NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Disease background

- Pancreatic cancer is a disease in which cancerous cells form in the tissues of the pancreas
  - The pancreas produces digestive juices and hormones that regulate blood sugar
- Risk factors include pancreatitis (chronic or hereditary), diabetes, BRCA mutation, obesity and smoking
- Symptoms include upper abdominal pain that radiates to the back, jaundice, loss of appetite, and blood clots
- Extremely aggressive and life-threatening
  - Often asymptomatic in early stages – most people diagnosed with advanced disease
- In 2014, 8,080 people were diagnosed with pancreatic cancer in England
- Affects men and women equally, and about 75% of people diagnosed with pancreatic cancer are aged 65 years or over

Clinical management

Treatment options for untreated advanced / metastatic pancreatic cancer

Gemcitabine (Gem)

- Standard of care for first line treatment of advanced pancreatic cancer
- Recommended in TA25 for people with Karnofsky score ≥50

Gemcitabine + capecitabine (Gem + Cap)

- Not licensed
- Modest use in NHS – company estimates [redacted]
- Company reports concerns about effectiveness vs Gem; ERG notes published meta-analysis showed significant survival gain with Gem + Cap

FOLFIRINOX*

- Not licensed
- Recommended in European and US clinical guidelines for people who are well enough for aggressive treatment
- High administration burden and considerable toxicity
- Usage not uniform across UK – company estimates [redacted]

Clinical experts stated that, in clinical practice:

- FOLFIRINOX is used for fitter and younger patients (ECOG ≤1, age ≤70–75)
- Gem monotherapy is used if FOLFIRINOX is unsuitable – majority of patients

*FOLFIRINOX: leucovorin, fluorouracil, irinotecan + oxaliplatin

Paclitaxel as albumin-bound nanoparticles (Nab-P; Abraxane, Celgene)

Description

- Paclitaxel inhibits cancer growth by blocking cell division and promoting cell death
- Albumin-bound nanoparticles: aims to improve chemotherapeutic effects and reduce common toxicities associated with solvent-based forms

Marketing authorisation

- In combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas

Dosage

- Nab-P: 125mg/m^2 IV infusion on Days 1, 8 and 15 of 28-day cycle
- Gem: 1000mg/m^2 IV infusion immediately after each nab-P administration

Average length of a course of treatment

- Treatment should be continued until disease progression or unacceptable toxicity (median time in pivotal trial 15 weeks)

Patients' perspective

- Highlights the devastating effect a diagnosis of pancreatic cancer has on patients and their families
  - most commonly reported feeling devastated, alone, helpless, and completely without hope
  - diagnosis often leads to depression
- Patients and carers reported that simply increasing treatment options available can help relieve some of the psychological impact of diagnosis by giving patients a new hope
- Outcomes of importance to patients are:
  - increased survival
  - hope / positive impact on mental health
  - lower toxicity / less pronounced side effects than FOLFIRINOX
  - improved symptom control
  - being able to socialise and attend family events

Recap of TA360 – clinical and economic evidence

- Clinical effectiveness evidence
  - 1 study: CA046 – Nab-P + Gem vs Gem
  - Indirect comparison: mixed treatment comparison of 16 studies comparing Nab-P + Gem vs Gem + Cap or FOLFIRINOX
- Cost effectiveness evidence
  - De novo Markov cost–utility analysis
  - Base case: Nab-P + Gem vs Gem alone
  - Scenario analyses: Nab-P + Gem vs FOLFIRINOX, and vs Gem + Cap, based on the mixed treatment comparison
- ERG comments
  - People in CA046 younger and fitter than those seen in clinical practice in England
  - Indirect comparisons relied on proportional hazards assumption, which was not met for CA046 – results were unreliable
  - Noted concerns about the utilities, drug costing assumptions and projection of time-to-event data in the economic model

Recap of TA360 – committee considerations (1)

- FOLFIRINOX, Gem + Cap and Gem alone are all appropriate comparators
- Nab-P + Gem more clinically effective than Gem alone, but associated with a higher rate of adverse events
- Although there is significant uncertainty, the mixed treatment comparison could be used to compare Nab-P + Gem with Gem + Cap and FOLFIRINOX
  - FOLFIRINOX more clinically effective than Nab-P + Gem
  - Nab-P + Gem and Gem+Cap showed similar OS and PFS, but Nab-P + Gem may be associated with higher rate of AEs
- Not appropriate to consider Nab-P + Gem for a subgroup defined only by performance status
- No HRQoL in CA046: difficult to judge people's preferences and the acceptability of the toxicity profile of Nab-P + Gem

Recap of TA360 – committee considerations (2)

- Company's model appropriate for decision-making
- Modelling assumptions:
  - Neither the company or ERG method for extrapolating time-to-event data was more appropriate: both taken into account
  - Vial sharing is not appropriate and the full cost without missed doses should be used
  - ERG utility values and terminal care costs were more appropriate
- Most plausible ICER for Nab-P + Gem vs Gem: £72,500–£78,500 per QALY gained
- Despite considerable uncertainty, committee was confident Nab-P + Gem would not be cost-effective compared with Gem + Cap or FOLFIRINOX
- End-of-life criteria were met for Nab-P + Gem vs Gem, but not for comparison with Gem + Cap or FOLFIRINOX (no evidence of life extension)

Nab-P + Gem was not recommended within its marketing authorisation for adults with previously untreated metastatic pancreatic cancer

Review proposed March 2016: company proposed a patient access scheme (PAS) and indicated that new evidence was available

Scope and decision problem

Population	People with previously untreated metastatic adenocarcinoma of the pancreas
Intervention	Paclitaxel as albumin-bound nanoparticles
Comparators	• Gemcitabine (Gem) • Gemcitabine plus capecitabine (Gem + Cap) • Oxaliplatin plus irinotecan, fluorouracil and leucovorin (FOLFIRINOX)
Outcomes	• Overall survival • Progression-free survival • Time to tumour progression • Response rate • Adverse effects of treatment • Health-related quality of life
Subgroups	None specified

Decision problem: comparators (1)

Company submission

- Considers that the appropriate comparator is gemcitabine monotherapy
- Gem + Cap and FOLFIRINOX:
  - Unlicensed and not widely used in the NHS
  - Would not be displaced by Nab-P
    - No decline in use when Nab-P was funded through the CDF
    - Patients for whom Nab-P is suitable are easily identifiable and clinically distinct from those having Gem + Cap or FOLFIRINOX
    - Expert panel of clinicians confirmed that patients would continue to have FOLFIRINOX if suitable if Nab-P is available
- Comparisons with Gem + Cap and FOLFIRINOX presented in scenario analyses

Clinical experts

- A significant number of patients are unable to have FOLFIRINOX, and so currently have Gem
  - Many of these patients would be fit enough for Nab-P + Gem

Decision problem: comparators (2)

ERG comments

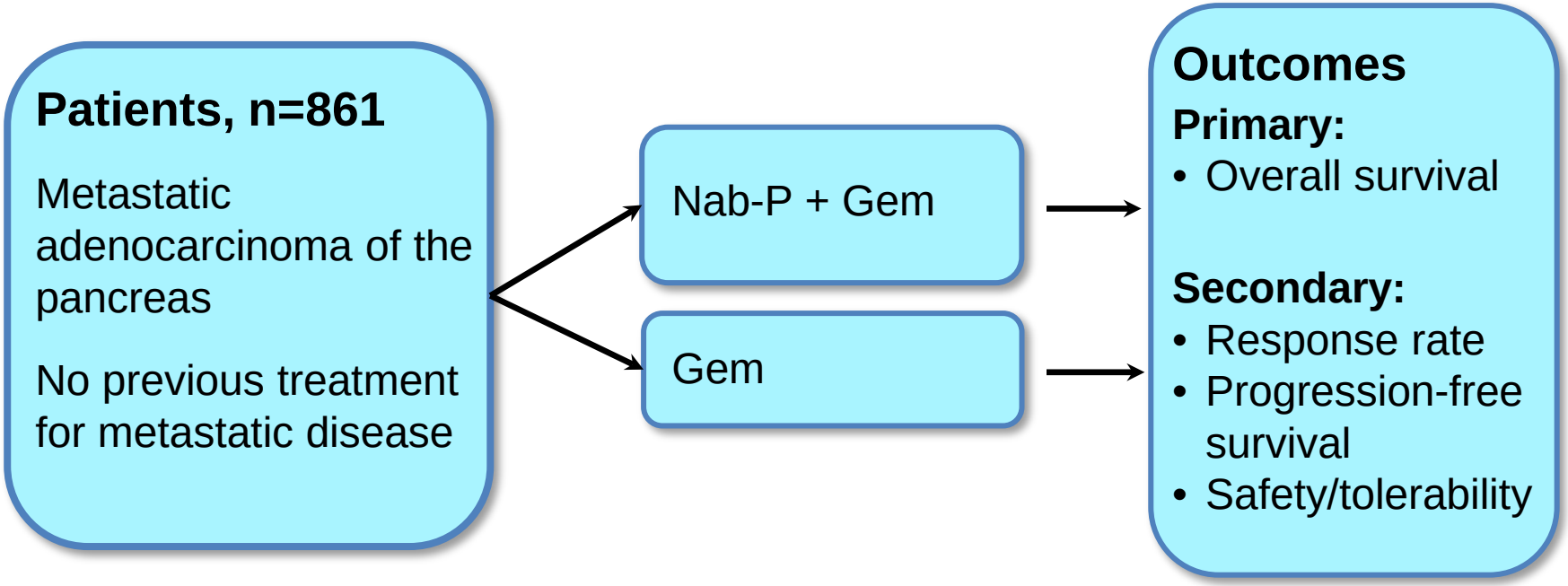
- Agrees that Gem + Cap and FOLFIRINOX are not licensed, and Gem + Cap is not commonly used
- Distinction between patients for whom FOLFIRINOX or Nab-P + Gem would be suitable is not clear
  - Patient populations in key trials for Nab-P + Gem and FOLFIRINOX are similar
- May have been some displacement of FOLFIRINOX by Nab-P, given trend towards increasing use of FOLFIRINOX

Recap: Committee considerations in TA360

- *Nab-P + Gem would be considered if fit enough for combination chemotherapy but FOLFIRINOX not suitable*
- *This group could not be defined just by performance status – other factors include comorbidities, age, patient preference and treatment availability*
- *Gem, Gem + Cap and FOLFIRINOX are all appropriate comparators*

Clinical trial evidence: CA046

Randomised open-label phase III study



Data analyses:

- Interim analysis (≥200 patients followed for ≥6 months)
- Primary endpoint (692 deaths - 80% of patients): September 2012
- Extension (774 deaths - 90% of patients): May 2013

(All 3 analyses were reported in the company submission for TA360)

CA046: baseline characteristics

	Nab-P + Gem N=431	Gem N=430	All N=861
Age, years			
Median	62	63	63
Range	27–86	32–88	27–88
≥65 – n (%)	177 (41)	188 (44)	365 (42)
Sex – n (%)			
Female	186 (43)	173 (40)	359 (42)
Karnofsky performance status – n/total n (%)			
100	69/429 (16)	69/429 (16)	138/858 (16)
90	179/429 (42)	199/429 (46)	378/858 (44)
80	149/429 (35)	128/429 (30)	277/858 (32)
70	30/429 (7)	33/429 (8)	63/858 (7)
60	2/429 (<1)	0/429	2/858 (<1)

Table 11, company submission

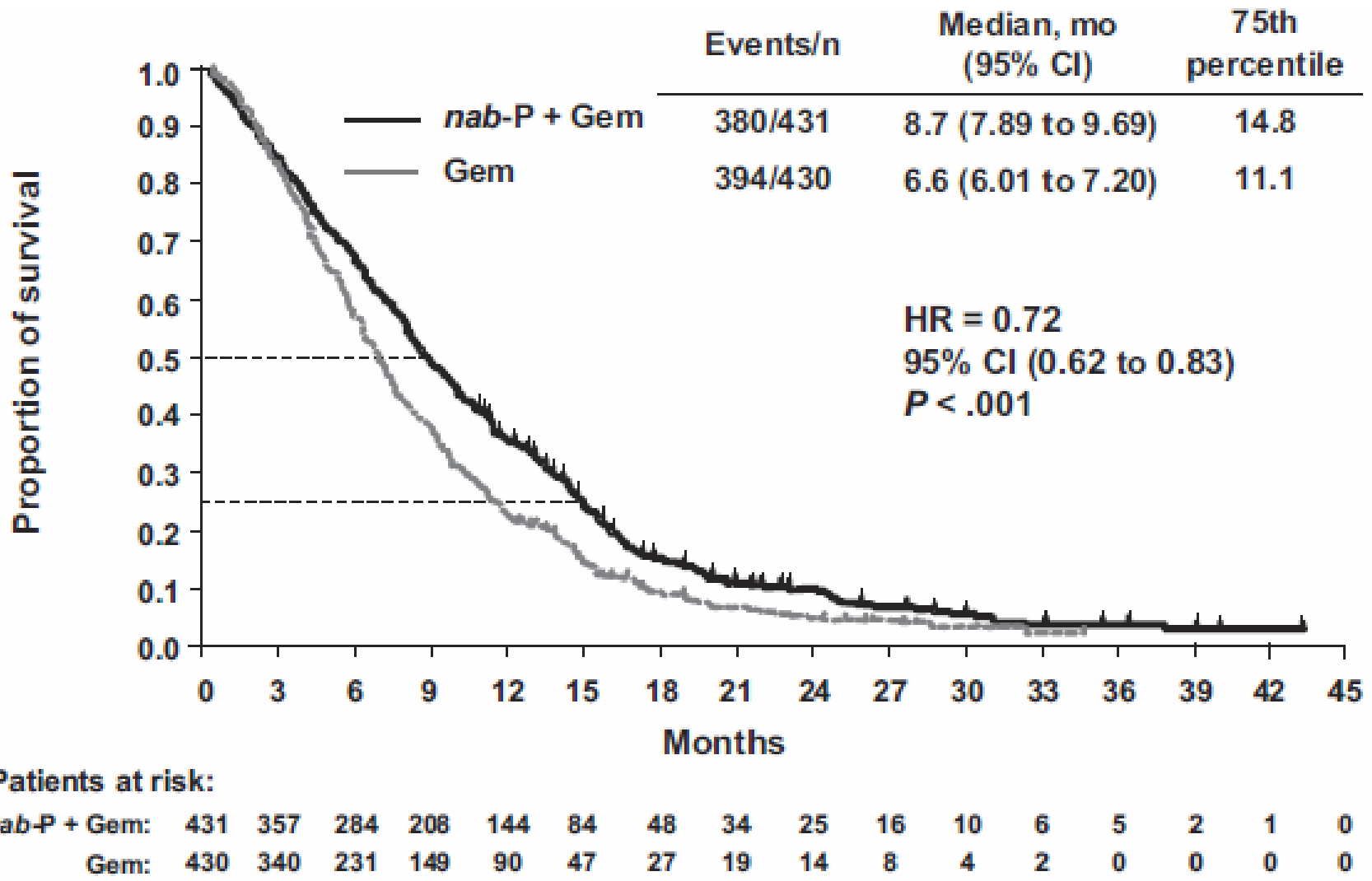
CA046: results

	Nab-P + Gem	Gem	Hazard ratio	P-value
Median overall survival (primary analysis)	8.5 months	6.7 months	0.72	P<0.001
Median overall survival (*extension)	8.7 months	6.6 months	0.72	P<0.0001
2-year survival	10%	5%	–	NR
Median progression-free survival	5.5 months	3.7 months	0.69	P<0.001
Overall response rate	23%	7%	*3.19	P<0.001

- In TA360 the company presented results from CA046 stratified by EGOG performance status, whereas the entire ITT population is presented here.

* Updated post-hoc overall survival analysis based on extended follow-up (data cut-off May 2013)

CA046: results



Based on May 2013 data cut-off; Figure 5, company submission

CA046: ERG comments

- CA046 was well designed and conducted, and trial data mature
  - Possible to draw reasonable conclusions about the clinical effectiveness of Nab-P + Gem versus Gem
- However:
  - Patients recruited to the trial were younger and fitter than the population with metastatic disease treated in the NHS – issue of generalisability
    - Only 10% of trial population aged ≥75 years, but this age group makes up nearly half of population diagnosed with pancreatic cancer in NHS
    - ERG highlighted consideration of patients ≥75 years in the EPAR and SPC: Lack of evidence of efficacy in this group (HR=1.08; 95% CI: 0.65 to 1.80), and patients should be carefully assessed before treatment
  - ERG assessment found proportional hazards assumption not met for progression free survival and overall survival, therefore hazard ratios should be interpreted with caution

Clinical trial evidence: SIEGE trial

- The company reported additional data from SIEGE trial – *not available at the time of TA360*
  - UK multicentre randomised phase II trial
  - Compared different schedules of Nab-P + Gem as first-line treatment for metastatic pancreatic cancer
  - Patients randomised either to the sequential arm (n=71) where Gem was administered 24 hours after Nab-P, or concomitant arm (n=75) where Gem was administered immediately after Nab-P
  - More severe patient population treated with Nab-P + Gem than in CA046
  - Company presents data on adverse events and health-related quality of life (EQ-5D-5L)
    - EQ-5D data used to generate health state utilities in economic model (scenario analysis)

Network meta-analysis (NMA)

- Company presented an NMA to provide comparisons of Nab-P + Gem vs Gem + Cap and vs FOLFIRINOX
  - *Updated since TA360 to include additional studies: 2 further studies included*
  - Fixed effects analysis
  - Extensive set of comparators (including others outside the scope) to provide feedback loops to explore consistency
  - Based on metastatic disease only *(consistent with committee and ERG preference in TA360)*
- Systematic review identified 10 trials of patients with metastatic disease that were included in the NMA
- Company considered trials were similar in terms of patient demographic (3 trials exclusively Asian populations) and clinical characteristics (some difference in extent of metastatic disease)
- Company performed sensitivity analyses:
  - Random effects analysis
  - Using a reduced network that included only the comparators listed in the final scope
  - Metastatic and locally advanced disease
- Results from the base-case NMA are used in the cost effectiveness model

Trials included in the NMA of patients with metastatic pancreatic cancer

Trial	Population	Intervention (n)	Primary outcome
CA046	Previously untreated mPC and KPS ≥70	Nab-P + Gem (431)	OS
*Chao 2013	Previously untreated mPC	Gem + Cisplatin (21)	ORR
Boeck 2008	Previously untreated mPC or LAPC and KPS ≥60	Gem + Cap (64) Gem + Oxaliplatin (63)	ORR, OS, Safety
CALGB 89904	Previously untreated mPC and ECOG 0-2	Gem + Cisplatin (66) Gem + Docetaxel (65) Gem + Irinotecan (64)	OS
FRE-GERCOR-GEMOX –D99-2	Previously untreated mPC or LAPC and WHO PS 0-2	Gem + Oxaliplatin (163)	OS

*****Exclusively Asian population; ECOG: Eastern Co-operative Group; Gem: gemcitabine; LAPC; Locally advanced pancreatic cancer; mPC: metastatic pancreatic cancer; OS: overall survival; ORR: overall response rate

Table 15, company submission

Trials included in the NMA of patients with metastatic pancreatic cancer Cont.

Trial	Population	Intervention (n)	Primary outcome
Heinemann 2006	Previously untreated mPC or LAPC and KPS ≥70	Gem + Cisplatin (98)	OS
Scheithauer 2003	Previously untreated mPC or LAPC and KPS ≥70	Gem + Cap (41)	PFS
*Wang 2002	Previously untreated mPC or uLAPC and KPS 60 -70	Gem + Cisplatin (22)	ORR
*Wang 2015	Previously untreated mPC and ECOG 0-2	Gem + Erlotinib (44)	ORR, OS
ACCORD	Previously untreated mPC or LAPC and WHO PS 0-1	FOLFIRINOX (171)	OS

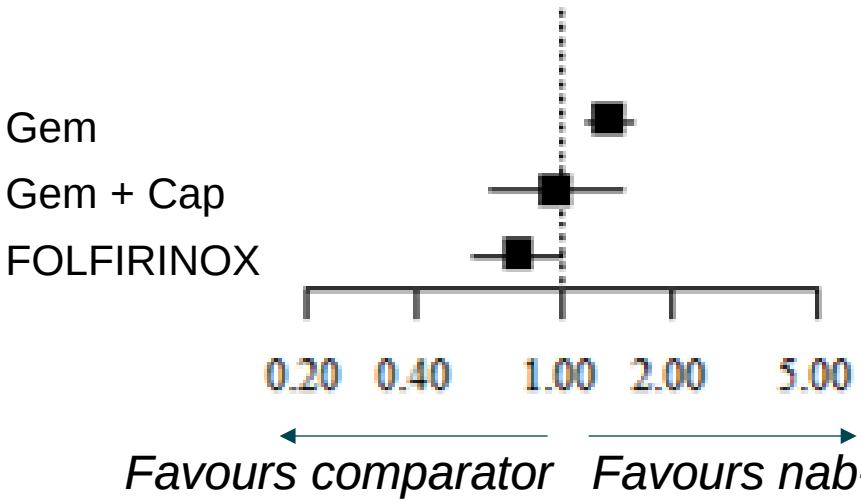
*****Exclusively Asian population; Cap: capecitabine; ECOG: Eastern Co-operative Group; FOLFIRINOX: leucovorin, fluorouracil, irinotecan and oxaliplatin; Gem: gemcitabine; LAPC; Locally advanced pancreatic cancer; mPC: metastatic pancreatic cancer; OS: overall survival; ORR: overall response rate; uLAPC: unresectable locally advanced pancreatic cancer

+

+*Additional studies included afterTA360*

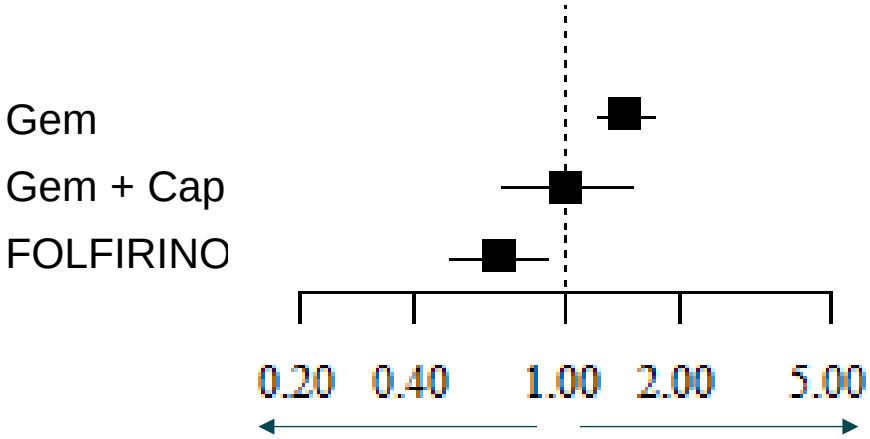
Summary of results of NMA

Overall survival: vs Nab-P + Gem



Recap: results presented in TA360*
1.39 [1.20, 1.60]
0.96 [0.60, 1.54]
0.79 [0.60,1.05]

Progression-free survival: vs Nab-P + Gem



1.64 [1.40, 1.92]
0.96 [0.58, 1.56]
0.77 [0.58, 1.02]

Network meta-analysis – ERG comments

- Considered methodology appropriate and included trials suitable
- Proportional hazards assumption not met in the CA046 trial for OS and PFS, therefore results should be treated with caution
- Not appropriate to include evidence for comparators not relevant to the decision problem
  - Not needed to produce connected network, and may introduce effect modifiers
  - Sensitivity analysis based on a reduced network (only trials that compared treatments in the decision problem) more valid
    - Overall survival results from this analysis mirror the results from the base case NMA analysis
    - Nab-P + Gem versus Gem + Cap: HR=1.10, 95% CrI: 0.67–1.84
    - Nab-P + Gem versus FOLFIRINOX: HR=0.77, 95% CrI: 0.58–1.01

Adverse events

- Primary safety data from CA046:
  - The company listed incidence of treatment-emergent adverse events of all grades experienced by ≥40% of patients in either treatment arm
  - More adverse events with Nab-p + gemcitabine than gemcitabine (89% versus 75%)
  - Most frequently reported events in Nab-p + gemcitabine arm: fatigue (59%), peripheral neuropathy (54%), nausea (54%), alopecia (50%), peripheral oedema (46%), diarrhoea (44%), anaemia (42%), neutropenia (42%) and pyrexia (41%)
- Additional data from SIEGE trial
  - Rate of grade ≥3 AEs similar to CA046 trial
  - 5.4% of patients experienced sepsis, but no cases reported in CA046

Key issues – Clinical effectiveness

- What are the relevant comparators for Nab-P + Gem?
  - What population will Nab-P + Gem be considered for? People for whom Gem, Gem + Cap and/or FOLFIRINOX would otherwise be considered?
  - Is gemcitabine monotherapy is the only relevant comparator?
- Strength of the clinical evidence for Nab-P + Gem compared with Gem
  - Are the results of CA046 generalisable to the UK clinical practice?
- Relative efficacy of Nab-P + Gem compared with Gem + Cap and FOLFIRINOX
  - How reliable are the results of the company's NMA?

Recap: Committee considerations in TA360

- *Nab-P + Gem would be considered if fit enough for combination chemotherapy but FOLFIRINOX not suitable*
- *Gem, Gem + Cap and FOLFIRINOX are all appropriate comparators*
- *Based on CA046, Nab-P + Gem was more effective than Gem, but was associated with more adverse events*
- *Recognising the uncertainty, the mixed treatment comparison could be used to compare Nab-P + Gem with Gem + Cap and FOLFIRINOX*

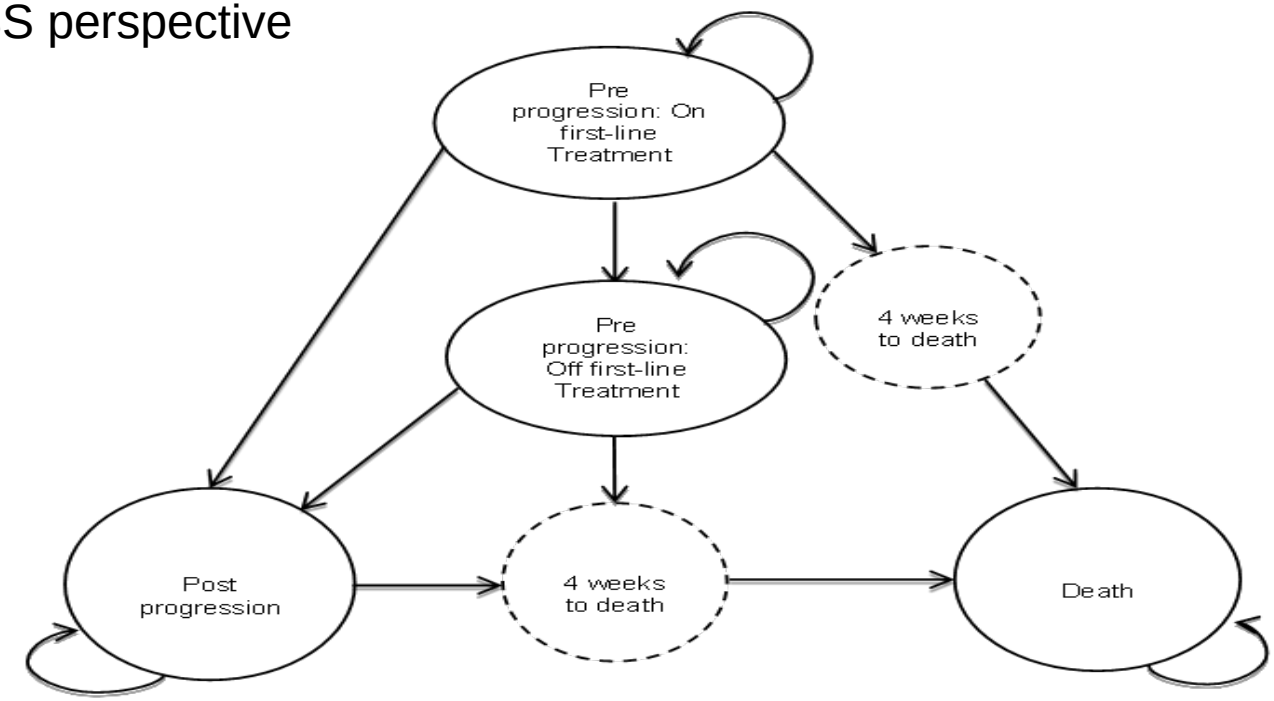
Additional evidence presented in this review

- *Further views on use of Nab-P + Gem in clinical practice*
- *NMA updated with additional studies*

Cost effectiveness evidence

Model structure

- Developed from model in TA360
- 1 week cycle length
- 10 year time horizon
- 3.5% discount in costs and QALYs after 1st year
- NHS & PSS perspective



ERG comment

- Total QALYs and life years slightly overestimated, as accrual begins at start of first cycle

Figure 21 , company submission

Clinical data in the model (1)

- Efficacy data for Nab-P + Gem compared with Gem from CA046
  - Overall survival, progression-free survival and time on treatment modelled using parametric distributions based on Kaplan–Meier data
  - 6 distributions assessed: stratified gamma selected based on statistical fit, clinical plausibility and non-proportional hazards
- Data from network meta-analysis used for the comparators Gem + Cap and FOLFIRINOX by applying hazard ratios from the NMA to parametric curves for Nab-P + Gem
- Area-under-the-curve approach used to estimate proportion of patients transitioning between health states
- Adverse event data from CA046

This is consistent with the company's approach in TA360, and incorporates the updated NMA including additional trial data

Clinical data in the model (2)

ERG comments

- Company's fully parametric model to estimate time to event data for Nab-P + Gem vs Gem is unnecessary
  - CA046 data 90% complete for OS and almost 100% for PFS
  - ERG presented exploratory analyses in which overall survival and progression-free survival from CA046 modelled using Kaplan–Meier data as far as possible and extrapolating the 'tail' only
- Company's application of hazard ratios from network meta-analysis to OS and PFS estimates for Nab-P + Gem is invalid
  - Approach relies on proportional hazards assumption
  - Proportional hazards assumption does not hold for Nab-P + Gem versus Gem in CA046
  - Use of hazard ratios directly applied to cycle probabilities is inappropriate – should be applied to treatment parameter for the curve

Recap: Committee considerations in TA360

- *Neither the company or ERG method for time to event data could be considered more appropriate than the other – took both into account*

Costs (1)

Vial sharing

- Vial sharing is not included in the base case
  - *In TA360, committee suggested that vial sharing was inappropriate due to the small patient population*

Dose intensity and missed doses

- Included cost savings for a proportion of dose reductions and missed doses (those that could be anticipated in advance)
  - *In TA360, committee considered that not all dose reductions or missed doses could be anticipated so, as a conservative approach, the costs of the full recommended treatment dose should be included*

Body surface area

- Dose of all drugs (with the exception of erlotinib and capecitabine) based on average BSA of 1.75m^2

Terminal care costs

- A micro-costing approach suggested by the ERG in TA360 is used to estimate the cost associated with end of life care

Costs (2)

ERG comments

- All first-line drug costs overestimated as not all available vial and packet sizes were included
- Dosage should be estimated using separate body surface areas for men and women
- Queried assumption that patients would not stay in hospital overnight with grade 3+ diarrhoea, dehydration and vomiting

Health-related quality of life (1)

- Health state utility values based on 3 sources:
  - Romanus et al (2012) with UK adjustment *– committee preferred in TA360*
  - SIEGE trial – phase II study of nab-P + gem, which collected EQ-5D-5L *– not available at the time of TA360*
    - A) Valued using EQ-5D-5L value set from Devlin et al. (2016)
    - *B)* Converted to EQ-5D-3L using 'crosswalk method'

Utility values in base case model and scenario analyses

	Health state utility	
	Pre-progression	Post-progression
Romanus et al (2012) with UK adjustment (used in base case)	0.74	0.67
SIEGE, with Devlin et al value set	0.79	0.75
SIEGE, with 'Crosswalk method'	0.70	0.65

Health-related quality of life (2)

ERG comments

- Health state utilities uncertain: none of the presented values are robust
  - ERG considers the values from Romanus and SIEGE with crosswalk more appropriate than SIEGE data with Devlin value set
- Company included adverse event disutilities as well as health state utility values from a clinical trial (which would have captured effect of adverse events) – results in double counting

Company base case results

	Total costs	Total LYG	Total QALYs	Incr cost	Incr LYG	Incr QALY	ICER (£/QALY)
Gem	[redacted]	0.725	0.396				
Nab-P + Gem	[redacted]	0.927	0.540	£6,717	0.202	0.144	**£46,657**

Following clarification, company presented an additional analysis:

- Incidence of adverse events based on number of events in CA046 (rather than number of patients with events)
- ICER for nab-P + gem vs gem: £46,932 per QALY gained

Recap: TA360

- *Company base case: £51,900 per QALY gained*
- *Most plausible ICER: £72,500–£78,500 per QALY gained*

ICER, incremental cost-effectiveness ratio; LYG, life years gained; nab-P + Gem, nab-Paclitaxel in combination with gemcitabine; QALYs, quality-adjusted life years

Company base case results

	Total costs	Total LYG	Total QALYs	Incr cost	Incr LYG	Incr QALY	ICER (£/QALY)
Gem + Cap	[redacted]	0.95	0.55				
Nab-P + Gem	[redacted]	0.93	0.54	£5,555	-0.02	-0.01	**Dominated**
FOLFIRINOX	[redacted]	1.15	0.69				
Nab-P + Gem	[redacted]	0.93	0.54	£1,543	-0.22	-0.15	**Dominated**

Recap: TA360

- *Company base case*
  - *Nab-P + Gem vs Gem + Cap: £87,084 per QALY gained*
  - *Nab-P + Gem vs FOLFIRINOX: Nab-P + Gem was dominated*
- *Committee considered that, although uncertain, it was confident that Nab-P + Gem would not be considered cost-effective compared with Gem + Cap or FOLFIRINOX*

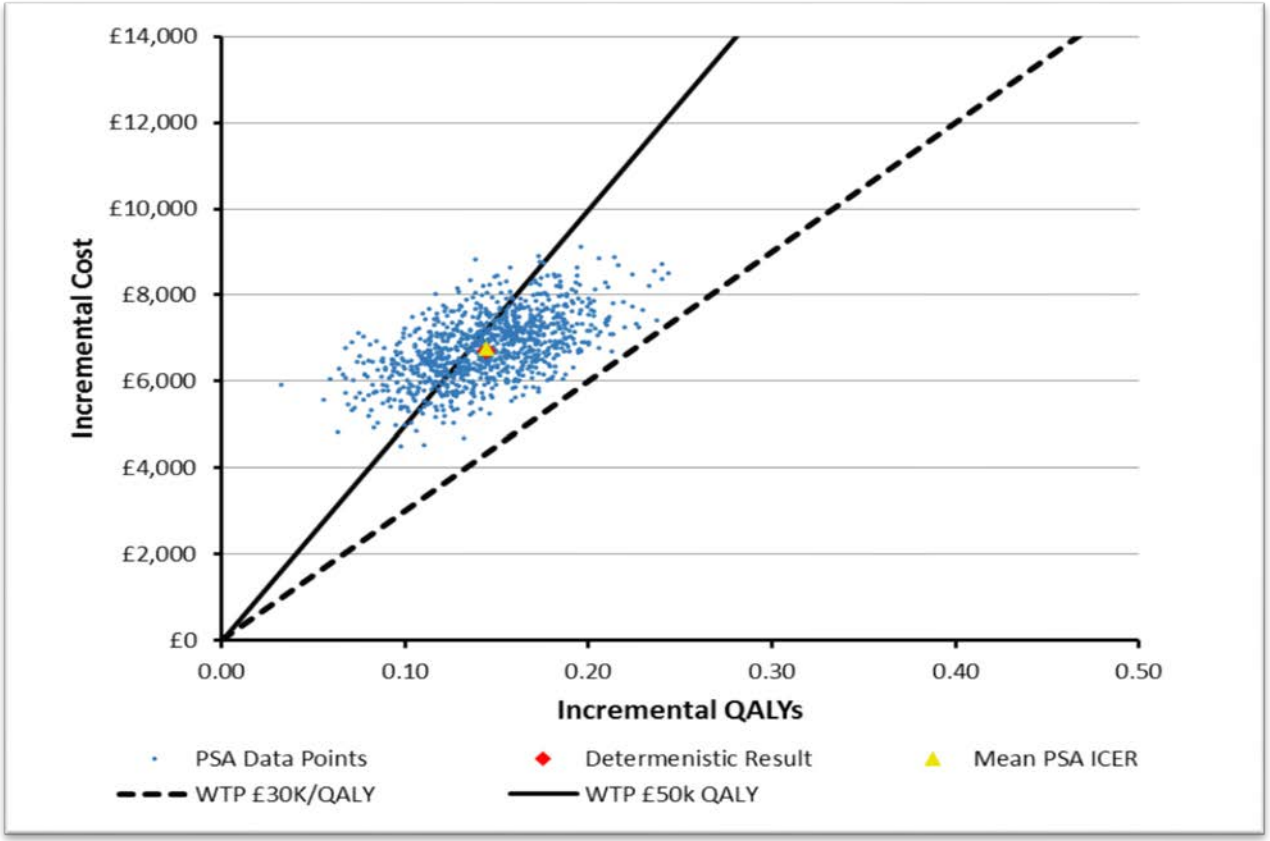
ICER, incremental cost-effectiveness ratio; LYG, life years gained; nab-P + Gem, nab-Paclitaxel in combination with gemcitabine; QALYs, quality-adjusted life years

Sensitivity analyses: Deterministic sensitivity analysis

Sensitivity analyses: Probabilistic analysis

Probabilistic sensitivity analysis

- Probabilistic ICER for Nab-P + Gem vs Gem: £46,801
- Nab-P + Gem has [redacted] probability of being cost effective compared to Gem at £50,000 per QALY gained



ERG exploratory analysis
Nab-P + Gem vs. Gem

ERG corrections:

- Total QALYs and life years accrual begins in first cycle, and corrected application of HRs

ERG revised analysis:

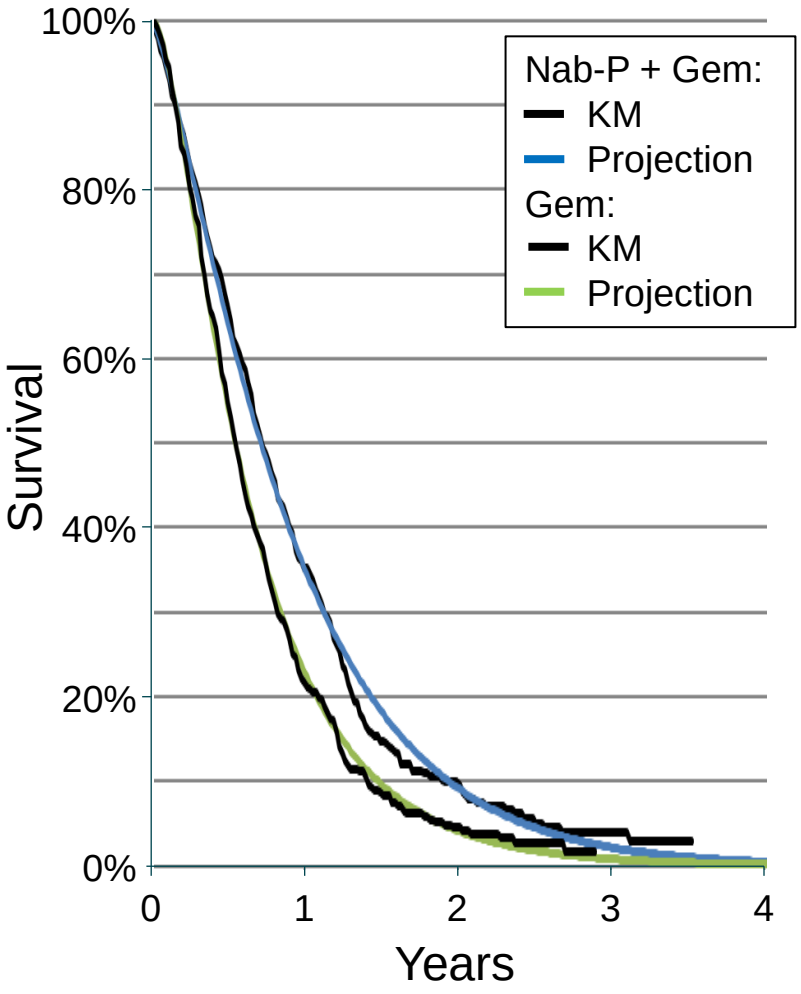
- Based on company's post-clarification model
- Overall survival and progression-free survival from CA046 modelled using Kaplan–Meier data as far as possible and extrapolating the 'tail' only
  - Consistent with ERG approach in TA360
  - *Company included this approach as a sensitivity analysis*
- Time on treatment taken directly from CA046
- Drug costs include all available vial/packet sizes and based on separate BSAs for men and women
- Remove adverse event disutilities

Scenario analyses:

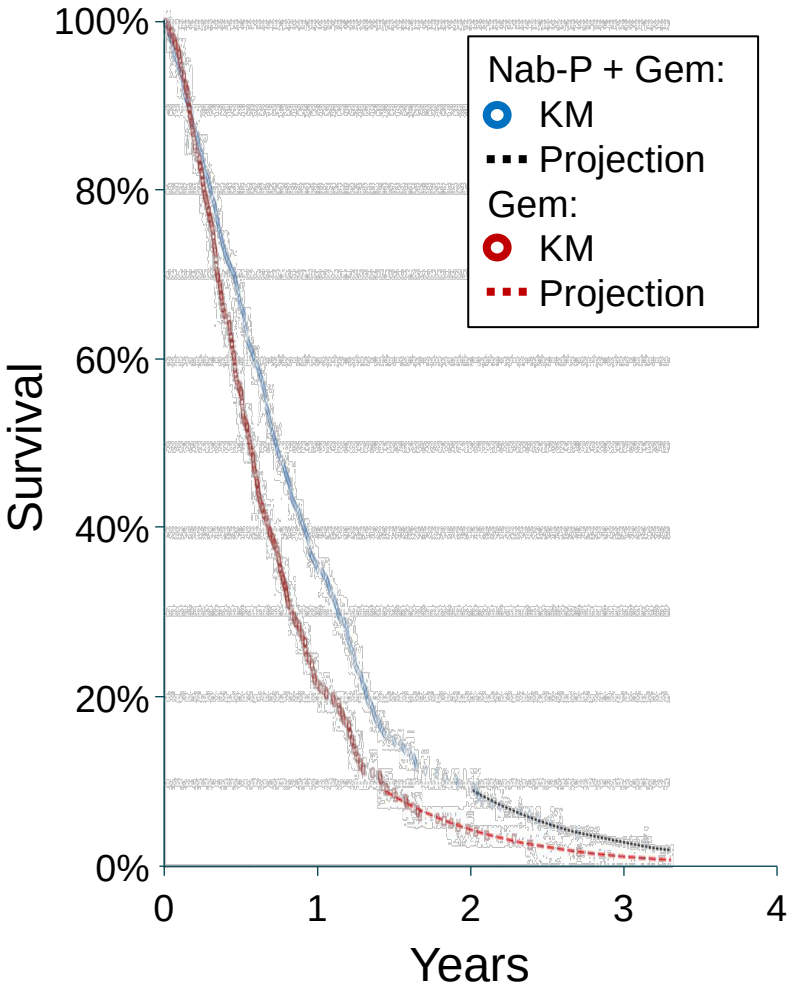
- An alternative cost for grade 3+ diarrhoea, dehydration and vomiting due to inclusion of overnight hospital stay
- Alternative SIEGE crosswalk health state utility estimates

ERG exploratory analysis: OS extrapolation

Company



ERG



Results of ERG exploratory analysis

Nab-P + Gem vs Gem

Description	Nab-P + Gem		Gem		Incremental		ICER	ICER change
	Costs	QALYs	Costs	QALYs	Costs	QALYs		
Company original base case	[redacted]	0.540	[redacted]	0.396	£6,717	0.144	£46,657	-
Company post-clarification	[redacted]	0.539	[redacted]	0.396	£6,755	0.144	£46,932	-
ERG amends								
ERG corrected company base case	[redacted]	0.527	[redacted]	0.383	£6,755	0.144	£47,011	-
ERG revised analysis	[redacted]	0.532	[redacted]	0.387	£5,985	0.145	£41,250	-£5,761
Scenarios: ERG revised analysis +								
1. ERG AE costs	[redacted]	0.532	[redacted]	0.387	£6,252	0.145	£43,088	-£3,923
2. SIEGE crosswalk utilities	[redacted]	0.500	[redacted]	0.363	£5,985	0.137	£43,626	-£3.385
3. SIEGE crosswalk utilities + ERG AE costs	[redacted]	0.500	[redacted]	0.363	£6,252	0.137	£45,571	-£1,440

ERG exploratory analysis Nab-P + Gem vs Gem + Cap and FOLFIRINOX

- All amendments as for ERG preferred and scenario analyses (previous slide)
- Also changed the way the comparator OS and PFS were calculated
  - Company base case applied hazard ratios from NMA to the nab-P + gem arm of CA046
    - However, this relies on proportional hazards assumption
  - ERG applied hazard ratios from published studies to the gem arm of CA046
    - Proportional hazards assumption doesn't hold in ACCORD trial, so comparison with FOLFIRINOX should be treated with caution

Comparator vs Gem	Source	Hazard ratio	
		OS	PFS
Gem+Cap	Scheithauer 2003	0.82	0.81
FOLFIRINOX	Conroy 2011 (ACCORD)	0.57	0.47

Table 42 ERG report

Results of ERG exploratory analysis

Nab-P + Gem vs FOLFIRINOX

Description	Nab-P + Gem		FOLFIRINOX		Incremental		ICER
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
Company original base case	[redacted]	0.540	[redacted]	0.693	£1,542	-0.153	Dominated
Company post-clarification	[redacted]	0.539	[redacted]	0.693	£1,479	-0.153	Dominated
ERG amends							
ERG corrected company base case	[redacted]	0.527	[redacted]	0.680	£1,479	-0.153	Dominated
ERG revised analysis	[redacted]	0.532	[redacted]	0.726	£383	-0.194	Dominated
Scenarios: ERG revised analysis +							
1. ERG AE costs	[redacted]	0.532	[redacted]	0.726	£436	-0.194	Dominated
2. SIEGE crosswalk utilities	[redacted]	0.500	[redacted]	0.684	£383	-0.184	Dominated
3. SIEGE crosswalk utilities + ERG AE costs	[redacted]	0.500	[redacted]	0.684	£435	-0.184	Dominated

ERG exploratory analysis – results cont.

Nab-P + Gem vs Gem + Cap

Description	Nab-Pac+Gem		Gem + cap		Incremental		ICER
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
Company original base case	[redacted]	0.540	[redacted]	0.551	£5,555	-0.011	Dominated
Company post-clarification	[redacted]	0.539	[redacted]	0.551	£5,567	-0.011	Dominated
ERG amends							
ERG corrected company base case	[redacted]	0.527	[redacted]	0.538	£5,567	-0.011	Dominated
ERG revised analysis	[redacted]	0.532	[redacted]	0.482	£5,072	0.051	£99,837
Scenarios: ERG revised analysis +							
1. ERG AE costs	[redacted]	0.532	[redacted]	0.482	£5,133	0.051	£101,037
2. SIEGE crosswalk utilities	[redacted]	0.500	[redacted]	0.453	£5,072	0.048	£106,616
3. SIEGE crosswalk utilities + ERG AE costs	[redacted]	0.500	[redacted]	0.453	£5,133	0.048	£107,898

End of life

NICE End of Life criteria	Data presented by the company
Treatment is indicated for patients with a short life expectancy, normally less than 24 months	Real world survival Median: 2 to 6 months depending on how much the cancer has grown and where it has spread Trial survival Median: 6.6 months Mean: 8.7 months Data source: CRUK (real world survival); CA046 extension trial data (trial survival)
Treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Survival extension Median: 2.1 months Mean: 2.4 months Data source: CA046 extension trial data (trial survival)

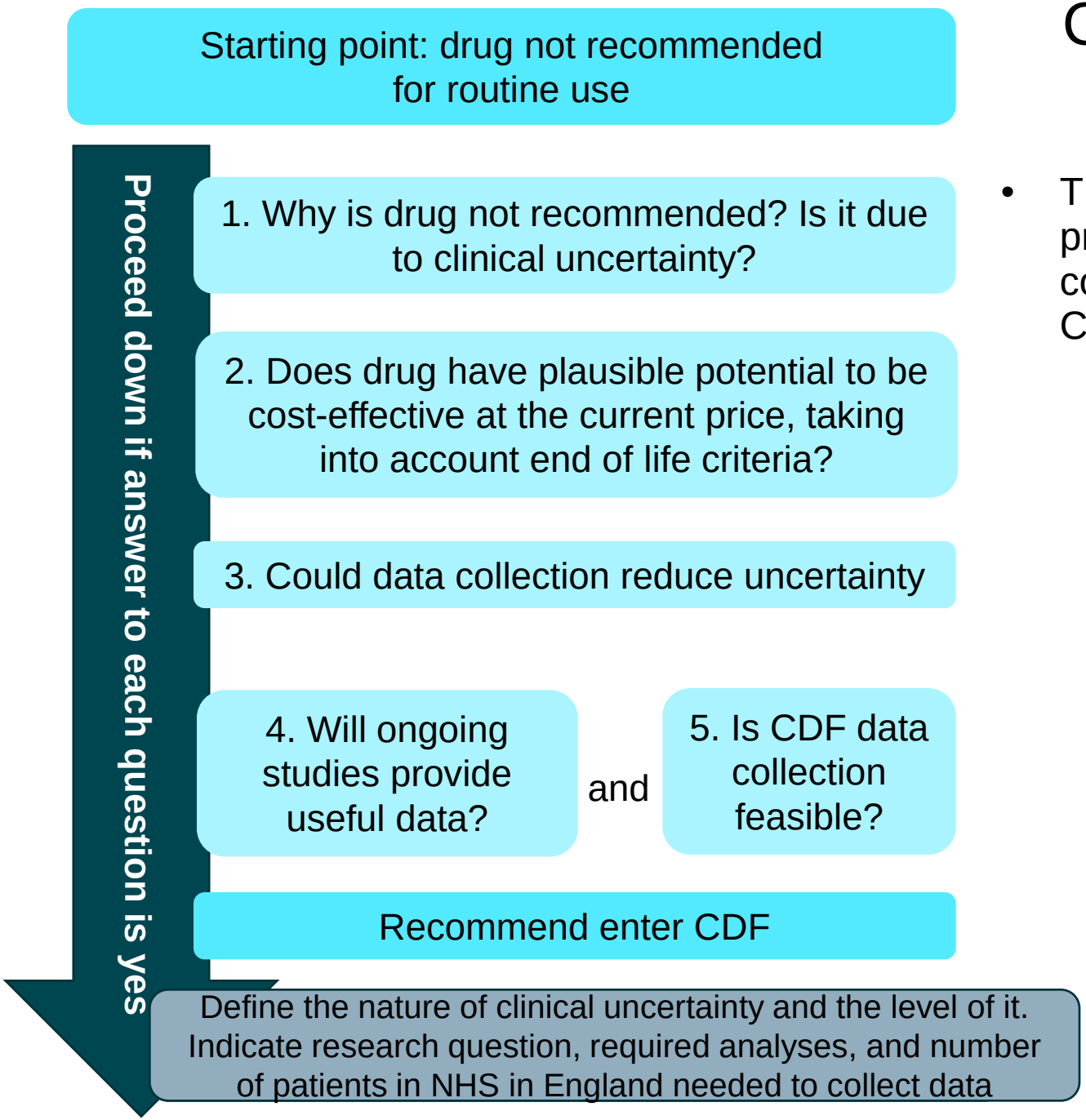
Recap: Committee considerations in TA360

- *End-of-life criteria were met for Nab-P + Gem vs Gem: survival gain was particularly significant relative to the average survival of people with this condition*
- *Criteria not met for Nab-P+ Gem vs Gam + Cap or FOLFIRINOX: no evidence of life extension*

Innovation and equalities

- Company considers Nab-P + Gem to be innovative because it:
  - has a distinct mechanism of action which results in a novel, synergistic effect
  - addresses a current unmet clinical need by providing an additional treatment option
- Company stated health-related benefits to patients were captured in QALYs
- Company and stakeholders did not identify any potential equality issues

Cancer Drugs Fund



- The company has not proposed that Nab-P be considered for the Cancer Drugs Fund

Key issues – cost effectiveness (1)

- Assumptions in the company economic model and ERG exploratory analysis
  - **Modelling time-to-event data:** fully parametric vs Kaplan–Meier + extrapolated tail
  - **Validity of indirect comparison** for Gem + Cap and FOLFIRINOX
  - **Source of utility values**: Romanus study vs SIEGE
  - **Costs**: ERG amends to vial sizes, BSA and adverse event costs

Recap: Committee considerations in TA360

- *Neither the company or ERG method for extrapolating time-to-event data could be considered more appropriate: both taken into account*
- *Utilities based on Romanus study, adjusted to UK values were appropriate [SIEGE data were not available]*

Key issues – cost effectiveness (2)

- What are the most plausible ICERs for Nab-P + Gem:
  - vs Gem?
  - vs Gem + Cap?
  - vs FOLFIRINOX ?
- End-of life criteria
- Innovative aspects of the technology

Recap: Committee considerations in TA360

- *End-of-life criteria were met for Nab-P + Gem vs Gem: survival gain was particularly significant relative to the average survival of people with this condition*
- *Criteria not met for Nab-P+ Gem vs Gam + Cap or FOLFIRINOX: no evidence of life extension*

Authors

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- with input from the Lead Team (Susan Dutton, Paula Ghaneh, Rebecca Harmston)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of paclitaxel formulated as albumin-bound nanoparticles in combination with gemcitabine within its marketing authorisation for previously untreated metastatic adenocarcinoma of the pancreas.

Background

The pancreas is a large gland located behind the stomach that is part of the digestive system. Pancreatic cancer does not usually cause any symptoms in its early stages, which can make it difficult to diagnose. The first symptoms may include pain in the back or stomach area, unexpected weight loss or jaundice (yellowing of the skin and whites of the eyes). The most common type of pancreatic cancer is adenocarcinoma.[1] About 45–55% have metastatic disease (meaning the cancer has spread to other parts of the body).[2]

In 2014, there were 8,080 people diagnosed with pancreatic cancer in England.[3] Pancreatic cancer affects men and women equally and about 75% of people diagnosed with pancreatic cancer are aged 65 years or over.[3] There were around 7,400 deaths due to pancreatic cancer in England in 2014.[4] The prognosis depends on how advanced the disease is when it is diagnosed. On average, about 21% of people with pancreatic cancer survive 12 months.[5]

Surgery is usually the only way pancreatic cancer can be cured, but it is only suitable for the 15-20% of people who have early stage disease. There is no established treatment pathway for treating metastatic pancreatic cancer. People may be offered chemotherapy, radiotherapy or palliative surgery to help control tumour growth and symptoms. These treatments may be given alone or in combination with each other.

NICE technology appraisal guidance 25 recommends gemcitabine for untreated advanced or metastatic adenocarcinoma of the pancreas, only if the person has a Karnofsky performance score of 50 or more and potentially curative surgery is not a suitable treatment. Other treatment options used in clinical practice, off-label, for treating metastatic pancreatic cancer include capecitabine in combination with gemcitabine and oxaliplatin in combination with irinotecan, fluorouracil and leucovorin (FOLFIRINOX).

NICE technology appraisal guidance 360 did not recommend paclitaxel as albumin bound nanoparticles in combination with gemcitabine for adults with previously untreated metastatic adenocarcinoma of the pancreas. The company has proposed a patient access scheme for paclitaxel as albumin bound nanoparticles and also indicated that there is new evidence available, which might lead to a change in the existing recommendations.

The technology

Paclitaxel as albumin-bound nanoparticles (Abraxane, Celgene) is a form of paclitaxel that inhibits cancer growth by blocking cell division and promoting cell death. The formulation contains albumin to help transport paclitaxel through the walls of blood vessels. This is thought to increase the amount of paclitaxel in the area of the tumour. Paclitaxel as albumin-bound nanoparticles is administered as an intravenous infusion.

Paclitaxel as albumin-bound nanoparticles in combination with gemcitabine has a marketing authorisation in the UK for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.

Intervention	Paclitaxel as albumin-bound nanoparticles
Population	People with previously untreated metastatic adenocarcinoma of the pancreas
Comparators	• Gemcitabine • Gemcitabine plus capecitabine • Oxaliplatin plus irinotecan, fluorouracil and leucovorin (FOLFIRINOX)
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • time to tumour progression • response rate • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention of comparator technologies will be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Guidance on the use of gemcitabine for the treatment of pancreatic cancer' (2001). NICE Technology Appraisal 25.Guidance on static list. Terminated appraisals: 'Pancreatic cancer – capecitabine' NICE technology appraisal guidance. Suspended. 'Masitinib for the treatment of locally advanced of metastatic pancreatic cancer' NICE technology appraisal guidance. Suspended. Appraisals in development: 'Pancreatic cancer (metastatic, untreated) - liposomal cisplatin (with gemcitabine)' NICE technology appraisals guidance [ID658] Publication expected TBC. 'Pancreatic cancer (metastatic) - nimotuzumab (1st line)' NICE technology appraisals guidance [ID513] Publication expected TBC. Related Guidelines: None Guidelines in development 'Pancreatic cancer'. Publication expected January 2018

	Related Interventional Procedures: 'Irreversible electroporation for treating pancreatic cancer' (2013). NICE interventional procedures guidance 442. Related NICE Pathways: Gastrointestinal cancers (2016) NICE pathway https://pathways.nice.org.uk/pathways/gastrointestinal-cancers
Related National Policy	NHS England (May 2016) Manual for prescribed specialised services 2016/17 Chapter 131: Specialist services for complex liver, biliary and pancreatic diseases in adults. NHS England 2013/14 NHS standard contract for cancer: pancreatic (adult) A02/S/b NHS England 2013/14 NHS standard contract for hepatobiliary and pancreas (adult) A02/S/a Department of Health (2016) NHS outcomes framework 2016 to 2017 Domains 1, 2, 4, 5.

References

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2. Pancreatic cancer UK (2015) Facts about pancreatic cancer. Accessed May 2015.
3. Office for National Statistics (2016) Cancer Registration Statistics, England. Accessed November 2016.
4. Cancer Research UK (2016) Pancreatic cancer mortality statistics. Accessed November 2016.
5. Cancer Research UK (2016) Pancreatic cancer survival statistics. Accessed November 2016.

APPENDIX A

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company/sponsor • Celgene (nab-paclitaxel) Patient/carer groups • Black Health Agency • Cancer Black Care • Cancer Equality • Cancer52 • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Macmillan Cancer Support • Maggie's Centres • Marie Curie • Muslim Council of Britain • Pancreatic Cancer Action • Pancreatic Cancer UK • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care Professional groups • Association of Cancer Physicians • Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society • British Society of Gastroenterology • Cancer Research UK • Pancreatic Society of Great Britain and Ireland • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists	General commentators • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparators • Accord Healthcare (capecitabine, fluorouracil, gemcitabine, irinotecan, oxaliplatin) • Actavis UK (capecitabine, gemcitabine, irinotecan, oxaliplatin) • Almirall Limited (fluorouracil) • Dr. Reddy's Laboratories (capecitabine) • Lilly UK (gemcitabine) • Meda Pharmaceuticals (fluorouracil) • Medac UK (capecitabine, gemcitabine, fluorouracil, irinotecan, oxaliplatin, leucovorin) • Pfizer (irinotecan) • Roche Products (capecitabine) • Seacross Pharmaceuticals (irinotecan) • Shire Pharmaceuticals (irinotecan)

• Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS Doncaster CCG • NHS England • NHS Surrey Heath CCG • Welsh Government	• Sun Pharmaceuticals (capecitabine, gemcitabine, oxaliplatin) <u>Relevant research groups</u> • Cochrane Upper Gastrointestinal and Pancreatic Diseases Group • CORE – Digestive Disorders Foundation • Institute of Cancer Research • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute of Health Research • Pancreatic Cancer Research Fund <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1] Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

Company evidence submission

File name	Version	Contains confidential information	Date
ID1058_nab-P_STASubmission_redacted	1	Yes	16/03/17

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

Tables and figures

Abbreviations

Abbreviation	Definition
5-FU	5-fluorouracil
AE	Adverse event
AIC	Akaike information criterion

Abbreviation	Definition
aPAC/APC	Advanced pancreatic cancer
ASCO	American Society of Clinical Oncology
AWMSG	All Wales Medical Strategy Group
BIC	Bayesian information criterion
BSA	Body surface area
CDF	Cancer Drugs Fund
CE	Cost-effectiveness
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CrI	Credible interval
CSR	Clinical study report
CT	Computed tomography
DCR	Disease control rate
DIC	Deviance Information Criterion
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC QLQ C30	European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire C30
EPAR	European Public Assessment Report
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FDR	Fixed dose rate
FOLFIRINOX	Leucovorin, fluorouracil, irinotecan and oxaliplatin
FOLFOX	Leucovorin, fluorouracil and oxaliplatin
G-CSF	Granulocyte-colony stimulating factor
Gem/Cap	Gemcitabine in combination with capecitabine
Gem/Erl	Gemcitabine in combination with erlotinib
GHS	Global health status
GI	Gastrointestinal
GP	General practitioner
HR	Hazard ratio
HRG	Healthcare Resource Group

Abbreviation	Definition
HRQL	Health-related quality of life
HTA	Health technology assessment
HTAi	Health Technology Assessment International
ICER	Incremental cost-effectiveness ratio
iHEA	International Health Economics Association
IPD	Individual patient data
IRR	Independent radiological review
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive voice response system
KM	Kaplan–Meier
KPS	Karnofsky Performance Status
LAPC	Locally advanced pancreatic cancer
LCH	Log-cumulative hazard
LCHP	Log-cumulative hazard plot
LSCCN	Lancashire and South Cumbria Cancer Network
LY	Life year
LYG	Life years gained
mAb	Monoclonal antibody
MAE	Mean absolute error
MIMS	Monthly Index of Medical Specialities
mPAC	Metastatic pancreatic adenocarcinoma
mPC	Metastatic pancreatic cancer
mPDAC	Metastatic pancreatic ductal adenocarcinoma
MRI	Magnetic resonance imaging
MTC	Mixed treatment comparison
nab-P/Gem	*nab*-Paclitaxel in combination with gemcitabine
NCI	National Cancer Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
ONS	Office of National statistics
OR	Odds ratio

Abbreviation	Definition
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PD	Progressive disease
PFS	Progression-free survival
PH	Proportional hazards
PhRMA	Pharmaceutical Research and Manufacturers of America
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance score
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumor
RMSE	Root mean squared error
RR	Relative risk
RRR	Response rate ratio
SACT	Systemic Anti-Cancer Therapy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SG	Standard gamble
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMDM	Society for Medical Decision Making
SmPC	Summary of product characteristics
SPARC	Secreted protein acidic and rich in cysteine
TEAE	Treatment-emergent adverse event
ToT	Time on treatment
TSD	Technical Support Document
TTO	Time trade-off
TTP	Time-to-progression

Abbreviation	Definition
uLAPC	Unresectable locally advanced pancreatic cancer
ULN	Upper limit of normal
VAS	Visual analogue scale
VTE	Venous thromboembolism
WHO	World Health Organization
WoS	Web of Science
WTP	Willingness to pay

Executive summary

Pancreatic cancer is a particularly aggressive and life-threatening malignancy for which there have been few therapeutic advances. Pancreatic cancer is responsible for an estimated 24 deaths every day in the UK (2014 data) and has one of the worst 5-year survival rates of all common cancers at <5%.[1, 2] This poor prognosis is associated with the fact that pancreatic cancer is often diagnosed at an advanced stage; only 30–40% of all patients present with disease confined to the pancreatic region.[3]

Gemcitabine monotherapy, which has been routinely funded in NHS England since 2001[4], remains the established standard of care for patients with advanced or metastatic pancreatic cancer (mPC) (who are eligible for chemotherapy treatment (Karnofsky Performance Status [KPS] ≥50). Although gemcitabine monotherapy demonstrated significant clinical benefit over conventional fluorouracil in clinical trials initiated over 20 years ago, it has limited effectiveness in clinical practice. The median survival of patients diagnosed with mPC in the UK remains at 2–6 months depending on the size of the tumour and where it has spread.[5]

In the pivotal, regulatory Phase III trial, CA046[6], gemcitabine plus *nab*-Paclitaxel (herein referred to as *nab*-P/Gem) became the first chemotherapy doublet to demonstrate both a statistically significant and clinically meaningful survival benefit (defined as 6–8 weeks by people affected by pancreatic cancer[7]) over gemcitabine monotherapy for the first-line treatment of metastatic pancreatic adenocarcinoma (mPAC).[6, 8] This benefit was observed across many patient groups, including those with markers of advanced disease and therefore worse prognosis. Some additive toxicity was observed (as expected *a priori*), but *nab*-P/Gem was generally well tolerated, with adverse events (AEs) considered manageable in the majority. While health-related quality of life (HRQL) data were not collected in CA046, supportive Phase II trial data show that a high proportion of advanced pancreatic cancer patients treated with *nab*-P/Gem report stable or improved HRQL.[9, 10] Additional real world evidence further supports the safety and efficacy profile of *nab*-P/Gem in clinical practice. Treatment with standard of care is generally associated with a life expectancy of ≤6 months. Nab-P/Gem should be considered a life-extending treatment in the context of this aggressive and life threatening malignancy, as it

demonstrates a clinically meaningful extension to life versus gemcitabine (a standard of care).

The appropriate comparator for *nab*-P/Gem is gemcitabine monotherapy.[11] During the original technology appraisal for *nab*-P/Gem, NICE acknowledged that there is a clinically recognisable group of patients who receive gemcitabine alone in clinical practice, rather than oxaliplatin plus irinotecan, fluorouracil and leucovorin (FOLFIRINOX) or gemcitabine plus capecitabine (Gem/Cap) (TA360).[12] Accessibility of *nab*-P/Gem will not displace either of these treatments in clinical practice[11], therefore they are not appropriate comparators, as we will outline in this submission. For certain patients currently treated with gemcitabine monotherapy, access to *nab*-P/Gem could significantly improve clinical prognosis and quality of life. In recognition of this critical medical need, previous concerns of uncertainty around the cost-effectiveness of *nab*-P/Gem have been directly addressed through a substantial price discount, and inclusion of additional HRQL data not previously available.

The economic evaluation was conducted from the National Health Service (NHS) and Personal Social Services (PSS) perspective and compares treatment with *nab-P*/Gem versus gemcitabine monotherapy. As mentioned above Gem/Cap is considered a secondary comparator in this analysis as it has not demonstrated a significant survival benefit over gem monotherapy in a Phase III RCT and is not recommended in European clinical guidelines. Thus, the use of Gem/Cap is limited to very few centres across the UK and is therefore not a national standard of care. Similarly, FOLFIRINOX is an intensive therapy that is suitable for a clinically defined group of appropriate patients (generally younger patients with a good performance status), who will continue to receive this treatment despite having access to *nab-P*/Gem and therefore is also considered a secondary comparator. Relative efficacy estimates for these analyses were obtained from an updated meta-analysis in the absence of head-to-head trial data.

The cost effectiveness analysis has been updated from the previous submission with the aim of keeping the base case as close to the Committee's preferred base case from the original submission (TA360) as possible (see section 5.11).

The results from the base case cost-effectiveness analysis show that the overall cost per patient for *nab-P/Gem* is [redacted] and for gemcitabine monotherapy is [redacted]. The

discounted quality-adjusted life year (QALY) gained per patient are 0.540 for *nab-P*/Gem and 0.396 for gemcitabine monotherapy, resulting in an incremental cost-effectiveness ratio (ICER) of £46,657 per QALY. In addition, results from the cost-effectiveness acceptability curve (CEAC) show that treatment with *nab-P*/Gem has a [redacted] probability to be cost-effective at a willingness to pay (WTP) threshold of £50,000 per QALY. Uncertainty was investigated around this estimate via probabilistic sensitivity analysis, and the result was shown to be robust; the ICER of £46,801 per QALY is comparable with the deterministic ICER. Several scenario analyses were also conducted including a comparison with the other comparators listed in the scope, even though they will not be replaced by *nab-P*/Gem in clinical practice.

The introduction of nabP/Gem in mPDAC will result in an average annual net budget impact of [redacted], when taking into account the additional savings of the PAS on the use of ABRAXANE in metastatic breast cancer in the NHS. This is based on a 5-year model of the net budget impact per year over 5 years across all indications for ABRAXANE.

1.1 Statement of decision problem

The decision problem addressed in this submission is summarised in Table 1.

It should be noted that while comparative efficacy and cost-effectiveness analyses versus FOLFIRINOX and Gem/Cap are provided within this submission to align to the final scope issued by NICE, these regimens are not considered to be relevant comparators. FOLFIRINOX is an intensive therapy, associated with high administration burden and considerable toxicity, and is therefore only suitable for a clinically defined group of appropriate patients. These generally younger and fitter patients will continue to receive this regimen despite the accessibility of *nab*-Paclitaxel (*nab*-P); that is, *nab*-P/Gem will not replace the use of FOLFIRINOX.[11] Gem/Cap has not demonstrated a significant survival benefit over gemcitabine monotherapy in a Phase III randomised controlled trial (RCT), and is not recommended in European clinical guidelines. Use of Gem/Cap is thus limited to very few centres across the UK, and this regimen does not represent a national standard of care. Select patients who may receive this regimen will continue to do so

despite the accessibility of *nab*-P; that is, *nab*-P/Gem will not replace the very limited use of Gem/Cap.[11]

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with previously untreated metastatic adenocarcinoma of the pancreas	People with previously untreated metastatic adenocarcinoma of the pancreas	-
Intervention	Paclitaxel as albumin-bound nanoparticles	Paclitaxel as albumin-bound nanoparticles	-
Comparator (s)	• Gemcitabine • Gemcitabine plus capecitabine • Oxaliplatin plus irinotecan, fluorouracil and leucovorin (FOLFIRINOX)	• Gemcitabine • Gemcitabine plus capecitabine • Oxaliplatin plus irinotecan, fluorouracil and leucovorin (FOLFIRINOX)	-
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • time to tumour progression • response rate • adverse effects of treatment • health-related quality of life.	The outcome measures to be considered include: • overall survival • progression-free survival • time to tumour progression • response rate • adverse effects of treatment • health-related quality of life.	-
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be	The present economic analysis was conducted in accordance with the NICE reference case. The effectiveness of treatment is expressed in terms of incremental costs per quality-adjusted life year. The economic model considers the clinical and cost effectiveness of *nab*-	-

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention of comparator technologies will be taken into account.	P/Gem versus the comparator treatments over a 10-year time horizon. This is in line with the aggressive late stage presentation of the malignancy which means that by year 10 all patients have transitioned to the death state. Costs are being evaluated from a UK National Health Services and the Personal Social Services (NHS & PSS) perspective. A discount rate of 3.5% will be used for both costs and benefits.	
Subgroups to be considered	None specified	None specified	-
Special considerations including issues related to equity or equality	None identified	None identified	-

1.2 Description of the technology being appraised

Nab-P is an innovative formulation of paclitaxel that facilitates selective and efficient accumulation of active treatment to promote cell death at the tumour site. When administered alongside gemcitabine, a novel, synergistic effect is observed (as indicated in a pre-clinical model).[13]

The indication for *nab*-P of interest to this submission is:

"in combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas"

This is summarised along with further details of *nab*-P in Table 2.

Table 2: Technology being appraised

UK approved name	Paclitaxel formulated as albumin-bound nanoparticles, commonly referred to as *nab*-Paclitaxel.
Brand name	ABRAXANE®
Indication	The licensed indication of interest to this submission is: *"in combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas"*.
Marketing authorisation	Marketing authorisation was granted on 20 December 2013.
Reimbursement status (UK)	*Nab*-P/Gem *is* accepted for use in NHS Scotland and NHS Wales for this indication. *Nab*-P/Gem *was* accessed through the CDF in NHS England from March 2014 to November 2015.
Method of administration and dosage	*Nab*-Paclitaxel: 125mg/m^2 IV infusion on Days 1, 8 and 15 of a 28-day cycle. Gemcitabine: 1000mg/m^2 IV infusion on Days 1, 8 and 15 of a 28-day cycle.
Key: CDF, Cancer Drugs Fund; IV, intravenous; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; NHS, National Health Service.	

1.3 Summary of the clinical effectiveness analysis

The clinical evidence supporting the use of *nab*-P/Gem primarily comes from a pivotal regulatory trial that provides evidence of direct relevance to the decision problem. This trial was a Phase III, multicentre, open-label RCT comparing the clinical efficacy and safety of *nab*-P/Gem with gemcitabine monotherapy in adult

patients with previously untreated mPAC. Data from this trial and its extension study (designed to give a more complete estimate of overall survival [OS]) are summarised below.

- Significant and clinically meaningful OS benefit observed for *nab*-P/Gem versus gemcitabine:
  - CA046 primary analysis: median OS, 8.5 months' vs 6.7 months; hazard ratio (HR), 0.72 (95% confidence interval [CI]: 0.62, 0.83); p<0.001[6]
  - CA046 extension study: median OS, 8.7 months' vs 6.6 months; HR, 0.72 (95% CI: 0.62, 0.83); p<0.0001; mean OS, 11.1 months vs 8.7 months (2.4 months life extension)[8]
  - OS benefit observed across many patient groups, including those with markers of advanced disease and therefore worse prognosis, such as extensive metastases and poor performance status.[6]
- Doubling of 2-year survival rates observed with *nab*-P/Gem versus gemcitabine: 10% vs 5%[8]
- Significant progression-free survival (PFS) benefit observed for *nab*-P/Gem versus gemcitabine: median PFS, 5.5 vs 3.7 months; HR (95% CI), 0.69 (0.58, 0.82); p<0.001[6]
- Significant overall response rate (ORR) benefit observed for *nab*-P/Gem versus gemcitabine
  - Independent review: 23% vs 7%; response rate ratio (RRR), 3.19 (95% CI: 2.18, 4.66); p<0.001; investigator assessment: 29% vs 8%[6]

In the absence of further direct data comparing *nab*-P/Gem to alternative chemotherapy doublets/regimens, a network meta-analysis (NMA) was conducted. As aforementioned, this NMA was only conducted for completeness with regard to scope alignment, with gemcitabine monotherapy considered to be the only relevant comparator to *nab*-P/Gem for this indication. Reflecting the direct data available, both *nab*-P/Gem and FOLFIRINOX demonstrated a significantly superior survival benefit over gemcitabine monotherapy; no significantly superior survival benefit was observed for Gem/Cap versus gemcitabine monotherapy. FOLFIRINOX demonstrated at least a numerically superior survival benefit over gemcitabine

doublets in indirect comparisons, as may be expected considering the multi-agent nature of this regimen. Comparisons between gemcitabine doublets were less conclusive but *nab*-P/Gem demonstrated at least comparable, if not superior benefit over Gem/Cap. As with most NMAs, potential sources of clinical and statistical bias across the mPC evidence base warrant caution to be applied when interpreting these indirect comparisons.

Assessment of adverse reactions in CA046 did show some additive toxicity with *nab*-P/Gem compared with gemcitabine monotherapy (as expected *a priori*). Treatment-emergent adverse events (TEAE) with the greatest observed differences between treatment groups were peripheral neuropathy (54% in the *nab*-P/Gem group and 13% in the gemcitabine group) and alopecia (50% in the *nab*-P/Gem group and 5% in the gemcitabine group).[6] Importantly, most TEAE were mild to moderate and generally manageable through dose modification. Such dose modification should be encouraged in clinical practice to maximize treatment exposure and optimize clinical effectiveness. Exploratory analyses conducted post-hoc demonstrate that patients with at least one dose delay or dose reduction have a significantly longer median OS time than patients who do not have any dose modifications (10.1 to 11.4 months vs 6.2 to 6.9 months, respectively); $p<0.0001$.[14] Such preservation of health status not only prolongs first-line treatment exposure, but also may allow patients to go onto receive second-line treatment and further improve their overall prognosis.

An omission of HRQL data collection is a limitation of the CA046 trial. HRQL data is currently being collected in two ongoing Phase II trials investigating the use of *nab*-P/Gem as a first-line treatment for advanced pancreatic cancer.[9, 10] This includes EuroQol-5 Dimension (EQ-5D) data which has been analysed to inform utility values within the cost-effectiveness modelling of this submission. It also includes European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) data which shows a high proportion of patients report stable or improved HRQL while receiving *nab*-P/Gem treatment.

1.4 Summary of the cost-effectiveness analysis

The cost effectiveness analysis has been updated from the previous submission with the aim of keeping the base case as close to the Committee's preferred base case from the original submission (TA360) as possible.

With application of the end of life criteria, gem/nab-P at its discounted price ([redacted] discount; [redacted] per 100mg) is cost effective vs. its relevant comparator gem mono with an ICER of £46,657/QALY. Uncertainty was investigated around this estimate, and the result was shown to be robust; probabilistic ICER of £46,801/QALY. Gem/nab-P has a [redacted] chance of being cost effective at a WTP threshold of £50,000/QALY.

In the original submission (TA360), the Committee concluded that the end of life criteria are met vs. gem monotherapy;

- The Committee accepted the cumulative total patient population in England is less than 7000.
- The Committee noted that the average survival rate of pancreatic cancer was up to 6 months and therefore concluded that the life expectancy criterion was met, because life expectancy for people with metastatic pancreatic cancer was normally substantially less than 24 months.
- The Committee noted that the survival gain was below what is normally considered appropriate for the extension-to-life criterion to be considered met (that is, the extension to life with nab-paclitaxel plus gemcitabine compared with gemcitabine alone was less than 3 months [approximately 2.4 months]). However, it agreed that the survival gain was particularly significant relative to the average survival of people with this condition, and therefore this criterion could be accepted as met in this circumstance.
- The Committee noted that the survival data were mature and therefore it considered that the survival gain estimate was robust

Note that the base case analysis shows results based upon only having a 100mg vial available. Currently, Celgene plan to release a 250mg vial in the future priced at the same price per mg as the 100mg vial, although the timelines are currently unknown. The cost-effectiveness of nab-P/Gem, including the availability of the 250mg vial, is explored in a separate scenario analysis (Table 81).

Table 3: Incremental cost-effectiveness results

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline (A)
***Nab*-P/Gem**	[redacted]	0.927	0.540				
Gem mono	[redacted]	0.725	0.396	£6,717	0.202	0.144	£46,657
Key: Gem**,** gemcitabine; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.							

As described in section 1.1 FOLFIRINOX and Gem/Cap are not considered relevant comparators to nab-P/gem. For completeness, results vs. these treatments are included in the sensitivity analyses of this report (see Section 5.8).

2. The technology

2.1 Description of the technology

Brand name: ABRAXANE®

UK approved name: Paclitaxel formulated as albumin-bound nanoparticles, (referred to throughout this submission as *nab*-Paclitaxel [*nab*-P]).

Therapeutic class: Antineoplastic agents, plant alkaloids and other natural products, taxanes, ATC Code: L01CD01

Mechanism of action:

Paclitaxel inhibits cancer growth by blocking cell division and promoting cell death. More specifically, paclitaxel binds to tubulin in cancerous cells and stabilises the mitotic spindle, preventing its breakdown during cell division and thus producing mitotic arrest, resulting in apoptosis or reversion to the G-phase of the cell cycle (cell growth). The unique mechanism of paclitaxel results in antineoplastic activity against a wide variety of malignancies, and it is widely used for the treatment of breast, lung and advanced ovarian cancers.[15]

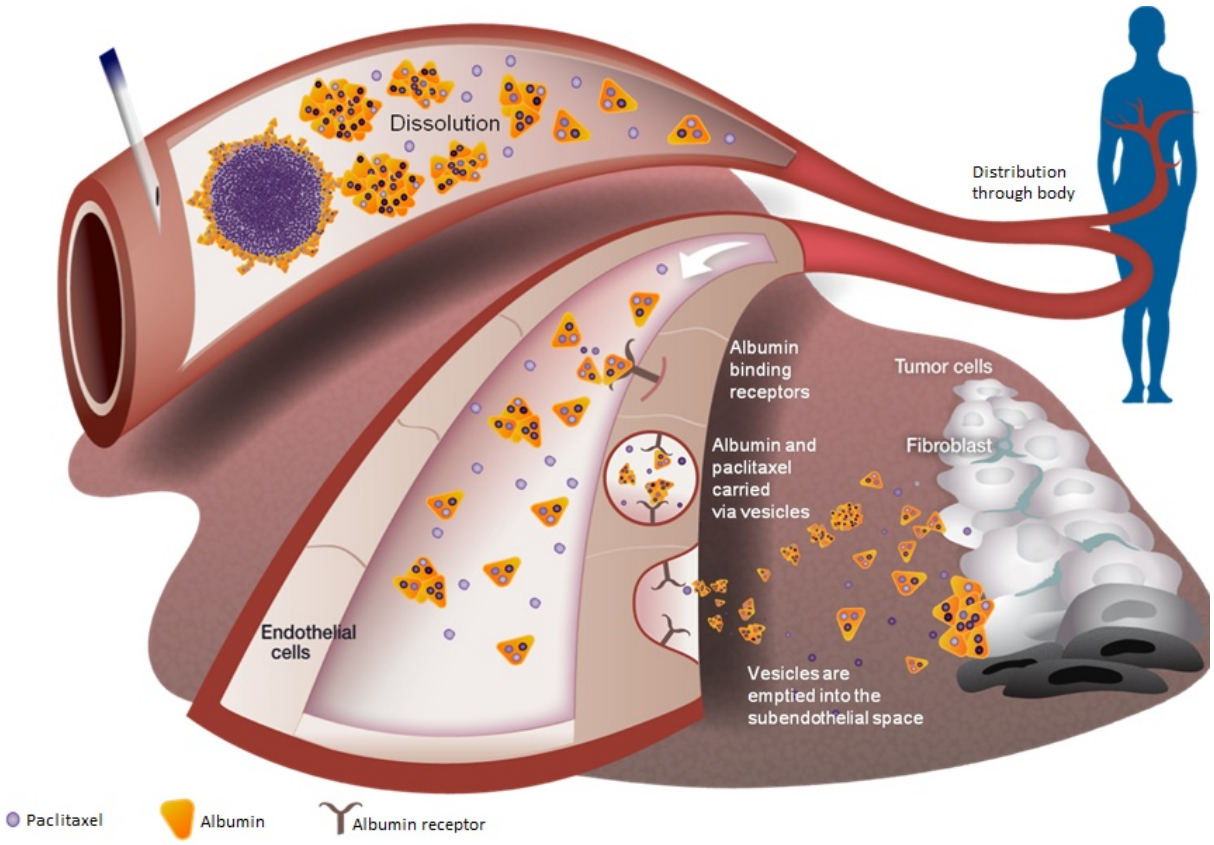
Nab-P is a novel, solvent-free formulation of paclitaxel in which the compound is attached to nanoparticles of albumin. This technology of attaching paclitaxel to nanoparticles of albumin was designed with the aim of improving the chemotherapeutic effects of paclitaxel and reducing common toxicities associated with solvent-based paclitaxel, such as hypersensitivity reactions. *Nab*-P nanoparticles are approximately 130 nm in size, with the paclitaxel present in a non-crystalline, amorphous state; upon intravenous (IV) administration, the nanoparticles rapidly dissociate into soluble, albumin bound paclitaxel complexes of approximately 10 nm in size, competent for tissue distribution. Albumin is known to mediate endothelial caveolar transcytosis of plasma constituents, and *in vitro* studies demonstrated that the presence of albumin in *nab*-P enhances transport of paclitaxel across endothelial cells. It is hypothesised that this enhanced transendothelial caveolar transport is mediated by the gp-60 albumin receptor.

Compared with conventional solvent-based paclitaxel, the novel formulation of *nab*-P demonstrates a shorter duration of high paclitaxel systemic exposure with

dose/exposure linearity over a clinically relevant dose range[16, 17], and a more rapid and greater tissue distribution of paclitaxel[16, 18, 19] due to enhanced transcytosis of paclitaxel across endothelial cells.[15] This results in more efficient and selective tumour accumulation of paclitaxel.[15, 20]

The proposed mechanism of action of *nab*-P is depicted in Figure 1.

Figure 1: Summary of the proposed mechanism of action of *nab*-Paclitaxel



When administered alongside gemcitabine, the metabolic interaction between *nab*-P and gemcitabine results in a novel, synergistic effect (as indicated in a pre-clinical model).[13] In a mouse model of pancreatic ductal adenocarcinoma, co-administration of gemcitabine plus *nab*-Paclitaxel (herein referred to as *nab*-P/Gem) uniquely demonstrates evidence of tumour regression. Combination treatment increases intra-tumoural gemcitabine levels attributable to a marked decrease in the primary gemcitabine metabolizing enzyme, cytidine deaminase. Correspondingly, *nab*-P reduced the levels of cytidine deaminase protein in cultured cells through reactive oxygen species-mediated degradation, resulting in the increased stabilisation of

gemcitabine. We have been advised by clinical experts that this represents an innovation in the context of treating metastatic pancreatic cancer (mPC).[11]

2.2 Marketing authorisation/CE marking and health technology assessment

The indication for *nab*-P of interest to this submission is:

"in combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas"

Marketing authorisation for this indication was granted by the European Commission on 20th December 2013 based on data from the pivotal Phase III trial, CA046 (see Section 4), and *nab*-P has been available for this indication in the UK since 27 January 2014. As part of their assessment of benefit-risk balance, the EMA considered the increase of 1.8 months in OS (primary analysis, see Section 4.7) associated with *nab*-P/Gem in comparison with gemcitabine alone to represent a significant clinical benefit over existing therapies for the treatment of patients with metastatic pancreatic adenocarcinoma (mPAC), where the population generally has a very short OS.

The EMA noted that in most subgroups, the treatment effect favoured *nab*-P/Gem; however, as clinical benefit was not demonstrated in patients ≥75 years of age, and the risk of toxicity is also greater in these patients, a warning/precaution for use regarding the use of *nab*-P/Gem for the treatment of patients 75 years and older was included in the summary of product characteristics (SmPC) (characteristic of many cancer drugs), as follows:

"For patients of 75 years and older, no benefit for the combination treatment of Abraxane and gemcitabine in comparison to gemcitabine monotherapy has been demonstrated. In the very elderly (≥75 years) who received Abraxane and gemcitabine, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation including haematologic toxicities, peripheral neuropathy, decreased appetite and dehydration. Patients with pancreatic adenocarcinoma aged 75 years and older should be carefully assessed for their ability to tolerate Abraxane in combination with gemcitabine with special consideration to performance status, co-morbidities and increased risk of infections"

It should be noted that these data are based on very few patients with only 10% of the CA046 population making up the ≥75 years cohort at trial initiation.[21] A lack of data indicating a clear benefit for *nab*-P/Gem in terms of prolonged OS in patients with normal carbohydrate antigen 19-9 (CA19-9) levels prior to the start of treatment is also highlighted; a similar lack of data in patients with renal or hepatic impairment was already reflected in the SmPC.

Regarding safety, the EMA concluded that *nab*-P/Gem mostly induced AEs known to be associated with gemcitabine or *nab*-P monotherapy but at higher frequencies compared to gemcitabine monotherapy, as may be expected *a priori* when adding chemotherapy agents. In recognition of frequent haematology AEs (primarily neutropenia), *nab*-P is contraindicated in patients who have baseline neutrophil counts <1500 cells/mm^3. While the higher rates of AEs were noted as a concern in a palliative setting, the EMA concluded that the majority of AEs may be considered manageable. Alongside the conclusion that the clinical benefit of *nab*-P/Gem is clinically relevant and of significant benefit to a patient population with generally very short OS and for whom only few treatment options are available, the EMA considered the benefit-risk balance of *nab*-P/Gem to be positive.

The European Public Assessment Report (EPAR) for the indication of interest to this submission and the SmPC for *nab*-P are provided in Appendix 1.

In addition to its mPAC indication, *nab*-P is also indicated as monotherapy 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, and in combination with carboplatin for the first-line treatment of non-small cell lung cancer (NSCLC) in adult patients who are not candidates for potentially curative surgery and/or radiation therapy. Outside of Europe, *nab*-P also has been granted regulatory licences in North America, South America, Australia and New Zealand, and Asia (including Japan and Hong Kong) for its mPAC indication.

In the UK, *nab*-P is accepted for use in combination with gemcitabine for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas within NHS Scotland and NHS Wales.[22, 23] *Nab*-P/Gem is not routinely funded in NHS England but could be accessed through the Cancer Drugs Fund (CDF) from March

2014 to November 2015, after which it was removed in preparation for the new approach to the appraisal and funding of cancer drugs in England.

2.3 Administration and costs of the technology

Administration details and costs of *nab*-P/Gem are summarised in Table 4.

Table 4: Costs of the technology being appraised

	Cost/detail	Source
Pharmaceutical formulation	*Nab*-Paclitaxel: powder for suspension for infusion Gemcitabine: solution for infusion	SmPC
Acquisition cost (excluding VAT)*	*Nab*-Paclitaxel: £246.00/100mg vial Gemcitabine: £3.99/200mg vial or £30.89/1g vial	MIMS
Method of administration	*Nab*-Paclitaxel: intravenous infusion (30 minutes) Gemcitabine: intravenous infusion (30 minutes)	SmPC
Doses	*Nab*-Paclitaxel: 125mg/m^2 Gemcitabine: 1,000 mg/m^2	SmPC
Dosing frequency	*Nab*-Paclitaxel: Days 1, 8 and 15 of each 28-day cycle Gemcitabine: Days 1, 8 and 15 of each 28-day cycle (immediately after the completion of *nab*-P administration)	SmPC
Average length of a course of treatment	Treatment should be continued until disease progression or unacceptable toxicity.	SmPC
	Median time on treatment in the pivotal trial was 15 weeks.	*Post hoc* trial analysis (9 May 2013 database lock)
Average cost of a course of treatment	Nab-P/Gem: [redacted]	Economic analysis
Anticipated average interval between courses of treatments	Retreatment is not anticipated.	-
Anticipated number of repeat courses of treatments	Retreatment is not anticipated.	-
Dose adjustments	Dose interruptions or reductions are recommended for neutropenia and/or thrombocytopenia, febrile neutropenia,	SmPC

	Cost/detail	Source
	peripheral neuropathy, cutaneous toxicity and gastrointestinal toxicity.	
Anticipated care setting	Hospital	SmPC
Key: MIMS, Monthly Index of Medical Specialities; SmPC, summary of product characteristics. **Note:** * List price for vial sizes currently available in the UK; 250mg vial for *nab*-Paclitaxel should be available in Q3 2017.		

The patient access scheme (PAS) is a simple financially-based scheme providing a confidential fixed net purchase price (excluding VAT) of [redacted] per 100mg vial (currently equivalent to a [redacted] discount), that will not change even if list prices change.

The discount is applied at the point of invoicing on all NHS supplies for this and all future indications. There is no administration burden above the usual supply of the product on the NHS.

2.4 Changes in service provision and management

No additional tests or investigations are needed outside of those required for the diagnosis of mPAC.

Nab-P should only be administered under the supervision of a qualified oncologist in units specialised in the administration of cytotoxic agents. Hospital oncology units already have the staffing and infrastructure needed for the administration of cancer treatments; *nab*-P would utilise this existing infrastructure.

Nab-P as an addition to gemcitabine unavoidably does involve some further resource use compared to gemcitabine monotherapy. Alongside acquisition of the drug itself, treatment requires an additional 30-minute infusion on each treatment day. Combination therapy is also associated with additional toxicity and, therefore, additional AE management needs. No additional monitoring is required outside of observation for common AEs that the patient would also undergo on gemcitabine monotherapy (safety monitoring is associated with all cancer drugs), and no concomitant medications are routinely prescribed. Most AEs are considered generally manageable, and circumstances in which temporary dose interruptions or dose reductions are recommended are outlined in the SmPC.

All additional resource requirements are fully accounted for in the economic modelling presented in Section 5.

2.5 Innovation

Pancreatic cancer is an aggressive and life-threatening malignancy for which there have been few therapeutic advances. mPC has an extremely poor prognosis, with median survival estimated at between 2 to 6 months.[5] The development of new treatments for mPC has been very limited in recent years, and despite numerous clinical trials, there has only been a modest improvement in life expectancy.[24]

Gemcitabine-based therapy has been the standard of care for the first-line treatment of patients with unresectable locally advanced pancreatic cancer (uLAPC) or mPC since 1997 and is still the only single agent licensed in Europe, associated with a median survival of 5–7 months.[24] A decade on, erlotinib added to gemcitabine achieved modest (yet significant) improvements in median OS compared with gemcitabine monotherapy (6.2 months vs 5.9 months[25]), resulting in a marketing authorisation being granted for this doublet[26]; however, this marginal benefit came at the expense of additive toxicity, and the risk-benefit of this doublet is a controversial topic[27] such that it is rarely used in UK practice. Prior to *nab*-P/Gem, no other chemotherapy doublet demonstrated a significant survival benefit over gemcitabine monotherapy for the treatment of mPAC in a Phase III trial setting. In a Phase II/III trial not designed for registration, a significant survival benefit for patients with mPAC was observed with the combination regimen of leucovorin, fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) compared with gemcitabine monotherapy (11.1 months vs 6.8 months[28]); however, this regimen has often been found to be poorly tolerated, except by very fit patients, and modified versions with unproven efficacy in the context of a randomised controlled Phase III clinical trial are often adopted in clinical practice in an attempt to improve tolerability of the regimen.[29]

There is clearly a high level of unmet need associated with mPAC. This was previously acknowledged by NICE, who recognised that current treatments are limited in efficacy or associated with significant AEs such that additional treatment options in this area would be of value.[12]

Nab-P is an innovative formulation of paclitaxel that facilitates selective and efficient accumulation of active treatment at the tumour site; pre-clinical modelling indicates

that when *nab*-P is administered alongside gemcitabine, a novel, synergistic effect is observed (see Section 2.1). We have been advised by clinical experts that this represents an innovation in the context of treating mPC.[11]

In the pivotal, regulatory Phase III trial, CA046, *nab*-P/Gem became the first chemotherapy doublet to demonstrate both a statistically significant *and* clinically meaningful survival benefit (defined as 6–8 weeks by people affected by pancreatic cancer[7]) over established standard of care (gemcitabine monotherapy) (see Section 4.7). While some additive toxicity was observed (as expected *a priori*), the *nab*-P/Gem regimen was generally well tolerated, with the majority of AEs potentially manageable through dose modification (see Section 4.12).

While the health-related benefits to patients should be captured in the QALY, the fact that *nab*-P/Gem offers a licensed treatment option with an innovative mechanism of action proven to improve life expectancy for patients with mPAC should be considered a 'step-change' in the management of this condition with extremely high unmet need. Furthermore, the more emotional aspects of an extension to life and the benefit of a life-extending medicine to the family and friends of a patient with a life-threatening malignancy should be considered, and these will not be captured in the QALY. These benefits were recognised by Pancreatic Cancer UK as part of their Two More Months campaign, launched in February 2014 in an attempt to ensure *nab*-P was available for use via the NHS across the UK.[30] This campaign illustrates how access to *nab*-P could give mPAC patients and their families the ability to achieve particular personal ambitions at the end of their life. More broadly, preventing people from dying prematurely is one of the NHS Outcomes Framework measures for 2016–2017, and access to novel medicines for cancer provides wider societal reassurance that the NHS remains true to the promise of healthcare for all.

3. Health condition and position of the technology in the treatment pathway

3.1 Disease overview

Pancreatic cancer is a disease in which malignant cells form in the tissues of the pancreas. Although pancreatic cancers can form in either the exocrine or endocrine parenchyma, the vast majority start in the cells of the exocrine pancreas, with

pancreatic adenocarcinoma (PAC) accounting for approximately 80–95% of all pancreatic cancers.[3, 5] Most commonly, cancer originates in the head of the pancreas (approximately 75% of all cases), but it can also start in the body or tail.[5] In the case of mPAC, cancer originates in the pancreas but thereafter spreads to other areas of the body, with the most common sites of metastases being the liver, peritoneum, lungs and bones.[5]

Cases of pancreatic cancer in the UK are evenly split between males and females, but pancreatic cancer is more common in White and Black people than in Asian people.[1] In England, pancreatic cancer is also more common in people living in the most deprived areas.[1] Approximately half (47%) of all pancreatic cancer cases are diagnosed in people aged ≥75 years, with cases in people under 40 years of age uncommon.[1]

There is no single known cause of pancreatic cancer, but there are a number of clinical, genetic and environmental risk factors alongside the demographic factors that increase the risk of pancreatic cancer. These include pancreatitis (chronic or hereditary), diabetes, *BRCA* mutation, obesity and smoking, and to a lesser extent previous cancer, hepatitis, *Helicobacter pylori* infection, alcohol (often associated with chronic pancreatitis) and diet.[3, 5, 31]

Pancreatic cancer is an extremely aggressive and life-threatening malignancy. With mortality rates stabilising or increasing rather than declining, it is thought that pancreatic cancer may become the third leading cause of death from cancer in the EU by 2025 (after lung and colorectal cancers).[32] As the disease often remains asymptomatic at early stages, a high percentage of patients are diagnosed at an advanced stage. Only 30–40% of all patients present with disease confined to the pancreatic region[3] and in England, 79% of patients are diagnosed at Stage III or IV.[1] Metastatic disease has a particularly poor prognosis, with median survival estimated at between 2 to 6 months[5]; this depends on the size of the tumour and where it has spread (see Section 3.4). In addition to the extent of metastases, worse prognosis is also associated with poor performance status, pancreatic head tumour location and presence of biliary stent, and elevated CA19-9.[33, 34]

3.2 Effect of disease on patients, carers and society

Patients with mPAC experience a variety of complications and disease-related symptoms, all of which affect normal living.

Pancreatic cancer is typically symptomless in the early stages, but as it grows and spreads, symptoms can manifest (hence why most cases are diagnosed at an advanced stage). The exact symptoms a patient may experience will depend on the type of pancreatic cancer as well as its location. Common symptoms associated with adenocarcinoma include pancreatic insufficiency, weight loss, jaundice (head tumours) and abdominal/back pain (body-tail tumours).[5, 31] Patients with mPAC may also experience additional symptoms associated with the site of metastases. For example, liver metastases can be associated with a swollen and painful abdomen, nausea, fatigue, and weight loss; while lung metastases can cause dyspnoea, persistent cough and chronic chest infections.[35]

We might expect patients with pancreatic cancer to experience some detrimental impact on quality of life as a result of their disease, and there are some reports of reduced quality of life in the literature; particularly with regard to mental health that appears to worsen with advanced disease, likely as a result of their poor prognosis.[36] However, formal assessment of health-related quality of life (HRQL), resulting in a single health index (utility), shows a similar index score between patients with advanced pancreatic cancer (APC) who are receiving active treatment (gemcitabine) and the general population (see Section 5.4).[37]

Alongside the direct economic burden captured in the economic modelling (see Section 5), it is also important to consider the wider societal burden. For patients who are actively employed, the cost of productivity loss has been estimated to be as high as €87,205 (approximately £74,228).[36] Given the poor prognosis of patients with mPC, there is also a societal burden of disease due to premature mortality. In Europe, the cost to society of premature death due to pancreatic cancer is estimated at €3.9 billion (approximately £3.3 billion) (2008 data).[38]

3.3 Clinical pathway of care

The NICE pathway for pancreatic cancer recommends that people with mPAC are treated with gemcitabine as a first-line treatment if they have a Karnofsky

Performance Status (KPS) score of 50 or more. This recommendation was made in 2001, and no positive recommendations for alternative treatments have been made since. As such, gemcitabine monotherapy is the established standard of care for the first-line treatment of mPAC in England.

European and US clinical guidelines do have additional recommendations for the first-line treatment of mPAC (see Section 3.5), most noticeably the preferential use of FOLFIRINOX or *nab*-P/Gem for patients considered well enough to tolerate a more aggressive treatment approach and the use of *nab*-P/Gem for patients with poor performance status caused by high tumour burden. These regimens are the only treatments to show both a statistically significant and a clinically meaningful survival benefit (6–8 weeks according to patients[7]) over gemcitabine monotherapy in the last 20 years.

FOLFIRINOX is not a licensed regimen, and as a combination of generic treatments, it is unlikely to go through regulatory approval. FOLFIRINOX is an intensive therapy, associated with high administration burden and considerable toxicity (see Section 3.6). It is therefore only suitable for a subgroup of mPAC patients who, while not strictly definable by one clinical parameter, can be easily identified in clinical practice. An expert panel of treating clinicians in NHS England recently confirmed that patients who are considered suitable for FOLFIRINOX will continue to receive this regimen despite the accessibility of *nab*-P; that is, *nab*-P/Gem will not replace the use of FOLFIRINOX, and FOLFIRINOX should therefore not be considered a relevant comparator to *nab*-P/Gem in this appraisal.[11] The same expert panel were involved in a workshop that confirmed patients who currently receive FOLFIRINOX are an easily identifiable, clinically distinct patient group to those who currently receive gemcitabine and could receive *nab*-P/Gem in clinical practice.[11] In summary (though of note, patient preference is also taken into account):

- FOLFIRINOX is used to treat patients who are ≤70 years old, have an ECOG performance status of 0-1 and have very minor comorbidities (e.g. well-controlled hypertension).
- Gemcitabine monotherapy is used to treat patients of any age, who have an ECOG performance status of ≥2.

- *Nab*-P/Gem would be used to treat patients of any age (with use in those over 80 years of age not necessarily excluded due to real world evidence supporting its use in an older population [see Section 4.12]), who have an ECOG performance status of 0-1 and for whom treatment with FOLFIRINOX is not considered suitable.

There is also some first-line use of gemcitabine plus capecitabine (Gem/Cap) in NHS England. As with FOLFIRINOX, Gem/Cap is not licensed for the treatment of mPAC, and is unlikely to go through regulatory approval, as generic versions of both treatments are available. Unlike FOLFIRINOX, Gem/Cap has not demonstrated a significant survival benefit over gemcitabine monotherapy in a Phase III randomised controlled trial (RCT), and is not recommended in clinical guidelines (see Section 3.6). Its use is therefore limited to very few centres across the UK, and it should not be considered a national standard of care. An expert panel of treating clinicians in NHS England recently confirmed that patients who do have access to Gem/Cap in current practice will continue to receive Gem/Cap despite the accessibility of *nab*-P; that is, *nab*-P/Gem will not replace the very limited use of Gem/Cap, and Gem/Cap should therefore not be considered a relevant comparator to *nab*-P/Gem in this appraisal.[11]

Market research based on patient chart audit, to provide treatment data based on real patient cases, clearly shows consistent use of FOLFIRINOX and gemcitabine doublet (likely to be Gem/Cap in the first-line setting), irrespective of *nab*-P/Gem funding, as depicted in Figure 2. Of the patients on treatment in the 6 months prior to Q2 2015 analysis in the UK (n=232), [redacted] of mPAC patients received gemcitabine monotherapy at first-line, [redacted] received the FOLFIRINOX regimen, and [redacted] received gemcitabine doublet therapy. During this time, *nab*-P/Gem was only funded through the CDF in England, with funding in Scotland coming in post SMC acceptance in February 2015, and funding in Wales coming in post AWMSG acceptance in September 2015. Of the patients treated in the 6 months prior to Q4 2015 analysis in the UK (n=186 in the chart audit), the proportion receiving gemcitabine monotherapy at first-line decreased to [redacted], while the proportion receiving the FOLFIRINOX regimen and gemcitabine doublet therapy remained practically the same, at [redacted] and [redacted], respectively. During this same period, uptake of *nab*-P/Gem increased, with [redacted] of mPAC patients treated with *nab*-P/Gem in the

first-line setting in the Q2 2015 analysis and [redacted] of mPAC patients treated with *nab*-P/Gem in the first-line setting in the Q4 2015 analysis. This market research demonstrates both the primary displacement of gemcitabine monotherapy with *nab*-P/Gem uptake and clear support from the clinical community for *nab*-P/Gem. This market research therefore clearly demonstrates that the accessibility of *nab*-P/Gem did not displace the use of either FOLFIRINOX or Gem/Cap in clinical practice.

The face validity of this market research is supported with data from the Systemic Anti-Cancer Therapy (SACT) dataset for NHS England, which reports that [redacted] of pancreatic cancer patients were treated with gemcitabine monotherapy in 2014 (irrespective of treatment line); [redacted] of pancreatic cancer patients were treated with FOLFIRINOX, [redacted] of patients were treated with gemcitabine doublet (other than *nab*-P/Gem), and [redacted] of patients were treated with *nab*-P/Gem.[39] However, interpretation of these data are limited by the fact that the SACT dataset does not collect line of therapy; thus, these data span settings from adjuvant treatment through to second-line treatment for metastatic disease.

[redacted]

[redacted]

[redacted]

Comparative efficacy and cost-effectiveness analyses versus FOLFIRINOX and Gem/Cap are provided within this submission for completeness. However, while their inclusion in the decision problem reflects a comprehensive insight into individual centres in England and individual patients, it is not applicable to all patients across NHS England, and these regimens should thus not be considered uniformly established standards of care. Moreover, considering that market research data and clinical consultation confirm that *nab*-P/Gem will not replace the use of FOLFIRINOX and Gem/Cap, these regimens are not relevant comparators to *nab*-P/Gem, which will only replace the use of gemcitabine monotherapy for appropriate patients. NICE previously acknowledged that there is a clinically recognisable group of patients who receive gemcitabine alone instead of FOLFIRINOX or Gem/Cap in clinical practice.[12] These are patients for whom *nab*-P/Gem would provide an alternative treatment with improved clinical benefit. In the pivotal, regulatory Phase III RCT, CA046, *nab*-

P/Gem demonstrated both a statistically significant *and* clinically meaningful survival benefit (defined as 6–8 weeks by people affected by pancreatic cancer[7]) over gemcitabine monotherapy (see Section 4.7). Gem/Cap, the only other chemotherapy doublet utilised at any level in the UK (albeit sparsely in a few centres), has failed to show a statistically significant survival benefit in a Phase III RCT.

3.4 Life expectancy and patient population

Pancreatic cancer is a particularly aggressive and life-threatening malignancy. In 2014, there were around 8,800 pancreatic cancer deaths in the UK (7,430 in England), which aligns to 24 deaths every day, making it the fifth most common cause of cancer death.[1] Of people diagnosed with pancreatic cancer in England between 2005 and 2009, less than 20% survived beyond 12 months, and less than 4% survived to 5 years.[2] Similar observations were made for people diagnosed between 2010 and 2011 in England and Wales, 21% of whom survived beyond 12 months, and 3% of whom survived to 5 years.[1] We can assume survival rates are still as low in current practice considering the lack of therapeutic advancement. One reason for this poor prognosis is that pancreatic cancer is often diagnosed at an advanced stage. For patients with mPC, median survival is estimated at only 2 to 6 months, depending on how much the cancer has grown and where it has spread.[5]

The latest incidence estimates for pancreatic cancer in the UK are based on 2013 data, when there were around 9,400 new cases (7,887 in England), which aligns to 26 people diagnosed every day.[1] Of all pancreatic cancer cases, 80–95% are adenocarcinoma[3, 5], and only 30–40% of all patients present with disease confined to the pancreatic region.[3] Therefore, the maximum number of patients with mPAC in England is estimated to be 5,245. Not all patients with mPAC are suitable for chemotherapy. Expert opinion is that 50–60% of patients with mPAC receive chemotherapy in NHS England. The maximum number of patients eligible for treatment within this indication in England is therefore estimated at 3,147.

3.5 Relevant NICE guidance and clinical guidelines

NICE is developing a guideline specific to pancreatic cancer, but publication is not expected until January 2018. At present, recommendations for the treatment of pancreatic cancer are captured within the NICE pathway for gastrointestinal cancers.

NICE guidance and additional clinical guidelines of relevance to this submission are summarised in Table 5.

Table 5: Relevant NICE guidance and clinical guidelines

Organisation	Title	Date	Summary
NICE guidance			
NICE STA No. 25[4]	Guidance on the use of gemcitabine for the treatment of pancreatic cancer	2001	NICE has recommended that: - People with advanced or metastatic pancreatic cancer may be treated with gemcitabine as a first-line treatment if they have KPS ≥50. - Gemcitabine should not be used for people with pancreatic cancer who are suitable for surgery that may cure their cancer, or those who have KPS <50. - Gemcitabine should not be used as a second-line treatment for people with pancreatic cancer, because there is insufficient evidence to support this practice.
Clinical guidelines			
ESMO[3]	Cancer of the pancreas: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up	2015	The following treatment options should be considered for the treatment of patients with metastatic pancreatic cancer according to their general status: - If the ECOG PS of the patient is 0 or 1 and the bilirubin level is below 1.5 x ULN, two types of combination chemotherapy – the FOLFIRINOX regimen or the combination of gemcitabine and *nab*-P – should be considered [I, A]. - For patients with ECOG PS of 2 and/or bilirubin level higher than 1.5 x ULN, monotherapy with gemcitabine could be considered [I, A]. - In very selected patients with ECOG PS 2 due to heavy tumour load, gemcitabine and *nab*-P can be considered for best chance of response [II, B]. - For patients with ECOG PS of 3/4 with significant morbidities and very short life-expectancy, only symptomatic treatment can be considered.
ASCO[41]	Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice	2016	Key treatment recommendations for first-line therapy: - FOLFIRINOX is recommended for patients who meet all the following criteria: ECOG PS 0/1, favourable comorbidity profile,

Organisation	Title	Date	Summary
	Guideline		patient preference and support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services (strong). - Gemcitabine plus *nab*-P is recommended for patients who meet all the following criteria: ECOG PS 0/1, relatively favourable comorbidity profile, patient preference and support system for relatively aggressive medical therapy (strong). - Gemcitabine alone is recommended for patients who have either an ECOG PS 2 or a comorbidity profile that precludes more-aggressive regimens and who wish to pursue cancer-directed therapy. The addition of either capecitabine or erlotinib to gemcitabine may be offered in this setting (moderate). - Patients with an ECOG PS ≥3 or with poorly controlled comorbid conditions despite ongoing active medical care should be offered cancer-directed therapy only on a case-by-case basis. The major emphasis should be on optimising supportive care measures (moderate).
NCCN[42]	NCCN Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 2.2016	2016	Preferred first-line therapy for patients with good PS (defined as ECOG PS 0/1 with good pain management, patent biliary stent, and adequate nutritional intake): - Clinical trial - FOLFIRINOX (category 1) - Gemcitabine plus *nab*-P (category 1) - FOLFIRINOX should be limited to patients with ECOG PS 0/1; gemcitabine plus *nab*-P is reasonable for patients with KPS ≥70 Alternative first-line therapy options for patients with good PS: - Gemcitabine plus erlotinib (category 1) - Gemcitabine-based combination therapy - Gemcitabine monotherapy (category 1) - Capecitabine or continuous infusion 5-FU (category 2B) - Fluoropyrimidine plus oxaliplatin (category 2B) First-line therapy options for patients with poor PS: - Gemcitabine (category 1) - Palliative and best supportive care

Organisation	Title	Date	Summary
Key: 5-FU, fluorouracil; ASCO, American Society of Clinical Oncology; ECOG, Eastern Cooperative Oncology Group; ESMO, European Society for Medical Oncology; FOLFIRINOX, leucovorin, fluorouracil, irinotecan and oxaliplatin; KPS, Karnofsky Performance Status; *nab*-P, *nab*-Paclitaxel; NCCN, National Comprehensive Cancer Network; NICE, National Institute of Health and Care Excellence; PS, performance status; STA, single technology appraisal; ULN, upper limit of normal.			

3.6 Issues relating to clinical practice

Established standard of care for patients with mPAC in NHS England is restricted to gemcitabine monotherapy as this is the only therapy that is licensed for the treatment of pancreatic cancer, and that is recommended by NICE (see Section 3.3).

Although gemcitabine monotherapy demonstrated significant clinical benefit over conventional fluorouracil in clinical trials initiated in the 1990s, this agent has limited effectiveness in clinical practice (current life expectancy of patients with mPC is estimated at ≤6 months[5]). Despite this limited effectiveness, very few alternative treatments have been able to demonstrate a significant improvement in OS over gemcitabine alone, such that gemcitabine monotherapy remains established standard of care in the absence of a better option.

Outside of *nab*-P/Gem (see Section 4.7), the only regimen to show both a statistically significant and a clinically meaningful survival benefit (6–8 weeks according to patients[7]) over gemcitabine monotherapy in a Phase II/III trial setting is FOLFIRINOX.[28] This regimen is not licensed for the treatment of mPAC and is an intensive therapy: the administration schedule of FOLFIRINOX requires chemotherapy port and infusion pump management services, and there are perceived toxicity concerns associated with concurrent administration of multiple, toxic chemotherapy agents. A recent survey of physician experience with intensified chemotherapeutic options for mPC across Europe reported that *"FOLFIRINOX was more toxic and associated with a higher burden of adverse events as reflected in the estimated higher likelihood of protocol deviation and higher rates of neutropenia, polyneuropathy, worsening performance status, and need for nutritional support"*.[43] In NHS England, there is some first-line use of FOLFIRINOX, but a lack of organisational infrastructure and clinical expertise to support the administration and AE management needs means the use of the FOLFIRINOX regimen is not uniform across all treatment centres in England.

There are reports of some treatment centres modifying the FOLFIRINOX regimen in an attempt to reduce its toxicity and administration burden, often after full dose induction; however, no standard modification can be defined, and the clinical efficacy of any modified versions of FOLFIRINOX is uncertain, with no conclusive RCT data supporting their use over established standard of care (gemcitabine monotherapy).[29] In the clinical systematic literature review (SLR) described in Section 4.1, no RCTs were identified that investigated a modified version of the FOLFIRINOX regimen. A single RCT was identified that investigated FOLFOX which consists of three of the four agents making up the FOLFIRINOX regimen (leucovorin, fluorouracil and oxaliplatin) (PAN1).[44] Within this study, a survival benefit was not observed with FOLFOX compared with gemcitabine alone. However, this study had to be prematurely terminated due to inability to recruit enough patients to make the trial scientifically viable; thus, final survival analyses are based on only 16 patients.

In a few centres in NHS England, there is some limited use of Gem/Cap. Again, this regimen is not licensed for the treatment of mPAC, but in addition, its clinical effectiveness (regarding survival benefit) has not been established in the metastatic setting, with Gem/Cap failing to show a significant OS benefit over gemcitabine monotherapy in several individual Phase III RCTs.[45-47] As such, it is not recommended in European clinical guidelines and has not been uniformly adopted in clinical practice. Although a positive meta-analysis combining three Phase II/III trials showed a marginally significant OS benefit for Gem/Cap versus gemcitabine[45], this meta-analysis retrospectively attempts to show a result (a statistically significant OS benefit between Gem/Cap and gemcitabine) that was not observed in any of the original individual prospective trial data. Thus this analysis was not that well received in clinical circles.

Such variation and uncertainty in clinical practice with respect to these off-licence regimens was acknowledged by the Evidence Review Group (ERG) during the previous appraisal for *nab*-P/Gem.[48] Therapeutic advancements have not been made since this time; thus, this variation and uncertainty is unchanged, and gemcitabine monotherapy remains the only uniformly established standard of care.

Limitations associated with treatments named in the decision problem are summarised in Table 6. This table has been validated by a group of treating clinicians in the UK.[11]

Table 6: Issues with treatments named in the decision problem

Treatment	Summary of key issues	Relevance to decision problem
Gemcitabine monotherapy	- Limited effectiveness with an associated median OS of ≤6 months	Key comparator
Gemcitabine plus capecitabine	- Not a licensed regimen for the treatment of mPAC - Uncertain effectiveness regarding OS benefit, with no single Phase III RCT showing a significant OS benefit - Not uniformly utilised across treatment centres in England	Cannot be considered national standard of care Would not be replaced by *nab*-P/Gem
FOLFIRINOX	- Not a licensed regimen for the treatment of mPAC - Only an appropriate treatment option for a clinically defined group of patients - Tolerability concerns associated with concurrent administration of multiple toxic chemotherapy agents means it is not a treatment option for many patients - Often modified but no uniform modification with proven effectiveness - Access to chemotherapy port and infusion pump management services required - Home administration burden with a district nurse home visit often required for each treatment cycle - Not uniformly accessible across treatment centres in England	Would not be replaced by *nab*-P/Gem

Key: FOLFIRINOX, leucovorin, fluorouracil, irinotecan and oxaliplatin; mPAC, metastatic pancreatic adenocarcinoma; OS, overall survival; RCT, randomised controlled trial.

3.7 Equality

No equality issues related to the use of *nab*-P have been identified or are foreseen. As part of the previous appraisal, no issues relating to equality considerations were raised during consultation or in the Committee meetings.[12]

4. Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1. Search strategy

An SLR designed to identify studies of *nab*-P/Gem and potential comparator therapies was initiated in May 2013 and updated in March 2014 and July 2016. Information retrieval methods were based upon the research question "what is the clinical efficacy and tolerability of *nab*-P/Gem and comparator therapies for the treatment of advanced pancreatic cancer?"

Searches were performed in the following electronic databases:

- MEDLINE and MEDLINE In-Process
- Embase
- The Cochrane Library, including:
  - Cochrane Central Register of Controlled Trials (CENTRAL)
  - The Cochrane Database of Systematic Reviews (CDSR)
  - Database of Abstracts of Reviews of Effectiveness (DARE)
  - Database of Health Technology Assessments (HTA)
- The Cumulative Index to Nursing and Allied Health (CINAHL)

In addition, 2012–2016 proceedings of the following conferences were hand-searched in order to identify any relevant, on-going research:

- The American Society of Clinical Oncology (ASCO) Annual Meeting
- ASCO Gastrointestinal Cancers Symposium (GICS or ASCO GI)
- The European Society for Medical Oncology (ESMO) Annual Meeting
- ESMO European Cancer Congress (ECC)
- ESMO World Congress on Gastrointestinal Cancer (World GI)

Reference lists of existing SLRs/meta-analyses identified through systematic searches were also hand-searched to identify any additional trials of relevance to the research question.

The search strategies used for clinical effectiveness searches are provided in Appendix 2. These strategies were developed by a team of information specialists at the School of Health and Related Research (ScHARR) and were endorsed by the ERG as part of the previous appraisal who were *"confident that the search strategies employed by the manufacturer are appropriate and sufficiently comprehensive to be able to identify all relevant studies"*.[48]

4.1.2. Study selection

At the time of protocol development, the exact indication for *nab*-P/Gem in pancreatic cancer, and the resulting comparators of interest to reimbursement agencies were unconfirmed. To accommodate all positioning options, primary eligibility of wide scope was applied in accordance with the criteria presented in Appendix 2. In summary, RCTs of any design that compared the clinical efficacy of the stated interventions (used either as monotherapy or in combination with any other therapy) with any other active treatment in adult patients with APC, of whom at least half had metastatic disease that appeared to be previously untreated, were included.

Following confirmation of a mPAC indication, and thus confirmation of comparators of interest to reimbursement agencies, secondary eligibility criteria of narrower scope were applied in accordance with Table 7. This allowed the identification of RCTs that directly compared the clinical efficacy and/or tolerability of two or more interventions of interest in adult patients with APC, of whom at least half had previously untreated metastatic disease. Of note, the inclusion criteria for the patient population is still wider in scope than the confirmed mPAC indication within these secondary eligibility criteria. This is because scoping exercises suggested a paucity of RCT evidence exclusive to mPAC patients for all named interventions of interest. Clinical efficacy/tolerability evidence for the mPAC patient population was therefore pre-determined as a specific subgroup of interest. As part of the previous appraisal, the ERG endorsed this approach, considering it *"logical and pragmatic"*.[48]

Table 7: Secondary eligibility criteria applied to systematic search results

	Inclusion criteria	Exclusion criteria
Population	Adult patients APC patients, of whom at least half had metastatic disease No prior systemic therapy for metastatic disease	Paediatric patients Non-pancreatic cancer patients LAPC patients only Prior systemic therapy for metastatic disease
Interventions	Gemcitabine + *nab*-Paclitaxel Gemcitabine monotherapy Gemcitabine + oxaliplatin Gemcitabine + capecitabine Gemcitabine + erlotinib Gemcitabine + cisplatin Gemcitabine + fluourouracil FOLFIRINOX	-
Comparators	Direct comparisons between named interventions of interest	Active treatment comparisons outside of named interventions of interest Non-active treatment comparisons Dosing regimen comparisons
Outcomes	Overall survival Progression-free survival Time to treatment failure Disease control rate Objective response rate Time to response Duration of response Serum CA19-9 Plasma SPARC Safety/tolerability	-
Study type	Randomised controlled trials of any design	Non-randomised trials Non-controlled trials Observational studies
Restrictions	Date: none Language: English abstract	-
Key: APC, advanced pancreatic cancer; CA19-9, carbohydrate antigen 19-9; LAPC, locally advanced pancreatic cancer; SPARC, secreted protein acidic and rich in cysteine.		

Two reviewers independently inspected each reference (title and abstract) identified by the systematic searches and applied study selection criteria. When abstracts were considered potentially relevant (or in the case of disagreement between the two reviewers), the full article was obtained and independently assessed against the eligibility criteria for primary and secondary inclusion. In the event of disagreement between the two reviewers, a third reviewer would have independently inspected the paper, and the applicability of selection criteria would have been attained by consensus. This was not necessary as no disagreements occurred.

Data were extracted from each included full text article by one reviewer, and all extracted data were verified against the original source by a second reviewer, with any discrepancies solved by consensus. If study duplication within publications were suspected, author names, location and setting, specific intervention details, participant numbers, baseline data and date and duration of study were assessed. If uncertainties remained, the authors would have been contacted, but such a need did not arise.

Secondary publications of studies meeting the eligibility criteria of the review were included if they provided data of interest; those providing data not meeting the eligibility criteria of the review and those providing interim data that have since been updated were excluded.

4.1.3. Initial search results (May 2013)

Initial electronic database searches were conducted on 28 May 2013. Conference proceedings of ASCO and ESMO 2011 and 2012 were also searched through the Web of Science (WoS) on this day; however, subsequent assessment of references from key publications highlighted an issue with these searches as a number of potentially relevant abstracts were not identified. As a result, the ASCO website was independently hand-searched for conference proceedings on 5 July 2013. This was not possible for the ESMO conference proceeding searches; therefore, the WoS service centre was asked to rectify the original issue, and searches were re-run via this portal on 9 July 2013.

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the number of studies included and excluded at each stage of the initial review is presented in Appendix 2.

In total, 4,943 unique citations were screened for relevance to the research question. Title and abstract screening resulted in the exclusion of 4,315 citations that were clearly not of relevance; common reasons for exclusion at this stage were non-APC patient populations and non-RCT study designs. A total of 628 citations were obtained in full (where applicable and necessary) for further evaluation. Of these citations, 97 were principal publications of studies meeting the primary eligibility criteria, and a further 12 were associated publications providing additional data of interest to the review. Of the 97 studies meeting the primary eligibility criteria, 16 also met the secondary eligibility criteria of the review.

Record of the 628 citations obtained in full and reasons for inclusion/exclusion against both the primary and secondary eligibility criteria is available as a separate Microsoft Excel® workbook that can be provided on request.

4.1.4. Updated search results (March 2014)

Electronic database searches were updated between 14–18 March 2014. Conference proceedings of ASCO and ESMO 2013 were also searched through the WoS at this time, but due to concerns with this platform (highlighted within the initial review), conference proceedings of the ASCO GICS 2014, the ESMO ECC 2013 and the ESMO World GI 2013 were also hand-searched on 1 April 2014.

A PRISMA flow diagram showing the number of studies included and excluded at each stage of the review update is presented in Appendix 2.

In total, 549 unique citations were screened for relevance to the research question. Title and abstract screening resulted in the exclusion of 407 citations that were clearly not of relevance for common reasons as per the initial review (non-APC patient populations and non-RCT study designs). A total of 142 citations were obtained in full (where applicable and necessary) for further evaluation. Of these citations, 6 were principal publications of studies meeting the primary eligibility criteria, and 2 were associated publications that provided additional data of interest. Of the 6 studies meeting the primary eligibility criteria, none met the secondary eligibility criteria of the review.

Of note, this PRISMA flow diagram has been updated from the original submission to reflect the mistaken identity of a citation reported by Chao *et al.*[49] as a principal publication rather than an associated publication to a trial identified in the initial

search results (Li *et al.* 2004[50]). This was flagged by the ERG as part of the previous appraisal but was not picked up during the review update due to the considerable differences in the data reported. This is discussed further in Section 4.10.

4.1.5. Updated search results (July 2016)

Electronic database searches were further updated between 13–24 July 2016. Due to previous issues with the WoS interface, conference proceedings of ASCO and ESMO 2014 to 2016 were hand-searched between 16–17 August 2016.

A PRISMA flow diagram showing the number of studies included and excluded at each stage of the review update is presented in Appendix 2.

In total, 1,227 unique citations were screened for relevance to the research question. Title and abstract screening resulted in the exclusion of 1,067 citations that were clearly not of relevance for common reasons as per the initial review and first update (non-APC patient populations and non-RCT study designs). A total of 137 citations were obtained in full (where applicable and necessary) for further evaluation. Of these citations, 18 were principal publications of studies meeting the primary eligibility criteria, and 31 were associated publications that provided additional data of interest to the review. Of the 18 studies meeting the primary eligibility criteria, 1 also met the secondary eligibility criteria.

4.2 List of relevant randomised controlled trials

The pivotal, regulatory Phase III RCT, CA046, provides direct evidence on the clinical benefits of *nab*-P/Gem versus gemcitabine monotherapy for the first-line treatment of mPAC, as detailed in Table 8. Enrolling 861 patients in total, CA046 (also known as MPACT but referred to as CA046 throughout this submission) provides the largest dataset for the first-line treatment of mPAC to date.

Table 8: List of relevant RCTs

Trial name (NCT number)	Population	Intervention	Comparator	Primary study reference
CA046 (NCT00844649)	Adult patients with previously untreated mPAC and KPS ≥70	*Nab*-Paclitaxel plus gemcitabine (n=431)	Gemcitabine monotherapy (n=430)	Von Hoff *et al.* 2013[6]
Key: KPS, Karnofsky Performance Status; mPAC, metastatic pancreatic adenocarcinoma.				

In addition to the primary study reference, data for CA046 have been published in numerous secondary study references, details of which are listed in Appendix 3. Further data required for submission completion are taken from the clinical study report (CSR).[21]

4.3 Summary of methodology of the relevant randomised controlled trials

Details of the methodology of CA046 are presented in Table 9.

CA046 is an international, multicentre, open-label Phase IIII RCT, designed to evaluate the efficacy and safety of *nab*-P/Gem in comparison with established standard of care (gemcitabine monotherapy) for the first-line treatment of mPAC.

Patients were randomised to treatment in a 1:1 ratio with stratification for key prognostic factors, pre-defined as geographical region, KPS and presence of liver metastases. Patients treated with *nab*-P/Gem initially received *nab*-P at a dose of 125mg/m^2, but dose modifications, including dose interruptions and a maximum of two dose reductions, were allowed for toxicity management. Similar dose modifications are detailed in the final SmPC (Appendix 1). Treatment continued until the patient experienced progressive disease (PD) or unacceptable toxicity.

The primary endpoint in CA046 was OS, and secondary endpoints were predefined as PFS and ORR, assessed against standard Response Evaluation Criteria in Solid Tumor (RECIST) (v1.0) by independent radiological review (IRR), and safety and tolerability. Other efficacy endpoints included further response analyses, investigator assessment of PFS and ORR, and investigations of correlations between various potential biomarkers for response and survival. HRQL data were not captured in the CA046 study.

Table 9: Summary of CA046 methodology

Location	151 sites in North America, Australia, Russia, Italy, Canada, Ukraine, Spain, Germany, Austria, France and Belgium.
Trial design	Phase III, international, multi-centre, open-label RCT. Randomisation was stratified by key prognostic factors: geographic region (North America vs other), baseline KPS (70–80 vs 90–100), and presence of liver metastases (yes vs no).
Eligibility criteria for participants	Inclusion criteria included: • Histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas; • Initial diagnosis of metastatic disease must have occurred ≤6 weeks prior to randomisation in the study; • One or more metastatic tumours measurable by CT scan; • No previous radiotherapy, surgery, chemotherapy, or investigational therapy for treatment of metastatic disease: - Prior treatment with fluorouracil or gemcitabine administered as a radiation sensitiser in the adjuvant setting allowed, provided at least 6 months had elapsed since completion of last dose and no lingering toxicities were present; - Patients having received cytotoxic doses of gemcitabine or any other chemotherapy in the adjuvant setting were not eligible; • Men or women (nonpregnant and nonlactating), age ≥18 years; • Baseline blood counts of: - Absolute neutrophil count ≥1.5 x 10^9/L; - Platelet count ≥100,000/mm^3 (100 x 10^9/L); - Haemoglobin ≥9g/dL; • Baseline chemistry of: - Aspartame aminotransferase, alanine aminotransferase ≤2.5 x ULN, unless liver metastases are clearly present, then, ≤5 x ULN; - Total bilirubin ≤ULN; - Serum creatinine within normal limits or calculated creatinine clearance ≥60 mL/min/1.73 m^2 for patients with serum creatinine levels above the institutional normal value; • Acceptable coagulation studies; • KPS ≥70. Exclusion criteria were: • Patients with islet cell neoplasms; • Known brain metastases unless previously treated and well controlled for at least 3 months; • Only locally advanced disease; • Coumadin use; • Known infection with HIV, hepatitis B, or hepatitis C; • Active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy; • Major surgery, excluding diagnostic surgery ≤4 weeks prior to Day 1

	of treatment; • History of allergy or hypersensitivity to the study drug; • Patients with serious medical risk factors involving any of the major organ systems; • History of malignancy in the last 5 years excluding prior history of in situ cancer or basal or squamous cell skin cancer: - Patients with other malignancies were eligible if they were cured by surgery alone or surgery plus radiotherapy and patients were continuously disease-free for ≥5 years; • History of connective tissue disorders; • History of interstitial lung disease, slowly progressive dyspnoea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies; • History of chronic leukaemias; • High cardiovascular risk; • History of peripheral artery disease.
Settings and location where the data were collected	Blinded, independent, central reviews of the CT/MRI/PET scans were performed globally by ICON Medical Imaging in Warrington, PA. Laboratory samples were analysed by a central laboratory: ACM Global Central Laboratory in Rochester, New York, US (US and Canada), ACM United Kingdom (Austria, Belgium, France, Germany, Italy, Spain, Russian Federation, and Ukraine), and Dorevitch, Heidelberg, Australia (Australia). However, local laboratory results were utilised to make immediate treatment decisions. Tissue samples for IHC analysis of tissue SPARC or osteonectin were prepared and stored by St. John's Health Center (Santa Monica, CA, USA). The IHC assay of SPARC was performed by Hospital De Madrid (Madrid, Spain). Plasma samples for potential SPARC analysis were stored at ACM Global Central Laboratory in Rochester, New York, US (US and Canada), ACM United Kingdom (Austria, Belgium, France, Germany, Italy, Spain, Russian Federation, and Ukraine), and Dorevitch, Heidelberg, Australia (Australia). CA19-9 analysis was performed locally. Statistical analyses of the clinical data and CSR preparation were performed by the manufacturer.
Trial drugs	***Nab*-Paclitaxel plus gemcitabine (n=431)**: 30–40 minute IV infusion of *nab*-Paclitaxel (125mg/m^2) followed by a 30–40 minute IV infusion of gemcitabine (1,000 mg/m^2) on Days 1, 8, 15, 29, 36 and 43 of a 56-day cycle in Cycle 1 only and on Days 1, 8 and 15 of a 28-day cycle in Cycle 2 and onward. **Gemcitabine (n=430)**: 30–40 minute IV infusion of gemcitabine (1,000 mg/m^2) on Days 1, 8, 15, 29, 36 and 43 of a 56-day cycle in Cycle 1 only and on Days 1, 8 and 15 of a 28-day cycle in Cycle 2 and onward. Treatment continued until PD or unacceptable toxicity. Dose modifications including a maximum of two dose reductions were allowed from the original dose for toxicity management, as detailed in the below table:

Dose level	*Nab*-P	Gemcitabine

	<table><tr><td>Study dose</td><td>125mg/m^2</td><td>1,000mg/m^2</td></tr><tr><td>-1</td><td>100mg/m^2</td><td>800mg/m^2</td></tr><tr><td>-2</td><td>75mg/m^2</td><td>600mg/m^2</td></tr></table> Following dose reduction, no dose re-escalation was permitted for the duration of the study.* Patients experiencing study drug-related AEs that required a dose delay >21 days were discontinued from further treatment.
Permitted and disallowed concomitant medication	Supportive care was administered at the discretion of the investigator; this included antiemetic prophylaxis, recommended due to the administration of gemcitabine. Anticoagulation medication was allowed as part of supportive care but low molecular weight heparin was used instead of Coumadin, which was prohibited. All concomitant medications and prior medications taken within 30 days of first study drug administration were recorded. Radiotherapy was not allowed during the study. Administration of other chemotherapy, immunotherapy, or antitumour hormonal therapy during the study was also prohibited.
Primary outcome	OS: defined as the time from randomisation to death from any cause. Survival assessments post-study treatment were conducted on a monthly basis for 6 months, then every 3 months thereafter until death, study closure or 3 years since treatment discontinuation (whichever happened first). This assessment was conducted by record review and/or telephone contact with the patient's treating physician.
Secondary outcomes	PFS: defined as the time from randomisation to progressive disease or death from any cause (whichever happened first). ORR: defined as the proportion of all randomised patients with a confirmed CR or PR. Safety and tolerability: including incidence of TEAEs, incidence of dose reductions and interruptions, and included of treatment discontinuation and reason for discontinuation. Response was evaluated based on IRR of CT scans (or MRI scans if patient contraindicated to CT contrast media) against RECIST v1.0 criteria, with assessments conducted every 8 weeks. Data for any TEAEs that start after initial study drug administration and up to 30 days after the last dose of study drug or study closure (whichever happened first) were collected. TEAEs were categorised through MedDRA v15.0 terms and graded according to NCI CTCAE v3.0.
Other efficacy outcomes	Other efficacy endpoints included: • PFS and ORR evaluated by investigator assessment; • Time to response and response duration (according to RECIST v1.0); • Disease control rate (i.e. SD for ≥16 weeks or confirmed CR or PR); • Time to treatment failure; • Changes in serum CA19-9; • Tumour response based on PET scans (evaluated according to EORTC criteria);

	• Correlation between ORR (RECIST) and tumour response (EORTC); • Changes in plasma SPARC levels; • Correlation between expression of molecular markers and efficacy outcomes; • Correlation between ORR, tumour response, changes in serum 19-9 and OS; • Correlation between ORR, tumour response, PFS, OS and expression of tumour markers (e.g. SPARC, nucleoside transporters).
Pre-planned subgroups	The following subgroups were specified in the protocol: • Geographic region (Australia, Eastern Europe, Western Europe, North America); • Age (<65 years, ≥65 to <75 years, and ≥75 years); • KPS (70 to 80 and 90 to 100); • Gender (male and female); • Pancreatic cancer primary location (head and other); • Stage at diagnosis (IV and other); • Level of CA19-9 (within normal limit, ULN to < 59 x ULN, ≥59 x ULN); • Presence of liver metastases (yes and no); • Peritoneal carcinomatosis (yes and no); • Previous Whipple procedure (yes and no); • Presence of biliary stent (yes and no) at baseline; • Presence of pulmonary metastases (yes and no); and • Number of metastatic sites (1, 2, 3 and above).
Key: AE, adverse event; CA19-9, carbohydrate antigen 19-9; CR, complete response; CT, computerised tomography; EORTC, European Organisation for Research and Treatment of Cancer; IRR, independent radiological review; IV, intravenous; KPS, Karnofsky Performance Status; MedDRA, Medical Dictionary for Regulatory Activities; MRI, magnetic resonance imaging; ORR, overall response rate; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; SPARC, secreted protein acidic and rich in cysteine; TEAE, treatment-emergent adverse event; RCT, randomised controlled trial; RECIST, Response Evaluation Criteria in Solid Tumor; ULN, upper limit of normal. **Note:** * with the exception that on Day 15, re-escalation with G-CSF support was permitted, after a previous dose reduction on Day 8 of the same cycle. **Sources:** Von Hoff *et al.* 2013[6]; CA046 CSR.[21]	

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

The hypothesis and associated statistical analysis methods adopted in CA046 are presented in Table 10.

All efficacy analyses were carried out in the intent-to-treat (ITT) population, defined as all randomised patients. Safety analyses were carried out in the treated

population, which consisted of all randomised patients who received at least one dose of study drug. Primary and secondary endpoint analyses were also carried out in the Treated population, as well as the Per-protocol population (defined as all treated patients who met all eligibility criteria and received the same treatment as assigned by randomisation) as sensitivity analyses.

It was calculated that a sample of 842 patients with 608 events would have 90% power to detect a HR for death with *nab*-P/Gem versus gemcitabine monotherapy of 0.769 at a two-sided alpha level of 0.049. Of note, the power was increased from 80 to 90% in a protocol amendment before any interim analyses were performed.

Time-to-event analyses including the primary endpoint of OS were estimated using the Kaplan–Meier (KM) method, with distributions for the two treatment arms compared using the stratified log-rank test; associated HR and 95% confidence interval (CI) were estimated using a stratified Cox proportional-hazard model. Patients without an event at the time of analysis were censored using pre-defined data management criteria. Differences in tumour response rates between treatment arms were tested using the chi-squared test with the relative risk (RR) and 95% CI provided.

Per-protocol, an interim analysis for OS was performed after at least 200 patients had been followed for at least 6 months from the date of randomisation. The purpose of this interim analysis was to evaluate futility with the possibility of stopping the study prematurely due to lack of efficacy (the interim analysis was not designed to stop the study early for outstanding efficacy). The final analysis for OS was to be performed when at least 608 deaths had occurred; all death events that occurred on or prior to projected clinical cutoff date were included.

Final OS analysis was based on 692 deaths (80% of patients) at a clinical cutoff date of 17 September 2012. At this time, the median follow-up was 9.1 months (range: 0.1–36.9) in the *nab*-P/Gem group and 7.4 months (range: 0.0–31.3) in the gemcitabine group. An extension study to collect further survival data was registered at study closure and provides an updated post-hoc OS analysis with an extended data cutoff date of 9 May 2013 (NCT02021500). At this time, 774 (90%) patients in the ITT population had died, and the median follow-up was 13.9 months.

As part of the previous appraisal, the ERG assessed whether the chosen analyses were appropriate for the data and concluded that the *"methods of analyses for both OS and PFS were appropriate"* and that *"the data from the study are fully mature"*.[48]

Table 10: Summary of statistical analyses in CA046

Hypothesis objective	Ho: $HR_{nab\text{-Paclitaxel + Gemcitabine/Gemcitabine alone}}$ ($HR_{n\text{-P+G/G}}$) = 1 Ha: $HR_{nab\text{-Paclitaxel + Gemcitabine/Gemcitabine alone}}$ ($HR_{n\text{-P+G/G}}$) ≠1 (superiority)
Statistical analysis	All efficacy analyses were carried out in the ITT population (i.e. all patients who underwent randomisation). OS was analysed using the KM method and a stratified log-rank test; the p-value was compared with the allocated Type 1 error rate of 0.049. The associated HR and 95% CI were estimated using a stratified Cox proportional-hazard model. A multivariate analysis of survival was performed with the use of a Cox proportional-hazard model to evaluate the treatment effect with adjustment for stratification factors. PFS was also analysed using the KM method and a stratified log-rank test with HR, and 2-sided CIs were estimated using a stratified Cox-proportional hazard model. ORR was summarised by the number and percentage of patients who achieved a confirmed CR or PR. Differences in tumour response rates between treatment arms were tested using the chi-squared test. The relative risk and 95% CI were provided. Statistical testing of secondary endpoints was to be performed only if the primary efficacy endpoint of OS displayed superiority of *nab*-P/Gem over gemcitabine alone for OS. To control the overall family-wise Type 1 error rate at 2-sided α = 0.050 for the two key secondary efficacy endpoints, PFS was tested first at α = 0.050; ORR was tested at α = 0.050 only if PFS showed statistically significant improvement.
Sample size, power calculation	A sample size of 421 patients randomised to each treatment arm (842 patients in total) provided 90% power with two-sided Type I error of 0.049 to reject the primary efficacy null hypothesis that the *nab*-P/Gem/ gemcitabine HR for OS was equal to 1.0. This sample size calculation assumed *nab*-P/Gem has 30% improvement in OS compared with gemcitabine alone (HR=0.769).
Data management, patient withdrawals	All randomised patients were included in the efficacy analyses. For OS, patients who were lost to follow-up were censored on the last date known-to-be-alive. For PFS, patients who were lost to follow-up were censored on the date of last tumour assessment; patients who dropped out early without any post baseline tumour assessment and/or died more than 120 days after the randomisation were censored on the date of randomisation; patients who had missing tumour assessments prior to PD or death and PD or death occurred more than 120 days after previous tumour assessment were censored on the date of previous tumour assessment; patients with ≥2 consecutive missing response assessments prior to a visit with documented progression (or death) were censored at the last date of tumour assessment when the patient was documented to be progression free.

	For ORR, patients who did not have post baseline tumour assessments were counted as non-responders.

Key: CI, confidence interval; CR, complete response; H_0, null hypothesis; H_a, alternative hypothesis; HR, hazard ratio; ITT, intention-to-treat; KM, Kaplan–Meier; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response.
Sources: Von Hoff *et al.* 2013[6]; CA046 CSR.[21]

4.5 Participant flow in the relevant randomised controlled trials

Figure 3 shows the Consolidated Standards of Reporting Trials (CONSORT) flow chart for patient disposition in CA046 at the time of the final analysis.

Of the 861 patients randomised, 420 were treated with *nab*-P/Gem, and 403 were treated with gemcitabine monotherapy. Over 90% of patients in both treatment groups had discontinued therapy at the time of the final analysis data cutoff; the majority due to progressive disease (47% in the *nab*-P/Gem group and 61% in the gemcitabine group). One patient was randomised to treatment with gemcitabine but received treatment with *nab*-P/Gem. According to the ITT principle, in primary efficacy analysis (based on the ITT population), the patient was analysed as randomised. In safety analysis (based on the treated population), this patient was analysed as treated. No patients were lost to follow-up.

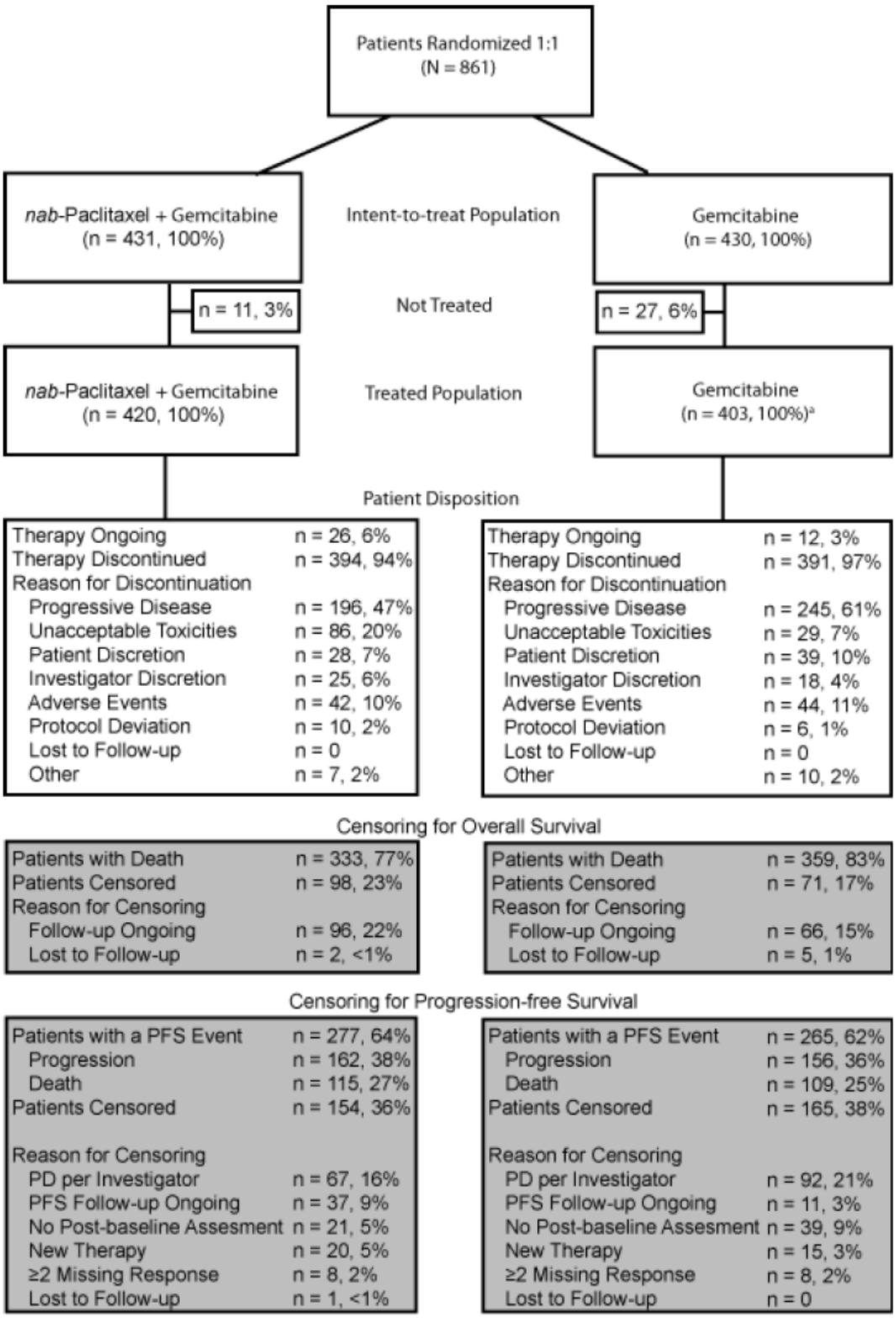
The median duration of treatment (defined as the time from the first study drug dose date to the end of treatment date) in CA046 was 3.9 months (range: 0.1–21.9) in the *nab*-P/Gem group and 2.8 months (range: 0.1–21.5) in the gemcitabine group, with 32% and 15% of patients, respectively, receiving treatment for at least 6 months. In the *nab*-P/Gem group, 41% of patients had reductions in the *nab*-P dose, and 47% of patients had reductions in the gemcitabine dose. In total, 71% of all nab-P doses administered during the study were at the full dose of 125 mg/m^2. The median relative dose intensity in the *nab*-P/Gem group was 81% for *nab*-P and 75% for gemcitabine. In the gemcitabine group, 33% of patients had dose reductions, resulting in a median relative dose intensity of 85%. The median cumulative dose of gemcitabine delivered was greater in the *nab*-P/Gem group than in the gemcitabine group (11,400 mg/m^2 vs 9,000 mg/m^2); this difference was related to the increased duration of treatment in the *nab*-P/Gem group.

Overall, the rate of the use of subsequent therapy was balanced between the treatment arms (38% and 42% of patients in the *nab*-P/Gem and gemcitabine

groups, respectively). Although not permitted by protocol, 6% of patients from the gemcitabine group crossed over to receive a regimen that included *nab*-P. To assess the impact of starting new anticancer therapy on OS, a pre-defined sensitivity analysis was conducted where patients who started a new anticancer therapy were censored at the initiation date of the new chemotherapy (see Section 4.7). Additional, post-hoc exploratory analysis evaluating second-line treatment of patients enrolled in CA046 is also provided in Section 4.7.

Although the extension study of CA046 was primarily designed to collect survival data, time on treatment (ToT) data were also collected and have been utilised within the economic model as the most mature data available. At the time of this post-hoc analysis (9 May 2013 data cutoff), the median duration of treatment (defined as above) was 3.4 months in the *nab*-P/Gem treatment group, and 2.3 months in the gemcitabine treatment group (see Section 5).

Figure 2: CONSORT diagram of patient disposition in CA046 (17 September 2012 data cutoff)



Key: PD, progressive disease; PFS, progression-free survival.
Source: Supplementary appendix of Von Hoff *et al.* 2013.[6]

Demographic and clinical characteristics of participants at baseline were well balanced between the treatment groups, as presented in Table 11.

The CA046 trial population directly represents the population for which marketing authorisation was granted, and thus the population outlined in the decision problem of interest to this submission. However, patients do appear younger and fitter on average than patients typically presenting in UK practice; this is often observed in clinical trial populations compared to 'real-life' populations but may also be attributed to geographical variation in demographics as no UK centres were involved in CA046. Despite these differences, the CA046 trial population is considered generally representative of mPAC patients treated in England (see Section 4.13). Of note, real world evidence reporting use of *nab*-P/Gem in patients ≥75 years of age is provided in Section 4.12.

Table 11: Baseline characteristics of participants in CA046

Characteristic	***Nab*-P/Gem N=431**	**Gem N=430**	**All N=861**
Age, years			
Median	62	63	63
Range	27–86	32–88	27–88
<65 – n (%)	254 (59)	242 (56)	496 (58)
≥65 – n (%)	177 (41)	188 (44)	365 (42)
Sex – n (%)			
Female	186 (43)	173 (40)	359 (42)
Male	245 (57)	257 (60)	502 (58)
Race or ethnic group – n (%)*			
Asian	8 (2)	9 (2)	17 (2)
Black	16 (4)	16 (4)	32 (4)
White	378 (88)	375 (87)	753 (87)
Hispanic	25 (6)	26 (6)	51 (6)
Other	4 (1)	4 (1)	8 (1)
Region – n (%)			
Australia	61 (14)	59 (14)	120 (14)
Eastern Europe	64 (15)	62 (14)	126 (15)
North America	268 (62)	271 (63)	539 (63)
Western Europe	38 (9)	38 (9)	76 (9)

Characteristic	*Nab*-P/Gem N=431	Gem N=430	All N=861
KPS score – n/total n (%)**			
100	69/429 (16)	69/429 (16)	138/858 (16)
90	179/429 (42)	199/429 (46)	378/858 (44)
80	149/429 (35)	128/429 (30)	277/858 (32)
70	30/429 (7)	33/429 (8)	63/858 (7)
60	2/429 (<1)	0/429	2/858 (<1)
Pancreatic tumour location – n (%)			
Head	191 (44)	180 (42)	371 (43)
Body	132 (31)	136 (32)	268 (31)
Tail	105 (24)	110 (26)	215 (25)
Unknown	3 (1)	4 (1)	7 (1)
Site of metastatic disease – n (%)			
Liver	365 (85)	360 (84)	725 (84)
Lung	153 (35)	184 (43)	337 (39)
Peritoneum	19 (4)	10 (2)	29 (3)
Number of metastatic sites – n (%)			
1	33 (8)	21 (5)	54 (6)
2	202 (47)	206 (48)	408 (47)
3	136 (32)	140 (33)	276 (32)
>3	60 (14)	63 (15)	123 (14)
Level of CA19-9 – n/total n (%)			
Normal***	60/379 (16)	56/371 (15)	116/750 (15)
ULN to <59 x ULN	122/379 (32)	120/371 (32)	242/750 (32)
≥59 ULN	197/379 (52)	195/371 (53)	392/750 (52)
Previous therapy – n (%)			
Radiation therapy	19 (4)	11 (3)	30 (3)
Chemotherapy	23 (5)	12 (3)	35 (4)
Whipple procedure	32 (7)	30 (7)	62 (7)
Biliary stent	80 (19)	68 (16)	148 (17)

Key: CA19-9, carbohydrate antigen 19-9; KPS, Karnofsky Performance Status; *nab*-P/Gem, *nab*-P in combination with gemcitabine; ULN, upper limit of normal.
Notes: * Race or ethnic group were self-reported; ** KPS range from 0–100, with higher scores indicating better performance status; two patients in the *nab*-P/Gem group had a score greater than 70 at the screening visit but a score of 60 at the baseline visit on Day 1 or Cycle 1; *** Defined as 0 to 35U/ml.
Source: Von Hoff *et al.* 2013.[6]

4.6 Quality assessment of the relevant randomised controlled trials

CA046 was conducted in accordance with good clinical practice (GCP) guidelines by qualified investigators using a single protocol to promote consistency across sites, and with measures taken to minimise bias.

Randomisation was successfully carried out such that baseline characteristics of patients randomised were well balanced across treatment groups. The most common reason for study withdrawal was disease progression, which is fully accounted for within efficacy assessments. Patient withdrawals for reasons other than disease progression were accounted for with pre-defined, standard censoring methods.

Although the trial was open-label in design, the primary endpoint of OS is not a subjectively assessed endpoint; therefore, lack of blinding was not thought to have a great impact on the outcome of the study. For secondary endpoints of PFS and ORR, assessments were conducted by IRR with independent assessors blinded to treatment allocation. All outcome assessments were conducted in accordance with trial-validated methodology, and an independent Data Monitoring Committee (DMC) was established with the responsibility of safeguarding the interests of study participants.

CA046 is thought to adequately reflect routine clinical practice in England with respect to population, comparator choice, treatment administration and outcomes assessed.

Quality assessment in accordance with the NICE-recommended checklist for RCT assessment of bias is presented in Table 12. The risk of bias in CA046 is considered to be low, and this conclusion was supported by the ERG as part of the previous appraisal, who stated that *"the ERG considers the CA046 study to be robust, well designed and well reported"* and that *"the study is at an overall low risk of bias".*[48]

Table 12: Quality assessment results for CA046

Study question	How is the question addressed in the study?	Risk of bias
Was randomisation carried out appropriately?	Yes. Randomisation schedule was generated by a randomisation statistician, with stratification for key prognostic factors.	Low
Was the concealment of treatment allocation adequate?	Yes. Randomisation was implemented via a centralised IVRS.	Low
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Patient demographics were well balanced, with no key differences between treatment groups.	Low
Were the care providers, participants and outcome assessors blind to treatment allocation?	Independent assessors were blinded; care providers and participants were not.	Low
Were there any unexpected imbalances in drop-outs between groups?	No. The most common reason for study withdrawal in both treatment arms was disease progression, which is fully accounted for within efficacy assessments.	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.	Low
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analyses were performed according to the intention-to-treat principle, with standard censoring methods used to account for missing data.	Low
Key: IVRS, interactive voice response system.		

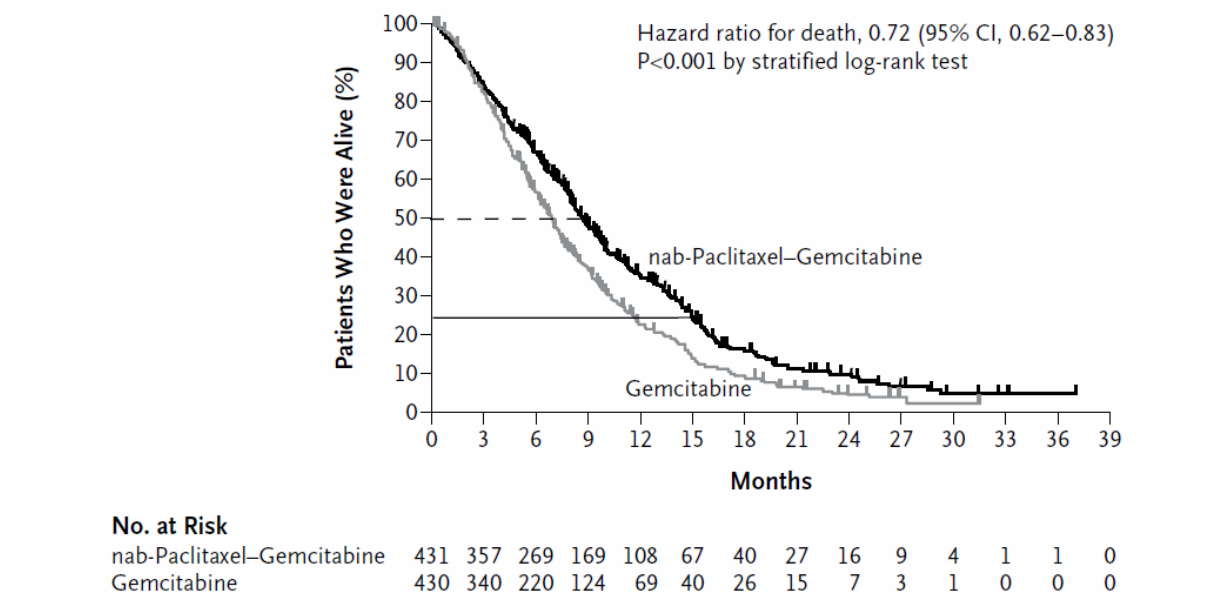
4.7 Clinical effectiveness results of the relevant randomised controlled trials

4.7.1. Final efficacy analysis as per the CA046 Study (17 September 2012 data cutoff)

Key efficacy results from the final analysis of CA046 as per protocol are presented in Table 13.

Final OS analysis was based on 692 deaths (80% of patients). The median OS was 8.5 months (95% CI: 7.9, 9.5) in the *nab*-P/Gem group and 6.7 months (95% CI: 6.0, 7.2) in the gemcitabine group; HR for death: 0.72 (95% CI: 0.62, 0.83); p<0.001. Treatment differences were seen as early as 2 months after the start of therapy, as can be seen in the KM plot presented as Figure 4. At the time point at which 25% of the patients were alive, a treatment difference of 3.4 months of survival was observed between treatment groups (in favour of *nab*-P/Gem). For this final analysis, data for 23% of the patients were censored for survival in the *nab*-P/Gem group, compared with data for 17% of the patients in the gemcitabine group. This shows that a greater percentage of patients in the *nab*-P/Gem group were alive at the time of analysis compared to the gemcitabine group.

Figure 3: KM plot of OS in CA046 (ITT population; 17 September 2012 data cutoff)



Key: CI, confidence interval; KM, Kaplan–Meier; OS, overall survival.
Source: Von Hoff *et al.* 2013.[6]

A multivariate analysis of OS was conducted (using a Cox proportional hazard model) to evaluate the treatment effect adjusted for the stratification factors (geographic region, KPS, presence of liver metastases). In this analysis, the treatment effect of *nab*-P/Gem remained positive and statistically significant; HR for death: 0.71 (95% CI: 0.61, 0.83); p<0.0001; KPS and presence of liver metastases were also shown to be independent predictors of survival. All sensitivity analyses for

OS similarly showed consistent and statistically significant improvement in the *nab*-P/Gem arm compared with the gemcitabine arm. This included a pre-planned sensitivity analysis based upon subsequent treatment. When the data for survival were censored at the time of the initiation of subsequent therapy, median OS was significantly longer with *nab*-P/Gem (9.4 months) than with gemcitabine (6.8 months); HR for death: 0.68 (95% CI: 0.56, 0.82); p<0.001. Post-hoc exploratory analysis of patients enrolled in CA046 showed that the median total survival in patients who went on to receive second-line treatment was significantly longer in the *nab*-P/Gem group (12.8 months) than in the gemcitabine group (9.9 months); HR for death: 0.76 (95% CI: 0.61, 0.95); p=0.015.[51] Further post-hoc exploratory analysis showed the median OS was also significantly longer for those patients treated until disease progression in the *nab*-P/Gem group (9.8 months) than in the gemcitabine group (7.5 months); p<0.001.[52] These analyses suggest that prolonged first-line treatment exposure and ability to receive subsequent therapies can further improve survival among mPAC patients.

The median PFS was significantly longer in the *nab*-P/Gem group (5.5 months) than in the gemcitabine group (3.7 months); HR for disease progression or death: 0.69 (95% CI: 0.58, 0.82); p<0.001. The PFS rate at 1-year in the *nab*-P/Gem group was almost double that of the gemcitabine group by independent review (16% vs 9%, respectively), and notably greater by investigator assessment (12% vs 4%, respectively). The ORR according to independent review was significantly higher with *nab*-P/Gem (23%) than with gemcitabine (7%); response rate ratio (RRR): 3.19 (95% CI: 2.18, 4.66); p<0.001. This was supported by the ORR analysis based on investigator assessment, which was also significantly higher with *nab*-P/Gem (29%) than with gemcitabine (8%); RRR: 3.81 (95% CI: 2.66, 5.46); p<0.001.

Table 13: Primary and secondary efficacy endpoints in CA046 (ITT population; 17 September 2012 data cutoff)

Efficacy variable	***Nab*-P/Gem (N=431)**	**Gem (N=430)**	**HR or RRR (95% CI)***	**p-value**
Overall survival				
Events, n (%)	333 (77)	359 (83)	-	-
Censored, n (%)	98 (23)	71 (17)	-	-
Median months	8.5 (7.9, 9.5)	6.7 (6.0, 7.2)	0.72 (0.62, 0.83)	<0.001

Efficacy variable	***Nab*-P/Gem (N=431)**	**Gem (N=430)**	**HR or RRR (95% CI)***	**p-value**
(95% CI)				
Survival rate, % (95% CI)				
6 months	67 (62, 71)	55 (50, 60)	-	<0.001
12 months	35 (30, 39)	22 (18, 27)	-	<0.001
18 months	16 (12, 20)	9 (6, 12)	-	0.008
24 months	9 (6, 13)	4 (2, 7)	-	0.02
Progression-free survival (Independent review)				
Events, n (%)	277 (64)	265 (62)	-	-
Censored, n (%)	154 (36)	165 (38)	-	-
Median months (95% CI)	5.5 (4.5, 5.9)	3.7 (3.6, 4.0)	0.69 (0.58, 0.82)	<0.001
PFS rate, % (95% CI)				
6 months	44 (39, 50)	25 (20, 30)	-	-
12 months	16 (12, 21)	9 (5, 14)	-	-
18 months	5 (2, 11)	7 (3, 13)	-	-
Progression-free survival (Investigators assessment)				
Events, n (%)	327 (76)	348 (81)	-	-
Censored, n (%)	104 (24)	82 (19)	-	-
Median months (95% CI)	5.3 (4.4, 5.5)	3.5 (3.3, 3.7)	0.61 (0.52, 0.71)	<0.001
PFS rate, % (95% CI)				
6 months	41 (35.6, 45.6)	18 (13.8, 21.9)	-	-
12 months	12 (8.3, 16.0)	4 (1.9, 6.5)	-	-
Response (Independent review)				
Number of patients with response	99	31	3.19 (2.18, 4.66)	<0.001
% (95% CI)	23 (19, 27)	7 (5, 10)	-	-
Number of patients with disease control**	206	141	1.46 (1.23, 1.72)	<0.001
% (95% CI)	48 (43, 53)	33 (28, 37)	-	-
Best response, n (%): Complete response Partial response Stable disease Progressive disease Not evaluable No post-baseline	 1 (<1) 98 (23) 118 (27) 86 (20) 56 (13)	 0 31 (7) 122 (28) 110 (26) 80 (19)	-	-

Efficacy variable	*Nab*-P/Gem (N=431)	Gem (N=430)	HR or RRR (95% CI)*	p-value
assessment	72 (17)	87 (20)		
Response (Investigator assessment)				
Number of patients with response	126	33	3.81 (2.66, 5.46)	<0.001
% (95% CI)	29 (25, 34)	8 (5, 11)	-	-
Best response, n (%):				
Complete response	6 (1)	0	-	-
Partial response	120 (28)	33 (8)		
Stable disease	96 (22)	105 (24)		
Progressive disease	96 (22)	156 (36)		
Not evaluable	43 (10)	50 (12)		
No post-baseline assessment	70 (16)	86 (20)		

Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; RRR, response rate ratio.
Notes: * HR for death is provided for OS, and the HR for progression or death is provided for PFS, with a HR of <1 favouring the *nab*-P/Gem group; the RRRs are provided for the ORRs, with a RRR of >1 favouring the *nab*-P/Gem group, compared with the gemcitabine group; ** Disease control included confirmed complete response, confirmed partial response, and stable disease for at least 16 weeks.
Sources: Von Hoff *et al.* 2013[6]; CA046 CSR.[21]

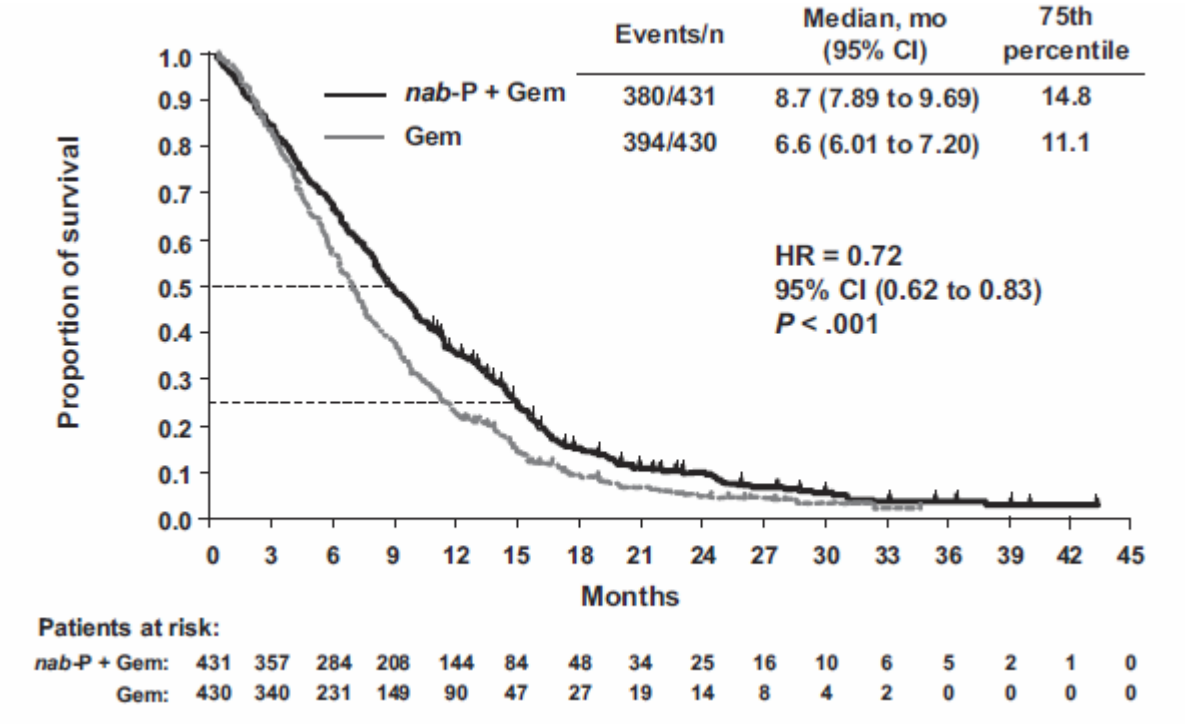
Additional exploratory analyses of CA046 trial data are provided in Appendix 3.

4.7.2. Updated survival analysis as per the CA046 Extension Study (9 May 2013 data cutoff)

An extension study registered at study closure provides a post-hoc analysis, with an extended follow-up (8 months longer) to give a more complete estimate of OS. This analysis was based on 774 deaths (90% of patients). The updated survival estimates from this analysis are shown in Table 14.

The median OS was 8.7 months (95% CI: 7.9, 9.7) in the *nab*-P/Gem group and 6.6 months (95% CI: 6.0, 7.2) in the gemcitabine group; HR for death: 0.72 (95% CI: 0.62, 0.83); p<0.0001, as depicted in Figure 5.

Figure 4: KM plot of OS in CA046 (ITT population; 9 May 2013 data cutoff)



Key: CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier; mo, months; OS, overall survival.
Source: Goldstein *et al.* 2015.[8]

Further post-hoc analysis on this extension study dataset showed the mean OS was 11.1 months in the *nab*-P/Gem group and 8.7 months in the gemcitabine group. These results confirm the previous analysis showing *nab*-P/Gem to be significantly superior to gemcitabine alone for the first-line treatment of patients with mPAC. With a median OS difference of 2.1 months and a mean OS difference of 2.4 months, this superiority is also considered to be clinically meaningful to people affected by pancreatic cancer, for whom Pancreatic Cancer UK noted that an improvement of 6–8 weeks would be seen as significant[7], and have since launched their Two More Months campaign to illustrate how important an extra 2 months of life is to patients affected by this fatal disease.[30]

At the time point at which 25% of the patients were alive, an even greater treatment difference of 3.7 months of survival was observed between treatment groups (in favour of *nab*-P/Gem). Extended follow-up also identified patients who survived longer than 24 months in the *nab*-P/Gem group, including 4% of patients who survived at least 36 months and 3% of patients who survived at least 42 months. No patient survived for 36 months in the gemcitabine monotherapy group.

Table 14: Updated survival estimates in CA046 (ITT population; 9 May 2013 data cutoff)

	***Nab*-P/Gem (N=431)**	**Gem (N=430)**	**HR (95% CI)***	**p-value**
Events, n (%)	380 (88)	394 (92)	-	-
Censored, n (%)	51 (12)	36 (8)	-	-
Median months (95% CI)	8.7 (7.9, 9.7)	6.6 (6.0, 7.2)	0.72 (0.62, 0.83)	<0.0001
Survival rate, % (95% CI)				
6 months	66 (62, 71)	55 (50, 60)	-	-
12 months	35 (31, 40)	22 (18, 26)	-	-
24 months	10 (6, 13)	5 (2, 7)	-	-
36 months	4 (2, 7)	0	-	-
42 months	3 (1, 6)	0	-	-

Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine.
Note: * The HR for death is provided with a HR <1 favouring the *nab*-P/Gem group.
Sources: Goldstein *et al.* 2015[8]; updated overall survival data on file.

As was observed in the primary analysis, OS showed consistent and statistically significant improvement in the *nab*-P/Gem arm compared with the gemcitabine arm across all sensitivity analyses. In multivariate analysis adjusting for stratification factors, the treatment effect of *nab*-P/Gem remained positive and statistically significant; HR for death: 0.68 (95% CI: 0.57, 0.80); p<0.001.

4.7.3. Health-related quality of life

HRQL data were not captured in the CA046 study. HRQL data from supportive trials are therefore summarised here to provide an estimate of how *nab*-P/Gem could impact HRQL in clinical practice.

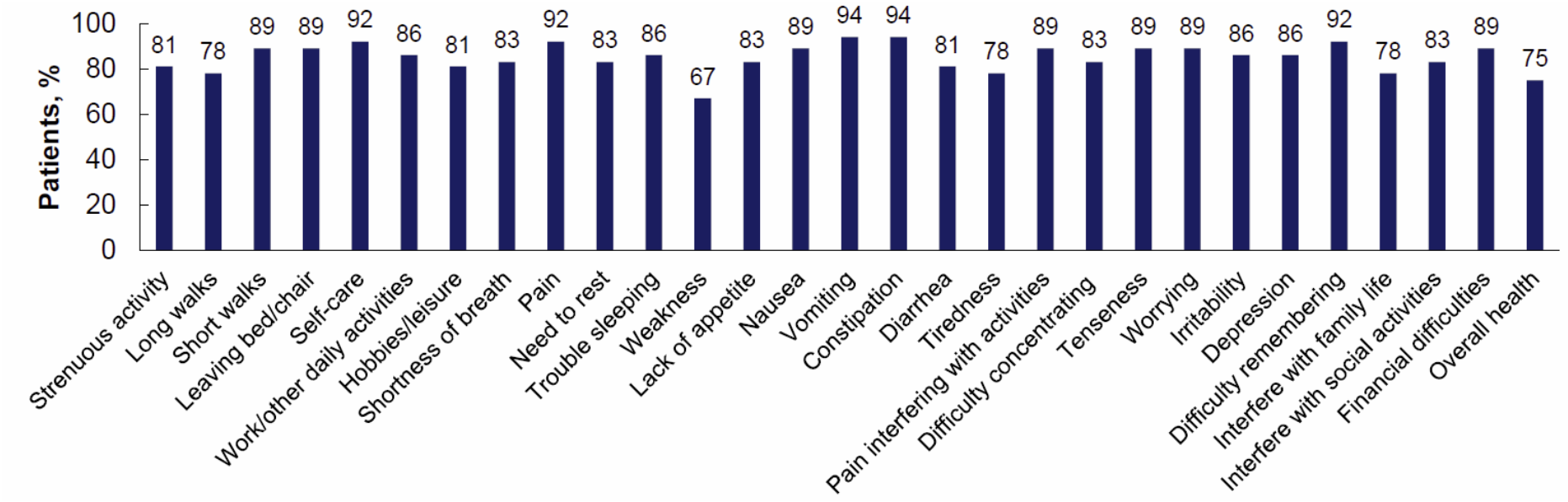
The SIEGE trial was referenced in the original submission as a potential source of HRQL data. This Phase II randomised trial is primarily designed to explore whether the scheduling of *nab*-P and gemcitabine may be critical to the mechanism of action and optimal clinical benefit. Therefore, it does not provide comparative data for *nab*-P/Gem versus gemcitabine monotherapy, but does provide UK-specific data for *nab*-P/Gem. The control arm in the study (known as the 'concomitant' arm) reflects the

licensed schedule of *nab*-P/Gem, and the experimental arm (known as the 'sequential' arm) consists of *nab*-P delivered 24 hours prior to Gem. A study schema for this trial is provided in Appendix 3. Early data from SIEGE were recently presented at ASCO GI 2017, including global health status (GHS) scores derived from the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30).[9] GHS scores were generally stable throughout treatment but data are hard to interpret towards the end of the 6 treatment cycle period due to small patient numbers (n=22 in the concomitant *nab*-P/Gem arm at Week 24). Aggregate HRQL data also fail to capture the patient's disease state. A more detailed analysis of EuroQol-5 Dimension (EQ-5D) data from SIEGE has been conducted to inform utility values within the cost-effectiveness modelling; these analyses are detailed in Section 5.4. Early effectiveness data from the SIEGE trial report a median OS of 7.9 months in patients treated with concomitant *nab*-P/Gem, and a 1-year OS rate of 21% (n=75). These data are viewed as very similar to, and supportive of, the CA046 trial by UK expert clinicians.[11] In absolute terms, these survival data are slightly lower than that observed in the CA046 trial. This is reflective of a more severe patient population treated with *nab*-P/Gem in SIEGE, but importantly still represents a clinically meaningful survival benefit (defined as 6-8 weeks by people affected by pancreatic cancer[7]) over current life expectancy for patients with mPC in clinical practice (≤6 months[5]). Additionally, SIEGE is a small (n=146) phase II study investigating different dose schedules of *nab*-P/Gem where the comparator is not gemcitabine, so it is difficult to compare efficacy results to a large phase III RCT such as CA046. Of interest, performance status was assessed against both the KPS and ECOG scales in SIEGE, and no clear or consistent mapping between these assessment measures was observed. This suggests that in clinical practice, performance status alone is not used to justify eligibility for a particular treatment. These data are summarised in Appendix 3.

Data are also available from the induction phase (6 treatment cycles) of an ongoing Phase II single-arm trial (Locally Advanced Pancreatic Adenocarcinoma Clinical Trial [LAPACT]) investigating *nab*-P/Gem as a first-line treatment for patients with LAPC.[10] A study schema for this trial is provided in Appendix 3. As depicted in Figure 6, a high proportion of patients treated with *nab*-P/Gem reported stable or improved

HRQL in accordance with individual items of the EORTC QLQ-C30. [redacted]

Figure 5: Stable or improvement rate for EORTC QLQ-C30 questions in patients with LAPC treated with *nab*-P/Gem in the first-line setting (n=36)



Key: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.
Source: Lacy *et al.* 2017.[10]

[redacted]

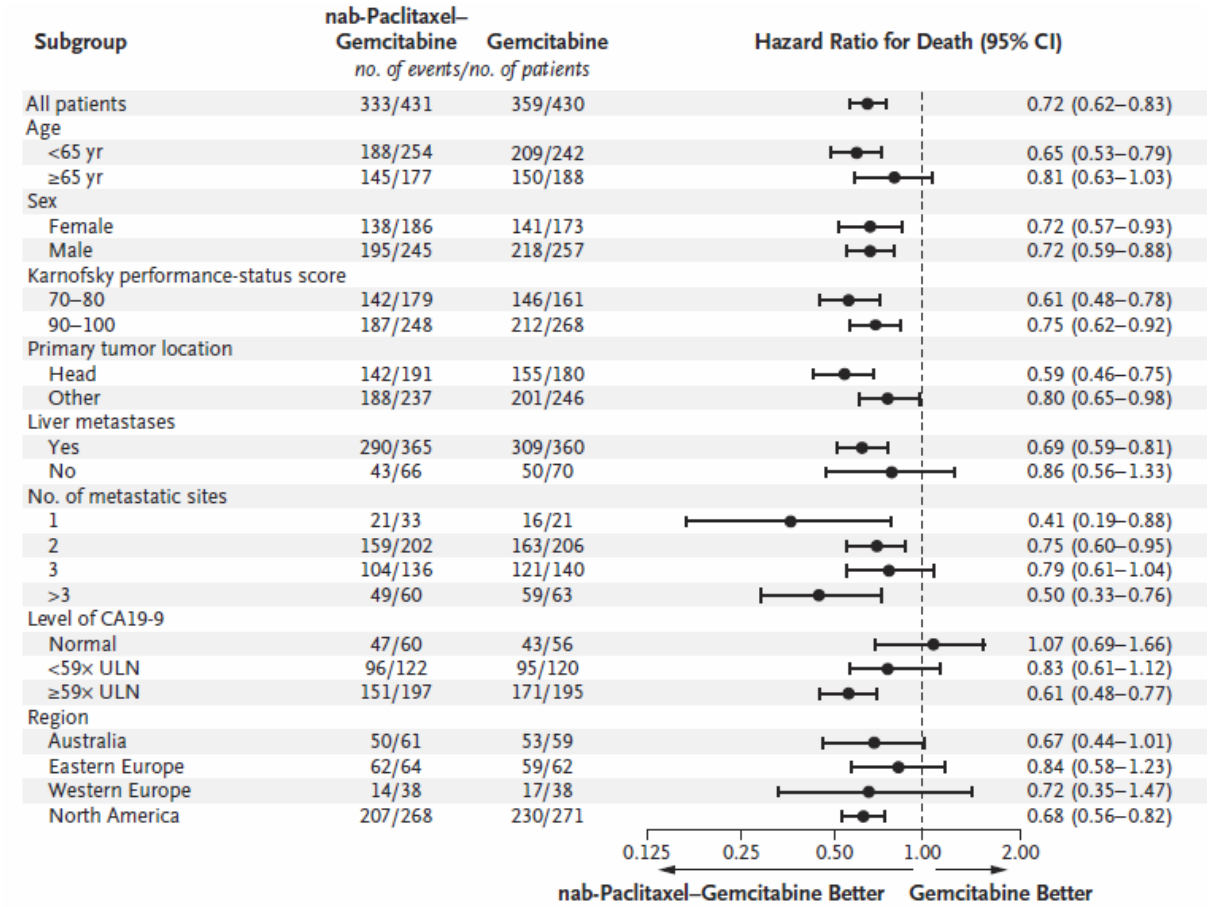
[redacted]

4.8 Subgroup analysis

As pre-specified in the Statistical Analysis Plan (SAP), analyses were performed to assess the potential influence of key prognostic factors on the primary efficacy endpoint of OS. In this analysis, stratification factors (geographic region, KPS and presence of liver metastases) were based on the clinical data, not the randomisation data (i.e. based on data in the clinical report file collected and verified on site rather than interactive voice response system (IVRS) information provided for randomisation).

As can be observed in the forest plot presented in Figure 8, the treatment effect favoured the *nab*-P/Gem group across the majority of pre-specified subgroups.

Figure 6: Forest plot of OS in pre-specified subgroups of CA046 (ITT population; 17 September 2012 data cutoff)



Key: CI, confidence interval; ITT, intention-to-treat; OS, overall survival; ULN, upper limit of normal.
Source: Von Hoff *et al.* 2013.[6]

Although no UK patients were enrolled in CA046, the subgroup of patients from Western Europe had the same reduction in the risk of death as the total patient population (HR for death: 0.72; Figure 8). In more detailed subgroup analysis of the extension study data by geography, the median OS in the Western Europe cohort was 3.8 months greater in patients receiving *nab*-P/Gem (n=38) than in those treated with gemcitabine alone (n=38), although this difference fell outside statistical significance; HR for death: 0.82 (95% CI: 0.48, 1.4); p=0.471.[54]

Interestingly, subgroups characterised by patients with more advanced disease generally had the greatest reduction in the risk of death; for example, patients with poorer KPS (70–80), patients with >3 metastatic sites and patients with elevated CA19-9. There is no definitive explanation for this observation; however, there are biologically plausible explanations that can be considered, based on a range of characteristics associated with more advanced disease, such as tumour size, more deranged biochemistry (e.g. albumin, alkaline phosphatise, aspartate transaminase and lactate dehydrogenase), and more prominent paraneoplastic features.[55]

4.9 Meta-analysis

Meta-analysis has not been performed because a single RCT provides evidence supporting the use of *nab*-P/Gem for the first-line treatment of mPAC.

4.10 Indirect and mixed treatment comparisons

4.10.1. Search strategy

The SLR methods used to identify trials for potential inclusion in an NMA are described in Section 4.1.

4.10.2. Study selection

In addition to CA046, 16 studies met the secondary eligibility criteria of the review, as summarised in Table 15. In the previous appraisal, the ERG considered it more appropriate to use the results of the NMA synthesising data from the metastatic population of interest to the submission, and the NICE committee agreed with this opinion. Therefore, the 10 studies (including CA046) that provide data for patients with mPC (Table 15) have been utilised for this NMA update.

Table 15: RCTs meeting the secondary eligibility criteria of the clinical SLR

Trial name (NCT number)	Design	Population	mPC data	Treatment arms	Primary outcome	Key secondary outcomes	Primary study reference
ACCORD (NCT00112658)	RCT Phase II/III Parallel-group	Adult patients with previously untreated mPAC and a WHO PS score of 0–1.	Yes	FOLFIRINOX (n=171) Gemcitabine monotherapy (n=171)	OS	PFS ORR HRQL Safety	Conroy *et al.* 2011[28]
Boeck 2008	RCT Phase II Parallel-group Open-label	Adult patients with previously untreated mPC or LAPC and a KPS score ≥60	Yes	Gemcitabine plus capecitabine (n=64) Gemcitabine plus oxaliplatin (n=63) Capecitabine plus oxaliplatin (n=61)	PFS	OS ORR Safety	Boeck *et al.* 2008[56]
CA046 (NCT00844649)	RCT Phase III Parallel-group Open-label	Adult patients with previously untreated mPAC and a KPS score ≥70	Yes	*Nab*-Paclitaxel plus gemcitabine (n=431) Gemcitabine monotherapy (n=430)	OS	PFS ORR Safety	Von Hoff *et al.* 2013[6]
CALGB 89904 (NCT00012220)	RCT Phase II Parallel-group Open-label	Adult patients with previously untreated mPAC and an ECOG PS of 0–2	Yes	Gemcitabine plus cisplatin (n=66) Gemcitabine plus docetaxel (n=65) Gemcitabine plus irinotecan (n=64) Gemcitabine FDR (n=64)	OS	TTP ORR Safety	Kulke *et al.* 2009[57]
CAN-NCIC-PA3 (NCT00026338)	RCT Phase III	Adult patients with previously untreated mPAC or LAPC and an	No	Gemcitabine plus erlotinib (n=285) Gemcitabine	OS	PFS ORR	Moore *et al.* 2007[25]

Trial name (NCT number)	Design	Population	mPC data	Treatment arms	Primary outcome	Key secondary outcomes	Primary study reference
	Parallel-group Double-blind	ECOG PS of 0–2		monotherapy (n=284)		HRQL Safety	
Chao 2013	RCT Parallel-group Open-label	Adult patients with previously untreated mPC in Taiwan	Yes	Gemcitabine plus cisplatin (n=21) Gemcitabine monotherapy (n=25)	ORR	OS TTP HRQL Safety	Chao *et al.* 2013[49]
Colluci 2002	RCT Phase III Parallel-group	Adult patients with previously untreated mPC or LAPC and a KPS score ≥50	No	Gemcitabine plus cisplatin (n=53) Gemcitabine monotherapy (n=54)	TTP	OS ORR	Colluci *et al.* 2002[58]
CRUK-GEM-CAP (NCT00032175)	RCT Phase III Parallel-group Open-label	Adult patients with previously untreated mPAC or LAPC and a WHO PS score of 0–2	No	Gemcitabine plus capecitabine (n=267) Gemcitabine monotherapy (n=266)	OS	PFS ORR HRQL Safety	Cunningham *et al.* 2009[45]
Di Contanzo 2005	RCT Phase II Parallel-group	Adult patients with previously untreated mPC or LAPC and a KPS score ≥50	No	Gemcitabine plus 5-FU (n=43) Gemcitabine monotherapy (n=48)	ORR	OS PFS Safety	Di Contanzo *et al.* 2005[59]
ECOG-6201 (NCT00058149)	RCT Phase III Parallel-group	Adult patients with previously untreated mPAC OR LAPC and an ECOG PS of 0–2	No	Gemcitabine plus oxaliplatin (n=261) Gemcitabine FDR (n=275) Gemcitabine monotherapy (n=261)	OS	PFS ORR Safety	Poplin *et al.* 2009[60]
ECOG E2297	RCT	Adult patients with previously untreated	No	Gemcitabine plus 5-FU (n=160)	OS	TTP	Berlin *et al.* 2002[61]

Trial name (NCT number)	Design	Population	mPC data	Treatment arms	Primary outcome	Key secondary outcomes	Primary study reference
	Phase III Parallel-group	mPC or LAPC and an ECOG PS of 0–2		Gemcitabine monotherapy (n=162)		ORR	
FRE-GERCOR-GEMOX-D99-2 (NCT00006117)	RCT Phase III	Adult patients with previously untreated mPAC or LAPC and a WHO PS score of 0–2	Yes	Gemcitabine plus oxaliplatin (n=163) Gemcitabine monotherapy (n=163)	OS	PFS ORR Safety	Louvet *et al.* 2005[62]
Heinemann 2006	RCT Phase III Parallel-group Open-label	Adult patients with previously untreated mPC or LAPC and a KPS score of 70 or more	Yes	Gemcitabine plus cisplatin (n=98) Gemcitabine monotherapy (n=97)	OS	PFS ORR	Heinemann *et al.* 2006[63]
SAKK 44/00 (NCT00030732)	RCT Phase III Parallel-group Open-label	Adult patients with previously untreated mPAC or uLAPC and a KPS score of 60–100	No	Gemcitabine plus capecitabine (n=160) Gemcitabine monotherapy (n=159)	OS	PFS ORR HRQL Safety	Herrmann *et al.* 2007[46]
Scheithauer 2003	RCT Phase II Parallel-group	Adult patients with previously untreated mPAC and a KPS score of 50 or more	Yes	Gemcitabine plus capecitabine (n=41) Gemcitabine monotherapy (n=42)*	PFS	OS ORR	Scheithauer *et al.* 2003[47]
Wang 2002	RCT Phase III Parallel-group	Adult patients with previously untreated mPC or LAPC and a KPS score of 60–80 in China	Yes	Gemcitabine plus cisplatin (n=22) Gemcitabine monotherapy (n=20)	ORR	OS TTP Safety	Wang *et al.* 2002[64]
Wang 2015 (NCT01608841)	RCT Phase II	Adult patients with previously untreated mPC and an ECOG PS	Yes	Gemcitabine plus erlotinib (n=44) Gemcitabine	DCR	ORR OS	Wang *et al.* 2015[65]

Trial name (NCT number)	Design	Population	mPC data	Treatment arms	Primary outcome	Key secondary outcomes	Primary study reference
	Parallel-group Open-label	of 0–2 in Taiwan		monotherapy (n=44)		PFS	

Key: 5-FU, fluorouracil; ECOG, Eastern Cooperative Oncology Group; FDR, fixed dose rate; HRQL, health-related quality of life; KPS, Karnofsky Performance Status; LAPC, locally advanced pancreatic cancer; mPAC, metastatic pancreatic adenocarcinoma; mPC, metastatic pancreatic cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; RCT, randomised controlled trial; TTP, time-to-progression; uLAPC, unresectable locally advanced pancreatic cancer; WHO, World Health Organization.
Note: * Gemcitabine monotherapy administered at the higher dose of 2,200mg.

4.10.3. Methods and outcomes of included studies

Full details of the trial methodology and patient characteristics for studies included in the NMA alongside CA046 are provided in Appendix 4.

Some differences were observed in the dosing regimens adopted for common drugs, either in dose size or scheduling (see Appendix 4). In the case of gemcitabine monotherapy, although most studies adopted the standard 1000mg dose administered by IV infusion over approximately 30 minutes, gemcitabine was also administered at the higher dose of 2200mg or at a fixed dose rate (FDR). Clinical advice sought by the ERG as part of the previous appraisal was that differences in the dosing regimen would have little impact on the NMA outcomes. Furthermore, we have been advised by an expert clinician that the gemcitabine FDR regimen adopted in the CALGB 89904 trial[57] is not used in UK practice. Substantial differences were observed in sample sizes that ranged from a total population of 42 patients to the 861 patients enrolled in CA046.

Regarding patient populations, seven trials exclusively enrolled patients with mPC or mPAC; three further studies reported subgroup analysis for this patient group (Table 15). Patient demographics were generally well balanced both within and across trials at baseline, but there were differences in race, with three trials exclusively enrolling Asian populations. Clinical characteristics at baseline were also generally well balanced within trials, but some differences were observed across trials in the extent of metastatic disease (number of metastatic sites and location of metastases), CA19-9 levels, and tumour location, which can be associated with presence of a biliary stent. In addition, comparisons of performance status are hampered by the different assessment criteria adopted. Poor performance status, the extent of metastatic disease, pancreatic head tumour location and the associated presence of a biliary stent, and elevated CA19-9 levels can be associated with worse prognosis[33, 34], and should thus be considered when naively comparing across trials. Importantly, the use of relative measures of treatment efficacy has been adopted for NMA that avoids the need for patients recruited to different trials within network to have the same prognosis on average.

Outcomes of included studies utilised for NMA are provided in Appendix 4. Of note, there were some differences in the way in which disease progression was measured;

some studies utilised the RECIST criteria as per the CA046 trial, while others adopted alternative criteria such as those developed by the World Health Organization (WHO). There was also a lack of clarity as to whether disease progression was investigator- or independently-assessed in most trials (see Appendix 4), and some trials provided time to progression (TTP) data.

4.10.4. Risk of bias

A complete quality assessment in accordance with the NICE-recommended checklist for RCT assessment of bias is presented for each trial in Appendix 4.

Although most trials were at a reasonably low risk of bias based on the assessment of selection bias, performance bias, attrition bias and detection bias, the applicability of all trials to routine clinical practice in England is questionable, particularly those conducted in Asia, and those comparing regimens not adopted in English practice. To provide a more focused analysis relevant to the UK setting, a NMA for the decision comparator set was performed (containing only trials comparing regimens adopted in English practice and enrolling European patients) and is presented as a sensitivity analyses (see methods of analysis in this section).

4.10.5. Methods of analysis and presentation of results

A series of NMAs were performed to estimate comparative efficacy between the relevant trials identified in the SLR. Comparative safety could not be estimated due to a paucity of comparable safety data.

The efficacy evidence base could be connected in a single network. Additional comparators not directly relevant to the decision problem were included in the network, which provided useful feedback loops from which inconsistency between direct and indirect evidence could be explored. All comparators formed the synthesis comparator set, even if not directly relevant to the decision problem; the decision comparator set was comprised of *nab*-P/Gem, gemcitabine monotherapy, FOLFIRINOX and Gem/Cap. These sets are defined in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 1.[66]

Within-trial HR data (for both OS and PFS) were extracted where reported. HRs were the primary outcome measure selected for analysis. However, not all studies reported these data; some trials included a KM curve for either OS and/or PFS from

which a HR could be estimated. This approach is described fully below. In the absence of both reported HRs and KM curves, median survival was explored. The hierarchy of data was as follows:

1) Reported HRs

2) Estimated HRs (from KM curves)

3) Median survival

The motivation for this hierarchy is that pairwise HRs were obtained from the NMAs and that median survival is a limited summary measure of time-to-event data. Where trials reported both HR data and median data, HR data were selected for inclusion in all analyses, as recommended by Woods *et al.*[67] The NMA model proposed by Woods *et al.* allows synthesis of a combination of different types of survival data, and using this approach, the evidence base is maximised, meaning that trials are not excluded due to a lack of reported HR data, despite the potential limitations of using median survival data. Where studies included a published KM curve, pseudo-individual patient data (IPD) was estimated using an algorithm for statistical software, R (version 3.3.2), proposed by Guyot *et al.*[68], along with digitisation software. An estimated HR (and a corresponding measure of uncertainty) was then calculated based on this pseudo-IPD using a Cox regression model. The recreated pseudo-IPD was inspected visually to verify that the estimated KM curves were consistent with those presented in each publication.

Results from a series of NMAs are presented for the following scenarios:

- Base case analysis:
  - Exclusively mPC population data within the mPC network
  - Extensive set of comparators (to provide feedback loops between comparators of interest)
  - Combination of HR and median survival data (HR data where reported/estimated, otherwise median survival) [statistical model 1a]
  - Fixed-effect model
- Sensitivity analysis 1:
  - Exclusively mPC population data within the mPC network

  - Extensive set of comparators (to provide feedback loops between comparators of interest)
  - Combination of HR and median survival data (HR data where reported/estimated, otherwise median survival) [statistical model 1b]
  - Random-effects model
- Sensitivity analysis 2:
  - Exclusively mPC population data within the mPC network
  - Reduced set of comparators relevant to the NICE scope (resulting in the absence of feedback loops)
  - Exclusively HR data (reported for all included studies) [statistical model 2]
  - Fixed-effect model
- Sensitivity analysis 3:
  - Combination of mPC and LAPC population data within the mPC network (mPC median survival data replaced with LAPC HR data where mPC HR data [absolute or KM curve] not reported)
  - Extensive set of comparators (to provide feedback loops between comparators of interest)
  - Exclusively HR data (estimated where not reported) [statistical model 2]
  - Fixed-effect model

Each sensitivity is based on one alteration to the base case analysis in order to test the stability of the NMA results.

Technical details of the methodology adopted for NMA are provided in Appendix 4.

Presentation of results

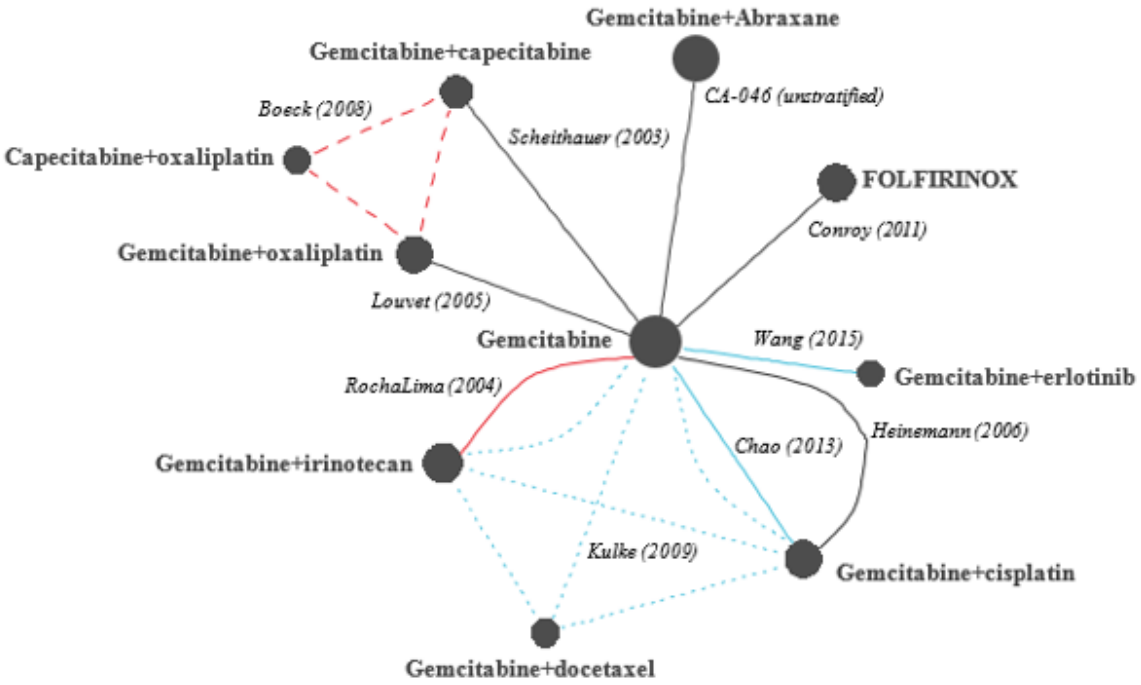
The network of evidence is presented for each analysis and identifies the format of data available for each trial. Only relative treatment effects were estimated within the NMA and are represented by pairwise HRs and corresponding 95% credible intervals (CrI) and take the form of forest plots. Relative treatment effects versus *nab*-P/Gem are provided in the main submission text; comparisons versus

gemcitabine are provided in Appendix 4. *Nab*-P/Gem is referred to as Gemcitabine plus Abraxane in the NMA figures and tables. The treatment ranking probabilities are also presented; the probability of each treatment being ranked as the best treatment is tabulated along with the expected (median) rank and corresponding 95% CrI.

Base case analysis – OS

The network of evidence is presented in Figure 9. The base case analyses for both OS and PFS rely upon synthesis of a combination of both HR data (reported and estimated) and median survival data. Ten studies are included in the analysis (eight two-arm, one three-arm, one four-arm), evaluating the efficacy of ten treatments.

Figure 7: Network of evidence – base case analysis – OS



Key: OS, overall survival.
Notes: Black lines represent reported HR data; blue lines represent HR data digitised from published KM curves; red lines represent median survival data; solid lines represent two-arm studies; dashed lines represent three-arm studies; dotted lines represent four-arm studies; node sizes are proportional to the number of patients treated with the respective intervention.

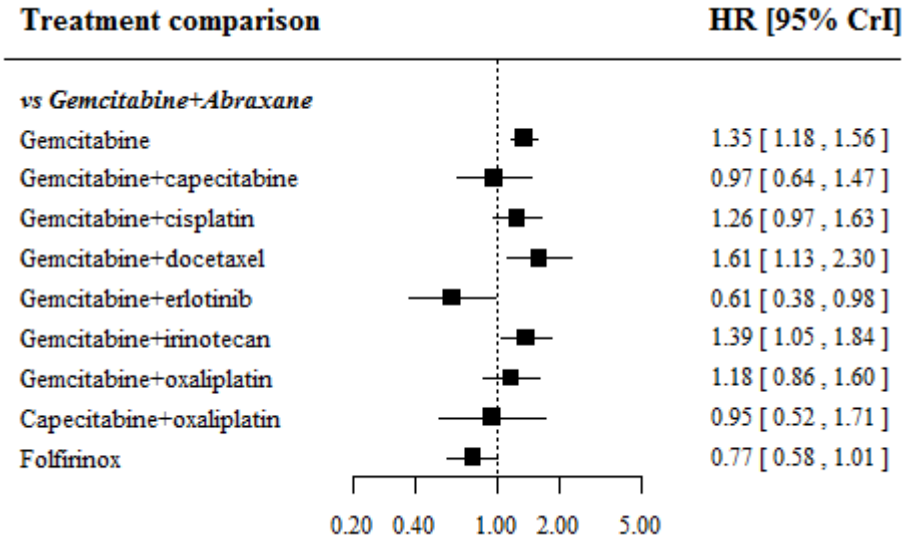
Relative effects versus *nab*-P/Gem are presented in Figure 10; relative effects versus gemcitabine are presented in Appendix 4. All but two interventions (gemcitabine plus docetaxel and gemcitabine plus irinotecan) show a trend of superiority versus gemcitabine. Three treatments (*nab*-P/Gem, gemcitabine plus

erlotinib, FOLFIRINOX) show a statistically significant reduction in the hazard of death versus gemcitabine.

Two interventions show a statistically significantly inferior HR versus *nab*-P/Gem: gemcitabine (HR=1.35, 95% CrI [1.18, 1.56]) and gemcitabine plus docetaxel (HR=1.61, 95% CrI [1.13, 2.30]). Additionally, three interventions (gemcitabine plus cisplatin, gemcitabine plus irinotecan, gemcitabine plus oxaliplatin) show a numerically inferior HR versus *nab*-P/Gem. One intervention (gemcitabine plus erlotinib) shows a statistically significant superior HR versus *nab*-P/Gem (HR=0.61, 95% CrI [0.38, 0.98]), and three interventions (Gem/Cap, capecitabine plus oxaliplatin, FOLFIRINOX) show a numerically superior HR versus *nab*-P/Gem.

The posterior probabilities that *nab*-P/Gem is numerically more efficacious than gemcitabine plus capecitabine and FOLFIRINOX are 0.45 and 0.03, respectively.

Figure 8: Relative effects versus gemcitabine plus Abraxane – base case – OS



Key: CrI, credible interval; HR, hazard ratio; OS, overall survival.
Notes: Point estimates lying to the left of 1 favour the treatment under observation over the reference treatment.

The probability of being the best treatment is presented in Table 16. Full treatment ranking histograms are presented in Appendix 4. *Nab*-P/Gem is expected to be ranked as the equal fourth best treatment, with a similar efficacy estimate to Gem/Cap and capecitabine plus oxaliplatin.

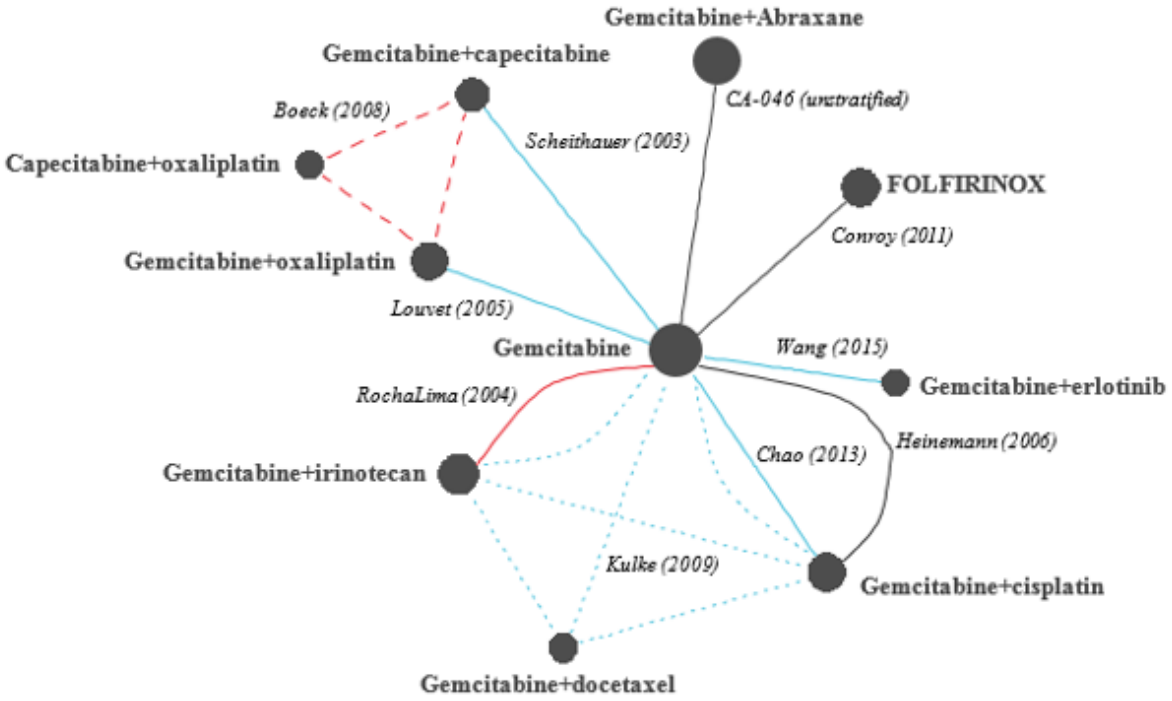
Table 16: Probability of being the best and median rank – base case – OS

Treatment	Probability best	Median rank [95% CrI]
Gemcitabine	0.000	8 [6, 10]
Gemcitabine+Abraxane	0.001	4 [3, 6]
Gemcitabine+capecitabine	0.024	4 [2, 8]
Gemcitabine+cisplatin	0.000	7 [4, 9]
Gemcitabine+docetaxel	0.000	10 [6, 10]
Gemcitabine+erlotinib	0.741	1 [1, 4]
Gemcitabine+irinotecan	0.000	9 [5, 10]
Gemcitabine+oxaliplatin	0.000	6 [4, 10]
Capecitabine+oxaliplatin	0.084	4 [1, 10]
FOLFIRINOX	0.150	2 [1, 4]
Key: CrI, credible interval; FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin.		

Base case analysis – PFS

The network of evidence is presented in Figure 11; 10 studies are included (eight two-arm, one three-arm, one four-arm), evaluating 10 interventions. Due to the varying definitions of PFS assessment across studies (see Appendix 4), this endpoint was analysed using two definitions of CA046 trial data: independent and investigator assessments. The independent assessment of PFS was the named secondary endpoint in the CA046 trial, but investigator assessment of PFS was utilised for the CE model as a better reflection of clinical practice; this approach was supported by the ERG during the previous NICE appraisal (see Section 5).

Figure 9: Network of evidence – base case analysis – PFS



Key: PFS, progression-free survival.
Notes: Black lines represent reported HR data; blue lines represent HR data digitised from published KM curves; red lines represent median survival data; solid lines represent two-arm studies; dashed lines represent three-arm studies; dotted lines represent four-arm studies; node sizes are proportional to the number of patients treated with the respective intervention.

Independent PFS assessment

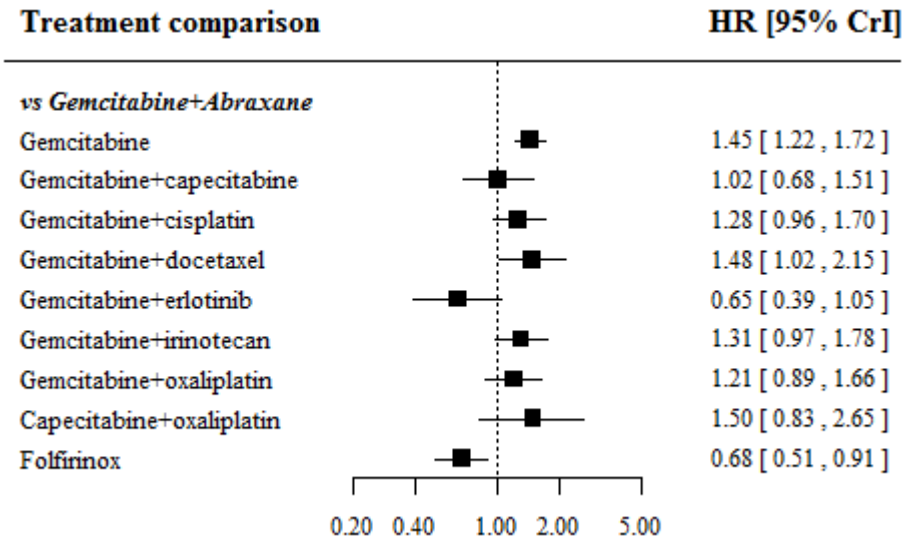
Relative effects versus *nab*-P/Gem are presented in Figure 12; relative effects versus gemcitabine are presented in Appendix 4. All but two interventions (gemcitabine plus docetaxel and capecitabine plus oxaliplatin) show a trend of superiority versus gemcitabine. Four treatments (*nab*-P/Gem, Gem/Cap gemcitabine plus erlotinib, FOLFIRINOX) show a statistically significant reduction in the hazard of progression versus gemcitabine.

Two interventions show a statistically significantly inferior HR versus *nab*-P/Gem: gemcitabine (HR=1.45, 95% CrI [1.22, 1.72]) and gemcitabine plus docetaxel (HR=1.48, 95% CrI [1.02, 2.15]). Additionally, five interventions (Gem/Cap, gemcitabine plus cisplatin, gemcitabine plus irinotecan, gemcitabine plus oxaliplatin, capecitabine plus oxaliplatin) show a numerically inferior HR versus *nab*-P/Gem.

One intervention (FOLFIRINOX) shows a statistically significant superior HR versus *nab*-P/Gem (HR=0.68, 95% CrI [0.51, 0.91]), and one intervention (gemcitabine plus erlotinib) shows a numerically superior HR versus *nab*-P/Gem.

The posterior probabilities that *nab*-P/Gem is numerically more efficacious than Gem/Cap and FOLFIRINOX are 0.53 and <0.01, respectively.

Figure 10: Relative effects versus gemcitabine plus Abraxane – base case – PFS (independent assessment)



Key: CrI, credible interval; HR, hazard ratio; PFs, progression-free survival.
Notes: Point estimates lying to the left of 1 favour the treatment under observation over the reference treatment.

Investigator PFS assessment

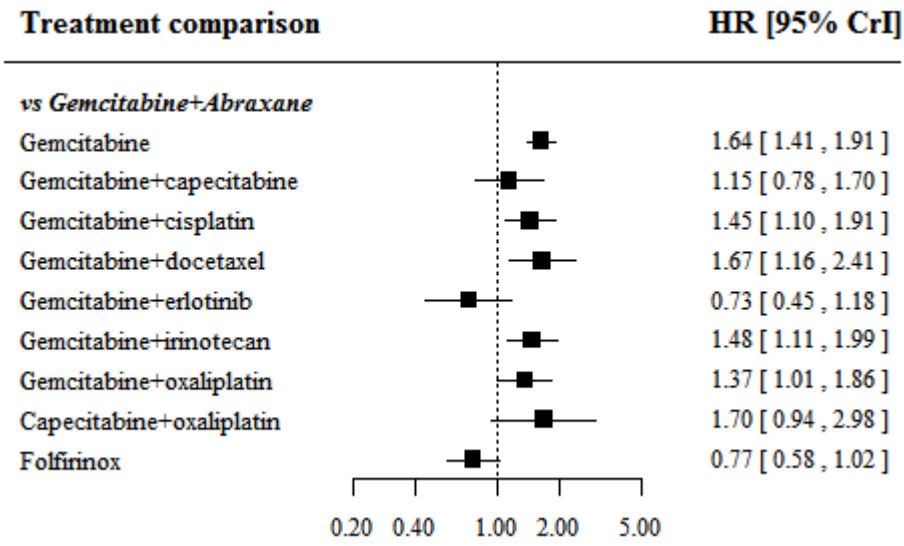
Relative effects versus *nab*-P/Gem are presented in Figure 13; relative effects versus gemcitabine are presented in Appendix 4. All but two interventions (gemcitabine plus docetaxel and capecitabine plus oxaliplatin) show a trend of superiority versus gemcitabine. Four treatments (*nab*-P/Gem, Gem/Cap, gemcitabine plus erlotinib, FOLFIRINOX) show a statistically significant reduction in the hazard of progression versus gemcitabine.

Five interventions show a statistically significantly inferior HR versus *nab*-P/Gem: gemcitabine (HR=1.64, 95% CrI [1.41, 1.91]), gemcitabine plus cisplatin (HR=1.45, 95% CrI [1.10, 1.91]), gemcitabine plus docetaxel (HR=1.67, 95% CrI [1.16, 2.41]), gemcitabine plus irinotecan (HR=1.48, 95% CrI [1.11, 1.99]) and gemcitabine plus

oxaliplatin (HR=1.37, 95% CI: 1.01, 1.86). Additionally, two interventions (Gem/Cap and capecitabine plus oxaliplatin) show a numerically inferior HR versus *nab*-P/Gem. While two interventions (FOLFIRINOX and gemcitabine plus erlotinib) show a trend of numerical superiority versus *nab*-P/Gem, these comparisons are not statistically significant.

The posterior probabilities that *nab*-P/Gem is numerically more efficacious than Gem/Cap and FOLFIRINOX are 0.76 and 0.03, respectively.

Figure 11: Relative effects versus gemcitabine plus Abraxane – base case – PFS (investigator assessment)



Key: CrI, credible interval; HR, hazard ratio; PFs, progression-free survival.
Notes: Point estimates lying to the left of 1 favour the treatment under observation over the reference treatment.

The probability of being the best treatment is presented in Table 17. Full treatment ranking histograms are presented in Appendix 4. *Nab*-P/Gem is expected to be ranked as the equal fourth best treatment (independent PFS assessment) or third best treatment (investigator PFS assessment), with a similar efficacy estimate to Gem/Cap.

Table 17: Probability of being the best and median rank – base case – PFS

Treatment	*Independent assessment*		*Investigator assessment*	
	Probability best	**Median rank [95% CrI]**	**Probability best**	**Median rank [95% CrI]**
Gemcitabine	0.000	9 [6, 10]	0.000	9 [6, 10]
Gemcitabine+Abraxane	0.001	4 [2, 6]	0.006	3 [2, 5]
Gemcitabine+capecitabine	0.011	4 [2, 8]	0.011	4 [2, 8]
Gemcitabine+cisplatin	0.000	6 [4, 10]	0.000	6 [4, 10]
Gemcitabine+docetaxel	0.000	9 [4, 10]	0.000	9 [5, 10]
Gemcitabine+erlotinib	0.571	1 [1, 4]	0.569	1 [1, 4]
Gemcitabine+irinotecan	0.000	7 [4, 10]	0.000	7 [4, 10]
Gemcitabine+oxaliplatin	0.000	6 [3, 9]	0.000	6 [4, 9]
Capecitabine+oxaliplatin	0.003	9 [3, 10]	0.003	9 [3, 10]
FOLFIRINOX	0.414	2 [1, 3]	0.411	2 [1, 3]

Key: FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin; CrI, credible interval; PFS, progression-free survival.

Sensitivity analysis 1 – OS

Random-effects model results are presented in Appendix 4. The network of evidence is identical, and the data utilised in the analysis remain consistent with the base case analysis; only the underlying model has changed (statistical model 1b). Point estimates (pairwise HRs) are comparable to those observed in the base case analysis; however, only gemcitabine plus erlotinib remains statistically significantly superior to gemcitabine, and there are no statistically significant comparisons versus *nab*-P/Gem. Additional uncertainty is observed (as expected) when fitting a random-effects model, which accounts for the presence of between-study heterogeneity.

Sensitivity analysis 1 – PFS

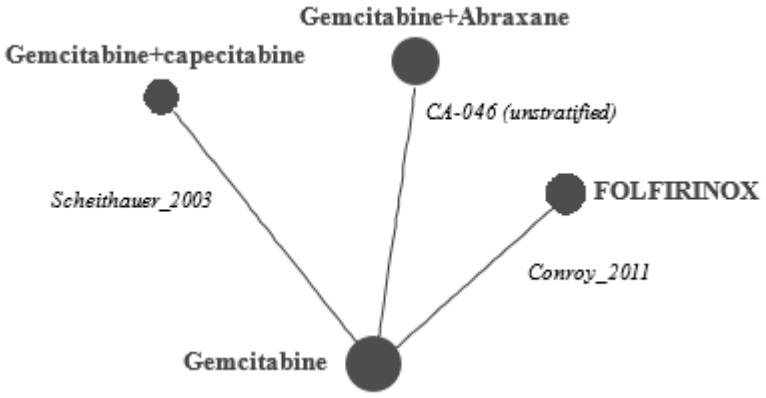
Random-effects model results are presented in Appendix 4. The network of evidence is identical, and the data utilised in the analysis remain consistent with the base case analysis; only the underlying model has changed (statistical model 1b). Point estimates are comparable to those observed in the base case analysis; however, only gemcitabine plus erlotinib and FOLFIRINOX remain statistically significantly

superior to gemcitabine, and there are no statistically significant comparisons versus *nab*-P/Gem. Additional uncertainty is observed (as expected) when fitting a random-effects model, which accounts for the presence of between-study heterogeneity.

Sensitivity analysis 2 – OS

A focused, reduced network of evidence was explored, including only comparators relevant to the NICE scope. As a result, the network is based on direct evidence only (no feedback loops are present between the comparators of interest) and is presented in Figure 14. Three two-arm studies are included in the NMA, all reporting HR data, and consequently, statistical model 2 was fitted to the data.

Figure 12: Network of evidence – sensitivity analysis 2 – OS



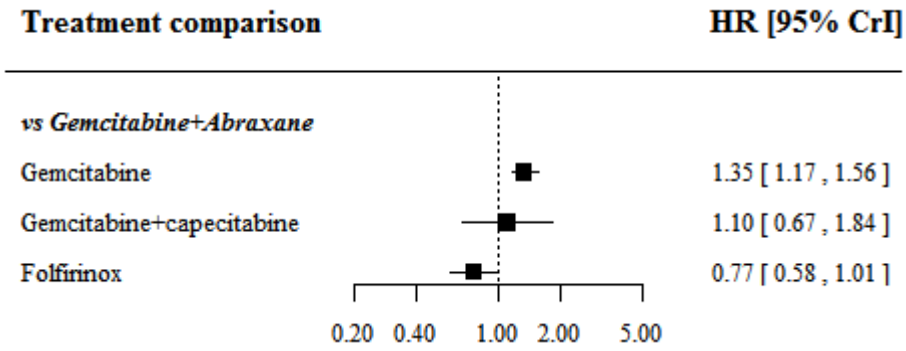
Key: OS, overall survival.
Notes: Black lines represent reported HR data; solid lines represent two-arm studies; node sizes are proportional to the number of patients treated with the respective intervention.

Relative effects versus *nab*-P/Gem are presented in Figure 15; relative effects versus gemcitabine are presented in Appendix 4. *Nab*-P/Gem and FOLFIRINOX show a statistically significant reduction in the hazard of death versus gemcitabine. Gem/Cap shows a numerically superior HR versus gemcitabine but this result is not statistically significant. *Nab*-P/Gem is numerically superior to Gem/Cap, and FOLFIRINOX is numerically superior to *nab*-P/Gem; however, neither comparison is statistically significant. Compared to the base case analysis, the HR for Gem/Cap versus gemcitabine is increased, and consequently, the HR between Gem/Cap and *nab*-P/Gem has changed direction and numerically favours *nab*-P/Gem.

This means that *nab*-P/Gem has a higher posterior probability (compared to the base case analysis) of being numerically superior to Gem/Cap. The posterior probabilities

that *nab*-P/Gem is numerically more efficacious than Gem/Cap and FOLFIRINOX are 0.65 and 0.03, respectively.

Figure 13: Relative effects versus gemcitabine plus Abraxane – sensitivity analysis 2 – OS



Key: CrI, credible interval; HR, hazard ratio; OS, overall survival.
Notes: Point estimates lying to the left of 1 favour the treatment under observation over the reference treatment.

The probability of being the best treatment is presented in Table 18. Full treatment ranking histograms are presented in Appendix 4. *Nab*-P/Gem is expected to be the second-best treatment (probability=0.63) (after FOLFIRINOX) out of this reduced, decision comparator set.

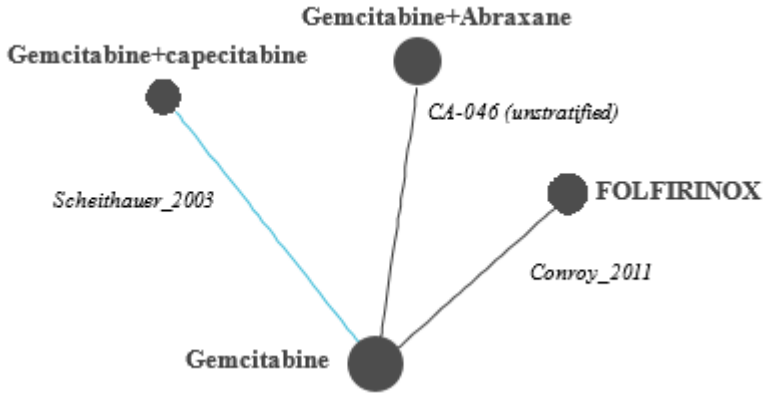
Table 18: Probability of being the best and median rank

Treatment	Probability best	Median rank (95% CrI)
Gemcitabine	0.000	4 (3, 4)
Gemcitabine+Abraxane	0.025	2 (2, 3)
Gemcitabine+capecitabine	0.097	3 (1, 4)
FOLFIRINOX	0.878	1 (1, 2)
Key: FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin; CrI, credible interval.		

Sensitivity analysis 2 – PFS

As for OS, this analysis relies on a reduced comparator list, and therefore, only direct evidence is available for synthesis. The network of evidence is presented in Figure 16. Two studies explicitly reported HR data, while one study presented a KM curve from which a HR could be estimated.

Figure 14: Network of evidence – sensitivity analysis 2 – PFS

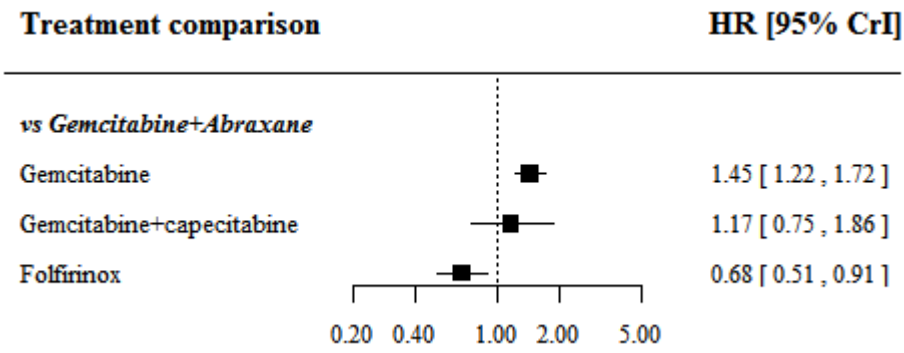


Key: PFS, progression-free survival.
Notes: Black lines represent reported HR data; blue line represent HR data digitised from published KM curves; solid lines represent two-arm studies; node sizes are proportional to the number of patients treated with the respective intervention.

Relative effects versus *nab*-P/Gem are presented in Figure 17; relative effects versus gemcitabine are presented in Appendix 4. *Nab*-P/Gem and FOLFIRINOX show a statistically significant reduction in the hazard of progression versus gemcitabine. Gem/Cap shows a numerically superior HR versus gemcitabine, but this result is not statistically significant. *Nab*-P/Gem is numerically superior to Gem/Cap, and FOLFIRINOX is statistically significantly superior to *nab*-P/Gem.

The posterior probabilities that *nab*-P/Gem is numerically more efficacious than Gem/Cap and FOLFIRINOX are 0.75 and <0.01, respectively.

Figure 15: Relative effects versus gemcitabine plus Abraxane – sensitivity analysis 2 – PFS



Key: CrI, credible interval; HR, hazard ratio; PFS, progression-free survival.
Notes: Point estimates lying to the left of 1 favour the treatment under observation over the reference treatment.

The probability of being the best treatment is presented in Table 19. Full treatment ranking histograms are presented Appendix 4. *Nab*-P/Gem is expected to be the second-best treatment (probability=0.75) (after FOLFIRINOX) out of this reduced, decision comparator set.

Table 19: Probability of being the best and median rank

Treatment	Probability best	Median rank [95% CrI]
Gemcitabine	0.000	4 [3, 4]
Gemcitabine+Abraxane	0.005	2 [2, 3]
Gemcitabine+capecitabine	0.013	3 [2, 4]
FOLFIRINOX	0.982	1 [1, 1]
Key: CrI, credible interval; FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin.		

Sensitivity analysis 3 – OS

NMA model results based on exclusively HR data are presented in Appendix 4. For this analysis, the network is identical to the base case, but data from two studies reporting median survival data for an mPC subgroup are superseded with HR data from the total trial population (LAPC) (statistical model 2). Point estimates (pairwise HRs) are comparable to those observed in the base case analysis but the HR between Gem/Cap and *nab*-P/Gem has changed direction and numerically favours

nab-P/Gem (HR: 1.02 [95% CrI: 0.70, 1.47]). Treatment ranking probabilities remain consistent.

Comparison of NMA sensitivity analysis results with base case analysis

All NMA results presented show stability of the pairwise relative treatment effects. Sensitivity analysis results are consistent with the base case analysis for both OS and PFS; however, the most notable difference is observed when synthesising only direct data (sensitivity analysis 2). Furthermore, all sensitivity analyses performed do show that while for some treatment comparisons, numerical trends alter in direction, the NMA results do not alter significantly.

The probability of superiority across analyses are summarised in Table 20. *Nab*-P/Gem has a greater probability of being more efficacious versus Gem/Cap when including only direct evidence in the NMA, and when exclusively populating the model with HR data. This suggests the NMA results may be sensitive to the type of data included in the analysis (e.g. direct evidence only versus combination of direct and indirect evidence or HR versus median survival).

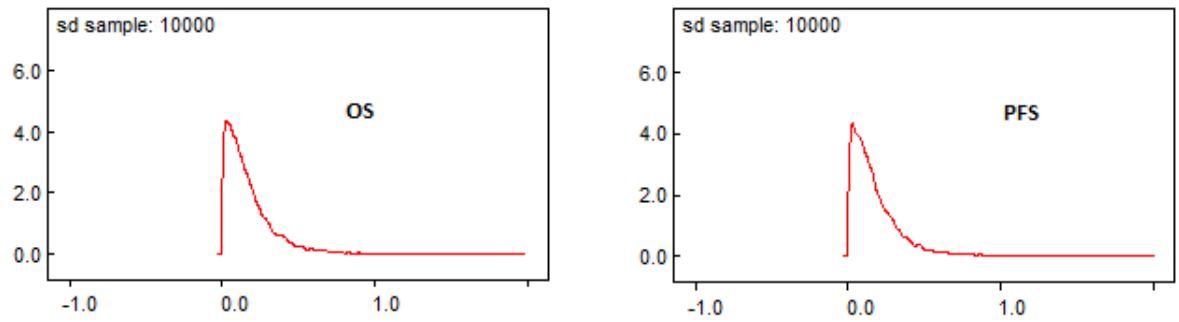
Table 20: Probability of superiority

Analysis	**Probability that gemcitabine plus Abraxane is numerically superior to Gem/Cap**	**Probability that gemcitabine plus Abraxane is numerically superior to FOLFIRINOX**
Base case analysis – OS	0.45	0.03
Sensitivity analysis 1 – OS	0.46	0.15
Sensitivity analysis 2 – OS	0.65	0.03
Sensitivity analysis 3 – OS	0.54	0.04
Base case analysis – PFS (independent/investigator)	0.53/0.76	<0.01/0.03
Sensitivity analysis 1 – PFS (independent)	0.52	0.10
Sensitivity analysis 2 – PFS (independent)	0.75	0.01
Key: FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin; Gem/Cap, gemcitabine plus capecitabine; OS, overall survival; PFS, progression-free survival.		

Statistical heterogeneity

In addition to the clinical heterogeneity that is observed between the trials included in the NMA, there is also statistical heterogeneity, which needs to be addressed. A fixed-effect model was fitted to the data in all analyses except sensitivity analysis 1. By their very nature, fixed-effect models do not account for any heterogeneity that may be present in the network; it is assumed that every trial estimates the same underlying treatment effects, and any deviations are assumed to arise from sampling error alone. These models are consequently likely to underestimate the uncertainty in the treatment effects. The DIC was assessed to select the best fitting model; the fixed-effect model yielded the lowest DIC value and was therefore selected as the base case analysis. The equivalent random-effects models for both OS and PFS (sensitivity analysis 1) showed that there was mild-to-moderate statistical heterogeneity present; the median posterior estimates of this heterogeneity parameter are 0.12 (95% CrI [0.01, 0.65]) and 0.13 (95% CrI [0.01, 0.67]) for OS and PFS, respectively. The posterior distributions of the between-study heterogeneity parameter are presented in Figure 18 and demonstrated adequate Bayesian updating.

Figure 16: Posterior distribution of between-study heterogeneity parameter



Key: OS, overall survival; PFS, progression-free survival.

Inconsistency between direct and indirect evidence

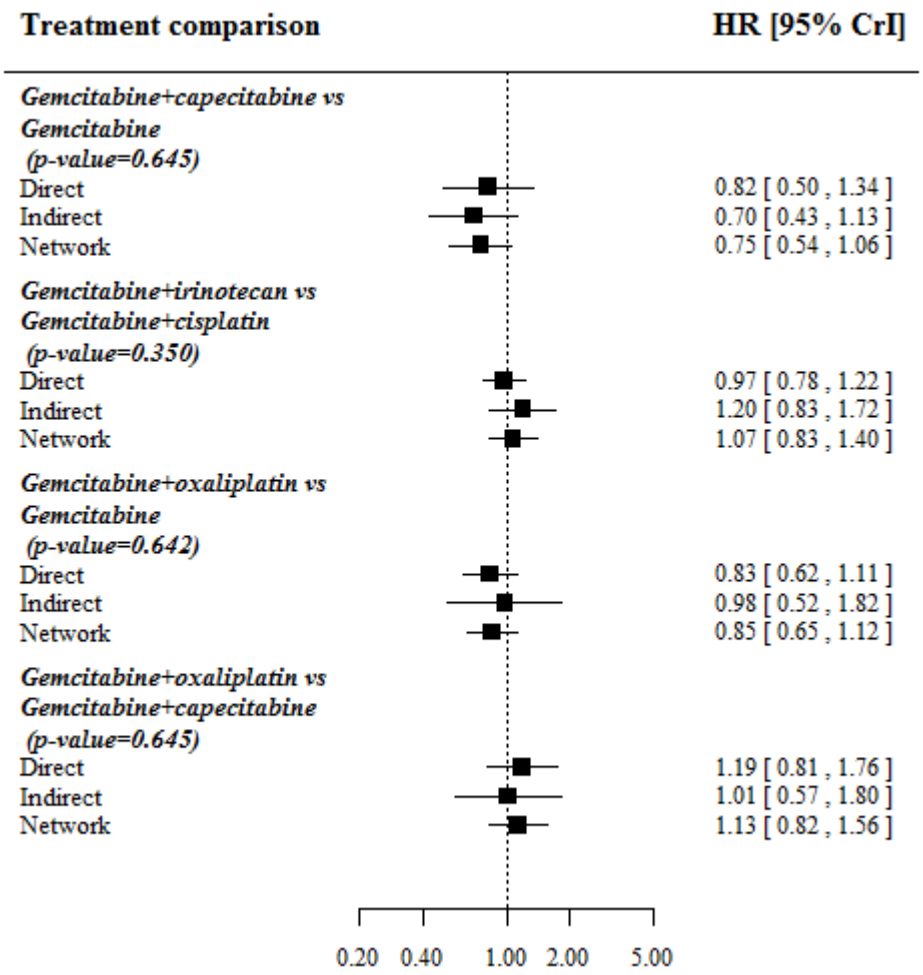
Statistical inconsistency between direct and indirect evidence could be explored within sensitivity analysis 3 for OS, using a model that relies on synthesis of HR data only (arising from both the mPC and the LAPC population).

Due to the presence of two feedback loops (from evidence not arising from multi-arm trials), inconsistency could be checked for the following four pairwise treatment comparisons:

- Gem/Cap versus gemcitabine
- Gemcitabine plus irinotecan versus gemcitabine plus cisplatin
- Gemcitabine plus oxaliplatin versus gemcitabine
- Gemcitabine plus oxaliplatin versus Gem/Cap

Since a Bayesian framework was adopted for the NMA, a node-splitting approach was utilised to explore any potential inconsistency between the direct and indirect evidence available for these comparisons, as described in NICE DSU TSD 4.[69] A forest plot including direct, indirect and NMA estimates is presented, along with a corresponding p-value. The results are shown in Figure 19; there is insufficient evidence to show that there is statistically significant inconsistency present in the network (assuming the treatment comparisons that could be explored are representative of all comparisons in the evidence base). The NMA estimate is a compromise between direct and indirect evidence, and although some of the indirect and direct HRs show a difference in direction around the line of no difference (HR=1) (e.g. in the second treatment comparison), none of the discrepancies are statistically significant; that is, there is a great deal of overlap of the 95% CrIs. The large amount of the uncertainty observed is likely due to the presence of only one trial for most of the treatment comparisons. Moreover, LAPC data contributed to each scenario where inconsistency could be checked, and these results suggest that these data may be representative of what might have been observed in the mPC population; that is, there is no inconsistency detected between direct and indirect evidence where the indirect evidence is comprised of LAPC data.

Figure 17: Inconsistency results (node-splitting model) – sensitivity analysis 3 – OS



Key: CrI, credible intervals; HR, hazard ratio; OS, overall survival.

Exploration of the proportional hazards assumption

The main assumption underpinning the statistical models adopted to estimate comparative efficacy (based on HRs) is the presence of within-study proportional hazards (PH). Should there be notable deviation away from the PH assumption, it would potentially undermine results obtained from the NMAs and question the reliability of the conclusions and inferences drawn from them. Access to IPD was limited to the CA-046 trial (evaluating *nab*-P/Gem and gemcitabine monotherapy); exploration of remaining comparator trial data relied upon digitisation methods to recreate pseudo-IPD.

The PH assumption was investigated for all studies that were included in at least one NMA. The following diagnostics were explored (as described further by Collet 2003[70]) as follows:

- Visual inspection of log-cumulative hazard (LCH) plots
- Visual inspection of Schoenfeld residual plots and corresponding correlation estimates and p-values assessing proportionality
- Comparison of observed and predicted KM curves (estimated from a Cox PH regression model)

LCH plots were created for each study (based on recreated, pseudo-IPD), which show the log of time versus the log of the negative log of the estimated survival distribution function for each treatment arm. If these curves are parallel, where the difference in log-cumulative hazards between treatments remains constant over time, this would suggest that the PH assumption may be reasonable. However, the interpretation and conclusions made regarding the LCH plots are subjective, and for many studies included in the NMAs, it is not definitively clear whether the PH assumption holds based on inspection of these curves. For both OS and PFS, the LCH plots fail to clearly show whether the PH assumption is supported. In cases where the lines cross, this could suggest deviation away from the PH assumption, and alternative non-PH approaches may be more appropriate, for example, adopting time-dependent models. LCH plots are presented for OS and PFS in Appendix 4. For some studies, the curves fail to clearly show whether the PH assumption appears valid. During the initial follow-up period, the LCH curves do not appear to be parallel in many trials, suggesting that there might be some evidence to suggest non-proportionality between treatment arms. Within-study curves do show some overlap, convergence and crossing of lines; however, the extent of this varies substantially. For example, the PH assumption for the study reported by Wang *et al.*[65] looks reasonable for OS and PFS as the curves are typically parallel; however, for the study reported by Chao *et al.*[49], the curves cross on numerous occasions, which may suggest that the estimated HR might not necessarily be the most appropriate measure of the treatment effect, thus questioning the validity of the NMA estimates.

In addition to the LCH plots, Schoenfeld residuals obtained from a Cox regression model were also investigated as a diagnostic measure of PH assessment. These

residuals may be used to detect whether the covariate(s) adjusted for within a Cox regression model are in fact time-dependent.[71] Schoenfeld residuals are defined as the difference between the time-independent treatment coefficient estimated within a Cox regression model and the expected time-dependent treatment coefficient at each death time. These residuals may be transformed so their variance is approximately 1, to give scaled Schoenfeld residuals. Should the treatment coefficient not be dependent upon time, it would be expected that the scaled residuals would be distributed with mean zero.

A chi-squared test may be used to test for significant correlation between the time-dependent coefficient and time[72]; a significant correlation would indicate that hazards are not proportional over time. The test is limited in that it can only assess whether a linear relationship between the variables exists; correlation may be deemed statistically non-significant when the relationship between the variables is non-linear, but this non-linearity would indeed suggest a violation of the PH assumption. To visually explore this relationship, the time-dependent coefficient should be plotted against each time corresponding to an event (e.g. death or progression). A smoothed curve (represented by a red solid line) with 95% CI (represented by red dashed lines) may show more clearly how the time-dependent coefficient changes over time. The smoothed curve may then be compared with the estimate of the time-independent coefficient (represented by the black dashed line), and this curve should produce an approximately horizontal straight line equal to the time-independent coefficient if the PH assumption is considered appropriate. Should the time-independent coefficient value not be contained exclusively within the 95% CI of the smoothed curve, this may be indicative of violation of the PH assumption.

The time-dependent treatment effect versus time (captured on the log scale) are presented for OS and PFS in Appendix 4. For multi-arm trials, separate figures are presented for each comparator treatment against the reference treatment of that study. The p-values assessing the correlation derived from a chi-squared test are also presented alongside the scaled Schoenfeld residuals.

All residual plots fail to show a statistically significant correlation (using a 5% significance level); the corresponding p-values derived from a chi-squared test suggest that no significant correlation is observed between the time-dependent treatment effects and time, which would suggest that there is insufficient evidence to

infer deviation away from the PH assumption. However, for the OS and PFS from the CA046 trial[6] and the ACCORD trial[28], the time-independent estimate fails to remain within the 95% CI of the smoothed curve across the entire duration of the study period, suggesting that the hazards might be non-linear, and therefore, the assumption might not be valid.

A third approach adopted for further exploration of the within-study PH assumption was based on visually assessing the fit of the KM curve based on a Cox regression model, stratified by treatment arm. As HR data were unreported for many of the studies included in the NMAs, these HRs were estimated based on pseudo-IPD (from published KM curves). Therefore, it is useful to assess the comparability between the observed KM curves and those predicted from the Cox regression model upon which the HR is estimated. Should the predicted curves provide a good approximation to the observed KM curves, this may suggest that the corresponding estimated HR may be a robust measure of the treatment effect. If there is sufficient evidence that the PH assumption is not valid, it is likely that the predicted KM curve would also provide a poor fit to the observed KM curve; however, the assessment of the comparability of curves is also subjective.

In all predicted KM curves, as presented for OS and PFS in Appendix 4, there appears to be considerable overlap and very little discrepancy between the predicted and observed KM curves, which may indicate that the proportionality assumption underpinning the estimated HR may not be violated. The most notable discrepancies are observed for the studies with small samples and in the tails of the KM curves, which results in greater uncertainty around KM estimates. The analysis of PFS by independent assessment for the CA046 trial has a much larger number of patients, and the differences between the observed and predicted KM curves is therefore likely to be the result of non-proportional hazards, particularly towards the end of the study period in which the survival probability is overestimated for *nab*-P/Gem and underestimated for gemcitabine monotherapy.

Assessment of all three diagnostics leads to a slightly uncertain conclusion; indeed, there is insufficient evidence to conclude statistically significant deviation away from the PH assumption; however, this is likely attributed to the small sample sizes in many of the studies and the nature of these diagnostics being reliant upon subjective interpretation.

Discussion

There are several limitations of the statistical analyses presented; primarily, the number of studies available for each treatment comparison is limited, and therefore, relative efficacy is based on a maximum of one or two studies. This paucity of data means there is little evidence upon which to estimate comparative efficacy and trials, and the uncertainty around the NMA estimates is large. Furthermore, there is some disparity between studies in how data are reported. Regarding disease progression, there is a mixture of investigator- and independently-assessed PFS, and the tools used to evaluate PFS vary between RECIST and WHO criteria. In addition, some studies report TTP instead; however, for the purposes of the NMAs, it is assumed that these measures are equivalent.

Additionally, there is some (limited) reliance on median survival data – although only used for two studies, median survival has been shown to not be a reliable summary statistic or measure of treatment effect. While this is addressed in a sensitivity analysis (3) for OS, the HR estimates superseding median survival times arise from the total trial population (LAPC) and may therefore not be fully representative of the mPC patient group. There is also a limitation when synthesising HR data – analysis of a single point estimate may not capture the treatment effect adequately. All conventional NMAs suffer from this; however, where underlying assumptions around HRs are violated, this may not be an appropriate measure of relative efficacy. One study (Heinemann *et al.* 2006[63]) did not report a measure of uncertainty around the HR estimate for both OS and PS, and therefore, imputation methods proposed by Altman *et al.*[73] were applied, which estimated the standard error based on the observed within-trial p-value. In addition, not all studies included in the NMAs reported HRs, and while digitisation methods have proved successful in recreating pseudo-IPD, estimation of HRs (and corresponding measures of uncertainty) based on such data may not be as accurate as those directly reported in the literature.

The base case NMA adopted a fixed-effect model, and as such, does not reflect any heterogeneity that might be present between the studies. This means that the uncertainty around the NMA HRs may be underestimated as it assumed that there is no between-study variation. While providing the best fit to the data (according to the DIC), the fixed-effect model may yield too much precision around the NMA results, particularly given the notable variation between studies from a clinical perspective.

The equivalent random-effects model (sensitivity analysis 1) showed that while the NMA point estimates were almost identical to those presented in the base case analysis, the additional uncertainty observed might be more realistic and does account for the presence of heterogeneity between studies. Adopting a vague prior distribution did result in some Bayesian updating and showed the presence of mild-to-moderate statistical heterogeneity among the evidence base.

According to the NMAs, gemcitabine plus erlotinib (Gem/Erl) was associated with a superior OS and PFS benefit compared to all other treatments. However, there are several potential sources of bias in the single study providing data for this comparison[65] that questions the robustness of this outcome and, therefore, the reliability of the relative efficacy estimate. In terms of patient population, this trial was conducted in Taiwan and thus exclusively enrolled Asian patients who may not be representative of patients in UK practice. In terms of trial design, the objective was to clarify the effects of adding erlotinib to gemcitabine, using the disease control rate (DCR) as the primary efficacy outcome measure, and the roles of EGFR and KRAS mutations as predictive biomarkers. The trial was not powered to detect differences in OS and PFS, and the efficacy in the Gem/Erl arm seems to be driven by the presence of an EGFR mutation, something that is not usually screened for in the UK mPAC population. Absolute outcomes also appear low when comparing across common treatment arms; the median OS in patients treated with gemcitabine monotherapy was 4.4 months in the trial reported by Wang *et al.*[65], which was the lowest observed across trials despite patients having a good performance status at baseline (83% of patients ECOG 0); for example, median OS associated with gemcitabine monotherapy in the CA046 trial was 6.6 months (see Appendix 4). In the regulatory trial for Gem/Erl that enrolled 569 advanced pancreatic cancer patients (of which 75% had metastatic disease), a far more modest survival benefit versus gemcitabine monotherapy was observed (HR for death: 0.82 [95% CI: 0.69, 0.99][25]) than estimated through NMA (HR for death: 0.45 [95% CrI: 0.29, 0.70]).

Alongside the limitations already discussed, this may also be associated with the short-term follow-up at the time of analyses in the Wang trial[65]; in the gemcitabine monotherapy arm, the median follow-up was only 4.5 months. In earlier analyses of the trial reported by Chao *et al.*[49], which was also set in Taiwan, a similarly low median OS of 4.6 months[50] was observed in the gemcitabine monotherapy arm

when median follow-up was 5.3 months. With an extended follow-up, this median OS extended to 7.7 months in the gemcitabine monotherapy group. Although this raises its own questions around the validity of the Chao *et al.* trial data, it does suggest short-term survival may be lower in Taiwan than in other countries.

There are some further statistical concerns regarding the validity of reported results in the Chao *et al.* trial.[49] The reported median OS estimates are 7.7 and 7.9 months for gemcitabine monotherapy and gemcitabine plus cisplatin, respectively; however, the KM curves presented show different estimates; 5.1 and 5.3 months for gemcitabine monotherapy and gemcitabine plus cisplatin, respectively. In addition, the reported median TTP estimates are 4.6 and 3.6 months for gemcitabine monotherapy and gemcitabine plus cisplatin, respectively; however, the KM curve presented shows very different estimates and shows that gemcitabine plus cisplatin yields a higher median estimate (2.8 months) versus gemcitabine monotherapy (2.1 months). While pseudo-IPD was recreated for this study (based on digitisation methods of KM curves) to estimate a HR (which avoids the use of median survival data), this inconsistent reporting for both endpoints may undermine the robustness of results for this study, which are subsequently used in the NMAs.

Regarding the comparisons of interest to English practice (and thus this technology appraisal), FOLFIRINOX and *nab*-P/Gem were both associated with a significantly superior OS and PFS benefit compared to gemcitabine monotherapy; Gem/Cap demonstrated a numerically superior OS and PFS benefit compared to gemcitabine monotherapy, but this failed to reach statistical significance. In this respect, the NMA outcomes reflect observations from direct trial data for these comparisons. In base case analysis, FOLFIRINOX was associated with a superior OS and PFS benefit compared to *nab*-P/Gem (HR for death: 0.77 [95% CrI: 0.58, 1.01]; HR for death or disease progression: 0.68 [95% CrI: 0.51, 0.91]). Although the difference fell outside statistical significance for some analyses, OS and PFS superiority was maintained when the network was focused to direct trial data of relevance to the decision problem, and in all other sensitivity analyses, supporting the robustness of this outcome. Superiority of FOLFIRINOX was expected *a priori* as a multi-agent regimen is likely to be more effective than a doublet regimen, and this outcome is in line with expectations of the clinical community. As previously discussed (see Section 3.3), patients who have access to FOLFIRINOX in current practice, and for whom this

treatment is considered suitable, will continue to receive FOLFIRINOX despite the accessibility of *nab*-P. The comparison of *nab*-P/Gem and Gem/Cap was far less conclusive. In the base case analysis, minimal difference in OS and PFS benefit was observed between these gemcitabine doublets, with a HR close to 1 for both outcomes (OS: 0.97; PFS: 1.02). However, when the network was focused to direct trial data of relevance to the decision problem, *nab*-P/Gem was associated with a numerical OS and PFS benefit (HR for death: 1.10 [95% CrI: 0.67, 1.84]; HR for death or disease progression: 1.17 [95% CrI: 0.75, 1.86]). This suggests the comparison of *nab*-P/Gem versus Gem/Cap is being heavily influenced by indirect data. The trial contributing indirect evidence to this comparison in the base case network is the three-arm trial reported by Boeck *et al.*[56] This was a small, Phase II RCT designed to compare the PFS benefit of capecitabine plus oxaliplatin versus Gem/Cap versus gemcitabine plus oxaliplatin in patients with APC, a proportion of whom had metastatic disease. The predefined endpoint in this trial was PFS rate after 3 months ≥70% in the total population (LAPC); none of the experimental arms (including Gem/Cap) met this primary endpoint. In addition, this study only reported median survival data for the mPC population and only presented KM curves for the LAPC population. The reliability of these data should therefore be considered when interpreting the base case NMA outcomes for the comparison of *nab*-P/Gem versus Gem/Cap. Additional uncertainty arises from differences in dosing schedules adopted for capecitabine. In the Gem/Cap arm of the trial reported by Boeck *et al.*[56], capecitabine was administered in a 3-week cycle, rather than the 2-week cycle adopted in the trial providing direct data for Gem/Cap versus gemcitabine monotherapy.[47] It is not clear what the impact of varying capecitabine dosing may have on clinical benefit, or what is considered ‘standard’ dosing in clinical practice with further trials in LAPC adopting a 4-week dosing regimen.[45] As part of the original submission, these further trials of Gem/Cap were incorporated within a wider network (LAPC) that resulted in a HR of death for the comparison of *nab*-P/Gem versus Gem/Cap of 1.17 (95% CrI: 0.96, 1.43). This is similar to that observed in the network analyses focused to direct trial of relevance to the decision problem in this resubmission. Uncertainty around the clinical efficacy of the Gem/Cap regimen is reflected in its limited use in current clinical practice (see Sections 3.3 and 3.6).

Conclusion

Although comparisons outside of direct trial data from CA046 are not considered relevant to this submission as *nab*-P/Gem would provide an alternative treatment for the clinically recognisable group of patients who receive gemcitabine alone instead of FOLFIRINOX or Gem/Cap in clinical practice (as defined by NICE[12]), a NMA has been conducted to provide additional comparisons for completeness in recognition of their inclusion in the final scope. Potential sources of clinical and statistical bias across the identified evidence base warrant caution to be applied when interpreting these indirect comparisons.

NMA outcomes versus gemcitabine monotherapy reflect head-to-head trials, with only FOLFIRINOX and Gem/Erl demonstrating a significantly superior clinical benefit (OS and PFS) over gemcitabine monotherapy in addition to *nab*-P/Gem. Regarding additional comparisons included in the final scope, FOLFIRINOX demonstrated at least a numerical superior clinical benefit over Gem/Cap and *nab*-P/Gem as expected *a priori* considering the multi-agent nature of this regimen. The comparison of *nab*-P/Gem versus Gem/Cap was far less conclusive, but *nab*-P/Gem demonstrated at least comparable, if not superior, clinical benefit over Gem/Cap.

4.11 Non-randomised and non-controlled evidence

Non-RCT evidence was not formally considered as part of comparative efficacy or cost-effectiveness assessments as RCT data were available for the intervention and for named comparators of interest to the decision problem. However, real world evidence providing supportive data for the safe and effective use of *nab*-P/Gem in clinical practice is presented in Section 4.12.

4.12 Adverse reactions

Summary safety data from CA046 are presented in Table 21. All safety data are taken from the final analysis of CA046 (17 September 2012 data cutoff).

Most patients in both groups reported at least 1 treatment-emergent adverse event (TEAE) during treatment, and the majority had events that were assessed by the investigator to be treatment-related. As expected *a priori*, higher rates of Grade ≥3 TEAEs and serious adverse events (SAE) were reported in the *nab*-P/Gem group compared with the gemcitabine group. Such additive toxicity is often observed when

administering anti-chemotherapy agents concurrently. Importantly, the higher rates of SAEs did not result in a higher rate of fatality in the *nab*-P/Gem group.

Table 21: Overview of TEAEs in CA046 (Treated population; 17 September 2012 data cutoff)

n (%)	***Nab*-P/Gem (N=421)**	**Gemcitabine (N=402)**
Patients with at least 1 TEAE	417 (99)	395 (98)
Patients with at least 1 treatment-related TEAE	403 (96)	371 (92)
Patients with at least 1 SAE	212 (50)	172 (43)
Patients with at least 1 treatment-related SAE	121 (29)	53 (13)
Patients with at least 1 Grade 3 or higher AE	374 (89)	303 (75)
Patients with at least 1 treatment-related Grade 3 or higher AE	325 (77)	203 (50)
Patients with at least 1 TEAE leading to treatment discontinuation	149 (35)	95 (24)
Patients with at least 1 TEAE with outcome of death	18 (4)	18 (4)

Key: AE, adverse event; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Sources: Von Hoff *et al.* 2013[6]; CA046 CSR.[21]

4.12.1. Treatment-emergent adverse events

In the EPAR, it was summarised that the combined treatment of *nab*-P/Gem induced mostly AEs known to be associated with gemcitabine or *nab*-P monotherapy, but at higher frequencies (see Appendix 1). All TEAEs reported by at least 10% of patients in either group are summarised in Appendix 3.

The most frequently reported TEAEs across both groups (≥ 40% of patients) were fatigue (59% in the *nab*-P/Gem group and 46% in the gemcitabine group), nausea (54% in the *nab*-P/Gem group and 48% in the gemcitabine group), peripheral oedema (46% in the *nab*-P/Gem group and 31% in the gemcitabine group), anaemia (42% in the *nab*-P/Gem and 33% in the gemcitabine group), neutropenia (42% in the *nab*-P/Gem group and 30% in the gemcitabine group), and pyrexia (41% in the *nab*-P/Gem group and 29% in the gemcitabine group). The TEAEs with the greatest observed differences between treatment groups were peripheral neuropathy (54% in

the *nab*-P/Gem group and 13% in the gemcitabine group) and alopecia (50% in the *nab*-P/Gem group and 5% in the gemcitabine group).

All Grade 3 or higher TEAEs reported by at least 5% of patients in either group are summarised in Table 22.

The most frequently reported Grade 3 or higher TEAEs (≥ 10% of patients) in the *nab*-P/Gem group were neutropenia (33%), fatigue (18%), peripheral neuropathy (17%), thrombocytopenia (13%) and anaemia (12%), as summarised in the Grade ≥3 TEAEs, and the greatest observed differences were between treatment groups were peripheral neuropathy (17% in the *nab*-P/Gem group and 1% in the gemcitabine group), neutropenia (33% in the *nab*-P/Gem group and 21% in the gemcitabine group) and fatigue (18% in the *nab*-P/Gem group and 9% in the gemcitabine group).

Table 22: Incidence of treatment-emergent Grade 3 or higher AEs by system organ class and preferred term in Study CA046 (at least 5% in either group) (Treated population; 17 September 2012 data cutoff)

n (%)	***Nab*-P/Gem (N=421)**	**Gemcitabine (N=402)**
At least 1 Grade 3 or higher AE	374 (89)	303 (75)
Blood and lymphatic system disorders	202 (48)	128 (32)
Neutropenia	138 (33)	85 (21)
Thrombocytopenia	53 (13)	33 (8)
Anaemia	49 (12)	32 (8)
Leukopenia	39 (9)	15 (4)
General disorders and administration site conditions	132 (31)	76 (19)
Fatigue	77 (18)	37 (9)
Asthenia	29 (7)	17 (4)
Gastrointestinal disorders	114 (27)	92 (23)
Abdominal pain	27 (6)	32 (8)
Diarrhoea	26 (6)	6 (1)
Nausea	27 (6)	14 (3)
Vomiting	25 (6)	15 (4)
Nervous system disorders	82 (19)	19 (5)
Peripheral neuropathy[a]	70 (17)	3 (1)
Metabolism and nutritional disorders	76 (18)	48 (12)

n (%)	*Nab*-P/Gem (N=421)	Gemcitabine (N=402)
Dehydration	31 (7)	10 (2)
Decreased appetite	23 (5)	8 (2)
Respiratory, thoracic and mediastinal disorders	41 (10)	45 (11)
Pulmonary embolism	19 (5)	26 (6)
Vascular disorders	41 (10)	39 (10)
Deep vein thrombosis	21 (5)	22 (5)

Key: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; SMQ, standardised MedDRA query.
Notes: [a], Peripheral neuropathy evaluated using the MedDRA SMQ in order to capture all events under a single term.
Source: CA046 CSR.[21]

The higher incidence of peripheral neuropathy was expected *a priori* as a common AE associated with taxane-based therapies. The majority of peripheral neuropathy cases were mild in nature, as 69% of the 227 patients with peripheral neuropathy were Grade 1 or 2. No patient experienced a Grade 4 or higher event of peripheral neuropathy. Of the 70 patients with a Grade 3 event of peripheral neuropathy (Table 22), 30 (43%) improved to Grade ≤1 peripheral neuropathy with dose modifications (dose delay [80%] and/or dose reduction [41%]); the median time to improvement was 29 days. In total, 44% of patients in whom peripheral neuropathy was improved from Grade 3 to Grade ≤1 resumed *nab*-P/Gem treatment within a median of 23 days following onset of the event. Of the patients who did not improve to Grade ≤1 (n=40), the majority discontinued study treatment. Of all patients randomised to *nab*-P/Gem, the incidence of peripheral neuropathy (all grades) leading to discontinuation of study treatment was 8%.

In post-hoc subset analysis, patients who developed Grade 3 peripheral neuropathy had increased treatment exposure and, thus, significantly better outcomes compared with those who did not, as summarised in Table 23. Rates of Grade 3 peripheral neuropathy doubled after Cycle 4 and peaked at Cycle 7.

Table 23: Treatment exposure and efficacy outcomes by grade of peripheral neuropathy in the *nab*-P/Gem group of CA046 (Treated population; 17 September 2012 data cutoff)

	Grade of peripheral neuropathy developed				HR or RRR (95% CI)* p-value
	0	1	2	3	
OS, median months (95% CI)	5.9 (4.7, 6.9)	9.0 (8.3, 12.3)	12.6 (9.6, 15.7)	14.9 (11.9, 19.2)	0.33 (0.23, 0.48) p<0.0001
PFS, median months (95% CI)	3.5 (3.1, 3.8)	5.6 (4.5, 6.2)	9.3 (7.2, 12.6)	9.1 (7.5, 11.5)	0.27 (0.18, 0.41) p<0.0001
ORR, % (95% CI)	8 (4.4, 1.24)	29 (20.3, 39.3)	43 (30.0, 55.9)	43 (31.1, 55.3)	5.54 (3.18, 9.67) p<0.0001
Median treatment cycles (range)	1 (1–13)	4 (1–17)	6 (1–2)	6 (1–22)	-

Key: CI, confidence interval; HR, hazard ratio; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RRR, response rate ratio.
Note: * Patients with Grade 3 peripheral neuropathy vs no peripheral neuropathy.
Source: Goldstein *et al.* 2015.[74]

In addition to peripheral neuropathy, toxicities that commonly led to dose modifications were neutropenia, thrombocytopenia and fatigue, and this was the case for both treatment groups. Only a small percentage of patients in both treatment arms (≤2%) had the study drug discontinued due to neutropenia or thrombocytopenia. These data suggest that the myelosuppression observed in this study was reversible and was effectively managed by adequate laboratory monitoring, dose delays, and subsequent dose reductions.

As toxicity management is an important part of the use of *nab*-P/Gem, an exploratory analysis examined the influence of dose modifications on treatment exposure and efficacy to better inform the use of this chemotherapy doublet in clinical practice. This exploratory analysis further confirms the observations of the post-hoc subset analysis of patients with peripheral neuropathy: dose modifications result in greater treatment exposure and thus greater clinical efficacy, as summarised in Table 24. Therefore, appropriate dose modifications should be encouraged to accommodate

the safe use of *nab*-P/Gem in clinical practice; moreover, the data do not suggest that dose reductions negatively influence patient outcomes.

Table 24: Treatment exposure and efficacy outcomes by dose modifications in the *nab*-P/Gem group of CA046 (treated population; 17 September 2012 data cutoff)

	Dose reductions			Dose delays		
	No dose reduction (n=249)	**≥1 dose reduction (n=172)**	**HR or RRR (95% CI) p-value**	**No dose delay (n=121)**	**≥1 dose delay (n=300)**	**HR or RRR (95% CI) p-value**
OS, median months	6.9	11.4	1.93 (1.53, 2.44) p<0.0001	6.2	10.1	2.05 (1.59, 2.63) p<0.0001
PFS, median months	3.8	8.8	2.62 (2.01, 3.42) p<0.0001	3.4	6.6	2.80 (2.13, 3.69) p<0.0001
ORR, %	16	34	0.49 (0.34, 0.69) p<0.0001	10	29	0.34 (0.19, 0.60) p<0.0001

Key: CI, confidence interval; HR, hazard ratio; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; RRR, response rate ratio.
Note: The HR for death is provided for OS, and the HR for progression or death is provided for PFS, with a HR of >1 favouring dose modification; the RRRs are provided for ORRs, with a RRR of <1 favouring dose modification.
Source: Scheithauer *et al.* 2016.[14]

4.12.2. Treatment-related TEAEs

Treatment-related TEAEs were those TEAEs considered by the investigator to have a possible, probable, or definite relationship to the study drug. In both treatment groups, most patients had treatment-related TEAEs (Table 21). The most frequently reported treatment-related TEAEs (≥25% of patients) in the *nab*-P/Gem group in decreasing order of frequency were fatigue (54%), alopecia (50%), nausea (49%), neutropenia (42%), anaemia (38%), diarrhoea (37%), peripheral oedema (33%), vomiting (32%), thrombocytopenia (30%), pyrexia (29%), decreased appetite (27%), peripheral neuropathy (27%), and peripheral sensory neuropathy (25%). Events reported more frequently in the *nab*-P/Gem group than in the gemcitabine group included fatigue (54% vs 37%), alopecia (50% vs 5%), neutropenia (42% vs 30%),

diarrhoea (37% vs 13%), peripheral oedema (33% vs 17%), vomiting (32% vs 21%), decreased appetite (27% vs 14%), peripheral neuropathy (27% vs 1%), peripheral sensory neuropathy (25% vs 3%) and rash (22% vs 8%).

4.12.3. Deaths

The number of patients with TEAEs with an outcome of death was the same in the two treatment arms of Study CA046; 18 in the *nab*-P/Gem group and 18 patients in the gemcitabine group (both 4% of patients).

Sepsis and pneumonitis were slightly more frequently reported as the cause of death in patients in the *nab*-P/Gem group than in the gemcitabine group (both 2 patients vs 0 patients). However, cause-specific mortality due to sepsis and pneumonitis was still very low (<1%) with *nab*-P/Gem treatment, showing that the risk of these events can be effectively managed by clinical vigilance (monitoring patient status), treatment discontinuation and steroid treatment, as per the CA046 study protocol.

4.12.4. Serious adverse events

The overall incidence of SAEs was similar in the two treatment arms (50% in the *nab*-P/Gem arm and 43% in the gemcitabine arm). All SAEs are summarised in Appendix 3.

Pyrexia was the most frequently reported SAE in the *nab*-P/Gem arm, reported by 6% of patients. SAEs reported by ≥2% more patients in the *nab*-P/Gem arm than in the gemcitabine arm were pyrexia (6% vs 2%) and febrile neutropenia (3% vs <1%). The SAE of pulmonary embolism was reported by 2% more patients in the gemcitabine arm than in the *nab*-P/Gem arm (5% vs 3%). All other SAEs were observed in similar percentages in the two treatment arms.

4.12.5. TEAEs by subgroup

Subgroup analysis for safety variables was not pre-planned in CA046 and thus was not considered as part of the SAP.

There was no upper age limit for enrolment in CA046; 42% of patients were ≥65 years of age, and 10% of patients were ≥75 years of age. As expected *a priori*, the rate of TEAEs was higher in the elderly population than in the overall Treated population, and the overall incidence of Grade 3 or higher TEAEs and SAEs was

higher in patients ≥ 65 years of age who received *nab*-P/Gem compared with gemcitabine alone. However, the relative differences observed between treatment groups for patients ≥ 65 years of age were similar in both severity and frequency when compared with those observed between the treatment arms for the overall Treated population.

Although the number of patients ≥75 years of age included in the study was small (n=84), and therefore, comparisons of TEAEs in this subgroup should be interpreted with caution, data suggest that there is a higher risk of Grade 3 TEAE, SAEs, TEAEs with an outcome of death and of TEAEs leading to study drug discontinuation in these older patients treated with *nab*-P/Gem compared with gemcitabine monotherapy. This is not unexpected when comparing a single agent with doublet chemotherapy in an elderly population. Nevertheless, the observed toxicities in patients ≥75 years of age were generally manageable using the same strategies for dose delays, dose adjustments and supportive treatment that were recommended for the overall population. As recommended in the SmPC, patients with mPAC aged ≥75 years should be carefully assessed for their ability to tolerate *nab*-P/Gem with special consideration to performance status, co-morbidities, and increased risk of infections. We have since been advised by clinical experts that age alone would not exclude patients from receiving *nab*-P/Gem in clinical practice, and that they would be comfortable treating certain patients over the age of 75, acknowledging that there are other (arguably more clinically appropriate) ways to assess age-associated increases in risk.[11]

The incidence and distribution of TEAEs, Grade 3 or higher TEAEs, SAEs, and TEAEs with an outcome of death were generally similar for men and women, and similar relationships were observed when comparing the *nab*-P/Gem arm to the gemcitabine arm. TEAEs reported with a ≥10% difference in women compared with men were neutropenia (49% vs 36%), anaemia (49% vs 36%), vomiting (44% vs 29%), and urinary tract infection (17% vs 4%). Cough was reported in 22% of men and 11% of women. Neutropenia was the only Grade 3 or higher TEAE reported with a >5% difference in women than men (40% vs 27%). Among women, there was a greater incidence of Grade 3 or higher TEAEs in the *nab*-P/Gem group than in the gemcitabine monotherapy group (90% vs 71%); neutropenia was the only Grade 3 or

higher TEAE reported with a >10% difference between the two treatment arms (41% vs 21%).

The overall incidence of TEAEs, Grade 3 or higher TEAEs, and SAEs was similar among patients enrolled at sites in the 4 geographic regions (North America, Eastern Europe, Australia and Western Europe). In general, the incidence of individual TEAEs for patients enrolled in sites in Eastern Europe was lower than for patients enrolled at sites in the other geographic regions, and similar relationships were observed when comparing the *nab*-P/Gem arm to the gemcitabine arm.

4.12.6. Safety data from the SIEGE trial

Supportive safety data specific to the UK population are provided from the SIEGE trial.[9] Of note, the average age of patients treated with *nab*-P/Gem in the SIEGE trial (concomitant arm as per license terms) was 67 years, supporting its common use in an older patient group (than the CA046 trial population) in clinical practice.

Of the 74 patients in the concomitant arm of SIEGE, 61 (82%) experienced a Grade ≥3 AE during treatment. The most common Grade ≥3 AEs (≥10%) were neutropenia (experienced by 22 patients [30%]), fatigue (experienced by 11 patients [15%]), febrile neutropenia (experienced by 9 patients [12%]), and vomiting (experienced by 8 patients [11%]). A higher rate of myelosuppression across the study as a whole was noted compared with the CA046 trial, and was reported to most likely reflect the lower use of growth factor support in SIEGE (G-CSF was received by 12 patients in the concomitant arm [16%]).

4.12.7. Real world evidence

As *nab*-P/Gem was granted marketing authorisation for the first-line treatment of mPAC at the end of 2013, there are some further safety data available relating to its use in clinical practice.

Between October 2013 and October 2015, 32 patients with mPAC were treated with *nab*-P/Gem across the Lancashire and South Cumbria Cancer Network (LSCCN).[75] Compared to the CA046 trial population, the LSCCN cohort had a greater proportion of patients aged >65 (84% vs 41%). No patients developed Grade 3 or 4 toxicities of neutropenia, rash or HFS, resulting in a conclusion that overall, *nab*-P/Gem treatment is well-tolerated in clinical practice. In this ‘real-life’ population, the rate of

Grade 3 peripheral neuropathy was only 3.1% (compared to 16.7% in the CA046 trial; p=0.047). Dose reduction rates were similar (40% compared to 41% in the CA046 trial; p=1), confirming that the dosing regimen is suitable across different patient populations. The median duration of treatment was 2.3 months, which may contribute to the lower survival observed with a median OS of 5.8 months, among other factors such as patient selection.

Between 1 September 2014 and 30 September 2015, 17 mPAC patients (12 male and 5 female) in South West Wales were treated with *nab*-P/Gem in the first-line setting.[76] All patients had good performance status (ECOG 0 or 1), and the mean age was 63.4 years. In this 'real-life' population, *nab*-P/Gem was generally well tolerated with lower rates of fatigue, Grade 3 myelosuppression (neutropenia and thrombocytopenia) and Grade 3 peripheral neuropathy compared with trial data, as summarised in Table 25. There were more cases of venous thromboembolism (VTE) observed in the 'real-life' population but this was considered potentially attributable to the high risk of VTE in pancreatic cancer, rather than due to treatment. There were also more cases of Grade 3/4 infection observed in the 'real-life' population. Details of these cases are not reported, but are being sought for further review. With a follow-up of 117 days, median OS is yet to be reached in this 'real-life' population, but radiological response rates were at least equivalent to trial outcomes with an ORR of 40% and durable response demonstrated. Additionally, the patient numbers included in both of these audits are very small (n=32 and n=17 respectively).

Table 25: Toxicity profile of *nab*-P/Gem in a 'real-life' population in South West Wales compared with the Treated population of CA046

	'Real-life' population (n=17)	**CA046 Treated population (n=421)**
Fatigue, %	18	59
Grade 3 neutropenia, %	24	33
Grade 3 thrombocytopenia, %	6	13
Grade 3 peripheral neuropathy, %	6	17
Grade 3/4 infection, %	53	16
Thrombosis, %	24	1
Diarrhoea, %	12	44
Arrhythmia, %	6	-

Key: *Nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine.
Note: Data presented are from a naive cross-trial comparison and thus should be interpreted with caution.
Sources: Quinton *et al.* 2015[76]; Von Hoff *et al.* 2013[6]; CA046 CSR.[21]

Additional real world evidence for a larger patient group (n=208) is available from a retrospective analysis of mPAC patients treated with *nab*-P/Gem 100 or 125mg/m^2 in the first-line setting across 19 centres in Italy.[77] As was observed in the South West Wales and Lancashire and South Cumbria cohorts, *nab*-P/Gem was shown to be safely used in clinical practice, with only four patients (2%) stopping treatment due to unacceptable toxicity. Dose reduction was adopted to manage toxicity in 25% of patients. Prophylactic use of G-CSF was initiated in 33% of patients, and 19% of patients received erythropoietin to treat anaemia. In general, rates of Grade 3 TEAEs observed in this 'real-life' population were equivalent or lower than rates observed in the CA046 trial population, as presented in Table 26. Thirteen patients in the 'real-life' population experienced a Grade 4 TEAE; the most common was Grade 4 neutropenia, observed in 4% of patients (n=8).

Table 26: Toxicity profile of *nab*-P/Gem in a 'real-life' population in Italy compared with the treated population of CA046

Grade 3 events, %	'Real-life' population (n=208)	CA046 Treated population (n=421)
Anaemia	2	12
Neutropenia	24	33
Thrombopenia	15	13
Nausea/vomiting	4	6
Diarrhoea	5	6
Neurotoxicity	16	<1
Fatigue	17	18
Mucositis	3	-
Skin rash	2	2

Key: *Nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine.
Note: Data presented are from a naive cross-trial comparison and thus should be interpreted with caution.
Sources: Giardano *et al.* 2015[77]; Von Hoff *et al.* 2013[6]; CA046 CSR.[21]

Of specific interest given the limited trial data for the patients ≥75 years of age (n=32), subgroup analysis of this Italian cohort reports data for this patient group.[78] In these patients, the toxicity profile of *nab*-P/Gem was shown to be generally the same as that observed in patients <75 years of age with no significantly worsened tolerability, as summarised in Table 27. Comparable tolerability was also observed in patients with poorer performance status (ECOG 2 vs ECOG 0 or 1) and biliary stent carriers (Table 27).

Table 27: Toxicity profile of *nab*-P/Gem in a 'real-life' population in Italy based on age

Grade 3/4 events, n (%)	Age		ECOG		Biliary stent	
	<75 years (n=176)	≥75 years (n=32)	0 or 1 (n=173)	2 (n=35)	No (n=164)	Yes (n=44)
Anaemia	3 (2)	2 (6)	3 (2)	2 (6)	2 (1)	2 (5)
Neutropenia	49 (28)	8 (25)	34 (31)	12 (34)	45 (27)	12 (27)
Thrombopenia	29 (17)	5 (16)	22 (16)	6 (17)	25 (15)	9 (21)
Nausea/vomiting	9 (5)	3 (9)	12 (7)	1 (2)	12 (7)	1 (2)
Diarrhoea	12 (7)	4 (13)	17 (10)	2 (5)	13 (8)	5 (11)
Neurotoxicity	21 (12)	3 (9)	23 (17)	6 (17)	25 (15)	8 (18)
Fatigue	21 (12)	2 (6)	25 (18)	6 (17)	25 (15)	7 (16)
Mucositis	5 (3)	1 (3)	6 (4)	1 (2)	5 (3)	0
Skin rash	2 (1)	0	2 (1)	0	2 (1)	0

Key: ECOG, European Cooperative Oncology Group; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine.
Source: Giardano *et al.* 2015.[78]

This analyses not only shows comparable tolerability across patient groups but also provides insight into the characteristics of patients being treated with *nab*-P/Gem in clinical practice. As can be seen in the comparison presented in Table 28, demographics and clinical characteristics of patients in the 'real-life' population were similar to those of patients enrolled in CA046, although patients were generally older (median age 67 vs 62) but had fewer metastatic sites (median 1 vs ≥2). There were also a higher proportion of patients in the 'real-life' population with primary tumours located in the head of the pancreas (59% vs 44%); however, the proportion of patients with biliary stent were equivalent in both datasets (21% vs 19%).

Table 28: Baseline characteristics of patients treated with *nab*-P/Gem in clinical practice (Italy) and patients randomised to *nab*-P/Gem in CA046

Characteristic	'Real-life' population N=208	CA046 ITT population N=431
Age, years		
Median	67	62
Range	37–86	27–86
Sex – n (%)		
Female	93 (45)	186 (43)
Male	115 (55)	245 (57)
Performance score – n (%)*		
KPS	Not reported	N=429 100: 69 (16) 90: 179 (42) 80: 149 (35) 70: 30 (7) 60: 2 (<1)
ECOG	0: 94 (45) 1: 77 (37) 2: 37 (18)	Not reported
Pancreatic tumour location – n (%)		
Head	122 (59)	191 (44)
Body-tail	86 (41)	237 (55)
Unknown	0	3 (1)
Site of metastatic disease – n (%)		
Liver	144 (69)	365 (85)
Lung	62 (30)	153 (35)
Peritoneum	55 (26)	19 (4)
Number of metastatic sites – n (%)		
1	103 (50)	33 (8)
2	73 (35)	202 (47)
>2	32 (15)	196 (46)
Previous therapy – n (%)		
Radiation therapy	7 (3)	19 (4)
Chemotherapy	Neoadjuvant: 23 (11) Adjuvant: 41 (20)	23 (5)
Surgery	57 (27)	32 (7)**

Characteristic	'Real-life' population N=208	CA046 ITT population N=431
Biliary stent	44 (21)	80 (19)

Key: ECOG, European Cooperative Oncology Group; KPS, Karnofsky Performance Status; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine.
Notes: Data presented are from a naive cross-trial comparison and thus should be interpreted with caution; * KPS range from 0–100, with higher scores indicating better performance status; ECOG range from 0–5, with lower scores indicating better performance status; ** Whipple procedure.
Sources: Giardano *et al.* 2015[77]; Von Hoff *et al.* 2013.[6]

Although not formally considered as part of comparative efficacy or cost-effectiveness assessments, it is also of interest to the decision problem to assess the clinical effectiveness of *nab*-P/Gem in this 'real-life' population. Key effectiveness results are presented in Table 29.

In the overall population, the median number of treatment cycles was 6 (range: 1–15) with 95% dose intensity; median duration of treatment was 22 weeks (range: 3–65). The median OS was 11.3 months (95% CI: 9.3, 11.2), and the median PFS was 6.7 months (95% CI: 6.2, 7.2). A majority of patients (64%) were well enough to go on to receive second-line treatment following progressive disease on *nab*-P/Gem. The ORR was 31%, and the DCR was 63%. Improvement in pain was reported by 57% of patients, and improvement in performance status was obtained in 35% of patients. In subgroup analyses, similar activity was observed regardless of age, performance status and biliary stent implantation (Table 29). Univariate analysis showed no relation between age (<75 vs ≥75), ECOG performance status (0 or 1 vs 2) or biliary stent implantation (no vs yes) and outcome both in terms of OS and PFS.

Table 29: Key effectiveness data for the first-line use of *nab*-P/Gem in a 'real-life' mPAC population in Italy

Efficacy variable	All (N=208)	Age		ECOG		Biliary stent	
		<75 years (n=176)	≥75 years (n=32)	0 or 1 (n=173)	2 (n=35)	No (n=164)	Yes (n=44)
Overall survival							
Median months	11.3	-	11.4	-	11.0	-	8.8
95% CI	9.3, 11.2	-	10.5, 12.3	-	7.4, 14.7	-	8.0, 9.7

Efficacy variable	All (N=208)	Age		ECOG		Biliary stent	
		<75 years (n=176)	≥75 years (n=32)	0 or 1 (n=173)	2 (n=35)	No (n=164)	Yes (n=44)
p-value*	-		0.71		0.59		0.97
Progression-free survival							
Median months	6.7	-	7.1	-	6.6	-	6.1
95% CI	6.2, 7.2	-	6.6, 7.6	-	5.9, 7.3	-	4.8, 7.4
Response							
ORR, n (%)	65 (31)	58 (35)	7 (22)	54 (31)	11 (31)	54 (35)	11 (26)
p-value*	-		0.15		0.70		0.20
DCR, n (%)	131 (63)	109 (61)	22 (69)	113 (65)	18 (52)	104 (66)	27 (63)
p-value*	-		0.64		0.09		0.69
Best response, n (%):							
CR	7 (3)	7 (4)	0	6 (4)	1 (3)	6 (4)	1 (2)
PR	58 (28)	51 (31)	7 (22)	48 (28)	10 (29)	48 (31)	10 (23)
SD	66 (32)	51 (35)	15 (47)	59 (36)	7 (20)	50 (32)	16 (37)
PD	77 (37)	67 (39)	10 (31)	59 (35)	17 (48)	69 (34)	17 (37)

Key: CI, confidence interval; CR, complete response; DCR, disease control rate; ECOG, European Cooperative Oncology Group; mPAC, metastatic pancreatic adenocarcinoma; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
Note: * Log rank test for comparisons within subgroups based on age, ECOG performance status and biliary stent status.
Sources: Giardano *et al.* 2015[77]; Giardano *et al.* 2015.[78]

Further analysis of the use of *nab*-P/Gem in the 'real-life' population of advanced pancreatic cancer patients in Italy evaluates the feasibility and efficacy of second-line treatment following *nab*-P/Gem at first-line.[79] At the time of data analysis, 55% of patients (122/221) who experienced disease progression went on to receive second-line treatment. Median OS in these patients was significantly longer that in patients who did not go on to receive further active treatment: 13.5 months (95% CI: 12.7, 14.3) versus 6.8 months (95% CI: 5.6, 8.0), respectively; p<0.0001. Patients who responded to *nab*-P/Gem treatment were more likely to respond to second-line treatment, and a significant correlation was observed between longer first-line PFS (≥6 months) and second-line PFS ≥4 months.

A number of smaller-scale studies provide further real world evidence, supporting the clinical effectiveness and tolerability of *nab*-P/Gem in clinical practice; some of the more recent data are summarised in Appendix 5.

4.13 Interpretation of clinical effectiveness and safety evidence

Pancreatic cancer is a particularly aggressive and life-threatening malignancy for which there have been few therapeutic advances. Gemcitabine monotherapy, which has been routinely funded in NHS England since 2001, remains the established standard of care for patients with mPAC, but has limited effectiveness in clinical practice (current life expectancy of patients with mPC is estimated at ≤6 months[5]). There is a clear unmet medical need for patients to get access to more effective treatments.

In the pivotal, regulatory Phase III trial, CA046, *nab*-P/Gem became the first chemotherapy doublet to demonstrate both a statistically significant and clinically meaningful survival benefit (defined as 6–8 weeks by people affected by pancreatic cancer[7]) over gemcitabine monotherapy for the first-line treatment of mPAC. This benefit was observed across patient groups, including those with markers of advanced disease and worse prognosis such as extensive metastases, poor performance status, pancreatic head tumour location and elevated CA19-9. Some additive toxicity was observed (as expected a priori), but the *nab*-P/Gem regimen was generally well tolerated, with AEs considered manageable in the majority. Real world evidence supports the safe and effective use of *nab*-P/Gem in clinical practice, including in older patients (≥75 years of age), patients with poorer performance status (ECOG 2) and biliary stent carriers. Dose modifications should be encouraged in clinical practice to accommodate the safe use of this chemotherapy doublet, while maximising treatment exposure to optimise clinical effectiveness. Importantly, this also helps to preserve the health status of patients such that they can go on to receive second-line treatment and further improve their overall prognosis.

The CA046 trial provides good quality RCT evidence supporting the use of *nab*-P/Gem. Although patients may appear younger and fitter on average than patients typically presenting in UK practice, an expert panel of treating clinicians in NHS England did not have concerns regarding the general applicability of CA046 trial data to patients presenting in clinical practice.[11] Real world evidence allows a comparison

of trial population characteristics to a ‘real-life’ population (albeit some data are from outside of the UK) and shows they are generally comparable, although patients were generally older in the real world evidence sets. Additionally, data from the concomitant arm of SIEGE, a UK based clinical trial, provides further reassurance that *nab*-P/Gem is generally well tolerated by the relevant patient population under assessment in this submission. As aforementioned, safe and effective use of *nab*-P/Gem was observed across patient groups that may be considered suitable for such therapy in clinical practice. The CA046 trial also provides comparator data of direct relevance to the decision problem for NHS England. Although additional comparators of FOLFIRINOX and Gem/Cap are also named in the final scope of this appraisal, the *nab*-P/Gem regimen will not replace the use of such treatments. *Nab*-P/Gem is intended for use in a group of patients (easily identified by clinicians) who currently only receive gemcitabine but may derive clinical benefit from receiving *nab*-P/Gem rather than gemcitabine monotherapy. This group of patients is clinically distinct from those who would receive FOLFIRINOX or Gem/Cap in clinical practice, as previously acknowledged by NICE.[12]

The CA046 trial assessed endpoints related to the clinical benefit and potential harms of *nab*-P/Gem that can be expected in clinical practice. The primary endpoint of OS assesses the outcome of most importance to patients and carers alike, and its subjective nature minimises assessment bias. For secondary endpoints of PFS and ORR, primary assessments were conducted by IRR in line with trial assessment recommendations, but were supplemented with investigator-assessed data, which are arguably more reflective of response to be expected in clinical practice. The omission of HRQL data collection is a limitation of the CA046 trial, which could not be addressed through alternative trial data at the time of the original submission. The impact of *nab*-P/Gem on HRQL has since been investigated in metastatic pancreatic ductal adenocarcinoma (mPDAC) patients as part of the SIEGE trial; and in LAPC patients as part of the LAPACT trial where a high proportion of patients treated with *nab*-P/Gem reported stable or improved HRQL in accordance with individual items of the EORTC QLQ-C30.

With a life-expectancy of ≤6 months associated with standard of care, and a clinically meaningful extension to life observed versus this standard of care in the CA046 trial, *nab*-P/Gem should be considered as a life-extending treatment at the end of life.

Supportive data for this conclusion are summarised in Table 30. Although the extension to life may be under 3 months, it is considered proportionally equivalent given the extremely short life-expectancy of this patient group. As part of the original submission, NICE concluded that the normal extension to life of an additional 3 months is not appropriate in order to meet end of life criteria in this instance. As noted in the Appeal Decision Paper *"First, the estimates before the Appraisal Committee were very robust, so that the actual benefit of 2.4 months was firmly established rather than an uncertain extrapolation. Secondly, the outlook in metastatic pancreatic cancer was very poor, and the gain in life was high in proportion to the life-expectancy. For that reason the Committee decided it would be right to apply the end-of-life policy, even though the product did not strictly fulfil all of the criteria".*[80]

Table 30: End of life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Real world survival Median: 2–6 months depending on how much the cancer has grown and where it has spread. Trial survival Median: 6.6 months Mean: 8.7 months Data source: CRUK (real world survival)[5]; CA046 extension trial data (trial survival).[8]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Survival extension Median: 2.1 months Mean: 2.4 months Data source: CA046 extension trial data (trial survival).[8]

4.14 Ongoing studies

The most relevant ongoing study from which additional evidence is likely to be available in the next 12 months is the SIEGE study, from which early HRQL data are presented in Section 4.7.

No other Phase II/III trials investigating the use of the *nab*-P/Gem doublet for the indication being appraised (first-line treatment of mPAC) are expected to provide additional evidence within the next 12 months. However, it should be acknowledged that there are numerous studies ongoing that are adding novel agents to the

backbone of *nab*-P/Gem for the first-line treatment of mPC, demonstrating that this regimen is a recognised standard of care for this patient group in the global market. Some of these studies are summarised in Table 31, but clinical intelligence suggests there are approximately 130 ongoing trials investigating the use of *nab*-P in pancreatic cancer (across treatment settings), targeting at least 12,000 patients.

Table 31: Ongoing early clinical trials of metastatic pancreatic cancer treatments with a *nab*-P/Gem backbone

Study drug	Sponsor	Mechanism	Setting	Phase	NCT #
BYL719	Moffit Cancer Center	PI3Kα inhibitor	1L	I	02155088
Enzalutamide (MDV3100)	Astellas	Androgen receptor antagonist	1L	I	02138383
TH‑302 (evofosfamide)	EMD Serono	Hypoxia activated 2‑nitroimidazole prodrug of DNA-alkylating Br-IDM	1L	I	02047500
Dovitinib (TK1258)	Rosswell Park	FGFR/VEGFR TKI	1L	Ib	02048943
OMP‑54F28	Oncomed	Frizzled‑8–Fc fusion protein	1L	Ib	02050178
Vantictumab (OMP‑18R5)	Oncomed	Anti-Frizzled‑1/2/5/7/8 antibody	1L	IB	02005315
Demcizumab (OMP‑21M18)	Oncomed	Anti-DLL4 antibody	1L	I/II	02289898
GS‑5745	Gilead	Anti-MMP‑9 mAb	1L	I/II	01803282
Indoximod (D-1MT)	NewLink Genetics	IDO inhibitor	1L	I/II	02077881
Necuparanib (M402)	Momenta	Heparan sulphate mimetic	1L	I/II	01621243
PF‑03084014	Pfizer	γ-secretase inhibitor	1L	I/II	02109445
Selinexor (KPT‑330)	NCI	Inhibitor of nuclear export	1L	I/II	02178436
Tarextumab (OMP‑59R5)	Oncomed	Anti-Notch 2/3 mAb	1L	I/II	01647828
Vismodegib (GDC‑0449)	SKCCC	Hedgehog inhibitor	1L	II	01088815
Apatorsen (OGX‑427)	SCRI	Antisense oligonucleotide	1L	RPII	01844817
Momelotinib	Gilead	JAK inhibitor	1L	RPII	02101021

Study drug	Sponsor	Mechanism	Setting	Phase	NCT #
(GS‑0387, CYT387)					
PEGPH20	Halozyme Therapeutics	PEGylated recombinant human hyaluronidase	1L	RPII	01839487
INCB039110	Incyte	JAK1 inhibitor	2L	IB	01858883
Ensituximab (NPC‑1C, NEO‑101)	Precision Biologics	Anti-MUC5AC mAb	2L	RPII	01834235
LCL161	Novartis	Pan-IAP inhibitor	Any	I	01934634
ADI-PEG 20	Polaris Group	PEGylated arginine deiminase; arginine degradation	Any	IB	02101580
Hydroxy-chloroquine	Abramson Cancer Center	Autophagy inhibitor	Any	I/II	01506973

Key: 1L, first line; 2L, second line; mAb, monoclonal antibody; SKCCC, Sidney Kimmel Comprehensive Cancer Center; TKI, tyrosine-kinase inhibitor.
Source: Garrido-Laguna *et al.* 2015.[81]

SECTION SUMMARY

- A cost-effectiveness evaluation was conducted from the perspective of the NHS and PSS to compare *nab*-P/Gem with Gem monotherapy for patients with previously untreated metastatic pancreatic cancer (mPAC)
- The analysis was based on a Markov state-transition cohort model with 1-week cycle length and a 10-year time horizon
- The model structure is the same as the model used in TA360 and includes three main clinically defined health states
    - Pre-progression
    - Post-progression
    - Death
- The transition probabilities between each health state are informed by a set of survival models fitted to Kaplan-Meier data from CA046 for the following clinical end-points
    1. Overall survival (OS)
    2. Progression-free survival (PFS)
    3. Time on treatment (ToT)
- *Nab*-P/Gem is compared with Gem monotherapy, Gem/Cap and FOLFIRINOX in line with the final scope. However, Gem/Cap and FOLFIRINOX are considered as secondary comparators due to limited available evidence base in the UK clinical setting.
- Direct medical costs including treatment costs, drug administration costs, monitoring costs, adverse events and end of life costs are included in line with TA360. Follow-up and monitoring resource use were estimated through clinician interviews and validated by a panel of experts at a UK advisory board.
- Health effects are measured in QALYs. The base case HRQL data are taken from Romanus et al. (2012) and were estimated using EQ-5D.
- Structural and parametric uncertainty within the model is assessed in a series of scenario analyses, deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA)
- End of life criteria are met as was accepted in the original submission (TA360)
- Incremental costs vs gem monotherapy are £6,717
- Incremental QALYs vs gem monotherapy are £0.144
- *Nab*-P/Gem at discounted price ([redacted] discount) is cost effective vs the relevant comparator, gem monotherapy; ICER = £46,657/QALY
- This result was investigated for uncertainty and remained true; probabilistic ICER vs gem monotherapy = £46,801/QALY

5. Cost effectiveness

5.1 Published cost-effectiveness studies

5.1.1. Identification of studies

An extensive SLR of the cost-effectiveness studies was conducted for the previous NICE review (TA360) in March 2014.[82] This has been updated to provide the evidence base for this resubmission using the same search strategy. Updated searches were carried out from March 2014 through to August 2016 to ensure that the latest available evidence is presented in the resubmission.

The SLR was performed to identify and summarise the relevant economic evidence for metastatic or locally aPAC, with the majority (>50%) of the population being mPAC patients. A precise search strategy was utilised, incorporating terms for *nab*-P and the treatment comparators across Europe (5-fluorouracil [5-FU], capecitabine [brand name XELODA®], gemcitabine [brand name GEMZAR®], oxaliplatin [brand name ELOXATIN®], erlotinib [brand name TARCEVA®]), as monotherapy or in combination with any other therapy. Included studies were full economic evaluations that provided either costs, life years gained, QALYs or ICERs with sufficient detail regarding methods and results.

The review included searches of the following electronic databases:

- MEDLINE and Embase (using Embase.com)
- MEDLINE In-Process (using PubMed.com)
- EconLit
- The Cumulative Index to Nursing and Allied Health Literature (CINAHL) (using EBSCO.com)
- The Cochrane Library, including the following:
  - National Health Service Economic Evaluations Database
  - Centre for Reviews and Dissemination – Health Technology Assessment Database

Additionally, conference proceedings from the last 4 years (2013–2016) were searched to identify recently completed or ongoing studies of interest. These will include:

- Health Technology Assessment International (HTAi)

- International Health Economics Association (iHEA)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual International Congress
- Society for Medical Decision Making (SMDM)

Appendix 11 describes the strategy used to search the databases. The search strategies are described by providing the structure and the terms used to search the MEDLINE, EconLit, CINAHL and Cochrane library databases.

Having identified relevant economic studies from the electronic database search, the titles and abstracts were reviewed by two independent reviewers to assess their relevance for informing the overall decision problem. Table 32 lists the inclusion and exclusion criteria used in the review to assess the relevance of the identified studies. Data extraction from the included full-text of articles was also performed independently by two reviewers to ensure that everything was captured.

Table 32: Inclusion and exclusion criteria for economic modelling studies

Criteria	Inclusion	Exclusion
Population	• Adult patients • aPAC patients, at least a proportion (50%) of whom have metastatic (or pancreatic ductal adenocarcinoma) disease • Potentially eligible for first-line therapy for metastatic disease	• Healthy volunteers • Children (age <18 years) • Diseases other than those specified in inclusion criteria
Intervention/ comparator	• *Nab*-Paclitaxel + gemcitabine • AND a relevant comparator from: Placebo, 5-FU, capecitabine (XELODA®), erlotinib (TARCEVA®), gemcitabine (GEMZAR®) and oxaliplatin (ELOXATIN®), monotherapy or in combination with any other therapy**	• Non-active comparisons • Comparisons outside of named list of interventions/comparators of interest
Outcomes	• ICER • Costs (unit and total) • QALYs • LYs • Incremental costs • Incremental QALYs/LYs • Model inputs (e.g. transition probabilities) • Sensitivity analyses results	

Criteria	Inclusion	Exclusion
Study type	• Full economic evaluations, such as: • Cost–consequence • Cost-effectiveness • Cost–utility • Cost–benefit • Cost-minimisation	• Non-systematic reviews*, letters and comment articles • Burden of illness studies and non-modelling will be excluded
Language	• Studies published in English will be included • Studies not published in English will be included and flagged***	• Studies will not be excluded based on publication language
Key: 5-FU, 5-fluorouracil; aPAC, advanced pancreatic cancer; FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin; Gem/Cap, gemcitabine in combination with capecitabine; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years. **Notes:** * Systematic reviews will be included and flagged for bibliography searches; ** The range of potential comparators is deliberately broad. When discussing the cost-effectiveness studies identified, we draw a distinction between studies that include comparators in the scope for TA360 (gemcitabine monotherapy; Gem/Cap and FOLFIRINOX) and those studies that only include the wider treatments not considered by NICE to be relevant to UK practice; *** Studies published in languages other than English will be explored only if sufficient evidence is not identified from studies published in English.		

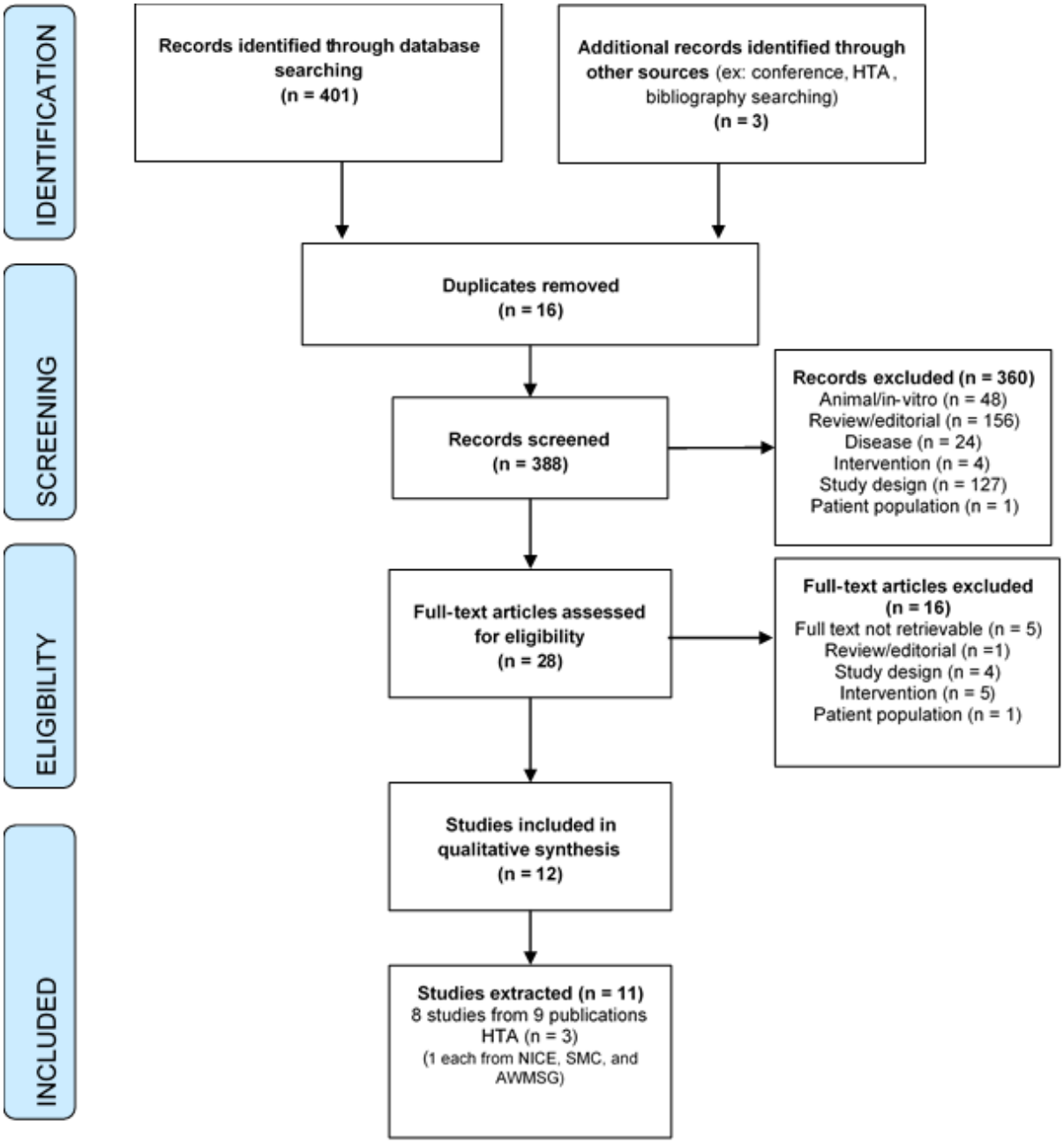
5.1.2. Description of identified studies

In total, 404 papers were identified from the electronic searches. Screening of the titles and abstracts against the pre-specified inclusion and exclusion criteria (as presented in Table 32) was performed for 388 records after removing 16 duplicates. Of these, 28 were included for full-text screening. The most common reasons for exclusion at primary screening were irrelevant publication style (review or editorial; n=156) and irrelevant study design (n=127).

After screening, only 11 papers were included for data extraction; nine studies and three HTAs. An additional paper was identified for data extraction[83], but described the same model as Cheng *et al.* (2016).[84] No additional data were presented in this additional secondary publication, and so data were only extracted from the original paper.

The flow diagram of the updated cost-effectiveness SLR is presented in Figure 20.[85]

Figure 18: PRISMA flow-diagram of the updated cost-effectiveness SLR[85]



Key: AWMSG, All Wales Medical Strategy Group; HTA, health technology assessment; n, number; NICE, National Institute for Health and Care Excellence; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review; SMC, Scottish Medicines Consortium.

5.1.3. Study results

A summary of the findings across the 11 identified papers is presented in Table 33.

All studies considered the full intention-to-treat (ITT) newly diagnosed mPAC population, eligible for first-line treatment. In addition, there was a lack of studies modelling second-line mPAC treatment that were found to meet the inclusion criteria of this search.

The most common comparison was between *nab*-P/Gem and gemcitabine (n=9), followed by *nab*-P/Gem compared with FOLFIRINOX (n=4). Other comparisons included: *nab*-P/Gem compared with Gem/Cap and gemcitabine compared with FOLFIRINOX and Gem/Cap.

Ten cost-utility Markov models were identified – nine *de novo* economic models and one considering an update to a previously published model. The remaining paper presented a cost-benefit analysis.

In all comparisons of *nab*-P/Gem with gemcitabine, efficacy was sourced from the CA046 (MPACT) study.[6] The ACCORD trial was referenced as the efficacy source for the paper that made comparisons with FOLFIRINOX.[28]

The final study included in these results considered a comparison of *nab*-P/Gem with gemcitabine in combination with erlotinib (Gem/Erl). As Gem/Erl was not included in the NICE scope due to limited relevance for the UK clinical setting, this study is considered separately for completeness.[86]

Table 33: Summary of cost-effectiveness data extractions

Study	Country	Summary	Patient population	Efficacy data source	Time horizon	Costs	QALYs	ICER
Carrato *et al.* (2015)[36]	Spain	Cost utility Markov model. Comparison of first-line *nab*-P/Gem with gemcitabine	First-line mPAC ITT population. Average age NR (based on MPACT trial)	MPACT study[6]	10 years	*Nab*-P/Gem: €16,885 Gemcitabine: €10,408	*Nab*-P/Gem: 0.718 Gemcitabine: 0.562	€41,519 per QALY gained
Cheng *et al.* (2016)[87]	US	Cost utility Markov model. Comparison of first-line FOLFIRINOX with *nab*-P/Gem	First-line mPAC ITT population. Average age NR	NR	3 years	FOLFIRINOX: $56,628 *nab*-P/Gem: $55,944	FOLFIRINOX: 0.51 *nab*-P/Gem: 0.40	$30,870 per QALY gained
Cowell *et al.* (2014)[88]	UK	Research paper considering weighting QALYs based on burden of illness using the Markov model comparing *nab*-P/Gem with gemcitabine submitted to the SMC as an example	NR. Average age NR	MPACT study	NR	NR	Partial QALY weighting: 0.221 incremental QALYs Full QALY weighting: 0.39 incremental QALYs	No QALY weighting: £52,885 per QALY gained Partial QALY weighting: £37,249 per QALY gained Full QALY weighting: £21,108 per QALY gained
Fragoulakis *et al.* (2014)[89]	Greece	Cost utility Markov model. Comparison of	First-line mPAC ITT population. Average age NR	MPACT study	NR	*Nab*-P/Gem: €15,628 (95% CI:	*Nab*-P/Gem: 0.71 (95% CI: 0.66, 0.78)	€47,120 per QALY gained

Study	Country	Summary	Patient population	Efficacy data source	Time horizon	Costs	QALYs	ICER
		first-line *nab*-P/Gem with gemcitabine				€14,377, €17,027) Gemcitabine: € 8,284 (95% CI: €7,455, €9,112)	Gem: 0.56 (95% CI: 0.52, 0.60)	
Gharaibeh *et al.* (2015)[90]	UK	Cost utility Markov model. Comparison of first-line *nab*-P/Gem with gemcitabine	First-line mPAC ITT population. Median age: 63 years old	MPACT study	Lifetime	*Nab*-P/Gem: £9,314 Gemcitabine: £3,848	*Nab*-P/Gem: 0.52 Gemcitabine: 0.45	£78,086 per QALY gained
Gharaibeh *et al.* (2015)[91]	US	Cost utility Markov model. Comparison of first-line *nab*-P/Gem with gemcitabine and FOLFIRINOX	First-line mPAC ITT population. Average age NR	MPACT study ACCORD trial Bucher indirect comparisons due to lack of head to head data with FOLFIRINOX	Lifetime	*Nab*-P/Gem vs gemcitabine: incremental cost $23,031 FOLFIRINOX vs gemcitabine: $42,846 FOLFIRINOX vs *nab*-P/Gem : $19,815	*Nab*-P/Gem vs gemcitabine: incremental +0.16 FOLFIRINOX vs gemcitabine: +0.26 FOLFIRINOX vs *nab*-P/Gem: +0.16	*Nab*-P/Gem vs gemcitabine: $141,338 FOLFIRINOX vs gemcitabine: $164,495 FOLFIRINOX vs *nab*-P/Gem: $202,187 *nab*-P/Gem vs FOLFIRINOX: $37,692
Stetka *et al.* (2015)[92]	Slovak Republic	Cost utility Markov model Comparison of	First-line mPAC ITT population KPS 70–80	MPACT	10 years	*nab*-P/Gem: €9,912.13 Gemcitabine:	*nab*-P/Gem: 0.629 Gemcitabine:	€27,769 per QALY gained

Study	Country	Summary	Patient population	Efficacy data source	Time horizon	Costs	QALYs	ICER
		nab-P/Gem with gemcitabine	Average age NR			€3,969.52	0.415	
NICE TA360 (2015)[82]	UK	Cost utility Markov model Comparison of *nab*-P/Gem with gemcitabine, Gem/Cap and FOLFIRINOX	First-line mPAC ITT population KPS 70–80 Average age NR	MPACT	10 years	*Nab*-P/Gem: £18,213 Gemcitabine: £10,078 FOLFIRINOX: £15,105	*Nab*-P/Gem: 0.713 Gemcitabine: 0.556 FOLFIRINOX: 0.857	*Nab*-P/Gem vs Gem: £51,900 per QALY gained *nab*-P/Gem vs Gem/Cap: £87,084 per QALY gained *nab*-P/Gem vs FOLFIRINOX: Dominated
SMC (no: 968/14)[22]	UK (Scotland)	Cost utility Markov model Comparison of *nab*-P/Gem with gemcitabine	First-line mPAC ITT population KPS 70–80 Average age NR	MPACT	10 years	Incremental cost of £8,232	Incremental QALYs of 0.156	£52,885 per QALY gained
AWMSG (no: 1999)[23]	UK (Wales)	Cost utility Markov model Comparison of *nab*-P/Gem with gemcitabine	First-line mPAC ITT population KPS 70–80 Average age NR	MPACT	10 years	*Nab*-P/Gem: £21,920 Gemcitabine: £13,630	*Nab*-P/Gem: 0.717 Gemcitabine: 0.561	£53,260 per QALY gained
Data extractions relating to secondary comparators (beyond previous NICE scope)								
Osterlund *et al.* (2016)[86]	Norway Sweden Finland Denmar	Cost benefit analysis Comparison of Gem/Erl and *nab*-Paclitaxel	First-line mPAC ITT population Average age NR	NR	NR	NR	NR	Cost per month of OS, average of Nordic countries (Gem/Erl): €1,232 Cost per month of

Study	Country	Summary	Patient population	Efficacy data source	Time horizon	Costs	QALYs	ICER
	k							PFS, average or Nordic countries (Gem/Erl): €2,103 Cost per month of PFS, average or Nordic countries (*nab*-P/Gem): €2,602

Key: AWMSG, All Wales Medical Strategy Group; FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin; Gem/Erl, gemcitabine in combination with erlotinib; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; KPS, Karnofsky Performance Status; mPAC, metastatic pancreatic adenocarcinoma; NICE, National Institute for Health and Care Excellence; NR, not reported; OS, overall survival; PFS, progression free survival; QALY, quality-adjusted life year; SMC, Scottish Medicines Consortium; TA, technology appraisal.

The three identified HTA submissions included the original NICE appraisal (TA360) for *nab*-P/Gem and the equivalent submissions for Scotland and Wales. Data were extracted from each appraisal, but as the limitations raised by the AWMSG and SMC formed a subset of those raised by NICE as part of the original submission, only the key issues raised by the ERG and the Appraisal Committee during the original NICE appraisal (TA360) were extracted to show how each issue has been addressed in this resubmission. Table 34 provides this information as a summary.

Table 34: Issues raised from the original TA360 appraisal[12, 48]

	Issues	**How this submission addresses these**
Comparative effectiveness data	The Committee considered that all data available at the time had been included in the submission. The ERG stated that proportional hazards were violated in the CA046 trial and so this cannot be assumed in other trials. The committee agreed with the ERG but concluded that for OS and PFS from CA046 there was not a gross violation of the proportional hazards assumption. The committee therefore decided that the MTC could be used to compare to secondary comparators Gem/Cap and FOLFIRINOX.	The clinical evidence base was updated for the re-submission; this included an update of the clinical SLR and the NMA.
Utility	The Committee and ERG considered that the CA046 (MPACT) study did not collect quality of life data and as a result the acceptability of the AE profile of *nab*-P/Gem was unknown. Further concerns were raised regarding the generalisability of the US utility values.	In the base case analysis, the re-submission considers quality of life data from the SIEGE trial.[93] The SIEGE trial includes patients that are receiving *nab*-P/Gem and so informs the quality of life evidence gap associated with the tolerability of *nab*-P/Gem in UK practice (see Section 5.4). Current analysis uses the February 2017 data cut. US values taken from Romanus *et al.* (2012) were converted to UK values using a mapping algorithm supplied by the ERG.[37]
Subgroups	The Committee and the ERG had concerns regarding selecting people for particular treatments based on their performance status, as it was noted that performance status is subjective and there are	Clinical feedback confirmed that although a subgroup effect is present this cannot be defined using standard performance status measures, such as KPS. Therefore, only the ITT population is

	Issues	How this submission addresses these
	no accepted performance status cut-off values for different treatments. In TA360, it was noted that "that FOLFIRINOX and Gem/Cap may be considered more effective treatment options, but there could be several reasons why people would choose gem alone instead (such as patient preference or from clinical judgment). It agreed that it was not possible to define this population (that is, people with a KPS of 70 to 100 who would have gemcitabine alone rather than FOLFIRINOX or Gem/Cap), and was unsure how generalizable the clinical trial data were to this population".	considered in the resubmission. The committee "considered that although the group of people who may have gemcitabine alone instead of FOLFIRINOX or gemcitabine plus capecitabine could not be defined, this group was clinically recognised…" (TA360, Guidance 4.19).
AEs	The Committee considered that firm conclusions were difficult to draw regarding AEs as the event rates and definitions varied across studies.	In the base-case analysis, the AE events for *nab*-P/Gem and gemcitabine are obtained from the CA046 trial.[6] The AE events for FOLFIRINOX are obtained from Conroy *et al.* (2011).[28] Where AE events are unavailable, the rate of AEs is assumed equal to *nab*-P/Gem. The AE event rate for Gem/Cap is assumed equal to *nab*-P/Gem. A scenario analysis considers assuming the same AE profile as *nab*-P/Gem for both FOLFIRINOX and Gem/Cap.
Dosing	The Committee considered that the base-case analysis should account for the costs of the full recommended treatment dose without missed doses, as it was considered that not all missed doses could be anticipated.	In the base case, the model uses data from a survey of pharmacists to inform the proportion of dose reductions and missed doses that are anticipated. Reductions or missed doses that are not anticipated are costed in full. These assumptions were independently validated by clinical experts.
Vial sharing	The Committee thought it inappropriate to apply vial sharing to patients receiving *nab*-Paclitaxel	In the base-case analysis, vial sharing is not included.

	Issues	How this submission addresses these
	only as other chemotherapy agents could be safely stored for 24 hours before use and could therefore be considered for vial sharing. Furthermore, it was considered that, due to the small patient population, vial sharing was inappropriate.	
Terminal care costs	The Committee considered that the terminal care cost should account for the proportion of people who die in hospital, hospice or at home.	In the base-case analysis, the micro-costing approach suggested by the ERG is used to estimate the cost associated with end of life care. A scenario analysis considers the estimate from the King's Fund, Addicott and Dewar (2008).[94]
Key: AE, adverse event; ERG, Evidence review group; FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin; Gem/Cap, gemcitabine in combination with capecitabine; MTC, mixed treatment comparison; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; ITT, intention-to-treat; KPS, Karnofsky Performance Status; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; SLR, systematic literature review; TA, technology appraisal.		

5.2 Update of de novo analysis

5.2.1. Patient population

Nab-P/Gem is indicated for the first-line treatment of adult patients with mPAC. Given this, the base-case analysis of cost effectiveness in the re-submission utilises the main ITT trial data from the pivotal clinical trial, study CA046, which is in line with this indication.[6] This population is in line with the scope for this appraisal.

5.2.2. Model structure

Based upon the models identified within the economic literature, it was decided to adapt the economic model submitted within the original submission to NICE for TA360 rather than constructing a new *de novo* economic model. This is in line with the intention to keep the base case as close to NICE's preferred base case from TA360 as possible.

The model was developed in Microsoft Excel® 2010 using a Markov structure and an area under the curve approach to estimate the proportion of treated patients transitioning between a series of health states from the start of treatment through to

death. Similar Markov models were identified in the economic literature; Markov models lend themselves to disease areas in which patients progress through distinct stages, such as mPAC which is characterised by pre-progression and post-progression health states. The ERG deemed this model structure acceptable within the original submission to NICE.[48]

The three main clinically-defined health states are:

1. Pre-progression
2. Post-progression
3. Death

A proportion of patients in the pre-progression health state may not be receiving active treatment as clinicians may withdraw treatment due to toxicity or other treatment-related issues. Therefore, to ensure drug costs are not overestimated, the "pre-progression health state" was split into:

- 'Pre-progression: on first-line treatment'
- 'Pre-progression: off first-line treatment'

Patients enter the model in the 'Pre-progression: On first-line treatment' health state and remain there for the duration of the first cycle (1 week). Thereafter, patients can transition between health states (as shown in Figure 21) in each weekly model cycle, with a given transition probability. The probabilities of transitioning between each state are informed by a set of survival models fitted to Kaplan–Meier (KM) data from the study CA046 for all three clinical end-points:[6]

1. OS
2. PFS
3. ToT

Disease progression was based on the RECIST guidelines and assessed by investigator review in the base case. Investigator review was considered in the base case as, in the initial scoping consultations for the original NICE submission (TA360), the ERG expressed a preference for PFS by investigator assessment based on the fact that this is a close representation of clinical practice.[7] However, in line with recommendations from the Pharmaceutical Research and Manufacturers of America

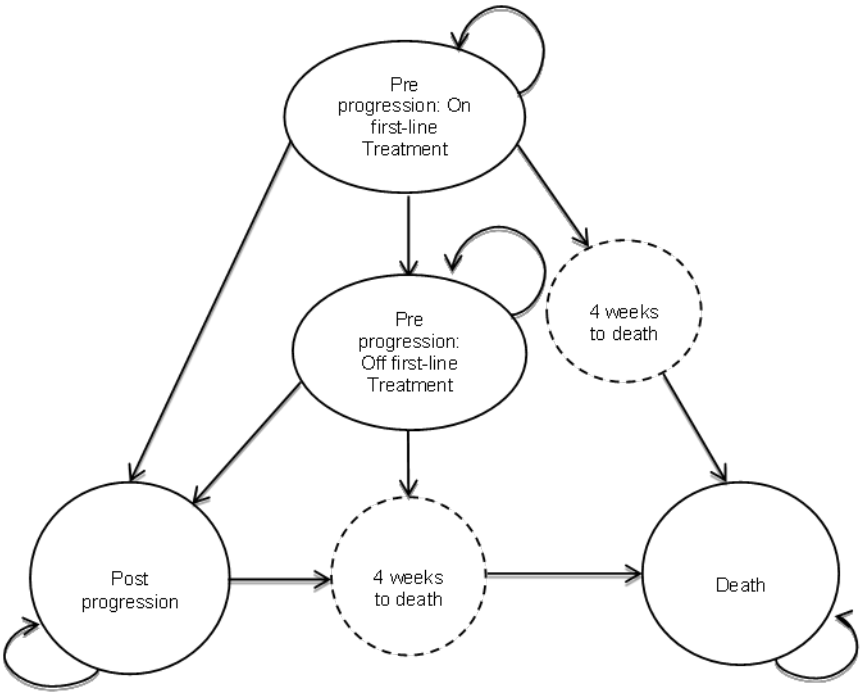
(PhRMA) PFS Working Group, PFS by independent review is used in an ‘audit capacity’ and is considered in a scenario analysis. Little difference was seen between investigator assessment and independent review.

The model structure also has a tunnel state at ‘4 weeks to death’, which is used to represent and capture the more intensive period of palliative care often required in the final stages of life. The duration of the tunnel state can be set at 4, 8 or 12 weeks to reflect the periods of time end of life outcomes are experienced over.

The three model health states are designed to capture the factors most important to patients with mPAC, including:

- Whether or not the patient is pre-progression (responding to treatment or maintaining stable disease) or post-progression: with impacts on quality of life and the costs of managing the disease
- Whether the patient is receiving treatment or not
- Survival

Figure 19: Model schematic



A cycle length of 1 week was considered sufficient to capture the progression of mPAC. In the base case, half-cycle correction was not applied as patients incur drug and administration costs of first-line treatment at the beginning of the cycle.

Furthermore, given the short cycle length, inclusion of half-cycle correction had a negligible impact on the ICER, as it did in the original submission. Table 35 summaries the key features of this economic analysis.

Table 35: Features of the *de novo* analysis

Factor	Chosen values	Justification
Time horizon	10 years	All patients have transitioned to the death state by Year 10 – in line with the aggressive and late-stage presentation of the disease
Model cycle length	1 week	The first-line treatments for mPAC are administered at different frequencies. A 1-week cycle length allowed the costs associated with each first-line treatment to be fully incorporated
Were health effects measured in QALYs; if not, what was used?	Yes	As per NICE reference case[95]
Discount of 3.5% for utilities and costs	Yes	As per NICE reference case
Perspective (NHS/PSS)	Yes	As per NICE reference case
Key: mPAC, metastatic pancreatic cancer; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years.		

5.2.3. Intervention technology and comparators

5.2.3.1. First-line treatment

In line with the decision problem outlined in the scope, the model compared *nab*-P/Gem with gemcitabine, Gem/Cap and FOLFIRINOX for the first-line treatment of mPAC. The main comparator is gemcitabine. FOLFIRINOX is an intensive therapy, associated with high administration burden and considerable toxicity, and is therefore only suitable for a defined group of clinically appropriate patients. These patients will continue to receive this regimen despite the accessibility of *nab*-P. Gem/Cap has not demonstrated a significant survival benefit over gemcitabine monotherapy in a Phase III RCT, and is not recommended in European clinical guidelines. Use of Gem/Cap is thus limited to very few centres across the UK, and

this regimen does not represent a national standard of care. Select patients who may receive this regimen will continue to do so despite the accessibility of *nab*-P/Gem; that is, *nab*-P/Gem will not replace the very limited use of Gem/Cap.[11]

Neither Gem/Cap nor FOLFIRINOX are licensed within the UK. Furthermore, Gem/Cap is only prescribed in a limited number of treatment centres and so the applicability of these comparators in a UK setting is considered limited. FOLFIRINOX use is reserved for the segment of patients who are considered fit enough to take it. Clinical experts suggest that treatment with FOLFIRINOX or Gem/Cap will not be replaced by *nab*-P/Gem.[11] Instead, *nab*-P/Gem will displace gemcitabine monotherapy in patients who are older or somewhat less fit, and thus less likely to be treated with FOLFIRINOX, as it did when it was available via the CDF.[11] This explained in more detail in Section 3.3.

Efficacy data for *nab*-P/Gem compared with gemcitabine is obtained from the CA046 study.[6] No direct head-to-head evidence is available comparing *nab*-P/Gem with Gem/Cap nor with FOLFIRINOX. Therefore, this re-submission considers an NMA using the results of the updated clinical SLR to estimate the relative efficacy of Gem/Cap and FOLFIRINOX with respect to *nab*-P/Gem (see Section 4.10). The assumptions underpinning an NMA require proportional hazards to hold between treatments – this assumption is not supported by the CA046 study used within the network; KM OS and PFS curves are shown to cross (see Section 4.10.5). Therefore, there is a risk the results from the NMA lack technical validity and so should be interpreted with caution.

Once patients have completed first-line treatment they are assumed in the model to spend a period of time off treatment. This is calculated in the model using the observed difference in the proportion of patients between the fitted ToT and PFS curves (%PFS - %ToT). During this time off treatment, patients are assumed to continue to be regularly monitored, but they do not receive any further active first-line therapy. This is an important aspect of the model's clinical validity; if it is assumed that all patients continue to receive treatment until disease progression, the amount of first-line drugs typically administered to the cohort of patients in clinical practice will be overestimated (and in clinical trial [CA046] evidence).[21]

5.2.3.2. Second-line treatment

Following clinician feedback, second-line treatment is initiated based on evidence of disease progression.[96] Therefore, upon transitioning into the post-progression health state, patients are modelled to receive second-line care.

To avoid any issues of confounding, data from study CA046 were used to estimate the level of use and range of second-line treatments. This ensures that the treatment costs included in the model reflect those associated with the OS benefit demonstrated in study CA046. However, since CA046 was an international study, there are some treatments included in second-line therapy (such as erlotinib) that are not routinely used as second-line treatment in the UK, although the actual percentage use of these therapies in CA046 is low (4%–5%).

The total percentage of patients moving on to active second-line therapy on the gemcitabine monotherapy arm and *nab*-P/Gem arm, as reported in study CA046, is 42% and 38%, respectively (Table 36). Therefore, the cohort of patients on the *nab*-P/Gem arm received marginally less survival benefit from second-line treatment. The seven most prevalent second-line treatments reported in study CA046 have been included in the model. The percentage of patients receiving each of the active second-line therapies has been adjusted such that the sum of the seven selected therapies is equal to the total percentage moving on to second-line treatment in each arm. Patients who do not move onto active second-line therapy are assumed to receive standard palliative care (see Section 5.5.5).

The model assumes that patients treated with either first-line Gem/Cap or FOLFIRINOX will receive a similar profile of second-line therapies (combinations and distribution percentages) (excluding the initial, first-line treatment) as those received by patients initially treated with *nab*-P/Gem (in the study CA046).

Table 36: Second-line treatments

Second-line treatment	**% Patients moving onto second-line therapies[6]**	
	Gemcitabine (Total=42%)	***Nab*-P/Gem (Total=38%*)**
5-FU	1.3%	7.3%
5-FU + oxaliplatin	17.1%	13.2%
Gem/Cap	3.9%	2.9%
Capecitabine	6.6%	4.4%

Gem/Erl	3.9%	2.9%
Erlotinib	1.3%	1.5%
FOLFIRINOX	0.0%	0.0%
Key: 5-FU, 5-fluorouracil; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; Gem/Cap, gemcitabine in combination with capecitabine; Gem/Erl, gemcitabine in combination with erlotinib; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine. **Note:** * The figures do not sum to 38% due to rounding.		

5.3 Clinical parameters and variables

The pivotal study used for cost-effectiveness analysis was study CA046; this is the largest study of first-line therapies for mPAC to date. The primary objective of the study was to evaluate the efficacy of *nab*-P/Gem compared with gemcitabine monotherapy. These data were used in the original NICE submission (TA360), and the updated clinical SLRs did not identify any new comparative efficacy data.

The primary endpoint in the CA046 study was OS analysed using KM methods and a stratified log-rank test. Secondary endpoints were PFS, objective response rate (tumour response, ORR) according to RECIST (Version 1) criteria, and the safety and tolerability of the combination.

5.3.1. Survival analysis

Patient-level data from study CA046 were used to generate KM data for each treatment arm for OS, PFS and ToT.[21]

In line with NICE DSU guidance, the applicability of a single parametric model or a Cox proportional hazards model was determined using visual inspection of the KM curves, the log cumulative hazard plots (LCHP) and the quantile-quantile curves (Q-Q).[97] LCHPs were assessed to determine the suitability of using a single parametric model for the two treatment arms in terms of the underlying hazard and in assessing the suitability of projecting using exponential, Weibull and Gompertz curves. Q-Q plots were assessed to determine the suitability of the use of accelerated failure time models.

Six parametric distributions (exponential, log-normal, log-logistic, Gompertz, gamma and Weibull) were examined for each clinical outcome (OS, PFS and ToT), in line with the NICE DSU guidance.[97] Where a pooled model was not appropriate, either

due to non-proportional hazards or poor visual fit, a single (stratified) approach was considered to improve the model fit. Stratified models were considered to allow for a more flexible approach, where the hazard varied between arms at baseline and across time.

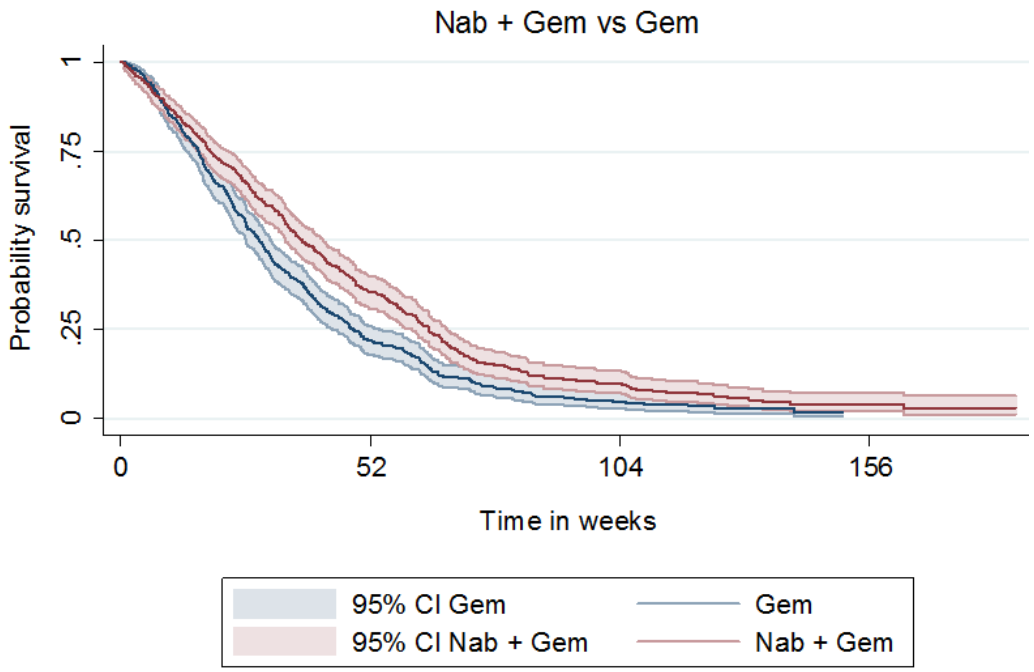
The fit of each parametric model to the KM data was explored using visual inspection, LCHPs, Q-Q plots, Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness of fit statistics and clinical plausibility. AIC and BIC provide an estimated relative fit of the alternative parametric models to the observed trial data. AIC and BIC have been criticised for use in selection of the most appropriate curve because they do not provide any measure of the relative merits of each functional form when used for extrapolation. While this is a valid criticism, updated OS data from study CA046 are relatively mature, with over 90% of patients followed to death. Furthermore, the validity of the selected curve was assessed by clinicians and economists to ensure that the predicted values from extrapolation were plausible. All curves were fitted using the statistical software package Stata.

The fitted parametric survival models enable the cost-effectiveness model to extrapolate beyond the trial period, and they therefore incorporate outcomes that occur after the trial over the patient's lifetime.

5.3.1.1. Overall survival

Data from study CA046 indicated that *nab*-P/Gem was associated with a significant improvement in median survival of 2.1 months compared to gemcitabine alone as shown in Figure 22 (median OS: 8.7 vs 6.6; HR: 0.72, 95% CI: 0.620, 0.825; P<0.0001).

Figure 20: OS Kaplan–Meier Survival plots by treatment group in ITT



Key: CI, confidence interval; ITT, intention to treat; Gem, gemcitabine; Nab, *nab*-Paclitaxel; OS, overall survival.

The applicability of using unstratified models for the comparison of OS for *nab*-P/Gem with gemcitabine was determined using visual inspection of the KM curves, the LCHPs and the Q-Q curves. The LCHPs and Q-Q plots for OS associated with *nab*-P/Gem are presented in Appendix 16. The LCHP suggests that a single parametric model may not be suitable for OS given the data, due to the lack of support for proportional hazards assumption indicated by the crossing of the LCHP curves. Using stratified models relaxed the proportional hazards assumption, and visual assessment of the parametric curve fits concluded that a stratified parametric model provides a reasonable fit to the data.

The AIC and BIC estimates associated with *nab*-P/Gem and gemcitabine are presented in Table 37. These estimates suggest that the gamma provides the most appropriate choice of model, as this curve had the lowest AIC/BIC and provides a good fit to the observed dataset (Figure 23). Stratified gamma curves were chosen because of the lack of support for the proportional hazards assumption. However, unstratified gamma also provides plausible estimates and a good visual fit and is therefore considered in a scenario analysis.

The mean modelled OS using the unstratified and stratified gamma distributions are extremely similar. Using either of the functional forms results in a survival gain of approximately 2.42 months for those receiving *nab*-P/Gem compared to gemcitabine monotherapy. The modelled survival using the stratified gamma curve plotted and compared to the underlying KM data is given in Figure 23, and shows a good visual fit for both CA046 treatment arms.

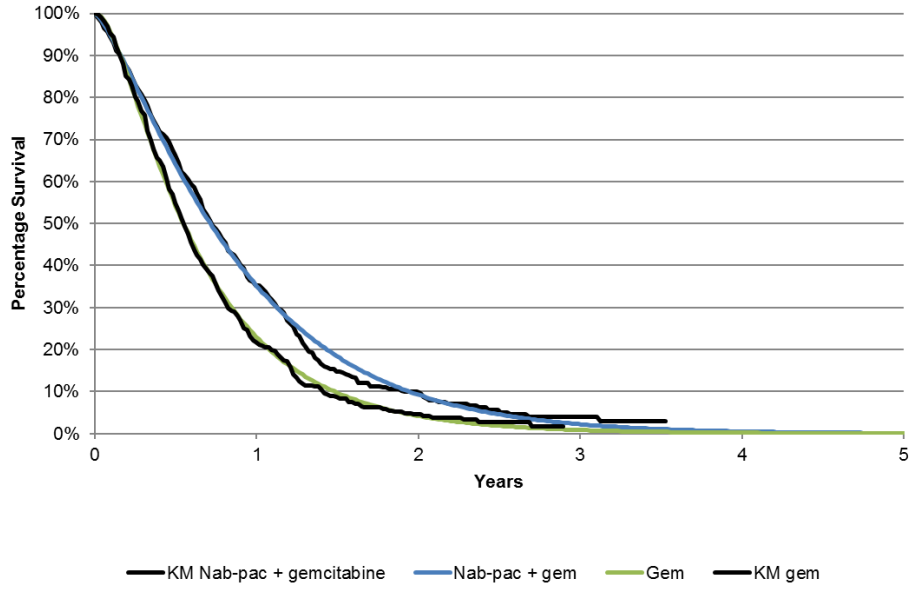
The ERG provided their own curve fits for OS in response to the economic model submitted as part of TA360. These curves are not considered in the base case analysis; the parameters associated with the underlying distribution were not provided, and therefore, the uncertainty associated with the ERG's OS curve cannot be captured. However, the impact on results of using the ERG's OS curve is assessed in a scenario analysis.

Table 37: AIC and BIC estimates for OS associated with *nab*-P/Gem and gemcitabine

	OS	
Model	**AIC**	**BIC**
Exponential	2,359.67	2,369.19
Weibull	2,300.06	2,314.33
Stratified Weibull	2,300.80	2,319.83
Gompertz	2,340.87	2,355.15
Lognormal	2,361.16	2,375.44
Log logistic	2,319.69	2,333.97
Gamma	2,293.47	2,312.50
Stratified gamma	2,290.93	2,319.48

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; OS, overall survival.

Figure 21: Kaplan–Meier versus base-case curves for OS associated with *nab*-P/Gem and gemcitabine



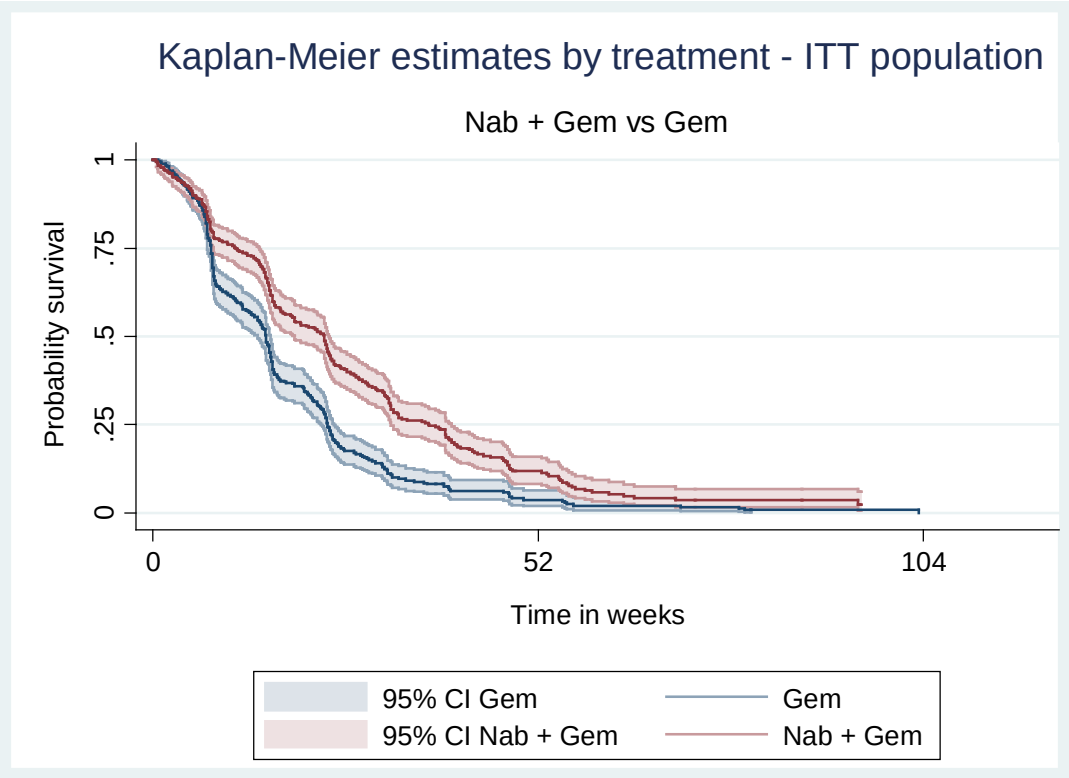
Key: KM, Kaplan–Meier; gem, gemcitabine; Nab-p/gem, *nab*-Paclitaxel in combination with gemcitabine; OS, overall survival.

5.3.1.2. Progression-free survival

PFS was one of two secondary endpoints in study CA046 (PFS and ORR) and was assessed by both independent reviewers and investigators. In both assessments, interpretation of radiological response for use in the PFS was completed using computed tomography (CT) alone or magnetic resonance imaging (MRI) scans. Independent review was conducted by two radiological reviewers who were blinded to treatment assignment (with a third reviewer for adjudication). In the base-case analysis, investigator assessment is considered in line with the original NICE submission (TA360).

Results from investigator assessment of PFS show patients receiving *nab*-P/Gem had a median PFS of 5.3 months compared to 3.5 months for patients receiving gemcitabine monotherapy. This resulted in a HR between treatment arms of 0.61 ($P<0.001$) and is demonstrated diagrammatically in Figure 24.

Figure 22: PFS Kaplan–Meier survival plots by treatment group



Key: CI, confidence interval; ITT, intention to treat; Gem, gemcitabine; Nab, *nab*-Paclitaxel; PFS, progression-free survival.

The applicability of using unstratified models for the comparison of PFS for *nab*-P/Gem with gemcitabine was determined using visual inspection of the KM curves, the LCHPs and the Q-Q curves. The LCHPs and Q-Q plots for PFS associated with *nab*-P/Gem are presented in Appendix 16. The LCHP indicates that a single parametric model may not be suitable for PFS given the data, due to the lack of support for proportional hazards assumption indicated by the crossing of the LCHP curves. Using stratified models relaxed the proportional hazards assumption, and visual assessment of the parametric curve fits concluded that a stratified parametric model provides a reasonable fit to the data.

The AIC and BIC PFS estimates associated with *nab*-P/Gem and gemcitabine are presented in Table 38. These estimates suggest that the stratified gamma provides the most appropriate choice of model as this curve had the lowest AIC/BIC and provided a good fit to the observed dataset (Figure 25). The modelled mean duration of PFS for patients on *nab*-P/Gem is 6.15 months compared to 4.17 months for

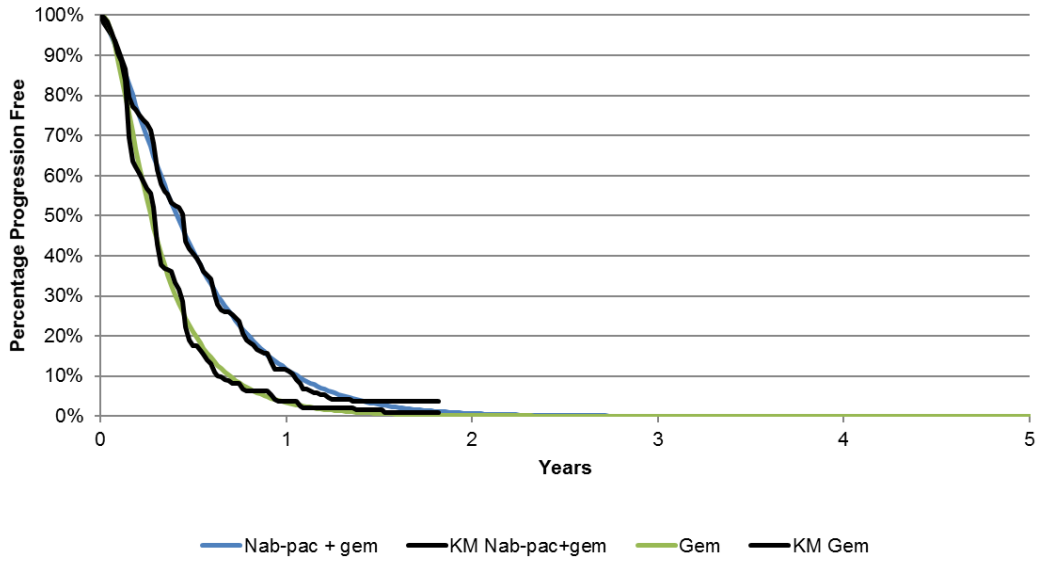
gemcitabine monotherapy, resulting in an incremental gain of 1.98 months of PFS. However, unstratified gamma also provides plausible estimates and a good visual fit and is therefore considered in a scenario analysis.

The ERG provided their own curve fits for PFS in response to the economic model submitted as part of TA360. These curves are not considered in the base-case analysis; the parameters associated with the underlying distribution were not provided, and therefore, the uncertainty associated with the ERG's PFS curve cannot be captured. The impact on results of using the ERG's PFS curve is assessed in a scenario analysis.

Table 38: AIC and BIC estimates for PFS associated with *nab*-P/Gem and gemcitabine

	PFS	
Model	**AIC**	**BIC**
Exponential	2,057.47	2,066.98
Weibull	1,974.00	1,988.27
Stratified Weibull	1,974.81	1,993.84
Gompertz	2,030.19	2,044.46
Lognormal	2,019.58	2,033.85
Log logistic	1,982.25	1,996.53
Gamma	1,962.75	1,981.79
Stratified gamma	1,952.27	1,980.82
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; PFS, progression-free survival.		

Figure 23: PFS KM versus base-case PFS curves

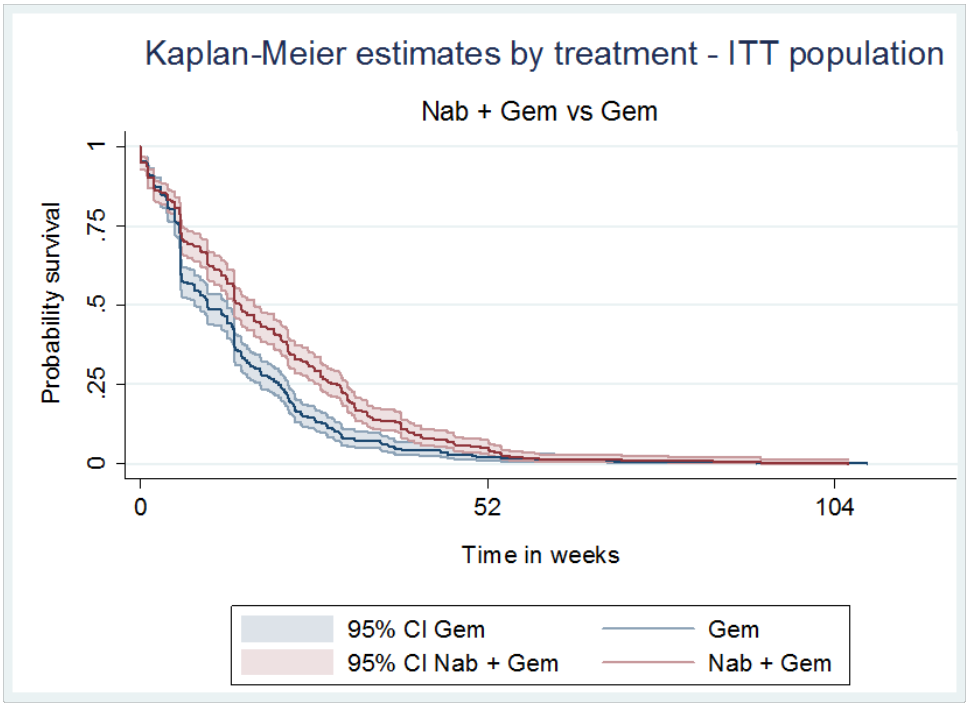


Key: KM, Kaplan–Meier; Gem, gemcitabine; Nab-pac+gem, *nab*-Paclitaxel in combination with gemcitabine; PFS, progression-free survival.

5.3.1.3. Time on treatment

ToT is a derived variable, calculated from the patient-level data as the difference between treatment end date and treatment start date. Where the treatment end date was not available, the date of progression was used. According to data from the pivotal study, patients receiving *nab*-P/Gem remained on treatment longer than those on gemcitabine monotherapy with median values of 3.4 and 2.3 months (0.71, 95% CI: 0.62, 0.81), respectively. KM data for the ToT for both arms are given in Figure 26.

Figure 24: ToT Kaplan–Meier survival plots by treatment group in ITT



Key: CI, confidence interval; Gem, gemcitabine; ITT, intention-to-treat; Nab, *nab*-Paclitaxel; ToT, time on treatment.

An identical approach to the parametric curve selection used for OS and PFS was used to assess the best functional survival form to model ToT from the study CA046.

The applicability of using unstratified models for the comparison of ToT for *nab*-P/Gem with gemcitabine was determined using visual inspection of the KM curves, the LCHPs and the Q-Q curves. The LCHPs and Q-Q plots for ToT associated with *nab*-P/Gem are presented in Appendix 16. The LCHP indicates that a single parametric model may not be suitable for ToT given the data, due to the lack of support for proportional hazards assumption indicated by the crossing of the LCHP curves. Using stratified models relaxed the proportional hazards assumption, and visual assessment of the parametric curve fits concluded that a stratified parametric model provides a reasonable fit to the data.

The AIC and BIC ToT estimates associated with *nab*-P/Gem and gemcitabine are presented in Table 39. These estimates suggest that the stratified gamma provides the most appropriate choice of model as this curve had the lowest AIC/BIC and provided a good fit to the observed dataset (Figure 27).

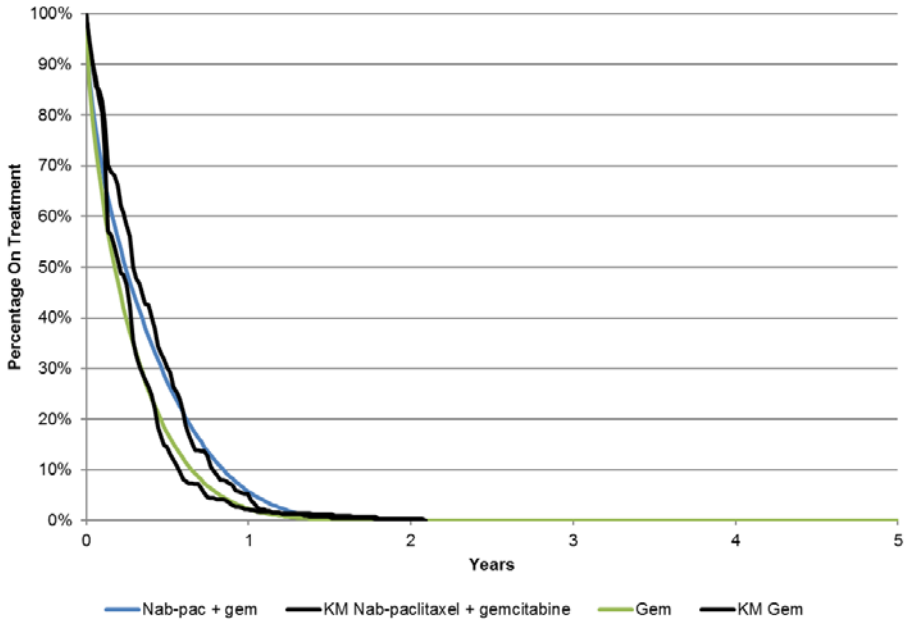
The modelled survival, using the stratified gamma curve plotted and compared to the underlying KM data, is given in Figure 27 and shows a good visual fit for both CA046 treatment arms. The modelled mean ToT for patients on *nab*-P/Gem is 4.15 months compared to 3.16 months for those on gemcitabine monotherapy.

The ERG provided their own curve fits for ToT in response to the economic model submitted as part of TA360. These curves are not considered in the base-case analysis; the parameters associated with the underlying distribution were not provided, and therefore, the uncertainty associated with the ERG's ToT curve cannot be captured. The impact on results of using the ERG's ToT curve is assessed in a scenario analysis.

Table 39: AIC and BIC estimates for ToT associated with *nab*-P/Gem and gemcitabine

	ToT	
Model	**AIC**	**BIC**
Exponential	3,215.93	3,225.45
Weibull	3,174.43	3,188.70
Stratified Weibull	3,176.36	3,195.39
Gompertz	3,210.92	3,225.19
Lognormal	4,039.76	4,054.03
Log logistic	3,514.41	3,528.68
Gamma	3,015.96	3,035.00
Stratified gamma	3,013.61	3,042.16
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; ToT, time on treatment.		

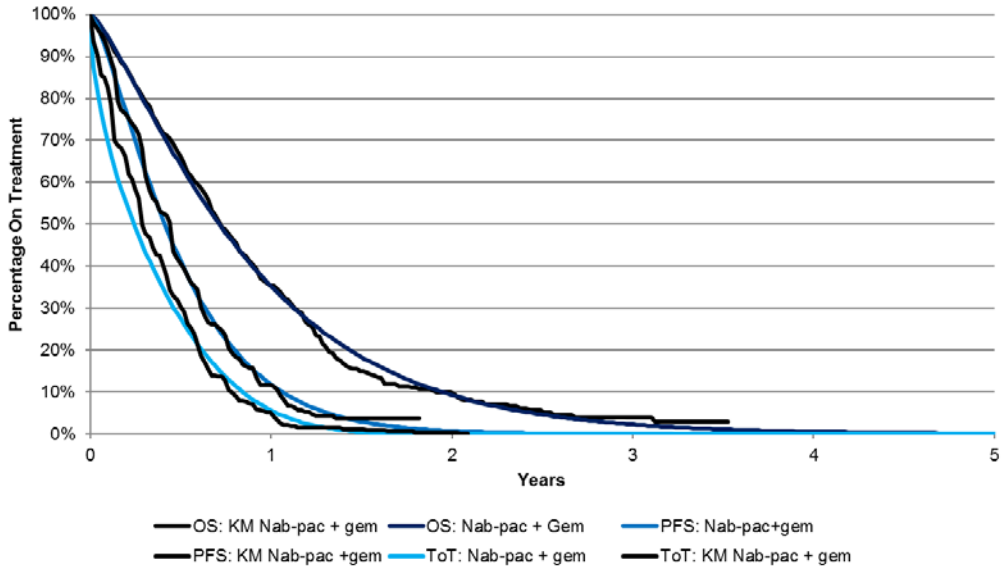
Figure 25: ToT KM versus base-case ToT curves



Key: KM, Kaplan–Meier; Gem, gemcitabine; Nab-pac, *nab*-Paclitaxel; ToT, time on treatment.

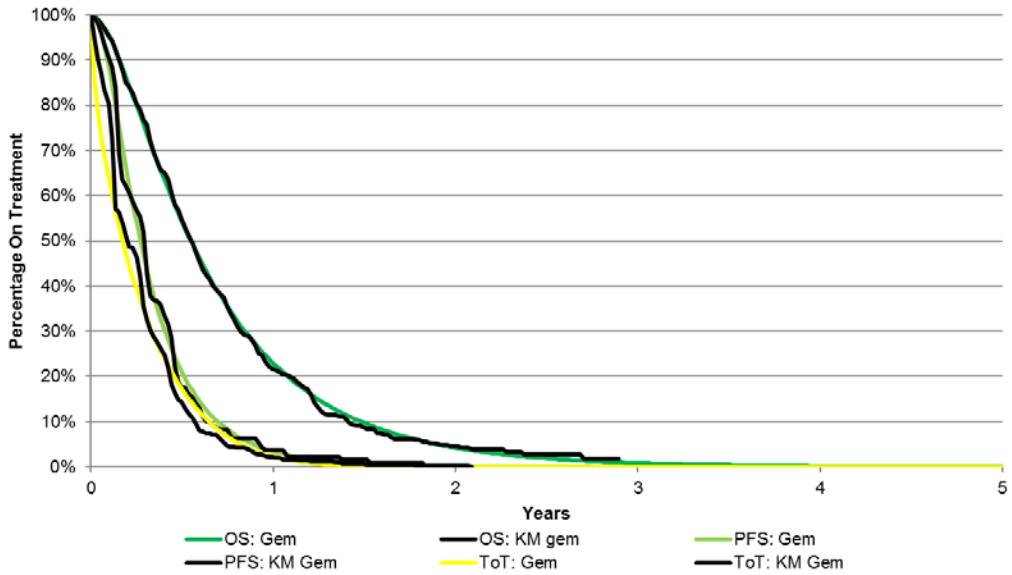
Figure 28 and Figure 29 compare the trial KM data for OS, PFS and ToT to the percentage of patients in the model who are respectively estimated to be alive, in pre-progression and on first-line treatment. The stopping rule for first-line treatment used in clinical practice is disease progression. However, in UK clinical practice, chemotherapy treatment is often stopped before this due to treatment-related toxicity or other AEs. Given this, the time on first-line treatment was modelled separately to pre-progression and was seen to be systematically lower across the cohort of patients on both treatment arms in study CA046 (Figure 28, Figure 29).

Figure 26: *nab*-P/Gem modelled time to event vs KM data (ITT)



Key: Nab-p/gem, *nab*-Paclitaxel in combination with gemcitabine; ITT, intention-to-treat; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.

Figure 27: Gemcitabine monotherapy modelled time to event vs KM data (ITT)



Key: Gem, gemcitabine; ITT, intention-to-treat; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.

5.3.2. Mixed treatment comparison

Gemcitabine monotherapy is the main comparator for *nab*-P/Gem (see Section 3.3). However, based on the scoping guidelines produced by NICE, Gem/Cap and FOLFIRINOX are also included as secondary comparators. This is despite the fact that Gem/Cap has not shown a statistically significant clinical benefit over gemcitabine monotherapy in a randomised Phase III trial and FOLFIRINOX, based on rationale presented in Section 3.3, is not considered an appropriate comparator. The pivotal trial used in the economic analysis is a head-to-head trial of *nab*-P/Gem compared to gemcitabine monotherapy, and thus provides no evidence of the relative efficacy of the intervention therapy to either Gem/Cap or FOLFIRINOX.

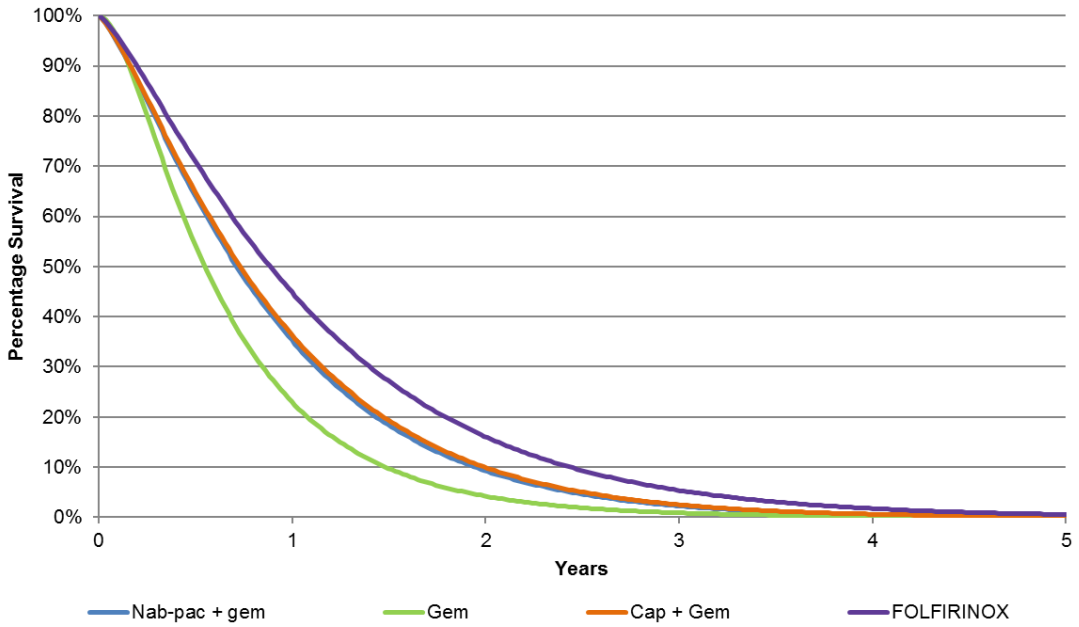
A meta-analysis and mixed treatment comparison (MTC) were undertaken as part of the original NICE submission (TA360) to incorporate these additional comparators into the economic model and estimate the HRs of Gem/Cap and FOLFIRINOX compared to:

(1) *Nab*-P/Gem for OS and PFS

(2) Gemcitabine monotherapy for OS and PFS

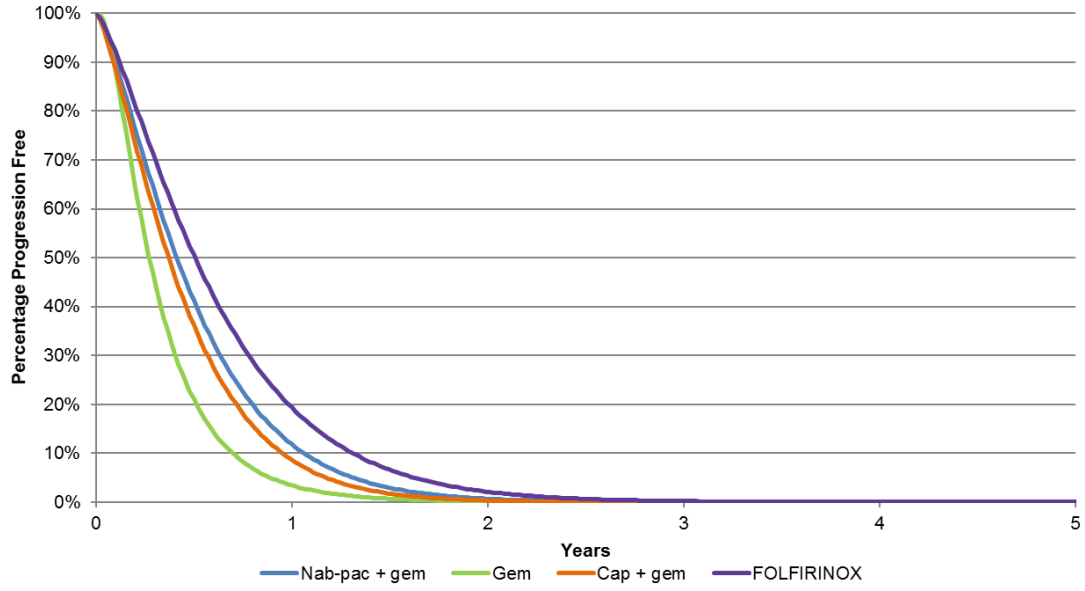
For this re-submission, the meta-analysis and MTC were updated to incorporate clinical evidence that became available since the original submission. See Section 4.10 for details of the MTC. OS, PFS and ToT curves produced by the base-case NMA settings are displayed in the figures below (Figure 30, Figure 31 and Figure 32), as well as mean estimates resulting from these curves (Table 40).

Figure 28: Base-case curves for OS associated with all comparators



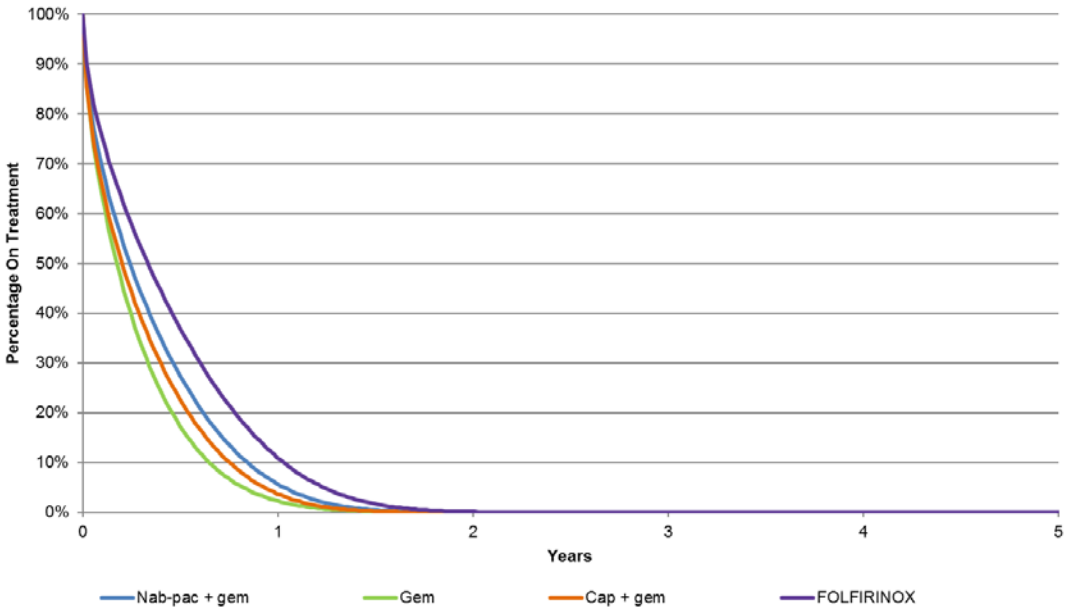
Key: cap + gem, gemcitabine in combination with capecitabine; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; gem, gemcitabine; Nab-p/gem, *nab*-Paclitaxel in combination with gemcitabine; Nab, *nab*-Paclitaxel; OS, overall survival.

Figure 29: Base-case curves for PFS associated with all comparators



Key: cap + gem, gemcitabine in combination with capecitabine; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; gem, gemcitabine; *nab*-Paclitaxel in combination with gemcitabine; Nab, *nab*-P; PFS, progression-free survival.

Figure 30: Base-case curves for ToT associated with all comparators



Key: cap + gem, gemcitabine in combination with capecitabine; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; gem, gemcitabine; Nab-p/gem, *nab*-Paclitaxel in combination with gemcitabine; Nab, *nab*-Paclitaxel; ToT, time on treatment.

Table 40: Base-case NMA outputs including hazard ratios reported versus *nab*-P/Gem

Outcome	Comparator	Median hazard ratio (vs *nab*-P/Gem)	95% Credible intervals	
			Lower Bound	Upper bound
OS	Gem/Cap	0.970	0.641	1.465
	FOLFIRINOX	0.769	0.580	1.015
PFS	Gem/Cap	1.148	1.698	1.004
	FOLFIRINOX	0.770	1.016	0.700
ToT	Gem/Cap	Assume same hazard ratio as PFS		
	FOLFIRINOX	Assume same hazard ratio as PFS		

Key: Gem/Cap, gemcitabine in combination with capecitabine; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.

Table 41: Mean OS, PFS and ToT associated with all comparators

Outcome	Model results			
	Gem	***nab*-P/Gem**	**Gem/Cap**	**FOLFIRINOX**
Mean survival (months)				
Overall survival	8.59	11.01	11.29	13.73
Progression-free survival	4.17	6.15	5.52	7.57
Time on treatment	3.16	4.15	3.63	5.29

Key: Gem/Cap, gemcitabine in combination with capecitabine; FOLFIRINOX, Folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; gem, gemcitabine; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.

Results of the NMA are used as inputs in the economic model to inform survival outcomes for secondary comparators Gem/Cap and FOLFIRINOX. The deterministic model uses median and 95% credible interval values. Uncertainty around the HR estimates is incorporated in the probabilistic sensitivity analysis (PSA) by randomly sampling from the 10,000 iterations from the posterior distribution of the Bayesian NMA.

Due to the lack of support for the assumption of proportional hazards in the OS and PFS data from the CA046 study, the proportional hazards assumption underpinning the MTC is questionable, and therefore, the comparison between *nab*-P/Gem and Gem/Cap or FOLFIRINOX cannot be relied upon to produce useful results.

5.3.3. Adverse events

Treatment with chemotherapy results in a variety of AEs. Furthermore, the type, severity and rate of AEs can vary between chemotherapy treatments, leading to differences in overall HRQL, resource use and costs. To capture these differences, AEs were included in the model based on the following criteria:

1. Treatment emergent
2. Grade 3+
3. Occur in >5% of patients on either arm

In addition, clinicians were presented with a list of AEs that met criteria (1) and (2) laid out above, but occurred in at less than 5% of patients (first advisory board).[96]

They were asked to identify any AEs that were originally omitted but should be included based on either:

- A substantial decrement in terms of HRQL
- A substantial impact on resource use or costs

Fifteen different AEs met the above criteria and were included in the analysis, as shown in Table 42. The modelled duration of ToT (gemcitabine=99.7 days, *nab*-P/Gem=129.9 days) and the total number of patients on each arm from CA046 (gemcitabine n=402, *nab*-P/Gem=421) were used to give the total ToT in patient years. The rate of occurrence for each AE was then calculated by dividing by the total number of each event per treatment arm by the patient years on each treatment. It was then converted into a cycle (weekly) probability using the rate to probability formula:

Cycle probability = 1-EXP (-rate*[cycle length/duration of 1 year]).

Table 42: Grade 3+ TEAEs

Grade 3+ TEAEs	***nab*-P/Gem**			**Gemcitabine**		
	Number of events*	**Rate**	**Cycle Probability**	**Number of events**	**Rate**	**Cycle Probability**
Neutropenia	138	0.922	0.018	85	0.775	0.01474
Fatigue	77	0.514	0.010	37	0.337	0.00644
Thrombocytopenia	53	0.354	0.007	33	0.301	0.00575
Anaemia	49	0.327	0.006	32	0.292	0.00557
Leukopenia	39	0.260	0.005	15	0.137	0.00262
Peripheral sensory neuropathy	34	0.227	0.004	1	0.009	0.00017
Neuropathy peripheral	32	0.214	0.004	0	0.000	0.00000
Dehydration	31	0.207	0.004	10	0.091	0.00175
Asthenia	29	0.194	0.004	17	0.155	0.00297
Abdominal pain	27	0.180	0.003	32	0.292	0.00557
Nausea	27	0.180	0.003	14	0.128	0.00244
Diarrhoea	26	0.174	0.003	6	0.055	0.00105
Vomiting	25	0.167	0.003	15	0.137	0.00262
Decreased appetite	23	0.154	0.003	8	0.073	0.00140

Grade 3+ TEAEs	*nab*-P/Gem			Gemcitabine		
	Number of events*	Rate	Cycle Probability	Number of events	Rate	Cycle Probability
Pulmonary embolism	19	0.127	0.002	26	0.237	0.00453
Pneumonia	15	0.100	0.002	9	0.082	0.00157
Febrile neutropenia	14	0.094	0.002	6	0.055	0.00105
Cholangitis	10	0.067	0.001	6	0.055	0.00105
Hyperbilirubinemia	9	0.060	0.001	12	0.109	0.00209

Key: *Nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; TEAE, treatment-emergent adverse event;
Note: * Taken from study CA046.[21]

Costs and utilities were assigned to each AE and multiplied by the cycle probability to get an average cost and disutility per cycle. For the utility calculation, the average durations of AEs were calculated from the patient-level data and used to weight the disutility associated with each AE.

As a simplifying assumption, the same AE profile is assumed for the gemcitabine doublets, therefore the observed profile of *nab*-P/Gem (in terms of both observed rate and AE duration) is applied to Gem/Cap in this exploratory analysis. Similarly, for second-line therapies where two agents are given in combination, they are assumed to have the same AE profile as *nab*-P/Gem. Where a monotherapy is given, the profile is assumed to be equal to gemcitabine.

The rate of AEs for FOLFIRINOX was calculated using the reported percentages of AEs from Conroy *et al.* (2011), where possible (Table 43).[28] An RR was calculated for each reported AE compared with gemcitabine and was then applied to the model. Where it was not possible for RRs to be calculated (data not reported for all AEs), the rates and durations of AEs observed in the Study CA046 in the *nab*-P/Gem arm were applied. A summary of the cycle probabilities used for each AE for each first-line treatment is given in Table 44.

Table 43: Calculation of AE rates for FOLFIRINOX[28]

AEs	Reported % of AEs (Conroy *et al.*, 2011)		Calculated RR
	Gemcitabine	FOLFIRINOX	

Neutropenia	21%	46%	2.18
Febrile neutropenia	1%	5%	4.58
Thrombocytopenia	4%	9%	2.55
Anaemia	6%	8%	1.32
Fatigue	18%	24%	1.33
Vomiting	8%	14%	1.75
Diarrhoea	2%	13%	7.17
Thromboembolism	4%	7%	1.60
Key: AE, adverse event; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; RR, relative risk.			

Table 44: AE cycle probabilities used in model

AEs	Cycle probabilities			
	***nab*-P/Gem**	**Gemcitabine**	**FOLFIRINOX**	**Gem/Cap**
Neutropenia	0.0175	0.0147	0.0322	0.0175
Fatigue	0.0098	0.0064	0.0086	0.0098
Thrombocytopenia	0.0068	0.0057	0.0146	0.0068
Anaemia	0.0063	0.0056	0.0073	0.0063
Leukopenia	0.0050	0.0026	0.0050	0.0050
Peripheral sensory neuropathy	0.0043	0.0002	0.0043	0.0043
Neuropathy peripheral	0.0041	0.0000	0.0041	0.0041
Dehydration	0.0040	0.0017	0.0040	0.0040
Asthenia	0.0037	0.0030	0.0037	0.0037
Abdominal pain	0.0035	0.0035	0.0035	0.0035
Nausea	0.0035	0.0035	0.0035	0.0035
Diarrhoea	0.0033	0.0033	0.0238	0.0033
Vomiting	0.0032	0.0032	0.0056	0.0032
Decreased appetite	0.0029	0.0029	0.0029	0.0029
Pulmonary embolism	0.0000	0.0045	0.0000	0.0000
Pneumonia	0.0024	0.0016	0.0024	0.0024
Febrile neutropenia	0.0018	0.0010	0.0072	0.0018
Cholangitis	0.0013	0.0010	0.0013	0.0013
Hyperbilirubinemia	0.0012	0.0021	0.0012	0.0012

Key: AE, adverse event; FOLFIRINOX, folinic acid, 5-fluorouracil; irinotecan and oxaliplatin; Gem/Cap, gemcitabine in combination with capecitabine; Gem/Cap, gemcitabine in combination with capecitabine; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine.

5.3.4. Validation of clinical parameters and variables

The clinical parameters and variables in the model were validated by:

- Comparing the clinical outcomes (OS, PFS, ToT and number of AEs) in the model with those from the clinical trials that informed the model
- Clinician validation (see Section 5.3.5)
- Internal quality-assured processes

Table 45 shows that the clinical outcomes in the model after 1 year closely match the trial outcomes of OS, PFS, ToT and number of AEs. In replicating these outcomes, the economic model accurately represents the clinical outcomes from the CA046 study.

The choice of base-case analysis parametric curve based on the KM data was assessed by clinicians who confirmed the suitability of the gamma curve for the OS, PFS and ToT. Due to the violation of proportional hazards the stratified model was chosen. It was further considered that the Weibull curve provided a plausible fit to the OS and PFS data. In line with ERG feedback, the curves suggested by the ERG were considered in a scenario analysis for OS, PFS and ToT.

In addition, clinicians were asked to identify any AEs that were originally omitted but should be included in the model based on either a substantial decrement in terms of HRQL or a substantial impact on resource use or costs. This updated list then constituted the final AEs included in the model.

Finally, the model was also quality-assured by internal processes at the company who built the economic model. In these processes, an economist not involved in the model's construction reviewed the model for coding errors, inconsistencies and the plausibility of inputs.

Table 45: Summary of model results compared with clinical data (updated data cut)

	Gemcitabine		*nab*-P/Gem	
Outcome	**Clinical trial result**	**Model result**	**Clinical trial result**	**Model result**
Mean survival (months)				
Overall survival	8.65	8.59	11.10	11.01
Progression-free survival	5.49	4.17	6.91	6.15
Time on treatment	3.45	3.16	4.61	4.15
Adverse events (number of events (gemcitabine n=402: *nab*-P/Gem n=421)				
Neutropenia	85	81	138	133
Fatigue	37	36	77	75
Thrombocytopenia	33	32	53	51
Anaemia	32	31	49	48
Leukopenia	15	14	39	38
Peripheral sensory neuropathy	1	1	34	33
Neuropathy peripheral	0	0	32	31
Dehydration	10	10	31	30
Asthenia	17	16	29	28
Abdominal pain	32	31	27	26
Nausea	14	13	27	26
Diarrhoea	6	6	26	25
Vomiting	15	14	25	24
Decreased appetite	8	8	23	22
Pulmonary embolism	26	25	19	18
Pneumonia	9	9	15	15
Febrile neutropenia	6	6	14	14
Cholangitis	6	6	10	10
Hyperbilirubinemia	12	12	9	9
Key: *Nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; N, number.				

5.3.5. Clinician validation

5.3.5.1. Advisory board 1: December 2013

Celgene Ltd conducted an advisory board as part of the original NICE submission (TA360) with eight clinical experts during December 2013. Table 46 provides the details of the expert selection and content for this advisory board. The specific objectives were to:

- Discuss and gain advice for Celgene's HTA strategy for *nab*-P/Gem in mPAC
- Discuss the clinical evidence identified for use within the submission
- Discuss the cost-effectiveness evidence identified for use within the submission
- Discuss the assumptions underpinning the economic model including: parametric curve fits and AE inclusion

Table 46: Details of expert selection and data extraction

Detail	Explanation
The criteria for selecting the experts	Oncologists with expertise in treating pancreatic cancer, oncology pharmacists and health economists to give a range of experiences and opinions at the advisory board meeting
The number of experts approached	Eleven experts were invited to attend the health technology assessment advisory board meeting. These experts comprised of clinicians, pharmacists and health economists
The number of experts who participated	Eight experts attended the meeting
Declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought	No declaration of potential conflicts of interest from the delegates were collated
The background information provided and its consistency with the totality of the evidence provided in the submission	No pre-reading (background information) was provided to the delegates in advance of the meeting. Delegates were informed about the objectives of the meeting in advance
The method used to collect the opinions	A medical writer from Succinct Medical Communications attended the meeting and produced a meeting report
The medium used to collect opinions	The advisory board meeting was the medium used to collect opinions from the experts. The opinions and discussions were then summarised into a meeting report
Whether iteration was used in the collation of opinions and, if so, how it was used	No iteration was used in the collation of opinions

The relevant comparators and clinical pathway associated with *nab*-P/Gem were discussed – this topic was discussed in greater detail in the more recent advisory board (see Sections 3.3 and 3.6).

Graphs depicting the comparison of KM OS data with the fitted gamma parametric curve, KM PFS data with the fitted gamma parametric curve and KM ToT data with the fitted gamma parametric curve were presented to the clinical experts. Clinical experts confirmed the plausibility of these parametric curve fits in the model.

In addition, clinicians were presented with a list of AEs that the data showed occurred in less than 5% of patients. Clinicians were asked to identify any AEs that should be included in the model based on either a substantial decrement in terms of HRQL or a substantial impact on resource use or costs. All AEs occurring in 5% or more of patients were included in the model. This updated list then constituted the final AEs included in the model. Where utility decrements associated with AEs were unavailable in the literature, clinicians advised on the most appropriate analogous AE taking into consideration the HRQL and costs associated with the AE.

The time taken to remove the initial infusion and set up the next one and the frequency of monitoring were obtained from this advisory board. Inputs were averaged across all clinicians in attendance.

5.3.5.2. Advisory board 2: October 2016

Celgene Ltd conducted an advisory board as part of this resubmission with seven clinicians; detailed minutes were recorded.[11]

The research objectives were:

- To seek feedback and advice on the clinical section of the *nab*-P/Gem for previously untreated mPAC STA NICE re-submission
- To seek advice regarding the most clinically appropriate and relevant comparator for *nab*-P/Gem in previously untreated metastatic pancreatic adenocarcinoma
- To seek feedback regarding the revised health economic modelling

- To seek feedback regarding any potential gaps in the *nab*-P/Gem for previously untreated mPAC STA NICE re-submission.
- To collect a consensus from the clinical attendees on the most appropriate and relevant answers to key issues and questions that are identified during the course of the meeting

The discussion included:

- *Nab*-P waste management procedures in hospital pharmacies
- Typical practices associated with *nab*-P dose modification/adjustment and dose cessation

Regarding service provisions, advisors agreed that with regard to perceived change requirements for service provision and management for *nab*-P/Gem:

- "No additional tests or investigations are needed outside of those required for the diagnosis of metastatic pancreatic adenocarcinoma (mPAC)"
- "*nab*-Paclitaxel+gemcitabine would utilise existing infrastructure in hospital oncology units for the administration of cancer treatments"
- "No additional resource use and costs are associated with *nab*-Paclitaxel+gemcitabine beyond the drug acquisition, additional infusion time and additional adverse event (AE) management". Celgene confirmed that treatment modifications, infusion preparation time and the use of granulocyte-colony stimulating factor (G-CSF) are included in the modelling for the submission

The other aspects of the advisory board are discussed elsewhere (see Sections 3.3, 3.6 and 5.5).

5.4 Measurement and valuation of health effects

Pancreatic cancer has been described as a 'silent cancer' because it is often symptomless in the early stages, but pancreatic cancer patients have reported problems in all five domains of the EQ-5D in comparison to American (Romanus *et al.*, 2012) and German (Muller-Nordhorn *et al.*, 2006) general population samples, with differences in pain/discomfort (Romanus *et al.*, 2012; Muller-Nordhorn *et al.*,

2006) and anxiety/depression (Romanus *et al.*, 2012) domains the most pronounced.[37, 98] In addition, the high intensity of treatments for non-resectable pancreatic cancer may expose patients to levels of toxicity that heighten the risk of health-related AEs.

The Phase II clinical trial investigating two dose schedules of *nab*-P/Gem in patients with mPAC (the SIEGE trial) collected EQ-5D data at baseline, at 4-weekly intervals during pre-progression and at 12-weekly intervals during post-progression over a 12-month period.[93] Analysis of these data indicated a slight deterioration in utility associated with patients with progressive disease. However, disease status was not found to be significant at the 5% level.

A study of HRQL in patients with advanced pancreatic cancer who were not deemed appropriate for surgical resection (Romanus *et al.*, 2012) found patient-reported overall HRQL to be stable in those with pre-progression disease over 8 weeks of chemotherapy treatment (gemcitabine plus placebo or gemcitabine plus bevacizumab), with symptoms of pain/discomfort and anxiety/depression improving and symptoms of physical functioning worsening. However, the same study reported lower HRQL in patients with progressive disease compared to patients with progression-free pancreatic cancer, suggesting patient utility decreases with disease progression. Changes in utility were reported over 8 weeks within disease states in this study and were not significant at the 5% level.[37]

Braun *et al.* (2013) explored longitudinal changes in quality of life of 127 patients with newly diagnosed Stage IV pancreatic cancer, using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).[99] Reported changes in EORTC QLQ-C30 scores over 3 months were small. Bonnetain *et al.* (2010) analysed EORTC QLQ-C30 to measure quality of life deterioration in 202 patients with mPAC receiving chemotherapy (either 5-FU, folinic acid and cisplatin in combination followed by gemcitabine, or the opposite sequence).[100] Median time until definitive deterioration in quality of life was estimated to be over 5 months. Neither Braun *et al.* (2013) nor Bonnetain *et al.* (2010) differentiated between stable and progressive disease patients; the slight deterioration in EORTC QLQ-C30 scores observed over 3 months by Braun *et al.*

(2013) and over 5 months observed by Bonnetain *et al.* (2010) are likely driven by disease progression within the samples.[99, 100]

These data, alongside findings from the SIEGE study, suggest longitudinal HRQL stability in patients within disease states in the economic model supporting this submission.

5.4.1. Health-related quality-of-life data from clinical trials

5.4.1.1. Identification of utility studies

The HRQL SLR that formed part of the previous NICE submission (TA360) was updated in order to capture new utility studies for patients with pancreatic cancer. Updated searches were carried out from March 2014 to August 2016 to ensure that the latest available evidence is presented in the resubmission.

The SLR was performed to identify and summarise the relevant HRQL evidence for metastatic or LAPC. The search strategy considered adult patients with advanced pancreatic cancer, at least 50% of whom have metastatic disease, and who are potentially eligible for first-line therapy. Included studies reported utility values with sufficient detail regarding the methodology used. Due to the preference of NICE for patient-reported EQ-5D data, the literature search undertook the approach of:

- Firstly, reviewing the literature to identify if there were studies in the relevant population that incorporated the EQ-5D with responses completed by patients.
- Secondly, if no such studies were available, reviewing the literature to identify patient-reported outcomes using other HRQL measures in the relevant population that could be mapped to EQ-5D values.

The review included searches of the following electronic databases:

- MEDLINE and Embase (using Embase.com)
- MEDLINE In-Process (using PubMed.com)
- EconLit
- CINAHL (using EBSCO.com)
- The Cochrane Library, including the following:
  - National Health Service Economic Evaluations Database
  - Centre for Reviews and Dissemination – HTA Database

Additionally, conference proceedings from the last 4 years (2013–2016) will be searched to identify recently completed or ongoing studies of interest. These will include:

- HTAi
- iHEA
- ISPOR Annual International Congress
- SMDM

Appendix 11 describes the strategy used to search the databases. The search strategies are described by providing the structure and the terms used to search the MEDLINE, EconLit, CINAHL and Cochrane library databases.

Having identified relevant HRQL studies from the electronic database search, the titles and abstracts were reviewed by two independent reviewers to assess their relevance for informing the overall decision problem. Table 47 lists the inclusion and exclusion criteria used in the review to assess the relevance of the identified studies. Data extraction from the included full-text of articles was also performed independently by two reviewers to ensure that everything was captured.

Table 47: Inclusion and exclusion criteria for utility studies

Criteria	Inclusion	Exclusion
Population	• Adult patients • aPAC patients, at least 50% of whom have metastatic (or pancreatic ductal adenocarcinoma) disease • Potentially eligible for first-line therapy for metastatic disease	• Healthy volunteers • Children (age <18 years) • Diseases other than those specified in inclusion criteria
Intervention/ comparator	• No specific inclusion criteria • Studies reporting utility values for non-treated patients will also be included to assess the burden of illness	• Studies will not be excluded on the basis of intervention/ comparator
Outcomes	• Utility values	
Study types	• Economic evaluations reporting utility values • RCTs and observational studies reporting utility data • Studies must present sufficient detail regarding the methodology used • Studies must provide extractable results	• Non-systematic reviews*, letters, comment or editorials • Studies not reporting adequate methodology or extractable data

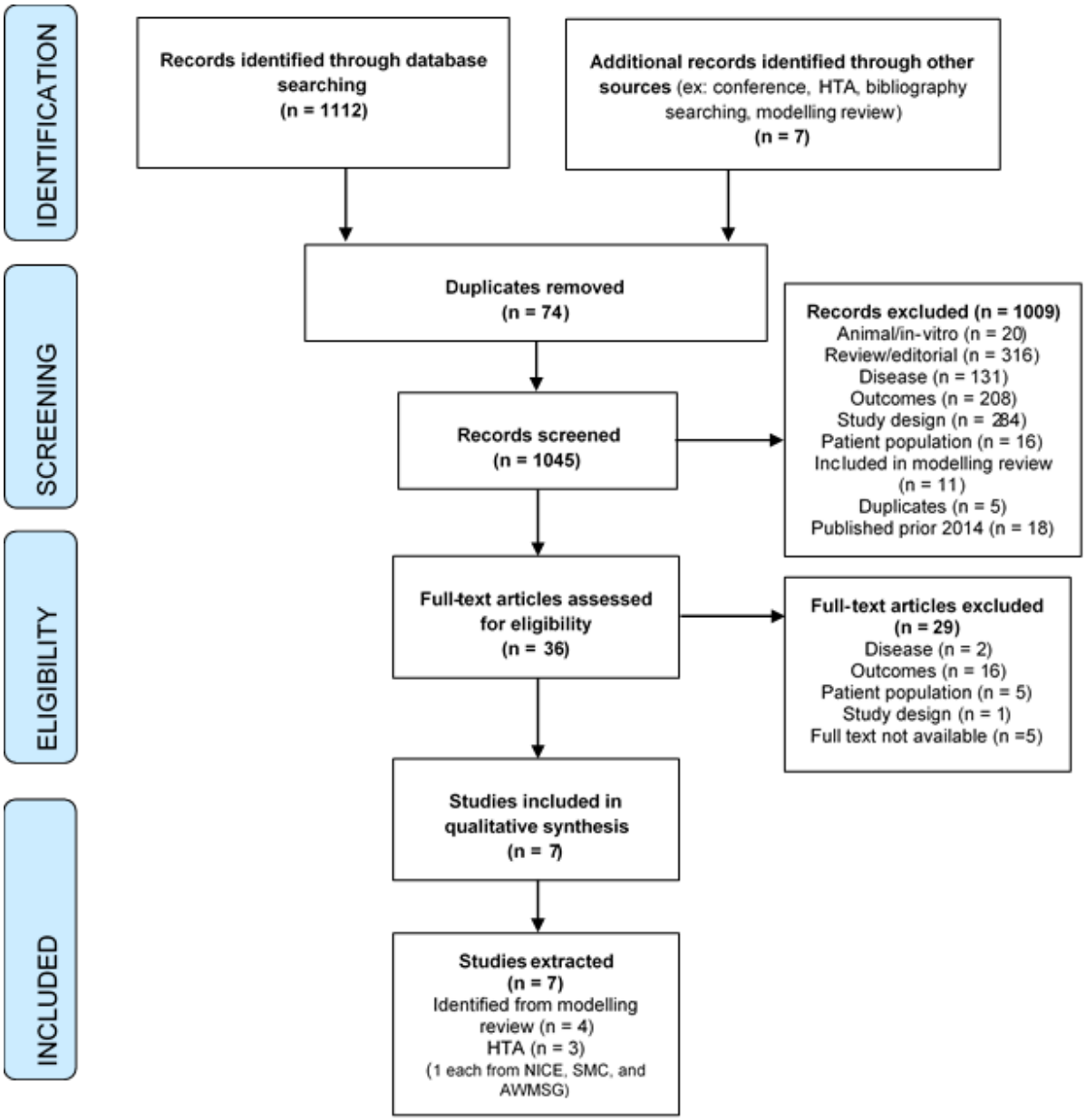
Criteria	Inclusion	Exclusion
Language	• Studies published in English will be included • Studies not published in English will be included and flagged**	• Studies will not be excluded on the basis of publication language
Key: aPAC, advanced pancreatic cancer; RCT, randomised controlled trials. **Notes:** * Systematic reviews will be included and flagged for bibliography searches; ** Studies published in languages other than English will be explored only if sufficient evidence is not identified from studies published in English.		

5.4.1.2. Description of the identified utility studies

In total, 1,119 papers were identified from the electronic searches. Screening of titles and abstracts against the pre-specified inclusion and exclusion criteria (as presented in Table 47) was performed for 1,045 records after removing 74 duplicates. Of these, 36 were included for full-text screening. The most common reasons for exclusion at primary screening were irrelevant publication style (review or editorial; n=316) and irrelevant study design (n=284).

After full-text screening, only seven papers were included for data extraction – four studies and three HTAs. The flow diagram of the updated cost-effectiveness SLR is presented in Figure 33.

Figure 31: PRISMA flow-diagram of the updated HRQL SLR[85]



Key: AWMSG, All Wales Medical Strategy Group; HRQL, health-related quality of life; HTA, health technology assessment; N, number; NICE, National Institute for Health and Care Excellence; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review; SMC, Scottish Medicines Consortium.

5.4.1.3. Study results

A summary of the findings across these seven papers is presented in Table 48 and Table 49. Full data extraction tables are available upon request.

Six of the seven identified studies pooled the baseline and 8-week HRQL estimates presented by Romanus *et al.* (2012)[37] for pre-progression and post-progression health states:

- Pre-progression = 0.80
- Post-progression = 0.75

Romanus *et al.* (2012) measured the HRQL of patients with aPAC participating in Cancer and Leukaemia Group B 80303, a multicentre, double blind, randomised trial comparing gemcitabine+bevacizumab with gemcitabine+placebo at baseline and at 8 weeks using the EQ-5D.[37] The work by Romanus *et al.* was not included in this SLR as it was identified as part of the SLR in the original NICE submission. However, given its application in the corresponding economic model, it has been added to Table 48 for completeness.[82]

The other study, by Lien *et al.* (2015), considered the impact of country-specific EQ-5D-3L tariffs on the cost per QALY of various first-line treatments for mPAC.[101] The EQ-5D data were obtained from a survey sent to 60 medical oncologists in Canada who were requested to use the EQ-5D-3L to report their perception of a patient's health state. The postal survey described eight scenarios of a patient with mPAC and varying symptoms undergoing one of four chemotherapy regimens. The methods are described in the original publication: Tam *et al.* (2013).[102] The EQ-5D-3L survey responses were then converted into utility scores using each of the country-specific tariffs. For the UK perspective, the tariff published by Dolan *et al.* (1997) was used.[103] The utilities were then averaged across clinicians to give: 0.643 for a stable disease. Decrements associated with AEs are presented in Table 48.

The differences between the utilities seen in the literature may be caused by disparities between clinicians and patients' perception of HRQL; patients complete the EQ-5D questionnaire in the work by Romanus *et al.* (2012), whereas clinicians complete the EQ-5D questionnaire assuming a patients' perspective in the work by Lien *et al.* (2015).[37, 101]

AE utility decrements are presented in four studies. These were obtained from the literature and, due to the lack of mPAC-relevant estimates, are obtained from various populations including: non-small cell lung cancer, renal cell carcinoma, lymphocytic leukaemia, mPAC and metastatic breast cancer. In the original NICE submission

(TA360), where utility decrement estimates were not available, clinician advice was sought to provide advice as to an analogous condition for which the utility decrement could be assumed equal to.

The information below is collected for primary studies (Lien *et al.* and Romanus *et al.*) while a separate summary of secondary studies which use utilities from Romanus *et al.* is captured in Table 49:

- Population in which health effects were measured
- Information on recruitment (e.g. participants of a clinical trial, approximations from clinical experts, utility elicitation exercises including members of the general public or patients)
- Interventions and comparators
- Sample size
- Response rates
- Description of health states
- Adverse reactions
- Appropriateness of health states given the condition and treatment pathway
- Method of elicitation
- Method of valuation
- Mapping
- Uncertainty around values
- Consistency with reference case
- Appropriateness for cost-effectiveness analysis
- Results with confidence intervals
- Appropriateness of the study for cost-effectiveness analysis

Table 48: Summary of primary HRQL data extractions

Study refs from SLR	Country	Population	Cohort size, N	Interventions and comparators	Recruitment	Completion rate/ response rate	Method of elicitation/valuation	Utilities included/ uncertainty	AE decrements	Appropriate for CE analysis	Consistent with NICE reference case
Lien *et al.* (2015)[101]	Canada, US, UK, Denmark, France, Germany, Japan, the Netherlands and Spain	1L mPAC	33	Gemcitabine Gem/Cap Gem/Erl FOLFIRINOX	Survey sent to 60 medical oncologists (experts in non-colorectal gastrointestinal cancers)	33 clinicians responded to the survey. It is assumed all fully completed the EQ-5D-3L questionnaire.	Clinicians completed EQ-5D-3L to report their perception of the patient's health state. The EQ-5D-3L responses were converted into utility scores using the Dolan *et al.* (1997) valuation set for UK values.[103] The utilities were then averaged across clinicians	Only UK utility decrements using the UK tariff are presented here. Stable disease = 0.643	Nausea and vomiting = 0.352 Diarrhoea = 0.328 Hand-foot syndrome = 0.179 Stomatitis = –0.038 Febrile neutropenia = 0.454 Fatigue = –0.053 Rash = 0.487 Neuropathy = 0.320 Supportive care = –0.250	Not appropriate given other utility data available. PROs data preferable.	No. EQ-5D-3L consistent with NICE reference case. Study does not use patient reported outcomes which is required.
Romanus *et al.* (2012)[82]	US	aPAC. (86% mPC, 12%	186	Gemcitabine+ bevacizumab vs gemcitabine + placebo	aPAC patients from Phase III RCT CALGB 80303	Of 366 who consented to HRQL: 267 (73%) patients	Patient-reported EQ-5D-3L scores recorded via telephone interview and	Reported mean (SD): Baseline progressive =	None reported	Appropriate in part. Patient-reported data	Yes, patient-reported EQ-5D -3L

Study refs from SLR	Country	Population	Cohort size, N	Interventions and comparators	Recruitment	Completion rate/ response rate	Method of elicitation/valuation	Utilities included/ uncertainty	AE decrements	Appropriate for CE analysis	Consistent with NICE reference case
		locally advanced, 2% unknown)				completed the baseline EQ-5D survey and 186 (70%) patients completed the 8-week follow-up EQ-5D interview. Baseline characteristics were comparable between those who did (n=186) and did not (n=64) complete the follow up visit. However, those who did complete follow-up had significantly longer OS and a	applied to the D1 US valuation set to generate preference based utility values. D1 value set elicited societal preferences using the TTO method.[104]	0.77(0.13) 8 week progressive = 0.73(0.18) Baseline stable = 0.79(0.14) 8 week stable 0.81(0.15). CR/PR baseline=0.79(0.14), CR/PR 8 week=0.81(0.15) Gemcitabine+bevacizumab: baseline=0.80(0.77), 8 weeks=0.80(0.15). Gemcitabine+placebo: baseline=0.77(0.15) 8 weeks= 0.77(0.18)		generated although application to UK patients debatable. Mapping from US value set to UK value set more suitable. Interventions not consistent with *nab*-P/Gem study of interest but no difference in HRQL found between treatment arms	values elicited and value set represents societal valuation. See previous comment regarding differences between US and UK societal values accounted for by a mapping approach

Study refs from SLR	Country	Population	Cohort size, N	Interventions and comparators	Recruitment	Completion rate/ response rate	Method of elicitation/valuation	Utilities included/ uncertainty	AE decrements	Appropriate for CE analysis	Consistent with NICE reference case
						higher proportion of stable disease (p<0.05)					

Key: 1L, first line; AE, adverse event; aPAC, advanced pancreatic cancer; CR, complete response; FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin; Gem/Cap, gemcitabine in combination with capecitabine; Gem/Erl, gemcitabine in combination with erlotinib; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; HRQL, health-related quality of life; mPAC, metastatic pancreatic adenocarcinoma; N, number; NICE, National Institute for Health and Care Excellence; OS, overall survival; PR, partial response; PRO, patient-reported outcome; RCT, randomised controlled trial; TTO, time trade-off.

Table 49: Summary of secondary HRQL data extractions

Study	Country	Population	Cohort size, N	Interventions and comparators	Method	Utilities included	Adverse event decrements
Carrato *et al.* (2015)[105]	Spain	1L mPAC	NR	*nab*-P/Gem Gemcitabine	Literature	From Romanus *et al.* (2012)[37] Progression free = 0.80 Progression = 0.75	Neutropenia = -0.090 Fatigue = -0.204 Thrombocytopenia = -0.108 Anaemia = -0.119 Leukopenia = -0.090 (assumed equal to neutropenia) Peripheral sensory neuropathy = -0.226 (assumed equal to peripheral

Study	Country	Population	Cohort size, N	Interventions and comparators	Method	Utilities included	Adverse event decrements
							neuropathy) Peripheral neuropathy = -0.226 Dehydration = 0.000 (assumed no reduction) Asthenia = -0.204 Abdominal pain = -0.069 Nausea = -0.048 Diarrhoea = -0.261 Vomiting = -0.103 Loss of appetite = 0.0 (assumed no reduction) Pulmonary embolism = -0.195 Pneumonia = -0.440 Febrile neutropenia = -0.150 Cholangitis = -0.440 (assumed equal to event with greatest impact on quality of life) Hyperbilirubinemia = -0.204 (assumed equal to fatigue)

Study	Country	Population	Cohort size, N	Interventions and comparators	Method	Utilities included	Adverse event decrements
Attard *et al.* (2014)[106]	Canada	1L mPAC 18–75 years	NR	1L FOLFIRINOX followed by 2L gemcitabine 1L gemcitabine followed by 2L platinum based chemotherapy, with use of G-CSF 1L gemcitabine followed by BSC	Literature	From Romanus *et al.* (2012) Progression free = 0.80 Progression = 0.73 Partial response = 0.83	Diarrhoea = –0.288 Vomiting = –0.152 Febrile neutropenia = –0.36 Neutropenia = –0.184 Thrombocytopenia = –0.184 Neuropathy = –0.24 Elevated alanine transaminase= 0 Fatigue = –0.115 Thromboembolism = –0.16
Stetka *et al.* (2015)[92]	Slovak Republic	1L mPAC	NR	*nab*-P/Gem Gemcitabine	Literature	From Romanus *et al.* (2012) Progression free = 0.80 Progression = 0.75	NR
NICE TA360 (2015)[82]	UK	1L mPAC	NR	*nab*-P/Gem Gemcitabine Gem/Cap FOLFIRINOX	Literature	From Romanus *et al.* (2012) Progression free = 0.80 Progression = 0.75	Neutropenia: -0.090 Fatigue: -0.204 Thrombocytopenia = -0.108 Anaemia = -0.204 (Assumed same as fatigue)

Study	Country	Population	Cohort size, N	Interventions and comparators	Method	Utilities included	Adverse event decrements
							Leukopenia = -0.090 (Assumed same as neutropenia) Peripheral sensory neuropathy (pain) = -0.226 (Assumed same as neuropathy peripheral) Neuropathy peripheral (pain) = -0.226 Dehydration = -0.204 (Assumed same as fatigue) Asthenia = -0.204 (Assumed same as fatigue) Abdominal pain = -0.069 Nausea = -0.048 Diarrhoea = -0.204 (Assumed same as fatigue) Vomiting = -0.048 (Assumed same as nausea) Decreased appetite = -0.204 (Assumed same as fatigue) Pulmonary embolism = -0.370

Study	Country	Population	Cohort size, N	Interventions and comparators	Method	Utilities included	Adverse event decrements
							Pneumonia = -0.402 Febrile neutropenia = -0.150 Cholangitis = -0.402 (assumed equal to most severe AE) Hyperbilirubinemia = -0.204 (Assumed same as fatigue)
SMC (no: 968/14)[22]	UK (Scotland)	1L mPAC	NR	*nab*-P/Gem Gemcitabine	Literature	From Romanus *et al.* (2012) Progression free = 0.80 Progression = 0.75	NR
AWMSG (no: 1999)([23]	UK (Wales)	1L mPAC	NR	*nab*-P/Gem Gemcitabine	Literature	From Romanus *et al.* (2012) Progression free = 0.80 Progression = 0.75	NR

Key: 1L, first line; 2L, second line; AE, adverse event; AWMSG, All Wales Medical Strategy Group; BSC, best supportive care; FOLFIRINOX, folinic acid, fluorouracil, irinotecan and oxaliplatin; G-CSF, granulocyte-colony stimulating factor; Gem/Cap, gemcitabine in combination with Capecitabine; Gem/Erl, gemcitabine in combination with erlotinib; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; HRQL, health-related quality of life; mPAC, metastatic pancreatic adenocarcinoma; N, number; NICE, National Institute for Health and Care Excellence; NR, not reported; SMC, Scottish Medicines Consortium.

The updated HRQL SLR added seven studies to the HRQL evidence base for mPAC and mPDAC. Three studies were identified in the HRQL SLR conducted as part of the original NICE submission (TA360). Six of these studies used the utility estimates presented by Romanus *et al.* (2012) in a paper identified in the original NICE submission.[82] Therefore, only one paper provided a *de novo* analysis of HRQL in patients with mPAC. This paper estimated utility values from EQ-5D questionnaires completed by clinicians from the perspective of a patient with mPAC. As the differentiation between clinicians' perceptions of a patient's health and the patient's experience is unknown, these data are not considered in the re-submission. Therefore, no additional data were identified in the HRQL SLR as relevant for inclusion in the re-submission model.

5.4.1.4 Description of updated HRQL data

The CA046 (MPACT) trial did not collect quality of life data. Therefore, in the original NICE submission (TA360), no *nab*-P/Gem-specific HRQL data were available. As a result, the NICE Committee and ERG commented that the acceptability of the AE profile of *nab*-P/Gem was unknown.

This re-submission considers newly available HRQL data available from an investigator-initiated randomised Phase II clinical trial investigating two dose schedules of *nab*-P/Gem in patients with mPAC (the SIEGE trial). Only data from the 'concomitant' treatment regimen, equivalent to that used in the CA046 trial, were analysed. The SIEGE trial collected quality of life data at baseline, at 4-weekly intervals during pre-progression and at 12-weekly intervals during post-progression over a 12-month period.[93] The European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire C30 (EORTC-QLQ C30) and the EQ-5D-5L were collected in the study. EORTC-QLQ C30 data were not considered in this submission as these data do not incorporate preference information and due to the NICE guidance stating its preference for EQ-5D as the measure of quality of life.[95]

Utility values were derived by two separate methods. First, using the EQ-5D-5L value set published in Devlin *et al.*[107] and, second, the 'crosswalk method' to derive EQ-5D-3L utility values from the EQ-5D-5L data collected from the SIEGE trial.[108]

The Devlin *et al.* value set was designed specifically for the EQ-5D-5L classification system and follows an international body of work to develop the new HRQL outcome measure. It employs novel methodology to incorporate a combination of preference elicitation techniques (TTO and discrete choice experiment) that strengthen the evidence used to support the development of the value set. Additionally, previous limitations of the EQ-5D-3L have been addressed by Devlin *et al.* The EQ-5D-3L predicted utility values worse than death for over 30% of all health states compared to less than 5% with the EQ-5D-5L. Consequently, this aids the EQ-5D-5L in providing HRQL data suitable for healthcare decision making.

The 'crosswalk method' was developed in order to utilise EQ-5D-5L data for economic evaluations prior to the development of a validated value set and UK based tariff system.[108] It allows the conversion of EQ-5D-5L patient-reported outcomes data to EQ-5D-3L utilities using an algorithm based on a statistical relationship between the two measures. It therefore suffers similar limitations to the EQ-5D-3L value set. Furthermore, by using the crosswalk algorithm, an additional dimension of uncertainty is incorporated into the health state utility estimates. The 'crosswalk method' does however allow comparability with previous economic evaluations conducted using the EQ-5D-3L.

Multivariate analysis was conducted to determine the most significant predictors of HRQL over all time points, using a 5% significance level. A multiple regression model was used, fitting a linear mixed-effect model to allow for non-linear relationships. The model includes a random-effect term for patients, which is appropriate when there are clustered data (i.e. observations taken over time on the same individual), as the majority of patients' utility scores were measured at more than one time point. Covariate selection for the multiple regression model was conducted using a forward selection technique, including covariates based on a significance level less than 0.20 in addition to progression status which was included irrespective of significance due to the requirements of the economic model. KPS was the only covariate found to significantly predict utility and was included as a pooled categorical variable of KPS ≤80 and KPS >80 based on clinical evidence reported in the CA046 CSR.[21]

The regression coefficients and results of the analyses associated with the crosswalk and Devlin data sets are presented in Table 50 and Table 51, respectively. Utility values were calculated by summing each coefficient multiplied by the CA046 mean trial value for that explanatory variable.

The results from these regressions show that KPS was a statistically significant covariate for both sets of utility values. The root mean squared error (RMSE) and mean absolute error (MAE) are reported to show an absolute measure of goodness of fit.

Table 50: Linear mixed-effects model fitted to crosswalk-derived utility values

	Regression coefficient	**Standard error**	**P value**
Fixed effects			
Intercept	0.6428237	0.03894721	0.000
Progression status (post-progression)*	-0.0524416	0.02861018	0.068
KPS (>80)**	0.0936729	0.04680484	0.049
Random effects			
	Intercept	**Residual**	
Standard deviation	0.1670882	0.127757	
Model fit			
	RMSE	**MAE**	
	0.1146039	0.08186478	

Key: MAE, mean absolute error; RMSE, root mean squared error.
Notes: Regression coefficients, standard error and p value for fixed effects model covariates. Random effects distributions and absolute goodness of fit are also reported. * Reference category for progression status is pre-progression. Regression coefficient applied to progressive observations; ** Reference category for KPS is ≤80. Regression coefficient applied to observations for KPS >80.

Table 51: Linear mixed-effects model fitted to Devlin valuation set-derived utility values

	Regression coefficient	**Standard error**	**P value**
Fixed effects			
Intercept	0.7445444	0.03264236	0.000
Progression status (post-progression)*	-0.0459902	0.02498116	0.066

KPS (>80)**	0.0780882	0.03918956	0.050
Random effects			
	Intercept	**Residual**	
Standard deviation	0.1385864	0.1118736	
Model fit			
	RMSE	**MAE**	
	0.1351484	0.1104661	

Key: MAE, mean absolute error; RMSE, root mean squared error.
Notes: Regression coefficients, standard error and p value for fixed effects model covariates. Random effects distributions and absolute goodness of fit are also reported. * Reference category for progression status is pre-progression. Regression coefficient applied to progressive observations; ** Reference category for KPS is ≤80. Regression coefficient applied to observations for KPS >80.

The results of diagnostic tests are present in Appendix 17. These suggest negligible differences between using the crosswalk method or the value set in the work by Devlin *et al.* (2016).[107]

The proportion of patients with KPS >80 was taken from the CA046 trial and applied to the model using the mean of covariates approach. Using these data, utility values for the pre-progression and post-progression health states estimated from the Devlin value set and 'crosswalk method' data are shown below alongside utilities reported by Romanus *et al.* (2012)[37] and converted to UK values:

Table 52: Health state utility values generated from SIEGE analysis in comparison to those by Romanus *et al.* (2012)

	Health state utility	
	Pre-progression	**Post-progression**
Romanus *et al.*, (2012) with UK adjustment	0.74	0.67
Devlin value set (SIEGE)	0.79	0.75
'Crosswalk method' (SIEGE)	0.70	0.65

The results of the SIEGE utility analysis are not used in the base-case model for a number of reasons, but they are investigated in separate scenario analyses. Results from the SIEGE utility analysis indicate a considerable level of uncertainty with respect to which method is used to derive the utility values. The choice between the

Devlin value set and the 'crosswalk method' is a subjective one, with each having a number of strengths and weaknesses. However, they also are shown as upper and lower bounds for the pre-progression utility estimates (0.79 and 0.70) and corresponding ICERs. As such, it is deemed appropriate that the health state utilities reported by Romanus *et al.* (2012) adjusted for a UK population are used in the base case analysis for pre-progression and progressive disease (see Section 5.4). This decision provides a compromised estimate of HRQL, while acknowledging the uncertainty between the three estimates and the limitations of the work by Romanus *et al.* (2012) not being specific to the intervention considered in this appraisal.

5.4.2. Mapping

The 'crosswalk method' was used to derive utility values from EQ-5D-5L data by mapping these data to EQ-5D-3L values for a sensitivity analysis; this is in accordance with the NICE Methods Guide.[95]

5.4.3. Adverse reactions

Treatment with chemotherapy results in various AEs. Furthermore, the type, severity and rate of AEs can vary between chemotherapy treatments leading to differences in overall HRQL. To capture this in the economic model, the health state utility value is assumed to be the same on both arms and is then retrospectively adjusted for differences in HRQL arising due to different AE profiles. Any Grade 3 and above TEAE is included in the economic model, as outlined in Section 5.3.3 and is assigned a disutility that is used to adjust the base HRQL in each health state in each cycle.

The HRQL studies identified in the original and updated SLRs did not provide estimates for AEs in an mPAC population. Therefore, an alternative approach was to undertake a targeted review of previous HTA submissions for AE HRQL data. Each of the sources identified were assessed for quality based on the method of valuation, patient number, disease area and country to determine whether they were relevant and reliable sources of evidence. A summary of each of the quality indicators for each of the included studies can be found in Table 53. This method was conducted in the original NICE submission (TA360) and updated as part of the re-submission.

No literature was identified for a number of AEs and therefore assumptions were made, based on the clinicians' descriptions of the conditions at advisory boards, for a number of unavailable utility decrements. Only one utility decrement was updated from the original NICE submission (TA360); this was the utility decrement associated with abdominal pain updated from -0.069 (Doyle *et al.*, 2008) to -0.051 (Sullivan *et al.*, 2011).[109, 110] A summary of the utility decrements and sources/assumptions used for each AE are outlined in Table 54.

For some AEs, disutility values were not reported; instead a utility value with and without the presence of the given AE was reported. In these cases, the disutility was calculated as the difference between the utility without the AE and with the AE (Table 53.).

Table 53: Utility decrement of Grade 3+ TEAEs

Grade 3+ treatment emergent AEs	Utility decrement	Source
Neutropenia	-0.090	Nafees *et al.* (2008)[111]
Fatigue	-0.204	Swinburn (2010)*[112]
Thrombocytopenia	-0.108	Tolley *et al.* (2013)**[113]
Anaemia	-0.204	Assumed same as fatigue
Leukopenia	-0.090	Assumed same as neutropenia
Peripheral sensory neuropathy (pain)	-0.226	Assumed same as peripheral neuropathy
Neuropathy peripheral (pain)	-0.226	Tam (2013)***[102]
Dehydration	-0.204	Assumed same as fatigue
Asthenia	-0.204	Assumed same as fatigue
Abdominal pain	-0.051	Sullivan *et al.* (2011)[110]
Nausea	-0.048	Nafees *et al.* (2008)[111]
Diarrhoea	-0.204	Assumed same as fatigue
Vomiting	-0.048	Assumed same as nausea vomiting
Decreased appetite	-0.204	Assumed same as fatigue
Pulmonary embolism	-0.370	Rivaroxaban ERG Report (2012)[114]
Pneumonia	-0.402	Edwards *et al.* (2012)[115]
Febrile neutropenia	-0.150	Lloyd *et al.* (2006)[116]
Cholangitis	-0.402	Assumed equal to most severe AE
Hyperbilirubinemia	-0.204	Assumed same as fatigue

Grade 3+ treatment emergent AEs	Utility decrement	Source
Key: AE, adverse event; TEAE, treatment-emergent adverse event. **Notes:** * Derived as difference from baseline utility of patients with metastatic renal cell cancer; ** Derived as difference from baseline utility of patients with late-stage chronic lymphocytic leukaemia; *** Derived as difference from baseline utility of patients with metastatic pancreatic cancer.		

Table 54: Quality assessment of primary HRQL studies used for AEs

Source	Disease area	N	Method of valuation	Country
Nafees *et al.* (2011)[111]	Small cell lung cancer	100	SG & VAS	UK
Swinburn (2010)[112]	Metastatic renal cell carcinoma	100	TT0	UK
Tolley *et al.* (2013)[113]	Late-stage chronic lymphocytic leukaemia	110	TTO	UK
Tam (2013)[102]	Metastatic pancreatic cancer	33	TTO	Canada
Sullivan *et al.* (2011)[110]	UK-based catalogue of utility scores. Decrement for other gastrointestinal disorders	79,197	EQ-5D	UK
Doyle *et al.* (2008)[109]	Non-small cell lung cancer	110	SG & VAS	UK
Lloyd *et al.* (2006) [116]	Breast cancer	100	SG & VAS	UK
Rivaroxaban ERG Report (2012)[114]	Venous thromboembolism	129	TTO	The Netherlands
Key: AEs, adverse events; ERG, Evidence Review Group; HRQL, health-related quality of life; N, number; SG, standard gamble; TTO, time trade-off; VAS, visual analogue score.				

The average duration of the included AEs was calculated from the patient-level data given in Study CA046 for both treatment arms and summarised in Table 55. Each disutility value was weighted by the average duration to give a disutility per cycle (1 week). The weekly disutility was then multiplied by the cycle probability for each AE and summed on each arm to give a total average AE-related disutility per cycle for each treatment.

Table 55: Accounting for duration of AEs

Grade 3+ TEAEs	*nab*-P/Gem	Gemcitabine

	Average duration (days)	Disutility per week	Average duration (days)	Disutility per week
Neutropenia	9.547	-0.0023	9.291	-0.0023
Fatigue	19.885	-0.0111	19.140	-0.0107
Thrombocytopenia	8.057	-0.0024	9.320	-0.0028
Anaemia	12.400	-0.0069	14.500	-0.0081
Leukopenia	10.041	-0.0025	10.400	-0.0026
Peripheral sensory neuropathy	26.917	-0.0167	28.000	-0.0173
Neuropathy peripheral	25.111	-0.0155	0.000	0.0000
Dehydration	7.645	-0.0043	7.300	-0.0041
Asthenia	17.629	-0.0098	14.368	-0.0080
Abdominal pain	10.452	-0.0015	13.140	-0.0018
Nausea	11.179	-0.0015	20.933	-0.0028
Diarrhoea	5.567	-0.0031	5.500	-0.0031
Vomiting	5.852	-0.0008	10.875	-0.0014
Decreased appetite	22.042	-0.0123	27.250	-0.0152
Pulmonary embolism	51.900	-0.0526	22.931	-0.0232
Pneumonia	9.813	-0.0108	12.333	-0.0136
Febrile neutropenia	7.154	-0.0029	8.000	-0.0033
Cholangitis	10.500	-0.0116	8.333	-0.0092
Hyperbilirubinemia	9.556	-0.0053	11.133	-0.0062

Key: TEAEs, treatment-emergent adverse events; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine.

Where possible the cycle rate for FOLFIRINOX has been calculated using data from Conroy *et al.* (2011).[28] A RR relative to gemcitabine monotherapy was calculated using the proportion of AEs observed for FOLFIRINOX in the ACCORD trial (Conroy *et al.*, 2011) and the proportion of AEs observed for gemcitabine monotherapy in the CA046 study. To estimate the cycle probability for FOLFIRINOX, each RR was then applied to the relevant gemcitabine AE cycle probability. Where it was not possible for RRs to be calculated (data not reported for all AEs) the cycle probabilities observed in the *nab*-P/Gem arm of Study CA046 were applied.

The duration and weekly decrement associated with AEs for Gem/Cap and FOLFIRINOX is assumed equal to *nab*-P/Gem and thus will give the same cyclical utility decrement as that reported for *nab*-P/Gem.

5.4.4. Health-related quality-of-life data used in cost-effectiveness analysis

Within the model, base-case HRQL data were obtained from Romanus *et al.* (2012) and data were adjusted to take into account a UK population. This is in line with the ERG feedback from the original NICE submission (TA360).

Romanus *et al.* (2012) measured the HRQL of patients with advanced pancreatic cancer (aPAC) participating in Cancer and Leukaemia Group B 80303, a multicentre, double blind, randomised trial comparing gemcitabine+bevacizumab with gemcitabine+placebo, at baseline and at 8 weeks using the EQ-5D.[13] The trial collected HRQL data in the US, and therefore, these data were converted to UK utilities using a simple linear regression model fitted between the two corresponding tariff scores.[29] The combined health state-specific UK adjusted means were estimated as:

- Pre-progression = 0.74
- Post-progression = 0.67

Data from the SIEGE analysis were not considered in the base case analysis due to the reasons stated above in Section 5.4.1.[15] A scenario analysis considers using the SIEGE data, with results provided for both the Devlin value set and those derived using the 'crosswalk method'.

Table 56 presents the base-case utility values and decrements associated with AEs. Using the base-case method (Romanus *et al.*, 2012), a patient HRQL is not constant over time as patients experience a utility decrement with disease progression. This is in line with the literature identified as part of the SLR and in line with the results from the SIEGE analysis.

Table 56: Base-case utility estimates and AE decrements

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Pre-progression	0.74	(0.73, 0.76)	See HRQL SLR report and Section 5.4.1	Utility values were obtained from Romanus *et al.* (2012) and adjusted for a UK population using the linear regression provided in the work by Shaw *et al.* (2005)[37, 104]
Progressive disease	0.67	(0.65, 0.69)	See HRQL SLR report and Section 5.4.1	
Neutropenia	-0.090	(-0.062,0.122)	Section 5.4.3	Identified through targeted published literature search or assumed equivalent to published estimate for similar AE validated by clinical experts
Fatigue	-0.204	Average utility with fatigue 0.591 (0.49, 0.68)	Section 5.4.3	
Thrombocytopenia	-0.108	Average utility with thrombocytopenia 0.563 (0.47, 0.65)	Section 5.4.3	
Anaemia	-0.204	Assumed same as fatigue	Section 5.4.3	
Leukopenia	-0.090	Assumed same as neutropenia	Section 5.4.3	
Peripheral sensory neuropathy (pain)	-0.226	Assumed same as neuropathy peripheral	Section 5.4.3	
Neuropathy peripheral (pain)	-0.226	Average utility with neuropathy peripheral 0.494 (0.37,0.62)	Section 5.4.3	
Dehydration	-0.204	Assumed same as fatigue	Section 5.4.3	
Asthenia	-0.204	Assumed	Section 5.4.3	

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
		same as fatigue		
Abdominal pain	-0.051	(-0.02, -0.10)	Section 5.4.3	
Nausea	-0.048	(-0.01, -0.10)	Section 5.4.3	
Diarrhoea	-0.204	Assumed same as fatigue	Section 5.4.3	
Vomiting	-0.048	Assumed same as nausea	Section 5.4.3	
Decreased appetite	-0.204	Assumed same as fatigue	Section 5.4.3	
Pulmonary embolism	-0.370	Average utility with pulmonary embolism 0.63 (0.55, 0.71)	Section 5.4.3	
Pneumonia	-0.402	(-0.34, -0.46)	Section 5.4.3	
Febrile neutropenia	-0.150	(-0.03, -0.34)	Section 5.4.3	
Cholangitis	-0.402	Assumed equal to most severe AE	Section 5.4.3	
Hyperbilirubinemia	-0.204	Assumed same as fatigue	Section 5.4.3	
Key: AE, adverse event; HRQL, health-related quality of life.				

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1. Resource identification, measurement and valuation studies

Appendix 18 presents a table with all cost and resource use parameters used to evaluate the cost effectiveness of *nab*-P/Gem.

The cost and resource use SLR conducted as part of the original NICE submission (TA360) did not identify any treatment-specific resource use relevant to the decision

problem. Instead, the resources used as part of follow-up and monitoring were estimated through clinician interviews and validated by a panel of experts at a UK advisory board (first advisory board) (see Section 5.3.5).

This approach is maintained in the re-submission, with resource use estimates further validated by the more recent UK advisory board.

5.5.2. Intervention and comparators' costs and resource use

Unit drug costs

A summary of the drug costs used in the economic model is presented in Table 57. A PAS is in place for *nab*-P that reduces the net price from the list price of £246.00 per 100mg to [redacted].

Table 57: Cost per mg calculations of chemotherapy treatment

Treatment	Unit cost including PAS	Unit price per mg	Weighted unit price per mg	Source
Gemcitabine				
1g powder for solution for infusion vials	£30.89	£0.03	£0.03	eMIT. Date accessed: 19 January 2017[117]
200mg powder for solution for infusion vials	£3.99	£0.02		
Nab-Paclitaxel				
Powder for reconstitution, paclitaxel, net price 100-mg vial	[redacted]	[redacted]	[redacted]	MIMS. Data accessed: 19 January 2017[118]
Capecitabine (XELODA®)				
150mg, 60-tab pack	£7.73	£0.0009	£0.001*	eMIT. Date accessed: 19 January 2017[117]
500mg, 120-tab pack	£29.59	£0.0005		
Erlotinib (TARCEVA®)				
25mg, 30-tab pack	£378.33	£0.50	£0.44	MIMS. Data accessed: 19 January 2017[118]
100mg, 30-tab pack	£1,324.14	£0.44		
150mg, 30-tab pack	£1,631.53	£0.36		
5-fluorouracil bolus injection				
1g/20ml (5%) solution for	£4.00	£0.02	£0.01	BNF January

Treatment	Unit cost including PAS	Unit price per mg	Weighted unit price per mg	Source
injection vials				2017[119]
500mg/10ml (5%) solution for injection vials/Pack size 1	£6.40	£0.01		
Oxaliplatin				
100mg/20ml solution for infusion vials	£15.50	£0.16	£0.17	eMIT. Date accessed: 19 January 2017[117]
50mg/10ml solution for infusion vials	£10.62	£0.21		
5-fluorouracil Infusion				
2.5g/50ml (5%) solution for infusion vials	£4.68	£0.002	£0.004*	eMIT. Date accessed: 19 January 2017[117]
5g/100ml (5%) solution for infusion vials	£4.53	£0.001		
Folinic acid (Leucovorin®)				
Calcium folinate 100mg/10ml solution for injection vials/Pack	£2.29	£0.02	£0.02	eMIT. Date accessed: 19 January 2017[117]
Calcium folinate 300mg/30ml solution for injection vials/ Pack	£4.59	£0.02		
Irinotecan				
100mg/5ml solution for infusion vials/Pack size 1	£7.52	£0.08	£0.07	eMIT. Date accessed: 19 January 2017[117]
300mg/15ml solution for infusion vials/Pack size 1	£18.64	£0.06		

Key: BNF, British National Formulary; eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialties.
Note: * Less than 1p per mg.

Dosing

Dosing data for *nab*-P/Gem and gemcitabine were obtained from the CA046 study reported by Von Hoff *et al.* (2013).[6] Dosing data for Gem/Cap were obtained from Cunningham *et al.* (2009) and for FOLFIRINOX from the ACCORD study reported by Conroy *et al.* (2011).[28, 45]

The dose of all drugs (with the exception of erlotinib and capecitabine) is based on a patient's body surface area (BSA) in metres squared (m^2). An average BSA of

1.75m^2 was used in the model based on results of the KANTAR study for the UK pancreatic cancer population.[40]

The economic model has two treatment arms with patients in the "pre-progression: on first-line treatment" health state receiving either:

1. Intervention

- *nab*-P/Gem: *nab*-P at a dose of 125mg/m^2 followed by 1,000mg/m^2 of gemcitabine administered sequentially as 30-minute IV infusions on Days 1, 8 and 15 of a 28-day treatment cycle.[6]

2. Comparator

- Gemcitabine monotherapy: gemcitabine at 1,000mg/m^2 as a 30-minute IV infusion on Days 1, 8, 15 and 21 of the initial 28-day cycle followed by Days 1, 8 and 15 of each subsequent 28-day treatment cycle.[6]

OR

- Gem/Cap: 1,000mg/m^2 of gemcitabine as a 30-minute IV infusion on Days 1, 8, 15 and 1,830mg/m^2 oral capecitabine twice per day on Days 1–21 of a 28-day treatment cycle.[45]

OR

- FOLFIRINOX: oxaliplatin, 85 mg/m^2; irinotecan,180mg/m^2; leucovorin, 400mg/m^2; and 5-fluorouracil, 400 mg/m^2 given as a bolus followed by 2,400 mg/m^2 given as a 46-hour continuous infusion on Day 1 of a 14-day treatment cycle.[28]
- First-line drug costs

The dosing regimens and resulting weekly doses for each first-line treatment are outlined in Table 58. The costs per treatment shown in Table 58 are not applied in the model as dosing is subject to dosing intensity and wastage before application.

Table 58: Cost per cycle of chemotherapy treatment (first-line treatments)

Drug	Dose (mg/m^2)*	Average dose (mg/week)	Cost per treatment*
Gemcitabine	1,000, Von Hoff *et al.* (2013)[6]	1,750	[redacted]

nab-Paclitaxel	125, Von Hoff *et al.* (2013)	219	[redacted]
Capecitabine	11,620, Cunningham *et al.* (2009)[45]	20,335	[redacted]
FOLFIRINOX			
Oxaliplatin	85, Conroy *et al.* (2011)[28]	148.75	[redacted]
Folinic acid (brand name LEUCOVORIN®)	400, Conroy *et al.* (2011)	700	[redacted]
Irinotecan	180, Conroy *et al.* (2011)	315	[redacted]
Fluorouracil (bolus)	400, Conroy *et al.* (2011)	700	[redacted]
Fluorouracil (infusion)	2,400, Conroy *et al.* (2011)	4,200	[redacted]

Key: FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, oxaliplatin.
Note: * The cost per treatment shown here is not applied in first line as dosing is subject to dosing intensity and wastage before application.

Vial sharing

The cost per treatment outlined above assumes that the entire content of each vial is used and thus may underestimate drug costs. In the original NICE submission (TA360), vial sharing was incorporated into the drug cost calculations. However, feedback from the NICE Committee and the ERG suggested that vial sharing was inappropriate due to the small patient population.[48] Therefore, vial sharing is not included in the base case in the re-submission and is investigated separately as scenario analyses.

Dosing intensity and missed doses

In study CA046 and in clinical practice, due to toxicity, patients may have their doses reduced or miss doses altogether. In the original NICE submission (TA360), the trial data from CA046 informed the extent of dose reductions and missed doses in the model. Costs savings were assumed to accrue from these dose reductions and missed doses. Feedback from the NICE Committee considered that not all dose reductions or missed doses could be anticipated, and therefore, as a conservative approach, the costs of the full recommended treatment dose should be considered in the base case.[12]

In response to this feedback, Celgene Ltd commissioned a survey collecting data on the waste management procedures in hospital pharmacies and typical practices associated with *nab*-P dose modification/adjustment and dose cessation in the UK.

The survey methodology used was divided into two stages. The first stage was a 10-minute online survey and the second stage was a 20-minute online survey including quantitative and qualitative elements similar to the first survey, as well as an option to complete case notes for pancreatic cancer patients who received *nab*-P and for whom a dose adjustment or dose cessation was made. Stage 2 also included four 20-minute deep-dive interviews with respondents from Stage 1 with pre-specified policies in place to avoid *nab*-P wastage.

Of the 26 pharmacists responding to the survey, 13 stated that they have pre-specified policies in place to avoid drug wastage for both dose adjustments and dose cessations. Key measures used to avoid drug wastage included drug preparation occurring on the same day as dosing and not until blood results have been received, and the appropriate dose prescribed in response to this, as well as oncology clinics providing sufficient notice of dose adjustments or dose cessation to the pharmacist.

These data informed the model for the:

- Proportion of first-time dose reductions that can be anticipated in UK practice (50%)[120]
- Proportion of missed doses that can be anticipated in UK practice (50%)[120]

It was assumed that all subsequent maintained dose reductions can be anticipated. These assumptions were verified with clinical experts in an advisory board (see Section 5.3.5):

Clinical advisors agreed that it is normally possible to anticipate dose reductions/delays prior to the infusion of *nab*-P being prepared. It was agreed that stating that 50% of dose reductions would occur prior to preparation of the drug was a fair assumption – although it is noted that several advisors stated that the proportion in their clinical experience would be greater than this, therefore they agreed that this was a conservative estimate. Advisors stated that the NHS England system of ‘dose banding’ for the most common 19 chemotherapy regimens, which

includes: oxaliplatin, gemcitabine, fluorouracil and irinotecan, has already started to be implemented to some extent, and they felt that this would continue.

It is assumed that 79.7% of reduced doses are subsequent maintained dose reductions; this was estimated using the patient-level data from CA046 (1,880 out of 2,360 dose reductions were subsequent maintained dose reductions). Therefore, the weighted proportion of total dose reductions that can be anticipated is 89.83%.

To incorporate this in the economic model, the average dose intensity in each cycle was calculated from the patient-level data in study CA046 as:

$$\frac{Dose\ given + \big((Recommended\ dose - Dose\ given) + (1 - \%Anticipated)\big)}{Recommended\ dose} \times 100$$

Where the %Anticipated was equal to the proportion of dose reductions that could be anticipated (89.83%).

This was calculated at a patient level and then averaged across each visit to ensure trends over time were captured. Similarly, the average number of doses missed was calculated from the patient-level data as:

$$\frac{Received\ treatment + \big((Total - Received\ treatment) + (1 - \%Anticipated)\big)}{Total} \times 100$$

Where the %Anticipated was equal to the proportion of missed doses that could be anticipated (50%).[120]

This was done for:

- % patients missing a gemcitabine dose
- % patients missing a *nab*-P dose (where applicable)
- % patients missing both doses

In the base case, the proportions of anticipated dose reductions/missed doses were estimated using the calculations outlined above. Furthermore, the proportion of anticipated dose reductions/missed doses observed for *nab*-P/Gem were applied to Gem/Cap and FOLFIRINOX.

This method is used to ascertain a realistic estimation of the cost savings accrued from anticipated dose reductions and missed doses in UK practice. In the base case, the cost of treatment and administration are saved from anticipated dose reductions and missed doses. A scenario analysis considers maintaining the pharmacy cost associated with anticipated missed doses. Dose reductions and missed doses that are not anticipated accrue the full cost associated with treatment and administration in the model.

For model parsimony, the approach above is only applied to first-line treatments.

Second-line drug costs

A proportion of patients are assumed to receive active second-line treatment upon disease progression (see Table 36 for combinations of second-line treatments). There are extremely limited data available on second-line pancreatic cancer chemotherapy regimens; therefore, in the absence of data, dosing in the second line is assumed to be the same as that in the first line. The weekly dose and cost per 1-week cycle for each second-line treatment are shown in Table 59.

Table 59: Cost per cycle of second-line chemotherapy treatments

Drug	Dose (mg/m^2)	Average dose (mg/week)	Cost per treatment	Cost per week*
Capecitabine (XELODA®)	11,620, Cunningham *et al.* (2009)[45]	20,335	£13.57	[redacted]
nab-Paclitaxel	125, Von Hoff *et al.* (2013)[6]	219	[redacted]	[redacted]
Gemcitabine	1,000, Von Hoff *et al.* (2013)	1,750	£46.75	[redacted]
Erlotinib	700, Moore *et al.* (2007)[25]	700	£305.29	[redacted]
Fluorouracil bolus	600, Berlin *et al.* (2002)[61]	1,050	£15.12	[redacted]
Oxaliplatin	100, Louvet *et al.* (2005)[62]	175	£30.32	[redacted]
FOLFIRINOX				
Oxaliplatin	85, Conroy *et al.* (2011)[28]	148.75	£25.77	[redacted]
Folinic Acid (LEUCOVORIN®)	400, Conroy *et al.* (2011)	700	£13.01	[redacted]
Irinotecan	180, Conroy *et al.* (2011)	315	£22.69	[redacted]
5-fluorouracil (bolus)	400, Conroy *et al.* (2011)	700	£10.08	[redacted]

Drug	Dose (mg/m^2)	Average dose (mg/week)	Cost per treatment	Cost per week*
Fluorouracil (infusion)	2,400, Conroy *et al.* (2011)	4,200	£18.74	[redacted]
Key: FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan and oxaliplatin. **Note:** * Cost per week is applied to the model and is the cost per treatment averaged according to the treatment regimen e.g. if treatment is given 3/4 weeks then cost per week = cost per treatment*3/4.				

Administration cost of chemotherapy

Each time a patient receives chemotherapy treatment, there is an associated cost in terms of resources used – mostly staff time. The model uses administration costs sourced from the English and Welsh NHS reference costs. The NHS reference costs 2015/16 provides a number of tariffs for each type of chemotherapy administered as outlined in Table 60.[121]

Where an infusion treatment is given as a monotherapy (e.g. gemcitabine), the cost of a simple infusion is applied at £253.32 (Deliver Simple Parenteral Chemotherapy; NHS reference costs 2015/16).[121] Similarly, where a drug is given in combination, the initial infusion is costed as a simple infusion at £253.32, with the exception of oxaliplatin, which is administered over 2 hours for infusion and is thus costed as a more complex chemotherapy at £336.57.

Table 60: NHS reference costs for administration of chemotherapy treatments

Description	Unit cost	NHS reference cost 2015/16 code[121]
Deliver simple parenteral chemotherapy at first attendance	£253.32	SB12Z
Deliver more complex parenteral chemotherapy at first attendance	£336.57	SB13Z
Deliver exclusively oral chemotherapy	£205.90	SB11Z
Key: NHS, National Health Service.		

For additional infusion treatments, a micro-costing approach is used to cost the additional staff time required. Any other infusion treatment given in addition to the primary treatment, for example a doublet such as *nab*-P, is assumed to take an

additional 30 minutes of staff time to remove the initial infusion and set up the next one, according to clinical opinion at the initial UK advisory board (see Section 5.3.5.1). Administration of chemotherapy is assumed to be done by a day ward nurse (£35 per hour; Personal Social Services Research Unit [PSSRU], 2016) costing a total of £17.50 per additional infusion.[122] The rationale for using a micro-costing approach for additional administrations is to ensure the fixed set-up costs for an infusion are not double counted as most infusions (with exception of FOLFIRINOX) are administered subsequently in the same visit.

For the administration of FOLFIRINOX the initial infusion, oxaliplatin, is costed as a complex chemotherapy administration with each sequential treatment given on the same day costed at £17.50, as previously described. An additional cost of £99.97 (outpatient nurse visit; NHS reference costs 2015/16) is included for the return visit where patients have the 46-hour infusion of 5-fluorouracil removed, giving a total cost of £551.54.[121] The total cost of administration for each first- and second-line treatment is outlined in Table 61 and Table 62, respectively.

Table 61: Administration cost of first-line chemotherapy treatments

Chemotherapy treatment	Component drug name	Administration cost[121]	Total cost per treatment
Gemcitabine	Gemcitabine	£253.32	£253.32
nab-P/Gem	*Nab*-Paclitaxel	£17.50	£270.82
	Gemcitabine	£253.32	
Gem/Cap	Capecitabine	£0.00	£253.32
	Gemcitabine	£253.32	
FOLFIRINOX	Oxaliplatin	£336.57	£506.54
	Irinotecan	£17.50	
	5-fluorouracil bolus	£17.50	
	Folinic acid	£17.50	
	5-fluorouracil continuous infusion	£117.47*	

Key: FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; Gem/Cap, gemcitabine in combination with capecitabine; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.
Note: * Costed using a micro-cost (£17.50) (PSSRU, 2016) approach plus outpatient nurse visit (£99.97) as the 46-hour infusion requires an additional return visit to remove infusion (NHS reference costs 2015/16).[121, 122]

In the post-progression health state for patients who receive second-line treatment, an average cost per cycle is used such that the administration cost is adjusted to account for the fact that the different treatments are given at different frequencies over a 4-week period. Each administration cost is therefore multiplied by the frequency of treatment; for example, gemcitabine is administered 3 out of every 4 weeks, and therefore, the cost applied per 1-week cycle is £192.83 (£257.11*3/4). The cost per cycle of each second-line therapy is summarised in Table 62.

For oral chemotherapies (erlotinib and capecitabine), there is assumed to be no additional cost where they are given in combination with an infusion as patients would receive their oral drugs at the same visit. Where oral drugs are given as a monotherapy, the NHS reference cost for oral administration is used and applied per cycle of chemotherapy treatment (once every 4 weeks).

Table 62: Administration cost of second-line chemotherapy treatments

Regimen name (dataset short version)	Component drug name	Administration cost (NHS reference costs 2015/16[121])	Total administration cost per treatment	Average administration cost per week*
Gem	Gemcitabine	£253.32	£253.32	£189.99
Gem/Erl	Erlotinib	£-	£253.32	£189.99
	Gemcitabine	£253.32		
Gem/Cap	Capecitabine	£-	£253.32	£189.99
	Gemcitabine	£253.32		
Oxaliplatin + fluorouracil	Fluorouracil	£17.50	£270.82	£203.12
	Oxaliplatin	£253.32		
Erlotinib	Erlotinib	£205.90	£205.90	£51.48
Capecitabine	Capecitabine	£205.90	£205.90	£51.48
Fluorouracil	Fluorouracil	£253.32	£253.32	£189.99
FOLFIRINOX	Oxaliplatin	£336.57	£506.54	£253.27
	Irinotecan	£17.50		
	5-fluorouracil	£17.50		
	Folinic acid	£17.50		
	5-fluouracil continuous infusion	£117.47		

Key: FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; Gem/Cap, gemcitabine in

combination with capecitabine; Gem/Erl, gemcitabine in combination with erlotinib.
Note: * The administration cost is adjusted to account for the fact that the different treatments are given at different frequencies over a 4-week period.

Each time an infusion is prepared, there is an associated pharmacy cost. *Nab*-P takes longer to prepare than some other infusions as it is reconstituted from a powder; this requires an additional 30 minutes of technician time based on the opinion of experts at the initial UK advisory board (see Section 5.3.5.1). Preparation of *nab*-P also requires a 15-micron filter, which costs approximately £2.04 and is added to the pharmacy cost shown in Table 63.

Table 63: NHS reference costs for administration of chemotherapy treatments

Description	Pharmacist cost (per hour)	Pharmacist time (minutes)	Technician cost (per hour)*	Technician time	Total cost
nab-Paclitaxel	£45.00 Curtis and Burns (2016)[122]	15	£30.00 Curtis and Burns (2016)[122]	30	£26.25
Other infusion-based chemotherapies		15		0	£11.25
Note: * Technician cost per hour based on cost of hospital support worker per hour.					

In the base case, administration costs are applied to all unanticipated received and missed doses. Administration cost savings are accrued for anticipated missed doses. If a component of the treatment is not administered, the cost of simple chemotherapy is applied at £253.32; where a cycle is skipped completely, no administration cost is applied (Table 61).

Monitoring costs

The resources used as part of follow-up and monitoring were estimated through clinician interviews and validated by a panel of experts at a UK advisory board (see Section 5.3.5). Monitoring costs are applied to all patients in the pre-progression health state, whether they are on treatment or not, as dictated by clinical practice. Patients who move on to active second-line therapy continue to have their disease progression monitored. Those patients who do not move onto active second-line therapy are assumed to receive palliative care.

Monitoring costs are split into:

- Immediate care prior to starting first-line chemotherapy treatment
- Follow-up and monitoring during first- and second-line treatment

The unit cost for each element of monitoring has been taken from the relevant English sources, where available, and multiplied by the number and percentage of patients requiring each type of care; this leads to £325.37 being applied in the first cycle only (see Table 64). The initial resource use for each treatment, both first- and second-line, is assumed to be the same, except for FOLFIRINOX, where all patients also have a baseline electrocardiogram (ECG; £40.35; NHS ref EY51Z)[121], and a further 5% require a follow-up echocardiogram (£72.45; NHS ref RD51A).[121] This leads to a cost of £369.35 being applied in the first cycle. Communication with leading clinicians has indicated that the current approach may somewhat underestimate the costs applied to FOLFIRINOX.

Additional resources may be required in addition to those that are costed. For example, the likely requirement of additional specialists' time for the insertion of a standard central venous line and for an X-ray following line insertion to check the tip of the line is in the correct place. The model has not extensively explored the additional costs that relate to FOLFIRINOX. This is because, for those patients who are suitable and can tolerate FOLFIRINOX, the treatment is highly cost effective compared to treatment with *nab*-P/Gem. For these patients, the full dose FOLFIRINOX would likely remain the cost-effective treatment option, even if complexity was added to the model and additional costs were incorporated.

Table 64: Immediate care prior to chemotherapy

Resource	Unit cost	Reference	N	% of patients	Cost per 1-week cycle
Outpatient visit (consultant)	£162.84	NHS reference costs 2015/16[121] (370:WF01A)	1	100%	£162.84
CT scan	£120.70	NHS reference costs 2015/16 (RD26Z)	1	100%	£120.70
Radiographic/MRI scan	£204.67	NHS reference costs 2015/16 (RD03Z)	1	10%	£20.47

Full blood count	£40.35	NHS reference costs 2015/16 (DAPS05)	1	100%	£0.00
Liver function test*	£72.45	NHS reference costs 2015/16 (DAPS05)	1	100%	£0.00
Ultrasound	£3.10	NHS reference costs 2015/16 (RD41Z)	1	5%	£3.10
Key: CT, computed tomography; MRI, magnetic resonance imaging; NHS, National Health Service. **Note:** Liver function test: five tests required (5* DAPS05).					

Following the initial cycle, patients on active treatment (first- or second-line) are monitored with follow-up visits and tests. The resource use associated with follow up and monitoring was validated at the UK advisory boards (first advisory board) (see Section 5.3.5.1) and is shown in Table 65. The resource use is assumed to be the same for all chemotherapy treatments, except for FOLFIRINOX, which is a triplet and therefore a more toxic treatment and, therefore, patients are monitored twice as often. For patients in the 'post-progression' health state on second-line therapy, the monitoring cost is weighted by the proportion of patients moving onto second-line therapy in each arm and applied as an average cost per cycle.

In the 'pre-progression: off first-line treatment' health state patients are not receiving any active therapy; however, it is assumed they will still require some monitoring and they are assumed to have one nurse visit per week at a cost of £44.00 (PSSRU, 2016).[122]

Table 65: Monitoring costs for first-line and second-line therapies

Resource	Unit cost	Source	N	Every X weeks	% of patients	Cost per 1-week cycle
Outpatient visit (consultant)	£162.84	NHS reference costs 2015/16[121] (370:WF01A)	1	4	100%	£40.71
Outpatient visit (nurse)	£99.97	Curtis and Burns (2016)[122]	1	4	50%	£12.50
Community visit (nurse)	£44.00	Curtis and Burns (2016)	1	4	50%	£5.50
CT scan	£120.70	NHS reference costs 2015/16 (RD26Z)	1	12	100%	£10.06

Full blood count	£3.10	NHS reference costs 2015/16 (DAPS05)	3	4	100%	£2.33
Liver function test*	£15.64	NHS reference costs 2015/16 (DAPS05)	3	4	100%	£11.73
Tumour Marker CA19-9 Test	£3.13	NHS reference costs 2015/16 (DAPS05)	6	4	100%	£4.69
Key: CT, computed tomography; N, number; NHS, National Health Service. **Note:** * Liver function test: five tests required (5* DAPS05).						

Palliative care costs

Palliative care is received by patients when they are no longer receiving active therapy (first- or second-line), but they require some support to maintain their quality of life. In the economic model, this is estimated to be 62% of patients in the intervention arm and 58% in the gemcitabine monotherapy arm based on results from the CA046 study. In the economic model, patients in the 'post-progression' health state who do not go on to receive active second-line treatment on each arm are assumed to have one GP home-care visit per week at a cost of £31.00 (PSSRU, 2016), based on clinical opinion at an advisory board.[122] This cost is weighted by the number of patients receiving palliative care on each arm and applied to the model as an average cost per cycle.

G-CSF

There are two approaches to the inclusion of G-CSF costs considered in the economic model:

1) Use according to trial data
2) Use according to clinical practice

According to clinical opinion, in current practice patients on treatments other than FOLFIRINOX receive G-CSF upon diagnosis of febrile neutropenia for the duration of the current active therapy. However, according to data from Von Hoff *et al.* (2013), the number of patients treated with G-CSF in study CA046 was much higher than would be expected given the clinical treatment pattern described above.[6] Given that

patient-level data from the pivotal trial (CA046) underpin the estimated benefits from *nab*-P/Gem treatment, it was deemed appropriate to use the trial data in the base case model while recognising that this would most likely lead to an overestimation of the cost of G-CSF. A scenario analysis considering G-CSF use according to current clinical practice is considered.

G-CSF estimated using trial data

In the economic model, to estimate the cost of G-CSF treatment, patient numbers were transformed to cycle probability rates, as with AEs (see Section 5.3.3), and multiplied by the average cost of G-CSF treatment, as shown in Table 66.

The average cost of G-CSF treatment was £191.04 for gemcitabine, gemcitabine doublets and FOLFIRINOX. This was estimated by multiplying the per treatment cost of G-CSF with the average number of treatments received by patients over a 28-day period. These calculations are explained in more detail below.

Over a 28-day period, the average number of days that patients were treated with G-CSF was assumed to be:

- 6 days for gemcitabine and gemcitabine doublets
- 6 days for FOLFIRINOX

The duration of treatment with G-CSF was assumed to be equal for all treatment arms (21.44 days).[106] Therefore, the average number of treatments was estimated as 4.59 for gemcitabine, gemcitabine doublets and FOLFIRINOX (6/28 x 21.44).

It was assumed G-CSF treatment was administered using filgrastim (brand name NEUPOGEN® injection); the cost per unit was estimated to be £0.88 using costs sourced from the Monthly Index of Medical Specialties (MIMS), accessed January 2017.[118] The associated dose of filgrastim is 0.50 millions of units per kg; this was multiplied by the average weight of patients with febrile neutropenia (74.76kg) to give the average cost per dose: £32.78.

An administration cost was accrued by patients who could not self-administer the treatment (assumed to be 20%); these patients incurred the cost of a community nurse (£44; PSSRU, 2016), resulting in an average administration cost of £8.80.[122]

Therefore, the average cost of G-CSF per treatment was £41.58. This was multiplied by the average number of treatments to give the average cost of G-CSF treatment (£191.04).

Table 66: G-CSF usage in study CA046 and clinical practice

	Number of patients treated (CA046 study)		Cycle probability		Average cost per treatment		Average cost per cycle	
	***Nab*-P/Gem**	**Gem**	***Nab*-P/Gem**	**Gem**	***Nab*-P/Gem**	**Gem**	***Nab*-P/Gem**	**Gem**
G-CSF treatment according to trial data	110	63	0.012	0.010	£191.04	£191.04	£2.33	£0.40
G-CSF treatment for febrile neutropenia (clinical practice)	14	6	0.002	0.001	£584.91	£477.12	£1.05	£0.50

Key: G-CSF, granulocyte-colony stimulating factor; gem, gemcitabine; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine.

[redacted]The use of G-CSF for patients treated with Gem/Cap is assumed to be equal to *nab*-P/Gem in the absence of patient-level data.

The trial use of G-CSF for FOLFIRINOX is taken from the work by Attard *et al.* (2014), which reports that 42.5% of patients (n=342) received treatment with G-CSF in the ACCORD trial.[106] This results in a cycle probability of 0.018. As with other treatments, this is multiplied by the average cost of G-CSF treatment (£191.04) to give the average cost per cycle.

Table 66 also presents the cost per cycle applied in the scenario analysis, where G-CSF treatment is modelled as per clinical practice.

5.5.3. Health-state unit costs and resource use

Table 67 describes each of the costs associated with the pre-progression and post-progression health states for *nab*-P/Gem compared with gemcitabine, Gem/Cap and FOLFIRINOX.

The model calculates the proportion of patients in each health state and applies the appropriate costs and resource use associated with that health state. This method is the same for all health states, but costs are weighted differently according to the proportion of patients in the respective health states.

Table 67: List of health states and associated costs in the economic model

Health states	Items	Value	Reference in report
Pre-progression: on first-line treatment	Technology (cost per treatment): Please note these costs are not adjusted for dose intensity or vial wastage	*Nab*-P/Gem: [redacted] Gemcitabine: [redacted] Gem/Cap: [redacted] FOLFIRINOX: [redacted]	Section 5.5.2
	Immediate care prior to chemotherapy	All other treatments: £325.37 FOLFIRINOX: £369.35	Section 5.5.2
	Administration per treatment: Please not these costs not adjusted for doses missed	*Nab*-P/Gem: £270.82 Gemcitabine: £253.32 Gem/Cap: £253.32 FOLFIRINOX: £506.54	Section 5.5.2
	Pharmacy cost	*Nab*-P/Gem: £39.54 Gemcitabine: £11.25 Gem/Cap: £11.25 FOLFIRINOX: £45.00	Section 5.5.2
	AEs	*Nab*-P/Gem: £44.49 Gemcitabine: £38.68 Gem/Cap: £44.49 FOLFIRINOX: £61.70	Section 5.5.4
	G-CSF	*Nab*-P/Gem: £2.33 Gemcitabine: £0.40 Gem/Cap: £2.33 FOLFIRINOX: £3.42 Please note these costs are included in the AE costs	Section 5.5.2
Post-progression: off first-line treatment	Palliative care	£31.00 per week	Section 5.5.2
Post progression	Cost of second-line treatment (average cost per cycle)	*Nab*-P/Gem: [redacted] Gemcitabine: [redacted] Gem/Cap: [redacted] FOLFIRINOX: [redacted]	Section 5.5.2

Health states	Items	Value	Reference in report
	Monitoring and testing	*Nab*-P/Gem: £38.37 Gemcitabine: £87.52 Gem/Cap: £87.52 FOLFIRINOX: £175.03	Section 5.5.2
	Administration and pharmacy cost (average cost per cycle)	*Nab*-P/Gem: £72.44 Gemcitabine: £198.43 Gem/Cap: £198.43 FOLFIRINOX: £ £275.77	Section 5.5.2
	AEs (average cost per week)	Gem doublets: £44.49 Monotherapies: £38.68	Section 5.5.4
	G-CSF	Gem doublets: £2.33 Monotherapies: £0.40 Please note these costs are included in the AE costs	Section 5.5.2
4 weeks to death health state	End of life costs	All treatments: £1,058.48	Section 5.5.5
Key: AEs, adverse events; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; G-CSF, granulocyte-colony stimulating factor; gem, gemcitabine; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine.			

5.5.4. Adverse reaction unit costs and resource use

Section 5.3.3 describes the inclusion of AEs in the economic model. To capture the cost impact of AEs on each arm, a cost was assigned to each AE and multiplied by the cycle probability of that event occurring.

Costs were taken from appropriate items in the NHS reference costs (NHS reference costs, 2015/16) and validated by clinicians at a UK advisory board.[96, 121] The NHS reference costs provide a tariff of average costs for a number of procedures available on the NHS for the financial year 2015/16. The cost assigned to each adverse event is summarised in Table 68.

Table 68: Cost of adverse events

Grade 3+ TEAEs	Cost	NHS reference cost 2015/16[121] description
Neutropenia	£97.29	HRG code: XD25Z Neutropenia drugs band 1, NHS Trusts High Cost Drugs: Admitted Patient Care[121]
Fatigue*	£35.00	Assumption: Fatigue assumed as one nurse visit per day of fatigue[122]
Thrombocytopenia	£498.81	HRG code SA12K, Thrombocytopenia with CC Score 0-1 non-elective inpatients (short-stay)
Anaemia	£481.06	HRG code SA04L, Iron Deficiency Anaemia with CC Score 0-1, Non-elective short stay
Leukopenia	£97.29	No specific data available – assumed to be equal to neutropenia
Peripheral sensory neuropathy (pain)	£139.12	HRG code: 191 NHS Reference Costs 2015/2016 Total outpatient procedures, pain management
Neuropathy peripheral (pain)	£139.12	HRG code: 191 NHS Reference Costs 2015/2016 Total outpatient procedures, pain management
Dehydration	£808.64	HRG code: KC05H, Fluid and Electrolyte Disorders, with Interventions, with CC Score 0-4, Non-elective inpatient short stay
Asthenia*	£35.00	Assumption: Asthenia assumed as one nurse visit per day of asthenia
Abdominal pain	£1,124.81	HRG Code: FZ90A, Abdominal Pain with Interventions, non-elective in patient (short stay)
Nausea***	£379.38	Assumption: same as diarrhoea
Diarrhoea	£379.38	HRG code FZ91M, Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2, day case
Vomiting***	£379.38	Assumption: same as diarrhoea
Decreased appetite***	£379.38	Assumption: same as diarrhoea
Pulmonary embolism	£1,549.87	HRG code DZ09K: Pulmonary Embolus with Interventions, with CC Score 0-8, non-elective inpatient
Pneumonia	£1,984.07	HRG code: DZ19L, Other Respiratory Disorders without Interventions, with CC Score 11+, Non- elective inpatient long stay
Febrile Neutropenia**	£2,067.07	HRG Code: SA08J, Other Haematological or Splenic Disorders, with CC Score 0-2, non-elective inpatient
Cholangitis	£1,530.00	Assumption: UK Advisory board estimate 5 x cost of 1 excess bed day from NHS reference manual 2015/2016
Hyperbilirubinemia***	£435.22	Assumption: UK Advisory board: 1 consultant visit, 5 community nurse visits plus 1 ultrasound

Grade 3+ TEAEs	Cost	NHS reference cost 2015/16[121] description
Key: CC, complexity and comorbidity; G-CSF, granulocyte colony-stimulating factor; HRG, Healthcare Resource Group; NHS, National Health Service; TEAE, treatment-emergent adverse event. **Notes:** * Cost shown is unit cost of 1-hour community nurse time, unit cost multiplied by duration of fatigue on each arm before application to model; ** Patients with febrile neutropenia treated with G-CSF from the start of the adverse event to the end of chemotherapy treatment. This cost is applied in addition to the HRG code (SA08F) and is not shown here – see Section 5.1; *** Based on clinical opinion from recent UK advisory board.		

5.5.5. Miscellaneous unit costs and resource use

An additional holding state of '4 weeks to death' is included in the model. In the original NICE submission (TA360), end of life costs were estimated by costing the frequency of nurse home care and hospice centre/palliative care costs relevant for a patient in the 4-weeks to death health state; frequencies were obtained at an advisory board (see Section 5.3.5).[82] The ERG responded to the original NICE submission (TA360) by stating that the terminal care cost should account for the proportion of patients who die in hospital, a hospice or at home.[48] The ERG provided the manufacturer with an example using a micro-costing approach – this method is used in the base case.

The micro-costing approach considered estimating the cost associated with death in hospital, a hospice and at home and then weighting these estimates based on the proportion of patients (sourced from the ERG example in response to TA360).

Death in hospital

The total cost associated with death in hospital was £929 per week; this was estimated by summing the total costs associated with hospital stay and home care prior to hospital stay.

The average length and cost of a hospital stay was obtained from the NHS reference costs (2015/16) and was calculated as the weighted average of non-elective inpatient long-stay cases for malignant gastrointestinal tract disorders without interventions (Code: FZ92).[121] This resulted in an average length of stay of 7.61 days, costing £3,332.

In the base-case analysis, it was assumed that end of life costs are accrued over the final 4 weeks of life. Therefore, on average, patients spent 20.39 days not in hospital (28 days minus 7.61 days). These patients required three nurse home-care visits

every week (obtained from an advisory board, see Section 5.3.5). The cost of a community nurse was accrued for each visit (£44.00; PSSRU, 2016), resulting in a cost of £384.49 per 4 weeks.[122] The weekly cost associated with death in hospital was therefore £929.

Death in a hospice

The total cost associated with death in a hospice was £1,137 per week; this was estimated by summing the total costs associated with a hospice stay and home care prior to the hospice stay.

The average length of a hospice stay was assumed to be the same as a hospital stay (7.61 days). In line with the ERG's feedback, the average cost of a hospice stay was assumed to be 25% higher than the cost associated with a hospital stay (£4,165).

As with the home care considered for hospital deaths, patients required three nurse home-care visits every week, which was applied over the 20.39 days a patient spent at home. This resulted in a cost of £384.49 per 4 weeks. The weekly cost associated with death in a hospice was therefore £1,137.

Death at home

For patients dying at home, Taylor *et al.* (2004) estimated that patients would require seven GP home visits, 28 community nurse visits (lasting 2 hours) and 50 hours of MacMillan nurse visits over a 28-day period.[123] The costs of the GP home visit and the community nurse visit were obtained from the PSSRU (2016).[122] In line with ERG feedback, the cost of a MacMillan nurse was assumed to be two thirds of the cost of a community nurse visit. The total weekly cost of death at home per patient was therefore £1,274.

The total weekly costs associated with death in a hospital, in a hospice and at home were weighted and summed to provide a lump cost associated with end of life care (£1,058.48; Table 69).

Table 69: End of life care costs

	Proportion	Total weekly cost	Weighted weekly cost
Death in hospital	56%	£929	£518
Death in hospice	17%	£1,137	£192

Death at home	27%	£1,274	£348
Total:			£1,058

Two scenario analyses are considered:

- End of life care costs modelled as per the original NICE submission (TA360)[82]
- End of life care costs modelled using the 8-week estimate provided in the King's Fund document (£6,153).[94] This estimate considers the average cost per patient with cancer over the last 8 weeks of life. Therefore, in this scenario the cost is applied over 8 weeks.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1. Summary of base-case *de novo* analysis inputs

Appendix 18 summarises the variables applied in the economic model and references the section in this document where it is explained in more detail.

In line with the NICE reference case, the model considers a UK treatment provider's perspective and discounts costs and QALYs using a 3.5% discount rate.[95] Results are presented over a 10-year time horizon.

5.6.2. Assumptions

The pivotal trial used in the economic analysis is a head-to-head trial of *nab*-P/Gem compared to gemcitabine monotherapy. This trial provides efficacy and dosing data utilised in the economic model. No direct head-to-head data were available for the intervention therapy to either Gem/Cap or FOLFIRINOX, and therefore, a meta-analysis and MTC were undertaken to incorporate the relative efficacy of these comparators. The resulting HRs were used in the economic model to produce the results relative to the secondary comparators: Gem/Cap and FOLFIRINOX. Table 70 details the assumptions used in the economic model and provides a justification for each one.

Table 70: Base-case assumptions

	Assumption	Justification

	Assumption	Justification
Relative efficacy	We assume that the lack of support for the proportional hazards assumption does not allow for reasonable comparison of *nab*-P/Gem with Gem/Cap or FOLFIRINOX	Due to the lack of support for the assumption of proportional hazards in the OS and PFS data from the CA046 study, the proportional hazards assumption underpinning the meta-analysis and MTC does not hold, and therefore, no reasonable comparison can be conducted between *nab*-P/Gem and Gem/Cap or FOLFIRINOX. Therefore, the model considers the comparison of *nab*-P/Gem with gemcitabine as the primary outcome, with comparisons with Gem/Cap and FOLFIRINOX presented as secondary analyses.
Time off treatment	Patients are assumed to have a length of time off treatment that is estimated as the difference between the PFS and ToT curves. Second-line treatment is assumed to be initiated upon progression.	In study CA046 it was evident that a proportion of patients stopped treatment prior to progression. Furthermore, this was considered the case in clinical practice following feedback with clinicians. Modelling a period of PFS off treatment is an important aspect of the model's clinical validity, as any assumption that patients would continue to receive treatment until disease progression is likely to overestimate the amount of first-line drugs typically administered to the cohort of patients in clinical practice. Initiation of second-line treatment upon disease progression was validated by clinical experts at two UK advisory boards (see Section 5.3.5).
Utility	We assume that utility is constant in the stable disease and progressive disease health states.	This is in line with the literature identified as part of the HRQL SLR and in line with the preliminary analysis of the SIEGE data.
Second-line treatment	a) To overcome issues of confounding, the model assumes second-line treatment patterns follow those observed in Study CA046 (see Section 5.2.3.2) b) In addition, data on dosing regimens in second-line treatment is rare and therefore were assumed to be equivalent to dosing in first-line treatment.	a) Assuming the second-line treatment proportions of Study CA046 allows the model to accurately reflect the cost of second-line treatment directly associated with the modelled efficacy inputs. This stops potential bias entering the model from second-line treatments, which may present different efficacy profiles from those seen in the CA046 study. b) While it is recognised these assumptions may not reflect clinical practice, the impact of second-line treatments on the cost-effectiveness

	Assumption	Justification
		results is minimal.
Administration of monotherapies	It was assumed that all administrations of monotherapies would be costed using "simple parenteral chemotherapy at first attendance" at a cost of £253.32 per administration from the NHS reference costs.[121] The cost associated with subsequent attendances was considered unsuitable.	This was based on the opinion of clinical experts that the first chemotherapy administration is the most time intensive and therefore most expensive (first advisory board) (Section 5.3.5.1). This was not reflected by the NHS reference costs, which showed subsequent administrations to cost more. Given this, a conservative approach was taken assuming that subsequent chemotherapy administrations incurred the same cost as the initial administration.
Administration of combination therapies	The initial infusion was costed using the simple infusion cost, with the exception of oxaliplatin, which was costed using the complex infusion cost. Additional therapies incurred 30 minutes of additional staff time and an additional cost was accrued to patients receiving FOLFIRINOX as these patients required a return outpatient visit to remove the 46-hour 5-FU infusion.	A micro-costing approach was undertaken to ensure that costs were not double counted as many of the combination therapies would be administered at the same appointment. The additional time per additional infusion (30 minutes) was estimated from the UK advisory boards (first advisory board) (Section 5.3.5.1).
Vial sharing	It is assumed that vial sharing is inappropriate due to the small patient population with mPAC.	Previous feedback from the ERG and appraisal committee confirmed that applying vial sharing was not appropriate given the small patient population with mPAC in the UK. Furthermore, the ERG commented that if vial sharing was considered it should be considered for all of the comparators that can be safely stored.[48]
Dose intensity and missed doses	It was assumed that a proportion of first-time dose reductions and missed doses could be anticipated. It was assumed that all subsequent dose reductions could be anticipated. The model considers the cost savings accrued from these anticipated dose reductions/missed doses.	In the original NICE submission (TA360), the trial data from CA046[21] informed the extent of dose reductions and missed doses in the model. Feedback from the NICE Committee considered that not all dose reductions or missed doses could be anticipated, and therefore, as a conservative approach, the costs of the full recommended treatment dose should be considered in the base case. In response to this feedback, Celgene Ltd commissioned a survey collecting data on the waste management procedures in

	Assumption	Justification
		hospital pharmacies and typical practices associated with *nab*-Paclitaxel dose modification/adjustment and dose cessation in the UK. It was determined that a proportion of first-time dose reductions and missed doses could be anticipated. It was also considered that all subsequent dose reductions could be anticipated. These assumptions were supported during a UK advisory board (second advisory board) (Section 5.3.5.2). Therefore, the economic model considers the cost savings accrued from the anticipated dose reductions and missed doses.
AEs	Where AE utility decrements or costs associated with AEs were unavailable in the literature, clinicians indicated analogous AEs where the data were available. Therefore, the model assumed the utility decrements and costs associated with these AEs were equal to the analogous AEs. We assume that Gem/Cap has the same AE profile as *nab*-P/Gem. Where data are unavailable from the ACCORD trial, we assume that FOLFIRINOX has the same AE profile as *nab*-P/Gem.	Clinicians were asked to provide their thoughts on an analogous condition in terms of the HRQL and costs accrued by the patient. This ensures that where the data are unavailable assumptions have been validated in line with clinical practice. Assuming the same AE profile as *nab*-P/Gem for Gem/Cap and FOLFIRINOX is conservative.
Key: AE, adverse event; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; HRQL, health-related quality of life; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.		

5.7 Base-case results

The modelled cost-effectiveness results reported below were generated using clinical survival and safety data from the CA046 study. Section 5.3.1 discusses the application of parametric curves to estimate survival based on patient-level data from Study CA046. Parametric curves allow for extrapolation beyond the trial period to predict the survival that would be observed if all patients were followed to death.

Data from Study CA046 are relatively mature, resulting in similar observed and modelled survival as shown in Table 72.

Nab-P/Gem meets the end of life criteria for the same reasons agreed upon in the original submission (TA360); the Committee concluded that the end of life criteria are met versus gem monotherapy; “The Committee considered whether the end of life criteria should be applied for the comparison of nab‑paclitaxel plus gemcitabine compared with gemcitabine alone. It considered that although the group of people who may have gemcitabine alone instead of FOLFIRINOX or gemcitabine plus capecitabine could not be defined, this group was clinically recognised. The Committee concluded that, for the group of people for whom FOLFIRINOX and gemcitabine plus capecitabine are not suitable treatment options, the end of life criteria could be applied” (TA360 Guidance 4.19).

- The Committee accepted the cumulative total patient population in England is less than 7,000.
- The Committee noted that the average survival rate of mPC was up to 6 months. Therefore, it concluded that the life expectancy criterion was met, because life expectancy for people with mPC was normally substantially less than 24 months.
- The Committee noted that the survival gain was below what is normally considered appropriate for the extension to life criterion to be considered met (that is, the extension to life with *nab*-P/Gem compared with gemcitabine alone was less than 3 months [approximately 2.4 months]). However, it agreed that the survival gain was particularly significant relative to the average survival of people with this condition, and therefore, this criterion could be accepted as met in this circumstance.
- The Committee noted that the survival data were mature, and therefore, it considered that the survival gain estimate was robust.

5.7.1. Base-case incremental cost effectiveness analysis results

Nab-P/Gem showed an incremental survival gain of 2.42 months compared to gemcitabine; therefore, patients using *nab*-P/Gem are expected to live almost 30% longer than those treated with gemcitabine alone. Base-case results are presented

versus the main comparator gemcitabine in Table 71. Section 5.2.3.1 states that FOLFIRINOX is an intensive therapy, associated with high administration burden and considerable toxicity, and is therefore only suitable for a defined group of clinically appropriate patients. These patients will continue to receive this regimen despite the accessibility of *nab*-P. Gem/Cap has not demonstrated a significant survival benefit over gemcitabine monotherapy in a Phase III RCT, and it is not recommended in clinical guidelines. Use of Gem/Cap is thus limited to very few centres across the UK, and this regimen does not represent a national standard of care. Select patients who may receive this regimen will continue to do so despite the accessibility of *nab*-P/Gem; that is, *nab*-P/Gem will not replace the very limited use of Gem/Cap[11] and, as such, their cost-effectiveness results are investigated in separate scenario analyses. Cost-effectiveness estimates for secondary comparators are presented in Table 81. The uncertainty around the structural assumptions has been included within the model (see Table 79).

Table 71: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Gemcitabine	[redacted]	0.725	0.396					
Nab-P/Gem	[redacted]	0.927	0.540	£6,717	0.202	0.144	£46,657	

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; QALYs, quality-adjusted life years.

5.7.2. Clinical outcomes from the model

Table 72 displays the clinical outcomes and the model outcomes for the three main outcome measures: OS, PFS and ToT, as well as AEs. Clinical outcomes are presented for the primary comparison of *nab*-P/Gem with gemcitabine assuming base-case parametric curve fits (gamma parametric curves assumed for OS, PFS and ToT).

The mean OS, PFS and ToT are comparable and consistent with the respective observed clinical outcomes reported in the CA046 trial dataset and in the literature.[21]

Table 72: Summary of model clinical outcomes and adverse events compared to clinical data

	Gemcitabine		***Nab*-P/Gem**	
Outcome	**Clinical trial result**	**Model result**	**Clinical trial result**	**Model result**
Mean survival (months)				
Overall survival	8.65	8.59	11.10	11.01
Progression-free survival	5.49	4.17	6.91	6.15
Time on treatment	3.45	3.16	4.61	4.15
Adverse events (number of events (gemcitabine n=402: *nab*-P/Gem n= 421)				
Neutropenia	85	81	138	133
Fatigue	37	36	77	75
Thrombocytopenia	33	32	53	51
Anaemia	32	31	49	48
Leukopenia	15	14	39	38
Peripheral sensory neuropathy	1	1	34	33
Neuropathy peripheral	0	0	32	31
Dehydration	10	10	31	30
Asthenia	17	16	29	28
Abdominal pain	32	31	27	26
Nausea	14	13	27	26
Diarrhoea	6	6	26	25
Vomiting	15	14	25	24
Decreased appetite	8	8	23	22
Pulmonary embolism	26	25	19	18
Pneumonia	9	9	15	15
Febrile neutropenia	6	6	14	14
Cholangitis	6	6	10	10
Hyperbilirubinemia	12	12	9	9
Key: *Nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; n, number.				

Markov traces

Figure 34 and Figure 35 present the Markov traces for the *nab*-P/Gem and gemcitabine comparison. These graphs illustrate how living patients move through

the model states over time when treated with gemcitabine monotherapy and *nab*-P/Gem, respectively. At baseline, 100% of patients are considered as no patients have yet moved to the death health state; over time, the proportion of living patients falls as patients transition to the death health state.

Figure 32: Patient distribution over time for patients on gemcitabine monotherapy

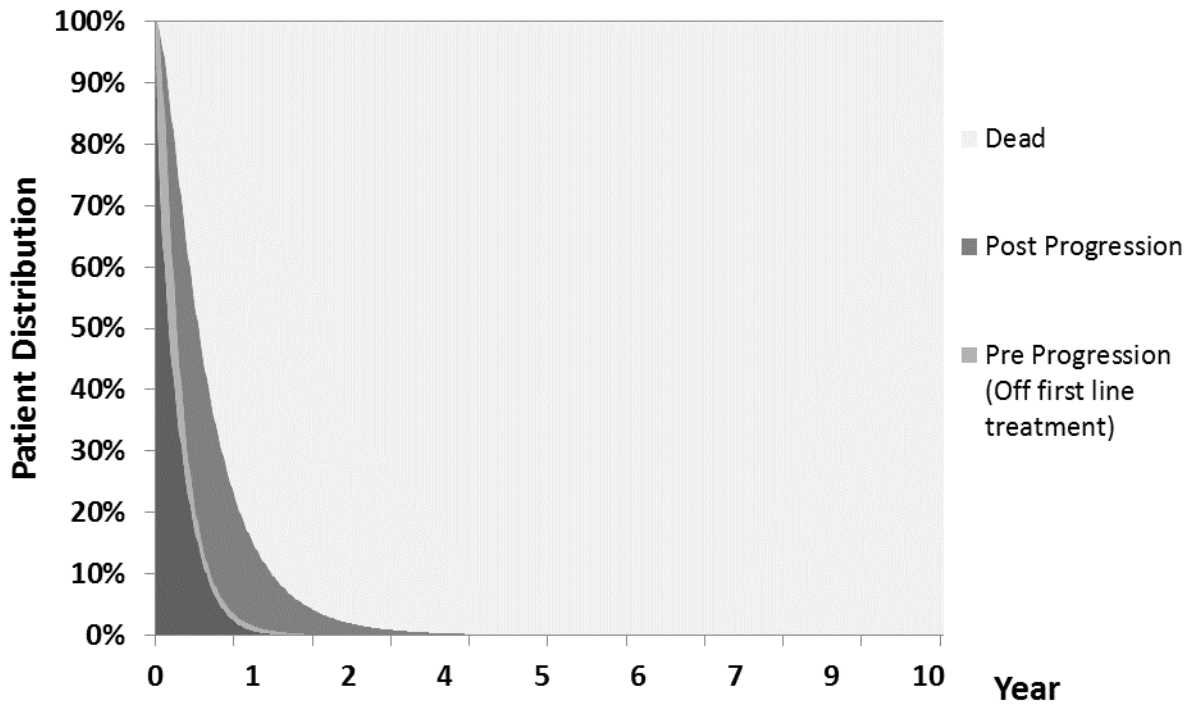
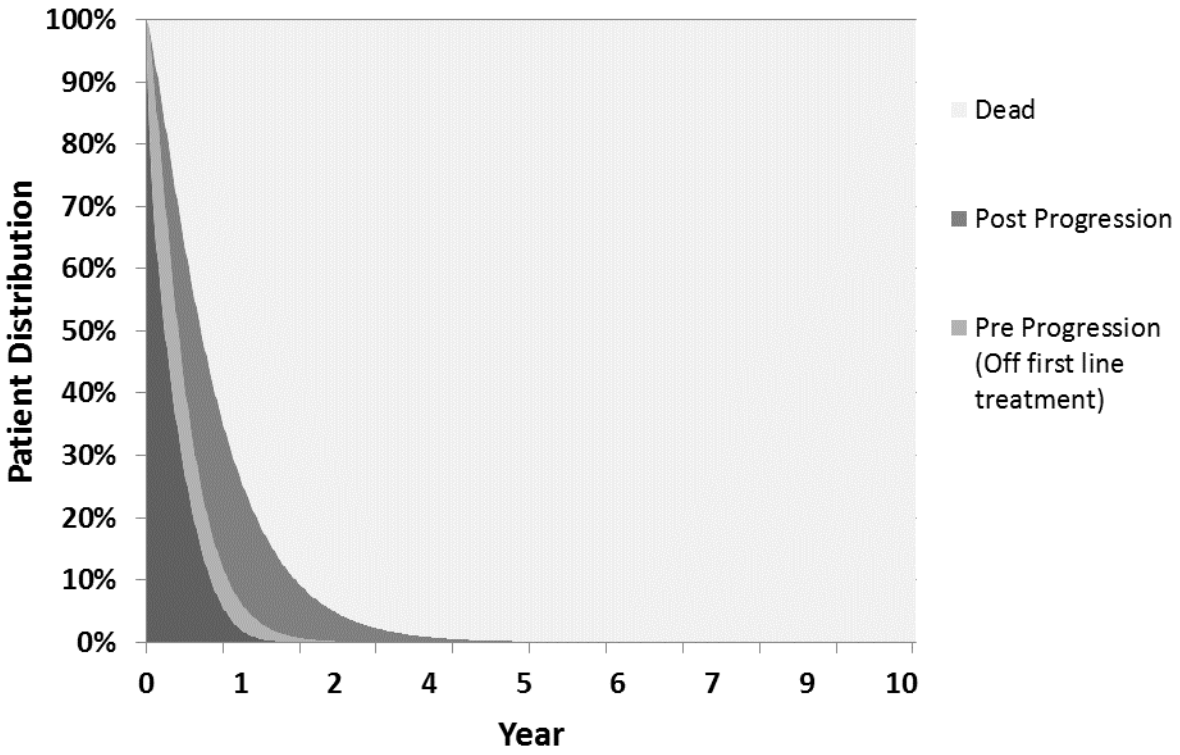


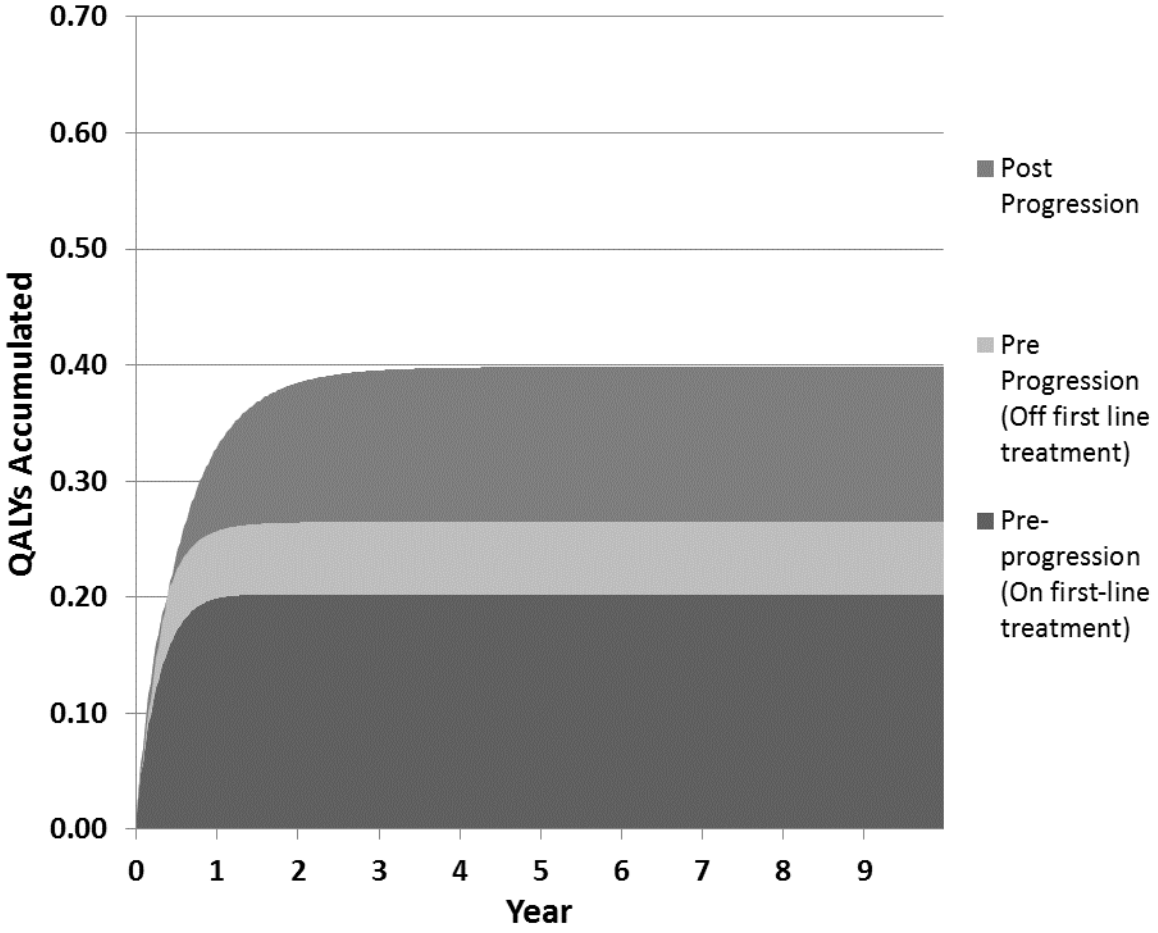
Figure 33: Patient distribution over time for patients on *nab*-P/Gem



Key: *Nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine.

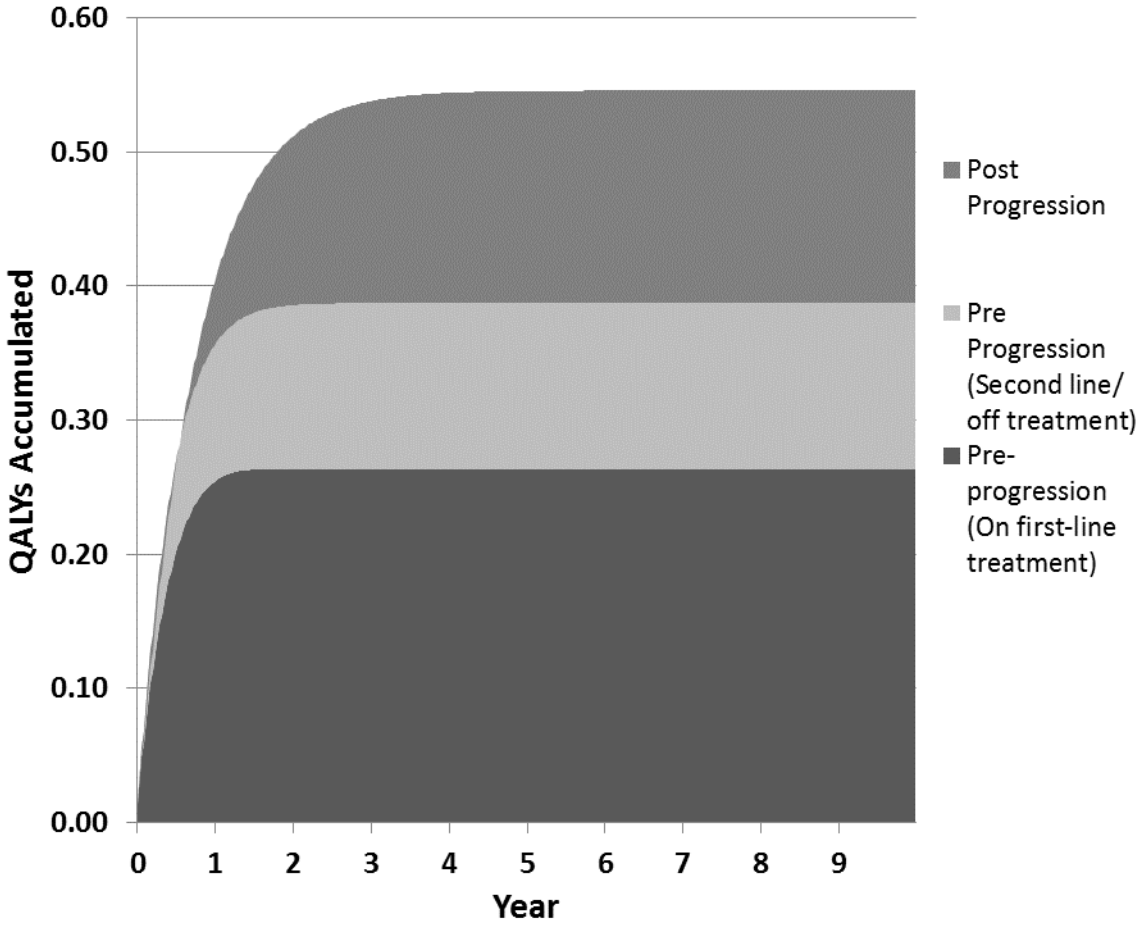
Figure 36 and Figure 37 illustrate how QALYs are accumulated over time when patients are treated with gemcitabine monotherapy and *nab*-P/Gem, respectively. As would be expected from Figure 36 and Figure 37, the QALYs are initially primarily accrued in the 'pre-progression: on first-line treatment' model state; as time continues, the QALYs are increasingly accrued in the 'pre-progression: off first-line treatment' and 'post-progression' model state. Compared with gemcitabine, the number of QALYs associated with *nab*-P/Gem at each cycle is consistently higher than the comparator treatment. The majority of QALYs are accrued within the first 2 years of the model.

Figure 34: QALY accumulation over time – gemcitabine monotherapy



Key: QALY, quality-adjusted life year.

Figure 35: QALY accumulation over time – *nab*-P/Gem



Key: *Nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; QALY, quality-adjusted life year.

5.7.3. Disaggregated results of the base case incremental cost effectiveness analysis

Life years

The total life years (LYs) gained by patients in each health state are shown below for *nab*-P/Gem compared with gemcitabine. LYs are not discounted in line with the NICE reference case. Table 73 demonstrates that *nab*-P/Gem produces an incremental gain in LYs versus gemcitabine monotherapy for each of the model health states. The majority of these gains are accumulated in pre-progression health states (81.84%).

Table 73: Summary of life years gained by health state

Health state	LY intervention (*nab*-P/Gem)	LY comparator (gemcitabine)	Increment	Absolute increment	% absolute increment
Pre-progression: first-line treatment	0.356	0.273	0.083	0.083	40.98%
Pre-progression: off treatment	0.167	0.084	0.082	0.082	40.86%
Post-progression	0.405	0.368	0.037	0.037	18.16%
Total:	0.927	0.725	0.202	0.202	100.00%

Key: *Nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; LY, life year.
Note: Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

QALYs

Table 74 shows the incremental QALYs gained by health state. These values are from the base case where QALYs are calculated using utilities obtained from Romanus *et al.* (2012)[37] and adjusted for a UK population. QALYs are discounted using a 3.5% discount rate. Treatment with *nab*-P/Gem is associated with higher QALYs across all health states, with the largest increment seen in "pre-progression: off first-line treatment" suggesting a continued treatment effect after treatment.

Table 74: Summary of QALY gain by health state

Health state	QALY intervention (*nab*-P/Gem)	QALY comparator (gemcitabine)	Increment	Absolute increment	% absolute increment
Pre-progression: on first-line treatment	0.263	0.202	0.061	0.061	42.45%
Pre-progression: off first-line treatment	0.123	0.062	0.061	0.061	42.07%
Post-progression	0.153	0.131	0.022	0.022	15.48%
Total:	0.540	0.396	0.144	0.144	100.00%

Key: *Nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; QALY, quality-adjusted life year.
Notes: Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Costs

Discounted total costs by health state between *nab*-P/Gem and gemcitabine are shown in Table 75. The majority of costs incurred by *nab*-P/Gem occur in "pre-progression: on first-line treatment"; this is primarily driven by the cost of treatment. This is evident in Table 76, showing the summary of predicted resource use by category of cost in the base-case analysis, where the costs incurred by *nab*-P/Gem patients are primarily driven by drug costs.

Table 75: Summary of costs by health state

Health state	Cost intervention (*nab*-P/Gem)	Cost comparator (gemcitabine)	Increment	Absolute increment	% absolute increment
Pre-progression: on first-line treatment	[redacted]	[redacted]	£6,703	£6,703	96.39%
Pre-progression: off first-line treatment	[redacted]	[redacted]	£132	£132	1.90%
Post-progression	[redacted]	[redacted]	-£119	£119	1.71%
Total:	[redacted]	[redacted]	£6,717	£6,955	100.00%

Key: *Nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine.
Notes: Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table 76: Summary of predicted resource use by category of cost

Item	Cost intervention (*nab*-P/Gem)	Cost comparator (gemcitabine)	Increment	Absolute increment	% absolute increment
Pre-progression: on first-line treatment					
Drug cost	[redacted]	[redacted]	£4,835	£4,835	69.41%
Administration costs	£4,230	£3,012	£1,218	£1,218	17.49%
Monitoring costs	£1,860	£1,483	£377	£377	5.41%
Adverse event costs	£825	£550	£274	£274	3.94%
Pre-progression: off first-line treatment					
Monitoring costs	£268	£136	£132	£132	1.90%
Post-progression					

Drug cost	[redacted]	[redacted]	£5	£5	0.07%
Administration costs	£1,492	£1,514	-£22	£22	0.32%
Monitoring costs	£790	£826	-£36	£36	0.52%
Terminal care	£4,118	£4,169	-£50	£50	0.72%
Adverse events	£353	£369	-£16	£16	0.23%
Total:	[redacted]	[redacted]	£6,717	£6,965	100.00%
Key: *Nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine.					

5.8 Sensitivity analyses

5.8.1. Probabilistic sensitivity analysis

To characterise uncertainty in model inputs, a PSA was performed for the comparison of *nab*-P/Gem with gemcitabine. PSA varies all inputs simultaneously, based upon their distribution information (Appendix 18), and records a resulting ICER that may conceivably be the 'true' underlying ICER. The results of 1,000 PSA iterations are presented in Table 77 and diagrammatically in Figure 38 and Figure 39. Cost-effectiveness planes show the incremental QALYs and costs of *nab*-P/Gem relative to gemcitabine, and cost-effectiveness acceptability curves show the likelihood of *nab*-P/Gem cost effectiveness at different WTP thresholds.

Results show the probabilistic mean ICER (£46,801) lies close to the expected ICER (£46,657), indicating that the deterministic result is a good approximation of the mean probabilistic value. In all cases, *nab*-P/Gem provided a QALY gain compared to gemcitabine monotherapy.

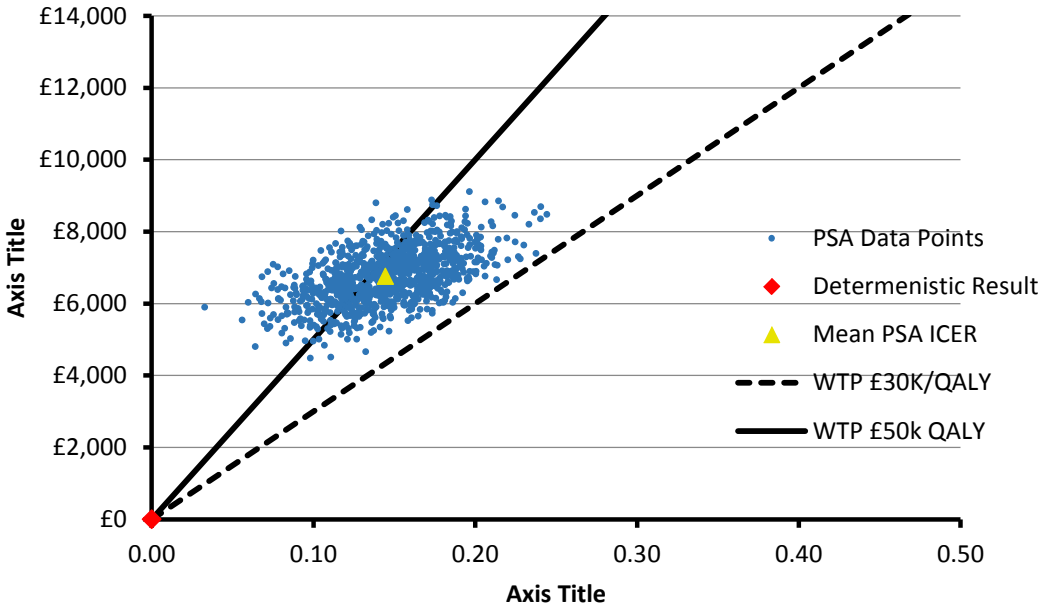
Based on these 1,000 PSA iterations, the cost-effectiveness acceptability curve (Figure 39) suggests that there is a [redacted] likelihood of *nab*-P/Gem cost effectiveness at a WTP threshold of £30,000/QALY (the top-end of the threshold recommended by NICE). At a WTP threshold of £50,000/QALY (the end of life threshold recommended by NICE) there is a [redacted] likelihood of *nab*-P/Gem cost effectiveness.

Table 77: Results from 1,000 PSA simulations

Model outcome	**PSA result**
Mean incremental costs (SD)	£6,758 (£756.69)

Mean incremental QALYs (SD)	0.14 (0.0328)
Mean ICER	£46,801
Observations cost effective at £30,000 threshold	[redacted]
Observations cost effective at £50,000 threshold	[redacted]
Key: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; SD, standard deviation; QALY, quality-adjusted life year.	

Figure 36: Cost-effectiveness plane



Key: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 37: Cost-effectiveness acceptability curve

[redacted]

5.8.2. Deterministic sensitivity analysis

A one-way sensitivity analysis was performed to evaluate the sensitivity of the model ICER to individual inputs, holding all else constant. Distribution information used in the model is provided in Appendix 18. Model results were recorded after changing each input to its upper and lower bound value in turn.

Figure 40 presents a tornado diagram with parameters shown in descending order of ICER sensitivity. Results from the deterministic sensitivity analysis (SA) show that the treatment variable used to parameterise OS (OS Gamma – Treat) has the most influence on the ICER. Results at the upper and lower bound range in ICER values from £39,624 to £59,286. This variable is used to estimate the survival benefit from treatment with *nab*-P/Gem compared with gemcitabine monotherapy; it would be expected to be highly influential on the ICER value as incremental survival underpins the QALY gain. All other parameter inputs have a substantially lower impact on the ICER value at their upper and lower bound, with most ICER values within £5,000 of the base-case value (see Table 78). This indicates that the model is relatively insensitive to the majority of parameters.

Figure 38: Tornado diagram (OWSA)

Key: 5-FU, 5-fluorouracil; Cons, constant; ICER, incremental cost-effectiveness ratio; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; ToT, time on treatment.

Table 78: OWSA: ten most influential parameters

Parameter name	Lower bound ICER	Upper bound ICER
OS Stratified Gamma-Kappa treat	£39,624	£59,286
OS Stratified Gamma-Ln(sigma) treat	£58,287	£39,469
OS Stratified Gamma-Treat	£55,396	£40,672
ToT Stratified Gamma-Kappa treat	£51,161	£42,304
ToT Stratified Gamma-Treat	£42,374	£51,182
Investigator PFS Stratified Gamma-Kappa treat	£44,114	£49,312
Investigator PFS Stratified Gamma-Ln(sigma) treat	£48,860	£44,331
Investigator PFS Stratified Gamma-Treat	£48,514	£44,696
Administration costs chemotherapy per treatment (simple)	£44,487	£47,903
ToT Stratified Gamma-Cons	£45,133	£48,518
Key: BSA, body surface area; ICER, incremental cost-effectiveness ratio; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; ToT, time on treatment.		

5.8.3. Scenario analysis

The uncertainty around the structural assumptions has been included within the model (see Table 79).

Table 79: Scenario analyses

Structural assumption in the base case	Scenario analysis
Model time horizon set at 10 years	Model time horizon set at 5 years
Costs and QALYs discounted at an annual rate of 3.5%	Discount rates of 3.5% or 5% for costs and QALYs investigated
The utility associated with pre-progression and progressive disease was obtained from Romanus *et al.* (2012)"[37]	A scenario analysis used alternative utility sources "SIEGE crosswalk (no AE utility decrement)" and "SIEGE Devlin value set (no AE utility decrement)"
Utility decrements associated with adverse events are/are not applied	Utility decrements are/are not applied
The PFS data as assessed by the investigator were used in the base case.	A scenario analysis considers the data from the independent review, in line with recommendations from the PhRMA PFS Working Group
The stratified gamma distribution is fit to OS, PFS and ToT data	A scenario analysis considers the impact on results of: the ERG's curves (from the response

Structural assumption in the base case	Scenario analysis
	to the original submission [TA360]), and unstratified gamma curves
BSA data obtained from UK data[40]	BSA data from CA046 used[21]
No 250mg vial of *nab*-P is available	A scenario analysis investigates the impact of making a 250mg vial of *nab*-P available
The primary comparison within the economic model is that of *nab*-P/Gem with gemcitabine	A scenario analysis compares *nab*-P/Gem with the secondary comparators: Gem/Cap and FOLFIRINOX using HR generated from the MTC. Scenarios investigate separately when both the core model and NMA use PFS data from independent review or from investigator assessment.
Percentage of reduced doses anticipated for first-dose reductions is 50% based on survey data from pharmacists[120]	Percentage of anticipated first-dose reductions set as 60% or 70% in line with advisory board (see Section 5.3.5.1)
Percentage of reduced doses anticipated for subsequent dose reductions is 100%	Scenario analysis considers that only 90% are anticipated
Percentage of reduced doses anticipated overall combined of 50% for first-dose reductions and 100% for subsequent dose reductions[120]	Scenario considers that 0% of dose reductions are anticipated
Filgrastim used as G-CSF treatment	Lenograstim used as G-CSF treatment
G-CSF dosed based on CA046 clinical trial data[21]	G-CSF use is equal to clinical practice in the UK; patients are only treated with G-CSF upon diagnosis of febrile neutropenia and for the duration of current active therapy
No vial sharing is assumed	*nab*-P vial sharing assumed as 0% while gemcitabine vial sharing considered as either 50% or 100%
End of life costs are captured over 4-weeks as per the micro-costing approach detailed by the ERG in response to the original NICE submission (TA360)	End of life costs are modelled using the method in the original NICE submission (TA360), following feedback at an advisory board. The implications of modelling end of life costs using the estimate from the King's Fund across all cancer subtypes is also considered[94]
Key: ERG, evidence review group; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; G-CSF, granulocyte colony-stimulating factor; MTC, mixed treatment comparison; *nab*-P, *nab*-Paclitaxel; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; TA, technology appraisal; ToT, time on treatment.	

The results from each of these scenarios are given in Table 80 below for *nab*-P/Gem compared with gemcitabine. Table 81 presents the secondary analyses results for *nab*-P/Gem compared with Gem/Cap and FOLFIRINOX.

Table 80: Scenario analyses results

Base Case	Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
Base case	-	£6,717	0.14	£46,657	0.00%
Time horizon - 10 years	5 years	£6,712	0.14	£46,675	0.04%
Discount rate (costs and QALYs) - 3.50%	0%	£6,789	0.15	£46,117	-1.16%
3.50%	5%	£6,687	0.14	£46,881	0.48%
Utilities - Romanus	SIEGE crosswalk (no AE utility decrement)	£6,717	0.14	£49,303	5.67%
Romanus	SIEGE Devlin value set (no AE utility decrement)	£6,717	0.15	£43,460	-6.85%
AE disutilities - Romanus with AE utility decrements	Romanus with no AE utility decrements	£6,717	0.14	£46,644	-0.03%
Romanus with AE utility decrements	SIEGE Devlin value set with AE utility decrements	£6,717	0.15	£43,471	-6.83%
Assessment of PFS – Investigator assessment	Independent assessment	£6,969	0.14	£48,968	4.95%
Parametric survival curves (OS, PFS, ToT) – Stratified Gamma	Gamma	£6,570	0.14	£46,107	-1.18%
Stratified Gamma	ERG curve fits	£7,308	0.15	£50,307	7.82%
Source of BSA data – UK data	Trial based BSA	£7,016	0.14	£48,739	4.46%

Base Case	Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
250mg vial availability – No 250mg vial	250mg vial	£6,250	0.14	£43,416	-6.95%
Network meta-analysis – Investigator assessment*	Investigator assessment	£6,717	0.14	£46,657	0.00%
Investigator assessment	Independent assessment	£6,969	0.14	£48,968	4.95%
Percentage of reduced doses anticipated for first-dose reduction – 50.00%	60.00%	£6,703	0.14	£46,562	-0.20%
50.00%	70.00%	£6,689	0.14	£46,469	-0.40%
Proportion of time reduced doses are anticipated for subsequent doses – 100.00%	90.00%	£6,772	0.14	£47,042	0.83%
Proportion of time missed doses anticipated overall (first and subsequent dose) - 50.00% and 100.00%	0.00% and 0.00%	£7,356	0.14	£51,097	9.52%
G-CSF treatment used - Filgrastim	Lenograstim	£6,761	0.14	£46,967	0.67%
Based on trial data	Based on clinical data	£6,682	0.14	£46,418	-0.51%
Vial sharing – Abraxane 0.00%, Gemcitabine 0.00%	Abraxane 0.00%, gemcitabine 50.00%	£6,715	0.14	£46,643	-0.03%
Abraxane 0.00%, Gemcitabine 0.00%	Abraxane 0.00%, gemcitabine 100.00%	£6,713	0.14	£46,629	-0.06%
Duration of end of life utility decrements and costs applied for – Utility decrement: 12 weeks	Utility decrement: 4 weeks	£6,717	0.14	£46,767	0.23%
End of life costs: 4 weeks	End of life costs: 12 weeks	£6,714	0.14	£46,641	-0.03%

Base Case	Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
	Key: AE, adverse event; BSA, body surface area; G-CSF, granulocyte-colony stimulating factor; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; ToT, time on treatment. * Base case for secondary comparators				

Table 81: Results compared to Gem/Cap and FOLFIRINOX

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Gem/Cap	[redacted]	0.95	0.55				
FOLFIRINOX	[redacted]	1.15	0.69	£4,014	0.20	0.14	£28,315
Nab-P/Gem	[redacted]	0.93	0.54	£1,542	-0.23	-0.15	Dominated

Key: FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; Gem/Cap, gemcitabine in combination with capecitabine; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

5.8.4. Summary of sensitivity analyses results

Model results were reasonably robust to SA with the key areas of uncertainty surrounding:

- The coefficient associated with treatment effect for OS
- The coefficient associated with treatment effect for ToT

The PSA indicated that simultaneous variation of parameter values resulted in *nab*-P/Gem having an incremental QALY gain compared to gemcitabine monotherapy across all iterations. This is illustrated by Figure 38, which shows all PSA points in the north-east quadrant of the cost-effectiveness plane. The PSA further indicated the probability of cost effectiveness for *nab*-P/Gem compared with gemcitabine to be [redacted] and [redacted] at a £30,000/QALY and a £50,000/QALY WTP threshold, respectively.

5.9 Subgroup analysis

No subgroup analyses were explored in the cost-effectiveness analysis following the feedback from the ERG in response to the original NICE submission (TA360).

The ERG accepted that while the KPS is routinely used to aid decision making, its subjective nature and lack of accepted cut-off values for treatment selection made it inappropriate to separate patients into subpopulations based on this measure. Furthermore, using a single measure to determine treatment selection was not appropriate, as decision making accounted for other factors such as comorbidities, patient preference and age, which were also important. This was validated by an expert group of clinicians at the second advisory board, October 2016: “It was agreed that these groups are not clearly defined by any one factor (i.e. age, KPS, comorbidities), but that the groups were clinically clearly definable” (see Section 5.3.5.2).[11] Considering the ITT population only is in line with the NICE decision problem.

5.10 Validation

5.10.1. Validation of *de novo* cost-effectiveness analysis

Internal validation

The model was quality-assured by the internal processes of the external economists who adapted the economic model. In these processes, an economist not involved in model adaptation reviewed the model for coding errors, inconsistencies and the plausibility of inputs. The model was also put through a checklist of known modelling errors, and questioning of the assumptions based upon the Phillips checklist.[124]

External validation of inputs

External validation of the inputs to the cost-effectiveness model included:

- An advisory board in the UK (second advisory board, see Section 5.3.5.2)
- Comparison of results with previously published economic model estimates (as identified as part of the economic SLR) considering patients with mPAC at first-line therapy

Advisory board validation

Advisory board 1: December 2013

Clinicians were further asked to provide their opinion on the relative efficacy of each treatment in terms of the modelled OS, PFS and ToT for *nab*-P/Gem compared with gemcitabine. Clinicians agreed that the single parametric model using a gamma distribution provided a plausible fit, based on their experience in UK clinical practice, for all three efficacy measures. The efficacy estimates were further validated through comparison with the trial estimates (Table 72).

Clinicians confirmed the final list of AEs for inclusion in the model, based upon the criteria of each AE having a significant impact on costs or quality of life. Assumptions associated with utility decrements and costs were validated where no published literature were available. Furthermore, all resource use associated with follow-up and monitoring were obtained from the average of values taken from the clinician's feedback.

Advisory board 2: October 2016

An advisory board was conducted in the UK to validate the updates to the economic model following the original NICE submission (TA360) and to gain advice for Celgene's HTA resubmission for *nab*-P/Gem in mPAC (see Section 5.3.5.2).

Clinicians were asked to provide their opinion on the most appropriate population and comparator relevant for *nab*-P/Gem based on their experience in UK clinical practice. Clinical experts suggest that treatment with FOLFIRINOX would not be replaced by *nab*-P/Gem. Instead, *nab*-P/Gem is likely to displace gemcitabine monotherapy () in patients who are somewhat less fit, and thus less likely to be treated with FOLFIRINOX. In addition, the advisors added that they felt Gem/Cap is not nationally used and therefore is not an appropriate comparator.[11]

Comparison of results with previously published economic evaluations

Since the original NICE submission (TA360), a number of economic evaluations have been published, as identified by the updated economic SLR. Results from this economic model are compared with the identified literature below.

Gharaibeh *et al.* (2016) conducted a critical review for economic evaluations for first-line chemotherapy regimens for pancreatic cancer – this study noted the divergence in ICERs observed across studies and considered this attributable to country-specific economic drivers.[125] Therefore, meaningful comparisons between the results reported in Section 5.7 and the published economic evaluations identified as part of the economic SLR are discussed only for those with a UK perspective.

Cowell *et al.* (2014) published an economic evaluation of *nab*-P/Gem versus gemcitabine monotherapy and reported an ICER of £52,885.[88] This a study is similar to the previously submitted model for TA360. Since the original submission, some changes (see section 5.11) have been made including a PAS discount (Cowell *et al.* (2014) uses list price for *nab*-P).

Using list price for *nab*-P, an ICER of £78,086 was reported by Gharaibeh *et al.* (2016) which is similar to the non-PAS ICER within this submission ([redacted]). The main methodological difference between the Gharaibeh *et al.* (2016) and Cowell *et al.* studies was the utility source, which Gharaibeh obtained from Tam *et al.* (2013).[102] This utility source was not considered appropriate, as it obtained EQ-5D values from postal surveys sent to academic medical oncologists across Canada, rather than patient-reported HRQL data, which are preferred by NICE. Cowell *et al.* (2014) used the health state-specific utility estimates from Romanus *et al.* (2012).[37, 88]

The original NICE submission (TA360), the SMC submission and the AWMSG submission all estimate ICERs based on the list price for *nab*-P (£51,900, £52,885 and £53,260, respectively). The original NICE submission reports very similar incremental costs to those estimated in this resubmission, but gives a greater incremental QALY gain for *nab*-P/Gem ([redacted]) compared to the 0.144 incremental QALYs estimated in this submission.[82] The difference in incremental QALYs, and therefore the difference in ICER, has largely resulted from the impact of converting the utility estimates from the Romanus *et al.* (2012) study to UK values.

Identified studies that compared gemcitabine monotherapy with *nab*-P/Gem use clinical trial data from CA046, and comparisons with FOLFIRINOX utilise the Phase II/III ACCORD study.[6, 45, 91] This is consistent with the efficacy sources used in this re-submission and indicates that all relevant efficacy sources are included in this resubmission. Results from the modelled survival data are consistent with published clinical data from Von Hoff *et al.* (2013) and Goldstein *et al.* (2015), with improvements in OS and PFS for *nab*-P/Gem compared to gemcitabine monotherapy (Table 36).[6]

The estimated LYs and QALYs were validated against the nine *de novo* cost-effectiveness economic models identified in the economic SLR considering patients with mPAC who require first-line treatment (Table 82). Incremental LYs are shown to vary from 0.17 to 0.27 for *nab*-P/Gem compared with gemcitabine. This is in line with the results from this report, where it is estimated that *nab*-P/Gem is associated with 0.20 additional LYs compared to gemcitabine. Incremental QALYs are shown to vary from 0.11 to 0.21 for *nab*-P/Gem compared with gemcitabine. This is also in line with the results from this report, where it is estimated that *nab*-P/Gem is associated with 0.15 additional QALYs. It follows that all the efficacy results from these studies are similar, as all studies used the results of the CA046 trial to inform the economic model.

Table 82: Comparison of LYs and QALYs across cost-effectiveness models identified in the economic systematic literature review

Study	Country	LYs	QALYs
NICE re-submission (TA360) – this report	UK	*Nab*-P/Gem: 0.927 Gemcitabine: 0.725	*Nab*-P/Gem: 0.540 Gemcitabine: 0.396
Carrato *et al.*	Spain	*Nab*-P/Gem: 0.918	*Nab*-P/Gem: 0.718

(2015)[36]		Gemcitabine: 0.719	Gemcitabine: 0.562
Cheng *et al.* (2016)[87]	US	*Nab*-P/Gem: 0.75 Gemcitabine: 0.58	*Nab*-P/Gem: 0.51 Gemcitabine: 0.40
Fragoulakis *et al.* (2014)[89]	Greece	NR	Nab-p/gem: 0.71 Gemcitabine: 0.56
Gharaibeh *et al.* (2015)[90]	UK	*Nab*-P/Gem: 0.97 Gemcitabine: 0.79	*Nab*-P/Gem: 0.52 Gemcitabine: 0.45
Gharaibeh *et al.* (2015)[91]	US	*Nab*-P/Gem associated with +0.27 LY compared with gemcitabine	*Nab*-P/Gem associated with +0.16 QALYs compared with gemcitabine
Stetka *et al.* (2015)[92]	Slovak Republic	NR	*Nab*-P/Gem: 0.629 Gemcitabine: 0.415
NICE TA360 (2015)[82]	UK	*Nab*-P/Gem: 0.928 Gemcitabine: 0.719	*Nab*-P/Gem: 0.713 Gemcitabine: 0.556
SMC (no: 968/14)[22]	UK (Scotland)	NR	Incremental QALYs: 0.156
AWMSG (no: 1999)[23]	UK (Wales)	*Nab*-P/Gem: 0.917 Gemcitabine: 0.718	*Nab*-P/Gem: 0.717 Gemcitabine: 0.561

Key: AWMSG, All Wales Medical Strategy Group; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine; LYs, life years; NICE, National Institute for Health and Care Excellence; NR, not reported; QALY, quality-adjusted life year; SMC, Scottish Medicines Consortium; TA, technology appraisal.

The base-case analysis uses utility estimates from Romanus *et al.* (2012)[37]; six of the seven identified studies in the updated HRQL SLR used the data presented in the Romanus *et al.* study, indicating that this study is generally well accepted in measuring the HRQL associated with pre-progression and progressive disease in the mPAC population.[37] The original data were adjusted for a UK population in line with the ERG's feedback from the original NICE submission (TA360).[48] The small utility decrement associated with progressive disease is further supported by Bonnetain *et al.* (2010), Braun *et al.* (2013) and the SIEGE analysis.[99, 100, 126]

The cost and resource use SLR, conducted as part of the original NICE submission (TA360), did not identify any treatment-specific or health state-specific resource use for the population relevant to *nab*-P/Gem. Therefore, it is difficult to make comparisons between economic studies based on costs and resource use.

All cost and resource use was validated at a UK advisory board (Section 5.3.5).

5.11 Interpretation and conclusions of economic evidence

Nab-P/Gem has been demonstrated to have a [redacted] chance of being cost effective at a WTP threshold of £30,000/QALY, and a [redacted] chance of being cost effective at a WTP threshold of £50,000/QALY. These estimates include the PAS being applied to *nab*-P and, as such, the price of *nab*-P being reduced from £246 for 100mg to [redacted]. Note that, in the previous submission (TA360), the Committee concluded that the end of life criteria are met (see Section 5.7). *Nab*-P/Gem can be considered a cost-effective treatment for the patient groups described in this submission.

The results from this submission provide up to date estimates and make use of the HRQL data obtained from the SIEGE trial, which were unavailable in the original NICE submission (TA360). The model included in this resubmission aims to match the Committee's preferred base case from the original submission (TA360) as closely as possible.

Updates to original NICE submission (TA360)

This submission differs from the original NICE submission (TA360) in that:

- Stratified parametric survival models were chosen due to the lack of support for the proportional hazards assumption
- The re-submission considered the entire ITT population from the CA046 trial only. Following feedback from the original NICE submission (TA360), it was considered that, although there may be a group of patients for whom *nab*-P/Gem would be more appropriate, this group cannot be defined only by performance status
- The clinical SLR was updated and informed an updated MTC and meta-analysis
- Cost savings were only accrued from anticipated dose reductions and anticipated missed doses. Following feedback from the original NICE submission (TA360), it was considered that only a proportion of dose reductions or missed doses could be anticipated. Celgene Ltd commissioned a survey to collect data on dose cessation and missed-dose practices in the UK, the results of which were implemented in the re-submission model

- Vial sharing was not included for any treatment. Following feedback from the original NICE submission (TA360), it was considered inappropriate to assume vial sharing given the small patient population in pancreatic cancer
- Health state-specific utility values estimated from the SIEGE trial were included using estimates derived from the [redacted]. Due to the uncertainty in the choice of which EQ-5D-5L value set is optimal, these data do not inform the model base case but are considered in a scenario analysis. The Romanus *et al.* (2012) source was selected as the utility values derived from this source are bounded by those derived when applying each of the differing value sets to the SIEGE EQ-5D-5L responses[37]
- End of life costs were updated in line with the method recommended by the ERG in response to the original NICE submission (TA360). Furthermore, a utility decrement associated with the final 12 weeks of life was applied. More flexibility was included for the time period associated with end of life costs and quality of life (4, 8 and 12 weeks)
- All costs and utility decrements were updated in line with the most up to date references
- A PAS is applied to the cost of *nab*-P

Strengths and limitations

The key strength of the economic evaluation lies within the maturity of the dataset available for *nab*-P/Gem compared with gemcitabine, including updated efficacy and safety data demonstrating significant median improvements in OS and PFS, at 2.1 and 1.8 months, respectively. This limits uncertainty around the benefit that can be achieved with *nab*-P/Gem.

Other strengths include the focus to estimate inputs that are considered valid in UK practice. The manufacturer commissioned two sets of exploratory data collection to form a clearer picture regarding UK clinical management of mPAC patients. Firstly, surveys were completed to ascertain the way in which missed doses and dose reductions were managed in the UK (see Section 5.5.2). Secondly, the KANTAR study was completed to more accurately define the patient demographics of the UK mPAC population.[40] Efficacy inputs, cost and resource use inputs and assumptions

were validated by a number of clinical experts at UK advisory boards (Section 5.3.5) to ensure the model reflected UK practice.

The use of the newly available HRQL data in scenario analyses, provided by the SIEGE study, is an additional strength of this model.[93] SIEGE recorded patient-level EQ-5D responses of patients with mPAC receiving *nab*-P/Gem. Data were available for patients who had both stable and progressive disease allowing health state utilities to be generated by using linear mixed-effects regression models. These data are UK-specific and inform the model regarding the tolerability profile of *nab*-P/Gem.

The probabilistic ICER of £46,801 was comparable to the deterministic ICER of £46,657, indicating a low level of parameter uncertainty within the model. The key model drivers were shown to be the parameters used to model OS and ToT, which demonstrates a degree of construct validity; it is logical that these parameters should influence the ICER the most, as OS directly impacts the LYs gained and the QALYs and ToT directly impact the cost of treatment and treatment-related AEs.

Limitations include the relative efficacy estimates obtained for *nab*-P/Gem compared with Gem/Cap and FOLFIRINOX. Due to the lack of available head-to-head data with *nab*-P/Gem, the relative efficacy estimates for Gem/Cap and FOLFIRINOX were obtained from an updated meta-analysis; however, the assumption of proportional hazards underpinning this analysis was not supported by the CA046 study, and therefore, results should be interpreted with caution. Following the feedback from the NICE Committee in response to the original NICE submission (TA360), these estimates are preferable to no relative data. Therefore, the comparisons of *nab*-P/Gem with Gem/Cap and FOLFIRINOX are considered in secondary analyses.

Both clinical experts and data on treatment utilisation, suggest that FOLFIRINOX would not be given to the same population eligible for *nab*-P/Gem and that Gem/Cap is not a relevant comparator. FOLFIRINOX is an intensive therapy, associated with high administration burden and considerable toxicity, and is therefore only suitable for a defined group of clinically appropriate patients. Gem/Cap has not demonstrated a significant survival benefit over gemcitabine monotherapy in a Phase III RCT, and it is not recommended in clinical guidelines. Use of Gem/Cap is thus limited to very few centres across the UK, and this regimen does not represent a national standard of care. Furthermore, as neither Gem/Cap nor FOLFIRINOX are licenced in UK practice, real world data are likely to be sparse.

6. Assessment of factors relevant to the NHS and other parties

Cancer Research UK statistics indicate that in 2014, the incidence rate of pancreatic cancer in England was 14.9 per 100,000[1]. Using a population size estimate of 54,786,300[127] the number of patients diagnosed with pancreatic cancer in England is approximately 8,163 per year. Additional consideration of prevalence rates is not necessary in this case due to the intervention's first-line indication, and typical survival prognoses of less than a year in this condition.

The estimated number of pancreatic cancer patients with metastatic adenocarcinoma patients who are actively treated is estimated to be 1891 (internal market research estimate). Of this number, it is estimated that 57% currently receive gem monotherapy (1078) (Celgene Abraxane EU tracker) and are thus eligible for *nab-P*/gem.

Costs included in the budget impact analysis were taken from the cost-effectiveness model and include drug acquisition and administration costs, monitoring costs, adverse events costs and end of life costs across the 3 health states (CE model sheets: PF_Gem, PF_AbraxaneGem, PF_GemCap and PF_Fol).

The following assumptions has been made in the budget impact analysis:

- Nab-P/Gem uptake only affects Gem monotherapy uptake
- Nab-P/Gem uptake is assumed to 33% in year one and remain constant from year 1 to year 5.
- Gem/Cap and FOLFIRINOX market shares remain constant over the 5 years
- Market share of FOLFIRINOX likely to be overestimated as it includes patients treated with other treatments. This does not influence the budget impact results.

Table 83: Uptake estimates (per year)

Year	*Nab*-P/Gem	Gem mono	Gem/Cap	FOLFIRINOX
World without Nab-P/Gem	0	1078	246	567
1	[redacted]	722	246	567
2	[redacted]	722	246	567
3	[redacted]	722	246	567
4	[redacted]	722	246	567
5	[redacted]	722	246	567

Key: FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; Gem, gemcitabine; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine.

Table 84: Total annual costs for each intervention for budget impact analysis

Year	*nab*-P/Gem	Gem mono	Gem/Cap	FOLFIRINOX
1	[redacted]	£11,307	£11,041	£13,789
2	[redacted]	£1,794	£2,738	£3,406
3	[redacted]	£320	£727	£1,096
4	[redacted]	£67	£183	£376
5	[redacted]	£15	£44	£122

Key: FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; Gem, gemcitabine; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine.

Table 85: Annual budget impact

Year	*1*	2	3	4	5	Total
World without Nab-P/Gem	£22,722,128	£27,260,753	£28,405,676	£28,736,232	£28,832,591	£135,957,380
World with Nab-P/Gem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: Gem, gemcitabine; *nab*-P/Gem, *nab*-Paclitaxel in combination with gemcitabine.

Treatment with Nab-P/Gem results in a net budget impact of [redacted] in Year 1 increasing to [redacted] in Year 5. Overall, the introduction of Nab-P/Gem is expected to result in a cumulative net budget impact of [redacted] over a 5-year period (Table 85).

In addition, the simple PAS scheme offers a discount for ABRAXANE when supplied on the NHS in metastatic breast cancer. This is estimated to be a net savings of [redacted] (converted to £ using the March 2017 exchange rate)[128] over the next 5 years based on Celgene commercial estimates. This results in a net budget impact of [redacted]).

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8. Appendices

Appendix 1: European public assessment report (EPAR) and Summary of product characteristics (SmPC) (Section 2.2)

Appendix 2: Clinical effectiveness searches (Section 4.1)

Appendix 3: Further details of clinical evidence (Sections 4.2, 4.7, and 4.12)

Appendix 4: Network meta-analysis (NMA) (Section 4.10)

Appendix 5: Real world evidence (Section 4.12)

Appendix 6: Appendix 6: Methods, results, outcomes and quality assessment of the relevant trials in the indirect or mixed treatment comparison (Section 4.10.9–10)

Appendix 7: Programming language used in the analysis (section 4.10.13)

Appendix 8: Quality assessment of the relevant non-randomised and non-controlled evidence (see Section 4.11.6–9)

Appendix 9: Search strategy for adverse reactions (Section 4.12.3)

Appendix 10: Quality assessment of adverse reaction data (Section 4.12.3)

Appendix 11: Search strategy for cost-effectiveness studies (Section 5.1.1)

Appendix 12: Quality assessment of cost-effectiveness studies (Section 5.1.3)

Appendix 13: Search strategy for measurement and valuation of health effects (section 5.4.3)

Appendix 14: Cost and healthcare resource identification, measurement and valuation (section 5.5.2)

Appendix 15: Checklist of confidential information

Appendix 16: LCHP and QQ plots

Appendix 17: SIEGE model diagnostics

Appendix 18: Parameters used in the economic model

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Single technology appraisal

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

Dear Company,

The Evidence Review Group, LRIG, and the technical team at NICE have looked at the submission received on 17 March 2017 from Celgene. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm on Friday 28 April 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

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Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Helen Tucker Technical Lead (helen.tucker@nice.org.uk). Any procedural questions should be addressed to Jenna Dilkes Project Manager (jenna.dilkes@nice.org.uk).

Yours sincerely

Helen Knight
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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

CA046 trial:

A1. Please provide the most up-to-date versions of the protocol and Statistical Analysis Plan (SAP) for the CA046 trial.

A2. If available, please provide the protocol, SAP and Clinical Study Report for the Extension Study (page 19) which was registered at the closure of the CA046 trial.

A3. On page 55 of the company submission, it is stated that Cox proportional hazards models were used for the analyses of overall survival and progression-free survival. Please clarify whether any testing of proportional hazards was conducted using overall survival or progression-free survival data from the CA046 study. If testing was performed, please provide the results of these tests.

A4. It is stated in the company submission (page 74), that clinical data were used for the subgroup analyses of geographic region, baseline Karnofsky Performance Score, and presence of liver metastases, rather than the randomisation data (i.e. subgroup analyses were based on data in the clinical report file collected and verified on site rather than interactive voice response system information provided for randomisation). Please provide the rationale for using this approach. Please also clarify the number of patients in each category for each subgroup according to the randomisation data.

Network Meta-Analysis (NMA)

A5. **Priority Question:** Please provide the results of sensitivity analysis 2 using random-effects models for: overall survival, progression-free survival using investigator assessment data from the CA046 trial, and independent assessment data from the CA046 trial. Please present the results as relative effects for each comparator in this reduced network versus Nab-Pac+Gem.

A6. In the company submission, and in the appendices to the company submission, results are presented for progression-free survival for sensitivity analysis 1 and sensitivity

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analysis 2 (Appendix 4: Figure 10, Figure 19, Figure 20, Figure 22; and company submission: Table 22 (page [70 to 72] and Figure 17 [page 93]). Please clarify if these results were calculated using progression-free survival determined by independent assessment or investigator assessment data from the CA046 trial.

A7. Please clarify which studies contribute data to the base-case NMA, specifically:
   i) Why the RochaLima 2004 study is presented in Figure 9 (page 83) and Figure 11 (page 86) as part of the network of evidence for the base-case NMA, but not listed in Table 15 (page 75)
   ii) Why the Wang 2002 is stated to provide data for the metastatic population in Table 15, but not included in the network of evidence presented in Figure 9 and Figure 11

A8. Please clarify whether the NMA analyses presented in the company submission and appendices were undertaken using the stratified or non-stratified hazard ratio for overall survival from the CA046 trial.

A9. In the file of appendices submitted by the company, Appendices 6-10 and Appendices 12-15 are referred to but are not provided. Please provide these Appendices.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question:** Section 4.7.2 (page 67) of the company submission includes a description of the CA046 Extension study with a data cutoff at 9 May 2013.
   a) Please clarify whether these data were used in the latest economic model, or if the earlier results (17th September 2012) have been retained in the economic model. If the latest overall survival data have been used in the economic model, have the progression-free survival, Post Progression Survival, and Time on Treatment data also been updated to ensure compatibility between the time-to-event data sets in the model?
   b) Please provide full Kaplan-Meier (K-M) analysis results showing updated K-M survival estimates at each event time (using the format shown in the sample table below) for both treatment arms in the CA046 trial for ***any of the following variables which were updated at the 9 May 2013 data cut:***

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- overall survival
- progression free survival;
- post progression survival;
- time on treatment.

For these K-M analyses, please use following analysis methods:

- the investigator assessment of disease progression;
- censoring any patient still at risk at the date of data cut, *not* the date of last contact/assessment.

NB: The ERG notes that K-M data are included in the submitted model. However, these relate only to weekly time points, and do not allow consideration of the timing of events and censored records, or accurate estimation of uncertainty for time-to-event statistics.

B2. **Priority Question:** Please provide an updated analysis at the 9 May 2013 data cut of the number of progression events in each treatment arm of the CA046 trial showing fatal and non-fatal events separately (a non-fatal event requires the patient to survive at least one day beyond the date of the progression event).

B3. **Priority Question:** Please provide an updated table of the CA046 trial 9 May 2013 data cut summarising the baseline patient characteristics of those patients who survived a progression event and entered PPS, stratified by treatment arm.

B4. **Priority Question:** The Kantar market research report (listed as reference 40 in the company submission) was not included within the references package for the company submission. Please provide a copy of this report. In particular the ERG wish to see the distribution of body surface area separately for men and women; if this is not included in the Kantar report, please provide this information.

B5. **Priority Question:** Please clarify the definitions used for the adverse event data in the model. Does the 'duration of adverse events' encompass the total number of days for all patients experiencing a particular adverse event at least once? If so, please indicate how many patients experienced multiple episodes of the same adverse event. Also, please

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provide the distribution of the length of separate episodes to indicate the relative severity of each type of AE.

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

Single technology appraisal

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Associate Director – Appraisals
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Encl. checklist for confidential information

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Provided as separate files.

A2. If available, please provide the protocol, SAP and Clinical Study Report for the Extension Study (page 19) which was registered at the closure of the CA046 trial.

The data which lead to the publication of reference 8, referred to on page 19 (Goldstein et al, nab-Paclitaxel plus Gemcitabine for metastatic pancreatic cancer: Long-term survival From a Phase III trial, JNCI J Natl Cancer Inst (2015) 107(2): dju413) is not a separate extension study to the CA046 study. This is an extended follow-up of the original MPACT clinical trial, and data was collected in accordance with the original CA046 MPACT protocol. This paper describes an updated analysis of OS from MPACT with an extended data cut-off (eight months longer) from the time the study was closed. At that time, 90% of patients in the intent to treat population had died (as opposed to 80% in the original MPACT publication, reference 6). The secondary endpoints of progression-free survival and overall response rate were not updated in this analysis. This was because they were not likely to have changed with extended follow-up, and additional scans were not collected to update either of these endpoints.

There was no separate protocol, and data was collected from the original MPACT database. Data cut-off for this updated analysis was May 9, 2013, which corresponded to the date the trial was closed following complete analysis of the post-study 120-day safety evaluation conducted as part of the standard regulatory process for the FDA. Statistical analyses were conducted in accordance with the statistical analysis plan for the original MPACT CA046 study and the clinical study report was not updated to include this information. The patient level data from this updated OS analysis was used in the economic modelling for the submission for OS.

For clarity, there was a separate extension study registered at the close of the CA046 study. This was called the CA046c study (NCT02021500). This study was called “MPACT EXTENSION STUDY: MULTICENTER, SURVIVAL DATA COLLECTION IN SUBJECTS PREVIOUSLY ENROLLED IN PROTOCOL CA046”. [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 1: Base case results in original submission (with corrected AE modelling; see answer to question B5)

	Costs	Lys	QALYs	Incremental (nab-P + gem vs. gem mono)			ICER (nab-P + gem vs. gem mono)
				Costs	Lys	QALYs	
Gem mono	[redacted]	0.725	0.396				
Nab-P + gem	[redacted]	0.927	0.539	[redacted]	0.202	0.144	[redacted]
Key: gem, gemcitabine; gem mono, gemcitabine monotherapy; Lys, life years; nab-P, nab-paclitaxel; QALYs, quality adjusted life years.							

Table 2: Model results directly applying KM data using the previous datacut

	Costs	Lys	QALYs	Incremental (nab-P + gem vs. gem mono)			ICER (nab-P + gem vs. gem mono)
				Costs	Lys	QALYs	
Gem mono	[redacted]	0.718	0.391				
Nab-P + gem	[redacted]	0.925	0.538	[redacted]	0.207	0.147	[redacted]
Key: gem, gemcitabine; gem mono, gemcitabine monotherapy; Lys, life years; nab-P, nab-paclitaxel; QALYs, quality adjusted life years.							

Table 3: Model results directly applying KM data using the updated datacut

- -	Costs	Lys	QALYs	Incremental (nab-P + gem vs. gem mono)			ICER (nab-P + gem vs. gem mono)
				Costs	Lys	QALYs	
Gem mono	[redacted]	0.725	0.396				
Nab-P + gem	[redacted]	0.959	0.559	[redacted]	0.233	0.163	[redacted]
Key: gem, gemcitabine; gem mono, gemcitabine monotherapy; Lys, life years; nab-P, nab-paclitaxel; QALYs, quality adjusted life years.							

A3. On page 55 of the company submission, it is stated that Cox proportional hazards models were used for the analyses of overall survival and progression-free survival. Please clarify whether any testing of proportional hazards was conducted using overall survival or progression-free survival data from the CA046 study. If testing was performed, please provide the results of these tests.

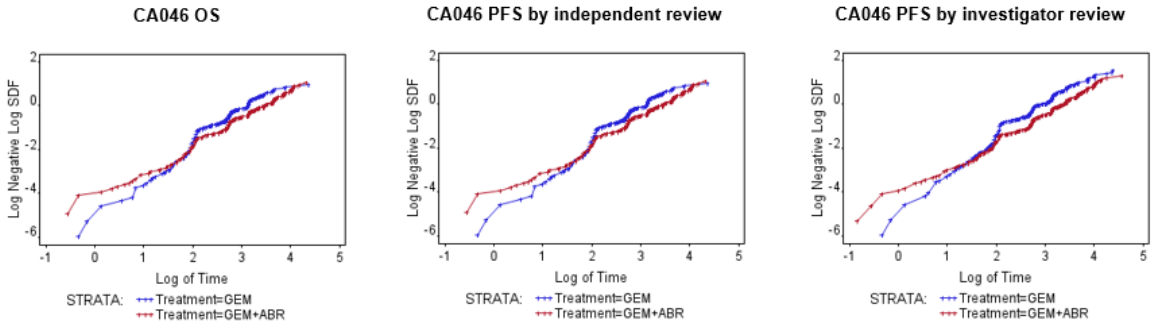
Prior to undertaking analyses specifically designed to inform this submission the proportional hazards (PH) assumption was explored as part of statistical model assumption testing of models adopted to estimate comparative efficacy. The following diagnostics were explored to assess the PH assumption for the CA046 study:

- Visual inspection of log-cumulative hazard (LCH) plots
- Visual inspection of Schoenfeld residual plots and corresponding correlation estimates and p-values assessing proportionality
- Comparison of observed and predicted KM curves (estimated from a Cox PH regression model)

Results of this testing are provided in Section 4.10.5 and Appendix 4 of the manufacturers submission, but those related to the CA046 study are presented below (Figure 1, **Key:** ABR, Abraxane; GEM, gemcitabine; OS, overall survival; PFS, progression-free survival; survival distribution function.

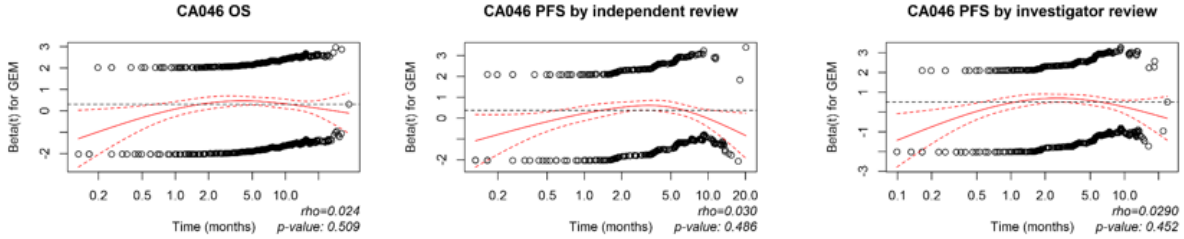
Figure 2, Figure 3) for ease of reference. In short, the analyses undertaken to investigate the assumption are inconclusive.

Figure 1: Visual inspection of log-cumulative hazard (LCH) plots



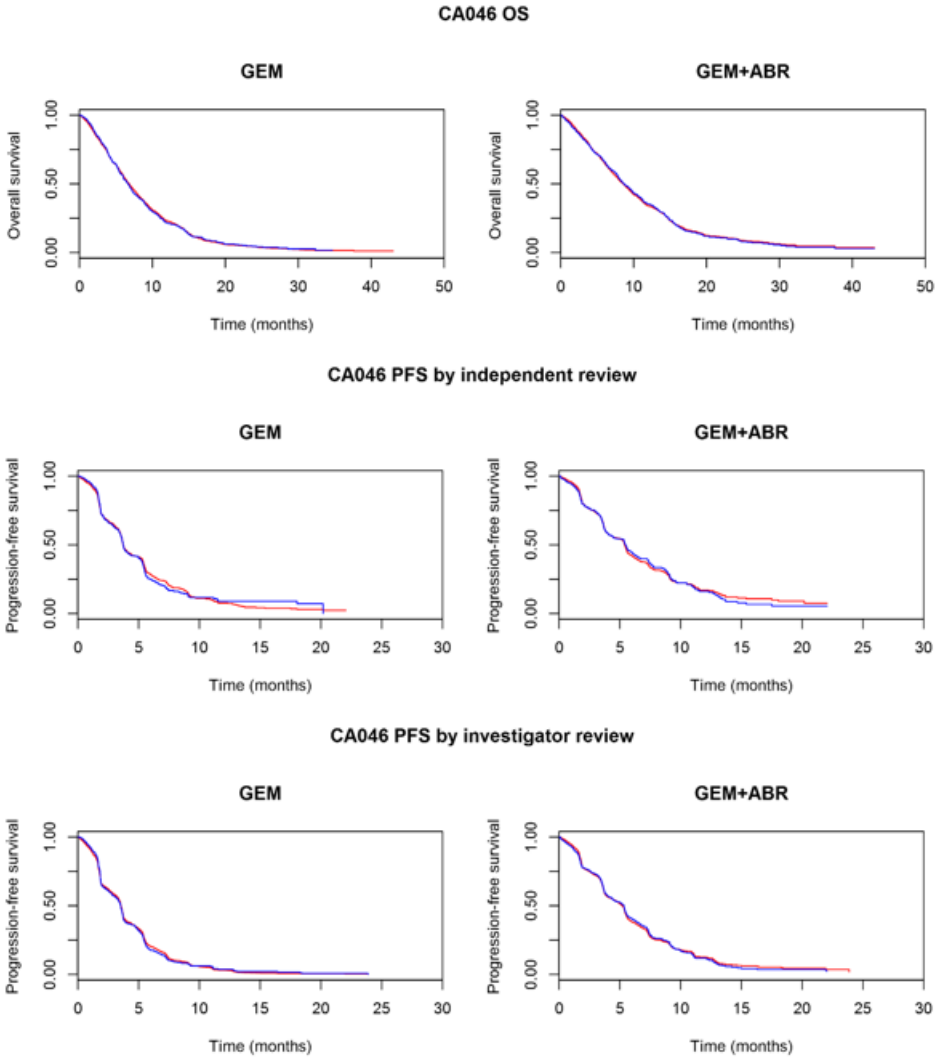
Key: ABR, Abraxane; GEM, gemcitabine; OS, overall survival; PFS, progression-free survival; survival distribution function.

Figure 2: Visual inspection of Schoenfeld residual plots and corresponding correlation estimates and p-values assessing proportionality



Key: ABR, Abraxane; GEM, gemcitabine; OS, overall survival; PFS, progression-free survival.
Notes: p-value calculated from a Chi-squared distribution; beta is the time-dependent treatment coefficient.

Figure 3: Comparison of observed and predicted KM curves



Key: ABR, Abraxane; GEM, gemcitabine; OS, overall survival; PFS, progression-free survival.
Notes: Blue line, observed KM; red line, predicted KM based on Cox regression model.

A4. It is stated in the company submission (page 74), that clinical data were used for the subgroup analyses of geographic region, baseline Karnofsky Performance Score and presence of liver metastases, rather than the randomisation data (i.e. subgroup analyses were based on data in the clinical report file collected and verified on site rather than interactive voice response system information provided for randomisation). Please provide the rationale for using this approach. Please also clarify the number of patients in each category for each subgroup according to the randomisation data.

The clinical data collected was source document verified and therefore considered the most accurate source of data to use for the subgroup analysis. The interactive voice response system randomisation data was not source document verified, and therefore considered less accurate. The rationale behind using the clinical report file data was therefore to ensure that the most accurate dataset was used for the subgroup analysis, once we had this information available. The below tables (Table 4, Table 5,Table 6) clarify the number of patients in each category for each subgroup according to the randomisation data and the clinical data, demonstrating the greater level of accuracy provided by the CRF data:

Table 4: Karnofsky Performance Clinical Data

	Karnofsky Performance (Clinical data)					
Karnofsky Performance at baseline (IRVS)	MISSING	_60	_70	_80	_90	_100
70-80	1	1	60	247	10	0
90-100	3	1	2	26	370	140

Table 5: Liver Metastasis at Baseline (Clinical Data)

	Liver metastasis at Baseline (Clinical data)	
Liver metastasis at Baseline (IRVS)	NO	YES
No	129	24
Yes	7	701

Table 6: Frequency by Geographical Region

Geographic Region (IRVS)	Geographic Region (Clinical data	Frequency Count
Australia/New Zealand	Australia	119
Eastern Europe	Eastern Europe	126
North America	Australia	1
North America	North America	539
Western Europe	Western Europe	76

Network Meta-Analysis (NMA)

A5. **Priority Question:** Please provide the results of sensitivity analysis 2 using random-effects models for: overall survival, progression-free survival using investigator assessment data from the CA046 trial, and independent assessment data from the CA046 trial. Please present the results as relative effects for each comparator in this reduced network versus Nab-Pac+Gem.

Results of sensitivity analysis 2 using random effects are presented in Table 7-Table 9. However, it should be noted that the results should be interpreted with caution. This is because, as can be seen in the network diagrams presented in Figure 4, only one trial is available for each comparison within the network. Therefore, the estimation of between trial heterogeneity is confounded with the estimation of the treatment effect. This results in issues with model convergence when estimating hazard ratio's and large uncertainty in the estimates. The point estimates, however, are similar to the fixed-effect analyses.

Table 7: Sensitivity analysis 2 using random-effects results – OS

Treatment comparison	HR (95% CrI)
Gemcitabine vs gemcitabine+Abraxane	1.33 (0.12, 15.43)
Gemcitabine+capectabine vs gemcitabine+Abraxane	1.10 (0.03, 35.88)
FOLFIRINOX vs gemcitabine+Abraxane	0.76 (0.02, 23.48)
Key: CrI, credible interval; HR, hazard ratio; OS, overall survival.	

Table 8: Sensitivity analysis 2 random-effects results – PFS (independent review)

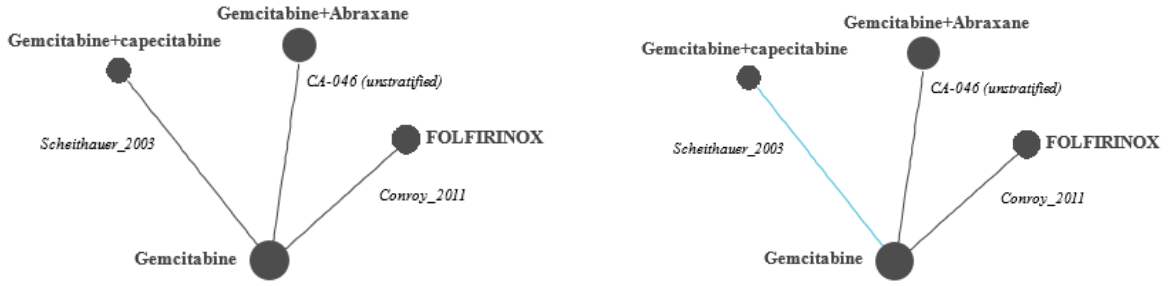
Treatment comparison	HR (95% CrI)
Gemcitabine vs gemcitabine+Abraxane	1.43 (0.13, 16.90)
Gemcitabine+capectabine vs gemcitabine+Abraxane	1.17 (0.04, 35.16)
FOLFIRINOX vs gemcitabine+Abraxane	0.67 (0.02, 18.90)
Key: CrI, credible interval; HR, hazard ratio; PFS, progression-free survival.	

Table 9: Sensitivity analysis 2 random-effects results – PFS (investigator review)

Treatment comparison	HR (95% CrI)
Gemcitabine vs	1.65 (0.14, 20.11)

gemcitabine+Abraxane	
Gemcitabine+capectabine vs gemcitabine+Abraxane	1.33 (0.04, 47.00)
FOLFIRINOX vs gemcitabine+Abraxane	0.77 (0.02, 29.96)
Key: CrI, credible interval; HR, hazard ratio; PFS, progression-free survival.	

Figure 4: Network of evidence – sensitivity analysis 2 – OS (left) and PFS (right)



Key: OS, overall survival; PFS, progression-free survival.
Notes: black lines represent trials reporting HR data; blue lines represent data digitised from published Kaplan Meier curves; node sizes are proportional to the number of patients treated with the respective intervention.

A6. In the company submission, and in the appendices to the company submission, results are presented for progression-free survival for sensitivity analysis 1 and sensitivity analysis 2 (Appendix 4: Figure 10, Figure 19, Figure 20, Figure 22; and company submission: Table 22 (page [70 to 72] and Figure 17 [page 93]). Please clarify if these results were calculated using progression-free survival determined by independent assessment or investigator assessment data from the CA046 trial.

These results were calculated using progression-free survival determined by independent assessment data from the CA046 trial (as the pre-determined assessment measure).

A7. Please clarify which studies contribute data to the base-case NMA, specifically:

i) Why the RochaLima 2004 study is presented in Figure 9 (page 83) and Figure 11 (page 86) as part of the network of evidence for the base-case NMA, but not listed in Table 15 (page 75)

ii) Why the Wang 2002 is stated to provide data for the metastatic population in Table 15, but not included in the network of evidence presented in Figure 9 and Figure 11

i) Studies contributing data to the base-case NMA are summarised in The Wang 2002 study was incorrectly stated to provided data for the metastatic population in Table 15; this

abstract only provides data for the advanced pancreatic cancer population (locally advanced or metastatic)

Table 10. With regard to the specific queries:

ii) The RochaLima 2004 study did not meet the secondary eligibility criteria of the clinical SLR as gemcitabine + irinotecan was not a named intervention of interest, hence why it was not captured in Table 15. However, following production of the evidence network, studies excluded based on intervention were re-assessed for inclusion within the synthesis comparator set network used for the base-case NMA. The RochLima 2004 study provided additional data for the comparison of gemcitabine versus gemcitabine + irinotecan in the metastatic population. This comparison was included in the synthesis comparator set network due to its inclusion in the four-arm trial reported by Kulke et al. 2009 that met the secondary eligibility criteria of the clinical SLR due to its gemcitabine + cisplatin intervention arm. No other studies (to the RochaLima 2004 study) contributed data to the base-case NMA on this basis.

iii) The Wang 2002 study was incorrectly stated to provided data for the metastatic population in Table 15; this abstract only provides data for the advanced pancreatic cancer population (locally advanced or metastatic)

Table 10: Studies contributing to the base-case NMA

	Overall survival			**Progression-free survival**		
	HR	**Median**	**KM curve**	**HR**	**Median**	**KM curve**
CA-046	✓	NN	NN	✓	NN	NN
Conroy_2011	✓	NN	NN	✓	NN	NN
Louvet_2005	✓	NN	NN	NR	NN	✓
Heinemann_2006	✓	NN	NN	✓	NN	NN
Scheithauer_2003	✓	NN	NN	NR	NN	✓
Chao_2013	NR	NN	✓	NR	NN	✓
RochaLima_2004	NR	✓	NR[a]	NR	✓	NR[a]
Wang_2015	NR	NN	✓	NR	NN	✓
Boeck_2008	NR	✓	NR[a]	NR	✓	NR[a]
Kulke_2009	NR	NN	✓	NR	NN	✓
Key: HR, hazard ratio; KM, Kaplan-Meier; NN, not needed for analysis (HR data available); NR, not reported.						

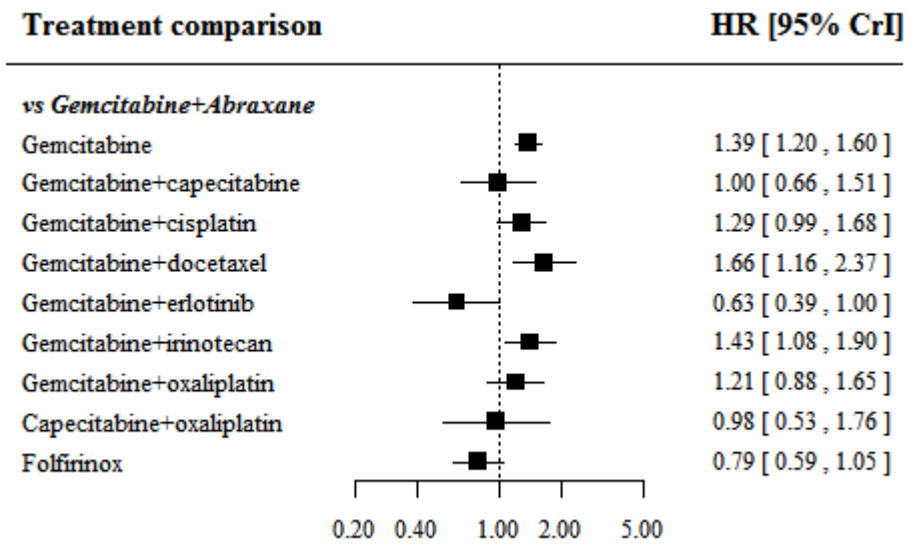
A8. Please clarify whether the NMA analyses presented in the company submission and appendices were undertaken using the stratified or non-stratified hazard ratio for overall survival from the CA046 trial.

The NMA analyses used the non-stratified hazard ratio for overall survival from the CA046 trial.

As there is no evidence to indicate that hazard ratios for overall survival from other studies are stratified (and they are likely to be non-stratified), these data were considered more appropriate.

Sensitivity analyses using the stratified hazard ratio for overall survival from the CA046 trial provided comparable outcomes to the base-case analyses, as presented in Figure 5.

Figure 5: Relative effects versus gemcitabine plus Abraxane – sensitivity analysis – non-stratified OS from CA046



Key: CrI, credible interval; HR, hazard ratio; OS, overall survival.
Notes: Point estimates lying to the left of 1 favour the treatment under observation over the reference treatment.

A9. In the file of appendices submitted by the company, Appendices 6-10 and Appendices 12-15 are referred to but are not provided. Please provide these Appendices.

These appendices are listed in error. They formed part of the original submission but are not referred to in this resubmission; hence why they are not provided. Programming language for the NMA is provided in Appendix A9.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question:** Section 4.7.2 (page 67) of the company submission includes a description of the CA046 Extension study with a data cutoff at 9 May 2013.

a) Please clarify whether these data were used in the latest economic model, or if the earlier results (17th September 2012) have been retained in the economic model. If the latest overall survival data have been used in the economic model, have the progression-free survival, Post Progression Survival, and Time on Treatment data also been updated to ensure compatibility between the time-to-event data sets in the model?

All outcomes except progression-free survival and overall response rate use the data from the 9th May 2013 cutoff. Progression-free survival and overall response rate were not updated in this analysis because they were not likely to have changed with extended follow-up.

b) Please provide full Kaplan-Meier (K-M) analysis results showing updated K-M survival estimates at each event time (using the format shown in the sample table below) for both treatment arms in the CA046 trial for ***any of the following variables which were updated at the 9 May 2013 data cut:***

- overall survival
- progression free survival;
- post progression survival;
- time on treatment.

For these K-M analyses, please use following analysis methods:

- the investigator assessment of disease progression;
- censoring any patient still at risk at the date of data cut, *not* the date of last contact/assessment.

NB: The ERG notes that K-M data are included in the submitted model. However, these relate only to weekly time points, and do not allow consideration of the timing of events and censored records, or accurate estimation of uncertainty for time-to-event statistics.

See separate file.

B2. **Priority Question:** Please provide an updated analysis at the 9 May 2013 data cut of the number of progression events in each treatment arm of the CA046 trial showing fatal and non-fatal events separately (a non-fatal event requires the patient to survive at least one day beyond the date of the progression event).

Table 11: Disease progression fatal and non-fatal events by treatment

	Treatment	
	ABI-007 + Gemcitabine	**Gemcitabine**
All Progressive Disease	303	310
Fatal	24	14
Non-fatal	279	296

B3. **Priority Question:** Please provide an updated table of the CA046 trial 9 May 2013 data cut summarising the baseline patient characteristics of those patients who survived a progression event and entered PPS, stratified by treatment arm.

Table 12: Demographic and Baseline Characteristics for Patients with Non-fatal Progression

Variable Category/Statistic	ABI-007/Gemcitabine (N=279)	Gemcitabine (N=296)	All Subjects (N=575)
Country, n (%)	279	296	575
Australia	45 (16)	49 (17)	94 (16)
Austria	3 (1)	2 (1)	5 (1)
Belgium	0	2 (1)	2 (<1)
Canada	24 (9)	19 (6)	43 (7)
France	4 (1)	1 (<1)	5 (1)
Germany	2 (1)	3 (1)	5 (1)
Italy	15 (5)	13 (4)	28 (5)
Spain	3 (1)	9 (3)	12 (2)
Russian Federation	39 (14)	43 (15)	82 (14)
Ukraine	7 (3)	10 (3)	17 (3)
United States	137 (49)	145 (49)	282 (49)

Variable Category/Statistic	ABI-007/Gemcitabine (N=279)	Gemcitabine (N=296)	All Subjects (N=575)
Region, n (%)	279	296	575
Australia	45 (16)	49 (17)	94 (16)

Variable Category/Statistic	ABI-007/Gemcitabine (N=279)	Gemcitabine (N=296)	All Subjects (N=575)
Eastern Europe	46 (16)	53 (18)	99 (17)
North America	161 (58)	164 (55)	325 (57)

Variable Category/Statistic	ABI-007/Gemcitabine (N=279)	Gemcitabine (N=296)	All Subjects (N=575)
Sex, n (%)	279	296	575
Female	116 (42)	128 (43)	244 (42)
Male	163 (58)	168 (57)	331 (58)
Race/Ethnicity, n (%)	279	296	575
Asian, Not Hispanic Or Latino	5 (2)	7 (2)	12 (2)
Black Or African American, Not Hispanic Or Latino	8 (3)	13 (4)	21 (4)
Native Hawaiian Or Other Pacific Islander, Not Hispanic Or Latino	0	0	0
North American Indian Or Alaska Native	0	0	0
White, Hispanic Or Latino	15 (5)	15 (5)	30 (5)
White, Not Hispanic Or Latino	248 (89)	257 (87)	505 (88)
Other, Unknown	3 (1)	4 (1)	7 (1)
< 75 Years	259 (93)	269 (91)	528 (92)
>= 75 Years	20 (7)	27 (9)	47 (8)
Western Europe	27 (10)	30 (10)	57 (10)

Variable Category/Statistic	ABI-007/Gemcitabine (N=279)	Gemcitabine (N=296)	All Subjects (N=575)

Weight (kg)

Variable Category/Statistic	ABI-007/Gemcitabine (N=279)	Gemcitabine (N=296)	All Subjects (N=575)
BMI (kg/m^2)			
n	279	296	575
Mean	25.82	25.49	25.65
STDEV	5.290	4.290	4.800
Median	24.90	25.10	25.00
Min, Max	14.0, 47.3	14.7, 42.4	14.0, 47.3
BSA (m^2)			
n	279	296	575
Mean	1.87	1.85	1.86
STDEV	0.250	0.225	0.238
Median	1.87	1.84	1.86
Min, Max	1.2, 2.7	1.1, 2.6	1.1, 2.7

Variable Category/Statistic	ABI-007/Gemcitabine (N=279)	Gemcitabine (N=296)	All Subjects (N=575)
Karnofsky Performance Status, n (%)	279	296	575
90 - 100	164 (59)	191 (65)	355 (62)
70 - 80	114 (41)	105 (35)	219 (38)
<70	1 (<1)	0	1 (<1)
100	42 (15)	45 (15)	87 (15)
90	122 (44)	146 (49)	268 (47)
80	93 (33)	85 (29)	178 (31)
70	21 (8)	20 (7)	41 (7)
60	1 (<1)	0	1 (<1)

Physician Assessment of Peripheral Neuropathy, n (%)	275	290	565
0	265 (96)	281 (97)	546 (97)
1	10 (4)	9 (3)	19 (3)
2	0	0	0
3	0	0	0
4	0	0	0

B4. **Priority Question:** The Kantar market research report (listed as reference 40 in the company submission) was not included within the references package for the company submission. Please provide a copy of this report. In particular the ERG wish to see the distribution of body surface area separately for men and women; if this is not included in the Kantar report, please provide this information.

The data outlined below reiterates the manufacturer's previous response to the Appraisal Consultation Document for TA360. Table 13 provides BSA distributions separated by gender, accompanied by density functions (Figure 6), as requested. The manufacturer regrets that it cannot provide the full report as permission was not obtained from the participants in the market research to provide the full report to NICE.

Table 13: Distribution of a UK sample of pancreatic cancer patients treated with chemotherapy (Kantar, 2014)

	Mean BSA	Standard Deviation (S.D.)	Number in group	% of sample
Whole sample	1.75	0.16	351	
Female	1.66	0.13	142	40%
Male	1.82	0.16	209	60%

In addition to providing the particular data of interest the manufacturer also wishes to briefly re-summarise the previous justification for the use of the whole sample BSA value from the Kantar report.

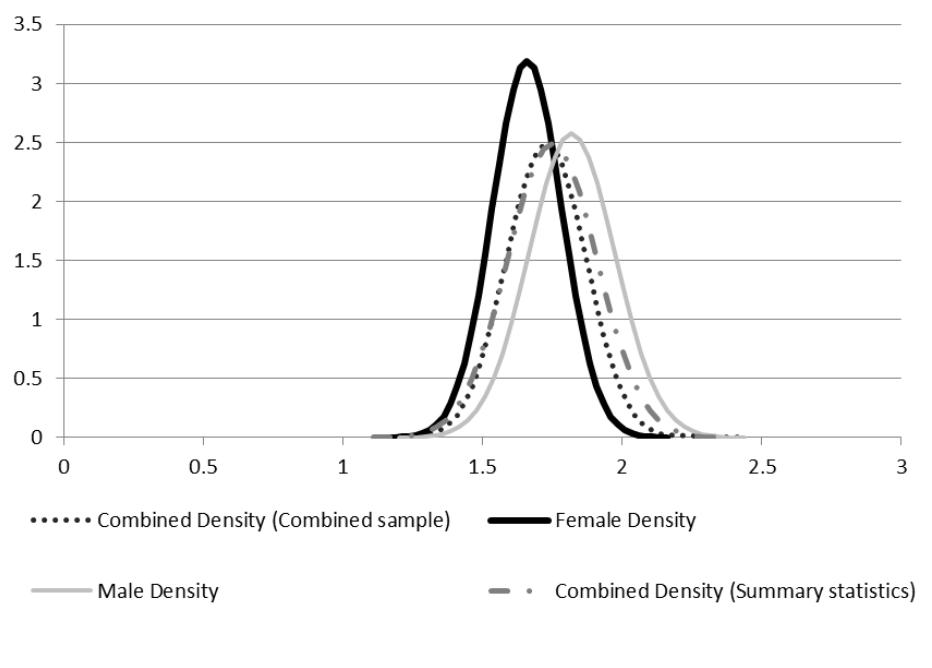
If the total sample used to estimate the population BSA is reflective, with respect to the gender split of women and men, of the wider population being treated there should be no need to explicitly model the female and male distributions separately.

The manufacturer notes that in both the sample of UK pancreatic cancer patients treated with chemotherapy (Kantar, 2014) and study CA046 the gender split was roughly 40:60 (female/male). To demonstrate that the sample statistics for the combined sample adequately capture the variation in BSA, even though female and male BSA differ, the following was done:

- the female distribution of BSA was estimated using a normal distribution and the summary statistics in Table 13,
- the male distribution of BSA was estimated using a normal distribution and the summary statistics in Table 13,
- the whole sample distribution of BSA was estimated using a normal distribution and the summary statistics in Table 13 (method 1: "summary statistics" in Figure 6)
- the whole sample distribution of BSA was estimated by additively combining the distributions of the female and male populations that had been estimated separately and weighting them for the different proportions of the sexes within the treated population (method 2: "combined sample" in Figure 6).

As can be seen in Figure 6, the population variance between the female and male BSA distributions are adequately captured by using the summary statistics of the combined sample as the distribution density estimated using this approach is exceptionally close to the distribution estimated by estimating the distributions separately and then combining them according to the sex split within the treated population.

Figure 6: BSA distributions



As was noted in the response to the appraisal committee document the effect on the ICER of alternating between the approaches is minimal. With the current model settings used, “method 1” led to an estimated mean per treatment cost of [redacted] while “method 2” (the ERG’s preferred approach) led to an estimated mean per treatment cost of [redacted]. This is deemed a negligible difference and as such the simplifying step adopted by the manufacturer does not seem unreasonable.

B5. **Priority Question:** Please clarify the definitions used for the adverse event data in the model. Does the ‘duration of adverse events’ encompass the total number of days for all patients experiencing a particular adverse event at least once? If so, please indicate how many patients experienced multiple episodes of the same adverse event. Also, please provide the distribution of the length of separate episodes to indicate the relative severity of each type of AE.

The economic model used patient level data from the CA046 trial to model adverse events. The duration of AEs was defined as the mean duration of each grade 3+ treatment emergent AE event.

The manufacturer, in responding to these clarification questions identified an inconsistency between the model and the submission dossier. The economic model used the number of patients experiencing each AE to model AEs, a commonly used and accepted methodology. However, this method makes the conservative assumption that each patient may not have multiple episodes.

Consequently, the manufacturer conducted additional analyses to investigate whether modelling separate AE episodes would impact on the CE model results. The analyses are shown below for nab-P + gem (Table 14) and gemcitabine monotherapy (Table 15). In addition, the standard deviation of the mean duration for each AE has been provided to indicate the relative severity of each type of AE.

The updated CE model results are outlined in
Table 16 and Table 17 and show additional analyses have a negligible impact on the ICER.

Table 14: Adverse events: nab-paclitaxel + gemcitabine

	nab-paclitaxel + gemcitabine				
Grade 3+ treatment emergent AEs	**Number of patients**	**Number of patients with multiple events**	**Number of events**	**Mean duration of event**	**SD of duration**
Neutropenia	138	72	348	9.13	6.97
Fatigue	80	18	101	17.29	15.03
Thrombocytopenia	55	18	93	7.77	6.44
Anaemia	54	13	70	11.00	11.21
Leukopenia	39	16	82	10.48	8.62
Peripheral sensory neuropathy	34	2	36	24.19	14.10
Neuropathy peripheral	32	8	45	20.98	9.66
Dehydration	31	0	31	9.35	10.93
Asthenia	31	5	37	16.22	11.58
Abdominal pain	28	2	32	13.31	11.55
Nausea	29	2	31	12.16	11.54
Diarrhoea	26	4	30	5.57	4.58
Vomiting	25	2	27	7.96	9.82
Decreased appetite	23	1	24	21.54	11.72
Pulmonary embolism	19	1	20	32.80	26.37
Pneumonia	15	1	16	10.88	9.50
Febrile Neutropenia	13	0	13	7.23	8.45
Cholangitis	10	2	12	13.67	13.42
Hyperbilirubinaemia	9	1	10	20.80	10.04
Key: AE, adverse event; SD, standard deviation.					

Table 15: Adverse events: gemcitabine monotherapy

	Gemcitabine monotherapy				
Grade 3+ treatment emergent AEs	**Number of patients**	**Number of patients with multiple events**	**Number of events**	**Mean duration of event**	**SD of duration**
Neutropenia	85	34	166	8.89	6.31
Fatigue	37	6	43	21.00	12.64
Thrombocytopenia	33	11	50	9.34	6.69
Anaemia	35	9	53	12.04	14.99
Leukopenia	15	6	25	9.56	8.92
Peripheral sensory neuropathy	1	0	1	28.00	NA
Neuropathy peripheral	0	0	0	0.00	0.00
Dehydration	11	0	11	7.82	11.03
Asthenia	17	2	21	18.43	11.71
Abdominal pain	35	7	44	14.11	13.07
Nausea	14	1	15	18.93	10.84
Diarrhoea	6	1	8	7.75	9.66
Vomiting	15	1	16	11.81	11.96
Decreased appetite	8	0	8	27.75	6.36
Pulmonary embolism	27	3	30	21.40	19.40
Pneumonia	9	0	9	14.33	12.07
Febrile Neutropenia	6	1	8	8.00	5.66
Cholangitis	6	0	6	8.33	8.96
Hyperbilirubinaemia	12	2	15	15.07	10.78

Key: AE, adverse event; SD, standard deviation.

Table 16: Cost and utility decrement per cycle for base case and updated AE analysis

	nab-P + gem		gemcitabine monotherapy	
	Base case	AE scenario	Base case	AE scenario
Cost per cycle	[redacted]	[redacted]	£38.68	£49.06
Utility decrement per cycle	-0.0005	-0.0007	-0.0004	-0.0006

Key: AE, adverse event; gem, gemcitabine; nab-P, nab-paclitaxel.
Note: Base case refers to original submitted model. AE scenario represents results with additional AE analyses using total number of events per AE rather than number of patients experiencing an AE.

Table 17: Base case discounted deterministic results (with PAS) compared to results using updated AE analysis

	Costs	Lys	QALYs	Incremental (nab-P + gem vs. gem mono)			ICER (nab-P + gem vs. gem mono)
				Costs	Lys	QALYs	
Base case (with PAS)							
Gem mono	[redacted]	0.725	0.396				
Nab-P + gem	[redacted]	0.927	0.540	£6,717	0.202	0.144	£46,656.94
AE scenario							
Gem mono	[redacted]	0.725	0.396				
Nab-P + gem	[redacted]	0.927	0.539	£6,755	0.202	0.144	£46,931.96

Key: AE, adverse event; gem, gemcitabine; gem mono, gemcitabine monotherapy; Lys, life years; nab-P, nab-paclitaxel; QALYs, quality adjusted life years.
Note: Base case refers to original submitted model. AE scenario represents results with additional AE analyses using total number of events per AE rather than number of patients experiencing an AE.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]
Name of your organisation: Pancreatic Cancer UK
Your position in the organisation: [redacted]

Your name: [redacted]
Name of your organisation: Pancreatic Cancer Action
Your position in the organisation: [redacted]

Brief description of the organisation: (For example: who funds the organisation? How many members does the organisation have?)
We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Pancreatic Cancer UK is fighting to make a difference. We're taking on pancreatic cancer together: by supporting those affected by the disease, investing in research, lobbying for greater recognition of pancreatic cancer, and being there for everyone involved in the fight.

We provide a UK-wide, expert and personalised support and information service, staffed by pancreatic cancer specialist nurses. This provides easy access to the best and most up-to-date information on pancreatic cancer to patients, their carers and families. We also run online discussion forums for pancreatic cancer patients, their families and carers to enable them to share experiences, information, inspiration and hope. We fund innovative research that makes the most impact with limited resources and leverages additional investment. Working closely with patients and their families and carers, clinicians and other healthcare professionals, researchers, politicians and policy makers, we seek to increase awareness of the disease and campaign to bring about improved outcomes in care and treatment.

Our funding comes from a variety of sources, although mostly from small donations and fundraisers. In 2015/16, 0.89% of our income came from pharmaceutical companies in the form of grants supporting our education work such as Nurse Study days etc. Full details of pharmaceutical contributions are available on request. Our policy is that pharmaceutical funding must not exceed 5% of our total budgeted income of the financial year and that any monies received cannot be used for campaigning.

Pancreatic Cancer Action is a national charity focussed on giving every pancreatic cancer patient the best chance of survival by improving earlier diagnosis and treatment.

Set up by a pancreatic cancer survivor, we raise awareness among the public and medical communities, fund research to improve early diagnosis, provide information for patients and develop educational courses for clinicians.

The majority of our funding comes from individual donors and supporters, most with a very personal connection to pancreatic cancer. While we do receive funding from pharmaceutical companies, the total amount we received equated to a mere 0.4% of

our total revenue in 2014. In 2015, while campaigning to keep the drug Abraxane® on the Cancer Drugs Fund list, Pancreatic Cancer Action made a conscious decision to refuse a grant from that drug manufacturer, Celgene even though the grant was not linked to any campaigning activity.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

Neither Pancreatic Cancer UK nor Pancreatic Cancer Action receive any funding – be it direct or indirect – from the tobacco industry.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Receiving a diagnosis of pancreatic cancer can be a devastating and bewildering time for patients and their family members. Pancreatic cancer patients often have complex supportive care needs, including support dealing with pain management, weight loss, nutritional issues, depression and other emotional and psychological needs.

A diagnosis of pancreatic cancer for many is seen as a death sentence with an average life expectancy among metastatic patients of two to six months. Patients often report feeling helpless and without hope due to the lack of effective treatment options available.

Being diagnosed with a disease that has such a poor prognosis is extremely difficult for both patients and their loved ones to deal with. In a 2014 survey[1] (n=130) run by Pancreatic Cancer UK and Pancreatic Cancer Action asking how patients and their family members felt on diagnosis, respondents most commonly reported feeling “devastated”, “alone”, “helpless”, “scared”, “shocked” and “completely without hope”.

As such, the psychological impact of a diagnosis of pancreatic cancer can be significant. We know from conversations with patients and carers, through calls made to the Pancreatic Cancer UK Support Line, and from participation in both organisations’ patient and carer forums, that a diagnosis of pancreatic cancer can lead to depression.[2] Simply increasing the treatment options available to patients can also help relieve some of the psychological impact of diagnosis by giving patients a new hope.

There are also many physical symptoms and side-effects associated with pancreatic cancer and treatment. For example, patients may experience symptoms related to diet (including Pancreatic Enzyme Insufficiency and diabetes); nausea and vomiting; changes to bowel habits; chronic fatigue; neuropathy; alopecia and pain.

[1] Pancreatic Cancer UK and Pancreatic Cancer Action, Abraxane Survey, 2014

[2] We recognise that depression can also be a symptom of pancreatic cancer. However our experience, and the point here, is that it can also be due to non-symptomatic reasons, especially the realisation of how few treatment options are available.

These symptoms and side-effects can have a significant impact on quality of life for both patients and carers. Patients and families often report that they find themselves unable to carry out simple day-to-day activities, with many patients and carers forced to give up work:

> *"I had to give up work to care for her, we all felt like a time bomb waiting to go off. I think we all felt like we were given a death sentence."* (Carer quote from 2014 survey)

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Pancreatic cancer is the fifth leading cause of cancer death in the UK[3] and has the worst survival outcomes of any of the 20 most common cancers, with a UK 5-year survival rate of less than 5%[4] (5.6% in England in 2014[5]) and a ten year survival of less than 1%[6]. Metastatic pancreatic cancer patients have a median survival of between just 2 – 6 months.[7]

Pancreatic cancer is not a rare cancer – around 9,600 cases were diagnosed in 2014[8] - and yet there are very few treatment options available. Surgery provides the only hope of a cure, and the best survival outcomes, and yet only around 10% of patients are eligible for surgery in the UK[9], largely because of late diagnosis of the disease.

This means that non-surgical treatments are of huge importance to the vast majority of pancreatic cancer patients. However, at the current time there are very few treatment options available.

Given those statistics, it is perhaps unsurprising that both Pancreatic Cancer UK and Pancreatic Cancer Action find from patient surveys, our forums and conversations with patients and carers, that extending overall survival is usually the number one, most desired treatment outcome.

Also of great importance is how a treatment can help manage or control side-effects of the disease itself.

A separate issue is how manageable the potential symptoms and side-effects from a treatment will be, and the impact these will have on quality of life, and this is also of significant consideration for patients.

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[3] CRUK The 20 Most Common Causes of Cancer Death: http://info.cancerresearchuk.org/cancerstats/mortality/cancerdeaths/
[4] https://www.nice.org.uk/guidance/ng12/evidence/full-guidance-74333341 (P66)
[5] ONS, Cancer Survival in England: Patients Diagnosed 2009–2014 and Followed up to 2015 www.ons.gov.uk
[6] CRUK, Cancer Statistics by Cancer Type, http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/pancreatic-cancer/survival#heading-Zero
[7] Spalding and Williamson (2007) Pancreatic Cancer, Medicine Vol 35, pp 325-329
[8] CRUK, Cancer Statistics by Cancer Type, http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/pancreatic-cancer/incidence#heading-Zero
[9] Ghaneh et al., (2008) Neoadjuvant and adjuvant strategies for pancreatic cancer EJSO 34 297-305

It is important to note that individual patients weigh these considerations slightly differently. That is why as patient representative organisations we constantly stress the need for patient choice and as wide a variety of treatment options for clinicians and patients as possible.

From our work with hundreds of patients and carers each year, we know that patients want to be the ones to make that choice about whether to have a potentially life-extending treatment, and weigh up the potential risks of experiencing significant side-effects.

Individual patients will tolerate side effects differently, both from a physical and psychological perspective but also based on their personal or family circumstances.

Both Pancreatic Cancer UK and Pancreatic Cancer Action firmly believe treatment decisions for metastatic pancreatic cancer should be about providing an informed choice for patients who, knowing the possible side effects of any given treatment, will then decide if they wish to undergo the treatment concerned.

In view of the limited number of treatments currently available for pancreatic cancer patients, it is vital that all effective treatment options are made available to patients on the NHS no matter where they live.

A 2017 survey[10] run by Pancreatic Cancer UK of 329 patients, carers and health practitioners found that only 5% of respondents **did not** believe Abraxane should be made available on the NHS. The most common reasons for supporting its inclusion were the increased survival and improved patient choice. Even patients for whom the treatment had proved unsuccessful supported its inclusion on the NHS, noting that the treatment had worked for others and arguing that the option should not be denied to patients.

These results echo findings of a 2014 joint survey run by Pancreatic Cancer UK and Pancreatic Cancer Action where only 1% of respondents said they would not want Abraxane to be made available to pancreatic cancer patients, based on reported side-effects[11]. Nineteen per cent said they were unsure, with the reason for their uncertainty being that they would want to assess the likely side effects with their families and doctors. However, even in those circumstances, respondents made it clear they felt that patients should have a choice and that the treatment should be made available on the NHS.

In our experience, we know that the majority of patients will, even when faced with potentially severe side effects, try the treatment if they are eligible. And should the side effects become intolerable, they will cease treatment or look for an alternative. The lack of treatment options currently available to pancreatic cancer patients means many are left feeling there is no choice for them:

> *"To have had another option which could potentially extend [my husband's] life would have given us hope. The utter despair when told there is nothing really on offer cannot be put into words." - Carer, 2014 survey*

> *"Poor availability. Poor choice. Feels like a lack of investment in this specific tumour site because of short survival rates which makes patients feel hugely undervalued." - Patient, 2017 survey*

[10] Pancreatic Cancer UK, Abraxane Survey 2017

[11] Pancreatic Cancer UK and Pancreatic Cancer Action, Abraxane Survey 2014

"The same treatment has been used for years! There is no improvement in survival rates and hearing that you or someone you love has pancreatic cancer is equal to hearing you've been given a death sentence. This has to change!" - Carer, 2017 survey

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Surgery followed by chemotherapy remains the only option for a cure. However, although it is estimated that whilst about 20% of patients diagnosed with the disease may be eligible for surgery, less than 10% go on to have it[12].

For those patients with metastatic pancreatic cancer, there are more limited options. Currently, the single agent gemcitabine, is the only treatment approved by NICE for patients with a Karnofsky performance score of >50. It is not approved by NICE as a second line therapy. Gemcitabine has proven to offer a modest survival benefit (median 7 months) as well as symptom control. However, currently only approximately 10% of patients will respond to gemcitabine chemotherapy[13].

An alternative is gemcitabine combined with capecitabine. This involves taking capecitabine in tablet form at home in addition to the administration of gemcitabine. Studies have shown that gemcitabine used in combination with capecitaine offers modest improved survival of 0.9 months compared to gemcitabine alone. However, gem-cap is not used that commonly in the UK. It is not recommended in any NICE guidance and is only used in a few centres. For this reason, we are concerned at its inclusion in the scope as a comparator.

Currently, oncologists' preferred first line treatment for pancreatic cancer is FOLFIRINOX, which is used off label. Evidence suggests that it provides the best overall survival outcome, around four extra months compared to gemcitabine alone, and a total of around 11 months on average[14]. However, this treatment is extremely toxic and only patients with a high performance status are eligible for this treatment.

Again, we do not feel FOLFIRINOX is an appropriate comparator for Abraxane, as it will always be the preferred option for patients fit enough to tolerate it. However, there is a significant group of patients who may not quite be fit enough to tolerate FOLFIRINOX but who would benefit from, and could tolerate a treatment option beyond gemcitabine. Based on the number of patients in England who received Abraxane when it was available on the Cancer Drugs Fund, we estimate that around 500 patients a year would benefit from having Abraxane as an additional treatment option. For this group of patients, Abraxane represents another treatment option that could extend survival where otherwise there would be none.

We strongly welcome the development of Abraxane, which robust trial data has shown offers a significant survival benefit of 2 months when used in combination with gemcitabine compared to gemcitabine alone, as well as a manageable safety profile. We hope that the NICE reappraisal will result in a positive recommendation for this

[12] Ghaneh et al., (2008) Neoadjuvant and adjuvant strategies for pancreatic cancer EJSO 34 297-305
[13] N Engl J Med. 2011 May 12;364(19):1817-25. doi: 10.1056/NEJMoa1011923.
[14] Ibid.

treatment, which patients in Scotland and Wales are already benefiting from access to.

What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

1. Increased survival
2. Additional treatment option
3. Hope/positive impact on mental health
4. Lower toxicity/less pronounced side effects than FOLFIRINOX / improved quality of life
5. Improved symptom control
6. Socialising/attending family events

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Increased survival

Trials have shown that Abraxane, used in combination with gemcitabine, increases survival by just over two months on average compared to treatment with gemcitabine alone (the standard chemotherapy treatment for metastatic pancreatic cancer patients), although in some cases patients do significantly better. It is also important

to note that trial data found one-year survival rates rose from 22% to 35% and two-year survival doubled from 5% to 10%.

Although an average survival gain of 2 months may seem modest, it is significant for a patient population with a median life expectancy of two to six months post diagnosis. It represents a substantial improvement in overall survival, which would make a huge difference to patients, their families and loved ones. Some patients do significantly better and we have heard stories of patients still alive one, two and three years since they first began treatment with Abraxane:

> *"I experienced a shrinking and stabilisation of my pancreatic tumour and the benefit of being here after 3 years of being diagnosed and being able to answer this questionnaire" – Patient, 2017 Abraxane Survey*

> *"He was told that he had little chance of survival, but that the NHS would not offer him Abraxane (…) On Abraxane 15 months later he is looking unbelievably well and is very much still alive." – Carer, 2017 Abraxane Survey*

> *"An additional 2 years of progression free survival, reduction in tumour size and pain. It is a life saver, literally" – Patient, 2017 Abraxane Survey*

> *"Given the advanced stage of his pancreatic cancer at diagnosis his life expectancy was very short, but with Abraxane he surprised us all surviving 15 months with the cancer actually shrinking." – Carer, 2017 Abraxane Survey*

Given the poor prognosis associated with pancreatic cancer, patients and carers are understandably keen for any new treatment which offers hope of more time to spend with their loved ones to be made available on the NHS. The value of this extra time to patients and carers is best explained in their own words:

> *"Two years increased lifespan so far. Ability for L to cope with her 2 year old child and home life as doing as much as possible with her daughter and husband whilst she is still alive" – Carer, 2017 Abraxane Survey*

> *"Adrian lived long beyond our expectations. Abraxane gave us hope at a time we never expected it and we feel so lucky to have had that extra time. It allowed him to get his affairs in order, we got married and he had time to prepare his children and those close to him for what was going to happen. Given the horrendous circumstances we felt lucky to have Abraxane." – Carer, 2017 Abraxane Survey*

"Time is precious and having more time with family means more than anything" - Patient, 2014 Survey

"I would give anything for two extra months with my wife and daughter" - Patient, 2014 Survey

"It would give me two more months to support my children at a critical stage in their lives" - Patient, 2014 Survey

"Two more months to any person with a terminal illness – is a long time, a bit of hope, precious" - Patient, 2014 Survey

''It is important to note a developing trend. …our support lines are being contacted more frequently by younger people being diagnosed with people in their late 30's to 50s, often people in prime of their professional career and with young families. Improvements in quality of life are important, as the more 'heavy duty' regimes often are being taken by those younger patients and side effects of treatment may impact quality of life. For these patients, when weighing up quality vs quantity of life, they will risk quality in the short term for any chance of increasing overall survival. The ability to increase their overall survival so that they are able to be involved in any memorable life event (such as births, marriages, holidays etc) is paramount for these patients.'' - Pancreatic Cancer Nurse Specialist

Additional treatment choice

As set out earlier, pancreatic cancer patients have extremely poor prognosis, with statistics showing no improvement in five-year survival rates over the past 40 years. Because diagnosis is often made so late, curative surgery is not an option for around 80% of patients. New treatments for metastatic patients are therefore particularly important.

At the present time, it appears to be that FOLFIRINOX is the most effective treatment for metastatic pancreatic cancer patients. However, as already discussed, because of its toxicity FOLFIRINOX treatment is limited to those with a very high performance status.

Because of less severe side-effects than the FOLFIRINOX regime, Abraxane potentially offers an additional treatment option for eligible patients with metastatic pancreatic cancer. In particular for those who are not quite fit enough to tolerate Folfirinox.

Patients who have experienced both regimes have told us that the Abraxane regime is easier to cope with.

Patients who responded to both our 2014 and 2017 surveys saying they had received both Abraxane and FOLFIRINOX said.

''Have had both regimes privately. Overall Abraxane has been easier.'' - Patient, 2014 Survey

''I am receiving gemcitabine & Abraxane and am finding that the side effects are far less debilitating than I expected.'' – Patient, 2014 Survey

> *"It felt physically easier on my body. Not so sick or tired."* - Patient, 2017 Survey

As previously eluded to, we have heard from many patients, carers and clinicians concerned at the lack of treatment options available to pancreatic cancer patients on the NHS in England:

> *"Pathetic range. The stats speak for themselves...9% 5-year survival in USA, 5% 5-year survival in U.K." - Patient on availability of treatments on the NHS, 2017 Survey*

> *"We are incredibly lucky that her health provider will allow her to have Abraxane otherwise we would now not have any options. We as a family are now trying to make the most of the time Abraxane is giving us." – Carer, 2017 Abraxane Survey*

> *"Not good at all. If she had stayed within the NHS she wouldn't have received FOLFIRINOX nor Abraxane and she wouldn't be alive now." – Carer on availability of treatments on the NHS, 2017 Abraxane Survey*

> *"There is a very poor choice of treatment available now, I believe that FOLFIRINOX is the only other recognised treatment for pancreatic cancer which I believe is even more toxic than the Gemcitabine/Abraxane regime" – Patient, 2017 Abraxane Survey*

> *"There are only two options neither of which address my needs" – Patient, Abraxane Survey 2017*

The 2017 survey also exposed frustration over unequal access to the treatment within the UK. Many respondents expressed anger at a "postcode lottery" when it comes to treatment options for pancreatic cancer, noting that the drug is available to patients in Wales and Scotland, but not England and Wales:

> *"We live in the United Kingdom. It is unfair for Abraxane to be available to patients in Scotland and Wales, and not in England." – Carer, 2017 Abraxane survey*

> *"I had researched this combination when my husband was undergoing chemo. He would have tried anything regardless of the side effects. We were frustrated that it was available if we had lived in Scotland but not to him as he lived in the U.K. This is unfair!" – Carer, 2017 Abraxane survey*

> *"It is so utterly unfair that patients in England don't have access. The time we will get with my mum is so precious." – Carer, 2017 Abraxane Survey*

Quality of life

Abraxane can offer patients a better quality of life in terms of coping with chemotherapy side-effects when compared to the possibly more effective but also more toxic FOLFIRINOX. This has enabled patients to stay well enough to enjoy social events, continue working and carry out everyday activities:

> *''Gemcitabine and Abraxane was much easier to tolerate than Folfirinox, gemcitabine alone easier still (although weekly Flu Like Symptoms and fever are typical).''* - Patient, 2014 Survey

> *"There can be no doubt in my mind that Abraxane has provided me with an extension of life beyond that originally envisaged and I have been able to retain a good quality of life whilst the treatment has been delivered." – Patient, 2017 Abraxane Survey*

> *"My brother worked full time for a year." – Carer, 2017 Abraxane Survey*

> *"Abraxane has given me an extension to my life whilst retaining a decent quality in my life." – Patient, 2017 Survey*

The way treatment is administered is slightly easier for Abraxane plus gemcitabine when compared with either the FOLFIRINOX or gemcitabine/capecitabine treatments. In the former case, there is no need for infusion at home for 48 hours after treatment in hospital, nor for nurses and carers to then remove the chemotherapy pump whilst at home. In the latter case, there is no additional oral treatment.

> *''Abraxane gemcitibine combo much easier to tolerate. No picc line, faster recovery and treatment time.''* – Patient, 2014 Survey

Mental health/hope:

As already discussed, there are very few treatment options for metastatic pancreatic cancer patients. A new option therefore represents new hope for these patients. The positive impact simply knowing another treatment option is available on both patients and carers is significant:

> *''The ability to be offered alternative treatments/having an additional option can have a huge psychological impact for patients that there are other choices available when a prior treatment regime has had limited response.''* – Pancreatic Cancer Nurse Specialist

Socialising/family events:

The potential for patients to live for a little longer and make important milestone family events cannot be overstated. Again, because pancreatic cancer median survival times are so short, even an additional two months can make all the difference:

> *"He lived to get married and see his son born (…) Without this treatment he would not have seen his son born or reach his 1st birthday. We only got the treatment due to BUPA insurance." – Carer, 2017 Abraxane Survey*

> *"The treatment has been such that I have retained a very reasonable quality of life. Apart from having to rest in the afternoons while treatment was ongoing, I have been able to garden, mow the lawn and attend social events. I was given a gap in treatment to cover my daughter's wedding and this treatment is ongoing." – Patient, 2017 Abraxane Survey*

Better symptom and pain control:

There is emerging, anecdotal evidence that where Abraxane has been used in conjunction with gemcitabine it can improve symptom control. This includes better pain management. It is worth quoting in full this observation from a palliative care consultant on the effect of Abraxane on his patient:

> *''I am a consultant in palliative medicine with 30 years' experience in the field. I am currently caring for a 50 year old gentleman with metastatic pancreatic carcinoma and I am writing to give some anecdotal evidence regarding his current chemotherapeutic regimen of gemcitabine/Abraxane. I am well aware that the trials of this regimen in pancreatic carcinoma failed to include meaningful quality of life measures and that anecdotal evidence may be of some help in its assessment for NHS use.*
>
> *My patient struggled badly with FOLFIRINOX with peripheral neuropathy and a very poor quality of life. During this period, he required hospice admission for several weeks to try and control subacute intestinal obstruction due to peritoneal disease. He was managed with TPN but vomited on a daily basis. Since he was converted to gemcitabine/Abraxane, his intestinal obstruction has settled to such an extent that he can now eat normally and he was able to be discharged from in-patient care. He is not vomiting and his overall quality of life has improved remarkably. He is tolerating the regimen well.*
>
> *In my years of treating patients with pancreatic cancer, I have seldom seen such an improvement in symptom control and general well-being in the presence of advanced disease.''* - Statement from Palliative Care Consultant.

> *"The pain level has gone down tremendously so we believe the treatment must be reducing the size of the tumour therefore relieving its pressure on the nerves." – Carer, 2017 Abraxane Survey*

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

The vast majority of patients and carers we have heard from have reported either an improvement in survival, an improvement in quality of life, or that they have managed to maintain a good quality of life despite the treatments side effects:

> *"Abraxane appears to make my mum more tired than her previous chemo and nauseous, but she is active and we enjoy time as a family." – Carer, Abraxane Survey 2017*

Of those patients and family members/friends of patients who have been treated with Abraxane only 5% reported that the treatment was both hard to cope with and did not help[15]. Nonetheless, it is important to note this difference in opinion regarding the potential benefits of Abraxane.

[15] Pancreatic Cancer UK, Abraxane Survey 2017

Overwhelmingly, the evidence we have received from patients, carers and clinicians alike emphasises the importance of patients being able to make an informed choice about whether a treatment option is suitable for them. It is telling that no patients who have been treated with Abraxane said they did not believe the treatment should be made available on the NHS. Even patients for whom the treatment did not work recognised the importance of others having that choice:

> *"Just because it didn't work for me if it helps others they should have that option." – Patient, Abraxane Survey 2017*

4. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Side effects

The side effects of a drug is one of the most significant considerations for both patients and carers when deciding whether to undergo treatment. Although our research has found that most patients and carers will opt for a treatment despite the associated side effects if it means more time to spend with their loved ones, it is also important to them that they are able to enjoy a good quality of life.

FOLFIRINOX is currently the preferred first-line treatment for pancreatic cancer, but is only available to patients with a high performance status due to the toxicity of the drug. The potentially severe side effects associated with the treatment is an important consideration for patients and carers.

Lack of choice

Patients and carers have voiced real concern over the lack of effective treatment options currently available to pancreatic cancer patients on the NHS. Asked by the

2017 Abraxane Survey what they thought of the range of treatment options available to pancreatic cancer patients on the NHS, the most common response from both patients and carers was “poor”.

The lack of effective treatment options has led to many reporting that they feel helpless, without hope, undervalued and as if they have been handed a death sentence. The impact of this on patients and carers’ mental health can be profound and have a significant negative impact on their quality of life.

Please list any concerns patients or carers have about the treatment being appraised.

Side effects

Side effects associated with Abraxane include fatigue, anaemia, shortness of breath, loss of appetite, diarrhoea, nausea and vomiting, sore mouth, joint and muscle pain, peripheral neuropathy (although this is reversible) and hair loss.

It is clear that the number and severity of side-effects are greater than those associated with patients using gemcitabine alone, which is the standard chemotherapy treatment, and the alternative gemcitabine/capecitabine combination.

However, evidence from clinical trials indicates that Abraxane is easier to tolerate than the FOLFIRINOX regime, with less severe or intense side-effects. This is backed up by our survey respondents who have had experience of both Abraxane and FOLFIRINOX treatments (see Section 3, pg. 12).

We find that patients are willing to accept some side effects as long as they are not completely debilitating and enable them to enjoy a reasonable quality of life. Despite finding them hard to cope with, patients appear willing to accept side effects such as fatigue, sickness, hair loss and neuropathy, but will end treatment when the side effects become too frequent and severe:

> *“Most of the side effects have remained consistent through the treatment. I have been hospitalised due high temps and generally felling unwell a few times. These have only ever been 1 or 2 night stays and treated with antibiotics.” – Patient, Abraxane Survey 2017*

> *“I found this treatment to be a bit tough at times, but feel it is saving my life without taking away too much quality.” – Patient, Abraxane Survey 2017*

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Individual patients will have different levels of tolerability, both from a physical and psychological perspective but also based on their personal or family circumstances.

Both Pancreatic Cancer Action and Pancreatic Cancer UK firmly believe treatment decisions for metastatic pancreatic cancer should be about providing an informed choice for patients who, knowing the possible side effects of any given treatment, will then decide if they wish to undergo the treatment concerned.

In view of the limited number of treatments available, it is vital that all treatment options should be made available to patients on the NHS.

In our experience, we know that the majority of patients will, even when faced with potentially severe side effects, try the treatment. And should the side effects become intolerable, they will cease treatment or look for an alternative.

5. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Clinical trials showed that all eligible patients can expect to benefit from Abraxane in terms of a mean survival advantage of 2.4 months compared to gemcitabine alone. We are aware from the MPACT clinical trial that a minority of patients responded better than others, where life was extended between one and two years.

As the average life expectancy for a pancreatic cancer patient is a mere 6 months, 2 more months represents a substantial relative survival gain for patients. We hope this will be taken into account when the NICE committee assesses the benefit of the drug and that the committee will consider allowing the drug to be appraised using its end of life criteria, even though it is less than the ‘’3 month life extension’’ suggested within the end of life guideline.

Likewise we would not want Abraxane restricted to patients with performance status of 0-1, mirroring the restriction previously imposed by the Cancer Drugs Fund. The MPACT trial on Abraxane included 8% patients with a Karnofsky score of 70 – 100, corresponding to a PS of 2. Whilst we recognise not all patients with a PS of 2 will be eligible for treatment, there are clearly some who can both tolerate and benefit from Abraxane. Their clinicians are in the best position to decide, along with the patient, whether to proceed, using their expertise to regulate the dose if required. Ultimately, we would not want patients to be denied the choice.

The treatment may prove especially beneficial to patients with a high performance status but who are not considered fit enough to tolerate treatment with FOLFIRINOX. For these patients, Abraxane represents an additional treatment option and hope where otherwise there would be none.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

We believe that all pancreatic cancer patients could benefit from access to Abraxane. Although FOLFIRINOX will be the preferred treatment for patients fit enough to tolerate it, it is important that all eligible pancreatic cancer patients have the additional option of treatment with Abraxane and are able to make an informed choice.

6. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Patients who have used Abraxane through private healthcare, the CDF or the NHS in Scotland and Wales have experienced similar side effects as those reported in the clinical trials.

The most common side effects reported through conversations with patients, the support line, forum and surveys have included peripheral neuropathy, fatigue, nausea, hair loss, diarrhoea, neutropenia and leukopenia. This correlates with the findings of the MPACT study.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

The clinical trial data effectively reports on survival outcomes and the side effects of using Abraxane, both issues we know to be of importance to patients. However, it does not adequately capture the impact the treatment can have on the quality of life of patients, their friends and families.

The value of additional time to spend with loved ones is not adequately demonstrated through the trial data. This can only be truly communicated through patient accounts of their experiences, as relayed to both Pancreatic Cancer UK and Pancreatic Cancer Action through our conversations with patients and surveys.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Abraxane is already available on the NHS in Wales and Scotland. It is also available to private patients in England and Northern Ireland. We are unaware of any additional side effects that have emerged through real world use.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

Yes

If yes, please provide references to the relevant studies.

Both Pancreatic Cancer UK and Pancreatic Cancer Action have conducted numerous online surveys collecting patient and carer views on their experiences of pancreatic cancer, treatment and treatment outcomes.

We know from these surveys that patients and carers hugely value treatments that can extend overall survival. As previously mentioned, the value patients and carers attach to improved survival is highlighted by responses to **surveys run in 2014[16] and 2017[17]**. Both surveys found that the vast majority of respondents would support the availability of Abraxane on the NHS due to the extra two month survival gain the drug offers eligible patients.

We often hear a great deal of frustration from patients and carers that survival rates for pancreatic cancer have not been improving at the same rate as those for other cancer types. Some patients and carers have also reported feeling that there is a nihilistic attitude towards pancreatic cancer treatment, due to so few treatments being available and the limited efficacy of those that are.

Pancreatic Cancer UK's 2011 Study for Survival[18], which drew on the experiences and views of over 1,000 people affected by pancreatic cancer and healthcare professionals, discovered many people were concerned patients are not always offered the full range of treatment options because of "nihilistic" clinician attitudes.

Nihilism extends to attitudes towards the likelihood of new effective treatments being made available on the NHS, reflected by responses to **Pancreatic Cancer UK's PCUK250 survey**[19]. The survey saw a panel of 250 patients, carers, clinicians, nurses and others who directly treat the disease or work in the wider health or cancer arena, answer questions on recent developments in pancreatic cancer.

One of the key findings to emerge from the survey was that, whilst 47% of panel members thought it likely new, tolerable, effective chemotherapy drugs would be licensed for use in the UK in the next five years, only 23% thought they would also be made available to patients on the NHS.

We heard concerns from patients that, although new treatments for pancreatic cancer are available, they are not being funded. Nihilism over new treatment prospects also seems to have been fuelled by the recent removal of Abraxane from the Cancer Drugs Fund:

> *"New treatments which improve survival outcome like Abraxane (nab-paclitaxel) have been removed from CDF and NICE, so effectively treatment outcomes and choices are going backwards."* (Survey respondent, PCUK250 report)

Through our case studies[20], patients and carers discuss the impact pancreatic cancer has had on their lives. They powerfully tell how scary a diagnosis of pancreatic

[16] Pancreatic Cancer UK and Pancreatic Cancer Action, Abraxane Survey 2014
[17] Pancreatic Cancer UK, Abraxane Survey 2017
[18] Pancreatic Cancer UK, Study for Survival, 2011
http://www.pancreaticcancer.org.uk/media/86664/study-for-surivial-report-final.pdf
[19] Pancreatic Cancer UK, The PCUK 250 Expert Panel: Tracking trends in pancreatic cancer, 2016
http://www.pancreaticcancer.org.uk/media/697010/pcuk-250-report.pdf
[20] pancreaticcanceruk.org.uk/informationandsupport/real-life-stories pancreaticcanceraction.org/about-pancreatic-cancer/cancer-stories/

cancer can be when you are faced with such appalling survival statistics and so few treatment options. They also look at patients' experiences of treatment, including different chemotherapy regimens, and of living with the condition.

The Pancreatic Cancer UK Discussion Forum[21] also gives patients and carers the opportunity to share their stories. It includes pages dedicated to the patient experience, treatments and side-effects and families, friends and carers.

The **APPG on Pancreatic Cancer's 2013 inquiry** raised particular concern over the lack of treatment options available to pancreatic cancer patients. The report, "Time to Change the Story: A plan of action for pancreatic cancer[22]" argues that "it is hard not to be struck by the lack of treatments that are available to pancreatic cancer patients". It goes on to conclude that "given the lack of options for curative treatment or for extending life, it is essential that any new treatments shown to be effective are made available to patients as quickly as possible".

Pancreatic Cancer Action has also carried out a patient and carer survey which explores attitudes and experience of diagnosis, care and the availability of treatments[23].

7. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

N/A

[21] http://forum.pancreaticcancer.org.uk/index.php
[22] APPG on Pancreatic Cancer, Time to Change the Story: A plan of action for pancreatic cancer, 2013 http://www.pancanappg.org.uk/wp-content/uploads/2014/10/2013-Inquiry-report.pdf
[23] Pancreatic Cancer Action Patient and Carer Survey 2015, https://pancreaticcanceraction.org/about-pancreatic-cancer/patient-experience-survey/

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

N/A

8. Other issues

Do you consider the treatment to be innovative?

Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

Pancreatic Cancer UK and Pancreatic Cancer Action believe Abraxane meets NICE's innovation criteria as it addresses a clear unmet need and has been shown to be clinically effective.

Not only does Abraxane represent an additional treatment option for a disease where survival has hardly improved in the last 40 years, it offers patients with a high performance status but who are not quite fit enough for treatment with FOLFIRINOX a treatment option beyond the less effective gemcitabine.

Moreover, the peripheral neuropathy associated with Abraxane has been shown to be reversible, unlike with other chemotherapy treatments for pancreatic cancer.

Are there any other issues that you would like the Appraisal Committee to consider?

Due to this unmet need and the extremely poor survival rates associated with pancreatic cancer, we strongly feel that Abraxane should be considered under end of life criteria.

Although the drug does not meet the '3 month' threshold for end of life rules, the significant relative survival gain it offers should be taken into account. We hope that the TA Committee will use its discretion when it comes to applying the 3 month threshold and the end of life criteria.

9. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

Pancreatic Cancer UK and Pancreatic Cancer Action strongly support the approval of Abraxane in combination with gemcitabine for routine use on the NHS in England. We believe it offers an important and tangible improvement in treatment for metastatic pancreatic cancer patients, potentially leading to:

- **Increased survival time for patients**: The median additional survival time of just over two months may not seem much. However, even a small amount of extra time will make a huge difference to patients, their families and loved ones, especially when taking into account the extremely poor median survival time from diagnosis of just 2-6 months. Given this relatively short prognosis,

an extra two months is a significant relative survival gain. Moreover, for a number of patients the additional survival time will be much longer than two months.

- **An additional treatment option** for a disease that has an extremely poor prognostic outcome and limited number of treatments. **There is a clear unmet need for pancreatic cance**r. Only 5% of patients survive five years or more. UK survival rates lag behind those of the rest of Europe and indeed the rest of the world. Survival rates have barely changed for the last 40 years. It is therefore essential that new effective treatments are made available to pancreatic cancer patients for the kind of improvements in survival we need to be achieved. Clinicians need more weapons in their arsenal and patients want to know that there are more treatment options open to them.
- **More patients could potentially benefit from Abraxane** as the current best treatment is only available to a small proportion of very fit patients with a high performance status.
- **Improved quality of life for patients:** in addition to being more tolerable than the current best available treatment, Abraxane can offer better symptom and pain control, leading to more quality time for the patient to spend with family and friends. It is also easier to administer than other alternatives, potentially freeing up carer or nurse time. Finally, it is important to note that the peripheral neuropathy from Abraxane is reversible, unlike with other treatments.
- **An end to the current inequitable situation**, where patients in Wales and Scotland and those with access to private healthcare are already benefitting from access to Abraxane.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: NCRI-ACP-RCP-RCR

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

There are three international established first line treatments for metastatic pancreatic cancer that in trials have been shown to provide survival benefit. These are gemcitabine, gemcitabine plus *nab*-paclitaxel (available as standard in Scotland and Wales, not currently available in England and Northern Ireland) and FOLFIRINOX. In phase III trials, patients treated with gemcitabine have an approximate median overall survival of 5-6 months, those receiving FOLFIRINOX (PRODIGE trial) 11 months, and gemcitabine + *nab*-paclitaxel (MPACT trial) 8.5 months.

In appropriately selected patients Gemcitabine + *nab*-paclitaxel is recommended as a first line treatment for metastatic pancreatic cancer by the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline (2016), the United States National Comprehensive Cancer Network Guideline (2017) and the European Society for Medical Oncology (ESMO) 2015 guideline.

The practice in England is fairly standard. In fitter (ECOG performance status 1 or better) and younger patients (generally under 70) the practice is to use FOLFIRINOX. Few, if any, UK clinicians use the classical FOLFIRINOX protocol as used in the pivotal phase III PRODIGE trial of gemcitabine versus FOLFIRINOX. In this trial, only patients with a WHO performance status of 1 or better were included. Almost all clinicians use modifications where doses of the FOLFIRINOX regimen components are either omitted or reduced. This is because the classical regimen is associated with excess toxicity. The

significant issue with the various modifications of FOLFIRINOX is that they have not been tested for efficacy in trials. Hence effects on survival and quality of life in comparison to gemcitabine are not defined.

A large proportion of patients with metastatic pancreatic cancer have either an impaired performance status (2 or more) and/or are older. These patients are rarely fit enough to tolerate even a modified FOLFIRINOX regimen.

There are therefore significant numbers of patients with metastatic pancreatic cancer who are either older or with impaired performance status who only receive gemcitabine monotherapy. However, many would be fit enough to tolerate gemcitabine + *nab*-paclitaxel. In subsequent analyses of the MPACT trial population, patients with worse performance status in particular benefited from gemcitabine + *nab*-paclitaxel. In addition there were significant toxicities in the MPACT trial necessitating dose reduction in 41% of patients. Of note, an exploratory post-hoc analysis of MPACT showed median survival in patients who received a dose reduction was longer than those who did not. These data suggest that for many older or frailer patients it is perfectly feasible to administer gemcitabine + *nab*-paclitaxel and if dose reductions are required, treatment efficacy is not compromised.

There is variation in administration of chemotherapy regimens for metastatic pancreatic cancer, not generally between regions, but between peripheral chemotherapy units and cancer centres. In peripheral chemotherapy units, there are barriers to receiving FOLFIRINOX. It is usually not administered, given its complexity and toxicity. Patients therefore either have to travel to a specialist centre to receive FOLFIRINOX or receive single agent gemcitabine. Administration of gemcitabine + *nab*-paclitaxel is very feasible in peripheral units. There are a small number of clinicians who use gemcitabine + capecitabine which is feasible to administer in peripheral chemotherapy units, but this is viewed as anomalous practice given the lack of survival benefit reported in comparison to gemcitabine alone.

In summary the expert reference groups represented here have the following views:

1. **The practice in England and Northern Ireland is different from Scotland and Wales where gemcitabine + *nab*-paclitaxel is a standard treatment.**
2. **It is also at variance with practice guidelines from Europe (ESMO 2015 guideline) and the USA (NCCN 2017 and ASCO 2016 guidelines).**
3. **Of the substantial population of patients either older or with a performance status below 1 who currently tend to receive gemcitabine alone as they are not suitable to receive FOLFIRINOX, a significant proportion would benefit and be able to receive gemcitabine + *nab*-paclitaxel.**
4. **There is no trial evidence to support the use of modified FOLFIRINOX regimens in comparison to gemcitabine, or as a substitute for gemcitabine**

+ *nab*-paclitaxel, whereas there is phase 3 trial data to support gemcitabine + *nab*-paclitaxel in comparison to gemcitabine.

5. **Gemcitabine + *nab*-paclitaxel use would relieve the barrier to treatment beyond single agent gemcitabine in peripheral chemotherapy units.**

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology

appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

We do not anticipate there being any issues in delivering this technology.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

No issues

Name: [redacted]

Name of organisation:

- **National Cancer Research Institute Clinical Studies Pancreatic Tumour Subgroup**
- **Barts Health NHS Trust.**

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **Yes**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
  Yes I am an expert witness representing:
  - **National Cancer Research Institute Clinical Studies Pancreatic Tumour Subgroup (member)**
  - **Royal College of Physicians (fellow)**
  - **Association of Cancer Physicians (member)**
  - **Royal College of Radiologists (designated representative)**
  - **Barts Health NHS Trust/Barts Cancer Institute (Consultant Medical Oncologist/Senior Lecturer)**

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: **None**

What is the expected place of the technology in current practice?

There are three international established first line treatments for metastatic pancreatic cancer that in trials have been shown to provide survival benefit. These are gemcitabine, gemcitabine plus nab-paclitaxel (available as standard in Scotland and Wales, not currently available in England and Northern Ireland) and FOLFIRINOX. In phase III trials, patients treated with gemcitabine have an approximate median overall survival of 5-6 months, those receiving FOLFIRINOX (PRODIGE trial) 11 months, and gemcitabine + nab-paclitaxel (MPACT trial) 8.5 months.

In appropriately selected patients Gemcitabine + nab-paclitaxel is recommended as a first line treatment for metastatic pancreatic cancer by the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline (2016), the United States National Comprehensive Cancer Network Guideline (2017) and the European Society for Medical Oncology (ESMO) 2015 guideline.

The practice in England is standard. In fitter (ECOG performance status 1 or better) and younger patients (generally under 70) the practice is to use FOLFIRINOX. Few, if any, UK clinicians use the classical FOLFIRINOX protocol as used in the pivotal phase III PRODIGE trial of gemcitabine versus FOLFIRINOX. In this trial, only patients with a WHO performance status of 1 or better were included. Almost all clinicians use modifications where doses of the FOLFIRINOX regimen components are either omitted or reduced. This is because the classical regimen is associated with excess toxicity. The significant issue with the various modifications of FOLFIRINOX is that they have not been tested for efficacy in trials. Hence effects on survival and quality of life in comparison to gemcitabine are not defined.

A large proportion of patients with metastatic pancreatic cancer have either an impaired performance status and/or are older. These patients are rarely fit enough to tolerate even a modified FOLFIRINOX regimen.

There are therefore significant numbers of patients with metastatic pancreatic cancer who are either older or with impaired performance status who only receive gemcitabine monotherapy. However, many would be fit enough to tolerate gemcitabine + nab-paclitaxel. In subsequent analyses of the MPACT trial population, patients with worse performance status in particular benefited from gemcitabine + nab-paclitaxel. In addition there were significant toxicities in the MPACT trial necessitating dose reduction in 41% of patients. Of note, an exploratory post-hoc analysis of MPACT showed median survival in patients who received a dose reduction was longer than those who did not. These data suggest that for many older or frailer patients it is perfectly feasible to administer gemcitabine + nab-paclitaxel and if dose reductions are required, treatment efficacy is not compromised.

There is variation in administration of chemotherapy regimens for metastatic pancreatic cancer, not generally between regions, but between peripheral chemotherapy units and cancer centres. In peripheral chemotherapy units, there are barriers to receiving FOLFIRINOX. It is usually not administered, given its complexity and toxicity. Patients therefore either have to travel to a specialist centre to receive FOLFIRINOX or receive single agent gemcitabine. Administration of gemcitabine + nab-paclitaxel is very feasible in peripheral units. There are a small number of clinicians who use gemcitabine + capecitabine which is feasible to administer in peripheral chemotherapy units, but this is viewed as anomalous practice given the lack of survival benefit reported in comparison to gemcitabine alone.

In summary the expert reference groups represented here have the following views:

1. The practice in England and Northern Ireland is different from Scotland and Wales where gemcitabine + *nab*-paclitaxel is a standard treatment.
2. It is also at variance with practice guidelines from Europe (ESMO 2015 guideline) and the USA (NCCN 2017 and ASCO 2016 guidelines).
3. Of the substantial population of patients either older or with an impaired performance status who currently tend to receive gemcitabine alone as they are not suitable to receive FOLFIRINOX, a significant proportion would benefit and be able to receive gemcitabine + *nab*-paclitaxel.
4. There is no trial evidence to support the use of modified FOLFIRINOX regimens in comparison to gemcitabine, or as a substitute for gemcitabine + *nab*-paclitaxel, whereas there is phase 3 trial data to support gemcitabine + *nab*-paclitaxel in comparison to gemcitabine.
5. Gemcitabine + *nab*-paclitaxel use would relieve the barrier to treatment beyond single agent gemcitabine in peripheral chemotherapy units.

Equality and Diversity

No issues.

Implementation issues

We do not anticipate there being any issues in delivering this technology**.**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your named [redacted]

Name of your organisation
Royal Marsden NHS Foundation Trust

Are you (tick all that apply):

- √a specialist in the treatment of people with the condition for which NICE is considering this technology?
- A specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- An employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- Other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Metastatic pancreatic cancer is still associated with very poor survival; median survival even with chemotherapy can be 6 months. Treatment options in this setting are limited. Those patients of good performance status and usually aged 75 or below with minimal co-morbidities receive triplet chemotherapy with FOLFIRINOX and this is associated with the best survival. Compared to other regimens
However a significant proportion of patients are not suitable for the triplet regimen, based on age, performance status and other factors.
Therefore for the majority of patients single agent gemcitabine is the alternative comprising of monotherapy and limited efficacy, (much shorter survival) compared to the triplet.
On the whole considering the whole of UK this would be given for those patients not suitable for triplet chemotherapy.
Gem / nab paclitaxel is a doublet chemotherapy option that can be given to some patients not suitable for triplet FOLFIRINOX, has greater efficacy and survival than gemcitabine monotherapy.
There are no major geographical differences across the UK in treating this disease and the regimens above are largely employed by oncologists in similar proportions allowing for slight variations in patient demographics regionally.

Gemcitabine monotherapy the alternative to Gem/Nab paclitaxel has lower response arte and overall survival than Gem /nab paclitaxel.
The increase ion survival with gem/nab paclitaxel is clinically relevant for advanced pancreatic cancer where the survival and landscape is poor.
However Gem monotherapy has a lower rate of grade 3/ 4 toxicity than Gem Nab Paclitaxel.
Nevertheless the toxicity experienced with gem/nab paclitaxel is manageable and there are clear guidelines for dose modifications and reduction and delays.
I found as did other oncologists that if these are carefully adhered to the toxicity does not negatively impact on quality of life for patients.
There still remains a group suitable for Gem monotherapy not suitable for doublet or triplet chemotherapy.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
No relevant subgroup population

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional

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professional input (for example, community care, specialist nursing, other healthcare professionals)?
Specialist hospital day unit administration
If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
Not available

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.
ESMO clinical guidelines
Cancer of the pancreas: ESMO Clinical Practice
Guidelines for diagnosis, treatment and follow-up†
M. Ducreux1,2, A. Sa. Cuhna2,3, C. Caramella4, A. Hollebecque1,5, P. Burtin1, D. Goéré6 T. Seufferlein7, K. Haustermans8, J. L. Van Laethem9, T. Conroy10 & D. Arnold11, on behalf of the ESMO Guidelines Committee*
Annals of Oncology 26 (Supplement 5): v56–v68, 2015 doi:10.1093/annonc/mdv295
Consensus statement produced by treating oncologists in this field (after reviewing all relevant literature of randomised trials) that states that Gem/ nab paclitaxel should be a treatment option for patients in this disease.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

As stated it provides treatment where there is a gap currently in this disease where some patients will only receive gemcitabine monotherapy and are not suitable for FOLFIRINOX .These patients would benefit form a doublet option.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.
No additional testing needed.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the

trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?
Important outcomes overall survival, response rate and toxicity measured in the trails.
Quality of life data extremely relevant and now available via SIEGE trial.
This is important as these patients have limited life expectancy.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The adverse effects are as expected in the trial ,
Neuropathy can be difficult but does appear to be reversible in some patients.
Myelosupression is seen in practice but can be managed by following the guidelines.
No adverse effects that were not in clinical trials providing the clinician follows the guidelines provided for dose modifications and delays.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed; No

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- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within

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3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No extra training as the staff used this under cancer drugs fund.
Increased chemotherapy day unit hours as treatment longer than gem monotherapy but not significantly.

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Single Technology Appraisal (STA)

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

Please sign and return to via NICE Docs/Appraisals

I confirm that:

- I agree with the content of the statement submitted by Pancreatic Cancer UK and consequently I will not be submitting a personal statement.

Name: ..[redacted].....

Signed: [redacted].....

Date: ....13/6/2017.....

ID1058 STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 14/90/01

Completed 5th June 2017

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

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Date completed: 5th June 2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 14/90/01

Declared competing interests of the authors: Dan Palmer has received consultancy fees from Celgene.

Acknowledgements: The authors would like to thank Dr Pauline Leonard, Consultant Medical Oncologist from The Whittington Hospital NHS Trust, who provided feedback on a final draft version of the report. Dr Leonard has no competing interests to declare.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Greenhalgh J, Bagust A, Stainthorpe A, Richardson M, Boland A, Beale S, Duarte R, Kotas E, Banks L, Palmer D. Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]: A Single Technology Appraisal. LRiG, University of Liverpool, 2017

Contributions of authors:

Janette Greenhalgh	Critical appraisal of the clinical evidence
Adrian Bagust	Critical appraisal of the economic evidence/model
Angela Stainthorpe	Critical appraisal of the economic evidence/model
Marty Richardson	Critical appraisal of the statistical evidence
Angela Boland	Ongoing source of methodological advice
Sophie Beale	Ongoing source of methodological advice
Rui Duarte	Critical appraisal of the adverse event evidence
Eleanor Kotas	Cross checking of the submission search strategies
Lindsay Banks	Critical appraisal of the company submission
Dan Palmer	Clinical advice and critical appraisal of the clinical sections of the company submission

All authors read and commented on draft versions of this report.

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LIST OF ABBREVIATIONS

5-FU	fluorouracil
AE	adverse event
AIC	Akaike information criterion
APC	advanced pancreatic cancer
ASCO	American Society of Clinical Oncology
BIC	Bayesian information criterion
BSA	body surface area
CA046 (MPACT)	Metastatic Pancreatic Adenocarcinoma Clinical Trial
CDF	Cancer Drugs Fund
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
Crl	credible interval
CRUK	Cancer Research UK
CS	company submission
CSR	clinical study report
DCR	disease control rate
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
EORTC	European Organisation for the Treatment of Cancer
EORTC QLQ-C30	European Organisation for the Treatment of Cancer quality of life questionnaire C30
EPAR	European Public Assessment Report
EQ-5D-5L	European quality of life-5 dimensions-5 levels questionnaire
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FAD	final appraisal determination
FOLFIRINOX	oxaliplatin, plus irinotecan, plus calcium folinate plus fluorouracil
Gem	gemcitabine
Gem+Cap	gemcitabine plus capecitabine
GHS	global health status
H-H	cumulative hazard versus cumulative hazard
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
ICER	incremental cost effectiveness ratio
ITT	intention-to-treat
IV	intravenous
IVRS	interactive voice recognition system
K-M	Kaplan-Meier
KPS	Karnofsky performance status
LCH	log-cumulative hazard
LCHP	log cumulative hazard plots
LY	life year
LYG	life years gained
MIMS	Monthly Index of Medical Specialities
Nab-Pac	nab-paclitaxel
Nab-Pac+Gem	nab-paclitaxel plus gemcitabine
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NR	not reported

NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PAS	patient access scheme
PD	progressive disease
PFS	progression-free survival
PH	proportional hazards
PS	performance status
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q	Quarter
Q-Q	quantile-quantile
QALY	quality adjusted life year
RCT	randomised controlled trial
RECIST	response evauation criteria in solid tumours
RR	relative risk
RRR	relative risk ratio
SA1	sensitivity analysis 1
SA2	sensitivity analysis 2
SA3	sensitivity analysis 3
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	summary of product characteristics
SPARC	secreted protein acid and rich in cysteine
STA	single technology appraisal
TOT	time on treatment
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
TTP	time to progression
ULN	upper limit of normal
WTP	willingness to pay

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the Single Technology Appraisal (STA) process. Clinical evidence and economic evidence have been submitted to NICE by Celgene Limited in support of the use of paclitaxel as albumin-bound nanoparticles (Abraxane®) with gemcitabine (Gem) for untreated metastatic adenocarcinoma of the pancreas. In this report, the formulation of paclitaxel as albumin-bound nanoparticles is referred to as Nab-Pac and the combination treatment is referred to as Nab-Pac+Gem.

Nab-Pac monotherapy is licensed in Europe as a second-line treatment for metastatic breast cancer and, in combination with carboplatin, for the first-line treatment of non-small cell lung cancer (NSCLC) in people whose disease is unsuitable for surgery or radiotherapy. On 2nd December 2013, the European Medicines Agency (EMA) approved an extension to the existing marketing authorisation allowing the use of Nab-Pac, co-administered with Gem, as a first-line treatment for people with metastatic adenocarcinoma of the pancreas.

The ERG notes that the appraisal under discussion in this report is an update of existing NICE guidance, TA360, published in October 2015. In TA360, NICE did not recommend the use of Nab-Pac+Gem as a treatment for previously untreated metastatic adenocarcinoma of the pancreas. The TA360 final appraisal determination (FAD) is available on the NICE website and a summary of the key points from the FAD and subsequent appeal is presented in Appendix 1 of this ERG report.

1.2 Critique of the decision problem in the company's submission

1.2.1 Population

The population described in the final scope issued by NICE is the same as the population recruited to the CA046 trial and discussed in the company submission (CS), i.e. patients with previously untreated metastatic adenocarcinoma of the pancreas.

Although 47% of all cases of pancreatic cancer are diagnosed in people aged ≥75 years, only 10% (n=84) of the patients recruited to the key trial (CA046) were aged ≥75 years. This means that the outcomes of the CA046 trial may not represent the outcomes of a substantial proportion of patients in the NHS who are diagnosed with metastatic adenocarcinoma pancreatic cancer.

In the European Public Assessment Report (EPAR) for Nab-Pac+Gem, the EMA cautions that there is no demonstrated benefit of treatment with Nab-Pac+Gem in people aged ≥75 years and that patients aged ≥75 years who were treated with Nab-Pac+Gem in the CA046 trial experienced more adverse events (AEs) and serious AEs (SAEs) than the overall trial population. The advice given in the Summary of Product Characteristics (SmPC) for Nab-Pac is that patients with pancreatic cancer who are aged ≥75 years should be carefully assessed for their ability to tolerate Nab-Pac+Gem, with special consideration given to performance status (PS), co-morbidities and increased risk of infection.

Clinical advice to the ERG is that most patients with metastatic adenocarcinoma of the pancreas who are seen by an oncologist are fit enough to be treated with Gem. Some patients are fit enough to tolerate a combination chemotherapy treatment (for example, gemcitabine plus capecitabine (Gem+Cap) or FOLFIRINOX). The company has not provided clear evidence to determine which patients are best suited to which of these treatments.

The company appears to consider that all patients who are fit enough to be treated with Gem, Gem+Cap or FOLFIRINOX are fit enough to be treated with Nab-Pac+Gem. However, the company considers that not all patients who are fit enough to tolerate treatment with Nab-Pac+Gem will be able to tolerate treatment with FOLFIRINOX. The ERG considers that the company has failed to clearly define the patient population for whom treatment with Nab-Pac+Gem is most appropriate.

1.2.2 Intervention

Nab-Pac was granted a UK marketing authorisation in 2013 for its use in combination with Gem for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. Hereafter referred to as Nab-Pac+Gem.

Nab-Paclitaxel is a formulation of paclitaxel in which paclitaxel is attached to nanoparticles of albumin and administered without the need for solvents. The company states that albumin-bound paclitaxel results in greater delivery of paclitaxel to the tumour site compared with conventional solvent-based paclitaxel formulations.

The treatment regimen for Nab-Pac+Gem is 125mg/m^2 intravenous (IV) infusion of Nab-Pac (over 30 minutes) immediately followed by Gem as a 1000mg/m^2 IV infusion (over 30 minutes) on Days 1, 8 and 15 of a 28-day cycle.

Nab-Pac+Gem is accepted for use in NHS Wales and NHS Scotland for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.

1.2.3 Comparators

The comparators specified in the final scope issued by NICE are Gem, Gem+Cap and a combination treatment consisting of four therapies known as FOLFIRINOX.

Gemcitabine

Direct clinical evidence is available for the comparison of the effectiveness of Nab-Pac+Gem versus Gem from the CA046 trial.

Gemcitabine+Capecitabine and FOLFIRINOX

In the absence of direct evidence for the comparison of Nab-Pac+Gem versus Gem+Cap or versus FOLFIRINOX, the company has conducted network meta-analyses (NMAs).

Gem+Cap and FOLFIRINOX are not licensed in the UK for the treatment of metastatic pancreatic cancer. As the components of both Gem+Cap and FOLFIRINOX are available as generics, there is no single company with an interest in supporting the use of either Gem+Cap or FOLFIRINOX. The use of Gem+Cap and FOLFIRINOX is not uniform across the NHS.

The company considers that Gem is the only valid comparator to Nab-Pac+Gem.

Outcomes

Direct evidence is available from the CA046 trial for the outcomes of overall survival (OS), progression-free survival (PFS), time to progression (TTP), objective response rate (ORR) and AEs. Health-related quality of life (HRQoL) data were not collected during the CA046 trial. In the clinical section of the CS, the company presents data from the SIEGE trial, collected using the European Organisation for Research and Treatment Cancer (EORTC) Quality of Life questionnaire (QLQ-C30). The SIEGE trial is an ongoing phase II study designed to explore different dosing schedules of Nab-Pac+Gem. Similar data are also presented from a US-based retrospective cross-sectional study of patients with metastatic pancreatic cancer that included patients treated with Nab-Pac+Gem, reported by Picozzi.

Other considerations

- An agreed patient access scheme (PAS) is in place for nab-paclitaxel
- The company has not identified any equality issues
- The company has presented a case for Nab-Pac+Gem to be assessed against the NICE End of Life criteria.

1.3 Summary of clinical effectiveness evidence submitted by the company

Results from the CA046 trial

The results of the most recent analysis of OS data from the CA046 trial (data cut-off: 9 May 2013) show that treatment with Nab-Pac+Gem statistically significantly improves median OS in comparison to treatment with Gem (8.7 months versus 6.6 months; hazard ratio [HR]=0.72, 95% confidence interval [CI]: 0.62 to 0.83) in patients with a Karnofsky PS (KPS) ≥70. Improvement in OS with Nab-Pac+Gem compared with Gem was generally consistent across patient baseline characteristics. At the time of the primary efficacy analysis, compared with treatment with Gem, treatment with Nab-Pac+Gem was shown, by independent review and by investigator assessment, to statistically significantly improve PFS.

The most common Grade 3 or 4 AEs associated with treatment with Nab-Pac+Gem were neutropenia, fatigue, metabolism and nutritional disorders, peripheral neuropathy, thrombocytopenia and anaemia. Although these AEs were also associated with treatment with Gem and Nab-Pac monotherapies, they occurred more frequently when patients were treated with Nab-Pac+Gem.

The company has presented early HRQoL results from the SIEGE trial within the clinical section of the CS. These data were collected using the EORTC QLQ-C30. The company reports that Global Health Scores (GHS) were generally stable throughout treatment; however, towards the end of the 6 treatment cycle period, data were difficult to interpret due to small patient numbers (n=22 in the concomitant Nab-Pac+Gem arm at Week 24).

In the absence of head-to-head clinical data that allow comparisons of the effectiveness of treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX, the company performed NMAs. Despite the fact that a connected network could be formed by including only trials that compared treatments relevant to the decision problem, the company base case network included seven trials that provided evidence for treatments that were not listed in the final scope issued by NICE. However, the company performed a sensitivity analysis using a reduced network (fixed effects) that included only the comparators listed in the final scope issued by NICE and the ERG considers the results from this analysis more valid than the company's base case NMA results. In terms of OS, the results from this sensitivity analysis mirror the results from the base-case analysis and do not suggest a statistically significant treatment effect for Nab-Pac+Gem versus Gem+Cap (HR=1.10, 95% credible interval [CrI]: 0.67 to 1.84) or for Nab-Pac+Gem versus FOLFIRINOX (HR=0.77, 95% CrI:

0.58 to 1.01). The results from the company's base case NMA are used in the company's cost effectiveness model.

1.4 Summary of the ERG's critique of submitted clinical effectiveness evidence

The ERG considers that the CA046 trial was of good quality and well conducted. The trial data are mature and, with no patient crossover, the results allow for reasonable conclusions to be drawn regarding the clinical effectiveness of Nab-Pac+Gem versus Gem in the trial population. Substantial numbers of patients were recruited to the CA046 trial and patient baseline characteristics were balanced across both trial arms. The statistical methods used to analyse trial data were generally appropriate. Clinical advice to the ERG is that patients recruited to the trial were younger and fitter than the population of patients with metastatic disease treated in the NHS. Most notably, only 10% of the patients recruited to the trial were aged ≥75 years, whereas Cancer Research UK (CRUK) statistics suggest that almost half (47%) of all patients diagnosed with pancreatic cancer are in this age band. None of the participating treatment centres were based in the UK. The ERG considers that the absence of HRQoL data from patients in the CA046 trial is disappointing.

The ERG conducted assessments to determine the validity of the company's assumption that survival hazards are proportional over time. The ERG's analyses showed that, over time, the OS and PFS hazards from the two arms of the CA046 trial are not proportional. Consequently, all HRs results derived from the CA046 trial should be interpreted with caution. Furthermore, the ERG highlights that all of the company's NMA results (base case and sensitivity analyses) are affected by the lack of proportional hazards (PHs) in the CA046 trial and these results should also be interpreted with caution.

1.5 Summary of cost effectiveness evidence submitted by the company

For the comparison of treatment with Nab-Pac+Gem versus Gem, Kaplan-Meier (K-M) data from the CA046 trial were used as the basis for estimating patient survival. Stratified gamma curves were used to model OS, PFS and time on treatment (TOT). Resource use and costs were estimated based on information from the CA046 trial, published sources and advice from clinical experts. A Department of Health PAS discount was applied to the cost of Nab-Pac+Gem and full list prices were used to represent the cost of the comparator drugs.

The company's base case analysis prediction is a mean of 0.927 life years gained (LYG) for patients receiving Nab-Pac+Gem, 0.725 LYG for patients receiving Gem, 0.950 LYG for patients receiving Gem+Cap and 1.154 LYG for patients receiving FOLFIRINOX.

HRQoL data were not collected as part of the CA046 trial. Instead, the company adjusted the health state utility values reported by Romanus et al (2012) for use in a UK population. These adjusted values were used in the base case analysis for pre-progression (0.74) and progressive disease (0.67). The company used EQ-5D-5L data from the concomitant arm of the SIEGE trial (phase II, dose-scheduling trial of Nab-Pac+Gem) in separate scenario analyses.

The company submitted an updated model as part of the clarification response. The company's updated base case incremental cost effectiveness ratio (ICER) for the comparison of treatment with Nab-Pac+Gem versus Gem is £46,932 per quality adjusted life year (QALY) gained; treatment with Nab-Pac+Gem generates 0.144 additional QALYs at an additional cost of £6,755. For the comparison of treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX, Nab-Pac+Gem is more costly and generates fewer QALYs.

For the comparison of treatment with Nab-Pac+Gem versus Gem, the company carried out a wide range of deterministic sensitivity analyses. The results show that the most influential parameter is the treatment variable used to parameterise OS. All of the other parameters that were varied had a lower impact on the size of the ICERs per QALY gained.

The results of the company's probabilistic sensitivity analysis show that Nab-Pac+Gem has a 64% probability of being cost effective compared to Gem at a willingness to pay threshold of £50,000 per QALY gained.

1.6 Summary of the ERG's critique of submitted cost effectiveness evidence

The company's model is generally well structured and correctly implemented. The ERG has corrected one error in the calculation of total LYs and QALYs. The three key issues that require exploration by the ERG in the company's model are: HRs used for treatment with Gem+Cap and with FOLFIRINOX, costing of drugs and modelling of TOT.

The company uses HRs from the NMA to estimate time-to-event outcomes for treatment with Gem+Cap and with FOLFIRINOX, which rely on the PH assumption holding for PFS and OS within the CA046 trial. Since PH has been shown not to hold for PFS or OS in the CA046 trial, using the results of the NMA in the model produces unreliable estimates for OS, PFS and TOT for treatment with Gem+Cap and with FOLFIRINOX. The ERG also has concerns about the company's use of HRs with a stratified Gamma model. The ERG has used published HRs for treatment with Gem+Cap versus Gem and with FOLFIRINOX versus Gem in the model to overcome the need for PH to hold in the CA046 trial; however, PH does not

hold in the ACCORD trial for either PFS or OS. Results for the comparison of treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX should be treated with caution.

The company has estimated average treatment costs for the intervention and comparators using only a limited range of the vial sizes available to the NHS for each drug. By incorporating all available vial sizes in the calculation of drug costs, the ERG has decreased the average weekly cost of each first-line treatment in the company model.

The ERG advocates the use of K-M data directly as far as possible when time-to-event evidence comes from a single trial, and especially when the trial data are mature. The TOT data from the CA046 trial are complete and so represent the best possible evidence of time spent on treatment for the patients in that trial. However, the company has used a fully parametric model to estimate TOT, which introduces unnecessary uncertainties into the analysis and results in an overestimation of TOT for both treatments. The ERG has re-estimated TOT for treatment with Nab-Pac+Gem and with Gem using K-M data directly from the CA046 trial.

The company has also used parametric models to estimate PFS and OS for treatment with Nab-Pac+Gem and with Gem using mature data from the CA046 trial. The ERG investigated remodelling PFS and OS for treatment with Nab-Pac+Gem and with Gem using K-M data as far as possible then appending a parametric tail to extrapolate beyond the trial data. The ERG found that its re-modelling of PFS and OS for treatment with Nab-Pac+Gem and with Gem had only a small impact on the size of the ICERs per QALY gained.

Other issues identified by the ERG include the double counting of AE disutilities. The ERG has also provided two scenario analyses that investigate the impact of using different costs for some AEs and of using a different source of utility values.

1.7 Summary of company's case for End of Life criteria being met

The company has put forward a case that Nab-Pac+Gem meets NICE's End of Life criteria based on the following points:

- The company quotes data that show the median survival for patients with metastatic adenocarcinoma pancreatic cancer is less than 24 months
- Base case results generated by the company's economic model suggest that the mean difference in OS between patients treated with Nab-Pac+Gem versus Gem is 2.4 months
- When Nab-Pac+Gem is compared with Gem+Cap or FOLFIRINOX, the results from the company's base case NMA show that there is no statistically significant OS gain from Nab-Pac+Gem.

1.8 ERG commentary on End of Life criteria

The ERG agrees with the company that patients with metastatic adenocarcinoma of the pancreas have a life expectancy of less than 24 months.

An examination of the ERG's remodelled OS data suggests that treatment with Nab-Pac+Gem generates a mean survival gain of 2.44 months compared to Gem. When Nab-Pac+Gem is compared with Gem+Cap or FOLFIRINOX, the results from the company base case NMA show that there is no statistically significant OS gain from Nab-Pac+Gem.

1.9 ERG commentary on the robustness of evidence submitted by the company

1.9.1 Strengths

Clinical evidence

- The CA046 trial was of good quality, was well conducted and recruited 861 patients
- The trial data are mature and free from patient crossover
- To enable the comparison of Nab-Pac+Gem versus treatments listed in the final scope issued by NICE, the company carried out a range of NMAs
- The company fulfilled the ERG's clarification requests to a good standard.

Cost effectiveness evidence

- The economic model was well constructed
- The company carried out a comprehensive range of deterministic sensitivity and scenario analyses.

1.9.2 Weaknesses and areas of uncertainty

Clinical evidence

- The company is unable to define the characteristics of the patient population who would be most suited to treatment with Nab-Pac+Gem
- Patients aged ≥75 years make up almost half of all patients diagnosed with pancreatic cancer; however, only 10% of patients in the CA046 trial were aged ≥75 years
- The PFS and OS HRs from the CA046 trial data were calculated using a pre-specified method that relies on the assumption that hazards are proportional. However, as demonstrated by the company and the ERG, this assumption does not hold and therefore OS and PFS HRs must be interpreted with caution
- The lack of PH in the CA046 trial means that results from the company's NMAs should also be treated with caution.

Cost effectiveness evidence

- Time-to-event evidence for treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX relies on results from the NMA, these results should be treated with caution due to the lack of PH in the CA046 trial
- Drug costs are not fully optimised, as the company calculated the cost of average doses based on a limited range of the vial sizes available to the NHS
- The company used parametric models to estimate time-to-event outcomes for treatment with Nab-Pac+Gem and Gem when data from the CA046 trial were mature or, in the case of TOT, complete and could be used directly in the model
- The model includes additional disutilities for AEs, which amounts to double counting because the base case utility values are derived from a trial and will already include any effect of AEs experienced by patients.

1.10 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG amended time-to-event estimates for all four first-line treatments in the company model. The ERG used published HRs from the Scheithauer and ACCORD trials to model OS, PFS and TOT for Gem+Cap versus Gem and FOLFIRINOX versus Gem respectively to overcome the issue of lack of PH in the CA046 trial. The PH assumption was found not to hold in the ACCORD trial, so results in the ERG's revised model for treatment with FOLFIRINOX should be treated with caution. The ERG's preferred method of modelling OS and PFS from the CA046 trial is to use K-M data for as long as possible, and then to append exponential curves to project outcomes for the remainder of the model time horizon. No projections were necessary for TOT, as data are complete in the CA046 trial.

The ERG re-estimated average weekly treatment costs for each of the four first-line treatments by taking into account all vial sizes for the constituent drugs for which prices are available. The ERG also removed added AE disutilities using a switch in the company model.

The ERG undertook two sensitivity analyses to investigate the impact of using amended AE resource-use costs and of using a different source of utility values.

1.11 Cost effectiveness conclusions

Application of the ERG model amendments in the base case results in an ICER for the comparison of Nab-Pac+Gem versus Gem of £41,250 per QALY gained. Application of the ERG's model amendments in the base case and all of the scenario analyses results in an ICER for the comparison of Nab-Pac+Gem versus Gem of £45,571 per QALY gained.

Application of the ERG model amendments results in an ICER for the comparison of Nab-Pac+Gem versus Gem+Cap of £99,837 per QALY gained. Application of the ERG's model amendments in the base case and all of the scenario analyses results in an ICER for the comparison of Nab-Pac+Gem versus Gem+Cap of £107,898 per QALY gained

Application of the ERG model amendments indicates that treatment with Nab-Pac+Gem is dominated by treatment with FOLFIRINOX. Application of the ERG's model amendments in the base case and all of the scenario analyses indicates that treatment with Nab-Pac+Gem is dominated by treatment with FOLFIRINOX.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

Section 3.1 of the company submission (CS) includes an overview of pancreatic cancer and Section 3.2 includes a description of the effects of metastatic pancreatic cancer on patients, carers and society. Section 3.4 includes UK epidemiology data for pancreatic cancer. Key points from these sections of the CS are included as bulleted items in Box 1 and Box 2. The Evidence Review Group (ERG) considers that these points are appropriate and relevant to the decision problem under consideration. The ERG notes that most (80 to 95%) pancreatic cancers are of adenocarcinoma histology.

Box 1 Company overview of pancreatic cancer

- Pancreatic cancers can form in either the exocrine or endocrine parenchyma, however, the vast majority start in the cells of the exocrine pancreas, with pancreatic adenocarcinoma accounting for approximately 80–95% of all pancreatic cancers.
- Most commonly, cancer originates in the head of the pancreas (approximately 75% of all cases), but it can also start in the body or tail. In the case of metastatic pancreatic adenocarcinoma, cancer originates in the pancreas but thereafter spreads to other areas of the body, with the most common sites of metastases being the liver, peritoneum, lungs and bones.
- Cases of pancreatic cancer in the UK are evenly split between males and females, but pancreatic cancer is more common in white and black people than in Asian people. In England, pancreatic cancer is also more common in people living in the most deprived areas. Approximately half (47%) of all pancreatic cancer cases are diagnosed in people aged ≥75 years, with cases in people under 40 years of age uncommon.
- There is no single known cause of pancreatic cancer, but there are a number of clinical, genetic and environmental risk factors, alongside the demographic factors, that increase the risk of pancreatic cancer. These include pancreatitis (chronic or hereditary), diabetes, mutation of the *BRCA* gene, obesity and smoking, and to a lesser extent previous cancer, hepatitis, Helicobacter pylori infection, alcohol and diet.
- Pancreatic cancer is an extremely aggressive and life-threatening malignancy. With mortality rates stabilising or increasing rather than declining, it is thought that pancreatic cancer may become the third leading cause of death from cancer in the European Union by 2025 (after lung and colorectal cancers).
- As the disease often remains asymptomatic at early stages, a high percentage of patients are diagnosed at an advanced stage. Only 30–40% of all patients present with disease confined to the pancreatic region and, in England, 79% of patients are diagnosed at Stage III or IV.
- Metastatic disease has a particularly poor prognosis, with median survival estimated at between 2 to 6 months; this depends on the size of the tumour and where it has spread. In addition to the extent of metastases, worse prognosis is also associated with poor performance status, pancreatic head tumour location, presence of biliary stent, and elevated levels of the CA19-9 antigen.
- In 2014, there were around 8,800 pancreatic cancer deaths in the UK (7,430 in England), which equates to 24 deaths every day, making it the fifth most common cause of cancer death. The latest incidence estimates for pancreatic cancer in the UK are based on 2013 data, when there were around 9,400 new cases (7,887 in England), which equates to 26 people diagnosed every day.

- Of people diagnosed with pancreatic cancer in England between 2005 and 2009, less than 20% survived beyond 12 months, and less than 4% survived to 5 years. Similar observations were made for people diagnosed between 2010 and 2011 in England and Wales.

Source: CS, Section 3.1 and Section 3.4

Box 2 Company overview of the effects of metastatic pancreatic cancer on patients, carers and society

- Patients with metastatic pancreatic cancer experience a variety of complications and disease-related symptoms, all of which affect normal living.
- Pancreatic cancer is typically symptomless in the early stages, but as it grows and spreads, symptoms can manifest (hence why most cases are diagnosed at an advanced stage). The exact symptoms a patient may experience will depend on the type of pancreatic cancer as well as its location. Common symptoms associated with adenocarcinoma include pancreatic insufficiency, weight loss, jaundice (head tumours) and abdominal/back pain (body-tail tumours). Patients with metastatic pancreatic adenocarcinoma may also experience additional symptoms associated with the site of metastases. For example, liver metastases can be associated with a swollen and painful abdomen, nausea, fatigue, and weight loss; while lung metastases can cause dyspnoea, persistent cough and chronic chest infections.
- We might expect patients with pancreatic cancer to experience some detrimental impact on quality of life as a result of their disease, and there are some reports of reduced quality of life in the literature; particularly with regard to mental health that appears to worsen with advanced disease, likely as a result of their poor prognosis. However, formal assessment of health-related quality of life resulting in a single health index (utility), shows a similar index score between patients with advanced pancreatic cancer who are receiving active treatment (gemcitabine) and the general population.
- For patients who are actively employed, the cost of productivity loss has been estimated to be as high as €87,205 (approximately £74,228). Given the poor prognosis of patients with metastatic pancreatic adenocarcinoma, there is also a societal burden of disease due to premature mortality. In Europe, the cost to society of premature death due to pancreatic cancer is estimated at €3.9 billion (approximately £3.3 billion).

Source: CS, Section 3.2

2.2 Company's overview of current service provision

The company presents an overview of the clinical care pathway in Section 3.3 of the CS. The ERG considers the company's overview to be relevant to the decision problem under consideration. The company discusses the use of three treatments for metastatic pancreatic cancer in the NHS in England: i) gemcitabine monotherapy (Gem); ii) gemcitabine+capecitabine (Gem+Cap); iii) a combination treatment of oxaliplatin, irinotecan, calcium folinate and flurouracil known as FOLFIRINOX. Details of the three treatments are summarised in Table 1.

The company reports that treatment options differ between NHS England, NHS Wales[1] and NHS Scotland[2] as nab-paclitaxel combined with gemcitabine (Nab-Pac+Gem) is currently available as a treatment option for patients with metastatic pancreatic cancer in both NHS Wales and NHS Scotland.

Table 1 Summary of company overview of current service provision

Treatment	Licensed in Europe	NICE guidance	Treatment regimen	Available uniformly across NHS?	Available as a generic product?
Gem	Yes	TA25[3] (2001)	IV 1000mg/m^2 (30 min). Weekly for 7 weeks followed by a week of rest. Thereafter once a week on a 3-weekly cycle	Yes	Yes
Gem+Cap	No	N/A	Gem IV 1000mg/m^2 (30 min) once a week on a 3-weekly cycle. Capecitabine tablets 1666mg/m^2 daily on a 3-weekly cycle	No	Yes
FOLFIRINOX	No	N/A	Oxaliplatin, irinotecan, leucovorin and flurouracil (5-FU) administered via central line, Portacath or PICC line. • Oxaliplatin 85mg/m^2 (2 hrs) • Leucovorin 400mg/m^2 (2 hrs) • Irinotecan 180mg/m^2 (90 min) • 5-FU 400mg/m^2 administered by IV bolus, then as a continuous IV infusion of 2400mg/m^2 over 46 hrs every 2 weeks	No. Modified treatment regimens are used in some centres	Yes

5-FU= flurouracil; IV=intravenous; PICC=peripherally inserted central catheter
Source: CS, Section 3.3

Gemcitabine monotherapy

The company states (CS, p34) that in NICE guidance published in 2001 (TA25[3]), Gem is recommended as a first-line treatment for people with advanced or metastatic pancreatic cancer if they have a Karnofsky Performance Status (KPS) of 50 or more. The ERG agrees with the company that gemcitabine remains the only treatment currently recommended by NICE for metastatic pancreatic cancer.

Gemcitabine+capecitabine

The company reports (CS, p35) that Gem+Cap is not a licensed treatment regimen for metastatic pancreatic cancer and, as generic versions of gemcitabine and capecitabine are available, there is no single company with a commercial interest in promoting or supporting the use of this regimen.

Clinical advice to the company (CS, p35), and to the ERG, is that there is modest use of Gem+Cap in the NHS. The company's market research data (CS, p35 and Section 2.4 of this ERG report) suggest that [redacted] of patients with metastatic pancreatic adenocarcinoma who receive treatment in the NHS are likely to receive Gem+Cap. Clinical advice to the ERG is that in the NHS, no more than [redacted] of patients are treated with Gem+Cap.

The company has reservations about the clinical effectiveness of treatment with Gem+Cap compared with the effectiveness of treatment with Gem (CS, p42). The company states that

there are three publications[4-6] that report the results of randomised controlled trials (RCTs) comparing Gem+Cap versus Gem in patients with advanced or metastatic pancreatic cancer; however, none of the three trials[4-6] has demonstrated evidence of a significant overall survival (OS) benefit from treatment with Gem+Cap compared with Gem. The company observes (CS, p42) that a 2009 meta-analysis (Cunningham[4]) of data from the three published trials[4-6] 'attempts' to demonstrate that there is a statistically significant OS benefit associated with treatment with Gem+Cap when compared with Gem even though no OS benefit was reported in the individual trials. The ERG notes that the results of the published meta-analysis[4] demonstrated a significant OS gain for Gem+Cap when compared with Gem (hazard ratio [HR]=0.86; 95% confidence interval [CI]: 0.75 to 0.98; p=0.02) in a mixed group of patients with locally advanced or metastatic disease. The company reports (CS, p43) that the results of the meta-analysis[4] were '*not that well received in clinical circles*.'

FOLFIRINOX

The ERG agrees with the company (CS, p34) that FOLFIRINOX is not licensed in Europe for the treatment of patients with metastatic pancreatic adenocarcinoma. Furthermore, as generic versions of all the components of FOLFIRINOX are available, there is no single company with a commercial interest in promoting or supporting the use of this regimen.

The ERG agrees with the company (CS, p41) that FOLFIRINOX is an intensive therapy that requires the use of chemotherapy port and infusion pump management services. The ERG is aware that the standard regimen of FOLFIRINOX for the treatment of metastatic pancreatic cancer, as described in Table 1, was established in the trial by Conroy.[7] In this trial,[7] median OS for patients treated with FOLFIRINOX was 11.1 months compared with 6.8 months for patients treated with Gem (HR=0.57; 95% CI: 0.45 to 0.73).

The company describes two main issues relevant to the use of FOLFIRINOX and these are set out in Box 3.

Box 3 Company identified issues with the use of FOLFIRINOX in the NHS

1. The use of FOLFIRINOX is not uniform across the NHS, mainly because there is no organisational infrastructure to support treatment administration and to manage the adverse events (AEs) associated with FOLFIRINOX.

2. A modified FOLFIRINOX regimen is given in some treatment centres to try to reduce the toxicity and the burden of administration; however, there is no randomised clinical trial evidence to support the clinical effectiveness of any modified version of FOLFIRINOX.

Source: CS, p42

The company states (Box 3, point 1) that FOLFIRINOX is not used uniformly across the NHS because of the lack of infrastructure to support treatment administration and manage the

associated AEs. Clinical advice to the ERG is that treatment centres that support the use of Nab-Pac+Gem also have the infrastructure to support the use of FOLFIRINOX.

The ERG agrees with the company's statements describing the availability and modification of FOLFIRINOX in UK clinical practice. However, clinical advice to the ERG is that there is no RCT evidence to support the dose reductions and dose omissions that are commonly required when treating patients with Nab-Pac+Gem. The ERG notes from the professional organisation submission to NICE[8] that patients seen at peripheral chemotherapy units who are eligible for treatment with FOLFIRINOX travel to specialist cancer centres to receive the treatment. Clinical advice to the ERG is that patients who are suitable for treatment with Nab-Pac+Gem will also be treated at specialist cancer centres.

The company states that FOLFIRINOX is offered to patients who are aged ≤70 years, have an Eastern Co-operative Group (ECOG) performance status (PS) of 0 or 1 and have very minor co-morbidities. Data from the company's market research (CS, p35 and Section 2.4 of this ERG report) suggest that, in the UK, between [redacted] of patients with metastatic pancreatic adenocarcinoma who receive treatment in the NHS are treated with FOLFIRINOX. Clinical advice to the ERG is that the use of FOLFIRINOX in the NHS may be limited by the toxicity of this treatment regimen which can only be offered to patients with PS of 0 or 1 with limited co-morbidities.

2.3 Place of Nab-Pac+Gem in the treatment pathway

The company describes Nab-Pac (CS, p19) as '…an innovative formulation of paclitaxel that facilitates selective and efficient accumulation of active treatment to promote cell death at the tumour site.' The company reports that the treatment effects of Nab-Pac are enhanced by the concomitant use of Gem.

It is specified in the Summary of Product Characteristics (SmPC[9]) for Nab-Pac that treatment is administered as a 125mg/m^2 IV infusion (over 30 minutes on Days 1, 8 and 15 of a 28-day cycle. Gem is administered as a 1000mg/m^2 IV infusion over 30 minutes immediately after Nab-Pac (CS, p19).

The company is clear that Gem is the only valid comparator to Nab-Pac+Gem in the first-line setting for patients with metastatic pancreatic cancer. The company states that the introduction of Nab-Pac+Gem into the NHS will only have an impact on the current NHS usage of Gem and will not affect the current NHS usage of either Gem+Cap or FOLFIRINOX. The company's rationale for this position on FOLFIRINOX (CS, p34-35) is set out in Box 4.

Box 4 Company's rationale for the place of Nab-Pac+Gem in the treatment pathway

- FOLFIRINOX treatment is intensive and only suitable for use in a subgroup of patients and, that the subgroup of patients who are suitable for treatment with FOLFIRINOX are easily identified in clinical practice
- Patients who are suitable for treatment with FOLFIRINOX are clinically distinct from patients who are treated with Gem but who could be treated with Nab-Pac+Gem
- Patients suitable for treatment with Nab-Pac+Gem are easily identified and are clinically distinct from patients who are suitable for treatment with Gem or with FOLFIRINOX

Source: CS, p34-35

Clinical advice to the ERG is that patients in the NHS who are better suited to treatment with FOLFIRINOX are easily identified from patients who are better suited to treatment with Gem. However, the distinction between patients who are better suited to treatment with FOLFIRINOX and patients who might be better suited to treatment with Nab-Pac+Gem is not clear, and it is difficult to formulate guidance for patient selection. The ERG notes that there is no known biomarker or patient characteristic that can be used to predict response to treatment with either Nab-Pac+Gem or FOLFIRINOX.[10]

The company's proposed use of Nab-Pac+Gem relative to other treatments is described in Table 2. The company's position is based on clinical expert advice given to the company. The ERG notes from Table 2 that the company claims that Nab-Pac+Gem can be used in patients of any age, including patients aged ≥75 years. The ERG questions the evidence supporting this claim (see Section 3.1 of this ERG report) and notes that the advice given in Section 4.4 of the SmPC[9] for Nab-Pac is that there is no demonstrated treatment benefit of Nab-Pac+Gem compared with Gem for patients with pancreatic cancer who are aged ≥75 years. The SmPC[9] for Nab-Pac includes the caution that patients who are ≥75 years should be carefully assessed for their ability to tolerate Nab-Pac+Gem, with special consideration given to PS, co-morbidities and increased risk of infection.

The company does not consider the use of Gem+Cap to be a standard of care in the NHS and does not fully discuss the characteristics of patients who are likely to receive treatment with Gem+Cap, except to say that these patients will continue to be offered treatment with Gem+Cap even if Nab-Pac+Gem becomes available for use in the NHS. Clinical advice to the ERG is that Gem+Cap is not commonly used to treat patients in the NHS. It may be used in patients with bulky symptomatic disease who are not fit for treatment with FOLFIRINOX.

Table 2 Proposed place of Nab-Pac+Gem in the treatment pathway with ERG comment

Treatment	Company proposed patient population	ERG comment
FOLFIRINOX	≤70 years ECOG PS 0 or 1 Minor co-morbidities (e.g. well controlled hypertension)	Clinical advice to the ERG is that in the NHS, FOLFIRINOX is used in patients who are ≥70 years if they have a PS of 0 or 1 and are aware of the potential side effects The company's market research shows that in the UK [redacted] of patients are treated with FOLFIRINOX
Gem	Any age ECOG PS ≥2	Agree
Nab-Pac+Gem	Any age (use in people aged over 80 years is supported by real-world evidence). ECOG PS 0 or 1 FOLFIRINOX treatment not suitable	The ERG notes that the SmPC for Nab-Pac includes a caution advising that there is no evidence of clinical efficacy of Nab-Pac+Gem in patients ≥75 years and that patients with pancreatic cancer who are aged ≥75 years should be carefully assessed for their ability to tolerate Nab-Pac+Gem with special consideration to performance status, co-morbidities and increased risk of infections. The company has not defined the patient population not suitable for treatment with FOLFIRINOX
Gem+Cap	Not discussed	Not in common usage in the NHS. May be used to treat patients with bulky symptomatic disease who are not fit enough for treatment with FOLFIRINOX The company's market research shows that in the UK [redacted] of patients are treated with Gem+Cap

ECOG=Eastern Co-operative Oncology Group; PS=performance status
Source: CS, p34-35

The ERG notes that the baseline characteristics of the patient populations recruited to the key trials of Nab-Pac+Gem (CA046[11,12]) and FOLFIRINOX (Conroy[7]) are very similar (Table 3). The ERG also notes that median OS for patients treated with Gem in the CA046 and Conroy trials is comparable (6.8 months and 6.6 months, respectively), underlining the similarities between the trial cohorts and the difficulty in distinguishing between patients in the NHS who are suited to treatment with FOLFIRINOX and Nab-Pac+Gem. Clinical advice to the ERG is that many of the patients recruited to the CA046 trial would have been suitable for treatment with FOLFIRINOX.

Table 3 Comparison of patient populations in the CA046 trial and in the Conroy 2011 trial

Characteristic	CA046 Nab-Pac+Gem vs Gem N=861 n (%)	Conroy 2011 FOLFIRINOX vs Gem N=342 n (%)	
Median age (years)	63	61	
Male	502 (58)	105 (61)	
Performance status			
KPS		**ECOG**	
100	138/858 (16)	0	65 (38)
90	378/858 (44)	1	106 (62)
80	277/858 (32)	2	1 (0)
70	63/858 (7)		
60	2/858 (<1)		
Tumour location			
Head	371 (43)	65 (38)	
Body	268 (31)	56 (32)	
Tail	215 (25)	45 (26)	
Unknown	4 (1)	NR	
Multicentric	NR	6 (3)	
Number of metastatic sites n%			
1	54 (6)		
2	408 (47)	Median of 2 (range 1 to 6)	
3	276 (32)		
>3	123 (14)		

ECOG=Eastern Cooperative Oncology Group; KPS=Karnofsky performance status; NR=not reported
Source: CS, Table 11 and Conroy 2011 Table 1

The ERG notes that guidelines[13] published by the European Society for Medical Oncology (ESMO) provide advice for the use of Nab-Pac+Gem and FOLFIRINOX in the treatment of metastatic pancreatic cancer. In these guidelines[13] the ESMO Committee states that there are no data to support the use of Nab-Pac+Gem over FOLFIRINOX. The Committee considered that either FOLFIRINOX or Nab-Pac+Gem could be offered to patients who have serum bilirubin levels of less than 1.5 times the upper limit of normal and are of good PS (ECOG 0 or 1). The ESMO guidelines[13] also include the statement that treatment with Nab-Pac+Gem could be considered to treat 'very selected patients' with ECOG PS 2.

In the 2014 ERG report for TA360,[14] it was noted that the company was unable to identify a single 'optimal' subgroup of patients who were suitable for treatment with Nab-Pac+Gem and the ERG considers that the company has yet to clearly identify this 'optimal' subgroup.

2.4 Impact of Nab-Pac+Gem on the use of Gem, Gem+Cap and FOLFIRINOX in the NHS

To support the claim that, in NHS clinical practice, the use of Nab-Pac+Gem will only have an impact on the use of Gem (CS, p35-37), the company has provided the results of market research conducted by Kantar.[15]

The company describes the research[15] as being based on an audit of Europe and UK patient chart data. The ERG understands that the data were derived from [redacted]. The company was unable to supply the source file for the market research when requested by the ERG (via the clarification process); the ERG is, therefore, unable to comment on the validity of the research, or to verify the results. However, the ERG notes that the presented data summarise the first-line treatments administered during each quarter (Q) of the audit year and the proportions of patients who received them. Data from the UK (Q2 2015 and Q4 2015) are shown in Table 4. The company states that during the 2015 data collection period, Nab-Pac+Gem was available via the Cancer Drugs Fund (CDF) in England and was recommended for use in Scotland in February 2015 and in Wales in October 2015.

The company reports that, in Q4, there was a [redacted] increase in the number of patients treated with Nab-Pac+Gem compared with the number treated in Q2. The company highlights that this increase coincided with an [redacted] decrease in patients treated with Gem. The use of FOLFIRINOX and Gem doublet (likely to be Gem+Cap) remained constant between Q2 and Q4.

The ERG notes that data presented by the company (CS, Figure 2) indicate an increasing trend towards the use of FOLFIRINOX in Europe between Q4 in 2014 and Q4 in 2015 [redacted]. The trend in the European data could suggest that the use of FOLFIRINOX in the UK might have also increased during 2015 (given the increasing experience of clinicians with administering FOLFIRINOX) and that the plateau in the usage of FOLFIRINOX in the UK may reflect some displacement by the use of Nab-Pac+Gem. The ERG also notes that the company did not provide any demographic information that would enable any comparison to be made between the patients who were treated with Nab-Pac+Gem and patients who were treated with FOLFIRINOX during 2015.

Table 4 Company market research data for first-line treatment of metastatic pancreatic adenocarcinoma in the UK

[redacted]	[redacted]	
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Q=quarter
*Note that the sum of each column is not 100% as the full audit includes other treatments not relevant to the present appraisal
Source: CS, Figure 2

2.5 Life expectancy

The company describes the life expectancy of people diagnosed with pancreatic cancer in Section 3.4 of the CS. The company presents information published by CRUK[16] that shows that pancreatic cancer was the fifth most common cause of cancer deaths in the UK in 2014 (approximately 8,800 deaths in the UK and 7,430 deaths in England). The company also presents the 12-month and 5-year survival data from CRUK for the years 2005 to 2009 (people in England) and 2010 to 2011 (people in England and Wales).[16] The company observes (CS, p38) that, in the absence of new treatments, the (low) current survival rates are likely to remain unchanged (Table 5). The company's observation is supported by details on the CRUK[16] website that highlight that, in the UK, survival from pancreatic cancer '…has not shown much improvement in the last 40 years.'

Table 5 12-month and 5-year survival rates in pancreatic cancer

Year	12-month survival rate	5-year survival rate
2005 – 2009 (England[16])	<20%	4%
2010 – 2011 (England and Wales[16])	21%	3%

Source: CS, p38

2.6 Summary of relevant clinical guidance and guidelines

The company provides details of relevant published guidance and treatment guidelines in Section 3.5 of the CS. These are reproduced in Table 6. The company observes that NICE expects to publish a guideline[17] specific to pancreatic cancer in January 2018.

Table 6 Company summary of guidance and guidelines relevant to metastatic pancreatic cancer

Organisation Year	Title	Summary
NICE guidance		
TA25[3] (2001)	Guidance on the use of gemcitabine for the treatment of pancreatic cancer	• People with advanced or metastatic adenocarcinoma of the pancreas may be treated with Gem as a first-line treatment if they have KPS ≥50 • Gem should not be used for people with pancreatic cancer who are suitable for surgery that may cure their cancer, or those who have KPS <50 • Gem should not be used as a second-line treatment for people with pancreatic cancer, because there is insufficient evidence to support this practice
International clinical guidelines		
European Society for Medical Oncology[13] (2015)	Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	The following treatment options should be considered for the treatment of patients with metastatic pancreatic cancer according to their general status: • If the ECOG PS of the patient is 0 or 1 and the bilirubin level is below 1.5 x ULN, two types of combination chemotherapy: the FOLFIRINOX regimen or the combination of Nab-Pac+Gem should be considered • For patients with ECOG PS of 2 and/or bilirubin level higher than 1.5 x ULN, monotherapy with Gem could be considered • In very selected patients with ECOG PS 2 due to heavy tumour load, Nab-Pac+Gem can be considered for best chance of response • For patients with ECOG PS of 3/4 with significant morbidities and very short life-expectancy, only symptomatic treatment can be considered
American Society of Clinical Oncology[18] (2016)	Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline	Key treatment recommendations for first-line therapy: • FOLFIRINOX is recommended for patients who meet all the following criteria: ECOG PS 0/1, favourable comorbidity profile, patient preference and support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services • Nab-Pac+Gem is recommended for patients who meet all the following criteria: ECOG PS 0/1, relatively favourable comorbidity profile, patient preference and support system for relatively aggressive medical therapy • Gem alone is recommended for patients who have either an ECOG PS 2 or a comorbidity profile that precludes more-aggressive regimens and who wish to pursue cancer-directed therapy. The addition of either capecitabine or erlotinib to gemcitabine may be offered in this setting • Patients with an ECOG PS ≥3 or with poorly controlled comorbid conditions despite ongoing active medical care should be offered cancer-directed therapy only on a case-by-case basis. The major emphasis should be on optimising supportive care measures

National Comprehensive Cancer Network[19] (2016)	NCCN Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 2. 2016	Preferred first-line therapy for patients with good PS (defined as ECOG PS 0/1 with good pain management, patent biliary stent, and adequate nutritional intake): • Clinical trial • FOLFIRINOX • Nab-Pac+Gem FOLFIRINOX should be limited to patients with ECOG PS 0/1; Nab-Pac+Gem is reasonable for patients with KPS ≥70 Options for patients with good PS: • Gemcitabine plus erlotinib • Gemcitabine-based combination therapy • Gemcitabine monotherapy • Capecitabine or continuous infusion 5-FU • Fluoropyrimidine plus oxaliplatin First-line therapy options for patients with poor PS: • Gemcitabine • Palliative and best supportive care

5-FU=fluorouracil; ECOG=Eastern Co-operative Oncology Group; KPS=Karnofsky Performance Status; PS=Performance Status; ULN=upper limit of normal
Source: CS, Table 5

2.7 Innovation

The company puts forward the case that Nab-Pac+Gem is an innovative treatment (CS, Section 2.5). The company's case is set out in Box 5.

Box 5 Company's case that Nab-Pac+Gem is an innovative treatment

- Metastatic pancreatic cancer has an extremely poor prognosis, with median survival estimated at between 2 to 6 months. The development of new treatments has been very limited in recent years, and despite numerous clinical trials, there has only been a modest improvement in life expectancy

- Gem-based therapy has been the standard of care for the first-line treatment of patients with unresectable locally advanced and/or metastatic pancreatic cancer since 1997 and is still the only single agent licensed in Europe. Its use is associated with a median survival of 5 to 7 months[10]

- In a phase II/III trial[7,14] not designed for registration, a significant survival benefit for patients with metastatic pancreatic cancer was observed with the combination regimen FOLFIRINOX compared with gemcitabine monotherapy (11.1 months vs 6.8 months); however, this regimen has often been found to be poorly tolerated, except by very fit patients, and modified versions with unproven efficacy in the context of a randomised controlled phase III clinical trial are often adopted in clinical practice in an attempt to improve tolerability of the regimen

- There is clearly a high level of unmet need associated with metastatic pancreatic cancer. This was previously acknowledged by NICE, who recognised that current treatments are limited in efficacy or associated with significant AEs such that additional treatment options in this area would be of value

- In the pivotal, regulatory phase III trial, CA046, Nab-Pac+Gem became the first chemotherapy doublet to demonstrate both a statistically significant and clinically meaningful survival benefit (defined as 6 to 8 weeks by people affected by pancreatic cancer over established standard of care (Gem). While some additive toxicity was observed (as expected a priori), the Nab-Pac+Gem regimen was generally well tolerated, with the majority of AEs potentially manageable through dose modification

- While the health-related benefits to patients should be captured in the QALY, the fact that

Nab-Pac+Gem offers a licensed treatment option with an innovative mechanism of action proven to improve life expectancy for patients with metastatic adenocarcinoma of the pancreas should be considered a 'step-change' in the management of this condition with extremely high unmet need • The more emotional aspects of an extension to life and the benefit of a life-extending medicine to the family and friends of a patient with a life-threatening malignancy should be considered, and these will not be captured in the QALY. These benefits were recognised by Pancreatic Cancer UK[20] as part of their Two More Months campaign, launched in February 2014 in an attempt to ensure Nab-Pac+Gem was available for use via the NHS across the UK. This campaign illustrates how access to Nab-Pac+Gem could give metastatic adenocarcinoma of the pancreas patients and their families the ability to achieve particular personal ambitions at the end of their life.

QALY=quality adjusted life year
Source: CS, p30-31

Clinical advice to the ERG is that treatment with Nab-Pac+Gem and FOLFIRINOX are associated with more AEs than treatment with Gem. Nab-Pac+Gem and FOLFIRINOX have similar AE profiles and both treatment regimens require dose reductions and modifications in managing the AEs.

2.8 Number of patients eligible for treatment with Nab-Pac+Gem

The company estimates that in England, the maximum number of patients who will be eligible for treatment with Nab-Pac+Gem is 3147 each year. The company's method for calculating this number is presented in Table 7 along with the ERG's estimate. The ERG estimate is based on the 2014 incidence rate of pancreatic cancer published by CRUK. The ERG considers that the company's estimate of 3147 is reasonable.

Table 7 Company estimate of numbers of patients eligible for treatment

	Number of patients	
Parameter	**Company estimate**	**ERG estimate**
Incidence of pancreatic cancer in England in 2013	7887[16]	8080[16]
Cases of pancreatic cancer that are adenocarcinoma = 80-95%[13,21]	7492	7676
Cases that are metastatic disease = 60-70%[13]	5245	5373
Patients suitable for chemotherapy = 50-60%*	3147	3224

ERG=Evidence Review Group
*Expert opinion to the company
Source: CS, Section 3.4

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the ERG's comparison of the decision problem outlined in the final scope issued by NICE[22] and that addressed within the CS is presented in Table 8. Each parameter in Table 8 is discussed in more detail in the text following the table (Section 3.1 to Section 3.6).

Table 8 Comparison between NICE scope and company decision problem

Final scope issued by NICE Parameter and specification	**Summary of a comparison between the decision problem stated in the NICE scope and addressed in the CS**
Population People with previously untreated metastatic adenocarcinoma of the pancreas	People with previously untreated metastatic adenocarcinoma of the pancreas
Intervention Paclitaxel as albumin-bound nanoparticles (Nab-Pac)	Nab-Pac+Gem (as specified in its marketing authorisation)
Comparators Gem Gem+Cap FOLFIRINOX	**Direct evidence** Nab-Pac+Gem versus Gem The CA046 trial was designed to compare the clinical effectiveness of Nab-Pac+Gem versus Gem **Indirect evidence** Nab-Pac+Gem versus Gem+Cap Nab-Pac+Gem versus FOLFIRINOX The company has carried out NMAs to compare the relative effectiveness of treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX. However, the company states (CS, p34-35) that only Gem is a relevant comparator to Nab-Pac+Gem

Final scope issued by NICE Parameter and specification	Summary of a comparison between the decision problem stated in the NICE scope and addressed in the CS
Outcomes OS PFS RR AEs HRQoL	The company has presented results for all the outcomes detailed in the final scope issued by NICE
Economic analysis The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY	Cost effectiveness has been assessed using ICERs per QALY gained
If appropriate, the appraisal should include consideration of the costs and implications of additional testing for biological markers, but will not make recommendations on specific diagnostic tests or devices	Not applicable – the anticipated marketing authorisation for Nab-Pac+Gem is the whole population of patients with metastatic adenocarcinoma of the pancreas
The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared	The model time horizon is 10 years
Costs will be considered from an NHS and Personal Social Services perspective	Costs have been considered from an NHS perspective
The availability of any patient access schemes (PAS) for the intervention or comparator technologies will be taken into account	Details relating to the PAS for Nab-Pac+Gem have been provided in a confidential appendix that form part of the CS
Subgroups to be considered None specified	None identified
Special considerations None identified	None identified

AE=adverse effects of treatment; CS=company submission; ERG=evidence review group; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; ITT=intention to treat; NICE=National Institute for Health and Care Excellence; NMA=network meta-analysis; OS=overall survival; PAS=patient access scheme; PFS=progression-free survival; QALY=quality adjusted life year; RR=response rate
Source: CS, pp17-18

3.1 Population

The population described in the final scope issued by NICE is people with previously untreated metastatic adenocarcinoma of the pancreas. The population discussed in the CS is the population recruited to the CA046 trial, which is identical to the population described in the final scope issued by NICE.

Use of nab-paclitaxel+ gemcitabine in patients aged ≥75 years

The company reports (CS, p32) that 47% of all cases of pancreatic cancer are diagnosed in people aged ≥75 years. These data are derived from figures available on the CRUK

website.[16] The ERG notes that only 10% (n=84) of the patients recruited to the CA046 trial were ≥75 years. The ERG is concerned that the outcomes of the CA046 trial may not represent the outcomes of a substantial proportion of patients in the NHS who are diagnosed with pancreatic cancer, i.e. patients aged ≥75 years.

The company discusses the consideration given to patients aged ≥75 years in the EPAR[9] and the SmPC[9] for Nab-Pac (CS, p27). In the EPAR,[9] it is stated that for people aged ≥75 years there is no demonstrated treatment benefit of Nab-Pac+Gem compared with Gem. The ERG notes that the results of a pre-specified subgroup analysis of OS for patients aged ≥75 years in the CA046 trial showed a poorer OS outcome for patients treated with Nab-Pac+Gem compared with treatment with Gem (HR=1.08; 95% CI: 0.65 to 1.80).

In the SmPC,[9] the European Medicines Agency (EMA) also cautions that patients aged ≥75 years who were treated with Nab-Pac+Gem in the CA046 trial experienced more adverse events (AEs) and serious adverse events (SAEs) than the overall trial population. The AEs and SAEs included haematological toxicities, peripheral neuropathy, decreased appetite and dehydration. The advice given in the SmPC[9] is that patients with pancreatic cancer who are aged ≥75 years should be carefully assessed for their ability to tolerate Nab-Pac+Gem, with special consideration given to PS, co-morbidities and increased risk of infection.

The company states (CS, p26) that the advice given in the SmPC[9] is based on a small number of patients. The company also reports (CS, p117) that data from a retrospective analysis[23] of Italian patients with advanced pancreatic cancer treated with Nab-Pac+Gem show that similar rates of Grade 3 and Grade 4 AEs were recorded for patients aged <75 years (n=176) and those aged ≥75 years (n=32). The ERG notes that the study[23] was based on data from clinical records, included patients with advanced pancreatic cancer and included only 32 patients aged ≥75 years.

Clinical advice to the company (CS, p113) is that, in NHS clinical practice, age would not be a barrier to treatment with Nab-Pac+Gem. The clinical experts advised the company (CS, p113) that they would consider patients aged ≥75 for treatment with Nab-Pac+Gem.

3.2 Intervention

The intervention specified in the final scope issued by NICE is Nab-Pac. The intervention discussed in the CS is Nab-Pac+Gem; this is appropriate and reflects the marketing authorisation[9] issued by the EMA on 20th December 2013. The licensed indication for Nab-Pac+Gem is for the first-line treatment of adults with metastatic adenocarcinoma of the pancreas.

Nab-Pac is administered intravenously over 30 minutes at a dose of 125mg/m^2 on days 1, 8 and 15 of each 28-day cycle. Gem is administered intravenously over 30 minutes at a dose of 1000mg/m^2. Gem is administered immediately after the administration of Nab-Pac has been completed.

The company states (CS, p24) that paclitaxel prevents the growth of cancer cells by obstructing cell division and fostering cell death. Paclitaxel is used to treat other types of cancer, including breast and lung cancer. The company describes Nab-Pac as a novel formulation of paclitaxel in which paclitaxel is attached to nanoparticles of albumin and administered without the need for solvents. Albumin-bound paclitaxel results in greater delivery of paclitaxel to the tumour site compared with conventional solvent-based paclitaxel formulations. The company reports that, when combined with Gem, a '…novel, synergistic effect' results in an increase in, and the stabilisation of, levels of intra-tumoural Gem.[24]

Nab-Pac+Gem in the UK

In the Final Appraisal Determination (FAD) for TA360[25] issued in October 2015, NICE did not recommend the use of Nab-Pac+Gem for patients in the NHS with previously untreated metastatic pancreatic cancer. The company reports (CS, p27) that Nab-Pac+Gem was available to patients via CDF between March 2014 and November 2015, and was then removed from the CDF '…in preparation for the new approach to the appraisal and funding of cancer drugs in England'. The ERG notes that Nab-Pac was one of 17 drugs removed from the CDF in November 2015 as a result of a review by a partnership between NHS England, NICE, Public Health England and the Department of Health.[26]

Nab-Pac+Gem is available for use in NHS Wales[1] and in NHS Scotland.[2]

Other licensed indications for nab-paclitaxel

Nab-Pac monotherapy is licensed in Europe[9] for the treatment of people with metastatic breast cancer whose disease has progressed following first-line treatment and who are unsuitable for treatments containing anthracyclines. Nab-Pac in combination with carboplatin is licensed in Europe[9] for the first-line treatment of NSCLC in people whose disease is unsuitable for surgery or radiotherapy. NICE has not appraised Nab-Pac for use in either of these licensed indications.

3.3 Comparators

The comparators specified in the final scope issued by NICE are Gem, Gem+Cap and FOLFIRINOX.

3.3.1 Included comparators

Gemcitabine

Direct clinical evidence is available for the comparison of the effectiveness of Nab-Pac+Gem versus Gem from the CA046 trial. Throughout the CS (pp14, 15, 20, 23, 34, 35, 38, 142, 248), the company is clear that it considers Gem to be the only relevant comparator to treatment with Nab-Pac+Gem.

Gem+Cap and FOLFIRINOX

In the absence of any direct evidence to allow the effectiveness of Nab-Pac+Gem to be compared with that of Gem+Cap or FOLFIRINOX, the company has conducted network meta-analyses (NMAs). However, the company states that the results of the comparative clinical effectiveness and cost effectiveness analyses of Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX are only presented in the CS for completeness. The ERG (and the company) consider that the results of the company's NMA should be treated with caution.

The company does not consider either Gem+Cap or FOLFIRINOX to be relevant comparators to Nab-Pac+Gem for the reasons described in Sections 2.2 and 2.3 of this ERG report.

The company contends that the limited use of Gem+Cap in the NHS means that it does not represent standard of care and that the current use of Gem+Cap in the NHS would not be displaced if Nab-Pac+Gem became available for use. The ERG notes that data presented by the company (CS, Figure 2) indicate that, in 2015, [redacted] of treated patients received Gem+Cap.

The company also contends that patients in the NHS who are suitable for treatment with Nab-Pac+Gem are easily identified and are clinically distinct from patients who would be considered suitable for treatment with Gem or with FOLFIRINOX. Clinical advice to the ERG is that patients who are suitable for treatment with FOLFIRINOX are clinically distinct from patients who are suitable for treatment with Gem monotherapy. However, the ERG is uncertain that patients with metastatic pancreatic cancer who may be considered suitable for treatment with Nab-Pac+Gem in the NHS are clinically distinct from patients who would currently be treated with FOLFIRINOX. Clinical advice to the ERG is that it would be difficult to clearly establish which patients in the NHS would better suited to treatment with Nab-Pac+Gem rather than with FOLFIRINOX.

3.4 Outcomes

The outcomes specified in the final scope issued by NICE are: OS, progression-free survival (PFS), time to tumour progression (TTP), objective response rate (ORR), AEs and health-related quality of life (HRQoL). Direct evidence for the effectiveness of Nab-Pac+Gem versus Gem is derived from the CA046 trial and details relating to OS, PFS, TTP, ORR (reported as overall response rate and disease control rate) and AEs associated with these two treatments are presented in the CS.

No HRQoL data were collected as part of the CA046 trial; the company has used EQ-5D[27] data from the SIEGE trial[28] to populate the economic model. The SIEGE trial[28] is a phase II randomised trial designed to compare two different treatment schedules of Nab-Pac+Gem; the trial does not provide a comparison of Nab-Pac+Gem with Gem. In the clinical section of the CS, (CS, p70-71) the company briefly discusses HRQoL data (EORTC QLQ-C30[29]) from LAPACT,[30] an ongoing phase II single arm trial of patients with locally advanced pancreatic cancer who were treated with Nab-Pac+Gem. The company also summarises HRQoL (EORTC QLQ-C30[29] and EORTC QLQ-PAN26)[31] results from a cross-sectional study[32] of patients with metastatic pancreatic cancer in the US who were treated with three cycles of Nab-Pac+Gem compared with patients who were newly diagnosed.

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained and outcomes were assessed over a 10-year time period (equivalent to a lifetime horizon). Costs were considered from an NHS perspective.

3.5 Subgroups

No patient subgroups were identified in the final scope issued by NICE. In the CS, the company has presented results from the CA046 trial for subgroups based on prognostic factors that were pre-specified in the trial protocol. These were age, sex, PS, tumour location, liver metastases, number of metastatic sites, level of CA19-9 and region of patient recruitment.

3.6 Other relevant factors

The company has not identified any equity or equality issues. Details relating to the patient access scheme (PAS) for Nab-Pac have been provided by the company in a confidential appendix that formed part of the CS.

4 CLINICAL EFFECTIVENESS SYSTEMATIC REVIEW METHODS

4.1 Systematic review methods

The company carried out a systematic search of the literature in May 2013 and updates were conducted in March 2014 and July 2016 to identify phase II-IV RCTs, systematic reviews and meta-analyses designed to investigate the efficacy and safety of pharmacological interventions for people with previously untreated metastatic adenocarcinoma of the pancreas. In addition to the electronic database searches, a number of conference proceedings were searched. The company states that hand searches of the reference lists of the systematic reviews and meta-analyses identified during the searches were performed to identify studies that were potentially relevant to the research question.

The data sources searched, and the time spans for the searches, are provided in Table 9 and a summary of, and ERG comments on, the review methods used by the company are presented in Table 10.

Table 9 Data sources for the clinical systematic review

Search strategy component	Source	Search date range	
		Start	End
Electronic database searches	EMBASE	1974	13 July 2016
	MEDLINE	1946	
	MEDLINE In-Process	1946	
	Cochrane Central Library of Controlled Trials (CENTRAL)	1996	13 July 2016
	Cochrane Database of Systematic Reviews (CDSR)		
	Database of Abstracts of Reviews of Effectiveness (DARE)	1995	13 July 2016
	Database of Health Technology Assessments (HTA)	1995	13 July 2016
	Cumulative Index to Nursing and Allied Health (CINAHL)	1981	24 July 2016
Congress proceedings	American Society of Clinical Oncology (ASCO) ASCO Gastrointestinal Cancers Symposium (GICS or ASCO GI) European Society for Medical Oncology (ESMO) ESMO World Congress on Gastrointestinal Cancer (World GI)	2012	Between 16-17 August 2016

Source: CS, pp44-45

Table 10 Summary of, and ERG comment on, the systematic review methods used by the company

Review method	Results	ERG comment
Searching		
Sources searched: • Electronic databases • Congress proceedings • Clinical trial registries	Initial search=4943 Update 03/2014=635 Update 07/2016=1227	• The last update was carried out in July 2016, meaning that there is a risk that some relevant studies may not have been included in the search results • It is unclear whether the time-periods for the update searches overlapped. Not including an overlap may result in some relevant studies being missed • Only CENTRAL was searched for ongoing trials. Any clinical trials that are only registered in other databases (e.g. ClinicalTrials.gov) will have been missed
Formal eligibility criteria		
Two analysts independently assessed study eligibility based on: - the primary eligibility criteria presented in Table 3, Appendix 2 of the CS (p15)	Unique studies Initial search=97 Update 03/2014=6 Update 07/2016=18	• Use of two independent assessors improves the quality of reviews
Additional eligibility criteria		
The company states that a narrower scope was employed following confirmation of the indication for Nab-Pac+Gem leading to changes in the following: • Population – changed from people with previously untreated metastatic adenocarcinoma of the pancreas to APC patients, of whom at least 50% patients with metastatic pancreatic cancer and must not have had prior systemic therapy for metastatic disease • Comparators - specific Gem-based chemotherapy combinations and FOLFIRINOX, rather than the less-defined list of comparators specified at the primary stage The secondary eligibility criteria are presented in Table 7 of the CS (p46)	Unique studies Initial search=16 Update 03/2014=0 Update 07/2016=1	• Only studies meeting the additional eligibility criteria were included and summarised in the CS
Quality assessment		
The company assessed the risk of bias of the CA046 trial using the minimum criteria recommended by NICE[33] The results of the assessment of risk of bias of the RCTs included in the company's NMA are presented in Appendix 4 of the CS		

APC=advanced pancreatic cancer; CS=company submission; ERG=Evidence Review Group; NMA=network meta-analysis; NICE=National Institute for Health and Care Excellence; RCT=randomised controlled trial
Source: CS, p44-49 and p62-63

4.1.1 Evidence synthesis

The company presents direct evidence to support the clinical efficacy of Nab-Pac+Gem from one RCT (the CA046 trial). The CS includes a narrative description of this trial. No evidence synthesis was undertaken.

4.2 ERG critique of direct clinical effectiveness evidence

4.2.1 Identified trials

Key trial: the CA046 trial

The company presents evidence for the clinical effectiveness of Nab-Pac+Gem from the CA046 trial (also known as mPACT). The CA046 trial was an open-label, multicentre, phase III RCT that was designed to investigate the efficacy and safety of Nab-Pac+Gem versus Gem in patients with untreated metastatic adenocarcinoma of the pancreas. Patients were randomised to receive either Nab-Pac+Gem (Nab-Pac at 125mg/m^2 and Gem at 1000mg/m^2) or Gem 1000mg/m^2. Treatment in both arms was given on days 1, 8 ,15, 29, 36 and 43 for the first 56 days (Cycle 1) and then on days 1, 8 and 15 of a 28-day cycle. Details relevant to the CA046 trial are reported in the CS, in the trial clinical study report (CSR[11]) and in a published paper.[12]

Other trials

Neither the company nor the ERG identified any other trials that directly compare Nab-Pac+Gem with any of the comparators listed in the final scope issued by NICE.

4.2.2 Key characteristics of the CA046 trial

The key characteristics of the CA046 trial are provided in the CS (CS, p50-59) and are summarised in Table 11.

The trial was conducted internationally, however, none of the treatment centres were located in the UK. Clinical advice to the ERG is that treatment centres based in Western Europe and Australia would be most like NHS treatment centres. Patients were randomised to receive either Nab-Pac+Gem (n=431) or Gem (n=430) using a centralised interactive voice recognition system (IVRS). Randomisation was stratified by geographic region (North America versus other), baseline KPS (70 to 80 versus 90 to 100) and presence or absence of liver metastases.

The ERG considers that the CA046 trial was well designed and well conducted. Substantial numbers of patients were recruited; patient crossover did not take place and the trial data are mature. These attributes mean that it is possible to draw reasonable conclusions about the clinical effectiveness of Nab-Pac+Gem versus Gem in the trial population.

Table 11 Key characteristics of the CA046 trial

Location	International, multicentre study involving 151 centres in the USA (n=68), Australia (n=20), Russian Federation (n=19), Italy (n=12), Canada (n=7), Ukraine (n=7), Spain (n=7),

	Germany (n=4), Austria (n=3), France (n=2) and Belgium (n=2).
Design	Randomised, open-label, phase III Stratification factors: geographic region (North America vs other), KPS (70 to 80 vs 90 to 100), presence of liver metastases (yes or no)
Patient eligibility criteria	Inclusion criteria • Metastatic adenocarcinoma of the pancreas (histologically or cytologically confirmed) • Initial diagnosis of metastatic disease ≤6 weeks prior to randomisation • One or more metastatic tumours measurable by CT scan • No previous treatment of metastatic disease • Men or women (nonpregnant and nonlactating), age ≥18 years • Baseline blood counts (see Table 9 of the CS for details) • Baseline chemistry (see Table 9 of the CS for details) • Acceptable coagulation studies • KPS ≥70. Exclusion criteria • Patients with islet cell neoplasms • Known brain metastases unless treated and well controlled for at least 3 months • Only locally advanced disease • Coumadin use • Known infection with HIV, hepatitis B, or hepatitis C • Active, uncontrolled infection(s) requiring systemic therapy • Major surgery ≤4 weeks prior to Day 1 of treatment • History of allergy or hypersensitivity to the study drug • Serious medical risk factors involving any of the major organ systems • History of malignancy in the last 5 years • History of connective tissue disorders • History of interstitial lung disease, slowly progressive dyspnoea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies; • History of chronic leukaemias • High cardiovascular risk • History of peripheral artery disease
Duration of study	Enrolment: May 2009 to March 2011 Primary analysis: 17th Sept 2012 (data cut-off) Follow-up analysis: 9th May 2013 (data cut-off) Death rate at final analysis: 90%

Intervention(s) and comparator(s)	**Nab-Pac+Gem** (n=431): 30 to 40 minute IV infusion of Nab-Pac (125mg/m^2) followed by a 30 to 40 minute IV infusion of Gem (1,000 mg/m^2) on Days 1, 8, 15, 29, 36 and 43 of a 56-day cycle in Cycle 1 only and on Days 1, 8 and 15 of a 28-day cycle in Cycle 2 and onward **Gem** (n=430): 30 to 40 minute IV infusion of Gem (1,000 mg/m^2) on Days 1, 8, 15, 29, 36 and 43 of a 56-day cycle in Cycle 1 only and on Days 1, 8 and 15 of a 28-day cycle in Cycle 2 and onward Treatment was continued until progressive disease or unacceptable toxicity. Dose modifications including a maximum of two dose reductions were allowed from the original dose for toxicity management
Primary outcome	OS (time from randomisation to death from any cause)
Secondary outcomes	PFS, objective tumour response, safety, tolerability
Other efficacy outcomes	PFS and ORR by investigator assessment, time to response and response duration, disease control rate, time to treatment failure, changes in serum CA19-9, tumour response based on PET scans
Duration of follow-up	Median follow-up at the primary analysis (17 September 2012) was 9.1 months (range, 0.1–36.9) in the Nab-Pac+Gem arm, and 7.4 months (range, 0.0–31.3) in the Gem arm

CS=company submission; CT=computed tomography; HIV=human immunodeficiency virus; IV=intravenous; KPS=Karnofsky performance score; ORR=objective response rate; OS=overall survival; PET=positron emission tomography; PFS=progression-free survival; vs=versus
Source: CS, Table 9

4.2.3 Characteristics of patients enrolled in the CA046 trial

The key baseline characteristics of patients included in the CA046 trial are listed in Table 12. The company reports (CS, p60) that the patients' baseline characteristics were well balanced between trial arms. The company is confident (and the ERG agrees) that the population of patients recruited to the CA046 trial matches the patient population identified in the final scope issued by NICE, whilst acknowledging that the patient population in the trial is younger and fitter than patients treated in the NHS.

The ERG notes from the CS (p32) that approximately half (47%) of all pancreatic cancer cases are diagnosed in people aged ≥75 years; however, the company reports (CS, p27) that only 10% of patients in the CA046 trial were aged 75 years or over. Clinical advice to the ERG is that in the NHS, almost half of patients diagnosed with pancreatic cancer are aged ≥75 years. In the SmPC[9] for Nab-Pac, the EMA cautions that there is a lack of evidence of clinical efficacy in people aged ≥75 years and that patients aged ≥75 years who were treated with Nab-Pac+Gem in the CA046 trial experienced more AEs and SAEs than the overall trial population. Consequently, it is not known if the treatment effect estimated for the population of the CA046 trial is generalisable to the population expected to be seen in clinical practice. Furthermore, the occurrence of AEs and SAEs that would be seen in clinical practice may be underestimated by the CA046 trial, due to the small proportion of people aged ≥75 years in the trial population.

Table 12 Key characteristics of patients in the CA046 trial

Characteristic		Nab-Pac+Gem N=431	Gem N=430	All N=861
Age (median) years (range)		62 (27 to 86)	63 (32 to 88)	63 (27 to 88)
Age categories	< 65 –n (%)	254 (59)	242 (56)	496 (58)
	≥ 65 –n (%)	177 (41)	188 (44)	365 (42)
Sex n (%)	Female	186 (43)	173 (40)	359 (42)
	Male	245 (57)	257 (60)	502 (58)
Race or ethnic group n (%)	Asian	8 (2)	9 (2)	17 (2)
	Black	16 (4)	16 (4)	32 (4)
	White	378 (88)	375 (87)	753 (87)
	Hispanic	25 (6)	26 (6)	26 (6)
	Other	4 (1)	4 (1)	8 (1)
Region n (%)	Australia	61 (14)	59 (14)	120 (14)
	Eastern Europe	64 (15)	62 (14)	126 (15)
	North America	268 (62)	271 (63)	539 (63)
	Western Europe	38 (9)	38 (9)	76 (9)
KPS score n/total n (%)	100	69/429 (16)	69/429 (16)	138/858 (16)
	90	179/429 (42)	199/429 (46)	378/858 (44)
	80	149/429 (35)	128/429 (30)	277/858 (32)
	70	30/429 (7)	33/429 (8)	63/858 (7)
	60	2/429 (<1)	0/429	2/858 (<1)
Pancreatic tumour location n (%)	Head	191 (44)	180 (42)	371 (43)
	Body	132 (31)	136 (32)	268 (31)
	Tail	105 (24)	110 (26)	215 (25)
	Unknown	3 (1)	4 (1)	7 (1)
Site of metastatic disease n (%)	Liver	365 (85)	360 (84)	725 (84)
	Lung	153 (35)	184 (43)	337 (39)
	Peritoneum	19 (4)	10 (2)	29 (3)
Number of metastatic sites n (%)	1	33 (8)	21 (5)	54 (6)
	2	202 (47)	206 (48)	408 (47)
	3	136 (32)	140 (33)	276 (32)
	>3	60 (14)	63 (15)	123 (14)
Previous therapy n (%)	Radiation therapy	19 (4)	11 (3)	30 (3)
	Chemotherapy	23 (5)	12 (3)	35 (4)
	Whipple procedure	32 (7)	30 (7)	62 (7)
	Biliary stent	80 (19)	68 (16)	148 (17)

KPS=Karnofsky performance status
Source: CS, Table 11

4.2.4 Statistical approach adopted

Information relevant to the statistical approach taken by the company to analyse data from the CA046 trial has been taken from the CS, the trial CSR, the trial protocol,[34] and the statistical analysis plan (SAP).[35]

Sample size calculation

Details of the sample size calculation performed by the company are reported in the CS (p56). The trial was powered (at the 90% level) to detect a HR for death, for the comparison of the effectiveness of Nab-Pac+Gem versus Gem, of 0.769 with a two-sided alpha level of 0.049. This required a sample size of 842, with 608 events. The ERG is satisfied that the company's pre-specified sample size calculation was carried out correctly.

Protocol amendments

A list of protocol amendments is included in the CSR (p58-62). The key protocol amendments that could have influenced the outcomes and analyses of CA046 are:

Protocol amendment 1 (20 Mar 2009)

- Added serum CA19-9 and plasma secreted protein acid and rich in cysteine (SPARC) levels as secondary objectives and endpoints
- Added an interim analysis (evaluated by independent data monitoring committee) with the possibility of stopping the study prematurely due to lack of efficacy
- Clarified the primary efficacy endpoint hypotheses and modified the confidence interval (CI) of the OS HR to account for the interim efficacy analysis

Protocol amendment 2 (17 Nov 2009)

- Added language to the randomisation stratification categories
- Modified the statistical procedure for testing the secondary efficacy endpoints from the Hochberg[36] procedure to a sequential step-down procedure, where PFS was tested first and ORR was tested only if PFS was statistically significant

Protocol amendment 4 (30 Sep 2010)

- Modified sample size (increased required number of deaths to at least 608, and enrolled patients to 842) to allow for an increase in statistical power from 80% to 90%

The ERG notes that the protocol amendment changes took place before any data analyses. Thus, they were not driven by the results of the trial and, therefore, are unlikely to be a cause for concern.

Outcomes and analyses

The intention-to-treat (ITT) population, which consisted of all randomised patients, was used in all efficacy analyses. Safety analyses were carried out in the treated population, which consisted of all randomised patients who received at least one dose of the trial drug.

The primary outcome of OS was analysed using the Kaplan-Meier (K-M) method, and a stratified log-rank test. A stratified Cox proportional hazards (PH) model was used to estimate the HR and corresponding 95% CI. Cox regression analyses, including adjustments for stratification factors, were also carried out to estimate treatment effects.

The secondary outcomes were PFS and ORR, which were assessed by independent review according to Response Evaluation in Solid Tumours (RECIST) criteria, and safety and tolerability of the administered treatments. Investigator-assessed PFS and ORR were also reported. Cox PH methods and a stratified log-rank test were used to generate PFS results. Patient ORRs were compared between the two arms of the trial using the chi-square test.

The ERG is satisfied that all outcomes were pre-specified in the SAP and reported in full in the CSR.

The analyses carried out by the company to generate OS and PFS HRs from CA046 trial data were conducted using Cox PH modelling. The validity of this method relies on the survival hazards of patients in the two arms of the trial being proportional over time. The company assessed the validity of the PH assumption using the following methods:

- Visual inspection of log-cumulative hazard (LCH) plots
- Visual inspection of Schoenfeld residual plots and corresponding correlation estimates and p-values assessing proportionality
- Comparison of observed and predicted K-M curves (estimated using a Cox PH regression model)

The company presents each of these plots for the outcomes of OS and PFS in Appendix 4 of the CS. However, in their interpretation of these plots (CS, p98-101), the company does not draw any firm conclusions about whether OS and PFS hazards for patients in the two arms of the CA046 trial can be considered to be proportional over time.

The ERG has assessed the validity of the OS and PFS PH assumptions by plotting the cumulative hazard associated with Nab-Pac+Gem treatment versus the cumulative hazard associated with Gem treatment (H-H plot) for each outcome, together with the constant PH trend line. If the PH assumption is valid for these data, the data points should lie close to the trend line and be evenly distributed either side of it. Figure 1 displays the H-H plot for the OS

data. The plot suggests that the PH assumption for OS data is violated; data points fall below the PH trend line in the first half of the analysis and then sit above the trend line in the second half. The violation is confirmed by a regression test of linearity, the result from which indicates statistically significant non-linearity (p<0.001).

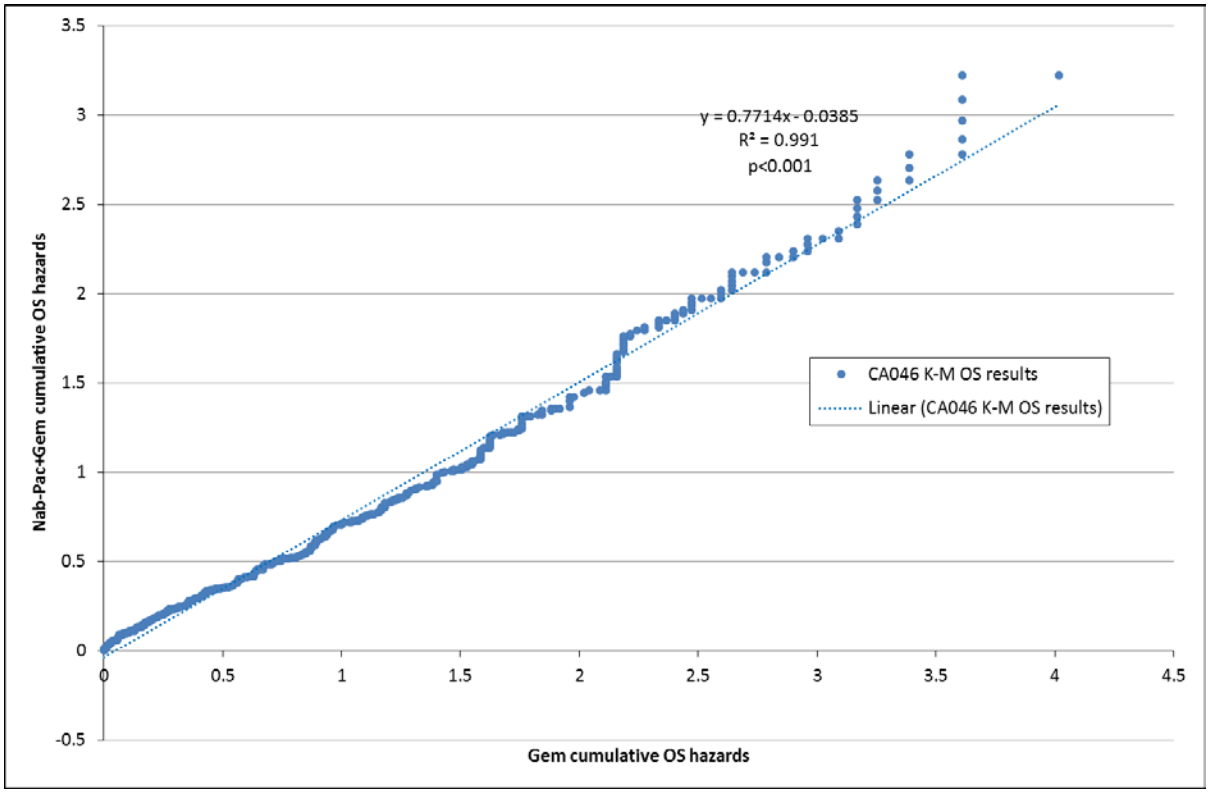

Figure 1 ERG comparative cumulative OS hazard plot for Nab-Pac+Gem vs Gem in CA046 trial

OS=overall survival

The H-H plot for PFS data (Figure 2) shows a systematic divergence from the PH trend line, suggesting that the PH assumption is violated. The violation is confirmed by a regression test of linearity, the result from which indicates statistically significant non-linearity (p<0.001).

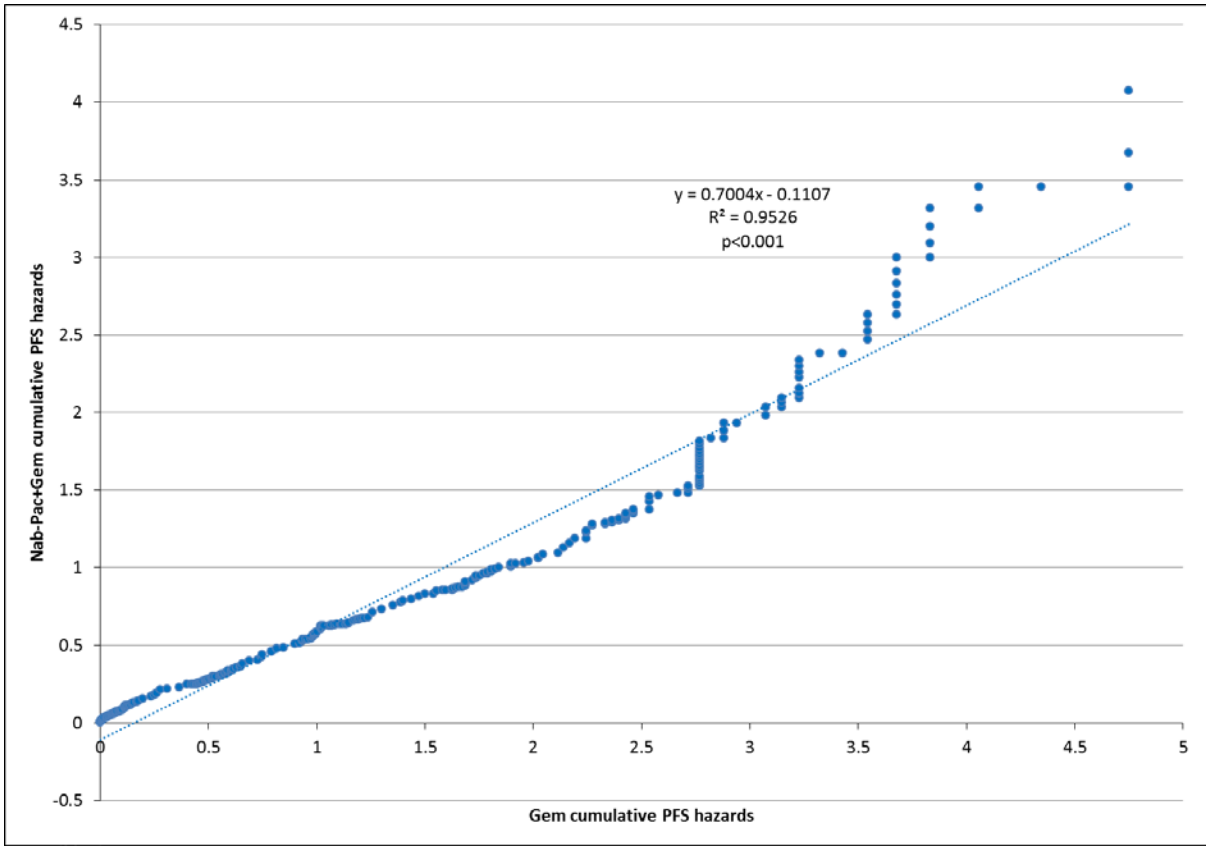

Figure 2 Comparative cumulative PFS hazard plot for Nab-Pac+Gem vs Gem in CA046 trial

PFS=progression-free survival

The ERG's H-H plots suggest that the PH assumption does not hold for the CA046 trial OS or PFS data and, consequently, HRs are not an appropriate summary of treatment effect for this trial. It is not possible to know whether the reported HRs would overestimate or underestimate the effect of Nab-Pac+Gem in comparison to Gem, and all CA046 trial HRs should be interpreted with caution.

Subgroup analyses

Subgroup analyses for the primary outcome of OS were pre-specified in the SAP. The ERG is satisfied that the results from these analyses are provided in full in the CSR. It is stated in the CS (p55) that, for the subgroup analyses of geographic region, baseline KPS, and presence of liver metastases, clinical data rather than randomisation data were used (i.e., analyses were based on data in the clinical report file collected and verified on site rather than on the IVRS information provided for randomisation). The company explained in their response to the ERG clarification letter that the clinical data were source document verified whilst the randomisation data were not and, therefore, the clinical data were considered to be the more accurate. The ERG is satisfied with the company's explanation.

Sensitivity analyses

Sensitivity analyses to investigate the robustness of the results of the primary outcome analyses were pre-specified in the SAP. The ERG is satisfied that the results of all of the sensitivity analyses were fully reported in the CSR.

Timing of analyses

An interim analysis for OS was pre-specified in the CA046 trial protocol. This was performed after at least 200 patients had been followed for at least 6 months from the date of randomisation. The interim analysis was designed to evaluate futility, with the possibility of stopping the trial early due to lack of efficacy. As determined by the pre-specified sample size calculation, the final analysis of OS was conducted when at least 608 deaths had occurred; all deaths that occurred on, or prior to, the projected clinical cut-off date, were included in the analysis.

The final OS analysis was based on 692 deaths (80% of patients, data cut-off: 17 September 2012). Median follow-up was 9.1 months in the Nab-Pac+Gem arm and 7.4 months in the Gem arm.

An updated analysis of OS from the CA046 trial with an extended data cut-off (8 months longer than the final OS analysis) was reported in a paper by Goldstein[37] (data cut-off: 9 May 2013). At the time of the updated analysis, 774 (90%) patients in the ITT population had died and median follow-up was 13.9 months. The ERG is aware that this is a post-hoc analysis; however, this is not a cause for concern as it is unlikely that the updated results could be subject to bias. The motivation for undertaking the follow-up analysis is clear - at this point, 90% of the ITT population had experienced an event compared with 80% at the time of the primary analysis.

Overall, the ERG considers that appropriate statistical methods were used for the analyses of CA046 trial data, with the exception of the inappropriate generation of HRs to compare survival (OS and PFS) between trial arms.

4.2.5 Risk of bias assessment for the CA042 trial

The company assessed the risk of bias in the CA046 trial using the minimum criteria set out in NICE's Guide to the Methods of Technology Appraisal.[33] The ERG agrees with the company that the risk of bias is low for all the criteria listed in Table 13. The ERG notes that the CA046 trial was of an open-label design; however, a blinded review of the investigator-assessed radiological outcomes was conducted. The ERG considers that a notable strength of the CA046 trial is that the study protocol prohibited treatment crossover.

Table 13 Risk of bias assessment of the CA046 trial

Study question	Company assessment		
	Addressed in the trial?	Risk of bias	ERG comment
Was randomisation carried out appropriately?	Yes. Randomisation schedule was generated by a randomisation statistician, with stratification for key prognostic factors.	Low	Agree
Was the concealment of treatment allocation adequate?	Yes. Randomisation was implemented via a centralised IVRS.	Low	Agree
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Patient demographics were well balanced, with no key differences between treatment groups.	Low	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	Independent assessors were blinded; care providers and participants were not.	Low	Agree
Were there any unexpected imbalances in drop-outs between groups?	No. The most common reason for study withdrawal in both treatment arms was disease progression, which is fully accounted for within efficacy assessments.	Low	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.	Low	Agree
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analyses were performed according to the ITT principle, with standard censoring methods used to account for missing data.	Low	Agree

IVRS=interactive voice response system; ITT=intention-to-treat
Source: CS, Table 12

4.2.6 Participant disposition in the CA046 trial

The company provided a Consolidated Standards of Reporting Trials (CONSORT) flow chart to show patient disposition in the CA046 at the time of the final analysis (CS, Figure 3). In summary:

- in total, 861 patients were randomised; 420 were treated with Nab-Pac+Gem, and 403 were treated with Gem
- over 90% of patients in both treatment arms had discontinued therapy at the time of the final analysis data cut-off; the majority due to progressive disease (47% in the Nab-Pac+Gem arm and 61% in the Gem arm)
- one patient was randomised to treatment with Gem but received treatment with Nab-Pac+Gem

- at the time of final analysis, median duration of treatment was 3.9 months (range: 0.1–21.9) in the Nab-Pac+Gem arm and 2.8 months (range: 0.1–21.5) in the Gem arm
- in the Nab-Pac+Gem arm, 41% of patients had reductions in the Nab-Pac dose, and 47% of patients had reductions in the Gem dose; in the Gem arm, 33% of patients had dose reductions
- the use of second-line therapies was balanced between the treatment arms (38% in the Nab-Pac+Gem arm and 42% in the Gem arm); although not permitted by protocol, a small number (6%) of patients in the Gem arm received Nab-Pac+Gem as a second-line treatment.

At the time of the updated survival analysis[37] (9 May 2013 data cut-off), the median duration of treatment was 3.4 months in the Nab-Pac+Gem arm, and 2.3 months in the Gem arm.

4.3 Results from the CA046 trial

The validity of the method used by the company to generate OS and PFS HRs relies on the assumption that the survival hazards for patients in the two arms of the trial are proportional over time. The ERG considers that this assumption does not hold for the OS or PFS data (see Section 4.2.4). Consequently, the HRs reported throughout Section 4.3.1 and Section 4.3.2 must be interpreted with caution.

4.3.1 Final efficacy analysis (17 September 2012 data cut-off)

A summary of the primary and secondary outcome data from the CA046 trial is presented in Table 14. All analyses were carried out using data from the ITT population.

Table 14 CA046 trial primary and secondary efficacy endpoints (ITT population: 17 September 2012 data cut-off)

Efficacy variable	Nab-Pac+ Gem (N=431)	Gem (N=430)	HR or RRR (95% CI)*	p-value
OS				
Events, n (%)	333 (77)	359 (83)	-	-
Censored, n (%)	98 (23)	71 (17)	-	-
Median months (95% CI)	8.5 (7.9 to 9.5)	6.7 (6.0 to 7.2)	0.72 (0.62 to 0.83)	<0.001
Survival rate, % (95% CI) 6 months 12 months 18 months 24 months	 67 (62 to 71) 35 (30 to 39) 16 (12 to 20) 9 (6 to 13)	 55 (50 to 60) 22 (18 to 27) 9 (6 to 12) 4 (2 to 7)	 - - - -	 <0.001 <0.001 0.008 0.02
PFS (independent review)				
Events, n (%)	277 (64)	265 (62)	-	-
Censored, n (%)	154 (36)	165 (38)	-	-
Median months (95% CI)	5.5 (4.5 to 5.9)	3.7 (3.6 to 4.0)	0.69 (0.58 to 0.82)	<0.001

Efficacy variable	Nab-Pac+ Gem (N=431)	Gem (N=430)	HR or RRR (95% CI)*	p-value
PFS rate, % (95% CI) 6 months 12 months 18 months	 44 (39 to 50) 16 (12 to 21) 5 (2 to 11)	 25 (20 to 30) 9 (5 to 14) 7 (3 to 13)	 - - -	 - - -
PFS (investigator assessment)				
Events, n (%)	327 (76)	348 (81)	-	-
Censored, n (%)	104 (24)	82 (19)	-	-
Median months (95% CI)	5.3 (4.4 to 5.5)	3.5 (3.3 to 3.7)	0.61 (0.52 to 0.71)	<0.001
PFS rate, % (95% CI) 6 months 12 months	 41 (35.6 to 45.6) 12 (8.3 to 16.0)	 18 (13.8 to 21.9) 4 (1.9 to 6.5)	 - -	 - -
ORR (independent review)				
No. of patients with response	99	31	3.19 (2.18 to 4.66)	<0.001
% (95% CI)	23 (19 to 27)	7 (5 to 10)	-	-
No. of patients with disease control**	206	141	1.46 (1.23 to 1.72)	<0.001
% (95% CI)	48 (43 to 53)	33 (28 to 37)	-	-
Best response, n (%): Complete response Partial response Stable disease Progressive disease Not evaluable No post-baseline assessment	 1 (<1) 98 (23) 118 (27) 86 (20) 56 (13) 72 (17)	 0 31 (7) 122 (28) 110 (26) 80 (19) 87 (20)	 - - - - - -	 - - - - - -
ORR (investigator assessment)				
No. of patients with response	126	33	3.81 (2.66 to 5.46)	<0.001
% (95% CI)	29 (25 to 34)	8 (5 to 11)	-	-
Best response, n (%): Complete response Partial response Stable disease Progressive disease Not evaluable No post-baseline assessment	 6 (1) 120 (28) 96 (22) 96 (22) 43 (10) 70 (16)	 0 33 (8) 105 (24) 156 (36) 50 (12) 86 (20)	 - - - - - -	 - - - - - -

CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RRR=response rate ratio.
* HRs are provided for OS and PFS; the RRRs are provided for the ORRs
** Disease control included confirmed complete response, confirmed partial response, and stable disease for at least 16 weeks
Source: CS, Table 13

Overall survival

Treatment with Nab-Pac+Gem statistically significantly improved median OS in comparison to treatment with Gem (8.5 months versus 6.7 months; HR=0.72, 95% CI: 0.62 to 0.83). The

incremental OS benefit of treatment with Nab-Pac+Gem was 1.8 months. The effect of Nab-Pac+Gem was consistent over time as survival rates were statistically significantly higher in the Nab-Pac+Gem arm than in the Gem arm at both 1 year and 2 years ($p<0.001$ and $p=0.02$, respectively).

The company also performed a multivariate analysis of OS (using a Cox PH regression model) to evaluate treatment effect adjusted for the stratification factors used at randomisation (geographic region, KPS, presence of liver metastases). The results of this analysis also suggest a statistically significant improvement in OS for patients in the Nab-Pac+Gem arm in comparison to patients in the Gem arm (HR=0.71, 95% CI: 0.61 to 0.83; $p<0.0001$). The results suggest that lower KPS (70 to 80) and presence of liver metastases are independently associated with a higher risk of death.

All the sensitivity analyses carried out by the company showed a statistically significant OS treatment effect in favour of patients treated with Nab-Pac+Gem. The analyses included a sensitivity analysis of subsequent therapy, where survival data were censored at the time that subsequent treatment began. Median OS was statistically significantly longer for patients treated with Nab-Pac+Gem than for patients treated with Gem (9.4 months vs 6.8 months; HR=0.68, 95% CI: 0.56 to 0.82; $p<0.001$).

The company also outlined details of post-hoc exploratory analyses (CS, p65). Median survival in patients who received second-line treatment was significantly longer in the Nab-Pac+Gem group than in the Gem group (12.8 months versus 9.9 months; HR=0.76, 95% CI: 0.61 to 0.95; $p=0.015$). Median OS was also statistically significantly longer for patients treated until disease progression in the Nab-Pac+Gem group than for patients in the Gem group (9.8 months versus 7.5 months, $p<0.001$).

The company states that the results of these post-hoc analyses suggest that prolonged first-line treatment exposure and ability to receive subsequent therapies can further improve survival. The ERG notes that, irrespective of first-line treatment, compared with the overall trial population, median OS is longer within both the subgroup of patients receiving second-line treatment and the subgroup of patients who were treated until disease progression. However, the ERG also notes that no formal statistical testing was performed to detect differences between these subgroups and the overall trial population and it is, therefore, not possible to conclude that prolonged treatment, or the use of subsequent therapy, improves survival in this patient population.

Subgroup analyses for overall survival

The results of the subgroup analyses are reported in the CS (Figure 8, p74). The estimate of treatment effect favoured treatment with Nab-Pac+Gem rather than Gem in all subgroups, except patients with normal CA19-9 levels for whom no conclusions could be drawn. The company highlights that patients with more advanced disease generally benefited from treatment with Nab-Pac+Gem more than patients with less advanced disease, i.e., patients with poorer KPS (70-80), patients with >3 metastatic sites, and patients with elevated CA19-9 levels. The ERG agrees with the company's observations but notes that these analyses were not powered to detect subgroup differences and, therefore, it is not possible to draw firm conclusions about treatment effect in patients with more advanced disease.

The company also highlights that although no UK patients were enrolled in the CA046 trial, the subgroup of patients from Western Europe had the same reduction in risk of death as the total patient population (HR=0.72) for Nab-Pac+Gem versus Gem alone. Furthermore, the company refers to a subgroup analysis of the dataset for the updated OS analysis (data cut-off: 9 May 2013), the results from which show that median OS in the Western Europe cohort was 3.8 months greater in the Nab-Pac+Gem group (n=38) than in the Gem group (n=38), although this difference was not statistically significant (HR=0.82, 95% CI: 0.48 to 1.4; p=0.471).[38] The ERG notes that the number of patients in this latter subgroup was relatively small, so the absence of a statistically significant result is not of concern.

Progression-free survival

Treatment with Nab-Pac+Gem statistically significantly improved median PFS in comparison to treatment with Gem. Table 14 shows an incremental PFS benefit of 1.8 months for both PFS by independent review (HR=0.69, 95% CI: 0.58 to 0.82) and PFS by investigator assessment (HR=0.61, 95% CI: 0.52 to 0.71). At 1 year, PFS rates were greater in the Nab-Pac+Gem group compared with the Gem group (16% versus 9%, independent review; 12% versus 4%, investigator assessment). The ERG is not concerned about the differences between investigator assessment and independent review as the independent reviewer often has less information to work with than the trial investigator.

The ORR assessed by independent review was statistically significantly higher for patients treated with Nab-Pac+Gem than for those treated with Gem (23% versus 7%; response rate ratio [RRR]=3.19, 95% CI: 2.18 to 4.66; p<0.001). This finding was supported by ORR assessed by investigator which was also statistically significantly higher for patients treated with Nab-Pac+Gem than for patients treated with Gem (29% versus 8%; RRR=3.81, 95% CI: 2.66 to 5.46; p<0.001).

4.3.2 Updated survival analysis (9 May 2013 data cut-off)

Results of the updated post-hoc OS analysis[37] (data cut-off: 9 May 2013) are provided in Table 15.

Table 15 Updated survival estimates in the CA046 trial (ITT population; 9 May 2013 data cut-off)

	Nab-Pac+Gem (N=431)	Gem (N=430)	HR (95% CI)	p-value
Events, n (%)	380 (88)	394 (92)	-	-
Censored, n (%)	51 (12)	36 (8)	-	-
Median months (95% CI)	8.7 (7.9 to 9.7)	6.6 (6.0 to 7.2)	0.72 (0.62 to 0.83)	<0.0001
Survival rate, % (95% CI) 6 months 12 months 24 months 36 months 42 months	 66 (62 to 71) 35 (31 to 40) 10 (6 to 13) 4 (2 to 7) 3 (1 to 6)	 55 (50 to 60) 22 (18 to 26) 5 (2, 7) 0 0	-	-

CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat
Source: CS, Table 14

The reported updated OS HR of 0.72 (95% CI: 0.62 to 0.83) is in accordance with the findings of the primary analysis, supporting the evidence for a statistically significant benefit of treatment with Nab-Pac+Gem in comparison to Gem (8.7 months versus 6.6 months). The incremental OS benefit for Nab-Pac+Gem versus Gem is 2.1 months. The company states that the results of the updated OS analysis[37] show mean OS to be 11.1 months in the Nab-Pac+Gem arm and 8.7 months in the Gem arm.

Results from all sensitivity analyses demonstrated a statistically significant improvement in OS for patients treated with Nab-Pac+Gem compared with those treated with Gem. Results from a multivariate regression analysis (using a Cox PH model) adjusting for the randomisation stratification factors also demonstrated a statistically significant treatment benefit in favour of Nab-Pac+Gem versus Gem (HR=0.68, 95% CI: 0.57 to 0.80; p<0.001).

4.4 Health-related quality of life

The company reports (CS, p69) that HRQoL data were not collected during the CA046 trial but has presented information from three different sources, namely the SIEGE[28] trial, the LAPACT[30] trial and a cross-sectional study[32] that was conducted in the USA. Key details about these trials are presented in Table 16.

The SIEGE[28] trial has the greatest relevance to the current appraisal as it is a UK-based randomised trial that recruited patients with metastatic pancreatic cancer. However, the

SIEGE[28] trial was designed to compare two dose schedules of Nab-Pac+Gem and only the 'concomitant arm' (i.e. treatment with Gem immediately after treatment with Nab-Pac) is relevant to the appraisal under discussion. The LAPACT[30] trial is an ongoing phase II single arm trial that is recruiting patients with locally advanced pancreatic cancer and the Picozzi[32] study is a small US-based retrospective study that compares data from patients treated with Nab-Pac+Gem with patients who did not receive treatment for their metastatic pancreatic cancer.

The company summarises (CS, p70) the HRQoL data from the SIEGE[28] trial that were presented at the 2017 American Society of Clinical Oncology (ASCO) conference. The company describes the data as 'early' and states that the Global Health Status scores collected using the EORTC QLQ-C30 questionnaire were stable across time; however, data were only available from a small number of patients (n=22) at week 24 of the trial. The EQ-5D-5L data from the SIEGE[28] trial were used as the basis for estimating utility values that were used in cost effectiveness scenario analyses.

Table 16 Key details about studies mentioned in the company submission that collected HRQoL data

	Patient population	**Geographical region**	**Study design** **Number patients**	**Data collected**	**ERG comment**
SIEGE[28]	Metastatic pancreatic ductal carcinoma	UK	Phase II randomised trial comparing sequential Nab-Pac+Gem (n=71) with concomitant Nab-Pac+Gem (n=75)	EORTC QLQ-C30 EQ-5D-5L	UK-based trial Non-comparative data only Only early results available
LAPACT[30]	Locally advanced pancreatic adenocarcinoma	Not reported	Phase II single arm ongoing Nab-Pac+Gem 36 respondents	EORTC QLQ-C30	Ongoing trial Small number of respondents Locally advanced disease
Picozzi[32]	Metastatic pancreatic cancer	USA	Cross sectional study Nab-Pac+Gem (n=26) No treatment (n=29)	EORTC QLQ-C30 EORTC QLQ-PAN26 EQ-5D	Real world evidence Small retrospective study Based in USA

4.5 Adverse events reported in the CA046 trial

Details of the AEs experienced by patients participating in the CA046 trial (data cut-off 17 September 2012) are presented in Section 4.12 of the CS (p106-121). The ERG notes from the CSR (p135) that the median treatment duration for patients treated with Nab-Pac+Gem was 3.9 months, compared to 2.8 months for patients treated with Gem. It is also stated in

the CSR that the median number of treatment doses given to patients in the Nab-Pac+Gem arm was 12; nine doses were given to patients in the Gem arm.

The company discusses AEs in terms of being treatment-emergent or treatment-related. Treatment-emergent AEs (TEAEs) are defined as any AEs that begin or increase in intensity after study drug initiation up to 30 days after the last dose or the end of the study, whichever is later. Treatment-related AEs (TRAEs) are defined as AEs that were considered by the trial investigator to be either possibly, probably or definitely related to the study drug.

Summary of safety data are summarised in Table 21 of the CS (p107) and are reproduced in Table 17. The company observes that 99% of patients treated with Nab-Pac+Gem reported at least one TEAE and that 96% of these were assessed as being treatment-related. Compared with patients in the Gem arm, patients in the Nab-Pac+Gem arm experienced more Grade ≥3 TRAEs (77% vs 50%) and more AEs (any grade) leading to treatment discontinuation (35% versus 24%), dose reduction (50% versus 31%) or dose delay (66% versus 48%). The proportion of treatment-emergent deaths was the same in both trial arms (4%). The company states that the higher rates of Grade ≥3 AEs and SAEs in the Nab-Pac+Gem arm compared with the Gem arm were expected as additive toxicity is often observed when administering anti-chemotherapy agents concurrently (CS, p106-107).

Table 17 Overview of safety data in CA046 trial

Category of event	**Nab-Pac+Gem N=421 n (%)**	**Gem N=402 n (%)**
Patients with at least one TEAE	417 (99)	395 (98)
Patients with at least one treatment-related TEAE	403 (96)	371 (92)
Patients with at least one SAE	212 (50)	172 (43)
Patients with at least one treatment-related SAE	121 (29)	53 (13)
Patients with at least one TRAE leading to dose reduction	209 (50)	125 (31)
Patients with at least one AE leading to dose delay	276 (66)	192 (48)
Patients with at least one Grade ≥3 AE	374 (89)	303 (75)
Patients with at least one Grade ≥3 TRAE	325 (77)	203 (50)
Patients with at least one TEAE leading to treatment discontinuation	149 (35)	95 (24)
Patients with at least one TEAE with outcome of death	18 (4)	18 (4)

AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TRAE-treatment-related adverse event.
Source: CS, Table 21

Treatment-emergent adverse events

The company lists the incidence of TEAEs of all grades experienced by 40% or more of patients in either treatment arm (CS, p107-108). The company reports that the most frequently reported events in the Nab-Pac+Gem arm (in descending order) were fatigue

(59%), peripheral neuropathy (54%), nausea (54%), alopecia (50%), peripheral oedema (46%), diarrhoea (44%), anaemia (42%), neutropenia (42%) and pyrexia (41%). The ERG notes that in the Gem arm, the most frequently reported TEAEs were nausea (48%), fatigue (46%), anaemia (33%), peripheral oedema (31%) and neutropenia (30%). The TEAEs with the greatest observed differences between treatment groups were peripheral neuropathy (54% in the Nab-Pac+Gem arm and 13% in the Gem arm) and alopecia (50% in the Nab-Pac+Gem arm and 5% in the Gem arm).

Table 22 in the CS (p108-109) lists the incidence of TEAEs assessed as Grade ≥3 in more than 5% of patients; this table is replicated in Table 18 of this ERG report. The company comments that there were more AEs reported by patients treated with Nab-Pac+Gem than by patients treated with Gem (89% versus 75%). The company points out that the most frequently reported AEs in the Nab-Pac+Gem arm were neutropenia (33%), fatigue (18%), metabolism and nutritional disorders (18%), peripheral neuropathy (17%), thrombocytopenia (13%) and anaemia (12%). The ERG notes that the most frequently reported AE in the Gem arm was neutropenia (21%).

Table 18 Treatment-emergent adverse events (Grade ≥3) in the CA046 trial (≥5% in either group)

Category of event	Nab-Pac+Gem N=421 n (%)	Gem N=402 n (%)
At least one Grade ≥3 AE	374 (89)	303 (75)
Blood and lymphatic system disorders	202 (48)	128 (32)
Neutropenia	138 (33)	85 (21)
Thrombocytopenia	53 (13)	33 (8)
Anaemia	49 (12)	32 (8)
Leukopenia	39 (9)	15 (4)
General disorders and administration site conditions	132 (31)	76 (19)
Fatigue	77 (18)	37 (9)
Asthenia	29 (7)	17 (4)
Gastrointestinal disorders	114 (27)	92 (23)
Abdominal pain	27 (6)	32 (8)
Diarrhoea	26 (6)	6 (1)
Nausea	27 (6)	14 (3)
Vomiting	25 (6)	15 (4)
Nervous system disorders	82 (19)	19 (5)
Peripheral neuropathy SMQ	70 (17)	3 (1)
Metabolism and nutritional disorders	76 (18)	48 (12)
Dehydration	31 (7)	10 (2)
Decreased appetite	23 (5)	8 (2)
Respiratory, thoracic and mediastinal disorders	41 (10)	45 (11)
Pulmonary embolism	19 (5)	26 (6)
Vascular disorders	41 (10)	39 (10)
Deep vein thrombosis	21 (5)	22 (5)

AE=adverse event; SMQ=standardised MeDRA (Medical Dictionary for Regulatory Activities) query
Source: CS, Table 22

Serious adverse events

Appendix 3 of the CS reports the overall incidence of SAEs to be 50% in the Nab-Pac+Gem arm and 43% in the Gem arm. The majority of SAEs were reported to have similar rates across both arms of the trial. The exception was pyrexia (6% Nab-Pac+Gem versus 2% Gem). Febrile neutropenia was experienced by 3% of patients in the Nab-Pac+Gem arm compared to <1% of patients in the Gem arm.

The company (CS, p112) reports the AE rates according to particular subgroups of patients that were not pre-planned. These include age (≤65 years, ≥65 years, and ≥75 years), males versus females and geographical region.

It is recorded in the CS (p112-113) that the rates of AEs and SAEs were higher in older patients (≥65 years) treated with Nab-Pac+Gem than in the overall treated population. The CS also reports that for patients aged ≥75 years, more frequent Grade 3 TEAEs, SAEs, TEAEs with an outcome of death and TEAEs leading to study discontinuation were recorded in the Nab-Pac+Gem arm than in the Gem arm. The number of patients aged ≥75 years of age included in the study was small (n=84), and therefore, comparisons of TEAEs in this subgroup should be interpreted with caution. The ERG notes that the EMA's marketing authorisation[9] for Nab-Pac+Gem contains a warning regarding the increased risk of AEs in the ≥75 years of age group and states that use of Nab-Pac for the treatment of patients ≥75 years should be carefully considered.

The company reports that TEAEs with a ≥10% difference in women compared with men were neutropenia (49% versus 36%), anaemia (49% versus 36%), vomiting (44% versus 29%), and urinary tract infection (17% versus 4%). Neutropenia was the only Grade 3 or higher TEAE reported with a >5% difference in women than men (40% versus 27%).

The overall incidence of TEAEs, Grade 3 or higher TEAEs, and SAEs was similar between patients from the four different geographic regions (North America, Western Europe, Eastern Europe and Australia) that were considered.

Peripheral neuropathy

The company states (CS, p109) that the majority of cases of Grade ≤3 neuropathy could be reversed and managed by delaying further treatment or reducing the dose until the condition improved to Grade ≤1. The company also reports that a (not pre-specified) subgroup analysis showed that patients who developed Grade 3 peripheral neuropathy had increased treatment exposure and thus experienced significantly better OS, PFS, ORR compared to those who did not develop peripheral neuropathy (CS, p109, Table 23, replicated in Table 19). The company reports that peripheral neuropathy was rapidly reversible with treatment interruption and that the median time to improvement to Grade 1 severity was 29 days. The ERG considers that 29 days is a substantial period for a patient with metastatic pancreatic cancer. The ERG notes from the CSR that peripheral neuropathy was the most common reason for treatment discontinuation (8%) in the Nab-Pac+Gem arm.

Table 19 Treatment exposure and efficacy outcomes by grade of peripheral neuropathy in the Nab-Pac+Gem group of the CA046 trial

	Grade of peripheral neuropathy				HR or RRR (95% CI)* p-value
	0	1	2	3	
OS, median months (95% CI)	5.9 (4.7 to 6.9)	9.0 (8.3 to 12.3)	12.6 (9.6 to 15.7)	14.9 (11.9 to 19.2)	0.33 (0.23 to 0.48) p<0.0001
PFS, median months (95% CI)	3.5 (3.1 to 3.8)	5.6 (4.5 to 6.2)	9.3 (7.2 to 12.6)	9.1 (7.5 to 11.5)	0.27 (0.18 to 0.41) p<0.0001
ORR, % (95% CI)	8 (4.4 to 1.24)	29 (20.3 to 39.3)	43 (30.0 to 55.9)	43 (31.1 to 55.3)	5.54 (3.18 to 9.67) p<0.0001
Median treatment cycles (range)	1 (1–13)	4 (1–17)	6 (1–2)	6 (1–22)	-

CI=confidence interval; HR=hazard ratio; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; RRR=response rate ratio
* Patients with Grade 3 peripheral neuropathy versus no peripheral neuropathy
Source: CS, Table 23

Toxicities

Further post-hoc subgroup analyses were conducted to evaluate the effect that dose modifications due to toxicities have on treatment exposure and efficacy (Table 20). The company states that toxicity management is an important part of the use of Nab-Pac+Gem and that results of dose modification due to toxicities are similar to the results of the post-hoc subgroup analysis of patients with peripheral neuropathy: dose modifications result in greater treatment exposure and thus greater clinical efficacy. The company suggests that appropriate dose modifications should be encouraged to accommodate the safe use of Nab-Pac+Gem in clinical practice and that dose reductions do not negatively influence patient outcomes.

Clinical advice to the ERG is that patients who benefit most from Nab-Pac+Gem are more likely to stay on treatment for longer with the resultant cumulative toxicity requiring dose reduction or delay. Patients with resistance or early disease progression are likely to discontinue treatment before dose modification is needed and would inevitably have poorer survival.

Table 20 Treatment exposure and efficacy outcomes by dose modifications in the Nab-Pac+Gem arm of the CA046 trial

	Dose reductions			Dose delays		
	No dose reduction (n=249)	**≥1 dose reduction (n=172)**	**HR or RRR (95% CI) p-value**	**No dose delay (n=121)**	**≥1 dose delay (n=300)**	**HR or RRR (95% CI) p-value**
OS, median months	6.9	11.4	1.93 (1.53 to 2.44) p<0.0001	6.2	10.1	2.05 (1.59 to 2.63) p<0.0001
PFS, median months	3.8	8.8	2.62 (2.01 to 3.42) p<0.0001	3.4	6.6	2.80 (2.13 to 3.69) p<0.0001
ORR, %	16	34	0.49 (0.34 to 0.69) p<0.0001	10	29	0.34 (0.19 to 0.60) p<0.0001

CI=confidence interval; HR=hazard ratio; OS=overall survival; ORR=overall response rate; PFS=progression-free survival; RRR=response rate ratio
Note: The HR for death is provided for OS, and the HR for progression or death is provided for PFS, with a HR of >1 favouring dose modification; the RRRs are provided for ORRs, with a RRR of <1 favouring dose modification
Source: CS, Table 24

Additional safety data

Additional safety data presented in the CS (p114-117) are summarised in Appendix 1 of this ERG report. Briefly, the additional AE data are derived from the SIEGE trial,[28] two small cohorts[39,40] of patients who were treated with Nab-Pac+Gem between October 2013 and October 2015 in the Lancashire and South Cumbria Cancer Network (n=32) and in South West Wales (n=17). Further data describing patients (n=208) who were treated in centres in Italy[23] are also presented.

The only data available from the SIEGE trial[28] are taken from a poster presented at the ASCO conference in January 2017. In comparison to the CA046 trial, the overall proportion of patients in the SIEGE trial[28] who experienced Grade ≥3 AEs was similar (89% versus 82% respectively). The rates of specific Grade ≥3 AEs reported by patients in the SIEGE trial[28] were also similar to, or lower than, rates reported in the CA046 trial. However, 5.4% of patients in the SIEGE trial[28] experienced sepsis, whilst no cases of sepsis were reported in the CA046 trial.

The only data available from the retrospective study of elderly patients (n=208) treated in Italian centres are from a poster presentation given at the 2015 ESMO conference. The safety data appear to be similar to those reported during the CA046 trial.

The ERG considers that the data available from the cohorts of patients based in Lancashire and South Cumbria and in Wales are difficult to interpret due to the small numbers of participants.

4.6 ERG summary and critique of the indirect evidence

4.6.1 Trials identified for inclusion in network meta-analysis

In addition to the CA046 trial, 16 trials met the secondary eligibility criteria for the company's systematic review. In the previous appraisal of Nab-Pac+Gem (TA360[14]), the ERG and the NICE Appraisal Committee considered that the most appropriate network of evidence to use in the company's NMA was the network that only included trials that reported data for the metastatic pancreatic cancer population. Therefore, in their NMA, the company only used data from such trials. The ERG notes that the company included trials that recruited metastatic pancreatic cancer patients, regardless of histology, whereas the population of interest to this appraisal is the metastatic pancreatic adenocarcinoma population. The ERG considers that the company's approach is appropriate as approximately 80–95% of all pancreatic cancers are of adenocarcinoma histology and, therefore, the populations of trials that recruited all metastatic pancreatic cancer patients consist largely of patients with metastatic adenocarcinoma of the pancreas.

Following production of the network of evidence, studies that had been excluded from the TA360[14] systematic review based on intervention were re-assessed for inclusion in the current NMA. One trial (Rocha Lima 2004[41]) which had previously been excluded was included in the current NMA as the trial provided data for the comparison of treatment with Gem versus Gem+Irinotecan in the metastatic pancreatic adenocarcinoma population. This comparison was included in the network of evidence due to its inclusion in the four-arm trial reported by Kulke (2009).[42] No other trials (in addition to the Rocha Lima 2004 trial[41]) were included in the NMA on this basis.

The 10 trials[6,7,12,41-47] included in the company's NMA are listed in Table 21. The company states that these trials either exclusively enrolled patients with metastatic pancreatic cancer or metastatic pancreatic adenocarcinoma, or reported a subgroup analysis for these patient populations.

Table 21 RCTs included in the company's NMA

Trial name	Design	Population	Treatment arms	Primary outcome	Key secondary outcomes
ACCORD[7]	Phase II/III, parallel-group RCT	Adult patients with previously untreated mPAC and a WHO PS score of 0–1	FOLFIRINOX (n=171) Gem (n=171)	OS	PFS, ORR, HRQoL, safety
Boeck 2008[43]	Phase II, parallel-group, open-label RCT	Adult patients with previously untreated mPC or LAPC and a KPS score ≥60	Gem+Cap (n=64) Gem+Oxaliplatin (n=63) Cap+Oxaliplatin (n=61)	PFS	OS, ORR, safety
CA046[12]	Phase III, parallel-group, open-label RCT	Adult patients with previously untreated mPAC and a KPS score ≥70	Nab-Pac+Gem (n=431) Gem (n=430)	OS	PFS, ORR, safety
CALGB 89904[42]	Phase II, parallel-group, open-label RCT	Adult patients with previously untreated mPAC and an ECOG PS of 0–2	Gem+Cisplatin (n=66) Gem+Docetaxel (n=65) Gem+Irinotecan (n=64) Gem FDR (n=64)	OS	TTP, ORR, safety
Chao 2013[44]	Parallel-group, open-label, RCT	Adult patients with previously untreated mPC in Taiwan	Gem+Cisplatin (n=21) Gem (n=25)	ORR	OS, TTP, HRQoL, safety
FRE-GERCOR-GEMOX-D99-2[45]	Phase III RCT	Adult patients with previously untreated mPAC or LAPC and a WHO PS score of 0–2	Gem+Oxaliplatin (n=163) Gem (n=163)	OS	PFS, ORR, safety
Heinemann 2006[46]	Phase III, parallel-group, open-label RCT	Adult patients with previously untreated mPC or LAPC and a KPS score of 70 or more	Gem+Cisplatin (n=98) Gem (n=97)	OS	PFS, ORR
Rocha Lima 2004[41]	Phase III, parallel-group, open-label RCT	Adult patients with previously untreated mPAC or LAPC and an ECOG PS of 0–2	Gem+Irinotecan (n=180) Gem (n=180)	OS	Tumour response, TTP, safety
Scheithauer 2003[6]	Phase II, parallel-group RCT	Adult patients with previously untreated mPAC and a KPS score of 50 or more	Gem+Cap (n=41) Gem (n=42)*	PFS	OS, ORR
Wang 2015[47]	Phase II, parallel-group, open-label RCT	Adult patients with previously untreated mPC and an ECOG PS of 0–2 in Taiwan	Gem+Erlotinib (n=44) Gem (n=44)	DCR	ORR, OS, PFS

DCR=disease control rate; ECOG=Eastern Cooperative Oncology Group; FDR=fixed dose rate; HRQoL=health-related quality of life; KPS=Karnofsky performance status; LAPC=locally advanced pancreatic cancer; mPAC=metastatic pancreatic adenocarcinoma; mPC=metastatic pancreatic cancer; NMA=network meta-analysis; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PS=performance status; RCT=randomised controlled trial; TTP=time-to-progression; WHO=World Health Organization
*Gem monotherapy administered at the higher dose of 2,200mg
Source: CS, adapted from Table 15, Rocha Lima (2004)[41]

The ERG notes that seven[41-47] of the 10 trials included in the company's NMA provide evidence for comparators that are not relevant to the decision problem. The set of comparators that are relevant to the decision problem, i.e. Nab-Pac+Gem, Gem, FOLFIRINOX and Gem+Cap, is referred to in the remainder of this report as the 'decision comparator set'.

4.6.2 ERG rationale for focusing on a reduced network of evidence

The company provides details of the patient characteristics and trial methodology for each of the 10 trials[6,7,12,41-47] included in the base case NMA (CS, Appendix 4). A summary of the key differences between the studies included in the base case NMA is provided in Appendix 10.4.

Generally, the ERG considers that the trial methodology and patient characteristics of the 10 included trials are similar enough that conducting a NMA that includes these trials is appropriate. However, as mentioned in Section 4.6.1, seven[41-47] of the trials included in the base case NMA provide evidence for comparators that are not relevant to the decision problem. The ERG notes that a connected network can be formed by including only trials that compare interventions included in the decision comparator set. According to guidance in NICE Technical Support document 1,[48] there is no specific need to include comparators other than those in the decision comparator set, unless such an extension is required to produce a connected network.

The company's rationale for including additional trials in the network is that evidence from these trials provides feedback loops, meaning that the consistency of direct and indirect evidence can be considered. While the ERG is aware that it is stated within NICE Technical Support Document 1[48] that one advantage of including additional comparators is the ability to investigate consistency in the network, it is also stated that such extension of the network should not be used in the base case analysis. The disadvantage of extending the network is the possibility that effect modifiers will be introduced as trials of more remotely connected treatments are likely to have different patient populations compared to the patient population of interest. This seems to be the case for the company's NMA as extending the network leads to the inclusion of some trials with exclusively Asian populations. Furthermore, extending the network results in the inclusion of trials[44,47] with primary outcomes other than OS and PFS (i.e. trials that were not powered to detect differences in OS or PFS), and trials that do not report HR data[6,41-44,47] (meaning that the company had to estimate HRs, or use median survival data, see Section 4.6.4). Consequently, the ERG considers that results from a NMA that includes only trials that compare treatments in the decision comparator set are

more informative than results from a NMA that includes data from all 10 of the trials[6,7,12,41-47] listed in Table 21.

The company performed a sensitivity analysis (sensitivity analysis 2 [SA2], see Section 4.6.4) that included only trials that compared treatments specified in the decision comparator set and the ERG considers that this sensitivity analysis should have formed the company's base case NMA. Restricting the network to only trials that compare treatments in the decision comparator set results in a network of trials that has patient populations that are relevant to the decision problem; all trials have at least some sites in European countries, and all comparators are relevant to UK clinical practice. In addition, for the base case NMA, the company incorporated median survival data due to the absence of both reported HRs and K-M data for some included studies. All studies in the reduced network report HR data (or provide K-M data from which HRs can be estimated) for both OS and PFS; therefore, analyses using this reduced network are not subject to the limitations of using median OS data for some comparisons. Further details of the analyses conducted by the company are provided in Section 4.6.4.

4.6.3 Characteristics of trials included in the reduced network of evidence

As the ERG considers the results of the company's analyses that use the reduced network of evidence to be the most valid, the ERG has presented a comparison of the trial methodology and baseline patient characteristics of studies included in this reduced network in the Appendices to this ERG report (Appendix 10.5 and Appendix 10.6). The ERG notes that the dosing regimen of Gem used in the Scheithauer trial[6] differs to the dosing regimen used in the other studies in the network. However, clinical advice to the ERG is that this difference would have little impact on the NMA results. Generally, the ERG considers that the trials in the reduced network are sufficiently similar for the data collected in these trials to be synthesised in a NMA.

4.6.4 Methodological approach to the network meta-analysis

The company's NMA was conducted to provide estimates of relative treatment efficacy (in terms of OS and PFS) between the comparators included in each network of evidence. The company states that it was not possible to use the NMA to compare the safety of the drugs of interest due to a paucity of comparable safety data.

The company performed the base case NMA and three sensitivity analyses; sensitivity analysis 1 (SA1), sensitivity analysis 2 (SA2) and sensitivity analysis 3 (SA3). Each of these analyses is described in Table 22.

Table 22 Base case NMA and sensitivity analyses

Analysis	Description
Base case analysis	Exclusively metastatic pancreatic cancer population data Extensive set of comparators (to provide feedback loops between comparators of interest) Combination of HR and median survival data (HR data where reported/estimated, otherwise median survival) Fixed-effects model
Sensitivity analysis 1 (SA1)	Identical to the base case analysis, but with a random-effects model instead of a fixed-effects model
Sensitivity analysis 2 (SA2)	Reduced set of comparators that are relevant to the NICE scope The network is a reduced version of the network used for the base case analysis and is limited to data from the metastatic pancreatic cancer population All trials included in the reduced network report HR data Fixed-effect model
Sensitivity analysis 3 (SA3)	Identical to the base case analysis, except that metastatic pancreatic cancer median survival data is replaced with locally advanced pancreatic cancer HR data where metastatic pancreatic cancer HR data [absolute or K-M data] were not reported

HR=hazard ratio; K-M=Kaplan-Meier; NMA=network meta-analysis
Source: CS, p82-83

The network of evidence used for the base case analysis, SA1 and SA3, is presented in Figure 3. The network of evidence used for SA2 and the ERG requested analysis is provided in Figure 4.

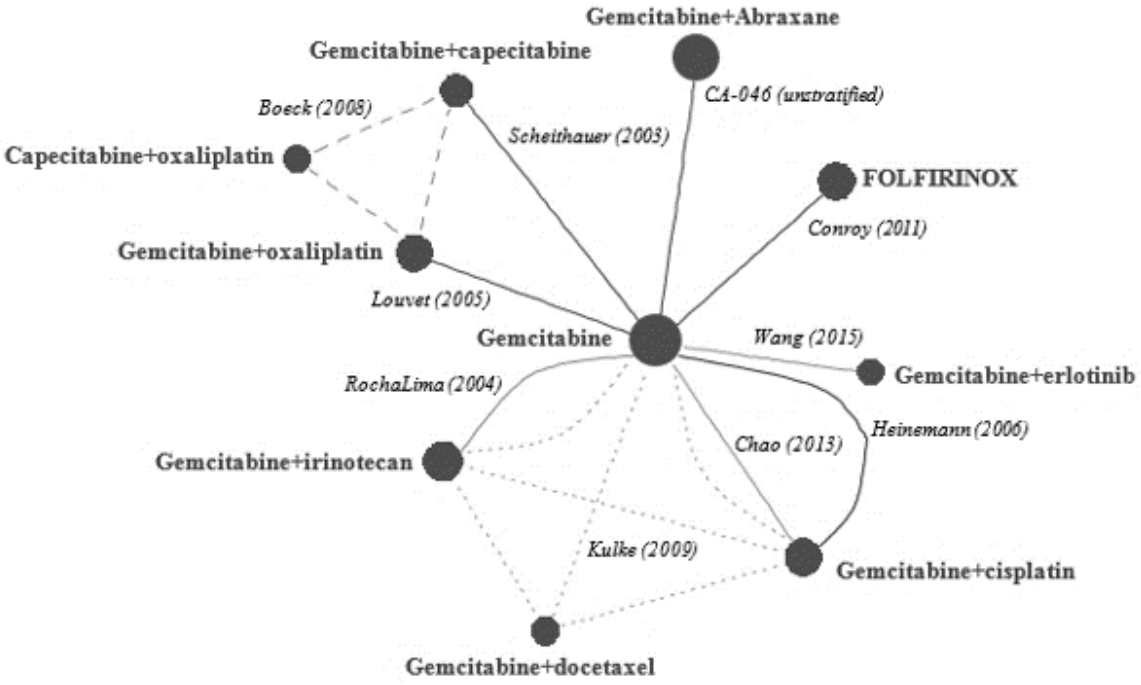

Figure 3 Network of evidence: base case analysis, SA1 and SA3

Solid lines represent two-arm studies; dashed lines represent three-arm studies; dotted lines represent four-arm studies; node sizes are proportional to the number of patients treated with the respective intervention.
Source: CS, adapted from Figure 9 (colours removed)

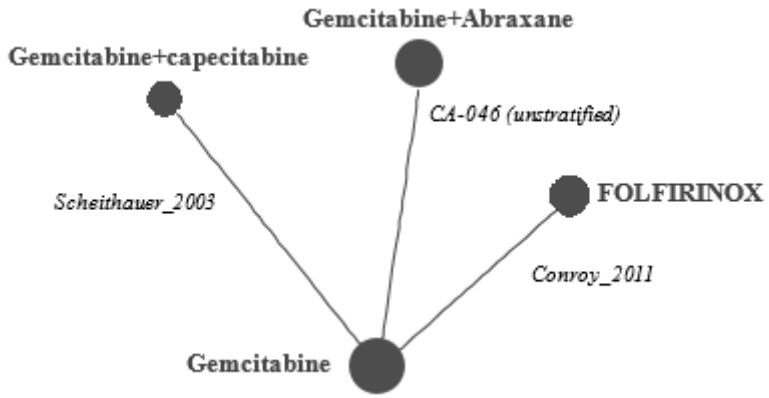

Figure 4 Network of evidence: SA2 and the ERG requested analysis

Node sizes are proportional to the number of patients treated with the respective intervention
HR=hazard ratio
Source: CS, adapted from Figure 14 (colours removed)

As previously mentioned, the ERG considers that using the reduced network (i.e. including only trials that make comparisons between treatments in the decision comparator set) provides more valid results than those derived from the analyses using the wider network (i.e. base case analysis, SA1 and SA3). As the company's analysis in the reduced network (SA2) used a fixed-effects model, the ERG asked the company to provide results for this reduced network using a random-effects model, so that the impact of this model choice on the analysis using the reduced network could be evaluated. The company provided this additional analysis, which from this point onwards, will be referred to as the "ERG requested analysis".

As previously discussed in Section 4.6.3, there was a lack of clarity as to whether disease progression was investigator- or independently-assessed in most of the trials included in the NMA, and so the company analysed the PFS endpoint using both independent-assessed and investigator-assessed PFS data from the CA046 trial. As the independent assessment of PFS was the named secondary endpoint in the CA046 trial, but investigator assessment of PFS was utilised in the company's cost effectiveness model to better reflect clinical practice, the ERG considers the company's approach to be suitable.

Proportional hazards assumption

The validity of the results of all of the indirect analyses conducted by the company (i.e. base case NMA, three sensitivity analyses, and the ERG requested analysis) relies on the assumption that OS and PFS hazards are proportional in each of the trials included in the network for each analysis. The network used in the company's base case NMA, the reduced network used in SA2, and the ERG requested analysis all include the CA046 trial as this trial links Nab-Pac+Gem to Gem. As previously shown in Section 4.2.4, the PH assumption is not valid for OS or PFS data from the CA046 trial. The violation of the PH assumption for OS

and PFS in this trial compromises the networks of evidence. HRs are not an appropriate summary of treatment effect within this network, and it is not possible to know whether the reported HRs would overestimate or underestimate treatment effects estimated by the NMA. The ERG, therefore, considers that all NMA results should be interpreted with caution.

4.6.5 Assessment of risk of bias of the trials included in the network meta-analysis

The company quality assessed all of the trials included in the base case NMA using the criteria recommended by NICE (CS Appendices, Appendix 4). The ERG's summary of the company's risk of bias assessment can be found in Appendix 10.7.

The assessment of risk of bias for studies included in the reduced network is also provided in Appendix 10.8 of the ERG report. In all of the studies, randomisation was carried out appropriately, patient characteristics were balanced between treatment groups and there was no evidence to suggest that selective reporting of outcomes had occurred. The ACCORD[7] trial (FOLFIRINOX versus Gem) was judged to be at high risk of bias for unexpected imbalances in drop-outs between treatment groups as more patients in the Gem arm discontinued treatment than in the FOLFIRINOX arm, with almost twice as many patients discontinuing treatment due to disease progression. In addition, the trial by Scheithauer 2003[6] was deemed not to represent UK practice; all patients were enrolled from study centres in Austria and the dosage of Gem monotherapy (2,200mg/m^2) was not reflective of UK practice. The ERG considers that it is important to take these issues into consideration when interpreting results from the reduced network NMAs in the reduced network (SA2 and the ERG requested analysis).

4.6.6 Results from the network meta-analysis

As the ERG considers results from the reduced network NMA including only trials that make comparisons between treatments in the decision comparator set to be the most valid, only results from SA2 and the ERG requested analysis are presented in this section. Results from analyses performed using the wider network of evidence (i.e. base case analysis, SA1, and SA3) are summarised in Appendix 10.9 of the ERG report.

SA2

SA2 uses a reduced network of evidence including only trials that compare treatments in the decision comparator set. Three trials[6,7,12] evaluating four treatments are included in this analysis (as shown previously in Figure 4). For OS, all included studies reported HR data; for PFS, two studies reported HR data,[7,12] while one trial[6] presented a K-M curve from which a HR could be estimated.

Relative effects for each of the treatments in the decision comparator set versus Nab-Pac+Gem are presented in Table 23, for the outcomes of OS and PFS by independent assessment. The company also presents the results for each treatment included in the network versus Gem for each of these outcomes in Appendix 4 of the CS.

Table 23 Results of SA2

Treatment comparison	HR (95% CrI)
OS	
Gem vs Nab-Pac+Gem	1.35 (1.17 to 1.56)
Gem+Cap vs Nab-Pac+Gem	1.10 (0.67 to 1.84)
FOLFIRINOX vs Nab-Pac+Gem	0.77 (0.58 to 1.01)
PFS by independent assessment	
Gem vs Nab-Pac+Gem	1.45 (1.22 to 1.72)
Gem+Cap vs Nab-Pac+Gem	1.17 (0.75 to 1.86)
FOLFIRINOX vs Nab-Pac+Gem	0.68 (0.51 to 0.91)

CrI=credible interval; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; vs=versus
Source: CS, Figure 15 and Figure 17

For OS, Gem was shown to be statistically significantly inferior to Nab-Pac+Gem (HR=1.35, 95% CrI: 1.17 to 1.56). For Gem+Cap versus Nab-Pac+Gem, there is no evidence to suggest a difference between these two treatments in terms of OS. For FOLFIRINOX versus Nab-Pac+Gem, the HR favoured FOLFIRINOX, although this result was not statistically significant (HR=0.77, 95% CrI: 0.58 to 1.01). Compared to the base case analysis, only the HR for Gem+Cap versus Nab-Pac+Gem has been affected by using the reduced network. The direction of effect is reversed in comparison to the base case analysis, and now favours Nab-Pac+Gem, although no statistically significant differences were identified between these two treatments in either analysis. This change is due to the fact that there is more indirect evidence in the network used for the base case analysis for the comparison of Gem+Cap versus Nab-Pac+Gem than is used in the reduced network used for SA2. The evidence that contributes to the Nab-Pac+Gem versus Gem, and FOLFIRINOX versus Nab-Pac+Gem remains constant between the two networks. As previously discussed, the ERG considers that results from SA2 are more valid than those from the base case NMA.

The probabilities of being the best treatment and median ranks for OS are provided in Table 18 of the CS. The probabilities of being the best treatment are: FOLFIRINOX (0.878), Gem+Cap (0.097), Nab-Pac+Gem (0.025), and Gem (0.000). Nab-Pac+Gem is expected to be the second best treatment (probability=0.63) after FOLFIRINOX.

For PFS, Gem was shown to be statistically significantly inferior to Nab-Pac+Gem (HR=1.45, 95% CrI: 1.22 to 1.72). For Gem+Cap versus Nab-Pac+Gem, no statistically significant

differences were observed between the treatments. FOLFIRINOX was shown to be statistically significantly superior to Nab-Pac+Gem (HR=0.68, 95% CrI: 0.51 to 0.91).

The probabilities of being the best treatment and median ranks for the outcome of PFS by independent assessment are provided in Table 19 of the CS. The probabilities of being the best treatment are: FOLFIRINOX (0.982), Gem+Cap (0.013), Nab-Pac+Gem (0.005), and Gem (0.000). Nab-Pac+Gem is expected to be the second best treatment (probability=0.75) after FOLFIRINOX.

ERG requested analysis

As the company's analysis in the reduced network (SA2) uses a fixed-effects model, the ERG asked the company to provide results for this reduced network using a random-effects model so that the impact of this model choice on the analysis using the reduced network could be evaluated. The results of the ERG requested analysis are provided in Table 24.

Table 24 Results of the ERG requested analysis

Treatment comparison	HR (95% CrI)
OS	
Gem vs Nab-Pac+Gem	1.33 (0.12 to 15.43)
Gem+Cap vs Nab-Pac+Gem	1.10 (0.03 to 35.88)
FOLFIRINOX vs Nab-Pac+Gem	0.76 (0.02 to 23.48)
PFS (independent review)	
Gemcitabine vs Nab-Pac+Gem	1.43 (0.13 to 16.90)
Gem+Cap vs Nab-Pac+Gem	1.17 (0.04 to 35.16)
FOLFIRINOX vs Nab-Pac+Gem	0.67 (0.02 to 18.90)
PFS (investigator review)	
Gemcitabine vs Nab-Pac+Gem	1.65 (0.14 to 20.11)
Gem+Cap vs Nab-Pac+Gem	1.33 (0.04 to 47.00)
FOLFIRINOX vs Nab-Pac+Gem	0.77 (0.02 to 29.96)

CrI=credible interval; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; vs=versus
Source=Question A5 of the company's response to the ERG clarification letter

The point estimates of the HRs are similar to those obtained in SA2, but the corresponding credible intervals are very wide. This company states that, when running this analysis, there were issues with model convergence when estimating HRs. In other words, there were not enough data in the random-effects model to obtain a precise CrI around estimates of HRs, resulting in large uncertainty in the estimates.

The company provided the ERG-requested analysis so that the impact of the choice of a fixed-effects or random-effects model on the analysis using the reduced network could be evaluated. The ERG agrees with the company that the ERG requested analysis has been

severely impacted by model convergence issues. Therefore, the ERG considers that the results of SA2 are more informative than those from the ERG requested analysis, i.e. from the fixed-effects model rather than the random-effects model because there are insufficient data to run the random-effects model. The ERG notes that slight differences in dosing regimens were identified between trials included in the reduced network but does not consider that these differences would invalidate the results of an analysis using a fixed-effects model.

4.6.7 ERG interpretation of NMA results

In summary, the ERG's considers that the OS and PFS data from the CA046 trial lack PH, and so the results of the company's NMAs should be interpreted with caution. In addition, the ERG has concerns about the relevance of the NMA results to the decision problem as there are few patients aged over 75 years of age in the trials which make up the network.

4.7 Conclusions of the clinical effectiveness section

The ERG considers that the submitted evidence largely reflects the decision problem defined in the final scope issued by NICE; however, the ERG notes the following points:

- Nab-Pac+Gem was not recommended for use in NHS England following the publication of TA360 but it has been recommended for use in NHS Wales and NHS Scotland
- the company has provided clinical effectiveness data pertaining to all comparators listed in the final scope issued by NICE; however, direct evidence is only available for the comparison of treatment with Nab-Pac+Gem versus Gem
- the company considers that Gem is the only relevant comparator to Nab-Pac+Gem
- the company considers that (i) FOLFIRINOX and Gem+Cap are not standards of care in the NHS and (ii) the introduction of Nab-Pac+Gem for use in the NHS will not displace the use of either of these comparators
- the company considers that patients who are suited to treatment with Nab-Pac+Gem are easily identified and are 'clinically distinct' from patients who are suited to treatment with FOLFIRINOX. The ERG considers that the company has yet to provide a definition of patients who are suited to treatment with Nab-Pac+Gem.

4.7.1 Clinical effectiveness evidence

Direct evidence

The direct evidence was derived from the CA046 trial. The ERG highlights the following points:

- patients in the CA046 trial were younger and fitter than patients treated in the NHS
- only 10% of patients recruited to the CA046 trial were aged ≥75 years. In the NHS, 47% of patients with pancreatic cancer are aged ≥75 years. This means that the evidence from the trial may not be relevant to a substantial number of NHS patients

- in the SmPC[9] for Nab-Pac, the EMA advises caution when considering using Nab-Pac+Gem to treat patients aged ≥75 years due to a lack of evidence of clinical efficacy and the AE profile
- results of the final efficacy analysis of the CA046 trial suggest that treatment with Nab-Pac+Gem statistically significantly improves median OS in comparison to treatment with Gem (8.5 months versus 6.7 months; HR=0.72, 95% CI: 0.62 to 0.83)
- results from the updated OS analysis are in accordance with the findings of the primary analysis, supporting the evidence for a statistically significant benefit from treatment with Nab-Pac+Gem compared to Gem (8.7 months versus 6.6 months; HR=0.72, 95% CI: 0.62 to 0.83)
- the ERG's assessment of the PH assumption for the CA046 trial data suggests that the PH assumption does not hold for either OS or PFS data and, consequently, the HRs from the CA046 trial for these outcomes should be interpreted with caution
- the most common Grade 3 and 4 AEs associated with treatment with Nab-Pac+Gem were neutropenia, fatigue, metabolism and nutritional disorders, peripheral neuropathy, thrombocytopenia and anaemia. Although these AEs are associated with treatment with either Gem or Nab-Pac monotherapies, they occur more frequently when patients are treated with the Nab-Pac+Gem combination
- no HRQoL data are available as part of the CA046 trial. The company has presented HRQoL evidence from one arm of the SIEGE trial,[28] an ongoing phase II single arm trial of patients with locally advanced pancreatic cancer who were treated with Nab-Pac+Gem and from a cross-sectional study[32] of patients with metastatic pancreatic cancer treated with Nab-Pac+Gem in the US.

Indirect evidence

The ERG highlights the following points:

- in the absence of head-to-head data for the comparisons of Nab-Pac+Gem versus FOLFIRINOX and Nab-Pac+Gem versus Gem+Cap, the company performed a NMA to obtain estimates of the relative efficacy of these comparators
- seven of the 10 trials included in the base case NMA provide evidence for comparators that are not relevant to the decision problem; the ERG considers that results from a NMA that includes only trials that compare treatments listed in the decision problem are more informative than results from a NMA that includes data from all 10 trials
- all NMA results are affected by a violation of the PH assumption within the CA046, and should be interpreted with caution.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by the company in support of the use of Nab-Pac+Gem to treat patients with previously untreated metastatic adenocarcinoma of the pancreas. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has also provided copies of its economic model, which were developed in Microsoft Excel.

The company submitted two copies of its economic model: the first at the beginning of the evidence review process and the second during the clarification period. The company submitted the updated model in response to an inconsistency it found between the model and the CS whilst responding to the ERG's clarification questions. The changes to the model constitute small amendments to the duration of AEs, to take into account the number of repeat events experienced by patients.

5.2 ERG comment on the company's review of the cost effectiveness evidence

5.2.1 Objective of the company's systematic review

The company performed a systematic literature review to identify and summarise the relevant cost effectiveness evidence for Nab-Pac+Gem as a treatment for previously untreated locally advanced or metastatic pancreatic cancer with the majority (>50%) of the population in any given study having metastatic disease.

Company searches

The company added to the review of cost effectiveness evidence included in the previous appraisal for this indication (TA360)[14] with updated searches from March 2014 to August 2016. The company searched MEDLINE and Embase (using Embase.com), MEDLINE In-Process (using PubMed.com), EconLit, The Cumulative Index to Nursing and Allied Health Literature (CINAHL) and The Cochrane Library (including the National Health Service Economic Evaluations Database and the Centre for Reviews and Dissemination – Health Technology Assessment Database). These searches were supplemented with searches of conference proceedings from 2013 to 2016. The search strategies used by the company are provided in Appendix 11 of the CS.

5.2.1 Eligibility criteria used in study selection

The inclusion/exclusion criteria used by the company for study selection are provided in Table 32 of the CS and are reproduced in Table 25.

Table 25 Eligibility criteria for the cost effectiveness systematic review

Criteria	Inclusion	Exclusion
Population	• Adult patients • aPAC patients, at least a proportion (50%) of whom have metastatic (or pancreatic ductal adenocarcinoma) disease • Potentially eligible for first-line therapy for metastatic disease	• Healthy volunteers • Children (age <18 years) • Diseases other than those specified in inclusion criteria
Intervention/ comparator	• Nab-Paclitaxel+gemcitabine • AND a relevant comparator from: Placebo, 5-FU, capecitabine (XELODA®), erlotinib (TARCEVA®), gemcitabine (GEMZAR®) and oxaliplatin (ELOXATIN®), monotherapy or in combination with any other therapy**	• Non-active comparisons • Comparisons outside of named list of interventions/comparators of interest
Outcomes	• ICER • Costs (unit and total) • QALYs • LYs • Incremental costs • Incremental QALYs/LYs • Model inputs (e.g. transition probabilities) • Sensitivity analyses results	•
Study type	• Full economic evaluations, such as: • Cost consequence analysis • Cost effectiveness analysis • Cost utility analysis • Cost benefit analysis • Cost minimisation analysis	• Non-systematic reviews,* letters and comment articles • Burden of illness studies and non-modelling will be excluded
Language	• Studies published in English will be included • Studies not published in English will be included and flagged***	• Studies will not be excluded based on publication language

5-FU=5-fluorouracil; aPAC=advanced pancreatic cancer; ICER=incremental cost-effectiveness ratio; LYs=life years; QALYs= quality adjusted life years
*Systematic reviews will be included and flagged for bibliography searches; **The range of potential comparators is deliberately broad. When discussing the cost effectiveness studies identified, we draw a distinction between studies that include comparators in the scope for TA360 (gemcitabine monotherapy; Gem/Cap and FOLFIRINOX) and those studies that only include the wider treatments not considered by NICE to be relevant to UK practice; *** Studies published in languages other than English will be explored only if sufficient evidence is not identified from studies published in English
Source: CS, Table 32

5.2.2 Included and excluded studies

The company's literature searches identified 404 papers. After removing duplicates, 388 papers were screened using titles and abstracts only, of which 28 papers were assessed for eligibility using the full-text version of the publication. The most common reasons for exclusion at the title and abstract stage were publication type (e.g., reviews or editorials

were excluded) or study design. After applying inclusion criteria, data from 11 papers were considered by the company to be relevant and were included in the data extraction table presented in the CS (Table 33).

5.2.3 Findings from cost effectiveness review

The company extracted data from 11 papers (Table 26). Further details of study characteristics and findings are reported in the CS, Table 33.

Table 26 Summary of company's findings from cost effectiveness review

Study	Country	Treatments	ICER per QALY gained
Carrato et al (2015)[49]	Spain	Nab-Pac+Gem vs Gem	€41,519
Cheng et al (2016)[50]	US	FOLFIRINOX vs Nab-Pac+Gem	$30,870
Cowell et al (2014) [51] [51] [51]	UK	Nab-Pac+Gem vs Gem	£52,885 (no QALY weighting) £37,249 (partial QALY weighting) £21,108 (full QALY weighting)
Fragoulakis et al (2014)[52]	Greece	Nab-Pac+Gem vs Gem	€47,120
Gharaibeh et al (2015)[53]	UK	Nab-Pac+Gem vs Gem	£78,086
Gharaibeh et al (2015)[54]	US	Nab-Pac+Gem vs Gem	$141,338
		FOLFIRINOX vs Gem	$164,495
		Nab-Pac+Gem vs FOLFIRINOX	$37,692
		FOLFIRINOX vs Nab-Pac+Gem	$202,187
Stetka et al (2015)[55]	Slovak Republic	Nab-Pac+Gem vs Gem	€27,769
NICE TA360 (2015)[14]	UK (England and Wales)	Nab-Pac+Gem vs Gem	£51,900
		Nab-Pac+Gem vs FOLFIRINOX	Dominated
		Nab-Pac+Gem vs Gem+Cap	£87,084
SMC (no: 968/14)[2]	UK (Scotland)	Nab-Pac+Gem vs Gem	£52,885
AWMSG (no: 1999)[1]	UK (Wales)	Nab-Pac+Gem vs Gem	£53,260
Osterlund et al (2016) [56] [56] [56]	Norway Sweden Finland Denmark	Erlotinib+Gem	€1,232 (cost per month of OS, average of Nordic countries)
		Erlotinib+Gem	€2,103 (cost per month of PFS, average of Nordic countries)
		Nab-Pac+Gem	€2,602 (cost per month of PFS, average of Nordic countries)

AWMSG=All Wales Medical Strategy Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; SMC=Scottish Medicines Consortium; TA=technology appraisal
Source: CS, Table 33

5.3 ERG critique of the company's review of cost effectiveness evidence

The company adequately describes the search strategies used to identify relevant studies related to the use of Nab-Pac+Gem for the treatment of patients with untreated metastatic

pancreatic cancer. The search strategies were originally run in March 2013 and then updated in March 2014 and July 2016. Considering the date of the last update search, there is a chance that relevant papers have not been picked up. Separate searches were conducted for the retrieval of cost effectiveness studies and HRQoL studies. The dates of the searches and the full date spans are included in the CS.

Full details of the separate search strategies used to locate cost effectiveness evidence and HRQoL evidence are reported in Section 5.1 and Appendix 11 of the CS. Both of the search strategies included population terms as well as indication terms and use MeSH and free text. The separate search strategies include a cost effectiveness filter and HRQoL search filter. The ERG considers the search terms used in the strategy and the use of the search filters to be appropriate.

Summary of searching

In summary, the ERG concludes that the company's cost effectiveness and HRQoL search strategies are appropriate and comprehensive enough to identify relevant studies as described in the final scope issued by NICE. However, given that the searches are slightly out of date, it is possible relevant studies may have been missed.

5.4 Summary and critique of the company's submitted economic evaluation by the ERG

The base-case cost effectiveness evaluation undertaken by the company compares the costs and benefits (in terms of QALYs) of treatment with Nab-Pac+Gem versus treatment with Gem in patients with previously untreated metastatic pancreatic cancer. The company also provides scenario analyses comparing the costs and benefits of treatment with Nab-Pac+Gem versus treatment with Gem+Cap, and treatment with Nab-Pac+Gem versus FOLFIRINOX.

5.4.1 Model structure

The company has adapted the model submitted within the original submission to NICE for appraisal TA360[14] rather than constructing a de novo economic model. The company uses a Markov structure in the model and employs an area under the curve approach to estimate the proportion of patients who transition between health states over time from the start of treatment until death. There are three primary health states in the model: pre-progression, post-progression and death. The company has divided the pre-progression state into two secondary health states (pre-progression: on first-line treatment and pre-progression: off first-line treatment) to more accurately estimate drug costs in cases where treatment is discontinued before progression. The company has also included a tunnel state at 4 weeks

to death to account for a period of intensive palliative care in the final stages of life (Figure 5).

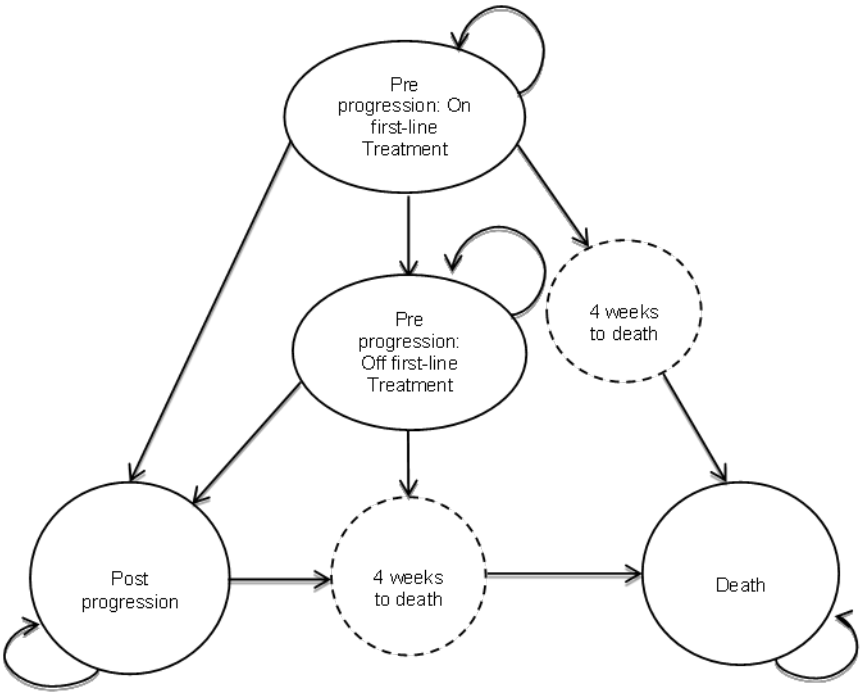

Figure 5 Model schematic

Source: CS, Figure 21

All patients enter the model in the 'pre-progression: on first-line treatment' health state and remain there for one cycle. Patients can then either stay in their current health state or transition to a worse health state at the beginning of each subsequent model cycle. Patients receive second-line treatments on progression. Transition probabilities between health states are informed by survival models fitted to OS, PFS and TOT K-M data from the CA046 trial.

The model cycle length is 1 week and no half-cycle correction has been applied, as the company notes that all drug and administration costs are incurred at the beginning of a cycle, and that using a half-cycle correction has a negligible impact on the ICER per QALY gained.

5.4.2 Population

The population reflected in the company model is adults with untreated metastatic cancer of the pancreas.

5.4.3 Interventions and comparators

Intervention

Nab-Pac is supplied as a powder for intravenous infusion and Gem is supplied as a solution for intravenous infusion. In line with the EMA marketing authorisation[9] for Nab-Pac, Nab-Pac (125mg/m^2) and Gem (1000mg/m^2) are administered sequentially for 30 minutes each on days 1, 8 and 15 of each 28-day cycle until disease progression or unacceptable toxicity.

Comparators

The final scope issued by NICE states that the comparators for this appraisal are Gem, Gem+Cap and FOLFIRINOX. The company considers Gem as the main comparator to Nab-Pac+Gem in the economic analysis with Gem+Cap and FOLFIRINOX considered only as secondary comparators due to a limited evidence base for these treatments in a UK clinical setting. Further details of the comparators are presented in Table 9 of the ERG report.

Second-line treatment

Data describing the seven most prevalent second-line treatments reported in the CA046 trial are used to estimate the range and use of second-line treatments in the model. The percentage of patients receiving second-line therapy in the CA046 trial differed according to study arm: 38% of patients who received Nab-Pac+Gem as a first-line treatment received a second-line treatment and 42% of patients who received Gem as a first-line treatment received a second-line treatment.[12] The proportions of each of the second-line treatments used in the model are shown in Table 27.

Table 27 Second-line treatments included in the company model

Second-line treatment	% of patients moving into second-line treatment	
	Nab-Pac+Gem (total=38%*)	Gem (total=42%)
5-FU	7.3%	1.3%
5-FU+oxaliplatin	13.2%	17.1%
Gem+Cap	2.9%	3.9%
Capecitabine	4.4%	6.6%
Gem+erlotinib	2.9%	3.9%
Erlotinib	1.5%	1.3%
FOLFIRINOX	0.0%	0.0%

5-FU=5-fluorouracil
* The figures do not sum to 38% due to rounding
Source: CS, Table 36

5.4.4 Perspective, time horizon and discounting

The company states that the economic evaluation was undertaken from the perspective of the NHS and PSS (Personal Social Services). The model time horizon was 10 years. Both costs and benefits were discounted at a rate of 3.5% per annum.

5.4.5 Treatment effectiveness and extrapolation

Nab-Pac+Gem and Gem

The company used K-M data from the CA046 trial as a basis for extrapolating survival for treatment with Nab-Pac+Gem and Gem. The company assessed the applicability of a single parametric model or a Cox PH model by visual inspection of the K-M curves, log cumulative hazard plots (LCHP) and quantile-quantile (Q-Q) plots. Six parametric distributions (exponential, log-normal, log-logistic, Gompertz, gamma and Weibull) were examined for each clinical outcome (OS, PFS and TOT). A single stratified approach was considered if a pooled model was deemed inappropriate due to non-PHs or poor visual fit. The company explored the fit of each parametric model using visual inspection, LCHP, Q-Q plots, Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness of fit statistics, and clinical plausibility.

The company concluded from examination of the LCHP curves that the PH assumption does not hold for OS, PFS or TOT in the CA046 trial; for each of these outcomes the LCHP curves cross. The company thus considered stratified versions of the six parametric models to allow for a more flexible approach to extrapolation. For OS, PFS and TOT, the stratified gamma model was considered to be the most appropriate choice as these curves had the lowest AIC/BIC and, according to the company, provided a good fit to the observed dataset. For OS and PFS, as the unstratified gamma curves also yielded plausible values and, according to the company, provided a good fit to the observed dataset and so use of the unstratified gamma model was considered in the scenario analyses conducted by the company. Use of the ERG's curves that were submitted during the earlier appraisal (TA360[14]) were also included as scenario analyses.

Gem+Cap and FOLFIRINOX

The company updated the NMA undertaken for TA360[14] to incorporate any clinical evidence that had become available since the original submission. Hazard ratios for treatment with Nab-Pac+Gem versus Gem+Cap or FOLFIRINOX from the updated NMA were used to model OS and PFS in the cost effectiveness model for Nab-PAC+Gem versus these two comparators. The company notes (CS, p160) …'that due to the lack of support for the assumption of PHs in the OS and PFS data from the CA046 trial, the PH assumption underpinning the NMA is questionable and therefore the comparison between Nab-Pac+Gem and Gem+Cap or FOLFIRINOX is questionable.'

5.4.6 Health-related quality of life

No HRQoL data were collected during the CA046 trial. The company updated the search for HRQoL data from the previous NICE submission (TA360) to ensure that the latest available data are presented in the CS. Details of the searches are given in Section 5.4.1 of the CS. The company also analysed HRQoL data from the Phase II SIEGE trial.[28] Three sets of health state utility values were considered by the company for use in the cost effectiveness model: two[57,58] from the SIEGE trial[28] and one from a paper by Romanus et al.[59]

The SIEGE trial[28] was designed to investigate the clinical effectiveness of two different dosing regimens for Nab-Pac+Gem, one of which matched the regimen used in the CA046 trial. The company derived utility values from answers to the EQ-5D-5L questionnaire; trial participants completed questionnaires at baseline, at 4-weekly intervals during pre-progression and at 12-weekly intervals during post-progression over a period of 12 months.

Two distinct methods were used to derive utility values from the collected data from patients in the SIEGE trial:[28] first, using the EQ-5D-5L value set published by Devlin et al;[57] and second, using the 'crosswalk method'[58] which allows EQ-5D-3L utility values to be generated from EQ-5D-5L data.

The company explains (CS, p184) that multivariate regression analysis was conducted to determine the most significant predictors of HRQoL over time; only progression status and KPS (KPS≤80 and KPS>80 based on clinical evidence from the CA046 trial CSR) were included in the final multivariate models. The results of the regression analysis were combined with the results generated by applying the Devlin[57] and crosswalk[58] methods to produce two sets of utility value estimates from the SIEGE trial[28] data (Table 28).

The company also considered the findings from a study by Romanus.[59] This RCT compared Gem+bevacizumab versus Gem+placebo in US patients via telephone interviews with advanced pancreatic cancer using the EQ-5D at baseline and at 8 weeks. The company has applied an (unexplained) adjustment to the values reported in the publication to represent a UK, rather than US, population (Table 28); the adjustment was made in line with the ERG feedback from the original NICE submission (TA360[14]).

Table 28 Health state utility values

	Health state utility	
	Pre-progression	**Post-progression**
Devlin57 value set (SIEGE)	0.79	0.75
Crosswalk method58 (SIEGE)	0.70	0.65
Romanus et al (2012)59 with UK adjustment	0.74	0.67

Source: CS, Table 52

The company notes that there is substantial uncertainty in the utility values derived from the SIEGE trial[28] depending on the method of analysis used. As the results from the Romanus[59] paper lie between the two sets of values derived from the HRQoL data collected in the SIEGE trial,[28] the company has used the Romanus[59] values in the base-case analysis and the values derived from the SIEGE trial data in the scenario analyses. The company acknowledges that all three approaches have strengths and weaknesses (not least that the adjusted utility values from the Romanus[59] paper are not specific to patients receiving Nab-Pac+Gem).

Baseline health state utility values were assumed to be the same for all patients irrespective of treatment. However, these values were then retrospectively adjusted to reflect the AE profiles of the treatments.

5.4.7 Adverse events

The company model includes AEs recorded during the CA046 trial that met the following criteria: treatment emergent; Grade ≥3; or occur in >5% of patients in either arm. Clinicians were consulted about any AEs that met the first two criteria but were present in <5% of patients in the CA046 trial. The purpose of this consultation was to identify any AEs that would have a substantial impact on HRQoL or on resource use and costs. In total, 19 AEs were identified that met the inclusion criteria.

The probability of an AE occurring was calculated based on incidence and mean length of exposure to treatment data collected in the CA046 trial. The rates of AEs for patients treated with Nab-Pac+Gem and Gem were taken from the CA046 trial. The rates of AEs for Gem+Cap were assumed to be the same as for patients treated with Nab-Pac+Gem.

The rates of AEs for patients treated with FOLFIRINOX were calculated as relative risks (RRs) compared with rates for patients treated with Gem, which were extracted from a published source,[7] which were then applied to the Gem AE data from the CA046 trial. For AEs where data were not reported, AE rates and durations were assumed to be the same as for Nab-Pac+Gem.

5.4.8 Resources and costs

The company did not present any treatment-specific resource use literature in the CS for TA360.[14] Instead, the company estimated resource use (as part of follow-up and monitoring) through clinician interviews and a panel of experts validated these estimates at a UK advisory board meeting. In the current submission, the company adopts the same approach.

Drug acquisition costs

The drug acquisition costs for first-line treatments are presented in Table 29. The list price for Nab-Pac is £246.00 per vial, which is reduced to [redacted] per mg with the application of a PAS.

Table 29 Drug acquisition costs

Treatment	Unit cost including PAS	Unit price per mg	Weighted unit price per mg	Source
				Gemcitabine
1g powder for solution for infusion vials	£30.89	£0.03	£0.03	eMIT.[60] Date accessed: 19 January 2017
200mg powder for solution for infusion vials	£3.99	£0.02		
Nab-Paclitaxel				
Powder for reconstitution, paclitaxel, net price 100-mg vial	[redacted]	[redacted]	[redacted]	MIMS.[61] Data accessed: 19 January 2017
Capecitabine				
150mg, 60-tab pack	£7.73	£0.0009	£0.001*	eMIT.[60] Date accessed: 19 January 2017
500mg, 120-tab pack	£29.59	£0.0005		
Erlotinib				
25mg, 30-tab pack	£378.33	£0.50	£0.44	MIMS.[61] Data accessed: 19 January 2017
100mg, 30-tab pack	£1,324.14	£0.44		
150mg, 30-tab pack	£1,631.53	£0.36		
5-fluorouracil bolus injection				
1g/20ml (5%) solution for injection vials	£4.00	£0.02	£0.01	BNF January 2017[62]
500mg/10ml (5%) solution for injection vials/Pack size 1	£6.40	£0.01		
Oxaliplatin				
100mg/20ml solution for infusion vials	£15.50	£0.16	£0.17	eMIT.[60] Date accessed: 19 January 2017
50mg/10ml solution for infusion vials	£10.62	£0.21		
5-fluorouracil Infusion				
2.5g/50ml (5%) solution for infusion vials	£4.68	£0.002	£0.004*	eMIT.[60] Date accessed: 19 January 2017
5g/100ml (5%) solution for infusion vials	£4.53	£0.001		
Folinic acid (Leucovorin®)				
Calcium folinate 100mg/10ml solution for injection vials/Pack	£2.29	£0.02	£0.02	eMIT.[60] Date accessed: 19 January 2017
Calcium folinate 300mg/30ml solution for injection vials/ Pack	£4.59	£0.02		
Irinotecan				
100mg/5ml solution for infusion vials/Pack size 1	£7.52	£0.08	£0.07	eMIT.[60] Date accessed: 19 January 2017
300mg/15ml solution for infusion vials/Pack size 1	£18.64	£0.06		

BNF=British National Formulary; eMIT=electronic market information tool; MIMS=Monthly Index of Medical Specialties
*Less than 1p per mg
Source: CS, Table 57

Second-line drug costs

In the absence of data detailing dosing regimens for second-line chemotherapy treatments (see Table 27), the company has assumed that dosing in the second-line setting is the same as dosing in the first-line setting.

Dosing

Dosing information for treatment with Nab-Pac+Gem and Gem was obtained from the CA046 trial as reported in the publication by Von Hoff.[12] Dosing information for Gem+Cap and FOLFIRINOX (ACCORD study) were obtained from published sources.[4,7]

Doses for all drugs (with the exception of capecitabine and erlotinib) are based on a patient's body surface area (BSA). The average BSA used in the cost effectiveness model is 1.75m^2, which was taken from the KANTAR study for the UK pancreatic cancer population.[15]

For full information on individual doses for the drugs, see Table 9 of this ERG report.

Vial sharing

Vial sharing is not included in the base-case analysis, but is investigated as a scenario analysis.

Dose intensity and missed doses

The company base-case analysis includes adjustments to the cost of each first-line treatment to take into account any cost-saving effect of reduced or missed doses. Data from the CA046 trial were used to inform the proportion of reduced or missed doses applied in the model. The proportions of reduced or missed doses that could be anticipated (and therefore would not lead to drug wastage) were estimated based on the results (n=26) of a survey of waste management procedures in hospital pharmacies, and of waste management procedures associated with Nab-Pac dose modification/adjustment and dose cessation in the UK. Clinical experts validated the survey results.

Half of the survey respondents stated that they had pre-specified waste management policies in place to avoid drug wastage (e.g., drug preparation on day of treatment, not preparing drugs until blood results were received). The company used these responses to inform the modelling assumption that 50% of first-time dose reductions and 50% of missed doses could be anticipated. The company has assumed that all subsequent dose reductions could be anticipated and would, therefore, not result in wastage. The adjustments were applied to patient level data for patients missing a Nab-Pac dose, Gem dose or both.

The average dose intensity used in the model to estimate the cost of reduced doses is 89.83%, weighted to include the 79.7% of subsequent doses (assumed 100% anticipated) and 20.3% of first-time reductions (assumed 50% anticipated).

The proportion of anticipated dose reductions and missed doses for patients receiving Gem+Cap and FOLFIRINOX were assumed to be the same as for patients receiving Nab-Pac. The assumption that no missed or reduced doses can be anticipated (and, therefore, no cost savings accrued) is explored in a scenario analysis.

Administration costs

The company has used NHS Reference Costs (2015/16)[63] and Personal Social Services Research Unit (PSSRU) costs (2016)[64] as estimates for the cost of administering chemotherapy. Table 30 shows the costs of administration associated with each first-line treatment.

Table 30 Administration costs of chemotherapy treatments

Chemotherapy	Component drug name	Administration cost	Source	Total cost per treatment
Gem	Gem	£253.32	NHS Reference Cost[63] SB12Z	£253.32
Nab-Pac	Nab-Pac	£17.50	PSSRU (day ward nurse)[64]	£270.83
	Gem	£253.32	NHS Reference Cost[63]SB12Z	
Gem+Cap	Gem	£253.32	NHS Reference Cost[63] SB12Z	
	Cap	£0	-	£253.32
FOLFIRINOX	Oxaliplatin	£336.57	NHS Reference Cost[63] SB13Z	£506.54
	Irinotecan	£17.50	PSSRU (day ward nurse)[64]	
	5-FU	£17.50	PSSRU (day ward nurse)[64]	
	Folinic acid	£17.50	PSSRU (day ward nurse)[64]	
	5-FU continuous infusion	£117.47	PSSRU (day ward nurse)[64] + NHS Reference Cost[63]	

PSSR=Personal Social Services Research Unit
Source: CS, Table 61

An extra 30 minutes pharmacy time is also included in the administration costs for Nab-Pac as the drug has to be reconstituted from powder, which takes longer to prepare than other infusions. Preparation of Nab-Pac also requires a 15-micron filter at a cost of £2.04.

Monitoring costs

Monitoring costs were applied in the 'pre-progression: on first-line treatment' health state and in the post-progression health state for those patients receiving second-line treatment. Monitoring costs for patients receiving active treatment are categorised as either first-line (immediately prior to initiation of chemotherapy), and first- and second-line (follow-up and monitoring).

First-line costs prior to chemotherapy are £325.37 for all treatments except FOLFIRINOX, which costs £369.35 due to additional requirement for ECG and echocardiogram. Weekly follow-up and monitoring costs in first- and second-line are £87.52 for all treatments except FOLFIRINOX, which costs £175.03. Patients treated with FOLFIRINOX are assumed to be monitored twice as often as patients receiving other treatments as the treatment is assumed to be more toxic.

Details of the individual elements of monitoring costs can be found in the company model (1^{st}_Line_Costs and 2^{nd}_Line_Costs), as Table 64 in the CS contains errors that lead to an underestimate of the total costs by £18.26.

Palliative care costs

Patients in the 'pre-progression: off first-line treatment' health state in the model were assumed to receive monitoring that was costed as palliative care provided by one GP home visit per week (at a cost of £31). However, in the CS (p207), the company states that these patients receive one nurse visit per week at a cost of £44, but this is an error as it is not borne out by the model. Patients who do not receive second-line treatment are also assumed to receive palliative care provided by one GP home visit per week.

G-CSF

The company states that G-CSF use in the CA046 trial was higher than would be expected in clinical practice (see Table 31 for details). However, because the estimated survival benefits of treatment with Nab-Pac+Gem are taken directly from the CA046 trial and used in the company model, it was deemed appropriate to include G-CSF use for patients treated with Nab-Pab+Gem and patients treated with Gem according to the CA046 trial data. The company considers G-CSF use according to current practice in a scenario analysis.

Table 31 G-CSF usage in the CA046 trial and in clinical practice

	Number of patients treated (CA046 trial)		**Cycle probability**		**Average cost per treatment**		**Average cost per cycle**	
	NPG	Gem	NPG	Gem	NPG	Gem	NPG	Gem
G-CSF treatment according to trial data	110	63	0.012	0.010	£191.04	£191.04	£2.33	£0.40
G-CSF treatment for febrile neutropenia (clinical practice)	14	6	0.002	0.001	£584.91	£477.12	£1.05	£0.50

NPG=Nab-Pac+Gem
Source: CS, Table 66

Due to the absence of any clinical data, the use of G-CSF by patients treated with Gem+Cap was assumed to be the same as for patients treated with Nab-Pac+Gem. G-CSF use by patients treated with FOLFIRINOX was taken from the ACCORD trial.[34]

Adverse events costs

The cost of AEs was included in the model as the cycle probability of an event occurring, multiplied by the cost of that event. Costs for AEs were taken from NHS Reference Costs (2015/16)[63] and validated by clinicians and are shown in Table 32.

Table 32 Adverse event costs

Grade 3+ TEAEs	Cost	NHS Reference Cost 2015/16[63] description
Neutropenia	£97.29	HRG code: XD25Z Neutropenia drugs band 1, NHS Trusts High Cost Drugs: Admitted Patient Care
Fatigue*	£35.00	Assumption: Fatigue assumed as one nurse visit per day of fatigue
Thrombocytopenia	£498.81	HRG code SA12K, Thrombocytopenia with CC Score 0-1 non-elective inpatients (short-stay)
Anaemia	£481.06	HRG code SA04L, Iron Deficiency Anaemia with CC Score 0-1, Non-elective short stay
Leukopenia	£97.29	No specific data available – assumed to be equal to neutropenia
Peripheral sensory neuropathy (pain)	£139.12	HRG code: 191 NHS Reference Costs 2015/2016 Total outpatient procedures, pain management
Neuropathy peripheral (pain)	£139.12	HRG code: 191 NHS Reference Costs 2015/2016 Total outpatient procedures, pain management
Dehydration	£808.64	HRG code: KC05H, Fluid and Electrolyte Disorders, with Interventions, with CC Score 0-4, Non-elective inpatient short stay
Asthenia*	£35.00	Assumption: Asthenia assumed as one nurse visit per day of asthenia
Abdominal pain	£1,124.81	HRG Code: FZ90A, Abdominal Pain with Interventions, non-elective in patient (short stay)
Nausea***	£379.38	Assumption: same as diarrhoea
Diarrhoea	£379.38	HRG code FZ91M, Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2, day case
Vomiting***	£379.38	Assumption: same as diarrhoea
Decreased appetite***	£379.38	Assumption: same as diarrhoea
Pulmonary embolism	£1,549.87	HRG code DZ09K: Pulmonary Embolus with Interventions, with CC Score 0-8, non-elective inpatient
Pneumonia	£1,984.07	HRG code: DZ19L, Other Respiratory Disorders without Interventions, with CC Score 11+, Non- elective inpatient long stay
Febrile Neutropenia**	£2,067.07	HRG Code: SA08J, Other Haematological or Splenic Disorders, with CC Score 0-2, non-elective inpatient
Cholangitis	£1,530.00	Assumption: UK Advisory board estimate 5 x cost of 1 excess bed day from NHS reference manual 2015/2016
Hyperbilirubinemia***	£435.22	Assumption: UK Advisory board: 1 consultant visit, 5 community nurse visits plus 1 ultrasound

CC=complexity and comorbidity; G-CSF=granulocyte colony-stimulating factor; HRG=Healthcare Resource Group; NHS=National Health Service; TEAE=treatment-emergent adverse event
* Cost shown is unit cost of 1-hour community nurse time, unit cost multiplied by duration of fatigue on each arm before application to model; ** Patients with febrile neutropenia treated with G-CSF from the start of the adverse event to the end of chemotherapy treatment. This cost is applied in addition to the HRG code (SA08F) and is not shown here – see Section 5.1 of the CS; *** Based on clinical opinion from recent UK advisory board
Source: CS, Table 68

Terminal care costs

An additional tunnel state of '4 weeks to death' is included in the model for the estimation of terminal care costs. In the base-case analysis, terminal care costs have been calculated based on a micro-costing approach that considers the cost of dying in hospital, at a hospice or at home, and weights these estimates based on the proportion of patients considered to die in each of these settings (Table 33). Full details of this approach are presented in Section 5.5.5 of the CS.

Table 33 Terminal care costs

	Proportion*	Total weekly cost	Weighted weekly cost
Death in hospital	56%	£929	£518
Death in hospice	17%	£1,137	£192
Death at home	27%	£1,274	£348
Total weighted weekly cost:			£1,058

*Proportions are taken from the ERG report in TA360[14]
Source: CS, Table 69

The company carried out two scenario analyses that model End of Life costs as per the company's original submission for TA360,[14] and as per an estimate of £6,153 for the last 8 weeks of life as modelled by the King's Fund.[65] These results are shown in Table 38.

5.4.9 Cost effectiveness results (PAS price)

The results presented in Section 5.4.9 to Section 5.4.12 are taken directly from the CS. However, the company updated the economic model during the clarification period. The **updated** incremental cost effectiveness ratio (ICER) per QALY gained (£46,932) for Nab-Pac+Gem versus Gem is slightly higher than the submitted base-case ICER per QALY gained (£46,657) for Nab-Pac+Gem versus Gem that is reported in the CS.

All of the company's cost effectiveness results are based on the PAS price of Nab-Pac. However, the company states (CS, p242) that the non-PAS ICER for Nab-PAC+Gem is £[redacted] per QALY gained. No further mention of this non-PAS ICER is made in the CS.

The base-case cost effectiveness results generated by the company's model are shown in Table 34. In the base-case analysis, treatment with Nab-Pac+Gem generates more benefits than treatment with Gem (+0.202 life years and +0.144 QALYs) at an increased cost (+£6,717). The company base-case ICER for the comparison of treatment with Nab-Pac+Gem versus Gem is £46,657 per QALY gained. Full details of the disaggregated results are presented in Section 5.7.3 of the CS.

Table 34 Base-case cost effectiveness results

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER per QALY gained
Gem	[redacted]	0.725	0.396				
Nab-Pac+Gem	[redacted]	0.927	0.540	£6,717	0.202	0.144	£46,657

ICER=incremental cost effectiveness ratio; LYG=life years gained; QALYs=quality adjusted life years; Inc=incremental
Source: CS, Table 71

The results of the company's cost effectiveness analysis for the comparison of treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX are given in Table 35 and Table 36. These comparisons are described as scenario analyses in the CS.

Treatment with Nab-Pac+Gem generates fewer benefits than treatment with Gem+Cap (-0.02 life years and -0.01 QALYs) at an increased cost (+£5,555). When compared to treatment with Gem+Cap, treatment with Nab-Pac+Gem is dominated (i.e., is more expensive and less effective).

Table 35 Company's cost effectiveness results for treatment with Nab-Pac+Gem vs Gem+Cap

Technology	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER per QALY gained
Gem+Cap	[redacted]	0.95	0.55				
Nab-Pac+Gem	[redacted]	0.93	0.54	+£5,555	-0.02	-0.01	Dominated

ICER=incremental cost effectiveness ratio; Inc=incremental; LYG=life years gained; QALYs=quality adjusted life years
Source: CS, adapted from Table 81

Treatment with Nab-Pac+Gem generates fewer benefits than treatment with FOLFIRINOX (-0.22 life years and -0.015 QALYs) at an increased cost (+£1,543). Compared with treatment with FOLFIRINOX, treatment with Nab-Pac+Gem is dominated (i.e., is more costly and less effective).

Table 36 Company's cost effectiveness results for treatment with Nab-Pac+Gem vs FOLFIRINOX

Technology	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER per QALY gained
FOLFIRINOX	[redacted]	1.15	0.69				
Nab-Pac+Gem	[redacted]	0.93	0.54	+£1,543	-0.22	-0.15	Dominated

ICER=incremental cost effectiveness ratio; Inc=incremental; LYG=life years gained; QALYs=quality adjusted life years
Source: CS, adapted from Table 81

5.4.10 Sensitivity analyses

Deterministic sensitivity analysis

The company performed one-way sensitivity analyses to explore the sensitivity of the cost effectiveness results generated by the model (240 individual inputs were varied). Results from varying the ten most influential parameters are presented in the CS as a tornado diagram, which is reproduced as Figure 6. The results show that the most influential parameters are the treatment variables used to parameterise OS, TOT and PFS.

Figure 6 Results from company's one-way sensitivity analyses

OS=overall survival; PFS=progression-free survival; TOT=time on treatment
Source: CS, Figure 40

Probabilistic sensitivity analysis

The company undertook a probabilistic sensitivity analysis (PSA) to derive the mean ICER per QALY gained for the comparison of the cost effectiveness of treatment with Nab-Pac+Gem versus Gem. The PSA was run for 1000 iterations. Results from the company's base-case deterministic analysis and PSA are shown in Table 37.

Table 37 Base-case deterministic versus PSA cost effectiveness results

	Incremental costs	Incremental QALYs	ICER per QALY gained
Deterministic result	£6,717	0.144	£46,657
Average value from PSA	£6,758	0.140	£46,801

ICER=incremental cost effectiveness ratio; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year
Source: CS, Table 71 and Table 77

Results from the PSA suggest a [redacted] likelihood of treatment with Nab-Pac+Gem being cost effective versus treatment with Gem at a willingness-to-pay (WTP) threshold of £30,000 per QALY gained and a [redacted] likelihood of treatment with Nab-Pac+Gem being cost effective versus treatment with Gem at a WTP threshold of £50,000 per QALY gained. The results from the PSA are presented as a cost effectiveness plane in Figure 7 and a cost effectiveness acceptability curve in Figure 8.

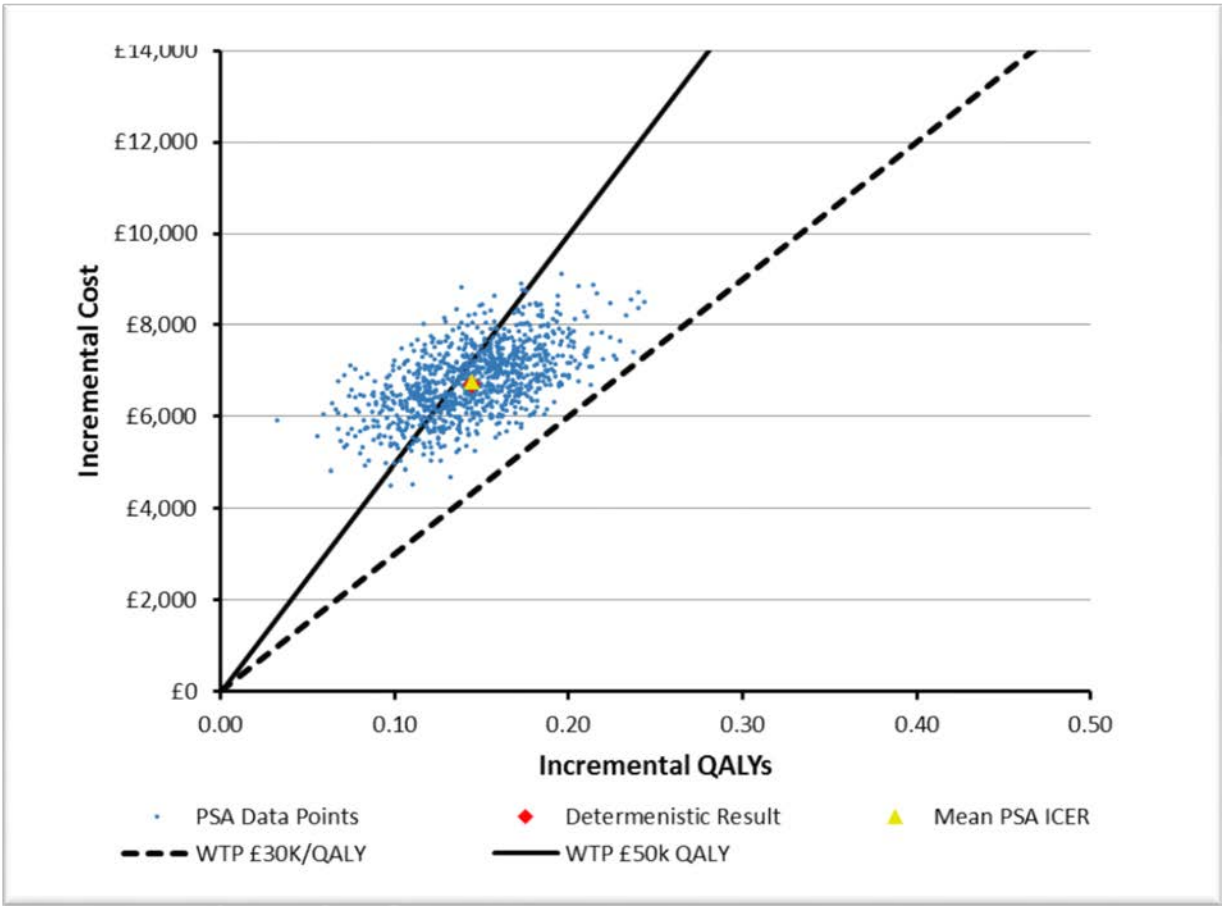

Figure 7 Cost effectiveness plane for treatment with Nab-Pac+Gem vs Gem

Figure 8 Cost effectiveness acceptability curve for treatment with Nab-Pac+Gem vs Gem

Source: CS, Figure 39

5.4.11 Scenario analyses

The company presents the results of 25 scenarios used to explore different structural assumptions for the comparison of treatment with Nab-Pac+Gem versus Gem. The structural scenario with the biggest impact on the ICER per QALY gained is the assumption of no anticipated missed doses. The second most influential change was the use of the ERG OS curve from TA360[14] and the third most influential change was the availability of a 250mg vial for Nab-Pac (Table 38).

Table 38 Structural scenario analyses results (top ten [and End of Life] impact on ICER per QALY gained)

Base case	Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base-case ICER
Base case	-	£6,717	0.14	£46,657	-
Proportion of time missed doses anticipated overall (first and subsequent dose) - 50.00% and 100.00%	0.00% and 0.00%	£7,356	0.14	£51,097	9.52%
Stratified Gamma	ERG curve fits	£7,308	0.15	£50,307	7.82%
250mg vial availability – No 250mg vial	250mg vial	£6,250	0.14	£43,416	-6.95%
Utilities - Romanus	SIEGE Devlin value set (no AE utility decrement)	£6,717	0.15	£43,460	-6.85%
Romanus with AE utility decrements	SIEGE Devlin value set with AE utility decrements	£6,717	0.15	£43,471	-6.83%
Utilities - Romanus	SIEGE crosswalk (no AE utility decrement)	£6,717	0.14	£49,303	5.67%
Assessment of PFS – Investigator assessment	Independent assessment	£6,969	0.14	£48,968	4.95%
Source of BSA data – UK data	Trial based BSA	£7,016	0.14	£48,739	4.46%
Parametric survival curves (OS, PFS, TOT) – Stratified Gamma	Gamma	£6,570	0.14	£46,107	-1.18%
Discount rate (costs and QALYs) - 3.50%	0%	£6,789	0.15	£46,117	-1.16%
Duration of end of life utility decrements and costs applied for – utility decrement: 12 weeks	Utility decrement: 4 weeks	£6,717	0.14	£46,767	0.23%
End of life costs: 4 weeks	End of life costs: 12 weeks	£6,714	0.15	£46,641	-0.03%

AE=adverse event; BSA=body surface area; G-CSF=granulocyte-colony stimulating factor; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; ToT=time on treatment
Source: Adapted from CS, Table 80

The company also considered the comparison of Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX to be scenario analysis. The results of these comparisons are presented in Table 35 and Table 36 of this ERG report.

5.4.12 Subgroup analyses

The company did not carry out any cost effectiveness subgroup analyses.

5.4.13 Model validation and face validity check

According to the company (CS, p241) …'The model was quality assured by the internal processes of the external economists who adapted the economic model.' These processes included review of the model for coding errors, inconsistencies and plausibility of inputs. The model was also subject to a checklist[66] of known modelling errors.

The model inputs were also validated by clinical advisory boards and by comparing results from the model with any previously published model estimates[51,67] that were identified by the company's literature search. The publication by Gharaibeh[67] reports an ICER of £78,086 per QALY gained for Nab-PAC+Gem versus Gem, which the company states is similar to the non-PAS ICER of [redacted] per QALY gained that is reported in the CS (p242).

5.5 ERG critique of company's submitted economic evaluation

Table 39 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by the Institute	Yes, although two of the comparators in the final scope are not considered in the company's base case analysis
Comparator(s)	Alternative therapies routinely used in the NHS	Yes
Perspective costs	NHS and PSS	PSS costs were not fully considered in the CS
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes
Synthesis of evidence on outcomes	Systematic review	Yes, for OS and PFS for treatment with Gem+Cap and FOLFIRINOX, and for HRQoL outcomes
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standard and validated instrument	Yes
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

EQ-5D=EuroQol-5 dimension; QALY=quality adjusted life year; HRQoL=health-related quality of life; OS=overall survival; PFS=progression-free survival: PSS=Personal Social Services; CS= company submission

Table 40 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partly	Effectiveness for treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX not robustly established due to issues with the NMA
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Partly	Error in the calculation of total LY and QALYs
Were the cost and consequences valued credibly?	Partly	Drug cost calculations did not take into account all available vial sizes
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

LY=life year; QALY=quality adjusted life year

The company's Microsoft Excel spreadsheet model is constructed according to conventional practice and is generally implemented correctly. The company provided two models as part of its submission: an original model, the results of which are given in the CS; and an updated model corrected for AE calculations, which was provided during the clarification process. The ERG has used the updated model as the basis for its critique and revisions. The original base case ICERs per QALY gained are presented in Table 46 (Nab-Pac+Gem versus Gem), Table 47 (Nab-Pac+Gem versus Gem+Cap), and Table 48 (Nab-Pac+Gem versus FOLFIRINOX) alongside the company's updated base case and the ERG's revisions.

5.5.1 ERG corrections

Application of HRs for treatment with Gem+Cap and FOLFIRINOX

The implementation of the company's estimates of OS, PFS and TOT for treatment with Gem+Cap and with FOLFIRINOX is incorrect. The company uses HRs from the NMA to estimate the relative treatment effect for Nab-Pac+Gem versus Gem+Cap or FOLFIRINOX and applies these treatment effects by raising each cycle probability for OS, PFS and TOT to the power of the relevant HR. However, the HR does not function as a multiplier in this way.

The HR should instead be applied to the treatment parameter within the definition of the curve.

The ERG has corrected the application of the HRs within the company model. Applying the ERG's correction to the modelling of time-to-event outcomes for treatment with Gem+Cap and with FOLFIRINOX

Total life year and QALY calculations

The company's area under the curve estimations of total QALYs and LYs are slightly overestimated, as they include a value for the first cycle. No QALYs or LYs should be accrued at the very beginning of the very first cycle, as patients have only just entered the model. However, it is correct that costs are accrued in the first cycle, as it is assumed that treatment is received on Day 1 of a cycle.

The ERG has corrected the calculation of total QALYs and life years so that accrual begins in the second cycle of the model. Applying the ERG's correction to the calculation of total QALYs and LYs increases the ICER per QALY gained for the comparison of treatment with Nab-Pac+Gem versus Gem by £79 to £47,011. Treatment both with Gem+Cap and with FOLFIRINOX continue to dominate treatment with Nab-Pac+Gem.

All ICERs per QALY gained in the ERG's critique are quoted with reference to the ERG's corrected company base case for each comparator (Nab-Pac+Gem versus Gem=£47,011, Nab-Pac+Gem versus Gem+Cap=Dominated, Nab-Pac+Gem versus

FOLFIRINOX=Dominated).

5.5.2 Major issues

Comparators

The final scope issued by NICE for this appraisal indicates that, for treatment with Nab-Pac+Gem, there are three appropriate comparators: Gem, Gem+Cap, and FOLFIRINOX. Evidence of relative clinical effectiveness for Nab-Pac+Gem, Gem+Cap and FOLFIRINOX compared with Gem is provided by data from three clinical trials.

The company argues for restricting consideration to the comparison of Nab-Pac+Gem versus Gem on the basis that there is a distinct subgroup of patients with metastatic adenocarcinoma of the pancreas currently receiving Gem who are most likely to be suitable for transfer to the Nab-Pac+Gem regimen. On this basis, the company base-case analysis is restricted to the analysis of evidence from the CA046 trial. This subgroup makes up approximately [redacted] of patients currently receiving treatment. The company does not

describe the characteristics of these patients for whom clinical effectiveness has been assessed.

For completeness, the company presents the results of a wider set of cost effectiveness analyses (CS, Table 81); Gem+Cap and FOLFIRINOX were considered to be comparators in separate scenario analyses. From this it can be deduced that the results of pair-wise comparisons of Nab-Pac+Gem versus Gem+Cap, and versus FOLFIRINOX indicate that Nab-Pac+Gem is dominated by both of these comparators, exhibiting inferior outcomes (incremental LYs and incremental QALYs per patient) as well as incurring higher costs per patient (Table 41).

Table 41 Company cost effectiveness results for Nab-Pac+Gem vs Gem-Cap and FOLFIRINOX

Treatment	Incremental costs	Incremental QALYs	ICER
Gem+Cap	[redacted]	-0.011	Dominated
FOLFIRINOX	[redacted]	-0.153	Dominated

Source: Updated company model

The comparison of treatment with Nab-Pac+Gem versus Gem uses modelled parametric curves based on data from the CA046 trial that do not rely on the PH assumption nor the results from the NMA.

However, the company applies HRs from the NMA to the OS and PFS estimates for treatment with Nab-Pac+Gem in order to create estimates of OS and PFS for treatment with Gem+Cap and FOLFIRINOX. This approach is not valid, as it relies on the PH assumption holding between treatment with Nab-Pac+Gem versus Gem in the CA046 trial when PH is shown to be violated in this trial (Section 4.2.4). The ERG is also concerned that the company's application of a HR is inappropriate. The ERG has used the company's approach to fitting an HR to the stratified Gamma model due to the limitations of the model; however, it urges that the results be interpreted with caution.

If PH can be shown to hold for treatment with Gem+Cap versus Gem and FOLFIRINOX versus Gem, then HRs could be applied to OS and PFS estimates for treatment with Gem from the CA046 trial to create estimates of OS and PFS for treatment with Gem+Cap and FOLFIRINOX. The ERG's approach to applying comparator HRs to the model is outlined in Appendix 10.10 of this ERG report. The ERG investigated whether the PH assumption holds in the two trials[6,7] included in the SA2 reduced network NMA (Section 4.6.6).

For treatment with Gem+Cap versus Gem, the ERG found that, given the limited data available, the PH assumption was not strongly violated for either OS or PFS. For treatment

with FOLFIRINOX versus Gem, it found the PH assumption to be strongly violated for both OS and PFS. The results of the ERG's PH tests are given in Appendix 10.11.

The ERG has provided cost effectiveness results from the model for treatment with Gem+Cap and with FOLFIRINOX (using published HRs versus treatment with Gem) for completeness and to provide a sensitivity analysis versus the company's base case using HRs from the NMA. However, these results should be treated with caution, as they apply a HR to a stratified Gamma model, which is not appropriate.

The ERG has applied the HRs shown in Table 42 to model estimates of OS and PFS for treatment with Gem (and assumed that the HRs for PFS also apply to TOT).

Table 42 HRs used in ERG amended model

Comparator vs Gem	Source	HR
Gem+Cap OS	Scheithauer 2003[6]	0.82
Gem+Cap PFS	Scheithauer 2003[6]	0.81
FOLFIRINOX OS	Conroy 2011[7]	0.57
FOLFIRINOX PFS	Conroy 2011[7]	0.47

Source: Figure 9 and Figure 10, CS Appendix 4;

The ERG's analysis generates a mean OS gain of 0.8 months and a mean PFS gain of 1.18 months for treatment with Nab-Pac+Gem generates versus Gem+Cap. Treatment with Gem+Cap no longer dominates treatment with Nab-Pac+Gem once the ERG's revised HRs are applied, as treatment with Nab-Pac+Gem shows increased benefit over Gem+Cap (+0.054 QALYs) albeit at a slightly higher incremental cost than in the base case (+£5,563 versus +£5,567). The ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem+Cap using revised HRs is £103,827.

The ERG's analysis generates a mean OS loss of 2.72 months and a mean PFS loss of 1.42 months for treatment with Nab-Pac+Gem versus FOLFIRINOX. These results should be treated with caution due to violation of PH in the ACCORD trial.[7] Applying revised HRs in the model results in extra time on treatment for patients receiving FOLFIRINOX, which generates high enough extra administration, monitoring and AE costs to outweigh the more expensive drugs used for treatment with Nab-Pac+Gem. It also increases OS and PFS for treatment with FOLFIRINOX, which in turn increases the incremental QALY difference between Nab-Pac+Gem and FOLFIRINOX. As treatment with Nab-Pac+Gem becomes cheaper than treatment with FOLFIRINOX once the revised HRs are applied (-£582), and remains less beneficial (-0.175 QALYs), it is no longer dominated by FOLFIRINOX. The ICER per QALY gained for treatment with Nab-Pac+Gem versus FOLFIRINOX using revised HRs is £3,327.

Costing of first-line treatments

All first-line drugs included in the company's model are overestimated in the base case. This is principally due to the company not including all available vial/packet sizes in its calculation of costs for first-line treatments, but there is also a small impact from using an average BSA for all patients to estimate average dosage rather than estimating doses based on sex. The ERG has re-estimated weekly drug costs using all vial/packet sizes available to the NHS and using separate BSA values for males and females, as recorded in the CA046 trial (Table 43).

Table 43 First-line treatment costs: company model and ERG estimates

	Nab-Pac+Gem	Gem	Gem+Cap	FOLFIRINOX
Company model	[redacted]	[redacted]	[redacted]	[redacted]
ERG	[redacted]	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]	[redacted]

Source: BNF; eMIT; MIMs; ERG calculations
Note: these costs do not include amendments for dose intensity or wastage

Applying the ERG's drug costing method decreases the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem by £7,721 to £39,289. Treatment with Nab-Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

Time on treatment

The company uses a stratified Gamma model to estimate time on treatment for patients receiving Nab-Pac+Gem or Gem, which is unnecessary, as the data from the CA046 is complete. The company's stratified Gamma model slightly overestimates time on treatment for both Nab-Pac+Gem and Gem by the same amount (0.23 months), but, given the magnitude of the cost differential between the two treatments, this difference has a sizable impact on the ICER per QALY gained.

Using the full K-M data for time on treatment rather than the company's stratified Gamma model increases the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem by £2,911 to £49,922. Treatment with Nab-Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

5.5.3 Minor issues

AE disutilities

The company base case analysis includes AE disutilities alongside health-state utility values from a clinical trial,[59] which the ERG considers to be double counting. The effects of AEs experienced during a trial will be included in patients' responses to the EQ-5D questionnaire and do not need to be estimated separately. The ERG has used an existing switch in the

company model to remove additional AE disutilities from the calculation of the ICER per QALY gained. Without additional AE disutilities, the ICER per QALY gained for the comparison of treatment with Nab-Pac+Gem versus Gem decreases by £17 to £46,994. Treatment with Nab-Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

5.5.4 ERG analyses

Survival estimates: CA046

The company's use of fully parametric models to estimate and extrapolate time-to-event data from the CA046 trial introduces unnecessary uncertainties into the cost effectiveness estimates for the comparison of Nab-Pac+Gem versus Gem. The CA046 trial data are 90% complete for OS and almost 100% complete for PFS, so it is only the very few remaining patients for whom outcomes need to be estimated. By using fully parametric models, the company is replacing with estimates information that already exists for most patients in the CA046 trial. The ERG's preference when modelling survival using data from a single trial is to use K-M data as far as possible before appending a parametric model to the end of the K-M data to project over the remaining time horizon. In NICE TA360,[14] the ERG explored the impact of modelling OS and PFS using only those data in the period towards the end of the survival curve in which it was apparent that a long-term trend had become established (Figure 9 and Figure 10). These estimates are included in the current company model as a sensitivity analysis and are preferred by the ERG in this appraisal.

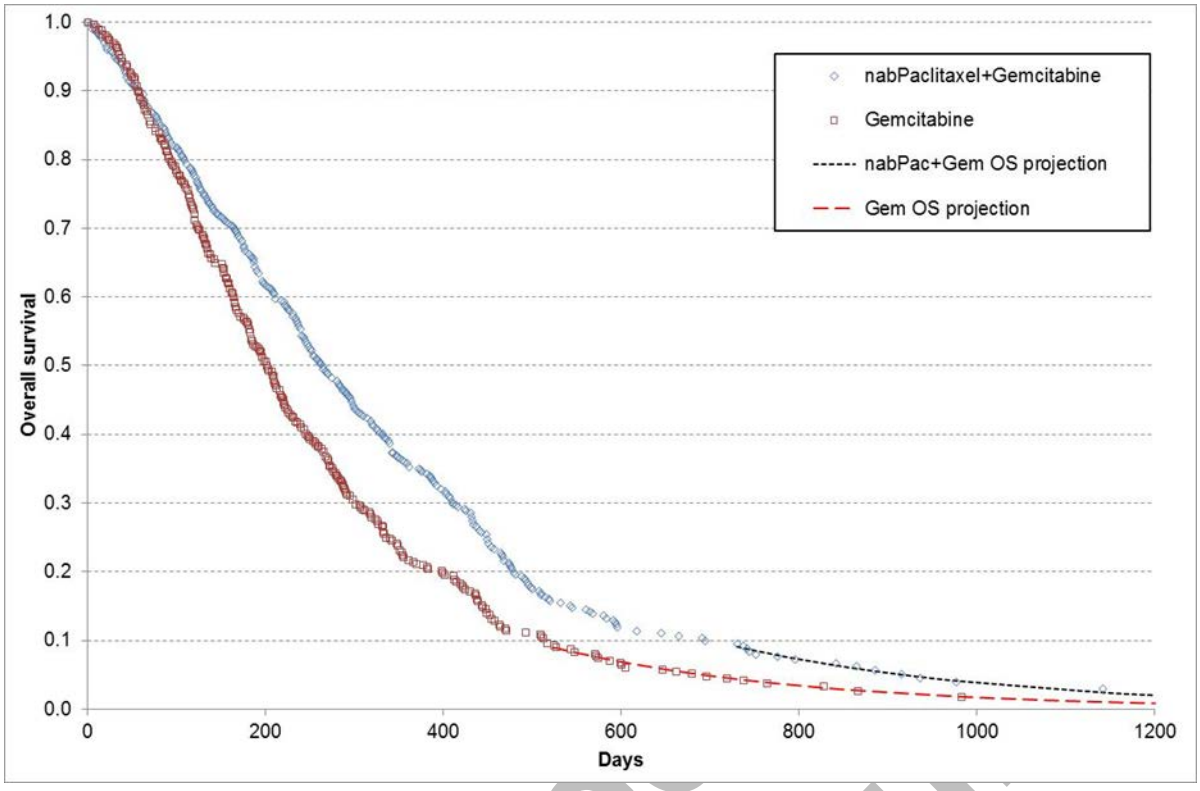

Figure 9 Overall survival in the whole CA046 trial population
Source: NICE TA360

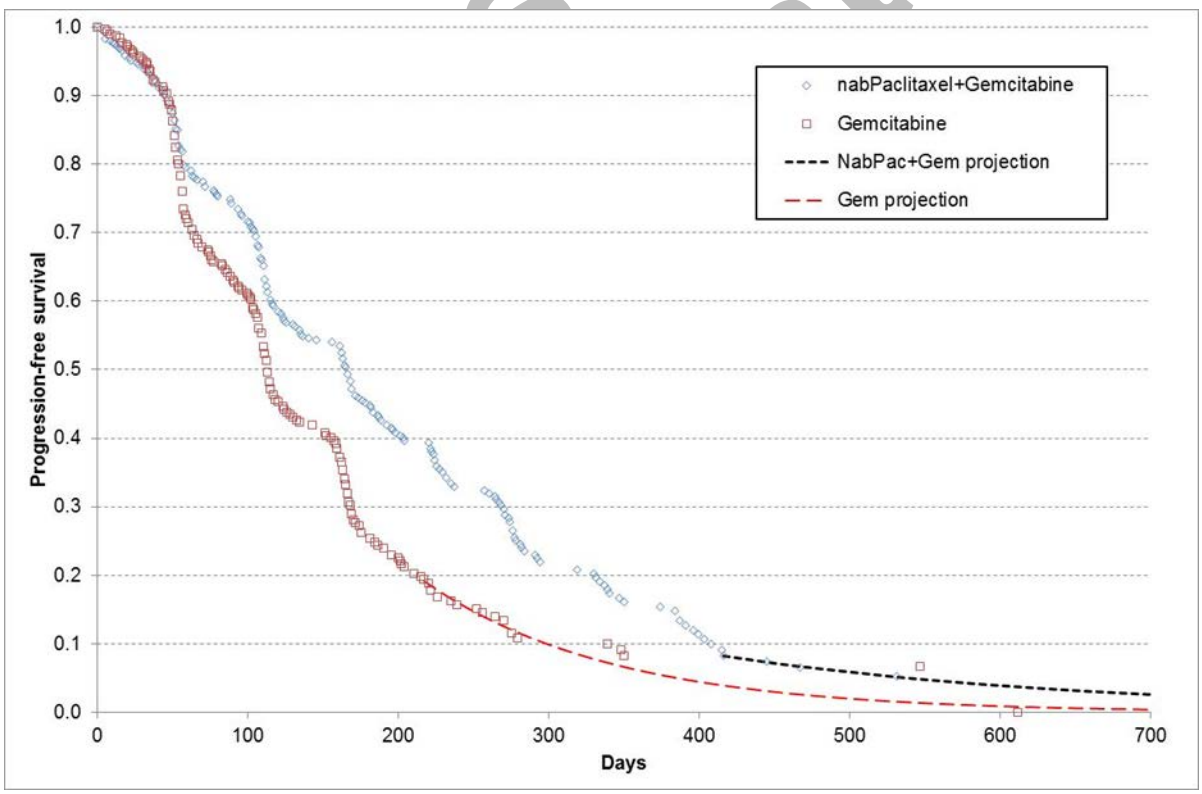

Figure 10 Progression free survival in the whole CA046 trial population
Source: NICE TA360

Using the ERG's OS projections from NICE TA360[14] gives mean OS for treatment with Nab-Pac+Gem of 10.91 months and mean OS for Gem of 8.47 months, resulting in an OS gain of

2.44 months. This is compared to an OS gain of 2.42 months in the company model. Using the ERG estimates of OS, the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem decreases by £330 to £46,681. Treatment with Nab-Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

Using the ERG's PFS projections from NICE TA360[14] gives mean PFS for treatment with Nab-Pac+Gem of 6.82 months and mean PFS for Gem of 4.74 months, resulting in a PFS gain of 2.52 months. This is compared to a PFS gain of 2.07 months in the company model. Using the ERG estimates of PFS, the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem increases by £77 to £46,933. Treatment with Nab-Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

5.5.5 Scenario analyses

AE costs

The ERG has investigated the sensitivity of the ICERs per QALY gained to the estimates of AE costs used in the model. used published sources[68-70] and discussions with a clinical expert to re-estimated the resource cost used in the model for some AEs. The major differences between the ERG estimates of AE costs and the company estimates is in the assumed length of stay in hospital for Grade 3+ diarrhoea, dehydration and vomiting: the ERG has assumed at least one overnight stay for these events, whereas the company has assumed that patients will not stay overnight in hospital. Table 44 gives the definitions of all the admission/appointment types used in the costing of AEs. Table 45 compares the costs used in the company base case versus the ERG revised costs.

Table 44 Definition of admission/appointment types

Type	Definition
Non-elective inpatient short stay	1 day (no overnight - patient allowed home on day of admission)[70]
Non-elective inpatient long stay	2 or more days[70]
Day case	Admitted electively, returns home as scheduled without stay overnight[69]
Outpatient procedure	Attendance at outpatient clinic (pre-booked or not)[70]

Table 45 Costs of Grade 3+ AEs: Company model and ERG revisions

	Company model		ERG	
Grade 3+ AE	**Reference**	**Cost**	**Reference**	**Cost**
Neutropenia	High cost drugs: Neutropenia Drugs, Band 1 (Admitted patient care, HRG code: XD25Z)	£97.29	High cost drugs: Neutropenia Drugs, Band 1 (Outpatient, HRG code: XD25Z)	£136.61
Fatigue	Assumption: Fatigue assumed as one nurse visit per day of fatigue	£35.00	As per CS	£35.00
Thrombocytopenia	Thrombocytopenia with CC Score 0-1 (Non-elective inpatient short stay, HRG code: SA12K)	£498.81	Thrombocytopenia with CC Score 0-1 (Day case, HRG code: SA12K)	£324.52
Anaemia	Iron Deficiency Anaemia with CC Score 0-1 (Non-elective inpatient short stay, HRG code: SA04L)	£481.06	As per CS	£481.06
Leukopenia	No specific data available – assumed to be equal to neutropenia	£97.29	Assume same as neutropenia	£136.61
Peripheral sensory neuropathy (pain)	Pain management (Total outpatient procedures, service code: 191)	£139.12	As per CS	£139.12
Neuropathy peripheral (pain)	Pain management (Total outpatient procedures, service code: 191)	£139.12	As per CS	£139.12
Dehydration	Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-4 (Non-elective inpatient short stay, HRG code: KC05H)	£808.64	Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-4 (Non-elective inpatient long stay, HRG code: KC05H)	£3,368.32
Asthenia	Assumption: Asthenia assumed as one nurse visit per day of asthenia	£35.00	As per CS	£35.00
Abdominal pain	Abdominal Pain with Interventions (Non-elective inpatient short stay, HRG code: FZ90A)	£1,124.81	Abdominal Pain with Interventions (Non elective long stay, HRG code: FZ90A)*	£2,407.05
Nausea	Assumption: same as diarrhoea	£379.38	As per CS	£379.38
Diarrhoea	Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2, day case [FZ91M]	£379.38	Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-4 (Non-elective inpatient long stay, HRG code: KC05H)	£3,368.32
Vomiting	Assumption: same as diarrhoea	£379.38	Assume same as diarrhoea	£3,368.32
Decreased appetite	Assumption: same as diarrhoea	£379.38	Assume same as nausea	£379.38
Pulmonary embolism	Pulmonary Embolus with Interventions, with CC Score 0-8, non-elective inpatient [DZ09K]	£1,549.87	Pulmonary Embolus with Interventions, with CC Score 0-8 (Non-elective inpatient short stay, HRG code: DZ09K)	£677.69
Pneumonia	Other Respiratory Disorders without Interventions, with CC Score 11+ (Non- elective inpatient long stay, HRG code: DZ19L)	£1,984.07	As per CS	£1,984.07

Febrile Neutropenia	Other Haematological or Splenic Disorders, with CC Score 0-2 (Non-elective inpatient long stay, HRG code: SA08J)	£2,067.07	As per CS	£2,067.07
Cholangitis	Assumption: UK Advisory board estimate 5 x cost of 1 excess bed day from NHS reference manual 2015/2016	£1,530.00	Gastrointestinal Infections without interventions, with CC Score 0-1 (Non-elective inpatient long stay, HRG code: FZ36Q)	£1,421.51
Hyperbilirubinemia	Assumption: UK Advisory board: 1 consultant visit, 5 community nurse visits plus 1 ultrasound	£435.22	Assume same as cholangitis	£1,421.51

* long stay assumed due to need for investigations before deciding on subsequent management
Source: CS Table 68; NHS Reference Costs 2015/2016

Applying all the ERG's revised AE costs increases the ICER per QALY gained for the treatment of Nab-Pac+Gem versus Gem by £1,762 to £48,773. Treatment with Nab-Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

Health state utility values

The ERG does not consider any of the utility values presented by the company to be robust. However, it has not identified a preferred source of utility values. The ERG considers the UK-adjusted Romanus[59] and SIEGE crosswalk[58] values to be more appropriate than the SIEGE Devlin[57] values. It has presented the Romanus[59] values in its base case analysis to maintain consistency with previous appraisal TA360[14] in the absence of detail that would allow critique of the values from the SIEGE trial.[28] The SIEGE crosswalk utility values are presented as a sensitivity analysis.

Table 46 Health state utility values

	Health state utility	
	Pre-progression	**Post-progression**
Devlin[57] value set (SIEGE)	0.79	0.75
Crosswalk method[58] (SIEGE)	0.70	0.65
Romanus et al (2012)[59] with UK adjustment	0.74	0.67

Source: CS, Table 52

The company's justification for choosing the Romanus[59] utility values is based on flawed reasoning. The company notes that the two methods of analysing the SIEGE[28] HRQoL data produce substantially different results and that the choice between them is subjective. It also notes that the UK-adjusted Romanus[59] utility values fall between the two sets of values derived from the SIEGE[28] trial, and uses this fact to inform its decision to use the UK-adjusted Romanus[59] values in its base case.

The ERG does not consider it appropriate to categorise the two sets of utility estimates from the SIEGE[28] trial as upper and lower bounds of the health state utility estimates. The Devlin[57] and crosswalk[58] methods are not attempting to produce estimates of the same thing. The Devlin[57] value set is a way of weighting the 3125 theoretically possible health states derived from the EQ-5D-5L questionnaire according to their value by the general UK population. The crosswalk method is a way of translating the results of the EQ-5D-5L into the weighting of the 243 theoretically possible health states derived from the EQ-5D-3L. Out of the three sets of utility values presented by the company, only the UK-adjusted Romanus[59] utility values and the utility values from the SIEGE[28] trial adjusted to the EQ-5D-3L UK-value set are comparable, since they are measured on the same scale.

Since the NICE cost-effectiveness thresholds are based on benefit calculations using HRQoL data derived from the EQ-5D-3L questionnaire, and because the results of the EQ-5D-5L and EQ-5D-3L have been found to produce substantially different estimates of cost effectiveness,[71] the ERG does not consider the Devlin[57] value set to be appropriate in this instance.

The UK-adjusted values from the Romanus paper[59] were the ERG's preferred estimates of health state utility in the original appraisal,[14] at which time the HRQoL data from the SIEGE trial were not available. The ERG noted in the original appraisal that there was still considerable uncertainty around patients' quality of life using these estimates. First, the patients in the trial reported by Romanus[59] were not treated with Nab-Pac+Gem; they received either Gemcitabine plus Placebo or Gemcitabine plus Bevacizumab. Second, the company itself had pointed out that the reported utility values for patients with stable disease in the Romanus[59] study were not significantly different from age-matched US general population values. Third, the utility values were mapped to the UK-value set from published summary values, which introduces further uncertainty.

The SIEGE[28] trial has the greatest relevance to the current appraisal, as it is a UK-based randomised trial that recruited patients with metastatic pancreatic cancer of whom half received the Nab-Pac+Gem regimen used in the CA046 trial. However, the reference provided by the company does not include any details of the EQ-5D from the SIEGE[28] trial, so the ERG has not been able to verify the derivation or mapping of the utility values from the trial.

Applying the switch in the company model to use the SIEGE crosswalk utility values instead of the base case UK-adjusted Romanus utility values increases the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem by £2,667 to £49,678. Treatment with Nab-

Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX. Applying the switch in the company model to use the SIEGE Devlin[57] utility values instead of the base case UK-adjusted Romanus utility values would decrease the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem. Treatment with Nab-Pac+Gem would remain dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Before incorporating any ERG amendments into the company model, the ERG has corrected an error in the company model, namely:

- Calculation of total LY and QALYs

The ERG has made the following amendments to the ERG corrected company base case for treatment with Nab-Pac+Gem versus Gem, Nab-Pac+Gem versus Gem+Cap and Nab-Pac versus Gem versus FOLFIRINOX:

- HRs for Gem+Cap vs Gem (R1)
- HRs for FOLFIRINOX vs Gem (R2)
- ERG drug costing method (R3)
- TOT from CA046 trial (R4)
- Do not apply AE disutilities (R5)
- ERG OS (R6)
- ERG PFS (R7)

The ERG has also included two scenario analyses to investigate the effect of changes to the ERG corrected base case of using:

- ERG AE costs (S1)
- SIEGE crosswalk utility values (S2)

Deterministic results

Cost effectiveness results for the base case comparisons of treatment with Nab-Pac+Gem versus Gem, Nab-Pact+Gem versus Gem+Cap and for Nab-Pac+Gem versus FOLFIRINOX are displayed in Table 47, Table 48 and Table 49 respectively. Cost effectiveness results for the sensitivity analyses for comparisons of treatment with Nab-Pac+Gem versus Gem, Nab-Pact+Gem versus Gem+Cap and for Nab-Pac+Gem versus FOLFIRINOX are displayed in Table 50, Table 51 and Table 52 respectively.

When all of the ERG's suggested amendments have been implemented in the base case, the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem is £41,250. When all of the ERG's suggested amendments have been implemented in the base case and all of the scenario analyses are implemented, the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem is £45,571.

The ERG urges caution when interpreting its revised cost effectiveness results for treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX, as there are fundamental issues within the time-to-event estimates (non-PH in the ACCORD[7] trial, and the use of HRs with a stratified Gamma model) that it could not resolve within the model.

Treatment with Nab-Pac+Gem is no longer dominated by treatment with Gem+Cap once all of the ERG revisions are applied in combination. This is principally due to the ERG's indirect treatment comparison method (R1), which uses HRs applied to the modelled Gem OS, PFS and TOT to estimate time-to-event outcomes for treatment with Gem+Cap. When all of the ERG's suggested amendments to the base case have been implemented, the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem+Cap is £99,837. When all of the ERG's suggested amendments have been implemented in the base case and all of the scenario analyses are implemented, the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem+Cap is £107,898.

Treatment with Nab-Pac+Gem is dominated by treatment with FOLFIRINOX when all but one of the ERG's revisions are applied either individually or in combination. This is because treatment with Nab-Pac+Gem is shown to be more costly and les beneficial than treatment with FOLFIRINOX. The only ERG revision that does not result in treatment with FOLFIRINOX dominating treatment with Nab-Pac+Gem is when the ERG's amended HRs are applied to the model in isolation (R2). This results in extra time on treatment for patients receiving FOLFIRINOX, which generates high enough extra administration, monitoring and AE costs to outweigh the more expensive drugs used for treatment with Nab-Pac+Gem. Treatment with Nab-Pac+Gem thus becomes cheaper than treatment with FOLFIRINOX due to this individual revision and remains less beneficial, and yields an ICER of £3,327. When all of the ERG's suggested amendments have been implemented in the base case and all of the scenario analyses are implemented, treatment with Nab-Pac+Gem is dominated by treatment with FOLFIRINOX.

Table 47 Cost effectiveness results: ERG revisions to company base case for the comparison of Nab-Pac+Gem vs Gem

Description	Nab-Pac+Gem			Gem			Incremental			ICER/QALY gained	ICER change
	Costs	LY	QALYs	Costs	LY	QALYs	Costs	LY	QALYs		
Company original base case	[redacted]	***0.927***	***0.540***	[redacted]	***0.725***	***0.396***	***£6,717***	***0.202***	***0.144***	***£46,657***	**-**
Company updated base case	[redacted]	***0.927***	***0.539***	[redacted]	***0.725***	***0.396***	***£6,755***	***0.202***	***0.144***	***£46,932***	**-**
ERG corrected company base case	[redacted]	***0.908***	***0.527***	[redacted]	***0.706***	***0.383***	***£6,755***	***0.202***	***0.144***	***£47,011***	**-**
R1) HRs for Gem+Cap vs Gem	[redacted]	-	-	[redacted]	-	-	**-**	-	-	**-**	**-**
R2) HRs for FOLFIRINOX vs Gem	[redacted]	0.908	0.527	[redacted]	0.706	0.383	***£6,755***	0.202	0.144	***£47,012***	***+£1****
R3) ERG drug costing method	[redacted]	0.908	0.527	[redacted]	0.706	0.383	***£5,646***	0.202	0.144	***£39,289***	***-£7,721***
R4) TOT from CA046 trial	[redacted]	0.908	0.527	[redacted]	0.706	0.383	***£7,173***	0.202	0.144	***£49,922***	***£2,911***
R5) Do not apply AE disutilities	[redacted]	0.908	0.527†	[redacted]	0.706	0.383†	***£6,755***	0.202	0.144	***£46,994***	***-£17***
R6) ERG OS	[redacted]	0.909	0.528	[redacted]	0.706	0.383†	***£6,750***	0.203	0.145	***£46,681***	***-£330***
R7) ERG PFS	[redacted]	0.908	0.531	[redacted]	0.706	0.387	***£6,765***	0.202	0.144	***£46,933***	***-£77***
ERG revised base case (R3:R7)	[redacted]	***0.909***	***0.532***	[redacted]	***0.706***	***0.387***	***£5,985***	***0.203***	***0.145***	***£41,250***	***-£5,761***

Costs and QALYs discounted; life years undiscounted
* Changing HRs for FOLFIRINOX affects results for other treatments due to calculation of G-CSF use in patients treated with FOLFIRINOX second line
† QALY change from ERG corrected company base case evident at greater than 3 decimal places
AE=adverse event; ERG=Evidence Review Group; LY=life years; PFS=progression free survival; OS=overall survival; QALYs=quality adjusted life years; TOT=time on treatment; ICER=incremental cost effectiveness ratio

Table 48 Cost effectiveness results: ERG revisions to company base case for the comparison of Nab-Pac+Gem vs Gem+Cap

Description	Nab-Pac+Gem			Gem+Cap			Incremental			ICER/QALY gained
	Costs	LY	QALYs	Costs	LY	QALYs	Costs	LY	QALYs	
Company original base case	[redacted]	***0.927***	***0.540***	[redacted]	***0.950***	***0.551***	***£5,555***	***-0.023***	***-0.011***	***Dominated***
Company updated base case	[redacted]	***0.927***	***0.539***	[redacted]	***0.950***	***0.551***	***£5,567***	***-0.023***	***-0.011***	***Dominated***
ERG corrected company base case	[redacted]	***0.908***	***0.527***	[redacted]	***0.931***	***0.538***	***£5,567***	***-0.023***	***-0.011***	***Dominated***
R1) HRs for Gem+Cap vs Gem	[redacted]	0.908	0.527	[redacted]	0.839	***0.473***	***£5,563***	0.068	0.054	***£103,827***
R2) HRs for FOLFIRINOX vs Gem	[redacted]	0.908	0.527	[redacted]	0.931	***0.538***	***£5,568****	-0.023	-0.011	***Dominated***
R3) ERG drug costing method	[redacted]	0.908	0.527	[redacted]	0.931	***0.538***	***£4,520***	-0.023	-0.011	***Dominated***
R4) TOT from CA046 trial	[redacted]	0.908	0.527	[redacted]	0.931	***0.538***	***£5,719***	-0.023	-0.011	***Dominated***
R5) Do not apply AE disutilities	[redacted]	0.908	0.527†	[redacted]	0.931	***0.538†***	***£5,567***	-0.023	-0.011	***Dominated***
R6) ERG OS	[redacted]	0.909	0.528	[redacted]	0.934	***0.539***	***£5,560***	-0.024	-0.012	***Dominated***
R7) ERG PFS	[redacted]	0.908	0.531	[redacted]	0.931	***0.542***	***£5,464***	-0.023	-0.010	***Dominated***
ERG revised base case (R1, R3:R7)	[redacted]	***0.909***	***0.532***	[redacted]	***0.845***	***0.482***	***£5,072***	***0.064***	***0.051***	***£99,837***

Costs and QALYs discounted; life years undiscounted
* Changing HRs for FOLFIRINOX affects results for other treatments due to calculation of G-CSF use in patients treated with FOLFIRINOX second line
† QALY change from ERG corrected company base case evident at greater than 3 decimal places
AE=adverse event; ERG=Evidence Review Group; LY=life years; PFS=progression free survival; OS=overall survival; QALYs=quality adjusted life years; TOT=time on treatment; ICER=incremental cost effectiveness ratio

Table 49 Cost effectiveness results: ERG revisions to company base case for the comparison of Nab-Pac+Gem vs FOLFIRINOX

Description	Nab-Pac+Gem			FOLFIRINOX			Incremental			ICER/QALY gained
	Costs	LY	QALYs	Costs	LY	QALYs	Costs	LY	QALYs	
Company original base case	[redacted]	***0.927***	***0.540***	[redacted]	***1.154***	0.693	£1,542	***-0.227***	***-0.153***	***Dominated***
Company updated base case	[redacted]	***0.927***	***0.539***	[redacted]	***1.154***	0.693	£1,479	***-0.227***	***-0.153***	***Dominated***
ERG corrected company base case	[redacted]	***0.908***	***0.527***	[redacted]	***1.135***	0.680	£1,479	***-0.227***	***-0.153***	***Dominated***
R1) HRs for Gem+Cap vs Gem	[redacted]	-	-	[redacted]	-	-	-	-	-	-
R2) HRs for FOLFIRINOX vs Gem	[redacted]	0.908	0.527	[redacted]	1.170	0.702	-£582	-0.262	-0.175	£3,327
R3) ERG drug costing method	[redacted]	0.908	0.527	[redacted]	1.135	0.680	£592	-0.227	-0.153	Dominated
R4) TOT from CA046 trial	[redacted]	0.908	0.527	[redacted]	1.135	0.680	£2,304	-0.227	-0.153	Dominated
R5) Do not apply AE disutilities	[redacted]	0.908	0.527†	[redacted]	1.135	0.680†	£1,479	-0.227	-0.152	Dominated
R6) ERG OS	[redacted]	0.909	0.528	[redacted]	1.150	0.688	£2,058	-0.225	-0.159	Dominated
R7) ERG PFS	[redacted]	0.908	0.531	[redacted]	1.135	0.686	£16	-0.227	-0.148	Dominated
ERG revised base case (R2:R7)	[redacted]	***0.909***	***0.532***	[redacted]	***1.201***	0.726	£383	***-0.291***	***-0.194***	***Dominated***

Costs and QALYs discounted; life years undiscounted

† QALY change from ERG corrected company base case evident at greater than 3 decimal places

AE=adverse event; ERG=Evidence Review Group; LY=life years; PFS=progression free survival; OS=overall survival; QALYs=quality adjusted life years; TOT=time on treatment; ICER=incremental cost effectiveness ratio

Table 50 Cost effectiveness results: ERG base case sensitivity analysis for the comparison of Nab-Pac+Gem vs Gem

Description	Nab-Pac+Gem			Gem			Incremental			ICER/QALY gained	ICER change
	Costs	LY	QALYs	Costs	LY	QALYs	Costs	LY	QALYs		
Company original base case	[redacted]	***0.927***	***0.540***	[redacted]	***0.725***	***0.396***	***£6,717***	***0.202***	***0.144***	***£46,657***	***-***
Company updated base case	[redacted]	***0.927***	***0.539***	[redacted]	***0.725***	***0.396***	***£6,755***	***0.202***	***0.144***	***£46,932***	***-***
ERG corrected company base case	[redacted]	***0.908***	***0.527***	[redacted]	***0.706***	***0.383***	***£6,755***	***0.202***	***0.144***	***£47,011***	***-***
ERG revised base case (R3:R7)	[redacted]	***0.909***	***0.532***	[redacted]	***0.706***	***0.387***	***£5,985***	***0.203***	***0.145***	***£41,250***	***-£5,761***
S1) ERG AE costs	[redacted]	0.908	0.527	[redacted]	0.706	0.383	***£7,008***	0.202	0.144	***£48,773***	***+£1,762***
S2) SIEGE crosswalk utility values	[redacted]	0.908	0.496	[redacted]	0.706	0.360	***£6,755***	0.202	0.136	***£49,678***	***+£2,667***
ERG revised base case + ERG AE costs (S1)	[redacted]	***0.909***	***0.532***	[redacted]	***0.706***	***0.387***	***£6,252***	***0.203***	***0.145***	***£43,088***	***-£3,923***
ERG revised base case + SIEGE crosswalk utilities (S2)	[redacted]	***0.909***	***0.500***	[redacted]	***0.706***	***0.363***	***£5,985***	***0.203***	***0.137***	***£43,626***	***-£3.385***
ERG revised base case + SIEGE crosswalk utilities + ERG AE costs (S1:S2)	[redacted]	***0.909***	***0.500***	[redacted]	***0.706***	***0.363***	***£6,252***	***0.203***	***0.137***	***£45,571***	***-£1,440***

Costs and QALYs discounted; life years undiscounted
AE=adverse event; ERG=Evidence Review Group; LY=life years; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio

Table 51 Cost effectiveness results: ERG base case sensitivity analysis for the comparison of Nab-Pac+Gem vs Gem+Cap

Description	Nab-Pac+Gem			Gem+Cap			Incremental			ICER/QALY gained
	Costs	LY	QALYs	Costs	LY	QALYs	Costs	LY	QALYs	
Company original base case	[redacted]	***0.927***	***0.540***	[redacted]	***0.950***	***0.551***	***£5,555***	***-0.023***	***-0.011***	***Dominated***
Company updated base case	[redacted]	***0.927***	***0.539***	[redacted]	***0.950***	***0.551***	***£5,567***	***-0.023***	***-0.011***	***Dominated***
ERG corrected company base case	[redacted]	***0.908***	***0.527***	[redacted]	***0.931***	***0.538***	***£5,567***	***-0.023***	***-0.011***	***Dominated***
ERG revised base case (R1, R3:R7)	[redacted]	***0.909***	***0.532***	[redacted]	***0.845***	***0.482***	***£5,072***	***0.064***	***0.051***	***£99,837***
S1) ERG AE costs	[redacted]	0.908	0.527	[redacted]	0.931	0.538	***£5,600***	***-0.023***	***-0.011***	***Dominated***
S2) SIEGE crosswalk utility values	[redacted]	0.908	0.496	[redacted]	0.931	0.508	***£5,567***	***-0.023***	***-0.012***	***Dominated***
ERG revised base case + ERG AE costs (S1)	[redacted]	***0.909***	***0.532***	[redacted]	***0.845***	***0.482***	***£5,133***	***0.064***	***0.051***	***£101,037***
ERG revised base case + SIEGE crosswalk utilities (S2)	[redacted]	***0.909***	***0.500***	[redacted]	***0.845***	***0.453***	***£5,072***	***0.064***	***0.048***	***£106,616***
ERG revised base case + SIEGE crosswalk utilities + ERG AE costs (S1:S2)	[redacted]	***0.909***	***0.500***	[redacted]	***0.845***	***0.453***	***£5,133***	***0.064***	***0.048***	***£107,898***

Costs and QALYs discounted; life years undiscounted
AE=adverse event; ERG=Evidence Review Group; LY=life years; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio

Table 52 Cost effectiveness results: ERG base case sensitivity analysis for the comparison of Nab-Pac+Gem vs FOLFIRINOX

Description	Nab-Pac+Gem			FOLFIRINOX			Incremental			ICER/QALY gained
	Costs	LY	QALYs	Costs	LY	QALYs	Costs	LY	QALYs	
Company original base case	[redacted]	***0.927***	***0.540***	[redacted]	***1.154***	***0.693***	***£1,542***	***-0.227***	***-0.153***	***Dominated***
Company updated base case	[redacted]	***0.927***	***0.539***	[redacted]	***1.154***	***0.693***	***£1,479***	***-0.227***	***-0.153***	***Dominated***
ERG corrected company base case	[redacted]	***0.908***	***0.527***	[redacted]	***1.135***	***0.680***	***£1,479***	***-0.227***	***-0.153***	***Dominated***
ERG revised base case (R2:R7)	[redacted]	***0.909***	***0.532***	[redacted]	***1.201***	***0.726***	***£383***	***-0.291***	***-0.194***	***Dominated***
S1) ERG AE costs	[redacted]	0.908	0.527	[redacted]	1.135	0.680	***£1,559***	***-0.227***	-0.153	Dominated
S2) SIEGE crosswalk utility values	[redacted]	0.908	0.496	[redacted]	1.135	0.641	***£1,479***	***-0.227***	-0.145	Dominated
ERG revised base case + ERG AE costs (S1)	[redacted]	***0.909***	***0.532***	[redacted]	***1.201***	***0.726***	***£436***	***-0.291***	***-0.194***	***Dominated***
ERG revised base case + SIEGE crosswalk utilities (S2)	[redacted]	***0.909***	***0.500***	[redacted]	***1.201***	***0.684***	***£383***	***-0.291***	***-0.184***	***Dominated***
ERG revised base case + SIEGE crosswalk utilities + ERG AE costs (S1:S2)	[redacted]	***0.909***	***0.500***	[redacted]	***1.201***	***0.684***	***£435***	***-0.291***	***-0.184***	***Dominated***

Costs and QALYs discounted; life years undiscounted
AE=adverse event; ERG=Evidence Review Group; LY=life years; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio

6.1 Conclusions of the cost effectiveness section

The various changes implemented by the ERG for the comparison of treatment with Nab-Pac+Gem versus Gem, treatment with Nab-Pac+Gem versus Gem+Cap and treatment with Nab-Pac+Gem versus FOLFIRINOX yield a mixture of effects. Incremental costs and incremental benefits both increase and decrease depending on the individual revision. However, none of the ERG's individual revisions or revised base case scenarios yield ICERs under £30,000 per QALY gained for treatment with Nab-Pac+Gem against any of the comparators. Only the comparison of Nab-Pac+Gem versus Gem yields ICERs under £50,000 per QALY gained once all the ERG's revisions and scenarios are applied.

7 END OF LIFE

The NICE End of Life criteria, and the data presented by the company to show that these criteria have been met, are presented in Table 53.

Table 53 End of Life criteria

NICE End of Life criteria	Data presented by the company
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Real world survival Median: 2 to 6 months depending on how much the cancer has grown and where it has spread Trial survival Median: 6.6 months Mean: 8.7 months Data source: CRUK (real world survival); CA046 extension trial data (trial survival)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Survival extension Median: 2.1 months Mean: 2.4 months Data source: CA046 extension trial data (trial survival)

Source: CS, Table 30

7.1 Short life expectancy

The ERG agrees with the company that patients with pancreatic metastatic adenocarcinoma have a life expectancy of less than 24 months.

7.2 Extension to life

An examination of the ERG's remodelled OS suggests that treatment with Nab-Pac+Gem generates a mean survival gain of 2.44 months when compared to gemcitabine.

When treatment with Nab-Pac+Gem is compared with Gem+Cap or FOLFIRINOX, the results from the company base-case NMA show that there is no statistically significant OS gain from Nab-Pac+Gem. The ERG is not aware of any other evidence to support or refute this claim.

8 OVERALL CONCLUSIONS

The ERG considers that the evidence submitted by the company largely reflects the decision problem defined in the final scope issued by NICE. However, direct clinical effectiveness evidence was only available for the comparison of the efficacy of Nab-Pac+Gem versus Gem.

8.1 Direct clinical evidence

The direct clinical effectiveness evidence for the treatment of Nab-Pac+Gem versus Gem was derived from the CA046 trial. This trial, which is complete, was of good quality and no patient crossover was permitted. These attributes mean that it is possible to draw reasonable conclusions from the data about the comparative efficacy of the two interventions in the trial population. Results from the most recent OS analysis (updated analysis) of the CA046 trial data suggest that treatment with Nab-Pac+Gem statistically significantly improves median OS in comparison to treatment with Gem (8.7 months versus 6.6 months; HR=0.72, 95% CI: 0.62 to 0.83). The ERG highlights that the company's OS HR should be viewed with caution as the method used to calculate the OS HR relies on an assumption of PH, which does not hold. The company states that updated OS analysis results[37] show mean OS to be 11.1 months in the Nab-Pac+Gem arm and 8.7 months in the Gem arm.

However, the ERG notes that only 10% of the trial population were aged ≥75 years. Figures from CRUK[16] indicate that, in the NHS, 47% of patients with pancreatic cancer are ≥75 years, and 80% of patients diagnosed with pancreatic cancer have late stage disease. This is of concern as the EMA cautions[9] that there is no demonstrated benefit of treatment with Nab-Pac+Gem in people aged ≥75 years and that patients aged ≥75 years who were treated with Nab-Pac+Gem in the CA046 trial experienced more AEs and SAEs than the overall trial population.

The ERG considers that the company has failed to clearly define the patient population for whom treatment with Nab-Pac+Gem is appropriate. Figures from the company's own market research, based on patient chart audit of first-line therapies, suggest [redacted] of patients received gemcitabine monotherapy, [redacted] received gemcitabine doublet therapy (other than Nab-Pac+Gem) and [redacted] received FOLFIRINOX. The company is confident that all patients who can tolerate FOLFIRINOX can be easily identified in clinical practice; however, the characteristics of these patients have not been described in the CS. The company says that all patients who are fit enough to be treated with FOLFIRINOX are fit enough to be treated with Nab-Pac+Gem. However, the company considers that not all patients who are fit enough to tolerate treatment with Nab-Pac+Gem will be able to tolerate

treatment with FOLFIRINOX. The company considers that Gem is the only relevant comparator but the ERG has not found their case to be compelling.

8.2 Indirect evidence

The company has provided indirect clinical evidence to allow the comparative efficacy of Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX to be assessed.

Despite the fact that a connected network could be formed by including only trials that compared treatments relevant to the decision problem, the company base-case network included seven trials[41-47] that provided evidence for treatments that were not listed in the final scope issued by NICE. However, the company performed a sensitivity analysis using a reduced network (fixed effects) that included only the comparators listed in the final scope issued by NICE and the ERG considers the results from this analysis are more valid than the company's base-case NMA results. In terms of OS, the results from this sensitivity analysis mirror the results from the base-case analysis and do not suggest a statistically significant treatment effect for Nab-Pac+Gem versus Gem+Cap (HR=1.10, 95% CrI: 0.67 to 1.84) or for Nab-Pac+Gem versus FOLFIRINOX (HR=0.77, 95% CrI: 0.58 to 1.01). The results from the company's base-case NMA are used in the company's cost effectiveness model.

However, the ERG highlights that all of the NMA OS results are affected by the lack of PH in the CA046 and ACCORD trials[7] and should be interpreted with caution. Furthermore, PFS results are affected by the lack of PH in the CA046 trial and these results should, therefore, also be interpreted with caution.

8.3 Economic evidence

Uncertainty in the modelling of time-to-event outcomes for treatment with Nab-Pac+Gem versus Gem is not limited by the maturity of the CA046 trial, as the trial data are almost complete. However, the company has introduced unnecessary uncertainty back into the model by using parametric models to estimate TOT data that were already complete.

The ERG considers the company's modelling of treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX to be flawed. The modelling relies on HRs from the NMA, which should be treated with caution due to violation of the PH assumption in the CA046 trial. The ERG notes that applying HRs directly from the relevant trials [6,7] to modelled time-to-event estimates for treatment with Gem produces results that do not rely on the PH assumption holding in the CA046 trial. However, the PH assumption does not appear to hold for time-to-event outcomes in the ACCORD[7] trial, so results for FOLFIRINOX should be treated with caution. Although the PH assumption appears to hold in the Scheithauer trial,[6]

the sample is small and data have been digitised, so the ERG's modelling will still be subject to some uncertainty.

There is an absence of HRQoL evidence from the CA046 trial, which introduces further uncertainty into the model. Utility values used in the company's base case and scenario analyses are either from published sources referencing populations treated in different geographies with different interventions,[59] or from unpublished EQ-5D-5L (rather than 3L) data to which the ERG has not had access.[28]

The company has estimated the cost of each treatment in the model based on only a selection of the vial sizes available for each drug. This means that full economies of scale cannot be taken into account in its calculations and that weekly treatment costs are overestimated in its model.

8.4 Implications for research

The ERG considers that further research is required to address several issues. First, there is no direct evidence that can be used to assess the clinical effectiveness of treatment with Nab-Pac+Gem versus Gem+Cap or versus FOLFIRINOX. Second, most of the patients recruited to the CA046 trial are younger than the patients likely to be treated in the NHS, as only 10% of patients of trial patients were aged ≥75 years. Third, the company claims that there are easily identifiable subgroups of patients with metastatic adenocarcinoma pancreatic cancer. However, the characteristics of these patients have not been described in the CS.

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10 APPENDICES

10.1 Key points from the Final Appraisal Determination

TA360 Paclitaxel as albumin-bound nanoparticles in combination with gemcitabine for previously untreated metastatic pancreatic cancer		Section
Key conclusion		
Paclitaxel as albumin-bound nanoparticles in combination with gemcitabine is not recommended within its marketing authorisation for adults with previously untreated metastatic adenocarcinoma of the pancreas. Nab-paclitaxel plus gemcitabine was more clinically effective compared with gemcitabine alone, but was associated with a higher rate of grade 3 or higher adverse effects. FOLFIRINOX was likely to be more clinically effective than nab-paclitaxel plus gemcitabine. Nab-paclitaxel plus gemcitabine and gemcitabine plus capecitabine showed similar progression-free survival and overall survival, but nab-paclitaxel plus gemcitabine may be associated with a higher rate of grade 3 or 4 adverse events. The Committee agreed that the most plausible ICER, allowing for the uncertainty of time-to-event modelling, would lie somewhere between £72,500 and the £78,500 per QALY gained. The company's analyses showed that nab-paclitaxel plus gemcitabine was dominated by FOLFIRINOX and had an ICER of £87,100 per QALY gained compared with gemcitabine plus capecitabine. Although these estimates were subject to considerable uncertainty, the Committee was confident that nab-paclitaxel plus gemcitabine would not be considered a cost effective use of NHS resources compared with these treatments.		1.1, 4.5, 4.7, 4.8, 4.16, 4.17
Current practice		
Clinical need of patients, including the availability of alternative treatments	Previously untreated metastatic pancreatic cancer is associated with a poor prognosis: many people are not diagnosed until the cancer is very advanced and, without treatment, survival may be only 2 to 6 months. Current treatments are limited in efficacy or associated with significant toxicity. Therefore there is value of additional treatment options in this area.	4.2
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee understood that nab-paclitaxel is a novel formulation of paclitaxel and that there was a high level of unmet need in this disease area. However, the Committee considered that all health-related benefits had been adequately captured by the quality-adjusted life years (QALYs) in the model, and it agreed that nab-paclitaxel did not offer a step change in the treatment of metastatic pancreatic cancer.	4.21
What is the position of the treatment in the pathway of care for the condition?	The Committee agreed that nab-paclitaxel plus gemcitabine would be considered for use in clinical practice for those people who were able to tolerate the associated adverse events.	4.3
Adverse reactions	The Committee heard from the clinical expert that the adverse effects of nab-paclitaxel plus gemcitabine, though serious, were mainly manageable. The Committee noted, on reviewing the adverse event profiles from study CA046 and the Conroy study, that both nab- paclitaxel plus gemcitabine and FOLFIRINOX were associated with considerable toxicity, and that a difference in the adverse event profiles could not be reliably determined from the data available.	2.3, 4.2, 4.7

	The most common clinically significant adverse reactions for nab-paclitaxel are: neutropenia, peripheral neuropathy, arthralgia/myalgia and gastrointestinal disorders.	
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The company's submission presented clinical effectiveness evidence from study CA046. Study CA046 was a phase III international, multicentre, open-label, randomised study comparing nab-paclitaxel plus gemcitabine with gemcitabine alone in people with metastatic pancreatic adenocarcinoma who had not been treated for metastatic disease before, and who had a Karnofsky performance status of 70 or more.	3.2
Relevance to general clinical practice in the NHS	Compared with people treated in clinical practice in England, people in study CA046 were younger and fitter. In addition, there were no participating treatment centres for study CA046 in the UK.	3.24
Uncertainties generated by the evidence	No head-to-head trial data were available comparing nab-paclitaxel plus gemcitabine with FOLFIRINOX or with gemcitabine plus capecitabine. No health-related quality of life data were collected in study CA046, and as such the Committee considered it difficult to judge people's preferences and the acceptability of the toxicity profile of nab-paclitaxel plus gemcitabine.	4.6, 4.5
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The company's submission presented an analysis for a subgroup of people with a Karnofsky performance status of 70 or 80. The Committee concluded that, based on the biological and clinical plausibility, and the strength of evidence of a subgroup effect, it could not justify excluding people with a Karnofsky performance status of 90 or 100 from its consideration, and therefore it was not appropriate to make recommendations for nab- paclitaxel plus gemcitabine in the subgroup of people with a Karnofsky performance status or 70 or 80. The Committee agreed that it was appropriate to consider the intention-to-treat analyses.	4.9
Estimate of the size of the clinical effectiveness including strength of supporting evidence	Study CA046 showed that nab-paclitaxel plus gemcitabine compared with gemcitabine alone had statistically significantly longer overall survival (median gain of 2.1 months) and progression-free survival (median gain of 1.8 months), and higher response rates (relative risk of 3.19 to 3.81). The mixed treatment comparison showed that nab-paclitaxel plus gemcitabine was likely to be associated with a shorter overall survival and progression-free survival compared with FOLFIRINOX, and with a similar overall survival and progression-free survival compared with gemcitabine plus capecitabine.	3.3, 4.7, 4.8
Evidence for cost effectiveness		
Availability and nature of evidence	The company submitted a de novo economic model to estimate the cost effectiveness of nab-paclitaxel plus gemcitabine with gemcitabine alone in people with metastatic pancreatic cancer that had not been treated	3.12, 3.14

	before. The company also presented scenario analyses comparing nab-paclitaxel plus gemcitabine with FOLFIRINOX and with gemcitabine plus capecitabine. The company used indirect methods to estimate overall survival, progression-free survival and time-on-treatment curves for these comparators which were then used in the model.	
Uncertainties around and plausibility of assumptions and inputs in the economic model	The company made assumptions relating to the costs, utilities and survival estimates in the model. The Committee agreed it was not appropriate to account for vial sharing or missed and reduced doses in the base case. The Committee agreed that the UK EQ-5D algorithm should be used to determine utility values, rather than that of the USA as provided by the company. The company's and ERG's methods of modelling time-to-event data were both associated with strengths and limitations and therefore the Committee considered them equally appropriate.	4.11 to 4.15
Incorporation of health- related quality-of-life benefits and utility values Have any potential significant and substantial health- related benefits been identified that were not included in the economic model, and how have they been considered?	The utility values provided by the Company used a US EQ-5D algorithm. The Committee agreed that the ERG's adjusted utility values, which used the UK algorithm, were the most appropriate. The Committee considered that all health-related benefits had been adequately captured by the quality-adjusted life years (QALYs) in the model.	4.14, 4.21
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee concluded that it was not appropriate to consider nab-paclitaxel plus gemcitabine for a subgroup defined only by performance status.	4.9
What are the key drivers of cost effectiveness?	Deterministic sensitivity analyses showed that the key driver of the cost effectiveness of nab-paclitaxel plus gemcitabine compared with gemcitabine alone was overall survival benefit.	3.20
Most likely cost- effectiveness estimate (given as an ICER)	The Committee agreed that the most plausible ICER for nab-paclitaxel plus gemcitabine compared with gemcitabine alone, allowing for the uncertainty of time-to-event modelling, would lie somewhere between £72,500 and £78,500 per QALY gained. The company's analyses showed that nab-paclitaxel plus gemcitabine was dominated by FOLFIRINOX and had an ICER of £87,100 per QALY gained compared with gemcitabine plus capecitabine. These analyses were estimated from the mixed treatment comparison using the results from the advanced pancreatic cancer population. If the results from the metastatic pancreatic cancer population were used, nab-paclitaxel plus gemcitabine may be dominated by gemcitabine plus capecitabine.	4.16, 4.17
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable to this appraisal.	
End-of-life considerations	Nab-paclitaxel plus gemcitabine did not meet the extension-to-life criterion when compared with FOLFIRINOX or gemcitabine plus capecitabine. For the comparison of nab-paclitaxel plus gemcitabine with	4.19, 4.20

	gemcitabine alone, the Committee accepted that the end-of-life criteria could be applied when taking into consideration both the relative magnitude of the overall survival gain, and the impact of giving proportionally greater weight to QALYs gained in this condition. The Committee agreed that this was an unusual circumstance and that applying the maximum weighting would not be appropriate. In addition, it noted that this would apply only to those people for whom FOLFIRINOX and gemcitabine plus capecitabine are not suitable treatment options.	
Equalities considerations and social value judgements	No issues relating to equality considerations were raised in the submissions, during consultation or in the Committee meetings.	

Source: NICE Final Appraisal Determination document[25]

Appeal by the company

The company lodged an appeal against the FAD issued by NICE. The appeal was based on the grounds set out in Box 6.

Box 6 Company's appeal grounds

- 1.1(a) The Institute had acted unfairly in failing to consider the impact of the 2014 Pharmaceutical Price Regulation Scheme (PPRS) in determining the cost effectiveness of the technology
- 1.2 (a) The Institute had acted unfairly in failing to obtain sufficient clinical expert input at the second Appraisal Committee meeting
- 2. The Institute had formulated guidance which cannot be reasonably justified in the light of the evidence submitted
- 2.1 That the Appraisal Committee had acted unreasonably in failing to accept a subgroup defined according to performance status, which was proposed by the company with an approvable level of cost effectiveness but not accepted by NICE
- 2.2 That the Appraisal Committee had acted unreasonably in failing to consider adequately the effect of dose adjustments and vial sharing on the calculation of ICERs
- 2.3 That the Appraisal Committee had acted unreasonably in failing to apply the appropriate level of weighting under the end-of-life policy to the QALY, given the extent of survival improvement conferred by Nab-Pac
- 2.4 That the Appraisal Committee had acted unreasonably in deciding that Nab-Pac does not represent a step change in the management of pancreatic cancer

Source: NICE appeal decision[14]

The findings of the Appeal Panel are set out in Box 7.

Box 7 Findings of the Appeal Panel

The Appeal Panel upheld the appeal on the grounds that The Institute had acted unfairly in failing to consider the impact of the 2014 Pharmaceutical Price Regulation Scheme (PPRS) in determining the cost effectiveness of the technology; and that the Appraisal Committee may have acted unreasonably in failing to apply the appropriate level of weighting under the end-of-life policy to the quality-adjusted life year (QALY), given the extent of survival improvement conferred by nab-paclitaxel in so far as it had failed to give clear reasons why it had failed to apply the full weighting.

The appeal was dismissed on all other grounds.

Source: NICE appeal decision[14]

10.2 Comparison of AEs of Grade 3 and above reported in the Conroy and the CA046 trials

Comparison of AEs of Grade 3 and above reported (by 5% patients) in the Conroy and the CA046 trials

Event	**FOLFIRINOX (Conroy) N=171**	**Nab-Pac+Gem N=421**
Neutropenia	45.7%	33%
Febrile Neutropenia	5.4%	NR
Thrombocytopenia	9.1%	13%
Anaemia	7.8%	12%
Fatigue	23.6%	18%
Vomiting	14.5%	6%
Diarrhoea	12.7%	6%
Peripheral neuropathy	9.0%	17%
Elevated alanine aminotransferase	7.3%	NR
Thromboembolism	6.6%	5%

NR=not reported
Source: Conroy 2011, CS, Table 22

10.3 Additional safety data

The company reports safety data from the SIEGE trial,[28] a UK multicentre randomised phase II trial comparing different schedules of nab-Paclitaxel combined with Gem as a first-line treatment for metastatic pancreatic cancer (CS, p114). In the SIEGE trial, patients were randomised either to the sequential arm (n=71) where Gem was administered 24 hours after Nab-Pac, or to the concomitant arm (n=75) where Gem was administered immediately after Nab-Pac. The median age of the participants in the SIEGE trial was 67 years (range: 48 to 82). Similar rates to the CA046 trial of Grade ≥3 AEs were observed (n=61, 82%) with the most common (≥10%) being neutropenia (30%), fatigue (15%), febrile neutropenia (12%), and vomiting (11%) (Table 54). A higher rate of myelosuppression across the study was noted; the authors of the publication suggested that this reflected the lower use of growth factor support (G-CSF received by 12 patients in the concomitant arm [16%]) compared to that received in the CA046 trial.

The CS also included safety data from retrospective studies (CS, pp114-121). There were some differences when compared to the CA046 trial. A study conducted in the UK (n=32) observed rates of Grade 3 peripheral neuropathy of 3.1% with no patients developing Grade 3 or 4 toxicities of neutropenia.[40] In an Italian setting, 13 out of 208 patients experienced a Grade 4 TEAE; with the most common being Grade 4 neutropenia observed in 4% of patients (n=8).[23] Subgroup analysis of the Italian cohort compared patients <75 years (n=176) to those ≥75 years of age (n=32) and the company suggested that the toxicity profile of Nab-Pac+Gem was similar across the patient groups (CS, p117).

Table 54 Adverse events (Grade ≥3) in the CA046 trial, SIEGE trial and from an Italian setting

Category of event	Nab-Pac+Gem N=421 n (%)	SIEGE concomitant arm N=74 n (%)	Italian setting N=208 n (%)
At least one Grade ≥3 AE	374 (89)	61 (82)	-
Neutropenia	138 (33)	22 (30)	50 (24)
Thrombocytopenia	53 (13)	7 (10)	31 (15)
Anaemia	49 (12)	4 (5)	5 (2)
Leukopenia	39 (9)	3 (4)	-
Fatigue	77 (18)	11 (15)	35 (17)
Diarrhoea	26 (6)	3 (4)	11 (5)
Nausea	27 (6)	2 (3)	-
Vomiting	25 (6)	8 (11)	-
Nausea / vomiting	-	-	9 (4)
Dehydration	31 (7)	3 (4)	-

AE=adverse event
Source: CS, p114, Table 22, Table 26

10.4 ERG summary of characteristics of studies included in the base case network of evidence

The company highlights that patient demographics were generally well balanced between the trials included in the NMA, although there were differences in the ethnicity of included patients (CS, p80). For example, two trials[44,47] included exclusively Asian populations. Differences in clinical characteristics were observed between the trials in terms of the extent of metastatic disease (number of metastatic sites and location of metastases), CA19-9 levels, and tumour location which can be associated with presence of a biliary stent. Furthermore, the company explains that it is difficult to make comparisons of performance status (PS) between patients in the included trials due to differences in the assessment criteria used by the trial investigators. There are also differences in the measurement of disease progression between patients in the included trials; some investigators used RECIST criteria (also used in the CA046 trial), while others used alternative criteria such as those developed by the World Health Organization (WHO). It also remains unknown whether disease progression was investigator- or independently-assessed in most of the included trials, and some trial investigators collected time to progression (TTP) data rather than PFS data.

10.5 Trial methodology of studies in the reduced network of evidence

Table 55 Summary of trial methodology for studies in the reduced network of evidence

	ACCORD[7]	Scheithauer 2003[6]	CA046[12]
Location	55 study locations in France	Austria	151 sites in North America, Australia, Russia, Italy, Canada, Ukraine, Spain, Germany, Austria, France and Belgium.
Trial design	A multicentre, randomised, Phase II-III trials to explore FOLFIRINOX compared with single-agent Gem as first-line treatment in patients with metastatic cancer	A multicentre, randomised Phase II trial to investigate the feasibility and therapeutic index of a bi-weekly high-dose Gem+Cap versus Gem alone in previously untreated patients with advanced metastatic adenocarcinoma	Phase III, international, multi-centre, open-label RCT. Randomisation was stratified by key prognostic factors: geographic region (North America vs other), baseline KPS (70–80 vs 90–100), and presence of liver metastases (yes vs no)
Eligibility criteria for participants	≥18 years of age; histologically and cytologically confirmed, measurable metastatic pancreatic adenocarcinoma that had not previously been treated with chemotherapy; ECOG PS of 0–1; adequate bone marrow (granulocyte count ≥1500/mm^3 and platelet count ≥100,000/mm^3), liver function (bilirubin ≤1.5 times the upper limit of the normal range, and renal function. Patients were excluded if they were aged 76 years of older; endocrine or acinar pancreatic carcinoma; previous radiotherapy for measurable lesions; cerebral metastases; history of another major cancer; active infection;	Histologically or cytologically ascertained metastatic adenocarcinoma of the exocrine pancreas; bidimensionally measurable disease; age between 19 and 75 years; an anticipated life expectancy of ≥3 months; a baseline KPS of ≥50%; adequate renal (serum creatinine level <1.5mg/dL), liver (total bilirubin level <1.5mg/dL and transaminase levels <2 X ULN) and bone marrow function (leucocyte count ≥4000/µl, absolute neutrophil count ≥2,000/µl and platelet count ≥100,000/µl); patients may have received adjuvant fluoropyrimidine-based chemotherapy and/or radiation therapy, but this must have been completed at least 6 months before study entry; a minimum of 2 weeks was required to have elapsed in cases of prior abdominal exploration or palliative surgery. Patients were excluded if they had resectable tumours; locally advanced inoperable disease; other serious or uncontrolled concurrent medical illness; central nervous system metastases; any prior palliative chemotherapy	Eligible adults (≥18 years of age) had a KPS score of 70 or more (on a scale from 0 to 100, with higher scores indicating better performance status), had not previously received chemotherapy for metastatic disease, and had histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas that was measurable according to RECIST version 1.0. Metastatic disease had to have been diagnosed within 6 weeks before randomization. Eligible patients could have received treatment with fluorouracil or Gem as a radiation sensitizer in the adjuvant setting if the treatment had been received at least 6 months before randomization. Patients who had received cytotoxic doses of Gem or any other chemotherapy in the adjuvant setting and those with islet-cell neoplasms or locally advanced disease were excluded. Patients had to have adequate hematologic, hepatic, and renal function (including an absolute neutrophil count of ≥1.5×10 per liter, a hemoglobin level of ≥9 g per deciliter, and a bilirubin level at or below the ULN range, according to the standards at the central laboratory)

<table>
<tr><th></th><th>ACCORD[7]</th><th>Scheithauer 2003[6]</th><th>CA046[12]</th></tr>
<tr><td></td><td>chronic diarrhoea; clinically significant history of cardiac disease; pregnancy or breast-feeding</td><td></td><td></td></tr>
<tr><td>Trial drugs</td><td>FOLFIRINOX: oxaliplatin 85mg/m^2 by 2-hour IV infusion, immediately followed by leucovorin 400mg/m^2 by 2-hour IV infusion, with the addition after 30 minutes of irinotecan 180mg/m^2 by 90-minute IV infusion, followed immediately by fluorouracil 400mg/m^2 by IV bolus, followed by a continuous IV infusion of 2400mg/m^2 over a 46-hour period every 2 weeks
Gem: Gem 100mg/m^2 BSA by 30-minute IV infusion weekly for 7 weeks, followed by a 1-week rest, then weekly for 3-weeks in subsequent 4-week courses</td><td>Gem+Cap: biweekly Gem 2200mg/m^2 as a 30 min IV infusion on Day 1 + oral capecitabine 2500mg/m^2/day in two equally divided daily doses approximately 12 hours apart from Days 1 to 7, repeated every 2 weeks for a maximum of 12 courses
Gem: biweekly Gem 2200mg/m^2 as a 30 min IV infusion on Day 1, repeated every 2 weeks for a maximum of 12 courses
NB: ondansetron 8mg was routinely given only on the day of IV chemotherapeutic drug administration</td><td>Nab-Pac+Gem: 30–40 minute IV infusion of Nab-Pac (125mg/m^2) followed by a 30–40 minute IV infusion of Gem (1,000 mg/m^2) on Days 1, 8, 15, 29, 36 and 43 of a 56-day cycle in Cycle 1 only and on Days 1, 8 and 15 of a 28-day cycle in Cycle 2 and onward.
Gem: 30–40 minute IV infusion of Gem (1,000 mg/m^2) on Days 1, 8, 15, 29, 36 and 43 of a 56-day cycle in Cycle 1 only and on Days 1, 8 and 15 of a 28-day cycle in Cycle 2 and onward.
Treatment continued until PD or unacceptable toxicity</td></tr>
<tr><td>Changes to treatment regimen</td><td>In the event of predefined toxic events, protocol-specified treatment modifications were permitted</td><td>Chemotherapeutic drug doses could be reduced by 25% or delayed with the occurrence of any severe non-haematological toxicity of low WBC and platelet counts</td><td>A maximum of two dose reductions were allowed from the original dose for toxicity management:
<table>
<tr><th>Dose level</th><th>Nab-Pac</th><th>Gem</th></tr>
<tr><td>Study dose</td><td>125mg/m^2</td><td>1,000mg/m^2</td></tr>
<tr><td>-1</td><td>100mg/m^2</td><td>800mg/m^2</td></tr>
<tr><td>-2</td><td>75mg/m^2</td><td>600mg/m^2</td></tr>
</table>
Following dose reduction, no dose re-escalation was permitted for the duration of the study.
Patients experiencing study drug-related AEs that required a dose delay >21 days were discontinued from further treatment.</td></tr>
<tr><td>Primary outcome</td><td>OS</td><td>PFS
Disease progression</td><td>OS</td></tr>
</table>

	ACCORD[7]	Scheithauer 2003[6]	CA046[12]
		measured using WHO criteria; independent assessment	
Secondary outcomes	PFS; tumour response; safety; QoL Disease progression measured using RECIST; independent assessment	OS and response rate; clinical benefit rate	PFS and ORR, assessed by an independent reviewer according to RECIST criteria; safety and tolerability of the administered treatments; investigator-assessed PFS and ORR
Survival follow-up	Median, months (95% CI): 26.6 (20.5–44.9) Death rate at final analysis: 79.8%	Randomisation: June 1999–May 2001	Death rate at final OS analysis: 80% Median follow-up was 9.1 months in the Nab-Pac+Gem group and 7.4 months in the Gem group. Death rate at updated post-hoc OS analysis: 90% (median follow-up was 13.9 months)

AE=adverse event; BSA=body surface area; CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group performance status; IV=intravenous; KPS=Karnofsky performance status; OS=overall survival; PD=progressive disease; PFS=progression-free survival; QoL=quality of life; RCT=randomised controlled trial; RECIST=Response Evaluation in Solid Tumours; ULN=upper limit of normal; WBC=white blood cell; WHO=World Health Organization
Source: Appendix 4 of the CS, adapted from Table 7 and Table 9; CS, adapted from Table 9; CS, page 55; CA046 original trial report[12]

10.6 Patient characteristics of studies in the reduced network of evidence

Table 56 Baseline characteristics of patients enrolled in studies in reduced network of evidence

	ACCORD		Scheithauer 2003		CA046	
	FOLFIRINOX (n=171)	**Gem (n=171)**	**Gem+Cap (n=41)**	**Gem (n=42)**	**Nab-Pac+Gem (n=431)**	**Gem (n=430)**
Age, median years (range)	61 (25–76)	61 (34–75)	64 (40–75)	66 (39–75)	62 (27-86)	63 (32-88)
Sex, male n (%)	106 (62.0)	105 (61.4)	27 (66)	23 (55)	245 (57)	257 (60)
Race, n (%)	NR	NR	NR	NR	Asian: 8 (2) Black: 16 (4) White: 378 (88) Hispanic: 25 (6) Other: 4 (1)	Asian: 9 (2) Black: 16 (4) White: 375 (87) Hispanic: 26 (6) Other: 4 (1)
Performance status, n (%)*	ECOG 0: 64 (37.4) ECOG 1: 106 (61.9) ECOG 2: 1 (0.6)	ECOG 0: 66 (38.6) ECOG 1: 105 (61.4) ECOG 2: 0	KPS 90-100: 11 (27) KPS 70-80: 22 (54) KPS 50-60: 8 (19)	KPS 90-100: 10 (24) KPS 70-80: 23 (55) KPS 50-60: 9 (21)	KPS 100: 69/429 (16) KPS 90: 179/429 (42) KPS 80: 149/429 (35) KPS 70: 30/429 (7) KPS 60: 2/429 (<1)	KPS 100: 69/429 (16) KPS 90: 199/429 (46) KPS 80: 128/429 (30) KPS 70: 33/429 (8) KPS 60: 0/429
Pancreatic tumour location, n (%)	Head: 67 (39.2) Body: 53 (31.0) Tail: 45 (26.3) Multicentric: 6 (3.5)	Head: 63 (36.8) Body: 58 (33.9) Tail: 45 (26.3) Multicentric: 5 (2.9)	NR	NR	Head: 191 (44) Body: 132 (31) Tail: 105 (24) Unknown: 3 (1)	Head: 180 (42) Body: 136 (32) Tail: 110 (26) Unknown: 4 (1)
Site of metastatic disease, n (%)**	Liver: 149/170 (87.6) Pancreas: 90/170 (52.9) Lymph node: 49/170 (28.8)	Liver: 150/171 (87.7) Pancreas: 91/171 (53.2) Lymph node: 39/171 (22.8)	Liver: 26 (63) Abdominopelvic mass: 32 (78) Lung: 9 (22)	Liver: 26 (62) Abdominopelvic mass: 27 (64) Lung: 6 (14)	Liver: 365 (85) Lung: 153 (35) Peritoneum: 19 (4)	Liver: 360 (84) Lung: 184 (43) Peritoneum: 10 (2)

	ACCORD		Scheithauer 2003		CA046	
	FOLFIRINOX (n=171)	**Gem (n=171)**	**Gem+Cap (n=41)**	**Gem (n=42)**	**Nab-Pac+Gem (n=431)**	**Gem (n=430)**
	Lung: 33/170 (19.4) Peritoneum: 33/170 (19.4) Other: 18/170 (10.6)	Lung: 49/171 (28.7) Peritoneum: 32/171 (18.7) Other: 29/171 (17.0)	Extra-abdominal lymph nodes/soft tissue: 2 (5) Adrenals: 2 (5) Spleen: 1 (2)	Extra-abdominal lymph nodes/soft tissues: 3 (7) Adrenals: 0 Spleen: 1 (2)		
Number of metastatic sites, n (%)	Median (range): 2 (1–6)	Median (range): 2 (1–6)	NR	NR	1 site: 33 (8) 2 sites: 202 (47) 3 sites: 136 (32) >3 sites: 60 (14)	1 site: 21 (5) 2 sites: 206 (48) 3 sites: 140 (33) >3 sites: 63 (15)
Level of CA19-9, n/N (%)	Normal: 24/164 (14.6) ULN to <59 x ULN: 72/164 (43.9) ≥59 ULN: 68/164 (41.5) Unknown: 7/171 (4.1)	Normal: 23/165 (13.9) ULN to <59 x ULN: 65/165 (39.4) ≥59 ULN: 77/165 (46.7) Unknown: 6/171 (3.5)	NR	NR	Normal: 60/379 (16) ULN to <59 x ULN: 122/379 (32) ≥59 ULN: 197/379 (52)	Normal: 56/371 (15) ULN to <59 x ULN: 120/371 (32) ≥59 ULN: 195/371 (53)
Presence of biliary stent, n (%)	Yes: 27 (15.8) No: 144 (84.2)	Yes: 22 (12.9) No: 149 (87.1)	10 (24)	7 (17)	80 (19)	68 (16)

*For CA046, KPS scores are presented as n/N (%); two patients in the Nab-Pac+Gem group had a score >70 at the screening visit but a score of 60 at the baseline visit on Day 1 or Cycle 1
** For ACCORD, site of metastatic disease is presented as n/N (%) where N is the number of patients with measurable metastatic sites
ECOG=Eastern Cooperative Oncology Group; KPS=Karnofsky performance status; NR=not reported; ULN=upper limit of normal
Source: Appendix 4 of the CS, adapted from Table 10 and Table 12; CS, adapted from Table 12

10.7 ERG summary of risk of bias of studies included in the base case network of evidence

The company considered that most trials were at a reasonably low risk of bias based on the assessment of selection bias, performance bias, attrition bias and detection bias. The ERG generally agrees with this statement, but notes that several of the included trials did not report important details concerning allocation concealment, blinding, and the extent of missing data.

The company's main concern related to the applicability of all trials to routine clinical practice in England. Specifically, the company judged five trials to be at high risk of bias due to the treatment setting not being representative of UK clinical practice, these trials were either conducted in Asia or compared regimens which are not currently used in UK clinical practice.

10.8 Quality assessment results for studies in the reduced network of evidence

Table 57 Quality assessment results for studies in the reduced network of evidence

Study question	ACCORD[7]		Scheithauer 2003[6]		CA046[12]	
	How is the question addressed in the study?	**Risk of bias**	**How is the question addressed in the study?**	**Risk of bias**	**How is the question addressed in the study?**	**Risk of bias**
Was randomisation carried out appropriately?	Yes. Randomisation was performed centrally in a 1:1 ratio with stratification according to centre, performance status (0 vs. 1), and primary tumour localisation (the head vs. the body or tail)	Low	Yes. Randomisation was stratified per KPS (90–100 vs. 50–80) and prior adjuvant treatment	Low	Yes. Randomisation schedule was generated by a randomisation statistician, with stratification for key prognostic factors.	Low
Was the concealment of treatment allocation adequate?	Unclear. No details provided	Unclear	Yes. Patients were assigned to treatment via a central office	Low	Yes. Randomisation was implemented via a centralised IVRS.	Low
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Overall patient demographics were well balanced; more patients in the FOLFIRINOX group had a biliary stent, more patients in the Gem group has measurable metastatic sites in the lung	Low	Yes. Baseline characteristics were well balanced between treatment groups	Low	Yes. Patient demographics were well balanced, with no key differences between treatment groups.	Low
Were the care providers, participants and outcome assessors blind to treatment allocation?	Unclear. No details provided	Unclear	Unclear. No details provided	Unclear	Independent assessors were blinded; care providers and participants were not.	Low
Were there any unexpected imbalances in drop-outs between groups?	Yes. More patients in the Gem group discontinued treatment, with almost twice as many patients discontinuing due to disease progression	High	No.	Low	No. The most common reason for study withdrawal in both treatment arms was disease progression, which is fully accounted for within efficacy assessments.	Low
Is there any evidence to suggest that the authors measured more	No.	Low	No.	Low	No.	Low

Study question	ACCORD[7]		Scheithauer 2003[6]		CA046[12]	
	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias
outcomes than they reported?						
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy analyses were performed according to the intention-to-treat principle	Low	Unclear. No details provided	Low	Yes. Efficacy analyses were performed according to the intention-to-treat principle, with standard censoring methods used to account for missing data.	Low
Did setting reflect UK practice?	Reasonably well. Although all patients were enrolled from French study centres, western Europe populations are considered generally comparable, and treatment arms and outcome assessments are reflective of UK practice.	Low	No. All patients were enrolled from study centres in Austria; comparator arm not reflective of UK practice and dosing of Gem monotherapy (2,200mg/m^2) not reflective of UK practice.	High	Not assessed by company	Not assessed by company

IVRS=interactive voice response system; KPS=Karnofsky performance status
Source: Appendix 4 of the CS, Table 14 and Table 16; CS, Table 12

10.9 Additional results from the network meta-analysis

For each analysis presented in the CS, the company provides results for each treatment included in the network versus Nab-Pac+Gem. However, as many of these treatments are of no relevance to the decision problem, throughout the following section the ERG presents results only for each of the treatments in the decision comparator set versus Nab-Pac+Gem.

Base case analysis

The company presents the results for each treatment included in the network versus Nab-Pac+Gem in Figure 10 (CS, p85), Figure 12 (CS, p88) and Figure 13 (CS, p89) of the CS for OS, PFS by independent assessment and PFS by investigator assessment, respectively.

For OS, Gem was shown to be statistically significantly inferior to Nab-Pac+Gem (HR=1.35, 95% CrI: 1.18 to 1.56). For Gem+Cap versus Nab-Pac+Gem, there is no evidence to suggest a difference between these two treatments in terms of OS. For FOLFIRINOX versus Nab-Pac+Gem, the HR favoured FOLFIRINOX, although this result was not statistically significant (HR=0.77, 95% CI: 0.58 to 1.01).

For PFS, Gem was shown to be statistically significantly inferior to Nab-Pac+Gem by both independent and investigator assessment. For Gem+Cap versus Nab-Pac+Gem, no statistically significant differences were observed between the treatments for PFS by either independent or investigator assessment. FOLFIRINOX was shown to be statistically significantly superior to Nab-Pac+Gem for PFS by independent assessment (HR=0.68, 95% CrI: 0.51 to 0.91). For PFS by investigator assessment, a trend in favour of FOLFIRINOX was observed, although this difference was no longer statistically significant (HR=0.77; 95% CI: 0.58 to 1.02).

SA1

The company presents the results of SA1 in Appendix 4 of the CS. For OS, estimated HRs for each of the treatments in the decision comparator set versus Nab-Pac+Gem are comparable to those observed in the base case analysis; however, there were no statistically significant differences between any of the treatments in the decision comparator set and Nab-Pac+Gem. Similarly, PFS by independent assessment results were comparable to those observed in the base case analysis; however, there were no statistically significant differences between any of the treatments in the decision comparator set and Nab-Pac+Gem.

SA3

For this analysis, the network of evidence is identical to the network used for the base case analysis, but data from two studies reporting median survival data for a metastatic pancreatic cancer subgroup are superseded with HR data from the total trial population. The company presents the results of SA3, which was performed for the outcome of OS only, in Appendix 4 of the CS.

10.10 Comparator method applied to model

The ERG has estimated OS and PFS for treatment with Gem+Cap and with FOLFIRINOX by applying HRs from relevant published papers [6,7] to the modelled OS and PFS estimates for Gem, which are based on data from the CA046 trial. This is in contrast to the company, which estimated OS and PFS for treatment with Gem+Cap and with FOLFIRINOX by combining HRs from relevant published papers [6,7] with HRs calculated from the CA046 trial and applying them to the modelled OS and PFS estimates for Nab-Pac+Gem, which are based on data from the CA046 trial. The difference in the approaches is illustrated by the following example.

If there are three treatments:

- treatment A (TxA) is the intervention of interest,
- treatment B (TxB) is a comparator and
- treatment C (TxC) is a comparator

and two trials:

- Trial 1 compares TxA and TxC, and
- Trial 2 compares TxB with TxC

then to compare TxA with TxB, there needs to be some sort of indirect comparison of effectiveness linked through TxC.

An NMA makes this comparison by first calculating HR_{AC} for TxA versus TxC from Trial 1 and HR_{BC} for TxB versus TxC from Trial 2. HR_{BC} is then adjusted by HR_{AC} to give HR_{AB}, an estimate of the effectiveness of TxA versus TxB (Figure 11).

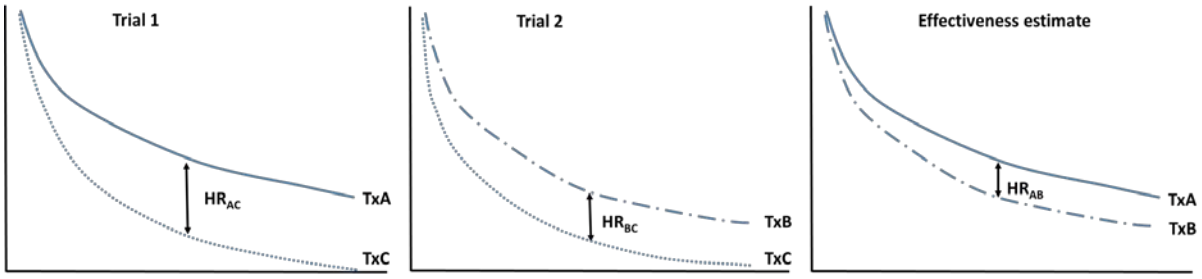

Figure 11 Simplified indirect comparison using HRs

Source: ERG
HR=hazard ratio; TxA=treatment A; TxB=treatment B; TxC=treatment C

This method of comparing the effectiveness of TxA with TxB requires that the PH assumption holds in both Trial 1 and Trial 2, as HRs are used from both these trials to calculate HR_{AB}.

If PH was shown not to hold in Trial 1 but could be shown to hold in Trial 2, an effectiveness comparison could be made between TxA and TxB in the cost effectiveness model by applying HR_{BC} from Trial 2 to the survival curve for TxC that had been estimated based on IPD from Trial 1.

10.11 PH test results FOLFIRINOX vs Gem and Gem+Cap vs Gem

A comparison of cumulative hazards on an H-H plot should yield an approximately straight line through the origin if hazards are proportional between the two treatments. A comparison of ln(-ln(OS)) or ln(-ln(PFS)) against ln(time) should yield approximately parallel lines if hazards are proportional between the two treatments. The comparisons are limited by the fact that the ERG has analysed data digitised from published papers,[6,7] so the following conclusions are based on visual inspection rather than statistical tests that might yield spurious precision.

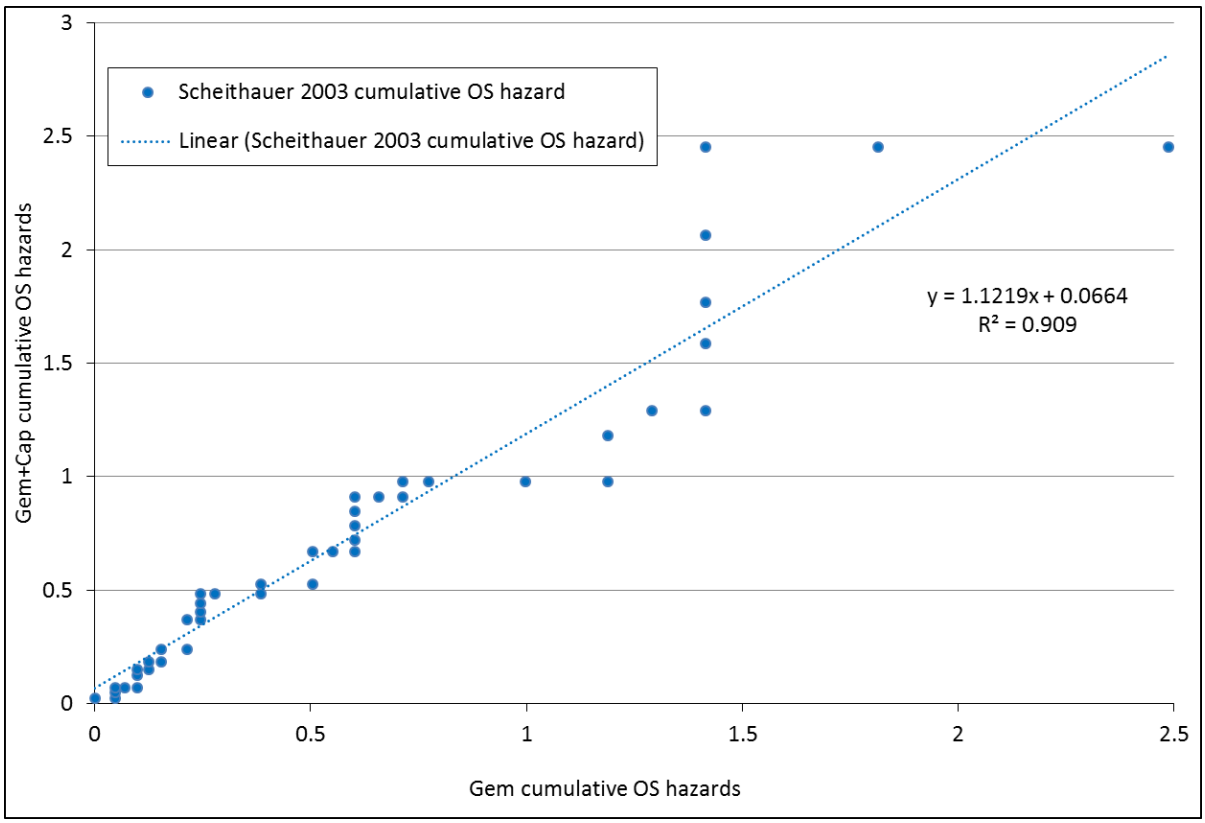

Figure 12 OS H-H plot Gem+Cap vs Gem

Source: ERG calculations; digitised data from Scheithauer 2003

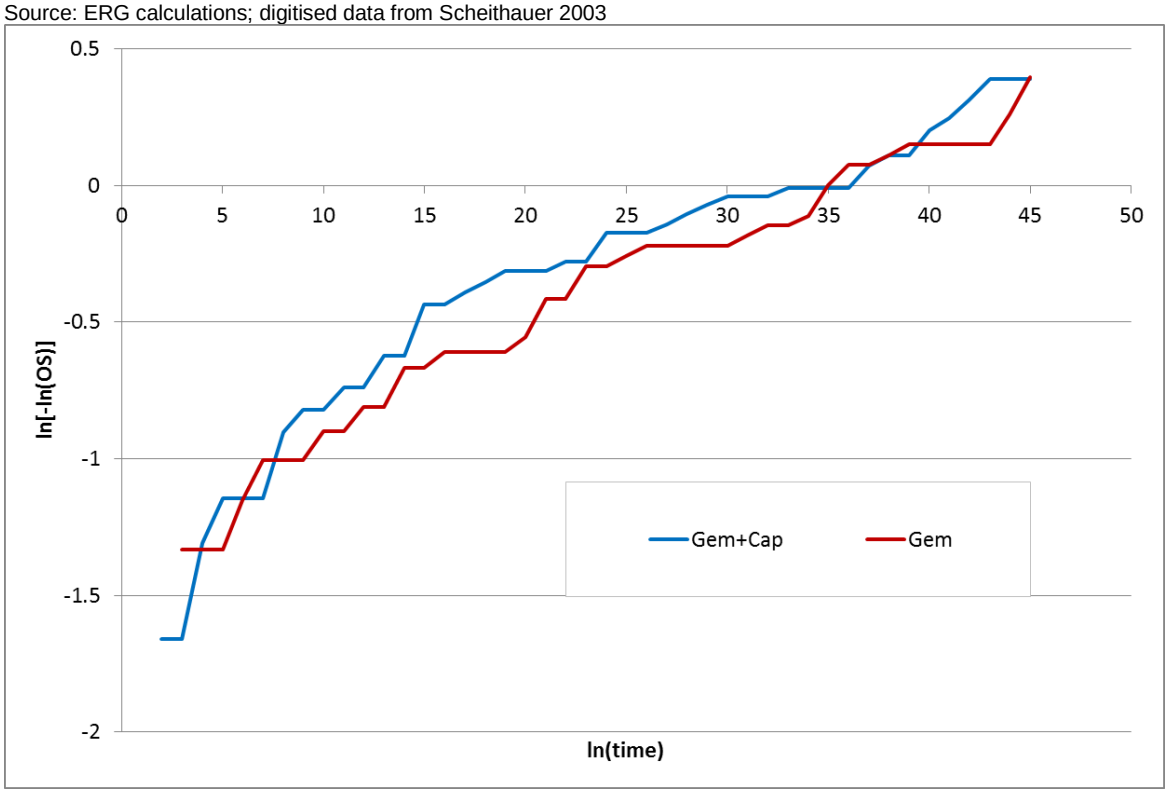

Figure 13 OS log-log plot Gem+Cap vs Gem

Source: ERG calculations; digitised data from Scheithauer 2003

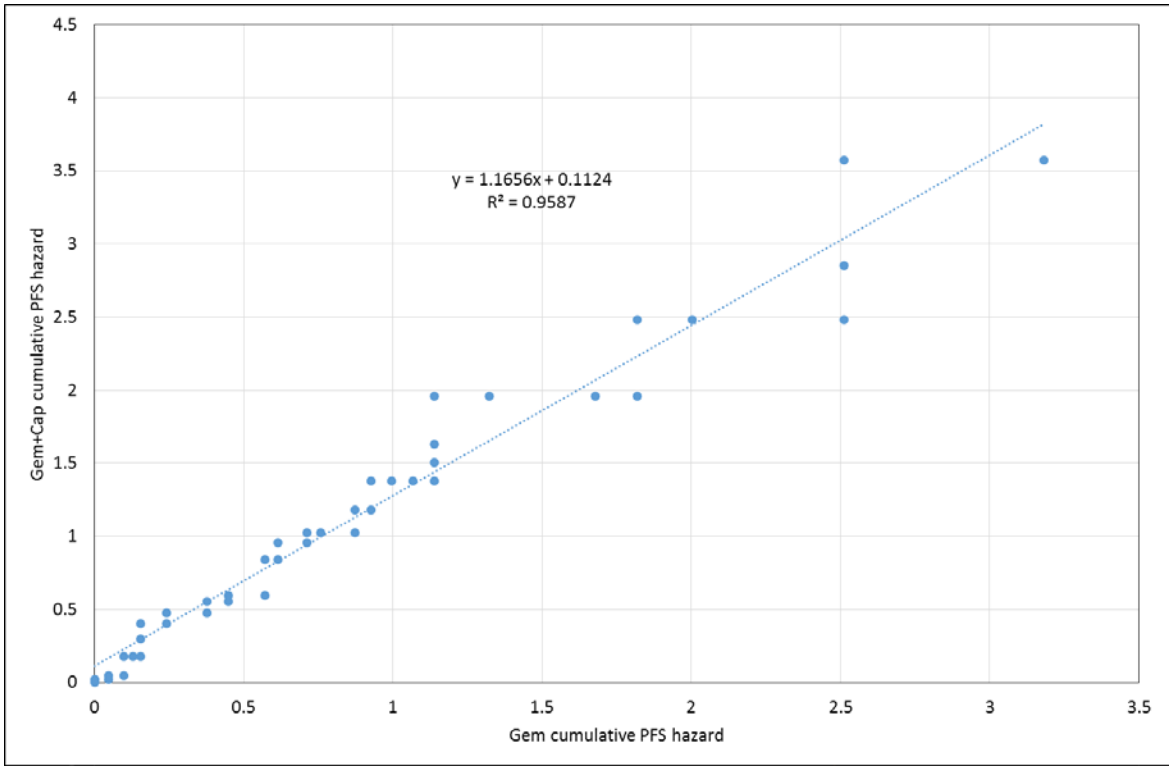

Figure 14 PFS H-H plot Gem+Cap vs Gem

Source: ERG calculations; digitised data from Scheithauer 2003

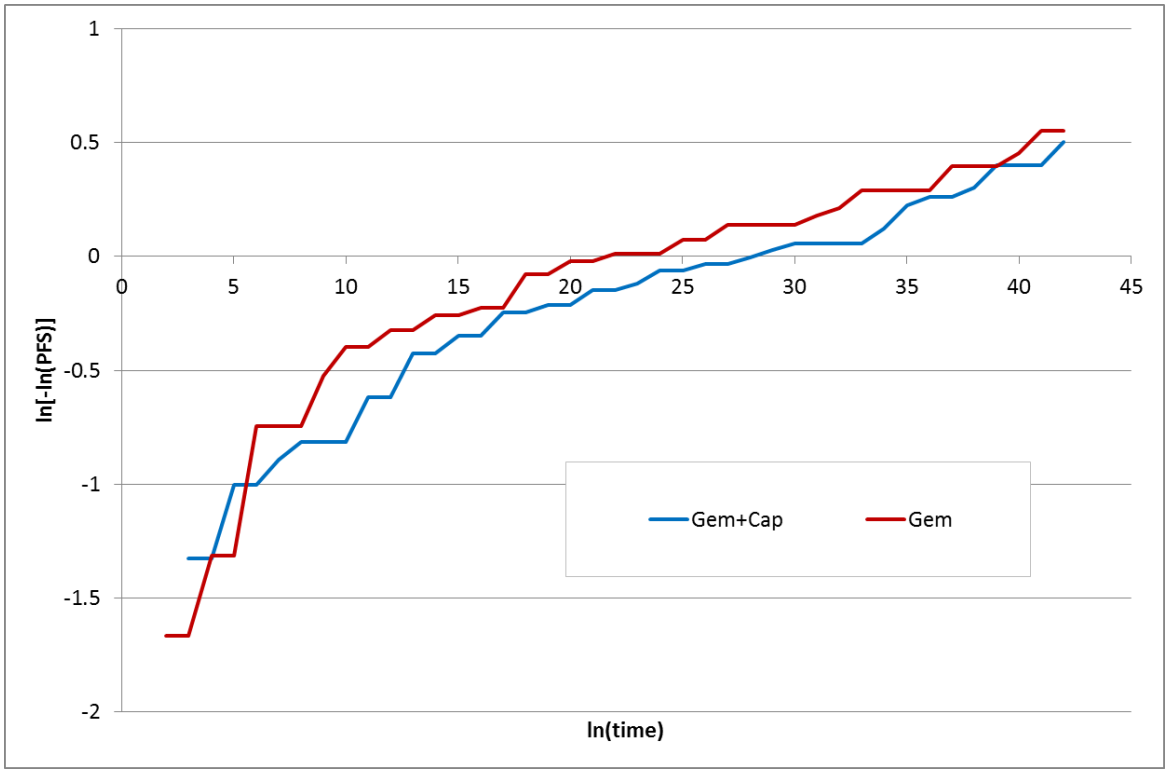

Figure 15 PFS log-log plot Gem+Cap vs Gem

Source: ERG calculations; digitised data from Scheithauer 2003

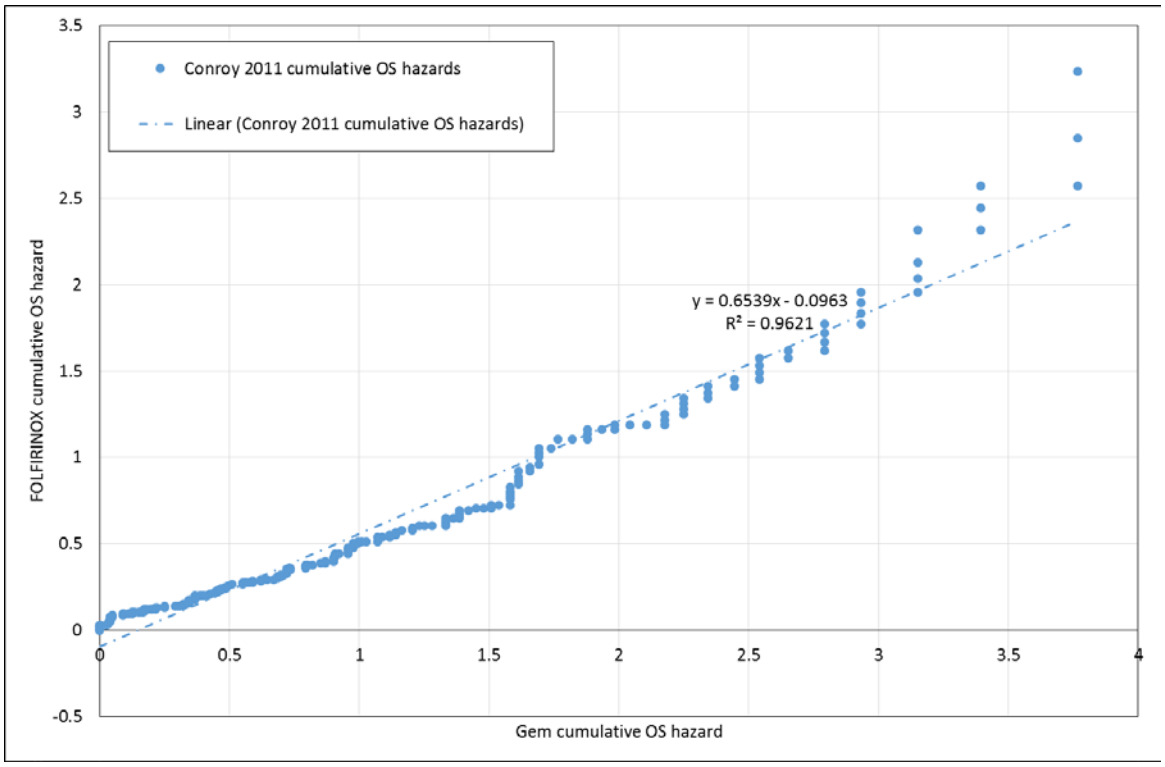

Figure 16 OS H-H plot FOLFIRINOX vs Gem

Source: ERG calculations using digitised data from Conroy 2011

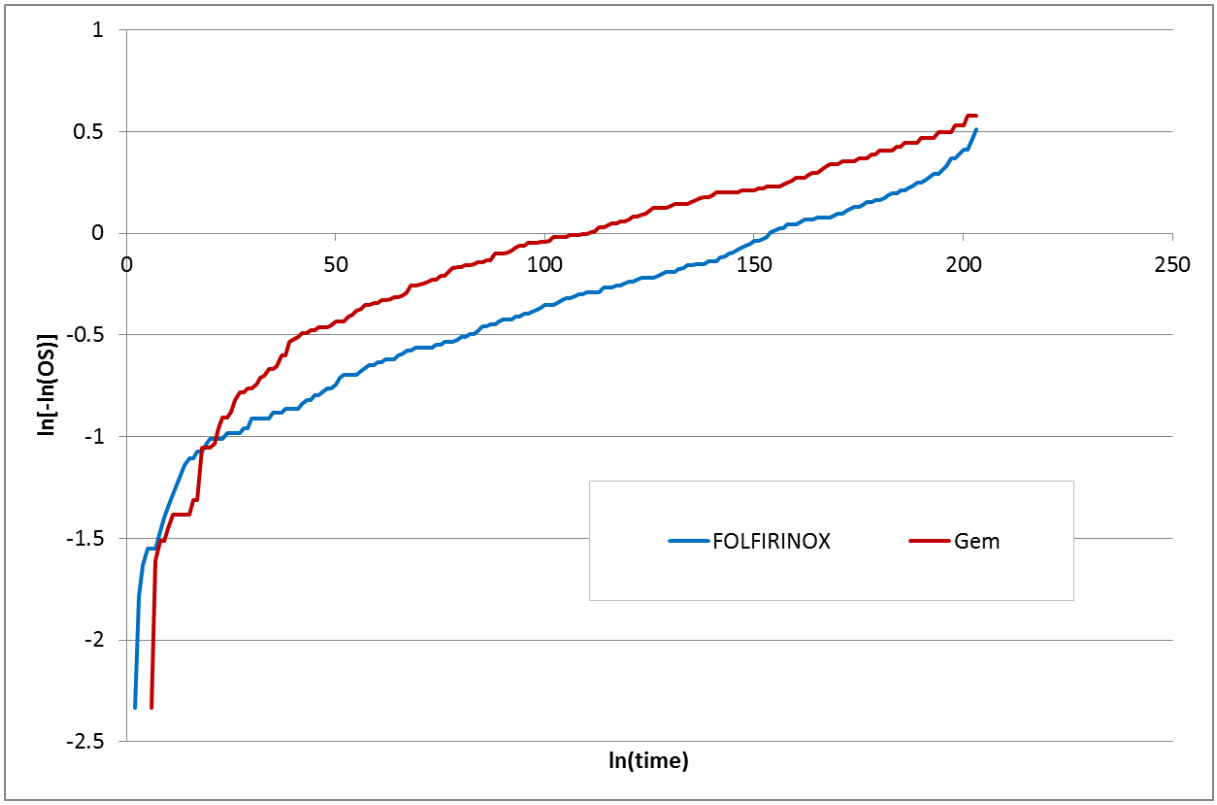

Figure 17 OS log-log plot FOLFIRINOX vs Gem

Source: ERG calculations using digitised data from Conroy 2011

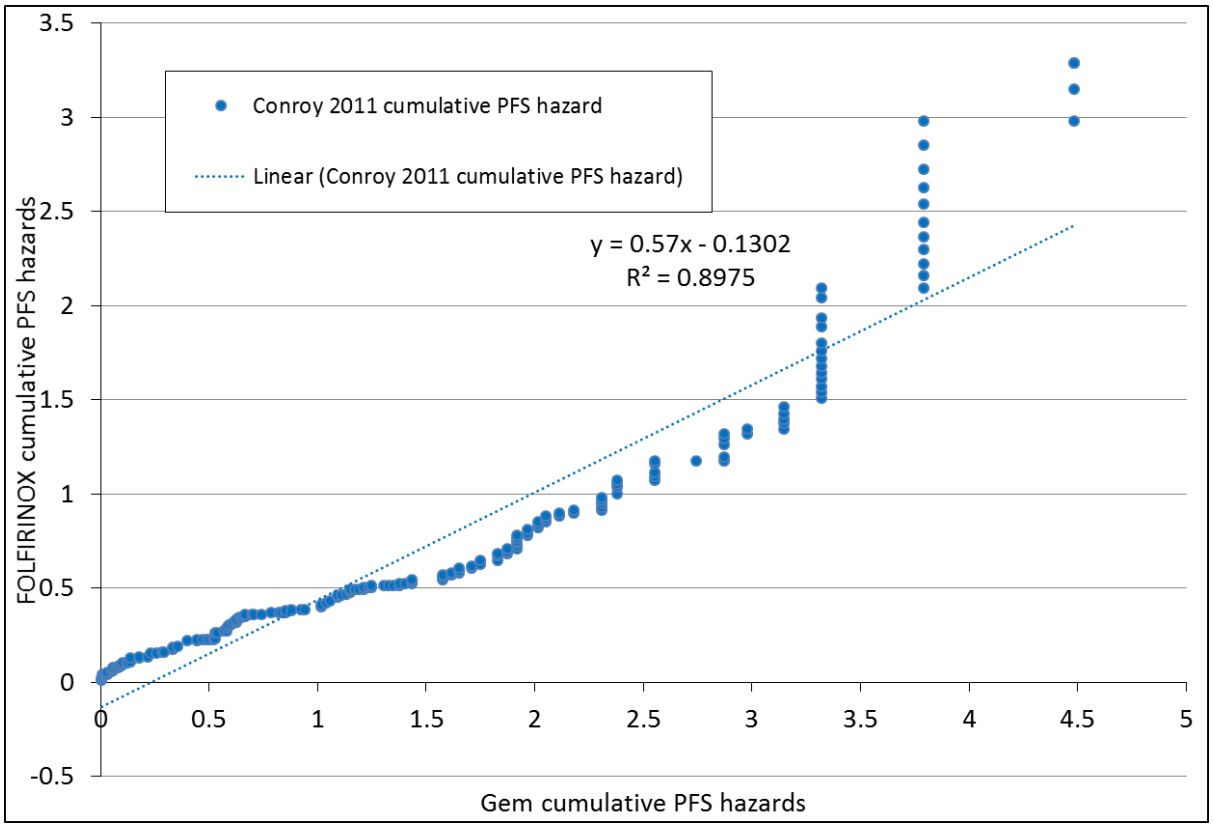

Figure 18 PFS H-H plot FOLFIRINOX vs Gem

Source: ERG calculations using digitised data from Conroy 2011

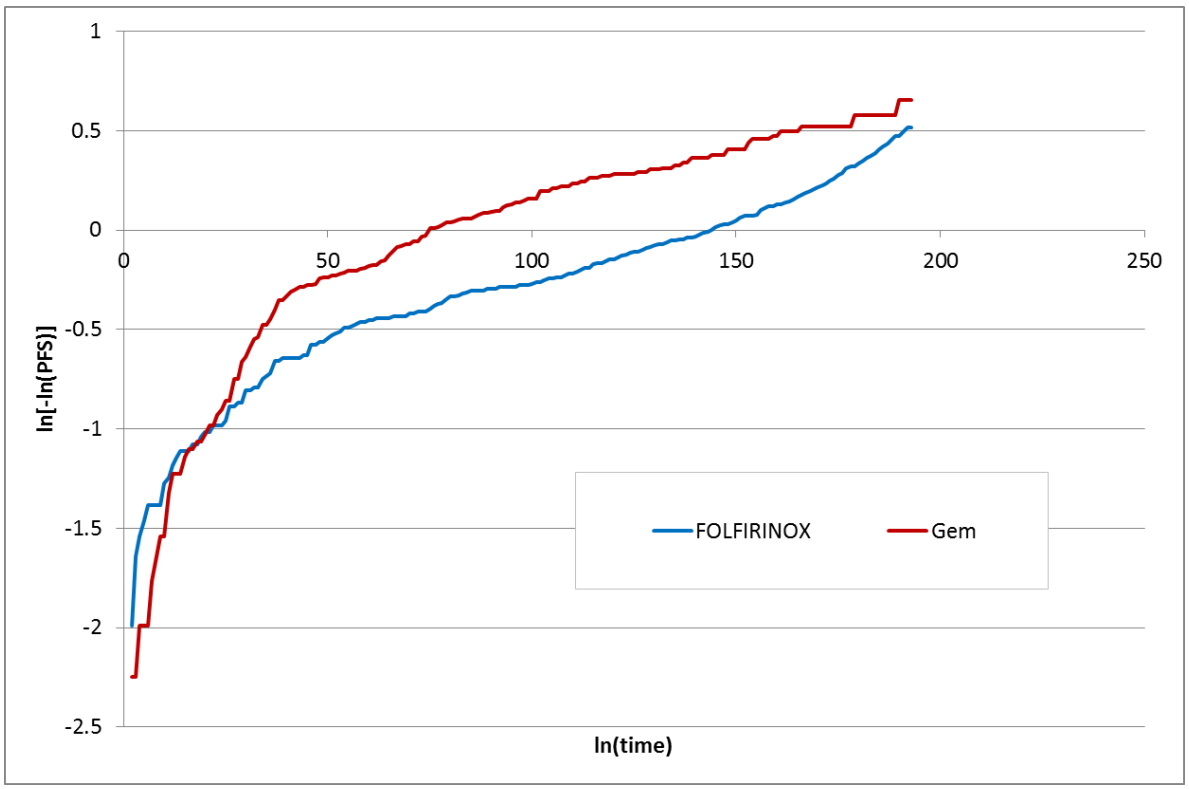

Figure 19 PFS log-log plot FOLFIRINOX vs Gem

Source: ERG calculations using digitised data from Conroy 2011

10.12 ERG Revisions to company's model

All revisions are activated by a logic switch. Logic switches are indicated by named range variables Mod_*letter* where letter = A - J.

A menu of revisions and Mod names appears below and on the 'Results' worksheet in the ERG amended model.

Instructions for modifying the updated company model (received during clarification)

1. Populate the following named switch values in the Results sheet

Revision #	Name	Switch value	Switch levels	Description
Correction	Mod_F	0	0, 1	Calculation of total LY and QALYs
R1	Mod_I	0	0, 1	HRs for Gem+Cap vs Gem
R2	Mod_B	0	0, 1	HRs for FOLFIRINOX vs Gem
R3	Mod_A	0	0, 1	ERG drug costing method
R4	Mod_E	0	0, 1	TOT from CA046 trial
R5	Mod_H	0	0, 1	Do not apply AE disutilities
R6	Mod_C	0	0, 1	ERG OS
R7	Mod_D	0	0, 1	ERG PFS
S1	Mod_G	0	0, 1	ERG AE costs
S2	Mod_J	0	0, 1	SIEGE crosswalk utility values *N.B. R5 (Mod_H) should also be applied*

2. Move all sheets from *ID1058_Nab-Pac_ERG additional model data.xlsx* into the model

3. Populate the following named ranges in the relevant sheets

Sheet	Value/formula	Name
OS	0.82	ERG_HR_OS_GemCap
OS	0.57	ERG_HR_OS_FOL
PFS	0.81	ERG_HR_PFS_GemCap
PFS	0.47	ERG_HR_PFS_FOL
ToT	0.81	ERG_HR_TOT_GemCap
ToT	0.47	ERG_HR_TOT_FOL

4. In sheet 'ToT', extend column AG to 522 cycles

5. In sheet 'Adverse_Events',
   - copy cells C45:C63
   - paste as values into cells R45:R63

6. For each sheet given in the 'Sheet' column below:
   - copy formulae from the 'Modified formulae' column in the table below
   - paste formulae into the cells referred to in the 'Cells' column in the table below

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
Correction	Mod_F	PF_Gem	Z15	=IF(Mod_F=0,1,0)*(O15*Cont.Cyclelength.PropYr*(p_u_stable+ae_gem_util))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
			AA15	=IF(Mod_F=0,1,0)*((p_u_stable+IF(Control.2ndLineOption="Once patient has failed on 1st line treatment",ae_gem_doublet2l*ae_gemdoublet_util+ae_gem_mono2l*ae_mono2l_util+ae_gem_FOLF*ae_FOLFIRINOX_util,0)) *P15*Cont.Cyclelength.PropYr)
			AB15	=IF(Mod_F=0,1,0)*(Q15*Cont.Cyclelength.PropYr *(p_u_progressed+ae_gem_doublet2l*ae_gemdoublet_util+ae_gem_mono2l*ae_mono2l_util+ae_gem_FOLF*ae_FOLFIRINOX_util) +IF(cont.utility.decrement.duration="4 weeks", (R15*p_u_terminal_decrement*Cont.Cyclelength.PropYr), IF(cont.utility.decrement.duration="8 weeks", (S15*p_u_terminal_decrement*Cont.Cyclelength.PropYr), IF(cont.utility.decrement.duration="12 weeks", (T15*p_u_terminal_decrement*Cont.Cyclelength.PropYr),0))))
			AI15	=IF(Mod_F=0,O15*Cont.Cyclelength.PropYr,0)
			AJ15	=IF(Mod_F=0,P15*Cont.Cyclelength.PropYr,0)
			AK15	=IF(Mod_F=0,Q15*Cont.Cyclelength.PropYr,0)
Correction	Mod_F	PF_AbraxaneGem	X18	=IF(Mod_F=0,1,0)*(O18*Cont.Cyclelength.PropYr*(p_u_stable+ae_gemabx_util))
			Y18	=IF(Mod_F=0,1,0)*((p_u_stable+IF(Control.2ndLineOption="Once patient has failed on 1st line treatment",ae_gemabx_doublet2l*ae_gemdoublet_util+ae_gemabx_mono2l*ae_mono2l_util+ae_gemabx_FOLF*ae_FOLFIRINOX_util,0))*P18*Cont.Cyclelength.PropYr)
			Z18	=IF(Mod_F=0,1,0)*(Q18*Cont.Cyclelength.PropYr*(p_u_progressed+ae_gemabx_doublet2l*ae_gemdoublet_util+ae_gemabx_mono2l*ae_mono2l_util+ae_gemabx_FOLF*ae_FOLFIRINOX_util)+IF(cont.utility.decrement.duration="4 weeks",(R18*p_u_terminal_decrement*Cont.Cyclelength.PropYr),IF(cont.utility.decrement.duration="8 weeks",(S18*p_u_terminal_decrement*Cont.Cyclelength.PropYr),IF(cont.utility.decrement.duration="12 weeks",(T18*p_u_terminal_decrement*Cont.Cyclelength.PropYr),0))))
			AF18	=IF(Mod_F=0,1,0)*(O18*Cont.Cyclelength.PropYr)
			AG18	=IF(Mod_F=0,1,0)*(P18*Cont.Cyclelength.PropYr)
			AH18	=IF(Mod_F=0,1,0)*(Q18*Cont.Cyclelength.PropYr)
Correction	Mod_F	PF_GemCap	X15	=IF(Mod_F=0,1,0)*(O15*Cont.Cyclelength.PropYr*(p_u_stable+IF(Control.Rate.Equivalent.AE="Gemcitabine Monotherapy",ae_gem_util,ae_gemabx_util)))
			Y15	=IF(Mod_F=0,1,0)*((p_u_stable+IF(Control.2ndLineOption="Once patient has failed on 1st line treatment",ae_gemcap_doublet2l*ae_gemdoublet_util+ae_gemcap_mono2l*ae_mono2l_util+ae_gemcap_FOLF*ae_FOLFIRINOX_util,0))*P15*Cont.Cyclelength.PropYr)
			Z15	=IF(Mod_F=0,1,0)*(Q15*Cont.Cyclelength.PropYr*(p_u_progressed+ae_gemcap_doublet2l*ae_gemdoublet_util+ae_gemcap_mono2l*ae_mono2l_util+ae_gemcap_FOLF*ae_FOLFIRINOX_util)+IF(cont.utility.decrement.duration="4 weeks",(R15*p_u_terminal_decrement*Cont.Cyclelength.PropYr),IF(cont.utility.decrement.duration="8 weeks",(S15*p_u_terminal_decrement*Cont.Cyclelength.PropYr),IF(cont.utility.decrement.duration="12 weeks",(T15*p_u_terminal_decrement*Cont.Cyclelength.PropYr),0))))
			AC15	=IF(Mod_F=0,1,0)*(O15*Cont.Cyclelength.PropYr)
			AD15	=IF(Mod_F=0,1,0)*(P15*Cont.Cyclelength.PropYr)
			AE15	=IF(Mod_F=0,1,0)*(Q15*Cont.Cyclelength.PropYr)
Correction	Mod_F	PF_Fol	Z15	=IF(Mod_F=0,1,0)*(O15*Cont.Cyclelength.PropYr*(p_u_stable+ae_mono2l_util))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
			AA15	=IF(Mod_F=0,1,0)*((p_u_stable+IF(Control.2ndLineOption="Once patient has failed on 1st line treatment",ae_FOLF_doublet2l*ae_gemdoublet_util+ae_folf_mono2l*ae_mono2l_util+ae_FOLF_FOLF*ae_FOLFIRINOX_util,0))*P15*Cont.Cyclelength.PropYr)
			AB15	=IF(Mod_F=0,1,0)*(Q15*Cont.Cyclelength.PropYr*(p_u_progressed+ae_FOLF_doublet2l*ae_gemdoublet_util+ae_folf_mono2l*ae_mono2l_util+ae_FOLF_FOLF*ae_FOLFIRINOX_util)+IF(cont.utility.decrement.duration="4 weeks",(R15*p_u_terminal_decrement*Cont.Cyclelength.PropYr),IF(cont.utility.decrement.duration="8nweeks",(S15*p_u_terminal_decrement*Cont.Cyclelength.PropYr),IF(cont.utility.decrement.duration="12 weeks",(T15*p_u_terminal_decrement*Cont.Cyclelength.PropYr),0))))
			AE15	=IF(Mod_F=0,1,0)*(O15*Cont.Cyclelength.PropYr)
			AF15	=IF(Mod_F=0,1,0)*(P15*Cont.Cyclelength.PropYr)
			AG15	=IF(Mod_F=0,1,0)*(Q15*Cont.Cyclelength.PropYr)
R1 HRs for Gem+Cap vs Gem	Mod_I	OS	E19:E541	=IF(Mod_I=0,1,0)*(C19^hr_os_GemCap)+IF(Mod_I=1,1,0)*(D19^ERG_HR_OS_GemCap)
R1 HRs for Gem+Cap vs Gem	Mod_I	PFS	E21:E543	=IF(Mod_I=0,1,0)*(C21^hr_pfs_GemCap)+IF(Mod_I=1,1,0)*(D21^ERG_HR_PFS_GemCap)
R1 HRs for Gem+Cap vs Gem	Mod_I	ToT	F20:F542	=IF(Mod_I=0,1,0)*(D20^hr_tot_GemCap)+IF(Mod_I=1,1,0)*(E20^ERG_HR_TOT_GemCap)
R2 HRs for FOLFIRINOX vs Gem	Mod_B	OS	F19:F541	=IF(Mod_B=0,1,0)*(C19^hr_os_FOL)+IF(Mod_B=1,1,0)*(D19^ERG_HR_OS_FOL)
R2 HRs for FOLFIRINOX vs Gem	Mod_B	PFS	F21:F543	=IF(Mod_B=0,1,0)*(C21^hr_pfs_FOL)+IF(Mod_B=1,1,0)*(D21^ERG_HR_PFS_FOL)
R2 HRs for FOLFIRINOX vs Gem	Mod_B	ToT	G20:G542	=IF(Mod_B=0,1,0)*(D20^hr_tot_FOL)+IF(Mod_B=1,1,0)*(E20^ERG_HR_TOT_FOL)
R3 ERG drug costing method	Mod_A	MoM_gem	BJ15:BJ537	=IF(Mod_A=0,IF(E15="","",(1-p_Perc_VialShare_Gem) *(AZ15*p_c_gem_1g+BA15*p_c_gem_200mg)+p_Perc_VialShare_Gem*BF15*c_gem_permg),IF(E15="","", (((1-p_Perc_VialShare_Gem) *ERG_weeklycost_gem_gem)+(p_Perc_VialShare_Gem*ERG_avgdose_gem_gem*ERG_costmg_gem_gem))* N15))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R3 ERG drug costing method	Mod_A	MoM_abxgem	CR15:CR537	=IF(Mod_A=0,IF(E15="","",(1-Perc_VialShare_Abx) *(BE15*p_c_abx_100mg+BF15*p_c_abx_250mg)+Perc_VialShare_Abx*CM15*c_abx_permg), IF(E15="","",(((1- Perc_VialShare_Abx)*ERG_weeklycost_npg_nabpac)+(Perc_VialShare_Abx*ERG_avgdose_npg_nabpac*ERG_costmg_npg_nabpac))*L15))
			CS15:CS537	=IF(Mod_A=0, IF(E15="", "", (1-p_Perc_VialShare_Gem) *(CA15*p_c_gem_1g+CB15*c_gem_200mg)+p_Perc_VialShare_Gem*CN15*c_gem_permg), IF(E15="","",(((1- p_Perc_VialShare_Gem)*ERG_weeklycost_npg_gem)+(p_Perc_VialShare_Gem*ERG_avgdose_npg_gem*ERG_costmg_npg_gem))*L15))
R3 ERG drug costing method	Mod_A	MoM_Cap	CC15:CC537	=IF(Mod_A=0,IF(E15="","", (L15*p_dose_cap*average_BSA*c_cap_permg)), IF(E15="","", (L15*ERG_weeklycost_gc_cap)))
			CE15:CE537	=IF(Mod_A=0, IF(E15="","",(1- p_Perc_VialShare_Gem)*(BU15*p_c_gem_1g+BV15*c_gem_200mg)+p_Perc_VialShare_Gem*BZ15*c_gem_permg), IF(E15="","",(((1- p_Perc_VialShare_Gem)*ERG_weeklycost_gc_gem)+(p_Perc_VialShare_Gem*ERG_avgdose_gc_gem*ERG_costmg_gc_gem))*L15))
R3 ERG drug costing method	Mod_A	MoM_FOLFIRINOX	CU15:CU537	=IF(Mod_A=0, IF($E15="","",(1- p_Perc_VialShare_Ox)*(AL15*p_c_ox_50mg+AM15*p_c_ox_100mg)+p_Perc_VialShare_Ox*CN15*c_ox_permg), IF($E15="","",(((1- p_Perc_VialShare_Ox)*ERG_weeklycosts_FOL_ox)+(p_Perc_VialShare_Ox*ERG_avgdose_FOL_ox*ERG_costmg_FOL_ox))*L15))
			CV15:CV537	=IF(Mod_A=0, IF($E15="","",(1- p_Perc_VialShare_flubol)*(AW15*p_c_flu_500mg+AV15*p_c_flu_250mg)+p_Perc_VialShare_flubol*$CO15*c_flu_permg), IF($E15="","",(((1- p_Perc_VialShare_flubol)*ERG_weeklycosts_FOL_5FUbol)+(p_Perc_VialShare_flubol*ERG_avgdose_FOL_5FUbol*ERG_costmg_FOL_5FUbol))*L15))
			CW15:Cw537	=IF(Mod_A=0, IF($E15="","",(1- p_Perc_VialShare_Flu)*(BC15*p_c_fluinf_2.5g+BD15*p_c_fluinf_5g)+p_Perc_VialShare_Flu*CP15*c_fluinf_permg), IF($E15="","",(((1- p_Perc_VialShare_Flu)*ERG_weeklycosts_FOL_5FUinf)+(p_Perc_VialShare_Flu*ERG_avgdose_FOL_5FUinf*ERG_costmg_FOL_5FUinf))*L15))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
			CX15:CX537	=IF(Mod_A=0, IF($E15="","",(1-p_Perc_VialShare_leu)*(BR15*p_c_leu_100mg+BS15*p_c_leu_300mg)+p_Perc_VialShare_leu*CQ15*c_fa_permg), IF($E15="","",(((1-p_Perc_VialShare_leu)*ERG_weeklycosts_FOL_folac)+(p_Perc_VialShare_leu*ERG_avgdose_FOL_folac*ERG_costmg_FOL_folac))*L15))
			CY15:Cy537	=IF(Mod_A=0, IF($E15="","",(1-p_Perc_VialShare_Iri)*(CB15*p_c_Iri_100mg+CC15*p_c_Iri_300mg)+p_Perc_VialShare_Iri*CR15*c_iri_permg), IF($E15="","",(((1-p_Perc_VialShare_Iri)*ERG_weeklycosts_FOL_iri)+(p_Perc_VialShare_Iri*ERG_avgdose_FOL_iri*ERG_costmg_FOL_iri))*L15))
R4 TOT from CA046 trial	Mod_E	ToT	D20:D542	=IF(Mod_E=0,1,0)*IF(Control.ToT.Curve="KM Data",L123,AU16)+IF(Mod_E=1,1,0)*VLOOKUP(C20,ERG_TTE_basecase,5)
			E20E542	=IF(Mod_E=0,1,0)*IF(Control.ToT.Curve="KM Data",M123,AV16)+IF(Mod_E=1,1,0)*VLOOKUP(C20,ERG_TTE_basecase,6)
R5 Do not apply AE disutilities	Mod_H	Controls	F56	Change company switch to 'No'
R6 ERG OS	Mod_C	Controls	F34	Change company switch to 'ERG curves'
R7 ERG PFS	Mod_D	Controls	F38	Change company switch to 'ERG curves'
S1 ERG AE costs	Mod_G	Adverse Events	C45	=IF(Mod_G=0, 1,0)*R45+IF(Mod_G=1, 1,0)*ERG_neutro
			C46	=IF(Mod_G=0, 1,0)*R46+IF(Mod_G=1, 1,0)*ERG_fatigue
			C47	=IF(Mod_G=0, 1,0)*R47+IF(Mod_G=1, 1,0)*ERG_thrombo
			C48	=IF(Mod_G=0, 1,0)*R48+IF(Mod_G=1, 1,0)*ERG_anaemia
			C49	=IF(Mod_G=0, 1,0)*R49+IF(Mod_G=1, 1,0)*ERG_leuko
			C50	=IF(Mod_G=0, 1,0)*R50+IF(Mod_G=1, 1,0)*ERG_psensneuro
			C51	=IF(Mod_G=0, 1,0)*R51+IF(Mod_G=1, 1,0)*ERG_neuroperi
			C52	=IF(Mod_G=0, 1,0)*R52+IF(Mod_G=1, 1,0)*ERG_dehydra
			C53	=IF(Mod_G=0, 1,0)*R53+IF(Mod_G=1, 1,0)*ERG_asthenia
			C54	=IF(Mod_G=0, 1,0)*R54+IF(Mod_G=1, 1,0)*ERG_abdopain
			C55	=IF(Mod_G=0, 1,0)*R55+IF(Mod_G=1, 1,0)*ERG_nausea
			C56	=IF(Mod_G=0, 1,0)*R56+IF(Mod_G=1, 1,0)*ERG_diarrhoea
			C57	=IF(Mod_G=0, 1,0)*R57+IF(Mod_G=1, 1,0)*ERG_vomiting
			C58	=IF(Mod_G=0, 1,0)*R58+IF(Mod_G=1, 1,0)*ERG_decappetite
			C59	=IF(Mod_G=0, 1,0)*R59+IF(Mod_G=1, 1,0)*ERG_pulembo

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
			C60	=IF(Mod_G=0, 1,0)*R60+IF(Mod_G=1, 1,0)*ERG_pneumonia
			C61	=IF(Mod_G=0, 1,0)*R61+IF(Mod_G=1, 1,0)*ERG_febneutro
			C62	=IF(Mod_G=0, 1,0)*R62+IF(Mod_G=1, 1,0)*ERG_cholangitis
			C63	=IF(Mod_G=0, 1,0)*R63+IF(Mod_G=1, 1,0)*ERG_hyperbili
S2 SIEGE crosswalk utility values	Mod_J	Controls	F54	Change company switch to 'SIEGE study (Crosswalk)'

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

You are asked to check the ERG report from LRIG to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Wednesday 21 June** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Definition of patient group suitable for treatment with *nab*-Paclitaxel and gemcitabine (*Nab-Pac+Gem*)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 11, 18, 25, 26, 27, 37, 72, 103, 124 and 126 the ERG makes several statements relating to identifying the patient population suitable for Nab-Pac+Gem and the patient populations suitable for FOLFIRINOX and gemcitabine monotherapy. Examples include the following statements: "The company has not provided clear evidence to determine which patients are best suited to which of these treatments" (page 11) "The ERG considers that the company has failed to clearly define the patient population for whom treatment with Nab-Pac+Gem is most appropriate" (page 11) "The company is unable to define the characteristics of the patient population who would be most suited to treatment with Nab-Pac+Gem" (Page 18) "The distinction between patients who are better suited to treatment with FOLFIRINOX and patients	The company has clearly defined the patient population for whom Nab-Pac+Gem is most appropriate. The company provides evidence of expert clinical validation (by 7 highly experienced clinicians in the field of pancreatic cancer) of the definitions regarding which patients are best suited to treatment with Nab-Pac+Gem, FOLFIRINOX and Gemcitabine monotherapy. The definitions are as follows: • FOLFIRINOX is used to treat patients who are ≤70 years old, have an ECOG performance status of 0-1 and have very minor comorbidities (e.g. well-controlled hypertension). • Gemcitabine monotherapy is used to treat patients of any age, who have an ECOG performance status of ≥2. • Nab-Pac+Gem would be used to treat patients of any age (with use in those over 80 years of age not necessarily excluded due to real world evidence supporting its use in an older population [see Section 4.12]), who have an ECOG performance status of 0-1 and for whom treatment with FOLFIRINOX is not considered suitable. Clinicians also noted that if a patient has an ECOG performance status of 2 due to disease burden they may consider treatment with Nab-Pac+Gem	<u>Factual Inaccuracy:</u> The company clearly identifies the group of patients suitable for treatment with Nab-Pac+Gem. Additionally, the ERG states that "patients in the NHS who are better suited to treatment with FOLFIRINOX are easily identified from patients who are better suited to treatment with Gem". Following the logic of this statement, as a group of 7 expert clinicians advise us that patients who currently receive FOLFRINIOX would never receive Nab-Pac+Gem and that the only relevant comparator is Gem (i.e. Nab-Pac+Gem will not displace FOLFIRINOX use, only Gem use), this would suggest that the ERG agree that the group of patients who would be suitable for Nab-Pac+Gem is clearly distinguishable from those patients who would receive FOLFIRINOX. Moreover, in the conclusions of the committee from the previous NICE submission, the committee stated the following: "the Committee concluded that nab-	This is not a factual error, no change made. Whilst the company may be clear on their intended target patient population for Nab-Pac+Gem, there is no trial subgroup evidence available to support use in this target group of patients in the CS. In addition, the company also recognises that it is not possible to define this or any subgroup by any one parameter.

who might be better suited to treatment with Nab-Pac+Gem is not clear and it is difficult to formulate guidance for patient selection" (Page 25) "Clinical advice to the ERG is that patients who are suitable for treatment with FOLFIRINOX are clinically distinct from patients who are suitable for treatment with Gem monotherapy. However, the ERG is uncertain that patients with metastatic pancreatic cancer who may be considered suitable for treatment with Nab-Pac+Gem in the NHS are clinically distinct from patients who would currently be treated with FOLFIRINOX. Clinical advice to the ERG is that it would be difficult to clearly establish which patients in the NHS would better suited to treatment with Nab-Pac+Gem rather than with FOLFIRINOX." (page 37) "The company appears to consider that all patients who are fit enough to be treated with Gem, Gem+Cap or FOLFIRINOX are fit enough to be treated with Nab-Pac+Gem. However, the company considers that not all patients who are fit enough to tolerate treatment with Nab-Pac+Gem will be able to tolerate	The company also references expert clinical advice that states no patient currently treated with FOLFIRINOX or Gem+Cap would receive Nab-Pac+Gem if it was made available, which therefore means that neither FOLFIRINOX nor Gem+Cap are relevant comparators to this decision problem. The same expert panel were involved in a workshop that confirmed patients who currently receive FOLFIRINOX are an easily identifiable, clinically distinct patient group to those who currently receive gemcitabine and could receive Nab-Pac+Gem in clinical practice (which the ERG and the original NICE committee agrees with). Furthermore, the above definitions were suggested and validated by a group of expert clinicians who have prescribed Nab-Pac+Gem, Gem and FOLFIRINOX in their clinical practice. In the company submission it is also noted that it is not possible to define the above patient groups by any one parameter. In the previous ERG report, the ERG accepted that "while the KPS is routinely used to aid decision making, its subjective nature and lack of accepted cut-off values for treatment selection made it inappropriate to separate patients into subpopulations based on this measure." Furthermore, using a single measure to determine treatment selection is not appropriate, as decision making accounts for many factors such as comorbidities, patient preference and age. This was validated by an expert group of clinicians: "It was agreed that these groups are not clearly defined by any one factor (i.e. age, KPS, comorbidities), but that the groups were	paclitaxel plus gemcitabine would be considered for use in clinical practice for those people who were fit enough to have chemotherapy with 2 agents but FOLFIRINOX was not suitable for them, irrespective of Karnofsky performance status. However, it also understood from the clinical expert that this group could not be defined just by performance status, given that other factors are also considered, including comorbidities, age, patient preference and treatment availability" The committee also stated: "There is a clinically recognisable group of patients who receive gemcitabine alone in clinical practice" It is therefore factually inaccurate to state that the CS fails to define the group of patients for whom Nab-Pac+Gem would be most suitable.	

treatment with FOLFIRINOX" (pages 11 and 124)	clinically clearly definable." The company suggests that all of the ERG's comments such as "The company has not provided clear evidence to determine which patients are best suited to which of these treatments" are removed or revised to reflect the information provided above.		

Issue 2 The representation of patients ≥75 in the CA046 clinical trial in the context of the decision problem

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 10, 14, 18, 34, 35, 43, 60 and 124 the ERG makes several statements about the fact that 10% of patients in the CA046 clinical trial are ≥75 and that this may not reflect the group of patients treated in clinical practice. Some examples are the following: "Although 47% of all cases of pancreatic cancer are diagnosed in people aged ≥75 years, only 10% (n=84) of the patients recruited to the key trial (CA046) were aged ≥75. This means that the outcomes of the CA046 trial may not represent the outcomes of a substantial proportion of patients in the NHS who are diagnosed with metastatic adenocarcinoma pancreatic cancer" (Page 10)	47% of all cases of pancreatic cancer are diagnosed in people aged ≥75 years, only 10% (n=84) of the patients recruited to the key trial (CA046) were aged ≥75. However, only 50-60% of patients diagnosed with metastatic pancreatic adenocarcinoma will be suitable to tolerate treatment with any chemotherapy. Therefore, in reality the percentage of patients over the age of 75 treated with chemotherapy will be substantially smaller than the 47% diagnosed (many of which will receive palliative care only). Market research data looking at patients treated with chemotherapy for metastatic pancreatic adenocarcinoma in the first line setting suggests that the percentage of patients over the age of 75 treated is between 17-22% of the treated patient population. Of this percentage, as these patients are older and therefore more likely to have significant co-morbidities and an ECOG PS of 2 not due to disease burden, a high proportion of them will only be suitable for	<u>Factual Inaccuracy:</u> While we agree with ERG that 47% of patients diagnosed with metastatic pancreatic adenocarcinoma are ≥75 years of age,,It is incorrect to suggest that all of these patients will be deemed suitable for treatment with chemotherapy. It is also misleading to suggest that all these patients would be suitable for treatment with Nab-Pac+Gem when many of them would only tolerate Gem monotherapy, if anything. We have market research data (which we are happy to provide) from between 203-288 patient notes across a 2-year period in the UK that suggests the proportion of patients ≥75 that are treated with chemotherapy is between 17-22%	Not a factual error, no change made. Whilst the ERG agrees that not all patients ≥75 years of age who are diagnosed with metastatic pancreatic adenocarcinoma will be eligible for treatment, the ERG is concerned that the patients ≥75 of years who <u>are</u> eligible for treatment are not fully represented in the CA046 trial.

“Clinical advice to the ERG is that patients recruited to t he trial were younger and fitter than the population of patients with metastatic disease treated in the NHS. Most notably, only 10% of the patients recruited to the trial were aged ≥75 year, whereas cancer research UK (CRUK) statistics suggest that almost half (47%) of all patients diagnosed with pancreatic cancer are in this age band.” (Page 14) “The ERG is concerned that the outcomes of the CA046 trial may not represent the outcomes of a substantial proportion of patients in the NHS who are diagnosed with pancreatic cancer, i.e. patients aged ≥75 years” (Page 35) “The ERG notes from the CS (p32) that approximately half (47%) of all pancreatic cancer cases are diagnosed in people aged ≥75 years; however, the company reports (CS, p27) that only 10% of patients in the CA046 trial were aged 75 years or over. Clinical advice to the ERG is that in the NHS, almost half of patients diagnosed with pancreatic cancer are aged ≥75 years... Consequently, it is not known if	Gem monotherapy. Therefore, the 10% of patients ≥75 in the CA046 study is likely to be roughly similar to the percentage of treated patients that would receive Nab-Pac+Gem in clinical practice on the NHS. Therefore, the percentage of AEs and SAEs seen in the clinical trial is likely to be representative of the proportion of these that would be seen in clinical practice. Data from the real world setting in Italy supports this, with 15% of the patients included being ≥75. Additionally, the CA046 study is the only clinical trial in the NMA that provides any evidence of patients treated with any of the treatments under consideration (Gem, Gem+Cap, FOLFIRINOX and Nab-Pac+Gem) in the patient group ≥75. The company proposes that all ERG comments such as those described are removed or revised to reflect the information provided above.	of the total population of treated patients. Therefore, the statement that the outcomes of the CA046 trial may not represent the outcomes of a substantial proportion of patients with metastatic disease treated on the NHS is misleading. Additionally, the statement that the number of AEs and SAEs may be under-represented is also factually inaccurate. The 10% of patients ≥75 recruited into the CA046 clinical trial may be roughly similar to the percentage of patients ≥75 that would receive Nab-Pac+Gem in clinical practice on the NHS. Therefore, the AEs and SAEs seen would also reflect what is likely to be seen on the NHS in clinical practice.	

the treatment effect estimated for the population of the CA046 trial is generalisable to the population expected to be seen in clinical practice. Furthermore, the occurrence of AEs and SAEs that would be seen in clinical practice may be underestimated by the CA046 trial, due to the small proportion of people aged ≥75 years in the trial population" (Page 43)			

Issue 3 The clinical efficacy of Nab-Pac+Gem in the patient population ≥75 years of age

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 11, 25, 26, 35, 43, 60, 72, 119, 124 the ERG makes similar statements about the following: "In the European Public Assessment Report (EPAR) for Nab-Pac+Gem, the EMA cautions that there is no demonstrated benefit of treatment with Nab-Pac+Gem in people aged ≥75 years and that patients aged ≥75 years who were treated with Nab-Pac+Gem in the CA046 trial experienced more adverse events (AEs) and serious AEs (SAEs) than the overall trial population. The advice given in the Summary	The following language from the ERG report (concerning the EPAR) should put the data into context as is done in the EPAR report as follows: In the European Public Assessment Report (EPAR) for Nab-Pac+Gem, the EMA cautions that there is no demonstrated benefit of treatment with Nab-Pac+Gem in people aged ≥75 years and that patients aged ≥75 years who were treated with Nab-Pac+Gem in the CA046 trial experienced more adverse events (AEs) and serious AEs (SAEs) than the overall trial population. The advice given in the Summary of Product Characteristics (SmPC) for Nab-Pac is that patients with pancreatic cancer who are aged ≥75 years should be carefully assessed for their ability to tolerate Nab-Pac+Gem, with special consideration given to performance status (PS),	<u>Failure to consider context:</u> It can be misleading to quote only part of the wording from the EPAR and SmPC as this does not contextualise the statements made by the EMA. Therefore, we ask whenever this is referred to, that the second paragraph is included for accuracy. This also provides additional accuracy and context around the AE profile of the patients aged ≥75. It also could be misleading not to discuss all the data on patients ≥75 that the company has provided when discussing efficacy and AEs in this patient population,	This is not a factual error, no change made.

of Product Characteristics (SmPC) for Nab-Pac is that patients with pancreatic cancer who are aged ≥75 years should be carefully assessed for their ability to tolerate Nab-Pac+Gem, with special consideration given to performance status (PS), co-morbidities and increased risk of infection." (Page 11) "patients aged ≥75 years who were treated with Nab-Pac+Gem in the CA046 trial experienced more AEs and SAEs than the overall trial population." (Page 35) "In the SmPC9 for Nab-Pac, the EMA cautions that there is a lack of evidence of clinical efficacy in people aged ≥75 years" (page 43)	co-morbidities and increased risk of infection. The EPAR goes on to note that the observed OS HR may have been impacted by confounding factors. The small sample size (41 patients ≥75 years of age received Abraxane/gemcitabine, and 49 gemcitabine) and high rate of early withdrawal prior to treatment in the gemcitabine arm (10% vs. 0%) may have contributed to a lack of precision around the estimate of OS in the gemcitabine arm. Additionally, imbalances in baseline characteristics were observed across the treatment arms in this patient group, including a number of prognostic factors identified to be predictors of poorer survival. Patients in the Abraxane/gemcitabine arm were more likely to have a worse performance status ((KPS score of 70-80), more extensive disease burden and a higher incidence of liver metastases. The ERG notes that Nab-Pac+Gem is not contra-indicated for patients ≥75 years of age in the EPAR. Additionally, the MPACT clinical trial was not powered for a sub-analysis of a ≥75 years of age subgroup. Additionally, the oldest patient recruited into the SIEGE trial, a trial carried out in 19 UK clinical treatment centres, was 82 years of age. Moreover, patients over 75 were not excluded from this trial. This demonstrates that UK clinicians perceive Nab-Pac+Gem to be of value in treating patients over the age of 75. Lastly, real world data from Italy (where 32 patients out of 208 were aged ≥75) demonstrates no significant difference in the overall toxicity	therefore, the Italian real world data should also be mentioned when this topic is discussed.	

	profile of Nab-Pac+Gem in patients ≥75 and <75 years of age, with no significantly worsened tolerability. Additionally, the outcomes in the ≥75 patient subgroup in this study (albeit small numbers) show an OS of 11.4 months and a PFS of 7.1 months, which demonstrated no difference when compared to the OS and PFS of patients <75 (n=176). The company proposes that all ERG comments such as those described are removed or revised to reflect the above information.		

Issue 4 Description of the Abraxane licenced indications

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 10 the ERG states the following: "Nab-Pac monotherapy is licensed in Europe as a second-line treatment for metastatic breast cancer and, in combination with carboplatin, for the first-line treatment of non-small cell lung cancer (NSCLC) in people whose disease is unsuitable for surgery or radiotherapy. On 2nd December 2013, the European Medicines Agency (EMA) approved an extension to the existing marketing authorisation allowing the use of	The appropriate licences are as follows and were granted in the following order: Abraxane monotherapy is indicated 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. Abraxane in combination with carboplatin is indicated for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy. On the 20th December 2013, the EMA approved	<u>Factual Inaccuracy:</u> It is important to fully and accurately quote the licence for all Abraxane indications – please amend this to match the full licence details. Secondly, the lung licence was granted after the pancreatic licence, therefore it is factually inaccurate to state that an extension to the lung licence was granted for the pancreatic licence. The date of EMA approval was the 20th December, not the 2nd.	For clarity and accuracy, text is reworded as follows: Page 10: Nab-Pac is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. Page 36: Nab-Pac+carboplatin is indicated for the first-line treatment of NSCLC in adult

Nab-Pac, co-administered with Gem, as a first-line treatment for people with metastatic adenocarcinoma of the pancreas." And on page 36 the ERG states the following: "Nab-Pac in combination with carboplatin is licensed in Europe for the first-line treatment of NSCLC in people whose disease is unsuitable for surgery or radiotherapy."	the use of Nab-Pac+Gem.		patients who are not candidates for potentially curative surgery and/or radiation therapy.

Issue 5 Availability of Gem+Cap and FOLFIRINOX across the NHS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 12 of the ERG report, the ERG states the following: "The use of Gem+Cap and FOLFIRINOX is not uniform across the NHS" Additionally, on page 22 of the ERG report in Table 1, the ERG notes that: FOLFIRINOX is not uniformly available across the NHS with the caveat that "modified treatment regimens are used in some centres."	The company proposes the following wording: "The use of Gem+Cap and FOLFIRINOX is not uniform across the NHS, but for different reasons. The use of Gem+Cap is not uniform across the NHS as it is only used in a few centres and therefore does not represent a national comparator. In addition, there is no single randomised controlled clinical trial that demonstrates any benefit of Gem+Cap over the standard of care (Gem). The use of FOLFIRINOX is not uniform across the NHS as it is an intensive therapy, associated with high administration burden and considerable toxicity, and can therefore only be offered in specialist cancer treatment centres	<u>Misleading statement:</u> The current wording in the report is misleading as it suggests that the use of Gem+Cap and FOLFIRINOX is not uniform across the NHS for similar reasons, when in fact the reasons for this are very different. It is also misleading in Table 1 on page 22 of the ERG report not to state that FOLFIRINOX is not given at all in some centres if the ERG are going to state that modified regimens are used in some centres.	This is not a factual error, no change made.

	across the NHS (as stated by the ERG). Therefore, FOLFIRINOX is not used at all in many NHS centres. Additionally, different modified versions of the FOLFIRINOX regimen with unproven efficacy in the context of a randomised controlled Phase III clinical trial are often adopted in clinical practice in an attempt to improve tolerability of the regimen."		

Issue 6 The SIEGE Trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 12 of the ERG report it states: "SIEGE is an ongoing phase II study"	"SIEGE is a phase II study that has now closed to recruitment and is continuing to report results."	Factual Inaccuracy: The current statement implies that the SIEGE trial is ongoing. It is not, it has closed to recruitment and is continuing to report results.	Text has been reworded as follows: The SIEGE trial is a [redacted] phase II study designed to explore different dosing schedules of Nab-Pac+Gem; the trial is now closed to recruitment and is continuing to report results.

Issue 7 Metabolism and Nutritional Disorder

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 13 and 58 of the ERG report it states: "the most common Grade 3 or 4	"metabolism and nutritional disorders (dehydration and decreased appetite)"	Misleading Statement: This statement is misleading as it could suggest that a wide range of	For clarity, text on page 13 and on page 58 has been reworded as suggested by the company.

AEs associated with treatment with Nab-Pac+Gem were… metabolism and nutritional disorders”		metabolism and nutritional disorders were seen in the clinical trial. According to the CA046 study, this means dehydration and decreased appetite and therefore would request that the ERG clarify the current wording by including the proposed amendment.	

Issue 8 Nab-P monotherapy was not investigated in the CA046 trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 of the ERG report: “Although these AEs were also associated with treatment with Gem and Nab-Pac monotherapies they occurred more frequently when patients were treated with Nab-Pac+Gem”	Nab-Pac monotherapy was not investigated in the CA046 trial, under which sub-heading this statement is included. Proposed amendment to clarify sources: “Although these AEs were also associated with treatment with Gem (and nab-Pac monotherapy outside of CA046), they occurred more frequently when patients were treated with Nab-Pac+Gem”	Factual inaccuracy	For clarity, text on page 13 has been amended as suggested by the company.

Issue 9 The company’s case for End of Life criteria being met

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 16-17 the ERG report states the following: The company has put forward a case that Nab-Pac+Gem meets	Please remove the last bullet point – we do not state this in the company submission as a reason for why we meet End of Life criteria.	<u>Factual Inaccuracy:</u> It is factually inaccurate to state that the company stated “When Nab-Pac+Gem is compared with	Final bullet point has been deleted from the text.

NICE's End of Life criteria based on the following points: • The company quotes data that show the median survival for patients with metastatic adenocarcinoma pancreatic cancer is less than 24 months • Base case results generated by the company's economic model suggest that the mean difference in OS between patients treated with Nab-Pac+Gem versus Gem is 2.4 months • When Nab-Pac+Gem is compared with Gem+Cap or FOLFIRINOX, the results from the company's base case NMA show that there is no statistically significant OS gain from Nab-Pac+Gem.	Please replace this with the following: "With a life-expectancy of ≤6 months associated with standard of care, and a clinically meaningful extension to life observed versus this standard of care in the CA046 trial, Nab-Pac+Gem should be considered as a life-extending treatment at the end of life. Although the extension to life may be under 3 months, it is considered proportionally equivalent given the extremely short life-expectancy of this patient group. As part of the original submission, NICE concluded that the normal extension to life of an additional 3 months is not appropriate in order to meet end of life criteria in this instance. As noted in the Appeal Decision Paper "First, the estimates before the Appraisal Committee were very robust, so that the actual benefit of 2.4 months was firmly established rather than an uncertain extrapolation. Secondly, the outlook in metastatic pancreatic cancer was very poor, and the gain in life was high in proportion to the life-expectancy. For that reason, the Committee decided it would be right to apply the end-of-life policy, even though the product did not strictly fulfil all of the criteria""	Gem+Cap or FOLFIRINOX, the results from the company's base case NMA show that there is no statistically significant OS gain from Nab-Pac+Gem" as one of the reasons why the company feels that Nab-Pac+Gem should qualify for EOL criteria, since it is not what was written in the submission. Details of what was written in the submission regarding EOL criteria are provided in the column to the left.	

Issue 10 Gem doublet market share

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 22, 26 (Table 2) and 37 of the ERG report:	The market research data did not distinguish between Gem doublets outside of Abraxane +	Factual inaccuracy	For clarity, text has been amended as suggested by the

Stated that the company's market research suggest/shows that in the UK xxxxxxxxxx of patients are treated with Gem+Cap.	gemcitabine; other Gem doublets could account for this use (e.g. Gem+Cisplatin) and while it is possible that some patients in this group were treated with Gem+Cap in the UK, this cannot be stated as fact. Please amend in line with the more accurate description of market share data on pages 28 and 29 of the ERG report that describe this group as *"Gem doublet (includes Gem+Cap)"*		company.

Issue 11 The flawed Gem+Cap Meta-Analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 23 the ERG notes: "The ERG notes that the results of the published meta-analysis4 demonstrated a significant OS gain for Gem+Cap when compared with Gem (hazard ratio [HR]=0.86; 95% confidence interval [CI]: 0.75 to 0.98; p=0.02) in a mixed group of patients with locally advanced or metastatic disease."	A sentence should be added to state: The fact that the meta-analysis includes studies with hazard ratios that include patients with LAPAC makes this meta-analysis irrelevant to the decision problem under discussion. Additionally, a meta-analysis is only as good as the contributing data, and should not change the outcomes tested by individual trial hypotheses. An aggregation of information (such as a meta-analysis) can lead to higher statistical power than individual studies[1]; this should not be confused with an increase in treatment effect. In the case of the meta-analysis presented by Cunningham et al, the point estimate of treatment effect was	<u>Inconsistency:</u> The ERG agree with the approach taken in the meta-analysis to exclude clinical trials where the population is not restricted to patients with mPAC, therefore it is inconsistent to not also apply this approach to the meta-analysis. <u>Factual Inaccuracy:</u> It is not correct to suggest that a meta-analysis can change the outcomes tested by individual trial hypotheses (explanation in column to the left)	This is not a factual error. This is a description of results so no change has been made to the text.

	identical to that reported in their Phase III trial with a hazard ratio of 0.86 for the comparison of Gem+Cap versus Gem, and we don't believe that the attainment of statistical significance via the use of meta-analysis 'elevates' the initial findings. This standpoint is reflected in the Cochrane Handbook[2] where it is suggested that a common misinterpretation in large studies such as meta-analyses is that a small P value for the summary effect estimate implies that the intervention has an important benefit, and that in a large study, a small P value may represent the detection of a trivial effect. The recommendation is that inspection of the point estimate and confidence intervals can help correct interpretations. 1. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003657.pdf. 2. Higgins J PT & Green S *ed.* Cochrane Handbook for Systematic Reviews of Interventions. P values and statistical significance, Available via URL: http://handbook.cochrane.org/chapter_12/12_4_2_p_values_and_statistical_significance.htm (last accessed 14Jun2017)		

Issue 12 Use of Nab-Pac+Gem and FOLFIRINOX on the NHS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 24 the ERG states the following: "Clinical advice to the ERG is that treatment centres that support the use of Nab-Pac+Gem also have the infrastructure to support the use of FOLFIRINOX" And "Clinical advice to the ERG is that patients who are suitable for treatment with Nab-Pac+Gem will also be treated at specialist cancer centres." (Implying that the use of Nab-Pac+Gem will be restricted to use in only centres that prescribe FOLFIRINOX).	"Nab-Pac+Gem is able to be prescribed more uniformly across the NHS compared to FOLFIRINOX. There are 63 district general hospitals who prescribed nab-P when it was available on the CDF, where it is unlikely that FOLFIRINOX was prescribed. Additionally, 7 clinical experts in the field of pancreatic cancer agree that 'Nab-Pac+Gem would utilise existing infrastructure in hospital oncology units for the administration of cancer treatments' and no caveats about the use of Nab-Pac+Gem in smaller hospitals were identified."	<u>Misleading Statement:</u> It is misleading to state that centres that support the use of Nab-Pac+Gem also have the infrastructure to support the use of FOLFIRINOX and to imply that treatment with Nab-Pac+Gem will be limited specialist centres like FOLFIRINOX. The company has evidence from when Nab-Pac+Gem was previously available via the CDF that many hospitals treated patients with metastatic pancreatic adenocarcinoma with Nab-Pac+Gem where it is unlikely patients were treated with FOLFIRINOX. Moreover, expert clinicians did not identify a barrier to prescribing Nab-Pac+Gem in less specialist hospitals, whereas they did for FOLFIRINOX. We have a list of 63 DGH hospitals that have used Nab-P that are unlikely to also use FOLFIRINOX. We are happy to provide this list on request.	This is clinical advice, not a factual error, no change made.

Issue 13 Dose Modifications of Nab-Pac+Gem

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 24 the ERG state the following: "clinical advice to the ERG is that there is no RCT evidence to support the dose reductions and dose omissions that are commonly required when treating patients with Nab-Pac+Gem."	This statement should be removed or replaced with: "The CA046 clinical trial reflects dose modifications and dose omissions that are commonly required in clinical practice. In addition, there are two papers (referenced in the CS) published outlining the optimal management of dose reductions and modifications and demonstrating that these improve outcomes, as well as demonstrating that keeping patients on treatment until disease progression improves outcomes. Both these papers come from CA046, a randomised controlled trial."	Factual Inaccuracy: There is RCT evidence to support the dose reductions and dose omissions that are commonly required when treating patients with Nab-Pac+Gem. The CA046 study accurately reflects the dose modifications and omissions that may be seen in clinical practice. Additionally, there is specific guidance in the SmPC for Abraxane about how to dose modify and omit doses in the context of specific clinical scenarios. Therefore, this comment in the ERG is misleading.	This is clinical advice, not a factual error, no change made.

Issue 14 The use of Gem+Cap

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 25 the ERG state the following regarding the use of gemcitabine: "It may be used in patients with bulky symptomatic disease who are not fit for treatment with FOLFIRINOX"	This sentence should be removed and replaced with the following statement: "No European clinical guidelines recommend the use of Gem+Cap and there is no single RCT demonstrating that this regimen demonstrates a statistically significant benefit over standard of care (gem), therefore there is no defined patient population for whom this regimen will be used and its use across the	Factual Inaccuracy: The statement that Gem+Cap may be used in patients with bulky disease is factually inaccurate as there is no evidence from any clinical guideline to back this statement up.	This is clinical advice, not a factual error, no change made.

	NHS is restricted to very few centres."		

Issue 15 Cross-trial comparisons between the Conroy study and CA046

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 26 the ERG state the following: "The ERG notes that the baseline characteristics of the patient populations recruited to the key trials of Nab-Pac+Gem (CA046[11,12]) and FOLFIRINOX (Conroy[7]) are very similar." On page 27 the ERG provide a table comparing the patient populations in the CA046 trial and in the Conroy 2011 trial.	Further information should be added to contextualise this data and reflect the fact that cross-trial comparisons must be interpreted with caution: On page 26 we propose the following amend: "The ERG notes that the baseline characteristics of the patient populations recruited to the key trials of Nab-Pac+Gem (CA046[11,12]) and FOLFIRINOX (Conroy[7]) are very similar. The ERG notes that cross-trial comparisons should be treated with caution. In addition, it is acknowledged that there are several differences between the patient populations in the Conroy and CA046 trial. These include the fact that patients included in the Conroy trial had to be ECOG PS 0 or 1 and aged ≤75 years. The CA046 trial did not have these restrictions and there were patients with a worse performance status and/or aged ≥ 75 years included in the trial. It is also noted that CA046 was an international trial with approximately 2.5 times more patients than the Conroy trial which was a single country trial."	<u>Caution with cross-trial comparison</u>: It must be noted that cross-trial comparisons should be interpreted with caution. We request that wherever the ERG has conducted cross-trial comparisons that the statement be added to interpret them with caution as it can be misleading. There a several differences between these trials which must be highlighted patient populations in the CA046 and Conroy trial and these must be highlighted as it is factually inaccurate to say they are 'very similar'.	This is not a factual error, no change made.

	On page 27 we propose the following amend: "Table 1 Comparison of patient populations in the CA046 trial and in the Conroy 2011 trial (cross trial comparisons must be interpreted with caution)"		

Issue 16 Patients in the CA046 study who would be eligible for treatment with FOLFIRINOX

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 26 the ERG state the following: "Clinical advice to the ERG is that many of the patients recruited to the CA046 trial would have been suitable for treatment with FOLFIRINOX."	Further information should be added to reflect the views of the expert advice added to the company from 7 clinical experts in the field of pancreatic cancer: Clinical advice to the ERG is that some of the patients recruited to the CA046 trial would have been suitable for treatment with FOLFIRINOX. The company submission notes clinical advice obtained from 7 clinical experts in the field of pancreatic cancer whom suggested that between 25-33% of patients included in the CA046 trial would be suitable for treatment with FOLFIRINOX (if it had been available and the data from the Conroy trial known at the time of the CA046 trial). The group of expert clinicians also advised that patients deemed suitable for FOLFIRINOX will still receive this, regardless of the availability of Nab-Pac+Gem. The efficacy of the CA046 study is not likely to be driven by the patients who would have	<u>Misleading statement:</u> It is incorrect to state that 'many' of the patients enrolled in the CA046 study would have been suitable for FOLFIRINOX. A sentence should be added to reflect the advice obtained by the company from 7 expert clinicians in the field of pancreatic cancer to add clarity regarding the percentage of patients in the CA046 trial who would have been suitable for treatment with FOLFIRINOX. Also, to clarify that a group of 7 expert clinicians have advised that patients deemed suitable for FOLFIRINOX will still receive it regardless of the availability of Nab-Pac+Gem.	This is clinical advice, not a factual error, no change made.

	received FOLFRINOX, as the patients with poorer performance status and more co-morbidities benefited more from treatment than the 'fitter' patients in the CA046 study. The ERG states this in their report (Page 57: The company highlights that patients with more advanced disease generally benefited from treatment with Nab-Pac+Gem more than patients with less advanced disease, i.e., patients with poorer KPS (70-80), patients with >3 metastatic sites, and patients with elevated CA19-9 levels) Therefore, the incremental efficacy in the CA046 study is being driven by the patients more likely to receive Nab-Pac+Gem in clinical practice.		

Issue 17 Patients suitable for treatment with FOLFIRINOX

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27 of the ERG state the following: "The Committee considered that either FOLFIRINOX or Nab-Pac+Gem could be offered to patients who have serum bilirubin levels of less than 1.5 times the upper limit of normal and are of good PS (ECOG 0 or 1)."	Addition of the second paragraph to clarify the data so it reads as follows: "The Committee considered that FOLFIRINOX could be offered to patients who have serum bilirubin levels of less than 1.5 times the upper limit of normal and are of good PS (ECOG 0 or 1). The Committee considers that Nab-Pac+Gem could be offered to patients who have serum bilirubin levels of less than 1.5 times the upper limit of normal and have a ECOG PS of 0-1, or 2 if caused by high disease burden. There are	<u>Inconsistency with clinical advice:</u> The company would like to note that this statement is contrary to the expert clinical advice that the company has received. Advice provided to the company from 7 expert clinicians in the field of pancreatic cancer in the UK is that patients deemed suitable for FOLFIRINOX will still receive it regardless of the availability of Nab-Pac+Gem. Therefore, FOLFIRINOX is not a relevant comparator as it	For clarity, the text has been amended as follows: The Committee considers that Nab-Pac+Gem could be offered to patients who have serum bilirubin levels of less than 1.5 times the upper limit of normal and have a ECOG PS of 0-1, or 2 if caused by high disease burden.

	patients who would be fit for Nab-Pac+Gem who would not be able to tolerate treatment with FOLFIRINOX. Advice sought by the company from 7 expert clinicians notes that 25-33% of patients included in the CA046 trial would be suitable for treatment with FOLFIRINOX should it have been available and the data from the Conroy trial known at the time of the CA046 trial. In addition, the group of 7 expert clinicians also advised that patients deemed suitable for FOLFIRINOX will still receive it regardless of the availability of Nab-Pac+Gem."	will not be displaced by the availability of Nab-Pac+Gem.	

Issue 18 Market research data presented by the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 28 of the ERG report states the following: "The ERG notes that data presented by the company (CS, Figure 2) indicate an increasing trend towards the use of FOLFIRINOX in Europe between Q4 in 2014 and Q4 in 2015 xxxxxxxxxxx. The trend in the European data could suggest that the use of FOLFIRINOX in the UK might have also increased during	The ERG notes that data presented by the company (CS, Figure 2) indicate an increasing trend towards the use of FOLFIRINOX in Europe between Q4 in 2014 and Q4 in 2015 xxxxxxxxxxx. Please add the following information to contextualise this statement: "The use of FOLFIRINOX in the UK increased from xxxxxxxxx in this time. Additionally, the use of modified FOLFIRINOX also increases. The company notes that the total FOLFIRINOX use (modified and full-dose) was xxx in the UK and the total FOLFIRINOX use (modified and	Misleading speculation: There is no evidence to support the suggestion that the European data "could suggest that the use of FOLFIRINOX in the UK might have also increased during 2015 (given the increasing experience of clinicians with administering FOLFIRINOX) and that the plateau in the usage of FOLFIRINOX in the UK may reflect some displacement by the use of Nab-Pac+Gem." The wording should be replaced with the	This is not a factual error, the text has been reworded as follows: The ERG notes that data presented by the company (CS, Figure 2) indicate an increasing trend towards the use of FOLFIRINOX in Europe between Q4 in 2014 and Q4 in 2015 xxxxxxxxxxx. [redacted]

2015 (given the increasing experience of clinicians with administering FOLFIRINOX) and that the plateau in the usage of FOLFIRINOX in the UK may reflect some displacement by the use of Nab-Pac+Gem."	full-dose) was xxx in Europe which is fairly similar and it should also be noted that the use of Nab-Pac+Gem in Europe is higher than in the UK. Additionally, the increase in use of Nab-Pac+Gem of xxx corresponds to an almost identical decrease in the use of Gem. As advice sought by 7 expert clinicians in the field of pancreatic cancer states that the availability of Nab-Pac+Gem will only displace Gem, it seems likely that Nab-Pac+Gem use accounts for this decrease in Gem use. "	amendment shown.	

Issue 19 5-year survival rate

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 29 (Table 5) of the ERG report: 5-year survival rate for 2005-2009 (England) noted as 4%	Data report that less than 4% survived to 5 years; therefore, this should be reported as <4%.	Factual inaccuracy	Thanks, this is a factual error. The data in Table 5 have been corrected as suggested by the company.

Issue 20 Include evidence levels for NCCN and ASCO guidelines

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 30 and 31 of the ERG report cites the key recommendations from the ESMO, ASCO and NCCN guidelines.	Add the levels of evidence/strength of recommendations as per the guidelines to add context for each recommendation: "The following treatment options should be considered for the treatment of patients with	<u>Contextualising weight of evidence:</u> The company would request that the evidence levels for the recommendations are added so that the strength of the	This is not a factual error, no change made.

	metastatic pancreatic cancer according to their general status: • If the ECOG PS of the patient is 0 or 1 and the bilirubin level is below 1.5 x ULN, two types of combination chemotherapy: the FOLFIRINOX regimen or the combination of Nab-Pac+Gem should be considered [Level of evidence I,A] • For patients with ECOG PS of 2 and/or bilirubin level higher than 1.5 x ULN, monotherapy with Gem could be considered [Level of evidence I,A] • In very selected patients with ECOG PS 2 due to heavy tumour load, Nab-Pac+Gem can be considered for best chance of response [Level of evidence II,B] • For patients with ECOG PS of 3/4 with significant morbidities and very short life-expectancy, only symptomatic treatment can be considered" "Key treatment recommendations for first-line therapy: • FOLFIRINOX is recommended for patients who meet all the following criteria: ECOG PS 0/1, favourable comorbidity profile, patient preference and support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services [Evidence quality: intermediate; Strength of recommendation: strong] • Nab-Pac+Gem is recommended for patients	recommendations are put into context. It is misleading to quote evidence from guidelines without listing the strength of the evidence stated.	

	who meet all the following criteria: ECOG PS 0/1, relatively favourable comorbidity profile, patient preference and support system for relatively aggressive medical therapy [Evidence quality: intermediate; Strength of recommendation: strong] • Gem alone is recommended for patients who have either an ECOG PS 2 or a comorbidity profile that precludes more-aggressive regimens and who wish to pursue cancer-directed therapy. The addition of either capecitabine or erlotinib to gemcitabine may be offered in this setting [Evidence quality: intermediate; Strength of recommendation: moderate] • Patients with an ECOG PS ≥3 or with poorly controlled comorbid conditions despite ongoing active medical care should be offered cancer-directed therapy only on a case-by-case basis. The major emphasis should be on optimising supportive care measures. Evidence quality: intermediate; Strength of recommendation: moderate" Preferred first-line therapy for patients with good PS (defined as ECOG PS 0/1 with good pain management, patent biliary stent, and adequate nutritional intake): • Clinical trial • FOLFIRINOX (category 1) • Nab-Pac+Gem (category 1) FOLFIRINOX should be limited to patients with ECOG PS 0/1; Nab-Pac+Gem is reasonable for		

	patients with KPS ≥70 Other first-line therapy options for patients with good PS: • Gemcitabine plus erlotinib (category 1) • Gemcitabine-based combination therapy • Gemcitabine monotherapy (category 1) • Capecitabine or continuous infusion 5-FU (category 2B) • Fluoropyrimidine plus oxaliplatin (category 2B) First-line therapy options for patients with poor PS: • Gemcitabine (category 1) • Palliative and best supportive care		

Issue 21 Adverse event profiles of Nab-Pac+Gem and FOLFIRINOX

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 32 the ERG report states the following: "Nab-Pac+Gem and FOLFIRINOX have similar AE profiles and both treatment regimens require dose reductions	Proposed amendment to clarify data: "Cross-trial comparisons between trials must be interpreted with caution. Nab-Pac+Gem and FOLFIRINOX treatment regimens require dose reductions and modifications in managing the AEs. The AE profiles of the two treatments	<u>Factual Inaccuracy:</u> It is incorrect to say that Nab-Pac+Gem has a similar AE profile to FOLFIRINOX when the incidence for seven of the ten reported grade ≥ 3 adverse events is higher in the	This is clinical advice, not a factual error, no change made.

and modifications in managing the AEs.”	differ with FOLFIRINOX generally being considered the more toxic regimen as it is three chemotherapy agents plus leucovorin compared to Nab-Pac+Gem which is a doublet chemotherapy treatment. Additionally, the report from the previous NICE committee meeting states *“the Committee heard from the clinical expert that the adverse effects of nab-paclitaxel, although serious, were mainly manageable, and its adverse event profile was better than FOLFIRINOX.”* Specifically, FOLFIRINOX is associated with a 45.7% rate of neutropenia and a 5.4% rate of febrile neutropenia, with a 33% rate of neutropenia and no febrile neutropenia reported in the CA046 study with Nab-Pac+Gem. There is also more diarrhoea (12.7% vs 6% in CA046) and vomiting (14.5% vs 6% in CA046) reported in the FOLFIRINOX clinical trial compared to the Nab-Pac+Gem study. There is more peripheral neuropathy reported in the Nab-Pac+Gem study compared to the FOLFIRINOX clinical trial (17% in CA046 vs 9%), however, a substantial proportion of the peripheral neuropathy in the CA046 study was reversible (in contrast to the peripheral neuropathy seen with FOLFIRINOX) and the median time to improvement from grade 3 to grade 2 was 21 days and to grade 1 or resolution of the event was 29 days. Of the patients who had grade 3 peripheral neuropathy, 44% resumed treatment at a reduced dose of nab-paclitaxel within a median of 23 days after the onset of a grade 3 event.”	Conroy trial than the CA046 trial. Additionally, this contradicts the opinion of the clinical expert that NICE accepted in the previous NICE submission (*“the Committee heard from the clinical expert that the adverse effects of nab-paclitaxel, although serious, were mainly manageable, and its adverse event profile was better than FOLFIRINOX”*).	

Issue 22 Systematic literature review population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 40 (Table 10) the ERG report states the following: "Population – changed from people with previously untreated metastatic adenocarcinoma of the pancreas to APC patients, of whom at least 50% patients with metastatic pancreatic cancer and must not have had prior systemic therapy for metastatic disease."	This is an incorrect interpretation of the eligibility criteria. Proposed amendment to clarify: Population – changed from studies of APC patients, of whom at least 50% had metastatic disease and were potentially eligible for first-line therapy for metastatic disease to studies of APC patients, of whom at least 50% had metastatic disease and who had received no prior systemic therapy for metastatic disease.	Factual Inaccuracy: The ERG statement is incorrect. To aid clarity, the description of the population looked at in the systematic literature review should be amended as per the proposed text.	For clarity, text in Table 10 has been amended as suggested.

Issue 23 CA046 not CA042

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 49 the ERG report states the following: "4.2.5 Risk of bias assessment for the CA042 trial"	Proposed amendment to correct the inaccuracy: 4.2.5 Risk of bias assessment for the CA046 trial	Factual Inaccuracy: It is a factual inaccuracy to state CA042 when the trial being referred to is CA046 therefore the company requests that this is changed to CA046.	This is a typographical error, the text has been corrected as suggested by the company.

Issue 24 Peripheral neuropathy and use of the term rapidly reversible

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 60 of the ERG report: "The company reports that peripheral neuropathy was rapidly reversible with treatment interruption and that the median time to improvement to Grade 1 severity was 29 days" Also on page 60 of the ERG report: *"The company states (CS, p109) that the majority of cases of Grade ≤3 neuropathy could be reversed and managed by delaying further treatment or reducing the dose until the condition improved to Grade ≤1."*	While data on the median time to improvement from Grade 3 to Grade ≤1 is reported (29 days), the company do not use the terminology 'rapidly reversible'. Please remove this statement, or replace with a more accurate interpretation: *"Data shows the median time to improvement from Grade 3 to Grade ≤1 peripheral neuropathy was 29 days."* Data is presented to show that 43% of Grade 3 peripheral neuropathy events were improved to Grade ≤1 with dose modifications, the statement referred to in the ERG report is not made. Proposed amendment to clarify data: *"The company presents data (CS, p109) that shows 43% of cases of Grade 3 peripheral neuropathy could be reversed and managed by delaying further treatment or reducing the dose until the condition improved to Grade ≤1."*	Factual inaccuracy	For clarity, the text has been amended as follows: "The company reports that peripheral neuropathy was [redacted] reversible with treatment interruption and that the median time to improvement from Grade 3 to Grade ≤1 severity was 29 days"

Issue 25 Treatment to progression

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61 of the ERG report states the following: "Clinical advice to the ERG is that patients who benefit most from Nab-Pac+Gem are more likely to stay on treatment for longer with the resultant cumulative toxicity requiring dose reduction or delay. Patients with resistance or early disease progression are likely to discontinue treatment before dose modification is needed and would inevitably have poorer survival."	Addition of proposed text in the second paragraph to clarify the data: However, data from the CS suggests that dose reductions and modifications help patients to stay on treatment for longer. Data from the CS from an exploratory analysis of the CA046 trial which shows that patients treated to progressive disease rather than unacceptable adverse events had a longer overall survival compared to Gem (median, 9.8 vs 7.5 months; P < 0.001) which highlights the importance of managing adverse events for patients receiving Nab-Pac+Gem according the dose modification/dose delay guidance in the Summary of Product Characteristics. The dose modification/dose delay analysis paper by Scheithauer et al on the CA046 trial supports dose modification/dose delay to keep patients on treatment until the disease progresses. This analysis suggests that dose modification helps patients to stay on treatment for longer.	<u>Misleading speculation:</u> It is misleading to speculate the reasons for why patients do not receive dose modifications. It is important to include evidence from the CA046 trial so that the clinical advice can be contextualised. Data from the CA046 study suggests that dose modifications or delays help patients to remain on treatment and therefore have better outcomes.	This is clinical advice, not a factual error, no change made.

Issue 26 Adverse events in SIEGE

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 62 of the ERG report states the following: "In comparison to the CA046 trial, the overall proportion of patients in the SIEGE trial[28] who experienced Grade ≥3 AEs was similar (89% versus 82% respectively). The rates of specific Grade ≥3 AEs reported by patients in the SIEGE trial[28] were also similar to, or lower than, rates reported in the CA046 trial. However, 5.4% of patients in the SIEGE trial[28] experienced sepsis, whilst no cases of sepsis were reported in the CA046 trial.	Please add a statement to contextualise this statement: It is suggested by the authors of the SIEGE study that the increased rate of sepsis may be related to a reduced use of G-CSF in the SIEGE trial compared to the CA046 study and the recommendations in the Summary of Product Characteristics.	Misleading Statement: It is important that we quote the opinions of the SIEGE authors on the reason for the increased rate of sepsis seen in SIEGE compared to CA046.	This is not a factual error, no change made.

Issue 27 Number of posters by Giordano regarding the Italian real world data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 62 of the ERG report states the following: "The only data available from the retrospective study of elderly patients (n=208) treated in Italian centres are from a poster	Proposed amendment to clarify data: Data available from the retrospective study of elderly patients (n=208) treated in Italian centres are from two posters presented at the 2015 ESMO conference. At ASCO 2016 an updated data set was presented where 221	Factual Inaccuracy: The company submission refers to three poster presentations regarding the Italian real world data set: two posters were presented at ESMO 2015 and the third poster	This is a factual error. Text has been reworded as suggested by the company.

presentation given at the 2015 ESMO conference"	patients were eligible for the analysis.	was presented at ASCO 2016.	

Issue 28 Standard of care

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 72 of the ERG report states the following: "the company considers that (i) FOLFIRINOX and Gem+Cap are not standards of care in the NHS and (ii) the introduction of Nab-Pac+Gem for use in the NHS will not displace the use of either of these comparators"	Proposed amendment to clarify data: "The company considers that (i) Gem+Cap is not a standard of care in the NHS due to a lack of positive phase III RCT evidence demonstrating a benefit over standard of care and thus it is therefore used in very few centres. FOLFIRINOX is acknowledged as a standard of care for younger, very fit patients, although many different non-standardised modified versions are often used with no phase III RCT evidence to support efficacy. Moreover, 7 expert clinicians in the field of pancreatic cancer have advised the company patients whom are suitable to receive FOLFIRINOX will continue to receive it despite the availability of Nab-Pac+Gem, thus it is not a standard of care for the patient population whom Nab-Pac+Gem is appropriate for and as a result (ii) the introduction of Nab-Pac+Gem for use in the NHS will not displace the use of either of these comparators."	<u>Factual Inaccuracy:</u> The company has been advised by 7 expert clinicians in the field of pancreatic cancer that patients who are suitable for FOLFIRINOX will still receive it regardless of the availability of Nab-Pac+Gem therefore it is not a standard of care for the patient population who Nab-Pac+Gem would be appropriate for. Gem+Cap is not a standard of care due to the limited evidence base it is not routinely used throughout the UK.	The text has been amended as follows: • the company considers that (i) [redacted] Gem+Cap is not a standard of care in the NHS and (ii) the introduction of Nab-Pac+Gem for use in the NHS will not displace FOLFIRINOX

Issue 29 Limited evidence base for Gem+Cap not FOLFIRINOX

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 81 of the ERG report states the following: "The company considers Gem as the main comparator to Nab-Pac+Gem in the economic analysis with Gem+Cap and FOLFIRINOX considered only as secondary comparators due to a limited evidence base for these treatments in a UK clinical setting."	Proposed amendment to clarify data: "The company considers Gem as the main comparator to Nab-Pac+Gem in the economic analysis with Gem+Cap and FOLFIRINOX considered only as secondary comparators. FOLFIRINOX is secondary comparator as the company have been advised by a group of 7 expert clinicians in the field of pancreatic cancer that patients who are suitable for FOLFIRINOX will still receive it regardless of the availability of Nab-Pac+Gem therefore the availability of Nab-Pac+Gem will not displace FOLFIRINOX and it is not a relevant comparator. Gem+Cap is considered a secondary comparator due to a limited evidence base (there is no single positive phase III randomised control trial) for this regimen and as a result this treatment is not uniformly used across the UK in a clinical setting and it is therefore not a relevant comparator."	<u>Factual Inaccuracy:</u> The company states the current evidence base for Gem+Cap is limited as there is no single positive phase III randomised control trial to support the use of this regimen. The company does *not* state that there is a limited evidence base for full dose FOLFIRINOX (although there is for 'modified' FOLFIRINOX, which is not a standard regimen and has no RCT evidence to demonstrate efficacy). The company acknowledges that there is a positive phase III trial for full dose FOLFIRINOX. The company has been advised by 7 expert clinicians in the field of pancreatic cancer that patients who are suitable for FOLFIRINOX will still receive it regardless of the availability of Nab-Pac+Gem, therefore it is not a relevant comparator. Neither is Gem+Cap, as due to the limited evidence base it is rarely used.	The text has been amended as follows: The company considers Gem as the main comparator to Nab-Pac+Gem in the economic analysis with Gem+Cap and FOLFIRINOX considered only as secondary comparators [redacted]

Issue 30 Addition of Hazard Ratios to confidence intervals

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 105 of the ERG report has table 42 which states the HR without the confidence interval	Please add an additional column with the confidence intervals for each hazard ratio stated	Misleading statement: The Hazard ratios should not be referenced without stating confidence intervals especially when some of the quoted hazard ratios are not statistically significant.	Confidence intervals for hazard ratios have been added to Table 42.

Issue 31 Re-estimation of AE costs in the model by the ERG

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 108-9 the ERG states the following: "The ERG has… re-estimated the resource cost used in the model for some AEs" Specifically, (on page 111-2): Neutropenia is changed from 'Admitted patient care, HRG code: XD25Z' to 'Outpatient, HRG code: XD25z' Leukopenia is 'as per CS', however as the ERG has changed the cost of	Please justify this change in codes – there is no explanation as to why the ERG considers this code more appropriate. Please keep CS estimate. This overestimates the cost of leukopenia with no explanation as to why the cost is increased. It would be more appropriate to keep this as £97.29 as in the CS	Applying increased AE charges: AE costs have been changed without justification for changes. Some changes result in inappropriate costings for AEs, which is a factual inaccuracy. Factual Inaccuracy: It is factually inaccurate to state that leukopenia would cost the same as neutropenia at this increased cost.	These costs are based on clinical advice, not a factual error. For clarity, the text has been amended as follows: The ERG has investigated the sensitivity of the ICERs per QALY gained to the estimates of AE costs used in the model. The ERG has made these amendments based on the mean duration of AEs in the CA046 trial, reference to published sources[68-70] and discussions with a clinical expert. The most substantial increases in the ERG estimates of AE costs versus the company's estimates [redacted] are for diarrhoea, dehydration and vomiting. The ERG notes from Table 14 and Table 15 of the company's clarification response that patients in both arms of the CA046 trial reported mean durations of Grade ≥3 diarrhoea, dehydration and vomiting between

neutropenia, this makes the cost of leukopenia now £136.61 Dehydration has changed from 'Non-elective inpatient short stay, HRG code: KC05H with a cost of £808.64' to 'Non-elective inpatient long-stay, HRG code: KC05H with a cost of £3,368.32' Abdominal pain is changed from 'Non-elective inpatient short stay, HRG code: FZ90A with a cost of '£1,124.81' to 'Non-elective long stay, HRG code: FZ90A with a cost of £2,407.05' Diarrhoea is changed from 'day case at a cost of £379.38' to 'Non-elective inpatient long stay, HRG code: KC05H at a cost of £3,368.32' The cost of vomiting is increased from £379.38 to £3,368.32 as it is assumed to be the same as diarrhoea Hyperbilirubinemia is changed to 'Assume the	Keep the CS estimate of £808.64 Keep the CS estimate of £1,124.81 Keep the CS estimate of £379.38. Keep the CS estimate of £379.38 Keep the CS estimate of £435.22	It is factually inaccurate to state that all dehydrated patients will be admitted for two or more days. Many receive IV rehydration and are discharged on the same day. It is factually inaccurate to state that all patients with abdominal pain will be admitted for two or more days. Many will be discharged the same day after investigations and treatment. It is factually inaccurate to assume that all patients with diarrhoea will be admitted to hospital for 2 or more days. Many will be managed as an outpatient or discharged the same day after management. It is factually inaccurate to assume that all patients with vomiting will be admitted to hospital for 2 or more days. Many will be managed as an outpatient or discharged the same day after management. It is factually inaccurate to treat cholangitis (inflammation of the gall-bladder from unknown causes) the same as hyperbilirubinemia, which	5.57 and 11.81 days. The ERG notes that Grade ≥3 AEs are generally considered severe enough to require hospitalization. [https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf]. This information, combined with the mean duration of the events in the CA046 and supported by clinical advice, indicates that patients with Grade ≥3 diarrhoea, dehydration or vomiting would be most appropriately treated by an overnight stay in hospital (non-elective inpatient long stay). However, the company has assumed that patients with Grade ≥3 diarrhoea, dehydration and vomiting would not stay overnight in hospital (non-elective inpatient short stay or day case). Table 44 gives the definitions of the relevant NHS admission types used in the costing of AEs. Other increased costs in the ERG's scenario analysis versus the company base case are for treating: neutropenia and leukopenia (changed from admitted patient care to outpatient treatment, based on clinical advice); abdominal pain (changed from non-elective inpatient short stay to long stay and including interventions, based on clinical advice); and hyperbilirubinemia (changed from a specific costing to assuming same cost as cholangitis, based on clinical advice). Decreased costs in the ERG's scenario analysis versus the company base case are for treating: thrombocytopenia (changed from non-elective inpatient short stay to day case, based on clinical advice); pulmonary embolism (source of company cost not clear, so changed to non-elective short stay based on clinical advice); cholangitis (changed from 5x excess bed days to an HRG code that includes interventions, based on

same as cholangitis'		is simply an increase in the level of bilirubin in the blood. This is likely be related to the patients underlying disease, and as such often does not require admission at all. Clinical experts have not advised that this condition requires admission (UK Advisory board), therefore it is inappropriate to treat this condition the same as cholangitis.	clinical advice). Table 45 compares the AE costs used in the company base case versus the costs used by the ERG in its scenario analysis. Table 44 has been amended for clarity.

Issue 32 Gem+Cap no single positive phase III randomised control trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 149 of the ERG report states the following: "For Gem+Cap versus Nab-Pac+Gem, there is no evidence to suggest a difference between these two treatments in terms of OS." "For Gem+Cap versus Nab-Pac+Gem, no statistically significant differences were observed between the treatments	Proposed amendments to clarify the statements on this page: "For Gem+Cap versus Nab-Pac+Gem, there is no evidence to suggest a difference between these two treatments in terms of OS. The ERG acknowledges that there is no single positive phase III randomised control trial for Gem+Cap." "For Gem+Cap versus Nab-Pac+Gem, no statistically significant differences were observed between the treatments for PFS by	<u>Failure to contextualise data:</u> To contextualise the statements made by the ERG it should be made clear that there is no positive randomised control phase III trial for Gem+Cap whereas there is a positive phase III trial for Nab-Pac+Gem.	Text has been amended as suggested by the company.

for PFS by either independent or investigator assessment."	either independent or investigator assessment. The ERG acknowledges that there is no single positive phase III randomised control trial for Gem+Cap."		

Issue 33 ERG sets QALYs accrued in first cycle to 0

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG argues that since treatments are administered at the beginning of each cycle, in the first cycle treatment costs should be accrued but no benefits (LYs) should be accrued	The company suggests that 2 alternatives are appropriate. First to adopt the original approach and assume both costs and benefits are accrued in the first cycle. Or to assume no costs and benefits are assumed in the first cycle and that only at the end of cycle 1 are costs and QALYs calculated.	While not applying half-cycle correction would overestimate the benefits accrued as a proportion of patients either die or progress. To assume no benefits are accrued would be an underestimation of the benefits accrued in the first cycle	This is not a factual error, no change made.

Issue 34 ERG questioning of Devlin method to calculate utility values

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 107 the ERG states "The ERG considers the UK-adjusted Romanus59 and SIEGE crosswalk58 values to be more appropriate than the SIEGE Devlin57 values."	Amend to: "There are limitations with all the potential approaches (and therefore uncertainty with each). For example, when using values derived from the cross walk approach there is uncertainty as regards the mapping of the EQ-5D-5L responses to their most likely EQ-5D-3L	It is misleading to disregard the Devlin methodology used; this method offers an alternative approach to calculating utilities which is important due to the considerable uncertainties associated with the other approaches. With the ERG's	This is not a factual error. Text has been amended for completeness as follows: Page 108 Applying the switch in the company model to use the SIEGE Devlin57 utility values

	equivalents. Similarly, when using the Romanus data there is uncertainty when attempting to adjust for differences between US and UK preferences concerning quality versus length of life. It therefore appropriate that the values derived from each of the three approaches are considered given: (i) the different sources of uncertainty associated with each of the three; (ii) the 2013 Methods guide implies both 5L and 3L may be acceptable as a reference case (taken from 2013 reference guide and DSU report); and (iii) the distribution of the preference weight values from the EQ-5D-5L face fewer issues than those typically derived from the EQ-5D-3L (i.e. the preference weights derived from the EQ-5D-3L are typically bimodal and show evidence of a ceiling effect) (from DSU report)."	preferred base case and using the Devlin based utilities the ICER vs. gem monotherapy is £38,473/QALY	instead of the base case UK-adjusted Romanus utility values would decrease the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem by £3,230 to £43,780.

Issue 35 Non-PAS ICER should be CiC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 95 the non-PAS ICER should be marked as CiC	On page 95 the non-PAS ICER should be marked as CiC	The non-PAS ICER is CiC	Text has been amended as suggested by the company.

Issue 36 Description of "Error is calculation of LY and QALYs"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 97, table 40. The ERG states "Error in calculation of total LY and QALYs"	The company suggests alternative wording to reflect the fact that this is not an error; rather it is subjective opinion	This is not an error; rather it is subjective opinion	The text has been amended as follows:

			Section 1.6, page 15 The ERG has amended one structural feature in the calculation of total LYs and QALYs. Table 40 Overestimation of total LY and QALYs Section 6, page 109 Before incorporating any ERG amendments into the company model, the ERG has amended a structural feature in the company model namely:

(please cut and paste further tables as necessary)

ID1058 STA ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 14/90/01

Erratum completed 16 June 20167

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The company identified 36 overall issues in relation to factual inaccuracies in the original Evidence Review Group (ERG) report. Not all were considered by the ERG to be factual inaccuracies but some were considered to require minor changes to the text. The pages of the ERG report that have been affected are presented here. Please note:

- Additional or replacement text added by the ERG is highlighted in grey
- Text deleted completely (as opposed to being reworded) is blacked out (for example, [redacted]).

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the Single Technology Appraisal (STA) process. Clinical evidence and economic evidence have been submitted to NICE by Celgene Limited in support of the use of paclitaxel as albumin-bound nanoparticles (Abraxane®) with gemcitabine (Gem) for untreated metastatic adenocarcinoma of the pancreas. In this report, the formulation of paclitaxel as albumin-bound nanoparticles is referred to as Nab-Pac and the combination treatment is referred to as Nab-Pac+Gem.

Nab-Pac is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. [redacted]

The ERG notes that the appraisal under discussion in this report is an update of existing NICE guidance, TA360, published in October 2015. In TA360, NICE did not recommend the use of Nab-Pac+Gem as a treatment for previously untreated metastatic adenocarcinoma of the pancreas. The TA360 final appraisal determination (FAD) is available on the NICE website and a summary of the key points from the FAD and subsequent appeal is presented in Appendix 1 of this ERG report.

1.2 Critique of the decision problem in the company's submission

1.2.1 Population

The population described in the final scope issued by NICE is the same as the population recruited to the CA046 trial and discussed in the company submission (CS), i.e. patients with previously untreated metastatic adenocarcinoma of the pancreas.

Although 47% of all cases of pancreatic cancer are diagnosed in people aged ≥75 years, only 10% (n=84) of the patients recruited to the key trial (CA046) were aged ≥75 years. This means that the outcomes of the CA046 trial may not represent the outcomes of a substantial proportion of patients in the NHS who are diagnosed with metastatic adenocarcinoma pancreatic cancer.

1.2.3 Comparators

The comparators specified in the final scope issued by NICE are Gem, Gem+Cap and a combination treatment consisting of four therapies known as FOLFIRINOX.

Gemcitabine

Direct clinical evidence is available for the comparison of the effectiveness of Nab-Pac+Gem versus Gem from the CA046 trial.

Gemcitabine+Capecitabine and FOLFIRINOX

In the absence of direct evidence for the comparison of Nab-Pac+Gem versus Gem+Cap or versus FOLFIRINOX, the company has conducted network meta-analyses (NMAs).

Gem+Cap and FOLFIRINOX are not licensed in the UK for the treatment of metastatic pancreatic cancer. As the components of both Gem+Cap and FOLFIRINOX are available as generics, there is no single company with an interest in supporting the use of either Gem+Cap or FOLFIRINOX. The use of Gem+Cap and FOLFIRINOX is not uniform across the NHS.

The company considers that Gem is the only valid comparator to Nab-Pac+Gem.

Outcomes

Direct evidence is available from the CA046 trial for the outcomes of overall survival (OS), progression-free survival (PFS), time to progression (TTP), objective response rate (ORR) and AEs. Health-related quality of life (HRQoL) data were not collected during the CA046 trial. In the clinical section of the CS, the company presents data from the SIEGE trial, collected using the European Organisation for Research and Treatment Cancer (EORTC) Quality of Life questionnaire (QLQ-C30). The SIEGE trial is a [redacted] phase II study designed to explore different dosing schedules of Nab-Pac+Gem; the trial is now closed to recruitment and is continuing to report results. Similar data are also presented from a US-based retrospective cross-sectional study of patients with metastatic pancreatic cancer that included patients treated with Nab-Pac+Gem, reported by Picozzi.

Other considerations

- An agreed patient access scheme (PAS) is in place for nab-paclitaxel
- The company has not identified any equality issues
- The company has presented a case for Nab-Pac+Gem to be assessed against the NICE End of Life criteria.

1.3 Summary of clinical effectiveness evidence submitted by the company

Results from the CA046 trial

The results of the most recent analysis of OS data from the CA046 trial (data cut-off: 9 May 2013) show that treatment with Nab-Pac+Gem statistically significantly improves median OS in comparison to treatment with Gem (8.7 months versus 6.6 months; hazard ratio [HR]=0.72, 95% confidence interval [CI]: 0.62 to 0.83) in patients with a Karnofsky PS (KPS) ≥70. Improvement in OS with Nab-Pac+Gem compared with Gem was generally consistent across patient baseline characteristics. At the time of the primary efficacy analysis, compared with treatment with Gem, treatment with Nab-Pac+Gem was shown, by independent review and by investigator assessment, to statistically significantly improve PFS.

The most common Grade 3 or 4 AEs associated with treatment with Nab-Pac+Gem were neutropenia, fatigue, metabolism and nutritional disorders (dehydration and decreased appetite), peripheral neuropathy, thrombocytopenia and anaemia. Although these AEs were also associated with treatment with Gem (and Nab-Pac monotherapy outside of CA046), they occurred more frequently when patients were treated with Nab-Pac+Gem.

The company has presented early HRQoL results from the SIEGE trial within the clinical section of the CS. These data were collected using the EORTC QLQ-C30. The company reports that Global Health Scores (GHS) were generally stable throughout treatment; however, towards the end of the 6 treatment cycle period, data were difficult to interpret due to small patient numbers (n=22 in the concomitant Nab-Pac+Gem arm at Week 24).

In the absence of head-to-head clinical data that allow comparisons of the effectiveness of treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX, the company performed NMAs. Despite the fact that a connected network could be formed by including only trials that compared treatments relevant to the decision problem, the company base case network included seven trials that provided evidence for treatments that were not listed in the final scope issued by NICE. However, the company performed a sensitivity analysis using a reduced network (fixed effects) that included only the comparators listed in the final scope issued by NICE and the ERG considers the results from this analysis more valid than the company's base case NMA results. In terms of OS, the results from this sensitivity analysis mirror the results from the base-case analysis and do not suggest a statistically significant treatment effect for Nab-Pac+Gem versus Gem+Cap (HR=1.10, 95% credible

interval [CrI]: 0.67 to 1.84) or for Nab-Pac+Gem versus FOLFIRINOX (HR=0.77, 95% CrI: 0.58 to 1.01).

HRQoL data were not collected as part of the CA046 trial. Instead, the company adjusted the health state utility values reported by Romanus et al (2012) for use in a UK population. These adjusted values were used in the base case analysis for pre-progression (0.74) and progressive disease (0.67). The company used EQ-5D-5L data from the concomitant arm of the SIEGE trial (phase II, dose-scheduling trial of Nab-Pac+Gem) in separate scenario analyses.

The company submitted an updated model as part of the clarification response. The company's updated base case incremental cost effectiveness ratio (ICER) for the comparison of treatment with Nab-Pac+Gem versus Gem is £46,932 per quality adjusted life year (QALY) gained; treatment with Nab-Pac+Gem generates 0.144 additional QALYs at an additional cost of £6,755. For the comparison of treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX, Nab-Pac+Gem is more costly and generates fewer QALYs.

For the comparison of treatment with Nab-Pac+Gem versus Gem, the company carried out a wide range of deterministic sensitivity analyses. The results show that the most influential parameter is the treatment variable used to parameterise OS. All of the other parameters that were varied had a lower impact on the size of the ICERs per QALY gained.

The results of the company's probabilistic sensitivity analysis show that Nab-Pac+Gem has a 64% probability of being cost effective compared to Gem at a willingness to pay threshold of £50,000 per QALY gained.

1.6 Summary of the ERG's critique of submitted cost effectiveness evidence

The company's model is generally well structured and correctly implemented. The ERG has amended one structural feature in the calculation of total LYs and QALYs. The three key issues that require exploration by the ERG in the company's model are: HRs used for treatment with Gem+Cap and with FOLFIRINOX, costing of drugs and modelling of TOT.

The company uses HRs from the NMA to estimate time-to-event outcomes for treatment with Gem+Cap and with FOLFIRINOX, which rely on the PH assumption holding for PFS and OS within the CA046 trial. Since PH has been shown not to hold for PFS or OS in the CA046 trial, using the results of the NMA in the model produces unreliable estimates for OS, PFS and TOT for treatment with Gem+Cap and with FOLFIRINOX. The ERG also has concerns about the company's use of HRs with a stratified Gamma model. The ERG has used published HRs for treatment with Gem+Cap versus Gem and with FOLFIRINOX versus Gem

in the model to overcome the need for PH to hold in the CA046 trial; however, PH does not hold in the

- The company quotes data that show the median survival for patients with metastatic adenocarcinoma pancreatic cancer is less than 24 months
- Base case results generated by the company's economic model suggest that the mean difference in OS between patients treated with Nab-Pac+Gem versus Gem is 2.4 months

[redacted]

1.8 ERG commentary on End of Life criteria

The ERG agrees with the company that patients with metastatic adenocarcinoma of the pancreas have a life expectancy of less than 24 months.

An examination of the ERG's remodelled OS data suggests that treatment with Nab-Pac+Gem generates a mean survival gain of 2.44 months compared to Gem. When Nab-Pac+Gem is compared with Gem+Cap or FOLFIRINOX, the results from the company base case NMA show that there is no statistically significant OS gain from Nab-Pac+Gem.

Table 1 Summary of company overview of current service provision

Treatment	Licensed in Europe	NICE guidance	Treatment regimen	Available uniformly across NHS?	Available as a generic product?
Gem	Yes	TA25[3] (2001)	IV 1000mg/m^2 (30 min). Weekly for 7 weeks followed by a week of rest. Thereafter once a week on a 3-weekly cycle	Yes	Yes
Gem+Cap	No	N/A	Gem IV 1000mg/m^2 (30 min) once a week on a 3-weekly cycle. Capecitabine tablets 1666mg/m^2 daily on a 3-weekly cycle	No	Yes
FOLFIRINOX	No	N/A	Oxaliplatin, irinotecan, leucovorin and flurouracil (5-FU) administered via central line, Portacath or PICC line. • Oxaliplatin 85mg/m^2 (2 hrs) • Leucovorin 400mg/m^2 (2 hrs) • Irinotecan 180mg/m^2 (90 min) • 5-FU 400mg/m^2 administered by IV bolus, then as a continuous IV infusion of 2400mg/m^2 over 46 hrs every 2 weeks	No. Modified treatment regimens are used in some centres	Yes

5-FU= flurouracil; IV=intravenous; PICC=peripherally inserted central catheter
Source: CS, Section 3.3

Gemcitabine monotherapy

The company states (CS, p34) that in NICE guidance published in 2001 (TA25[3]), Gem is recommended as a first-line treatment for people with advanced or metastatic pancreatic cancer if they have a Karnofsky Performance Status (KPS) of 50 or more. The ERG agrees with the company that gemcitabine remains the only treatment currently recommended by NICE for metastatic pancreatic cancer.

Gemcitabine+capecitabine

The company reports (CS, p35) that Gem+Cap is not a licensed treatment regimen for metastatic pancreatic cancer and, as generic versions of gemcitabine and capecitabine are available, there is no single company with a commercial interest in promoting or supporting the use of this regimen.

Clinical advice to the company (CS, p35), and to the ERG, is that there is modest use of Gem+Cap in the NHS. The company's market research data (CS, p35 and Section 2.4 of this ERG report) suggest that XXXXX of patients with metastatic pancreatic adenocarcinoma who receive treatment in the NHS are likely to receive Gem doublet (likely to be Gem+Cap). Clinical advice to the ERG is that in the NHS, no more than XXXX of patients are treated with Gem+Cap.

Table 2 Proposed place of Nab-Pac+Gem in the treatment pathway with ERG comment

Treatment	Company proposed patient population	ERG comment
FOLFIRINOX	≤70 years ECOG PS 0 or 1 Minor co-morbidities (e.g. well controlled hypertension)	Clinical advice to the ERG is that in the NHS, FOLFIRINOX is used in patients who are ≥70 years if they have a PS of 0 or 1 and are aware of the potential side effects The company's market research shows that in the UK XXXXXXX of patients are treated with FOLFIRINOX
Gem	Any age ECOG PS ≥2	Agree
Nab-Pac+Gem	Any age (use in people aged over 80 years is supported by real-world evidence). ECOG PS 0 or 1 FOLFIRINOX treatment not suitable	The ERG notes that the SmPC for Nab-Pac includes a caution advising that there is no evidence of clinical efficacy of Nab-Pac+Gem in patients ≥75 years and that patients with pancreatic cancer who are aged ≥75 years should be carefully assessed for their ability to tolerate Nab-Pac+Gem with special consideration to performance status, co-morbidities and increased risk of infections. The company has not defined the patient population not suitable for treatment with FOLFIRINOX
Gem+Cap	Not discussed	Not in common usage in the NHS. May be used to treat patients with bulky symptomatic disease who are not fit enough for treatment with FOLFIRINOX The company's market research shows that in the UK XXXXXX of patients are treated with Gem doublet (likely to be Gem+Cap)

ECOG=Eastern Co-operative Oncology Group; PS=performance status
Source: CS, p34-35

The ERG notes that the baseline characteristics of the patient populations recruited to the key trials of Nab-Pac+Gem (CA046[11,12]) and FOLFIRINOX (Conroy[7]) are very similar (Table 3). The ERG also notes that median OS for patients treated with Gem in the CA046 and Conroy trials is comparable (6.8 months and 6.6 months, respectively), underlining the similarities between the trial cohorts and the difficulty in distinguishing between patients in the NHS who are suited to treatment with FOLFIRINOX and Nab-Pac+Gem. Clinical advice to the ERG is that many of the patients recruited to the CA046 trial would have been suitable for treatment with FOLFIRINOX.

Table 3 Comparison of patient populations in the CA046 trial and in the Conroy 2011 trial

Characteristic	CA046 Nab-Pac+Gem vs Gem N=861 n (%)	Conroy 2011 FOLFIRINOX vs Gem N=342 n (%)	
Median age (years)	63	61	
Male	502 (58)	105 (61)	
Performance status			
KPS		**ECOG**	
100	138/858 (16)	0	65 (38)
90	378/858 (44)	1	106 (62)
80	277/858 (32)	2	1 (0)
70	63/858 (7)		
60	2/858 (<1)		
Tumour location			
Head	371 (43)	65 (38)	
Body	268 (31)	56 (32)	
Tail	215 (25)	45 (26)	
Unknown	4 (1)	NR	
Multicentric	NR	6 (3)	
Number of metastatic sites n%			
1	54 (6)		
2	408 (47)	Median of 2 (range 1 to 6)	
3	276 (32)		
>3	123 (14)		

ECOG=Eastern Cooperative Oncology Group; KPS=Karnofsky performance status; NR=not reported
Source: CS, Table 11 and Conroy 2011 Table 1

The ERG notes that guidelines[13] published by the European Society for Medical Oncology (ESMO) provide advice for the use of Nab-Pac+Gem and FOLFIRINOX in the treatment of metastatic pancreatic cancer. In these guidelines[13] the ESMO Committee states that there are no data to support the use of Nab-Pac+Gem over FOLFIRINOX. The Committee considers that Nab-Pac+Gem could be offered to patients who have serum bilirubin levels of less than 1.5 times the upper limit of normal and have a ECOG PS of 0-1, or 2 if caused by high disease burden. The ESMO guidelines[13] also include the statement that treatment with Nab-Pac+Gem could be considered to treat 'very selected patients' with ECOG PS 2.

In the 2014 ERG report for TA360,[14] it was noted that the company was unable to identify a single 'optimal' subgroup of patients who were suitable for treatment with Nab-Pac+Gem and the ERG considers that the company has yet to clearly identify this 'optimal' subgroup.

2.4 *Impact of Nab-Pac+Gem on the use of Gem, Gem+Cap and FOLFIRINOX in the NHS*

To support the claim that, in NHS clinical practice, the use of Nab-Pac+Gem will only have an impact on the use of Gem (CS, p35-37), the company has provided the results of market research conducted by Kantar.[15]

The company describes the research[15] as being based on an audit of Europe and UK patient chart data. The ERG understands that the data were derived from XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXX. The company was unable to supply the source file for the market research when requested by the ERG (via the clarification process); the ERG is, therefore, unable to comment on the validity of the research, or to verify the results. However, the ERG notes that the presented data summarise the first-line treatments administered during each quarter (Q) of the audit year and the proportions of patients who received them. Data from the UK (Q2 2015 and Q4 2015) are shown in Table 4. The company states that during the 2015 data collection period, Nab-Pac+Gem was available via the Cancer Drugs Fund (CDF) in England and was recommended for use in Scotland in February 2015 and in Wales in October 2015.

The company reports that, in Q4, there was a XXXX increase in the number of patients treated with Nab-Pac+Gem compared with the number treated in Q2. The company highlights that this increase coincided with an XXXX decrease in patients treated with Gem. The use of FOLFIRINOX and Gem doublet (likely to be Gem+Cap) remained constant between Q2 and Q4.

The ERG notes that data presented by the company (CS, Figure 2) indicate an increasing trend towards the use of FOLFIRINOX in Europe between Q4 in 2014 and Q4 in 2015 XXXX). [redacted] The ERG also notes that the company did not provide any demographic information that would enable any comparison to be made between the patients who were treated with Nab-Pac+Gem and patients who were treated with FOLFIRINOX during 2015.

Table 4 Company market research data for first-line treatment of metastatic pancreatic adenocarcinoma in the UK

XXXXXXXXX	XXXXXXXX	
	XXXXX XXXX	XXXXX XXXX
XXXXXXXX	XXXX	XXXX
XXXXXXXX	XXXX	XXXX
XXX	XXXX	XXXX
XXXXXXXXXXX	XXXX	XXXX

Q=quarter
*Note that the sum of each column is not 100% as the full audit includes other treatments not relevant to the present appraisal
Source: CS, Figure 2

2.5 Life expectancy

The company describes the life expectancy of people diagnosed with pancreatic cancer in Section 3.4 of the CS. The company presents information published by CRUK[16] that shows that pancreatic cancer was the fifth most common cause of cancer deaths in the UK in 2014 (approximately 8,800 deaths in the UK and 7,430 deaths in England). The company also presents the 12-month and 5-year survival data from CRUK for the years 2005 to 2009 (people in England) and 2010 to 2011 (people in England and Wales).[16] The company observes (CS, p38) that, in the absence of new treatments, the (low) current survival rates are likely to remain unchanged (Table 5). The company's observation is supported by details on the CRUK[16] website that highlight that, in the UK, survival from pancreatic cancer '…has not shown much improvement in the last 40 years.'

Table 5 12-month and 5-year survival rates in pancreatic cancer

Year	12-month survival rate	5-year survival rate
2005 – 2009 (England[16])	<20%	<4%
2010 – 2011 (England and Wales[16])	21%	3%

Source: CS, p38

2.6 Summary of relevant clinical guidance and guidelines

The company provides details of relevant published guidance and treatment guidelines in Section 3.5 of the CS. These are reproduced in Table 6. The company observes that NICE expects to publish a guideline[17] specific to pancreatic cancer in January 2018.

Nab-Pac is administered intravenously over 30 minutes at a dose of 125mg/m^2 on days 1, 8 and 15 of each 28-day cycle. Gem is administered intravenously over 30 minutes at a dose of 1000mg/m^2. Gem is administered immediately after the administration of Nab-Pac has been completed.

The company states (CS, p24) that paclitaxel prevents the growth of cancer cells by obstructing cell division and fostering cell death. Paclitaxel is used to treat other types of cancer, including breast and lung cancer. The company describes Nab-Pac as a novel formulation of paclitaxel in which paclitaxel is attached to nanoparticles of albumin and administered without the need for solvents. Albumin-bound paclitaxel results in greater delivery of paclitaxel to the tumour site compared with conventional solvent-based paclitaxel formulations. The company reports that, when combined with Gem, a '…novel, synergistic effect' results in an increase in, and the stabilisation of, levels of intra-tumoural Gem.[24]

Nab-Pac+Gem in the UK

In the Final Appraisal Determination (FAD) for TA360[25] issued in October 2015, NICE did not recommend the use of Nab-Pac+Gem for patients in the NHS with previously untreated metastatic pancreatic cancer. The company reports (CS, p27) that Nab-Pac+Gem was available to patients via CDF between March 2014 and November 2015, and was then removed from the CDF '…in preparation for the new approach to the appraisal and funding of cancer drugs in England'. The ERG notes that Nab-Pac was one of 17 drugs removed from the CDF in November 2015 as a result of a review by a partnership between NHS England, NICE, Public Health England and the Department of Health.[26]

Nab-Pac+Gem is available for use in NHS Wales[1] and in NHS Scotland.[2]

Other licensed indications for nab-paclitaxel

Nab-Pac monotherapy is licensed in Europe[9] for the treatment of people with metastatic breast cancer whose disease has progressed following first-line treatment and who are unsuitable for treatments containing anthracyclines. Nab-Pac+carboplatin is indicated for the first-line treatment of NSCLC in adult patients who are not candidates for potentially curative surgery and/or radiation therapy. NICE has not appraised Nab-Pac for use in either of these licensed indications.

3.3 Comparators

The comparators specified in the final scope issued by NICE are Gem, Gem+Cap and FOLFIRINOX.

3.3.1 Included comparators

Gemcitabine

Direct clinical evidence is available for the comparison of the effectiveness of Nab-Pac+Gem versus Gem from the CA046 trial. Throughout the CS (pp14, 15, 20, 23, 34, 35, 38, 142, 248), the company is clear that it considers Gem to be the only relevant comparator to treatment with Nab-Pac+Gem.

Gem+Cap and FOLFIRINOX

In the absence of any direct evidence to allow the effectiveness of Nab-Pac+Gem to be compared with that of Gem+Cap or FOLFIRINOX, the company has conducted network meta-analyses (NMAs). However, the company states that the results of the comparative clinical effectiveness and cost effectiveness analyses of Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX are only presented in the CS for completeness. The ERG (and the company) consider that the results of the company's NMA should be treated with caution.

The company does not consider either Gem+Cap or FOLFIRINOX to be relevant comparators to Nab-Pac+Gem for the reasons described in Sections 2.2 and 2.3 of this ERG report.

The company contends that the limited use of Gem+Cap in the NHS means that it does not represent standard of care and that the current use of Gem+Cap in the NHS would not be displaced if Nab-Pac+Gem became available for use. The ERG notes that data presented by the company (CS, Figure 2) indicate that, in 2015, XXXXXXXX of treated patients received Gem doublet (likely to be Gem+Cap).

The company also contends that patients in the NHS who are suitable for treatment with Nab-Pac+Gem are easily identified and are clinically distinct from patients who would be considered suitable for treatment with Gem or with FOLFIRINOX. Clinical advice to the ERG is that patients who are suitable for treatment with FOLFIRINOX are clinically distinct from patients who are suitable for treatment with Gem monotherapy. However, the ERG is uncertain that patients with metastatic pancreatic cancer who may be considered suitable for treatment with Nab-Pac+Gem in the NHS are clinically distinct from patients who would currently be treated with FOLFIRINOX. Clinical advice to the ERG is that it would be difficult to clearly establish which patients in the NHS would better suited to treatment with Nab-Pac+Gem rather than with FOLFIRINOX.

3.4 Outcomes

The outcomes specified in the final scope issued by NICE are: OS, progression-free survival (PFS), time to tumour progression (TTP), objective response rate (ORR), AEs and health-

Table 10 Summary of, and ERG comment on, the systematic review methods used by the company

Review method	Results	ERG comment
Searching		
Sources searched: • Electronic databases • Congress proceedings • Clinical trial registries	Initial search=4943 Update 03/2014=635 Update 07/2016=1227	• The last update was carried out in July 2016, meaning that there is a risk that some relevant studies may not have been included in the search results • It is unclear whether the time-periods for the update searches overlapped. Not including an overlap may result in some relevant studies being missed • Only CENTRAL was searched for ongoing trials. Any clinical trials that are only registered in other databases (e.g. ClinicalTrials.gov) will have been missed
Formal eligibility criteria		
Two analysts independently assessed study eligibility based on: - the primary eligibility criteria presented in Table 3, Appendix 2 of the CS (p15)	Unique studies Initial search=97 Update 03/2014=6 Update 07/2016=18	• Use of two independent assessors improves the quality of reviews
Additional eligibility criteria		
The company states that a narrower scope was employed following confirmation of the indication for Nab-Pac+Gem leading to changes in the following: • Population – changed from studies of APC patients, of whom at least 50% had metastatic disease and were potentially eligible for first-line therapy for metastatic disease to studies of APC patients, of whom at least 50% had metastatic disease and who had received no prior systemic therapy for metastatic disease • Comparators - specific Gem-based chemotherapy combinations and FOLFIRINOX, rather than the less-defined list of comparators specified at the primary stage The secondary eligibility criteria are presented in Table 7 of the CS (p46)	Unique studies Initial search=16 Update 03/2014=0 Update 07/2016=1	• Only studies meeting the additional eligibility criteria were included and summarised in the CS
Quality assessment		
The company assessed the risk of bias of the CA046 trial using the minimum criteria recommended by NICE[33] The results of the assessment of risk of bias of the RCTs included in the company's NMA are presented in Appendix 4 of the CS		

APC=advanced pancreatic cancer; CS=company submission; ERG=Evidence Review Group; NMA=network meta-analysis; NICE=National Institute for Health and Care Excellence; RCT=randomised controlled trial
Source: CS, p44-49 and p62-63

Sensitivity analyses

Sensitivity analyses to investigate the robustness of the results of the primary outcome analyses were pre-specified in the SAP. The ERG is satisfied that the results of all of the sensitivity analyses were fully reported in the CSR.

Timing of analyses

An interim analysis for OS was pre-specified in the CA046 trial protocol. This was performed after at least 200 patients had been followed for at least 6 months from the date of randomisation. The interim analysis was designed to evaluate futility, with the possibility of stopping the trial early due to lack of efficacy. As determined by the pre-specified sample size calculation, the final analysis of OS was conducted when at least 608 deaths had occurred; all deaths that occurred on, or prior to, the projected clinical cut-off date, were included in the analysis.

The final OS analysis was based on 692 deaths (80% of patients, data cut-off: 17 September 2012). Median follow-up was 9.1 months in the Nab-Pac+Gem arm and 7.4 months in the Gem arm.

An updated analysis of OS from the CA046 trial with an extended data cut-off (8 months longer than the final OS analysis) was reported in a paper by Goldstein[37] (data cut-off: 9 May 2013). At the time of the updated analysis, 774 (90%) patients in the ITT population had died and median follow-up was 13.9 months. The ERG is aware that this is a post-hoc analysis; however, this is not a cause for concern as it is unlikely that the updated results could be subject to bias. The motivation for undertaking the follow-up analysis is clear - at this point, 90% of the ITT population had experienced an event compared with 80% at the time of the primary analysis.

Overall, the ERG considers that appropriate statistical methods were used for the analyses of CA046 trial data, with the exception of the inappropriate generation of HRs to compare survival (OS and PFS) between trial arms.

4.2.5 Risk of bias assessment for the CA046 trial

The company assessed the risk of bias in the CA046 trial using the minimum criteria set out in NICE's Guide to the Methods of Technology Appraisal.[33] The ERG agrees with the company that the risk of bias is low for all the criteria listed in Table 13. The ERG notes that the CA046 trial was of an open-label design; however, a blinded review of the investigator-assessed radiological outcomes was conducted. The ERG considers that a notable strength of the CA046 trial is that the study protocol prohibited treatment crossover.

peripheral neuropathy (54%), nausea (54%), alopecia (50%), peripheral oedema (46%), diarrhoea (44%), anaemia (42%), neutropenia (42%) and pyrexia (41%). The ERG notes that in the Gem arm, the most frequently reported TEAEs were nausea (48%), fatigue (46%), anaemia (33%), peripheral oedema (31%) and neutropenia (30%). The TEAEs with the greatest observed differences between treatment groups were peripheral neuropathy (54% in the Nab-Pac+Gem arm and 13% in the Gem arm) and alopecia (50% in the Nab-Pac+Gem arm and 5% in the Gem arm).

Table 22 in the CS (p108-109) lists the incidence of TEAEs assessed as Grade ≥3 in more than 5% of patients; this table is replicated in Table 18 of this ERG report. The company comments that there were more AEs reported by patients treated with Nab-Pac+Gem than by patients treated with Gem (89% versus 75%). The company points out that the most frequently reported AEs in the Nab-Pac+Gem arm were neutropenia (33%), fatigue (18%), metabolism and nutritional disorders (dehydration and decreased appetite) (18%), peripheral neuropathy (17%), thrombocytopenia (13%) and anaemia (12%). The ERG notes that the most frequently reported AE in the Gem arm was neutropenia (21%).

It is recorded in the CS (p112-113) that the rates of AEs and SAEs were higher in older patients (≥65 years) treated with Nab-Pac+Gem than in the overall treated population. The CS also reports that for patients aged ≥75 years, more frequent Grade 3 TEAEs, SAEs, TEAEs with an outcome of death and TEAEs leading to study discontinuation were recorded in the Nab-Pac+Gem arm than in the Gem arm. The number of patients aged ≥75 years of age included in the study was small (n=84), and therefore, comparisons of TEAEs in this subgroup should be interpreted with caution. The ERG notes that the EMA's marketing authorisation[9] for Nab-Pac+Gem contains a warning regarding the increased risk of AEs in the ≥75 years of age group and states that use of Nab-Pac for the treatment of patients ≥75 years should be carefully considered.

The company reports that TEAEs with a ≥10% difference in women compared with men were neutropenia (49% versus 36%), anaemia (49% versus 36%), vomiting (44% versus 29%), and urinary tract infection (17% versus 4%). Neutropenia was the only Grade 3 or higher TEAE reported with a >5% difference in women than men (40% versus 27%).

The overall incidence of TEAEs, Grade 3 or higher TEAEs, and SAEs was similar between patients from the four different geographic regions (North America, Western Europe, Eastern Europe and Australia) that were considered.

Peripheral neuropathy

The company states (CS, p109) that the majority of cases of Grade ≤3 neuropathy could be reversed and managed by delaying further treatment or reducing the dose until the condition improved to Grade ≤1. The company also reports that a (not pre-specified) subgroup analysis showed that patients who developed Grade 3 peripheral neuropathy had increased treatment exposure and thus experienced significantly better OS, PFS, ORR compared to those who did not develop peripheral neuropathy (CS, p109, Table 23, replicated in Table 19). The company reports that peripheral neuropathy was [redacted] reversible with treatment interruption and that the median time to improvement from Grade 3 to Grade ≤1 severity was 29 days. The ERG considers that 29 days is a substantial period for a patient with metastatic pancreatic cancer. The ERG notes from the CSR that peripheral neuropathy was the most common reason for treatment discontinuation (8%) in the Nab-Pac+Gem arm.

Table 6 Treatment exposure and efficacy outcomes by dose modifications in the Nab-Pac+Gem arm of the CA046 trial

	Dose reductions			Dose delays		
	No dose reduction (n=249)	**≥1 dose reduction (n=172)**	**HR or RRR (95% CI) p-value**	**No dose delay (n=121)**	**≥1 dose delay (n=300)**	**HR or RRR (95% CI) p-value**
OS, median months	6.9	11.4	1.93 (1.53 to 2.44) p<0.0001	6.2	10.1	2.05 (1.59 to 2.63) p<0.0001
PFS, median months	3.8	8.8	2.62 (2.01 to 3.42) p<0.0001	3.4	6.6	2.80 (2.13 to 3.69) p<0.0001
ORR, %	16	34	0.49 (0.34 to 0.69) p<0.0001	10	29	0.34 (0.19 to 0.60) p<0.0001

CI=confidence interval; HR=hazard ratio; OS=overall survival; ORR=overall response rate; PFS=progression-free survival; RRR=response rate ratio
Note: The HR for death is provided for OS, and the HR for progression or death is provided for PFS, with a HR of >1 favouring dose modification; the RRRs are provided for ORRs, with a RRR of <1 favouring dose modification
Source: CS, Table 24

Additional safety data

Additional safety data presented in the CS (p114-117) are summarised in Appendix 1 of this ERG report. Briefly, the additional AE data are derived from the SIEGE trial,[28] two small cohorts[39,40] of patients who were treated with Nab-Pac+Gem between October 2013 and October 2015 in the Lancashire and South Cumbria Cancer Network (n=32) and in South West Wales (n=17). Further data describing patients (n=208) who were treated in centres in Italy[23] are also presented.

The only data available from the SIEGE trial[28] are taken from a poster presented at the ASCO conference in January 2017. In comparison to the CA046 trial, the overall proportion of patients in the SIEGE trial[28] who experienced Grade ≥3 AEs was similar (89% versus 82% respectively). The rates of specific Grade ≥3 AEs reported by patients in the SIEGE trial[28] were also similar to, or lower than, rates reported in the CA046 trial. However, 5.4% of patients in the SIEGE trial[28] experienced sepsis, whilst no cases of sepsis were reported in the CA046 trial.

Data available from the retrospective study of elderly patients (n=208) treated in Italian centres are from two posters presented at the 2015 ESMO conference. At ASCO 2016 an updated data set was presented where 221 patients were eligible for the analysis. The safety data appear to be similar to those reported during the CA046 trial.

severely impacted by model convergence issues. Therefore, the ERG considers that the results of SA2 are more informative than those from the ERG requested analysis, i.e. from the fixed-effects model rather than the random-effects model because there are insufficient data to run the random-effects model. The ERG notes that slight differences in dosing regimens were identified between trials included in the reduced network but does not consider that these differences would invalidate the results of an analysis using a fixed-effects model.

4.6.7 ERG interpretation of NMA results

In summary, the ERG's considers that the OS and PFS data from the CA046 trial lack PH, and so the results of the company's NMAs should be interpreted with caution. In addition, the ERG has concerns about the relevance of the NMA results to the decision problem as there are few patients aged over 75 years of age in the trials which make up the network.

4.7 Conclusions of the clinical effectiveness section

The ERG considers that the submitted evidence largely reflects the decision problem defined in the final scope issued by NICE; however, the ERG notes the following points:

- Nab-Pac+Gem was not recommended for use in NHS England following the publication of TA360 but it has been recommended for use in NHS Wales and NHS Scotland
- the company has provided clinical effectiveness data pertaining to all comparators listed in the final scope issued by NICE; however, direct evidence is only available for the comparison of treatment with Nab-Pac+Gem versus Gem
- the company considers that Gem is the only relevant comparator to Nab-Pac+Gem
- the company considers that (i) [redacted] Gem+Cap is not a standard of care in the NHS and (ii) the introduction of Nab-Pac+Gem for use in the NHS will not displace FOLFIRINOX
- the company considers that patients who are suited to treatment with Nab-Pac+Gem are easily identified and are 'clinically distinct' from patients who are suited to treatment with FOLFIRINOX. The ERG considers that the company has yet to provide a definition of patients who are suited to treatment with Nab-Pac+Gem.

4.7.1 Clinical effectiveness evidence

Direct evidence

The direct evidence was derived from the CA046 trial. The ERG highlights the following points:

- patients in the CA046 trial were younger and fitter than patients treated in the NHS
- only 10% of patients recruited to the CA046 trial were aged ≥75 years. In the NHS, 47% of patients with pancreatic cancer are aged ≥75 years. This means that the evidence from the trial may not be relevant to a substantial number of NHS patients

- in the SmPC[9] for Nab-Pac, the EMA advises caution when considering using Nab-Pac+Gem to treat patients aged ≥75 years due to a lack of evidence of clinical efficacy and the AE profile

- results of the final efficacy analysis of the CA046 trial suggest that treatment with Nab-Pac+Gem statistically significantly improves median OS in comparison to treatment with Gem (8.5 months versus 6.7 months; HR=0.72, 95% CI: 0.62 to 0.83)
- results from the updated OS analysis are in accordance with the findings of the primary analysis, supporting the evidence for a statistically significant benefit from treatment with Nab-Pac+Gem compared to Gem (8.7 months versus 6.6 months; HR=0.72, 95% CI: 0.62 to 0.83)
- the ERG's assessment of the PH assumption for the CA046 trial data suggests that the PH assumption does not hold for either OS or PFS data and, consequently, the HRs from the CA046 trial for these outcomes should be interpreted with caution
- the most common Grade 3 and 4 AEs associated with treatment with Nab-Pac+Gem were neutropenia, fatigue, metabolism and nutritional disorders, peripheral neuropathy, thrombocytopenia and anaemia. Although these AEs are associated with treatment with either Gem or Nab-Pac monotherapies, they occur more frequently when patients are treated with the Nab-Pac+Gem combination
- no HRQoL data are available as part of the CA046 trial. The company has presented HRQoL evidence from one arm of the SIEGE trial,[28] a [redacted] phase II single arm trial of patients with locally advanced pancreatic cancer who were treated with Nab-Pac+Gem and from a cross-sectional study[32] of patients with metastatic pancreatic cancer treated with Nab-Pac+Gem in the US.

Indirect evidence

The ERG highlights the following points:

- in the absence of head-to-head data for the comparisons of Nab-Pac+Gem versus FOLFIRINOX and Nab-Pac+Gem versus Gem+Cap, the company performed a NMA to obtain estimates of the relative efficacy of these comparators
- seven of the 10 trials included in the base case NMA provide evidence for comparators that are not relevant to the decision problem; the ERG considers that results from a NMA that includes only trials that compare treatments listed in the decision problem are more informative than results from a NMA that includes data from all 10 trials
- all NMA results are affected by a violation of the PH assumption within the CA046, and should be interpreted with caution.

Comparators

The final scope issued by NICE states that the comparators for this appraisal are Gem, Gem+Cap and FOLFIRINOX. The company considers Gem as the main comparator to Nab-Pac+Gem in the economic analysis with Gem+Cap and FOLFIRINOX considered only as secondary comparators [redacted]. Further details of the comparators are presented in Table 9 of the ERG report.

Second-line treatment

Data describing the seven most prevalent second-line treatments reported in the CA046 trial are used to estimate the range and use of second-line treatments in the model. The percentage of patients receiving second-line therapy in the CA046 trial differed according to study arm: 38% of patients who received Nab-Pac+Gem as a first-line treatment received a second-line treatment and 42% of patients who received Gem as a first-line treatment received a second-line treatment.[12] The proportions of each of the second-line treatments used in the model are shown in Table 27.

Table 7 Second-line treatments included in the company model

Second-line treatment	% of patients moving into second-line treatment	
	Nab-Pac+Gem (total=38%*)	Gem (total=42%)
5-FU	7.3%	1.3%
5-FU+oxaliplatin	13.2%	17.1%
Gem+Cap	2.9%	3.9%
Capecitabine	4.4%	6.6%
Gem+erlotinib	2.9%	3.9%
Erlotinib	1.5%	1.3%
FOLFIRINOX	0.0%	0.0%

5-FU=5-fluorouracil
* The figures do not sum to 38% due to rounding
Source: CS, Table 36

5.4.4 Perspective, time horizon and discounting

The company states that the economic evaluation was undertaken from the perspective of the NHS and PSS (Personal Social Services). The model time horizon was 10 years. Both costs and benefits were discounted at a rate of 3.5% per annum.

5.4.5 Treatment effectiveness and extrapolation

Nab-Pac+Gem and Gem

The company used K-M data from the CA046 trial as a basis for extrapolating survival for treatment with Nab-Pac+Gem and Gem. The company assessed the applicability of a single parametric model or a Cox PH model by visual inspection of the K-M curves, log cumulative hazard plots (LCHP) and quantile-quantile (Q-Q) plots. Six parametric distributions

The company also considered the comparison of Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX to be scenario analysis. The results of these comparisons are presented in Table 35 and Table 36 of this ERG report.

5.4.12 Subgroup analyses

The company did not carry out any cost effectiveness subgroup analyses.

5.4.13 Model validation and face validity check

According to the company (CS, p241) …'The model was quality assured by the internal processes of the external economists who adapted the economic model.' These processes included review of the model for coding errors, inconsistencies and plausibility of inputs. The model was also subject to a checklist[66] of known modelling errors.

The model inputs were also validated by clinical advisory boards and by comparing results from the model with any previously published model estimates[51,67] that were identified by the company's literature search. The publication by Gharaibeh[67] reports an ICER of £78,086 per QALY gained for Nab-PAC+Gem versus Gem, which the company states is similar to the non-PAS ICER of XXXXX per QALY gained that is reported in the CS (p242).

Table 8 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partly	Effectiveness for treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX not robustly established due to issues with the NMA
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Partly	Overestimation of total LY and QALYs
Were the cost and consequences valued credibly?	Partly	Drug cost calculations did not take into account all available vial sizes
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

LY=life year; QALY=quality adjusted life year

The company's Microsoft Excel spreadsheet model is constructed according to conventional practice and is generally implemented correctly. The company provided two models as part of its submission: an original model, the results of which are given in the CS; and an updated model corrected for AE calculations, which was provided during the clarification process. The ERG has used the updated model as the basis for its critique and revisions. The original base case ICERs per QALY gained are presented in Table 46 (Nab-Pac+Gem versus Gem), Table 47 (Nab-Pac+Gem versus Gem+Cap), and Table 48 (Nab-Pac+Gem versus FOLFIRINOX) alongside the company's updated base case and the ERG's revisions.

5.5.1 ERG corrections

Application of HRs for treatment with Gem+Cap and FOLFIRINOX

The implementation of the company's estimates of OS, PFS and TOT for treatment with Gem+Cap and with FOLFIRINOX is incorrect. The company uses HRs from the NMA to estimate the relative treatment effect for Nab-Pac+Gem versus Gem+Cap or FOLFIRINOX and applies these treatment effects by raising each cycle probability for OS, PFS and TOT to the power of the relevant HR. However, the HR does not function as a multiplier in this way.

The HR should instead be applied to the treatment parameter within the definition of the curve.

The ERG has provided cost effectiveness results from the model for treatment with Gem+Cap and with FOLFIRINOX (using published HRs versus treatment with Gem) for completeness and to provide a sensitivity analysis versus the company's base case using HRs from the NMA. However, these results should be treated with caution, as they apply a HR to a stratified Gamma model, which is not appropriate.

The ERG has applied the HRs shown in Table 42 to model estimates of OS and PFS for treatment with Gem (and assumed that the HRs for PFS also apply to TOT).

Table 9 HRs used in ERG amended model

Comparator vs Gem	Source	HR (95% CI)
Gem+Cap OS	Scheithauer 2003[6]	0.82 [0.50, 1.35]
Gem+Cap PFS	Scheithauer 2003[6]	0.81 [0.53, 1.27]
FOLFIRINOX OS	Conroy 2011[7]	0.57 [0.45, 0.73]
FOLFIRINOX PFS	Conroy 2011[7]	0.47 [0.37, 0.59]

Source: Figure 9 and Figure 10, CS Appendix 4;

The ERG's analysis generates a mean OS gain of 0.8 months and a mean PFS gain of 1.18 months for treatment with Nab-Pac+Gem generates versus Gem+Cap. Treatment with Gem+Cap no longer dominates treatment with Nab-Pac+Gem once the ERG's revised HRs are applied, as treatment with Nab-Pac+Gem shows increased benefit over Gem+Cap (+0.054 QALYs) albeit at a slightly higher incremental cost than in the base case (+£5,563 versus +£5,567). The ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem+Cap using revised HRs is £103,827.

The ERG's analysis generates a mean OS loss of 2.72 months and a mean PFS loss of 1.42 months for treatment with Nab-Pac+Gem versus FOLFIRINOX. These results should be treated with caution due to violation of PH in the ACCORD trial.[7] Applying revised HRs in the model results in extra time on treatment for patients receiving FOLFIRINOX, which generates high enough extra administration, monitoring and AE costs to outweigh the more expensive drugs used for treatment with Nab-Pac+Gem. It also increases OS and PFS for treatment with FOLFIRINOX, which in turn increases the incremental QALY difference between Nab-Pac+Gem and FOLFIRINOX. As treatment with Nab-Pac+Gem becomes cheaper than treatment with FOLFIRINOX once the revised HRs are applied (-£582), and remains less beneficial (-0.175 QALYs), it is no longer dominated by FOLFIRINOX. The ICER per QALY gained for treatment with Nab-Pac+Gem versus FOLFIRINOX using revised HRs is £3,327.

Costing of first-line treatments

All first-line drugs included in the company's model are overestimated in the base case. This is principally due to the company not including all available vial/packet sizes in its calculation

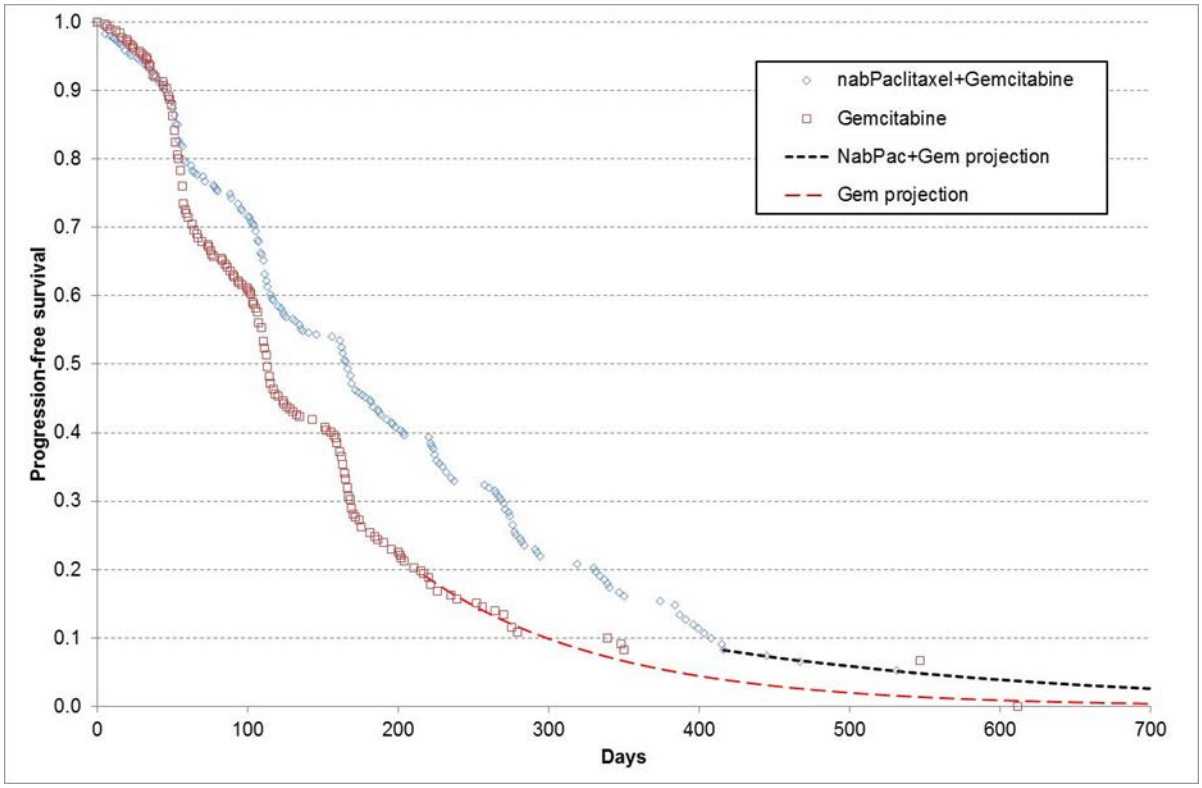

Figure 1 Progression free survival in the whole CA046 trial population
Source: NICE TA360

Using the ERG's OS projections from NICE TA360[14] gives mean OS for treatment with Nab-Pac+Gem of 10.91 months and mean OS for Gem of 8.47 months, resulting in an OS gain of 2.44 months. This is compared to an OS gain of 2.42 months in the company model. Using the ERG estimates of OS, the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem decreases by £330 to £46,681. Treatment with Nab-Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

Using the ERG's PFS projections from NICE TA360[14] gives mean PFS for treatment with Nab-Pac+Gem of 6.82 months and mean PFS for Gem of 4.74 months, resulting in a PFS gain of 2.52 months. This is compared to a PFS gain of 2.07 months in the company model. Using the ERG estimates of PFS, the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem increases by £77 to £46,933. Treatment with Nab-Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

5.5.5 Scenario analyses

AE costs

The ERG has investigated the sensitivity of the ICERs per QALY gained to the estimates of AE costs used in the model. The ERG has made these amendments based on the mean duration of AEs in the CA046 trial, reference to published sources[68-70] and discussions with a clinical expert. The most substantial increases in the ERG estimates of AE costs versus the

company's estimates [redacted] are for diarrhoea, dehydration and vomiting. The ERG notes from Table 14 and Table 15 of the company's clarification response that patients in both arms of the CA046 trial reported mean durations of Grade ≥3 diarrhoea, dehydration and vomiting between 5.57 and 11.81 days. The ERG notes that Grade ≥3 AEs are generally considered severe enough to require hospitalisation. This information, combined with the mean duration of the events in the CA046 and supported by clinical advice, indicates that patients with Grade ≥3 diarrhoea, dehydration or vomiting would be most appropriately treated by an overnight stay in hospital (non-elective inpatient long stay). However, the company has assumed that patients with Grade ≥3 diarrhoea, dehydration and vomiting would not stay overnight in hospital (non-elective inpatient short stay or day case). Table 44 gives the definitions of the relevant NHS admission types used in the costing of AEs.

Other increased costs in the ERG's scenario analysis versus the company base case are for treating: neutropenia and leukopenia (changed from admitted patient care to outpatient treatment, based on clinical advice); abdominal pain (changed from non-elective inpatient short stay to long stay and including interventions, based on clinical advice); and hyperbilirubinemia (changed from a specific costing to assuming same cost as cholangitis, based on clinical advice).

Decreased costs in the ERG's scenario analysis versus the company base case are for treating: thrombocytopenia (changed from non-elective inpatient short stay to day case, based on clinical advice); pulmonary embolism (source of company cost not clear, so changed to non-elective short stay based on clinical advice); cholangitis (changed from 5x excess bed days to an HRG code that includes interventions, based on clinical advice).

Table 45 compares the AE costs used in the company base case versus the costs used by the ERG in its scenario analysis.

Table 10 Definition of admission/appointment types

Type	Definition
Non-elective inpatient short stay*	1 day (no overnight - patient allowed home on day of admission)[70]
Non-elective inpatient long stay**	2 or more days[70]
Day case	Admitted electively, returns home as scheduled without stay overnight[69]
Outpatient procedure	Attendance at outpatient clinic (pre-booked or not)[70]

* recorded as one day for auditing purposes, but relates to admissions where patients are allowed home on the same day as they were admitted
** recorded as 2 days for auditing purposes, but relates to admissions where patients have at least one overnight stay

and crosswalk[58] methods are not attempting to produce estimates of the same thing. The Devlin[57] value set is a way of weighting the 3125 theoretically possible health states derived from the EQ-5D-5L questionnaire according to their value by the general UK population. The crosswalk method is a way of translating the results of the EQ-5D-5L into the weighting of the 243 theoretically possible health states derived from the EQ-5D-3L. Out of the three sets of utility values presented by the company, only the UK-adjusted Romanus[59] utility values and the utility values from the SIEGE[28] trial adjusted to the EQ-5D-3L UK-value set are comparable, since they are measured on the same scale.

Since the NICE cost-effectiveness thresholds are based on benefit calculations using HRQoL data derived from the EQ-5D-3L questionnaire, and because the results of the EQ-5D-5L and EQ-5D-3L have been found to produce substantially different estimates of cost effectiveness,[71] the ERG does not consider the Devlin[57] value set to be appropriate in this instance.

The UK-adjusted values from the Romanus paper[59] were the ERG's preferred estimates of health state utility in the original appraisal,[14] at which time the HRQoL data from the SIEGE trial were not available. The ERG noted in the original appraisal that there was still considerable uncertainty around patients' quality of life using these estimates. First, the patients in the trial reported by Romanus[59] were not treated with Nab-Pac+Gem; they received either Gemcitabine plus Placebo or Gemcitabine plus Bevacizumab. Second, the company itself had pointed out that the reported utility values for patients with stable disease in the Romanus[59] study were not significantly different from age-matched US general population values. Third, the utility values were mapped to the UK-value set from published summary values, which introduces further uncertainty.

The SIEGE[28] trial has the greatest relevance to the current appraisal, as it is a UK-based randomised trial that recruited patients with metastatic pancreatic cancer of whom half received the Nab-Pac+Gem regimen used in the CA046 trial. However, the reference provided by the company does not include any details of the EQ-5D from the SIEGE[28] trial, so the ERG has not been able to verify the derivation or mapping of the utility values from the trial.

Applying the switch in the company model to use the SIEGE crosswalk utility values instead of the base case UK-adjusted Romanus utility values increases the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem by £2,667 to £49,678. Treatment with Nab-Pac+Gem remains dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX. Applying the switch in the company model to use the SIEGE Devlin57 utility

values instead of the base case UK-adjusted Romanus utility values would decrease the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem by £3,230 to £43, 780.

Treatment with Nab-Pac+Gem would remain dominated by both treatment with Gem+Cap and treatment with FOLFIRINOX.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Before incorporating any ERG amendments into the company model, the ERG has amended a structural feature in the company model, namely:

- Calculation of total LY and QALYs

The ERG has made the following amendments to the ERG corrected company base case for treatment with Nab-Pac+Gem versus Gem, Nab-Pac+Gem versus Gem+Cap and Nab-Pac versus Gem versus FOLFIRINOX:

- HRs for Gem+Cap vs Gem (R1)
- HRs for FOLFIRINOX vs Gem (R2)
- ERG drug costing method (R3)
- TOT from CA046 trial (R4)
- Do not apply AE disutilities (R5)
- ERG OS (R6)
- ERG PFS (R7)

The ERG has also included two scenario analyses to investigate the effect of changes to the ERG corrected base case of using:

- ERG AE costs (S1)
- SIEGE crosswalk utility values (S2)

Deterministic results

Cost effectiveness results for the base case comparisons of treatment with Nab-Pac+Gem versus Gem, Nab-Pact+Gem versus Gem+Cap and for Nab-Pac+Gem versus FOLFIRINOX are displayed in Table 47, Table 48 and Table 49 respectively. Cost effectiveness results for the sensitivity analyses for comparisons of treatment with Nab-Pac+Gem versus Gem, Nab-Pact+Gem versus Gem+Cap and for Nab-Pac+Gem versus FOLFIRINOX are displayed in Table 50, Table 51 and Table 52 respectively.

When all of the ERG's suggested amendments have been implemented in the base case, the ICER per QALY gained for treatment with Nab-Pac+Gem versus Gem is £41,250. When

all of the ERG's suggested amendments have been implemented in the base case and all of the

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10.9 Additional results from the network meta-analysis

For each analysis presented in the CS, the company provides results for each treatment included in the network versus Nab-Pac+Gem. However, as many of these treatments are of no relevance to the decision problem, throughout the following section the ERG presents results only for each of the treatments in the decision comparator set versus Nab-Pac+Gem.

Base case analysis

The company presents the results for each treatment included in the network versus Nab-Pac+Gem in Figure 10 (CS, p85), Figure 12 (CS, p88) and Figure 13 (CS, p89) of the CS for OS, PFS by independent assessment and PFS by investigator assessment, respectively.

For OS, Gem was shown to be statistically significantly inferior to Nab-Pac+Gem (HR=1.35, 95% CrI: 1.17 to 1.56). For Gem+Cap versus Nab-Pac+Gem, there is no evidence to suggest a difference between these two treatments in terms of OS. The ERG acknowledges that there is no single positive phase III RCT for Gem+Cap. For FOLFIRINOX versus Nab-Pac+Gem, the HR favoured FOLFIRINOX, although this result was not statistically significant (HR=0.77, 95% CI: 0.58 to 1.01).

For PFS, Gem was shown to be statistically significantly inferior to Nab-Pac+Gem by both independent and investigator assessment. For Gem+Cap versus Nab-Pac+Gem, no statistically significant differences were observed between the treatments for PFS by either independent or investigator assessment. The ERG acknowledges that there is no single positive phase III RCT for Gem+Cap. FOLFIRINOX was shown to be statistically significantly superior to Nab-Pac+Gem for PFS by independent assessment (HR=0.68, 95% CrI: 0.51 to 0.91). For PFS by investigator assessment, a trend in favour of FOLFIRINOX was observed, although this difference was no longer statistically significant (HR=0.77; 95% CI: 0.58 to 1.02).

SA1

The company presents the results of SA1 in Appendix 4 of the CS. For OS, estimated HRs for each of the treatments in the decision comparator set versus Nab-Pac+Gem are comparable to those observed in the base case analysis; however, there were no statistically significant differences between any of the treatments in the decision comparator set and Nab-Pac+Gem. Similarly, PFS by independent assessment results were comparable to those observed in the base case analysis; however, there were no statistically significant differences between any of the treatments in the decision comparator set and Nab-Pac+Gem.

ID1058 STA ERRATUM 2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 14/90/01

Erratum completed 26 June 20167

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

This document contains an erratum for the ERG report following a query by the NICE technical team.

Please note:

- Additional or replacement text added by the ERG is highlighted in grey
- Text deleted completely (as opposed to being reworded) is blacked out (for example, [redacted])

Table 1 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partly	Effectiveness for treatment with Nab-Pac+Gem versus Gem+Cap and versus FOLFIRINOX not robustly established due to issues with the NMA
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Partly	Overestimation of total LY and QALYs
Were the cost and consequences valued credibly?	Partly	Drug cost calculations did not take into account all available vial sizes
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

LY=life year; QALY=quality adjusted life year

The company's Microsoft Excel spreadsheet model is constructed according to conventional practice and is generally implemented correctly. The company provided two models as part of its submission: an original model, the results of which are given in the CS; and an updated model corrected for AE calculations, which was provided during the clarification process. The ERG has used the updated model as the basis for its critique and revisions. The original base case ICERs per QALY gained are presented in Table 46 (Nab-Pac+Gem versus Gem), Table 47 (Nab-Pac+Gem versus Gem+Cap), and Table 48 (Nab-Pac+Gem versus FOLFIRINOX) alongside the company's updated base case and the ERG's revisions.

5.5.1 ERG corrections

[redacted]

[redacted]

Total life year and QALY calculations

The company's area under the curve estimations of total QALYs and LYs are slightly overestimated, as they include a value for the first cycle. No QALYs or LYs should be accrued at the very beginning of the very first cycle, as patients have only just entered the model. However, it is correct that costs are accrued in the first cycle, as it is assumed that treatment is received on Day 1 of a cycle.

The ERG has corrected the calculation of total QALYs and life years so that accrual begins in the second cycle of the model. Applying the ERG's correction to the calculation of total QALYs and LYs increases the ICER per QALY gained for the comparison of treatment with Nab-Pac+Gem versus Gem by £79 to £47,011. Treatment both with Gem+Cap and with FOLFIRINOX continue to dominate treatment with Nab-Pac+Gem.

All ICERs per QALY gained in the ERG's critique are quoted with reference to the ERG's corrected company base case for each comparator (Nab-Pac+Gem versus Gem=£47,011, Nab-Pac+Gem versus Gem+Cap=Dominated, Nab-Pac+Gem versus FOLFIRINOX=Dominated).

1.2.1 Major issues

Comparators

The final scope issued by NICE for this appraisal indicates that, for treatment with Nab-Pac+Gem, there are three appropriate comparators: Gem, Gem+Cap, and FOLFIRINOX. Evidence of relative clinical effectiveness for Nab-Pac+Gem, Gem+Cap and FOLFIRINOX compared with Gem is provided by data from three clinical trials.

The company argues for restricting consideration to the comparison of Nab-Pac+Gem versus Gem on the basis that there is a distinct subgroup of patients with metastatic adenocarcinoma of the pancreas currently receiving Gem who are most likely to be suitable for transfer to the Nab-Pac+Gem regimen. On this basis, the company base-case analysis is restricted to the analysis of evidence from the CA046 trial. This subgroup makes up approximately XXX of patients currently receiving treatment. The company does not

describe the characteristics of these patients for whom clinical effectiveness has been assessed.