	Off-label use
	Concomitant therapy and interactions requiring dose adjustments
Important Missing Information	
	Patients with impaired renal function
	Use in children
	CNS metastases

OPR evaluator's comment

In comparison to the AU-RMP previously reviewed for this product, the important potential risks: '*Stevens-Johnson syndrome/toxic epidermal necrolysis*' and '*Infusion site reactions/extravasation*' have now been categorised as important identified risks. In addition the newly identified safety concern: '*Pneumonitis*' has now been added as an important identified risk based on ongoing clinical trial data. The ASA states the sponsor has also agreed to include the important potential risk: '*Use in patients with hepatic impairment*' as an ongoing safety concern in response to the previous evaluation of the AU-RMP.

Notwithstanding the evaluation of the clinical aspects of the SS, the OPR considers that this list of ongoing safety concerns is acceptable.

Pharmacovigilance plan

The sponsor states that routine pharmacovigilance activities, consistent with the activities outlined in 3.1.2 *Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)*, are proposed to monitor all the specified ongoing safety concerns.

The ASA states that in Australia additional pharmacovigilance activity is proposed: "*In addition, the Sponsor has designed and will implement an Abraxane Drug Utilisation Study (ADUS) to determine off label usage, the use in combination therapies and as a concomitant medication and the requirement for pre-medication for gastrointestinal events*".

Risk minimisation activities

The ASA states: *“Routine risk minimisation activities are proposed since there is no need for a risk minimisation plan for Abraxane.”* However, it would appear that additional risk minimisation activities are also proposed to minimise medication error and for the important identified risks: ‘Cranial nerve palsies’, ‘Cardiotoxicity’ & ‘Stevens-Johnson syndrome/toxic epidermal necrolysis’, while no routine risk minimisation is proposed for the important potential risk: ‘Off-label use’ and the important missing information: ‘Central Nervous System (CNS) metastases’.

Routine risk minimisation activities will comprise labelling, including contraindications, special warning and precaution statements, instructions for use, overdose statements and/or notification of undesirable effects for all the specified ongoing safety concerns. A Health Care Practitioners (HCP) brochure to address the education of physicians on the rare and important side effects caused by Abraxane has also been prepared.

Summary of first round recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the draft PI and consumer medicine information documents (CMI) should not be revised until the Delegates Overview has been received:

1. Safety considerations may be raised by the clinical evaluators through the consolidated TGA request for further information and/or the Clinical Evaluation Report. It is important to ensure that the information provided in response to this includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.
2. The limited information provided about the proposed ADUS could only be considered as a draft synopsis and does not lend itself to detailed assessment. Given the stated anticipated timeframe the sponsor should provide at least a draft protocol for review and include it as an appendix to an updated ASA.
3. It appears the sponsor has maintained the position that there is no need for a risk minimisation plan in the ASA despite previous TGA advice to the contrary. This review concurs with the previous evaluation that the proposed additional risk minimisation activities for the important identified risks: ‘Cranial nerve palsies’, ‘Cardiotoxicity’ and ‘Stevens-Johnson syndrome/toxic epidermal necrolysis’ triggers the need for a risk minimisation plan to be included in the ASA. The sponsor should provide to the TGA an updated ASA to that effect. The risk minimisation plan should be in accordance with the format required in the EMA Annex C: TEMPLATE FOR EU RISK MANAGEMENT PLAN (EU – RMP), including how the effectiveness of the HCP educational brochure as a measure to reduce risk will be assessed. This is consistent with the previous evaluation’s recommendation: *“Planned outcome measures for the success or otherwise of the education need to be provided”*.
4. The sponsor should update the ASA to include a risk minimisation plan in accordance with the ‘Risk management plan (RMP) questions & answers’ (Version 1.3, October 2012) document on the TGA website. Complete assessment of the proposed additional risk minimisation activity cannot be conducted until such information is provided, although the approved indications for Abraxane will need to be updated in the HCP brochure if the proposed NSCLC indication is approved.

5. In regard to the proposed routine risk minimisation activities, revisions were recommended to several statements in the draft PI. Details of these are beyond the scope of the AusPAR.

Second round review

A summary of the sponsor's responses to the recommendations outlined above it as follows:

- *Recommendation 1:* The sponsor has provided an assurance that it will address any issues raised by the Clinical Evaluator once the evaluation reports have been received, and incorporate into the RMP as considered relevant and necessary. This is acceptable.
- *Recommendation 2:* The sponsor submitted an updated ASA Version: 2.1, dated 18 December 2012, and this recommendation has not been adequately addressed.

The ASA Version: 2.0, dated 24 May 2012, stated:

In addition, the Sponsor has designed and will implement an ADUS to determine off label usage, the use in combination therapies and as a concomitant medication and the requirement for pre-medication for gastrointestinal events.

The sponsor was advised that the limited information provided about the proposed ADUS could only be considered as a draft synopsis and did not lend itself to detailed assessment. Given the stated anticipated timeframe the sponsor was asked to provide at least a draft protocol for review and include it as an appendix to an updated ASA.

Consequently the sponsor should now submit the supporting protocol or state when the draft protocol is anticipated to be available, and provide a revised anticipated timeframe for this project, preferably before this application is approved.

- *Recommendation 3:* The sponsor updated the ASA to reflect additional risk minimisation activities for the following important identified risks to be covered in a HCP brochure: Cranial nerve palsies, Severe skin reactions (Stevens Johnson and Lyell syndrome), and cardiotoxicity. The sponsor proposed to conduct a brief survey to measure the effectiveness of this risk communication.

In general the Yes/No questions included in the brief survey are considered to be an inappropriate measure of the effectiveness of the proposed additional risk minimisation activities to reduce such risk. Questions interrogating the HCP's specific understanding of the content of the safety messages in the HCP brochure should instead be asked. In addition the sponsor should propose and justify the quantitative criteria to be used to verify the success (pass/fail) of the proposed additional risk minimisation activities. Consequently a revised Risk Minimisation Plan in the ASA and a HCP Brochure Survey Protocol satisfactory to the TGA should be submitted for review, preferably before this application is approved.

- *Recommendation 4:* As discussed in *Recommendation 3*, the ASA has been amended to include the details of the planned additional risk minimisation activities. Nevertheless a revised Risk Minimisation Plan in the ASA and a HCP Brochure Survey Protocol satisfactory to the TGA should be submitted for review, preferably before this application is approved. The sponsor has also provided an assurance that revision to the HCP brochure will be made as required, including an update to the approved indication in the brochure if the NSCLC indication is approved. This is acceptable.

Recommendation regarding the implementation of the RMP as a condition of registration

The RMP proposed by the sponsor was considered generally acceptable by the OPR. The following condition of registration was advised:

The European Risk Management Plan identified as Version: 11.0, dated 5 April 2012, with an ASA Version: 2.1, dated 18 December 2012, and amended details of a Risk Minimisation Plan as agreed with the TGA, must be implemented.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Overview of data

- Study CA031 was a Phase III, randomised, open-label, Taxol-controlled trial in patients with advanced NSCLC. This study has been published (Socinski *et al* 2012¹³). There is an accompanying editorial by Levine and Juergens¹⁴, which refers in part to the Socinski Study.
- Three efficacy and safety Studies CA028; CA015; CA018 considered supportive by the sponsor, but not considered influential by the clinical evaluator.
- Four clinical studies relating to other indications, such as breast cancer (not evaluated).
- Four clinical pharmacology studies.

The relevant European Union (EU) Guidelines (beside the general guidelines) to this application are as follows:

- EMEA/EWP/205/95 Rev.3 Corr; Guideline on the Evaluation of Anticancer Medicinal Products in Man, Published: TGA Internet site, Effective: June 2006
- CPMP/EWP/482/99; Points to Consider on Switching between Superiority and Non-inferiority; Published: TGA Internet site; Effective: 29 June 2001
- EMEA/CPMP/EWP/2158/99; Guideline on the Choice of the Non-Inferiority Margin; Published: TGA Internet site; Effective: January 2006

¹³ Socinski *et al* 2012. Weekly Nab-Paclitaxel In Combination With Carboplatin Versus Solvent-Based Paclitaxel Plus Carboplatin As First-Line Therapy In Patients With Advanced Non-Small Cell Lung Cancer: Final Results Of A Phase III Trial. *JCO* 2012; 30 (17): 2055-2062

¹⁴ Levine MN and Juergens R. Method to Our Madness or Madness in Our Methods? Pitfalls in Trial Methodology. *JCO* 2012; 30 (17): 2025-2027

Pharmacokinetics

Abraxane/carboplatin PK interactions: Study 08DA33 provided PK interaction data for Abraxane/carboplatin (in 12 Japanese NSCLC patients enrolled in pivotal Study CA031). Mean Maximum Concentration (C_{max}) and AUC values for paclitaxel (Abraxane) were approximately 15% lower when administered directly before carboplatin than when administered without carboplatin. The evaluator notes that carboplatin could not influence C_{max} of paclitaxel on Day 1 due to timing of infusions versus sampling, and proposes that higher paclitaxel exposure on Day 15 is due to accumulation. An effect of Abraxane on carboplatin PK was not formally excluded.

Sub-study BIO-VT-5 also gathered PK information in NSCLC patients given Abraxane/carboplatin (the patients were drawn from the pivotal Study CA031), but sampling was sparse and results were considered difficult to interpret.

The evaluator concluded that carboplatin is unlikely to significantly affect the plasma PK of paclitaxel.

There was some evidence of proportionality between Abraxane dose (from 80 to 300 mg/m²) and paclitaxel exposure. Dose reductions for toxicity are to 75 mg/m² then 50 mg/m², both outside the range in which there is evidence of dose proportionality.

There was some evidence that the PK of paclitaxel is similar in patients with NSCLC and with solid tumours. The evaluator also concluded that the PK of paclitaxel is similar in White and Japanese subjects.

Pharmacodynamics

In a non-clinical study, Shao *et al* (2011¹⁵) found that anti-tumour activity of Abraxane did not correlate with tumour expression of SPARC (Secreted Protein Acidic and Rich in Cysteine). Consistent with this, PD Report BIO-VT-6 was a Sub-study of CA031; the patients consenting to participation in the sub-study tended to do better than others. High versus low SPARC expression was not found to have any predictive value.

Koukourakis *et al* (2003) found that 5% of neoplastic cells from NSCLC tissue expressed SPARC, but 37% of stromal fibroblasts expressed/produced SPARC.

Efficacy

The sponsor's justifications for selection of Abraxane, Taxol and carboplatin doses were noted.

Study CA031

This is an ongoing Phase III, open-label study conducted in six countries (Russia, USA, Japan, Ukraine, Canada, and Australia [1% of patients]). Data cut-off for the primary efficacy endpoint was 12 October 2009, and for other endpoints 31 January 2011 (>15 months difference).

Inclusion and exclusion criteria were noted. Eligible patients were adults with Stages IIIB-IV NSCLC who had not received prior chemotherapy for metastatic disease (adjuvant chemotherapy was allowed if had been completed 12 months prior to study entry). Prior radiation was allowed if to a non-target lesion or to a target lesion with progression of the lesion since radiation was completed. Stage IIIB implies significant spread to regional

¹⁵ Shao H., Salavaggiione O.E., Yu C., Hylander B., Tan W., Repasky E., Adjei A.A. and Dy G.K. Improved response to nab-paclitaxel compared with cremophor-solubilised paclitaxel is independent of secreted protein acidic and rich in cysteine expression in non-small cell lung cancer *Thorac. Oncol.* 2011;6:998-1005

lymph nodes (N3¹⁶), or at least moderate nodal spread (N2) with tumour invasion of significant structures, and is essentially inoperable. The study did not involve genetic testing of tumours for mutation status. A key exclusion was active brain metastases.

1052 subjects were enrolled, stratified by Stage (IIIB/IV), age (<70 yrs, ≥70 yrs), gender, histology (adenocarcinoma/squamous cell carcinoma (SCC)/other) and region, and randomised 1:1 as follows:

- Arm A (n=521): Abraxane/carboplatin
 - Abraxane: 100 mg/m² (unless modified due to toxicity); IV over 30 minutes; no steroid premedication; without routine granulocyte colony-stimulating factor (G-CSF) prophylaxis; once weekly on Days 1, 8 and 15 of each three-week cycle
 - Carboplatin: to reach AUC 6 mg.min/mL on Day 1 of each three-week cycle
- Arm B (n=531): Taxol/carboplatin
 - Taxol: 200 mg/m² (unless modified due to toxicity); IV over three hours; standard premedication; given every three weeks
 - Carboplatin: to reach AUC 6 mg.min/mL on Day 1 of each three-week cycle

Treatment could continue until progression, unacceptable toxicity or withdrawal of consent. Median number of cycles was six across arms (in contrast with eviQ¹⁷ advice to treat metastatic cancer for four cycles unless otherwise indicated, but somewhat closer to the National Comprehensive Cancer Network (NCCN¹⁸) advice to consider maintenance therapy after four-six cycles). Irradiation was not allowed during treatment.

Median age was 60 years; 79% of subjects had Stage IV disease at randomisation and 21% had Stage IIIB. Median number of lesions was five in the Taxol arm and four in the Abraxane arm (p=0.011). 97-98% of patients had received no prior medication for cancer; 7-9% had received prior radiation (such as lung, bone, brain). Many of the 89/1052 patients who had prior radiation had that radiation directed to metastases. 3% of patients had brain metastases (presumably inactive, that is, treated and stable and off therapy for a month or more).

There were disparities in the use of concomitant medications. For example, corticosteroids were used in 45% of Abraxane patients but in 99% of Taxol patients. Presumably some of this disparity related to premedication in the Taxol arm; but this does not explain the more frequent use of “anti-anaemic preparations” in the Abraxane arm (see ‘*Safety*’ below).

The primary efficacy endpoint was ORR based on blinded and independent radiological review, using RECIST criteria, confirmed by the next assessment. The study was designed as a superiority study; (see under ‘*Issues*’ for discussion of the addendum to the Statistical Analysis Plan that allowed a non-inferiority analysis).

Objective response rate: Results for the primary endpoint: 170/521 patients (33%) in the Abraxane arm had a PR, and 131/531 (25%) in the Taxol arm had a PR (as well as 1/531 with a CR). The lower bound of the 95.1% CI around the response rate ratio was

¹⁶ N: degree of spread to regional lymph nodes: N2 Metastatic carcinoma in ipsilateral mediastinal or subcarinal nodes; N3 Metastatic carcinoma in contralateral mediastinal or hilar nodes or Ipsilateral or contralateral scalene nodes or Supraclavicular nodes. ‘TNM Classification for Lung Cancer’ developed by the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC).

¹⁷ eviQ Cancer Treatments Online. Treatment Algorithms for the Management of Lung Cancer in NSW, Guide for Clinicians. Available from: URL: <<https://www.eviq.org.au/>>. Accessed May 13, 2013.

¹⁸ NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-small cell lung cancer, Version 2.2013. Available from: URL: <<http://www.nccn.org/>>. Accessed May 9, 2013.

1.082, that is, this difference was statistically significant. The evaluator described the clinical significance of this difference as '*uncertain*'.

In subgroup analysis, it was notable that differences in ORR, favouring Abraxane, were more prominent in patients with SCC. Bevacizumab is indicated in NSCLC with squamous cell histology.

Duration of OR was not formally assessed; instead, the sponsor analysed PFS in those with an OR, as a proxy. PFS outcomes were very similar across arms in this regard.

Progression-free survival: There was no statistically significant difference in PFS between arms (Hazard Ratio (HR) 0.902, 95% CI 0.767-1.060). Setting this fundamental limitation aside, the clinical evaluator considered that the difference in point estimates of median PFS (6.3 months for the Abraxane arm versus 5.8 months for the Taxol arm) was not clinically significant. Strictly, if the statistical significance of a difference (using an acceptable p-value) cannot be concluded, the clinical significance of the difference should be considered cautiously: it cannot be assumed that any difference exists. Abraxane was non-inferior to Taxol, in terms of PFS, accepting the sponsor's choice of delta (see '*Issues*').

Overall survival: Median OS was 12.1 months in the Abraxane arm and 11.2 months in the Taxol arm (HR 0.92, CI 0.80-1.07). This was not a statistically significant difference; setting this basic issue aside, the clinical evaluator's view was that this was not a clinically meaningful difference.

Quality of life was not reported.

Study CA028

This was an uncontrolled, open-label study of Abraxane/carboplatin in advanced NSCLC, from Russia. Escalating Abraxane doses were given one-three times in a three week cycle to seven patient cohorts each of 25 subjects. 98% had received no prior chemotherapy. There were 25 patients in the cohort with a regimen same as that proposed in this submission; the ORR in that cohort was 48%, made up of one CR and 11 PR patients. Median PFS in the cohort of most interest was 6.2 months; OS was 11.3 months.

Other studies

Single centre, open-label, uncontrolled Study CA015 did not examine use in conjunction with carboplatin and analysed only three patients treated with the proposed 100 mg/m² weekly dose of Abraxane. The clinical evaluator considered this meant the study provided no meaningful efficacy data.

Study CA018 suffered from similar shortcomings (open-label, uncontrolled; no carboplatin; no patients on proposed Abraxane regimen) and again was considered unresponsive.

Safety

Exposure

In the four efficacy/safety studies discussed above, 539 subjects received treatment using the proposed dosing regimen; 514/539 were from the pivotal Study CA031. Appropriately, the clinical evaluator has focused on safety data from this study. In Study CA031, median number of cycles given was six across arms. Median cumulative taxane dose was higher in the Abraxane arm (1325 mg/m² versus 1125 mg/m²), but not as high as the comparison of dosing regimens might predict (300 mg versus 200 mg per three week cycle), whereas the median cumulative carboplatin dose was slightly lower in the Abraxane arm (3140 mg versus 3315 mg). Dose reductions were more common in the Abraxane arm for both components (46% each) than in the Taxol arm (23% each), perhaps because weekly dosing for Abraxane allows greater scope for dose modification based on toxicity.

Overview of AEs

The overview suggests no major difference in AEs across arms, except that twice as many in the Abraxane arm (46% versus 23%) had one AE resulting in dosage reduction, and 71% (Abraxane) versus 41% (Taxol) had an AE resulting in delayed taxane administration.

Drilling down to PTs, there were distinctly more reports in the Abraxane arm than the Taxol arm of anaemia (44% versus 21% for Taxol arm), thrombocytopenia (40% versus 23%), peripheral oedema (7% versus 2%) and some other AEs. Conversely, there were distinctly more reports in Taxol arm patients of peripheral sensory neuropathy (40% versus 26%), arthralgia (25% versus 13%) and myalgia (19% versus 10%). Analysis of severe AEs revealed a similar picture, with the increases in severe anaemia (25% versus 6%) and thrombocytopenia (17% versus 6%) in Abraxane arm patients offsetting decreases in peripheral sensory neuropathy/peripheral neuropathy (>3% versus 12%). Treatment-related AEs followed this broad pattern.

Haematological toxicity

A convincing picture emerged that in the Abraxane arm, anaemia (including severe anaemia and anaemia requiring treatment, such as transfusion) was more prominent than in the Taxol arm. Despite more thrombocytopenia in the Abraxane arm patients, incidence of haemorrhagic AEs was similar (13% for Abraxane, 10% for Taxol), suggesting an alternative cause for anaemia (bone marrow suppression is implied by the sponsor). This translated into <1% of Abraxane arm subjects discontinuing due to anaemia, versus no Taxol arm subjects.

While there was some evidence of less severe neutropenia in the Abraxane arm, this did not translate into any difference in infections or immunostimulant use, or into any distinct difference in discontinuation due to neutropenia (2-3% across arms). Rather, dose reductions due to neutropenia were more prominent in the Abraxane arm (24% versus 9%), as were dose delays. Few patients reported febrile neutropenia.

In the Abraxane arm, thrombocytopenia (including both severe and treated events) was more evident than in the Taxol arm. This resulted in taxane discontinuation in 3% for the Abraxane arm and <1% for the Taxol arm.

Peripheral neuropathy

Peripheral neuropathy was more frequent, more severe, of earlier onset and slower to resolve in the Taxol arm, and this had an impact on quality of life. This was a relatively major cause of discontinuation in the Taxol arm.

In the pivotal study of metastatic breast cancer as reported in the Abraxane PI, Abraxane 260 mg/m² every three weeks resulted in 10% incidence of severe sensory neuropathy, whereas Taxol 175 mg/m² every three weeks resulted in 2% incidence (Table 6). This contrasts with CA031 where Taxol 200 mg/m² every three weeks (with carboplatin) resulted in 12% incidence. Potentially, addition of carboplatin makes peripheral neuropathy more likely (but carboplatin was also given to the Abraxane arm, where incidence was 3%); differences in study populations could also explain the contrasting findings.

Table 7: Incidence of severe sensory neuropathy

Sensory neuropathy	Metastatic breast cancer		Advanced NSCLC	
Abraxane	260 mg/m ² q3wk	71% any; 10% severe	100 mg/m ² q1wk, plus carboplatin	48% any; 3% severe
Taxol	175 mg/m ² q3wk	56% any; 2% severe	200 mg/m ² q3wk, plus carboplatin	64% any; 12% severe

Other

Arthralgia, myalgia and hypersensitivity were less of a problem in the Abraxane arm than in the Taxol arm. Hypersensitivity was rare even in the Taxol arm.

Many of these differences across arms in AE frequency were magnified in patients ≥ 65 yrs of age, for example, severe anaemia in 24% (older Abraxane patients) versus 4% (older Taxol patients), or severe peripheral sensory neuropathy in 12% (older Taxol patients) versus 1% (older Abraxane patients).

It is unclear whether these differences in toxicities are due to the differences in dose regimen between arms, or due to formulation differences (see 'Issues' below).

Clinical evaluator's recommendation

The clinical evaluator recommends approval of the sponsor's proposed new indication.

Risk management plan

The RMP proposed by the sponsor was considered generally acceptable by the OPR. The following condition of registration was advised:

- The European Risk Management Plan identified as Version: 11.0, dated 5 April 2012, with an ASA Version: 2.1, dated 18 December 2012, and amended details of a Risk Minimisation Plan as agreed with the TGA, must be implemented.

Risk-benefit analysis**Delegate considerations*****Efficacy – pivotal study – choice of comparator***

Taxol/carboplatin as used in Study CA031 is a reasonable comparator in metastatic disease. In Stage IIIB disease (21% of study patients), the choice is dubious. The sponsor has made no comparison of its proposed regimen with the established treatment of Stage IIIB disease. The relevance of concluding broadly comparable efficacy in Stage IIIB versus full dose Taxol/carboplatin is limited.

Efficacy – pivotal study – choice of primary endpoint

The evaluator notes that ORR is not endorsed by TGA-adopted EU guidelines¹⁹ as a primary endpoint in the setting of NSCLC treatment. The sponsor justifies the choice, weakly – the fact that paclitaxel is active/effective is tangential to the issue (it remains difficult to translate differences between Taxol and Abraxane arms in ORR into differences in ‘clinical benefit’) and the fact that the study was designed after talks with the FDA has no direct relevance.

The editorial by Levine and Juergens²⁰ that discusses the published report of Study CA031 notes that:

The use of ORR alone as the primary outcome measure is not commonly done in 2012. Most clinical investigators would not consider this outcome as an adequate choice for a definitive trial evaluating a chemotherapy agent and might choose instead end points such as PFS or OS. In this regard, the clinical relevance of an 8% difference in ORR with no survival benefit is uncertain.

Applications with one pivotal study should ensure that that pivotal study is robust in design and conduct²¹. Having a primary endpoint that does not allow direct comparison of ‘clinical benefit’ means it is difficult to gauge whether the relative treatment benefit of Abraxane/carboplatin versus Taxol/carboplatin is large enough to be clinically valuable. In this case, the analysis of secondary endpoints was helpful in understanding the overall benefit of Abraxane versus comparator; the secondary endpoint results generally supported the primary ones.

Efficacy – pivotal study – study design and dose regimen

The editorial by Levine and Juergens that discusses the published Report of CA031 also notes:

The schedules of the two regimens were different—weekly nab-paclitaxel versus every three weeks solvent-based (sb)-paclitaxel. There is evidence that weekly paclitaxel is more efficacious and associated with less adverse effects than paclitaxel administered every three weeks in breast cancer, but not in NSCLC. It is unknown how nab-paclitaxel as administered in this trial would fare against weekly sb-paclitaxel.

The referenced study of paclitaxel dosing frequency is by Belani *et al*²². In Arm 1, paclitaxel 100 mg/m² was given weekly for three of four weeks, with carboplatin (AUC = 6 mg.min/mL) on Day 1 of each four week cycle. In Arm 2, patients were given paclitaxel 225 mg/m² and carboplatin to AUC = 6 mg.min/mL, on Day 1 of each three week cycle. After four cycles, maintenance therapy was given (lower dose weekly paclitaxel).

In this randomised study of patients with untreated advanced NSCLC, ORR was 27.6% in Arm 1 and 19.2% in Arm 2 (p=0.037). The primary endpoint (OS) was similar across arms (median survival, 38.6 weeks versus 42.9 weeks; two-year survival, 16.2% versus 17.6%). Grade 3-4 anaemia was more common with Arm 1 (8% versus 3%; p=0.026), but Grade 2-

¹⁹ Guideline on the evaluation of anticancer medicinal products in man
<<http://www.tga.gov.au/pdf/euguide/ewp020595enrev3.pdf>>

²⁰ Levine MN and Juergens R. Method to Our Madness or Madness in Our Methods? Pitfalls in Trial Methodology. *JCO* 2012; 30 (17): 2025-2027

²¹ Points to consider on application with 1. Meta-analyses; 2. One pivotal study.
<<http://www.tga.gov.au/pdf/euguide/ewp233099en.pdf>>

²² Belani CP, Ramalingan S, Perry MC, LaRocca RV, Rinaldi D, Gable PS, *et al*. Randomized Phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small cell lung cancer. *J Clin Oncol* 2008;26(3):468-73.

3 neuropathies (12% versus 18%; 1-sided $p=0.05$; italicised in Table 8 below) and Grade 2-3 arthralgias (1% versus 6%; $p=0.017$) were less common.

Table 8: Incidence of Grade 2-3 neuropathies

Sensory neuropathy	Metastatic breast cancer		Advanced NSCLC	
	Abraxane	260 mg/m ² q3wk	71% any; 10% severe	100 mg/m ² q1wk, plus carboplatin
Taxol	175 mg/m ² q3wk	56% any; 2% severe	200 mg/m ² q3wk, plus carboplatin	64% any; 12% severe
	-	-	100 mg/m ² q1wk, plus carboplatin (3 weeks out of 4)	12% moderate to severe
	-	-	225 mg/m ² q3wk, plus carboplatin	18% moderate to severe

This Belani Study has not been evaluated; but it raises the suspicion that many findings in Study CA031 can be put down to differences in dose regimen (rather than formulation).

Efficacy – pivotal study – addendum to Statistical Analysis Plan

An addendum to the statistical analysis plan (SAP) was included on 11 April 2011, to cater for EU guidelines. This was done before PFS and OS analyses but after a pre-specified interim analysis of response. The argument that potential inferiority of Abraxane/carboplatin versus Taxol/carboplatin, in terms of PFS or OS, of up to 17.6%, is ‘acceptable’ because crudely speaking it only reduces its efficacy to that seen with etoposide/cisplatin, and is weak. Such a reduction in efficacy, when endpoints such as PFS and OS with established clinical benefit are considered, would have to be offset by major gains in other clinically valuable endpoints (such as quality of life and specific toxicities).

There is a TGA-adopted guideline on switching between superiority and non-inferiority²³. Of note is Section III, Relevance of Pre-definition: “*Plausible arguments may often be advanced for a retrospective choice [of delta]*”.

Efficacy – conclusions

Despite the above major methodological concerns, the Delegate considers that the proposed regimen has been shown to be non-inferior and broadly comparable in efficacy to Taxol/carboplatin in advanced NSCLC. Given that the pivotal study was large and that statistical significance of superior efficacy was not found, it is reasonable only to conclude that the proposed regimen is non-inferior. However, the comparison is only relevant for Stage IV disease. There was no appropriate comparator for Stage IIIB disease. So, efficacy has not been demonstrated in Stage IIIB disease (relative to an appropriate comparator).

²³ CPMP/EWP/482/99; Points to Consider on Switching between Superiority and Non-Inferiority; Published: TGA Internet site; Effective 29 June 2001

Incidentally, PFS was not shown to be improved in Stage IIIB disease, though this may be a consequence of sub-group analysis.

Use has not been examined in patients with active brain metastases and this should be noted in the PI, as a caveat in the indication and accompanied by a suitable precaution.

It is not clear whether the marginal differences in efficacy are due to the differences in dose regimen between arms or due to formulation differences, or both.

Safety

As noted by the clinical evaluator, in the pivotal study the proposed regimen appears to have a different toxicity profile to the comparator regimen. Those in the Abraxane arm of CA031 had more and more severe anaemia and thrombocytopenia, in particular. On the other hand, those in the Taxol arm had more and more severe peripheral neuropathy. Of relevance in this regard, the recommended taxane dose in Stage IIIB disease treated with chemo-radiation may be considerably lower than that used in Study CA031: potentially, the risk of peripheral nerve damage is also lower in that setting (so the benefit of weekly Abraxane in reducing peripheral neuropathy may be less apparent in that setting).

Indications

The Delegate considered that the data support the following indication:

Abraxane, in combination with carboplatin, is indicated for the first-line treatment of metastatic non-small cell lung cancer in patients. Use has not been studied in patients with active CNS metastases.

The sponsor's proposed indication was:

Abraxane, in combination with carboplatin, is indicated for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation.

The sponsor's proposed indication endorses use in Stage IIIB disease despite the absence of clinical data comparing Abraxane/carboplatin versus an appropriate comparator.

The sponsor's indication would also endorse use in patients with earlier stage disease, despite the pivotal study not including such patients, where "potentially curative" treatment cannot be given. Chemo-radiation in Stage IIIA can produce a cure in a small number of patients but is palliative in most. Again, there is no indication from the sponsor's data that Abraxane/carboplatin when given as proposed provides any net benefit to such patients compared to the currently accepted best practice.

There is a relatively modest net positive benefit-risk profile seen in Stage IV disease relative to an acceptable comparator. Extrapolation to assume that the proposed regimen is no worse than currently accepted best practice in other situations where patients are not candidates for potentially curative surgery and/or radiation is inappropriate.

Taxol is indicated broadly, in NSCLC. An alternative view to that described above is that the Abraxane/carboplatin regimen in Study CA031 was no worse than the Taxol/carboplatin regimen, so Abraxane should be allowed the Taxol indication. Possibly this was the sponsor's logic, since the proposed indication reflects the Taxol indication in the US and EU.

Use with bevacizumab has not been tested. The bevacizumab indication is:

*Avastin (bevacizumab), in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with **unresectable advanced, metastatic or recurrent, non-squamous, non-small cell lung cancer.***

It is therefore appropriate to highlight that studies with Avastin have not been conducted.

Overall risk-benefit

The benefit of much shorter infusion time for Abraxane is recognised; as is the reduced need for pre-medication and the ability to use standard tubing and IV bags (Taxol and its generics require non-Polyvinyl chloride (PVC) containing infusion sets).

The Delegate considered there is a positive benefit-risk balance in the indication:

Abraxane, in combination with carboplatin, is indicated for the first-line treatment of metastatic NSCLC in patients. Use has not been studied in patients with active CNS metastases.

In patients susceptible to peripheral neuropathy, or in whom peripheral neuropathy would be a bad outcome, Abraxane/carboplatin as proposed could be advantageous. In patients in whom risks posed by thrombocytopenia and anaemia are higher, it may be preferable to use Taxol/carboplatin as per Study CA031. Patients with a bleeding diathesis, a history of bleeding, predictable sources of bleeding (such as active peptic ulcer disease), baseline low Hgb or platelet count could fall into this group. This could be addressed by appropriate PI precautions.

Proposed action

The Delegate proposed to approve the application but restrict the indication as follows:

Abraxane, in combination with carboplatin, is indicated for the first-line treatment of metastatic non-small cell lung cancer in patients. Use has not been studied in patients with active CNS metastases.

Request for advice

The advice of the Advisory Committee on Prescription Medicines (ACPM) is requested, to help inform a decision about the application:

1. Is the comparator arm in pivotal Study CA031 appropriate for (a) Stage IV patients, and (b) Stage IIIB or other patients?
2. In what NSCLC population, if any, does the ACPM see a positive benefit-risk profile for the proposed treatment regimen?

Advice is requested from the ACPM about whether it is appropriate to accept the sponsor's indication on the basis that Abraxane seems no worse than Taxol in the pivotal Study CA031, or whether, as above, it is appropriate to approve an indication more specifically supported by the pivotal study.

Given the apparent differences in toxicity profile between Abraxane and Taxol regimens as used in the pivotal study, can the ACPM advise about optimising the recommended use of Abraxane/carboplatin (for example, in terms of *Indications, Precautions, et cetera*).

The ACPM was also requested to consider, specifically, the status of the current Precaution about substituting solvent-based paclitaxel.

Response from sponsor

This document includes Celgene's responses to the questions directed to the ACPM by the Delegate.

Introduction

Abraxane nab paclitaxel powder for Injection (suspension) is a proprietary solvent-free, protein-stabilised formulation of paclitaxel comprised of paclitaxel and human albumin. Abraxane has been developed to improve the therapeutic index of paclitaxel, by reducing the toxicities associated with the solvent-based paclitaxel, Taxol (paclitaxel) Injection, manufactured by Bristol-Myers Squibb (New York) and the Cremophor EL (BASF, Ludwigshafen, Germany) and ethanol vehicle while improving the chemotherapeutic effect of the drug. This is achieved by taking advantage of endogenous transport pathways to deliver higher doses of paclitaxel to the tumour. The formulation of Abraxane is a lyophilised powder consisting of paclitaxel bound to human albumin in each vial.

The impetus to develop Abraxane emanated from the goal to produce a therapeutic paclitaxel formulation devoid of solvents. The development of a nanoparticle form of unmodified paclitaxel that is stabilised using human albumin accomplished this goal and provided the opportunity to take advantage of endogenous transport pathways to potentially deliver higher doses of paclitaxel to the tumour. Furthermore, the nab formulation of Abraxane eliminated micellar entrapment of paclitaxel associated with Cremophor EL-based formulations. The unique characteristics of the Abraxane formulation enhance the chemotherapeutic effect of the drug as well as reduce the toxicities associated with solvent-based formulations, leading to an improvement in the therapeutic index.

Non-small cell lung cancer is a serious and life-threatening disease for which there is an unmet medical need for new effective and well tolerated treatment options. The majority of patients with lung cancer are diagnosed once the tumour has progressed beyond the primary site. In the treatment of advanced NSCLC, paclitaxel/carboplatin is a commonly used platinum-doublet chemotherapy regimen. Despite recent advances in identifying optimal chemotherapy regimens, patients with advanced NSCLC continue to have a poor prognosis.

Based on the experience with Abraxane in MBC, and the promising activity demonstrated in a Phase I/II study and two Phase II studies in NSCLC, a large international, well-controlled Phase III trial (CA031) was designed and conducted as a superiority trial in consultation with global regulatory authorities, including TGA, on the study design and analysis plan.

Study CA031 enrolled patients with Stage IIIB and IV NSCLC who were not candidates for potentially curative surgery and/or radiation therapy. The comparator arm of paclitaxel/carboplatin used reflects treatment recommendations in guidelines for the treatment of patients with NSCLC including guidelines from Australia, the US, and Scotland and treatment currently utilised in clinical practice. These guidelines recommend combination chemotherapy for patients with Stage III NSCLC who are ineligible for curative surgery or radiation.

The study met the primary endpoint of ORR, determined by independent radiologic review, with high statistical significance. Nonsignificant trends for PFS and OS in favour of the Abraxane/carboplatin regimen compared to the Taxol/carboplatin regimen were also observed in the pivotal Phase III Study CA031. The greatest improvement in ORR and strongest trends in PFS and OS were observed in the group of patients with the largest unmet need, those with squamous cell histology. In addition, there were notable differences in the safety profile between the two combinations, with the Abraxane/carboplatin regimen showing distinct advantages for a reduced risk of neutropenia, peripheral neuropathy, and musculoskeletal pain in comparison to the Taxol/carboplatin regimen that showed a lower risk of thrombocytopenia and anaemia.

Based on the totality of efficacy and safety data from Study CA031, Celgene believes that the Abraxane/carboplatin regimen has a favourable benefit-risk profile in comparison

with the Taxol/carboplatin regimen and is supportive of the Sponsor's proposed indication of "*Abraxane, in combination with carboplatin, for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and or radiation*".

The addition of Abraxane/carboplatin as a treatment option would expand the clinical armamentarium in the underserved patient population with NSCLC.

Celgene's responses to the questions directed to the ACPM by the Delegate

Delegate's Question 1. Is the comparator arm in pivotal Study CA031 appropriate for (a) Stage IV patients, and (b) Stage IIIB or other patients?

The sponsor's proposed indication is:

"Abraxane, in combination with carboplatin, is indicated for the first line treatment of NSCLC in patients who are not candidates for potentially curative surgery and/or radiation."

Study CA031 evaluated patients with Stage IIIB and IV NSCLC, randomising them to Abraxane in combination with carboplatin compared to an established standard, Taxol in combination with carboplatin, at recommended doses for metastatic NSCLC and therefore the comparator arm is appropriate for Stage IV patients.

The application of surgery and/or radiation (or chemo-radiation) in earlier stage disease (Stages I-III), is typically for curative intent. The sponsor-proposed indication specifically excludes all patients who may be eligible for such treatment. As the Delegate mentioned, the guidelines stipulate that either surgery or chemo-radiation are the standard of care for such patients with earlier stage disease. However, guidelines for the treatment of patients with NSCLC also recommend combination chemotherapy for some patients with Stage III NSCLC clinical practice guidelines for the treatment of lung cancer commissioned and co-funded by Cancer Australia and developed by Cancer Council Australia (Lehman, 2012²⁴) define three groups of Stage III NSCLC patients:

- a. Patients with good performance status (PS), adequate pulmonary function and localised tumour who should be considered for radical treatment with the accepted "standard of care" being the concurrent administration of chemotherapy and radiotherapy (RT) to doses ≥ 60 Gray (Gy).
- b. Patients with poor PS, substantial weight loss ($>10\%$) and advanced disease for whom simple palliative measures are appropriate; and
- c. An intermediate group of patients who have a good PS but locally advanced disease for whom radical chemo-radiation (≥ 60 Gy) is not feasible either due to tumour extent or patient factors (such as poor respiratory function).

These guidelines further state that chemotherapy is recommended for some Stage III patients based on the following evidence:

- *"In advanced NSCLC, systemic chemotherapy improves survival and maintains quality of life compared with best supportive care. In a meta-analysis of 16 trials involving 2714 patients, chemotherapy reduced the risk of death (HR = 0.77; 95% CI 0.71-0.83; $p \leq 0.0001$), resulting in an absolute improvement in one year survival of 9% (from 20% - 29%). Studies which prospectively evaluate intrathoracic tumour-related symptoms demonstrate an improvement from baseline scores with palliative chemotherapy."*

²⁴ Lehman, M. What is the optimal treatment approach for patients with stage III inoperable NSCLC who, because of patient or tumour factors, are not suitable for curative treatment with concurrent chemo-radiotherapy? [Version URL: <http://wiki.cancer.org.au/australiawiki/index.php?oldid=47749>, cited 2013 May 12]. Clinical practice guidelines for the treatment of lung cancer. Sydney: Cancer Council Australia. Accessed May 11, 2013.

- *“For patients with stage III disease who because of performance status or disease extent are not suitable for treatment with curative intent and who are not experiencing symptoms specifically related to chest disease, referral for chemotherapy opinion should be considered.”*

The eviQ Cancer Treatments Online *“Treatment Algorithms for the Management of Lung Cancer in NSW, Guide for Clinicians”* also supports the option for patients with Stage IIIB NSCLC of palliative chemotherapy if radiation therapy is contraindicated (eviQ, 2013.²⁵).

Other guidelines also address that such patients should be treated with combination chemotherapy, the comparator used in Study CA031 (SIGN, 2005; Alberta Provincial Thoracic Tumour Team, 2012). Therefore, combination chemotherapy is clinically acceptable for patients with Stage IIIB disease who are ineligible for curative surgery or radiation treatment.

Study CA031 enrolled Stage III patients for whom combination chemotherapy would be an option. Thus the population in the proposed indication of first-line treatment of NSCLC in patients who are not candidates for potentially curative surgery and/or radiation is appropriately supported by the randomised Study CA031 and is consistent with treatment guidelines.

Delegate’s Question 2: In what NSCLC population, if any, does the ACPM see a positive benefit-risk profile for the proposed treatment regimen?

Advice is requested from the ACPM about whether it is appropriate to accept the sponsor's indication on the basis that Abraxane seems no worse than Taxol in the pivotal Study CA031, or whether, as above, it is appropriate to approve an indication more specifically supported by the pivotal study.

The standard of care for patients with advanced NSCLC who are ineligible for curative surgery, radiation or chemo-radiation is a platinum-based chemotherapy doublet. Prior Phase III randomised trials showed similar ORRs and survival for many platinum-doublet combinations, with differences in toxicity, dosing schedule, and convenience. The NCCN Guidelines for NSCLC mention that *“clinicians can individualise therapy for their patients”* (NCCN, Guidelines Version 2.2013 – Non-small Cell Lung Cancer).

The Abraxane/carboplatin combination represents another option for clinicians to consider as they individualise therapy for their patients in the following ways:

- The Abraxane regimen differs from the solvent-based paclitaxel based regimen in toxicity, dosing schedule and convenience. In Study CA031, the combination of Abraxane/carboplatin had an improved ORR compared to solvent based paclitaxel/carboplatin. An analysis of ORR showed the strongest trend towards a beneficial treatment effect in patients with SCC, a subgroup that has the highest unmet need. For the overall and SCC populations, the median and HRs for PFS and OS trended toward an improvement in the Abraxane/carboplatin arm, but were not significantly improved.
- There were notable differences in the safety profile between the two combinations, with patients on Abraxane showing distinct advantages for a reduced risk for neutropenia, peripheral neuropathy, and musculoskeletal pain compared to patients on solvent-based paclitaxel that showed a lower risk of thrombocytopenia and anaemia. While the sponsor would agree that the clinical relevance of the difference of haematologic parameters remains to be established, the advantages of a significantly

²⁵ eviQ Cancer Treatments Online. Treatment Algorithms for the Management of Lung Cancer in NSW, Guide for Clinicians. Available from: URL: <<https://www.eviq.org.au/>>. Accessed May 13, 2013.

lower risk and fewer dose modifications for peripheral neuropathy in a regimen including carboplatin remain unquestionable.

Common to most advanced oncology protocols, patients with active CNS metastases were excluded. NSCLC frequently involves the CNS and there were patients who were enrolled on Study CA031 with CNS metastases noted at baseline or as new lesions in follow-up scans. The number of patients with disease progression due to CNS/brain metastases either due to unequivocal progression of disease of an existing lesion, or due to a new CNS lesion was similar in each arm (17 cases in the Abraxane-containing arm versus 16 cases in the solvent-based paclitaxel containing arm). Thus, there was no disadvantage for patients on the Abraxane Arm as the frequency of disease progression due to CNS/brain metastases was similar between the two regimens. The sponsor acknowledges that the effectiveness and safety of Abraxane has not been formally studied in patients with CNS metastases. This is prominently represented in the *Precautions* section of the current Abraxane PI that includes the following:

“The effectiveness and safety of Abraxane in patients with CNS metastases has not been established.”

Delegate’s Question 3: Given the apparent differences in toxicity profile between Abraxane and Taxol regimens as used in the pivotal study, can the ACPM advise about optimising the recommended use of Abraxane/carboplatin (for example, in terms of *Indications, Precautions, et cetera*).

Could the ACPM please consider, specifically, the status of the current precaution about substituting solvent-based paclitaxel?

The current precaution in the PI to not substitute Abraxane for or with other solvent-based paclitaxel formulations is important language that was included to ensure the safe use of Abraxane. This language is incorporated as a black box warning in both the US Package Insert and the Canadian Product Monograph for Abraxane, and is included the EMA Summary of Product Characteristics (SmPC) *“Posology and method of administration”* section.

Celgene believes patient safety is paramount. Revising the current precaution language to allow substitution of Abraxane with solvent-based paclitaxel would unnecessarily compromise patient safety and place patients at undue risk for toxicities. Celgene requests that the Delegate and the ACPM respectfully consider maintaining the original language in the proposed PI for the following reasons:

- Celgene does not agree that Abraxane is the same as solvent-based paclitaxel. In particular, the albumin component of the nanoparticles is more than an auxiliary substance to improve stability, duration and/or absorption of the active component. Rather, the albumin plays an active biological role in the pharmacology of Abraxane, and alters the pharmacology compared to solvent-based paclitaxel.
- While not covalently bound, paclitaxel and albumin are nevertheless bound with high affinity. Abraxane should be considered an active complex, which persists in the circulation and is transported across the endothelium into the tumour interstitium as a complex, behaving much like a covalently linked conjugate (Desai, 2006²⁶).
- The sponsor notes that the drug utilisation of Abraxane and solvent-based paclitaxel is distinct, since Abraxane and solvent-based paclitaxel are not clinically interchangeable. In particular, Abraxane is being used in settings where conventional

²⁶ Desai N, Trieu V, Yao, Z, Louie L, Ci s, Yang A, *et al*. Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. *Clin Cancer Res* 2006;12(4):1317-24.

solvent-based paclitaxel has showed limited or no activity, including chemo-naive metastatic melanoma and pancreatic adenocarcinoma. Based on this activity, Abraxane, in combination with gemcitabine, was recently added to the NCCN Guidelines as a Category 1 recommendation for patients with metastatic adenocarcinoma of the pancreas with good performance status (*NCCN Guidelines Version 1.2013 – Pancreatic Adenocarcinoma*).

The following points further illustrate the differentiation between Abraxane and solvent based paclitaxel:

- The novel, Cremophor EL-free, nab particle formulation of paclitaxel in Abraxane conferred the ability to achieve a higher MTD based on every three-weeks dosing: 300 mg/m² for Abraxane versus 175 mg/m² for Taxol (Nyman, 2004²⁷).
- The use of nab paclitaxel also enables Abraxane to be given in a shorter, more convenient infusion time of 30 minutes compared with 3 to 24 hours with Taxol.
- Abraxane is given without steroid and anti-histamine premedication, which is required for solvent-based paclitaxel to prevent solvent-related hypersensitivity reactions which, while rare, can be fatal (Taxol Label, 2011). Even with such premedication, the FDA label for conventional solvent-based paclitaxel notes in a Black Box warning “Fatal reactions have occurred in patients despite premedication”.
- Cremophor EL has been shown to leach plasticisers, specifically di(2-ethylhexyl) phthalate (DEHP), from polyvinyl chloride (PVC) bags and polyethylenelined tubing (Gelderblom, 2001²⁸; Venkataramanan, 1986²⁹; Pfeifer, 1993³⁰; Allwood, 1996³¹; Song, 1996³²; and Xu, 1998³³). Although no controlled epidemiologic toxicity studies have been conducted in humans exposed to DEHP, severe effects (such as, carcinogenicity, cardiopulmonary toxicity, hepatotoxicity, and nephrotoxicity) have been observed in experimental models. The prescribing information for solvent-based paclitaxel instructs users to prepare, store, and administer solutions in glass, polypropylene, or polyolefin containers; non-PVC-containing infusion sets (for example, those with polyethylene lining) should be used. By comparison, standard tubing and intravenous (IV) bags may be used for the IV administration of Abraxane (Ibrahim, 2002³⁴; Nyman, 2004³⁵).

These considerations point to drugs with significantly different pharmacological, dosing and administration properties such that Abraxane and conventional solvent-based

²⁷ Nyman DW, Campbell KJ, Hersh E, Richardson K, Patrick K, Trieu V, *et al.* A phase I trial of ABI-007, nanoparticle paclitaxel, administered to patients with advanced non-hematologic malignancies. *J Clin Oncol* 2004;22(Suppl 14):2027.

²⁸ Gelderblom H, Verweij J, Nooter K, Sparreboom A. Cremophor EL: The drawbacks and advantages of vehicle selection for drug formulation. *Eur J Cancer* 2001;37:1590-98.

²⁹ Venkataramanan R, Burckart GJ, Ptachcinski RJ, Blaha R, Logue LW, Bahnson A, *et al.* Leaching of diethylhexylphthalate from polyvinyl chloride bags into intravenous cyclosporine solution. *Am J Hosp Pharm* 1986;43(11):2800-2.

³⁰ Pfeifer RW, Hale KN, Cronquist SE, Daniels M. Precipitation of paclitaxel during infusion by pump. *Am J Hosp Pharm* 1993;50(12):2518-21.

³¹ Allwood MC, Martin H. The extraction of diethylhexylphthalate (DEHP) from polyvinyl chloride components of intravenous infusion containers and administration sets by paclitaxel injection. *Int J Pharm* 1996;127:65-71.

³² Song D, Hsu LF, Au JL. Binding of Taxol to plastic and glass containers and protein under in vitro conditions. *J Pharm Sci* 1996;85(1):29-31.

³³ Xu QA, Trissel LA, Zhang Y. Paclitaxel Compatibility with IV Express™ Filter Unit. *Int J Pharm Compounding* 1998;2:243-5.

³⁴ Ibrahim NK, Desai N, Legha S, Soon-Shiong P, Theriault RL, Rivera E, *et al.* Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. *Clin Cancer Res* 2002;8(5):1038-44.

³⁵ Nyman DW, Campbell KJ, Hersh E, Richardson K, Patrick K, Trieu V, *et al.* A phase I trial of ABI-007, nanoparticle paclitaxel, administered to patients with advanced non-hematologic malignancies. *J Clin Oncol* 2004;22(Suppl 14):2027.

paclitaxel are not safely clinically interchangeable. It is the intent of product labelling to accurately guide physicians and patients on the safe and effective use of the drug based on adequately and well-controlled clinical studies. Study CA031, a controlled, randomised, multicenter, open-label, Phase III Study to evaluate Abraxane compared to solvent-based paclitaxel, did not investigate substitution of Abraxane with that of solvent-based paclitaxel. Thus, any proposed language allowing a statement that suggests interchange of Abraxane and solvent-based paclitaxel in prescribing information cannot be supported by scientific data.

The pivotal Study CA031 was used as the basis of approval of Abraxane/carboplatin by the FDA in October 2012 and subsequently by Japan and Argentina for the treatment of NSCLC in February and April 2013. That Abraxane and solvent-based paclitaxel are distinguished from both a safety and efficacy perspective has ultimately been accepted and is reflected globally in labelling of Abraxane as a new product rather than as a generic equivalent to conventional solvent-based paclitaxel.

In conclusion, Celgene requests that the Delegate and members of the ACPM consider the points above in their assessment of the revised wording in the precautionary statement for Abraxane that has been proposed by the Delegate.

Advisory committee considerations

The ACPM having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM taking into account the submitted evidence of clinical efficacy and safety considered this product to have an overall negative benefit-risk profile.

In making this recommendation the ACPM

- expressed concern over the design of the single Phase III Study submitted, which does not conform to the relevant guidelines, in particular
 - the use of an inappropriate primary efficacy endpoint,
 - the confounding effects of using different dosing regimens in the two arms
- was of the view that the efficacy results were inadequate.

Post ACPM considerations

A meeting held with TGA on 12 July 2013 was requested by Celgene Corporation to discuss the outcomes of the ACPM's response to the Delegate's request for advice on the application to extend the indication for Abraxane.

The Delegate asked Celgene to comment on the ACPM's view of an unacceptable study design, inadequate efficacy data and an overall negative risk-benefit. Celgene stated that Study CA031 was not designed to look for superiority in PFS and OS and was intended to evaluate if Abraxane/carboplatin was at least as good as paclitaxel/carboplatin. Celgene noted that the FDA had agreed that while superiority in response rate would be acceptable for approval of Abraxane/carboplatin in NSCLC; demonstration of superiority for OS was not expected. The change from superiority to non-inferiority for PFS and OS was reviewed and found to be acceptable by the EMA. In the pre-submission meeting to discuss the plan for the NSCLC application in November 2011, TGA concurred that that the justification for the switch from superiority to non-inferiority was sound.

Abraxane/carboplatin was statistically superior to solvent-based paclitaxel/carboplatin in ORR (33% versus. 25%, $p = 0.005$; $pA/pT = 1.31$), which met the primary endpoint of this study. The 8% increase in ORR is clinically relevant particularly in patients who do not

tolerate other therapies. The ORR for Abraxane/carboplatin is almost double that of paclitaxel/carboplatin for squamous patient subset. Advantages in benefit were also seen for elderly patients and patients with large tumour burden. For the key secondary endpoints of PFS and OS, a statistically non-significant trend favouring the Abraxane/carboplatin treatment arm was observed. The forest plots of PFS and OS show a favourable positive trend for Abraxane/carboplatin for most patient subgroups, which indicates that Abraxane/carboplatin is at least as effective as paclitaxel/carboplatin.

Study CA031 demonstrates improvement in severe peripheral neuropathy compared to paclitaxel. A decrease in neuropathy may be clinically meaningful to patients and this was borne out in the data collected on the Functional Assessment of Cancer Therapy (FACT) taxane questionnaire. The incidence for anaemia and thrombocytopenia was higher for Abraxane; however, anaemia and thrombocytopenia are clinically manageable conditions. Although there were more blood transfusions on the Abraxane/carboplatin arm, there were no apparent increases in platelet transfusions or excess risk of haemorrhage compared to the paclitaxel/carboplatin arm.

Based on the efficacy results together with the safety profile, Celgene believes that some patients with NSCLC who do not tolerate other therapies, including the current standard of care, would benefit from the Abraxane/carboplatin combination.

The Delegate noted that he had accepted the ACPM advice that it is reasonable and appropriate to treat patients who are not suitable for surgery or radiation (such as some patients with Stage IIIb disease) and that the statement about CNS metastases would be more appropriate in the *Precautions* section. This will be reflected in the indication statement, if the application is approved. It was agreed that no further information or discussion was required on these items.

By email dated 18 July 2013, the Delegate advised the sponsor of his view that the extension of indication for Abraxane to include NSCLC can be approved subject to necessary PI changes as the PI has a bearing on the benefit-risk balance of this extension of indication. The PI influences the safety of the product as it is an important way in which to manage risk, via communicating issues to clinicians.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Abraxane containing nab paclitaxel for the new indication:

Non-Small Cell Lung Cancer

Abraxane, in combination with carboplatin, is indicated for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation.

Indications

The full indications are now:

Metastatic Breast Cancer

Abraxane is indicated for the treatment of metastatic carcinoma of the breast after failure of anthracycline therapy.

Non-small Cell Lung Cancer

Abraxane, in combination with carboplatin, is indicated for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation.

Specific conditions applying to these therapeutic goods

- The Abraxane Risk Management Plan (RMP), version 11.0, dated 5 April 2012, with an ASA Version: 2.1, dated 18 December 2012, included with submission PM-2012-01185-3-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1: Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2: Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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