All Wales Therapeutics and Toxicology Centre
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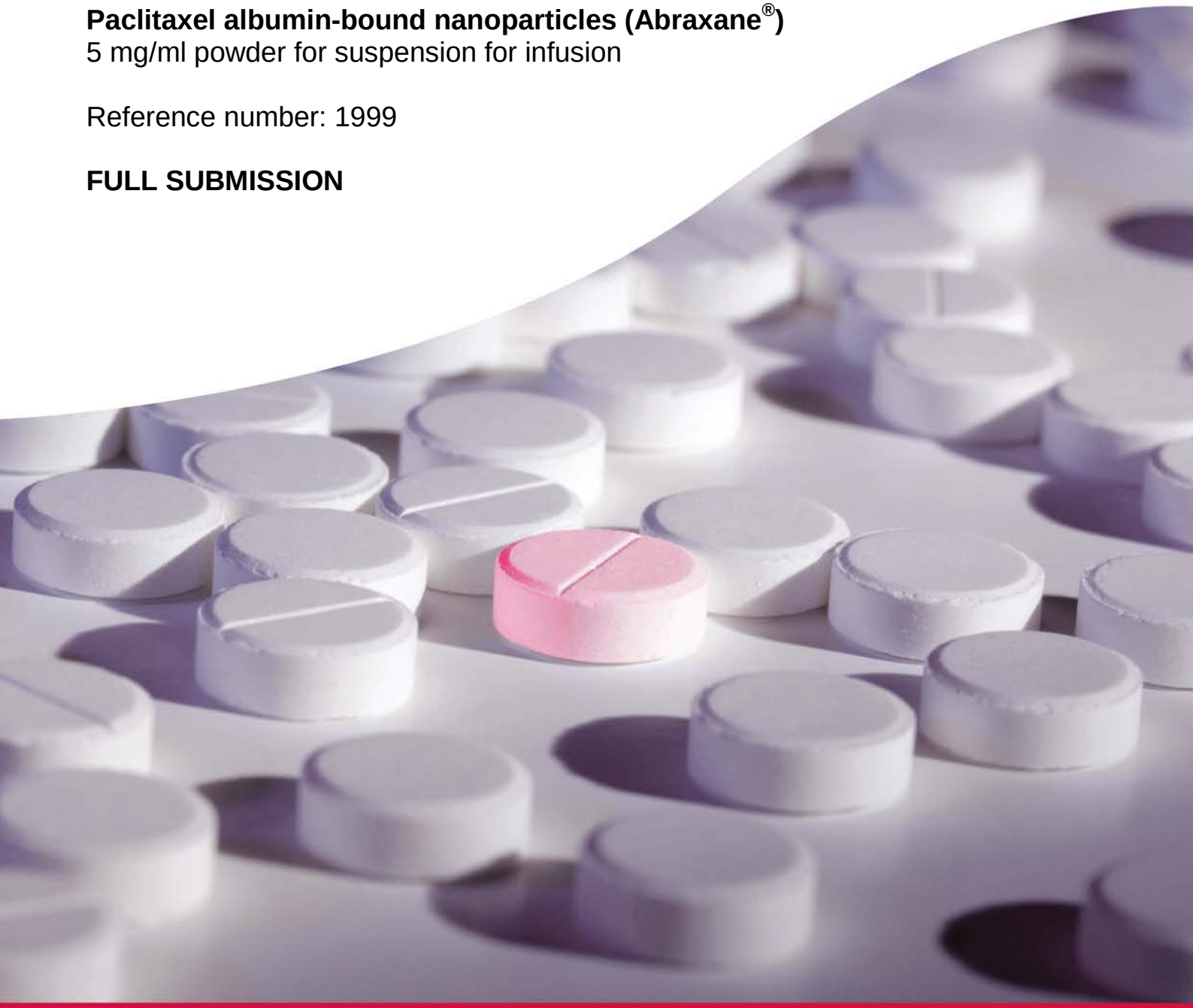
AWMSG SECRETARIAT ASSESSMENT REPORT

Paclitaxel albumin-bound nanoparticles (Abraxane®)

5 mg/ml powder for suspension for infusion

Reference number: 1999

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Paclitaxel albumin-bound nanoparticles (Abraxane®) 5 mg/ml powder for suspension for infusion. Reference number: 1999. July 2014.

AWMSG Secretariat Assessment Report
Paclitaxel albumin-bound nanoparticles (Abraxane®)
5 mg/ml powder for suspension for infusion

This assessment report is based on evidence submitted by Celgene Ltd on 31 March 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Paclitaxel albumin-bound nanoparticles (Abraxane®) in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas[2].
Dosing	The recommended dose of Abraxane® in this indication is 125 mg/m^2 administered intravenously as an infusion over 30 minutes on days 1, 8 and 15 of each 28-day cycle. The concurrent recommended dose of gemcitabine is 1000 mg/m^2 administered by intravenous infusion over 30 minutes on days 1, 8 and 15 of each 28-day cycle, immediately after the completion of Abraxane® administration. It should not be substituted for or with other paclitaxel formulations. Refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	20 December 2013[3] (licensed on 11 January 2008 for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated[2,4]).

2.0 DECISION CONTEXT

2.1 Background

Pancreatic cancer is a relatively uncommon form of cancer, affecting 394 patients in Wales (12.9 per 100,000 people) as of 31 December 2011 (diagnosed within past 20 years and still alive)[5], and diagnosed in an additional 487 patients during 2012[6]. Most commonly, pancreatic cancer arises from exocrine cells, and around 95% of these exocrine tumours are adenocarcinomas[7].

Surgical resection is the only potentially curative treatment for these patients, and most patients (80–85%) have unresectable disease at the time of diagnosis[7]. Median survival for patients presenting with metastatic disease is 3–6 months and the five-year overall survival (OS) rate is 1.6%[7]. Gemcitabine has been the standard chemotherapy for first-line treatment of pancreatic adenocarcinoma[7,8] and is recommended in this indication by the National Institute for Health and Care Excellence (NICE)[9]. More recent European guidance also recommends the off-label use of a combination of fluorouracil (5-FU), irinotecan, folinic acid and oxaliplatin (FOLFIRINOX); additionally, erlotinib (Tarceva®) in combination with gemcitabine is recommended under certain circumstances[8].

Abraxane® contains paclitaxel formulated as human serum albumin-bound nanoparticles[2]. Paclitaxel is an antimicrotubule agent that prevents cell division and promotes cell death, thereby suppressing cancer growth[2,10]. Albumin-bound paclitaxel is suggested to be more water-soluble and enhance transport of paclitaxel across endothelial cells to achieve higher delivery of paclitaxel to the tumour[2,7]. Additionally,

the absence of solvent present in standard paclitaxel formulations is suggested to cause less frequent hypersensitivity reactions[7]. Standard formulations of paclitaxel are not licensed for use in the indication under consideration at the time of writing[11]. Abraxane® should not be substituted for or with other paclitaxel formulations[2].

Although the company submission provides evidence for the use of Abraxane® in the entirety of the licensed indication under consideration, the applicant company has highlighted the subgroup of patients with a Karnofsky performance status (KPS) score of 70–80 (see Glossary), in whom the clinical and cost-effectiveness of Abraxane® may be particularly favourable[1].

2.2 Comparators

The comparators included in the company submission were:

- Gemcitabine monotherapy
- Gemcitabine combination therapy, specifically gemcitabine plus capecitabine (GEMCAP; off-label use)
- FOLFIRINOX (off-label use)

2.3 Guidance and related advice

- NICE. Single Technology Appraisal (TA) in development. Paclitaxel formulated as albumin-bound nanoparticles in combination with gemcitabine for treating previously untreated adenocarcinoma of the pancreas (ID680). Expected publication date: January 2015[12].
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Pancreatic adenocarcinoma. Version 1.2014 (2014)[13].
- NICE. Gastrointestinal cancers overview (2014)[14].
- European Society for Medical Oncology (ESMO) and European Society of Digestive Oncology (ESDO). Pancreatic adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2012)[8].
- Pancreatic Section of the British Society of Gastroenterology, Pancreatic Society of Great Britain and Ireland, Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, Royal College of Pathologists, and Special Interest Group for Gastro-Intestinal Radiology. Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas (2005)[15].
- NICE. TA25. Guidance on the use of gemcitabine for the treatment of pancreatic cancer (2001)[9].

The All Wales Medicines Strategy Group (AWMSG) has previously issued the following recommendations:

- Erlotinib (Tarceva®) in combination with gemcitabine has not been endorsed for use within NHS Wales for the treatment of patients with metastatic pancreatic cancer. The holder of the marketing authorisation has not made a submission to AWMSG for the appraisal of erlotinib (Tarceva®) in the above indication. As a result, AWMSG cannot advise the Minister for Health and Social Services whether this medicine should be available for use within NHS Wales (2008)[16].
- Paclitaxel albumin (Abraxane®) monotherapy is recommended as an option for use within NHS Wales for the treatment of metastatic breast cancer in patients who have failed first-line treatment for metastatic disease and for who standard, anthracycline containing therapy is not indicated[17].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

As evidence of the clinical effectiveness of Abraxane® for the first-line treatment of metastatic pancreatic adenocarcinoma, the company submission includes a phase III study (CA046)[1]. Additionally, the applicant company has provided a mixed treatment comparison (MTC) to evaluate Abraxane® versus gemcitabine monotherapy, FOLFIRINOX and GEMCAP. The company submission also includes a phase I/II dose-escalation study (CA040); this study does not add to the evidence of the clinical effectiveness of Abraxane® in comparison with a relevant comparator and so will not be discussed further[1].

3.1 Study CA046

This was an international, multicentre, open-label, randomised, active-controlled, phase III study that compared Abraxane® in combination with gemcitabine versus gemcitabine monotherapy for the treatment of metastatic pancreatic adenocarcinoma[7,18]. Patients (n = 861) were randomised (1:1) to receive either Abraxane® plus gemcitabine (125 mg/m^2 Abraxane® by intravenous infusion over 30–40 minutes, followed by 1000 mg/m^2 gemcitabine by intravenous infusion over 30 minutes) or gemcitabine monotherapy (1000 mg/m^2 gemcitabine by intravenous infusion over 30 minutes). The Abraxane® plus gemcitabine group received treatment on days 1, 8, 15, 29, 36, and 43 of cycle 1 (duration: 56 days), while the gemcitabine monotherapy arm received treatment on days 1, 8, 15, 22, 29, 36, and 43; both treatment groups received treatment on days 1, 8, and 15 of subsequent cycles (duration: 28 days). Eligible patients (≥ 18 years of age) had confirmed metastatic adenocarcinoma of the pancreas, a KPS score of 70 or better (see Glossary) and had not previously received surgery, radiotherapy or chemotherapy for the treatment of metastatic disease[7,18].

The primary endpoint was median OS (see Glossary for endpoint definitions), which was significantly greater in the Abraxane® plus gemcitabine group (8.5 months versus 6.7 months in the gemcitabine monotherapy group; treatment difference: 1.8 months; hazard ratio [HR]: 0.72; 95% confidence interval [CI]: 0.62–0.83; p < 0.001). This was supported by analysis of secondary endpoints, including progression-free survival (PFS) and overall response rate (ORR); see Table 1 for summary of results[7,18]. The benefit of adding Abraxane® was also confirmed in a post-hoc updated analysis, where the difference in median OS between the treatment groups was extended to 2.1 months (Abraxane® plus gemcitabine group: 8.7 months; gemcitabine monotherapy: 6.6 months; p < 0.0001)[1]. In the subgroup of patients with a KPS score of 70–80 (n = 340), median OS was also significantly longer in patients receiving Abraxane® plus gemcitabine (7.6 months versus 4.3 months in the gemcitabine monotherapy group; HR: 0.61; p < 0.0001)[1].

Table 1. Summary of endpoints from study CA046[1,7,18].

Endpoint	Abraxane® plus gemcitabine (n = 431)	Gemcitabine monotherapy (n = 430)	Treatment difference	95% CI (p-value)
Primary endpoint				
Median OS	8.5 months	6.7 months	1.8 months HR: 0.72	0.62–0.83 (p < 0.001)
Total number of deaths	333 (77%)	359 (83%)	Not reported	Not reported
Rate of survival at one year	35%	22%	Not reported	p < 0.001
Rate of survival at two years	9%	4%	Not reported	p = 0.02
Secondary endpoints				
Median PFS	5.5 months	3.7 months	1.8 months HR: 0.69	0.58–0.82 (p < 0.001)
ORR by independent review	99 patients (23.0%)	31 patients (7.2%)	Response-rate ratio: 3.19	2.18–4.66 (p < 0.001)
Subgroup analysis: patients with a KPS score of 70–80				
Number of patients	179	161		
Median OS	7.6 months	4.3 months	3.3 months HR: 0.61	0.48–0.78 (p < 0.0001)
Median PFS	4.3 months	3.0 months	1.3 months HR: 0.65	0.50–0.84 (p = 0.0012)
ORR by independent review	37 patients (20.7%)	9 patients (5.6%)	Response-rate ratio: 3.70	1.84–7.42 (p < 0.0001)

CI: confidence intervals; HR: hazard ratio; ORR: overall response rate; OS: overall survival; PFS: progression-free survival.

3.2 Systematic review and mixed treatment comparison

In the absence of data directly comparing Abraxane® plus gemcitabine versus gemcitabine combination therapy or FOLFIRINOX for the treatment of metastatic pancreatic adenocarcinoma, a systematic literature review and MTC have been included in the company submission to evaluate the relative efficacy of these treatments[1].

The systematic literature review identified all randomised controlled trials of any design that directly evaluated any of the interventions of interest (either as monotherapy or as part of a combination therapy) against any other active treatment in adult patients with advanced pancreatic cancer, of whom at least a proportion had metastatic disease that appeared to be previously untreated. The two outcomes of interest were OS and PFS, and data from relevant studies were incorporated into the MTC.

Results are summarised in Table 2. Abraxane® plus gemcitabine offered improved OS and PFS versus most comparator treatments; this was only statistically significant versus gemcitabine monotherapy. However, FOLFIRINOX offered slightly improved outcomes versus Abraxane® plus gemcitabine, but this was only statistically significant for PFS[1].

Table 2. Overview of results from MTC using Abraxane® plus gemcitabine as reference treatment[1].

Comparator treatment	OS		PFS	
	Mean HR	95% CrI	Mean HR	95% CrI
Abraxane® plus gemcitabine	Reference treatment			
Gemcitabine monotherapy	1.36	1.12–1.64	1.46	1.13–1.87
FOLFIRINOX	0.78	0.62–0.97	0.69	0.56–0.84
GEMCAP	1.15	0.91–1.45	1.15	0.89–1.49

CrI: credible intervals; FOLFIRINOX: fluorouracil (5-FU), irinotecan, folinic acid and oxaliplatin; GEMCAP: gemcitabine plus capecitabine; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.

3.3 Comparative safety

Evidence of comparative safety in the company submission comes from Study CA046, where 403/421 (95.7%) patients in the Abraxane® plus gemcitabine group experienced treatment-emergent adverse events (AEs) considered treatment-related, compared with 371/402 (92.3%) in the gemcitabine monotherapy group[7]. AEs reported as grade 3 severity or higher were more commonly reported in the paclitaxel albumin plus gemcitabine arm (374 [88.8%] versus 303 [74.1%]). Further, the proportion of treatment-emergent AEs leading to treatment discontinuation was higher in the Abraxane® plus gemcitabine treatment arm (149 [35.4%] versus 95 [23.6%] in the gemcitabine monotherapy arm). However, the incidence of treatment-emergent AEs leading to an outcome of death was equal between the groups (18 patients in each treatment arm)[7].

The treatment-related AEs reported more commonly (≥ 10% difference) in the Abraxane® plus gemcitabine arm than in the gemcitabine monotherapy group were alopecia (50.1% versus 5.0%, respectively), peripheral neuropathy (27.3% versus 0.7%), diarrhoea (37.1% versus 13.2%), peripheral sensory neuropathy (24.7% versus 2.7%), fatigue (53.7% versus 36.6%), peripheral oedema (33.5% versus 17.4%), rash (22.1% versus 14.4%), decreased appetite (36.1% versus 25.9%), neutropenia (41.6% versus 30.3%) and vomiting (31.6% versus 20.6%)[7].

Several AEs of interest were observed at higher frequencies in the Abraxane® plus gemcitabine arm than in the gemcitabine monotherapy arm of the study, including myelosuppression (66.3% versus 59.0%). At the time of licensing, the Committee for Medicinal Products for Human Use (CHMP) concluded that most of the AEs and serious AEs reported were known safety signals for Abraxane® or gemcitabine, but these were reported at higher frequencies than would be expected, and this was reflected by a higher rate of dose reductions and discontinuations in the Abraxane® plus gemcitabine treatment arm[7]. However, CHMP noted that the mean duration of treatment and mean number of cycles administered were both longer in the Abraxane® plus gemcitabine group than the gemcitabine monotherapy group (145.9 days versus 111.6 days and 4.4 cycles versus 3.3 cycles, respectively). CHMP suggested that this might have affected the level of AE reporting in the two groups and could add uncertainties as to the actual differences in safety profiles, but this uncertainty was not considered to have significantly affected the safety results[7].

3.4 AWTTC critique

- The company submission provides evidence for the use of Abraxane® in the entirety of the licensed indication under consideration[1]. Additionally, the applicant company has provided a subgroup analysis of patients with a KPS score of 70–80 (see Glossary), which demonstrated that median OS difference for Abraxane® plus gemcitabine versus gemcitabine monotherapy was extended from 1.8 months in the full population to 3.3 months in this patient subgroup (see Table 1)[1].

- Gemcitabine is the standard chemotherapy for first-line treatment of pancreatic adenocarcinoma[7,8] as recommended by NICE[9]; clinical experts contacted by AWTTC have confirmed gemcitabine monotherapy as the most relevant comparator in NHS Wales. During the pivotal study, CA046, patients receiving Abraxane® plus gemcitabine had significantly improved outcomes compared with gemcitabine monotherapy (see Table 1), including median OS, which was extended from 6.7 months to 8.5 months[18]. At the time of licensing, CHMP considered the increase of 1.8 months in both OS and PFS to be clinically relevant in patients with metastatic pancreatic adenocarcinoma[7].
- The prognosis for patients with advanced pancreatic adenocarcinoma who are ineligible for surgery, including those with metastatic disease, is poor, and the range of available treatment options is limited[7]. At the time of licensing, CHMP noted that other chemotherapy combinations failed to achieve improvement in OS greater than three weeks or were accompanied by increased toxicity, limiting the number of patients that can actually use these therapy regimens. CHMP concluded that a new chemotherapy regimen showing substantial improvement in OS with acceptable toxicity would therefore be of benefit to patients with advanced pancreatic adenocarcinoma[7].
- European guidance, issued in 2012, recommends off-label use of the FOLFIRINOX regimen for the treatment of metastatic pancreatic adenocarcinoma (see Section 2.1)[8]. In the absence of direct comparative data versus off-label use of the comparators gemcitabine combination therapy (specifically, GEMCAP) or FOLFIRINOX for the treatment of metastatic pancreatic adenocarcinoma, a systematic review and MTC has been included in the company submission to evaluate the relative efficacy of these treatments versus Abraxane®[1].
- The MTC provided by the applicant company appears to favour FOLFIRINOX, but this is only statistically significant for PFS. Although a common approach to the lack of direct head-to-head comparison data, an MTC has inherent limitations. Further, the full text of included studies has not been provided to AWTTC to comment on limitations on the MTC, such as differences in study design or baseline population characteristics, such as performance status or age differences[1]. In addition, no comparison of safety profiles of the two regimens can be made based on available evidence and no comparative evidence has been provided for the subgroup of patients highlighted by the company (i.e. patients with a KPS score of 70–80).
- In Wales, the mean age at pancreatic cancer diagnosis is 72.3 years[19] and, during 2012, 211 of the 487 patients diagnosed with pancreatic cancer were aged 75 years and older[6]. However, few patients aged 75 years or more were enrolled in study CA046 (41 patients in the Abraxane® plus gemcitabine treatment group and 49 in the gemcitabine monotherapy group)[7]. In this subgroup of patients, survival was comparable between the treatment groups, but higher frequencies of serious AEs were observed. At the time of licensing, CHMP suggested that the use of Abraxane® in patients with metastatic pancreatic adenocarcinoma aged 75 years or older should be carefully considered taking into account the individual patient characteristics and additional risk factors[7].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a primary cost-utility analysis (CUA) of Abraxane® in combination with gemcitabine compared against gemcitabine monotherapy as first-line treatment of metastatic adenocarcinoma of the pancreas[1]. Alternative comparisons against GEMCAP and FOLFIRINOX are considered in scenario analyses. An additional analysis is presented in a subgroup of patients with KPS of 70–80, using gemcitabine monotherapy as the comparator[1].

A Markov model has been developed, consisting of three main health states through which patients may transition over time: pre-progression; post-progression and death. Pre-progression is subdivided into time on-treatment (TOT) and time off-treatment to reflect treatment discontinuations for reasons other than disease progression. During pre-progression off-treatment, it is assumed that patients maintain their health-related quality of life but not the costs of active treatment. In the post-progression state, a proportion of patients are assumed to receive second-line chemotherapy, as observed in the CA046 study of Abraxane® versus gemcitabine. The model also incorporates a four-week tunnel state involving more intensive palliative care prior to death[1].

The efficacy of Abraxane® plus gemcitabine and gemcitabine monotherapy in the primary CUA and the subgroup analysis in patients with KPS 70–80 is derived directly from the CA046 trial. Parametric curves have been fitted to the OS, PFS and TOT data to determine the proportion of patients in each of the modelled health states over time and to extrapolate treatment effects over a ten-year (lifetime) time horizon. In the absence of direct comparative data for Abraxane® and the alternative comparators, indirect estimates of the risk of progression and death have been made using an MTC of data identified via systematic literature reviews. Due to a lack of data, TOT for the alternative comparators is estimated based on HR for PFS data for the comparators relative to Abraxane® plus gemcitabine, derived from the MTC[1].

The rate and duration of grade 3 or worse treatment-emergent AEs with Abraxane® plus gemcitabine and gemcitabine monotherapy are included where they occurred in over 5% of patients in the CA046 trial, or where company-sought expert opinion considered they were of such high severity or cost to warrant inclusion irrespective of observed frequency in the trial. It is assumed that GEMCAP has the same AE profile as modelled for Abraxane® plus gemcitabine, as do any second-line therapies involving two agents in combination. The rates of AEs for FOLFIRINOX are based on the relative risks compared with gemcitabine monotherapy observed in a trial of these two regimens[20], with the observed relative risk applied to the gemcitabine data from trial CA046 where possible, or else assumed to be the same as for Abraxane®.

A systematic literature search was conducted to identify utility values for weighting the pre- and post-progression health states. In the base case analysis, these are based on EuroQol-5 Dimension (EQ-5D) data collected in a published study of gemcitabine plus bevacizumab versus gemcitabine monotherapy in patients with advanced pancreatic cancer[21]. Alternative health-state values from other studies, and a weighted average of these, are explored in scenario analyses. Utility decrements for the AEs included in the model are based on values reported in a wide range of other Health Technology Assessment submissions, or else expert opinion, and are applied for durations observed from patient-level data from trial CA046[1].

Treatment doses are estimated assuming a mean body surface area of 1.75 m^2, reportedly based on company market research in UK patients, applied to all intended doses in each regimen[1]. The dose intensity and number of missed doses observed in

the CA046 trial for gemcitabine monotherapy and for Abraxane® plus gemcitabine is assumed, with Abraxane® plus gemcitabine dose intensity assumed to apply also to GEMCAP and FOLFIRINOX comparator regimens. Drug costs are estimated on a per milligram basis using British National Formulary (BNF) list prices, which assumes no vial wastage, except for Abraxane®, for which 22% of vials are assumed to be shared in the base case analysis. Administration and pharmacy preparation time, monitoring requirements, palliative care and resource use associated with AEs are based on expert opinion, costed using published unit costs. FOLFIRINOX treatment is assumed to require routine filgrastim as primary prophylaxis against neutropenia[1].

Costs and outcomes beyond one year are discounted at 3.5% per annum.

4.1.2 Results

The results of the base case analyses are presented in Table 3. Over a ten-year (lifetime) time horizon of analysis, the incremental cost per quality-adjusted life-year (QALY) gained for Abraxane® plus gemcitabine compared with gemcitabine alone is around £53,000. This is based on additional costs of around £8,300 due mainly to the greater acquisition costs of Abraxane® plus gemcitabine, combined with longer modelled TOT, and a gain of 0.156 QALYs, due mainly to the modelled difference in survival of 2.4 months.

Table 3. Base case primary CUA results in all patients over ten-year (lifetime) horizon[1].

	Abraxane® plus gemcitabine	Gemcitabine monotherapy	Difference
Total costs	£21,920	£13,630	£8,290
Total LYs gained	0.917	0.718	0.198
Total QALYs gained	0.717	0.561	0.156
ICER	**£53,260/QALY gained**		
PSA: Probability ICER < £30,000/QALY gained	0%		
ICER: incremental cost-effectiveness ratio (incremental cost per QALY gained) for Abraxane® plus gemcitabine versus comparator; LY: life-year; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life-year			

One-way sensitivity analyses were conducted across all parameters, by varying their values within the range of their 95% CI or, if unavailable, within +/-10%. These indicate that the model is highly sensitive to the treatment variable used in the parametric curve that has been fit to the OS data; the incremental cost-effectiveness ratio (ICER) is reported to range from £42,500 to £80,900 per QALY gained. The model was relatively insensitive to variation of all other parameters, deviating from the base case ICER estimate by £2,000 or less[1].

Scenario analyses indicate that the primary base case analysis is relatively insensitive to the assumed annual discount rate (range 0–6%), a reduced time horizon of five years, and the assumed proportion of Abraxane® vials that are shared (0–44%). Table 4 summarises the key scenario analyses presented by the company that do have a significant influence on the estimated ICERs, and associated plausibility considerations.

Table 4. Key scenario analyses.

Scenario description	Scenario details	Incremental cost per QALY	Plausibility considerations
Primary base case analysis	Comparison against gemcitabine monotherapy in all patients with KPS 70–100; utility values 0.8 for pre-progression and 0.75 for post-progression states.	£53,260	Based on direct comparative trial data. Represents a blended analysis of those with KPS 70–80 and those with KPS > 80. Unclear if this is appropriate. ICER sensitive to approach used to model TOT. Base case ICER possibly biased in favour of Abraxane® plus gemcitabine. Utility values from US population and pre-progression value similar to population norm.
Primary analysis with alternative utility values	Comparison against gemcitabine monotherapy in all patients with KPS 70–100; alternative utility values assumed: a) German study values: 0.65 for pre-progression and 0.6 for post-progression states[22]. b) 0.74 for pre-progression and 0.69 for post-progression states.	a) £65,834 (incremental cost: £8,290; QALY gain: 0.126) b) £57,346 (incremental cost: £8,290; QALY gain: 0.145)	a) German patients' utility values, possible reflect patients with worse performance status than those in Abraxane® trial? b) Pooled analysis of three sources of utility values; values midway between base case and a). Unclear that these are more plausible than values assumed in base case?
Alternative comparator: GEMCAP	Comparison against gemcitabine plus capecitabine in all patients with KPS 70–100; utility values: 0.8 for pre-progression and 0.75 for post-progression states.	£101,441 (incremental cost: £7,661; QALY gain: 0.076)	Based on company market research, GEMCAP is used in around 25% of all patients, irrespective of performance status, and so is a relevant comparator. Analysis relies on indirect comparison of trial data in MTC, which has limitations; unclear if trial populations are comparable.
Alternative comparator: FOLFIRINOX	Comparison against FOLFIRINOX in all patients with KPS ≥ 70; utility values: 0.8 for pre-progression and 0.75 for post-progression states.	£47,017 (Abraxane® plus gemcitabine is less costly and less effective; cost saved: £7,834; QALY foregone: 0.167)	FOLFIRINOX is a relevant comparator, particularly in those with good performance status. Analysis relies on indirect comparison of trial data in MTC, which has limitations; unclear if trial populations are comparable.
Subgroup analysis: patients with KPS 70–80	Comparison against gemcitabine monotherapy in patients with KPS 70–80; utility values: 0.8 for pre-progression and 0.75 for post-progression states.	£42,293 (incremental cost: £9,051; QALY gain: 0.214)	Based on pre-specified subgroup analysis of direct comparative trial data. Would only apply to patients with KPS 70–80 who are not candidates for GEMCAP or FOLFIRINOX. ICER sensitive to approach used to model TOT. Utility values from US population and pre-progression value similar to population norm. As this subgroup of patients has poorer performance status, the base case utility values may be less relevant than alternative sources?

Table 4. Continued.

Scenario description	Scenario Details	Incremental cost per QALY	Plausibility considerations
Subgroup analysis: patients with KPS 70–80 with alternative utility values	Comparison against gemcitabine monotherapy in patients with KPS 70–80; alternative utility values assumed: a) German study values: 0.65 for pre-progression and 0.6 for post-progression states[22]. b) 0.74 for pre-progression and 0.69 for post-progression states.	a) £52,474 (incremental cost: £9,051; QALY gain: 0.172) b) £45,593 (incremental cost: £9,051; QALY gain: 0.199)	a) German patients' utility values. b) Pooled analysis of three sources of utility values; values midway between base case and a). As this subgroup of patients has poorer performance status, these utility values may be more reflective than the base case values? ICER sensitive to approach used to model TOT.
ICER: incremental cost-effectiveness ratio (incremental cost per QALY gained) for Abraxane® plus gemcitabine versus comparator; KPS: Karnofsky performance status (see Glossary); MTC: mixed treatment comparison; QALY: quality-adjusted life-year; time on-treatment (TOT).			

4.1.3 AWTTC critique

The primary base case analysis of Abraxane® plus gemcitabine compared with gemcitabine monotherapy reflects a blended analysis of distinct patient groups defined by performance scores. A key subgroup of patients with KPS 70–80 has been identified, in which Abraxane® plus gemcitabine is estimated to be more cost-effective than in the wider population; however, the actual estimate of incremental cost per QALY gained in this group is uncertain and few sensitivity/scenario analyses have been conducted by the company to explore this. The company has made efforts to explore the incremental cost-effectiveness of Abraxane® compared with GEMCAP and FOLFIRINOX based on the limited available evidence, but acknowledges limitations. These exploratory analyses are based on data from all the whole patient population with KPS 70–100, and cannot be extrapolated to apply to subgroups of patients with KPS 70–80, or KPS > 80. All ICER estimates are subject to uncertainty related to the assumed utility values applied to health states and are sensitive to the approach to modelling TOT and OS.

The company suggests that Abraxane® plus gemcitabine should be considered under the AWMSG policy for appraising life-extending, end-of-life medicines[23], as life expectancy of patients with metastatic adenocarcinoma of the pancreas is typically less than two years, the improvement in OS in the subgroup of patients with KPS 70-80 exceeds three months, and the mean improvement in OS for the whole licensed indication is close to three months (2.4 months)[1]. This is discussed in detail in Section 6.5.

Strengths of the economic evidence include:

- The modelled pathway appears to be appropriate.
- The company has conducted systematic literature reviews to inform its approach to modelling and identify parameter values. MTCs have been attempted to provide indirect estimates of relative treatment effects in the absence of direct comparative data for Abraxane® plus gemcitabine versus GEMCAP and FOLFIRINOX.
- A wide range of sensitivity and scenario analyses have been conducted to explore some of the key assumptions used in the base case model.
- A key subgroup analysis has been conducted in those with baseline KPS 70–80.

Limitations and uncertainties in the economic evidence include:

- The company provides a primary base case analysis of Abraxane® plus gemcitabine in all patients with KPS 70–100 and a separate analysis in a subgroup with poorer performance status (KPS 70–80). These produce somewhat different cost-effectiveness estimates. No analyses have been provided to isolate the estimate of cost-effectiveness in patients with KPS > 80, but it would be anticipated that the ICER in that group would be somewhat greater than that in the primary base case analysis compared against gemcitabine. There are no data with which to model alternative comparators in this patient group.
- The ICER estimates are sensitive to the modelling of TOT and OS data. Parametric curves have been tested and the best fitting curves statistically have been used; however, use of actual mature TOT data from the trial, rather than a parametric extrapolation of the TOT data, and sensitivity analyses exploring the treatment variable used in the parametric curve that has been fit to the immature OS data, indicate that the modelled outputs are significantly influenced by these.
- There is uncertainty in the utility values assumed. The base case analysis in the whole population with KPS 70–100 uses utility values that are similar to population norms. The subgroup analysis, in patients with KPS 70–80, assumes the same utility values as for the whole population with KPS 70–100. The alternative values may be more reflective of patients with poorer performance status, and these increase the ICER estimates.
- No sensitivity or scenario analyses beyond the alternative utility values have been conducted around the ICER estimate for the key subgroup of patients with KPS 70–80.
- The company acknowledges the limitations of its MTC, which contribute to the estimates of cost-effectiveness of Abraxane® plus gemcitabine compared with the alternative comparators[1]. It is not clear that the trial populations were comparable, which introduces uncertainty into the ICER estimates.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any fully published cost effectiveness analyses of Abraxane® in this indication relevant to the UK.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company assumes there are 501 incident cases of pancreatic cancer in Wales[1], based on a mean average of estimates from Welsh Cancer Intelligence and Surveillance Unit[6] and Cancer Research UK data from 2011[24]. It further assumes that 92.5% of these present with adenocarcinoma (463 patients), and 68% (315) have metastatic disease, based on a mean average of several estimates in the literature[1]. It reports that 65% (205) have a KPS score of 60 or more, and so are suitable for chemotherapy, and further, that uptake amongst these patients would be 50% (102 patients), to reflect use in those with KPS score 70–90 and to account for variable uptake between different centres.

From the economic model in Section 4, drug acquisition costs for Abraxane® plus gemcitabine are estimated to be £7,010 greater than for gemcitabine monotherapy per patient treated. Total costs (including administration, monitoring, AEs, second-line treatments, and terminal care) are estimated in the model to be £8,290 greater than gemcitabine monotherapy per patient treated.

5.1.2 Results

The company estimates net budget impact in Wales in each of the next five years as in Table 5.

Table 5. Company estimates of net cost implications associated with Abraxane® in the treatment of metastatic adenocarcinoma of the pancreas.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	205	205	205	205	205
Treated patients	102	102	102	102	102
Net drug acquisition costs	£717,226	£717,226	£717,226	£717,226	£717,226
Overall net cost	£848,189	£848,189	£848,189	£848,189	£848,189

5.1.3 AWTTC critique

- There are several estimates of the prevalence and incidence of metastatic adenocarcinoma of the pancreas in the literature. The company has adopted a pragmatic approach to its estimates for Wales, but these are associated with an unknown degree of uncertainty.
- The analysis is intended to reflect use in patients with KPS scores 70-90. In response to AWTTC queries the company has also provided a budget impact estimate relating to patients with KPS 70-80. The company suggests similar numbers of patients would be treated as estimated for KPS 70-90, as uptake in the KPS 70-80 group would be higher. No further details are provided. Net acquisition costs are estimated to be £647,038 and total net costs £935,873 in each year.
- The assumed net costs per patient are based on estimates from the company's economic model. The uncertainties and limitations of the economic model therefore feed through to the budget impact estimates.
- Collectively, the budget impact estimates are subject to uncertainty.

5.2 Comparative unit costs

Comparator regimens for Abraxane® plus gemcitabine include gemcitabine monotherapy, GEMCAP and FOLFIRINOX. Treatment cycles vary depending on defined regimen schedule, and different treatment exposures and intensities are to be expected due to differences in AE profiles. Therefore, Table 6 provides only an illustrative example of comparative costs, based on lowest available BNF list prices for the first 12 weeks of treatment, for an adult of 1.75 m^2, assuming 100% dose intensity and no vial sharing.

Table 6. Example comparative costs per for adult of 1.75 m^2 over 12 weeks.

Regimens	Doses and treatment schedules	Approximate 12-week costs
Abraxane® plus gemcitabine	Regimen administered weekly for three weeks of a four-week cycle: • Nab-paclitaxel 125 mg/m^2 intravenous infusion • Gemcitabine 1,000 mg/m^2 intravenous infusion	£9,425
Gemcitabine monotherapy	Gemcitabine 1,000 mg/m^2 intravenous infusion weekly for seven weeks of the first eight-week cycle, followed by 1,000 mg/m^2 weekly for three weeks of each subsequent four-week cycle	£3,092
GEMCAP	Regimen administered for three weeks of a four-week cycle: • Gemcitabine 1,000 mg/m^2 intravenous infusion weekly • Capecitabine tablets 830 mg/m^2 twice daily	£3,539
FOLFIRINOX	Regimen administered every two weeks: • Oxaliplatin 85 mg/m^2 intravenous infusion • Folinic acid 400 mg/m^2 intravenous infusion • Irinotecan 180 mg/m^2 intravenous infusion • Fluorouracil 400 mg/m^2 intravenous bolus followed by 2,400 mg/m^2 intravenous infusion	£7,780
Note: not all regimens may be licensed for use in this patient population. See relevant SPCs for full licensed indications and dosing details[2,26–32]; unlicensed regimens are based on those used during clinical trials[20,33]. Costs are based on BNF list prices as of May 2014[34]. Costs of administration are not included. This table does not imply therapeutic equivalence of the drug regimens or doses.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, paclitaxel albumin-bound nanoparticles (Abraxane®) are appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipate that paclitaxel albumin-bound nanoparticles (Abraxane®) may be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 22 April 2014
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy on life-extending, end-of-life medicines

The company suggests that Abraxane® plus gemcitabine should be considered under the AWMSG policy for appraising life-extending, end-of-life medicines[23], as life expectancy of patients with metastatic adenocarcinoma of the pancreas is typically less than two years, the improvement in survival in the subgroup of patients with KPS 70-80 exceeds three months (3.3 months), and the mean improvement in survival for the whole licensed indication is close to three months (2.4 months)[1].

The criteria for appraising life-extending, end-of-life medicines apply when the most plausible ICER estimate exceeds £30,000 per QALY gained, and all the following conditions are satisfied:

- The medicine is indicated for patients with a short life expectancy, normally less than 24 months (e.g. estimated from the median survival of patients in the control group of the pivotal study).
- There is sufficient evidence to indicate that the medicine offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment. The estimates of the extension to life (e.g. based on the difference in median survival in the pivotal trial, or projected life-years gained) should be robust and shown (or reasonably inferred) from either progression free survival or overall survival.
- AWMSG/NMG will consider the cumulative population of each licensed indication of the medicine to be small[23].

Based on the economic evidence from the applicant company, the most plausible ICER for Abraxane® plus gemcitabine exceeds £30,000 per QALY when compared with gemcitabine monotherapy in both the full population and the subgroup with KPS 70-80[1]. Median survival for patients presenting with metastatic disease is 3–6 months and the five-year overall survival (OS) rate is 1.6%[7]. Therefore the first two criteria of the policy would appear to be met.

For the full licensed indication, post-hoc updated analyses of the CA046 trial data estimate the difference in median OS between Abraxane® and gemcitabine monotherapy was 2.1 months (8.7 vs 6.6 months)[1]. The modelled mean OS benefit was 2.4 months[1] (but the model is very sensitive to the OS modelling). In the subgroup of patients with a KPS score 70–80 the difference in median OS was 3.3 months (7.6 vs. 4.3 months)[1]. Consideration needs to be given to whether Abraxane® in the given licensed indication meets the criterion of sufficient evidence to indicate that it offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

AWMSG has no formal definition of a 'small' patient population under its end-of-life policy. The National Institute for Health and Care Excellence (NICE) considers that ≤ 7,000 patients in England would be considered to meet the definition of 'small' under its end-of-life policy. Based on Office for National Statistics mid-2012 population estimates (53.5 million in England; 3.1 million in Wales)[35], this would equate to a cumulative 406 patients in Wales.

Cancer research UK figures indicate there were 514 cases of pancreatic cancer in Wales in 2011[24]. The NICE scoping document for Abraxane® plus gemcitabine suggests that 95% of cases are ductal adenocarcinomas[9]. It further notes that only 10–20% are suitable for surgery, suggesting 80% are not. This accords with a review article which states that more than 80% of these patients present with an unresectable primary tumour along with distant metastasis at the time of diagnosis[25]. Based on these figures, of the 514 cases estimated in Wales, 488 (95%) have pancreatic adenocarcinoma and 415 (85%) have metastatic disease, meeting the licensed indication for Abraxane®. The company has provided revised estimates of the eligible patient population, based on alternative published estimates of incident cases of pancreatic cancer, the proportion that are ductal adenocarcinomas, and the proportion that are not resectable. Based on a mean average of these various estimates, the company calculates there are 501 incident cases of pancreatic cancer, of which 92.5% (463) are adenocarcinomas, and of which 68% (315) are unresectable. There is, therefore, uncertainty in the number of patients estimated to meet the licensed indication for Abraxane® in the treatment of metastatic pancreatic adenocarcinoma.

The AWMSG policy for appraising life-extending, end-of-life medicines indicates that the *cumulative* population of each licensed indication should be considered to be small. Both estimates above exclude the other licensed indication for this medicine: the treatment of breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated[2]. In its 2010 submission to AWMSG for this indication, the applicant company estimated that 95 breast cancer patients would be eligible for treatment with Abraxane® in 2014[17], bringing the cumulative population to around 510 using the first estimate of the metastatic adenocarcinoma population, or 410 using the company's revised estimates. Consideration therefore needs to be given to whether the cumulative population of each licensed indication of Abraxane® is small for the purposes of the AWMSG policy for appraising life-extending, end-of-life medicines.

GLOSSARY

Karnofsky performance status (KPS) scale

The KPS scale assesses the health of a patient using a score from 100 to 0, where a score of 100 is healthy and 0 is death (see Table 7)[9,36].

Table 7. Performance scales: KPS and ECOG scores[9,36].

	Karnofsky performance status (KPS) scale	Eastern Cooperative Oncology Group (ECOG) performance status score			
Grade	Karnofsky Status	ESMO conversion scale		NICE conversion scale	
		Grade	ECOG Status	Grade	ECOG Status
100	Normal, no complaints	0	Fully active, able to carry on all pre-disease performance without restriction	0	Normal activity
90	Able to carry on normal activities. Minor signs or symptoms of disease	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work		
80	Normal activity with effort			1	Symptoms demonstrated, but the patient remains ambulatory, and able to perform self care
70	Care for self. Unable to carry on normal activity or to do active work	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours		
60	Requires occasional assistance, but able to care for self			2	Ambulatory > 50% of the time and requires occasional assistance
50	Requires considerable assistance and frequent medical care	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours		
40	Disabled. Requires special care and assistance			3	Ambulatory < 50% of the time and requires nursing care
30	Severely disabled. Hospitalisation indicated though death nonimminent	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair		
20	Very sick. Hospitalisation necessary. Active supportive treatment necessary			4	Bedridden
10	Moribund				
0	Dead	5	Dead	5	Dead

Overall response rate (ORR)

ORR was defined during study CA046 as the percentage of participants who achieved a confirmed complete (CR; the disappearance of all known disease and no new sites or disease related symptoms confirmed at least 4 weeks after initial documentation) or partial response (PR; at least a 30% decrease in the sum of the longest diameters of target lesions and no progression in non-target lesions) based on an independent blinded radiology assessment of response using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines[37].

Overall survival (OS)

OS was defined during study CA046 as the time from the date of randomisation to the date of death from all causes. OS was summarised using Kaplan-Meier methods[37].

Progression-free survival (PFS)

PFS was defined during study CA046 as the time from the date of randomisation to the date of disease progression, as assessed by independent radiological review, or death (due to any cause), whichever occurred earlier. PFS was summarised using Kaplan-Meier methods[37].

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