PharmacoEconomics
https://doi.org/10.1007/s40273-018-0646-1

REVIEW ARTICLE

Paclitaxel as Albumin-Bound Nanoparticles with Gemcitabine for Untreated Metastatic Pancreatic Cancer: An Evidence Review Group Perspective of a NICE Single Technology Appraisal

Angela Stainthorpe[1] · Janette Greenhalgh[1] · Adrian Bagust[1] · Marty Richardson[1] · Angela Boland[1] · Sophie Beale[1] · Rui Duarte[1] · Eleanor Kotas[1] · Lindsay Banks[2] · Daniel Palmer[1]

Abstract As part of the single technology appraisal (STA) process, the National Institute for Health and Care Excellence (NICE) invited Celgene Ltd to submit clinical and cost-effectiveness evidence for paclitaxel as albumin-bound nanoparticles (Nab-Pac) in combination with gemcitabine (Nab-Pac + Gem) for patients with untreated metastatic pancreatic cancer. The STA was a review of NICE's 2015 guidance (TA360) in which Nab-Pac + Gem was not recommended for patients with untreated metastatic pancreatic cancer. The review was prompted by a proposed Patient Access Scheme (PAS) discount on the price of Nab-Pac and new evidence that might lead to a change in the guidance. The Liverpool Reviews and Implementation Group at the University of Liverpool was the Evidence Review Group (ERG). This article summarises the ERG's review of the company's evidence submission for Nab-Pac + Gem, and the Appraisal Committee (AC) decision. The final scope issued by NICE listed three comparators: gemcitabine monotherapy (Gem), gemcitabine in combination with capecitabine (Gem + Cap), and a combination of oxaliplatin, irinotecan, leucovorin and fluorouracil (FOLFIRINOX). Clinical evidence for the comparison of Nab-Pac + Gem versus Gem was from the phase III CA046 randomized controlled trial. Analysis of progression-free survival (PFS) and overall survival (OS) showed statistically significant improvement for patients treated with Nab-Pac + Gem versus Gem. Clinical evidence for the comparison of Nab-Pac + Gem versus FOLFIRINOX and versus Gem + Cap was derived from a network meta-analysis (NMA). Results of the NMA did not indicate a statistically significant difference in OS or PFS for the comparison of Nab-Pac + Gem versus either Gem + Cap or FOLFIRINOX. The ERG's main concerns with the clinical effectiveness evidence were difficulties in identifying the patient population for whom treatment with Nab-Pac + Gem is most appropriate, and violation of the proportional hazards (PH) assumption in the CA046 trial. The ERG highlighted methodological issues in the cost-effectiveness analysis pertaining to the modelling of survival outcomes, estimation of drug costs and double counting of adverse-event disutilities. The AC accepted all the ERG's amendments to the company's cost-effectiveness model; however, these did not make important differences to the incremental cost-effectiveness ratios (ICERs). The company's base-case ICER was £46,932 per quality-adjusted life-year (QALY) gained for the comparison of Nab-Pac + Gem versus Gem. Treatment with Nab-Pac + Gem was dominated both by treatment with Gem + Cap and with FOLFIRINOX in the company's base case. The AC concluded that the most plausible ICER for treatment with Nab-Pac + Gem versus Gem was in the range of £41,000–£46,000 per QALY gained. The AC concluded that Nab-Pac + Gem was not cost effective compared with Gem + Cap or FOLFIRINOX, and accepted that treatment with Nab-Pac + Gem met the end-of-life criteria versus Gem but did not consider Nab-Pac + Gem to meet the end-of-life criteria compared with Gem + Cap or FOLFIRINOX. The AC also concluded that although patients who would receive Nab-Pac + Gem rather than FOLFIRINOX or Gem + Cap were difficult to distinguish, they were identifiable in clinical practice. The AC recommended treatment with Nab-Pac + Gem for patients with untreated metastatic pancreatic cancer for whom other combination chemotherapies were unsuitable and who would otherwise receive Gem.

✉ Angela Stainthorpe
angela.stainthorpe@liverpool.ac.uk

[1] Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, Brownlow Hill, Liverpool L69 3GB, UK

[2] North West Medicines Information Centre, Liverpool L69 3GF, UK

Published online: 29 March 2018

Key Points for Decision Makers

There are no clear clinical parameters that can be used to identify patients with untreated metastatic pancreatic cancer for whom treatment with paclitaxel as albumin-bound nanoparticles in combination with gemcitabine (Nab-Pac + Gem) is suitable. Recognising the difficulty in identifying the appropriate patient population and taking into account that treatment with Nab-Pac + Gem was only shown to be cost effective versus treatment with Gem, the Appraisal Committee recommended that treatment with Nab-Pac + Gem be made available to patients for whom other combination chemotherapies were unsuitable and who would otherwise be treated with gemcitabine monotherapy (Gem).

Findings from the CA046 trial, which is of good-quality and mature, demonstrated that treatment with Nab-Pac + Gem is more efficacious than treatment with Gem; however, lack of proportional hazards in the trial means that hazard ratios for overall survival and progression-free survival should be treated with caution.

Only 10% of patients recruited to the CA046 trial were aged ≥ 75 years. In the National Health Service (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. The European Medicines Agency 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 adverse event profile.

No robust trial evidence is available to compare treatment with Nab-Pac + Gem with treatment with a combination of oxaliplatin, irinotecan, leucovorin and fluorouracil (FOLFIRINOX) or gemcitabine in combination with capecitabine (Gem + Cap). The true effectiveness of treatment with Nab-Pac + Gem compared with Gem + Cap or FOLFIRINOX remains to be established.

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.

1 Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organization responsible for providing national guidance to the National Health Service (NHS) in England and Wales on a range of clinical and public health issues, as well as appraisal of new health technologies. The NICE Single Technology Appraisal (STA) process is specifically designed for the appraisal of a single health technology for a single indication, where most of the relevant evidence lies with one company or sponsor and typically covers new technologies shortly after UK market authorisation is granted [1]. Within the STA process, the company provides a written submission (including a decision-analytic model) that summarizes the company's estimate of the clinical effectiveness and cost effectiveness of the technology. An external independent organisation (typically an academic group) known as the Evidence Review Group (ERG), provides a critique of the company's submission (the ERG report).

Following a specification developed by NICE (the final scope), the NICE Appraisal Committee (AC) considers the company's submission (CS), the ERG report, and testimonies from experts and stakeholders to determine whether the technology represents clinical and cost effective use of NHS resources. All stakeholders and the public have an opportunity to comment on the preliminary guidance issued by NICE in the form of an Appraisal Consultation Document (ACD), after which the AC meets again to produce the final guidance (Final Appraisal Determination [FAD]). The final guidance constitutes a legal obligation for NHS providers in England and Wales to provide a technology that is approved within its licensed indication [1].

This article presents a summary of the ERG report by the Liverpool Reviews and Implementation Group at the University of Liverpool for the STA of paclitaxel as albumin-bound nanoparticles with gemcitabine (Nab-Pac + Gem) for untreated metastatic pancreatic cancer. Celgene Ltd was the sponsoring company for this STA.

This STA was a review of existing NICE guidance TA360 [2], published in October 2015, in which NICE did not recommend the use of Nab-Pac + Gem as a treatment for untreated metastatic pancreatic cancer. The review of TA360 was prompted by a proposed Patient Access Scheme (PAS) discount on the price of Nab-Pac and an indication by the company that there was new evidence available that might lead to a change in the existing recommendation. Full details of all documents relevant to this appraisal (including the appraisal scope, ERG report, company and consultee submissions, NICE guidance, and

comments on each of these) can be found on the NICE website [3].

2 The Decision Problem

Pancreatic cancer is the seventh most common cause of cancer death worldwide [4]. More than 330,000 people died of the disease in 2012, with mortality rates at their highest in Europe and lowest in Africa (although these statistics partly reflect the quality of data worldwide) [4].

In Europe, pancreatic cancer is the fifth most common cause of cancer-related death and more than 104,000 people died from the disease in 2012 [4]. Pancreatic cancer is also the fifth most common cause of cancer death in the UK, with 8817 people dying from the disease in 2014 [5].

Pancreatic cancer survival rates have not improved in the UK for 40 years. Less than 1% of patients in England and Wales are expected to survive more than 10 years beyond diagnosis, which ranks pancreatic cancer survival rates the poorest of the 20 most common cancers [6]. This poor prognosis is partly due to the proportion of patients who are diagnosed with advanced disease. Approximately 69% of patients with pancreatic cancer in England and Wales (whose stage is recorded) have stage IV disease at diagnosis. Almost half (47%) of patients with pancreatic cancer in England are diagnosed after presenting as an emergency [7].

Early-stage pancreatic cancer is typically symptomless, and the symptoms of late-stage disease are non-specific. If the tumour compresses the bile duct, patients can present with jaundice. Other symptoms include abdominal pain, back pain and weight loss. Patients may also experience diabetes or pancreatitis [8].

When considering treatment options for patients with metastatic pancreatic cancer, factors including performance status (PS), age, bilirubin level, previous treatment, cardiac status and immune function are considered.

The standard of care in the NHS in England and Wales is gemcitabine monotherapy (Gem). Gem was first recommended by NICE in 2001 for patients with a Karnofsky PS (KPS) $\geq$ 50 [9]. Two other (combination) cytotoxic chemotherapy treatments are used in clinical practice in England and Wales: gemcitabine + capecitabine (Gem + Cap) and FOLFIRINOX, a combination of oxaliplatin, irinotecan, leucovorin and fluorouracil (5-FU). Neither Gem + Cap nor FOLFIRINOX are licensed in Europe for the treatment of pancreatic cancer, and neither treatment has been appraised by NICE. In UK clinical practice, where treatment with Gem + Cap is available, it would be considered as an option for patients with a good PS (e.g. Eastern Cooperative Oncology Group [ECOG] PS 0/1) [10]. Where treatment with FOLFIRINOX is available, it is an option for patients with a good PS and very few minor comorbidities [10]. Many of the treatment centres in the UK offer a modified dose schedule of FOLFIRINOX to reduce toxicity. A common modification is the omission of the bolus dose of 5-FU. However, the clinical efficacy of any modifications to the FOLFIRINOX regimen is not established.

The treatment considered in this appraisal was Nab-Pac + Gem. Nab-Pac is a novel formulation that allows paclitaxel to be administered without solvents. It is licensed in Europe, in combination with Gem, for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. Nab-Pac + Gem is accepted for use in NHS Scotland and NHS Wales, but was not recommended by NICE for use in NHS England after its original appraisal in 2015. The appraisal discussed in the present paper was prompted by the company's provision of new health-related quality of life (HRQoL) evidence and a proposed PAS discount on the price of Nab-Pac.

3 Independent Evidence Review Group (ERG) Report

The evidence provided by the company comprised an initial submission, a cost-effectiveness model (which is commercial in confidence) and the company's response to the ERG's clarification requests. The ERG report is a summary and critical review of the evidence for the clinical and cost effectiveness of the technology provided by the company. The aims of the report were to:

- assess whether the evidence submitted by the company conforms to the methodological guidelines issued by NICE;
- assess whether the company's interpretation and analysis of the evidence are appropriate;
- indicate the presence of other sources of evidence or alternative interpretations of the evidence that could help inform the development of NICE guidance.

In addition to providing this detailed critique, the ERG modified several key assumptions and parameters within the company's economic model in order to explore the robustness of the company's results.

3.1 Clinical Evidence

The comparators specified in the final scope issued by NICE were Gem, Gem + Cap and FOLFIRINOX.

The company presented evidence for the clinical effectiveness of Nab-Pac + Gem from the CA046 trial (also known as mPACT) [11]. The CA046 trial was an open-label, multicentre, phase III, randomized controlled trial

that was designed to investigate the efficacy and safety of Nab-Pac + Gem versus Gem in patients with untreated metastatic adenocarcinoma of the pancreas. A total of 831 patients were randomized to receive either Nab-Pac + Gem (n = 431) or Gem (n = 430).

The final overall survival (OS) analysis from the CA046 trial was based on 692 deaths (80% of patients; data cut-off: 17 September 2012) [11]. 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 was also reported (data cut-off: 9 May 2013) [12]. At the time of the updated analysis, 774 (90%) patients in the ITT population had died and median follow-up was 13.9 months.

Treatment with Nab-Pac + Gem was shown to improve median OS significantly compared with treatment with Gem (8.5 months vs. 6.7 months; hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.62–0.83) [11]. The incremental OS benefit of treatment with Nab-Pac + Gem was 1.8 months in the final analysis and 2.1 months in the updated analysis [11, 12]. 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) [11]. All sensitivity analyses carried out by the company showed a statistically significant OS treatment effect in favour of patients treated with Nab-Pac + Gem. 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. Key results from the final OS analysis are shown in Table 1 and from the updated OS analysis in Table 2.

Treatment with Nab-Pac + Gem was shown to improve median progression-free survival (PFS) significantly compared with treatment with Gem in the CA046 trial [11]. Table 1 shows an incremental PFS benefit of 1.8 months for both PFS by independent review (HR 0.69, 95% CI 0.58–0.82) and PFS by investigator assessment (HR 0.61, 95% CI 0.52–0.71). At 1 year, PFS rates were greater in the Nab-Pac + Gem group compared with the Gem group (16 vs. 9%, independent review; 12 vs. 4%, investigator assessment).

The most common grade 3 or 4 adverse events (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.

No HRQoL data were collected in the CA046 trial [11]. Instead, the company presented early HRQoL results from the SIEGE trial [13], a phase II randomized 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. These data were collected using the European Organisation for Research and Treatment Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30). The company reported that Global Health Scores were generally stable throughout treatment; however, towards the end of the six-treatment-cycle period, data were difficult to interpret due to small patient numbers (n = 22 in the appropriate arm at week 24).

To allow a comparison of the effectiveness of treatment with Nab-Pac + Gem versus Gem + Cap and versus FOLFIRINOX, the company performed a network meta-analysis (NMA). Although a connected network could be formed by including only trials that compared treatments relevant to the decision problem, the company base-case network of ten trials [11, 14–22] included only three trials [11, 15, 16] that provided evidence for comparators listed in the final scope issued by NICE (i.e. Gem, Gem + Cap and FOLFIRINOX). The company also performed a sensitivity analysis using a reduced network that included only the comparators listed in the final scope issued by NICE. In terms of OS, the results from this sensitivity analysis mirrored the results from the base-case analysis and did not suggest a statistically significant treatment effect for Gem + Cap versus Nab-Pac + Gem (HR 1.10, 95% credible interval [CrI] 0.67–1.84) or for FOLFIRINOX versus Nab-Pac + Gem (HR 0.77, 95% CrI 0.58–1.01). For PFS, the results of the sensitivity analysis also mirrored the results from the base-case analysis which did not suggest a statistically significant treatment effect for Gem + Cap versus Nab-Pac + Gem (HR 1.17, 95% CrI 0.75–1.86); however, the results of the sensitivity analysis did suggest a statistically significant treatment effect for FOLFIRINOX versus Nab-Pac + Gem (HR 0.68, 95% CrI 0.51–0.91), unlike in the company's base-case analysis. The results of the company's base-case NMA and reduced network sensitivity analysis are shown in Table 3. The results from the company's base-case NMA were used in the company's cost-effectiveness model.

Throughout the CS, the company maintained the position that the only comparator to treatment with Nab-Pac + Gem was Gem. The company claimed that Gem + Cap was used only rarely within the NHS, therefore did not represent standard of care and was not a relevant comparator. The company contended that patients who are suitable for treatment with FOLFIRINOX are easily identified in clinical practice and are clinically distinct from patients who would be treated with Gem but who could be treated with Nab-Pac + Gem. The company contended that the use of Nab-Pac + Gem in the NHS would only displace the use of Gem and would not affect

Table 1 CA046 trial primary and secondary efficacy endpoints (17 September 2012) Source: Company submission, Table 13

Efficacy variable	Nab-Pac + Gem [*N* = 431]	Gem [*N* = 430]	HR (95% CI)	*p* value
OS				
Events [*n* (%)]	333 (77)	359 (83)	–	–
Censored [%]	23	17	–	–
Months [median (95% CI)]	8.5 (7.9–9.5)	6.7 (6.0–7.2)	0.72 (0.62–0.83)	< 0.001
12-month survival rate [% (95% CI)]	35 (30–39)	22 (18–27)	–	< 0.001
PFS (independent review)				
Events [*n* (%)]	277 (64)	265 (62)	–	–
Censored [%]	36	38	–	–
Months [median (95% CI)]	5.5 (4.5–5.9)	3.7 (3.6–4.0)	0.69 (0.58–0.82)	< 0.001
12-month PFS rate [% (95% CI)]	16 (12–21)	9 (5–14)	–	–
PFS (investigator assessment)				
Events [*n* (%)]	327 (76)	348 (81)	–	–
Censored [%]	24	19	–	–
Months [median (95% CI)]	5.3 (4.4–5.5)	3.5 (3.3–3.7)	0.61 (0.52–0.71)	< 0.001
12-month PFS rate [% (95% CI)]	12 (8.3–16.0)	4 (1.9–6.5)	–	–

CI confidence interval, *Gem* gemcitabine, *HR* hazard ratio, *Nab-Pac + Gem* paclitaxel as albumin-bound nanoparticles in combination with gemcitabine, *OS* overall survival, *PFS* progression-free survival

Table 2 Updated survival estimates in the CA046 trial (9 May 2013) Source: Company submission, Table 14

	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)	–	–
Months [median (95% CI)]	8.7 (7.9–9.7)	6.6 (6.0–7.2)	0.72 (0.62–0.83)	< 0.0001
Survival rate, months [% (95% CI)]				
6	66 (62–71)	55 (50–60)	–	–
12	35 (31–40)	22 (18–26)		
24	10 (6–13)	5 (2–7)		
36	4 (2–7)	0		
42	3 (1–6)	0		

CI confidence interval, *Gem* gemcitabine, *HR* hazard ratio, *Nab-Pac + Gem* paclitaxel as albumin-bound nanoparticles in combination with gemcitabine

Table 3 Results of company network meta-analysis Source: Company submission, Figure 15, Figure 17 and Table 40

Outcome	Comparator	Median HR vs. Nab-Pac + Gem (95% CrI)	
		Company base case	Reduced network sensitivity analysis
OS	Gem + Cap	0.970 (0.640–1.47)	1.10 (0.67–1.84)
	FOLFIRINOX	0.77 (0.580–1.01)	0.77 (0.58–1.01)
PFS	Gem + Cap	1.15 (1.00–1.70)	1.17 (0.75–1.86)
	FOLFIRINOX	0.77 (0.58–1.02)	0.68 (0.51–0.91)

CrI credible interval, *FOLFIRINOX* combination of oxaliplatin, irinotecan, leucovorin and fluorouracil, *Gem + Cap* gemcitabine in combination with capecitabine, *HR* hazard ratio, *Nab-Pac + Gem* paclitaxel as albumin-bound nanoparticles in combination with gemcitabine, *OS* overall survival, *PFS* progression-free survival

the current NHS usage of either Gem + Cap or FOLFIRINOX.

3.2 Critique of the Clinical Evidence and Interpretation

The ERG considered that the company's argument that Gem was the only relevant comparator was not compelling. The ERG noted that the company's own market research data suggested that although many patients in the NHS receive Gem monotherapy, a proportion of patients receive Gem doublet therapy (such as Gem + Cap). The ERG therefore considered the argument that Gem + Cap was not a relevant comparator due to its limited use to be invalid. The ERG also considered that the company had failed to define the patients who would be suited to treatment with Nab-Pac + Gem but not FOLFIRINOX. Clinical advice to the ERG was that it would be difficult to clearly establish which patients in the NHS would be better suited to treatment with Nab-Pac + Gem rather than with FOLFIRINOX. The ERG considered that the issue of identifying which patients are suitable for treatment with Nab-Pac + Gem, but not with FOLFIRINOX, remained unresolved from TA360, and the ERG was unconvinced by the company's argument that FOLFIRINOX was not a relevant comparator to Nab-Pac + Gem.

The ERG considered that the CA046 trial [11] was of good quality and well conducted. The trial data were mature and, with no patient crossover, the results allowed 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 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 was that patients recruited to the CA046 trial [11] were younger and fitter than the population of patients with metastatic disease treated in the NHS. Most notably, only 10% of patients recruited to the trial were aged $\geq$ 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 [23]. None of the participating treatment centres were based in the UK. The ERG considered the absence of HRQoL data from patients in the CA046 trial to be disappointing. The ERG also considered the HRQoL data from the phase II, dose-scheduling SIEGE trial to have the greatest relevance to the appraisal as it is a UK-based randomized trial that recruited patients with metastatic pancreatic cancer. However, it noted that only the 'concomitant arm' (i.e. treatment with Gem immediately after treatment with Nab-Pac) of the trial was relevant to this appraisal, which did not provide comparative data, and that only early results were available.

The ERG conducted assessments to determine the validity of the company's assumption that survival hazards were proportional over time, and thus that the HRs presented in the CS were appropriate. The ERG's analyses showed that over time the OS and PFS hazards from the two arms of the CA046 trial [11] were not proportional. Consequently, all HR results derived from the CA046 trial [11] should be interpreted with caution. Furthermore, the ERG highlighted that all of the company's NMA results (base-case and sensitivity analyses) were affected by the lack of proportional hazards (PH) in the CA046 trial [11] and these results should also be interpreted with caution. Additionally, the ERG considered the results from the company's reduced NMA to be more appropriate than the company's base-case NMA results.

3.3 Cost-Effectiveness Evidence

The company adapted the model submitted within the original submission to NICE for appraisal TA360 [2] rather than constructing a de novo economic model. The company used a Markov structure and employed an area under the curve approach to estimating the proportion of patients who transition between health states over time from the start of treatment until death. There were three primary health states in the model: pre-progression, post-progression and death. The pre-progression state was divided 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 was discontinued before progression. The company 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.

Kaplan–Meier (K–M) data from the CA046 trial [11] were used as the basis for estimating patient survival for the comparison of treatment with Nab-Pac + Gem versus Gem. 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 [11], published sources and advice from clinical experts. A confidential Department of Health PAS discount was applied to the cost of Nab-Pac. Full list prices, accessed via the drugs and pharmaceutical electronic market information tool [24], the MIMS database [25] and the British National Formulary [26] in January 2017, were used to calculate the cost of all other drugs. No vial sharing was assumed. Overall drug costs in the first-line setting were subject to the assumption that 50% of all first-time dose reductions and all subsequent dose reductions could be anticipated, meaning that there would be no drug wastage

from these reductions. The company also assumed that 50% of all missed doses could be anticipated. Chemotherapy administration costs, monitoring costs, AE costs, and the cost of palliative and end-of-life care were sourced from NHS reference costs 2015/2016 [27] and the Personal Social Services Research Unit 2016 [28].

The company's base-case analysis prediction was a mean of 0.927 life-years (LYs) gained for patients receiving Nab-Pac + Gem, 0.725 LYs gained for patients receiving Gem, 0.950 LYs gained for patients receiving Gem + Cap and 1.154 LYs gained for patients receiving FOLFIRINOX.

As HRQoL data were not collected as part of the CA046 trial, the company instead adjusted published health state utility values [29] 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 in separate scenario analyses.

The company submitted an updated model during the clarification process to correct an error. The company's base-case incremental cost-effectiveness ratio (ICER) for the comparison of treatment with Nab-Pac + Gem versus Gem from the updated model was £46,932 per quality-adjusted life-year (QALY) gained. Treatment with Nab-Pac + Gem was dominated (more costly and generated fewer QALYs) by treatment with both Gem + Cap and with FOLFIRINOX.

The company carried out a wide range of deterministic sensitivity analyses for the comparison of treatment with Nab-Pac + Gem versus Gem. The results showed that the most influential parameter was the treatment variable used to parameterise OS.

The results of the company's probabilistic sensitivity analysis showed that Nab-Pac + Gem had a 64% probability of being cost effective compared with Gem at a willingness-to-pay threshold of £50,000 per QALY gained.

3.4 Critique of the Cost-Effectiveness Evidence and Interpretation

The ERG considered the company's model to be generally well-structured and correctly implemented. The ERG amended one structural feature in the calculation of total LYs and QALYs. The three key issues that required exploration by the ERG in the company's model were HRs used for treatment with Gem + Cap and with FOLFIRINOX, costing of drugs, and modelling of TOT.

The company used HRs from its base-case NMA to estimate time-to-event outcomes for treatment with Gem + Cap and with FOLFIRINOX, which relied on the PH assumption holding for PFS and OS within the CA046 trial [11]. Since PH had been shown not to hold for PFS or OS in the CA046 trial [11], using the results of the NMA in the model produced unreliable estimates for OS, PFS and TOT for treatment with Gem + Cap and with FOLFIRINOX. The ERG also had concerns about the company's use of HRs with a stratified Gamma model as the Gamma model is an accelerated failure time model rather than a PH model. The ERG applied published HRs for treatment with Gem + Cap versus Gem [15] and with FOLFIRINOX versus Gem [16] in the model to overcome the need for PH to hold in the CA046 trial [11]; however, PH did not hold for FOLFIRINOX versus Gem for either PFS or OS. The ERG considered that results for the comparison of treatment with Nab-Pac + Gem versus Gem + Cap and versus FOLFIRINOX should be treated with caution.

The company 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 estimated lower average weekly costs for each first-line treatment in the company model.

The ERG prefers the use of K–M data directly as far as possible when time-to-event evidence comes from a single trial, especially when the trial data are mature. The TOT data from the CA046 trial (supplied by the company during the clarification process) were complete and therefore represented the best possible evidence of time spent on treatment for the patients in that trial. However, the company used a fully parametric model to estimate TOT, which introduced unnecessary uncertainties into the analysis and resulted in an overestimation of TOT for both treatments. The ERG re-estimated TOT for treatment with Nab-Pac + Gem and with Gem using K–M data directly from the CA046 trial.

The company 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 remodelling 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 included the double counting of AE disutilities. The ERG provided two scenario analyses that investigate the impact of using different costs for some AEs and using a different source of utility values. The impact of the ERG's various amendments on the company's base-case ICER per QALY gained are shown in Table 4.

Table 4 Cost-effectiveness results: ERG revisions to company base case Source: ERG report, Table 47, Table 48 and Table 49

Description	Nab-Pac + Gem vs. Gem	Nab-Pac + Gem vs. Gem + Cap	Nab-Pac + Gem vs. FOLFIRINOX
Company original base case	£46,657	Dominated	Dominated
Company updated base case	£46,932	Dominated	Dominated
ERG corrected company base case	£47,011	Dominated	Dominated
R1) HRs for Gem + Cap vs. Gem	–	£103,827	–
R2) HRs for FOLFIRINOX vs. Gem	£47,012	Dominated	£3327
R3) ERG drug-costing method	£39,289	Dominated	Dominated
R4) TOT from CA046 trial	£49,922	Dominated	Dominated
R5) Do not apply AE disutilities	£46,994	Dominated	Dominated
R6) ERG OS	£46,681	Dominated	Dominated
R7) ERG PFS	£46,933	Dominated	Dominated
ERG revised base case (R3, R4, R5, R6, R7)	£41,250	–	–
ERG revised base case (R1, R3, R4, R5, R6, R7)	–	£99,837	–
ERG revised base case (R2, R3, R4, R5, R6, R7)	–	–	Dominated

AE adverse event, *ERG* Evidence Review Group, *FOLFIRINOX* combination of oxaliplatin, irinotecan, leucovorin and fluorouracil, *Gem* gemcitabine, *Gem + Cap* gemcitabine in combination with capecitabine, *HRs* hazard ratios, *Nab-Pac + Gem* paclitaxel as albumin-bound nanoparticles in combination with gemcitabine, *Nab-Pac + Gem* paclitaxel as albumin-bound nanoparticles in combination with gemcitabine, *PFS* progression-free survival, *OS* overall survival, *TOT* time on treatment

3.5 Conclusions of the ERG Report

The ERG considered that the evidence submitted by the company largely reflected the decision problem defined in the final scope issued by NICE, although direct clinical effectiveness evidence was only available for the comparison of the efficacy of Nab-Pac + Gem versus Gem.

The ERG noted that since the PH assumption for OS and PFS in the CA046 trial was violated, any HRs resulting from that trial should be treated with caution. This was true for the CA046 trial and the company's NMA. The true clinical effectiveness of Nab-Pac + Gem compared with Gem, Gem + Cap or FOLFIRINOX remains to be established.

The ERG considered that the company had failed to clearly define the patient population for whom treatment with Nab-Pac + Gem is appropriate. The ERG remained unconvinced by the company's case for Gem as the only comparator to Nab-Pac + Gem.

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 yielded a mixture of effects. Incremental costs and incremental benefits both increased and decreased depending on the individual revision. However, none of the ERG's individual revisions or revised base-case scenarios yielded 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 yielded ICERs under £50,000 per QALY gained once all the ERG's revisions and scenarios were applied.

4 National Institute for Health and Care Excellence Guidance

The AC reviewed the evidence available on the clinical and cost effectiveness of Nab-Pac + Gem alongside expert testimony from clinical experts and patient representatives.

4.1 Clinical Need and Patient Perspective

The AC accepted that metastatic pancreatic cancer carries a poor prognosis and that there are concerns with current treatment options, i.e. that treatment with FOLFIRINOX is more effective but can result in serious AEs, whereas treatment with Gem is better tolerated but is less effective. It heard from the patient expert that many patients would be willing to accept some additional side effects from treatment if it resulted in a longer life expectancy. The AC recognised the value of additional treatment options in this area.

4.2 Current Practice and Comparators

The AC heard from the clinical experts that FOLFIRINOX was the preferred choice in clinical practice for treating

patients with untreated metastatic pancreatic cancer. It understood that FOLFIRINOX is associated with better survival rates but that it can be associated with serious AEs. It heard that patients who were not considered fit enough for treatment with FOLFIRINOX would be offered Gem monotherapy. The clinical experts indicated that there exists a group of patients in clinical practice who are not fit enough to tolerate FOFIRINOX but who would be fit enough to tolerate Nab-Pac + Gem. The AC heard that this group of patients is not easy to define using specific criteria as it depends on the interaction of a number of factors, such as age, PS, comorbidities and patient willingness to accept the considerable toxicity. Clinical experts explained that Gem + Cap is rarely used in clinical practice, but the AC noted that there is evidence that Gem doublet therapy is used in the NHS in England to treat pancreatic cancer.

The AC concluded that, although Gem monotherapy, FOLFIRINOX and Gem + Cap were all potentially relevant comparators for patients with untreated metastatic pancreatic cancer, Gem monotherapy was the most appropriate comparator for a subpopulation of patients for whom other combination therapies were not suitable.

4.3 Clinical Effectiveness

The AC noted that the CA046 trial [11] showed that patients treated with Nab-Pac + Gem had statistically significantly longer OS and PFS, and higher response rates, than those treated with Gem monotherapy. The AC noted the ERG's concern that older patients were under represented in the CA046 trial; however, the AC understood that clinicians would be cautious about using Nab-Pac + Gem in an older population, therefore the evidence from the CA046 trial was suitable for decision making. The AC concluded that Nab-Pac + Gem was more clinically effective than Gem monotherapy.

The AC understood that there was uncertainty in the effectiveness estimates for treatment with FOLFIRINOX and with Gem + Cap; however, it considered that the NMAs presented were preferable to having no data at all on the effectiveness of treatment with Nab-Pac + Gem versus FOLFIRINOX and versus Gem + Cap. Noting the results of the NMAs, the AC concluded that Nab-Pac + Gem was likely to be less clinically effective than treatment with FOLFIRINOX, and similarly effective to Gem + Cap.

The AC noted that Nab-Pac + Gem was associated with more AEs than Gem monotherapy. It heard that combination therapies were likely to result in increased AE rates over monotherapies. The AC recognised that it was difficult to draw firm conclusions about the rates of AEs between treatment with Nab-Pac + Gem and Gem + Cap given the available data. The AC concluded that Nab-Pac + Gem may be associated with more AEs than Gem or Gem + Cap. The AC recalled that it concluded in TA360 [2] that a difference in AE profiles between treatment with Nab-Pac + Gem and FOLRINOX could not be reliably determined from the available data.

4.4 Cost Effectiveness

The AC agreed that the company's model was structured appropriately and that the assumptions were generally reasonable. The AC accepted the ERG's amendments to the company base case but noted that they did not make a substantial difference to the cost-effectiveness estimates.

The AC noted that neither the company base case nor any of the ERG scenarios took the estimated ICER for treatment with Nab-Pac + Gem versus Gem above £50,000 per QALY gained. The AC concluded that the most plausible ICER for treatment with Nab-Pac + Gem versus Gem was between £41,000 and £46,000 per QALY gained. The AC noted that both the company base case and ERG revised base case showed that treatment with Nab-Pac + Gem was dominated by treatment with FOLFIRINOX. It also noted that the company base case showed that treatment with Nab-Pac + Gem was dominated by treatment with Gem + Cap, whereas the ERG revised base case yielded an ICER of £99,837 per QALY gained for the same comparison. The AC was confident that, despite the uncertainty in the analyses, treatment with Nab-Pac + Gem would not be considered a cost-effective treatment versus Gem + Cap or versus FOLFIRINOX.

4.5 End-of-Life Criteria

The AC noted that life expectancy for patients with untreated metastatic pancreatic cancer was up to 6 months, therefore the short life expectancy criterion was met. It understood that the expected mean survival gain for treatment with Nab-Pac + Gem versus Gem was < 3 months (2.4 months), but recognised that this survival gain should be considered in the context of the average survival of patients with the condition. It therefore considered that the life-extending criterion was met in the comparison of Nab-Pac + Gem versus Gem. However, the AC concluded that there was no survival benefit shown in the comparison of Nab-Pac + Gem versus Gem + Cap or versus FOLFIRINOX, therefore the life-extending criterion was not met for these comparators. The AC therefore concluded that treatment with Nab-Pac + Gem met the end-of-life criteria when compared with treatment with Gem, but not when compared with treatment with Gem + Cap or FOLFIRINOX.

4.6 Final Guidance

The AC recommended Nab-Pac + Gem for patients with untreated metastatic pancreatic cancer for whom other combination therapies were unsuitable and who would otherwise receive Gem monotherapy. The final guidance was published by NICE in September 2017.

5 Conclusions

The key issue in this appraisal was not methodological but rather about how to identify the appropriate population for treatment with Nab-Pac + Gem. Although the ERG considered that some of the company's cost-effectiveness methods and assumptions had limitations, none of the ERG's model amendments made important differences to the estimated ICERs per QALY gained for the comparison of Nab-Pac + Gem versus Gem, Gem + Cap or FOLFIRINOX. Since treatment with Nab-Pac + Gem was only shown to be cost-effective versus treatment with Gem, it remained to identify a population for whom only Gem would be a suitable treatment in current clinical practice. Neither the company nor the clinical experts present at the AC meeting could provide evidence or advice to help definitively categorise the population who would have been fit enough for treatment with Nab-Pac + Gem, and for whom treatment with FOLFIRINOX or Gem + Cap would not have been suitable and who would otherwise have received treatment with Gem. Ultimately, the AC left the decision about the appropriate population up to individual clinicians on a case-by-case basis.

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 ERG report. Dr Leonard has no competing interests to declare.

Author Contributions AS: Critical appraisal of the economic evidence/model. JG: Project lead, drafted the clinical results section and supervised production of the final report. AB: Critical appraisal of the economic evidence/model. MR: Critical appraisal of the statistical evidence. AB: Ongoing source of methodological advice. SB: Ongoing source of methodological advice. RD: Critical appraisal of the AE evidence. EK: Cross-checking of the submission search strategies. LB: Critical appraisal of the company submission. DP: Critical appraisal of the clinical evidence. All authors read and commented on draft versions of this paper. This summary has not been externally reviewed by *PharmacoEconomics*.

Compliance with Ethical Standards

Funding This project was funded by the National Institute for Health Research Health Technology Programme (project number 14/90/01; see the Health Technology Assessment programme website for further project information, http://www.hta.ac.uk). The views and opinions expressed are those of the authors and do not necessarily reflect those of the National Institute of Health and Care Excellence or the Department of Health.

Conflict of interest Daniel Palmer has received consultancy fees from Celgene. Angela Stainthorpe, Janette Greenhalgh, Adrian Bagust, Marty Richardson, Angela Boland, Sophie Beale, Rui Duarte, Eleanor Kotas, Lindsay Banks have no competing interests.

References

1. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal. 2013. Available at: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. Accessed May 2017.
2. National Institute for Health and Care Excellence (NICE). Paclitaxel as albumin-bound nanoparticles in combination with gemcitabine for previously untreated metastatic pancreatic cancer [TA360]. 2015. Available at: https://www.nice.org.uk/guidance/ta360/history. Accessed May 2017.
3. National Institute for Health and Care Excellence (NICE). Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]. 2017. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10116. Accessed June 2017.
4. World Health Organisation (WHO) International Agency for Research on Cancer. Cancer Today. 2017. Available at: http://gco.iarc.fr/today/home. Accessed June 2017.
5. Cancer Research UK (CRUK). Pancreatic cancer mortality statistics. 2017. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/pancreatic-cancer/mortality. Accessed June 2017.
6. Cancer Research UK (CRUK). Pancreatic cancer survival statistics. 2017. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/pancreatic-cancer/survival. Accessed June 2017.
7. England PH. National Cancer Registration and Analysis Service: Routes to Diagnosis 2006–2013 workbook (a). 2017. Available at: http://www.ncin.org.uk/publications/routes_to_diagnosis. Accessed 21 Aug 2017.
8. Macmillan Cancer Support. Symptoms of pancreatic cancer. 2016. Available at: http://www.macmillan.org.uk/information-and-support/pancreatic-cancer/understanding-cancer/symptoms-of-pancreatic-cancer.html. Accessed 21 Aug 2017.
9. National Institute for Health and Care Excellence (NICE). Guidance on the use of gemcitabine for the treatment of pancreatic cancer [TA25]. 2001. Available at: https://www.nice.org.uk/guidance/ta25. Accessed May 2017.
10. National Institute for Health and Care Excellence (NICE). Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer [ID1058]: Committee Papers. 2017. Available at: https://www.nice.org.uk/guidance/gid-ta10116/documents/committee-papers. Accessed 21 Aug 2017.
11. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.

12. Goldstein D, El-Maraghi RH, Hammel P, Heinemann V, Kunzmann V, Sastre J, et al. Nab-paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. J Natl Cancer Inst. 2015;107(2) **(pii: dju413)**.
13. Corrie P, Qian W, Basu B, Jodrell DI, Falk S, Iwuji C, et al. A Randomised phase II trial comparing different schedules of nab-paclitaxel combined with gemcitabine as first line treatment for metastatic pancreatic cancer. In: ASCO Gastrointestinal Cancers Symposium 2017; San Francisco, CA.
14. Boeck S, Hoehler T, Seipelt G, Mahlberg R, Wein A, Hochhaus A, et al. Capecitabine plus oxaliplatin (CapOx) versus capecitabine plus gemcitabine (CapGem) versus gemcitabine plus oxaliplatin (mGemOx): final results of a multicenter randomized phase II trial in advanced pancreatic cancer. Ann Oncol. 2008;19(2):340–7.
15. Scheithauer W, Schull B, Ulrich-Pur H, Schmid K, Raderer M, Haider K, et al. Biweekly high-dose gemcitabine alone or in combination with capecitabine in patients with metastatic pancreatic adenocarcinoma: a randomized phase II trial. Ann Oncol. 2003;14(1):97–104.
16. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. Folfirinox versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
17. Wang JP, Wu CY, Yeh YC, Shyr YM, Wu YY, Kuo CY, et al. Erlotinib is effective in pancreatic cancer with epidermal growth factor receptor mutations: a randomized, open-label, prospective trial. Oncotarget. 2015;6(20):18162–73.
18. Heinemann V, Quietzsch D, Gieseler F, Gonnermann M, Schonekas H, Rost A, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol. 2006;24(24):3946–52.
19. Chao Y, Wu CY, Wang JP, Lee RC, Lee WP, Li CP. A randomized controlled trial of gemcitabine plus cisplatin versus gemcitabine alone in the treatment of metastatic pancreatic cancer. Cancer Chemother Pharmacol. 2013;72(3):637–42.
20. Kulke MH, Tempero MA, Niedzwiecki D, Hollis DR, Kindler HL, Cusnir M, et al. Randomized phase II study of gemcitabine administered at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in patients with metastatic pancreatic cancer: CALGB 89904. J Clin Oncol. 2009;27:5506–12.
21. Rocha Lima CM, Green MR, Rotche R, Miller WH Jr, Jeffrey GM, Cisar LA, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol. 2004;22(18):3776–83.
22. Louvet C, Labianca R, Hammel P, Lledo G, Zampino MG, Andre T, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol. 2005;23(15):3509–16.
23. Cancer Research UK (CRUK). Pancreatic cancer. 2015. Available at: http://www.cancerresearchuk.org/about-cancer/type/pancreatic-cancer/. Accessed May 2017.
24. Department of Health. Commercial Medicines Unit. Electronic market information tool (eMit). Available at: http://cmu.dh.gov.uk/electronic-market-information-tool-emit/. Accessed Oct 2017.
25. MIMS UK. 2016. Available at: https://www.mims.co.uk/.
26. Joint Formulary Committee. British National Formulary (BNF). 2017. Available at: https://www.evidence.nhs.uk/formulary/bnf/current. Accessed May 2017.
27. Department of Health. NHS reference costs 2015 to 2016. 2016. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-collection-guidance-for-2015-to-2016. Accessed May 2017.
28. Curtis L, Burns A. Unit costs of health and social care. 2016. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2016/. Accessed May 2017.
29. Romanus D, Kindler HL, Archer L, Basch E, Niedzwiecki D, Weeks J, et al. Does health-related quality of life improve for advanced pancreatic cancer patients who respond to gemcitabine? Analysis of a randomized phase III trial of the cancer and leukemia group B (CALGB 80303). J Pain Symptom Manag. 2012;43(2):205–17.