NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pegylated liposomal irinotecan hydrochloride trihydrate for treating pancreatic cancer after gemcitabine [ID778]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Pegylated liposomal irinotecan hydrochloride trihydrate for treating pancreatic cancer after gemcitabine

This premeeting briefing presents:

- 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.

Key issues for consideration

Clinical effectiveness

Generalisability of the NAPOLI-1 trial

- The ERG noted that the NAPOLI-1 trial, compared pegylated liposomal irinotecan hydrochloride trihydrate plus 5-fluorouracil + leucovorin (nal-iri plus 5-FU/LV) with 5-FU/LV, in people with pancreatic cancer after gemcitabine treatment was the only direct evidence. It also noted that a greater proportion of patients, who had previously received gemcitabine, received combination therapy (54.2%) and fewer patients had received gemcitabine monotherapy (45.8%), with the latter being considered more common treatment in the NHS in England. Is the population in the NAPOLI-1 trial generalisable to the population in England?

Relevant comparators

- The company carried out a direct comparison of nal-iri plus 5-FU/LV with 5-FU/LV using data from the NAPOLI-1 trial. However the company and the ERG considered oxaliplatin plus 5-FU/LV to be the current standard of care in England and the most appropriate comparator. Which treatment does the committee consider to be the most relevant comparator for nal-iri plus 5-FU/LV?

Indirect comparison

- There are no published trials to compare the effectiveness of nal-iri plus 5-FU/LV with some of the comparators in the NICE final scope (oxaliplatin plus 5-FU/LV, capecitabine monotherapy or oxaliplatin plus capecitabine). The company considered that there were no suitable trials to carry out an indirect comparison (but for cost-effectiveness analysis did conduct one anyway for nal-iri plus 5-FU/LV compared with oxaliplatin plus 5-FU/LV). The company also did not consider oxaliplatin plus capecitabine or capecitabine alone to be suitable comparators. Does the committee agree that an indirect comparison could not be performed for nal-iri plus 5-FU/LV with oxaliplatin plus capecitabine or capecitabine?

Cost effectiveness

Parametric curve fitting of trial data

- The company fitted parametric curves (log-normal curves in base case and log-logistic in a scenario analysis) to the progression-free survival, overall survival and time to treatment failure data from the NAPOLI-1 trial. The ERG considered this inappropriate because most of the data from the trial were complete. It also noted that the use of the Kaplan-Meier data from the NAPOLI-1 trial, rather than using the parametric models, reduced the mean survival gain for nal-iri plus 5-FU/LV compared with 5-FU/LV from 2.5 to 1.807 months. Is it acceptable to use parametric curves fitted to the Kaplan-Meier curves rather than the direct trial data?

Drug costs

- The ERG noted a number of issues with the drug costs included in the company's submission:
  - The company assumed that a reduction in nal-iri plus 5-FU/LV, 5-FU/LV or oxaliplatin plus 5-FU/LV dosing, based on the NAPOLI-1 trial, would in turn reduce drug costs. The ERG commented that this would only happen in the NHS if the dose reduction was known far enough in advance to allow the pharmacy to alter the parenteral formulations.
  - All drugs used in the company's submission except for nal-iri are available in generic form. The ERG noted that the company's model overestimated the cost of generic drugs by using the British National Formulary (BNF) rather than the drugs and pharmaceutical electronic market information (eMiT) as a pricing source.
  - The model also excludes the most economical treatment achievable by mixing different vial sizes, for the comparator drugs, and only uses the smallest vial sizes, which excludes potential cost savings.

  Are the costs in the company's model a true reflection of the costs to the NHS?

Hazard ratios

- The company developed progression-free survival and overall survival hazard ratios, using the Bucher adjusted indirect comparison method, to generate estimates for the effectiveness of nal-iri plus 5-FU/LV compared with oxaliplatin plus 5-FU/LV. The company and the ERG noted a number of limitations with this comparison including the possible heterogeneity both reported (trial location, patient characteristics, prior treatment with gemcitabine monotherapy compared with combination therapy) and unreported, across the included trials and also the use of hazard ratios in the company's model even though the proportional hazards assumption is violated. Are the hazard ratios for this comparison credible and does the indirect comparison hold?

Health-related quality of life data and utility values

- The cancer-specific EORTC-QLQ-C30 questionnaire was used during the NAPOLI-1 trial to collect HRQoL data but the company did not map this to the EQ-5D because of missing information and the lack of a suitable algorithm. Instead the company used data from the literature:
  - Utility values from a US study, adjusted to reflect values of the UK population and to include disutility associated with adverse events, were used in the company model. However, the ERG considered these utility values for untreated patients to be an overestimate of patient health-related quality of life.
  - In the company's model the pre-progression health state for all treatments was assigned a utility value of 0.742, and the post-progression health state for all treatments was assigned a value of 0.671 in the company's base case (corrected by the company during clarification because a value of 0.672 was originally included in company's submission), regardless of the treatment. The ERG's preferred values were 0.671 and 0.600 respectively.

  Are the company's utility values appropriate?

Plausible ICER

- The company considered its most plausible ICER (using log-normal parametric curve models) to be £[redacted] per QALY gained for the comparison of nal-iri plus 5-FU/LV with 5-FU/LV and £[redacted] per QALY gained for the comparison of nal-iri plus 5-FU/LV with oxaliplatin plus 5-FU/LV
  - The ERG updated the post-progression utility value in the company's model which altered the ICERs slightly (£[redacted] per QALY gained for of nal-iri plus 5-FU/LV with 5-FU/LV and £[redacted] per QALY gained for oxaliplatin plus 5-FU/LV)
- The ERG considered its most plausible ICER for the comparison of nal-iri plus 5-FU/LV compared with 5-FU/LV, including all the ERG's assumptions (using Kaplan-Meier data for survival analyses, updated costs and updated utility values) to be £[redacted] per QALY gained.

- The ERG did not consider it possible to determine a most plausible ICER for the comparison with oxaliplatin plus 5-FU/LV because of the uncertainties of the indirect comparison.

What does the committee consider to be the most plausible ICER?

End of life

- Does nal-iri plus 5-FU/LV meet the end of life criteria?
- The company stated that:
  - Patients have a short life expectancy - median life expectancy at diagnosis 4.6 months in patients with pancreatic cancer irrespective of stage of diagnosis, and the median survival for patients with metastatic disease was 2.8–5.7 months
  - NAPOLI-1 trial showed a 1.9 month gain in median overall survival for nal-iri plus 5-FU/LV compared with 5-FU/LV (representing a 45% increase in overall survival). The company's model for this comparison showed a median of 2.09 months and a mean of 2.51 months (these were reported in the company's submission as 1.57 months and 2.52 months respectively)
- The ERG noted:
  - Life expectancy for patients with pancreatic cancer after gemcitabine treatment is short
  - In the amended model, including the ERG's changes, the mean survival gain for nal-iri plus 5-FU/LV compared with 5-FU/LV was 1.807 months
  - The ERG could not provide a reliable comparison of survival between nal-iri plus 5-FU/LV and oxaliplatin plus 5-FU/LV but noted that in the oxaliplatin trials the median overall survival was similar to nal-iri plus 5-FU/LV
  - The most appropriate comparator was oxaliplatin plus 5-FU/LV and the ERG acknowledged that there is a lack of reliable evidence for this comparison. The weight of evidence from the ERG's crude comparisons suggests that overall survival for patients treated with oxaliplatin plus 5-FU/LV is very similar in magnitude to overall survival for patients who were treated with nal-iri plus 5-FU/LV in the NAPOLI-1 trial

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of nal-iri within its marketing authorisation for treating metastatic adenocarcinoma of the pancreas after prior treatment with gemcitabine-based treatments.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	People with metastatic adenocarcinoma of the pancreas that has been treated with gemcitabine-based treatments		NA	NA
Int.	Nal-iri in combination with fluorouracil and folinic acid		NA	NA
Com.	• Oxaliplatin in combination with fluorouracil and folinic acid • Oxaliplatin in combination with capecitabine • Fluoropyrimidine monotherapy	• Oxaliplatin in combination with fluorouracil and folinic acid • Fluoropyrimidine monotherapy: 5-fluorouracil + leucovorin (5-FU/LV)	There were no available data suitable for an indirect comparison for nal-iri + 5-FU/LV vs oxaliplatin + capecitabine. In addition, clinical expert opinion is that oxaliplatin + capecitabine is infrequently in clinical practice for post-gemcitabine treatment in pancreatic cancer	The ERG considered that oxaliplatin in combination with fluorouracil and folinic acid is the standard of care in England and therefore the most appropriate comparator. It considered that 5-FU/LV is rarely used in clinical practice.
Out.	• overall survival • progression-free survival • response rates • adverse effects of treatment health-related quality of life		NA	NA

2 The technology and the treatment pathway

2.1 Pegylated liposomal irinotecan hydrochloride trihydrate (nal-iri) (Onivyde, Shire) consists of the anti-cancer medicine irinotecan contained within tiny fat particles called nanoliposomes. The nanoliposomes are expected to accumulate within the tumour and release the irinotecan slowly over time. Irinotecan blocks an enzyme called topoisomerase I, which causes DNA strands to break. This prevents the cancer cells from dividing and they eventually die. Nal-iri received a positive CHMP opinion as follows: for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5 fluorouracil (5-FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine based therapy.

2.2 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 pancreatic ductal adenocarcinoma. 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. There is no set pathway for treating locally advanced or metastatic pancreatic cancer. 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. Alternatively in clinical practice people can receive a combination treatment including oxaliplatin with 5-fluorouracil (5-FU), leucovorin (LV) and irinotecan, also known as FOLFIRINOX. NICE technology appraisal guidance 25 states that there is insufficient evidence to support the use of gemcitabine as a second-line treatment in patients with pancreatic adenocarcinoma. For patients whose pancreatic cancer has relapsed after initial treatment oxaliplatin plus 5-FU/LV (FOLFOX) is a possible treatment and comes in different regimens (modified FOLFOX4

(mFOLFOX4), modified FOLFOX6 (mFOLFOX6) and oxaliplatin plus 5-FU/LV (OFF) (see page 26 of ERG report for further regimen details). Capecitabine monotherapy or in combination with oxaliplatin are also options for treating patients if oxaliplatin plus 5-FU/LV is not used.

Table 2 Technology

	Nal-iri	**Oxaliplatin in combination with fluorouracil and folinic acid**	**5-fluorouracil + leucovorin (folinic acid)**
Marketing authorisation	Positive CHMP opinion expected July 2016: for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5 fluorouracil (5-FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine based therapy	Oxaliplatin in combination with 5-fluorouracil and folinic acid does not have a marketing authorisation for pancreatic cancer. It does have a marketing authorisation for adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour and treatment of metastatic colorectal cancer	Fluorouracil has a marketing authorisation for the treatment of advanced pancreatic cancer Folinic acid has a marketing authorisation for use in combination with 5-fluorouracil in cytotoxic therapy
Administration method and dosing frequency	Intravenous infusion. 80 mg/m^2 nal-iri, 400 mg/m^2 LV, followed by 2400 mg/m^2 5-FU over 46 hours given every 2 weeks	Intravenous infusion or bolus injection. 85 mg/m^2 oxaliplatin on day 1, 200 mg/m^2 LV followed by 1000 mg/m^2 5-FU on day 1 over 46 hours given every 2 weeks	Intravenous infusion. LV at a dose of 200 mg/m^2 followed by 2,000 mg/m^2 5-FU over 24 hours administered on days 1, 8, 15 and 22, followed by 2 weeks of rest, in a 6-week cycle
Price and cost per cycle	Indicative cost per vial from company submission is [redacted] Cost per course is [redacted]. The company anticipates an average course of 8 treatments.	Oxaliplatin £10.62* per 50mg/10ml vial 5-FU - £0.93* per 500mg/10ml vial Leucovorin - £0.27* for 28 pack of 5mg tablets	5-FU - £0.93* per 500mg/10ml vial Leucovorin - £0.27* for 28 pack of 5mg tablets

See summary of product characteristics for details on adverse reactions and contraindications.

*from eMiT

3 Comments from consultees

3.1 The clinical experts indicated that gemcitabine has been the first-line treatment for patients with metastatic pancreatic cancer until recently when two combination chemotherapy treatments, FOLFIRINOX and gemcitabine plus nab-paclitaxel, became available. However gemcitabine plus nab-paclitaxel has now been removed from the Cancer Drugs Fund and had previously received negative NICE guidance so is only available through clinical trials. One clinical expert commented that one third of pancreatic cancer patients would be able to tolerate second-line treatment although there are currently no standard second-line treatments in the UK. Patients who have previously received gemcitabine-based chemotherapy may be offered a 5-FU-based chemotherapy regimen as second-line treatment and this can include capecitabine for patients with an ECOG 2 or combination regimens such as FOLFOX (oxaliplatin + 5FU/LV).

3.2 A patient and carer group noted how few treatments are currently available for metastatic advanced pancreatic cancer. The patient group commented that the most important outcomes to patients are extension in overall survival, management of side effects of therapy (neuropathy is a common side effect of oxaliplatin treatment) and the impact of treatment on quality of life. Patients also consider a licensed and recommended second-line treatment as important.

3.3 A clinical expert commented that there are no particular concerns or issues regarding use of nal-iri compared with other similar cytotoxic drugs. They also noted that the NAPOLI-1 trial was generally representative of UK clinical practice and contained some UK patients, although some patients had received gemcitabine plus nab-paclitaxel as first-line treatment, which is no longer funded via the CDF in the UK. The clinical experts also noted that the main toxicities of nal-iri; myelosuppression, diarrhoea, nausea and vomiting, fatigue, decreased appetite and fever are

common to cytotoxic chemotherapy treatments and should be straightforward to manage.

3.4 One clinical expert noted that delivery of nal-iri plus 5FU/LV does not pose any significant issues. Staff would require minimal education and training and no new facilities or equipment would be required. Patients would also receive the standard blood tests and CT scans. Another clinical expert commented that nal-iri would be used in oncology units accredited through the national peer review process for the administration of systemic chemotherapy but that the number of metastatic pancreatic cancer patients accessing second-line treatment is small meaning little impact on capacity.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company included one randomised controlled trial, NAPOLI-1, which was a multi-centre, multi-national study (4 sites in UK with 28 patients) comparing nal-iri plus 5-FU/LV (n=117) with 5-FU/LV (n=119) (and also nal-iri alone but this is not a relevant comparator and will not be discussed further). The trial included people whose pancreatic cancer was metastatic and had previously been treated with gemcitabine. All patients were required to have UGT1A1 genotype testing prior to enrolment in the study, because of a probable link between homozygosity of the UGT1A1*28 allele and irinotecan toxicity. People with pancreatic cancer that was homozygous for the UGT1A1*28 allele, and randomised to the nal-iri plus 5-FU/LV group started treatment at a reduced dose, which was increased if no drug-related toxicity was experienced after the first administration of nal-iri. Patients were randomised in the trial by baseline albumin levels (≥4.0 g/dL vs <4.0 g/dL), ethnicity and the karnofsky performance score, to classify function (70 and 80 vs ≥90). Some of the baseline characteristics of the patients in the study are shown in Table 3:

Table 3. Baseline characteristics of patients in NAPOLI-1 trial (intention to treat population). See company submission page 59 for full details.

Characteristic	Nal-iri + 5-FU/LV (n=117)	5-FU/LV control (n=119)[†]
Gender, n (%)		
Female	48 (41.0)	52 (43.7)
Male	69 (59.0)	67 (56.3)
Age, years, mean (SD)	63.2 (9.06)	61.0 (9.46)
Karnofsky Performance Score, n (%)		
50	1 (0.9)	0
60	2 (1.7)	0
70	7 (6.0)	10 (8.4)
80	38 (32.5)	51 (42.9)
90	51 (43.6)	40 (33.6)
100	18 (15.4)	17 (14.3)
Previous anti-cancer therapy, n (%)		
Gemcitabine alone	53 (45.3)	55 (46.2)
Gemcitabine combination	64 (54.7)	64 (53.8)
Fluorouracil-based	50 (42.7)	52 (43.7)
Irinotecan-based	12 (10.3)	17 (14.3)
Platinum-based	38 (32.5)	41 (34.5)

4.2 The primary endpoint of the trial was overall survival (time from patient randomisation to death or last known date alive). Overall survival was censored at the date of last contact if it was not known whether the patient had died.

4.3 Secondary endpoints in the trial were progression-free survival, time to treatment failure, objective response rate, tumour marker response of CA19-9, clinical benefit response rate, patient reported outcomes (using the European Organisation for Research and Treatment of Cancer [EORTC] quality-of-life core questionnaire [EORTC-QLQ-C30]) and the safety and adverse event profile of nal-iri.

4.4 There were several pre-specified populations included in the NAPOLI-1 trial (for definitions of the populations see Box 3, page 41 of ERG report). The intention-to-treat (ITT) population and safety population were used in the majority of the company's analyses.

ERG comments

4.5 The ERG agreed with the company that the NAPOLI-1 trial was the only randomised controlled trial relevant to the NICE final scope and that overall the patient baseline characteristics were equal across the two groups. The ERG considered the trial could be biased because it was open label and there was not an independent assessment of disease progression. It also considered that this might explain why more people withdrew from the 5-FU/LV group than the nal-iri plus 5-FU/LV group.

4.6 The ERG noted that in clinical practice in England and Wales approximately 49% of patients would receive gemcitabine monotherapy and 25% receive gemcitabine in combination with capecitabine. However, in the NAPOLI-1 trial 45.8% of patients received gemcitabine monotherapy and 54.2% of patients received combination therapy. Patients in the NHS given combination therapy often have a good performance status which might explain why a greater proportion of the people in the trial had combination treatment. The ERG also noted that patients in the 5-FU/LV group were more likely to have metastatic lesions compared to the nal-iri plus 5-FU/LV group. The ERG therefore considered that the population in the trial differed from that seen in NHS clinical practice.

4.7 The ERG noted a couple of further inconsistencies between the NAPOLI-1 trial and clinical practice in England. Patients were tested for the UGT1A1*28 allele in the NAPOLI-1 trial however this testing is not routinely conducted in NHS clinical practice. It also noted that 5-FU/LV monotherapy is rarely used as a second-line treatment for locally advanced and metastatic pancreatic cancer in England but that this was the only comparator included in the NAPOLI-1 trial.

4.8 The ERG commented that the dose scheduling of 5-FU/LV in the control group was different to that in the nal-iri plus 5-FU/LV group but notes that the company did not consider this would bias either group. The ERG

agreed with the company's conclusion that the dosing was unlikely to bias the nal-iri plus 5-FU/LV group because the planned and recorded dose intensities for the 5-FU/LV group were higher (see Table 4, page 32 of ERG report for regimens).

4.9 The ERG also noted that in both groups of the NAPOLI-1 trial, a relatively high proportion of patients received subsequent therapy after disease progression. This may reflect that patients in the trial were younger and fitter than those treated in clinical practice and may have an effect on the overall survival of patients. However the ERG noted that the subsequent treatments received in each group were fairly balanced and unlikely to bias either group.

Clinical trial results

The company presented data taken at 3 different time points. The primary analyses were carried out using a data cut-off of 14th February 2014, after 305 deaths and updated results were analysed up to May 2015 after 378 deaths. The final analysis was carried out in March 2016 when all the patients in the trial had died.

4.10 Overall survival (cut-off February 2014) was significantly longer for nal-iri plus 5-FU/LV group (6.1 months) than the 5-FU/LV alone group (4.2 months) with a hazard ratio of 0.67 (p=0.0122; calculated using the log-rank test and presuming proportional hazards assumption applies). Overall survival was censored for each patient who was not known to have died at the cut-off point. Overall survival results with a data cut-off of 25th May 2015 were in accordance with the results from the primary efficacy analysis, with median overall survival found to be 6.2 months (95% CI: 4.8 to 8.4) for nal-iri plus 5-FU/LV compared with 4.2 months (95% CI: 3.3 to 5.3) for 5-FU/LV. The company also presented median overall survival results from the final data cut (March 2016); these results are [redacted] to the interim results presented.

4.11 The company carried out a number of sensitivity analyses for overall survival for the different pre-specified populations in the trial (see section

4.4). In all the groups median overall survival was longer for patients in the nal-iri plus 5-FU/LV group than in the 5-FU/LV group (see Table 4). Median overall survival was longer for the per protocol population than the ITT population (2.8 months overall survival gain in the nal-iri plus 5-FU/LV group and 0.9 months gain in the 5-FU/LV group). However, the number of patients in the per protocol population was small with the main reason for exclusion being insufficient dosing.

Table 4. Clinical trial outcomes (see company submission Table 17 and company response to the ERG clarification letter, Table 10).

Sensitivity analysis	Nal-iri+5-FU/LV	5-FU/LV
Stratified analysis on ITT population		
Median OS, months (95% CI)	6.1 (4.76 to 8.87)	4.2 (3.29 to 5.32)
HR (95% CI; p-value)¶	0.57 (0.41 to 0.80; p=0.0009)	
Safety population		
Median OS, months (95% CI)	6.2 (4.86 to 8.87)	4.2 (3.29 to 5.29)
HR (95% CI; p-value)	0.66 (0.48 to 0.91; p=0.0108)	
PP population		
Median OS, months (95% CI)	8.9 (6.44 to 10.5)	5.1 (3.98 to 7.16)
HR (95% CI; p-value)	0.57 (0.37 to 0.88; p=0.0106)	
ITT population (censoring at change in therapy)		
Median OS, months (95% CI)	6.1 (4.70 to 12.68)	4.0 (3.06 to 5.88)
HR (95% CI; p-value)	0.5665 (0.39 to 0.83; p=0.0033)	

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; OS=overall survival; PP=per protocol

4.12 In the ITT population median progression-free survival (results from February 2014) was greater for the group treated with nal-iri plus 5-FU/LV than for the 5-FU/LV group (3.1 months; 95% CI: 2.7, 4.2, compared with 1.5 months; 95% CI: 1.4, 1.8; p=0.0001). The final data cut in March 2016 had [redacted] results with a median progression-free survival of [redacted] months (95% CI: [redacted]) with nal-iri plus 5-FU/LV compared with [redacted] months (95% CI: [redacted]) with 5-FU/LV. Progression-free survival was also statistically significantly longer for those treated with nal-iri plus 5-FU/LV

for the subgroups analysed in the sensitivity analyses (see table 19 in company submission and table 10 in clarification responses).

4.13 Other secondary outcomes included time to treatment failure (TTF), objective response rate, tumour marker response and clinical benefit response. Median TTF for the ITT population was statically significantly longer for nal-iri plus 5-FU/LV compared with 5-FU/LV (2.3 months compared with 1.4 months; p=0.0002). The nal-iri plus 5-FU/LV group also achieved a statistically significantly higher confirmed overall response rate (at least 4 weeks after investigator assessment of partial or complete response) of 7.7% compared with 0.8% in the 5-FU/LV group. A statistically significantly greater proportion of tumour marker response evaluable patients treated with nal-iri plus 5-FU/LV had reductions of at least 50% from baseline in CA19-9 levels than patients treated with 5-FU/LV.

4.14 The company also carried out an additional analysis to investigate the effect of baseline CA19-9 level on overall survival. Patients who received study medication and had a recorded baseline CA19-9 measurement were categorised according to baseline CA19-9 measurement, and HRs and corresponding 95% CI were calculated for each quartile (see figure 5, page 68 of company submission).

4.15 The company also included, as supportive evidence but not in its systematic review, one non-randomised controlled trial (NCT00813163) observing nal-iri monotherapy, 120 mg/m^2 intravenous infusion over 90 min every 21 days, in patients whose metastatic adenocarcinoma pancreatic cancer had progressed after gemcitabine treatment. The primary endpoint was 3 month overall survival. The study met its primary endpoint with 75% of patients surviving at least 3 months and 42.5% of patients still alive at 6 months and 25% alive at 12 months.

4.16 Health-related quality of life data were collected during the NAPOLI-1 trial with patients required to complete the EORTC-QLQ-C30 questionnaire at

the start of treatment, every 6 weeks thereafter and at 30 days post follow-up. The questionnaire was completed prior to study drug administration on days that the patient received the study drug. When evaluating the data the company only included the ITT population who had completed the EORTC-QLQ-C30 questionnaire at baseline and on at least one subsequent occasion: nal-iri plus 5-FU/LV, [redacted]; 5-FU/LV: [redacted]. Baseline EORTC-QLQ-C30 scores were [redacted] between treatment groups. Results at 6 weeks and 12 weeks showed no real differences suggesting no negative effect on health-related quality of life. When comparing the symptom scale for nausea and vomiting and diarrhoea the scores [redacted] for the nal-iri plus 5-FU/LV group compared with the 5-FU/LV group.

4.17 To support the trial evidence the company also carried out a 'quality-adjusted time without symptoms or toxicity' (Q-TWiST) analysis. The ITT population were divided into 3 groups: time with adverse events of at least grade 3 toxicity (TOX), time in relapse after disease progression (REL) and time without symptoms or adverse events of at least grade 3 toxicity (TWiST). Mean Q-TWiST was then calculated by multiplying the time spent in each health state by its respective utility value (0.5 for TOX, 0.5 for REL and 1.0 for TWiST). The results showed that people in the nal-iri plus 5-FU/LV group spent more time in TOX then those receiving 5-FU/LV. There was little difference for the REL group marginally favouring the 5-FU/LV group and TWiST favoured nal-iri+5-FU/LV by 1.0 month. Overall, nal-iri+5-FU/LV patients had a 1.3 months (95% CI: 0.4 to 2.1) greater Q-TWiST (range threshold analyses: 0.9 to 1.6 months), with a relative Q-TWiST gain of 24% (range threshold analyses: 17% to 31%).

ERG comments

4.18 The ERG noted that a number of people in the 5-FU/LV group had received no study treatment compared with the nal-iri plus 5-FU/LV group. Therefore the ITT population results may have been biased towards the nal-iri plus 5-FU/LV group. The ERG considered it important to take into

account the safety population included in the company's sensitivity analyses, which included only people who had received at least one dose of study treatment (see Table 4). The findings from the analysis of the safety population supported those of the ITT population.

4.19 The ERG also noted that a relatively high proportion of patients received subsequent therapy after disease progression, which may have prolonged overall survival. However, the numbers were similar for both the nal-iri plus 5-FU/LV group and the 5-FU/LV group and unlikely to have caused any bias.

4.20 The ERG noted that the results of the subgroup group analyses [redacted] suggest that there were any subgroups of patients who [redacted] receive nal-iri plus 5-FU/LV. The ERG's clinical experts considered that if a patient had previously received irinotecan it was unlikely that they would receive it again.

4.21 The ERG questioned whether the health-related quality of life data were robust because of the [redacted] numbers included. The ERG also questioned why the company did not provide, in its submission, p values for the Q-TWIST data considered statistically significant. However, the ERG did acknowledge that the company provided confidence intervals which appeared to show statistical significance. The ERG also queried whether the Q-TWIST was a post-hoc analysis and if so should be treated with caution.

Indirect comparison

4.22 The company identified 13 randomised controlled trials that could potentially be included in an indirect comparison (ITC) and then undertook a network-meta analysis feasibility assessment. The company considered that evidence from three trials (NAPOLI-1, CONKO-003 and PANCREOX) could, theoretically, be included in an ITC to generate evidence for the effectiveness of nal-iri plus 5-FU/LV compared with oxaliplatin plus 5-FU/LV (see figure 14 in company submission). However, the company

considered that an indirect comparison to compare clinical efficacy was not feasible after advice from 3 clinical experts suggesting combining the 3 trials would be flawed because the trials were not homogeneous (unknown follow-up durations, differing previous treatment, patient ages and other characteristics). The company did carry out the comparison using the Bucher adjusted indirect comparison method to allow a cost effectiveness analysis to be undertaken but noted that the proportional hazards assumption was violated invalidating the comparison.

ERG comments

4.23 The ERG noted that although the comparator in the NAPOLI-1 trial was 5-FU/LV this is rarely used in clinical practice. Instead the ERG agreed with the company that oxaliplatin plus 5-FU/LV is the most commonly used second-line treatment for patients with metastatic pancreatic cancer in England and therefore to be the most suitable comparator. The ERG noted that an indirect comparison was consequently required to inform the cost-effectiveness analysis. The ERG also commented that different formulations of oxaliplatin plus 5-FU/LV exist in clinical practice with mFOLFOX4 and FOLFOX6 being the most common in England but this was dependent on geographical area.

4.24 The ERG noted that 3 trials investigating oxaliplatin plus 5-FU/LV (CONKO-003, PANCREOX and SWOG S1115) reported overall survival results between 5.9 months and 6.7 months. These results were similar to the result for nal-iri plus 5-FU/LV in the NAPOLI-1 trial (6.1 months). The trials reported a progression-free survival of 2.9 months for OFF in the CONKO-003 trial and between 2.0 months and 3.1 months for mFOLFOX6. Again these results were similar to those reported for nal-iri plus 5-FU/LV in the NAPOLI-1 trial (3.1 months). Response rates in the trials were generally the same.

4.25 The ERG carried out work to assess the validity of the proportional hazards assumptions that must be applicable for the indirect comparison

to hold. The ERG used 'cumulative hazard versus cumulative hazard' plots to show the relationships between the cumulative hazard for each group in each trial event at common time points in the two trial groups. After observing the 5-FU/LV survival data from the 3 trials (NAPOLI-1, CONKO-003 and PANCREOX) the ERG determined that the assumption that the survival data were compatible with the assumption of proportional hazards and therefore equivalent for the trials was not valid. The ERG concluded that the indirect comparison was not reliable and did not provide credible estimates of clinical effectiveness for the comparison of nal-iri plus 5-FU/LV and oxaliplatin plus 5-FU/LV.

Adverse effects of treatment

4.26 The NAPOLI-1 trial included 95% (n=398) of the patients in the safety analysis. The mean duration of exposure to study drug was longer in the nal-iri plus 5-FU/LV group (15.0 weeks) than in the 5-FU/LV group (10.4 weeks). The proportion of people experiencing a treatment emergent adverse event (TEAE) was similar in both groups and nearly all patients experienced at least 1 TEAE in the trial. The percentage of subjects who experienced any Grade 3 or higher TEAE was greater in the nal-iri plus 5-FU/LV group (76.9%) than those in the 5-FU/LV group (56.0%).

4.27 TEAEs that were reported by at least 10% of patients in the nal-iri plus 5-FU group and at least 5% more than in the 5-FU/LV control group were diarrhoea (59.0 vs 26.1%), vomiting (52.1 vs 26.1%), nausea (51.3 vs 34.3%), decreased appetite (44.4 vs 32.1%), fatigue (40.2 vs 27.6%), anaemia (37.6 vs 23.1%) and neutropenia (23.1 vs 3.0%). Grade 3 or higher TEAEs that were reported by a higher percentage (greater than 2%) of patients in the combination arm than the control arm were neutropenia (14.5 compared with 0.7%), fatigue (13.7 compared with 3.7%), diarrhoea, (12.8 compared with 4.5%), vomiting (11.1 compared with 3.00%), anaemia (9.4 compared with 6.7%) and nausea (7.7 compared with 3.0%). Treatment-emergent serious adverse events were more common in the nal-iri plus 5-FU/LV group than in the 5-FU/LV group

(47.9% compared with 44.8%). One death was attributed to the nal-iri plus 5-FU/LV group and none to the 5-FU/LV group. The company said a safety comparison with patients heterozygous for UGT1A1*28 was difficult to perform because of the [redacted] of patients in this subgroup ([redacted]).

ERG comments

4.28 The ERG noted that the draft summary of product characteristics (SmPC) highlighted that individuals who are [redacted] are at [redacted]. The ERG also noted a safety comparison with patients heterozygous for UGT1A1*28 was difficult to perform because of the small number of patients in the subgroup of patients homozygous for UGT1A1*28.

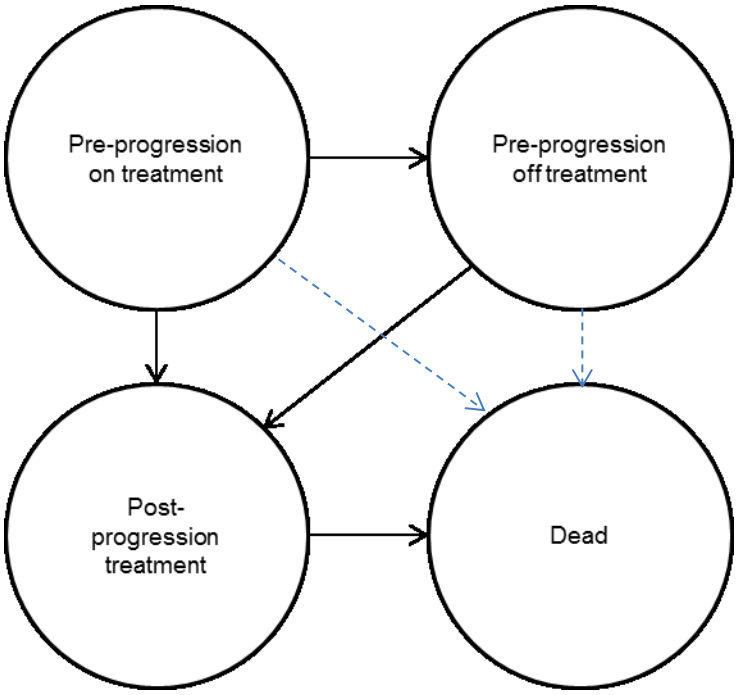
4.29 The ERG compiled tables to allow the comparison of safety data from the trials included in the comparison of nal-iri plus 5-FU/LV and oxaliplatin plus 5-FU/LV (see page 65 of ERG report). The ERG considered the comparison to have limitations knowing it was not possible to come to a reliable conclusion about relative safety. The main issues were differences in the trial populations and the different oxaliplatin plus 5-FU/LV regimens used, however it allowed a crude comparison across the trials. The most notable difference across trials seemed to be related to the baseline performance status scores of patients. The ERG also noted that there were more cases of diarrhoea for patients treated with oxaliplatin plus 5-FU/LV but fewer neutropenia and neurotoxicity (see Table 30, page 82 of ERG report for further details). However the ERG urged caution when interpreting the findings (see ERG report pages 73 to 77 for more information).

5 Cost-effectiveness evidence

Model structure

5.1 The company presented a de-novo, partitioned, survival model containing 4 mutually-exclusive health states: pre-progression ('on treatment' and 'off treatment'), post-progression and death. The model allowed the comparison of nal-iri plus 5-FU/LV with both 5-FU/LV and oxaliplatin plus 5-FU/LV. The model included 1-week cycles, a 10 year time horizon, a discount of 3.5% for utilities and costs and was from the perspective of the NHS. The model structure is shown below (Figure 1).

Figure 1. Company's model structure (from CS figure 8).



ERG comments

5.2 The ERG considered the company's model appropriate and to reflect the population in the NICE final scope. However the ERG added 2 arrows (dashed lines) to the company's schematic of the model to show that patients could move from either of the pre-progression treatment states to death.

Model details

Data from the final cut-off in March 2016 was used to inform the company's model.

5.3 All patients entered the model in the pre-progression 'on treatment' health state. At the beginning of each time period patients could either remain in the same health state or progress to a worse health state. The proportion of patients in the pre-progression 'on treatment' health state was estimated as the difference between progression-free survival and time to treatment failure using parametric models fitted to the Kaplan-Meier data from the NAPOLI-1 trial. For the comparison with oxaliplatin plus 5-FU/LV the hazard ratios from the indirect comparison were applied to the 5-FU/LV NAPOLI-1 trial data to determine the survival with oxaliplatin plus 5-FU/LV. The proportion of patients in the post-progression treatment state was estimated as the difference between overall survival and progression-free survival using the trial data or indirect comparison data.

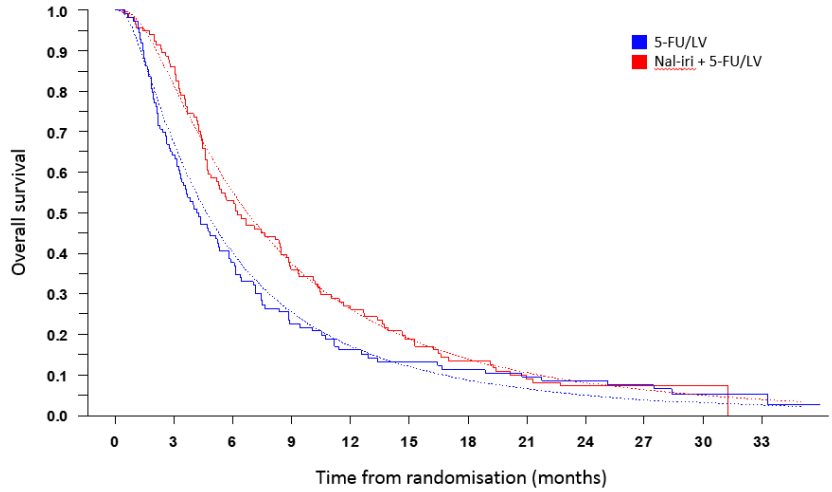
5.4 Based on the NAPOLI-1 trial the company had presumed that, of the people in the post-progression state of the model, 38% of patients receiving treatment with nal-iri plus 5-FU/LV (same assumption made for oxaliplatin plus 5-FU/LV) and 31% of people receiving 5-FU/LV also received post-progression anti-cancer treatment.

The company fitted six parametric models (exponential, Weibull, Gompertz, log-logistic, log-Gompertz, log-logistic, log-normal and gamma) to the overall survival and progression-free progression-free survival Kaplan-Meier data from the NAPOLI-1 trial to consider the consider the goodness of fit. For both the overall survival, progression-free survival data (see free survival data (see Figure 2) and time to treatment failure the company considered the log-normal to be the best fit and was used in its base case. A comparison of the NAPOLI-1 trial data and modelled survival data are shown in

5.5 Table 5.

Figure 2. Log-normal fit to overall survival and progression-free survival Kaplan-Meier curves (from CS page 100)

a) Overall survival from NAPOLI-1 trial



b) Progression-free survival from NAPOLI-1 trial

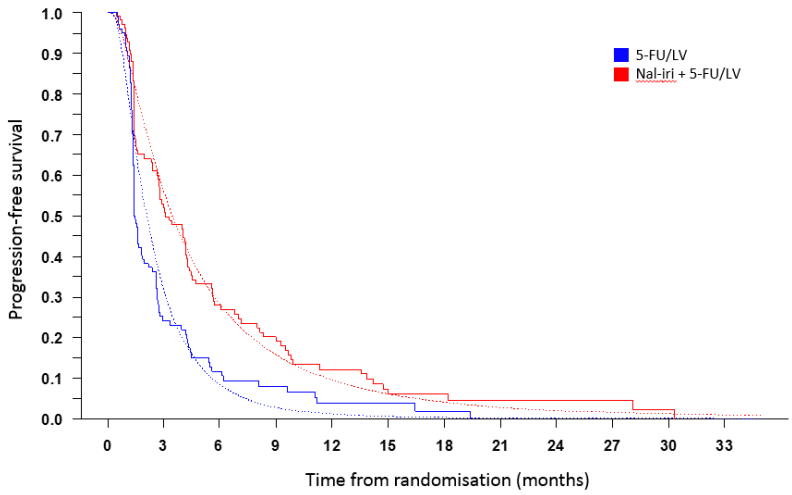


Table 5. Comparison of NAPOLI-1 trial data and the log-normal model fitted to the survival data

Log-normal survival function parameters	Nal-iri + 5-FU/LV	5-FU/LV
PFS		
Observed median, months	3.1	1.5
Median, months	3.47	2.09
Mean, months	5.45	2.81
AIC	496	369
OS		
Observed median, months	6.2	4.2
Median, months	6.24	4.67
Mean, months	10.18	7.66
AIC	675	598
Time on treatment		
Observed median, months	1.6	0.76
Median, months	1.7	1.10
Mean, months	4.6	2.0
AIC	534	344

5.6 Although the company could not derive clinical data from an indirect comparison of nal-iri plus 5-FU/LV and oxaliplatin plus 5-FU/LV it carried out an indirect analysis to allow an economic comparison between the 2 treatments. The company used the indirect comparison to calculate hazard ratios for progression-free survival and overall survival for the comparison of nal-iri plus 5-FU/LV and oxaliplatin plus 5-FU/LV (see Table 6). Although the company used hazard ratios it noted that the proportional hazards assumption was not met, because the overall survival Kaplan-Meier curves crossed, making the analysis invalid. The hazard ratios were used to adjust the 5 FU/LV base case overall and progression-free survival to generate survival estimates for oxaliplatin plus 5-FU/LV. The company also noted that it had assumed that the oxaliplatin plus 5-FU/LV dosing was the same in the CONKO-003 and PANCREOX trials (OFF and FOLFOX6 regimes respectively).

Table 6. Company's hazard ratios for comparison of nal-iri plus 5-FU/LV with oxaliplatin plus 5-FU/LV (from CS page 104, table 39)

Comparison	HR of PFS	HR of OS
Nal-iri + 5-FU/LV vs oxaliplatin + 5-FU/LV	0.70	0.63

5.7 Although EORTC-QLQ-C30 was used to measure health-related quality of life in the NAPOLI-1 trial a majority of the data were missing. The company found one potential mapping algorithm to map the data collected in the trial but the full details of the algorithm were not available. The company therefore used utility values from a US study and adjusted them to reflect the UK population and to include disutilities (see section 0). The company noted that the same utility values, without taking account of the disutility adjustments, were used in the technology appraisal for paclitaxel as albumin-bound nanoparticles in combination with gemcitabine for previously untreated metastatic pancreatic cancer (TA360). The pre-progression health state for all treatments was assigned a utility value of 0.742, and the post-progression health state for all treatments was assigned a value of 0.672 regardless of the treatment.

The company's model took account of adverse events by applying a disutility for every grade disutility for every grade 3 or greater adverse event reported by at least 5% of patients. The 5% of patients. The adverse events duration and exposure data were taken from the NAPOLI- taken from the NAPOLI-1 trial and the disutility values were taken from the literature and literature and weighted by the time the patient spent with the adverse event during the trial event during the trial (see

5.8 Table 7).

Table 7. Disutilities associated with adverse events included in the company's model (CS, table 42, page 116)

	Utility value	[95% CI]	Reference	Justification
Abdominal pain	–0.069	[-0.093, -0.045]†	Doyle et al, 2008 (106)	
Anaemia	–0.204	[-0.156, -0.252]	-	Assumed equivalent to fatigue
Diarrhoea	–0.204	[-0.156, -0.252]	-	Assumed equivalent to fatigue
Fatigue	–0.204	[-0.156, -0.252]	Swinburn et al, 2010 (107)	
Nausea	–0.048	[-0.079,-0.016]	Nafees et al, 2008 (108)	
Neutropenia	–0.090	[-0.122, -0.058]	Nafees et al, 2008 (108)	
Vomiting	–0.048	[–0.079, –0.016]	-	Assumed equivalent to nausea

5.9 The company included a number of drug costs in its model (see Table 8). The company used these costs to calculate average drug costs using the average number of vials per patient (based on the normal distribution of the dose per patient). The average number of vials used also took into account the recommended dose per m^2 and assumed that 5-FU came only in 500mg vials and all other drugs came in 50mg vials. The average dose per patient was based on mean body surface area ($1.79m^2$) and the recommended dose of the drug was adjusted using a dose intensity multiplier (85% of nal-iri plus 5-FU/LV based on the NAPOLI-1 trial and assumed the same for oxaliplatin plus 5-FU/LV and 95% for 5-FU/LV from the NAPOLI-1 trial) to allow adjustment for missed or reduced doses.

Table 8. Technology costs included in the company's model (from CS page 123, table 45).

Items	Cost per vial	Cost per unit (mg)
Nal-iri	[redacted]	[redacted]
5-FU bolus injection	£12.80*	£0.012*
5-FU infusion	£64.00*	£0.012*
LV	£100.00*	£0.375*
Oxaliplatin	£311.00*	£3.135*

*Taken from BNF 2016 by company

5.10 When considering administration costs the company used NHS Reference Costs. The first drug administered in any regimen was costed as simple parental chemotherapy (£239.12) and subsequent drugs were assumed to require 30 minutes of nurse time (£18.00). Because of the long infusion time associated with 5-FU treatment, an additional cost of £97.14 was applied for removal of the infusion pump.

5.11 Monitoring costs were applied to all patients in the model until the termination of active treatments. Monitoring costs were split into two parts: immediate monitoring costs prior to the start of therapy, and monitoring costs during the follow-up period before discontinuation of treatment. For more information see page 125 of the company submission.

5.12 Only grade 3 or greater adverse events were costed in the model (see section 0). Based on treatment exposure in NAPOLI-1 trial (17.7 weeks for nal-iri plus 5-FU/LV and 12.9 weeks for 5-FU/LV) the weekly adverse events costs were estimated to be £14.17 for nal-iri plus 5-FU/LV and £9.29 for 5-FU/LV (see table 50, page 126 of company submission for more details). The costs associated with adverse events with oxaliplatin plus 5-FU/LV was assumed to be the same as the costs for nal-iri plus 5-FU/LV.

5.13 Other costs included in the model were post-progression, palliative care and terminal costs. Post-progression costs were the same regardless of

the treatment the patient had received ([redacted]). The company based the estimates of people receiving palliative care on the number of people in the NAPOLI-1 trial (69% in the nal-iri plus 5-FU/LV and oxaliplatin plus 5-FU/LV and 62% in the 5-FU/LV group). The average palliative cost per week for nal-iri plus 5-FU/LV and oxaliplatin plus 5-FU/LV was £30.36 and for 5-FU/LV was £27.28. A cost of £426.54 was applied to patients in the final 4 weeks before death.

ERG comments

5.14 When considering the proportion of patients who entered the post-progression health state it was unclear to the ERG whether these proportions took account of the whole population or only those whose progression event was not fatal (see section 5.4).

5.15 The ERG noted that the figures provided in the company's submission and in the clarification response were different. In the company's clarification response the number of patients receiving treatment post-progression was 35.9% (38% in submission) in the nal-iri+5-FU/LV group and 42.0% (31% in submission) in the 5-FU/LV group respectively.

5.16 The ERG commented that the violation of the proportional hazards assumption for the overall survival results cast doubt on the validity of the hazard ratios developed. The company tested the proportional hazards assumption for the NAPOLI-1 trial for overall survival data and provided results of the test for various populations, as described in section 4.4. For the ITT population (analysed using un-stratified log-rank tests), the test rejected the null hypothesis that the proportional hazards assumption is valid (p=0.0169).

5.17 The ERG also noted that almost all the trial data were complete so there was only one instance where extrapolation was required (for a single patient). Therefore it considered parametric models were not required and the trial data should directly have been used. The ERG also noted the company provided no biological rationale for using the log-normal model

and noted the model overestimated progression-free survival for both groups in the trial, for the first 4 months, and underestimated survival from 6 months onwards (see Figure 10, page 101 of ERG report). The company's model also estimated a 4.8% greater progression-free survival gain when comparing nal-iri plus 5-FU/LV with 5-FU/LV than the trial data showed. The ERG also noted that the company's approach to modelling time to treatment underestimated the overall time on treatment (15% for the 5-FU/LV group and 1.4% for the nal-iri plus 5-FU/LV group) particularly for the first 15 months of the trial. The model also accrued benefit even after the patient had stopped treatment.

5.18 The ERG considered that the log-normal parametric model, when applied to the time on treatment data, exceeded the proportion of patients in the progression-free state. The ERG commented that the use of a model correction by the company to overcome this issue indicated that either the method used to calculate progression-free survival or pre-progression on treatment was incorrect. The ERG also disagreed with the company's assumption that the duration of exposure to nal-iri plus 5-FU/LV and oxaliplatin plus 5-FU/LV and dose intensity was equivalent.

5.19 The ERG also disagreed with the company's assumption that a reduction in nal-iri plus 5-FU/LV, 5-FU/LV or oxaliplatin plus 5-FU/LV dosing corresponded with a decrease in drug acquisition costs. In the NHS this only occurs if the reduction in dose is known far enough in advance of the treatment. The ERG considered the use of pro-rata reductions in drug costs in the company's model to be questionable.

5.20 All drugs used in the company's submission except for nal-iri are available in generic form. However the ERG noted that the company's model overestimated the cost of generic drugs by using the BNF as the source rather than eMiT. The model also excluded the most economic treatment achievable by not mixing different vile sizes and only used the smallest vial sizes, which excluded potential savings.

5.21 The ERG disagreed with the company's assumption that the average weekly cost per patient for post-progression treatment was equivalent to the weekly cost of treatment with nal-iri plus 5-FU/LV. The ERG considered it more appropriate to assume these patients would receive palliative therapy.

5.22 The ERG had concerns about the Healthcare Resource Groups (HRG) codes used by the company to cost adverse events. The ERG noted that the company used a weighted average of day case HRG codes, whilst the definition of grade 3 or higher adverse events was that they required hospital admission. The ERG considered that the use of the weighted average of costs for all types of admission is more reflective of the costs to the NHS (see table 56, page 112 or ERG report for updated costs).

5.23 The ERG considered that the utility values used by the company were unsuitable as they were for a first-line treatment population and would likely overestimate patient quality of life when applied to a second-line patient population. The ERG also noted that the company model did not include the effects of terminal disutility on patient quality of life.

5.24 The ERG disagreed with the company's use of a mean body surface area (BSA) of 1.79m^2, taken from a study of adult cancer patients in the UK. The ERG noted that although the company had selected a BSA that did not differentiate between tumour type or site or take account of the male to female distribution this information was available from the study (1.898m^2 for males and 1.654m^2 for females).

5.25 The ERG noted seven minor concerns in the company's submission (see ERG report page 114-117 for more information). However these were not included in the ERG's cost effectiveness analyses because their impact on the ICER per QALY gained was expected to be minimal.

Company's base-case results and sensitivity analysis

5.26 Nal-iri plus 5-FU/LV is associated with a QALY gain of 0.1341 compared with 5-FU/LV and 0.2013 compared with oxaliplatin plus 5-FU/LV, respectively. Nal-iri plus 5-FU/LV is associated with an incremental cost of £[redacted] compared with 5-FU/LV and £[redacted] compared with oxaliplatin plus 5-FU/LV, leading to incremental cost-effectiveness ratios (ICERs) of £[redacted]/QALY and £[redacted]/QALY, respectively (see Table 9).

Table 9. Company's base case ICERs (taken from CS page 131)

Technologies	Total		Incremental		ICER (Cost/QALY)
	Costs	QALYs	Costs	QALYs	
Nal-iri + 5-FU/LV	£[redacted]	0.5635	-	-	-
5-FU/LV	£13,338.32	0.4294	£[redacted]	0.1341	£[redacted]
Oxaliplatin + 5-FU/LV	£13,974.83	0.3621	£[redacted]	0.2013	£[redacted]

5.27 One-way sensitivity analyses showed that the ICER was most sensitive to varying pre-progression utility values and body surface area (see company submission table 62).

5.28 The company undertook probabilistic sensitivity analyses using 1000 simulations. The probabilistic mean ICER was £[redacted] per QALY gained when comparing nal-iri plus 5-FU/LV with 5-FU/LV. For the comparison of nal-iri plus 5-FU/LV with oxaliplatin plus 5-FU/LV the probabilistic mean ICER was £[redacted] per QALY gained.

Company scenarios

5.29 The company undertook 3 scenario analyses and the results are shown in Table 10.

Table 10. Company's scenario analyses (taken from CS page 139)

Scenario	Nal-iri + 5-FU/LV vs 5-FU/LV	Nal-iri + 5-FU/LV vs oxaliplatin + 5-FU/LV
Base case	£[redacted]	£[redacted]

February 2014 data cut from NAPOLI-1 trial using log-normal distribution	£[redacted]	£[redacted]
AE utility decrements omitted	£[redacted]	£[redacted]
Log-logistic distribution for nal-iri + 5-FU/LV vs 5-FU/LV	£[redacted]	–

ERG exploratory analyses

5.30 Based on the issues identified in its critical appraisal of the company's model (see sections 5.14 to 5.25) the ERG performed 11 sets of additional analyses (10 scenarios and an additional 1 containing all the changes) (see sections 5.31 to 5.34 and Table 11).

Table 11. Summary of the ERG's exploratory analyses

	Description	**ERG critique of company methods (PMB section number)**
R1	Use of OS, PFS and time on treatment data from trial	5.15, 5.16, 5.17
R1a	Use of OS data from trial	5.15, 5.16, 5.17
R1b	Use of PFS data from trial	5.15, 5.16, 5.17
R1c	Use of time on treatment data from trial	5.18
R2	Full dose intensity	5.18
R3	ERG's preferred BSA & drug acquisition costs (dose reduction and generic drugs)	5.24, 5.19, 5.20
R4	Assume post-progression treatment costs equivalent to palliative therapy	5.21
R5	ERG's preferred use of HRG codes to cal'c AE costs	**Error! Reference source not found.**
R6	ERG's preferred health state utilities	5.23
R7	ERG's preferred terminal disutility	5.23

5.31 In its exploratory analyses the ERG replaced the parametric models with the complete trial Kaplan-Meier data. The ERG noted there were 3 possible approaches to calculate overall survival: 1. using the NAPOLI-1 trial data, 2. using this data and extrapolating for the one remaining patient or 3. replace the trial data with parametric models of survival.

5.32 For method 1 the overall survival difference between the 2 treatment groups was a net gain of 2.212 months (95% CI 0.173 to 4.251) for the nal-iri plus 5-FU/LV group compared with 5-FU/LV. For method 2 the results showed a net gain in overall survival of 1.807 months for the nal-iri plus 5-FU/LV group compared with 5-FU/LV and for method 3 there was a net overall survival gain of 2.745 months for the nal-iri plus 5-FU/LV group compared with 5-FU/LV. The ERG considered that the difference in these results showed the uncertainty with estimating overall survival, particularly when comparing to the company's base case survival gain of 2.503 months. The ERG's preferred method was method 2 (see page 105 of ERG report for more information).

5.33 The ERG calculated progression-free survival, post-progression survival and overall survival for each treatment group and noted that in all cases the ERG's approach was less optimistic than the company's approach. The ERG also noted that in both its and the company's model the post-progression estimates were inconsistent with the finding that each patient entering the post-progression state had an equal chance of survival regardless of the treatment group (see section 5.21).

5.34 The ERG recalculated the drug costs used in the company's model using data from eMiT. The differences between the average weekly treatment costs per patient in the company's model and those used by the ERG are shown below in Table 12:

Table 12. Weekly average treatment costs used in the model by the company and ERG (see ERG report Table 55, page 109).

Item	Company model			ERG (revised BSA)		
Nal-iri+5-FU/LV	**Nal-iri**	**5-FU**	**LV**	**Nal-iri**	**5-FU**	**LV**
Weekly drug cost	[redacted]	£24.97	£118.80	[redacted]	£2.24	£5.19
Weekly treatment cost	[redacted]			[redacted]		
Oxaliplatin+5-FU/LV	**Oxaliplatin**	**5-FU**	**LV**	**Oxaliplatin**	**5-FU**	**LV**
Weekly drug cost	£238.84	£11.35	£61.74	£13.14	£1.19	£2.72
Weekly treatment cost	£311.93			£17.04		
5-FU/LV	**5-FU**	**LV**		**5-FU**	**LV**	
Weekly drug cost	£31.16	£91.27		£2.94	£4.19	
Weekly treatment cost	£122.43			£7.12		

5.35 The ERG identified an error in the utility value used by the company for the post-progression health state (0.672 was used instead of 0.671). The ERG also considered that a utility value of 0.671 (taken from the progressed disease state in TA360) would more accurately reflect the quality of life of patients with metastatic pancreatic adenocarcinoma after gemcitabine treatment. It also considered a utility value of 0.600 should have been used for the post-progression health state. The ERG estimated the mean EQ-5D disutility during the 4 weeks before death to be 0.146 using results from the study by Van den Hout et al. but recognised that those values related to lung cancer patients.

5.36 The ERG generated a range of cost-effectiveness results for the comparison of nal-iri plus 5-FU/LV compared with 5-FU/LV. See Table 13 for the results.

5.37 The ERG considered that the company's indirect comparison for nal-iri plus 5-FU/LV with oxaliplatin plus 5FU/LV was unreliable and that the ICERs per QALY gained for this comparison should not be used for decision-making. However the ERG generated a range of cost effectiveness results for the comparison of nal-iri plus 5-FU/LV compared with oxaliplatin plus 5-FU/LV based on assumptions that treatment with

oxaliplatin plus 5-FU/LV results in 10% more, 10% fewer or an equal number of QALYs to treatment with nal-iri plus 5-FU/LV (see Table 14 and Table 15).

Table 13. ERG exploratory analyses for nal-iri plus 5-FU/LV compared with 5-FU/LV: revisions to company's base case (taken from ERG report page 120)

Model scenario ERG revision	Nal-iri+5-FU/LV			5-FU/LV			Incremental			ICER	
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change
****Original CS base case***	[redacted]	***0.564***	***0.847***	***£13,338***	***0.429***	***0.639***	[redacted]	***0.134***	***+0.209***	[redacted]	--
A. Company base case**	[redacted]	***0.563***	***0.847***	***£13,338***	***0.429***	***0.639***	[redacted]	***0.134***	***+0.209***	[redacted]	--
R1. ERG OS, PFS, time on treatment	[redacted]	0.529	0.782	£13,655	0.429	0.637	[redacted]	+0.100	+0.145	[redacted]	[redacted]
R1a. ERG OS	[redacted]	0.527	0.782	£13,261	0.426	0.637	[redacted]	+0.101	+0.145	[redacted]	[redacted]
R1b. ERG PFS	[redacted]	0.565	0.847	£12,891	0.431	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R1c. ERG time on treatment	[redacted]	0.563	0.847	£14,212	0.429	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R2. Full dose intensity	[redacted]	0.563	0.847	£14,317	0.429	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R3. ERG BSA & drug acquisition costs	[redacted]	0.563	0.847	£12,436	0.429	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R4. ERG post-progression treatment costs	[redacted]	0.563	0.847	£6,643	0.429	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R5. ERG AE costs	[redacted]	0.563	0.847	£13,597	0.429	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R6. ERG health state utilities	[redacted]	0.504	0.847	£13,338	0.384	0.639	[redacted]	+0.120	+0.209	[redacted]	[redacted]
R7. ERG terminal disutility	[redacted]	0.552	0.847	£13,338	0.418	0.639	[redacted]	+0.135	+0.209	[redacted]	[redacted]
B. R1:R7	[redacted]	**0.465**	**0.782**	**£6,648**	**0.374**	**0.637**	[redacted]	**+0.091**	**+0.145**	[redacted]	[redacted]

Costs and QALYs discounted; life years undiscounted
BSA=body surface area; ERG=Evidence Review Group; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; TTF=time to treatment failure
*original base case estimate with error **This is the new company base case ICER estimate due to an error in post progression utility value in company model

Table 14 ERG exploratory analyses for nal-iri plus 5-FU/LV compared with oxaliplatin plus 5-FU/LV: revisions to company's base case (taken from ERG report page 119)

Model scenario ERG revision	Nal-iri+5-FU/LV			Oxaliplatin+5-FU/LV			Incremental			ICER	
	Cost	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**£/QALY**	**Change**
****Original CS base case***	[redacted]	***0.564***	***0.847***	***£13,975***	***0.362***	***0.535***	[redacted]	***+0.201***	***+0.312***	[redacted]	--
A. Company base case**	[redacted]	***0.563***	***0.847***	***£13,975***	***0.362***	***0.535***	[redacted]	***+0.201***	***+0.312***	[redacted]	--
R1. 5-FU/LV pre-progression time on treatment curve for oxaliplatin+5-FU/LV	[redacted]	0.563	0.847	£10,416	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
R2. Full dose intensity	[redacted]	0.563	0.847	£15,082	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
R3. ERG BSA & drug acquisition costs	[redacted]	0.563	0.847	£9,773	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
R4. ERG post-progression treatment costs	[redacted]	0.563	0.847	£11,034	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
R5. ERG AE costs	[redacted]	0.563	0.847	£14,957	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
R6. ERG health state utilities	[redacted]	0.504	0.847	£13,975	0.324	0.535	[redacted]	+0.180	+0.312	[redacted]	[redacted]
R7. ERG terminal disutility	[redacted]	0.552	0.847	£13,975	0.356	0.535	[redacted]	+0.196	+0.312	[redacted]	[redacted]
R8. ERG OS	[redacted]	0.527	0.782	£13,975	0.362	0.535	[redacted]	+0.165	+0.247	[redacted]	[redacted]
R9. ERG PFS	[redacted]	0.565	0.847	£13,975	0.362	0.535	[redacted]	+0.203	+0.312	[redacted]	[redacted]
R10. ERG Time on treatment	[redacted]	0.563	0.847	£13,975	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
B. R1:R10	[redacted]	**0.465**	**0.782**	**£5,809**	**0.318**	**0.535**	[redacted]	**+0.147**	**+0.247**	[redacted]	[redacted]
C. R2:R10	[redacted]	**0.465**	**0.782**	**£7,838**	**0.318**	**0.535**	[redacted]	**+0.147**	**+0.247**	[redacted]	[redacted]

Costs and QALYs discounted; life years undiscounted
BSA=body surface area; CS=company submission; ERG=Evidence Review Group; QALYs=quality adjusted life years
*Original base case estimate with error **This is the company base case ICER estimate following correction of an error in post progression utility value in company model

Table 15. ERG cost effectiveness results for the comparison of nal-iri+5-FU/LV compared with oxaliplatin+5-FU/LV (based on assumptions that treatment with oxaliplatin plus 5-FU/LV results in 10% more, 10% fewer or an equal number of QALYs to treatment with nal-iri plus 5-FU/LV; see ERG report page 118 and 121)

Scenario	ICER per QALY gained
Base case	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	[redacted]
ERG scenario B	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	[redacted]
ERG scenario C	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	[redacted]

Innovation

5.38 Justifications for considering nal-iri to be innovative:

- The company considers nal-iri to be innovative because it will provide a step change in the treatment pathway and will be the first treatment licensed for treating pancreatic cancer that has progressed following gemcitabine treatment.

- A patient and carer group considers nal-iri to innovative because it is able to bypass the stroma and attack the tumour making it more effective than some treatments.

6 End-of-life considerations

Table 16 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	**Company submission:** A systematic review of real-world, peer reviewed, observational European studies (n=91) found that the median life expectancy at diagnosis was 4.6 months in patients with pancreatic cancer irrespective of stage of diagnosis, and the median survival for patients with metastatic disease was 2.8–5.7 months **ERG:** Agreed with company that life expectancy is less than 24 months for this patient population
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	**NAPOLI –1 trial:** Median OS was 6.1 months in the nal-iri + 5-FU/LV group compared with 4.2 months in the 5-FU/LV group **Company model:** mean overall survival 2.5 months for nal-iri plus 5-FU/LV compared with 5-FU/LV **ERG model:** mean overall survival 1.8 months for nal-iri plus 5-FU/LV compared with 5-FU/LV. ERG cautions that 5-FU/LV not commonly used in NHS clinical practice. ERG noted that the overall survival for patients treated with oxaliplatin+5-FU/LV reported in the oxaliplatin trials were similar in magnitude to the overall survival outcomes of patients who were treated with nal-iri plus 5-FU/LV in the NAPOLI-1 trial

7 Equality issues

7.1 No equalities issues were raised during the scoping process or by consultees and commentators.

8 Authors

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Technical Lead

Sally Doss

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with input from the Lead Team (Tracey Cole, Susan Dutton and Alexander Dyker).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pegylated liposomal irinotecan hydrochloride trihydrate for treating pancreatic cancer after gemcitabine [ID778]

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Shire (pegylated liposomal irinotecan hydrochloride trihydrate) 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 Cancer Care • Muslim Council of Britain • Pancreatic Cancer Action • Pancreatic Cancer UK • Rarer Cancers Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care Professional groups • Association of Cancer Physicians • 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 • Primary Care Society for Gastroenterology • Royal College of General Practitioners	General • 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 Comparator companies • Accord (capecitabine, fluorouracil, oxaliplatin) • Allergan UK (capecitabine, oxaliplatin) • Dr. Reddy's Laboratories (capecitabine) • Hospira (calcium folinate, fluorouracil, oxaliplatin) • Medac GmbH (fluorouracil, folinic acid) • Pfizer (folinic acid) • Roche Products (capecitabine) • Sun Pharmaceuticals (capecitabine, oxaliplatin) • Zentiva (capecitabine) Relevant research groups • Cochrane Upper Gastrointestinal and

Consultees	**Commentators (no right to submit or appeal)**
• Royal College of Nursing • Royal College of Pathologists • 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 Cumbria CCG • NHS England • NHS Mansfield & Ashfield CCG • Welsh Government	Pancreatic Diseases Group • CORE (The 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

Nanoliposomal irinotecan for treating pancreatic cancer after prior treatment with gemcitabine

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of nanoliposomal irinotecan within its marketing authorisation for treating metastatic adenocarcinoma of the pancreas after prior treatment with gemcitabine-based treatments.

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 pancreatic ductal adenocarcinoma.[1]

In 2012, 7371 people were diagnosed with pancreatic cancer in England.[2] Pancreatic cancer affects men and women equally and about 75% of people diagnosed with pancreatic cancer are aged 65 years or over.[2] There were around 7200 deaths because of pancreatic cancer in 2013 in England.[3] 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.[4]

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. At the time of diagnosis, about 35–40% of people have locally advanced disease (meaning the cancer has grown into the tissues surrounding the pancreas) and about 45–55% have metastatic disease (meaning the cancer has spread to other parts of the body).[1]

There is no set pathway for treating locally advanced or metastatic pancreatic cancer and people with locally advanced or metastatic disease 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. NICE technology appraisal guidance 25 states that there is insufficient evidence to support the use of gemcitabine as a second-line treatment in patients with pancreatic adenocarcinoma.

There is no consensus about the preferred treatment for patients with pancreatic cancer that has previously been treated with gemcitabine. Options used in clinical practice include oxaliplatin in combination with 5-fluorouracil and folinic acid, oxaliplatin in combination with capecitabine, or fluoropyrimidine monotherapy.

The technology

Nanoliposomal irinotecan (Onivyde, Baxalta) consists of the anti-cancer medicine irinotecan contained within tiny fat particles called nanoliposomes. The nanoliposomes are expected to accumulate within the tumour and release the irinotecan slowly over time. Irinotecan blocks an enzyme called topoisomerase I, which causes DNA strands to break. This prevents the cancer cells from dividing and they eventually die. Nanoliposomal irinotecan is administered intravenously.

Nanoliposomal irinotecan does not currently have a marketing authorisation in the UK. It has been studied in a clinical trial that compared a regimen of nanoliposomal irinotecan, fluorouracil and folinic acid with a regimen of fluorouracil and folinic acid. The trial recruited patients with metastatic adenocarcinoma of the pancreas that had previously been treated with gemcitabine.

Intervention(s)	Nanoliposomal irinotecan in combination with fluorouracil and folinic acid
Population(s)	People with metastatic adenocarcinoma of the pancreas that has been treated with gemcitabine-based treatments
Comparators	• Oxaliplatin in combination with fluorouracil and folinic acid • Oxaliplatin in combination with capecitabine • Fluoropyrimidine monotherapy
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • 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.
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 Appraisal: Paclitaxel as albumin-bound nanoparticles in combination with gemcitabine for previously untreated metastatic pancreatic cancer (2015). NICE Technology Appraisal 360. Review date October 2018. Guidance on the use of gemcitabine for the treatment of pancreatic cancer (2001). NICE Technology Appraisal 25. Moved to static list in March 2006. Guideline in development: Pancreatic cancer. Publication expected January 2018. Related Interventional Procedure: Irreversible electroporation for treating pancreatic cancer (2013). NICE interventional procedures guidance 442. Related NICE Pathway: Gastrointestinal cancers (2015) NICE pathway http://pathways.nice.org.uk/
Related National Policy	NHS England Manual for Prescribed Specialised Services 2013/14. Chapter 105: Specialist cancer services (adults) http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf NHS England Standard Contract For Cancer: Pancreatic (Adult) 2013/14. Section B Part 1 - Service Specifications

	http://www.england.nhs.uk/wp-content/uploads/2013/06/a02-cncr-panc.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1, 4 and 5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

References

1. Pancreatic cancer UK (2015) Facts about pancreatic cancer. Accessed May 2015.
2. Office for National Statistics (2012) Cancer Registration Statistics, England.
3. Cancer Research UK (2015) Pancreatic cancer mortality statistics. Accessed May 2015.
4. Cancer Research UK (2015) Pancreatic cancer survival statistics. Accessed May 2015.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Nanoliposomal irinotecan for the treatment of metastatic pancreatic cancer following gemcitabine-based therapy [ID778]

Company evidence submission

20th April 2016

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Abbreviations

5-FU	5-fluorouracil
AE	Adverse event
AIC	Akaike Information Criterion
AICR	American Institute for Cancer Research
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APPG	All-Party Parliamentary Group
AST	Aspartate aminotransferase
AUC	Area under the curve
BIC	Bayesian Information Criterion
BLQ	Below quantification limit
BMI	Body mass index
BSA	Body surface area
BSC	Best supportive care
BSG	British Society of Gastroenterology
CBR	Clinical benefit response
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Human Medicinal Products
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variance
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EP	Evaluable patient
EPAR	European Public Assessment Report
EQ-5D	EuroQol-5 dimensions questionnaire
ERG	Evidence review group
ESMO	European Society for Medical Oncology
EU	European Union
FOLFOX	A regimen of oxaliplatin + 5-fluorouracil/leucovorin

GCP	Good clinical practice
G-CSF	Granulocyte-colony stimulating factor
GI	Gastrointestinal
GP	General practitioner
hENT1	human equilibrative nucleoside transporter 1
HEPES	2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulphonic acid
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
IARC	International Agency for Research on Cancer
ICE	Irinotecan, cetuximab and everolimus
ICER	Incremental cost-effectiveness ratio
ICH	International Conference on Harmonisation
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive web response system
KM	Kaplan-Meier
KPS	Karnofsky Performance Status
LV	Leucovorin
MPEG-2000-DSPE	A-(2-[1,2-distearoyl-sn-glycero(3)phosphooxy]ethylcarbamoyl-ω-methoxypoly(oxyethylen)-40 sodium salt
MRI	Magnetic resonance imaging
Nal-iri	Nanoliposomal irinotecan
NHS	National Health Service
NMA	Network meta-analysis
NYHA	New York Heart Association
OFF	A regimen of oxaliplatin + 5-fluorouracil/leucovorin
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PEG-DSPE	Poly(ethylene glycol)-distearoylphosphatidylethanolamine
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetic
PP	Per protocol
PR	Partial response
PRO	Patient-reported outcome

QALY	Quality-adjusted life year
QoL	Quality of life
Q-TWiST	Quality-adjusted time without symptoms or toxicity
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
REL	Time in relapse after disease progression
SAE	Serious adverse event
SD	Standard deviation
SF-6D	Short form-6 dimensions questionnaire
SG	Standard gamble
SmPC	Summary of product characteristics
SOS	Sucrose octasulphate
TEAE	Treatment-emergent adverse event
TMRE	Tumour marker response evaluable
TTF	Time to treatment failure
TTO	Time trade-off
ULN	Upper limit of normal
VAS	Visual analogue scale
WCRF	World Cancer Research Fund

1 Executive summary

1.1 *Statement of the decision problem*

The objective of this technology appraisal is to appraise the clinical and cost effectiveness of nanoliposomal irinotecan within its marketing authorisation for treating metastatic adenocarcinoma of the pancreas in combination with 5-fluorouracil and leucovorin in adults who have progressed following gemcitabine-based treatments. The NICE decision problem is summarised in Table 1.

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	Adults with metastatic adenocarcinoma of the pancreas who have progressed following gemcitabine-based treatments	The population reflects the therapeutic indication in the draft SmPC: Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) in adult patients who have progressed following gemcitabine-based therapy.	Indication in SmPC revised since scoping meeting.
Intervention	Nanoliposomal irinotecan in combination with 5-fluorouracil (5-FU) and leucovorin (LV)	As per scope	N/A
Comparator(s)	• Oxaliplatin in combination with fluorouracil and folinic acid • Oxaliplatin in combination with capecitabine • Fluoropyrimidine monotherapy	• Oxaliplatin in combination with fluorouracil and folinic acid • Fluoropyrimidine monotherapy: 5-fluorouracil + leucovorin (5-FU/LV)	There were no available data suitable for an indirect comparison for nal-iri + 5-FU/LV vs oxaliplatin + capecitabine. In addition, clinical expert opinion is that oxaliplatin + capecitabine is infrequently in clinical practice for post-gemcitabine treatment in pancreatic cancer.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	As per scope	N/A
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.	As per scope	N/A
Subgroups to be considered	None	None	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Special considerations including issues related to equity or equality	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.	–	The Cancer Patient Experience Survey in 2010 found that people with rarer forms of cancer reported a poorer experience of their treatment and care than people with more common forms of cancer (1). An All Party Parliamentary Group on Pancreatic Cancer report in 2013 found that care was not patient-centred, poorly co-ordinated and inefficient (2). The National Cancer Patient Experience Survey in 2014 questioned 4,310 patients in the UK with upper gastrointestinal cancer. The proportion of patients who replied negatively to a question was significantly lower than the average for cancer patients for eight questions, whereas the proportion of patients responding positively was only significantly higher than average for one question. In addition, pancreatic cancer presents primarily in the elderly population, with 80% of cases occurring in people aged between 60 and 80 years (3). Equity of treatment of the elderly is a concern, as evident from a report published by the National Audit Office in January 2015 (4). Pancreatic cancer is also an orphan disease (5). Therefore, access where appropriate to a treatment such as nal-iri should help to promote equality for both elderly patients and those with rarer forms of cancer.

Abbreviations: APPG, All-Party Parliamentary Group; 5-FU, 5-fluorouracil; LV, leucovorin; N/A, not applicable; NICE, National Institute for Health and Care Excellence; SmPC, summary of product characteristics.

1.2 *Description of the technology being appraised*

Nanoliposomal irinotecan (nal-iri) is a nanoliposomal formulation of irinotecan, a reversible topoisomerase I inhibitor, in the form of a sucrosofate salt. Approximately 80,000 molecules of irinotecan are encapsulated in a lipid bilayer vesicle or liposome. The cytotoxic effect of irinotecan on tumour cells is thought to be mediated by double-strand DNA damage that cannot efficiently be repaired.

Table 2: Technology being appraised

UK approved name	Irinotecan hydrochloride trihydrate as sucrosofate in a liposomal formulation (nanoliposomal irinotecan, nal-iri, also known as MM-398). In this submission, the name nal-iri will be used for this technology.
Brand name	Onivyde™
Marketing authorisation/CE mark status	Committee for Human Medicinal Products (CHMP) approval is expected circa 21st July 2016.
Indications and any restriction(s) as described in the summary of product characteristics	Indication: Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-FU and LV, also known as folinic acid, in adult patients who have progressed following gemcitabine-based therapy. Contraindications: • History of severe hypersensitivity reaction to irinotecan or any of the excipients: - 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) - Cholesterol - A-(2-[1,2-distearoyl-sn-glycero(3)phosphooxy]ethylcarbamoyl-ω-methoxypoly(oxyethylen)-40 sodium salt (MPEG-2000-DSPE) - Sucrose octasulphate potassium salt (SOS-potassium) - 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulphonic acid (HEPES) - Sodium chloride • Baseline neutrophil count of <1,500 cells/mm^3, and severe bone marrow failure • Bowel obstruction and chronic inflammatory bowel disease • Breastfeeding
Method of administration and dosage	Intravenous (IV) infusion. Nal-iri must not be administered as a bolus injection or an undiluted solution. Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with saline and/or sterile water and applications of ice are recommended.

Abbreviations: CHMP, Committee for Human Medicinal Products; DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; 5-FU, 5-fluorouracil; HEPES, 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulphonic acid; IV, intravenous; LV, leucovorin; MPEG-2000-DSPE, A-(2-[1,2-distearoyl-sn-glycero(3)phosphooxy]ethylcarbamoyl-ω-methoxypoly(oxyethylen)-40 sodium salt.

1.3 *Background summary*

Pancreatic cancer is the tenth most common cancer in the UK, and accounts for 3% of all new cases of cancer (6). It is a very severe and life-threatening disease with an extremely short life expectancy at diagnosis of median 4.6 months (7).

Patients with pancreatic cancer are usually asymptomatic in the early stages of the disease, which, along with the deep anatomical position of the pancreas, makes the cancer difficult to detect (8). Because of this and the aggressive nature of the tumour, pancreatic cancer is usually at a late stage at the time of diagnosis (either locally advanced or metastatic, where tumours have also appeared in other places in the body), and 80–90% of patients have inoperable or metastatic disease when diagnosed (9).

Pancreatic cancer is a condition associated with particularly high burden of illness, since the vast majority of patients present with advanced disease and the symptoms experienced significantly reduce a patient's quality of life (10, 11). Symptoms include jaundice, nausea, weight loss, poor appetite, diarrhoea and severe pain. Depression and anxiety are also common (7, 10). The symptoms that most significantly affect a patient's quality of life compared with the general population are pain, appetite loss, and insomnia, and global health is low, as measured by the European Organisation for Research and Treatment of Cancer (EORTC) (7).

Surgery is the only potentially curative option for pancreatic cancer, but it is only possible for the 10–20% of people who present with early stage disease (9). Of these patients, 53–87.5% have recurrence of their disease despite surgical removal of the tumour (12-14).

In the UK, gemcitabine is the most commonly prescribed first-line chemotherapy for pancreatic cancer, and is also the only first-line treatment option that is recommended by NICE (10). However, there is a poor response rate (20% or less) to gemcitabine-based treatment in the first-line setting and a short progression-free survival (PFS; <4 months). In addition, an increased use of gemcitabine as adjuvant treatment means that a different treatment is required on progression (15). As such, patients who progress on gemcitabine form a substantial patient pool, yet are currently poorly served, with no licenced or NICE recommended treatments available. Therefore, unlicensed treatments are currently used, and their use is supported by lower and conflicting levels of evidence than is considered acceptable in many other cancer indications.

Clinical expert opinion has revealed that in the UK, 20–40% of patients are well enough to receive active treatment post-gemcitabine. Of these, the majority receive one of the FOLFOX regimens containing folinic acid (leucovorin, LV), 5-FU and oxaliplatin. The most commonly used FOLFOX regimen in England is modified FOLFOX-4 (mFOLFOX-4). Very few patients, if any, receive oxaliplatin in combination with capecitabine or fluoropyrimidine monotherapy as post-gemcitabine treatment. It is important to recognise that peripheral neuropathy is a frequent treatment-related adverse event (AE) for oxaliplatin-containing chemotherapy regimens (16, 17), and is often a cause for dose reductions within the chemotherapy treatment (11).

The outlook for patients with pancreatic cancer has not improved since the 1970s, despite incidence rates rising by 8% in the last decade in the UK (6). This is in contrast to other cancers that have seen significant improvements in overall survival (OS) over the last 5 years (18). An All-Party Parliamentary Group (APPG) report in 2014 (19) called for more and better treatments for pancreatic cancer, and an earlier APPG report in 2013 (2) recommended that once diagnosed, patients should receive the most prompt and up-to-date treatment possible. As such, there is a substantial unmet need for a new treatment that can provide extended survival in a patient population that is currently underserved.

1.4 *Summary of the clinical effectiveness analysis*

1.4.1 *Efficacy demonstrated in nal-iri + 5-FU/LV*

NAPOLI-1 was designed as an open-label, randomised two-arm trial of nal-iri vs 5-FU/LV in metastatic pancreatic cancer patients previously treated with gemcitabine-based therapy. However, a protocol amendment was made to introduce a third combination therapy arm, nal-iri + 5-FU/LV. The licensed indication for nal-iri is in combination with 5-FU/LV, therefore results from this combination arm and the control arm (5-FU/LV) only are relevant for efficacy results. All three arms are presented in the safety profile to provide a complete overview of toxicity data for nal-iri. 5-FU/LV was used as the control arm due to its history of being one of the mainstays of therapy for pancreatic cancer, and at the time of the development of the trial protocol for NAPOLI-1, 5-FU was one of the standard treatments for pancreatic cancer (20, 21).

Of 577 patients screened, 417 were randomised and included in the intention-to-treat (ITT) population. Overall, the baseline characteristics of these patients were considered representative of a pre-treated, metastatic pancreatic cancer population and were balanced across treatment groups.

Primary endpoint – overall survival:

- Nal-iri + 5-FU/LV was superior to 5-FU/LV in OS (6.1 months vs 4.2 months, respectively; p=0.012)
- A clinically relevant 45% proportional increase in OS
- A 12-month survival estimate of 26% of patients with nal-iri + 5-FU/LV compared with 16% for 5-FU/LV
- All sensitivity analyses supported the primary OS analysis

Secondary endpoints:

- PFS was twice as long with nal-iri + 5-FU/LV compared with 5-FU/LV (3.1 months vs 1.5 months, respectively; p=0.0001)
- 16.2% of patients achieved unconfirmed objective response with nal-iri + 5-FU/LV vs 0.8% with 5-FU/LV
- Time to treatment failure was 2.3 months with 5-FU/LV vs 1.4 months with 5-FU/LV
- 28.9% of patients achieved CA19-9 tumour marker response with nal-iri + 5-FU/LV vs 8.6% with 5-FU/LV

Further data supporting the efficacy of nal-iri in patients with metastatic pancreatic cancer previously treated with gemcitabine were provided by the phase II trial, NCT00813163. This study also met its primary endpoint, with 75% of patients achieving a 3-month OS. Median PFS and OS were 2.4 and 5.2 months, respectively, and disease control was achieved by 50% of patients. In addition, 31.3% of patients with elevated CA19-9 at baseline showed >50% biomarker decline, and 20% of CBR-evaluable patients achieved significant clinical benefit.

Quality of life results generally showed no difference between the treatment arms. Baseline median Global Health Status scores were similar between the arms and there

were no appreciable changes from baseline after 12 weeks, suggesting that there were no negative effects of treatment on Global Health Status. As supporting evidence, an additional analysis was performed for quality of life outcomes, quality-adjusted time without symptoms or toxicity (Q-TWiST). It was found that patients in the nal-iri + 5-FU/LV arm had significantly more time in TWiST compared with the 5-FU/LV arm (3.4 vs 2.4 months, respectively), and 1.3 months longer Q-TWiST (5.1 vs 3.9 months, respectively), with a relative Q-TWiST gain of 24%.

These results support the primary analysis of quality of life, and show that nal-iri + 5-FU/LV resulted in statistically significant and clinically important gains in quality-adjusted survival compared with 5-FU/LV (22).

1.4.2 *Safety profile of nal-iri + 5-FU/LV vs 5-FU/LV*

The safety profile of nal-iri monotherapy and the nal-iri + 5-FU/LV combination in NAPOLI-1 was consistent with prior experience with nal-iri and 5-FU/LV. Gastrointestinal AEs (diarrhoea, nausea and vomiting) were the most common adverse reactions in the nal-iri-containing arms; however they were generally tolerated, and the number of patients discontinuing treatment due to gastrointestinal AEs was low. In addition, as described above, AEs did not show a detrimental effect on the patient's quality of life, which is an important factor for patients with pancreatic cancer, who are generally in poor health from the effects of the underlying disease and previous treatments.

More frequent and severe gastrointestinal AEs were observed in the nal-iri monotherapy arm compared with the nal-iri + 5-FU/LV combination arm, suggesting that the more frequent administration of nal-iri with a lower dose results in fewer and less severe gastrointestinal AEs. Electrolyte abnormalities, such as hypokalaemia, hypomagnesaemia, and hyponatraemia, which are commonly associated with diarrhoea, were more frequently observed in the nal-iri-containing arms compared with the 5 FU/LV control arm, and they too were most frequent and severe with nal-iri monotherapy.

Myelosuppression, especially neutropenia, was more frequent and severe in the nal-iri-containing arms than in the 5 FU/LV control arm, and were most frequent in the nal-iri + 5-FU/LV combination arm. Dose delay, dose reduction, and colony stimulating factors were used to manage myelosuppression. Treatment discontinuation due to myelosuppression was low. Thrombocytopenia was infrequent, as has been documented with non-liposomal irinotecan.

There were four deaths assessed as related to treatment in the nal-iri monotherapy arm, one in the nal-iri + 5-FU/LV arm, and none in the 5-FU/LV control arm.

In trial NCT00813163, as expected, gastrointestinal and haematologic AEs were among the most common toxicities reported during nal-iri monotherapy. Fatigue and abdominal pain were also common.

Overall, the results of NAPOLI-1 show that nal-iri in combination with 5-FU/LV is a clinically efficacious and manageable treatment for patients with metastatic pancreatic cancer who have previously been treated with gemcitabine. The phase II trial NCT00813163 supported this.

1.5 *Summary of the cost-effectiveness analysis*

Comparators in the economic evaluation described in Section 5 included 5-FU/LV and oxaliplatin + 5-FU/LV. NAPOLI-1 compared nal-iri + 5-FU/LV with 5-FU/LV, and so direct comparative evidence could be used in the economic analysis. 5-FU/LV was used as the control arm in NAPOLI-1 due to its history of being one of the mainstays of therapy for pancreatic cancer, and at the time of the development of the trial protocol for NAPOLI-1, 5-FU was one of the standard treatments for pancreatic cancer (20, 21). Despite a feasibility assessment and KOL feedback demonstrating that an indirect comparison between oxaliplatin + 5-FU/LV with nal-iri + 5-FU/LV was not feasible due to heterogeneity of the trials, an indirect comparison was performed in order to compare these two treatments, since clinical expert opinion is that FOLFOX is the most commonly used treatment post-gemcitabine. As such, several major assumptions for this comparison were required, as described in Section 5.6.2, and hence the results should be treated with caution.

The main strength of the evaluation is that it is relevant to UK decision-makers, since the model includes the current standard of care for UK patients following progression on gemcitabine-based therapy (oxaliplatin + 5-FU/LV) as evidenced by clinical expert opinion, and also uses associated UK-specific data, where available.

The main limitations are in the lack of head-to-head data for nal-iri + 5-FU/LV vs oxaliplatin + 5-FU/LV, as well as the methods used to incorporate the oxaliplatin + 5 FU/LV arm into the model (as described in Section 5.3.2.3).

The base case demonstrated that nal-iri + 5-FU/LV was more effective than both 5-FU/LV and oxaliplatin + 5-FU/LV (Table 3).

Table 3: Incremental cost-effectiveness results

Technologies	Total		Incremental		ICER (Cost/QALY)
	Costs	QALYs	Costs	QALYs	
Nal-iri + 5-FU/LV	[redacted]	0.5635	-	-	-
5-FU/LV	£13,338.32	0.4294	[redacted]	0.1341	[redacted]
Oxaliplatin + 5-FU/LV	£13,974.83	0.3621	[redacted]	0.2013	[redacted]

Abbreviations: 5-FU, 5-fluorouracil; ICER, incremental cost-effectiveness ratio; LV, leucovorin; QALY, quality-adjusted life year.

In order to evaluate the uncertainty, we also undertook extensive sensitivity analyses, which showed that the results of the model were robust in the face of uncertainty in both the parameter inputs and the structural assumptions required to construct the model. All scenarios indicate that nal-iri + 5-FU/LV is cost-effective below a willingness-to-pay threshold of [redacted] vs 5-FU/LV, and [redacted] vs oxaliplatin + 5-FU/LV.

2 The technology

2.1 *Description of the technology*

Brand name: Onivyde™

UK approved name: Irinotecan hydrochloride trihydrate as sucrosofate salt in a liposomal formulation (nanoliposomal irinotecan, nal-iri, also known as MM-398). In this submission, the name nal-iri will be used for this technology.

Therapeutic class: Reversible topoisomerase I inhibitor

Mechanism of action: Nal-iri is a nanoliposomal formulation of irinotecan, a reversible topoisomerase I inhibitor, in the form of a sucrosofate salt. Approximately 80,000 molecules of irinotecan are encapsulated in a lipid bilayer vesicle or liposome. The cytotoxic effect of irinotecan on tumour cells is thought to be mediated by double-strand DNA damage that cannot efficiently be repaired.

Irinotecan is a derivative of camptothecin, which inhibits the DNA enzyme topoisomerase I. It is converted by non-specific carboxylesterases present in the liver, blood and macrophages (23) into its metabolite SN-38, which is 100- to 1000-fold more active than irinotecan (24). Topoisomerase I relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and SN-38 bind to the topoisomerase I–DNA complex and prevent re-ligation of the breaks, leading to exposure time-dependent double-strand DNA damage and cell death.

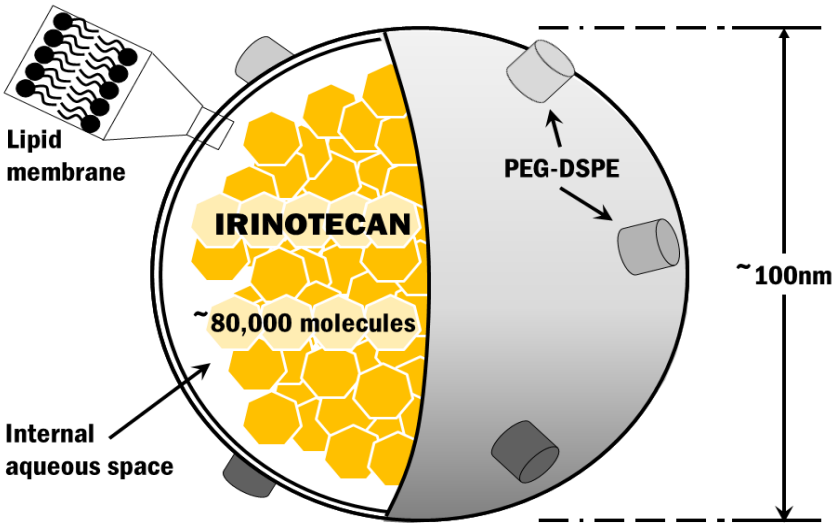
The rationale for developing a nanoliposomal formulation of irinotecan (nal-iri) was to:

- extend the circulation of irinotecan through sheltering it from conversion to SN-38 in plasma (25)
- increase delivery in tumours to take advantage of the compromised vasculatures of tumours (26)
- increase local intra-tumoral conversion of irinotecan to SN-38 leading to an increased and extended tumour concentration of SN-38 (26).

All of these attributes of nal-iri should result in a higher concentration of chemotherapeutic agent in the tumour, which should result in better tumour shrinkage or slower tumour growth.

The structure of nal-iri is shown in Figure 1.

Figure 1: Structure of nal-iri



Abbreviations: PEG-DSPE, poly(ethylene glycol)-distearoylphosphatidylethanolamine.

The half-life of nal-iri is approximately 26 hours in humans, and at least 90% of the drug remains liposome-encapsulated during circulation. It is hypothesised that because of their small size (ca. 100 nm) and persistence in the circulation, the PEGylated liposomes are able to penetrate the altered and often compromised vasculature of tumours, resulting in an extended duration of high drug concentration inside a tumour. A study in humans found that SN-38 levels in tumour biopsies were approximately 5-fold higher than plasma levels 72 hours after nal-iri infusion (27).

2.2 *Marketing authorisation/CE marking and health technology assessment*

2.2.1 *Marketing authorisation/CE marking*

The Marketing Authorisation Application is currently under review by the Committee for Human Medicinal Products (CHMP) under the European centralised procedure. The applicant has received the day 180 questions and the procedure is in 'clock stop' pending the company response to the questions received. It is anticipated that the CHMP will complete their review and issue an opinion on the application circa 21 July 2016. The European Public Assessment Report (EPAR) will be published by the EMA following the Commission Decision on nal-iri.

2.2.2 *(Anticipated) indication(s) in the UK*

Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine based therapy.

2.2.3 *(Anticipated) restrictions or contraindications*

2.2.3.1 Contraindications

- History of severe hypersensitivity reaction to irinotecan or any of the excipients:

- 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)
- Cholesterol
- α-(2-[1,2-distearoyl-sn-glycero(3)phosphooxy]ethylcarbamoyl)-ω-methoxypoly(oxyethylen)-40 sodium salt (MPEG-2000-DSPE)
- Sucrose octasulphate potassium salt (SOS-potassium)
- 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulphonic acid (HEPES)
- Sodium chloride

- Baseline neutrophil count of <1,500 cells/mm^3, and severe bone marrow failure
- Bowel obstruction and chronic inflammatory bowel disease
- Breastfeeding

2.2.3.2 Warnings and precautions

Warnings and precautions associated with nal-iri are discussed in full in the summary of product characteristics in Appendix 1.

2.2.4 *SmPC/Information for use and (Draft) assessment report*

The draft summary of product characteristics (SmPC) is provided in Appendix 1.

2.2.5 *Main issues discussed by regulatory authorities*

The Marketing Authorisation Application is currently under review, and therefore no issues have been discussed to date.

2.2.6 *Anticipated date of availability in the UK*

The anticipated date of availability in the UK is November 2016.

2.2.7 *Regulatory approval outside the UK*

Nal-iri in combination with 5-FU/LV was approved by the US FDA on 22 October 2015, and by the Taiwan FDA on 22 October 2015.

2.2.8 *Ongoing HTAs in the rest of the UK*

A submission for nal-iri to the SMC is planned for August 2016.

2.3 *Administration and costs of the technology*

Table 4: Costs of the technology being appraised

	Cost	Source

	Cost	Source
Pharmaceutical formulation	Concentrate for solution for infusion (white to slightly yellow opaque isotonic liposomal dispersion). One 10 mL pack contains one sterile single-use vial containing 50 mg irinotecan hydrochloride trihydrate (as sucrosofate salt in a liposomal formulation), which corresponds to 43 mg irinotecan. This must be diluted prior to administration with 5% glucose solution for injection or 0.9% w/v sodium chloride solution for injection to a final volume of 500 mL. The product should be used as soon as possible after dilution, but can be stored at ambient temperature for up to 6 hours or at 2–8°C for no more than 24 hours prior to use. It must be protected from light and it must not be frozen.	SmPC
Acquisition cost (excluding VAT)[†]	[redacted] – This is an indicative price only as the price has not been approved by the Department of Health to date.	N/A
Method of administration	Intravenous (IV) infusion. Nal-iri must not be administered as a bolus injection or an undiluted solution.	SmPC
Doses	80 mg/m^2 (body surface area)	SmPC
Dosing frequency, average length of a course of treatment and anticipated average interval between courses of treatments	Recommended dose and regimen is nal-iri 80 mg/m^2 IV infusion over 90 min, followed by LV 400 mg/m^2 IV over 30 min, followed by 5-FU 2400 mg/m^2 IV over 46 hours, administered every 2 weeks.	SmPC
Average cost of a course of treatment	[redacted] - This is an indicative cost estimate only as the list price has not been approved by the Department of Health to date	
Anticipated number of repeat courses of treatments	8 – Based on the average overall survival from the NAPOLI-1 trial results	Assumption
Dose adjustments	In patients known to be homozygous for the UGT1A1*28 allele, the recommended starting dose of nal-iri is 60 mg/m^2. A dose increase to 80 mg/m^2 should be considered as tolerated in subsequent cycles. In addition, dose adjustments of nal-iri and 5-FU are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia, and other Grade 3 or 4 toxicities judged to be related to nal-iri. There are no dose adjustments recommended for LV or for Grade 1 or 2 toxicities.	SmPC
Anticipated care setting	Nal-iri treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents.	

Abbreviations: 5-FU, 5-fluorouracil; IV, intravenous; LV, leucovorin; N/A, not applicable; SmPC, summary of product characteristics; VAT, value added tax.

2.3.1 *Patient access scheme*

A patient access scheme will be submitted to the Department of Health in April 2016. Further details will follow as soon as possible, and will hopefully be ministerially approved so that it can be considered during the first ACD meeting.

2.4 *Changes in service provision and management*

2.4.1 *Additional test/investigations*

No additional tests or monitoring are required for nal-iri beyond those that are already part of current clinical practice. Therefore, it is anticipated that no additional NHS resources will be required.

2.4.2 *Main resource use to the NHS associated with the technology*

Nal-iri, LV and 5-FU should be administered sequentially. The recommended dose and regimen of nal-iri is 80 mg/m^2 intravenously over 90 minutes, followed by LV 400 mg/m^2 intravenously over 30 minutes, followed by 5-FU 2,400 mg/m2 intravenously over 46 hours, administered every 2 weeks. As is standard practice for anticancer therapy, nal-iri should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents. Prior to and during treatment, patients should be monitored for treatment response and toxicities. Frequent monitoring of liver function and complete blood counts should be conducted in patients with hyperbilirubinemia to reduce the risk of neutropenia.

Monitoring of renal function is recommended in all patients, as nal-iri is not recommended for use in patients with severe renal impairment (CLcr <30 ml/min).

2.4.3 *Additional infrastructure requirements*

No additional NHS infrastructure is required to accommodate nal-iri when compared with other chemotherapy regimens.

2.4.4 *Patient monitoring requirements*

The level of monitoring required for nal-iri is consistent with other treatments prescribed for pancreatic cancer.

2.4.5 *Need for concomitant therapies*

The SmPC states that it is recommended that patients receive pre-medication for nausea and vomiting prior to nal-iri infusion with standard doses of dexamethasone (or an equivalent corticosteroid) together with a 5-HT3 antagonist (or other anti-emetic), unless contraindicated. Pre-medication is common with chemotherapy regimens, and should be given on the day of treatment, starting at least 30 minutes before administration of nal-iri.

Atropine may be prescribed prophylactically for patients who have experienced acute cholinergic symptoms in previous cycles. Physicians should also consider providing patients with an antiemetic regimen for subsequent use, as well as loperamide (or equivalent) for treatment of late diarrhoea, if necessary.

The use of granulocyte-colony stimulating factor (G-CSF) was permitted in the clinical trial to treat patients with neutropenia or neutropenic fever; prophylactic use of G-CSF

was permitted only in those patients with at least one episode of Grade 3 or 4 neutropenia or neutropenic fever while receiving study therapy.

2.5 *Innovation*

The nanoliposomal formulation of irinotecan is innovative and represents a step change in the management of this condition in the post-gemcitabine setting, being the first licensed treatment for pancreatic cancer in this setting. The 45% proportional increase in OS seen in NAPOLI-1 compared with 5-FU/LV and the anticipated increase in the real world setting with this technology would represent a significant improvement in survival for these currently underserved patients, and thus represents a step change in the prognosis for patients with pancreatic cancer, especially in the advanced stage of post-gemcitabine-based treatment.

There is published evidence showing distinctly modified pharmacokinetic characteristics for nal-iri compared with non-liposomal irinotecan, including slow clearance, extended plasma circulation, small volume of distribution, and prolonged terminal half-life (28, 29). Another study showed that the total levels of irinotecan and SN-38 were higher in tumour tissue than in plasma 72 hours after nal-iri dosing (27).

NAPOLI-1 is the largest trial in this setting with the most robust evidence, and nal-iri is the only proven treatment option in this patient population. Many other development programs for a range of molecules have failed in these patients, exacerbated by an extremely short life expectancy and small patient numbers, especially in the post-gemcitabine setting. Therapeutic options therefore remain extremely limited, and the use of other off-label agents in this setting are supported by lower levels of evidence than is seen in other cancer indications.

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

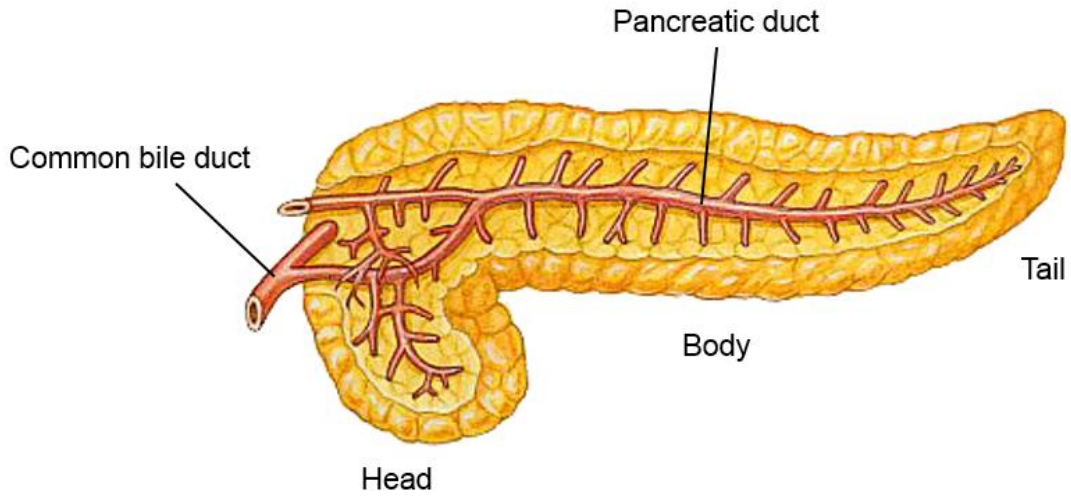
3.1 *Disease overview*

Pancreatic cancer is the tenth most common cancer in the UK, and accounts for 3% of all new cases of cancer; there were 9,408 new cases of pancreatic cancer in the UK in 2013 (6). It is a very severe and life-threatening disease with an extremely short life expectancy at diagnosis of median 4.6 months (7). Nal-iri was granted orphan designation in 2011. At this time, pancreatic cancer affected approximately 1.4 in 10,000 people in the EU, which is below the ceiling for orphan designation (5 people in 10,000) (5).

Tumours of the pancreas are highly heterogeneous; a global genomic analysis of 24 advanced pancreatic adenocarcinomas has shown that tumours contain an average of 63 genetic alterations (30). However, they can be broadly divided into two general groups. Exocrine tumours originate in the enzyme-producing cells of the pancreas, and endocrine tumours begin in the hormone-producing cells (31). Over 95% of pancreatic cancers are exocrine tumours, the most common of which are pancreatic ductal adenocarcinomas, accounting for approximately 90% of all pancreatic tumours (32).

There are three groups that pancreatic cancer can be anatomically classified into based on the tumour location: head, body or tail (Figure 2). The majority (60–70%) of tumours present in the head of the pancreas, while 20–25% present in the body or tail of the pancreas (33). The remainder diffusely involve the pancreas.

Figure 2: The pancreas



Pancreatic cancer tumours are dominated by stroma, the connective, functionally supportive framework of the pancreas. This creates a dense, poorly perfused, and nearly impenetrable tumour microenvironment that not only limits the ability of current

chemotherapies to reach the tumour and achieve effective concentrations, but also stimulates tumour growth (34).

Patients with pancreatic cancer are usually asymptomatic in the early stages of the disease, which, along with the deep anatomical position of the pancreas, makes the cancer difficult to detect (8). Because of this and the aggressive nature of the tumour, pancreatic cancer is usually at a late stage at the time of diagnosis (either locally advanced or metastatic, where tumours have also appeared in other places in the body), and 80–90% of patients have inoperable or metastatic disease when diagnosed (9).

Symptoms experienced in the later stages of pancreatic cancer include jaundice, abdominal pain, weight loss, poor appetite, diarrhoea, nausea and vomiting, dyspepsia, back pain, fever, blood clots, fatigue, and new onset diabetes mellitus (35).

The incidence of pancreatic cancer increases with age; it is rare in people younger than 45 years of age and 80% of cases occur in people aged between 60 and 80 years (3). The mean age of onset is 71 years for men and 75 years for women (33).

In addition to age, there are other risk factors for pancreatic cancer, and 37% of cases each year in the UK are linked to lifestyle and are preventable (6). Cigarette smoking is the strongest environmental risk factor for pancreatic cancer; an estimated 29% of cases in the UK are linked to smoking (6). A meta-analysis of 82 studies reported a 74% increased risk of pancreatic cancer in current smokers, with an odds ratio of 1.74 (95% CI: 1.61, 1.87) (36). Obesity is another lifestyle risk factor, and body fatness is classified as a cause of pancreatic cancer by the International Agency for Research on Cancer (IARC) and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) (37, 38). A meta-analysis found that for every 5-unit body mass index (BMI) increase, the risk of pancreatic cancer increases by 10%, and the risk increases by 11% per 10 cm waist circumference increase, and by 19% per 0.1 unit waist-to-hip ratio increment (39). In addition, obesity (BMI >30 kg/m^2) is associated with a 20–40% higher rate of death from pancreatic cancer (33). Other lifestyle choices that may relate to a higher pancreatic cancer risk include the consumption of alcohol and red meat (6).

3.2 *Burden to patients, carers and society*

Pancreatic cancer is a condition associated with particularly high burden of illness, since the vast majority of patients present with advanced disease and the symptoms experienced significantly reduce a patient's quality of life (10, 11). Symptoms include jaundice, nausea, weight loss, poor appetite, diarrhoea and severe pain, and depression and anxiety are also common (7, 10). The symptoms that most significantly affect a patient's quality of life compared with the general population are pain, appetite loss, and insomnia, and global health is low, as measured by the European Organisation for Research and Treatment of Cancer (EORTC) (7). Additionally, improvements in baseline global health and cognitive function after 3 months of treatment were found to be significant predictors of survival in a multivariate analysis (40). For every 10-point increase in baseline global quality of life (QoL) score, there was an associated 12% decrease in the risk of death (hazard ratio 0.88; 95% CI: 0.81, 0.95; p=0.001), and for every 10-point improvement in cognitive function, there was an associated 11% decrease in the risk of death (hazard ratio 0.89; 95% CI: 0.79, 0.99; p=0.04).

The direct medical costs associated with pancreatic cancer are substantial. A systematic review of burden of illness studies found that hospitalisation was the greatest contributor to direct medical costs, followed by interventions (radiology, surgery, and chemotherapy) (7). In the UK in 2008, the total cost of first emergency admissions for pancreatic cancer was £14,651,635, and of all emergency admissions occurring within 365 days of the first admission was £20,724,058 (41). The cost of care over the residual lifetime of the patient was estimated as €16,066 in Sweden (42) and €31,375 in Germany (43).

The healthcare resource utilisation for patients with pancreatic cancer is high from the time of diagnosis until death. In a 2015 study, 86.5% of patients in the UK had at least one healthcare visit unrelated to the administration of chemotherapy, 54.0% had at least one inpatient hospitalisation, 28.5% had at least one emergency department visit, and 42.5% received end-of-life care, as defined by enrolment in either hospice care or a long-term care facility (8). Of the 54.0% of patients that had at least one inpatient hospitalisation, 41.7% had one, 33.3% had two, and 25.0% had three or more, and the median length of stay was 6 days (8).

A 2009 study in Sweden found that patients had an average of 21.9 hospital days, 4.9 radiological investigations, and 18.8 chemotherapy doses per patient (42). The same study estimated indirect costs in patients aged ≤64 years, including absenteeism due to sickness and the loss of productive life years due to premature mortality. Short-term productivity loss per patient was €87,205 for men and €49,895 for women, and the mean productivity loss per patient due to mortality was €238,843 in men and €220,543 in women (42). A study in Germany found that 24% of diagnosed patients were actively employed, resulting in a mean productivity loss of €3,210 per patient, or €416 per month of observation (43). There is no reason to anticipate that Swedish or German patients are different from UK patients, and so these data are assumed to also be of relevance to the UK and indicative of this population.

3.3 *Clinical pathway of care*

Surgery is the only potentially curative option for pancreatic cancer, but it is only possible for the 10–20% of people who present with early stage disease (9), and, of these patients, 53–87.5% have recurrence of their disease despite surgical removal of the tumour (12-14). Patients with locally advanced or metastatic disease are not suitable for surgical resection, and at the time of diagnosis, 35–40% of people have locally advanced disease and 45–55% have metastases (9). As such, the vast majority of patients are only suitable for treatment aimed at improving survival and palliation.

In the UK, gemcitabine is the most commonly prescribed first-line chemotherapy for pancreatic cancer; 46% of patients are administered gemcitabine as first-line therapy, and a further 34% are given gemcitabine in combination with another cytotoxic agent (8). Gemcitabine is also the only treatment option that is recommended by NICE as first-line therapy in patients who are not suitable for potentially curative surgery and who have a Karnofsky performance score of ≥50 (10). Karnofsky performance status rates disease severity on a scale of 0 to 100 where 0 represents death and 100 represents no evidence of disease.

However, most metastatic pancreatic cancer patients progress following treatment with a gemcitabine-based therapy (44), and a retrospective study suggested that gemcitabine may only be effective in patients with high levels of human equilibrative nucleoside

transporter 1 (hENT1), which is the major mediator of gemcitabine uptake into human cells (45). As such, patients who fail on gemcitabine form a substantial patient pool, yet are currently poorly served, with no licenced or NICE recommended treatments available. Therefore, unlicensed treatments are currently used and their use is supported by lower levels of evidence than is deemed acceptable in many other cancer indications.

Clinical expert opinion has revealed that in the UK, 20–40% of patients are well enough to receive active treatment post-gemcitabine. Of these the majority receive one of the FOLFOX regimens containing folinic acid (leucovorin, LV), 5-FU and oxaliplatin. The most commonly used FOLFOX regimen in England is modified FOLFOX-4 (mFOLFOX-4). Very few patients receive oxaliplatin in combination with capecitabine or fluoropyrimidine monotherapy as post-gemcitabine treatment.

Evidence for the efficacy of the combination of folinic acid, 5-FU and oxaliplatin is inconsistent, and only two randomised controlled trials have been conducted that are relevant to be compared with nal-iri + 5-FU/LV, CONKO-003 and PANCREOX (the search to identify trials with oxaliplatin + 5-FU/LV is described in Section 4.1 and the network showing the relevant trials is shown in Section 4.10.1).

CONKO-003 was a study in Germany (n=168) comparing 5-FU, folinic acid and oxaliplatin in an OFF regimen with 5-FU and folinic acid. Results showed significantly extended OS with OFF compared with 5-FU and folinic acid (5.9 vs 3.3 months, respectively; p=0.01) (11). However, the OFF regimen differs from the most commonly used regimen in England, mFOLFOX-4, in the accumulative dose of 5-FU, the use of bolus 5-FU, the total dose of oxaliplatin, and the overall scheduling of treatment. These key technical differences may lead to important differences in treatment-related outcomes in terms of both safety and efficacy.

In stark contrast, PANCREOX, a more recent Canadian phase III trial (n=108) that is only published in abstract form, found that overall survival (OS) was inferior in gemcitabine-refractory patients treated with FOLFOX compared with 5-FU and folinic acid (6.1 vs 9.9 months, respectively; p=0.02) (46).

It is also important to recognise that peripheral neuropathy is a frequent treatment-related adverse event (AE) for oxaliplatin-containing chemotherapy regimens (17). Oxaliplatin-induced Grade 2 or worse neuropathy occurs in approximately 40–50% of patients, with Grade 3 neuropathy occurring in 10–20% of patients (16). In addition, a significant proportion of these patients are left with some symptoms more than 2 years after completing therapy (16). The symptoms experienced can range from sensory alterations and loss of reflexes (Grade 1) to severe symptoms limiting self-care, life-threatening consequences, or even death (Grade 3-5). The frequency of adverse events in CONKO-003 is broadly in line with that reported in a review of oxaliplatin-induced neuropathy in colorectal cancer (16). In addition, peripheral neuropathy is frequently a cause for dose reductions within the chemotherapy treatment. CONKO-003 reported a 75% dose reduction for 10% of the administrations, and a further 9% of planned oxaliplatin administrations were not given (11).

Given the conflicting results of these unlicensed treatments and the evidence supporting OS improvements with nal-iri, it is expected that nal-iri will provide the best option for the treatment of gemcitabine-refractory patients with a much more substantial evidence base. This is supported by the European Society for Medical Oncology (ESMO)

guidelines, which state that nal-iri may be the best option for the treatment of gemcitabine-refractory patients when nal-iri is available in all countries (33).

3.4 *Life expectancy*

The incidence of pancreatic cancer in the UK was 14.7 per 100,000 people in 2013 (47), equating to 9,408 new cases, of which 8,389 were in England (7,887) and Wales (502) (6). As described in Section 3.3, the majority of patients with pancreatic cancer present with advanced or metastatic disease, and of the small proportion who undergo surgery, the majority experience recurrence. Therefore, the prognosis for these patients is extremely poor and pancreatic cancer is the fifth most common cause of cancer death in the UK (6).

Pancreatic cancer was responsible for 8,662 deaths in the UK in 2012, almost half of which were in people aged ≥75 years (6). Only 21% of patients diagnosed with pancreatic cancer in England and Wales survive for 1 year or more after diagnosis, 3% survive for 5 years or more, and only 1% survive for 10 years or more (6). A systematic review of real-world, peer reviewed, observational European studies (n=91) found that the median life expectancy at diagnosis was 4.6 months in patients with pancreatic cancer irrespective of stage of diagnosis, compared with 15.1 years for an age-matched healthy population (7), and the median survival for patients with metastatic disease was 2.8–5.7 months.

The outlook for patients with pancreatic cancer has not improved since the 1970s, despite incidence rates rising by 8% in the last decade in the UK (6). This is in contrast to other cancers that have seen significant improvements in OS over the last 5 years (18). As such, there is a substantial unmet need for a new treatment that can provide extended survival in a patient population that is currently underserved.

3.5 *Relevant NICE guidance, pathways or commissioning guides*

NICE guidance TA25 concerns the use of gemcitabine for the treatment of pancreatic cancer (10), and provides the following recommendations:

- Gemcitabine may be considered as a treatment option for patients with advanced or metastatic adenocarcinoma of the pancreas and a Karnofsky performance score of 50 or more, where first-line chemotherapy is to be used.
- Gemcitabine is not recommended for patients who are suitable for potentially curative surgery, or patients with a Karnofsky performance score of less than 50.
- There is insufficient evidence to support the use of gemcitabine as a second-line treatment in patients with pancreatic adenocarcinoma.

There is currently no standard of care for treatment following disease progression on gemcitabine-based therapy, and it is not anticipated that wider guidance will be given, outside of this review, until NICE guidelines for the treatment of pancreatic cancer are published in 2018.

In addition, NICE published guidance TA360 in October 2015, which stated that 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 (48). While this may be revisited, it does not influence the introduction of nal-iri + 5-FU/LV as a treatment option since it considers a different point in the treatment pathway as it is combined with gemcitabine rather than following it.

An interventional procedure guidance document (IPG442) was published in 2013 for irreversible electroporation for treating pancreatic cancer (49). It was recommended that this procedure should only be used in the context of research due to the current safety and efficacy data being inadequate in quantity and quality.

3.6 *Clinical guidelines*

3.6.1 *UK guidelines*

The British Society of Gastroenterology (BSG) published guidelines for the management of patients with pancreatic cancer in 2005 (3), following the approval of gemcitabine by NICE in 2001 (10). The BSG guidelines recommend that gemcitabine should be used as chemotherapy for palliation, and that therapy with novel treatments should only be offered to patients within clinical trials (3).

3.6.2 *European guidelines*

The European Society for Medical Oncology (ESMO) published guidelines more recently in September 2015 (33). These guidelines state that when nal-iri is available in all countries, it may be the best option for the treatment of gemcitabine-refractory pancreatic cancer.

Recommendations on the first choice of treatment are also provided; although not of direct relevance to this submission, they are included here for completeness:

- Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 3–4 and significant morbidities and a very short life expectancy should only receive symptomatic treatment.
- Patients with ECOG performance status 2 should receive gemcitabine and nab-paclitaxel.
- Patients with ECOG performance score of 2 and/or a bilirubin level higher than 1.5 times the upper limit of normal (ULN) should receive monotherapy with gemcitabine.
- Patients with ECOG performance status of 0–1 and a bilirubin level below 1.5 times ULN should receive either FOLFIRINOX (folinic acid, 5-FU, irinotecan and oxaliplatin) or gemcitabine plus nab-paclitaxel.

It should be noted that, as stated in Section 3.5, nab-paclitaxel with gemcitabine is not recommended by NICE for the treatment of pancreatic adenocarcinoma that has not been treated before (48). Therefore, this treatment combination is not an option in England and Wales.

3.7 *Issues relating to current clinical practice*

Pancreatic cancer grows within a dense, poorly perfused, and nearly impenetrable stroma that limits the ability of current chemotherapies to effectively reach the tumour

and achieve effective concentrations (34). As such, currently available treatment options for patients with metastatic pancreatic cancer are inadequate. Gemcitabine is recommended as first-line therapy for pancreatic adenocarcinoma in the UK (10). However, there is a poor response rate (20% or less) of gemcitabine-based treatment in the first-line setting, a short progression-free survival (PFS; <4 months) and an increased use of gemcitabine as adjuvant treatment (15). This means that there is an unmet need for effective treatment alternatives following failure with gemcitabine-based therapy. There is currently no licenced or approved therapies in this setting. New therapies that enhance drug delivery and drug retention in tumour tissue are needed to improve clinical outcomes for patients with advanced and metastatic pancreatic cancer.

3.8 *Equality*

The Cancer Patient Experience Survey in 2010 found that people with rarer forms of cancer reported a poorer experience of their treatment and care than people with more common forms of cancer (1). In addition, an APPG report in 2013 found that care was not patient-centred, poorly co-ordinated and inefficient (2).

The National Cancer Patient Experience Survey in 2014 questioned 4,310 patients in the UK with upper gastrointestinal cancer. The proportion of patients who replied negatively to a question was significantly lower than the average for cancer patients for eight questions, whereas the proportion of patients responding positively was only significantly higher than average for one question (Table 5).

Table 5: Significant results from the 2014 National Cancer Patient Experience Survey

	Percentage of patients agree	
	Upper GI cancer	**Cancer average**
The proportion of patients answering positively was significantly lower for patients with upper GI cancer compared with the cancer average		
Patient saw GP no more than twice before being told they had to go to hospital	68.0%	75.0%
Patients thought they were seen as soon as necessary	78.0%	83.0%
Patient's health got better or remained about the same while waiting	68.0%	80.0%
Patient felt they were told sensitively that they had cancer	81.0%	84.0%
Patient given written information about the type of cancer they had	66.0%	72.0%
Doctors did not talk in front of the patients as if they were not there	78.0%	84.0%
Patient never thought that they were given conflicting information	73.0%	79.0%
Patient given clear written information about what they should/should not do post-discharge	79.0%	85.0%
The proportion of patients answering positively was significantly higher for patients with upper GI cancer compared with the cancer average		
All staff asked patient what name they preferred to be called by	69.0%	60.0%

Abbreviations: GI, gastrointestinal; GP, general practitioner.

In addition, pancreatic cancer presents primarily in the elderly population, with 80% of cases occurring in people aged between 60 and 80 years (3). Equity of treatment of the elderly is a concern, as evident from a report published by the National Audit Office in January 2015 (4). Pancreatic cancer is also an orphan disease (5). Therefore, access where appropriate to a treatment such as nal-iri should help to promote equality for both elderly patients and those with rarer forms of cancer.

4 Clinical effectiveness

4.1 *Identification and selection of relevant studies*

A systematic review was conducted to retrieve relevant clinical randomised controlled trials (RCTs), non-randomised trials, and observational data from the published literature regarding the efficacy and safety of nal-iri and relevant comparators for treatment of patients with metastatic pancreatic cancer who have previously received gemcitabine-based therapy. The systematic review had no date restrictions.

4.1.1 *Search strategy*

To identify relevant studies, the following electronic databases were searched via the OVID platform: MEDLINE®, MEDLINE® In-Process and Other Non-Indexed Citations, Embase, and the Cochrane Library, incorporating Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessment (HTA).

Electronic searches were supplemented by hand searching conference proceedings, clinical trial registries, and reference lists of included studies and relevant systematic reviews identified in the electronic search.

Full details of the search are provided in Appendix 2.

4.1.2 *Study selection*

Studies identified by the electronic searches were initially assessed based on title and abstract. Papers not meeting the inclusion criteria were excluded, and allocated a "reason code" to document the rationale for exclusion. Papers included after this stage were then assessed based on the full text; further papers were excluded, yielding the data set for inclusion that consisted of clinical studies for nal-iri and relevant comparators. The full texts of these comparator studies were screened and those suitable for indirect comparison were selected.

Inclusion and exclusion selection criteria are shown in Table 6.

Table 6: Eligibility criteria used in search strategy

	Inclusion criteria	Exclusion criteria
Population	Patients with advanced or metastatic[†] (stage IV) pancreatic cancer who have been previously treated with gemcitabine-containing treatment at any line of therapy (including gemcitabine in non-adjuvant/adjuvant/locally advanced patients who are now diagnosed with metastatic disease)	Studies in which it is unclear whether the population meets the inclusion criteria
Interventions	Nal-iri in combination with 5-FU and LV	Nal-iri monotherapy or nal-iri in different treatment combinations (excluded but tagged for reference)

Comparators	• Oxaliplatin in combination with 5-FU and LV (FOLFOX; OFF)
	• Capecitabine in combination with oxaliplatin (CAPOX)
	• Fluoropyrimidine therapy, including:
	  ○ Capecitabine monotherapy
	  ○ 5-FU monotherapy[‡]
	  ○ S-1 (in any treatment combination)[§]
		–

Outcomes	Including, but not limited to: • Overall survival (OS) • Progression-free survival (PFS) • Response rates • Adverse events (AEs) • HRQoL	–
Study design	• RCTs • Non-RCTs	• Single patient case studies • Editorials, reviews, letters, commentaries
Language restrictions	English language; English language abstracts of non-English language publications will also be included	Non-English language abstracts

Abbreviations: AE, adverse event; 5-FU, fluorouracil; HRQoL, health related quality of life; LV, leucovorin; nal-iri, nanoliposomal irinotecan; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial.
[†]Studies reporting any patients with metastatic disease, or reporting 'advanced' or 'unresectable' disease only, were included. Studies reporting results for a locally advanced population only were excluded.
[‡]Including in combination with LV. [§]Studies investigating S-1 combination therapy were included during title and abstract screening but were subsequently excluded at full text review, as the final NICE scope specifies fluoropyrimidine monotherapy only.

Clinical studies that investigated at least one intervention or comparator of interest and reported results for patients with pancreatic cancer who had previously been treated with gemcitabine-based therapy were eligible for inclusion provided the patients were reported to have advanced, metastatic, or unresectable pancreatic cancer (disease stage not specified), or a percentage of the study population were reported to have metastatic (stage IV) disease.

At full text review, studies investigating S-1 combination therapy were excluded, as the final NICE scope specifies fluoropyrimidines as monotherapy only.

The electronic database searches identified 4,736 records. Following the removal of 1,045 duplicates, 3,691 were screened based on title and abstract. Full texts of 141 publications were screened; 104 records were excluded, yielding 37 eligible publications identified by the electronic searches. An additional seven publications were identified through hand-searching, resulting in 44 included publications of 40 unique studies. Of the 40 included studies, 18 (22 publications) were RCTs and 22 studies had a non-RCT study design.

The systematic review was designed to identify studies investigating nal-iri or comparators that may be relevant to the decision problem for NICE and other HTA bodies. This included three fluoropyrimidines: 5-FU, capecitabine, and S-1. As S-1 is not currently approved for use in the EU, it may not be considered a relevant comparator for nal-iri in England. Therefore, the included S-1 studies were subsequently excluded from the systematic review. Following exclusion of 12 S-1 studies (13 publications), 31 included publications remained, consisting of 13 RCTs (16 publications) (11, 15, 44, 46, 50-61) and 15 non-RCTs (62-76).

Nal-iri in combination with 5-FU and LV was investigated in only one RCT (NAPOLI-1), and was compared with 5-FU + LV and nal-iri monotherapy. The main efficacy and safety results were reported in a full publication (44); expanded analyses (61) and updated overall survival (OS) results were available in abstract form (59). Results regarding the effects of baseline CA19-9 level on OS were also presented as an abstract (60). A single-arm study investigating nal-iri was also identified in patients with metastatic pancreatic cancer who had progressed following gemcitabine-based therapy (77); however, it reported results for nal-iri monotherapy only and was therefore excluded from the systematic review, but is summarised in Section 4.11.

There were six RCTs that reported results for oxaliplatin in combination with 5-FU and LV (11, 15, 46, 50, 53, 57); this treatment combination was also investigated in 10 non-RCTs (63, 65, 67-73, 76). Capecitabine in combination with oxaliplatin was reported in one RCT (51) and five non-RCTs (62, 63, 66, 69, 75), while results for fluoropyrimidine monotherapies (5-FU or capecitabine) were reported in 11 studies (14 publications), of which eight studies (11 publications) were RCTs (11, 44, 46, 52, 54-56, 58-61) and three studies had a non-RCT study design (64, 68, 74). However, one of these non-RCTs treated only four patients, therefore efficacy results were untenable and only toxicity data were reported (74).

There were two RCTs where the majority of patients did not have metastatic pancreatic cancer (50, 51), and this was also the case for one single-arm study (65). There were also two RCTs, available as abstracts only, that did not specify that patients had metastatic disease, and instead the population was described as having either advanced or unresectable pancreatic cancer (56, 58). Results from these five studies should therefore be interpreted with caution as it is not clear whether the included patients are representative of the population specified in the final NICE scope.

Searches of the clinical trial registries identified an additional ongoing phase III study investigating the efficacy and safety of glucophosphamide vs bolus 5-FU monotherapy (NCT01954992) as second-line treatment for patients with metastatic pancreatic cancer who have previously been treated with gemcitabine-based therapy. No study results are currently available, therefore the study was not included in the systematic review.

The included studies are presented in Table 7.

Table 7. Studies included in the systematic review

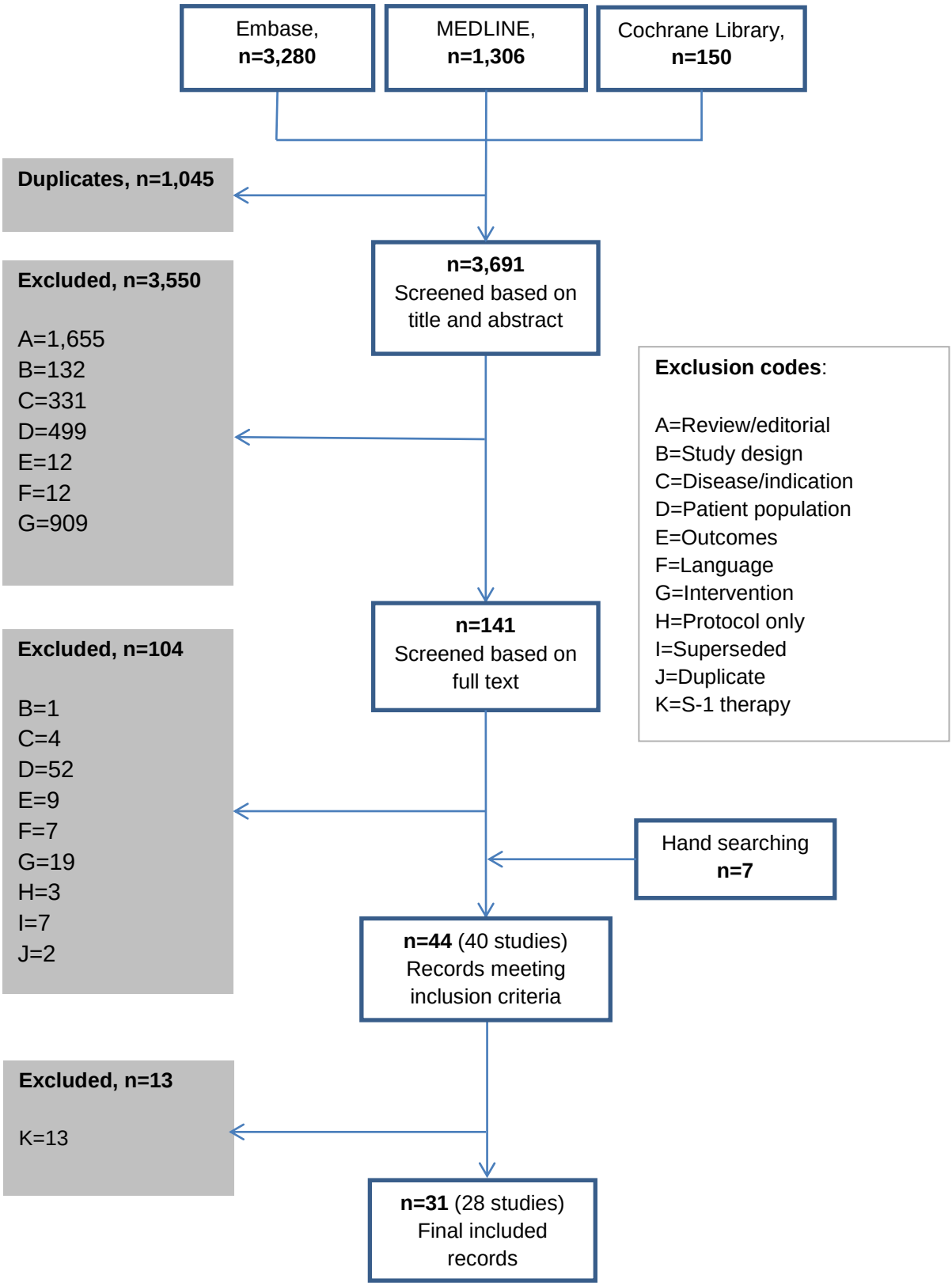
Reference	Country	Interventions and comparators
RCTs (n=13 [16 publications])		
Azmy 2013† (50)	Egypt	• Oxaliplatin + 5-FU + LV (FLOX) • Oxaliplatin + 5-FU + LV (3 week bolus regimen)
Bjerregaard 2014† (51)	Denmark‡	• Capecitabine + oxaliplatin (CAPOX) • Irinotecan + cetuximab + everolimus
Bodoky 2012 (52)	Multinational	• Capecitabine monotherapy • Selumetinib
Chen 2015 (61) (NAPOLI-1: expanded analyses, linked to (44))	Multinational	• Nal-iri + 5-FU + LV • 5-FU + LV • Nal-iri monotherapy
Chen 2016 (60) (NAPOLI-1: effects of CA19-9 on OS, linked to (44))	Multinational	• Nal-iri + 5-FU + LV • 5-FU + LV • Nal-iri monotherapy
Chung 2015 (53) (SWOG S1115)	USA‡	• Oxaliplatin + 5-FU + LV (mFOLFOX) • Selumetinib + MK-2206
Gill 2014 (46) (PANCREOX)	Canada	• Oxaliplatin + 5-FU + LV (mFOLFOX6) • 5-FU + LV
Heinemann 2013 (54) (AIO-PK0104)	Germany	• Gemcitabine + erlotinib (first line) followed by capecitabine monotherapy (second line) • Capecitabine + erlotinib (first line) followed by gemcitabine monotherapy (second line)§
Hurwitz 2015 (55)	USA	• Capecitabine + placebo • Capecitabine + ruxolotinib
Ioka 2013† (56)	Japan‡	• Fluoropyrimidine monotherapy (5-FU, capecitabine, or S-1)¶ • Gemcitabine monotherapy
Oettle 2014 (11) (CONKO-003)††	Germany	• Oxaliplatin + 5-FU + LV (OFF) (+BSC) • 5-FU + LV (+BSC)
Pelzer 2011 (57) (CONKO-003)††	Germany	• Oxaliplatin + 5-FU + LV (OFF) • BSC
Shi 2013† (58)	China	• Capecitabine monotherapy • Capecitabine + thalidomide
Wang-Gillam 2015 (44) (NAPOLI-1)	Multinational	• Nal-iri + 5-FU + LV • 5-FU + LV • Nal-iri monotherapy
Wang-Gillam 2016 (59) (NAPOLI-1: updated OS data, linked to (44))	Multinational	• Nal-iri + 5-FU + LV • 5-FU + LV • Nal-iri monotherapy
Yoo 2009 (15)	South Korea	• Oxaliplatin + 5-FU + LV (mFOLFOX) • Irinotecan + 5-FU + LV (mFOLFIRI)
Non-RCTs (n=15)		

Reference	Country	Interventions and comparators
Bayoglu 2014 (62)	Turkey	• Capecitabine + oxaliplatin (CAPOX)
Berk 2012 (63)	Turkey	• Capecitabine + oxaliplatin (CAPOX) • Oxaliplatin + 5-FU + LV (FOLFOX4)
Boeck 2007 (64)	Germany	• Capecitabine monotherapy
El-Hadaad 2013† (65)	Egypt	• Oxaliplatin + 5-FU + LV (OFF)
Gasent Blesa 2009 (66)	Spain	• Capecitabine + oxaliplatin (CAPOX)
Gebbia 2007 (67)	Italy	• Oxaliplatin + 5-FU + LV (FOLFOX4)
Goldstein 2016 (68) (MPACT extension)	Multinational	• Oxaliplatin + 5-FU + LV (FOLFOX/OFF) • 5-FU or capecitabine monotherapy‡‡
Maier-Stocker 2014 (69)	Germany	• Oxaliplatin + 5-FU + LV (FOLFOX) • Capecitabine + oxaliplatin (CAPOX)
Novarino 2009 (70)	USA‡	• Oxaliplatin + 5-FU + LV (FOLFOX)
Pelzer 2009 (71)	Germany	• Oxaliplatin + 5-FU + LV (OFF)
Schmidt 2016 (72)	USA	• Oxaliplatin + 5-FU + LV (FOLFOX)
Tsavaris 2005 (73)	Greece‡	• Oxaliplatin + 5-FU + LV (FOLFOX)
Weekes 2011 (74)	USA	• Capecitabine monotherapy
Xiong 2008 (75)	USA‡	• Capecitabine + oxaliplatin (CAPOX)
Zaanan 2014 (76)	France	• Oxaliplatin + 5-FU + LV (FOLFOX)

Abbreviations: 5-FU, fluorouracil; BSC, best supportive care; CA19-9, carbohydrate antigen 19-9; LV, leucovorin; nal-iri, nanoliposomal irinotecan; RCT, randomised controlled trial.
†Study population reported to have 'advanced' or 'unresectable' pancreatic cancer (disease stage not specified) or the majority of patients did not have metastatic disease. ‡Country not specified in publication, therefore country(s) of authors' affiliations have been extracted. §Study arm not eligible as patients receiving second line therapy had not previously received gemcitabine-based therapy. ¶Patients were randomised to a treatment arm, and those in the fluoropyrimidine arm were allocated a therapy (5-FU, capecitabine, or S-1) by their doctor – the results of all patients receiving a fluoropyrimidine monotherapy were analysed as one treatment arm. ††Original CONKO-003 trial compared OFF with BSC and was terminated early as a result of slow recruitment due to low acceptance of the trial containing a BSC arm (57) – the trial was reinitiated with 5-FU+LV as the control arm (11). ‡‡Results analysed as one treatment arm.

The systematic review schematic is shown in Figure 3.

Figure 3: Schematic for the systematic review of clinical evidence



A full list of studies excluded at full text review is provided in Appendix 2.

4.2 *List of relevant randomised controlled trials*

The systematic review identified only one RCT of nal-iri in combination with 5-FU + LV in patients with metastatic pancreatic cancer who have previously been treated with gemcitabine, NAPOLI-1 (44). The comparators in this trial were 5-FU + LV and nal-iri monotherapy. The efficacy and safety data presented in this section has a data cut-off date of 14 February 2014. There have been some updated interim results for OS, PFS and overall response rate (ORR) presented as a poster and abstract with a data cut-off date of 25 May 2015 after 378 OS events (59). These interim results showed no change from the previous results.

Another abstract presented in 2015 reported an expanded analysis of OS using the per protocol (PP) population (61), and an abstract presented in 2016 reported the effect of baseline carbohydrate antigen 19-9 (CA19-9) level on OS (60). These results are described in Sections 4.7.1.1 and 4.7.2.4, respectively.

In March 2016, a final analysis of the data set was performed, as all patients included in the trial had died at this stage. These results for OS and PFS were used in inform the cost-effectiveness analysis in Section 5, and the results from the clinical study report that are presented in this section (with a data cut-off of 14 February 2014) are used in a scenario cost-effectiveness analysis, presented in Section 5.8.3. The final results for OS and PFS are described in Sections 4.7.1 and 4.7.2.1, respectively.

4.3 *Summary of methodology of the relevant randomised controlled trials*

NAPOLI-1 was designed as a two-arm trial of nal-iri vs 5-FU/LV. However, a protocol amendment was made to introduce a third combination therapy arm, nal-iri + 5-FU/LV. The licensed indication for nal-iri is in combination with 5-FU/LV, therefore results from this combination arm and the control arm (5-FU/LV) only are relevant for efficacy results and are presented in Sections 4.3.5 to 4.7. All three arms are presented in the safety section (Section 4.12) to provide a complete overview of toxicity data for nal-iri. Further information regarding the protocol amendment is included in Section 4.3.3.2.

4.3.1 *Trial design*

NAPOLI-1 was an open-label, randomised, three-arm, phase III trial of nal-iri, with or without 5-fluorouracil (5-FU) and leucovorin (LV; also known as folinic acid) versus 5-FU and LV (5-FU/LV) in metastatic pancreatic cancer patients previously treated with gemcitabine-based therapy.

The trial was originally designed with two treatment arms, nal-iri vs 5-FU/LV, with patients randomised in a 1:1 ratio. The third arm, nal-iri + 5-FU/LV, was added after safety data became available for this combination in an ongoing study in metastatic colorectal cancer (78), which found that the most commonly reported Grade 3–4 AEs were lower with nal-iri + 5-FU/LV than FOLFIRI, and no additional safety concerns were identified. Further data regarding the safety of nal-iri + 5-FU/LV in NAPOLI-1 are provided in Section 4.12. After the new protocol was approved, patients were randomised in a 1:1:1 ratio to the three arms. The addition of the nal-iri + 5-FU/LV arm is described in Section 4.3.3.2, and other major protocol amendments are described in Section 4.3.5.

All patients were required to have UGT1A1 genotype testing prior to enrolment in the study, because there is a probable link between homozygosity of the UGT1A1*28 allele and irinotecan toxicity (79). The active metabolite of irinotecan, SN-38, is responsible for the direct toxicity associated with irinotecan therapy in normal tissues. The enzyme produced by the UGT1A1 gene regulates the effects of SN-38 by forming a glucuronide metabolite, which has 1/50 to 1/100 the activity of SN-38 (80). The activity of UGT1A1 is reduced in patients with the UGT1A1*28 polymorphism, who are therefore at risk of a higher exposure to SN-38 compared with those with the wild type UGT1A1 allele. This means that patients who were homozygous for the UGT1A1*28 allele were to be treated at a lower initial dose of nal-iri (see Table 10).

Patients were randomised by interactive web response system (IWRS) after all screening assessments were completed and UGT1A1*28 results were available. The randomisation was stratified based on the following prognostic factors:

- Baseline albumin levels (≥4.0 g/dL vs <4.0 g/dL)
- Karnofsky Performance Score (70 and 80 vs ≥90)
- Ethnicity (Caucasian vs East Asian vs all others)

The data cut-off for the results presented in this submission was 14 February 2014, which corresponds to the date on which the sponsor received confirmation regarding the occurrence of the required number of death events for the primary analysis.

4.3.2 *Participants*

NAPOLI-1 was a multi-centre, multi-national study conducted at 76 study sites in North America (20 sites), Europe (30 sites), Asia (12 sites), South America (8 sites) and Oceania (6 sites). There were 4 sites in the UK, which enrolled 28 patients: 1 patient in Liverpool, 5 in London (King's College), 10 in Manchester, and 12 in Sutton (Royal Marsden).

Inclusion criteria for NAPOLI-1 are shown in Table 8 and exclusion criteria in Table 9.

Table 8: Inclusion criteria for NAPOLI-1

Inclusion criteria

• Histologically or cytologically confirmed adenocarcinoma of exocrine pancreas
• Documented metastatic disease; disease status was permitted to be measurable or non-measurable as defined by RECIST v. 1.1 guidelines (81):
  ○ Measurable – tumour lesions must be accurately measured in at least one dimension with a minimum size of:
  ▪ 10 mm by CT scan
  ▪ 10 mm calliper measurement by clinical exam (lesions that cannot be accurately measured with callipers should be recorded as non-measurable)
  ▪ 20 mm by chest X-ray
  ○ Non-measurable – all other lesions, including small lesions (longest diameter <10 mm)
• Documented disease progression after prior gemcitabine or gemcitabine-containing therapy in locally advanced or metastatic setting. Examples of permitted therapies included, but were not limited to:
  ○ Single-agent gemcitabine

- Any gemcitabine-based regimen, with or without maintenance gemcitabine
- Single-agent gemcitabine to which a platinum agent, a fluoropyrimidine, or erlotinib was subsequently added
- Gemcitabine administered in the adjuvant setting, if disease recurrence occurred within 6 months of completing the adjuvant therapy

- KPS ≥70
- Adequate bone marrow reserves, as evidenced by:
  - ANC >1,500 cells/μL without the use of hematopoietic growth factors; and
  - Platelet count >100,000 cells/μL; and
  - Haemoglobin >9 g/dL (blood transfusions were permitted for patients with haemoglobin levels <9 g/dL
- Adequate hepatic function, as evidenced by:
  - Serum total bilirubin within normal range for the institution (biliary drainage was allowed for biliary obstruction)
  - Albumin levels ≥3.0 g/dL
  - AST and ALT ≤2.5 x ULN (≤5 x ULN was acceptable if liver metastases were present)
- Adequate renal function, as evidenced by a serum creatinine ≤1.5 x ULN
- Normal ECG or ECG without any clinically significant findings
- Recovered from the effects of any prior surgery, radiotherapy, or other anti-neoplastic therapy
- 18 years of age or older
- Able to understand and sign an informed consent (or have a legal representative who is able to do so)

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CT, computerised tomography; ECG, electrocardiogram; KPS, Karnofsky Performance Status; RECIST, response evaluation criteria in solid tumours; ULN, upper normal limit.

Table 9: Exclusion criteria for NAPOLI-1

Exclusion criteria
• Active CNS metastases (indicated by clinical symptoms, cerebral oedema, steroid requirement, or progressive disease); the patient should not have taken steroids within 28 days prior to starting study therapy • Clinically significant gastrointestinal disorder, including hepatic disorders, bleeding, inflammation, occlusion, or diarrhoea >Grade 1 • History of any second malignancy within 5 years prior to study commencement, with the exceptions of in-situ cancer or basal or squamous cell skin cancer • Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) within 6 months prior to study commencement • NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure • Active infection or unexplained fever >38.5°C during the screening visits or on the first scheduled day of study therapy, which in the investigator's opinion may have compromised the patient's participation in the study or affected the study outcome • Known hypersensitivity to any of the components of nal-iri, other liposomal products, fluoropyrimidines, or leucovorin • Investigational therapy administered within 4 weeks, or within a time interval less than 5 half-lives of the investigational agent, whichever was longer, prior to starting study therapy • Any other medical or social condition deemed by the investigator to be likely to interfere with

a patient's ability to sign informed consent, cooperate, and participate in the study, or interfere with the interpretation of the results • Pregnant or breastfeeding; female patients of child-bearing potential were required to test negative for pregnancy at screening based on a urine or serum pregnancy test, and both male and female patients of reproductive potential were required to use a reliable method of birth control during the study and for 3 months following the last dose of study drug

Abbreviations: CNS, central nervous system; NYHA, New York Heart Association.

In addition, patients were to be discontinued from study treatment in the following circumstances:

- Patient had evidence of disease progression based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria (81)
- Patient showed symptomatic deterioration
- Patient experienced intolerable toxicity, or an AE that required:
  - A third dose reduction; or
  - Treatment to be withheld for more than 21 days from the start of the next cycle, unless, in the opinion of the investigator, the patient was receiving benefit from study treatment
- Patient was significantly non-compliant with study procedures per principal investigator (PI) assessment
- The patient or patient's attending physician requested that the patient be withdrawn from study treatment
- The investigator or sponsor, for any reason, but considering the rights, safety, and well-being of the patient(s), and in accordance with ICH/GCP (International Conference on Harmonisation/Good Clinical Practice) guidelines and local regulations, stopped the study or stopped the patient's participation in the study.

4.3.3 *Interventions*

4.3.3.1 Study drugs

There were three treatment arms:

- Arm A (experimental arm): Nal-iri
- Arm B (control arm); 5-FU/LV
- Arm C (experimental arm): Nal-iri + 5-FU/LV (added as protocol amendment, as described in Section 4.3.3.2)

The method of administration in each treatment arm is shown in Table 10.

Table 10: Treatments administered

Treatment arm	Administration
A: Nal-iri	• 120 mg/m^2 intravenous nal-iri on Day 1 of each 3-week cycle • Patients homozygous for UGT1A1*28 allele were to start treatment at a reduced dose of 80 mg/m^2 for the first cycle • If the patient did not experience any drug-related toxicity after the first administration of nal-iri, the dose could be increased in increments of 20 mg/m^2 from cycle 2, up to a maximum of 120 mg/m^2
B: 5-FU/LV	• 2,000 mg/m^2 intravenous 5-FU over 24 hours, administered weekly for 4 weeks (Days 1, 8, 15 and 22), followed by 2 weeks of rest, in a 6-week treatment cycle • 200 mg/m^2 intravenous LV over 30 minutes, administered weekly for 4 weeks (Days 1, 8, 15 and 22), followed by 2 weeks of rest, in a 6-week treatment cycle • LV was to be administered prior to 5-FU
C: Nal-iri + 5-FU/LV	• 80 mg/m^2 intravenous nal-iri every 2 weeks • 2,400 mg/m^2 intravenous 5-FU over 46 hours every 2 weeks • 400 mg/m^2 intravenous LV over 30 minutes every 2 weeks • Nal-iri was to be administered first, followed by LV and then 5-FU • Patients homozygous for UGT1A1*28 allele were to start treatment at a reduced dose of 60 mg/m^2 of nal-iri, but if the patient did not experience any drug-related toxicity after the first administration of nal-iri, the dose could be increased to 80 mg/m^2 from cycle 2

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin.

Treatment was to be continued until disease progression, intolerable toxicity or other reason for study termination. Following treatment discontinuation, a 30-day post therapy follow-up visit was required. Subsequently, all patients were to be followed up every 1 month for OS until death or study closure, whichever occurred first. Patients who withdrew from study treatment due to reasons other than objective disease progression were to be assessed every 6 weeks during the follow-up period for radiological progression.

For this submission, only the nal-iri + 5-FU/LV and the control 5-FU/LV arms are of relevance, and only data for these arms will be presented for efficacy. Toxicity results from the nal-iri monotherapy arm are included in the safety section (Section 4.12) to provide a more complete overview of the safety of this drug.

4.3.3.2 Rationale for choice of treatment arms

Best supportive care was not considered to be a reasonable control, since it is becoming less acceptable to both patients and oncologists for patients with a high enough performance status to undergo further treatment. Historically, 5-FU was one of the mainstays of therapy for pancreatic cancer. 5-FU/LV was used as a control in the recent CONKO-003 trial (11), and the demonstrated responses suggested that it was effective.

Arm C (nal-iri + 5-FU/LV) was added as a protocol amendment because of investigators and other opinion leaders having an interest in combination therapies for pancreatic cancer in patients who can tolerate the potentially additive toxicity. Safety data became available for the combination of nal-iri and 5-FU/LV from an ongoing study in metastatic colorectal cancer (78), which indicated that the most commonly reported Grade 3–4 AEs were similar or lower with nal-iri + 5-FU/LV compared with non-liposomal irinotecan + 5-FU/LV. There is also a relative absence of overlapping toxic effects among 5-FU, LV and nal-iri. A requirement for an intensive safety review of the first 15 patients enrolled in each arm by the independent Data Safety Monitoring Board (DSMB) was added to ensure the safety of the new combination arm.

Pre-clinical evidence supports the hypothesis that nal-iri modifies the tumour microenvironment in a manner that should make tumours more susceptible to 5-FU/LV, through decreasing tumour hypoxia and increasing small molecule perfusion (82). Preclinical studies have also indicated that irinotecan has synergistic activity when administered prior to 5-FU and LV (83, 84), and liposomal irinotecan has been shown to alter the hypoxic environment of pancreatic cancer in xenografts (85).

There is also encouraging clinical evidence for the activity of the 5-FU + LV + non-liposomal irinotecan combination (FOLFIRI) in pancreatic cancer (15, 86-88). The nanoliposomal formulation of nal-iri is expected to act for longer than non-liposomal irinotecan because the nanoliposomes are expected to accumulate within the tumour and release irinotecan slowly over time, thereby decreasing the rate at which it is removed from the body.

4.3.3.3 Permitted concomitant therapy

Patients could receive analgesics, anti-emetics, antibiotics, anti-pyretics, and blood products, as necessary, during the trial. Although warfarin-type anticoagulant therapies were permitted, careful monitoring of coagulation parameters was imperative in order to avoid complications of any possible drug interactions.

4.3.3.4 Disallowed concomitant therapy

The prescribing information for nal-iri was not developed at the start of NAPOLI-1, so the Camptosar® (non-liposomal irinotecan) prescribing information (79) was used as a guide. Treatments listed as being known to interact with irinotecan were to be avoided wherever possible:

- St. John's Wort
- CYP3A4-inducing anticonvulsants (phenytoin, phenobarbital and carbamazepine)
- Ketoconazole (a CYP3A4 and UGT1A1 inhibitor)
- Itraconazole (a CYP3A4 inhibitor)
- Troleandomycin and erythromycin (antibiotics)
- Diltiazem and verapamil (calcium channel blockers to treat high blood pressure, angina and certain heart rhythm disorders)

Treatment with any other agents that interact with irinotecan were also to be avoided wherever possible, and caution was exercised if concomitant use of warfarin was necessary due to an interaction with 5-FU.

In addition, the following therapies were not to be permitted during the trial:

- Other anti-neoplastic therapy, including cytotoxics, targeted agents, endocrine therapy or other antibodies
- Potentially curative radiotherapy; palliative radiotherapy was permitted
- Any other investigational therapy.

4.3.4 *Endpoints*

4.3.4.1 Primary endpoint

The primary efficacy endpoint was OS. This was defined as the time from the date of patient randomisation to the date of death or the date last known alive. The last known alive date was identified as the latest qualifying date from examination of the OS case report form (CRF), laboratory sample dates, AE start and stop dates, concomitant medication start and stop dates, as well as normal visit/follow-up dates. In addition, death dates were permitted to be obtained from public records.

OS is considered the most reliable cancer endpoint (89).

4.3.4.2 Secondary endpoints

Secondary endpoints were:

- Progression-free survival (PFS)
- Time to treatment failure (TTF)
- Objective response rate (ORR)
- Tumour marker response of CA19-9
- Clinical benefit response (CBR) rate
- Patient-reported outcomes (PROs) using the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (EORTC-QLQ-C30)
- Safety and AE profiles
- To determine the pharmacokinetic properties of nal-iri and 5-FU/LV in this population.

These measures are widely accepted as evidence of efficacy in clinical studies in the field of oncology.

In addition, an exploratory objective was specified to explore the biomarkers associated with toxicity and efficacy following treatment with nal-iri in combination with 5-FU/LV. However, results for this objective have not been included in this submission because NAPOLI-1 did not provide evidence to select patients or differentiate therapy based on biomarkers.

Progression-free survival (PFS)

PFS was defined as the time in months from the date of patient randomisation to the date of death or disease progression, whichever occurred earlier. Analyses of PFS were based on tumour and disease progression assessments per investigator according to RECIST guidelines v1.1 (81), which define disease progression as at least a 20% increase and at least a 5 mm absolute increase in the sum of diameters of target lesions, taking as reference the smallest sum in the study. The appearance of one or more new lesions is also considered disease progression. These were assessed by the investigator by computed tomography (CT) or magnetic resonance imaging (MRI) at treatment start, every 6 weeks thereafter, and at 30 days post follow-up.

Time to treatment failure (TTF)

TTF was defined as the time in months to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death. In the event the patient discontinued study treatment for reasons other than disease progression or death, a tumour assessment was to be completed as soon as possible relative to the date of study termination, unless performed within the prior 4 weeks, to ensure disease progression was not present and to assess overall disease status.

Objective response rate (ORR)

ORR was defined by the percentage of patients in the study population with a best overall response of complete response (CR) or partial response (PR) as assessed by the investigator from randomisation until progression or end of study, and as defined by RECIST guidelines v1.1 (81). CR is defined as the disappearance of all target lesions, and any pathological lymph nodes (whether target or not) must have a reduction in short axis to <10 mm. PR is defined as at least a 30% decrease in the sum of diameters of target lesions. Tumour assessments by CT or MRI took place at treatment start, every 6 weeks thereafter, and at 30 days post follow-up.

Tumour marker response of CA19-9

Tumour marker response was evaluated by the change in CA19-9 serum levels, which was assessed at treatment start, every 6 weeks thereafter, and at 30 days post follow-up. Response was defined as a decrease of ≥50% of CA19-9 in relation to the baseline level at least once during the treatment period. Only patients with an elevated baseline CA19-9 value (>30 U/mL) were included in the tumour marker response-evaluable (TMRE) population for this endpoint.

Clinical benefit response (CBR) rate

Clinical benefit response is a composite parameter based on four characteristic features of pancreatic cancer:

- Primary measures of clinical benefit
    - Change in pain,
        - Change in pain intensity
        - Change in analgesic consumption,
    - Change in performance status

- Secondary measure of clinical benefit
    - Change in weight.

Pain

All patients were asked to complete a daily pain assessment and analgesic consumption diary throughout their participation in the study. Pain was measured by patient record on a 100 mm visual analogue scale (VAS) for pain with higher measurements indicative of greater pain. Pain intensity classifications will be determined as follows:

- Positive: an improvement of 50% or more over baseline, maintained for at least 4 weeks (providing baseline is greater than 20 out of 100)
- Negative: any worsening from baseline, maintained for at least 4 weeks, occurring earlier than 12 weeks after the start of treatment (providing the sustained scores were higher than 20)
- Stable: if a patient was neither Positive nor Negative for pain intensity.

The following information was captured for analgesic consumption each day: medication name, route, strength, unit, and total dose. For standardisation in the analysis, opioid medications were converted to oral morphine equivalents, where there was sufficient information to do so. The use of non-opioid medications was recorded, but not considered in the assessment of clinical benefit response. Analgesic consumption classifications were determined as follows:

- Positive: an improvement of 50% or more over baseline, maintained for at least 4 weeks (providing baseline was at least 10 mg per day)
- Negative: any worsening from baseline, maintained for at least 4 weeks, occurring earlier than 12 weeks after start of treatment (providing the sustained scores were higher than 10 mg per day)
- Stable: if a patient was neither Positive nor Negative for analgesic consumption.

If either of the two categories (pain intensity or analgesic consumption) were Negative, then the overall pain improvement classification was Negative (Table 11). If at least one of the two pain categories were Positive (and the other was not Negative) the overall pain improvement classification was Positive. If both the categories were Stable, then the overall pain improvement classification was Stable.

Table 11: Pain classification

		Analgesic consumption		
		Positive	**Stable**	**Negative**
Pain intensity	**Positive**	P	P	N
	Stable	P	S	N
	Negative	N	N	N

P = Positive for pain classification; N = Negative for pain classification; S = Stable for pain classification.

It should be noted that these rules result in a conservative classification of pain. For example, a patient who is Positive for pain intensity but Negative for analgesic consumption may have gained improvement in pain intensity at the cost of increased

doses of analgesic. Conversely, a patient who is Positive for analgesic consumption but Negative for pain intensity may have gained improvement in total analgesic consumed at the expense of overall pain severity. In both cases, the patient will be classified as Negative. A Positive classification for pain is reserved for the patient that has demonstrated improvement in one dimension without any worsening in the other.

Performance status

Once the patient was classified for pain, performance status was considered to determine whether clinical benefit response had been achieved. The performance status classification was determined for each patient by measurements of Karnofsky Performance Status (KPS) at each site visit. The KPS on Day 1 before the start of treatment was considered as the baseline value. Performance status classification was determined as follows:

- Positive: an improvement in KPS of at least 20 points over baseline, or an improvement to a KPS of 100 from 90, maintained for at least 4 weeks (providing baseline was 90 or less)
- Negative: worsening of at least 20 points from baseline, maintained for at least 4 weeks, occurring earlier than 12 weeks after the start of treatment
- Stable: if a patient was neither Positive nor Negative for performance status.

The performance status classification was then combined with the pain classification (from Table 11) to determine clinical benefit response (Table 12). A patient was defined to be a clinical benefit non-responder is either pain or performance status is classified as Negative. If neither is Negative and either pain or performance status are Positive, the patient will be defined to be a clinical benefit responder. If both pain and performance status are stable, then the classification for primary measures of clinical benefit will be Stable, and the secondary measure of weight will be taken into account, as described below.

Table 12: Primary measures of classification of clinical benefit response

		Performance status		
Pain classification		**Positive**	**Stable**	**Negative**
	Positive	R	R	NR
	Stable	R	S	NR
	Negative	NR	NR	NR

R = Clinical benefit responder; NR = Clinical benefit non-responder; S = Stable.

These classification criteria are also conservative. For example, a patient who is Positive for pain but Negative for performance status may have gained improvement in pain due to a lack of effort associated with decreased mobility. Conversely, a patient who is Positive for performance status but Negative for pain may have gained improvement in performance at the expense of overall pain associated with increased mobility. In both cases, the patient would be classified as a clinical benefit non-responder. A clinical benefit responder classification is for patients that have demonstrated sustained and significant improvement in at least one dimension without any worsening in any of the others.

Weight change

If a patient was considered to be Stable based on the primary measures of clinical benefit, the secondary measure of weight change was considered, and the patient was defined to be a clinical benefit responder if the weight change was classified as Positive. Weight was measured at each study visit, and classifications were determined as follows:

- Positive: an increase of at least 7% over baseline, maintained for at least 4 weeks (providing the patient did not develop third-space fluid accumulation during the study)
- Non-positive: any other change in weight.

There were only two classifications for weight, in order to make a final determination of clinical benefit response for a patient whose response to all the primary measured were Stable (and therefore inconclusive).

Patient-reported outcomes (PROs)

The EORTC QLQ-C30 questionnaire consists of 15 subscales in three independent domains: global health-related quality of life, functional scales (cognitive, emotional, physical, role and social functioning), and symptom scales (appetite loss, constipation, diarrhoea, dyspnoea, fatigue, insomnia, nausea and vomiting, financial difficulties, and pain).

Patients were required to complete the EORTC-QLQ-C30 questionnaire at treatment start, every 6 weeks thereafter and at 30 days post follow-up. On days that the patient received study drug, assessments were to be completed prior to study drug administration.

Safety and adverse event profiles

The investigator was to elicit information regarding the occurrence of AEs through open-ended questioning of the patient, physical examination, and review of laboratory results. Treatment-emergent adverse events (TEAEs) were recorded, as defined as events that occurred or worsened on or after the day of the first dose of study drug and within 30 days after the last administration of study drug, with the exception of AEs believed by the investigator to be related to nal-iri, which were to be reported at any time, even more than 30 days after the last dose of study drug. All AEs were followed until resolution, or until the patient discontinued from the OS follow-up portion of the study. Treatment procedures for managing nal-iri toxicities followed the prescribing information for Camptosar® (non-liposomal irinotecan) (79).

In addition, clinical safety laboratory parameters were measured, including:

- Haematology: haemoglobin, haematocrit, leukocytes, differential white blood cell count, absolute neutrophil count, platelets
- Chemistry: sodium, potassium, chloride, bicarbonate, alkaline phosphatase, alanine aminotransferase (SGPT), aspartate aminotransferase (SGOT), uric acid, blood area nitrogen, creatinine, LDH, glucose (random), calcium, magnesium, phosphate, total bilirubin, direct bilirubin, total protein, albumin

- Vital signs: resting systolic and diastolic blood pressure, respiratory rate, body temperature, weight, pulse rate, ECG.

Pharmacokinetic (PK) properties of nal-iri

To evaluate the pharmacokinetics of nal-iri, plasma concentrations were measured for total irinotecan (both encapsulated and non-liposomal), its active metabolite SN38, and SN38G, the glucuronidated (inactive) form of SN38.

Plasma pharmacokinetic (PK) samples were collected in Cycle 1 from all randomised patients at the following timepoints:

- Arm A: immediately prior to infusion, during infusion (80–90 minutes after start of infusion), 2.5–4 hours after the start of infusion, and on Day 8
- Arm B: at the end of 5-FU infusion (Day 2)
- Arm C: immediately prior to nal-iri infusion, during nal-iri infusion (80–90 minutes after start of infusion), 2.5–4 hours after the start of nal-iri infusion, at the end of 5-FU infusion, and on Day 8.

In addition, an optional sample was collected in Cycle 1 at 8–72 hours following administration of nal-iri in Arm A and Arm C if additional consent for collection of this sample was provided.

4.3.5 *Major protocol amendments*

4.3.5.1 Addition of third treatment arm (nal-iri + 5-FU/LV)

A third treatment arm, Arm C (nal-iri + 5-FU/LV) was added to the study, as described in Section 4.3.3.2.

4.3.5.2 Other amendments

- In the initial protocol, patients who had received prior irinotecan were excluded from participating in the study. This restriction was removed to be consistent with the absence of restriction to including subjects who had previously been treated with 5-FU and LV.
- The new RECIST 1.1 guidelines (81) stated that confirmation of response was no longer required in studies where response was a secondary endpoint; therefore confirmation of a PR or CR was no longer required.
- In the original protocol, if a patient discontinued study treatment for reasons other than disease progression, they were required to continue to undergo tumour assessments every 6 weeks until objective disease progression was documented. However, since post-study therapy can affect the tumour response status, the protocol was amended so that patients would be censored for tumour response analysis at the time of commencement of new anti-neoplastic therapy, and were not required to undergo tumour assessments from then onwards. Also, a sensitivity analysis was added to censor the OS at a date where any post-treatment anti-cancer therapy was first administered.
- Pharmacokinetic (PK) assessments were originally only required for patients in Arm A; however this was amended to also require assessments for patients in

Arms B and C. In addition, an optional PK sample could be taken any time between 8 and 72 hours following administration of nal-iri from patients who provided additional consent.

- All ECG abnormalities would now be reported as AEs.
- Originally only patients receiving nal-iri who became pregnant during the study were required to discontinue study treatment. This was amended so that all patients who became pregnant were required to immediately discontinue study treatment, regardless of treatment arm.
- The protocol originally required patients to complete a pain assessment diary for a minimum of 7 days prior to randomisation. This was shortened to 3−7 days, since expeditious treatment is often necessary for this group of patients.
- Due to the ongoing global shortages of oncology drugs, including leucovorin, the *ℓ* + *d* racemic form might not be available at all times. Therefore, the dose for the *ℓ* isomeric form was added in case this needed to be used as an alternative.

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

4.4.1 *General considerations*

As described in Section 4.3.3.1, only the nal-iri + 5-FU/LV combination arm and the 5-FU/LV control arm are relevant for this submission, and so efficacy data from only these two arms are presented. In order to accurately compare the nal-iri + 5-FU/LV arm to a control arm, an analysis group was used including all patients randomised to 5-FU/LV under protocol version 2 or later, who could have been randomised to the active treatment combination. Therefore patients that were randomised to the control arm prior to the protocol amendment were not included in the efficacy analyses in this document.

Unless otherwise specified, baseline was the last observation before the start of study drug. Presented p-values were two-sided. All efficacy analyses were pairwise comparisons.

4.4.2 *Analysis populations*

- **Intent-to-treat (ITT) population:** All randomised patients, as defined by the confirmation of a successful allocation of a randomisation number through IWRS. This population was the primary population for all efficacy parameters unless otherwise stated.
- **Safety population:** Patients that received at least one dose (including partial dose) of study medication. All safety analyses were performed on this population.
- **Per protocol (PP) population:** Patients who received treatment for at least 6 weeks and did not violate any inclusion/exclusion criteria nor significantly deviate from the protocol, including significant deviations in study drug administration.
- **Evaluable patient (EP) population for tumour response**: All randomised and treated patients who met all inclusion/exclusion criteria, had measurable disease

at baseline and were evaluable for response, i.e. patients with at least one tumour evaluation while on treatment and those with early (≤12 weeks) disease progression, including symptomatic deterioration and death.

- **Tumour marker response evaluable (TMRE) population:** Patients who had CA19-9 >30 U/mL at baseline.
- **Clinical benefit response evaluable (CBRE) population:** Patients who met at least one of the following criteria:
  - Baseline pain intensity ≥20 (out of 100)
  - Baseline morphine consumption ≥10 mg/day PO morphine equivalents
  - Baseline KPS of 70–90 points
- **PRO population:** All ITT patients that provided baseline and at least one subsequent assessment on the EORTC-QLQ-C30 instrument.
- **PK population:** All treated patients with at least one PK assessment.

The term 'All Screened Patients' was used to describe the set of all patients who signed informed consent, including randomised patients, patients who failed screening and any others who initiated screening.

4.4.3 *Primary endpoint analysis*

For each patient who was not known to have died as of the cut-off date for a particular analysis, OS was censored for that analysis at the date of last contact.

The study primary analysis used an un-stratified log-rank test for superiority of nal-iri + 5-FU/LV (Arm C) over 5-FU/LV (Arm B) in the ITT population.

The corresponding null hypothesis was:

$$H_0:S_C (t) = S_B (t)$$

Where S_B (t) and S_C (t) represent the survivor curves for Arms B and C, respectively. Kaplan-Meier analyses were performed on each treatment group to obtain non-parametric estimates of the survival function and the median survival time. Corresponding 95% CIs were computed using the log-log method. Un-stratified Cox proportional hazards regressions were used to estimate hazard ratios and their corresponding 95% CIs.

4.4.3.1 Sensitivity analyses

The following additional sensitivity analyses were carried out for OS on the ITT population (except where indicated), to evaluate the robustness of the primary analysis results:

- Log-rank test comparisons of treatments on the safety population
- Log-rank test comparisons of treatments on the PP population
- Stratified log-rank analyses, using randomisation stratification factors (with hazard ratio estimates from stratified Cox model)
- Wilcoxon pairwise comparisons of treatments

- Log-rank test comparisons of treatments with OS censored at the date any post-treatment anti-cancer therapy is first administered
- Cox regression model with a time-dependent covariate to account for post-baseline therapy
- Cox regression model with stepwise selection of model terms (p-value to enter <0.25, p-value to remain <0.15)

4.4.4 *Secondary endpoint analyses*

4.4.4.1 Progression-free survival

PFS was compared pairwise using un-stratified log-rank tests. Kaplan-Meier analyses were performed on each treatment group to obtain non-parametric estimates of the PFS function and the median PFS time. Corresponding 95% CIs were computed using the log-log method. Un-stratified Cox proportional hazards regressions were used to estimate hazard ratios and their corresponding 95% CIs. Summaries were presented for the ITT, PP and EP populations.

The following sensitivity analyses of PFS were performed on the ITT population:

- Stratified log-rank analysis with estimate of hazard ratio from stratified Cox proportional hazards model (based on randomisation strata)
- Early discontinuation sensitivity analysis: patients without documented progressive disease (PD) who had subsequent therapy or were discontinued from treatment due to clinical or symptomatic progression were considered as PD at the time of these events
- Missing data sensitivity analysis: date of PD was backdated to the expected date of the first missed tumour assessment if one or more tumour assessment were missing immediately preceding PD
- Cox regression model with stepwise selection (p-value to enter 0.25, p-value to remain 0.15) of model terms
- Log-rank analysis using progression computationally derived from target lesion, non-target lesion, and new lesion data

4.4.4.2 Objective response rate

The 95% CI for the proportion experiencing objective response was calculated based on the normal approximation. Objective response rates were pairwise compared using Fisher's exact tests. The analyses were performed for ITT, PP and EP populations.

4.4.4.3 Time to treatment failure

TTF was compared pairwise using un-stratified log-rank tests. Kaplan-Meier analyses were performed on each treatment group to obtain non-parametric estimates of the TTF function and the median TTF time. Corresponding 95% CIs were computed using the log-log method. Cox proportional hazards regressions were used to estimate the hazard ratios and their corresponding 95% CIs. Summaries were presented for the ITT, PP and EP populations.

4.4.4.4 Clinical benefit response

Objective CBR rates were pairwise compared for the CBRE population using Fisher's exact tests. Contingency tables for pain classification (analgesic consumption by pain intensity), primary measures of classification (KPS), and overall CBR (primary measures by weight) were also presented for each treatment group. Median time to CBR and median duration of CBR were computed using data from patients with CBR.

4.4.4.5 Tumour marker response

Tumour marker response rates were pairwise compared for the TMRE population using Fisher's exact tests. Time to first tumour marker response was summarised using Kaplan-Meier methods.

4.4.5 *Safety analysis*

All data were analysed and presented using the safety population.

4.4.6 *Pharmacokinetic analysis*

Descriptive summary statistics and listings of pharmacokinetic concentrations for the PK population were produced.

4.4.7 *Quality of life analyses*

Pairwise treatment group comparisons were performed on the PRO population for each subscale using Cochran Mantel Haenszel testing.

4.4.8 *Determination of sample size*

Preliminary results from a single arm study of patients with metastatic pancreatic cancer treated with nal-iri as a second-line treatment after prior gemcitabine therapy showed a median survival time of 5.2 months, a 6-month survival rate of 42% and a 1-year survival rate of 25% (77). Therefore, for the study sample size considerations, it was assumed that the median OS times were 3 months (Arm B) and 6 months (Arm C). These corresponded to a hazard ratio of 0.5 in favour of Arm C relative to Arm B.

The planned study size provided at least 99% power to detect the OS advantage for Arm C relative to Arm B. With a 14-month patient accrual and up to 3 months follow-up time, it was expected that a total of approximately 405 patients (across the three arms included in the original study design) would be randomised. This was an increase from the original calculation (270 patients) due to the protocol amendment of the addition of Arm C, as described in Section 4.3.3.2. In addition, the primary analysis for OS was now to take place once 305 deaths had occurred (220 deaths were required prior to protocol amendment).

4.4.9 *Changes in the planned analyses*

The definition of the PP population was modified to require a minimum exposure threshold during the first 6 weeks of treatment of at least 80% of the planned dose. Requiring patients to receive doses as planned through 6 weeks removed patients who could not tolerate treatment early on, as well as patients who failed treatment (PD or death) before adequate dosing during the first 6 weeks could be completed.

The CBRE population was modified to require post-baseline assessments for each component (pain, morphine consumption, and KPS), which was the original intention.

The CBR evaluation period was re-defined as 4 weeks beyond the time of last exposure to study drug. This provides a standard evaluation period relative to study drug exposure, provides a finite period for imputation of missing data, and removes from evaluation data that were collected well beyond the last exposure to treatment.

4.5 *Participant flow in the relevant randomised controlled trials*

4.5.1 *Patient disposition*

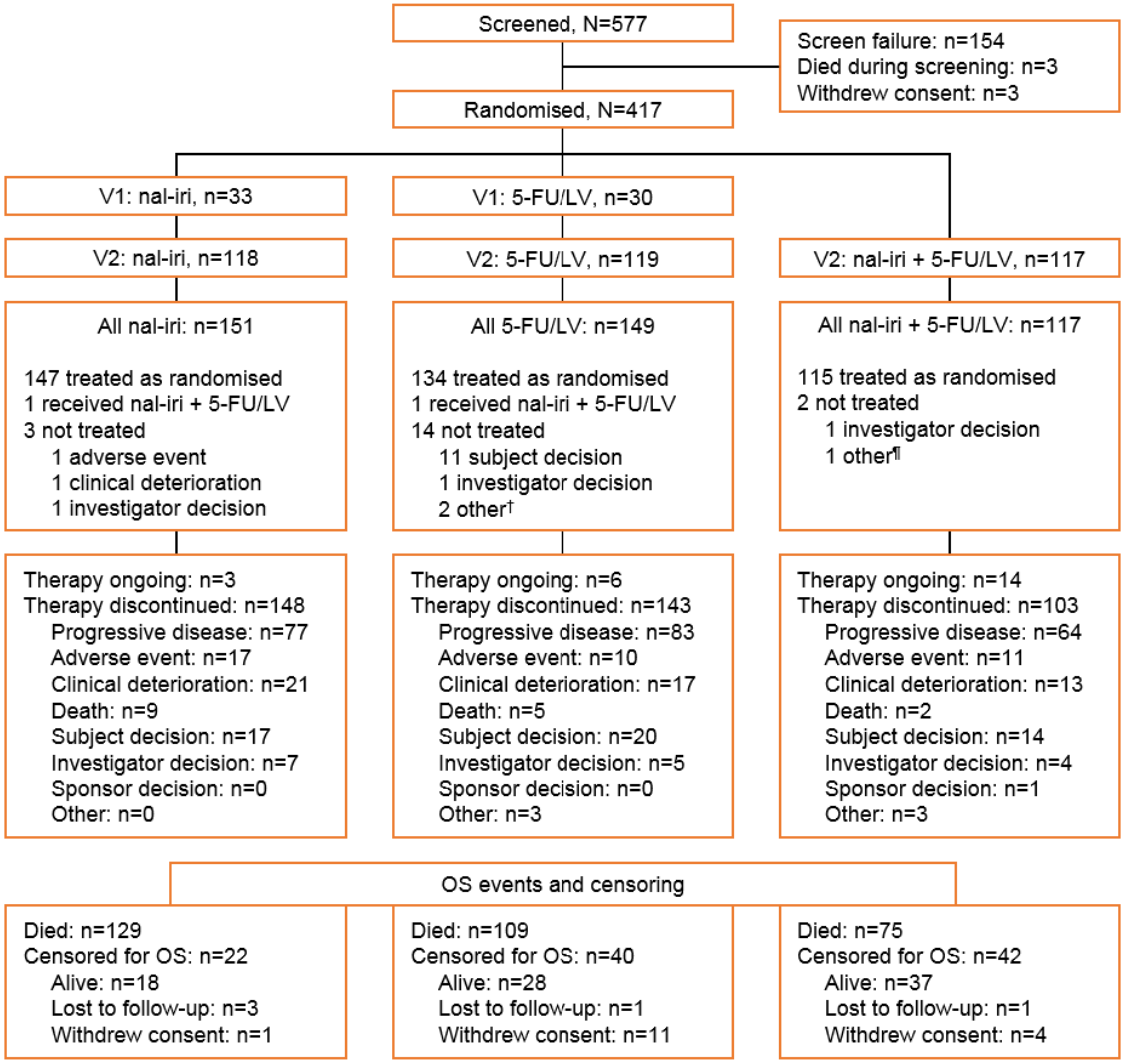
A total of 577 patients were screened, of which 417 were randomised and included in the ITT population. Figure 4 shows the patient enrolment and randomisation disposition flow.

At data cut-off on February 14 2014, 313 deaths had occurred, which is in line with the minimum requirement of 305 deaths defined in the protocol.

Of the 417 randomised patients, 63 were randomised under protocol version 1 and 354 under version 2 or later (after the addition of the nal-iri + 5-FU/LV treatment arm). Based on patients randomised after amendment to protocol version 2, there were 117 patients included in the ITT population of the nal-iri + 5-FU/LV arm, and 119 in the 5-FU/LV control arm.

Overall, there were 19 patients who were never treated, mostly due to the patient's decision. More patients withdrew consent once they were randomised to therapy, and of the 19 patients who were never treated, the majority (14 patients) were randomised to 5-FU/LV therapy. The patient flow for all three arms included in the original protocol is shown in Figure 4.

Figure 4: Patient enrolment and disposition



Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; OS, overall survival.
V1: Version 1 of the protocol; V2: Version 2 of the protocol, after the introduction of the nal-iri + 5-FU/LV arm.
†One patient became ineligible post-randomisation, one patient had an adverse event that delayed dosing for >7 days from randomisation. ¶One patients became ineligible post-randomisation.

In the two treatment arms presented in this submission (nal-iri + 5-FU/LV and s-FU/LV), the most common reason for the termination of treatment was progressive disease based on RECIST v1.1 criteria (121 patients, 51.3%) (81), followed by clinical deterioration (25 patients, 10.6%). Only two patients were lost to follow-up. A summary of patient disposition for the nal-iri + 5-FU/LV treatment group and the 5-FU/LV control group (patients enrolled after amendment to protocol version 2) is provided in Table 13 for the ITT population.

Table 13: Patient treatment and study disposition – ITT population

	Nal-iri + 5-FU/LV (N=117)	5-FU/LV control (N=119)[†]
Subjects who terminated treatment, n (%)	**103 (88.0)**	**113 (95.0)**
Reason for treatment termination, n (%)		
Adverse event	11 (9.4)	7 (5.9)
Clinical deterioration	13 (11.1)	12 (10.1)
Death	2 (1.7)	5 (4.2)
Investigator decision	4 (3.4)	4 (3.4)
Other	1 (0.9)	2 (1.7)
Progressive disease based on RECIST v1.1 criteria (81)	57 (48.7)	64 (53.8)
Sponsor decision	1 (0.9)	0 (0.0)
Subject decision	14 (12.0)	19 (16.0)
Time from randomisation to treatment termination		
Median, weeks	10.1	6.1
(95% CI)	(7.3, 12.7)	(6.1, 6.9)
Overall study disposition, n (%)		
Death	70 (59.8)	78 (65.6)
Lost to follow-up	1 (0.9)	1 (0.8)
Subject withdrew consent from follow-up	8 (6.8)	12 (10.1)
Other reasons	1 (0.9)	1 (0.8)
Subjects in study at analysis cut-off date (February 14, 2014), n (%)	**38 (32.5)**	**27 (22.7)**

Abbreviations: CI, confidence interval; 5-FU, 5-fluorouracil; ITT, intent-to-treat; LV, leucovorin; RECIST, Response Evaluation Criteria in Solid Tumours.
[†]This group is a subset of the 5-FU/LV total control group, containing patients who were enrolled in the study after protocol version 2 was activated (the addition of the nal-iri + 5-FU/LV combination arm).

In the nal-iri + 5-FU/LV combination arm there was a median of 10.1 weeks from randomisation to treatment discontinuation, whereas in the 5-FU/LV control arm, the median time to treatment discontinuation was 6.1 weeks.

The distribution of patients with respect to the randomisation strata of albumin level, KPS or ethnicity was balanced across both treatment groups. The majority of patients (93.2%) did not express the UGT1A1*28 genotype and this was also balanced between the two treatment arms.

4.5.2 *Baseline characteristics and demographics*

Patient characteristics at baseline are summarised in Table 14. Overall, the treatment groups were comparable in terms of demographic characteristics, indicating a well-balanced study population and one reflective of the general patient population with metastatic pancreatic cancer.

Table 14: Baseline demographics – ITT population

Characteristic	Nal-iri + 5-FU/LV (n=117)	5-FU/LV control (n=119)[†]
Gender, n (%)		
Female	48 (41.0)	52 (43.7)
Male	69 (59.0)	67 (56.3)
Race, n (%)		
American Indian or Alaska Native	0	0
Asian	34 (29.1)	36 (30.3)
Black or African American	4 (3.4)	3 (2.5)
White	72 (61.5)	76 (63.9)
Other	7 (6.0)	4 (3.4)
Age, years, mean (SD)	63.2 (9.06)	61.0 (9.46)
BMI, kg/m^2, mean (SD)	23.33 (4.134)	23.57 (5.054)
KPS, n (%)		
50	1 (0.9)	0
60	2 (1.7)	0
70	7 (6.0)	10 (8.4)
80	38 (32.5)	51 (42.9)
90	51 (43.6)	40 (33.6)
100	18 (15.4)	17 (14.3)
Albumin, g/dL, mean (SD)	3.97 (0.459)	3.98 (0.506)
Measurable lesions, n (%)	113 (96.6)	114 (95.8)
Measurable metastatic lesions, n (%)	97 (82.9)	103 (86.6)
Location of metastatic lesions, n (%)		
Distant lymph node	32 (27.4)	31 (26.1)
Liver	75 (64.1)	83 (69.7)
Lung	36 (30.8)	36 (30.3)
Pancreas	75 (64.1)	72 (60.5)
Peritoneal	28 (23.9)	32 (26.9)
Regional lymph node	13 (11.1)	14 (11.8)
Other	27 (23.1)	39 (32.8)

Characteristic	Nal-iri + 5-FU/LV (n=117)	5-FU/LV control (n=119)[†]
Previous anti-cancer therapy, n (%)		
Gemcitabine alone	53 (45.3)	55 (46.2)
Gemcitabine combination	64 (54.7)	64 (53.8)
Fluorouracil-based	50 (42.7)	52 (43.7)
Irinotecan-based	12 (10.3)	17 (14.3)
Platinum-based	38 (32.5)	41 (34.5)

Abbreviations: BMI, body mass index; 5-FU, 5-fluorouracil; ITT, intent-to-treat; KPS, Karnofsky Performance Score; LV, leucovorin; SD. Standard deviation.
[†]This group is a subset of the 5-FU/LV total control group, containing patients who were enrolled in the study after protocol version 2 was activated (the addition of the nal-iri + 5-FU/LV combination arm).
[§]Patients had only received treatment for metastatic cancer with gemcitabine or a gemcitabine-containing regimen in the neoadjuvant or adjuvant setting, therefore the study treatment was classed as first line.
Source: Wang-Gillam et al, 2015 (44).

4.6 *Quality assessment of the relevant randomised controlled trials*

Table 15: Quality assessment results for parallel group RCTs

	NAPOLI-1, Wang-Gillam 2015 (44)
Was randomisation carried out appropriately?	Yes. Patients were randomised 1:1 in the nal-iri + 5-FU/LV and 5-FU/LV arms by IWRS after all screening assessments were completed and UGT1A1*28 results were available.
Was the concealment of treatment allocation adequate?	Open-label study. Blinding of study treatment was not feasible due to different dosing schedules in the different arms. Using a double-dummy design would result in an unacceptable number of infusions lasting up to 46 hours.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Patient demographics in both groups were well balanced in terms of sex, race, age and BMI. The nal-iri+ 5-FU/LV and 5-FU/LV groups were also comparable for all baseline disease characteristics, including KPS, albumin level, number and anatomical location of metastatic lesions, measurable metastatic lesions, previous anti-cancer treatment, best response to prior therapy, prior radiotherapy, prior surgery, prior Whipple procedure, has biliary stent, and number and type of concomitant medical conditions (including anaemia, gastrointestinal disorders, fatigue, type 2 diabetes, hypertension, and psychiatric disorders).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Open-label trial. However, sponsor personnel did not have access to the randomisation code for treatment assignment. In the course of data cleaning and statistical programming development, limited sponsor clinical and biometrics personnel had access to data for individual patients that could be unblinded due to the uniqueness of the visit schedules for each arm. Access to the data in the EDC system was controlled and limited only to authorised personnel for specified data review.

	NAPOLI-1, Wang-Gillam 2015 (44)
Were there any unexpected imbalances in drop-outs between groups?	There was a lower rate of discontinuation with nal-iri + 5-FU/LV (88.0%) than with 5-FU/LV (95.0%). This is mainly due to a lower percentage of patients discontinuing due to progressive disease (48.7% vs 53.8%). Other differences were higher discontinuation due to an adverse event (9.4% vs 5.9%), lower discontinuation due to death (1.7% vs 4.2%), and lower discontinuation due to subject decision (12.0% vs 16.0%).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The ITT population was used for the analyses for the primary endpoint (OS) and the secondary endpoints PFS, TTF, and ORR. The ITT population was the most appropriate population for these endpoints as it included all randomised patients. The evaluation of tumour marker response used the tumour marker response evaluable population, which only included patients who had elevated CA19-9 level (>30 U/mL) at baseline. The evaluation of clinical benefit response used the clinical benefit response evaluable population, which only included patients who had at least one of: baseline pain intensity ≥20 (out of 100); baseline morphine consumption ≥10 mg/day oral morphine equivalents; baseline KPS of 70–90 points. The evaluation of quality of life used the patient-reported outcome population, which only included ITT patients that provided baseline and at least one subsequent assessment on the EORTC-QLQ-C30 instrument.

Abbreviations: BMI, body mass index; EDC, electronic data capture; EORTC-QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; 5-FU, 5-fluorouracil; ITT, intention-to-treat; IWRS, interactive web response system; KPS, Karnofsky performance score; LV, leucovorin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.

A complete quality assessment for each RCT is provided in Appendix 3.

4.7 *Clinical effectiveness results of the relevant randomised controlled trials*

4.7.1 *Primary efficacy outcome*

Median OS was significantly longer (p=0.0122) with the nal-iri + 5-FU/LV combination arm (6.1 months) compared with the 5-FU/LV control arm (4.2 months), with a corresponding hazard ratio of 0.67 (Table 16).

OS was censored for each patient who was not known to have died as of the cut-off date. Censoring occurred at the date of last contact with the patient prior to the cut-off date.

Table 16: Primary efficacy analysis – overall survival – ITT population

	Nal-iri + 5-FU/LV (n=117)	5-FU/LV control (n=119)[¶]
Median OS, months[†] (95% CI)	6.1 (4.76, 8.87)	4.2 (3.29, 5.32)
Comparison (hazard ratio)[§]	0.67 (p=0.0122)	
Died, n (%)	75 (64.1)	80 (67.2)
Reason for censoring, n (%)		
Alive	37 (31.6)	27 (22.7)
Lost to follow-up	1 (0.9)	1 (0.8)
Consent withdrawn from follow-up	4 (3.4)	11 (9.2)

Abbreviations: CI, confidence interval; 5-FU, 5-fluorouracil; ITT, intent-to-treat; LV, leucovorin; OS, overall survival.
[†]Median OS is the Kaplan-Meier estimate of the median survival time. [§]Hazard ratios are derived from the un-stratified Cox proportional hazards model with treatment as the independent variable. P-values are derived from the two-sided un-stratified log-rank test. [¶]This group is a subset of the 5-FU/LV total control group, containing patients who were enrolled in the study after protocol version 2 was activated (the addition of the nal-iri + 5-FU/LV combination arm).

Interim results with a data cut-off of 25th May 2015 showed a median OS of 6.2 months (95% CI: 4.8, 8.4) with nal-iri + 5-FU/LV compared with 4.2 months (95% CI: 3.3, 5.3) with 5-FU/LV (59). The final data cut analysed in March 2016 showed a median OS of [redacted] months (95% CI: [redacted]) with nal-iri + 5-FU/LV compared with [redacted] months (95% CI: [redacted]) with 5-FU/LV.

4.7.1.1 Sensitivity analyses of the primary efficacy outcome

Sensitivity analyses supported the robustness of the results of the primary efficacy analysis. The combination of nal-iri + 5-FU/LV achieved statistically significantly longer median OS than 5-FU/LV for all analyses (Table 17).

Table 17: Sensitivity analyses of the primary efficacy outcome – overall survival

Sensitivity analysis	Nal-iri + 5-FU/LV	5-FU/LV control[¶]
Stratified analysis on ITT population		
N	117	119
Median OS, months[†] (95% CI)	6.1 (4.76, 8.87)	4.2 (3.29, 5.32)
Comparison (hazard ratio)[¶]	0.57 (p=0.0009)	

Sensitivity analysis	Nal-iri + 5-FU/LV	5-FU/LV control[¶]
Safety population		
N	117	105
Median OS, months[†] (95% CI)	6.2 (4.86, 8.87)	4.2 (3.29, 5.29)
Comparison (hazard ratio)[§]	0.66 (p=0.0108)	
PP population (61)		
N	66	71
Median OS, months[†] (95% CI)	8.9 (6.44, 10.5)	5.1 (3.98, 7.16)
Comparison (hazard ratio)[§]	0.57 (0.0106)	
ITT population (censoring at change in therapy)		
N	117	119
Median OS, months[†] (95% CI)	6.1 (4.70, 12.68)	4.0 (3.06, 5.88)
Comparison (hazard ratio)[§]	0.5665 (0.0033)	

Abbreviations: CI, confidence interval; 5-FU, 5-fluorouracil; ITT, intent-to-treat; LV, leucovorin; OS, overall survival; PP, per protocol.
[†]Median OS is the Kaplan-Meier estimate of the median survival time. [¶]For the stratified analysis on the ITT population, the p-values are derived from the two-sided stratified log-rank test, incorporating randomisation strata; hazard ratios are derived using the stratified Cox proportional hazards model with treatment as the independent variable. [§]Hazard ratios and the associated p-values (from the two-sided log-rank test) are derived using Cox proportional hazards model with treatment as the independent variable. [¶]This group is a subset of the 5-FU/LV total control group, containing patients who were enrolled in the study after protocol version 2 was activated (the addition of the nal-iri + 5-FU/LV combination arm).

4.7.2 *Secondary efficacy outcomes*

4.7.2.1 Progression-free survival

Median PFS was over twice as long with the nal-iri + 5-FU/LV arm (3.1 months) than with the 5-FU/LV control arm (1.5 months). The difference was statistically significant (p=0.0001), with a corresponding hazard ratio of 0.56 (Table 18).

Table 18: Secondary efficacy analysis – progression-free survival – ITT population

	Nal-iri + 5-FU/LV (n=117)	5-FU/LV control[¶] (n=119)
Median PFS, months[†] (95% CI)	3.1 (2.69, 4.17)	1.5 (1.41, 1.84)
Comparison (hazard ratio)[§]	0.56 (p=0.0001)	
Progressed (n (%))	65 (55.6)	59 (58.0)
Died (n (%))	18 (15.4)	23 (19.3)
Reason for censoring (n (%))		
Clinical deterioration	3 (2.6)	2 (1.7)
Last non-PD assessment within 12 weeks of cut-off date	15 (12.8)	7 (5.9)
Not treated and no post-baseline tumour assessment	1 (0.9)	10 (8.4)
Other	15 (12.8)	8 (6.7)

Abbreviations: CI, confidence interval; 5-FU, 5-fluorouracil; ITT, intent-to-treat; LV, leucovorin; PD, progressive disease; PFS, progression-free survival.
[†]Median PFS is the Kaplan-Meier estimate of the median progression-free survival time. [§]Hazard ratios are derived from the un-stratified Cox proportional hazards model with treatment as the independent variable. P-values are derived from the two-sided un-stratified log-rank test. [¶]This group is a subset of the 5-FU/LV total control group, containing patients who were enrolled in the study after protocol version 2 was activated (the addition of the nal-iri + 5-FU/LV combination arm).

Interim results with a data cut-off of 25th May 2015 showed a median PFS of 3.1 months (95% CI: 2.7, 4.2) with nal-iri + 5-FU/LV compared with 1.5 months (95% CI: 1.4, 1.8) with 5-FU/LV (59). The final data cut analysed in March 2016 showed a median PFS of [redacted] months (95% CI: [redacted]) with nal-iri + 5-FU/LV compared with [redacted] months (95% CI: [redacted]) with 5-FU/LV.

Sensitivity analyses: progression-free survival

Sensitivity analyses supported the main PFS results, and showed that they were robust. The combination of nal-iri + 5-FU/LV achieved statistically significantly longer median PFS than 5-FU/LV in all sensitivity analyses conducted (Table 19).

Table 19: Sensitivity analyses – progression-free survival

Sensitivity analysis	Nal-iri + 5-FU/LV	5-FU/LV control[‡]
Stratified analysis on ITT population		
N	117	119
Median PFS, months[†] (95% CI)	3.1 (2.69, 4.17)	1.5 (1.41, 1.84)
Comparison (hazard ratio)[¶]	0.51 (p<0.0001)	
PP population		
N	66	71
Median PFS, months[†] (95% CI)	4.3 (3.06, 5.72)	1.6 (1.41, 2.60)
Comparison (hazard ratio)[§]	0.46 (p<0.0001)	

Sensitivity analysis	Nal-iri + 5-FU/LV	5-FU/LV control‡
Evaluable population		
N	104	92
Median PFS, months† (95% CI)	3.1 (2.66, 4.21)	1.4 (1.41, 1.81)
Comparison (hazard ratio)§	0.53 (p<0.0001)	
ITT population (early discontinuation)		
N	117	119
Median PFS, months† (95% CI)	3.1 (2.66, 4.14)	1.4 (1.41, 1.68)
Comparison (hazard ratio)§	0.55 (p<0.0001)	
ITT population (missing data)		
N	117	119
Median PFS, months† (95% CI)	3.1 (2.69, 4.17)	1.5 (1.41, 1.84)
Comparison (hazard ratio)§	0.56 (p=0.0001)	
ITT population (progression directly derived from lesion data)		
N	117	119
Median PFS, months† (95% CI)	3.3 (2.66, 4.21)	1.4 (1.41, 1.84)
Comparison (hazard ratio)§	0.56 (p=0.0001)	

Abbreviations: CI, confidence interval; 5-FU, 5-fluorouracil; ITT, intent-to-treat; LV, leucovorin; PFS, progression-free survival; PP, per protocol.
†Median PFS is the Kaplan-Meier estimate of the median progression-free survival time. ¶For the stratified analysis on the ITT population, the p-values are derived from the two-sided stratified log-rank test, incorporating randomisation strata; hazard ratios are derived using the stratified Cox proportional hazards model with treatment as the independent variable. §Hazard ratios and the associated p-values (two-sided from log-rank test) are derived using Cox proportional hazards model with treatment as the independent variable. ‡This group is a subset of the 5-FU/LV total control group, containing patients who were enrolled in the study after protocol version 2 was activated (the addition of the nal-iri + 5-FU/LV combination arm).

4.7.2.2 Time to treatment failure

Median TTF was significantly longer (p=0.0002) with the nal-iri + 5-FU/LV arm (2.3 months) compared with the 5-FU/LV control arm (1.4 months), with a corresponding hazard ratio of 0.60 (Table 20).

Table 20: Secondary efficacy analysis – time to treatment failure – ITT population

	Nal-iri + 5-FU/LV (n=117)	5-FU/LV control¶ (n=119)
Median TTF, months† (95% CI)	2.3 (1.58, 2.79)	1.4 (1.31, 1.41)
Comparison (hazard ratio)§	0.60 (p=0.0002)	
Progressed, n (%)	61 (52.1)	65 (54.6)
Died, n (%)	1 (0.9)	5 (4.2)
Other reason for treatment termination (n (%))	41 (35.0)	43 (36.1)

Abbreviations: CI, confidence interval; 5-FU, 5-fluorouracil; ITT, intent-to-treat; LV, leucovorin; TTF, time to treatment failure.
†Median TTF is the Kaplan-Meier estimate of the median time to treatment failure. §Hazard ratios and the associated p-values (from the two-sided log-rank test) are derived using Cox proportional hazards model with treatment as the independent variable. ¶This group is a subset of the 5-FU/LV total control group, containing patients who were enrolled in the study after protocol version 2 was activated (the addition of the nal-iri + 5-FU/LV combination arm).

Sensitivity analyses: time to treatment failure

Sensitivity analyses supported the main TTF results, and showed that they were robust. The combination of nal-iri + 5-FU/LV achieved statistically significantly longer median TTF than 5-FU/LV in both sensitivity analyses conducted (Table 21).

Table 21: Sensitivity analyses – time to treatment failure

Sensitivity analysis	Nal-iri + 5-FU/LV	5-FU/LV control[¶]
PP population		
N	66	71
Median TTF, months[†] (95% CI)	4.1 (2.79, 5.53)	1.4 (1.41, 2.43)
Comparison (hazard ratio)[§]	0.49 (p=0.0001)	
Evaluable population		
N	104	92
Median TTF, months[†] (95% CI)	2.5 (1.68, 2.89)	1.4 (1.35, 1.45)
Comparison (hazard ratio)[§]	0.58 (p=0.0004)	

Abbreviations: CI, confidence interval; 5-FU, 5-fluorouracil; LV, leucovorin; PP, per protocol; TTF, time to treatment failure.
[†]Median TTF is the Kaplan-Meier estimate of the median time to treatment failure. [§]Hazard ratios and the associated p-values (from the two-sided log-rank test) are derived using Cox proportional hazards model with treatment as the independent variable. [¶]This group is a subset of the 5-FU/LV total control group, containing patients who were enrolled in the study after protocol version 2 was activated (the addition of the nal-iri + 5-FU/LV combination arm).

4.7.2.3 Objective response rate

The nal-iri + 5-FU/LV arm achieved a statistically significantly higher confirmed ORR (≥4 weeks after investigator assessment of PR or CR) of 7.7% compared with 0.8% in the 5-FU/LV control arm (Table 22).

Table 22: Objective response – ITT population

	Nal-iri + 5-FU/LV (n=117)	5-FU/LV control (n=119)[§]
Best overall response, n (%)		
Partial response	9 (7.7)	1 (0.8)
Stable disease[†]	47 (40.2)	26 (21.8)
Non-complete response/non-progressive disease	3 (2.6)	2 (1.7)
Progressive disease	35 (29.9)	56 (47.1)
Not evaluable[¶]	23 (19.7)	34 (28.6)

	Nal-iri + 5-FU/LV (n=117)	5-FU/LV control (n=119)[§]
Objective response rate[¶]		
N	9	1
Rate, % (95% CI)	7.69 (2.86, 12.52)	0.84 (0.0, 2.48)
Rate difference (95% CI)	6.85 (1.75, 11.95)	
p-value[§]	0.0097	

Abbreviations: CI, confidence interval; 5-FU, 5-fluorouracil; ITT, intention to treat; LV, leucovorin; RECIST, Response Evaluation Criteria in Solid Tumours.
[†]Designation of stable disease required at least one assessment of stable disease according to RECIST v1.1 criteria (81) at least 6 weeks after starting treatment. [¶]Subjects with insufficient data for response classification were classified as not evaluable for best overall response, and as a non-responder for objective response in the ITT population. [§]Two-sided p-values from pairwise Fisher's exact test. [§]This group is a subset of the 5-FU/LV total control group, containing patients who were enrolled in the study after protocol version 2 was activated (the addition of the nal-iri + 5-FU/LV combination arm).

4.7.2.4 Tumour marker response

A statistically significantly greater proportion of tumour marker response evaluable patients treated with nal-iri + 5-FU/LV had reductions of ≥50% from baseline in CA19-9 levels than patients treated with 5-FU/LV alone (Table 23).

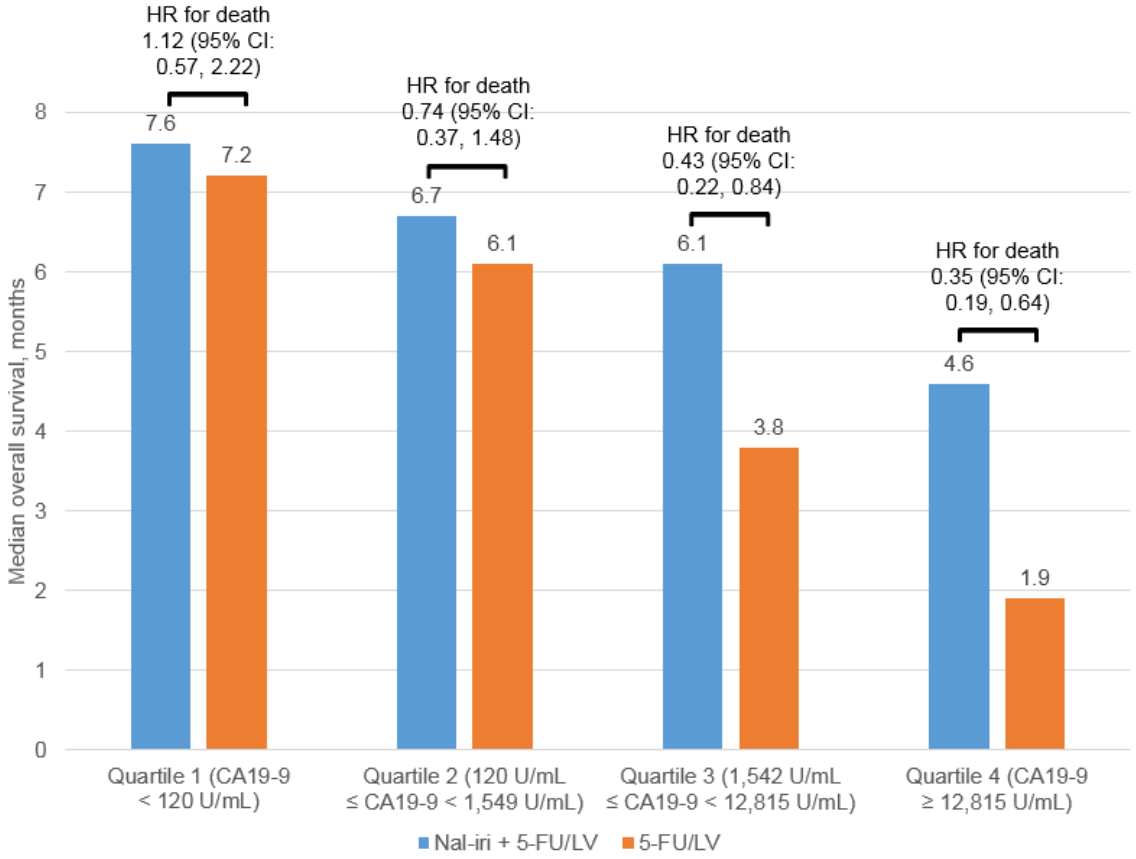
Table 23: Tumour marker (CA19-9) response – TMRE population

	Nal-iri + 5-FU/LV (n=97)	5-FU/LV control (n=81)
Tumour marker response, n (%)	28 (28.9)	7 (8.6)
p-value[†]	0.0006	
Median time to first tumour marker response[¶], months (95% CI)	4.3 (2.92, –)	3.91, –
Log-rank p-value[§]	0.0392	
Wilcoxon p-value[§]	0.0180	

Abbreviations: CI, confidence interval; 5-FU, 5-fluorouracil; LV, leucovorin; TMRE, tumour marker response evaluable.
[†]Two-sided p-values from pairwise comparisons of tumour marker response rates using Fisher's exact test. [¶]Median time to first tumour response is Kaplan-Meier estimate of the median time to first tumour marker response, in months. [§]Two-sided p-values from pairwise comparisons of time to first tumour marker response.

A further analysis was undertaken to investigate the effects of baseline CA19-9 level on overall survival (60). Patients that received study drug and had a recorded baseline CA19-9 measurement (n=218 in the nal-iri + 5-FU/LV and 5-FU/LV arms) were divided into quartiles based on 404 available CA19-9 values from randomised patients (N=417). Un-stratified Cox proportional hazards regression was used to calculate estimated hazard ratios for death and corresponding 95% CIs. Results showed that there was a greater treatment effect on OS with higher CA19-9 level relative to 5-FU/LV (Figure 5).

Figure 5: Effect of baseline CA19-9 level on overall survival



Abbreviations: CA19-9, carbohydrate antigen 19-9; 5-FU, 5-fluorouracil; HR, hazard ratio; LV, leucovorin.

4.7.2.5 Clinical benefit response

The nal-iri + 5-FU/LV arm showed a CBR rate of 14.1% compared with 11.7% in the 5-FU/LV arm (Table 24).

Table 24: Clinical benefit response – CBRE population

	Nal-iri + 5-FU/LV (n=78)			5-FU/LV control (n=60)		
	Analgesic consumption					
Pain intensity, n (%)	**Positive**	**Stable**	**Negative**	**Positive**	**Stable**	**Negative**
Positive	6 (7.69)	3 (3.85)	3 (3.85)	0	3 (5.00)	2 (3.33)
Stable	2 (2.56)	31 (39.74)	10 (12.82)	2 (3.33)	21 (35.00)	8 (13.33)
Negative	0	5 (6.41)	18 (23.08)	0	7 (11.67)	17 (28.33)
	Performance status					
Pain classification, n (%)	**Positive**	**Stable**	**Negative**	**Positive**	**Stable**	**Negative**
Positive	1 (1.28)	9 (11.54)	1 (1.28)	0	4 (6.67)	1 (1.67)
Stable	0	27 (34.62)	4 (5.13)	0	16 (26.67)	5 (8.33)
Negative	0	24 (30.77)	12 (15.38)	0	15 (25.00)	19 (31.67)

	Nal-iri + 5-FU/LV (n=78)			5-FU/LV control (n=60)		
	Primary measure					
Weight, n (%)	**Response**	**Stable**	**Non-response**	**Response**	**Stable**	**Non-response**
Positive	1 (1.28)	1 (1.28)	0	0	3 (5.00)	0
Non-positive	9 (11.54)	26 (33.33)	41 (52.56)	4 (6.67)	13 (21.67)	40 (66.67)
Clinical benefit response, n (%)	11 (14.10)			7 (11.67)		
p-value	0.8007					

Abbreviations: CBRE, clinical benefit response evaluable; 5-FU, 5-fluorouracil; LV, leucovorin.

The evaluation of CBR has a number of limitations. The pain component of the CBR assessment was based on patient-reported daily diary data. Diary compliance was low (60% of ITT patients were in the CBRE population), resulting in a large set of data that was highly variable in quality. Another limitation was the precision of the CBR classification rules (see Section 4.3.4.2). The algorithm required observed maintenance of 4 consecutive weeks with robust criteria in each category for classification of improvement. Classification of negative CBR was less robust due to the categorisation of 'any worsening' without a general equivalence window except for the thresholds of 20 cm VAS and 10 mg/day morphine equivalents, as negative for pain. With these limitations, gross improvements may be detected, but conclusions regarding negative classification should be treated with caution and the individual data should be explored more deeply.

4.7.2.6 Quality of life

Quality of life results generally showed no difference between the treatment arms. Baseline median Global Health Status scores were similar between the arms and there were no appreciable changes from baseline after 12 weeks, suggesting that there were no negative effects of treatment on Global Health Status.

Baseline median Functional Scale scores were similar between treatment arms and were high (≥75) for physical functioning, emotional functioning, and cognitive functioning, indicating a high/healthy level for functioning. Median scores for role functioning and social functioning were lower, but still above the midpoint of the scale. There were no appreciable changes from baseline after 12 weeks, suggesting that the effects of the treatments on Functional Scale scores were negligible.

Baseline median Symptom scores were also similar between the treatment arms and were between 0 and 33 for all symptoms, indicating low levels of symptomatology. There were no appreciable changes from baseline in the scores for pain, dyspnoea, insomnia, appetite loss and constipation, suggesting that the effects of the treatments on these symptoms were negligible. Baseline median symptom scores for nausea and diarrhoea were 0 (indicating no symptomatology), but there were slight increases post-baseline with median scores between 16.7 and 33.3 in the nal-iri + 5-FU/LV arm. Increases in median scores for fatigue and financial difficulties were low or transient.

As supportive evidence, an additional analysis was performed to analyse quality of life outcomes in NAPOLI-1: quality-adjusted time without symptoms or toxicity (Q-TWiST).

Total survival in the ITT population over 12 months was partitioned into time with AE Grade ≥3 toxicity (TOX), time in relapse after disease progression (REL), and time without symptoms or adverse event grade ≥3 toxicity (TWiST). Mean Q-TWiST was calculated by multiplying the time spent in each health state by its respective utility (0.5 for TOX, 0.5 for REL and 1.0 for TWiST). A scenario analysis was also conducted using the PP population.

Patients in the nal-iri + 5-FU/LV arm had significantly more time in TWiST compared with the 5-FU/LV arm (3.4 vs 2.4 months, respectively). Patients in the nal-iri + 5-FU/LV arm also had more time in TOX (1.0 vs 0.3 months, respectively), but similar time in REL (2.5 vs 2.7 months, respectively). Patients in the nal-iri + 5-FU/LV arm had 1.3 months longer Q-TWiST than patients in the 5-FU/LV arm (5.1 vs 3.9 months, respectively), with a relative Q-TWiST gain of 24%. The analysis using the PP population supported that for the ITT population, in that Q-TWiST was also significantly superior in the nal-iri + 5-FU/LV arm compared with the 5-FU/LV arm (Q-TWiST gain 1.8 months).

These results support the primary analysis of quality of life, and show that nal-iri + 5-FU/LV resulted in statistically significant and clinically important gains in quality-adjusted survival compared with 5-FU/LV (22).

4.7.2.7 Pharmacokinetics

Pharmacokinetics of 5-FU

The concentration of 5-FU was lower in the nal-iri + 5-FU/LV arm (geometric mean 0.14 mg/L) than in the 5-FU/LV control arm (0.22 mg/L). The geometric mean ratio for nal-iri + 5-FU/LV compared with 5-FU/LV is 0.63 (95% CI: 0.28, 1.39), which is consistent with the theoretical ratio obtained from the difference in the infusion rate between the two arms (ratio of steady-state concentrations 0.626).

Pharmacokinetics of total irinotecan, SN-38 and SN-38G

The pharmacokinetics of total irinotecan, SN-38 and SN-38 glucuronide (SN-38G) were consistent with the pharmacokinetics observed in previous studies, and are shown in Table 25.

The contribution of UGT*28 homozygosity status on the pharmacokinetics of nal-iri, SN-38 and SN-38G concentration at the time when C_{max} occurred (T_{max}; Day 1 for SN-38 and Day 2 for SN-38G) were evaluated as a function of UGT*28 homozygosity and race. Overall, reduced incidence of homozygosity for UGT1A1*28 was observed in Asians compared with Caucasians; a homozygosis state was observed in 23/243 (9.5%) Caucasians, 2/129 (1.6%) Asians, and 2/26 (7.7%) in all other races. The number of patients with SN-38 or SN-38G pharmacokinetic collections on Day 1 or 2 were too few to report (Day 1: 0 patients with homozygosity; Day 2: 3 out of 54 patients with homozygosity).

Table 25: Summary statistics of pharmacokinetic parameters of total irinotecan, SN-38 and SN-38G

Analyte	Time	N	Geometric mean	% CV	Median	Inter-quartile dispersion	% BLQ
Total	Week 1	98	0.45	127%	0.30	462%	41%

Analyte	Time	N	Geometric mean	% CV	Median	Inter-quartile dispersion	% BLQ
irinotecan (mg/L)	Max	116	26.06	33%	31.10	28%	0%
SN-38 (ng/mL)	Day 0	114	1.44	153%	1.25	69%	0%
	Day 1	12	3.27	73%	3.10	70%	0%
	Day 2	54	2.10	81%	2.00	55%	0%
	Week 1	98	0.72	70%	0.64	81%	34%
SN-38G (ng/mL)	Day 0	114	3.08	69%	2.50	34%	71%
	Day 1	12	21.49	54%	18.03	93%	0%
	Day 2	54	21.13	67%	21.49	85%	0%
	Week 1	98	5.03	109%	4.11	119%	18%

Abbreviations: BLQ, below quantification limit; CV, coefficient of variance.

4.8 *Subgroup analysis*

No subgroups are included for this submission; there were no subgroups identified in the NICE scope.

4.9 *Meta-analysis*

There was only one trial identified for nal-iri + 5-FU/LV (NAPOLI-1), so no meta-analysis of results was possible.

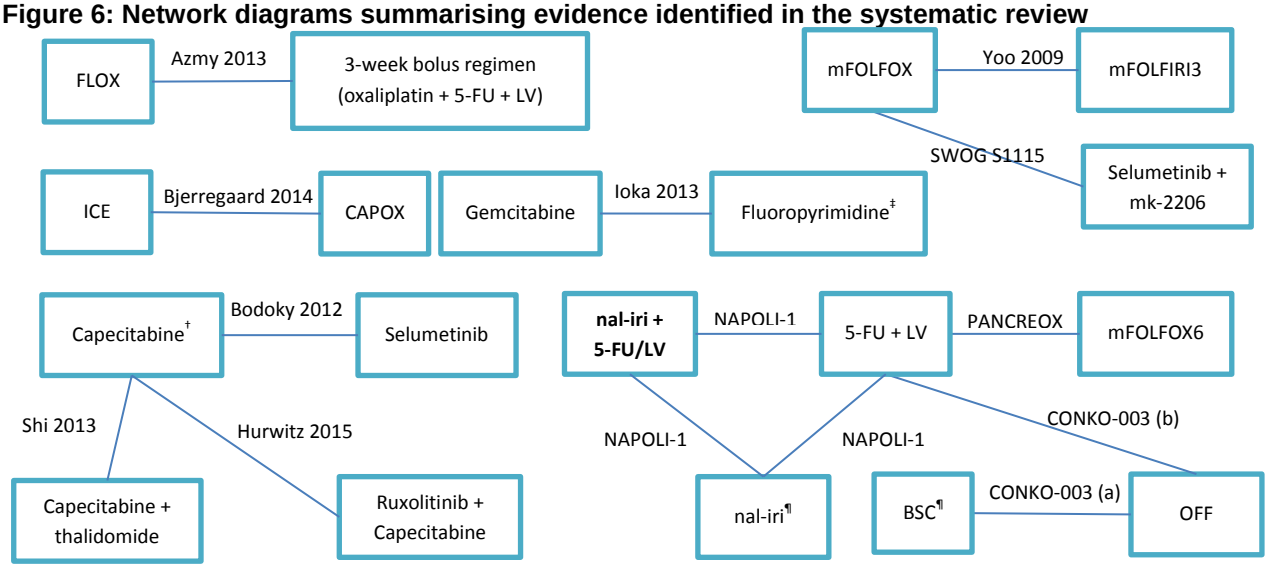
4.10 *Indirect and mixed treatment comparisons*

An indirect treatment comparison was not conducted because a network meta-analysis was deemed unfeasible.

4.10.1 *NMA feasibility assessment*

A systematic review of clinical evidence of treatments for metastatic adenocarcinoma of the pancreas (as described in Section 4.1) identified a total of 14 publications of 13 RCTs (11, 15, 44, 46, 50-58). A network meta-analysis (NMA) feasibility assessment was explored based on 12 randomised controlled trials that enrolled patients with advanced or metastatic pancreatic cancer that have been previously treated with gemcitabine-containing treatment at any line of therapy (11, 15, 44, 46, 50-53, 55-58). The best-case evidence network scenario included NAPOLI-1 (44), CONKO-003 (11), and PANCREOX (46), which are connected by the common comparator 5-FU + LV (Figure 6).

Figure 6: Network diagrams summarising evidence identified in the systematic review



Abbreviations: BSC, basic supportive care; 5-FU, 5-fluorouracil; ICE, irinotecan, cetixumab and everolimus; LV, leucovorin.

Suitability of trials for inclusion in indirect treatment comparisons and NMA is determined by considering whether studies are broadly homogeneous. It is difficult to conclude whether the trials are sufficiently homogeneous in this case due to the inconsistent reporting of the study designs and patient characteristics.

Based on the available papers and abstract, the NMA feasibility assessment concluded that the trial design and outcomes are insufficiently homogeneous in this case, due to the inconsistent reporting of the study designs and patient characteristics. This was confirmed independently by the assessment of the studies by an expert panel, with the conclusions summarised in section 4.10.2.

4.10.1.1 Outcomes

PFS: The calculation of hazard ratios from patient data is usually based on the proportional hazards assumption. Upon inspection of the Kaplan-Meier curves for PFS, it is evident that the curves cross in both CONKO-003 and PANCREOX. Therefore, the proportional hazards assumption is not likely to hold within/between trials.

OS: Similarly, the Kaplan-Meier curves for OS cross in NAPOLI-1, and therefore the proportional hazards assumption is not likely to hold.

Response rate: There was inconsistent reporting of response rates across the three trials, with NAPOLI-1 being the only trial to report both the objective response rate and CA19-9 response. The follow-up duration of CONKO-003 was reported as a median of 54.1 months, but the follow-up durations of NAPOLI-1 and PANCREOX were not reported. Therefore, an indirect comparison would require the assumption that the follow-up durations of NAPOLI-1 and PANCREOX are comparable to CONKO-003, or that differences in follow-up durations are not important (i.e. further follow-up would have no impact on the relative treatment effects in each of these studies).

Safety: Similarly, for comparison of safety outcomes, it would have to be assumed that the follow-up durations of all trials are comparable or that any differences are unimportant.

4.10.1.2 Heterogeneity

It is difficult to assess the heterogeneity of the trials; however some key aspects to consider are described below:

- NAPOLI-1 was multi-national including four sites in the UK, whereas CONKO-003 was conducted in Germany and PANCREOX was conducted in Canada
- As described earlier, the follow-up durations of CONKO-003 and PANCREOX were not reported
- The median age of patients was 62 years in CONKO-003 and NAPOLI-1, and 65 years in PANCREOX
- There was inconsistent reporting of additional clinically important patient characteristics, such as Eastern Cooperative Oncology Group (ECOG) performance score, CA19-9 levels, and the number and type of metastatic sites
- The treatment regimen details of the common comparator arm (5-FU + LV) across the three studies are inconsistently reported and therefore it is difficult to comment on the comparability of dosing.
- The trial populations for NAPOLI-1 and CONKO-003 differ substantially, as CONKO-003 enrolled patients with prior gemcitabine monotherapy only, whereas NAPOLI-1 recruited any prior gemcitabine combination therapy.

4.10.2 *Key opinion leader feedback*

A panel of three UK key opinion leaders (KOLs) were consulted to provide feedback on the feasibility of an indirect treatment comparison. Key feedback included:

- There is missing information for potentially key variables, which can make it harder to compare the trials
- Important variables that weren't provided for all trials include the time gap between first and second line treatment, the duration and intensity of treatment, prior lines of treatment
- It is very difficult to draw conclusions on trial and outcome similarity from the published information provided for CONKO-003 and PANCREOX

In summary, the KOLs concluded that potentially relevant information is not consistently provided for all trials, making it difficult to compare the similarity of the trials. In addition, due to the severity of the disease in these patients and the complexities in the treatment regimens, it is difficult to point out treatment effect modifying variables, which further hinders similarity assessment. Overall, the KOLs felt that combining the three trials in a meta-analysis may be considered flawed and "naïve".

4.11 *Non-randomised and non-controlled evidence*

4.11.1 *List of relevant non-randomised and non-controlled evidence*

There is one relevant non-randomised, non-controlled phase II trial of nal-iri monotherapy in patients with gemcitabine-refractory metastatic pancreatic cancer (NCT00813163) (77). A summary of the trial design is shown in Table 26.

Table 26: Trial design of NCT00813163

Trial design	International, multi-centre, open-label, phase II study.
Objective	To establish the efficacy and toxicity of single-agent nal-iri in patients with metastatic pancreatic cancer after progression on first-line gemcitabine-based therapy.
Population	Patients with histologically confirmed adenocarcinoma of the exocrine pancreas refractory to gemcitabine-based (either alone or in combination) systemic chemotherapy, including those with disease progression within 6 months after post-operative adjuvant therapy.
Intervention	Nal-iri 120 mg/m^2 intravenous infusion over 90 min every 21 days.
Comparator	Not applicable, this was a non-controlled trial.
Primary endpoint	3-month survival rate ($OS_{3\text{-month}}$).
Secondary endpoints	• Objective tumour response • Progression-free survival • Overall survival • Clinical benefit response • CA19-9 tumour marker response • Safety profile
Key inclusion criteria	• Age ≥18 years • KPS ≥50 (subsequently amended to ≥70 to ensure patient safety and to be consistent with the eligibility criteria of other clinical trials for this patient population) • Extra-pancreatic metastases diagnosed either radiographically or by biopsy confirmation • Absolute neutrophil count ≥1,500 ml^{-1} • Platelets ≥100,000 ml^{-1} • Serum bilirubin within ULN • Transaminase ≤2.5 x ULN (≤5 x ULN in patients with liver metastases)
Key exclusion criteria	• Prior treatment with irinotecan • Prior major surgery, radiotherapy (except palliative) or investigational drug therapy within previous 4 weeks • Treatment-related toxicities higher than grade 1 • Central nervous system metastases • Pregnancy • Uncontrolled active infection • Another primary malignancy within the past 5 years except curatively treated non-melanoma skin cancer or cervical carcinoma in situ • Other concomitant serious diseases

Primary study reference	Ko et al, 2013 (77).
Justification for inclusion	The positive results from this trial prompted the initiation of NAPOLI-1.

Abbreviations: KPS, Karnofsky Performance Status; OS, overall survival; ULN, upper normal limit.

4.11.2 *List of RCTs excluded from further discussion*

No further trials have been excluded.

4.11.3 *Summary of methodology of the relevant non-randomised and non-controlled evidence*

A summary of the methodology of NCT00813163 is shown in Table 27.

Table 27: Methodology of NCT00813163

Treatment	Nal-iri 120 mg/m^2 diluted in 500 mL of 5% dextrose, delivered as a 90 min intravenous infusion every 21 days
Pre-medication	Dexamethasone and a serotonin antagonist
Dose adjustments	Dose reductions were required for grade 3 or 4 toxicities. Dose escalation to 150 mg/m^2 was allowed in patients who did not experience drug-related toxicities worse than grade 1, at the discretion of the treating physician
Discontinuation	Treatment was continued until evidence of disease progression, unacceptable toxicity, treatment delay for >2 weeks, patient withdrawal of consent, or death

4.11.4 *Statistical analysis of the non-randomised and non-controlled evidence*

For the primary endpoint ($OS_{3\text{-month}}$), the null hypothesis (H_0) was $OS_{3\text{-month}}$ of 40% and the alternative hypothesis (H_a) was $OS_{3\text{-month}}$ of 65%. These values were estimated based on an $OS_{3\text{-month}}$ of ~35% in CONKO-003 (57). The study used an optimal Simon 2-stage design, and with a significance level of α=0.05 and a type 2 error β=0.10, at least 21 of 39 patients were required to survive 3 months or longer to allow rejection of the null hypothesis.

The primary analysis used the PP population for descriptive statistics, defined as patients who met all inclusion and exclusion criteria and didn't significantly deviate from the study protocol.

4.11.5 *Participant flow in the studies*

The baseline characteristics for the patients in trial NCT00813163 are shown in Table 28.

Table 28: Baseline characteristics for trial NCT00813163

Baseline characteristic	NCT00813163 (N=40)
Age in years, median (range)	58.8 (39–82)
Sex, n (%)	
Male	19 (47.5)
Female	21 (52.5)
Ethnicity, n (%)	
Asian	25 (62.5)
Caucasian	15 (37.5)
Karnofsky Performance Status, n (%)	
100	7 (17.5)
90	17 (42.5)
80	6 (15.0)
70	10 (25.0)
Prior treatment, n (%)	
Chemotherapy	40 (100)
Radiotherapy	10 (25.0)
Surgery	17 (42.5)
First-line chemotherapy	
Gemcitabine monotherapy, n (%)	9 (22.5)
Gemcitabine monotherapy duration in months, median (range)	2 (1.5–24)
Gemcitabine-based combination, n (%)	31 (77.5)
Gemcitabine-based combination duration in months, median (range)	6 (1–6)
Baseline clinical benefit parameters, n (%)	
Pain intensity ≥20 (out of 100)	17 (42.5)
Morphine consumption ≥10 mg per day	14 (35.0)

4.11.6 *Quality assessment of the relevant non-randomised and non-controlled evidence*

A quality assessment of NCT00813163 is provided in Appendix 5.

4.11.7 *Clinical effectiveness results of the relevant non-randomised and non-controlled evidence*

The study met its primary endpoint, with 30 patients (75.0%) surviving at least 3 months (Table 29). In addition, 17 patients (42.5%) were alive at 6 months and 10 (25.0%) at 12 months. Median progression-free and overall survival were 2.4 and 5.2 months, respectively.

Disease control (objective response plus stable disease for more than two cycles) was achieved by 50% of the patients, including three patients (7.5%) who achieved a

confirmed objective response (Table 29). Of the 17 patients with stable disease as their best response, 14 demonstrated disease stability for at least four cycles. There were 32 patients with elevated CA19-9 at baseline, 10 (31.3%) of which had >50% biomarker decline. A total of 5 (20%) of 25 CBR-evaluable patients achieved significant clinical benefit.

Table 29: Efficacy results from NCT00813163

Outcome	NCT00813163 (N=40)
Survival, months	
Median progression-free survival	2.4
Median overall survival	5.2
Proportion of patients alive at:	
3 months, n (%)	30 (75.0)
6 months, n (%)	17 (42.5)
12 months, n (%)	10 (25.0)
Best tumour response, n (%)	
Partial response	3 (7.5)
Stable disease	17 (42.5)[†]
Disease progression	10 (25.0)
Non-evaluable[¶]	10 (25.0)
Disease control (partial response + stable disease)	20 (50.0)
Clinical benefit response, n (%), n=25 evaluable	5 (20.0)
CA19-9 decline >50%, n (%), n=32 with elevated level at baseline	10 (31.3)

[†]Including eight patients with minor response. [¶]Non-evaluable patients for tumour response included those patients with non-measurable disease at baseline or in whom at least one post-treatment radiographic evaluation was not performed.

4.12 *Adverse reactions*

All safety data are derived from the phase III study, NAPOLI-1, and the phase II study, NCT00813163. The methodology of NAPOLI-1 is described in Section 4.3, and that of NCT00813163 in Section 4.11. No further studies that are of relevance to the decision problem are available. Safety data have been presented for all three arms of NAPOLI-1 (including the nal-iri monotherapy arm), in order to provide all safety information for nal-iri in the treatment of metastatic pancreatic cancer that is currently available.

4.12.1 *Summary of adverse events*

4.12.1.1 NAPOLI-1

The safety analysis population included 398 (95%) of the 417 patients randomly assigned who received at least one dose of study drug. A summary of AEs is provided in Table 30, and a detailed list of AEs occurring in ≥10% of patients in any treatment group is provided in Table 31. A summary of serious AEs occurring in ≥1% of patients in any treatment group is presented in Appendix 6.

Table 30: Summary of adverse events

n (%)	Nal-iri (n=147)	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=134)
≥1 AE	146 (99.3)	116 (99.1)	132 (98.5)
≥1 TEAE	145 (98.6)	116 (99.1)	132 (98.5)
≥1 treatment-related TEAE	128 (87.1)	107 (91.5)	93 (69.4)
≥1 CTCAE Grade 3 or higher TEAE	112 (76.2)	90 (76.9)	75 (56.0)
≥1 CTCAE Grade 3 or higher treatment-related TEAE	76 (51.7)	63 (53.8)	24 (17.9)
≥1 Grade 3 as most severe toxicity	54 (36.7)	53 (45.3)	21 (15.7)
≥1 Grade 4 as most severe toxicity	18 (12.2)	9 (7.7)	3 (2.2)
≥1 Grade 5 as most severe toxicity	4 (2.7)	1 (0.9)	0 (0.0)
≥1 serious TEAE	90 (61.2)	56 (47.9)	60 (44.8)
≥1 TEAE leading to any dose modification	81 (55.1)	83 (70.9)	48 (35.8)
≥1 TEAEs resulting in dose delay	49 (33.3)	72 (61.5)	43 (32.1)
≥1 TEAE leading to dose reduction	46 (31.3)	39 (33.3)	5 (3.7)
≥1 TEAE leading to dose discontinuation	17 (11.6)	13 (11.1)	10 (7.5)

Abbreviations: AE, adverse event; CTCAE, common terminology criteria for adverse events; 5-FU, 5-fluorouracil; LV, leucovorin; TEAE, treatment-emergent adverse event.

Table 31: Summary of adverse events occurring in ≥10% of patients

n (%)	Nal-iri (n=147)	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=134)
TEAEs occurring in ≥10% of subjects in any treatment group[†]			
Any TEAEs	145 (98.6)	116 (99.1)	132 (98.5)
Diarrhoea	103 (70.1)	69 (59.0)	35 (26.1)
Vomiting	80 (54.4)	61 (52.1)	35 (26.1)
Nausea	89 (60.5)	60 (51.3)	46 (34.3)
Decreased appetite	72 (49.0)	52 (44.4)	43 (32.1)
Fatigue	54 (36.7)	47 (40.2)	37 (27.6)
Anaemia	48 (32.7)	44 (37.6)	31 (23.1)
Abdominal pain	50 (34.0)	27 (23.1)	42 (31.3)
Pyrexia	29 (19.7)	27 (23.1)	15 (11.2)
Neutropenia	22 (15.0)	27 (23.1)	4 (3.0)
Constipation	26 (17.7)	26 (22.2)	32 (23.9)
Asthenia	35 (23.8)	24 (20.5)	22 (16.4)
Weight decreased	29 (19.7)	20 (17.1)	9 (6.7)
Neutrophil count decreased	15 (10.2)	17 (14.5)	2 (1.5)
White blood cell count decreased	10 (6.8)	17 (14.5)	2 (1.5)
Alopecia	32 (21.8)	16 (13.7)	6 (4.5)
Stomatitis	5 (3.4)	16 (13.7)	8 (6.0)

n (%)	Nal-iri (n=147)	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=134)
Dizziness	17 (11.6)	15 (12.8)	13 (9.7)
Back pain	12 (8.2)	15 (12.8)	16 (11.9)
Hypokalaemia	32 (21.8)	14 (12.0)	12 (9.0)
Oedema peripheral	28 (19.0)	13 (11.1)	20 (14.9)
Mucosal inflammation	8 (5.4)	12 (10.3)	5 (3.7)
Leukopenia	6 (4.1)	12 (10.3)	1 (0.7)
Platelet count decreased	3 (2.0)	12 (10.3)	3 (2.2)
Abdominal pain upper	17 (11.6)	11 (9.4)	10 (7.5)
Dehydration	15 (10.2)	9 (7.7)	9 (6.7)
Hypomagnesaemia	20 (13.6)	7 (6.0)	5 (3.7)
Hypoalbuminemia	19 (12.9)	7 (6.0)	8 (6.0)
TEAEs Grade 3 or higher occurring in ≥10% of subjects in any treatment group			
Any TEAE Grade 3 or higher	112 (76.2)	90 (76.9)	75 (56.0)
Blood and lymphatic system disorders	**29 (19.7)**	**31 (26.5)**	**10 (7.5)**
Agranulocytosis	0 (0.0)	1 (0.9)	0 (0.0)
Anaemia	16 (10.9)	11 (9.4)	9 (6.7)
Coagulopathy	1 (0.7)	0 (0.0)	0 (0.0)
Disseminated intravascular coagulation	1 (0.7)	0 (0.0)	0 (0.0)
Febrile neutropenia	6 (4.1)	2 (1.7)	0 (0.0)
Granulocytopenia	0 (0.0)	1 (0.9)	0 (0.0)
Leukocytosis	1 (0.7)	0 (0.0)	0 (0.0)
Leukopenia	4 (2.7)	1 (0.9)	0 (0.0)
Lymphopenia	2 (1.4)	2 (1.7)	0 (0.0)
Neutropenia	8 (5.4)	17 (14.5)	1 (0.7)
Pancytopenia	0 (0.0)	2 (1.7)	0 (0.0)
Thrombocytopenia	1 (0.7)	1 (0.9)	0 (0.0)
Gastrointestinal disorders	**68 (46.3)**	**38 (32.5)**	**29 (21.6)**
Abdominal distension	0 (0.0)	1 (0.9)	0 (0.0)
Abdominal pain	12 (8.2)	8 (6.8)	8 (6.0)
Abdominal pain upper	3 (2.0)	0 (0.0)	0 (0.0)
Ascites	5 (3.4)	2 (1.7)	2 (1.5)
Caecitis	1 (0.7)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	2 (1.5)
Diarrhoea	31 (21.1)	15 (12.8)	6 (4.5)
Duodenal ulcer	0 (0.0)	1 (0.9)	1 (0.7)
Enteritis	1 (0.7)	0 (0.0)	0 (0.0)
Gastric ulcer	1 (0.7)	0 (0.0)	0 (0.0)

n (%)	Nal-iri (n=147)	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=134)
Gastric varices haemorrhage	0 (0.0)	0 (0.0)	1 (0.7)
Gastrointestinal haemorrhage	1 (0.7)	1 (0.9)	1 (0.7)
Gastrointestinal obstruction	0 (0.0)	0 (0.0)	1 (0.7)
Gastrointestinal toxicity	1 (0.7)	0 (0.0)	0 (0.0)
Haematochezia	1 (0.7)	0 (0.0)	0 (0.0)
Ileus	1 (0.7)	0 (0.0)	1 (0.7)
Impaired gastric emptying	1 (0.7)	0 (0.0)	0 (0.0)
Intestinal obstruction	1 (0.7)	0 (0.0)	1 (0.7)
Intestinal ulcer	0 (0.0)	1 (0.9)	0 (0.0)
Melaena	1 (0.7)	0 (0.0)	0 (0.0)
Nausea	8 (5.4)	9 (7.7)	4 (3.0)
Obstruction gastric	0 (0.0)	0 (0.0)	2 (1.5)
Oesophagitis	1 (0.7)	0 (0.0)	1 (0.7)
Pancreatic haemorrhage	0 (0.0)	1 (0.9)	0 (0.0)
Pancreatitis	0 (0.0)	0 (0.0)	1 (0.7)
Pancreatitis acute	0 (0.0)	1 (0.9)	1 (0.7)
Pneumoperitoneum	1 (0.7)	0 (0.0)	0 (0.0)
Rectal haemorrhage	0 (0.0)	0 (0.0)	1 (0.7)
Small intestinal obstruction	2 (1.4)	0 (0.0)	0 (0.0)
Stomatitis	0 (0.0)	3 (2.6)	1 (0.7)
Upper gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	3 (2.2)
Varices oesophageal	0 (0.0)	0 (0.0)	1 (0.7)
Vomiting	20 (13.6)	13 (11.1)	4 (3.0)
General disorders and administration site conditions	**26 (17.7)**	**29 (24.8)**	**20 (14.9)**
Asthenia	10 (6.8)	9 (7.7)	9 (6.7)
Device dislocation	1 (0.7)	0 (0.0)	0 (0.0)
Fat necrosis	0 (0.0)	0 (0.0)	1 (0.7)
Fatigue	9 (6.1)	16 (13.7)	5 (3.7)
General physical health deterioration	5 (3.4)	0 (0.0)	0 (0.0)
Malaise	0 (0.0)	1 (0.9)	0 (0.0)
Mucosal inflammation	0 (0.0)	2 (1.7)	0 (0.0)
Non-cardiac chest pain	0 (0.0)	0 (0.0)	2 (1.5)
Oedema peripheral	1 (0.7)	0 (0.0)	1 (0.7)
Pain	0 (0.0)	0 (0.0)	1 (0.7)
Pyrexia	2 (1.4)	2 (1.7)	1 (0.7)

n (%)	Nal-iri (n=147)	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=134)
Infections and infestations	**21 (14.3)**	**20 (17.1)**	**16 (11.9)**
Bacteraemia	0 (0.0)	0 (0.0)	1 (0.7)
Biliary sepsis	1 (0.7)	1 (0.9)	0 (0.0)
Biliary tract infection	1 (0.7)	3 (2.6)	2 (1.5)
Brain abscess	1 (0.7)	0 (0.0)	0 (0.0)
Bronchitis	0 (0.0)	1 (0.9)	0 (0.0)
Bronchopneumonia	2 (1.4)	0 (0.0)	0 (0.0)
Cholangitis suppurative	1 (0.7)	0 (0.0)	1 (0.7)
Cholecystitis infective	0 (0.0)	1 (0.9)	0 (0.0)
Clostridial infection	1 (0.7)	0 (0.0)	0 (0.0)
Clostridium difficile colitis	2 (1.4)	0 (0.0)	0 (0.0)
Device-related infection	2 (1.4)	3 (2.6)	0 (0.0)
Enterocolitis infectious	1 (0.7)	0 (0.0)	0 (0.0)
Escherichia bacteraemia	0 (0.0)	0 (0.0)	1 (0.7)
Escherichia sepsis	0 (0.0)	1 (0.9)	1 (0.7)
Febrile infection	0 (0.0)	1 (0.9)	0 (0.0)
Gastroenteritis	1 (0.7)	3 (2.6)	0 (0.0)
Infection	0 (0.0)	1 (0.9)	1 (0.7)
Klebsiella bacteraemia	1 (0.7)	0 (0.0)	0 (0.0)
Klebsiella sepsis	0 (0.0)	0 (0.0)	1 (0.7)
Liver abscess	1 (0.7)	0 (0.0)	1 (0.7)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	1 (0.7)
Meningitis	1 (0.7)	0 (0.0)	0 (0.0)
Neutropenic sepsis	0 (0.0)	1 (0.9)	0 (0.0)
Oral candidiasis	0 (0.0)	1 (0.9)	1 (0.7)
Peritonitis bacterial	0 (0.0)	0 (0.0)	1 (0.7)
Peritonsillar abscess	0 (0.0)	1 (0.9)	0 (0.0)
Pneumonia	2 (1.4)	2 (1.7)	2 (1.5)
Pseudomonal sepsis	0 (0.0)	0 (0.0)	1 (0.7)
Respiratory tract infection	0 (0.0)	1 (0.9)	0 (0.0)
Sepsis	3 (2.0)	4 (3.4)	1 (0.7)
Septic shock	3 (2.0)	2 (1.7)	1 (0.7)
Urinary tract infection	1 (0.7)	0 (0.0)	3 (2.2)
Urosepsis	1 (0.7)	0 (0.0)	0 (0.0)
Investigations	**26 (17.7)**	**23 (19.7)**	**5 (3.7)**
Alanine aminotransferase increased	2 (1.4)	1 (0.9)	0 (0.0)
Aspartate aminotransferase increased	1 (0.7)	1 (0.9)	0 (0.0)

n (%)	Nal-iri (n=147)	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=134)
Blood alkaline phosphatase increased	2 (1.4)	0 (0.0)	2 (1.5)
Blood amylase increased	0 (0.0)	0 (0.0)	1 (0.7)
Blood bilirubin increased	3 (2.0)	1 (0.9)	0 (0.0)
Blood magnesium decreased	1 (0.7)	0 (0.0)	0 (0.0)
Gamma-glutamyltransferase increased	4 (2.7)	2 (1.7)	2 (1.5)
International normalised ratio increased	3 (2.0)	0 (0.0)	0 (0.0)
Lipase increased	1 (0.7)	0 (0.0)	1 (0.7)
Lymphocyte count decreased	0 (0.0)	1 (0.9)	0 (0.0)
Neutrophil count decreased	12 (8.2)	12 (10.3)	1 (0.7)
Nutritional condition abnormal	0 (0.0)	0 (0.0)	1 (0.7)
Weight decreased	2 (1.4)	2 (1.7)	0 (0.0)
White blood cell count decreased	4 (2.7)	9 (7.7)	0 (0.0)
Metabolism and nutrition disorders	**53 (36.1)**	**22 (18.8)**	**16 (11.9)**
Cachexia	1 (0.7)	1 (0.9)	0 (0.0)
Decreased appetite	13 (8.8)	5 (4.3)	3 (2.2)
Dehydration	5 (3.4)	5 (4.3)	2 (1.5)
Diabetes mellitus	0 (0.0)	2 (1.7)	0 (0.0)
Hyperglycaemia	8 (5.4)	1 (0.9)	3 (2.2)
Hyperkalaemia	2 (1.4)	1 (0.9)	1 (0.7)
Hypernatraemia	1 (0.7)	0 (0.0)	1 (0.7)
Hyperuricaemia	1 (0.7)	0 (0.0)	1 (0.7)
Hypoalbuminaemia	4 (2.7)	1 (0.9)	0 (0.0)
Hypocalcaemia	2 (1.4)	0 (0.0)	0 (0.0)
Hypoglycaemia	4 (2.7)	0 (0.0)	0 (0.0)
Hypokalaemia	17 (11.6)	4 (3.4)	3 (2.2)
Hypomagnesaemia	4 (2.7)	0 (0.0)	1 (0.7)
Hyponatraemia	9 (6.1)	3 (2.6)	2 (1.5)
Hypophagia	0 (0.0)	0 (0.0)	1 (0.7)
Hypophosphataemia	2 (1.4)	0 (0.0)	0 (0.0)
Metabolic disorder	0 (0.0)	0 (0.0)	1 (0.7)
Type 1 diabetes mellitus	0 (0.0)	1 (0.9)	0 (0.0)
Treatment-related TEAEs occurring in ≥10% of subjects in any treatment group[†]			
Any treatment-related TEAE(s)	128 (87.1)	107 (91.5)	93 (69.4)
Diarrhoea	91 (61.9)	55 (47.0)	20 (14.9)
Nausea	69 (46.9)	53 (45.3)	35 (26.1)
Vomiting	63 (42.9)	50 (42.7)	22 (16.4)
Fatigue	40 (27.2)	36 (30.8)	22 (16.4)

n (%)	Nal-iri (n=147)	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=134)
Decreased appetite	44 (29.9)	32 (27.4)	16 (11.9)
Neutropenia	22 (15.0)	25 (21.4)	3 (2.2)
Anaemia	27 (18.4)	20 (17.1)	12 (9.0)
Asthenia	20 (13.6)	18 (15.4)	5 (3.7)
White blood cell count decreased	10 (6.8)	17 (14.5)	2 (1.5)
Neutrophil count decreased	15 (10.2)	16 (13.7)	1 (0.7)
Alopecia	30 (20.4)	14 (12.0)	6 (4.5)
Weight decreased	12 (8.2)	14 (12.0)	3 (2.2)
Stomatitis	4 (2.7)	14 (12.0)	6 (4.5)
Abdominal pain	17 (11.6)	7 (6.0)	5 (3.7)

[†]Ordered by decreasing frequency in the nal-iri + 5-FU/LV combination treatment group.
Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; TEAE, treatment-emergent adverse event.

4.12.1.2 NCT00813163

A summary of TEAEs occurring in ≥10% of patients in NCT00813163 is shown in Table 32, and Grade 3–4 TEAEs occurring in ≥10% of patients is shown in Table 33.

Table 32: TEAEs occurring in ≥10% of patients in NCT00813163 (N=40)

TEAE	n (%)
Diarrhoea	30 (75.0)
Fatigue	25 (62.5)
Nausea	24 (60.0)
Anorexia	23 (57.5)
Vomiting	23 (57.5)
Alopecia	17 (42.5)
Neutropenia	16 (40.0)
Leukopenia	15 (37.5)
Abdominal pain	15 (37.5)
Weight decreased	15 (37.5)
Anaemia	13 (32.5)

Abbreviations: TEAE, treatment-emergent adverse event.

Table 33: Grade 3–4 TEAEs occurring in ≥10% of patients in NCT00813163 (N=40)

TEAE	n (%)
Any grade 3 or higher TEAE	26 (65.0)
Neutropenia	12 (30.0)
Leukopenia	10 (25.0)
Abdominal pain	6 (15.0)
Fatigue/asthenia	8 (20.0)
Anaemia	6 (15.0)
Hyponatremia	6 (15.0)
Diarrhoea	6 (15.0)
GGT elevated	5 (12.5)
Anorexia	4 (10.0)
Nausea	4 (10.0)

Abbreviations: GGT, gamma-glutamyl transferase; TEAE, treatment-emergent adverse event.

4.12.2 *Safety overview*

4.12.2.1 NAPOLI-1

The safety profile of nal-iri and the nal-iri + 5-FU/LV combination is consistent with prior experience with nal-iri and 5-FU/LV, and the most common AEs in the nal-iri-containing arms were similar to the known safety profile of irinotecan.

The mean duration of exposure to study drug was longer in the nal-iri + 5-FU/LV arm compared with the other treatment arms (15.0 weeks vs 11.9 weeks in the nal-iri arm and 10.4 weeks in the 5-FU/LV control arm). As a result, patients randomised to receive nal-iri + 5-FU/LV received a greater mean dose of nal-iri than patients in the nal-iri monotherapy arm (478.8 mg/m^2 vs 410.7 mg/m^2, respectively).

Almost all patients experienced one TEAE in each treatment arm (98.6% in the nal-iri monotherapy arm, 99.1% in the nal-iri + 5-FU/LV combination arm, and 98.5% in the 5-FU/LV control arm). The percentage of subjects who experienced any Grade 3 or higher TEAE was similar in the nal-iri-containing arms (76.2% in the monotherapy arm and 76.9% in the combination arm) and greater than those in the 5-FU/LV control arm (56.0%).

TEAEs related to study drug were common in each treatment arm, with a higher percentage occurring in the nal-iri-containing arms (87.1% in the monotherapy arm and 91.5% in the nal-iri + 5-FU/LV combination arm) compared with the 5-FU/LV control arm (69.4%). Grade 4 and 5 drug-related TEAEs were reported most frequently in the nal-iri monotherapy arm (12.2% and 2.7%, respectively), followed by the nal-iri + 5-FU/LV combination arm (7.7% and 0.9%, respectively), and were least frequent in the 5-FU/LV control arm (2.2% and 0%, respectively). Serious TEAEs followed the same pattern and were reported by 61.2% of patients in the nal-iri monotherapy arm, 47.9% in the nal-iri + 5-FU/LV combination arm, and 44.8% in the 5-FU/LV control arm.

TEAEs that were reported by ≥10% of patients in the nal-iri + 5-FU arm and occurred at a higher frequency (≥5%) than in the 5-FU/LV control arm were diarrhoea (59.0 vs

26.1%), vomiting (52.1 vs 26.1%), nausea (51.3 vs 34.3%), decreased appetite (44.4 vs 32.1%), fatigue (40.2 vs 27.6%), anaemia (37.6 vs 23.1%), pyrexia (23.1 vs 11.2%), neutropenia (23.1 vs 3.0%), weight decreased (17.1 vs 6.7%), neutrophil count decreased (14.5 vs 1.5%), white blood cell count decreased (14.5 vs 1.5%), alopecia (13.7 vs 4.5%), stomatitis (13.7 vs 6.0%), mucosal inflammation (10.2 vs 3.7%), and platelet count decreased (10.3 vs 2.2%). Grade 3 or higher TEAEs that were reported by a higher percentage (≥2%) of patients in the combination arm than the control arm were neutropenia (14.5 vs 0.7%), fatigue (13.7 vs 3.7%), diarrhoea, (12.8 vs 4.5%), vomiting (11.1 vs 3.00%), neutrophil count decreased (10.3 vs 0.7%), anaemia (9.4 vs 6.7%), nausea (7.7 vs 3.0%), decreased appetite (4.3 vs 2.2%), dehydration (4.3 vs 1.5%), sepsis (3.4 vs 0.7%), white blood cell count decreased (7.7 vs 0%), and gastroenteritis (2.6 vs 0%).

The most common TEAEs were generally similar in the nal-iri monotherapy arm compared with the nal-iri + 5-FU/LV combination arm with some notable differences. Certain gastrointestinal AEs (such as diarrhoea and nausea), alopecia, hypoalbuminemia, hypomagnesaemia, hypokalaemia and asthenia were more commonly reported in the monotherapy arm, while myelosuppression (such as neutropenia, leukopenia, white blood cell count decreased, anaemia and platelet count decreased) and stomatitis were more common in the combination arm. It is important to note that the frequency of severe TEAEs (Grade 3 or higher) was generally higher in the monotherapy arm than in the combination arm (with the exception of neutropenia, white cell count decreased, neutrophil count decreased, and fatigue). This suggests that the more frequent administration of nal-iri (every 2 weeks compared with every 3 weeks) with a lower dose, as in the nal-iri + 5-FU/LV combination arm compared with the nal-iri monotherapy arm, results in fewer and less severe gastrointestinal AEs. Also of note is that there were no reports of hand-foot syndrome during the study, which can be associated with irinotecan and PEGylated liposomal doxorubicin therapy.

Overall, 85.7% of patients in the nal-iri monotherapy arm, 64.1% in the nal-iri + 5-FU/LV arm, and 76.9% in the 5-FU/LV control arm died during the study. The majority of deaths were attributed to pancreatic cancer in each treatment arm. Treatment-emergent deaths that were attributed to AEs were more frequently reported in the nal-iri monotherapy arm (6.8%) than the nal-iri + 5-FU/LV combination arm (2.6%) and the 5-FU/LV control arm (2.2%). Treatment-emergent serious adverse events (SAEs) were more common in the nal-iri monotherapy arm (61.2%) than in the combination arm (47.9%) and the 5-FU/LV control arm (44.8%). The most commonly reported (>5%) treatment-emergent SAEs reported in the nal-iri-containing arms were diarrhoea and vomiting, while the most common treatment-emergent SAE in the control arm was abdominal pain (4.5%).

Study treatment discontinuation due to a TEAE was infrequent (11.6% in the nal-iri monotherapy arm, 11.1% in the combination arm, and 7.5% in the 5-FU/LV control arm). The higher frequency of discontinuation in the nal-iri-containing arms was most likely due to gastrointestinal disorders and infections. Dose delay was most common in the nal-iri + 5-FU/LV arm (61.5% vs 31.3% in the nal-iri monotherapy arm and 32.1% in the 5-FU/LV control arm), which was primarily due to neutropenia and neutrophil count decreased. Dose reduction was more common in the nal-iri-containing arms (31.3% in the monotherapy arm and 33.3% in the combination arm) compared with the 5-FU/LV control arm (3.7%). As anticipated, the most common reasons for dose reduction in the nal-iri-

containing arms were myelosuppression (primarily neutropenia and neutrophil count decreased) and gastrointestinal disorders (primarily nausea, vomiting and diarrhoea).

There were 7 patients in each nal-iri-containing arm who were homozygous for the UGT1A1*28 allele and therefore initiated nal-iri therapy at a lower dose. Only 1 of these 14 patients discontinued study treatment due to an AE. A safety comparison with patients with the heterozygous phenotype is difficult because of the small number of patients in this subgroup, however no obvious large differences in the frequency or severity of TEAEs were detected.

Among haematological abnormalities, decreased haemoglobin was very common in all treatment arms, reported by 95.2% of patients in the nal-iri monotherapy arm, 96.5% in the nal-iri + 5-FU/LV combination arm, and 85.7% in the 5-FU/LV control arm. However, the frequency of Grade 3 decreased haemoglobin was low (6.8%, 6.1%, and 4.5%, respectively), and no Grade 4 events were reported.

Laboratory evaluation results that were more frequently reported in the nal-iri-containing arms than the control arm were decreased neutrophils, increased ALT, decreased albumin, decreased potassium, decreased magnesium, decreased sodium, and weight decrease.

Overall, the safety profiles of nal-iri monotherapy and nal-iri + 5-FU/LV combination therapy were consistent with prior experience with nal-iri and with the safety profile of irinotecan and 5-FU. The nal-iri + 5-FU/LV combination was better tolerated than nal-iri monotherapy, most likely due to less frequent and less severe gastrointestinal AEs, despite a higher incidence of neutropenia overall.

4.12.2.2 NCT00813163

Patients received a mean of 5.875 cycles of nal-iri monotherapy, with 11 patients (27.5%) receiving at least eight treatment cycles. The starting dose of 120 mg/m^2 showed cause for concerns of excess toxicity, primarily asthenia, and so the protocol was amended to permit a lower starting dose of 100 mg/m^2. A total of 27 patients (67.5%) were able to maintain a dose of 120 mg/m^2 throughout their entire treatment course, and the majority of patients (75.0%) discontinued due to disease progression rather than toxicity.

As expected, gastrointestinal and haematologic events were among the most common toxicities observed during nal-iri treatment. Fatigue and abdominal pain were also common, which may have been related to the study treatment or the underlying cancer. A total of 26 patients (65%) reported at least one Grade 3 or higher TEAE during the study, and six patients died within 30 days of the last dose of study treatment. Cause of death was disease progression in three of these patients; the other three deaths were due to respiratory failure, aspiration pneumonia, and sepsis, all in the setting of neutropenia.

Overall, nal-iri was generally well tolerated in most patients, with manageable and predictable toxicities.

4.13 *Interpretation of clinical effectiveness and safety evidence*

4.13.1 *Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

NAPOLI-1 evaluated the efficacy and safety of nal-iri 80 mg/m^2 in combination with 5-FU 2,400 mg/m^2 over 46 hours and leucovorin 400 mg/m^2 IV every 2 weeks, compared with an active control arm consisting of 5-FU 2,000 mg/m^2 IV over 24 hours and leucovorin 200 mg/m^2 IV administered weekly for 4 weeks, followed by 2 weeks of rest, in patients with metastatic pancreatic cancer who have previously been treated with gemcitabine. A third arm in the trial with patients receiving nal-iri monotherapy 120 mg/m^2 administered every 3 weeks was not relevant for this submission, but was included in the safety section to increase the amount of safety data available for nal-iri.

Of 577 patients screened, 417 were randomised and included in the ITT population. Overall, the baseline characteristics of these patients were considered representative of a pre-treated, metastatic pancreatic cancer population and were balanced across treatment groups.

The nal-iri + 5-FU/LV arm met its primary endpoint of superiority over 5-FU/LV with a median OS of 6.1 months compared with 4.2 months in the control arm, representing a clinically relevant 45% increase that was statistically significant (p=0.012). Additionally, all sensitivity analyses supported this primary OS analysis of the nal-iri + 5-FU/LV combination.

The secondary endpoint of PFS was approximately twice as long with nal-iri + 5-FU/LV (3.1 months) compared with 5-FU/LV (1.5 months), and the difference was statistically significant (p=0.0001). The objective response rate was also higher, with 16.2% achieving unconfirmed objective response in the nal-iri + 5-FU/LV arm compared with 0.8% in the 5-FU/LV arm. These results strongly support the primary endpoint analysis.

The other secondary endpoints, TTF and CA19-9 response rate, also support the superior efficacy of nal-iri + 5-FU/LV compared with 5-FU/LV shown by the primary endpoint of OS. TTF indicated that patients stayed on treatment for longer with nal-iri + 5-FU/LV (2.3 months) compared with 5-FU/LV (1.4 months), and a higher proportion of patients achieved CA19-9 tumour marker response (28.9% vs 8.6%, respectively).

Although the dose and schedule of infusional 5-FU and LV regimens were different in both arms, the superior efficacy observed in the nal-iri + 5-FU/LV arm is due to the addition of nal-iri to 5-FU/LV and not to the difference in the 5-FU dose and schedule, since the dose intensity of 5-FU was substantially higher in the 5-FU/LV control arm.

Further data supporting the efficacy of nal-iri in patients with metastatic pancreatic cancer previously treated with gemcitabine were provided by the phase II trial, NCT00813163. This study also met its primary endpoint, with 75% of patients achieving $OS_{3\text{-month}}$. Median PFS and OS were 2.4 and 5.2 months, respectively, and disease control was achieved by 50% of patients. In addition, 31.3% of patients with elevated CA19-9 at baseline showed >50% biomarker decline, and 20% of CBR-evaluable patients achieved significant clinical benefit.

The safety profile of nal-iri monotherapy and the nal-iri + 5-FU/LV combination in NAPOLI-1 was consistent with prior experience with nal-iri and 5-FU/LV. Nal-iri is liposomal irinotecan, so, as anticipated, the most common AEs in the nal-iri-containing arms were similar to the known safety profile of irinotecan. Gastrointestinal events (diarrhoea, nausea and vomiting) were the most common adverse reactions in the nal-iri-containing arms. More frequent and severe gastrointestinal AEs were observed in the nal-iri monotherapy arm compared with the nal-iri + 5-FU/LV combination arm, suggesting that the more frequent administration of nal-iri with a lower dose results in fewer and less severe gastrointestinal AEs. As specified in the protocol, dose delays, dose reductions, and use of prophylactic measures including adequate hydration and symptomatic treatment are warranted when using nal-iri. Gastrointestinal AEs were generally tolerated, and the number of patients discontinuing treatment due to gastrointestinal events was low. Electrolyte abnormalities, such as hypokalaemia, hypomagnesaemia, and hyponatraemia, which are commonly associated with diarrhoea, were more frequently observed in the nal-iri-containing arms compared with the 5-FU/LV control arm, and they too were most frequent and severe with nal-iri monotherapy.

Myelosuppression, especially neutropenia, was more frequent and severe in the nal-iri-containing arms than in the 5-FU/LV control arm, and were most frequent in the nal-iri + 5-FU/LV combination arm. Dose delay, dose reduction, and colony stimulating factors were used to manage myelosuppression. Treatment discontinuation due to myelosuppression was low. Thrombocytopenia was infrequent, as has been documented with non-liposomal irinotecan.

There were four deaths assessed as related to treatment in the nal-iri monotherapy arm, one in the nal-iri + 5-FU/LV arm, and none in the 5-FU/LV control arm.

Despite additional toxicity, health-related quality of life (HRQoL) assessment showed no substantial differences in the proportion of patients who demonstrated improvement or decline in the QoL scores between the nal-iri + 5-FU/LV arm and the 5-FU/LV arm. This is an important measure in patients with metastatic pancreatic cancer, who are generally in poor health from the effects of the underlying disease and previous treatments.

In trial NCT00813163, as expected, gastrointestinal and haematologic AEs were among the most common toxicities reported during nal-iri monotherapy. Fatigue and abdominal pain were also common.

Overall, the results of NAPOLI-1 show that nal-iri in combination with 5-FU/LV is a clinically efficacious and manageable treatment for patients with metastatic pancreatic cancer who have previously been treated with gemcitabine. The phase II trial NCT00813163 supported this.

The NICE scope outlines the following comparators:

- Oxaliplatin in combination with fluorouracil and folinic acid
- Oxaliplatin in combination with capecitabine
- Fluoropyrimidine monotherapy

After a systematic literature review of the clinical evidence available for these treatments (Section 4.1), a feasibility assessment was performed for an indirect comparison between the treatments (Section 4.10.1). This feasibility assessment clearly showed that

an indirect comparison was not possible between nal-iri + 5-FU/LV and any capecitabine treatment regimens. In addition, it was not feasible for a comparison between nal-iri + 5-FU/LV and oxaliplatin + 5-FU/LV due to heterogeneity and limited reporting of the studies, which was supported by a panel of experts (Section 4.10.2).

Clinical expert opinion has revealed that in the UK, 20–40% of patients are well enough to receive active treatment post-gemcitabine. Of these, the majority receive one of the FOLFOX regimens containing folinic acid (leucovorin, LV), 5-FU and oxaliplatin. Very few patients receive oxaliplatin in combination with capecitabine or fluoropyrimidine monotherapy as post-gemcitabine treatment.

Comparators in the economic evaluation described in Section 5 included 5-FU/LV and oxaliplatin + 5-FU/LV. NAPOLI-1 compared nal-iri + 5-FU/LV with 5-FU/LV, and so direct evidence could be used in the economic analysis. 5-FU/LV was used as the control arm in NAPOLI-1 due to its history of being one of the mainstays of therapy for pancreatic cancer, and at the time of the development of the trial protocol for NAPOLI-1, 5-FU was one of the standard treatments for pancreatic cancer (20, 21). Despite a feasibility assessment and KOL feedback demonstrating that an indirect comparison between oxaliplatin + 5-FU/LV with nal-iri + 5-FU/LV was not feasible due to heterogeneity of the trials, an indirect comparison was performed in order to compare these two treatments, since clinical expert opinion is that FOLFOX is the most commonly used treatment post-gemcitabine. As such, several major assumptions for this comparison were required, as described in Section 5.6.2, and hence the results should be treated with caution. Limitations of this analysis are described in Section 5.6.3. There were no available data suitable for a comparison between nal-iri + 5-FU/LV and oxaliplatin + capecitabine.

4.13.2 *Strengths and limitations of the clinical evidence base for the technology*

4.13.2.1 Strengths

1. Design features of NAPOLI-1

    - NAPOLI-1 is a high quality, multi-centre, multi-national, randomised controlled trial that provides the pivotal evidence supporting the regulatory approval of nal-iri for the treatment of metastatic pancreatic cancer in adult patients who have previously been treated with gemcitabine.
    - The primary endpoint of OS is considered the most reliable endpoint for cancer studies, as it is an objective and direct measure of the treatment benefit that is most clinically meaningful to this patient population (89).
    - The relatively large number of patients in this trial and the consistency of the results in a diverse population at multiple medical centres worldwide supports the robustness of the results.
    - The current standard of care for patients with pancreatic cancer is gemcitabine, however there is currently no approved treatment for patients following gemcitabine therapy. At the time of the development of the trial protocol for NAPOLI-1, 5-FU was one of the standard treatments for pancreatic cancer (20, 21), therefore this comparator was deemed to be the most appropriate. In addition, 5-FU/LV is used in combination with

nal-iri in the experimental arm, and so the extra effect from the addition of nal-iri can be determined, even though 5-FU/LV was dosed in a slightly different way in the two arms.

2. Representativeness of patient population and generalisability to UK clinical practice
    - The patient population recruited to NAPOLI-1 is representative of patients included in the licensed indication and the population that would be treated in routine clinical practice in the UK.
3. Value of clinical outcomes observed with nal-iri
    - Patients with pancreatic cancer typically have a very short survival time, and this is likely to be even shorter in patients with metastases that have previously been treated with gemcitabine. Therefore a 45% proportional increase in overall survival, as seen in NAPOLI-1 with nal-iri + 5-FU/LV over 5-FU/LV, represents a significant improvement in survival in these currently under-served patients and is likely to be of great value to the patient and their family.

4.13.2.2 Limitations

Comparator regimen used in the 5-FU/LV control arm of NAPOLI-1 is different to the 5-FU/LV dosing schedule used in the experimental nal-iri + 5-FU/LV arm

- The control arm was set up to be dosed in the same way as the 5-FU/LV control arm in CONKO-003, but 5-FU/LV in the experimental arm with nal-iri + 5-FU/LV was optimised for the combination. When the nal-iri + 5-FU/LV arm was added to the trial (after protocol amendment as described in Section 4.3.3.2), the control regimen was not changed because 63 patients had already been treated with the original schedule, and so changing it would render the data from these patients invalid for the final analysis of the trial results.
- Although the 5-FU/LV dosing schedules were different between the two arms, it is highly unlikely that this created a bias in favour of the nal-iri + 5-FU/LV arm, since the planned and recorded dose intensities of 5-FU were higher in the control arm. In addition, patients in the control arm of NAPOLI-1 performed better than patients in the control arm of CONKO-003, with overall survival being 4.2 months in NAPOLI-1 and 3.3 months in CONKO-003.

4.13.2.3 End-of-life criteria

Table 34: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	A systematic review of real-world, peer reviewed, observational European studies (n=91) found that the median life expectancy at diagnosis was 4.6 months in patients with pancreatic cancer irrespective of stage of diagnosis, and the median survival for patients with metastatic disease was 2.8–5.7 months (7).
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	Median OS was 6.1 months in the nal-iri + 5-FU/LV group compared with 4.2 months in the 5-FU/LV group. While the increased survival of 1.9 months is below the 3 months specified in the end-of-life criteria, it represents a 45% increase that would be of substantial benefit to these patients, given the very short life expectancy at diagnosis.
The treatment is licensed or otherwise indicated for small patient populations	The 10-year prevalence of pancreatic cancer in 2006 was 4,349 (47). In 2012 the 5-year prevalence was 3,522 (90).

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; NHS, National Health Service; OS, overall survival.

4.14 *Ongoing studies*

There are no completed or ongoing company-sponsored trials of nal-iri + 5-FU/LV in patients with pancreatic cancer from which new evidence will be reported in the next 12 months. There is one phase I study (NCT02640365) investigating dose escalation of nal-iri + irinotecan in patients with unresectable advanced non-colorectal cancer (not necessarily pancreatic cancer). The study is currently recruiting 33–57 patients for this arm.

5 Cost effectiveness

5.1 *Published cost-effectiveness studies*

5.1.1 *Identification of studies*

A systematic review was conducted to identify cost-effectiveness studies from the published literature relevant to the decision problem. There were no date restrictions for the systematic review.

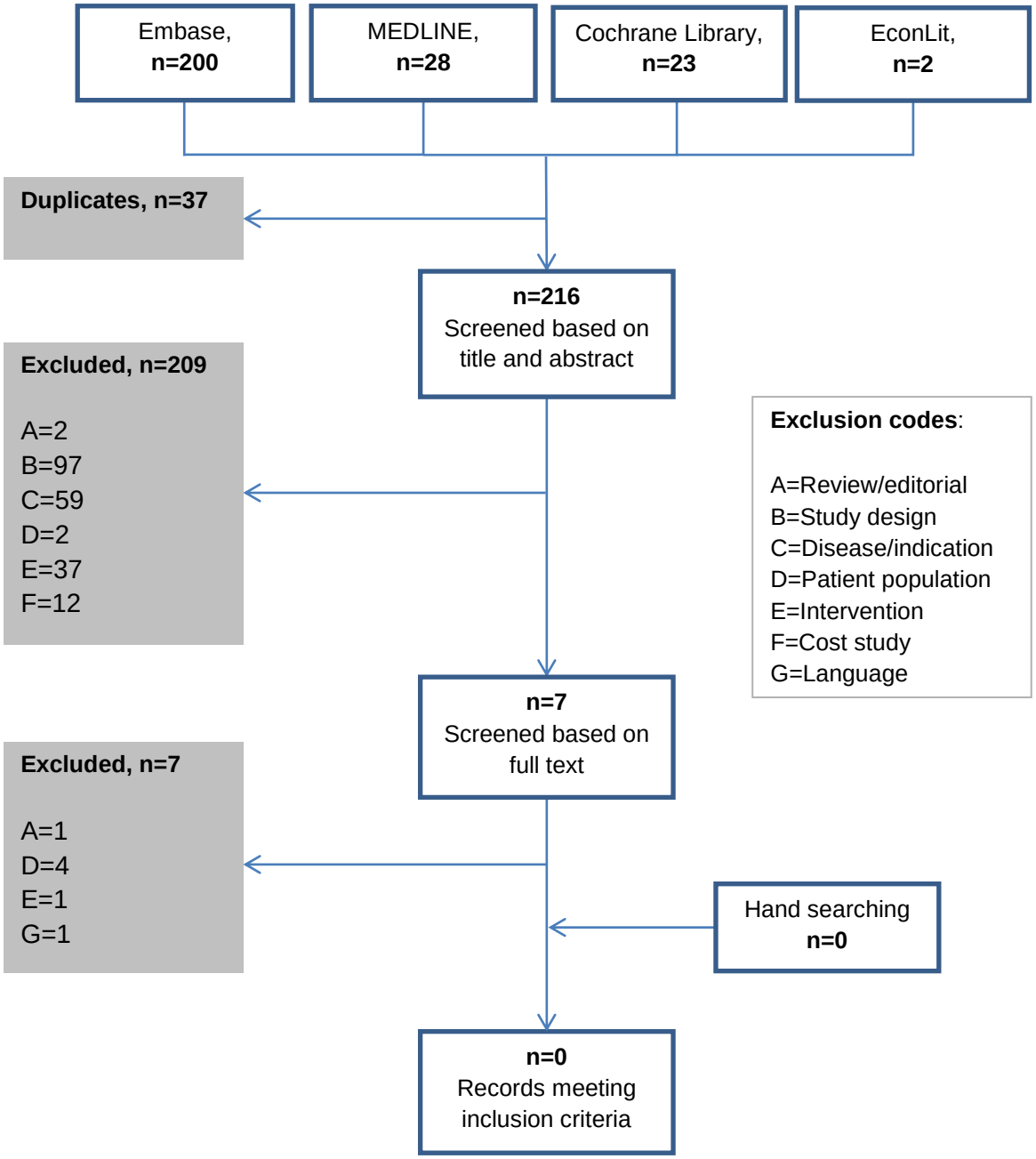
The following electronic databases were searched via the OVID platform: MEDLINE®, MEDLINE® In-Process and Other Non-Indexed Citations, Embase, EconLit, and The Cochrane Library, incorporating Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), and NHS Economic Evaluation Database (EED).

Electronic searches were supplemented by hand searching the following sources: reference lists of included studies and relevant systematic reviews, the Cost-Effectiveness Analysis (CEA) Registry, Research Papers in Economics (RePEc), conference proceedings, and previous HTA submissions/appraisals.

Full details of the search are provided in Appendix 7.

In total, 253 papers were identified through the electronic searches. Upon the removal of 37 duplicate papers, 216 titles and abstracts were reviewed. Seven records were ordered for full paper review, of which all seven were excluded, resulting in no relevant papers identified for final inclusion. In addition, no publications meeting the eligibility criteria were identified via hand searching (Figure 7).

Figure 7: Schematic for the systematic review of cost-effectiveness evidence



A full list of records excluded at full text review is provided in Appendix 7.

5.2 *De novo analysis*

The cost-effectiveness model was developed according to guidance published by NICE (91), the NICE Decision Support Unit (DSU) (92-94), and international good research practices for modelling (95, 96), to ensure that the analysis was as methodologically rigorous as possible.

5.2.1 *Patient population*

The population in the model is the patient population from NAPOLI-1. This is in line with the target indication (adult patients with metastatic adenocarcinoma of the pancreas who have progressed following gemcitabine-based therapy).

5.2.1.1 Inclusion criteria

In order to be included in NAPOLI-1, patients were required to have:

1. Histologically or cytologically confirmed adenocarcinoma of exocrine pancreas
2. Documented metastatic disease; disease status was permitted to be measurable or non-measurable as defined by RECIST v1.1 guidelines (81)
3. Documented disease progression after prior gemcitabine or gemcitabine-containing therapy, in locally advanced or metastatic setting. Examples of permitted therapies included, but were not limited to:
    - Single agent gemcitabine
    - Any one gemcitabine-based regimen, with or without maintenance gemcitabine
    - Single agent gemcitabine to which a platinum agent, a fluoropyrimidine, or erlotinib was subsequently added
    - Gemcitabine administered in the adjuvant setting, if disease recurrence occurred within 6 months of completing the adjuvant therapy
4. Karnofsky Performance Status (KPS) ≥70
5. Adequate bone marrow reserves as evidenced by:
    - Absolute neutrophil count (ANC) >1,500 cells/µL without the use of hematopoietic growth factors; and
    - Platelet count > 100,000 cells/µL; and
    - Haemoglobin > 9 g/dL (blood transfusions were permitted for patients with haemoglobin levels below 9 g/dL)
6. Adequate hepatic function as evidenced by:
    - Serum total bilirubin within normal range for the institution (biliary drainage was allowed for biliary obstruction)
    - Albumin levels ≥3.0 g/dL
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN; ≤5 x ULN was acceptable if liver metastases were present
7. Adequate renal function as evidenced by serum creatinine ≤1.5 x ULN
8. Normal ECG, or ECG without any clinically significant findings
9. Recovered from the effects of any prior surgery, radiotherapy or other anti-neoplastic therapy
10. At least 18 years of age

11. Able to understand and sign an informed consent (or have a legal representative who is able to do so).

5.2.1.2 ITT population

The summary demographics of the ITT population are provided in Table 35.

Table 35: Summary demographics – ITT population

Characteristic	Nal-iri + 5-FU/LV N=117	5-FU/LV N=119†
Sex, n (%)		
Female	48 (41.0)	52 (43.7)
Male	69 (59.0)	67 (56.3)
Age, years		
Mean (SD)	63.2 (9.06)	61.0 (9.46)
Median	63.0	62.0
Min, Max	41, 81	34, 80
Height, cm		
Mean (SD)	167.5 (9.64)	166.7 (10.10)
Min, Max	142, 189	147, 193
Weight, kg		
Mean (SD)	65.9 (14.87)	66.1 (18.33)
Min, Max	40, 123	37, 151
BMI, kg/m^2		
Mean (SD)	23.33 (4.134)	23.57 (5.054)
Min, Max	16.0, 43.5	16.7, 42.9

Abbreviations: BMI, body mass index; 5-FU, 5-fluorouracil; LV, leucovorin; SD, standard deviation.
†This group is a subset of the 5-FU/LV total control group, containing patients who were enrolled in the study after protocol version 2 was activated (the addition of the nal-iri + 5-FU/LV combination arm).

5.2.2 *Model structure*

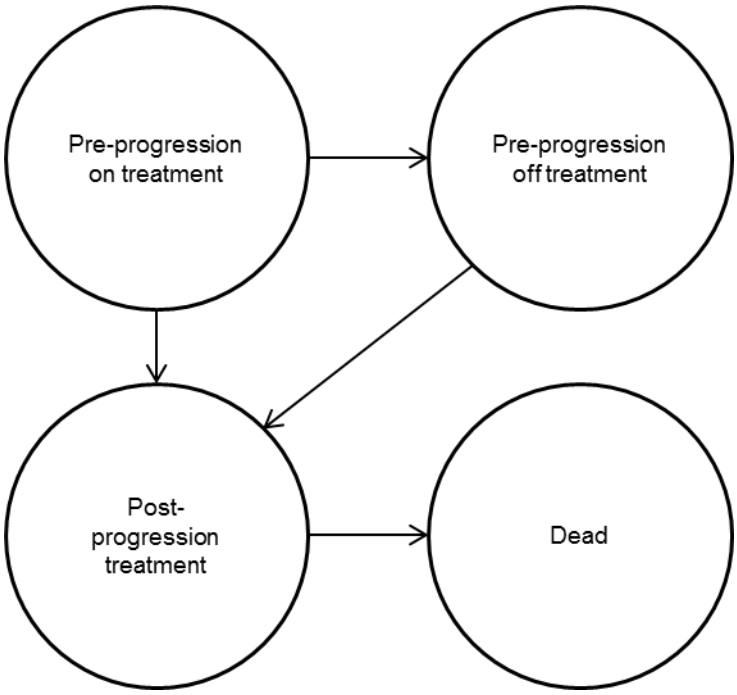
The objective of the cost-effectiveness model is to evaluate the combination therapy of nal-iri + 5-FU/LV as a treatment in metastatic pancreatic carcinoma (mPC) patients who have progressed following gemcitabine-based therapy. The model adopts the perspective of the UK NHS, and uses partitioned survival analysis to project the expected clinical and health economic outcomes of nal-iri + 5-FU/LV or 5-FU/LV in the model defined population.

A partitioned survival analysis model was used for the economic evaluation because it allows the long-term projection of the proportion of patients in health states defined by progression status and death. Additionally, using a model with states defined by PFS and OS is consistent with clinical outcomes employed in oncology trials, and specifically with those used in NAPOLI-1.

Partitioned survival analysis models commonly feature three mutually-exclusive health states: ‘alive with no progression’, ‘alive with progression’, and ‘dead’. In reality, some

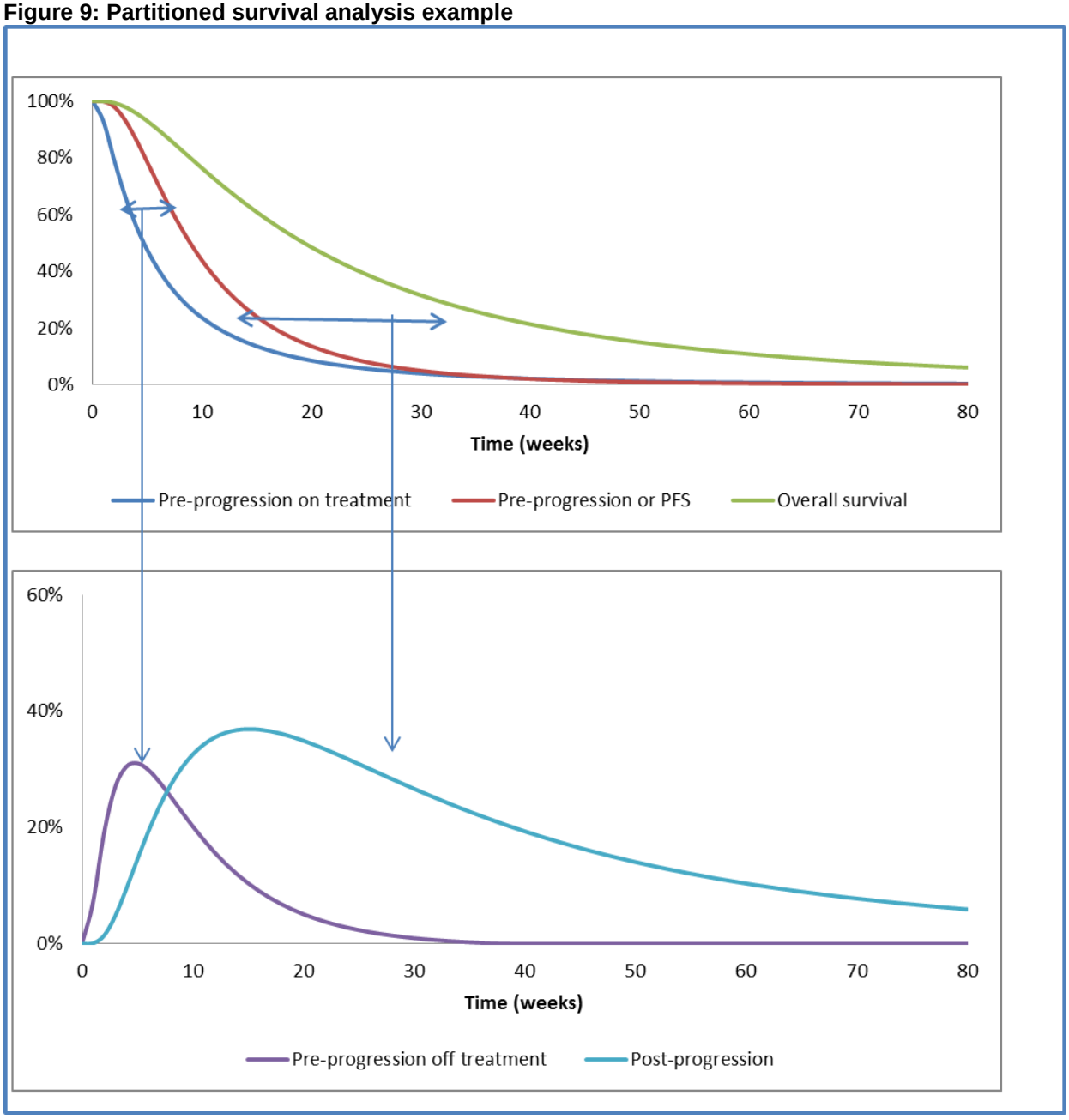
patients in the ‘alive with no progression’ state may discontinue treatment earlier due to toxicity and other treatment-related issues. To avoid overestimation of drug costs, we split the ‘alive with no progression’ into two states: ‘pre-progression on treatment’ and ‘pre-progression off treatment’, resulting in a four-state partitioned survival analysis model (Figure 8).

Figure 8: Model structure



The partitioned survival analysis model estimates the expected proportion of patients in each health state at any time point after the initiation of treatment. An example of a partitioned survival analysis model is shown in Figure 9.

Figure 9: Partitioned survival analysis example



Abbreviations: PFS, progression-free survival.

The mean survival time after progression can be calculated as the difference between the area under the OS curve and the PFS curve. Area under the curve (AUC) was calculated based on numerical integration, following the trapezoidal rules. Taking the example of the mean life year estimated in the first year, approximated by 52 weeks, the formula is shown as below:

$$\sum_{i=1}^{52}(t_i - t_{i-1})(S(t_i) + S(t_{i-1}))/2 = (\sum_{i=1}^{52} t_i S(t_{i-1}) - \sum_{i=1}^{52} t_{i-1} S(t_i) + t_{52} S(t_{52}) - t_0 S(t_0))/2$$

Given the limited life expectancy after diagnosis, a short model time cycle of one week was used to allow for the more precise capture of the changes in life years, quality-adjusted life years (QALYs), and costs, avoiding the need for a half-cycle correction.

5.2.2.1 Key features of the de novo analysis

A summary of the de novo analysis is shown in Table 36.

Table 36: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	10 years	mPC has a very poor prognosis and is uniformly fatal with a short life expectancy. Patients have a mean survival of 2–6 months and an overall survival rate of less than 4% at 5 years. Assuming a relatively constant monthly hazard of death, almost all patients would be deceased within 10 years, and therefore this model approximates a lifetime projection for mPC patients. This is consistent with the recommended good practice for cost-effectiveness analysis.
Were health effects measured in QALYs; if not, what was used?	Health effects are measured in QALYs	As per NICE reference case.
Discount of 3.5% for utilities and costs	3.5% discount for utilities and costs	As per NICE reference case.
Perspective	NHS	As per NICE reference case.

Abbreviations: mPC, metastatic pancreatic adenocarcinoma; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; PSS, Personal Social Services; QALY, quality-adjusted life year.

5.2.3 *Intervention technology and comparators*

The model is based directly on evidence from NAPOLI-1, with 5-FU/LV as the main comparator in the base case analysis. To confirm the most appropriate comparators in UK clinical practice, KOL interviews were performed to obtain clinical expert opinion. KOLs estimated that approximately 40% of post-gemcitabine mPC patients that are eligible for further treatment would receive the FOLFOX 4 or 6 regimens containing folinic acid, 5-fluorouracil and oxaliplatin. FOLFOX was also used in the reference case analysis.

5.3 *Clinical parameters and variables*

5.3.1 *Endpoints*

OS and PFS data from the final data cut (March 2016) of NAPOLI-1 were used to inform the clinical parameters in the de novo analysis. Parametric distributions were used to fit the OS and PFS curves from NAPOLI-1, which were used to model the transition of patients between health states.

5.3.2 *How are clinical data incorporated into the model?*

To decide the format of parametric model used for the partitioned survival analysis, patient-level data from NAPOLI-1 were used to generate Kaplan-Meier curves for the treatment and control arms, and parametric models were then fitted to the data to compare the goodness of fit. The parametric models enable the cost-effectiveness models to extrapolate beyond the trial period to capture the full survival benefits.

A wide range of parametric models are available and each has its own characteristics suitable to different datasets. Six standard parametric models (exponential, Weibull, Gompertz, log-logistic, log-normal and gamma) were compared according to the goodness of fit to the observed data and clinical and biological plausibility of the extrapolation data. Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics were used to assess the goodness of fit between observed Kaplan-Meier data and the parametric model estimates over time. However, neither measure is ideal for use in model selection, because neither provide any measure of the relative appropriateness of the functional form for the extrapolated portion (93).

Of the six parametric forms considered, gamma, log-normal, and log-logistic had the three lowest AIC and BIC (the lower the AIC and BIC, the better model fit), suggesting a superior fit to the observed data than the other model forms. Despite the best data fit, gamma function was considered inappropriate because its expected survival on the control arm was much longer than that on the intervention arm, resulting in a survival deficit of 0.1 years. In addition, unlike other parametric models in which all patients decease soon after treatment initiation, the gamma model allows a chance, albeit very small, of survival beyond 20 years, which is deemed to be clinically implausible. Therefore, a log-normal model was selected as the base case for survival modelling. Results using log-logistic were also presented as a scenario analysis (see Section 5.8.3).

5.3.2.1 Log-normal

The log-normal distribution has two parameters: μ and σ, the hazard initially increases to a maximum and then decreases as time increases. The survival function for this distribution can be written as:

$$\boldsymbol{S(t) = 1 - \Phi((\log(t) - \mu)/\sigma)},$$

where Φ is the standard normal distribution function.

Mean	$\text{Exp}(\mu + \sigma^2/2)$
Median	$\text{Exp}(\mu)$

Table 37 shows the log-normal survival function parameters, and Figure 10 and Figure 11 show the log-normal fit to OS and PFS, respectively.

Table 37: Log-normal survival function parameters

Log-normal survival function parameters	Nal-iri + 5-FU/LV	5-FU/LV
PFS		
mu (μ)	1.25	0.74
sigma (σ)	0.949	0.768

Observed median, months	3.1	1.5
Median, months	3.47	2.09
Mean, months	5.45	2.81
AIC	496	369
OS		
mu (μ)	1.91	1.54
sigma (σ)	0.908	1.00
Observed median, months	6.2	4.2
Median, months	6.24	4.67
Mean, months	10.18	7.66
AIC	675	598
Time on treatment		
mu (μ)	0.553	0.093
sigma (σ)	1.394	1.096
Observed median, months	1.6	0.76
Median, months	1.7	1.10
Mean, months	4.6	2.0
AIC	534	344

Abbreviations: AIC, Akaike information criteria; 5-FU, 5-fluorouracil; LV, leucovorin; OS, overall survival; PFS, progression-free survival.

Figure 10: Log-normal fit to overall survival

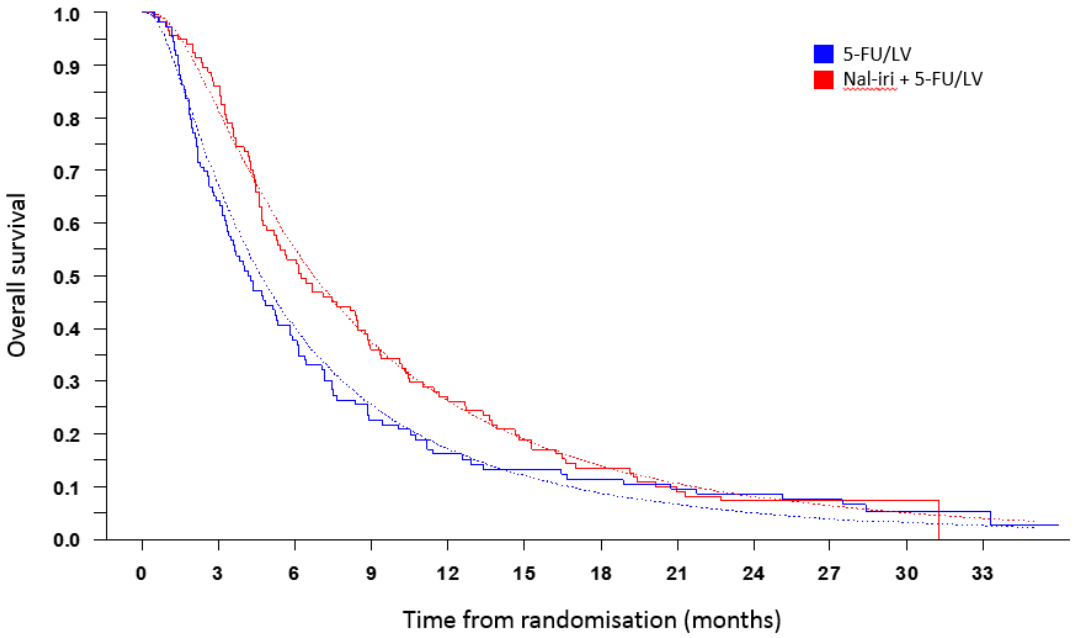
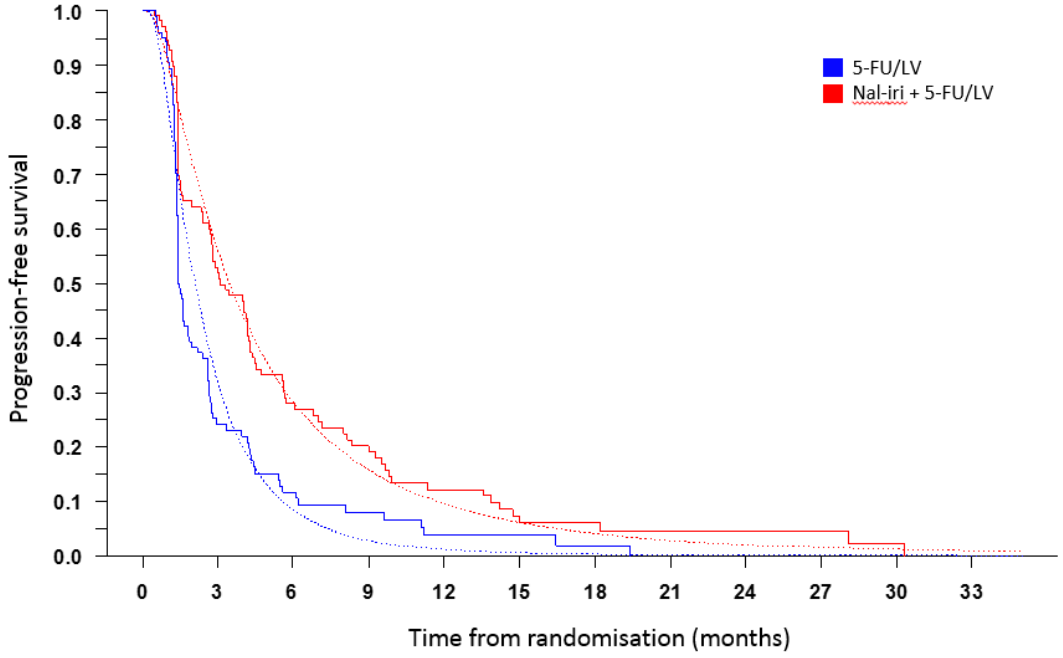


Figure 11: Log-normal fit to progression-free survival



5.3.2.2 Log-logistic

The log-logistic model is similar to the log-normal model as it has a hazard function that can be non-monotonic over time. The survivor function for this distribution can be written as:

$$S(w) = (1 + \exp((\log(t) - \mu)/\sigma))^{(-1)}.$$

Mean	Exp(μ)*π*σ / sin(π*σ)
Median	Exp(μ)

Table 38 shows the log-logistic survival function parameters, and Figure 12 and Figure 13 show the log-logistic fit to OS and PFS, respectively.

Table 38: Log-logistic survival function parameters

Log-logistic survival function parameters	Nal-iri + 5-FU/LV	5-FU/LV
PFS		
mu (μ)	1.20	0.64
sigma (σ)	0.562	0.421
Observed median, months	3.1	1.5
Median, months	3.32	1.89
Mean, months	5.98	2.59
AIC	501	365
OS		
mu (μ)	1.91	1.49

sigma (σ)	0.518	0.576
Observed median, months	6.2	4.2
Median, months	6.72	4.42
Mean, months	10.95	8.22
AIC	675	600
Time on treatment		
mu (μ)	0.599	0.045
sigma (σ)	0.791	0.599
Observed median, months	1.6	0.76
Median, months	1.8	1.0
Mean, months	7.4	2.1
AIC	536	341

Abbreviations: AIC, Akaike Information Criteria; 5-FU, 5-fluorouracil; LV, leucovorin; OS, overall survival; PFS, progression-free survival.

Figure 12: Log-logistic fit to overall survival

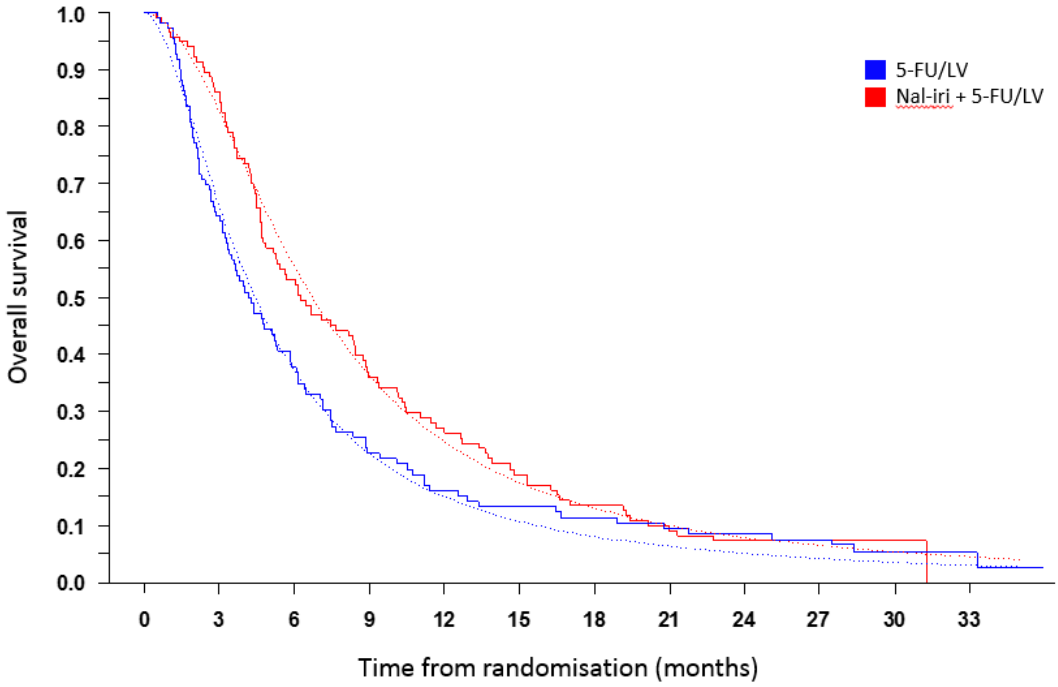
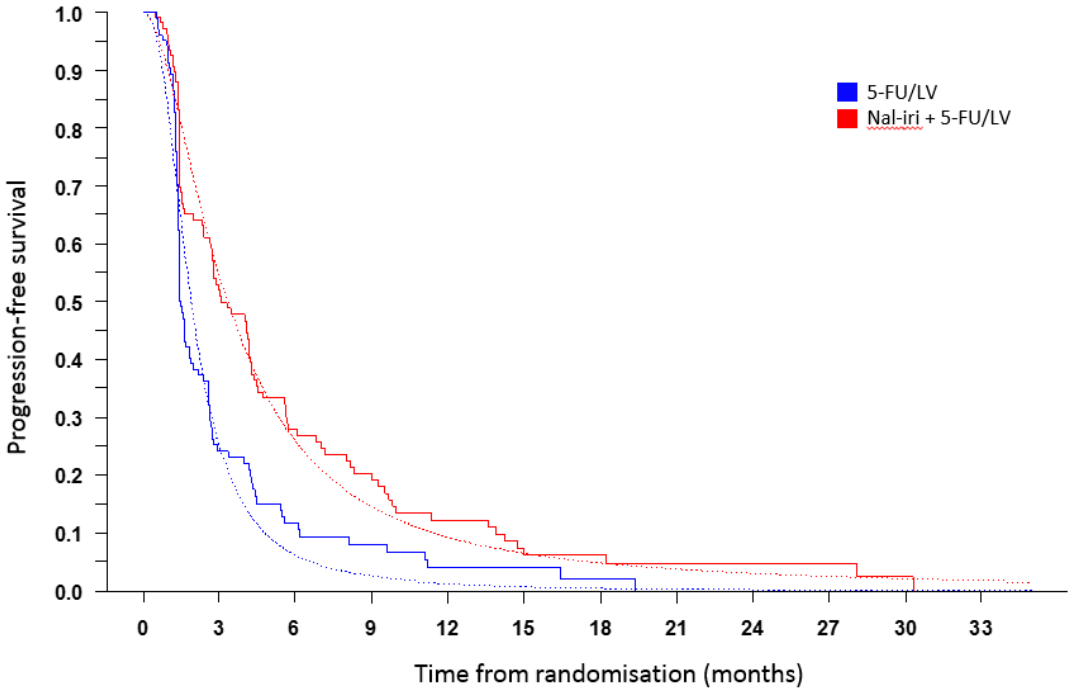


Figure 13: Log-logistic fit to progression-free survival



5.3.2.3 Including oxaliplatin + 5-FU/LV

To include oxaliplatin + 5-FU/LV in the economic evaluation, an indirect analysis was performed combining the results from NAPOLI-1, CONKO-003 and PANCREOX. To conduct this analysis, it was necessary to assume that the dosing regimens were equivalent for oxaliplatin + 5-FU/LV, i.e. the dosing regimen for mFOLFOX6 was the same as for OFF. The Bucher adjusted indirect comparison method (97) was utilised to calculate a hazard ratio for PFS and OS between nal-iri + 5-FU/LV and oxaliplatin + 5-FU/LV. Figure 14 shows the indirect treatment comparison (ITC) network.

Figure 14: ITC network: Combining CONKO-003 and PANCREOX

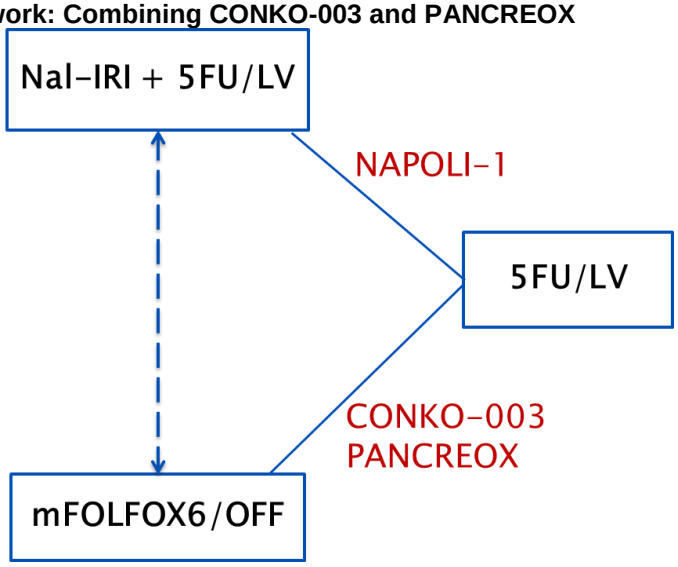


Table 39 shows the results of the indirect analysis.

Table 39: Hazard ratios for nal-iri vs oxaliplatin + 5-FU/LV

Comparison	ITC HR of PFS	ITC HR of OS
Nal-iri + 5-FU/LV vs oxaliplatin + 5-FU/LV	0.70	0.63

Abbreviations: 5-FU, 5-fluorouracil; HR, hazard ratio; ITC, indirect treatment comparison; LV, leucovorin; OS, overall survival; PFS, progression-free survival.

The hazard ratios have been applied to the log-normal distribution used for nal-iri + 5-FU/LV; however, underlying assumptions must be made. These include assuming proportional hazards when applying the hazard ratios, however the proportional hazards assumption is broken due to the KM curves for overall survival crossing in NAPOLI-1. This is the main limitation of including oxaliplatin + 5-FU/LV in the model.

5.3.3 *Transition probabilities*

Transition probabilities were not used in the model. Instead, the partitioned survival analysis model estimates the expected proportion of patients in each health state at any time point after the initiation of treatment.

5.3.4 *Clinical expert assessment of applicability of clinical parameters*

Clinical experts were not used to assess the applicability of values or to estimate values.

5.4 *Measurement and valuation of health effects*

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

NAPOLI-1 used EORTIC-QLQ-C30 to measure HRQoL. However, there was a significant amount of missing data, which precludes the practical use of this measure to generate utility values. There is a substantial and rapid decrease in patient-reported outcome (PRO) data in NAPOLI-1. Specifically, the remaining population is 48.7% by Week 6, 28.5% by Week 12, and 8.9% by Week 30. On average, each patient reported 2 time points of PRO data. Conclusions of extensive analyses of missing data in NAPOLI-1 revealed that the majority of missing data is due to discontinuation of treatment because of disease progression, adverse events, or death; i.e. the data not missing at random. Consequently, it was not possible to use multiple imputation for the missing data.

5.4.2 *Mapping*

There was no mapping carried out for HRQoL data; QoL data used in the model were derived from the literature (Section 5.4.3). The fact that the missing data were not at random precludes multiple imputation and meant that it was not possible to undertake any mapping activity. In addition, one potential mapping algorithm from EORTC-QLQ-C30 to EQ-5D was identified, Kind 2005 (98); however, this was an ASCO abstract and the algorithm was not provided.

5.4.3 *Health-related quality-of-life studies*

A systematic review was conducted to identify from the published literature HRQoL studies relevant to the decision problem. In particular, studies reporting health state utility values (HSUVs) relating to patients with metastatic (stage IV) pancreatic cancer were

considered eligible for inclusion. There were no date restrictions for the systematic review.

The following electronic databases were searched via the OVID platform: MEDLINE®, MEDLINE® In-Process and Other Non-Indexed Citations, Embase, and the Cochrane Library, consisting of the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), HTA, and the NHS Economic Evaluation Database (NHS EED).

To supplement the electronic database searches, hand-searching of the following sources was conducted: reference lists of included publications; reference lists of relevant economic evaluations and systematic reviews identified in the electronic searches; pre-specified websites; previous HTA submissions; and proceedings from three conferences. Any relevant abstracts identified through the electronic database search or supplementary hand searching were also checked for available associated posters.

Full details of the search are provided in Appendix 9.

The electronic database search identified 748 citations. Following removal of 179 duplicates, 569 citations were screened on the basis of title and abstract. Full texts of 61 publications were obtained and screened, of which 56 were excluded. One additional publication was identified via hand-searching, resulting in six relevant records for final inclusion. The study flow is presented in Figure 15.

A full list of studies excluded on the basis of full publication review is available in Appendix 9, along with a rationale for exclusion.

5.4.3.1 Studies that met the inclusion criteria of the review

A total of six full publications of four unique studies were identified (99-104). The four publications reporting primary study results reported utilities for Norway (101), Germany and the UK (99), the USA (103), and Canada (104). In addition, one publication reported utility results for Sweden (100), using Swedish health state valuations to adapt values from the German study (99) (and from an excluded study that reported utilities for resectable pancreatic cancer (105)), and one publication adapted results from the Canadian study (104) to report utilities for the UK, the USA, Denmark, France, Germany, Japan, the Netherlands, and Spain (102). Of the four studies reporting primary utility data (99, 101, 103, 104), one study reported HRQoL data collected from the CALGB 80303 RCT (103), two were prospective cohort studies designed to assess HRQoL (99, 101), and one was a cost-utility analysis that conducted a HRQoL survey to generate utility data for its economic evaluation (104).

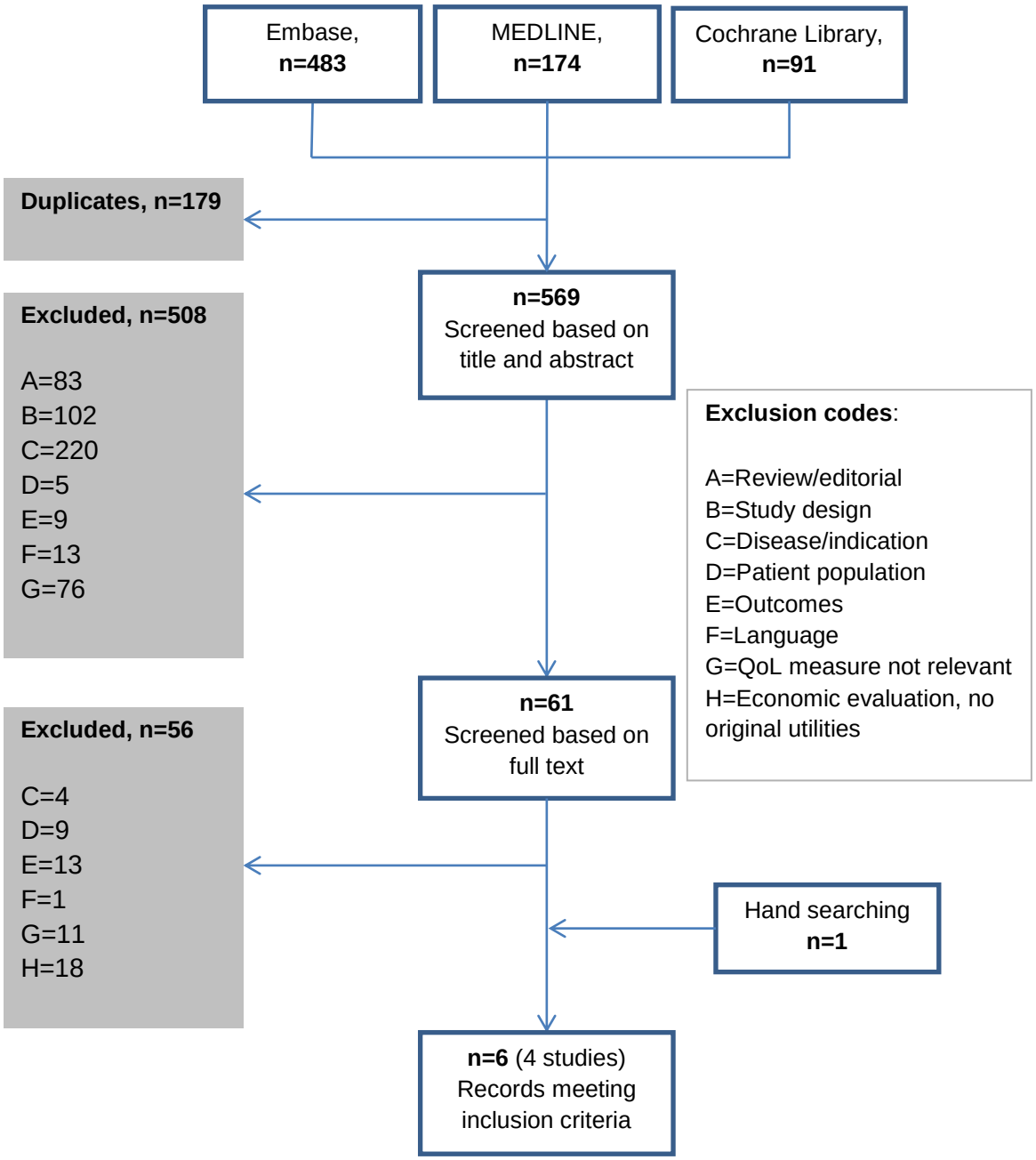
No studies were identified that met the population in the NICE scope exactly. In all included studies, the study population consisted of patients with pancreatic cancer, of which at least some were reported to have metastatic disease. In two studies, fewer than 50% of the study population were reported to have metastatic pancreatic cancer (99, 101); one study reported a population in which 86% had metastatic disease (103); and one study (two publications) reported results in a metastatic population only (102, 104). The publication reporting utilities adapted for Sweden (100) reports a utility value for patients with metastatic disease, however it is not clear how this was derived from the primary study (99). It is also unclear whether the results from studies in which some

patients were not metastatic are fully representative of the population of interest, particularly studies in which <50% of patients had metastatic disease. No studies were identified that investigated HRQoL in patients who had previously been treated with gemcitabine-based therapy and subsequently received another treatment. However, one study reported results following 8 weeks of treatment with gemcitabine plus bevacizumab or gemcitabine plus placebo (103), which may be representative of patients prior to receiving subsequent therapy for metastatic pancreatic cancer. None of the other included studies reported intervention-specific utilities.

The EQ-5D was used to derive utilities in all four included studies (and the publication reporting utilities adapted for several countries (102)), consistent with the NICE reference case. It is not clear whether the utilities reported in the Swedish adaptation publication (100) were derived using the EQ-5D or the SF-6D, however it is assumed that the health state for metastatic disease was adapted from the German study, which used the EQ-5D (99). Health states were described by patients with pancreatic cancer in the majority of studies, however one study (two publications) collected HRQoL data from a survey of medical oncologists specialising in non-colorectal gastrointestinal malignancies (102, 104). This is not consistent with the NICE reference case and the results from this study may not accurately reflect the HRQoL experienced by patients. Health states were valued using societal preferences elicited using the time trade-off (TTO) method in three studies (five publications) (99, 100, 102-104), as required in the NICE reference case; methods of valuation were not clearly reported in the remaining study (101). Utilities valued using UK tariffs were reported in two studies (99, 102). No studies were identified that reported mapping techniques.

The results reported in the six included publications are detailed in Table 40. The relevance of each study to the NICE reference case, and the comparability of the population to the NICE scope, was assessed and is presented in Table 41. Quality assessment of the included studies is provided in Appendix 9.

Figure 15: Schematic for the systematic review of HRQoL evidence



Abbreviations: HRQoL, health related quality of life; QoL, quality of life.

Table 40: Summary of HSUVs associated with patients with advanced/metastatic pancreatic cancer

Study, Country, Study design	Population	Interventions/ comparators	Sample size	Health states	Utility score [SD]
Ghatnekar 2013 (100), Sweden, Cost-utility analysis	Patients with resectable, locally advanced, or metastatic pancreatic cancer. Utilities from Ljungman 2011[†] (excluded) and Müller-Nordhorn 2006 (99) were adapted to Swedish-norm population	None	NR	Resectable pancreatic cancer	0.834
				Locally advanced pancreatic cancer	0.798
				Metastatic pancreatic cancer	0.762
Heiberg 2013 (101), Norway, Prospective cohort	Patients with confirmed pancreatic cancer (26.8% metastatic, sample 1; 10% metastatic, sample 2)	None	Sample 1, N=41 Sample 2, N=80[‡]	Pancreatic cancer (sample 1)	0.61 [0.26]
				Pancreatic cancer (sample 2)	0.60 [0.26]
Lien 2015 (102), UK[§] (results for Canada, Denmark, France, Germany, Japan, the Netherlands, Spain, and USA also reported), Utility values adapted from Tam 2013 (104)	Patients with metastatic pancreatic cancer (see Tam 2013 (104)). Utilities from Tam 2013 (104) were adapted to other countries' populations	None	N=60	Stable disease	0.643
				Supportive care	–0.250
				Grade 3–4 nausea and vomiting	0.352
				Grade 3–4 diarrhoea	0.328
				Grade 3–4 stomatitis	–0.038
				Grade 3–4 febrile neutropenia	0.454
				Grade 3–4 fatigue	–0.053
				Grade 3–4 rash	0.487
				Grade 3–4 hand-foot syndrome	0.179
				Grade 3–4 neuropathy	0.320
Müller-Nordhorn 2006 (99), Germany (UK	Patients with confirmed pancreatic cancer	None	N=45 (Male, n=21;	Women with pancreatic cancer (52% metastatic): German tariff	0.8 [0.2]

Study, Country, Study design	Population	Interventions/ comparators	Sample size	Health states	Utility score [SD]
utility weights also applied), Prospective cohort	(Stage IVa, 12%; Stage IVb [with metastases], 44%)		Female, n=24)	Women with pancreatic cancer (52% metastatic): UK tariff	0.7 [0.3]
				Men with pancreatic cancer (35% metastatic): German tariff	0.8 [0.3]
				Men with pancreatic cancer (35% metastatic): UK tariff	0.6 [0.3]
Romanus 2012 (103), USA, RCT†† (CALGB 80303)	Patients with advanced (stage III-IV) pancreatic cancer (86% metastatic) and ECOG performance status 0–2. No prior chemotherapy for metastatic disease; no gemcitabine for adjuvant therapy	• Gemcitabine plus bevacizumab • Gemcitabine plus placebo	N=186¶	All patients: baseline	0.78 [0.13]
				All patients: 8 weeks	0.79 [0.16]
				Progressive disease: baseline	0.77 [0.13]
				Progressive disease: 8 weeks	0.73 [0.18]
				Stable disease: baseline	0.79 [0.14]
				Stable disease: 8 weeks	0.81 [0.15]
				Complete/ Partial response: baseline	0.79 [0.14]
				Complete/ Partial response: 8 weeks	0.81 [0.15]
				Gemcitabine plus bevacizumab: baseline	0.80 [0.12]
				Gemcitabine plus bevacizumab: 8 weeks	0.80 [0.15]
				Gemcitabine plus placebo: baseline	0.77 [0.15]
				Gemcitabine plus placebo: 8 weeks	0.77 [0.118]

Study, Country, Study design	Population	Interventions/ comparators	Sample size	Health states	Utility score [SD]
Tam 2013 (104), Canada, Cost-utility analysis (prospective survey)	Patients with metastatic pancreatic cancer (hypothetical patients – survey of medical oncologists)	None‡‡	N=60	Stable disease	0.720 [0.185]
				Supportive care	0.136 [0.184]
				Grade 3–4 nausea and vomiting	0.526 [0.235]
				Grade 3–4 diarrhoea	0.508 [0.207]
				Grade 3–4 stomatitis	0.279 [0.231]
				Grade 3–4 febrile neutropenia	0.589 [0.171]
				Grade 3–4 fatigue	0.247 [0.239]
				Grade 3–4 rash	0.626 [0.166]
				Grade 3–4 hand-foot syndrome	0.409 [0.210]
				Grade 3–4 neuropathy	0.494 [0.177]

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EQ-5D, European Quality of Life-5 Dimensions; ERG, Evidence Review Group; HSUV, health state utility value; NICE, National Institute for Health and Care Excellence; NR, not reported; OS, overall survival; PFS, progression free survival; SD, standard deviation; SF-36; 36-item Short Form Health Survey; SF-6D, Short Form 6 Dimensions questionnaire; RCT, randomised controlled trial; TTO, time trade-off.
†Ljungman D, Lundholm K, Hyltander A. Cost-utility estimation of surgical treatment of pancreatic carcinoma aimed at cure. World journal of surgery. 2011 Mar;35(3):662-70.
‡EQ-5D data only available in 40 and 49 patients in sample 1 and sample 2, respectively. §For the purposes of this submission, only UK values have been extracted. ¶Patients who completed HRQoL questionnaire both at baseline and at 8 weeks and were then analysed - an additional 64 patients completed the questionnaire at baseline but not at follow-up. †† A total of 154 randomised patients were not enrolled into the HRQoL protocol - HRQoL assessments were conducted in a consecutive subset of enrolled patients.
‡‡Some interventions are used in the cost-utility analysis (gemcitabine, gemcitabine plus erlotinib, gemcitabine plus capecitabine, FOLFIRINOX), but health states are not estimated based on intervention; §Information regarding methods for health state valuation are reported in the linked study only (102), not in the primary study publication.

Table 41. Relevance of identified HSUVs to NICE reference case and comparability to the NICE scope

Is the study consistent with NICE reference case?					Summary of comparability to the NICE scope and quality assessment
EQ-5D used?	**Patients describe health states?**	**Societal preferences used?**	**TTO/SG used?**	**Consistent?**	
Ghatnekar 2013 (100); Sweden					
Unclear[†]	Yes	Yes	Yes - TTO	Unclear	• A utility value is reported for metastatic pancreatic cancer, however Müller-Nordhorn 2006 (99)), from which this population was derived, did not report results for patients only with metastatic disease. No information on previous treatment was reported. It is not clear whether the results are comparable to the population in the NICE scope. • Utility values were adapted to a Swedish-norm population, so it is unclear whether the results are generalisable to the UK setting. • Other limitations include: o No measures of uncertainty around utility values reported o Methods of utility derivation, incl. response rates, are unclear
Heiberg 2013 (101); Norway					
Yes	Yes	Unclear	Unclear	Unclear	• The study population consisted of patients with pancreatic cancer, however <30% had metastatic disease. Information on previous treatments was not reported. The results are unlikely to be representative of the population in the NICE scope. • The study was conducted in a Norwegian population, so it is unclear whether the results are generalisable to the UK setting. • A limitation is that EQ-5D values were not available for all sampled patients.

Is the study consistent with NICE reference case?					Summary of comparability to the NICE scope and quality assessment
EQ-5D used?	**Patients describe health states?**	**Societal preferences used?**	**TTO/SG used?**	**Consistent?**	
Lien 2015 (102); UK, Canada, Denmark, France, Germany, Japan, the Netherlands, Spain, and the USA, Utilities adapted from Tam 2013 (104)					
Yes	No – survey of medical oncologists (experts in non-colorectal GI malignancies)	Yes	Yes - TTO	No	• The study population consisted of hypothetical patients with metastatic pancreatic cancer, but previous treatment was not reported, therefore the results may not be fully representative of the population in the NICE scope. • The study recruited Canadian clinicians, however the health states were valued using UK tariffs, so the results may be generalisable to the UK. • Limitations include: o Absence of response rates to the EQ-5D survey o Absence of measures of uncertainty around utility values o Health states were described by clinicians instead of patients, so results may not be equivalent to patient-described health states
Müller-Nordhorn 2006 (99); Germany (UK values also reported)					
Yes	Yes	Yes	Yes - TTO	Yes	• The study population consisted of patients with pancreatic cancer, however <50% had metastatic disease and no information on previous treatment was reported, so the results may not be representative of the population in the NICE scope. • The study was conducted in a German population, but health states are valued using UK preferences so the results may be generalisable to a UK setting. • Other limitations include: o Risk of selection bias as only patients first admitted for pancreatic cancer in gastroenterology department were surveyed; patients presenting in the surgical or oncology departments may have a different profile. o Relatively small sample size of study

Is the study consistent with NICE reference case?					Summary of comparability to the NICE scope and quality assessment
EQ-5D used?	**Patients describe health states?**	**Societal preferences used?**	**TTO/SG used?**	**Consistent?**	
Romanus 2012 (103); USA					
Yes	Yes	Yes	Yes - TTO	Yes	• The study population consisted of patients with advanced pancreatic cancer, of which 86% had metastatic disease. Patients had not previously been treated with gemcitabine. However, study treatment was gemcitabine-based, therefore 8 week results may be representative of the population in the NICE scope. • The study was conducted in a USA population and used USA health state valuations, so it is unclear whether the results are generalisable to the UK setting. Utilities from this study were used in TA360; the ERG criticised the use of USA utility values to represent a UK population, and adjusted these to estimate values more appropriate for NICE appraisals (0.742 and 0.671 for PFS and post-progression survival, respectively). • Other limitations include: ○ Response rate was approximately 70%; only patients who had both baseline and 8 week EQ-5D results were analysed. These patients had a significantly longer OS, and a higher proportion had response to chemotherapy or stable disease, compared with patients who had baseline EQ-5D results only.

Is the study consistent with NICE reference case?					Summary of comparability to the NICE scope and quality assessment
EQ-5D used?	**Patients describe health states?**	**Societal preferences used?**	**TTO/SG used?**	**Consistent?**	
Tam 2013 (104); Canada					
Yes	No – survey of medical oncologists (experts in non-colorectal GI malignancies)	Yes‡	Yes - TTO‡	No	• The study population consisted of hypothetical patients with metastatic pancreatic cancer, but previous treatment was not reported, therefore the results may not be fully representative of the population in the NICE scope. • The study was conducted in a Canadian setting using USA health state valuations‡, so it is unclear whether the results are generalisable to the UK setting. • Limitations that may restrict the usefulness of the study for informing economic evaluation include: • Absence of information regarding response rates to the EQ-5D survey

Abbreviations: EQ-5D, European Quality of Life-5 Dimensions; ERG, Evidence Review Group; GI, gastrointestinal; HSUV, health state utility value; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; SF-36, short form-36; SF-6D, short form-6 dimensions; SG, standard gamble; TTO, time trade off.

† The use of EQ-5D is unclear in Ghatnekar 2013 (100) because two studies are used to derive the Swedish utility values: Muller-Nordhorn 2006 (99), that used the EQ-5D, and Ljungman 2011 (105) that used SF-6D mapped from SF-36. ‡Information regarding methods of health state valuation are reported in the linked study (102), not in the primary study publication.

5.4.4 *Key differences*

Due to the limitations with NAPOLI-1 QoL data stated in Sections 5.4.1 and 5.4.2, differences between literature and the trial data could not be explored.

5.4.5 *Adverse reactions*

A disutility for each Grade 3+ AE (reported by >5% patients) was identified from literature research, and then weighted by the time the patient spent with the corresponding AE over the study period. Several AEs were included in the model:

- Abdominal pain
- Anaemia
- Diarrhoea
- Fatigue
- Nausea
- Neutropenia
- Vomiting

The AE duration and exposure data were taken from NAPOLI-1. The decrement value for abdominal pain was taken from Doyle et al, 2008 (106). The decrements for anaemia and diarrhoea were assumed to be equivalent to that for fatigue, which was sourced from Swinburn et al, 2010 (107). The utility decrements for both nausea and neutropenia were provided by Nafees et al, 2008 (108). (2008), and the decrement for vomiting was assumed to be the same as for nausea.

5.4.6 *Health-related quality-of-life data used in cost-effectiveness analysis*

For the economic modelling, utility values associated with pre and post-progression were obtained from a US study of HRQoL in patients with advanced pancreatic cancer who were not deemed to be appropriate for surgical resection (103). This study found that patient-reported HRQoL, as measured by EQ-5D, was relatively stable over 8 weeks of chemotherapy (gemcitabine plus placebo or gemcitabine plus bevacizumab), but decreased in patients with progressive disease, suggesting that patient utility dropped with disease progression. The utility values from this study were also used in the base-case analysis in the NICE submission for Abraxane®. The pre-progression health state was assigned a utility value of 0.8, and the post-progression health state was assigned a value of 0.75. Using utility values from this US trial was criticised by the Evidence Review Group (ERG) because UK EQ-5D utility values tend to be lower than US values for the same health states. Therefore, the ERG adjusted these values for the UK NICE appraisal. The ERG estimated the utility values to be 0.742 for pre-progression and 0.671 for post-progression. These values were then adjusted by treatment-related disutility due to AEs. The ERG had noted some limitations with this method, including the fact that the source of the utility values included patients receiving active treatment (e.g. gemcitabine + bevacizumab) and accounted for treatment-related AEs, therefore the

utility decrements approach is considered to be double counting. An analysis without utility decrement was also performed as a scenario analysis (see Section 5.8.3).

Table 42: Summary of utility values for cost-effectiveness analysis

	Utility value	[95% CI]	Reference	Justification
5-FU/LV				
Baseline utility value				
Pre-progression	0.742	NR	TA360 ERG report	Utility data from NAPOLI-1 could not be used.
Post-progression	0.672	NR	TA360 ERG report	Utility data from NAPOLI-1 could not be used.
Nal-iri + 5-FU/LV				
Baseline utility value				
Pre-progression	0.742	NR	TA360 ERG report	Utility data from NAPOLI-1 could not be used.
Post-progression	0.672	NR	TA360 ERG report	Utility data from NAPOLI-1 could not be used.
Oxaliplatin + 5-FU/LV				
Baseline utility value				
Pre-progression	0.742	NR	TA360 ERG report	Assumed to be equivalent to nal-iri + 5-FU/LV
Post-progression	0.672	NR	TA360 ERG report	Assumed to be equivalent to nal-iri + 5-FU/LV
Adverse events (utility decrements)				
Abdominal pain	–0.069	[-0.093, -0.045]†	Doyle et al, 2008 (106)	
Anaemia	–0.204	[-0.156, -0.252]	-	Assumed equivalent to fatigue
Diarrhoea	–0.204	[-0.156, -0.252]	-	Assumed equivalent to fatigue
Fatigue	–0.204	[-0.156, -0.252]	Swinburn et al, 2010 (107)	
Nausea	–0.048	[-0.079,-0.016]	Nafees et al, 2008 (108)	
Neutropenia	–0.090	[-0.122, -0.058]	Nafees et al, 2008 (108)	
Vomiting	–0.048	[–0.079, –0.016]	-	Assumed equivalent to nausea

Abbreviations: AE, adverse event; 5-FU, ERG, Evidence Review Group; 5-fluorouracil; LV, leucovorin; NR, not reported.
†This was calculated due to not being reported in the manuscript.

5.4.6.1 Clinical expert assessment of applicability of health state utility values

Clinical experts were not used to assess the applicability of health state utility values.

5.5 *Cost and healthcare resource use identification, measurement and valuation*

5.5.1 *Resource identification, measurement and valuation studies*

A systematic review was conducted to identify resource use and cost data from the published literature relevant to the decision problem. There were no date restrictions for the systematic review.

The following electronic databases were searched via the OVID platform: MEDLINE®, MEDLINE® In-Process and Other Non-Indexed Citations, Embase, EconLit, and The Cochrane Library, incorporating Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), and NHS Economic Evaluation Database (EED).

Electronic searches were supplemented by hand searching the following sources: reference lists of included studies and relevant systematic reviews, the Cost-Effectiveness Analysis (CEA) Registry, Research Papers in Economics (RePEc), conference proceedings, and previous HTA submissions/appraisals.

Full details of the search are provided in Appendix 10.

In total, 791 papers were identified through the electronic searches. Upon the removal of 212 duplicate papers, 579 titles and abstracts were reviewed. There were 67 ordered for full paper review, of which 58 were excluded. No additional studies were identified by hand-searching, resulting in nine relevant papers for final inclusion (8, 42, 109-115). The systematic review study flow is illustrated in Figure 16. The included studies are detailed in Appendix 10.

All included studies reported results for patients with metastatic pancreatic cancer, however no studies were identified that investigated costs or resource use associated with post-gemcitabine treatment specifically. There were 6 studies that reported results in the USA setting (109, 110, 112-115), and two studies used a Swedish perspective (42, 111). Only one of the studies included data applicable to clinical practice in the UK (8), reporting treatment patterns and detailed resource utilisation data relating to 200 patients treated for metastatic pancreatic cancer between 2009 and 2012.

Figure 16: Schematic for the systematic review of resource identification, measurement and valuation

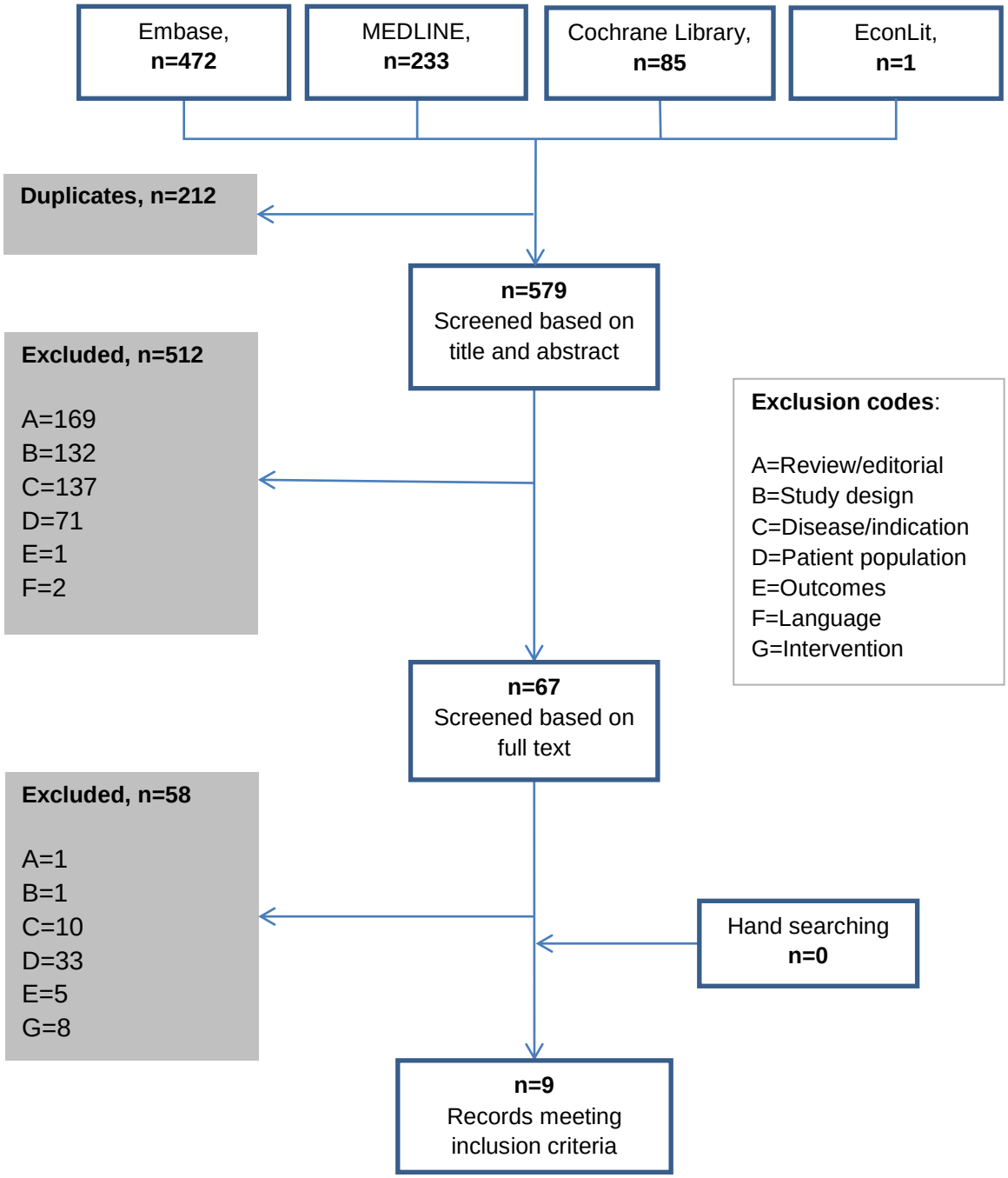


Table 43: Studies reporting resource data

Reference	Country, currency	Year of valuation	Patient population	Study design	Total costs and cost drivers
DaCosta Byfield 2013 (109)	USA, USD	2010	3,227 patients with metastatic pancreatic cancer	• Retrospective COI study using medical and pharmacy claims data. • Direct costs only.	Total cost PP per month, mean (SD): $21,637 ($29,814) Inpatient stays were the most costly resource.
Du 2000 (110)	USA, USD	1998	44 patients with metastatic pancreatic cancer	• COI study conducted at one USA cancer institute. • Direct costs only.	Total lifetime cost PP, mean: $35,809
Hjelmgren 2003 (111)	Sweden, Euros	2001	24 patients with metastatic pancreatic cancer	• Retrospective longitudinal COI study using registry data from 4 Swedish hospitals. • Direct costs only.	Total lifetime treatment cost PP, mean: €13,876 Inpatient stays were the most costly resource.
Oglesby 2010 (112) (Abstract)	USA, USD	Year NR	4,938 patients with metastatic pancreatic cancer	• Retrospective COI study using medical claims database.	Total cost of treatment PP per month, mean (SD): $16,192 (21,639) Inpatient stays contributed to 57.8% of total costs; outpatient visits contributed to 35.0%.
O'Neill 2011 (113) (Abstract)	USA, USD	2006	6,979 patients with metastatic pancreatic cancer	• Retrospective COI study using medical claims data.	Total cancer-related lifetime cost PP, mean: $45,100 Inpatient stays were the most costly resource, contributing 39% of the total cost.

Reference	Country, currency	Year of valuation	Patient population	Study design	Total costs and cost drivers
O'Neill 2012 (114)	USA, USD	2009	8,725 patients with metastatic pancreatic cancer	• Retrospective, population-based, COI study using medical claims data. • Direct medical costs only.	Total direct medical cost PP, mean (SD): Lifetime: $49,000 Per month: $25,300 (57,900) Inpatient stays were the most costly resource.
Seal 2014 (115) (Abstract)	USA, USD	2012	Patients with metastatic pancreatic cancer (n=NR; 2,901, 6,119, and 464 in overall study population, in each database respectively)	• Retrospective COI study using 3 medical claims databases.	Total costs PP per month, mean: $9,478 – $12,042 Medical costs contributed to the largest proportion of costs.
Smyth 2015 (8)	UK and France	NA	400 patients with metastatic pancreatic cancer (200 UK; 200 France)	• Retrospective resource utilisation study using a sample of patient medical records from participating physicians. • Direct resource use only.	No costs reported. Resource use reported for: • Emergency department visits • Outpatient visits • Inpatient stays Treatment pattern data also reported.
Tingstedt 2011 (42)	Sweden, Euros	2009	Patients with metastatic pancreatic cancer (n=NR; 83 in overall study population)	• Retrospective, incidence-based, COI study using registry data from one Swedish university hospital. • Direct medical costs only; productivity losses not reported by disease stage.	Total treatment cost PP, mean (SD): Lifetime: €16,179 (8,837) Per month: €10,154 (13,298) Inpatient stays were the most costly resource.

Abbreviations: COI, cost of illness; NR, not reported; PP, per patient; SD, standard deviation.

5.5.1.1 Appropriateness of NHS Ref costs/PbR tariffs

Due to the similar disease area, all costs used in the model were obtained directly from the NICE submission for Abraxane® (NICE ID680) and updated from the 2012–13 National Schedule of Reference Costs to the 2014–15 National Schedule of Reference Costs.

Table 44: Costs used in the model

Description	Unit Cost	Reference
Deliver simple parental chemotherapy at first attendance	£239.12	National Schedule of Reference Costs 2014-15. HRG code: SB12Z.
Deliver more complex parental chemotherapy at first attendance	£308.73	National Schedule of Reference Costs 2014-15. HRG code: SB13Z.
5-FU continuous infusion	£97.14	National Schedule of Reference Costs 2014-15. Service code: 370. Medical oncology. Non consultant outpatient attendance.
Outpatient visit (consultant)	£170.85	National Schedule of Reference Costs 2014-15. Service code: 370. Medical oncology. Consultant led outpatient attendance.
CT scan	£108.71	National Schedule of Reference Costs 2014-15. HRG code: RD25Z. Computerised Tomography Scan of three areas, without contrast.
Radiographic/MRI scan	£181.76	National Schedule of Reference Costs 2014-15. HRG code: RD03Z. Magnetic Resonance Imaging Scan of one area, with pre and post contrast.
Full blood count	£3.01	National Schedule of Reference Costs 2014-15. HRG code: DAPS05. Haematology.
Liver function test	£6.89	National Schedule of Reference Costs 2014-15. HRG code: DAPS07. Microbiology.
Ultrasound	£53.74	National Schedule of Reference Costs 2014-15. HRG code: RD40Z. Ultrasound Scan with duration of less than 20 minutes, without contrast.
Outpatient visit (nurse)	£97.14	National Schedule of Reference Costs 2014-15. Service code: 370. Medical oncology. Non consultant outpatient attendance.
Tumour Marker CA19-9 test	£1.38	National Schedule of Reference Costs 2014-15. HRG code: DAPS07. Microbiology. (1/5 of Liver function test which represents 5 tests).
Hospice centre/palliative care unit	£103.01	National Schedule of Reference Costs 2014-15. HRG code: SD03A. Hospital Specialist Palliative Care Support, age 19 years and over.
Neutropenia	£127.70	National Schedule of Reference Costs 2014-15. HRG code: XD25Z. Neutropenia Drugs, Band 1.
Thrombocytopenia	£479.13	National Schedule of Reference Costs 2014-15. HRG code: SA12K. Thrombocytopenia with CC Score 0-1. Non-elective short stay.

Description	Unit Cost	Reference
Anaemia	£528.15	National Schedule of Reference Costs 2014-15. HRG code: SA04L. Iron Deficiency Anaemia with CC Score 0-1. Non-elective short stay.
Peripheral sensory neuropathy (pain)	£111.32	National Schedule of Reference Costs 2014-15. HRG code: AB15Z - AB23Z. Weighted average of procedures for pain management. Outpatient procedures.
Neuropathy peripheral (pain)	£111.32	National Schedule of Reference Costs 2014-15. HRG code: AB15Z - AB23Z. Weighted average of procedures for pain management. Outpatient procedures.
Dehydration	£1,167.70	National Schedule of Reference Costs 2014-15. HRG code: KC05KZ - KC05M. Weighted average of Fluid or Electrolyte Disorders, without Interventions, with CC Score 2 - 9.
Abdominal pain	£387.25	National Schedule of Reference Costs 2014-15. HRG code: FZ90A - FZ90B. Weighted average of Abdominal Pain with Interventions and without Interventions. Regular Day or Night Admissions.
Diarrhoea	£319.34	National Schedule of Reference Costs 2014-15. HRG code: FZ49D - FZ49H. Weighted average of Nutritional Disorders with and without Interventions. Day case.
Pulmonary embolism	£1,093.10	National Schedule of Reference Costs 2014-15. HRG code: DZ09K - DZ09Q. Weighted average of Pulmonary Embolus with Interventions, with CC Score 0-8 and without Interventions, with CC Score 0-2.
Pneumonia	£1,315.93	National Schedule of Reference Costs 2014-15. HRG code: DZ19L. Other Respiratory Disorders without Interventions, with CC Score 11+.
Febrile Neutropenia	£633.26	National Schedule of Reference Costs 2014-15. HRG code: SA08J. Other Haematological or Splenic Disorders, with CC Score 0-2.
Cholangitis	£1,479.01	National Schedule of Reference Costs 2014-15. Non-Elective Excess Bed Days. 5 x cost of 1 excess bed day.

Abbreviations: CC, complexity and comorbidity; CT, computed tomography; 5-FU, 5-fluorouracil; HRG, Health Research Group; MRI, magnetic resonance imaging.

5.5.1.2 Clinical expert assessment of applicability of cost and healthcare resource use values

Clinical experts were not used to assess the applicability of cost and healthcare resource use values.

5.5.2 *Intervention and comparators' costs and resource use*

5.5.2.1 Treatment costs

There are three arms in the economic model, where patients in the 'pre-progression on treatment' health states will receive:

1. Intervention (Nal-iri + 5-FU/LV): 80 mg/m^2 nal-iri, 400 mg/m^2 LV, followed by 2400 mg/m^2 5-FU over 46 hours given every 2 weeks.
2. Comparator (5-FU/LV): LV at a dose of 200 mg/m^2 followed by 2,000 mg/m^2 5-FU over 24 hours administered on days 1, 8, 15 and 22, followed by 2 weeks of rest, in a 6-week cycle.
3. Comparator (Oxaliplatin + 5-FU/LV): 85 mg/m^2 oxaliplatin on day 1, 200 mg/m^2 LV followed by 1000 mg/m^2 5-FU on day 1 over 46 hours given every 2 weeks.

Table 45: Unit costs associated with the technology in the economic model

Items	Cost per vial	Cost per unit	Reference
Nal-iri	[redacted]	[redacted]	
5-FU bolus injection	£12.80	£0.012	BNF 2016
5-FU infusion	£64.00	£0.012	BNF 2016
LV	£100.00	£0.375	BNF 2016
Oxaliplatin	£311.00	£3.135	BNF 2016

Abbreviations: BNF, British National Formulary; 5-FU, 5-fluorouracil; LV, leucovorin.

The dose is based on a patient's body surface area (BSA), which is assumed to be 1.79 m^2 (SD=0.21), taken from a UK study measuring BSA of adult UK cancer patients (116). Due to toxicity, patients may have their dose reduced. Mean dose intensity was obtained for two arms from the trial (80% for nal-iri + 5-FU/LV, 95% for 5-FU/LV) and incorporated into the economic model. It was assumed that the mean dose intensity for oxaliplatin + 5-FU/LV was the same as for nal-iri + 5-FU/LV (80%).

Table 46: Cost per administration

Regimen	Average dose, mg	Cost per admin
Nal-iri + 5-FU/LV		
Nal-iri	[redacted]	[redacted]
5-FU infusion	3652	£49.94
LV	609	£237.60
Total	-	£2,057.13
5-FU/LV		
5-FU infusion	3401	£46.73
LV	340	£136.91
Total	-	£183.65
Oxaliplatin + 5-FU/LV		
Oxaliplatin	129	£481.52
5-FU infusion	1522	£22.69
LV	304	£123.49
Total	-	£627.71

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin.

The contents of each vial may not be entirely used due to the specific dosing needs for different regimens, causing drug wastage. Thus, vial sharing has not been included in the model. The method used to calculate the number of vials was based on a normal distribution of the average dose needed. An average number of vials (no sharing) was calculated using the calculated average dose and corresponding probabilities estimated from the distribution. The resulting expected numbers of vials without sharing were: 7.3 and 7.3 for 5-FU and LV, respectively, in the 5-FU/LV arm; 2.95, 7.80, and 12.67 for nal-iri, 5-FU, and LV, respectively, in the nal-iri + 5-FU/LV arm; and 3.07, 3.55 and 6.59 for oxaliplatin, 5-FU, and LV, respectively, in the oxaliplatin + 5-FU/LV arm.

5.5.3 *Health-state costs and resource use*

5.5.3.1 Administration costs

There are some costs for resource use associated with the administration of chemotherapy. NHS reference costs provide a number of costs for each type of chemotherapy administered. When the chemotherapy is given as a monotherapy or as simple parental chemotherapy in combination, the cost of this infusion is applied as £239.12. If the chemotherapy is considered as complex, the cost is applied as £308.73. For each chemotherapy given in addition to the parental chemotherapy, the cost is applied as £18.00. Nursing cost per hour is £36.00, and it is assumed that an additional 30 minutes is required to remove the initial infusion and to set up the next. This approach is consistent with that used in the NICE submission for Abraxane® (NICE ID680). Because of the long infusion time for 5-FU, an additional cost of £97.14 was applied to account for resource use associated with the patient's return to hospital.

Table 47: Administration costs of chemotherapy

Description	Unit Cost	Reference
Deliver simple parental chemotherapy at first attendance	£239.12	National Schedule of Reference Costs 2014-15. HRG code: SB12Z.
Deliver more complex parental chemotherapy at first attendance	£308.73	National Schedule of Reference Costs 2014-15. HRG code: SB13Z.
Admin nursing cost per hour	£36.00	Curtis L. PSSRU. Unit Costs of Health & Social Care 2015. Section 14 Hospital-based nurses. Band 5 hospital nurse.
5-FU continuous infusion	£97.14	National Schedule of Reference Costs 2014-15. Service code: 370. Medical oncology. Non consultant outpatient attendance.
Pharmacist cost for each infusion per hour	£44.00	Curtis L. PSSRU. Unit Costs of Health & Social Care 2015. Section 13.6 Hospital Pharmacist.

Abbreviations: 5-FU, 5-fluorouracil; HRG, Health Research Group; PSSRU, Personal Social Services Research Unit.

5.5.3.2 Monitoring costs

Monitoring costs were applied to all patients after model entry until the termination of active treatments. Monitoring costs were split into two parts: immediate monitoring costs prior to the start of therapy, and monitoring costs during the follow-up period before discontinuation of treatment. The former accounts for the costs associated with monitoring and laboratory tests preparing for the initiation of treatment, and it is only applied to the first cycle of the model. Following the first cycle or after the initiation of treatment, patients are monitored with follow-up visits and laboratory tests for as long as they remain on active treatments. Patients who discontinue treatment are assumed to receive palliative care with some level of monitoring, such as having one nurse home visit per week at a cost of £44.00. Unit costs of each monitoring service (e.g. outpatient visit, CT scan, MRI, etc.) were then adjusted by the percentage of patients requiring such service to get the expected weekly monitoring costs.

Table 48: Initial monitoring and lab test costs

Immediate care costs prior to chemo	Unit costs	Reference	% of patients that will receive	Cost per week
Outpatient visit (consultant)	£170.85	Curtis, 2015 (117)	100%	£170.85
CT scan	£108.71	NHS reference costs, 2014-15	100%	£108.71
Radiographic/MRI scan	£181.76	NHS reference costs, 2014-15	10%	£18.18
Full blood count	£3.01	NHS reference costs, 2014-15	100%	£3.01
Liver function test	£6.89	NHS reference costs, 2014-15	100%	£6.89
Ultrasound	£53.74	NHS reference costs, 2014-15	5%	£2.69

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; NHS, National Health Service.

Table 49: Monitoring costs during follow-up

Monitoring costs during follow-up	Unit costs	Reference	No.	Frequency (every X weeks)	% patients	Cost per week
Outpatient visit (consultant)	£170.85	Curtis, 2015 (117)	1	4	100%	£42.71
Outpatient visit (nurse)	£97.14	NHS reference costs, 2014-15	1	4	50%	£12.14
Community visit (nurse)	£44.00	Curtis, 2015 (117)	1	4	50%	£6.60
CT scan	£108.71	NHS reference costs, 2014-15	1	12	100%	£9.06
Full blood count	£3.01	NHS reference costs, 2014-15	3	4	100%	£2.26
Liver function test	£6.89	NHS reference costs, 2014-15	3	4	100%	£5.17
Tumour Marker CA19-9 test	£1.38	NHS reference costs, 2014-15	6	4	5%	£2.07

Abbreviations: CT, computed tomography; NHS, National Health Service.

5.5.4 *Adverse reaction unit costs and resource use*

Only Grade 3+ TEAEs reported by ≥5% of patients were included in the economic model. Costs for managing each AE are listed in Table 50. The expected number of each AE per patient in both arms was estimated. Based on an average of 17.7 weeks of treatment exposure in the intervention arm and 12.9 weeks in the control arm in NAPOLI-1, the weekly AE costs were estimated to be £14.17 for nal-iri + 5-FU/LV and £9.29 for 5-FU/LV. The costs associated with AEs with oxaliplatin + 5-FU/LV was assumed to be the same as the costs for nal-iri + 5-FU/LV (£14.17 per week).

Table 50: List of adverse reactions and summary of costs included in the economic model

Adverse events	Value	Reference
Anaemia	£528.15	NHS Reference Costs 2014-15. HRG code: SA04L
Neutropenia	£127.70	NHS Reference Costs 2014-15. HRG code: XD25Z
Abdominal pain	£387.25	NHS Reference Costs 2014-15. HRG code: FZ90A – FZ90B
Diarrhoea	£319.34	NHS Reference Costs 2014-15. HRG code: FZ49D - FZ49H
Nausea	£319.34	Assumed to be the same as diarrhoea
Vomiting	£319.34	Assumed to be the same as diarrhoea
Fatigue	£44.00	1 nurse visit per day for the duration of the adverse event; Curtis, 2015 (117)

Abbreviations: HRG, Health Research Group; NHS, National Health Service.

5.5.5 *Miscellaneous unit costs and resource use*

5.5.5.1 Palliative care costs

Palliative care is end of life treatment, and in this analysis was assumed to be received when patients were no longer on active treatment. In NAPOLI-1, it was estimated that 69% of patients in the intervention arm and 62% of patients in the control arm did not switch to another anti-cancer therapy following disease progression, and therefore were assumed to receive palliative care. It has been assumed that the percentage of patients on oxaliplatin + 5-FU/LV who did not switch to another anti-cancer therapy following disease progression is equivalent to those in the intervention arm of NAPOLI-1 (69%). Patients who receive palliative care are assumed to receive one nurse home care visit every week until death (Table 51).

Table 51: Palliative care costs

Item	5-FU/LV	Nal-iri + 5-FU/LV	Oxaliplatin + 5-FU/LV	Reference
Nurse home care visit per week	1			Advisory board
Costs per nurse home care visit	£44.00			NHS reference costs, 2014-15
Percent of patients	62%	69%	69%	NAPOLI-1[†]
Average cost per week	£27.28	£30.36	£30.36	

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; NHS, National Health Service.
[†]Percentages are for patients who did not switch to anti-cancer therapy following disease progression.

Patients at the end of their life tend to generate higher costs by having more frequent palliative nursing, moving to a hospice, etc. A cost of £426.54 was applied to patients in the final 4 weeks before death to better capture the change in health care use during this particular period, as used in the NICE submission for Abraxane®.

Table 52: Costs incurred in the 4 weeks before death

Items	No.	Every X weeks	% of patients	Unit cost	Reference	Cost per week
Nurse home care	3	1	50%	£44.00	Curtis, 2015 (117)	£66.00
Hospice centre/ palliative care unit	7	1	50%	£103.01	NHS reference costs, 2014-15	£360.54
Total						£426.54

Abbreviations: NHS, National Health Service.

5.5.5.2 Post-progression treatment costs

In NAPOLI-1, 38% of patients in the intervention arm and 31% in the control arm received other treatments after disease progression. Because a wide range of treatments were available and no corresponding costs were collected in the trial, we assumed that the average weekly costs of post-progression treatments were the same as the weekly drug costs of nal-iri + 5-FU/LV. These costs were then multiplied by the

percentage of patients receiving post-progression treatments to calculate the expected post-progression treatment costs per cycle.

Table 53: Costs for post-progression treatment

	5-FU/LV	Nal-iri + 5-FU/LV	Oxaliplatin + 5-FU/LV	Reference
Cost for post-progression treatments	£884.79	£884.79	£884.79	Assumed equal to nal-iri
Percent of patients	38%	31%	31%	NAPOLI-1 trial[†]
Average cost per week	£336.22	£274.29	£274.29	

[†]Percentages are for patients who did not switch to anti-cancer therapy following disease progression.

5.6 *Summary of base-case de novo analysis inputs and assumptions*

5.6.1 *Summary of base-case de novo analysis inputs*

A list of all variables used in the economic analysis is provided in Table 54.

Table 54: Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Time horizon, years	10	N/A	5.2.2.1
Discount rate	3.5%	N/A	5.2.2.1
Mean BSA, m^2	1.79	N/A	-
BSA SD, m^2	0.21	N/A	-
Dosing			
Nal-iri + 5-FU/LV arm: nal-iri dose	80	N/A	5.5.2.1
Nal-iri + 5-FU/LV arm: 5-FU dose	2400	N/A	5.5.2.1
Nal-iri + 5-FU/LV arm: LV dose	400	N/A	5.5.2.1
5-FU/LV arm: 5-FU dose	2000	N/A	5.5.2.1
5-FU/LV arm: LV dose	200	N/A	5.5.2.1
Oxaliplatin + 5-FU/LV arm: oxaliplatin dose	85	N/A	5.5.2.1
Oxaliplatin + 5-FU/LV arm: LV dose	400	N/A	5.5.2.1
Oxaliplatin + 5-FU/LV arm: 5-FU dose (IV)	2400	N/A	5.5.2.1
Survival parameters			
Nal-iri + 5-FU/LV arm: PFS, intercept	1.25	SD: 0.09 (Normal)	5.3.2.1

Variable	Value	CI (distribution)	Reference to section in submission
Nal-iri + 5-FU/LV arm: PFS, slope	0.949	SD: 0.07 (Normal)	5.3.2.1
Nal-iri + 5-FU/LV arm: OS, intercept	1.91	SD: 0.09 (Normal)	5.3.2.1
Nal-iri + 5-FU/LV arm: OS, slope	0.908	SD: 0.07 (Normal)	5.3.2.1
5-FU/LV arm: PFS, intercept	0.74	SD: 0.07 (Normal)	5.3.2.1
5-FU/LV arm: PFS, slope	0.768	SD: 0.06 (Normal)	5.3.2.1
5-FU/LV arm: OS, intercept	1.54	SD: 0.09 (Normal)	5.3.2.1
5-FU/LV arm: OS, slope	1	SD: 0.08 (Normal)	5.3.2.1
Oxaliplatin + 5-FU/LV: HR vs. Nal-iri, PFS	0.700	SD: 0.07 (Normal)	5.3.2.3
Oxaliplatin + 5-FU/LV: HR vs. Nal-iri, OS	0.630	SD: 0.06 (Normal)	5.3.2.3

Abbreviations: BSA, body surface area; CI, confidence interval; 5-FU, 5-fluorouracil; IV, intravenous; LV, leucovorin; N/A, not applicable; OS, overall survival; PFS, progression-free survival; SD, standard deviation.

5.6.2 *Assumptions*

The assumptions in the de novo economic model were:

- The relative dose intensity of oxaliplatin + 5-FU/LV was equivalent to the relative dose intensity observed in the nal-iri + 5-FU/LV arm of NAPOLI-1.
- The administration costs of oxaliplatin + 5-FU/LV were equivalent to the nal-iri + 5-FU/LV arm.
- The number of AEs experienced with oxaliplatin + 5-FU/LV was equivalent to that reported by patients in the nal-iri + 5-FU/LV arm of NAPOLI-1.
- The exposure to treatment (in weeks) for oxaliplatin + 5-FU/LV was equivalent to that observed in the nal-iri + 5-FU/LV arm of NAPOLI-1 trial.
- Time exposure to treatment (week) with oxaliplatin + 5-FU/LV was equivalent to nal-iri + 5-FU/LV.
- Monitoring costs for oxaliplatin + 5-FU/LV were equivalent to nal-iri + 5-FU/LV.
- Palliative care costs for oxaliplatin + 5-FU/LV were equivalent to nal-iri + 5-FU/LV.
- Costs of 4 weeks before death for oxaliplatin + 5-FU/LV were equivalent to nal-iri + 5-FU/LV.
- Costs for post-progression treatment for oxaliplatin + 5-FU/LV were equivalent to nal-iri + 5-FU/LV.
- Pre- and post-progression utility values for oxaliplatin + 5-FU/LV were equivalent to nal-iri + 5-FU/LV.

These assumptions were all due to a lack of available comparator data.

5.6.3 *Limitations*

2. Comparison of the nal-iri + 5-FU/LV with oxaliplatin + 5-FU/LV in the economic evaluation, using CONKO-003 and PANCREOX

    - There is currently no standardised FOLFOX treatment protocol available for the treatment of patients with pancreatic cancer in UK. The FOLFOX regimen may therefore differ in dose, frequency, administration time and cycle-length between treatment centres. The clinical experts that were consulted prior to this submission indicated that the most common regimen used in clinical practice in the UK is FOLFOX6. Therefore this regimen was used in the economic evaluation of nal-iri + 5-FU/LV vs oxaliplatin + 5-FU/LV.
    - The treatment regimen details of the common comparator arm (5-FU + LV) across the three studies are inconsistently reported and therefore this submission assumes comparability to allow the combined OS and PFS analysis.
    - In the network meta-analysis feasibility assessment and KOL feedback it was established that the trial populations between the studies were too heterogeneous to be used in an indirect comparison. However, for the purpose of the economic evaluation it was assumed that the baseline characteristics of the study populations were equivalent.
    - The OS and PFS results of CONKO-003 are not consistent with wider published evidence. Several studies reported OS and PFS values that were similar to that reported in PANCREOX, such as Yoo et al 2009 (15), Zaanan et al 2014 (76) and Conroy et al 2011 (118). The median OS in these studies was around 4 months for the mFOLFOX regimen, which contrasts to the 5.9 months reported in CONKO-003 for the OFF regimen. Therefore, the OS and PFS results of both CONKO-003 and PANCREOX were combined for the economic analysis in order to closer reflect better clinical outcomes of the FOLFOX regimen.

5.7 *Base case results*

5.7.1 *Base case incremental cost effectiveness analysis results*

The base case results are presented in Table 55.

Nal-iri + 5-FU/LV is associated with a QALY gain of 0.1341 and 0.2013 vs 5-FU/LV and oxaliplatin + 5-FU/LV, respectively. Nal-iri + 5-FU/LV is associated with an incremental cost of £17,746 vs 5-FU/LV and £17,110 vs oxaliplatin + 5-FU/LV, leading to incremental cost-effectiveness ratios (ICERs) of £132,360/QALY and £84,986/QALY, respectively.

Table 55: Base case results

Technologies	Total		Incremental		ICER (Cost/QALY)
	Costs	QALYs	Costs	QALYs	
Nal-iri + 5-FU/LV	[redacted]	0.5635	-	-	-
5-FU/LV	£13,338.32	0.4294	[redacted]	0.1341	[redacted]
Oxaliplatin + 5-FU/LV	£13,974.83	0.3621	[redacted]	0.2013	[redacted]

Abbreviations: 5-FU, 5-fluorouracil; ICER, incremental cost-effectiveness ratio; LV, leucovorin; QALY, quality-adjusted life year.

5.7.2 *Clinical outcomes from the model*

Table 56 compares the results of the de novo cost-effectiveness analysis with the clinical data from NAPOLI-1.

Table 56: Summary of model results compared with clinical data from NAPOLI-1

Outcome	Clinical trial result		Model result		
	5-FU/LV	Nal-iri + 5-FU/LV	5-FU/LV	Nal-iri + 5-FU/LV	Oxaliplatin + 5-FU/LV
Mean time on treatment	9.0 weeks	16.8 weeks	8.0 weeks	18.4 weeks	11.57 weeks
Mean PFS	13.6 weeks	24.7 weeks	11.3 weeks	21.9 weeks	15.3 weeks
Mean OS	32.4 weeks	40.8 weeks	30.8 weeks	40.8 weeks	25.7 weeks

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; OS, overall survival; PFS, progression-free survival.

5.7.3 *Disaggregated results of the base case incremental cost effectiveness analysis*

The disaggregate QALYs and costs by health state for the comparison between nal-iri + 5-FU/LV and 5-FU/LV are shown in Table 57 and Table 59, respectively, and the corresponding QALYs and costs by health state for the comparison between nal-iri + 5-FU/LV and oxaliplatin + 5-FU/LV are shown in Table 58 and Table 60, respectively.

Table 57: Summary of QALY gain by health state for nal-iri + 5-FU/LV vs 5-FU/LV

Health state	Nal-iri + 5-FU/LV	5-FU/LV	Increment	Absolute increment	% absolute increment
Pre-progression	0.3297	0.1732	0.1565	0.1565	113%
Post-progression	0.2413	0.2587	-0.0174	0.0174	-13%
Total	0.5710	0.4319	0.1391	0.1391	100%

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; QALY, quality-adjusted life year.

Table 58: Summary of QALY gain by health state for nal-iri + 5-FU/LV vs oxaliplatin + 5-FU/LV

Health state	Nal-iri + 5-FU/LV	Oxaliplatin + 5-FU/LV	Increment	Absolute increment	% absolute increment
Pre-progression	0.3297	0.2318	0.0980	0.0980	48%
Post-progression	0.2413	0.1348	0.1064	0.1064	52%
Total	0.5710	0.3666	0.2044	0.2044	100%

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; QALY, quality-adjusted life year.

Table 59: Summary of costs by health state for nal-iri + 5-FU/LV vs 5-FU/LV

Health state	Nal-iri + 5-FU/LV	5-FU/LV	Increment	Absolute increment	% absolute increment
Drug	[redacted]	£971	[redacted]	[redacted]	[redacted]
Admin	£3,174	£1,874	£1,300	£1,300	[redacted]
AE	£242	£74	£168	£168	[redacted]
Monitoring	£1,675	£945	£730	£730	[redacted]
Palliative	£2,492	£2,372	£120	£120	[redacted]
Post-progression	£5,578	£7,103	-£1,525	£1,525	[redacted]
Total	[redacted]	£13,338	[redacted]	[redacted]	100%

Abbreviations: AE, adverse event; 5-FU, 5-fluorouracil; LV, leucovorin.

Table 60: Summary of costs by health state for nal-iri + 5-FU/LV vs oxaliplatin + 5-FU/LV

Health state	Nal-iri + 5-FU/LV	Oxaliplatin + 5-FU/LV	Increment	Absolute increment	% absolute increment
Drug	[redacted]	£4,478	[redacted]	[redacted]	[redacted]
Admin	£3,174	£2,655	£518	£518	[redacted]
AE	£242	£202	£39	£39	[redacted]
Monitoring	£1,675	£1,452	£223	£223	[redacted]
Palliative	£2,492	£2,098	£394	£394	[redacted]
Post-progression	£5,578	£3,117	£2,461	£2,461	[redacted]
Total	[redacted]	£14,002	[redacted]	[redacted]	100%

Abbreviations: AE, adverse event; 5-FU, 5-fluorouracil; LV, leucovorin.

5.8 *Sensitivity analyses*

5.8.1 *Probabilistic sensitivity analysis*

5.8.1.1 Inputs

The base case value, standard deviation, and distribution for each parameter is presented in Table 61.

Table 61: Parameter value, standard deviation and distribution

Parameter	Base	SD	Distribution
BSA, m^2	1.79	0.21	Normal
Oxaliplatin cost	£3.11	0.31	Gamma
LV cost	£0.38	0.04	Gamma
5-FU cost, bolus	£0.01	0.00	Gamma
5-FU cost, IV	£0.01	0.00	Gamma
Cost to deliver simple parental chemotherapy at first attendance	£239.12	35.43	Gamma
Cost to deliver more complex parental chemotherapy at first attendance	£308.73	45.74	Gamma
Admin nursing cost per hour	£36.00	3.60	Gamma
Cost for 5-FU continuous infusion	£97.14	9.71	Gamma
Pharmacist cost for each infusion (per hour)	£44.00	4.40	Gamma
Outpatient visit cost (consultant)	£170.85	17.09	Gamma
Cost of CT scan	£108.71	28.99	Gamma
Cost of radiographic/MRI scan	£181.76	88.36	Gamma
Cost of full blood count	£3.01	1.60	Gamma
Cost of liver function test	£6.89	3.56	Gamma
Ultrasound cost	£53.74	5.37	Gamma
Cost of tumour marker CA19-9 test	£1.38	0.14	Gamma
Outpatient visit cost (nurse)	£97.14	9.71	Gamma
Community visit cost (nurse)	£44.00	4.40	Gamma
Costs per nurse home care visit	£44.00	4.40	Gamma
Cost of nurse home care	£44.00	4.40	Gamma
Cost of hospice centre/palliative care unit	£103.01	10.30	Gamma
Neutropenia cost	£127.70	12.77	Gamma
Fatigue cost	£44.00	4.40	Gamma
Anaemia cost	£528.15	52.82	Gamma
Abdominal pain cost	£387.25	38.73	Gamma
Nausea cost	£319.34	31.93	Gamma
Diarrhoea cost	£319.34	31.93	Gamma
Vomiting cost	£319.34	31.93	Gamma
Pre-progression utility values	0.742	0.07	Beta
Post-progression utility values	0.672	0.07	Beta
5-FU/LV arm: PFS, intercept	0.740	0.07	Normal
5-FU/LV arm: PFS, slope	0.768	0.06	Normal
5-FU/LV arm: OS, intercept	1.540	0.09	Normal

5-FU/LV arm: OS, slope	1.000	0.08	Normal
Nal-iri + 5-FU/LV arm: PFS, intercept	1.250	0.09	Normal
Nal-iri + 5-FU/LV arm: PFS, slope	0.949	0.07	Normal
Nal-iri + 5-FU/LV arm: OS, intercept	1.910	0.09	Normal
Nal-iri + 5-FU/LV arm: OS, slope	0.908	0.07	Normal
HR oxaliplatin + 5-FU/LV vs nal-iri; PFS	0.70	0.07	Normal
HR oxaliplatin + 5-FU/LV vs nal-iri; OS	0.63	0.06	Normal

Abbreviations: BSA, body surface area; CT, computed tomography 5-FU, 5-fluorouracil; IV, intravenous; LV, leucovorin; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; SD, standard deviation.

5.8.1.2 Results

Results for nal-iri + 5-FU/LV vs 5-FU/LV

The results of 1,000 simulations were plotted for nal-iri + 5-FU/LV vs 5-FU/LV on the cost-effectiveness plane (Figure 17), and the cost-effectiveness acceptability curve (CEAC) was calculated (Figure 18). It was found that 98% of the simulations lie in the North-East quadrant, indicating that nal-iri + 5-FU/LV more effective than 5-FU/LV in almost all simulations. The probabilistic mean ICER is [redacted]/QALY, which is greater than the base case ICER. The CEAC shows that nal-iri + 5-FU/LV has a 50% probability of being cost-effective at a willingness to pay threshold of [redacted] when compared with 5-FU/LV.

Figure 17: The cost-effectiveness plane for nal-iri + 5-FU/LV vs 5-FU/LV

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; QALY, quality-adjusted life year.

Figure 18: Cost-effectiveness acceptability curve for nal-iri + 5-FU/LV vs 5-FU/LV

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; QALY, quality-adjusted life year.

Results for nal-iri + 5-FU/LV vs oxaliplatin + 5-FU/LV

The results of 1,000 simulations were plotted for nal-iri + 5-FU/LV vs oxaliplatin + 5-FU/LV on the cost-effectiveness plane (Figure 19), and the cost-effectiveness acceptability curve (CEAC) was calculated (Figure 20). It was found that 100% of the simulations lie in the North-East quadrant, indicating that nal-iri + 5-FU/LV is always more effective than oxaliplatin + 5-FU/LV. The probabilistic mean ICER is [redacted]/QALY, which is comparable to the base case ICER, increasing the confidence that can be put in this result. The CEAC shows that nal-iri + 5-FU/LV has a 50% probability of being cost-effective at a willingness to pay threshold of [redacted] when compared with oxaliplatin + 5-FU/LV.

Figure 19: Cost-effectiveness plane for nal-iri + 5-FU/LV vs oxaliplatin + 5-FU/LV

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; QALY, quality-adjusted life year.

Figure 20: Cost-effectiveness acceptability curve for nal-iri + 5-FU/LV vs oxaliplatin + 5-FU/LV

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; QALY, quality-adjusted life year.

5.8.1.3 Discussion of variation between base case and PSA results

The results from the PSA and base case analysis are very similar for the comparison to oxaliplatin + 5-FU/LV; however, there is more uncertainty in the comparison to 5-FU/LV. The probabilistic mean for nal-iri + 5-FU/LV vs. 5-FU/LV produced a greater cost increment [redacted] and a lower QALY gain (0.1348), producing an ICER of [redacted]/QALY; while the probabilistic mean for nal-iri + 5-FU/LV vs oxaliplatin + 5-FU/LV produced a slightly greater cost increment [redacted] and a marginally greater QALY gain (0.2035), producing an ICER of [redacted]/QALY.

5.8.2 *Deterministic sensitivity analysis*

5.8.2.1 Inputs

Deterministic sensitivity analysis (DSA) was performed on many inputs included in the model apart from the dosing and treatment regimens, and a tornado diagram was produced. Table 62 summarises the variables included in the tornado diagram and the relative variation used for each.

Table 62: Parameter variation for deterministic sensitivity analysis

Parameter	Base	Lower bound	Upper bound	Justification
BSA, m^2	1.79	1.611	1.969	A common variation in parameter inputs was included in the DSA to determine the relative sensitivity of model outcomes to different model inputs. Exploration of uncertainty in parameter inputs was assessed through the PSA and three scenario analyses.
Discount rate	3.50%	2%	5%	
Nal-iri cost	[redacted]	[redacted]	[redacted]	
Oxaliplatin cost	£3.14	£2.82	£3.45	
LV cost	£0.38	£0.34	£0.41	
5-FU cost, bolus	£0.01	£0.01	£0.01	
5-FU cost, IV	£0.01	£0.01	£0.01	
Relative dose intensity: Nal-iri + 5-FU/LV	85%	80%	90%	
Relative dose intensity: 5-FU/LV	95%	90%	100%	
Relative dose intensity: oxaliplatin + 5-FU/LV	95%	90%	100%	
Cost to deliver simple parental chemotherapy at first attendance	£239.12	£215.21	£263.03	
Cost to deliver more complex parental chemotherapy at first attendance	£308.73	£277.86	£339.60	
Admin nursing cost per hr	£36.00	£32.40	£39.60	
Cost for 5-FU continuous infusion	£97.14	£87.43	£106.85	
Pharmacist cost for each infusion (per hour)	£44.00	£39.60	£48.40	
Outpatient visit cost (consultant)	£170.85	£153.77	£187.94	

CT scan cost	£108.71	£63.32	£102.46	
Radiographic/MRI scan cost	£181.76	£117.17	£236.46	
Full blood count cost	£3.01	£1.71	£3.87	
Liver function test cost	£6.89	£4.15	£8.95	
Ultrasound cost	£53.74	£48.37	£59.11	
Tumour Marker CA19-9 test cost	£1.38	£1.24	£1.52	
Outpatient visit cost (nurse)	£97.14	£87.43	£106.85	
Community visit cost (nurse)	£44.00	£39.60	£48.40	
% receiving outpatient visit (consultant)	100%	90%	100%	
% receiving CT scan	100%	90%	100%	
% receiving radiographic/MRI scan	10%	5%	15%	
% receiving full blood count	100%	90%	100%	
% receiving liver function test	100%	90%	100%	
% receiving ultrasound	5%	0%	10%	
% tumour Marker CA19-9 test	100%	90%	100%	
Costs per nurse home care visit	£44.00	£39.60	£48.40	
Cost of hospice centre/palliative care unit	£103.01	£92.71	£113.31	
Neutropenia cost	£127.70	£114.93	£140.47	
Fatigue cost	£44.00	£39.60	£48.40	
Anaemia cost	£528.15	£475.34	£580.97	
Abdominal pain cost	£387.25	£348.53	£425.98	
Nausea cost	£319.34	£287.41	£351.27	
Diarrhoea cost	£319.34	£287.41	£351.27	
Vomiting cost	£319.34	£287.41	£351.27	
% receiving nurse home care	50%	40%	60%	
% staying in hospice centre/palliative care unit	50%	40%	60%	
Pre-progression utility values	0.742	0.6678	0.8162	
Post-progression utility values	0.672	0.6048	0.7392	

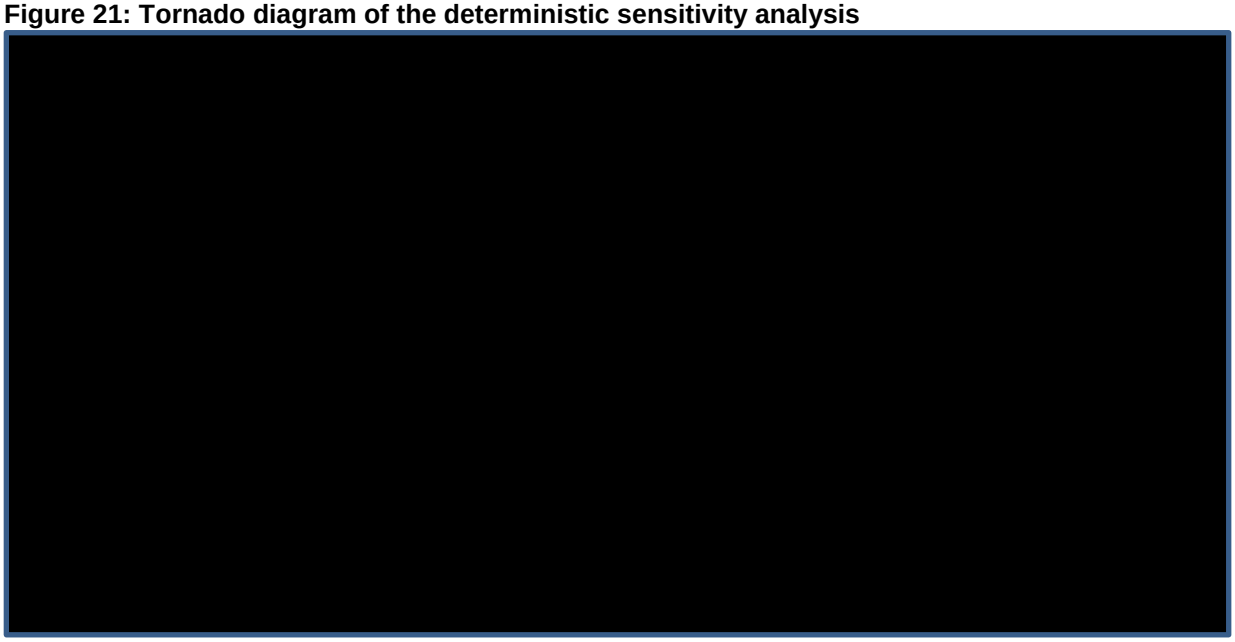
Abbreviations: BSA, body surface area; CT, computed tomography; 5-FU, 5-fluorouracil; IV, intravenous; LV, leucovorin; MRI, magnetic resonance imaging.

5.8.2.2 Results

The results of deterministic sensitivity analysis are presented as a tornado diagram in Figure 21. The main driver of the model is the pre-progression utility values, followed by the cost of nal-iri and the mean BSA. When the pre-progression utility value is set to 0.8162, i.e. greater than the 0.742 base rate used, the ICER reaches £[redacted]. Varying

the BSA appears to have a large effect on the ICER and this is due to its impact on the cost of treatment. The value used in the base case (1.79 m^2) from Sacco et al, 2010 (116), is commonly used in economic models and is very similar to the BSA of the ITT population in NAPOLI-1 (1.75 m^2).

Figure 21: Tornado diagram of the deterministic sensitivity analysis



Abbreviations: BSA, body surface area; chemo, chemotherapy; 5-FU, 5-fluorouracil.

5.8.3 *Scenario analysis*

There were three scenarios run to explore the uncertainty in model parameters. Table 63 presents the ICER for each scenario for nal-iri + 5-FU/LV vs the other treatment strategies. The results shows that the ICERs are similar to the base case.

Table 63: Scenario analysis

Scenario	Nal-iri + 5-FU/LV vs 5-FU/LV	Nal-iri + 5-FU/LV vs oxaliplatin + 5-FU/LV
Base case	[redacted]	[redacted]
February 2014 data cut from NAPOLI-1 trial using log-normal distribution	[redacted]	[redacted]
AE utility decrements omitted	[redacted]	[redacted]
Log-logistic distribution for nal-iri + 5-FU/LV vs 5-FU/LV	[redacted]	–

Abbreviations: AE, adverse event; 5-FU, 5-fluorouracil; HR, hazard ratio; LV, leucovorin.

5.8.4 *Summary of sensitivity analyses results*

The results of the model are robust in the face of uncertainty in both the parameter inputs and the structural assumptions required to construct the model. All scenarios indicate that nal-iri + 5-FU/LV is cost-effective below a willingness-to-pay threshold of [redacted] vs 5-FU/LV, and [redacted] vs oxaliplatin + 5-FU/LV.

5.9 *Subgroup analysis*

No subgroups were considered as part of this submission.

5.10 *Validation*

The model was validated through a multi-step process to verify the structure and underlying modelling and economic assumptions; this was followed by verification of all numerical data included in the model and mark-up of the reference publication.

5.10.1 *Internal Validation*

The model development team was supported by a quality control team that was not involved in model development. A model verification checklist was followed; this included tasks such as:

- All default data inputs were documented in cell comments and values were confirmed to match their corresponding Reference Data worksheets and referenced sources.
- All navigation and input cells were tested.
- Individual input were replaced with large and small values to show the results change appropriately.
- Results were traced back to their parameter and survival sheets.

5.11 *Interpretation and conclusions of economic evidence*

The main strength of the evaluation is that it is relevant to UK decision-makers, since the model includes the current standard of care for UK patients following progression on gemcitabine-based therapy (oxaliplatin + 5-FU/LV) as evidenced by clinical expert opinion, and also uses associated UK-specific data, where available.

The main limitations are in the lack of head-to-head data for nal-iri + 5-FU/LV vs oxaliplatin + 5-FU/LV, as well as the methods used to incorporate the oxaliplatin + 5-FU/LV arm into the model (as described in Section 5.3.2.3).

The base case demonstrated that nal-iri + 5-FU/LV was more effective than both 5-FU/LV and oxaliplatin + 5-FU/LV. In order to evaluate the uncertainty, we also undertook extensive sensitivity analyses, as shown in Section 5.8. These sensitivity analyses showed stability in all of the ICERs and results obtained.

6 Assessment of factors relevant to the NHS and other parties

6.1 *Population: people eligible for treatment*

It is expected that the total number of patients eligible for treatment with nal-iri will be 1,137 in year 1, rising to 1,230 in year 5. These figures are estimates of the total population of post-gemcitabine patients with mPC. Incidence and prevalence figures were obtained from Cancer Research UK (47).

Table 64: Estimation of patients eligible for treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population, n	6,587	6,719	6,854	6,990	7,130
Incident cases, n	132	134	137	140	143
Mortality, n	6,587	6,719	6,854	6,990	7,130
Patients recovering, n	0	0	0	0	0
Net population with the condition	0	0	0	0	0
Eligible for treatment, n (%)	1,137 (21%)	1,159 (21%)	1,182 (21%)	1,206 (21%)	1,230 (21%)

6.2 *Costs included*

Treatment costs for each regimen considered in the model are detailed in Table 65. Detailed breakdowns of each of these costs can be found in Section 5.5.

Table 65: Costs included in the budget impact

Treatment	Drug	Admin	AEs	Monitoring	Palliative	Total cost
5-FU/LV	£971	£1,874	£74	£945	£2,372	£13,338
Nal-iri + 5-FU/LV	[redacted]	£3,174	£242	£1,675	£2,492	[redacted]
Oxaliplatin + 5-FU/LV	£4,450	£2,655	£202	£1,452	£2,098	£13,975

Abbreviations: AE, adverse event; 5-FU. 5-fluorouracil; LV, leucovorin.

Nal-iri is assumed to displace 4.2% of the market share of oxaliplatin + 5-FU/LV in Year 1, increasing to 21% in Year 5, and is also expected to displace 0.8% of the market share of 5-FU/LV in Year 1, increasing to 4% in Year 5. As the treatments are end-of-life, treatment switching was not considered in the model due to short patient lifespan. Table 66 and Table 67 illustrate the estimated displaced medicines cost per patient per annum.

Table 66: Estimated displaced medicine cost: oxaliplatin + 5-FU/LV

Year	1	2	3	4	5
Estimated cost per patient per annum	£4,450	£4,450	£4,450	£4,450	£4,450
Estimated % displaced	4.2%	8.4%	12.6%	16.8%	21%
Estimated displaced medicine cost per patient per annum	£186.90	£373.80	£560.70	£747.60	£934.50

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin.

Table 67: Estimated displaced medicine cost: 5-FU/LV

Year	1	2	3	4	5
Estimated cost per patient per annum	£971	£971	£971	£971	£971
Estimated % displaced	0.8%	1.6%	2.4%	3.2%	4%
Estimated displaced medicine cost per patient per annum	£7.80	£15.50	£23.30	£31.10	£38.80

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin.

6.3 *Resource savings*

There are no other additional resource savings expected from the use of Nal-Iri.

6.4 *Budget impact*

The net annual budget impact for the NHS in England and Wales following the introduction of nal-iri in the anticipated licenced population is estimated to be £555,409 in Year 1, rising to £3,028,077 in Year 5, with a cumulative budget impact of £8,770,184 over 5 years. Costs without nal-iri are presented in Table 68, costs with nal-iri are presented in Table 69, and the budget impact is presented in Table 70.

Table 68: Costs without nal-iri

	Year 1	Year 2	Year 3	Year 4	Year 5
Oxaliplatin + 5-FU/LV, % uptake	84%	84%	84%	84%	84%
5-FU/LV, % uptake	16%	16%	16%	16%	16%
No. of patients treated with oxaliplatin + 5-FU/LV	955	974	993	1013	1033
No. of patients treated with 5-FU / LV	182	185	189	193	197
Annual net cost	**£24,723,375**	**£25,206,855**	**£ 25,703,861**	**£26,224,177**	**£26,744,493**
Cumulative net cost	**£24,723,375**	**£49,930,231**	**£75,634,092**	**£101,858,269**	**£128,602,763**

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; nal-iri: nanoliposomal irinotecan.

Table 69: Costs if Nal-iri becomes available

	Year 1	Year 2	Year 3	Year 4	Year 5
Nal-iri + 5-FU/LV, % uptake	5%	10%	15%	20%	25%
Oxaliplatin + 5-FU/LV, % uptake	80%	76%	71%	67%	63%
5-FU/LV, % uptake	15%	14%	14%	13%	12%
No. of patients treated with Nal-iri + 5-FU/LV	57	116	177	241	308
No. of patients treated with oxaliplatin + 5-FU/LV	907	876	844	810	775
No. of patients treated with 5-FU/LV	173	167	161	154	148
Annual net cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative net cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; nal-iri: nanoliposomal irinotecan.

Table 70: Net budget impact

Diagnosis year	Year 1	Year 2	Year 3	Year 4	Year 5
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.5 *Additional factors not included in analysis*

No further opportunities for resource savings or redirection of resources have been identified.

6.6 *Limitations of the analysis*

The same assumptions apply to the budget impact section as to the model (see Section 5.6.2), in that due to a lack of available comparator data, many costs and other data had to be assumed to be the same for oxaliplatin + 5-FU/LV as for nal-iri + 5-FU/LV.

In addition, the following assumptions were made for the budget impact analysis:

- Overall population and incidence rate from the reference sources are constant

- The percentage of mPC is assumed to be 81% the annual incidence of pancreatic cancers in the UK
- The percentage of patients receiving post-gemcitabine therapies was set as 21%
- The current post-gemcitabine market share was assumed to be 70% FOLFOX, 10% 5FU/LV and 20% BSC
- Due to the short life span for mPC population it is assumed that all treatments terminate within one year
- Costs associated with mortality and other comorbidities are not included.

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8 Appendices

Appendix 1: SmPC

Appendix 2: Search strategy for relevant studies

Appendix 3: Quality assessment of RCTs

Appendix 4: Details of relevant trials in the indirect or mixed treatment comparison

Appendix 5: Quality assessment of the relevant non-randomised and non-controlled evidence

Appendix 6: Summary of serious adverse events

Appendix 7: Search strategy for cost-effectiveness studies

Appendix 8: Quality assessment of cost-effectiveness studies

Appendix 9: Search strategy for measurement and valuation of health effects

Appendix 10: Cost and healthcare resource identification, measurement and valuation

Appendix 11: Checklist of confidential information

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Single technology appraisal

Nanoliposomal irinotecan for treating pancreatic cancer after prior treatment with gemcitabine [ID778]

Dear [redacted],

The Evidence Review Group, Liverpool Reviews and Implementation Group, and the technical team at NICE have looked at the submission received on 20th April 2016 from Baxalta. 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 would like to express their appreciation to Baxalta for providing the clinical study report for the key trial.

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 **1st June 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

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 Caroline Hall, Technical Lead (caroline.hall@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
Associate Director – Appraisals
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Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

Decision problem: comparators

A1. **Priority question.** The company submission states that the most commonly used regimen for patients with pancreatic cancer treated after prior treatment with gemcitabine in England is oxaliplatin with 5-fluorouracil (5-FU) and folinic acid (Leucovorin [LV]). The company submission also states (on page 29) that the most common type of oxaliplatin + 5-FU/LV regimen is mFOLFOX-4 but this is contradicted on page 130, of the submission, where FOLFOX-6 is stated to be the most common regimen. The company submission also states, on page 98, that in the opinion of 3 UK clinical experts, 40% of patients receive either of these regimens. However, on page 144 of the submission it is stated that the current market share is assumed to be 70% FOLFOX, 10% 5-FU/LV and 20% best supportive care (BSC). This suggests that the other comparators in the NICE scope (oxaliplatin + capecitabine and fluoropyrimidine monotherapies other than 5-FU/LV such as capecitabine monotherapy) are not used.

a. Please provide all the results from the interviews with the clinical experts for all treatments (including different oxaliplatin regimens and fluoropyrimidine monotherapies) considered to be used after prior treatment with gemcitabine in England (with %).
b. Please provide any additional supporting evidence (e.g. market research) for the regimens that are used after prior treatment with gemcitabine in England.
c. Please clarify whether the company considers the modified FOLFOX-6 regimens used in either the PANCREOX trial (described at https://clinicaltrials.gov/show/NCT01121848) or SWOG trial (https://clinicaltrials.gov/ct2/show/NCT01658943) to be similar to the FOLFOX-6 regimens it considers are most used in England?

Search strategy and study selection

A2. Please clarify why a search filter for randomised controlled trials (RCTs) was applied to the search strategy (see appendix 2) when both RCTs and non-RCTs were included in the company's systematic review. Please provide details explaining how the non-RCTs were identified.

NAPOLI-1 trial

A3. **Priority question.** Please provide the median follow-up for the NAPOLI-1 trial for the primary analysis (14 February 2014), interim analysis (25 May 2015) and final analysis (March 2016).

A4. **Priority question.** Study disposition for the NAPOLI-1 trial is given in Figure 4 (page 57 of submission) and Table 13 (page 58 of submission). The former, unlike the latter, includes patients who were enrolled prior to Protocol Version 2. Nonetheless, the numbers in Figure 13 and Table 4 should be identical for the nanoliposomal

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irinotecan (nal-iri) + 5-FU/LV arm but a number of discrepancies have been found, inlcuding:

a. "Other" reason for treatment discontinuation is lower in Table 13 (1 compared with 3 in Figure 4).
b. Progressive disease based on RECIST v1.1 criteria is lower in Table 13 (57 compared with 64 in Figure 4).
c. Number who died is lower in Table 13 (70 compared with 75 in Figure 4).
d. Patients who withdrew their consent is higher Table 13 (8 compared with 4 in Figure 4).

In addition, in the nal-iri + 5-FU/LV arm, Figure 4 states that 103 patients discontinued therapy but summing the reasons for discontinuation totals 117 and not 103. Please explain the differences in these numbers and provided any correct data if required.

A5. **Priority question.** The company submission details (page 56) that 14 patients in the control arm were never treated. This number includes patients who were enrolled prior to Protocol Version 2.

a. Please provide the number of patients who were never treated, excluding those enrolled prior to the implementation of Protocol Version 2.
b. Please also clarify whether the patient who was randomised to the control arm but received the nal-iri + 5-FU/LV (and identified in Figure 4, page 57) was enrolled prior to the implementation of Protocol Version 2.
c. Please provide baseline characteristics (with the same information as reported in Table 14 of the company submission plus that requested in question A9 below) for the nal-iri + 5-FU/LV and 5-FU/LV arms including only patients enrolled and who received their allocated study treatment following the implementation of Protocol Version 2.

A6. **Priority question.** Page 52 of the company submission states: "*In order to accurately compare the nal-iri + 5-FU/LV arm to a control arm, an analysis group was used including all patients randomised to 5-FU/LV under Protocol Version 2 or later, who could have been randomised to the active treatment combination. Therefore patients that were randomised to the control arm prior to the protocol amendment were not included in the efficacy analyses in this document*." Please provide details about why the company excluded these data in the efficacy analyses. Please also clarify why analyses of NAPOLI-1 presented in the company submission are only performed using an analysis population of patients who were randomised to 5-FU/LV under Protocol Version 2 or later.

A7. **Priority question.** The number of patients included in the per protocol population analysis is relatively small when compared with the numbers of patients included in the other analyses. Please provide a table with a breakdown of the reasons why patients from the intention-to-treat (ITT) population of NAPOLI-1 were not included in the per protocol population analysis.

A8. Please provide more detailed information regarding how the required sample size for NAPOLI-1 was calculated. Specifically:

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a. What parameters were used for the original sample size calculation performed as part of Protocol Version 1 i.e. power, patient accrual and follow-up times?
b. After Protocol Version 2, how did the new sample size calculation take into consideration that approximately 65 patients had already been randomised under Protocol Version 1 to a two-arm trial, and that the remainder of participants recruited would be randomised to one of three arms? Please provide any relevant references that describe the methodology implemented, and software code used to perform the calculations.

A9. Please provide the following additional baseline information by treatment arm for the ITT population:
a. Time since diagnosis.
b. Duration of advanced disease.
c. Proportion of patients who had had primary surgery.
d. Duration of time on treatment with gemcitabine.

A10. Page 62 of the company submission states: "*The combination of nal-iri + 5-FU/LV achieved statistically significantly longer median OS [overall survival] than 5-FU/LV for all analyses*". Similar statements are made on page 64 and page 65 regarding median PFS [progression-free survival] and median TTF [time to treatment failure]. Please clarify how the company has determined median OS/PFS/TTF to be statistically significantly longer for the nal-iri + 5-FU/LV arm than the 5-FU/LV arm. Please provide any formal statistical comparisons of median OS/PFS/TTF values between treatment groups that have been performed including the log-rank test and the differences in hazard ratios rather than in median survival time.

A11. Please clarify whether any formal testing of the proportional hazards assumption for the outcomes for which analyses were performed using Cox proportional hazards methods for the NAPOLI-1 trial were conducted. If so, please provide these results.

A12. The company has not presented any confidence intervals for the hazard ratios for any time-to-event outcomes (including OS and PFS). For all such analyses included in the company submission, including sensitivity analyses, please provide these data.

A13. Please provide the results of the following sensitivity analyses, including confidence intervals, for OS as described in section 4.4.3.1 of the company submission:
a. Wilcoxon pairwise comparisons of treatments.
b. Cox regression model with a time-dependent covariate to account for post-baseline therapy.
c. Cox regression model with stepwise selection of model terms (p-value to enter <0.25, p-value to remain <0.15).

A14. Were tests for interaction performed for the analysis of NAPOLI-1 trial data, which was undertaken to investigate the effects of baseline carbohydrate antigen 19-9 (CA19-9) level on OS (page 68 of company submission)? If so, please provide the results of the test for interaction.

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A15. Please clarify in Table 23 (page 67) of the company submission what the median time to first tumour marker response was and corresponding 95% confidence interval for the 5-FU/LV arm? Only one value is presented in Table 23 for the 5-FU/LV arm (3.91) and it is not clear if this is the median time to first tumour marker response, or the lower limit of the confidence interval
   a. .

A16. The findings for the final analysis of OS and PFS (March 2016) reported on pages 62 and 64 of the company submission **are identical** to those reported for the interim analyses (May 2015). Please clarify that this is correct and not a typographical error.

A17. Table 30 (page 78) of the company submission reports the total number of ≥1 treatment emergent adverse events (AEs) resulting in a dose delay, dose reduction and dose discontinuation. Please provide similar data by treatment arm for treatment-related AEs, i.e., the total number of ≥1 treatment-related AEs resulting in a dose delay, the total number of ≥1 treatment-related AEs resulting in a dose reduction and the total number of ≥1 treatment-related AEs resulting in a dose discontinuation.

Indirect treatment comparison

A18. In the network meta-analysis feasibility assessment (page 71 of company submission), please clarify what is meant by "best-case evidence network", and how this was identified from the wider evidence base.

A19. Please provide the data inputs for the indirect comparison described on page 103 of the company submission.

Non-randomised controlled trial evidence

A20. Please clarify which tool was used for assessing the quality of NCT00813163 (Appendix 5 of the company submission).

A21. It appears from the information provided for the NCT00813163 study that the 3 weekly regimen for nal-iri was the same as that used for the monotherapy arm in NAPOLI-1 and that patients were not tested for the UGT1A1*28 allele prior to treatment. Please can you confirm whether this is the case?

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** Please provide full Kaplan-Meier results (see example below) for the following populations of patients:
   a. All patients
   b. Patients with a KPS 70-80
   c. Patients with a KPS 90-100

   showing survival estimates at each event time, for all the treatment arms in the NAPOLI-1 trial for:

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i. OS.
ii. PFS.
iii. Post-Progression Survival (PPS).
iv. Time to treatment discontinuation.

Please use the most recent data cut and base on investigator assessment of disease progression. Please present analysis outputs using the following format:

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

B2. **Priority question.** Please provide analyses of body surface area (number of patients, mean, standard deviation and minimum and maximum values) for each of the randomised populations in all treatment arms of the NAPOLI-1 trial. Please show results separately for males and females.

B3. **Priority question.** Page 123 of the company submission (paragraph 2) states:
"*Mean dose intensity was obtained for two arms from the trial (80% for nal-iri + 5-FU/LV, 95% for 5-FU/LV) and incorporated into the economic model. It was assumed that the mean dose intensity for oxaliplatin + 5-FU/LV was the same as for nal-iri + 5-FU/LV (80%)*." However on page 137 (Table 62) of the company submission the relative dose intensity for nal-iri + 5-FU/LV is 85% and the mean dose intensity of 5-FU/LV and oxaliplatin + 5-FU/LV is 95%. Please clarify the appropriate dose intensity for the base case analysis and the required parameter variation values for the deterministic sensitivity analysis.

B4. **Priority question.** Page 123 of the company submission states that the dosing for the FOLFOX comparator regimen is:
"*85mg/m^2 oxaliplatin on day 1, 200mg/m^2 LV followed by 1000mg/m^2 5FU on day 1 over 46 hours given every 2 weeks*."

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However, in Table 54 (page 128) of the company submission the LV dose of the oxaliplatin + 5-FU/LV arm is 400mg/m^2 and the dose of 5FU is 2400mg/m^2. Please indicate the appropriate dosing regimen and associated costs for all of the components of the oxaliplatin + 5-FU/LV comparator.

B5. **Priority question.** Please provide tables, using data from the most recent data cut of the NAPOLI-1 trial, showing Grade 3+ adverse events which occurred in greater than 5% of patients. Please also provide the number of episodes per patient affected and mean duration per episode in days stratified by treatment arm.

B6. **Priority question.** Please provide number of patients, mean (standard deviation) time from diagnosis to randomisation and mean (standard deviation) age for patients in the NAPOLI-1 trial as a frequency table in 6 months segments stratified by treatment arm and gender. The rationale for this request is as follows: *The survival profile is likely to change depending on how long a patient has survival since diagnosis. It is important to understand if and how patients who have already lived with the disease for varying amounts of time might have influenced survival data.*

B7. **Priority question.** Please provide details of any unplanned treatment crossover or subsequent therapies received by patients in the intervention and control arms of NAPOLI-1 trial. Please provide the number (and proportion) of patients who received subsequent treatment on progression for each arm, with a breakdown of subsequent treatments received.

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B8. **Priority question.** Please provide details by treatment cycle of the number of patients receiving full or reduced doses of nal-iri + 5-FU/LV and 5-FU/LV, tabulated as follows:

a) Nal-iri + 5-FU/LV (taking UGT1A1*28 allele status into account)

	Nal-iri							5-FU			All therapies
	Not Homozygous for UGT1A1*28			Homozygous for UGT1A1*28				All patients			All patients
Cycle	80mg/ m^2	60mg/ m^2	50mg/ m^2	80mg/ m^2	60mg/ m^2	50mg/ m^2	40mg/ m^2	Full dose	25% reduction	50% reduction	Discontinued
1 2 . .											

b) 5-FU/LV

	5-FU			All therapy
Cycle	Full dose	25% reduction	50% reduction	Discontinued
1 2 . .				

B9. **Priority question.** On page 128, the footnote for Table 53 states "*Percentages are for patients who did not switch to anti-cancer therapy following disease progression*." Please clarify whether this statement is correct.

B10. Please clarify whether the post progression utility in the model should be 0.671 (in line with ERG amended values as a result of the ID680 Abraxane submission) or 0.672 (which is the utility in the model and company submission, Table 42, page 116). Using a utility value of 0.671 results in a slight decrease in the ICER from £132,360.39 to £132,345.80 compared with 5-FU/LV and from £85,057.19 to £84,986.38 compared with oxaliplatin+5-FU/LV.

Section C: Textual clarifications and additional points

C1. **Priority question.** Please provide the protocol and statistical analysis plan (SAP) for the NAPOLI-1 trial.

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C2. Please ensure the ‘expected date of marketing authorisation’ is marked consistently on pages 15 and 21 of the company submission. Please also reconsider the confidential marking on page 21 because full sentences cannot be marked as confidential, only key data or words.

C3. Please provide an updated checklist to reflect any changes in confidential marking and for the ‘academic in confidence’ data included in your submission, please provide the title of the journal to which the relevant paper will be/has been submitted.

Single technology appraisal

Nanoliposomal irinotecan for treating pancreatic cancer after prior treatment with gemcitabine [ID778]

Baxalta's response to ERG questions

01 June 2016

Section A: Clarification on effectiveness data

Decision problem: comparators

A1. **Priority question.** The company submission states that the most commonly used regimen for patients with pancreatic cancer treated after prior treatment with gemcitabine in England is oxaliplatin with 5-fluorouracil (5-FU) and folinic acid (Leucovorin [LV]). The company submission also states (on page 29) that the most common type of oxaliplatin + 5-FU/LV regimen is mFOLFOX-4 but this is contradicted on page 130, of the submission, where FOLFOX-6 is stated to be the most common regimen. The company submission also states, on page 98, that in the opinion of 3 UK clinical experts, 40% of patients receive either of these regimens. However, on page 144 of the submission it is stated that the current market share is assumed to be 70% FOLFOX, 10% 5-FU/LV and 20% best supportive care (BSC). This suggests that the other comparators in the NICE scope (oxaliplatin + capecitabine and fluoropyrimidine monotherapies other than 5-FU/LV such as capecitabine monotherapy) are not used.

a. Please provide all the results from the interviews with the clinical experts for all treatments (including different oxaliplatin regimens and fluoropyrimidine monotherapies) considered to be used after prior treatment with gemcitabine in England (with %).

A total of six UK clinical experts were consulted regarding the treatment they used in clinical practice for patients failing on gemcitabine. These have been anonymised and are summarised in Table 1.

Capecitabine + oxaliplatin (CAPOX) is used by some clinicians for a small number of patients. However, no economic comparison was possible between nal-iri + 5-FU/LV and CAPOX for this submission due to a lack of evidence for inclusion in an indirect treatment comparison. This was discovered in the NMA feasibility assessment included in the submission (Section 4.10.1). Therefore this small percentage of patients was not included in the budget impact calculations that are referred to on page 144.

Table 1: Clinical expert opinion

Clinician	Treatment used following gemcitabine (for patients who are well enough for further treatment)	FOLFOX regimen used
1	• 80% FOLFOX • 20% CAPOX	mFOLFOX4
2	• Only FOLFOX	mFOLFOX4
3	• 80–90% FOLFOX • 20% CAPOX	mFOLFOX6
4	• Only FOLFOX	mFOLFOX4
5	• Mainly FOLFOX • Sometimes capecitabine monotherapy	mFOLFOX4
6	• Mainly FOLFOX • Rarely fluoropyrimidine monotherapy – less than 10% • Extremely rare use of CAPOX	mFOLFOX6

Abbreviations: CAPOX, capecitabine plus oxaliplatin; FOLFOX, oxaliplatin + 5-fluorouracil/leucovorin.

b. Please provide any additional supporting evidence (e.g. market research) for the regimens that are used after prior treatment with gemcitabine in England.

There is no additional supporting evidence for the regimens used following failure on gemcitabine in England.

c. Please clarify whether the company considers the modified FOLFOX-6 regimens used in either the PANCREOX trial (described at https://clinicaltrials.gov/show/NCT01121848) or SWOG trial (https://clinicaltrials.gov/ct2/show/NCT01658943) to be similar to the FOLFOX-6 regimens it considers are most used in England?

The oxaliplatin + 5-FU/LV regimens used in PANCREOX, SWOG and CONKO-003 (for completeness) are shown in Table 2, along with the mFOLFOX4 and mFOLFOX6 regimens used in UK clinical practice.

Table 2: Oxaliplatin + 5-FU/LV regimens

	Clinical trial			UK clinical practice	
	PANCREOX	**SWOG**	**CONKO-003**	**mFOLFOX4**	**mFOLFOX6**
Oxaliplatin dose	85 mg/m^2 on Day 1	85 mg/m^2 on Day 1	85 mg/m^2 on Days 8 and 22	85 mg/m^2 on Day 1	85 mg/m^2 on Day 1
Oxaliplatin infusion time	2 hours	2 hours	Not specified	2 hours	2 hours
5-FU bolus dose	400 mg/m^2 on Day 1	–	–	400 mg/m^2 on Day 1	400 mg/m^2 on Day 1
5-FU bolus infusion time	2 hours (with oxaliplatin)	–	–	2 hours	2 hours
5-FU dose	2,400 mg/m^2 on Day 1–2	2,400 mg/m^2 on Day 1–2	2,000 mg/m^2 on Days 1, 8, 15 and 22	1,600 mg/m^2 on Day 1	2,400 mg/m^2 on Day 1
5-FU infusion time	46 hours	46–48 hours	24 hours	46 hours	46 hours
Leucovorin dose	400 mg/m^2 on Day 1	–	200 mg/m^2 on Days 1, 8, 15 and 22	200 mg/m^2 on Day 1	350 mg/m^2 on Day 1
Leucovorin infusion time	2 hours (with oxaliplatin)	–	Not specified	2 hours	2 hours
Cycle length	14 days	14 days	42 days	14 days	14 days
Cumulative 6-week dose:					
Oxaliplatin	255 mg/m^2	255 mg/m^2	170 mg/m^2	255 mg/m^2	255 mg/m^2
5-FU	8,400 mg/m^2	7,200 mg/m^2	8,000 mg/m^2	6,000 mg/m^2	8,400 mg/m^2
Leucovorin	1,200 mg/m^2	–	800 mg/m^2	600 mg/m^2	1,050 mg/m^2

Abbreviations: 5-FU, 5-fluorouracil.

As can be seen from Table 2, the clinical trial that most closely resembles mFOLFOX4 and mFOLFOX6 that are used in UK clinical practice is PANCREOX, due to the inclusion of a bolus 5-FU dose and the same infusion time of 5-FU and leucovorin. CONKO-003 does not resembles clinical practice, in that the dose of oxaliplatin received is lower, a bolus 5-FU dose is not given, the infusion time of 5-FU is not the same, and the cycle length is 42 days with a resting period of 20 days between Day 23 and Day 42. The regimen used in PANCREOX is more similar to mFOLFOX6 than to mFOLFOX4 because it includes an identical dose of 5-FU and a similar dose of leucovorin but, as the table shows, both mFOLFOX4 and mFOLFOX6 are more similar to the regimen used in PANCREOX than the regimen used in CONKO-003.

Search strategy and study selection

A2. Please clarify why a search filter for randomised controlled trials (RCTs) was applied to the search strategy (see appendix 2) when both RCTs and non-RCTs were included in the company's systematic review. Please provide details explaining how the non-RCTs were identified.

Both an RCT and non-RCT filter were applied to the search strategy to exclude other non-relevant publications (economic evaluations, epidemiological studies, cost studies, etc.).

The non-RCTs were identified using the same methodology as that used for the RCT evidence:

- Citations were identified via the search strategies in Medline, Embase, and the Cochrane library, and via hand-searching;
- The titles and abstracts of the retrieved citations were screened;
- Potentially relevant full text articles were screened;
- Studies meeting the eligibility criteria were included.

NAPOLI-1 trial

A3. **Priority question.** Please provide the median length of follow-up for the NAPOLI-1 trial for the primary analysis (14 February 2014), interim analysis (25 May 2015) and final analysis (March 2016).

The duration of treatment exposure for each analysis is presented in Table 3.

Table 3: Duration of treatment exposure

	Nal-iri + 5-FU/LV (N=117)	5-FU/LV control (N=119)[†]
Primary analysis (cut-off 14 February 2014)		
Median duration of treatment exposure, months (min, max)	[redacted]	[redacted]
Interim analysis (cut-off 25 May 2015)		
Median duration of treatment exposure, months (min, max)	[redacted]	[redacted]
Final analysis (cut-off March 2016)		
Median time from randomisation to treatment termination, months (95% CI)	[redacted]	[redacted]

Abbreviations: CI, confidence interval; 5-FU, 5-fluorouracil; LV, leucovorin.
[†]This group is a subset of the 5-FU/LV total control group, containing patients who were enrolled in the study after protocol version 2 was activated (the addition of the nal-iri + 5-FU/LV combination arm).

A4. **Priority question.** Study disposition for the NAPOLI-1 trial is given in Figure 4 (page 57 of submission) and Table 13 (page 58 of submission). The former, unlike the latter, includes patients who were enrolled prior to Protocol Version 2. Nonetheless,

the numbers in Figure 13 and Table 4 should be identical for the nanoliposomal irinotecan (nal-iri) + 5-FU/LV arm but a number of discrepancies have been found, including:

a. "Other" reason for treatment discontinuation is lower in Table 13 (1 compared with 3 in Figure 4).

Table 13 in the submission is correct. There appears to be a transcription error in the CSR, which was carried over to Figure 4.

b. Progressive disease based on RECIST v1.1 criteria is lower in Table 13 (57 compared with 64 in Figure 4).

Table 13 in the submission is correct. There appears to be a transcription error in the CSR, which was carried over to Figure 4.

c. Number who died is lower in Table 13 (70 compared with 75 in Figure 4).

Table 13 summarises study disposition using the data reported for 'Study discontinuation'. The number of deaths in Figure 4 is from the OS analysis, based on the reported death dates. Most patients discontinued the study due to death, but there were occasions where a patient discontinued the study for a non-death reason, but the death date was subsequently identified (for example during a survival sweep or death identified via public record).

d. Patients who withdrew their consent is higher in Table 13 (8 compared with 4 in Figure 4).

This is due to the same reason as in (c); patients who withdrew consent for 'Study discontinuation' but had death dates recorded were considered as death for OS status.

In addition, in the nal-iri + 5-FU/LV arm, Figure 4 states that 103 patients discontinued therapy but summing the reasons for discontinuation totals 117 and not 103. Please explain the differences in these numbers and provided any correct data if required.

There appears to be transcription errors in the CSR, which were carried over to Figure 4 of the submission. There were 103 treatment discontinuations, 57 of which were due to progressive disease (64 is incorrect) and 1 due to other reasons (3 is incorrect).

A5. **Priority question.** The company submission details (page 56) that 14 patients in the control arm were never treated. This number includes patients who were enrolled prior to Protocol Version 2.

a. Please provide the number of patients who were never treated, excluding those enrolled prior to the implementation of Protocol Version 2.

The number of patients not treated excluding those enrolled prior to the implementation of Protocol Version 2 are provided in Table 4.

Table 4: Subjects not treated – ITT population

	Nal-iri + 5-FU/LV (N=117)	5-FU/LV control (N=119)†
Subjects not treated, n (%)	**2 (1.7)**	**13 (10.9)**
Reason, n (%)		
Adverse event	0	0
Clinical deterioration	0	0
Investigator decision	0	1 (0.8)
Subject decision	1 (0.9)	11 (9.2)
Other	1 (0.9)	1 (.0.8)

Abbreviations: 5-FU, 5-fluorouracil; ITT, intention to treat; LV, leucovorin.
†This group is a subset of the 5-FU/LV total control group, containing patients who were enrolled in the study after protocol version 2 was activated (the addition of the nal-iri + 5-FU/LV combination arm).

b. Please also clarify whether the patient who was randomised to the control arm but received the nal-iri + 5-FU/LV (and identified in Figure 4, page 57) was enrolled prior to the implementation of Protocol Version 2.

The patient who was randomised to the control arm but received nal-iri + 5-FU/LV was enrolled after the protocol amendment to include the nal-iri + 5-FU/LV combination arm (Protocol Version 2).

c. Please provide baseline characteristics (with the same information as reported in Table 14 of the company submission plus that requested in question A9 below) for the nal-iri + 5-FU/LV and 5-FU/LV arms including only patients enrolled and who received their allocated study treatment following the implementation of Protocol Version 2.

Response to follow.

A6. **Priority question.** Page 52 of the company submission states: "*In order to accurately compare the nal-iri + 5-FU/LV arm to a control arm, an analysis group was used including all patients randomised to 5-FU/LV under Protocol Version 2 or later, who could have been randomised to the active treatment combination. Therefore patients that were randomised to the control arm prior to the protocol amendment were not included in the efficacy analyses in this document*." Please provide details about why the company excluded these data in the efficacy analyses. Please also clarify why analyses of NAPOLI-1 presented in the company submission are only performed using an analysis population of patients who were randomised to 5-FU/LV under Protocol Version 2 or later.

As the submission is for the combination of nal-iri + 5-FU/LV, only this arm and the control arm (5-FU/LV) were presented for the efficacy analyses (and not the nal-iri monotherapy arm). To make an accurate comparison between nal-iri + 5-FU/LV and 5-FU/LV, only patients in the 5-FU/LV arm who were enrolled under Protocol Version 2 or later were used for the control group. This is because only patients enrolled under Protocol Version 2 or later were able to be randomised to either the nal-iri + 5-FU/LV arm, the nal-iri monotherapy arm, or the 5-FU/LV arm. Patients enrolled prior to Protocol Version 2 could only be randomised

to receive either nal-iri monotherapy or 5-FU/LV, and so including these patients in the comparison between nal-iri +5-FU/LV and 5-FU/LV may have led to randomisation bias.

A7. **Priority question.** The number of patients included in the per protocol population analysis is relatively small when compared with the numbers of patients included in the other analyses. Please provide a table with a breakdown of the reasons why patients from the intention-to-treat (ITT) population of NAPOLI-1 were not included in the per protocol population analysis.

A breakdown of the reasons why patients from the ITT population of NAPOLI-1 were not included in the PP analysis are provided in Table 5. The main reason for exclusion was insufficient dosing.

Table 5: Reasons to exclude subjects from the PP population

	Nal-iri + 5-FU/LV (N=117)	5-FU/LV control (N=119)†
Subjects excluded from the PP population, n (%)	**51 (43.6)**	**48 (40.3)**
Reason, n (%)		
Did not meet eligibility criteria: adequate hepatic function	1 (0.9)	1 (0.8)
Enrolled with Vater-Papilla tumour	0	1 (0.8)
Insufficient dosing	47 (40.2)	31 (26.1)
Insufficient evidence of distal metastases	1 (0.9)	1 (0.8)
Not dosed	2 (1.7)	13 (10.9)
Randomised to 5-FU/LV, treated with nal-iri + 5-FU/LV	0	1 (0.8)

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; PP, per protocol.
†This group is a subset of the 5-FU/LV total control group, containing patients who were enrolled in the study after protocol version 2 was activated (the addition of the nal-iri + 5-FU/LV combination arm).

A8. Please provide more detailed information regarding how the required sample size for NAPOLI-1 was calculated. Specifically:

a. What parameters were used for the original sample size calculation performed as part of Protocol Version 1 i.e. power, patient accrual and follow-up times?

A total of 270 patients were to be enrolled under Protocol Version 1, randomised to receive nal-iri or 5-FU/LV. A total of 220 death events were required to detect a median OS difference between the two treatment arms of 3 months vs 4.5 months. Assuming an exponential survival, 14–18 month patient accrual, and up to 3 months follow up, this provides at least an 85% chance (power = 1–β = 0.85; β = 0.15 = the probability of accepting the null hypothesis of no survival difference when it is not true) of detecting a 33% shift in hazard ratio in favour of the best treatment arm. These calculations use an event driven, two-sided un-stratified log rank test with a $\alpha = 0.05$ chance of rejecting the null hypothesis H_0 of no difference in survival between the two treatment arms when H_0 is actually true.

b. After Protocol Version 2, how did the new sample size calculation take into consideration that approximately 65 patients had already been randomised under Protocol Version 1 to a two-arm trial, and that the remainder of

participants recruited would be randomised to one of three arms? Please provide any relevant references that describe the methodology implemented, and software code used to perform the calculations.

For the study sample size considerations after Protocol Version 2, it was assumed that the median OS times were 4.5 months (nal-iri arm), 3 months (5-FU/LV arm) and 6 months (nal-iri + 5-FU/LV arm). These correspond to hazard ratios of 0.67 and 0.5 in favour of the nal-iri arm and the nal-iri + 5-FU/LV arm, respectively, relative to the 5-FU/LV arm. The sample size and power calculations also assumed that approximately 65 patients were randomised under Protocol Version 1 and that the remaining patients were randomised under Protocol Version 2 or later. Power was assessed via simulation in R version 2.13.1. The planned study size provides at least 95% power to detect the OS advantage for the nal-iri + 5-FU/LV arm relative to the 5-FU/LV arm. These power statements are based on pairwise un-stratified log-rank tests using a Bonferroni-Holm adjustment that strongly controls the family-wise error rate for the planned comparisons at the two-sided 0.05 level.

A9. Please provide the following additional baseline information by treatment arm for the ITT population:

a. Time since diagnosis.

b. Duration of advanced disease.

c. Proportion of patients who had had primary surgery.

d. Duration of time on treatment with gemcitabine.

The time since diagnosis, duration of advanced disease (time since first metastatic diagnosis), the proportion of patients who had received prior surgery (including the proportion receiving prior surgery for curative reason, proportion receiving previous Whipple procedure, and proportion with a biliary stent), and the cumulative time on gemcitabine for the ITT population are provided in Table 6.

Table 6: Additional baseline information – ITT population

	Nal-iri + 5-FU/LV (N=117)	**5-FU/LV (N=119)†**
Time since first cytological or histo-pathological diagnosis, months		
N	117	117
Mean (SD)	13.33 (10.839)	12.81 (10.316)
Median	10.3	10.3
Q1, Q3	6.2, 17.1	6.2, 15.1
Min, max	0.5, 67.8	2.5, 57.7
Time since first metastatic diagnosis, months		
N	116	118
Mean (SD)	8.40 (7.432)	7.74 (7.120)
Median	6.9	6.2
Q1, Q3	3.1, 10.9	2.5, 10.6
Min, max	0.3, 46.2	0.2, 48.1

Patients who had received prior surgery, n (%)	94 (80.3)	93 (78.2)
For curative reason	40 (34.2)	43 (36.1)
Whipple procedure	29 (24.8)	33 (27.7)
Biliary stent	15 (12.8)	8 (6.7)
Cumulative time on gemcitabine, weeks[¶]		
N	117	118
Mean (SD)	25 (19.9)	24 (20.7)
Median	22.1	21.4
Q1, Q3	11.1, 31.3	10.1, 28.9
Min, max	0.1, 129.3	2.1, 147.9

Abbreviations: 5-FU, 5-fluorouracil; ITT, intent to treat; LV, leucovorin; SD, standard deviation.
[†]This group is a subset of the 5-FU/LV total control group, containing patients who were enrolled in the study after protocol version 2 was activated (the addition of the nal-iri + 5-FU/LV combination arm). [¶]Time is cumulative, i.e. if a patient had multiple courses with gemcitabine, the value is the sum of the durations of all courses.

A10. Page 62 of the company submission states: "*The combination of nal-iri + 5-FU/LV achieved statistically significantly longer median OS [overall survival] than 5-FU/LV for all analyses*". Similar statements are made on page 64 and page 65 regarding median PFS [progression-free survival] and median TTF [time to treatment failure]. Please clarify how the company has determined median OS/PFS/TTF to be statistically significantly longer for the nal-iri + 5-FU/LV arm than the 5-FU/LV arm. Please provide any formal statistical comparisons of median OS/PFS/TTF values between treatment groups that have been performed including the log-rank test and the differences in hazard ratios rather than in median survival time.

The study primary analysis involved a pairwise comparison of survival in the ITT population using un-stratified log-rank test. The nal-iri + 5-FU/LV arm was tested for superiority to the 5-FU/LV arm, with the corresponding null hypothesis H_0: S_C (t) = S_B (t), where S_C (t) represents the survivor curve for the nal-iri + 5-FU/LV arm and S_B (t) represents the survivor curve for the 5-FU/LV arm. The testing will be according to a Bonferroni-Holm procedure, which strongly controls the family-wise error rate at 0.05 (two-sided) level. H_0 was rejected if the log-rank p-value for this test was less than 0.025.

The hazard ratios, 95% confidence intervals and two-sided p-values from log-rank test are provided in Table 7.

Table 7: Hazard ratios for OS, PFS and TTF

	Value
OS	
Hazard ratio (95% CI)	0.6696 (0.4882, 0.9183)
Two-sided p-value from log-rank test	0.0122
PFS	
Hazard ratio (95% CI)	0.5554 (0.4109, 0.7507)
Two-sided p-value from log-rank test	0.0001
TTF	
Hazard ratio (95% CI)	0.5957 (0.4545, 0.7809)
Two-sided p-value from log-rank test	0.0002

Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.

A11. Please clarify whether any formal testing of the proportional hazards assumption for the outcomes for which analyses were performed using Cox proportional hazards methods for the NAPOLI-1 trial were conducted. If so, please provide these results.

Tests for proportional hazards for the OS endpoint are provided in Table 8.

Table 8: Overall survival: Assessments of proportional hazard assumptions

	Comparison of nal-iri + 5-FU/LV vs 5-FU/LV
Unstratified, ITT population	0.0169
Unstratified, safety population	0.0111
Unstratified, PP population	0.0034
Stratified, ITT population	0.1712
Censoring at change in therapy, ITT population	0.0951
Post-baseline therapy as time-dependent covariate, ITT population	0.0162

Abbreviations: 5-FU, 5-fluorouracil; ITT, intention to treat; LV, leucovorin; PP, per protocol.

A12. The company has not presented any confidence intervals for the hazard ratios for any time-to-event outcomes (including OS and PFS). For all such analyses included in the company submission, including sensitivity analyses, please provide these data.

The 95% confidence intervals for the hazard ratios for time-to-event outcomes and their sensitivity analyses are provided in Table 9.

Table 9: Hazard ratios and 95% confidence intervals for time-to-event outcomes

	Comparison of nal-iri + 5-FU/LV vs 5-FU/LV, hazard ratio (95% CI)
Overall survival	0.6696 (0.4882, 0.9183)
Stratified analysis on ITT population	0.5741 (0.4118, 0.8005)
Safety population	0.6610 (0.4796, 0.9111)
PP population	0.5683 (0.3663, 0.8817)
ITT population (censoring at change in therapy)	0.5665 (0.3858, 0.8319)
Progression-free survival	0.5554 (0.4109, 0.7507)
Stratified analysis on ITT population	0.5107 (0.3701, 0.7046)
PP population	0.4582 (0.3119, 0.6733)
Evaluable population	0.5263 (0.3857, 0.7183)
ITT population (early discontinuation)	0.5542 (0.4145, 0.7410)
ITT population (missing data)	0.5580 (0.4128, 0.7543)
ITT population (progression directly derived from lesion data)	0.5574 (0.4113, 0.7555)
Time to treatment failure	0.5957 (0.4545, 0.78109)
PP population	0.4934 (0.3422, 0.7112)
Evaluable population	0.5809 (0.4310, 0.7829)

Abbreviations: CI, confidence interval; 5-FU, 5-fluorouracil; ITT, intention to treat; LV, leucovorin; PP, per protocol.

A13. Please provide the results of the following sensitivity analyses, including confidence intervals, for OS as described in section 4.4.3.1 of the company submission:

a. Wilcoxon pairwise comparisons of treatments.

The two-sided p-values from Wilcoxon tests for OS, PFS and TTF are provided in Table 10.

Table 10: Wilcoxon test results

	Two-sided p-value from Wilcoxon test: Nal-iri + 5-FU/LV vs 5-FU/LV
Overall survival	0.0009
Progression-free survival	<0.0001
Time to treatment failure	<0.0001

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin.

b. Cox regression model with a time-dependent covariate to account for post-baseline therapy.

The results for the OS Cox regression model with a time-dependent covariate to account for post-baseline therapy for nal-iri + 5-FU/LV vs 5-FU/LV are provided in Table 11.

Table 11: OS Cox regression model with a time-dependent covariate to account for post-baseline therapy

	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=119)
Patients with change in therapy, n (%)	36 (30.77)	45 (37.82)
Died	22 (18.80)	27 (22.69)
Censored	14 (11.97)	18 (15.13)
Alive	14 (11.97)	17 (14.29)
Lost to follow-up	0	1 (0.84)
Subject withdrew consent from follow-up	0	0
Patients with no change in therapy, n (%)	81 (69.23)	74 (62.18)
Died	53 (45.30)	53 (44.54)
Censored	28 (23.93)	21 (17.65)
Alive	23 (19.66)	10 (8.40)
Lost to follow-up	1 (0.85)	0
Subject withdrew consent from follow-up	4 (3.42)	11 (9.24)
Hazard ratio for study treatment (95% CI)	0.6802 (0.4921, 0.9402)	
Two-sided p-value	0.0196	
Hazard ratio for change in therapy (95% CI)	1.0872 (0.7515, 1.5728)	
Two-sided p-value	0.6574	

Abbreviations: CI, confidence interval; 5-FU, 5-fluorouracil; LV, leucovorin; OS, overall survival.

c. Cox regression model with stepwise selection of model terms (p-value to enter <0.25, p-value to remain <0.15).

Results from the Cox regression model including covariates are provided in Table 12 for overall survival, Table 13 for progression-free survival and Table 14 for time to treatment failure.

Table 12: OS Cox regression model including covariates

	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=119)
Excluded from analysis, n (%)	5 (4.27)	10 (8.40)
Died, n (%)	73 (62.39)	78 (65.55)
Censored, n (%)	39 (33.33)	31 (26.05)
HR (p-value) for other model selected terms		
Treatment group: nal-iri + 5-FU/LV	0.580 (0.0012)	
Baseline KPS ≥90	0.639 (0.0089)	
Baseline albumin ≥4 g/dL	0.697 (0.0305)	
Stage 4 at diagnosis	2.042 (0.0003)	
Time since last anti-cancer therapy >1.3 months	0.737 (0.0724)	
Presence of liver metastases	1.873 (0.0012)	
Baseline CA19-9 ≥40 U/mL	1.925 (0.0038)	
Age >65 years	1.338 (0.0781)	

Abbreviations: 5-FU, 5-fluorouracil; HR, hazard ratio; KPS, Karnofsky performance score; LV, leucovorin; OS, overall survival.

Table 13: PFS Cox regression model including covariates

	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=119)
Excluded from analysis, n (%)	5 (4.27)	10 (8.40)
Censored, n (%)	31 (26.50)	21 (17.65)
Progressed, n (%)	65 (55.56)	66 (55.46)
Died, n (%)	16 (13.68)	22 (18.49)
HR (p-value) for other model selected terms		
Treatment group: nal-iri + 5-FU/LV	0.399 (<0.0001)	
BMI ≥22.9 kg/m^2	0.744 (0.0792)	
Time since last anti-cancer therapy >1.3 months	0.785 (0.1291)	
Age >65 years	1.297 (0.1135)	
Prior radiotherapy	1.875 (0.0023)	
Location: N America	1.891 (0.0044)	
Stage 4 at diagnosis	1.931 (0.0002)	
Baseline CA19-9 ≥40 U/mL	2.192 (0.0004)	
Presence of liver metastases	2.205 (<0.0001)	

Abbreviations: BMI, body mass index; 5-FU, 5-fluorouracil; HR, hazard ratio; LV, leucovorin; PFS, progression-free survival.

Table 14: TTF Cox regression model including covariates

	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=119)
Excluded from analysis, n (%)	5 (4.27)	10 (8.40)
Censored, n (%)	13 (11.11)	6 (5.04)
Progressed, n (%)	61 (52.14)	62 (52.10)
Died, n (%)	0	5 (4.20)
HR (p-value) for other model selected terms		
Treatment group: nal-iri + 5-FU/LV	0.471 (<0.0001)	
Time since histopathological diagnosis ≥10.1 months	0.743 (0.0625)	
Baseline albumin ≥4 g/dL	0.807 (0.1468)	
Age >65 years	1.256 (0.1415)	
Location: Europe	0.776 (0.1420)	
Location: N America	1.533 (0.0477)	
Prior exposure to 5-FU	1.559 (0.0045)	
Baseline CA19-9 ≥40 U/mL	1.777 (0.0037)	
Presence of liver metastases	1.911 (0.0001)	

Abbreviations: 5-FU, 5-fluorouracil; HR, hazard ratio; LV leucovorin; TTF, time to treatment failure.

A14. Were tests for interaction performed for the analysis of NAPOLI-1 trial data, which was undertaken to investigate the effects of baseline carbohydrate antigen 19-9 (CA19-9) level on OS (page 68 of company submission)? If so, please provide the results of the test for interaction.

There were no tests for interaction performed for the analysis of the effects of baseline CA19-9 level on OS.

A15. Please clarify in Table 23 (page 67) of the company submission what the median time to first tumour marker response was and corresponding 95% confidence interval for the 5-FU/LV arm? Only one value is presented in Table 23 for the 5-FU/LV arm (3.91) and it is not clear if this is the median time to first tumour marker response, or the lower limit of the confidence interval

The median time to first tumour marker response for the 5-FU/LV control arm was not reached, and 3.91 is the lower limit of the confidence interval. This analysis includes all patients in the tumour marker response evaluable population, with patients who did not achieve tumour marker response censored at their last CA19-9 evaluation. For additional information, Table 15 provides the median time to tumour marker response for patients who responded.

Table 15: Time to tumour marker (CA19-9) response for patients who responded

	Nal-iri + 5-FU/LV (n=117)	5-FU/LV control (n=119)†
Number of patients who responded	28	7
Median time to tumour marker response, months	1.7	2.8
Q1, Q3	1.5, 2.9	2.4, 3.9

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin.
†This group is a subset of the 5-FU/LV total control group, containing patients who were enrolled in the study after protocol version 2 was activated (the addition of the nal-iri + 5-FU/LV combination arm).

A16. The findings for the final analysis of OS and PFS (March 2016) reported on pages 62 and 64 of the company submission **are identical** to those reported for the interim analyses (May 2015). Please clarify that this is correct and not a typographical error.

This is correct and is not a typographical error.

A17. Table 30 (page 78) of the company submission reports the total number of ≥1 treatment emergent adverse events (AEs) resulting in a dose delay, dose reduction and dose discontinuation. Please provide similar data by treatment arm for treatment-related AEs, i.e., the total number of ≥1 treatment-related AEs resulting in a dose delay, the total number of ≥1 treatment-related AEs resulting in a dose reduction and the total number of ≥1 treatment-related AEs resulting in a dose discontinuation.

The number of patients with ≥1 treatment-related AE resulting in a dose delay, dose reduction and dose discontinuation are shown in Table 16.

Table 16: Treatment-related TEAEs

n (%)	Nal-iri (n=147)	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=134)
≥1 treatment related TEAE resulting in dose delay	28 (19.0)	59 (50.4)	19 (14.2)
≥1 treatment-related TEAE leading to dose reduction	43 (29.3)	35 (29.9)	3 (2.2)
≥1 treatment-related TEAE leading to dose discontinuation	10 (6.8)	5 (4.3)	2 (1.5)

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; TEAE, treatment-related adverse event.

The number of treatment-related TEAEs resulting in dose delay and dose reduction per patient are shown in Table 17. The majority of patients experiencing treatment-related TEAEs leading to dose delay (71.93%) and dose reduction (82.86%) in the nal-iri + 5-FU/LV arm only experienced ≤2 treatment-related TEAEs leading to these outcomes.

Table 17: Treatment-related TEAEs per patient

n (%) of patients experiencing treatment-related TEAEs leading to these outcomes	Nal-iri (n=147)	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=134)
Treatment-related TEAEs resulting in dose delay			
1 AE	13 (46.43)	23 (40.35)	12 (63.16)
2 AEs	5 (17.86)	18 (31.58)	5 (26.32)
≤2 AEs	18 (64.29)	41 (71.93)	17 (89.47)
Treatment-related TEAEs leading to dose reduction			
1 AE	22 (51.16)	20 (57.14)	2 (66.67)
2 AEs	11 (25.58)	9 (25.71)	1 (33.33)
≤2 AEs	33 (76.74)	29 (82.86)	3 (100.0)

Abbreviations: AE, adverse event; 5-FU, 5-fluorouracil; LV, leucovorin; TEAE, treatment-emergent adverse event.

Indirect treatment comparison

A18. In the network meta-analysis feasibility assessment (page 71 of company submission), please clarify what is meant by "best-case evidence network", and how this was identified from the wider evidence base.

A best-case evidence network is usually constructed at the first stage of meta-analysis feasibility assessment. The evidence identified from the SR is reviewed in terms of the studies available, and a network is constructed (where common comparators are available across trials). The best case scenario network does not consider the comparability of the study populations or the outcomes reported across the trials. Therefore the best-case scenario provides an overview of the evidence available, but when outcome-specific evidence networks are explored these may differ from the best-case scenario network (because not all of the studies may report a given outcome).

A19. Please provide the data inputs for the indirect comparison described on page 103 of the company submission.

To include oxaliplatin + 5-FU/LV in the economic evaluation, it was necessary to assume equivalent dosing regimens for mFOLFOX6 and OFF. The hazard ratios for PFS and OS in the comparison between oxaliplatin +5-FU/LV and 5-FU/LV were estimated by pooling the data from PANCREOX [1] and CONKO-003 [2], using the standard meta-analysis method. The random effects model was used to account for differences between studies. The results are summarised in Table 18.

Table 18: Random effects model for oxaliplatin + 5-FU/LV vs 5-FU/LV

Study	Number of patients		HR for PFS (95% CI)	HR for OS (95% CI)
	Oxaliplatin + 5-FU/LV	5-FU/LV		
PANCREOX: mFOLFOX6 vs 5-FU/LV	54	54	1 (0.66, 1.53)	1.78 (1.08, 2.93)
CONKO-003: OFF vs 5-FU/LV	76	84	0.68 (0.50, 0.94)	0.66 (0.48, 0.91)
Pooled (random effects)	130	138	0.80 (0.55, 1.17)	1.06 (0.40, 2.81)

Abbreviations: CI, confidence interval; 5-FU, 5-fluorouracil; HR, hazard ratio; LV, leucovorin; OS, overall survival; PFS, progression-free survival.

Hazard ratios for the comparison between nal-iri + 5-FU/LV and oxaliplatin + 5-FU/LV were then estimated by combining the hazard ratios for nal-iri + 5-FU/LV vs 5-FU/LV sourced from NAPOLI-1 with the pooled estimated hazard ratios for oxaliplatin + 5-FU/LV vs 5-FU/LV, using the "adjusted" indirect comparison methodology described by Bucher [3]. The difference in the hazard ratios between nal-iri + 5-FU/LV vs 5FU/LV and oxaliplatin + 5-FU/LV vs 5-FU/LV provides an estimate of the comparison between nal-iri + 5-FU/LV and oxaliplatin + 5-FU/LV. Results are shown in Table 19.

Table 19: Estimated hazard ratios for nal-iri + 5-FU/LV vs oxaliplatin vs 5-FU/LV

	HR for PFS (95% CI)	HR for OS (95% CI)
Nal-iri + 5-FU/LV vs oxaliplatin + 5-FU/LV	0.7 (0.42, 1.17)	0.63 (0.23, 1.76)

Abbreviations: CI, confidence interval; 5-FU, 5-fluorouracil; HR, hazard ratio; LV, leucovorin; OS, overall survival; PFS, progression-free survival.

The technical equations that were used for the adjusted indirect comparison are:

$$HR\ (A\ vs\ B) = HR(A\ vs\ C) / HR(B\ vs\ C)$$

$$Var\ (ln(HR(A\ vs\ B)) = Var(ln(HR(A\ vs\ C)) + Var(ln(HR(B\ vs\ C))$$

Non-randomised controlled trial evidence

A20. Please clarify which tool was used for assessing the quality of NCT00813163 (Appendix 5 of the company submission).

The assessment used to assess the quality of NCT00813163 was developed by Chambers et al [4].

A21. It appears from the information provided for the NCT00813163 study that the 3 weekly regimen for nal-iri was the same as that used for the monotherapy arm in NAPOLI-1 and that patients were not tested for the UGT1A1*28 allele prior to treatment. Please can you confirm whether this is the case?

We can confirm that the 3 weekly regimens for nal-iri was the same as that used for the monotherapy arm in NAPOLI-1. A further response will follow about the testing.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** Please provide full Kaplan-Meier results (see example below) for the following populations of patients:

a. All patients
b. Patients with a KPS 70-80
c. Patients with a KPS 90-100

showing survival estimates at each event time, for all the treatment arms in the NAPOLI-1 trial for:

i. OS.
ii. PFS.
iii. Post-Progression Survival (PPS).
iv. Time to treatment discontinuation.

The full Kaplan-Meier results for the requested outcomes and patient populations are provided in an Excel spreadsheet submitted as a separate document. All analyses are based on the ITT population, the dataset is the final cut (March 2016), KPS score is based on randomisation strata, and PPS is summarised only for patients who had progression according to RECIST v1.1.

B2. **Priority question.** Please provide analyses of body surface area (number of patients, mean, standard deviation and minimum and maximum values) for each of the randomised populations in all treatment arms of the NAPOLI-1 trial. Please show results separately for males and females.

Body surface area data are provided by treatment arm in Table 20.

Table 20: Body surface area

	Nal-iri monotherapy			Nal-iri + 5-FU/LV			5-FU/LV total			5-FU/LV after Protocol Version 2		
	Males	**Females**	**Total**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**
Number of patients	87	64	151	69	48	117	81	68	149	67	52	119
Body surface area, m^2												
Mean (SD)	1.83 (0.212)	1.58 (0.176)	1.72 (0.233)	1.84 (0.197)	1.61 (0.195)	1.74 (0.226)	1.83 (0.269)	1.61 (0.185)	1.73 (0.259)	1.85 (0.268)	1.60 (0.187)	1.74 (0.266)
Min, max	1.4, 2.5	1.3, 1.9	1.3, 2.5	1.5, 2.5	1.3, 2.3	1.3, 2.5	1.3, 2.8	1.2, 2.2	1.2, 2.8	1.3, 2.8	1.3, 2.2	1.2, 2.8

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; SD, standard deviation.

B3. **Priority question.** Page 123 of the company submission (paragraph 2) states:

> "*Mean dose intensity was obtained for two arms from the trial (80% for nal-iri + 5-FU/LV, 95% for 5-FU/LV) and incorporated into the economic model. It was assumed that the mean dose intensity for oxaliplatin + 5-FU/LV was the same as for nal-iri + 5-FU/LV (80%)*." However on page 137 (Table 62) of the company submission the relative dose intensity for nal-iri + 5-FU/LV is 85% and the mean dose intensity of 5-FU/LV and oxaliplatin + 5-FU/LV is 95%. Please clarify the appropriate dose intensity for the base case analysis and the required parameter variation values for the deterministic sensitivity analysis.

This appears to be a typographical error. In the economic model, a relative dose intensity of 85% was used for both nal-iri + 5-FU/LV and oxaliplatin + 5-FU/LV, and a relative dose intensity of 95% was assumed for 5-FU/LV.

B4. **Priority question.** Page 123 of the company submission states that the dosing for the FOLFOX comparator regimen is:

> "*85mg/m^2 oxaliplatin on day 1, 200mg/m^2 LV followed by 1000mg/m^2 5FU on day 1 over 46 hours given every 2 weeks*."

However, in Table 54 (page 128) of the company submission the LV dose of the oxaliplatin + 5-FU/LV arm is 400mg/m^2 and the dose of 5FU is 2400mg/m^2. Please indicate the appropriate dosing regimen and associated costs for all of the components of the oxaliplatin + 5-FU/LV comparator.

Table 54 (page 128) contains errors. The doses used in the model were 85 mg/m^2 oxaliplatin, 200 mg/m^2 LV and 1,000 mg/m^2 5-FU every 2 weeks (as per page 123).

B5. **Priority question.** Please provide tables, using data from the most recent data cut of the NAPOLI-1 trial, showing Grade 3+ adverse events which occurred in greater than 5% of patients. Please also provide the number of episodes per patient affected and mean duration per episode in days stratified by treatment arm.

Grade 3+ adverse events occurring in >5% of patients, the number of episodes per patient affected and the mean duration per episode are shown in Table 21 for nal-iri monotherapy, Table 22 for nal-iri + 5-FU/LV, and Table 23 for 5-FU/LV. If there was no end date for the adverse event, then the input for this value was the date of death or the date of the last study drug plus 30 days, whichever was earlier.

Table 21: Grade 3+ TEAEs for nal-iri monotherapy

		Number of patients experiencing:				Episode duration, days	
Grade 3+ TEAE	**n (%)**	**1 episode**	**2 episodes**	**3 episodes**	**Total no. of episodes**	**Mean (SD)**	**Min, max**
Abdominal pain	12 (8.2)	10	2	–	14	25 (42.3)	1, 167
Anaemia	16 (10.9)	11	4	1	22	15 (23.3)	2, 111
Asthenia	10 (6.8)	9	1	–	11	25 (18.0)	3, 60
Decreased appetite	13 (8.8)	12	–	1	15	25 (20.4)	4, 71
Diarrhoea	31 (21.1)	28	3	–	34	22 (46.8)	2, 276
Fatigue	9 (6.1)	9	–	–	9	42 (40.9)	5, 136
Nausea	8 (5.4)	6	2	–	10	7 (3.0)	3, 11
Neutropenia	8 (5.4)	6	2	–	10	10 (6.9)	1, 22
Neutrophil count decreased	12 (8.2)	7	4	1	18	21 (17.2)	3, 64
Vomiting	20 (13.6)	17	3	–	23	9 (8.3)	1, 38
WBC count decreased	4 (2.7)	3	–	1	6	24 (19.5)	7, 60

Abbreviations: SD, standard deviation; TEAE, treatment-emergent adverse event; WBC, white blood cell.

Table 22: Grade 3+ TEAEs for nal-iri + 5-FU/LV

		Number of patients experiencing:				Episode duration, days	
Grade 3+ TEAE	**n (%)**	**1 episode**	**2 episodes**	**3 episodes**	**Total no. of episodes**	**Mean (SD)**	**Min, max**
Abdominal pain	8 (6.8)	6	2	–	10	31 (39.8)	3, 113
Anaemia	11 (9.4)	8	2	1	15	24 (21.4)	1, 68
Asthenia	9 (7.7)	8	1	–	10	30 (26.8)	4, 85
Decreased appetite	6 (5.1)	6	–	–	6	25 (17.5)	8, 49
Diarrhoea	15 (12.8)	12	3	–	18	10 (7.8)	1, 25
Fatigue	16 (13.7)	13	3	–	19	26 (23.1)	6, 78
Nausea	9 (7.7)	8	1	–	10	24 (45.7)	2,153
Neutropenia	18 (15.4)	15	2	1	23	13 (8.3)	2, 29
Neutrophil count decreased	12 (10.3)	9	2	1	16	20 (22.8)	6, 98
Vomiting	14 (12.0)	11	3	–	17	12 (9.2)	3, 42
WBC count decreased	9 (7.7)	6	2	1	13	15 (9.2)	2, 29

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; SD, standard deviation; TEAE, treatment-emergent adverse event; WBC, white blood cell.

Table 23: Grade 3+ TEAEs for 5-FU/LV

Grade 3+ TEAE		Number of patients experiencing:				Episode duration, days	
	n (%)	1 episode	2 episodes	3 episodes	Total no. of episodes	Mean (SD)	Min, max
Abdominal pain	9 (6.7)	8	1	–	10	11 (8.8)	2, 25
Anaemia	9 (6.7)	7	2	–	11	24 (28.5)	2, 99
Asthenia	9 (6.7)	8	1	–	9	20 (11.2)	3, 38
Decreased appetite	3 (2.2)	3	–	–	3	38 (32.6)	10, 74
Diarrhoea	6 (4.5)	4	2	–	8	6 (5.5)	1, 17
Fatigue	5 (3.7)	5	–	–	5	25 (11.8)	8, 39
Nausea	4 (3.0)	4	–	–	4	8 (4.5)	3, 14
Neutropenia	1 (0.7)	1	–	–	1	15 (–)	–
Neutrophil count decreased	1 (0.7)	1	–	–	1	21 (–)	–
Vomiting	5 (3.7)	4	–	1	7	5 (5.0)	2, 15
WBC count decreased	0	–	–	–	–	–	–

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; SD, standard deviation; TEAE, treatment-emergent adverse event; WBC, white blood cell.

B6. **Priority question.** Please provide number of patients, mean (standard deviation) time from diagnosis to randomisation and mean (standard deviation) age for patients in the NAPOLI-1 trial as a frequency table in 6 months segments stratified by treatment arm and gender. The rationale for this request is as follows: *The survival profile is likely to change depending on how long a patient has survival since diagnosis. It is important to understand if and how patients who have already lived with the disease for varying amounts of time might have influenced survival data.*

Survival data are shown in Table 24.

Table 24: Survival data in 6-month segments

	Nal-iri + 5-FU/LV (n=117)			5-FU/LV (n=119)		
	Males	**Females**	**Total**	**Males**	**Females**	**Total**
Time from randomisation: 0 to <6 months						
Number of patients	36	30	66	51	33	84
Time from diagnosis to randomisation, months, mean (SD)	1.048 (0.9447)	0.998 (0.6496)	1.025 (0.8182)	0.783 (0.6088)	0.962 (0.6712)	0.854 (0.6364)
Age, mean (SD)	63.2 (9.12)	65.5 (7.42)	64.2 (8.40)	61.9 (8.50)	60.1 (8.74)	61.2 (8.59)
Patients with missing diagnosis date	0	0	0	1	0	1
Time from randomisation: 6 to <12 months						
Number of patients	27	16	43	12	17	29
Time from diagnosis to randomisation, months, mean (SD)	1.497 (1.1275)	0.913 (0.7544)	1.280 (1.0352)	1.760 (1.2177)	1.257 (0.7995)	1.472 (1.0118)
Age, mean (SD)	64.4 (8.96)	58.4 (10.79)	62.2 (9.98)	60.9 (9.45)	60.2 (13.24)	60.5 (11.63)
Patients with missing diagnosis date	0	0	0	0	1	1

	Nal-iri + 5-FU/LV (n=117)			5-FU/LV (n=119)		
Time from randomisation: 12 to <18 months						
Number of patients	6	2	8	4	2	6
Time from diagnosis to randomisation, months, mean (SD)	0.670 (0.6739)	1.636 (0.6485)	0.911 (0.7645)	2.103 (1.4445)	2.209 (1.8237)	2.138 (1.3857)
Age, mean (SD)	60.3 (10.41)	60.0 (4.24)	60.3 (8.94)	58.8 (11.32)	67.0 (12.73)	61.5 (11.29)
Patients with missing diagnosis date	0	0	0	0	0	0

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin; SD, standard deviation.

B7. **Priority question.** Please provide details of any unplanned treatment crossover or subsequent therapies received by patients in the intervention and control arms of NAPOLI-1 trial. Please provide the number (and proportion) of patients who received subsequent treatment on progression for each arm, with a breakdown of subsequent treatments received.

There were no unplanned treatment crossovers in NAPOLI-1. The details of subsequent treatment received by patients in each arm are shown in Table 25.

Table 25: Post-treatment anti-cancer therapy

	Nal-iri monotherapy (n=151)	Nal-iri + 5-FU/LV (n=117)	5-FU/LV total (n=149)	5-FU/LV after Protocol Version 2 (n=119)
Received post-treatment anti-cancer therapy, n (%)[†]	56 (37.1)	42 (35.9)	60 (40.3)	50 (42.0)
Gemcitabine-based	18 (11.9)	11 (9.4)	19 (12.8)	14 (11.8)
5-FU-based	41 (27.2)	28 (23.9)	42 (28.2)	35 (29.4)
Irinotecan-based	9 (6.0)	10 (8.5)	15 (10.1)	12 (10.1)
Platinum-based	26 (17.2)	24 (20.5)	29 (19.5)	24 (20.2)
Other non-investigational agents	15 (9.9)	14 (12.0)	14 (9.4)	12 (10.1)
Investigational	5 (3.3)	5 (4.3)	5 (3.4)	4 (3.4)
No record of post-treatment anti-cancer therapy, n (%)	95 (62.9)	75 (64.1)	89 (59.7)	69 (58.0)
Time from last study drug exposure to first post-treatment anti-cancer therapy, weeks[¶]				
N	56	42	58	48
Mean (SD)	5.04 (2.316)	4.93 (4.653)	4.66 (4.212)	4.62 (4.462)
Median	4.6	3.4	3.8	3.7
Q1, Q3	3.2, 6.1	2.7, 5.9	2.9, 4.9	2.9, 4.9
Min, max	2.0, 11.0	0.7, 24.1	0.9, 28.6	0.9, 28.6

[†]Subjects who received therapy in combination are counted in more than one therapy category. [¶]Includes only subjects treated with study drug and who had recorded post-treatment anti-cancer therapy. Two subjects randomised to 5-FU/LV under Protocol Version 2 did not receive study drug and had some record of post-treatment anti-cancer therapy post-randomisation were not included in the analysis.

B8. **Priority question.** Please provide details by treatment cycle of the number of patients receiving full or reduced doses of nal-iri + 5-FU/LV and 5-FU/LV, tabulated as follows:

a) Nal-iri + 5-FU/LV (taking UGT1A1*28 allele status into account)

Dose by treatment cycle for nal-iri (taking UGT1A1*28 allele status into account) and 5-FU in the nal-iri + 5-FU/LV arm are shown in Table 26.

Table 26: Dose details for the nal-iri + 5-FU/LV arm

	Nal-iri dose, mg/m^2								5-FU				All therapy	
	Not homozygous for UGT1A1*28				Homozygous for UGT1A1*28									
Cycle	80	60	50	40	80	60	50	40	Full dose	75%	50%	25%	Discontinued	Total dosed
1	107	3	0	0	0	7	0	0	116	1	0	0	0	117
2	80	17	2	0	3	3	0	0	88	17	0	0	12	105
3	57	17	3	0	4	0	1	0	62	19	1	0	23	82
4	35	15	3	0	3	0	0	1	39	15	3	0	25	57
5	28	16	3	0	2	1	0	1	32	18	1	0	6	51
6	22	17	5	0	2	0	0	1	25	18	4	0	4	47
7	20	13	5	1	1	1	0	1	21	16	5	0	5	42
8	20	10	5	1	1	0	1	0	22	11	5	0	4	38
9	19	11	3	1	1	0	1	0	22	10	4	0	2	36
10	13	7	4	0	1	0	1	0	14	9	3	0	10	26
11	13	6	2	0	1	0	1	0	14	4	5	0	3	23
12	13	6	1	0	1	0	1	0	14	4	4	0	1	22
13	10	4	1	1	1	0	1	0	12	2	4	0	4	18
14	10	3	2	0	1	0	1	0	11	2	4	0	1	17

Cycle	Nal-iri dose, mg/m^2								5-FU				All therapy	
	Not homozygous for UGT1A1*28				Homozygous for UGT1A1*28									
	80	60	50	40	80	60	50	40	Full dose	75%	50%	25%	Discontinued	Total dosed
15	9	2	1	0	1	0	1	0	10	1	3	0	3	14
16	8	2	1	0	1	0	1	0	9	1	3	0	1	13
17	7	2	1	0	1	0	1	0	9	1	2	0	1	12
18	7	2	1	0	1	0	0	0	9	1	1	0	1	11
19	5	2	0	0	1	0	0	0	7	1	0	0	3	8
20	4	2	0	0	1	0	0	0	6	1	0	0	1	7

Abbreviations: 5-FU. 5-fluorouracil; LV, leucovorin.

b) 5-FU/LV

The dose of 5-FU in the 5-FU/LV arm is shown by cycle in Table 27 and by dose in Table 28.

Table 27: Dosing of 5-FU in the 5-FU/LV arm by cycle

Cycle	Full dose	75%	50%	25%	Discontinued	Total dosed
1	96	19	11	8	0	134
2	35	8	5	4	82	52
3	17	4	2	1	28	24
4	12	1	2	2	7	17
5	9	0	2	0	6	11
6	5	0	0	3	3	8
7	3	2	0	0	3	5
8	3	0	0	0	2	3
9	3	0	0	0	0	3

Cycle	Full dose	75%	50%	25%	Discontinued	Total dosed
10	1	2	0	0	0	3
11	0	0	0	1	2	1

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin.

Table 28: Dosing of 5-FU in the 5-FU/LV arm by dose

Dose	Full dose	75%	50%	25%	Discontinued	Total dosed
1	134	0	0	0	0	134
2	123	3	0	1	7	127
3	115	1	0	0	11	116
4	99	2	0	0	15	101
5	50	2	0	0	49	52
6	45	1	1	0	5	47
7	42	1	0	0	4	43
8	38	1	0	0	4	39
9	24	1	0	0	14	25
10	23	1	0	0	1	24
11	20	1	0	0	3	21
12	18	0	0	0	3	18
13	16	0	0	0	2	16
14	14	1	0	0	1	15
15	14	1	0	0	0	15
16	13	1	0	0	1	14
17	10	1	0	0	3	11
18	9	1	0	0	1	10

Dose	Full dose	75%	50%	25%	Discontinued	Total dosed
19	9	1	0	0	0	10
20	8	1	0	0	1	9
21	6	1	0	0	2	7
22	5	1	0	0	1	6
23	5	1	0	0	0	6
24	5	1	0	0	0	6
25	4	0	0	0	2	4
26	4	0	0	0	0	4
27	4	0	0	0	0	4
28	3	0	0	0	1	3
29	3	0	0	0	0	3
30	3	0	0	0	0	3
31	3	0	0	0	0	3
32	3	0	0	0	0	3
33	3	0	0	0	0	3
34	3	0	0	0	0	3
35	3	0	0	0	0	3
36	3	0	0	0	0	3
37	3	0	0	0	0	3
38	3	0	0	0	0	3
39	3	0	0	0	0	3
40	3	0	0	0	0	3
41	2	0	0	0	1	2

Dose	Full dose	75%	50%	25%	Discontinued	Total dosed
42	2	0	0	0	0	2
43	1	0	0	0	1	1

Abbreviations: 5-FU, 5-fluorouracil; LV, leucovorin.

B9. **Priority question.** On page 128, the footnote for Table 53 states "*Percentages are for patients who did not switch to anti-cancer therapy following disease progression*." Please clarify whether this statement is correct.

This appears to be a typographical error. The footnote should read 'Percentages are for patients who did switch to anti-cancer therapy following disease progression; the remaining patients received palliative care. The percentage of patients receiving post-progression treatment after treatment with oxaliplatin + 5-FU/LV is assumed to be the same as after treatment with nal-iri + 5-FU/LV in NAPOLI-1.'

B10. Please clarify whether the post progression utility in the model should be 0.671 (in line with ERG amended values as a result of the ID680 Abraxane submission) or 0.672 (which is the utility in the model and company submission, Table 42, page 116). Using a utility value of 0.671 results in a slight decrease in the ICER from £132,360.39 to £132,345.80 compared with 5-FU/LV and from £85,057.19 to £84,986.38 compared with oxaliplatin+5-FU/LV.

The company agree with the ERG. The post-progression utility should be 0.671 in line with ERG amended values as a result of the ID680 Abraxane submission; this was a typographic error in the model for nal-iri + 5-FU/LV that was carried over to the submission.

Section C: Textual clarifications and additional points

C1. **Priority question.** Please provide the protocol and statistical analysis plan (SAP) for the NAPOLI-1 trial.

Protocol Version 1, Protocol Version 2 and the statistical analysis plan have been submitted as separate documents.

C2. Please ensure the 'expected date of marketing authorisation' is marked consistently on pages 15 and 21 of the company submission. Please also reconsider the confidential marking on page 21 because full sentences cannot be marked as confidential, only key data or words.

The full company submission with consistent marking has been submitted as a separate document.

C3. Please provide an updated checklist to reflect any changes in confidential marking and for the 'academic in confidence' data included in your submission, please provide the title of the journal to which the relevant paper will be/has been submitted.

An updated checklist has been submitted.

References

1. Gill S, Ko Y-J, Cripps MC, et al. PANCREOX: A randomized phase 3 study of 5FU/LV with or without oxaliplatin for second-line advanced pancreatic cancer (APC) in patients who have received gemcitabine-based chemotherapy. J Clin Oncol. 2014; 32.

2. Oettle H, Riess H, Stieler JM, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. J Clin Oncol. 2014; 32: 2423-9.

3. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997; 50: 683-91.

4. Chambers D, Rodgers M, Woolacott N. Not only randomized controlled trials, but also case series should be considered in systematic reviews of rapidly developing technologies. J Clin Epidemiol. 2009; 62: 1253-60 e4.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Nanoliposomal irinotecan for treating pancreatic cancer after prior treatment with gemcitabine [ID778]

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

This is a joint response from Pancreatic Cancer UK and Pancreatic Cancer Action

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 (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.[1] 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.

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[i] 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%[ii] (5.4% in England in 2014[iii]) and a ten year survival of less than 1%[iv]. Metastatic pancreatic cancer patients have a median survival of between just 2 – 6 months.[v]

Pancreatic cancer is not a rare cancer – around 9,400 cases were diagnosed in 2013[vi] - 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[vii], 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.

[1] 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.

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.

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 of having a life-extending treatment, even if it often means that treatment has significant side-effects.

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 currently available for pancreatic cancer patients, we believe that it is vital that all treatment options should be made available to patients on the NHS no matter where they live.

The previously mentioned joint Pancreatic Cancer Action/Pancreatic Cancer UK survey of 2014 found that over 80 per cent of patients, carers and family members would want to see a new drug that offered an extra two months' survival gain approved for use on the NHS, without reservation (the background to the survey at that time was nab-paclitaxel being appraised by NICE). Only 1% of respondents said they would not want the treatment to be made available, based on reported side-effects. The remaining 19% 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.

Given the potential life-extending benefit of nanoliposomal irinotecan, as displayed in the NAPOLI-1[2] trial, has also been shown to be around two months vs the control of 5FU and Folinic Acid, we felt it appropriate to reproduce some of the comments from that 2014 survey here:

[2] Wang-Gillam A et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *The Lancet* 2015

> *"Time is precious and having more time with family means more than anything"*
>
> *"I would give anything for two extra months with my wife and daughter"*
>
> *"It would give me two more months to support my children at a critical stage in their lives"*
>
> *"Two more months to any person with a terminal illness – is a long time, a bit of hope, precious"*

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 quote from 2014 survey)*

In particular there is currently no recognised standard of care for second line treatment of metastatic pancreatic cancer in the UK, let alone a licensed option. A NICE approval of nanoliposomal irinotecan would therefore be of particular importance, providing an extra option – above and beyond the limited off-label treatments - for patients who had had prior treatment with gemcitabine.

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[3].

For those patients with metastatic pancreatic cancer, there are more limited options. Currently, the only standard treatment is with single agent gemcitabine, which 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[4].

[3] Ghaneh et al., (2008) Neoadjuvant and adjuvant strategies for pancreatic cancer EJSO 34 297-305

[4] N Engl J Med. 2011 May 12;364(19):1817-25. doi: 10.1056/NEJMoa1011923.

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.

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[5]. However, this treatment is extremely toxic and only patients with a very high performance status are eligible for this treatment.

Importantly, and of most relevance to this technology appraisal, there is no recognised second line treatment option for metatstatic pancreatic cancer patients who have previously received gemcitabine-based therapy, let alone a licensed option, although Oxaliplatin in combination with flurouracil and folinic acid (FOLFOX) is often used as an off-label, second-line treatment where patients are fit enough. However, clinical trial data on the survival benefit of FOLFOX as a second line for metastatic cancer is ambiguous. Whilst the CONKO[6] trial shows an overall survival benefit similar to that shown by nanolipsomal irinotecan in the NAPOLI-1 trial, a separate trial, PANCREOX, concluded that there was no benefit to FOLFOX vs 5FU and folinic acid alone[7].

A NICE approval of nanoliposomal irinotecan would therefore be of particular importance, providing an extra option – above and beyond the limited off-label treatments - for patients who had had prior treatment with gemcitabine. This might be as a second line treatment for patients who have been treated with mono-gemcitabine therapy and who have responded well; for those who have been treated with gemcitabine-based combination therapy; or perhaps those who have previously been treated with gemcitabine as an adjuvant or neo-adjuvant therapy following surgery.

As such we welcome the development of nanoliposomal irinotecan, which robust trial data has shown offers a significant survival benefit, as well as a manageable safety profile[8]. We hope that the NICE Technology Appraisal will result in a positive recommendation for this new treatment.

[5] Ibid.

[6] Oettle H et al. Secon-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol* 2014; 32:2423-29

[7] Gill S et al. PANCREOX: A randomised phase 3 study of 5FU/LV with or without oxaliplatin for second-line advanced pancreatic cancer (APC) in patients (pts) who have received gemcitabine (GEM)-based chemotherapy (CT). *J Clin Oncol* 32:5s, 2014 (suppl; abtr 4022)

[8] Wang-Gillam A et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *The Lancet* 2015

Yet again, as patient representative organisations we would also stress the importance of choice, for both patients and their clinicians, in ensuring that treatment is best suited to their needs.

4. 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.

There is little widespread patient or carer knowledge of nanoliposomal irinotecan at this time, as it currently has no marketing authorisation in the UK. However, as patient representative organisations, both Pancreatic Cancer Action and Pancreatic Cancer UK have worked to inform patients and carers of the drug, its benefits and side effects as reported in trials. Some patients and carers are also aware of it having been already approved for use in the US and welcome the treatment's reported life extending qualities. The following areas highlight the main benefits patients have told us they expect from the new treatment.

Additional choice

Patients have told us they want to see the introduction of new second line treatments, stressing the importance of all new treatments being fully explored so they can offer patients choice and hope.

Clinical trial data has shown that Nanoliposomal irinotecan therapy could be an alternative second line treatment option for patients who have previously received gemcitabine-based therapy.

This is important as there is no consensus on a second line treatment option for patients who have previously received gemcitabine-based therapy, let alone a licensed option. As noted before, FOLFOX is sometimes used off-label. Nanoliposomal irinotecan offers patients an effective additional option, based on robust trial data. We believe that if NICE approved Nanoliposomal irinotecan as a post gemcitabine treatment, based on the robust evidence from the NAPLOI-1 trial, this could lead to more of a sound basis on which clinicians can make decisions on providing second line treatment for their patients.

Giving patients with advanced disease an extra treatment choice is an advantage in itself, considering the limited number of treatment options currently available.

As previously highlighted, patients and carers tell us of the psychological benefit of knowing that there is another treatment option available to them. This can give them hope where otherwise there is none.

Overall survival

As already noted, the number one benefit patients and carers want to see from new treatments is an extension to overall survival.

Trial data (NAPOLI-1[9]) shows that Nanoliposomal irinotecan in combination with fluorouracil and folnic acid (5FU and Folinic acid) extends overall survival by an average of 1.9 months, compared with 5FU and Folinic acid alone. The benefit presented by giving metastatic patients who have a life expectancy of just two to six months the chance to live up to 50% longer than that average cannot be overstated.

Updated data from the trial presented at the ASCO GI 2016 conference showed that one in four patients treated with Nanoliposomal irinotecan plus 5FU and folinic acid survived one year or more[10]. The data shows a 12-month overall survival estimate of 26% for Nanoliposomal irinotecan combination therapy, a 63% improvement when compared to 16% one year survival for 5FU and folinic acid alone.

This updated data and expanded analysis offers further confirmation of the survival benefit offered by Nanoliposomal irinotecan. Considering the few treatment options currently available to metastatic pancreatic cancer patients and the lack of a licensed standard of care for second line treatment, the introduction of a new treatment with life extending qualities as proven in a

[9] Wang-Gillam A et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *The Lancet* 2015

[10] Wang-Gillam A et al. Updated Data Shows NANOLIPOSOMAL IRINOTECAN Combination Regimen Increased One Year Survival by 63% in Patients with Metastatic Pancreatic Cancer. http://www.prnewswire.com/news-releases/updated-data-shows-nanoliposomal irinotecan-irinotecan-liposome-injection-combination-regimen-increased-one-year-survival-by-63-in-patients-with-metastatic-pancreatic-cancer-300206741.html

robust clinical trial setting would be of benefit to patients who might otherwise be placed on a less effective regimen, or not have a second line treatment offered to them at all.

And whilst two more months may not sound like a lot, it would represent a small, incremental improvement in patient survival that we all want to see, in a disease area that has seen practically no improvement in survival for over 40 years.

Quality of life

Whilst some patients experienced side-effects associated with Nanoliposomal irinotecan, the NAPOLI-1 clinical trial concludes that Nanoliposomal irinotecan combination therapy has a manageable safety profile.

Importantly, the NAPOLI-1 trial also concluded that Nanoliposomal irinotecan combination therapy showed similar toxicity to FOLFOX, with the main difference being that Nanoliposomal irinotecan resulted in less neuropathy[11]. Neuropathy is a particularly common side-effect of treatment with Oxaliplatin, and anecdotal evidence suggests is often the most troublesome for patients receiving the drug.

Neuropathy is nerve damage that can lead to numbness and tingling in the feet or hands, burning or shooting pain, loss of balance and muscle weakness. It can have a significant impact on quality of life and often affects patients' ability to carry out everyday activities, such as buttoning a shirt or making a cup of tea.

As such, Nanoliposomal irinotecan represents an important treatment option for patients who have previously undergone a chemotherapy regimen with high neuropathy, or for whom neuropathy is a particular issue.

Simply knowing there is an approved second line treatment option available would also be beneficial to patients, providing reassurance.

> *"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, Pancreatic Cancer UK)

Having more time to spend with their families can also positively impact on both patients and carers' quality of life. Patients and carers tell us how extra time can allow them to get their affairs in order, attend significant family events or say goodbye to loved ones:

[11] Wang-Gillam A et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *The Lancet* 2015

"We would have had the chance to say a proper goodbye and create some lasting memories" (Carer response, 2014 survey).

"Time to come to terms with it as she was beginning to do. She was very frightened and this may have been lessened with a little more time. A last Christmas with her grandchildren and family. Time to discuss what she wanted as she had not made a will. Time for her family to come to terms with it so we could have been more supportive". (Carer response, 2014 survey).

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Increased survival

Currently, as noted above, there is not a huge amount of information available to patients and carers on the benefits of Nanoliposomal irinotecan. Most patients will not have heard anything about the drug other than that it is available in the US and the topline trial data, namely it can extend overall survival by an average of two months compared to 5FU plus folinic acid. However, we know that patients who have heard of the drug welcome its life extending qualities.

Additional treatment option/patient choice

At the moment, there is no standard of care for second line treatment of metastatic pancreatic cancer, although FOLFOX is the most common second line therapy used off-label despite conflicting evidence surrounding its effectiveness.

The CONKO-003 trial[12] showed an overall survival in patients treated with FOLFOX (5.9 months), which is similar to the survival gain shown by nanoliposomal irinotecan in the NAPOLI-1 trial. However, it is worth noting that a separate trial, PANCREOX, concluded that there was no benefit to FOLFOX vs 5FU and folinic acid alone[13].

That ambiguity over FOLFOX trial data means that nanoliposomal irinotecan combination therapy could represent an overall survival benefit greater than FOLFOX, based on the very robust NAPOLI-1 trial data, and suggests that the regimen is well-positioned to become the standard of care for Gemcitabine-refractory patients[14].

[12] Oettle H et al. Secon-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol* 2014; 32:2423-29

[13] Gill S et al. PANCREOX: A randomised phase 3 study of 5FU/LV with or without oxaliplatin for second-line advanced pancreatic cancer (APC) in patients (pts) who have received gemcitabine (GEM)-based chemotherapy (CT). *J Clin Oncol* 32:5s, 2014 (suppl; abtr 4022)

[14] Wang-Gillam A et al. Updated Data Shows NANOLIPOSOMAL IRINOTECAN Combination Regimen Increased One Year Survival by 63% in Patients with Metastatic Pancreatic Cancer. http://www.prnewswire.com/news-releases/updated-data-shows-nanoliposomal irinotecan-irinotecan-

Furthermore, in March 2016, the National Comprehensive Cancer Network (NCCN) included Nanoliposomal irinotecan combination therapy in its Clinical Practice Guidelines in Oncology as a category 1 second-line therapy for patients with metastatic pancreatic cancer. The move has been seen to validate the importance of the treatment option to pancreatic cancer patients in the USA[15].

Quality of life

The NAPOLI-1 trial concluded that Nanoliposomal irinotecan combination therapy showed similar toxicity to FOLFOX, with the main difference being that Nanoliposomal irinotecan resulted in less neuropathy[16]. Neuropathy is a particularly common side-effect of treatment with Oxaliplatin, and anecdotal evidence suggests is often the most troublesome for patients receiving the drug.

Neuropathy is nerve damage that can lead to numbness and tingling in the feet or hands, burning or shooting pain, loss of balance and muscle weakness. It can have a significant impact on quality of life and often affects patients' ability to carry out everyday activities, such as buttoning a shirt or making a cup of tea.

As such, Nanoliposomal irinotecan represents an important treatment option for patients who have previously undergone a chemotherapy regimen with high neuropathy, or for whom neuropathy is a particular issue.

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.

N/A

5. 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

liposome-injection-combination-regimen-increased-one-year-survival-by-63-in-patients-with-metastatic-pancreatic-cancer-300206741.html

[15] http://www.prnewswire.com/news-releases/merrimack-announces-inclusion-of-nanoliposomal irinotecan-irinotecan-liposome-injection-as-a-category-1-treatment-option-in-the-2016-nccn-guidelines-for-pancreatic-adenocarcinoma-300240814.html

[16] Wang-Gillam A et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *The Lancet* 2015

- 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.

The main concerns patients diagnosed with pancreatic cancer have is that there are a limited number of treatment options available. We have previously heard concern from patients, carers and clinicians that there is a nihilistic attitude towards pancreatic cancer treatment, as so few treatments are available and new treatments shown to be effective are not being approved for use on the NHS.

Please list any concerns patients or carers have about the treatment being appraised.

As previously mentioned, there is little knowledge among patients and carers of the treatment being appraised. However, the main concern patients and carers will have about the treatment is whether they can access it, how toxic the regime may be, and how it will impact on quality of life.

Despite such concerns, patients are still keen for the drug to be made available on the NHS. They highlight that patients should be supported to make an informed choice about whether the treatment is right for them, arguing that this is better than having no choice at all.

As noted above, there is currently no consensus on a second line treatment option for patients who have previously received gemcitabine-based therapy, let alone a licensed option.

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.

N/A

6. 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.

N/A

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

N/A

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☒ Yes ☐ No

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.

Nanoliposomal irinotecan is currently unavailable in the UK, meaning it is not possible to consider whether patients' experience reflect the experiences of patients in clinical trials.

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 NAPOLI-1 trial does capture the most important treatment outcomes for patients and carers by considering overall survival as its primary endpoint and looking at side-effects and progression free survival as secondary endpoints.

However, one limitation to the trial data is that the Nanoliposomal irinotecan combination therapy was only assessed against a combination of 5FU and Folinic acid, not the comparators listed in the final NICE scope (FOLFOX, Oxaliplatin in combination with capecitabine, Fluoropyrimidine monotherapy). This makes it difficult to directly assess the benefits over these comparator drugs.

Nonetheless, it is important to note that there is currently no licensed standard of second line treatment for pancreatic cancer patients and that there seems

to be contradictory trial evidence regarding the benefits of the FOLFOX regime.

There is therefore a strong case for developing a licensed standard of care for second line treatment. A NICE approval for nanoliposomal irinotecan would create this second line treatment for metastatic pancreatic cancer patients previously treated with gemcitabine. This would offer greater clinician and patient choice, and will create more hope of improved overall survival and quality of life for patients and their carers.

We understand that the NAPOLI-1 trial did collect quality of life data, but that has not as yet been published with the rest of the trial results, even though it is expected to be published at a future date. We hope that the relevant data will be made available to NICE to assist them in their deliberations as part of this technology appraisal.

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?

N/A

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 ☐ No

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 can carers attach to improved survival is highlighted by responses to a joint Pancreatic cancer Action and Pancreatic Cancer UK 2014 survey, which saw 80% of respondents state that they 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[17], 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. We believe having a recognised, NICE approved second line treatment for metastatic pancreatic cancer, may lead to more eligible patients being offered the treatment by clinicians. This can only be good news and will add to the currently limited choices patients currently have.

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[18]. 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[19], patients and carers discuss the impact pancreatic cancer has had on their lives. They powerfully tell how scary a diagnosis of pancreatic 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[20] 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.

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[17] Pancreatic Cancer UK, Study for Survival, 2011
http://www.pancreaticcancer.org.uk/media/86664/study-for-surivial-report-final.pdf

[18] 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

[19] pancreaticcanceruk.org.uk/informationandsupport/real-life-stories pancreaticcanceraction.org/about-pancreatic-cancer/cancer-stories/

[20] http://forum.pancreaticcancer.org.uk/index.php

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[21]" 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[22].

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] 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

[22] 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 ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

The particular biology of pancreatic cancer tumours and the way the stroma develops makes the delivery of drugs directly to the tumour difficult and therefore makes pancreatic cancer particularly hard to treat. This is one of the reasons there have been so few new, effective drugs brought forward for pancreatic cancer over the past few decades.

Any new treatment that allows a drug to bypass the stroma and attack the tumour should be treated as innovative, at least when dealing with a cancer as persistently deadly and recalcitrant as pancreatic cancer.

As such, we believe that nanoliposomal irinotecan, which allows for more effective drug delivery to the tumour, should be considered a novel treatment.

Are there any other issues that you would like the Appraisal Committee to consider?

It is vital that when making its decision the Appraisal Committee considers the significant level of unmet need when it comes to pancreatic cancer and the burden of the disease in terms of lack of survival and the lack of treatment options available to patients. The disease has the worst survival of any of the 20 most common cancers and there are very few treatment options available to patients. New treatments are desperately needed to improve survival statistics, which have hardly changed in the last half a century.

Due to this unmet need and the extremely poor survival rates associated with pancreatic cancer, we also feel the treatment 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 as should the fact that this is the very first treatment for second line therapy that comes from a very sound evidence base in the form of the NAPOLI-1 trial. 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.

- There is a clear unmet need for pancreatic cancer. Only 5% of patients survive five years or more. UK survival rates lag behind those of the rest of Europe and indeed the world. Survival rates have barely changed for the last 40 years, which has not been helped by the fact that there has been no newly approved drug for pancreatic cancer (including those that demonstrate a survival advantage) by NICE since gemcitabine in 2001. It is essential that new treatments, where there is robust clinical evidence showing they are effective, 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 and need to know that there are more treatment options open to them.
- There is no approved/standard second line treatment available for pancreatic cancer. Nanoliposomal irinotecan offers the opportunity for an approved treatment option, based on robust clinical data, for this patient population.
- The NAPOLI-1 trial found that nanoliposomal offers a survival benefit of 1.9 months over F5U and Folinic Acid. This may seem a small additional survival gain but as the average life expectancy of pancreatic cancer patients diagnosed with metastatic disease is just two to six months, the survival benefit offered by nanoliposomal irinotecan to this patient group cannot be overstated. Such an increase in overall survival would represent an incremental but significant step towards boosting overall survival rates in pancreatic cancer.
- Trial data indicates benefits of nanoliposomal iriniotecan over the FOLFOX regime. Clinical trial data on the benefits provided by FOLFOX is ambiguous, and there continues to be uncertainty over the survival benefit the drug combination provides. Nanoliposomal Irinotecan causes significantly less neuropathy in patients than FOLFOX, meaning it may prove more tolerable to patients.
- Given the survival gain shown in the NAPOLI-1 trial, we believe that Nanoliposomal irinotecan should be considered under NICE end of life criteria. We believe the usual ‘3 month’ threshold for end-of-life criteria should be waived given the burden of the disease: extremely poor survival rates and the few treatment options available.

[i] CRUK The 20 Most Common Causes of Cancer Death: http://info.cancerresearchuk.org/cancerstats/mortality/cancerdeaths/

[ii] https://www.nice.org.uk/guidance/ng12/evidence/full-guidance-74333341 (P66)

[iii] ONS Cancer Survival in England: adults diagnosed between 2009 and 2013 and followed up to 2014

[iv] http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/pancreatic-cancer/survival#heading-Zero

[v] Spalding and Williamson (2007) Pancreatic Cancer, Medicine Vol 35, pp 325-329

[vi] [vi] http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/pancreatic-cancer/incidence#heading-Zero

[vii] Ghaneh et al., (2008) Neoadjuvant and adjuvant strategies for pancreatic cancer EJSO 34 297-305

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nanoliposomal irinotecan for treating pancreatic cancer after prior treatment with gemcitabine [ID778]

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 name: Dr Pippa Corrie

Name of your organisation

Cambridge University Hospitals 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? YES
- 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.)? YES: Consultant medical Oncologist
- 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?

Patients with metastatic pancreatic cancer generally have a poor prognosis, with life expectancy under 6 months untreated in most cases. Systemic chemotherapy can extend life, although benefits are limited to additional months only. Unfortunately, many patients present at a late stage when they are becoming symptomatic of the disease and poor performance status (PS) limits tolerance to chemotherapy.

In 2001, NICE approved gemcitabine as the first treatment shown to improve survival of patients with metastatic pancreatic cancer and this drug has been the mainstay of treatment up until recently. It is a well tolerated drug, but the definitive clinical trial showed an improvement in survival of 6 weeks compared with 5-fluorouracil (median OS 5.6 versus 4.4 months).

More recently, two combination chemotherapy regimens have reported superior survival compared with gemcitabine: FOLFIRINOX (median OS 11.1 versus 6.8 months) and gemcitabine+nab-paclitaxel (median OS 8.7 versus 6.6 months). Both combination regimens have been tested in fitter patients and drug-induced toxicity is significant with both combination regimens, so they are being adopted as standard of care internationally for ECOG PS 0-1 patients. There is a suggestion that some ECOG PS 2 patients may tolerate gemcitabine+nab-paclitaxel, but the UK experience suggests this is unlikely to be the case.

Therefore, current treatment of metastatic pancreatic cancer is generally as follows:
Around one third of patients diagnosed with metastatic pancreatic cancer are too poorly to be considered for any chemotherapy.
One third of patients are likely to tolerate gemcitabine monotherapy
One third of patients are sufficiently fit to tolerate combination chemotherapy.

For those patients fit for combination chemotherapy, gemcitabine+nab-paclitaxel is more straightforward to administer (a central venous access device is not required and the overall tolerance is probably better than with FOLFIRINOX), but nab-paclitaxel is not approved by NICE and was removed from the CDF last year, so this regimen is only available via clinical trials. FOLFIRINOX is being used particularly in specialist centres, often with modifications to the regimen to ensure tolerability.

Disease progression after first line chemotherapy is pretty much inevitable. Around one third of treated patients may be sufficiently fit to be candidates for second line chemotherapy. There is currently no standard second line chemotherapy in the UK. Patients who have previously received gemcitabine-based chemotherapy may be offered a 5fluoruracil (5FU) -based chemotherapy regimen, which may include capecitabine for less fit patients or combination regimens such as FOLFOX

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(oxaliplatin + 5FU), based on data from the CONKO 03 trial which reported improved survival with an oxaliplatin+5FU regimen compared with 5FU alone in patients progressing after gemcitabine.

Patients progressing after FOLFIRINOX may be offered gemcitabine-based 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?

The main patient subgroups are described above and patient performance status is the main factor limiting access to optimal treatment.

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)?

Nanoliposomal irinotecan (Nal-Iri) combined with 5FU/FA would only be used in secondary care, by specialist pancreatic oncologists experiences in treating patients with this disease.

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?

Nal-Iri is not currently available to NHS patients. I understand the manufacturer has recently opened a compassionate access programme but I have so far been unable to access this and cannot comment further on access critieria.

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.

The most recent UK pancreatic cancer guidelines date back to 2005 and predate modern systemic therapies. The current NICE pancreatic cancer guidelines committee is required not to address the role of any agents undergoing NICE technology appraisals.

The European ESMO 2015 pancreatic cancer guidelines do address second line chemotherapy and idenfity Nal-Iri as an appropriate second line chemotherapy drug t offer patients who have progressed following gemcitabine-based chemotherapy.

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Single Technology Appraisal (STA)

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?

There are no particular concerns or issues regarding use of this agent compared with other similar cytotoxic drugs in this setting.

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.

The main starting rules are that the patient has progressed after gemcitabine-based chemotherapy and performance status is sufficient to offer combination chemotherapy.
Discontinuation should occur on disease progression or lack of tolerance

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?

The NAPOLI-1 phase 3 mulitcentre international trial did involve at least 1 UK centre. Overall, the study does reflect UK practice. The trial confirmed superior OS, PFS, and RR with nalIri+5FU/FA versus 5FU/FA, with acceptable toxicity.

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 main toxicities – myelosuppression, diarrhoea, nausea and vomiting - are those that are very familiar to oncologists dealing with cytotoxic chemotherapy and should be straightforward to manage.

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Single Technology Appraisal (STA)

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;
- 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

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 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.

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Single Technology Appraisal (STA)

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)?

Positive NICE guidance would establish for the first time a second line chemotherapy regimen for patients progressing after gemcitabine-based chemotherapy and would be strongly welcomed by the clinical community. Delivery of the chemotherapy regimen does not pose any specific significant issues. NHS staff would require minimal education and traing and no new facilities/equipment would be required. In reality, for any one hospital, the number of metastatic pancreatic cancer patients accessing second line therapy is extremely small so any impact on capacity is likely to be negligible.

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Single Technology Appraisal (STA)

Nanoliposomal irinotecan for treating pancreatic cancer after prior treatment with gemcitabine [ID778]

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 name: Stephen Falk

Name of your organisation

UHBristol NHS foundation trust/NCRI

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?

x

- 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)
  Chair national Cancer Research Institute Pancreas cancer sub group

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

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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?

Despite its relatively low incidence, pancreatic cancer is the fourth leading cause of cancer mortality and is expected to become the second leading cause of cancer death in the next 2 decades. Poor prognosis for pancreatic cancer is caused by the disease's late stage at presentation, aggressive biology, and poor response to standard therapies. Pancreas cancer is a tumour with significant unmet need. There is widespread clinical nihilism. The national SACT database shows first line gemcitabine is the most commonly employed sole therapy. More aggressive combination treatments such as FOLFIRINOX and Abraxane previously available through the cancer drugs fund are not widely used. Second line therapies are variably used throughout the UK most commonly with Oxaliplatin and a fluouropyrimidine.

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?
Whilst often combined in trials locally advanced inoperable disease should be considered separately to metastatic disease. In general chemotherapy is confined to fit patients (WHO PS0-2). No reliable biomarkers are used in clinical practice.

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)?
This would be used in oncology units accredited through the national peer review process for the administration of systemic chemotherapy..

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?
Technology not available currently

*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.*
Pancreatic cancer NICE guideline in development and actively supported by the NCRI group I chair
https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0802/documents

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Single Technology Appraisal (STA)

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?

Single-arm phase II studies have been conducted after gemcitabine-based therapy; they include single-agent capecitabine, CAPOX (oxaliplatin and capecitabine), FOLFIRI (5-fluorouracil, leucovorin, and irinotecan), other gemcitabine combinations such as GTX (gemcitabine, docetaxel, and capecitabine), and targeted therapies. Randomized clinical trial data have been relatively limited in this setting. A small randomized German study comparing BSC alone versus 5-FU, folinic acid and oxaliplatin plus BSC after gemcitabine failure had to be terminated prematurely owing to low accrual. Several centers participating in this study refused to further accept a 'standard' arm with BSC only after gemcitabine failure. Preliminary results from this trial showed a prolongation of median survival by approximately 2.6 months with the use of chemotherapy (2.3 vs 4.9 months).
Standard practice is in some centres to consider this therapy in previously responding patients.
Irinotecan liposomal in combination with 5-FU/LVF represents a novel attractive treatment option after first-line gemcitabine. The NAPOLI 1 trial is the first to demonstrate in a reasonable number of patients therapeutic benefit. Median survival in the combination therapy arm was reported at 8.9 months versus 5.9 months with the 5-FU/LVF alone (hazard ratio [HR], 0.47; p = 0.0018). There was also an improvement in PFS to a median of 3.1 months with the irinotecan liposomal plus 5-FU/LVF group as compared with 1.5 months for those receiving 5-FU/LVF alone. These results were statistically significant and resulted in FDA approval for irinotecan liposomal this year. Common toxicities with irinotecan liposomal include diarrhea, fatigue, vomiting, nausea, decreased appetite, stomatitis, and fever.

The drug is thus manageable in UK oncology units as a standard of care without additional clinical requirements and good acceptability.

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.
Criteria: standard monitoring of bloods and CT scan after two to three months of treatment representing usual care. Stops at progression of disease or unacceptable toxicity/patient choice. Standard oncology approach.Treatment reserved for metastatic rather than locally advanced disease.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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?
The NAPOLI 1 trial fairly reflects the clinical scenario that patients would be treated. However many patients will have received Abraxane in the first line with gemcitabine in the trial and it is now not available in the UK following its withdrawal from the cancer drugs fund.

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 trial database summarises the toxicities. The drug is not available in the UK to comment on personal experience

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;
- 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 potential impact

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.

Not to my knowledge

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 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)?

Would be provided in existing chemotherapy facilities in oncology units in the UK. There is steady growth in demand in such units in any respect

STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pegylated liposomal irinotecan hydrochloride trihydrate for treating pancreatic cancer after gemcitabine [ID778]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/121/02

Completed 1st July 2016

CONTAINS ACADEMIC AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Pegylated liposomal irinotecan hydrochloride trihydrate for treating pancreatic cancer after gemcitabine [ID778]

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Contributions of authors

Fleeman N	Project lead, drafted clinical results section and supervised the final report
Abdulla A	Critique of the company economic model and proposal of alternative interpretations of the economic evidence
Bagust A	Checking and validation of the economic model and critique
Beale S	Critical appraisal of the clinical and economic evidence, editorial input
Richardson M	Critical appraisal of the statistical evidence
Stainthorpe A	Summary and critical appraisal of economic evidence
Boland A	Critical appraisal of the clinical and economic evidence, editorial input
Kotas E	Critical appraisal of the database searching
McEntee J	Critical appraisal of the submission
Palmer D	Clinical advice and critical appraisal of the clinical sections of the company submission

All authors read and commented on draft versions of the ERG report.

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LIST OF ABBREVIATIONS

5-FU	5-fluorouracil
AE	adverse event
ASCO	American Society of Clinical Oncology
BSA	body surface area
CA19-9	cancer antigen 19-9
CHMP	Committee for Human Medicinal Products
CI	confidence interval
CS	company submission
CSR	clinical study report
ECOG	Eastern Cooperative Oncology Group
eMIT	Electronic Market Information Tool
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
EQ-5D	EuroQol-5 dimension
ERG	Evidence Review Group
FOLFIRINOX	folinic acid (leucovorin) plus 5-fluorouracil plus irinotecan plus oxaliplatin
FOLFIRI	folinic acid (leucovorin) plus 5- fluorouracil plus irinotecan
FOLFOX	folinic acid (leucovorin) plus 5-fluorouracil plus oxaliplatin
H-H	cumulative hazard versus cumulative hazard
HR	hazard ratio
HRQoL	health related quality of life
ICER	incremental cost-effectiveness ratio
ITC	indirect treatment comparison
ITT	intention-to-treat
IVRS	interactive voice recognition system

K-M	Kaplan-Meier
KOLS	key opinion leaders
KPS	Karnofsky performance status
LV	leucovorin
LY	life year
Nal-iri	pegylated liposomal irinotecan hydrochloride trihydrate
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OFF	oxaliplatin plus folinic acid (leucovorin) plus 5-fluorouracil
ORR	objective response rate
OS	overall survival
PAS	Patient Access Scheme
PFS	progression-free survival
PH	proportional hazards
PS	performance status
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life year
Q-TWiST	quality adjusted time without symptoms or toxicity
RECIST	response evaluation criteria in solid tumours
SmPC	summary of product characteristics
TSAP	trial statistical analysis plan
STA	single technology appraisal
TEAE	treatment-emergent adverse event
TR-TEAE	treatment-related treatment-emergent adverse event
TTF	time to treatment failure

1 SUMMARY

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 and economic evidence has been submitted to NICE by Baxalta in support of the use of pegylated liposomal irinotecan hydrochloride trihydrate (Onivyde^{TM}) (hereafter referred to as nal-iri) for use within its anticipated marketing authorisation, i.e. in combination with 5-fluorouracil (5-FU) and folinic acid (also known as leucovorin [LV]) for the treatment of metastatic adenocarcinoma of the pancreas, in adult patients who have progressed following gemcitabine-based therapy.

1.1 Critique of the decision problem in the company submission

The decision problem addressed by the company is similar to the decision problem described in the final scope issued by NICE. Reflecting the anticipated licensed indication for nal-iri+5-FU/LV, the population of interest is adult patients with metastatic adenocarcinoma of the pancreas who have progressed following gemcitabine-basedtherapy. The main difference between the two decision problems is the stated range of comparators. The final scope lists the following comparators:

- oxaliplatin in combination with fluorouracil and folinic acid (oxaliplatin+5-FU/LV),
- oxaliplatin in combination with capecitabine (oxaliplatin+capecitabine)
- fluoropyrimidine monotherapy (e.g. capecitabine or 5-FU).

Evidence provided by the company and clinical advice to the ERG suggest that in the NHS, oxaliplatin+5-FU/LV is the treatment most often given to treat patients with metastatic adenocarcinoma of the pancreas who have progressed following gemcitabine-based chemotherapy (approximately 75% of cases). Oxaliplatin+5-FU/LV is administered in one of three formulations: mFOLFOX6, mFOLFOX4 or OFF. The former two regimens are most frequently used and the specifics of the regimen (and the extent to which it is used) vary by geographical area. Capecitabine monotherapy and oxaliplatin+capecitabine are less frequently used treatment alternatives and 5-FU/LV monotherapy is only rarely used, if at all. The company has only provided evidence for the clinical effectiveness of nal-iri+5-FU/LV versus 5-FU/LV.

The company explored the feasibility of an indirect treatment comparison (ITC) to compare the effectiveness of nal-iri+5-FU/LV with the other comparators detailed in the final scope

issued by NICE. Outputs from these analyses were used in the company model to generate cost effectiveness results for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company conducted a systematic review to identify randomised controlled trials (RCTs) and non-randomised studies (including observational studies) investigating the effectiveness of nal-iri+5-FU/LV and/or comparators relevant to the decision problem. The company identified 13 RCTs and 15 non-randomised studies. Only one RCT was considered directly relevant to the decision problem: the NAPOLI-1 trial.

The NAPOLI-1 trial was a multinational phase III open-label RCT comparing the efficacy and safety of nal-iri+5-FU/LV versus 5-FU/LV and also nal-iri monotherapy versus 5-FU/LV in patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy. Only the former comparison is relevant to the decision problem and only these results are reported in the company submission (CS), although safety data from the nal-iri monotherapy arm are also presented. Randomisation was stratified according to baseline albumin levels (≥4.0 g/dL versus <4.0 g/dL), Karnofsky performance score (KPS) (70 and 80 versus ≥90), and ethnicity (Caucasian versus East Asian versus all others). The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), time to treatment failure (TTF), objective response rate (ORR), tumour marker response, clinical benefit rate (CBR), adverse events (AEs) and health related quality of life (HRQoL). The primary analysis was performed using data from the 14 February 2014 data cut. The primary population for OS, PF, TTF and ORR was the intention-to-treat (ITT) population. According to the company's risk of bias assessment, the NAPOLI-1 trial was of reasonable quality.

Results from the primary analysis of NAPOLI-1 trial data (n=236) show that median OS was longer for patients in the nal-iri+5-FU/LV arm than for patients in the 5-FU/LV arm (6.1 months versus 4.2 months). The difference was statistically significant (hazard ratio [HR] 0.67; 95% confidence interval [CI] 0.49 to 0.92; p=0.0122). Results from subgroup analyses suggest that the treatment effect [redacted] nal-iri+5-FU/LV [redacted] 5-FU/LV [redacted]. Median PFS was longer for patients treated with nal-iri+5-FU/LV than for patients treated with 5-FU/LV (3.1 months versus 1.5 months). The difference was statistically significant (HR 0.56; 95% CI 0.41 to 0.75; p=0.0001). Sensitivity analyses included, but were not limited to, generating results for the per protocol (PP) population. The PP population consisted of patients who received treatment for at least 6 weeks and did not violate any inclusion/exclusion criteria nor

significantly deviate from the protocol, including significant deviations in study drug administration. The company also presented median OS and median PFS results for the ITT population generated from analyses of final data cut (March 2016) data; these results are [redacted] to the interim results presented in the CS.

Safety results are reported in the CS for the safety population (n=251), i.e. patients who received at least one dose (including partial dose) of study medication. In the nal-iri arm, the incidence of AEs was higher than in the 5-FU/LV arm. For patients treated with nal-iri+5-FU/LV the primary reason for dose delay was myelosuppression (e.g. neutropenia), the main reasons for dose reductions were myelosuppression and gastrointestinal disorders and the primary reasons for discontinuation of treatment were gastrointestinal disorders, and infections and infestations.

The primary health related quality of life evidence was derived from the patient-reported outcomes (PRO) population, which only included ITT patients who had completed the EORTC-QLC-C30 questionnaire at baseline and on at least one subsequent occasion ([redacted]). No statistically significant differences were reported between arms in scores at 6 or 12 weeks; comparative EORTC-QLC-C30 data after 12 weeks were not reported. The company also undertook a quality adjusted time without symptoms or toxicity (Q-TWiST) analysis for the ITT population (n=236). The company states that the results from the Q-TWiST analysis (relative Q-TWiST gain of 24%) show that treatment with nal-iri+5-FU/LV results in statistically significant and clinically important gains in quality-adjusted survival compared with treatment with 5-FU/LV. The company reported that a sensitivity analysis conducted in the PP population supported this finding.

The company explored the feasibility of conducting a network meta-analysis (NMA) or ITC to compare nal-iri+5-FU/LV with other relevant comparators (e.g. oxaliplatin+5-FU/LV). The company considered a network of evidence formed by 12 of the 13 RCTs included in its systematic review and presented network diagrams summarising the identified evidence. Three trials could be linked by a common comparator (5-FU/LV): the NAPOLI-1 trial, CONKO-003 trial and PANCREOX trial. The company stated that the proportional hazards (PH) assumptions necessary to generate reliable results were violated for both OS and PFS. In addition, the company considered that trials were too heterogeneous in terms of trial location, patient characteristics, prior treatment with gemcitabine (monotherapy versus combination therapy) and length of trial follow-up for results to be used in an ITC. These limitations led the company to conclude that an ITC was “unfeasible”. Advice, sought by the company, from a panel of three UK key opinion leaders (KOLS) was that it was difficult to

compare the key trials and combining data from them in an ITC might be considered flawed and “naïve”.

Evidence from one phase II non-RCT (NCT00813163) is also presented in the CS, including safety data. This non-randomised study was not included in the company’s systematic review because it only investigated the effectiveness of nal-iri monotherapy. The company states that results from this study show that, overall, the safety profiles of nal-iri+5-FU/LV and nal-iri monotherapy in the NAPOLI-1 trial were consistent with prior experience (i.e. consistent with the results of this study (NCT00813163).

1.3 Summary of the ERG’s critique of clinical effectiveness evidence submitted

The ERG is not aware of any additional RCTs or non-randomised studies that the company should have included as part of the evidence base.

Overall, the ERG agrees with the company that the NAPOLI-1 trial is of reasonable quality, although there is a risk of bias arising from the fact that it was an open-label trial. This may explain why a greater proportion of patients withdrew from the 5-FU/LV arm (10.9%) before treatment than from the nal-iri+5-FU/LV arm (1.7%). The open-label nature of the trial, combined with a lack of independent assessment of disease progression, may also have introduced bias into the assessment of disease progression, favouring nal-iri+5-FU/LV over 5-FU/LV.

Despite slight differences in some baseline characteristics, the ERG is satisfied that the treatment groups in the NAPOLI-1 trial were relatively well balanced. The patient population in the NAPOLI-1 trial was generally similar to the population that is likely to be considered for treatment with nal-iri+5-FU/LV in NHS clinical practice in England, aside from the usual caveat that only suitably fit patients are recruited to clinical trials which means the trial population may be slightly younger and fitter than the population seen in clinical practice.

The ERG is generally satisfied with the statistical approach employed by the company to analyse the data from the NAPOLI-1 trial, with the exception that the results of formal testing of PH for OS, PFS and TTF were not presented in the CS. The ERG’s own analyses show that the assumptions of PH for OS, PFS and TTF in the nal-iri+5-FU/LV and 5-FU/LV arms are not supported and, therefore, the log-rank test results that the company uses to demonstrate statistical significance in terms of median OS, PFS and TTF are not valid.

While the company states that the results of the sensitivity analyses support the primary analyses, the ERG notes that the analyses of data from the PP population generated median

OS and PFS results that were longer (in both treatment arms) than those for the ITT population (OS: 8.9 versus 5.1 months; PFS: 4.3 versus 1.6 months). However, the number of patients in the PP population was relatively small, indicating that only 56% of the nal-iri+5-FU/LV arm (66/117 patients) and 60% of the 5-FU/LV arm (71/117) received treatment for at least 6 weeks and did not violate any inclusion/exclusion criteria nor significantly deviate from the protocol. The most common reason for exclusion from the PP population was "insufficient dosing" or receiving no dose of the study drug. Thus patients in the NAPOLI-1 trial may have experienced considerably more treatment benefit had they been able to receive at least 80% of the planned dose throughout the duration of the study, particularly in the nal-iri+5-FU/LV arm.

Whilst, theoretically, HRQoL data from the NAPOLI-1 trial is useful, the ERG questions whether the EORTC-QLQ-C30 questionnaire results can be considered robust, given the relatively small number of patient responses. The ERG agrees that the Q-TWiST score of 24% suggests a clinically important result. However, the ERG cautions that the Q-TWiST analysis was not presented in the Clinical Study Report (CSR) of the NAPOLI-1 trial and so appears to be a post-hoc exploratory analysis; the findings should therefore be treated with caution.

Despite some apparent differences in the incidence rates of some AEs for patients treated with nal-iri monotherapy in the NAPOLI-1 trial compared with those in the NCT00813163 study, the ERG generally agrees with the company's overall assessment that the safety profiles of nal-iri+5-FU/LV and nal-iri monotherapy are consistent with prior experience with nal-iri, non-liposomal irinotecan and 5-FU.

Regarding the feasibility of conducting an ITC to allow the efficacy of nal-iri+5-FU/LV to be compared with that of other relevant comparators, the ERG agrees with the company that trial heterogeneity is a limitation. However, the ERG's primary reason for rejecting the validity of the results from the ITC relate to the PH assumptions being violated both within and between the arms of the three trials included in the ITC (i.e. the NAPOLI-1, CONKO-003 and PANCREOX trials) for both OS and PFS data. Thus the ERG considers that it is not possible to derive a credible estimate of clinical or cost effectiveness for nal-iri+5-FU/LV compared with oxaliplatin+5-FU/LV.

To enable a crude comparison of efficacy and safety data across key RCTs, the ERG extracted relevant data from RCTs of oxaliplatin+5-FU/LV that were identified in the company's systematic review (i.e. the CONKO-003, PANCREOX, SWOG S1115 and Yoo trials). Overall, the PFS and OS outcomes for patients treated with oxaliplatin+5-FU/LV

reported in these trials are similar in magnitude to the PFS and OS outcomes of patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial. Neutropenia is recognised as a very common AE for patients treated with nal-iri+5-FU/LV, this AE appears to be even more common in patients receiving oxaliplatin+5-FU/LV, and the same is true of the incidence of neurotoxicity. The proportion of patients with grade 3 to 4 neutropenia reported with mFOLFOX6 in the PANCREOX trial was 32.7% compared with 14.5% with nal-iri+5-FU/LV (14.5%) in the NAPOLI-1 trial. Grade ≥3 peripheral neuropathy was reported to be ~4% with the OFF and mFOLFOX6 without 5-FU bolus regimens in the CONKO-003 and SWOG S1115 trials but there were no cases of grade ≥3 peripheral neuropathy (a common neurotoxicity) with nal-ire+5-FU/LV in the NAPOLI-1 trial. Diarrhoea, on the other hand, appears to be more common for patients treated with nal-iri+5-FU/LV than for patients receiving oxaliplatin+5-FU/LV; grade ≥3 diarrhoea was 12.8% with nal-iri+5-FU/LV in the NAPOLI-1 trial, compared with no more than 6.5% with mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial. The ERG urges caution in interpreting the findings from these crude comparisons due to potential differences in the trial populations and advises that they should be considered, at best, to be exploratory.

1.4 Summary of submitted cost effectiveness evidence

The company developed a de novo partitioned survival model in Microsoft Excel to compare the cost effectiveness of treatment with nal-iri+5-FU/LV with (i) oxaliplatin+5-FU/LV (NHS standard care) and (ii) 5-FU/LV (company base case). The model comprised four mutually exclusive health states: pre-progression on treatment, pre-progression off treatment, post-progression treatment (including patients receiving second-line therapy and those receiving palliative care) and death. All patients enter the model in the pre-progression on treatment health state. The model time horizon set at 10 years with a 1-week cycle length. The model perspective was that of the UK NHS. Outcomes were measured in quality adjusted life years (QALYs), and both costs and QALYs discounted at an annual rate of 3.5%, as recommended by NICE. Survival for patients treated with nal-iri+5-FU/LV and those treated with 5-FU/LV was estimated based on data from the NAPOLI-1 trial. Survival for patients treated with oxaliplatin+5-FU/LV was based on data from the company's ITC. Utility values were taken from a previous NICE STA (nab-paclitaxel in combination with gemcitabine for previously untreated metastatic pancreatic cancer [TA360]). Resource use and costs were estimated based on information from the NAPOLI-1 trial, published sources and clinical experts.

The company's (corrected) incremental cost effectiveness ratio (ICER) for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV is £[redacted] per QALY gained and the ICER for

the comparison of nal-iri+5-FU/LV versus 5-FU/LV is £[redacted] per QALY gained. The company did not provide any deterministic sensitivity analyses for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, but one-way sensitivity analyses were conducted for the comparison of nal-iri+5-FU/LV versus 5-FU/LV. The company base case ICER per QALY gained for nal-iri+5-FU/LV versus 5-FU/LV was most sensitive to varying the pre-progression utility values. The results were also sensitive to the cost of nal-iri and to mean body surface area (BSA).

The company conducted probabilistic sensitivity analyses (PSAs). The (corrected) ICER from the PSA for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV is £[redacted] per QALY gained. The company's (corrected) probabilistic ICER for the comparison of nal-iri+5-FU/LV versus 5-FU/LV is £[redacted] per QALY gained. At a cost effectiveness threshold of £50,000 per QALY gained, treatment with nal-iri+5-FU/LV has a [redacted]% probability of being cost effective compared with treatment with oxaliplatin+5-FU/LV or with 5-FU/LV.

The company carried out three scenario analyses comparing nal-iri+5-FU/LV with oxaliplatin+5-FU/LV and with 5-FU/LV. The resultant (uncorrected) ICERs per QALY gained for treatment with nal-iri+5-FU/LV versus treatment with oxaliplatin+5-FU/LV varied from £[redacted] (AE utility decrements omitted) to £[redacted] (using data from the February 2014 data cut from the NAPOLI-1 trial with a log-normal distribution for modelling time-to-event data). The ICERs per QALY gained for the comparison of treatment with nal-iri+5-FU/LV versus treatment with 5-FU/LV varied from £[redacted] (AE utility decrements omitted) to £[redacted] (using log-logistic rather than log-normal distribution for modelling time-to-event data).

1.5 Summary of the ERG's critique of cost effectiveness evidence

The company's decision analytic model is structured appropriately according to conventional practice. An error was detected in the model with regards to the health state utility value for the post-progression health state resulting in an amendment in the base case ICER per QALY gained estimate to £[redacted]. The ERG identified several areas of the concern within the cost effectiveness analysis, namely: (i) the ITC for the nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV comparison (ii) the use of time to event data from the NAPOLI-1 trial, (iii) drug costing and (iv) use of inappropriate health state utility values.

The ERG considers the company's base case ICER for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV to be unreliable due to the use of an invalid ITC. Furthermore, the company's use of the PH assumption is inappropriate since log-normal models are accelerated failure-time models. The ERG conducted a scenario analyses to aid decision

making; the results suggest that any interpretation surrounding the ICER estimate should be made with caution.

The ERG questions the company's use of the log-normal parametric curves to reflect patient survival rather than the mature K-M data from the NAPOLI-1 trial for the nal-iri+5-FU/LV and 5-FU/LV treatment arms. The ERG notes that the use of the K-M data from the NAPOLI-1 trial reduces the mean survival gain for nal-iri+5-FU/LV versus 5-FU/LV from 2.5 to 1.67 months. The company's approach to modelling survival data therefore overestimates the OS of nal-iri+5-FU/LV and underestimates the overall ICER per QALY gained estimate for nal-iri+5-FU/LV versus 5-FU/LV.

In the company model it is assumed that the pre-progression time on treatment for oxaliplatin+5-FU/LV is equivalent to nal-iri+5-FU/LV. This assumption results in the proportion of patients on treatment in the pre-progression on treatment state to exceed the proportion of patients in the PFS state. The requirement of a correction in the company model to prevent this suggests that the company's approach has no logical basis.

The ERG considers several issues attributable to treatment costs in the company model to be unrepresentative of clinical practice in the UK. These include dosing intensity adjustments, undifferentiated BSA calculations (relevant to dosing), drug acquisition costs which do not take into account the availability of generic drug costs or different vial sizes, and the assumption that, in NHS clinical practice, patients are likely to receive further chemotherapy following the failure of second-line treatment.

The ERG also considers the utility values used in the company model to be an overestimate of patient HRQoL. The utility values were obtained from the ERG report for the appraisal of nab-paclitaxel in combination with gemcitabine for previously untreated metastatic pancreatic cancer in a first-line patient population (TA360). The ERG notes that alternative utility values are available that better reflect the target population. Furthermore, the ERG also considers that terminal disutility should have been accounted for in the company model.

1.6 Summary of company's case for end of life criteria being met

The company has put forward a case that nal-iri+5-FU/LV meets the NICE's End of Life criteria. The company states that nal-iri+5-FU/LV will be indicated for patients with a short life expectancy, normally less than 24 months and for a small patient population (10-year prevalence of pancreatic cancer in the UK in 2006 was 4349). The company considers that while the 1.9 month gain in median OS reported in the NAPOLI-1 trial for nal-iri+5-FU/LV compared with 5-FU/LV does not meet the 3 month OS gain stipulated in the End Of Life

guidance criteria, it represents a 45% increase in OS that would be of substantial benefit, given their very short life expectancy at the time diagnosis.

1.7 ERG commentary on end of life criteria

The ERG notes that the life expectancy of patients with metastatic pancreatic cancer is short and that that the anticipated licenced population will be small. The ERG also concurs that the gain in OS for nal-iri+5-FU/LV compared with 5-FU/LV is less than 3 months (both mean and median). However, a more appropriate comparison is nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV. There is a lack of reliable evidence for this comparison. The weight of evidence from the ERG's admittedly exploratory crude comparisons suggests that OS for patients treated with oxaliplatin+5-FU/LV reported in these trials is very similar in magnitude to OS for patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial.

1.8 ERG commentary on the robustness of evidence submitted by the company

1.8.1 Strengths

Clinical evidence

- The company appears to have identified all relevant RCTs that assess the effectiveness of nal-iri+5-FU/LV, and relevant comparators, for the treatment of patients with metastatic pancreatic cancer who have progressed following treatment with gemcitabine
- The key trial of nal-iri+5-FU/LV (the NAPOLI-1 trial) is a phase III multi-centre, multinational, RCT of reasonable quality. The relatively large number of patients in the NAPOLI-1 trial, and the consistency of the results in a diverse population at multiple medical centres worldwide, supports the robustness of the results. Patients from the UK were recruited to the trial.

Cost effectiveness evidence

- The economic model was well constructed and easy to navigate
- The ERG's requests for further data, made via the clarification letter, were fulfilled promptly and to a good standard
- The company made an attempt to compare the cost effectiveness of nal-iri+5-FU/LV with standard NHS care (oxaliplatin+5-FU/LV) despite the absence of head-to-head effectiveness data.

1.8.2 Weaknesses and areas of uncertainty

Clinical evidence

- There is no published RCT that compares the effectiveness of nal-iri+5-FU/LV with oxaliplatin+5-FU/LV, capecitabine monotherapy or oxaliplatin+capecitabine

- Direct evidence for the clinical effectiveness of treatment with nal-iri+5-FU/LV is only available compared with 5-FU/LV, which, in clinical practice in England, is rarely given to patients who have previously received treatment with gemcitabine
- In the NAPOLI-1 trial a greater proportion of patients had received prior gemcitabine combination therapy and fewer patients had received gemcitabine monotherapy than would be seen in the NHS in England
- It is not possible to derive a credible estimate of the relative clinical or cost effectiveness of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV (which is the most commonly used regimen in this setting in NHS clinical practice). The findings from the company's ITC cannot be considered to be reliable as PH assumptions are violated and possible heterogeneity exists. The heterogeneity is both reported (in terms of trial location, patient characteristics, prior treatment with gemcitabine monotherapy versus combination therapy) and possibly unreported across the included trials
- Crude comparisons across trials conducted by the ERG suggested the PFS and OS outcomes for patients treated with oxaliplatin+5-FU/LV reported in these trials are similar in magnitude to the PFS and OS outcomes of patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial. The comparisons are very uncertain and may lack reliability because of potential differences in trial populations

Cost effectiveness evidence

- The use of log-normal models instead of virtually complete NAPOLI-1 trial data only served to add uncertainty to the company's cost effectiveness results
- A number of errors were made when costing treatments and adverse events
- The ERG identified an error in the utility value for the post-progression health state in the company model
- The utility values used in the company model were more reflective of the experience of patients receiving first-line, rather than second-line, treatment for pancreatic cancer
- The company's cost effectiveness results for the comparison of nal-iri+5-FU/LV with oxaliplatin+5-FU/LV must be treated with caution due to lack of effectiveness evidence and the flawed methodology used to model assumed effectiveness.

1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has identified seven areas of concern relating to the approach used by the company to compare the cost effectiveness of nal-iri+5-FU/LV with 5-FU/LV. The result of implementing the ERG's preferred approach to modelling in these areas is a revised ICER of £[redacted] per QALY gained.

The ERG considers that the results (HRs) from the ITC used by the company to facilitate a comparison of the cost effectiveness of treatment with nal-iri+5-FU/LV versus oxaliplatin+5FU/LV are unreliable. The ERG cautions that the ICERs per QALY gained for this comparison are also unreliable and should not be used to inform decision-making.

2 BACKGROUND

2.1 Summary and critique of the company's description of the underlying health problem

The company's description of the underlying health problem is presented in Sections 1.3, 3.1, 3.2 and 3.4 of the company submission (CS).[1] Key points from these sections of the CS are reproduced (as bulleted items) in Box 1.

Box 1 Summary of company's description of underlying health problem

Symptoms

- Patients with pancreatic cancer are usually asymptomatic in the early stages of the disease, which, along with the deep anatomical position of the pancreas, makes the cancer difficult to detect
- Symptoms experienced in the later stages of pancreatic cancer include jaundice, abdominal pain, weight loss, poor appetite, diarrhoea, nausea and vomiting, dyspepsia, back pain, fever, blood clots, fatigue, and new onset diabetes mellitus

Incidence and survival

- Pancreatic cancer is the tenth most common cancer in the UK, and accounts for 3% of all new cases of cancer
- The incidence of pancreatic cancer in the UK was 14.7 per 100,000 people in 2013, equating to 9,408 new cases; 8,389 new cases were recorded in England and Wales (England, n=7,887 and Wales, n=(502)
- Pancreatic cancer is usually at a late stage at the time of diagnosis … 80% to 90% of patients have inoperable or metastatic disease when diagnosed
- The incidence of pancreatic cancer increases with age; it is rare in people younger than 45 years of age and 80% of cases occur in people aged between 60 and 80 years
- The mean age of onset is 71 years for men and 75 years for women
- Pancreatic cancer was responsible for 8,662 deaths in the UK in 2012, almost half of which were in people aged ≥75 years
- Only 21% of patients diagnosed with pancreatic cancer in England and Wales survive for 1 year or more after diagnosis, 3% survive for 5 years or more, and only 1% survive for 10 years or more
- The authors of a systematic review of real-world, peer reviewed, observational European studies (n=91) found that the median life expectancy at diagnosis was 4.6 months in patients with pancreatic cancer irrespective of stage of diagnosis, compared with 15.1 years for an age-matched healthy population, and the median survival for patients with metastatic disease was 2.8 to 5.7 months

Effects of disease on patients, carers and society

- Pancreatic cancer is a condition associated with particularly high burden of illness, since the vast majority of patients present with advanced disease and the symptoms experienced significantly reduce a patient's quality of life
- As well as physical symptoms in later stages of disease, depression and anxiety are also common
- The symptoms that most significantly affect a patient's quality of life compared with the general population are pain, appetite loss, and insomnia, and global health is low, as measured by the European Organisation for Research and Treatment of Cancer (EORTC-QLQ-C30) questionnaire
- The direct medical costs associated with pancreatic cancer are substantial
- The healthcare resource utilisation for patients with pancreatic cancer is high from the time of diagnosis until death

Source: CS, Sections 1.3, 3.1, 3.2 and 3.4

The Evidence Review Group (ERG) considers that the company's description largely presents an accurate picture of the underlying health problem. However, the company's statement that 80% of cases of pancreatic cancer occur in people aged between 60 and 80 years[2] is not supported by recent data. The figure of 80% is reported in guidelines published by the Pancreatic Section of the British Society of Gastroenterology in 2005 and is derived from information published in 1977[3] and 1984.[4] More recent Cancer Research UK data suggest that, between 2011 and 2013, the proportion of new cases in this age range in the UK was 55% and that 31% of new cases occur in people aged 80 years and over.[5] In the pivotal phase III NAPOLI-1 trial[6] of nal-iri+5-FU/LV described in the CS, the ERG notes that in the intention-to-treat (ITT) population, the median age was [redacted] years and the interquartile range was [redacted] years, indicating 50% of patients were aged [redacted] whereas 34% were aged 55 to 70 in the UK, 2011 to 2013.[5] Furthermore, the mean age was 63.2 and 61.0 years in the intervention and control arms of the NAPOLI-1 trial respectively, while as noted by the company in Box 1, the mean age of onset of pancreatic cancer is 71 years for men and 75 years for women.[7]

2.2 Summary and critique of the company's overview of current service provision

In addition to the summary of the company's description of the underlying health problem (see Box 1), a key message conveyed by the company is that, in contrast to many other cancers, the outlook for patients with pancreatic cancer has not improved since the 1970s. The company considers (on page 16 and on page 30 of the CS) that "there is a substantial unmet need for a new treatment that can provide extended survival in a patient population that is currently underserved." The company makes the point that pancreatic cancer grows within a dense, poorly perfused, and nearly impenetrable stroma that limits the ability of current chemotherapies to effectively reach the tumour and achieve effective concentrations.[8] The company highlights that the authors of two All-Party Parliamentary Group (APPG) reports (one published in 2013[9] and the other in 2014[10]) called for more and better treatments for patients with pancreatic cancer and recommended that patients should receive prompt and up-to-date treatment.

The company's overview of current service provision is presented in Sections 1.3, 3.3, 3.5, 3.6 and 3.7 of the CS. Key points from these sections are reproduced (as bulleted items) in Box 2. Overall, the ERG agrees with the company's overview of current service provision but makes three additional points in relation to first-, second- and third- line treatments (see Sections 2.2.1, 2.2.2 and 0 of the ERG report).

Box 2 Summary of company's overview of current service provision

Treatment for patients with early stage disease

- Surgery is the only potentially curative option for pancreatic cancer, but it is only possible for the 10% to 20% of people who present with early stage disease
- Of these patients, 53% to 87.5% have recurrence of their disease despite surgical removal of the tumour

First-line treatment for pancreatic cancer

- Patients with locally advanced or metastatic disease are not suitable for surgical resection, and at the time of diagnosis, 35% to 40% of people have locally advanced disease and 45% to 55% have metastases
- In the UK, gemcitabine is the most commonly prescribed first-line chemotherapy for pancreatic cancer; 46% of patients are administered gemcitabine as first-line therapy, and a further 34% are given gemcitabine in combination with another cytotoxic agent
- Gemcitabine is also the only treatment option that is recommended by NICE as first-line therapy in patients who are not suitable for potentially curative surgery and who have a Karnofsky performance score of ≥50
- The British Society of Gastroenterology (BSG) published guidelines for the management of patients with pancreatic cancer in 2005, following the approval of gemcitabine by NICE in 2001
- The BSG guidelines recommend that gemcitabine should be used as chemotherapy for palliation, and that therapy with novel treatments should only be offered to patients within clinical trials
- There is a poor response rate (20% or less) to gemcitabine-based treatment in the first-line setting and a short progression-free survival (PFS= <4 months)
- An increased use of gemcitabine as adjuvant treatment means that a different treatment may be required on progression

Second-line treatment for advanced and metastatic disease

- Patients who progress on gemcitabine form a substantial patient pool, yet are currently poorly served, with no licensed or NICE recommended treatments available
- Clinical expert opinion has revealed that in the UK, 20% to 40% of patients treated with gemcitabine are well enough to receive active treatment post-gemcitabine
- There is currently no licensed or approved therapies in this setting
- There is currently no standard of care for treatment following disease progression on gemcitabine-based therapy
- Unlicensed treatments are currently used, and their use is supported by lower and conflicting levels of evidence than is considered acceptable in many other cancer indications
- The majority of patients receive one of the FOLFOX regimens containing folinic acid (leucovorin, LV), 5-FU 5-fluorouracil and oxaliplatin. The most commonly used FOLFOX regimen in England is modified FOLFOX4 (mFOLFOX4)
- Very few patients…receive oxaliplatin in combination with capecitabine or receive fluoropyrimidine monotherapy as post-gemcitabine treatment
- It is important to recognise that peripheral neuropathy is a frequent treatment-related adverse event (AE) for oxaliplatin-containing chemotherapy regimens, and is often a cause for dose reductions within the chemotherapy treatment
- Given the conflicting results of these unlicensed treatments and the evidence supporting overall survival improvements with pegylated liposomal irinotecan hydrochloride trihydrate, (nal-iri), it is expected that nal-iri will provide the best option for the treatment of gemcitabine-refractory patients
- The European Society for Medical Oncology (ESMO) guidelines state that nal-iri may be the best option for the treatment of gemcitabine-refractory patients

Source: CS, Sections 1.3, 3,3, 3.5, 3.6 and 3.7

2.2.1 First-line treatment for metastatic pancreatic cancer

The company states that the majority of patients are treated with gemcitabine at first-line. Those who are not treated with gemcitabine are mostly treated with oxaliplatin in combination with 5-fluorouracil (5-FU), leucovorin (LV) and irinotecan, also known as FOLFIRINOX (FOL=Folinic acic [LV], F=5-FU, IRIN=irinotecan, OX=oxaliplatin.)

In the study (Smyth 2015[11]) cited by the company, 80% of 191 UK patients with metastatic pancreatic cancer who were diagnosed between 1 January 2009 and 31 December 2012 were treated with gemcitabine (46% monotherapy, 34% combination therapy), 12% were treated with FOLFIRINOX and other treatments accounted for the remaining 8% of the population. The ERG notes that the data from the Smyth study are derived from a purposive sample (of 50 physicians in the UK and 53 physicians in France) rather than a random sample. The ERG is aware that the first randomised controlled trial (RCT) to show evidence of the effectiveness of FOLFIRINOX versus gemcitabine as a first-line treatment was not published until 2011,[12] and so prior to this, and at the time of the Smyth 2015 study,[11] FOLFIRINOX was less commonly used than it is now. Clinical advice to the ERG is that FOLFIRINOX is used in the NHS in England in approximately 15% to 20% of cases (being an option only for fitter patients, most likely those with ECOG PS 0 to 1). Indeed, the ERG notes that in the 2014 STA for nab-paclitaxel in combination with gemcitabine for the treatment of metastatic pancreatic cancer,[13] it was reported by the manufacturer that, in clinical practice in England and Wales, 49% of patients received gemcitabine monotherapy, 25% received combination therapy (gemcitabine in combination with capecitabine) and 19% received FOLFIRINOX. Nab-paclitaxel in combination with gemcitabine was not recommended by NICE. Expert advice received by the ERG is that in some geographical areas of England, the proportion of patients treated with FOLFIRINOX in the NHS may be higher than 20%.

2.2.2 Second-line treatment for metastatic pancreatic cancer

The company argues that:

> "Patients who progress on gemcitabine form a substantial patient pool, yet are currently poorly served, with no licensed or NICE recommended treatments available. Therefore, unlicensed treatments are currently used, and their use is supported by lower and conflicting levels of evidence than is considered acceptable in many other cancer indications." (CS, page 16)

The company notes that in England, oxaliplatin in combination with 5-FU/LV (oxaliplatin+5-FU/LV) is the most commonly used treatment for this patient population. Oxaliplatin+5-FU/LV regimens are commonly known as FOLFOX (FOL=Folinic acid [LV], F=5-FU, OX=oxaliplatin). Modified versions of FOLFOX regimens exist, e.g. modified FOLFOX4 (mFOLFOX4), modified FOLFOX6 (mFOLFOX6) and a regimen known as OFF (oxaliplatin, folinic acid [LV], fluorouracil [5-FU]). These regimens differ in terms of the cumulative dose of 5-FU, the use of bolus 5-FU, the total dose of oxaliplatin, and the overall scheduling of treatment. A comparison of the different regimens is presented in Table 1. The ERG is not aware of any RCT evidence to suggest that any particular regimen is more effective than any other in terms of efficacy or safety.

Table 1 Typical oxaliplatin+5-FU/LV regimens described in the literature and used in clinical practice

Regimen details	UK clinical practice		Clinical trials (unpublished)		Published trial
	mFOLFOX4	mFOLFOX6	mFOLFOX6 (PANCREOX)	mFOLFOX6 (SWOG S1115)	OFF (CONKO-003)
Oxaliplatin dose	85 mg/m^2 Day 1	85 mg/m^2 Day 1	85 mg/m^2 Day 1	85 mg/m^2 Day 1	85 mg/m^2 Days 8 and 22
Oxaliplatin infusion time	2 hours	2 hours	2 hours	2 hours	Not specified
5-FU bolus dose	400 mg/m^2 Day 1	400 mg/m^2 Day 1	400 mg/m^2 Day 1	--	--
5-FU bolus time	2 hours	2 hours	2 hours (with oxaliplatin)	--	--
5-FU infusion dose	1600 mg/m^2 Day 1	2400 mg/m^2 Day 1	2400 mg/m^2 Day 1 to 2	2400 mg/m^2 Day 1 to 2	2000 mg/m^2 Days 1, 8, 15 and 22
5-FU infusion time	46 hours	46 hours	46 hours	46 to 48 hours	24 hours
Leucovorin dose	200 mg/m^2 Day 1	350 mg/m^2 Day 1	400 mg/m^2 Day 1	--	200 mg/m^2 Days 1, 8, 15 and 22
Leucovorin infusion time	2 hours	2 hours	2 hours (with oxaliplatin)	--	Not specified
Cycle length	14 days	14 days	14 days	14 days	42 days
Cumulative 6-week dose					
Oxaliplatin	255 mg/m^2	255 mg/m^2	255 mg/m^2	255 mg/m^2	170 mg/m^2
5-FU	6000 mg/m^2	8400 mg/m^2	8400 mg/m^2	7200 mg/m^2	8000 mg/m^2
Leucovorin	600 mg/m^2	1050 mg/m^2	1200 mg/m^2	--	800 mg/m^2

-- Not applicable (i.e. no use of bolus 5-FU and/or no explicit mention is made that 5-FU was modulated with leucovorin)
Source: Company response to ERG clarification letter, adapted from Table 2

Clinical advice to the ERG is that the OFF regimen is rarely used in England, if at all. Within the CS there is a lack of clarity as to which is the most commonly used FOLFOX regimen in the NHS:

- mFOLFOX4 is stated to be the most commonly used FOLFOX regimen in England (CS, page 16)

- FOLFOX6 is stated to be the most commonly used FOLFOX regimen in the UK (CS, page 130)
- Key opinion leaders (KOLS) estimate that 40% of post-gemcitabine metastatic pancreatic cancer patients who are eligible for further treatment would receive either mFOLFOX4 or FOLFOX6 (CS, page 98)

In response to the ERGs clarification request, the company presented findings from the opinions of six KOLS based in the UK who were consulted regarding the treatment they used in clinical practice for patients with disease progression on gemcitabine (Table 2). The findings clearly show that practice varies within the UK but that, essentially, the most common regimen is either mFOLFOX4 or mFOLFOX6, depending on geographical area. Clinical advice to the ERG (Table 2) is that mFOLFOX6 is the most common treatment regimen.

Table 2 Most commonly used post-gemcitabine treatments cited by clinical experts

Clinician	Treatment used following gemcitabine (for patients who are well enough for further treatment)	Oxaliplatin+5-FU/LV regimen used
1	80% oxaliplatin+5-FU/LV 20% oxaliplatin+capecitabine	mFOLFOX4
2	Only oxaliplatin+5-FU/LV	mFOLFOX4
3	80% to 90% oxaliplatin+5-FU/LV 20% oxaliplatin+capecitabine	mFOLFOX6
4	Only oxaliplatin+5-FU/LV	mFOLFOX4
5	Mainly oxaliplatin+5-FU/LV Sometimes capecitabine monotherapy	mFOLFOX4
6	Mainly oxaliplatin+5-FU/LV Rarely fluoropyrimidine monotherapy – less than 10% Extremely rare use of oxaliplatin+capecitabine	mFOLFOX6
ERG*	75% oxaliplatin+5-FU/LV 25% capecitabine monotherapy	mFOLFOX6

Source: Company response to ERG clarification letter' Table 1 and *clinical advice received by the ERG

The findings in Table 2 also show that the extent of treatment other than oxaliplatin+5-FU/LV also varies by geographical area. As the company has stated: "Very few patients, if any, receive oxaliplatin in combination with capecitabine [oxaliplatin+capecitabine] … as post-gemcitabine treatment" (CS, page 16). However, the company also states in the CS that very few patients receive fluoropyrimidine monotherapy as post-gemcitabine treatment. Fluoropyrimidine monotherapy tends to be preferred where patients are not considered able to tolerate oxaliplatin and may comprise capecitabine monotherapy or 5-FU/LV. Capecitabine monotherapy tends to be the fluoropyrimidine monotherapy used by most clinicians in such situations. Indeed, the ERG notes that in the Smyth 2015[11] study, the most commonly used second-line treatments (not necessarily post-gemcitabine) for patients with metastatic pancreatic cancer were capecitabine monotherapy (27.6%),

oxaliplatin+capecitabine (24.1%) and gemcitabine (10.3%). Clinical advice received by the ERG is that gemcitabine is most commonly used for patients previously treated with FOLFIRINOX. It is not commonly used for patients who have previously been treated with gemcitabine but may be used again in some instances where patients have been disease-free after completing treatment with gemcitabine for a relatively long time (e.g. 12 months).

2.2.3 Third-line treatment for metastatic pancreatic cancer

The ERG notes that very few patients with metastatic pancreatic cancer live long enough to receive third-line treatment. In the aforementioned Smyth 2015[11] study only 1 (0.5%) out of 191 patients in the UK sample received a third-line treatment. The specific regimen received by the patient is not known.

2.2.4 Pegylated liposomal irinotecan hydrochloride trihydrate

Pegylated liposomal irinotecan hydrochloride trihydrate (nal-iri) does not currently have a marketing authorisation from the Committee for Human Medicinal Products (CHMP). CHMP positive opinion is expected circa 21 July 2016. If approved, it is anticipated that it will be provided in combination with 5-fluorouracil (5-FU) and folinic acid (also known as leucovorin [LV]) for the treatment of metastatic adenocarcinoma of the pancreas, in adult patients who have progressed following gemcitabine-based therapy, i.e. after previous treatment with gemcitabine in any setting: adjuvant, neoadjuvant, first-line metastatic, second-line metastatic or even later.

Nal-iri is a nanoliposomal formulation of the anti-cancer drug irinotecan. Irinotecan is a derivative of camptothecin, which inhibits the DNA enzyme topoisomerase I. It is converted by non-specific carboxylesterases present in the liver, blood and macrophages[14] into its metabolite SN-38, which is 100- to 1000-fold more active than irinotecan. Whilst non-liposomal irinotecan is sometimes used as a component drug of the FOLFIRINOX regimen (i.e. in combination with oxaliplatin+5-FU/LV) as a first-line treatment for metastatic pancreatic cancer, it is rarely used as a second-line or later treatment. It has, however, been studied in combination with 5-FU/LV (but not with oxaliplatin) as part of a regimen known as FOLFIRI (folinic acid [LV], 5-FU, irinotecan).[12,15-17]

The rationale for developing a nanoliposomal formulation of irinotecan is that nanoliposomes are expected to accumulate within the tumour and release irinotecan slowly over time. This should yield a higher concentration of chemotherapeutic agent in the tumour, decrease the rate at which it is removed from the body and result in better tumour shrinkage or slower

tumour growth than could be obtained with non-liposomal irinotecan. The ERG is not, however, aware of any clinical trial that has compared nal-iri with non-liposomal irinotecan.

As highlighted in Box 2, the company expects that nal-iri in combination with 5-FU/LV (nal-iri+5-FU/LV) will provide the best option for the treatment of gemcitabine-refractory patients, a statement supported in the European Society for Medical Oncology (ESMO) guidelines. However, based on clinical opinion received, the ERG considers nal-iri+5-FU/LV is likely to be preferred for patients who are considered to be at risk of peripheral neuropathy, which is a frequent treatment-related adverse event (AE) for patients treated with regimens containing oxaliplatin. The company also expects that, if recommended by NICE, take-up of nal-iri+5-FU/LV will be gradual. It estimates that only 5% of patients potentially eligible for treatment post-gemcitabine would actually receive nal-iri+5-FU/LV in the first year it becomes a treatment option.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

Table 3 summarises the decision problem described by the company in the CS in relation to the final scope issued by NICE. Each parameter is discussed in more detail (Section 3.1 to Section 3.7) in the text following Table 3.

Table 3 Final scope issued by NICE and company's decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission
Population	People with metastatic adenocarcinoma of the pancreas that has been treated with gemcitabine-based treatments	Adult patients who have progressed following gemcitabine-based therapy (reflecting trial evidence and the anticipated therapeutic indication in the draft Summary of Product Characteristics; nal-iri does not currently have a marketing authorisation)
Intervention	Pegylated liposomal irinotecan hydrochloride trihydrate in combination with fluorouracil and folinic acid	As per scope
Comparator (s)	• Oxaliplatin in combination with fluorouracil and folinic acid [leucovorin] • Oxaliplatin in combination with capecitabine • Fluoropyrimidine monotherapy	• Oxaliplatin in combination with fluorouracil and folinic acid (oxaliplatin+5-FU/LV) • 5-fluorouracil+leucovorin (5-FU/LV) (a fluoropyrimidine monotherapy) Oxaliplatin in combination with capecitabine is not included a comparator due to a lack of evidence to enable a comparison; this regimen is not commonly used in clinical practice in England
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • Health related quality of life	As per scope
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	As per scope
Subgroups to be considered	None specified	As per scope
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	A Patient Access Scheme (PAS) is currently being considered by the PAS Liaison Unit The company highlights appropriate access to a treatment such as nal-iri+5-FU/LV should improve the patient experience for patients with rarer forms of cancer, such as metastatic pancreatic cancer and therefore for elderly patients (i.e. improve equity)

Source: Final scope issued by NICE and CS, Table 1

3.1 Population

The company has provided evidence for the population for which it expects the intervention to be licensed (since nal-iri does not currently have a marketing authorisation; CHMP positive opinion is expected circa 21 July 2016), i.e. treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) in adult patients who have progressed following gemcitabine-based therapy. The company highlights that patients who have progressed following gemcitabine-based therapy can include patients previously treated with monotherapy or combination therapy. The ERG notes that the licence, if granted, will be largely based on the clinical results from the NAPOLI-1 trial. In the NAPOLI-1 trial, patients were allowed to have received previous gemcitabine therapy in any setting, i.e. in the adjuvant or neoadjuvant setting (12.2%) first-line (56.1%) or second- line or later (31.7%) treatment for metastatic pancreatic cancer.

3.2 Intervention

The intervention is pegylated liposomal irinotecan hydrochloride trihydrate (nal-iri) in combination with 5-FU and folinic acid (also known as leucovorin [LV]). As noted above, the intervention is not currently licensed.

The recommended dose and regimen of nal-iri is 80 mg/m^2 administered intravenously over 90 minutes, diluted prior to administration with 5% glucose solution or 0.9% sodium chloride solution for injection to a final volume of 500 mL; it must not be administered as a bolus injection or an undiluted solution. Nal-iri is then followed by LV 400 mg/m^2 administered intravenously over 30 minutes, followed by 5-FU 2400 mg/m^2 administered intravenously over 46 hours. Nal-iri+5-FU/LV is administered every 2 weeks.

A reduced starting dose of nal-iri of 60 mg/m^2 should be considered for patients known to be homozygous for the *UGT1A1*28* allele (since patients homozygous for this allele have been found to be at increased risk of developing haematological (e.g. neutropenia) and/or digestive toxicities).[18] A dose increase of nal-iri to 80 mg/m^2 should be considered if tolerated in subsequent cycles. The ERG notes that testing for *UGT1A1*28* is not routinely conducted in NHS clinical practice. Therefore, if nal-iri+5-FU/LV was to be used in clinical practice without prior testing, this may mean that some AEs reported in the NAPOLI-1 trial would occur more often in clinical practice, resulting in more dose reductions which would likely be required as a result. The ERG also notes that in healthy individuals, it has been estimated that the proportion of people homozygous for *UGT1A1*28* is higher in people with varying degrees of African ancestry (18.1%) than Caucasians of European ancestry (11.3%) or Asians of Chinese and Japanese descent (2.1%).[19]

As described in Section 2.2 of this ERG report, 5-FU/LV is also used as a first-line treatment as part of the FOLFIRINOX regimen and as a second-line treatment as part of the FOLFOX regimen. The cumulative dose of 5-FU/LV, and whether bolus 5-FU is used, varies in the FOLFOX regimens (see Section 2.2, Table 1). The dose and scheduling for 5-FU/LV in combination with nal-iri is similar to the dose and scheduling for 5-FU/LV in combination with oxaliplatin in the mFOLFOX6 regimen. The only difference is that the mFOLFOX6 regimen used in England typically includes a bolus injection of 5-FU prior to it being infused over 46 hours, whereas in combination with nal-iri, there is no bolus injection of 5-FU prior to it being infused over 46 hours.

3.3 Comparators

The final scope issued by NICE and the company's decision problem identify three comparators:

- oxaliplatin+5-FU/LV
- oxaliplatin+capecitabine
- fluoropyrimidine monotherapy.

The company only compares the clinical effectiveness of nal-iri+5-FU/LV with 5-FU/LV (a fluoropyrimidine monotherapy). Both 5-FU/LV and oxaliplatin+5-FU/LV are comparators to nal-iri+5-FU/LV in the company's economic evaluation.

As highlighted in Section 2.2, oxaliplatin+5-FU/LV is the most commonly used second-line treatment for patients with metastatic pancreatic cancer in England and different formulations of oxaliplatin+5-FU/LV exist; mFOLFOX4 and FOLFOX6 are the most commonly used formulations in England, depending on geographical area. Nal-iri+5-FU/LV has not been compared with any oxaliplatin+5-FU/LV regimen in clinical trials. To allow a comparison of cost effectiveness to be undertaken, the company has conducted an indirect treatment comparison (ITC) to generate clinical effectiveness results for treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV. In its approach, the company assumes the OFF and mFOLFOX6 regimens administered in the CONKO-003 and PANCREOX trials are representative of the efficacy of oxaliplatin+5-FU/LV. As oxaliplatin+5-FU/LV is the most commonly used regimen in England, the ERG acknowledges that the company's attempt to make this comparison was appropriate and that, in the absence of evidence to the contrary, all oxaliplatin+5-FU/LV regimens may be considered to be of equal efficacy in clinical practice (see also Section 4.7 of this ERG report). However, for reasons outlined in Section 4.3 of this ERG report, the ERG agrees with the company that the results from the ITC cannot be considered reliable.

Clinical advice to the ERG and clinical advice received by the company suggests 5-FU/LV monotherapy is only rarely used as a second-line treatment for metastatic pancreatic cancer in England (see Section 2.2.2 of this ERG report). 5-FU/LV was, however, the comparator to nal-iri+5-FU/LV in the NAPOLI-1 trial. The rationale for choosing 5-FU/LV as the comparator in the NAPOLI-1 trial was that 5-FU was historically one of the mainstays of therapy for pancreatic cancer until the approval of gemcitabine. Moreover, it had been used as a comparator to the OFF regimen in the recently completed CONKO-003 trial, and the demonstrated responses in the 5-FU/LV control arm were argued by the company to suggest that it was effective and, therefore, the optimal choice when the NAPOLI-1 trial was planned. The ERG notes that at the time the NAPOLI-1 trial was designed, the results from the CONKO-003 trial comparing OFF with 5-FU/LV had not actually been published but results comparing OFF with BSC and OFF with 5-FU/LV had been presented at the conference of the American Society of Clinical Oncology (ASCO) in 2005[20] and 2008[21] respectively. These were suggestive of a survival benefit for OFF and so it could be argued that OFF may have been a more appropriate comparator.

The ERG notes that, when gemcitabine was recommended as a first-line regimen by NICE in 2001,[22] evidence was primarily derived from one published trial (Burris 1997[23]) comparing gemcitabine with 5-FU. The dose and scheduling of 5-FU/LV used in the CONKO-003 trial, and adopted for use as a comparator in the NAPOLI-1 trial, differed markedly to the regimen in the Burris trial. However, the regimen in the CONKO-003 and NAPOLI-1 trials is more typical of that used in NHS clinical practice (Table 4).

In the NAPOLI-1 trial, the scheduling of 5-FU/LV in the control arm of the NAPOLI-1 trial differed to that in the intervention arm (in combination with nal-iri) (Table 4). The company argues that the difference in scheduling is highly unlikely to have created a bias in favour of the nal-iri+5-FU/LV arm, since the planned and recorded dose intensities of 5-FU were higher in the control arm.

Table 4 5-FU/LV regimens used in trials versus gemcitabine, and in combination with and versus oxaliplatin and nal-iri

Regimen details	Burris 1997	CONKO-003		NAPOLI-1	
	Versus gemcitabine	Versus oxaliplatin+5-FU/LV	With oxaliplatin+5-FU/LV	Versus nal-iri+5-FU/LV	With nal-iri+5-FU/LV
5-FU bolus dose	600 mg/m^2 Days 1, 8, 15, 22	--	--	--	--
5-FU bolus time	30 mins	--	--	--	--
5-FU infusion dose	--	2,000 mg/m^2 Days 1, 8, 15 and 22	2,000 mg/m^2 Days 1, 8, 15 and 22	2,000 mg/m^2 Days 1, 8, 15 and 22	2,400 mg/m^2 Day 1 to 2
5-FU infusion time	--	24 hours	24 hours	24 hours	48 hours
Leucovorin dose	--	200 mg/m^2 Days 1, 8, 15 and 22	200 mg/m^2 Days 1, 8, 15 and 22	200 mg/m^2 Days 1, 8, 15 and 22	400 mg/m^2 Day 1
Leucovorin infusion time	--	Not specified	Not specified	Not specified	Not specified
Cycle length	4 weeks	2 weeks	2 weeks	6 weeks	2 weeks
Cumulative 6-week dose					
5-FU	3,600 mg/m^2	8,000 mg/m^2	8,000 mg/m^2	8,000 mg/m^2	7,200 mg/m^2
Leucovorin	--	1,200 mg/m^2	1,200 mg/m^2	1,200 mg/m^2	800 mg/m^2

-- Not applicable
Note: Bolus 5-FU was not used in any of the three trials.

The company states that it was unable to derive comparative evidence for nal-iri+5-FU/LV versus oxaliplatin+capecitabine or capecitabine monotherapy. As highlighted in Section 2.2.2, whilst the ERG understands that neither capecitabine nor oxaliplatin+capecitabine are commonly used in England in this patient population, both regimens are more commonly used than 5-FU/LV.

A third fluoropyrimidine therapy that could, theoretically, have been considered by the company is S-1 which, like capecitabine, is an oral treatment. The company stated that it excluded S-1 from consideration (CS, Table 6) because it is only used in combination with other treatments. Clinical advice to the ERG is that S-1 can also be used as a monotherapy. However, it is rarely used in England, if at all, and so the ERG considers it was appropriate for the company not to have included this potential comparator.

3.4 Outcomes

The outcomes specified in the final scope issued by NICE are overall survival (OS), progression-free survival (PFS), response rates, AEs and health related quality of life (HRQoL); these are standard outcomes used in oncology clinical trials. Clinical evidence is reported in the CS for all outcomes specified in the final scope issued by NICE.

3.5 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments is expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes are assessed over a 10-year time horizon (equivalent to a lifetime horizon) and costs are considered from an NHS perspective. Effectiveness evidence from the NAPOLI-1 trial was used in the company model to generate results for the comparison of the cost effectiveness of nal-iri+5-FU/LV versus 5-FU/LV. Outputs from the company's ITC (which both the company and the ERG consider to be unreliable) were used to generate cost effectiveness results for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV.

3.6 Subgroups

No subgroups were specified in the final scope issued by NICE. The company also states that no subgroup analyses were considered in its decision problem. The ERG concurs with the company that there were no relevant subgroups.

3.7 Other considerations

The company has submitted a Patient Access Scheme (PAS) application. This is currently undergoing consideration by the PAS Liaison Unit. The cost effectiveness results presented in the CS have not been generated using the proposed PAS price.

Regarding equity, the company highlights that pancreatic cancer is also an orphan disease[24] (i.e. a disease that is considered to be relatively rare, defined as no more than 5 people in 10,000). The company reports findings from the 2014 National Cancer Patient Experience Survey[25] in which people with rarer forms of cancer (including 4310 patients with upper gastrointestinal cancer) tended to report a poorer experience of their treatment and care than people with more common forms of cancer. In addition, the company notes that pancreatic cancer presents primarily in the elderly population[2] and equity of treatment of the elderly is a concern, citing a report published by the National Audit Office in January 2015. For example, in the report it is stated that across all cancers, patients aged 55 to 64 years are 20% more likely to survive for at least 1 year after diagnosis than those aged 75 to 99 years. Therefore, the company argues that the provision of nal-iri+5-FU/LV as a treatment for patients with pancreatic cancer will address some of these equity issues. However, the ERG notes that while pancreatic cancer does present more often in older patients, with a mean onset of 71 years for men and 75 years for women, evidence for the clinical effectiveness of nal-iri+5-FU/LV in the NAPOLI-1 trial is derived from a patient population with a median age of [redacted] years. The ERG further cautions, based on clinical advice received,

that clinicians would be wary of using combination chemotherapy in many older adults aged over 75 years of age since they tend to be frailer and therefore less likely to cope with this type of treatment.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Systematic review methods

A summary of the systematic review methods employed by the company, along with ERG comments, is presented in Table 5. Overall, the ERG is satisfied that the company's review was comprehensive and that the eligibility criteria employed were consistent with the final scope issued by NICE and with the company's decision problem.

Table 5 Summary of, and ERG comments on, the company's systematic review methods

Review method	ERG comment
Searching	
• The systematic review was designed to identify studies investigating nal-iri+5-FU/LV and/or comparators that may be relevant to the NICE decision problem and that of other HTA bodies • One search was carried out to identify RCTs, non-randomised studies and observational studies on 21 January 2016 Databases searched (along with date limits) were: MEDLINE® In-Process & Other Non-Indexed Citations, and MEDLINE®: 1946 to present; Embase: 1980 to 2016 and the Cochrane Library, incorporating: Cochrane Central Register of Controlled Trials (CENTRAL) – December 2015; Cochrane Database of Systematic Reviews – 2005 to 13 January 2016; Database of Abstracts of Reviews of Effects (DARE) – 2nd Quarter 2015; Health Technology Assessment (HTA) – 4th Quarter • Grey literature sources were also searched: ASCO, ESMO, ISPOR, Clinicaltrials.gov, NCI trials database, ISRCTN registry, UKCCR, EORTC and UK clinical trials gateway	• Where available, appropriate search terms were used; however, the search strategy reported by the company in its appendices to the CS includes a search filter for RCTs • Company included RCT filter for the Cochrane library which is not relevant for the Cochrane library search database • The company searched the appropriate conference abstracts • The ERG was able to replicate the searches • The ERG verified the data in the PRISMA flowchart presented in the CS via the clarification process • The ERG is confident that no relevant studies were missed
Eligibility criteria	
• Studies identified by the electronic searches were independently assessed by two reviewers to ascertain whether they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party	• Use of two independent assessors improves quality of review • A two-stage method for including studies as employed by the company (initially identifying references from title/abstracts and then full text) is considered to be good practice
Data extraction	
• A reviewer extracted relevant information into the STA template. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion	• Use of two independent assessors improves quality of data extraction
Quality assessment and risk of bias	
• Descriptive critical appraisal of the only included RCT was undertaken using the method recommended by NICE[26] • Descriptive critical appraisal of two RCTs used to derive evidence for oxaliplatin+5-FU/LV in the company's cost effectiveness analysis was also undertaken using the NICE recommended method	• An appropriate method for assessing risk of bias in RCTs was used • Unclear if two independent assessors were employed for assessing risk of bias

CS=company submission; RCT=randomised controlled trial; PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ASCO= American Society of Clinical Oncology; ESMO= European Society for Medical Oncology; ISPOR= International Society For Pharmacoeconomics and Outcomes Research; NCI trials database=National Cancer Institute trials database; UKCCR= United Kingdom Coordinating Committee On Cancer Research; EORTC=European Organisation for Research and Treatment of Cancer

4.1.2 Evidence synthesis

The company's literature search led to the identification of one RCT that was considered to be directly relevant to the decision problem (the NAPOLI-1 trial). This trial compared treatment with nal-iri+5-FU/LV with 5-FU/LV; the company considered 5-FU/LV to be a relevant comparator (but, as explained in Section 3.3 of this ERG report, this decision is disputed by the ERG). With the inclusion of only one relevant study, it was not possible for the company to carry out a meta-analysis.

The methods and results from a non-randomised study (NCT00813163[27]) that was designed to assess the effectiveness of nal-iri monotherapy, was reported in the CS and was described as 'supporting evidence'. (The ERG notes that this study was excluded from the company's systematic review).

To compare the effectiveness of nal-iri+5-FU/LV with other comparators, a "best-case evidence network scenario" was constructed (reproduced in this ERG report in Section 4.3, Figure 1). This network showed that an ITC allowing the comparison of the effectiveness of nal-iri+5-FU/LV with oxaliplatin+5-FU/LV (but no other relevant comparators) might, theoretically, be possible. However, the company states that it was not feasible to conduct an ITC due to the PH assumptions being violated for both OS and PFS data and also due to heterogeneity between trials and limited reporting. This view was supported by the panel of three KOLS who were consulted by the company. No clinical efficacy results are presented in the clinical effectiveness section of the CS for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV (although, results from an ITC conducted by the company are used in the company's cost effectiveness model). The clinical effectiveness section of the CS comprises narrative descriptions and findings from the NAPOLI-1 trial and the non-randomised NCT00813163.

The ERG considers that the company's approach to evidence synthesis is appropriate. The ERG is satisfied that appropriate steps were taken to compare nal-iri+5-FU/LV with relevant comparators and agrees that there were methodological issues precluding the conduct of an ITC which could produce credible results (detailed further in Section 4.3 of this ERG report). However, the ERG considers that it would have been useful if the company had presented results tables describing the efficacy and safety of relevant comparators, in particular for oxaliplatin+5-FU/LV. Therefore, to facilitate a crude comparison of nal-iri+5-FU/LV with other relevant comparators (in particular, oxaliplatin+5-FU/LV) the ERG has extracted efficacy and safety data from the key trials identified by the company's systematic review and presented these data in Section 4.7.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Identified studies in the systematic review

The company states that 31 records, reporting 28 different studies, were included in its systematic review (CS, Figure 3). These included 16 publications of 13 RCTs and reports for 15 non-randomised studies (CS, Table 7). As noted in Section 4.1.1 (Table 5) of this ERG report, the systematic review was designed to identify studies investigating the effectiveness of nal-iri+5-FU/LV and/or its comparators. Only one RCT (the NAPOLI-1 trial) included nal-iri+5-FU/LV as an intervention and none of the non-randomised studies investigated nal-iri+5-FU/LV. Thus, the ERG considers that the NAPOLI-1 trial is the only study directly relevant to the final scope issued by NICE and the company's decision problem. The comparator in this trial was 5-FU/LV (a fluoropyrimidine monotherapy which, as highlighted in Section 2.2.2 and Section 3.3 is rarely used in this setting in England). To compare the effectiveness of nal-iri+5-FU/LV with other (more) relevant comparators (e.g. oxaliplatin+5-FU/LV), the company explored the feasibility of conducting a network meta-analysis (NMA) or ITC (see Section 4.3 of this ERG report).

4.2.2 Characteristics of the NAPOLI-1 trial

The NAPOLI-1 trial is a phase III open-label RCT that investigated the use of nal-iri, with or without 5-FU/LV versus 5-FU/LV in patients with metastatic pancreatic cancer previously treated with a gemcitabine-based therapy. The NAPOLI-1 trial was conducted in 76 study sites across North America, Europe, Asia, South America and Oceania. There were four sites in the UK and these enrolled a total of 28 patients.

The NAPOLI-1 trial was originally designed to compare the effectiveness of nal-iri monotherapy versus 5-FU/LV, and patients were initially randomised to these two treatment arms in a 1:1 ratio. However, when safety data for the combination of nal-iri+5-FU/LV became available (from a phase II RCT of metastatic colorectal cancer known as PEPCOL[28]), this combination treatment was shown to have a favourable safety profile compared to FOLFIRI in terms of common grade 3 to 4 AEs, with no additional safety concerns identified. For this reason, the NAPOLI-1 trial protocol was amended so that a third treatment arm could be added to the study (version 2); patients in this new treatment arm received nal-iri+5-FU/LV. The company explains in the CS that only data from the nal-iri+5-FU/LV and the 5-FU/LV arms are of relevance to this appraisal and so efficacy data are presented for these two arms only; the ERG has adopted the same approach in the ERG report. The company also explains that, in order to accurately compare the efficacy of nal-

iri+5-FU/LV with 5-FU/LV, an analysis group was used that only included the patients who were randomised to 5-FU/LV under protocol version 2 or later. Therefore patients that were randomised to the control arm prior to the protocol amendment are not included in the efficacy analyses presented in the CS. The ERG considers that this approach is appropriate, as it maintains the benefit of randomisation (i.e. balancing baseline characteristics between treatment groups).

Due to a possible association between homozygosity of the *UGT1A1*28* allele and irinotecan toxicity, patients were required to undergo *UGT1A1* genotype testing prior to enrolment in the NAPOLI-1 trial. Patients who were identified as being homozygous for the *UGT1A1*28* allele, and who were randomised to either the nal-iri+5-FU/LV arm or the nal-iri monotherapy arm started treatment at a reduced dose, which was increased if no drug-related toxicity was experienced after the first administration of nal-iri. Clinical advice to the ERG is that no such testing is currently performed in clinical practice in England and so the nal-iri dose would likely be initiated at 80mg/m^2 and reduced when drug-related toxicity occurred. The company reports that in the NAPOLI-1 trial, homozygosity of the *UGT1A1*28* allele was observed in 23/243 (9.5%) Caucasians, in 2/129 (1.6%) Asians and in 2/26 (7.7%) of all other races. These results are in line with those reported elsewhere in the literature; for example, Beutler (1998)[19] reports a prevalence of homozygosity of the *UGT1A1*28* allele in 11.3% of Europeans, and in 2.1% of Asians.

Randomisation was stratified according to baseline albumin levels (≥4.0 g/dL versus <4.0 g/dL), KPS (70 and 80 versus ≥90), and ethnicity (Caucasian versus East Asian versus all others).

The primary endpoint of the NAPOLI-1 trial was OS. Secondary endpoints included PFS, time to treatment failure (TTF), objective response rate (ORR), tumour marker response, CBR, AEs and HRQoL.

4.2.3 Patient characteristics in the NAPOLI-1 trial

The company provided baseline characteristics for the patients included in the two relevant arms of the NAPOLI-1 trial (see Table 6).

As noted in Section 2.2.1, it has been reported that in clinical practice in England and Wales, 49% of patients received gemcitabine monotherapy and 25% received gemcitabine in combination with capecitabine for metastatic pancreatic cancer. This equates to two thirds of patients treated with gemcitabine receiving monotherapy and one-third receiving combination therapy. However, in the NAPOLI-1 trial, 45.8% of patients received

gemcitabine monotherapy compared with 54.2% of patients who received combination therapy. Thus, in this respect, the patient population appears to differ to that expected to be seen in NHS clinical practice in England although it should be noted that [redacted] of patients in the NAPOLI-1 trial only received gemcitabine as an adjuvant or neo-adjuvant treatment. Clinical advice to the ERG is that gemcitabine monotherapy is more commonly used in the adjuvant setting and gemcitabine combination therapy is more commonly used in the neo-adjuvant setting.

Previous use of gemcitabine monotherapy versus combination therapy could reflect performance status (PS) to some extent. In the NHS, patients offered combination therapy are likely to have a good PS. As a KPS of ≥70 was required for trial entry, this could in part explain why there was a greater proportion of patients treated with gemcitabine combination therapy than with monotherapy. It could also be a reason why [redacted] of patients in the NAPOLI-1 trial received the study drug as a third-line or later treatment, this is a higher proportion than would be expected to be treated in NHS clinical practice.

The higher proportion of patients treated with gemcitabine combination therapy than monotherapy in NAPOLI-1 could simply be a result of different treatment practices in the countries involved in the trial. In particular, it is noted that nab-paclitaxel in combination with gemcitabine is now commonly used outside of England but is not recommended by NICE for treating patients with metastatic pancreatic cancer in England.

The company states that, overall, the baseline patient characteristics were similar across treatment arms. The ERG agrees with this assessment but notes slight imbalances between treatment groups with regards to the site of metastatic lesions and KPS.

Patients in the 5-FU/LV arm were more likely to have metastatic lesions in sites other than the pancreas compared with patients in the nal-iri+5-FU/LV arm. In particular, more patients in the 5-FU/LV arm had metastatic lesions in the “other” category of metastatic sites than patients in the nal-iri+5-FU/LV arm (32.8% versus 23.1%). The proportion of patients with a baseline KPS 90 was higher in the nal-iri+5-FU/LV arm than in the 5-FU/LV arm, but the opposite was the case in terms of KPS 80 (KPS 90, 43.6% versus 33.6%; KPS 80, 32.5% versus 42.9%). Taken together, the differences in the site of the lesion and the greater proportion of patients with KPS 90 in the 5-FU/LV arm could suggest patients were less fit than those in the nal-iri+5-FU/LV arm although the ERG recognises there is a large degree of subjectivity in determining PS. Furthermore, it is noted that the proportion of patients with KPS ≤70 (i.e. the least fit) were similar between arms (8.6% versus 8.4%).

Table 6 Baseline characteristics of the NAPOLI-1 trial – ITT population

Characteristic	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Gender, n (%)		
• Female	48 (41.0)	52 (43.7)
• Male	69 (59.0)	67 (56.3)
Race, n (%)		
• American Indian or Alaska Native	0	0
• Asian	34 (29.1)	36 (30.3)
• Black or African American	4 (3.4)	3 (2.5)
• White	72 (61.5)	76 (63.9)
• Other	7 (6.0)	4 (3.4)
Age, years, mean (SD)	63.2 (9.06)	61.0 (9.46)
BMI, kg/m^2, mean (SD)	23.33 (4.134)	23.57 (5.054)
KPS, n (%)		
• 50	1 (0.9)	0
• 60	2 (1.7)	0
• 70	7 (6.0)	10 (8.4)
• 80	38 (32.5)	51 (42.9)
• 90	51 (43.6)	40 (33.6)
• 100	18 (15.4)	17 (14.3)
Albumin, g/dL, mean (SD)	3.97 (0.459)	3.98 (0.506)
Measurable lesions, n (%)	113 (96.6)	114 (95.8)
Measurable metastatic lesions, n (%)	97 (82.9)	103 (86.6)
Location of metastatic lesions, n (%)		
• Distant lymph node	32 (27.4)	31 (26.1)
• Liver	75 (64.1)	83 (69.7)
• Lung	36 (30.8)	36 (30.3)
• Pancreas	75 (64.1)	72 (60.5)
• Peritoneal	28 (23.9)	32 (26.9)
• Regional lymph node	13 (11.1)	14 (11.8)
• Other	27 (23.1)	39 (32.8)
Previous anti-cancer therapy, n (%)		
• Gemcitabine alone	53 (45.3)	55 (46.2)
• Gemcitabine combination	64 (54.7)	64 (53.8)
• Fluorouracil-based	50 (42.7)	52 (43.7)
• Irinotecan-based	12 (10.3)	17 (14.3)
• Platinum-based	38 (32.5)	41 (34.5)

BMI=body mass index; ITT=intent-to-treat; KPS=Karnofsky performance score; SD=standard deviation
Source: CS, Table 14

Overall, the ERG is satisfied that the treatment groups are relatively well balanced. The patient population in the NAPOLI-1 trial was generally similar to the population that is likely to be considered for treatment with nal-iri+5-FU/LV in clinical practice in England, aside from previous gemcitabine use and the usual caveat that only suitably fit patients are recruited to clinical trials, so the trial population may be slightly younger and fitter than the population seen in clinical practice.

4.2.4 Statistical approach adopted for the conduct and analysis of NAPOLI-1

In this section, the ERG provides a description and critique of the statistical approach adopted to analyse data collected during the NAPOLI-1 trial in relation to the outcomes stipulated in the NICE scope. Information relevant to the statistical approach taken by the company has been extracted from the CSR,[29] the trial statistical analysis plan (TSAP),[30] the trial protocol (version 2.2)[31] and the CS.

Trial population

The various trial populations used to analyse efficacy and safety outcomes are defined in Box 3.

Box 3 Definitions of trial populations in the NAPOLI-1 trial

- **Intent-to-treat (ITT) population**: all randomised patients, as defined by the confirmation of a successful allocation of a randomisation number through interactive web response system (IWRS). This population was the primary population for all efficacy parameters unless otherwise stated
- **Safety population**: patients that received at least one dose (including partial dose) of study medication. All safety analyses were performed on this population
- **Per protocol (PP) population**: patients who received treatment for at least 6 weeks and did not violate any inclusion/exclusion criteria nor significantly deviate from the protocol, including significant deviations in study drug administration
- **Evaluable patient (EP) population for tumour response**: all randomised and treated patients who ml inclusion/exclusion criteria, had measurable disease at baseline and were evaluable for response, i.e. patients with at least one tumour evaluation while on treatment and those with early (≤12 weeks) disease progression, including symptomatic deterioration and death
- **Tumour marker response evaluable (TMRE) population**: patients who had CA19-9 >30 U/mL at baseline
- **Clinical benefit response evaluable (CBRE) population**: patients who met at least one of the following criteria: baseline pain intensity ≥20 (out of 100); baseline morphine consumption ≥10 mg/day oral morphine equivalents; baseline KPS of 70–90 points
- **Patient-reported outcomes (PRO) population**: all ITT patients that provided baseline and at least one subsequent assessment on the EORTC-QLQ-C30 instrument
- **Pharmacokinetic (PK) population**: all treated patients with at least one PK assessment

Efficacy outcomes

The definitions and methods of analysis for the primary and secondary efficacy outcomes from the NAPOLI-1 trial are listed in Table 7. For OS, PFS, TTF and ORR, the company presents results for the ITT population and results are fully reported for the PP and EP populations for PFS, TTF and ORR in the CS and CSR. The ERG is satisfied that all

outcomes were pre-specified in the TSAP and that all outcomes were fully reported in the CSR.

In addition to the outcomes reported in Table 7, the company also reported on tumour marker response and clinical benefit rate. Additional information on these outcomes is reported in the Appendices of this ERG report in Section 11.1.

Table 7 Analysis strategy for NAPOLI-1 trial efficacy end points specified in the NICE scope

Endpoint	Definition	Statistical method	Population used for analysis
Primary outcome			
OS	Defined as the time from the date of patient randomisation to the date of death or the date last known alive	OS was compared using un-stratified log-rank tests. KM analyses were performed for each arm to obtain non-parametric estimates of the OS function and median OS. 95% CIs were computed using the log-log method. Un-stratified Cox PH regressions were used to estimate HRs and 95% CIs	ITT
Secondary outcomes			
PFS	Time from the date of patient randomisation to the date of death or disease progression, whichever occurred earlier. PFS was based on tumour and disease progression assessments per investigator according to RECIST guidelines v1.1	PFS was compared using un-stratified log-rank tests. KM analyses were performed for each arm to obtain non-parametric estimates of the PFS function and median PFS. 95% CIs were computed using the log-log method. Un-stratified Cox PH regressions were used to estimate HRs and 95% Cis	ITT, PP, EP
TTF	Defined as the time to discontinuation of treatment for any reason, including disease progression, toxicity, and death	TTF was compared using un-stratified log-rank tests. KM analyses were performed for each arm to obtain non-parametric estimates of the TTF function and median TTF. 95% CIs were computed using the log-log method. Cox PH regressions were used to estimate HRs and 95% CIs	ITT, PP, EP
ORR	Defined by the percentage of patients with a best overall response of CR or PR as assessed by the investigator from randomisation until progression or end of study, and as defined by RECIST guidelines v1.1	The 95% CI for the proportion experiencing objective response was calculated based on the normal approximation. ORRs were pairwise compared using Fisher's exact tests	ITT, PP, EP

CI=confidence interval; CR=complete response; EP=evaluable patient for tumour response; HR=hazard ratio; ITT=intent-to-treat; KM=Kaplan-Meier; KPS=Karnofsky performance score; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; PP=per protocol; PR=partial response; RECIST=response evaluation criteria in solid tumours; TTF=time to treatment failure
Source: CS Sections 4.3.4, 4.4.3 and 4.4.4

Outline of analyses

It was planned that the primary analysis would take place once 305 deaths had occurred. The efficacy and safety data presented in the CS are from this primary analysis, which was performed using a data cut-off point of 14 February 2014.

The company highlights that there have also been some updated results for OS, PFS and ORR presented as a poster and abstract with a data cut-off date of 25 May 2015 after 378 OS events.[32]

In March 2016, a final analysis of the NAPOLI-1 trial data set was performed as all patients included in the trial had died by this time. The March 2016 results for OS and PFS were used to inform the company's cost effectiveness analysis (see Section 5.3.4).

Cox proportional hazard modelling

The analyses carried out by the company to generate OS, PFS, and TTF hazard ratios (HRs) were conducted using Cox PH modelling. The validity of this method relies on the hazards of the two comparative drugs being proportional. The company mentions in the CS (Section 4.10.1.1) that the K-M curves for the NAPOLI-1 trial OS data cross, indicating that the PH assumption is unlikely to hold. This potential violation of PH casts doubt on the validity of the generated HRs for OS.

As part of the clarification process, the ERG requested details of any testing of the PH assumption that was carried out by the company. In response, the company tested the PH assumption for the NAPOLI-1 trial OS data and provided results of the test for various analysis populations (see Appendices to this ERG report, Section 11.2). For the ITT population (analysed using un-stratified log-rank tests), the test rejected the null hypothesis that the PH assumption is valid (p=0.0169). The results of the ERG's own analyses of the OS data are in agreement with those of the company.

As the company did not report any test of the PH assumption for PFS or TTF, the ERG carried out its own testing of the PFS and TTF data from the NAPOLI-1 trial (see Appendices to this ERG report, Section 11.3.1) and found the PH assumption to be violated for both outcomes. Consequently, the ERG is of the opinion that HRs are not an appropriate measure of survival benefit for nal+iri+5-FU/LV versus 5-FU/LV.

ERG assessment of statistical approach

A summary of the checks made by the ERG in relation to the statistical approach adopted by the company to analyse data from the NAPOLI-1 trial is provided in Table 8. Having carried out these checks, the ERG is satisfied with the statistical approach employed by the company, with the exception of the violation of the PH assumption for OS, and the lack of testing of PH for PFS and TTF.

Table 8 ERG assessment of statistical approach used to analyse the NAPOLI-1 trial data

Component	Statistical approach	ERG comments
Sample size calculation	Provided in the CSR (page 74). The sample size calculation was adjusted to account for the introduction of a third treatment, in order to take into consideration that some patients would have been randomised under protocol version 1 to either nal-iri monotherapy or 5-FU/LV, and that the remainder of patients would be randomised to one of three treatment groups, nal-iri monotherapy, 5-FU/LV, or nal-iri+5-FU/LV	The ERG is satisfied with the approach taken by the company to calculate sample size, and the adjustments made to the sample size calculation after protocol version 2
Protocol amendments	A third treatment arm, nal-iri+5-FU/LV, was added to the study, as described in Section 4.2.2 of this ERG report. Other protocol amendments are provided in the CS (pages 51 to 52)	The ERG is satisfied with the company's justification for introducing a third treatment arm Other amendments were carried out prior to analysis being conducted. Therefore, they are unlikely to have been driven by the results of the trial and are not a cause for concern
Changes in planned analyses	The company outlines changes in the planned analyses in the CS (pages 55-56). In particular, the definition of the PP population was modified to require a minimum exposure threshold during the first 6 weeks of treatment of at least 80% of the planned dose. Requiring patients to receive doses as planned through 6 weeks removed patients who could not tolerate treatment early on, as well as patients who failed treatment (PD or death) before adequate dosing during the first 6 weeks could be completed	The ERG notes that the number of patients included in the PP population was fairly small, and consequently explored the reasons for exclusion from the PP population (see Section 4.2.6)
Sensitivity analyses for OS	The CS (pages 53 to 54) states the following sensitivity analyses were carried out for OS on the ITT population (except where indicated): • Log-rank test comparisons of treatments on the safety population • Log-rank test comparisons of treatments on the PP population • Stratified log-rank analyses, using randomisation stratification factors (with HR estimates from stratified Cox model) • Wilcoxon pairwise comparisons of treatments • Log-rank test comparisons of treatments with OS censored at the date any post-treatment anti-cancer therapy is first administered • Cox regression model with a time-dependent covariate to account for post-baseline therapy • Cox regression model with stepwise selection of model terms (p-value to enter <0.25, p-value to remain <0.15)	The ERG asked the company to provide results for some of the pre-specified sensitivity analyses as part of the ERG clarification letter to the company, which the company provided in their response. All other sensitivity analyses were fully reported in the CS and CSR
Subgroup analyses for OS	Provided in the CSR (page 123)	The ERG is satisfied that all subgroup analyses were pre-specified in the TSAP and were fully reported in the CSR
AEs	Safety was assessed using several summary measures of AEs, and frequencies of AEs occurring in ≥10% of patients in any treatment group were also presented. All data were analysed and presented using the safety population (CS, pages 55 and 77)	The ERG is satisfied that the results of all the AE data analyses are provided in the CSR
HRQoL	Patients were required to complete the EORTC-QLQ-C30 questionnaire at treatment start, every 6 weeks thereafter and at 30 days post follow-up. On days that the patient received the study drug, assessments were to be completed prior to study drug administration Pairwise treatment group comparisons were performed on the PRO population for each subscale using Cochran MH testing (CS, pages 50 and 55)	The ERG is satisfied that the methodology used to analyse HRQoL data is appropriate

AE=adverse event; CS=company submission; CSR=clinical study report; ERG=evidence review group; HR=hazard ratio; HRQoL=Health related quality of life; ITT=intent-to-treat; MH=Mantel-Haenszel; OS=overall survival; PP=per protocol; PRO=patient-reported outcomes; TSAP=trial statistical analysis plan
Source: CS, pages 50 to 56 and page 77 and CSR, page 123

4.2.5 Assessment of risk of bias of the NAPOLI-1 trial

The company's assessments of risk of bias presented in the CS (Table 15) are reproduced, along with ERG comments, in the Appendices to this ERG report (Section 11.4, Table 66). Overall, the ERG agrees with the company's assessments and considers that the trial was of reasonable quality. The ERG considers that the greatest risks of bias occur from the fact that the NAPOLI-1 trial was an open-label trial. This may explain why a much larger proportion of patients withdrew from the 5-FU/LV arm (13/119, 10.9%) before being treated than from the nal-iri+5-FU/LV arm (2/117, 1.7%). It is possible that patients recruited to the 5-FU/LV arm may have withdrawn from the trial upon being told that they had been randomised to receive the control treatment. Indeed, the reason for withdrawal given for 11 of the 14 (78.6%) patients in the 5-FU/LV arm who did not receive any study treatment was "subject decision". The open-label nature of the NAPOLI-1 trial may also have introduced bias into the assessment of disease progression, favouring nal-iri+5-FU/LV over 5-FU/LV. There is no independent assessment of disease progression. The company highlights that blinding of study treatment was not feasible due to different dosing schedules in the different arms. The ERG recognises the company's assertion that, as a result of the new RECIST 1.1 guidelines,[33] central independent confirmation of objective tumour response is no longer required for RCTs that do not have tumour response as their primary endpoint since it is considered that the control arm serves as an appropriate means to interpret data.

As highlighted in Section 3.3 of this report, the dosing schedule for 5-FU/LV in the nal-iri+5-FU/LV arm was different to that used in the 5-FU/LV arm. However, as argued by the company, the ERG considers it is highly unlikely that this created a bias in favour of the nal-iri+5-FU/LV arm, since the planned and recorded dose intensities of 5-FU were higher in the control arm.

4.2.6 Results from the NAPOLI-1 trial

As reported in Section 4.2.4, both the company and the ERG agree that the PH assumption is violated for the OS data. The ERG's calculations indicated that the PH assumption is also violated for PFS and TTF (Appendices to this ERG report, Section 11.3.1). For this reason, the ERG has not interpreted the HRs that are presented for these outcomes in the CS, as the HRs were calculated assuming that the PH assumption is valid.

Primary efficacy outcome

The results of the primary analysis of OS for the ITT population performed using a data cut-off point of 14 February 2014 are provided in Table 9. Median OS was longer for nal-iri+5-FU/LV patients in comparison to 5-FU/LV patients (6.1 months versus 4.2 months). The

company states that the difference in median OS between treatment groups is statistically significant. However, the company has tested this difference using the log-rank test, which relies on the PH assumption. As previously discussed, the PH assumption is invalid for OS data from NAPOLI-1, and it is therefore not possible to use the results of the log-rank test to demonstrate statistical significance in terms of median OS.

Table 9 Overall survival in the NAPOLI-1 trial – ITT population

	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Median OS, months (95% CI)	6.1 (4.76 to 8.87)	4.2 (3.29 to 5.32)
HR (95% CI; p-value)	0.67 (0.49 to 0.92; p=0.0122)	
Died, n (%)	75 (64.1)	80 (67.2)
Reason for censoring, n (%)		
Alive	37 (31.6)	27 (22.7)
Lost to follow-up	1 (0.9)	1 (0.8)
Consent withdrawn from follow-up	4 (3.4)	11 (9.2)

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; OS=overall survival
Source: CS, Table 16 and company response to the ERG clarification letter, Table 8

Interim results with a data cut-off of 25th May 2015 were in accordance with the results from the primary efficacy analysis, median OS was found to be 6.2 months (95% CI: 4.8 to 8.4) for nal-iri+5-FU/LV compared with 4.2 months (95% CI: 3.3 to 5.3) for 5-FU/LV. The company also presents median OS results from the final data cut (March 2016); these results are [redacted] to the interim results presented in the CS.

The ERG notes that a larger percentage of patients in the 5-FU/LV arm received no study treatment compared to patients in the nal-iri+5-FU/LV arm; results from the ITT population may therefore be biased in favour of the nal-iri+5-FU/LV arm. Therefore, the ERG considers that it is important to take into account the results of the sensitivity analysis of OS (Table 11) that use the safety population (including only patients who received at least one dose of study medication).

The ERG also notes that in both arms of the trial, a relatively high proportion of patients received subsequent therapy on disease progression. This may reflect the fact that, as is common in clinical trials, patients in the trial were younger and fitter than those treated in clinical practice. Relatively similar proportions of patients received subsequent therapy in some trials of oxaliplatin+5-FU/LV (see Section 4.7). There was however no treatment crossover, i.e. no patient in the 5-FU/LV arm subsequently received either nal-iri monotherapy or nal-iri+5-FU/LV. Furthermore, the types of treatment received following progression were similar between arms. Therefore, whilst it is possible that subsequent treatment prolonged OS, it is unlikely that it resulted in bias favouring one arm over another.

The details of subsequent treatments received by patients in each arm are shown in Table 10.

Table 10: Post-treatment anti-cancer therapy in the NAPOLI-1 trial

	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Received post-treatment anti-cancer therapy, n (%)*	42 (35.9)	50 (42.0)
Gemcitabine-based	11 (9.4)	14 (11.8)
5-FU-based	28 (23.9)	35 (29.4)
Irinotecan-based	10 (8.5)	12 (10.1)
Platinum-based	24 (20.5)	24 (20.2)
Other non-investigational agents	14 (12.0)	12 (10.1)
Investigational	5 (4.3)	4 (3.4)
No record of post-treatment anti-cancer therapy, n (%)	75 (64.1)	69 (58.0)

*Subjects who received therapy in combination are counted in more than one therapy category.
Source: Company response to the ERG clarification letter, adapted from Table 26

Sensitivity analyses of the primary efficacy outcome

The results of the sensitivity analyses of OS are provided in Table 11. Median OS was longer for patients in the nal-iri+5-FU/LV arm than patients in the 5-FU/LV arm for all analyses. The ERG notes that in the safety population, results were almost identical to those presented for the ITT population. Therefore, it seems that despite the fact a larger percentage of patients in the 5-FU/LV arm did not receive any study treatment in comparison to the nal-iri+5-FU/LV arm, bias has not been introduced.

Median OS times were considerably longer for both treatment groups in the PP population in comparison to the ITT population (2.8 months OS gain in the nal-iri+5-FU/LV arm and 0.9 months OS gain in the 5-FU/LV arm). However, the number of patients in the PP population was relatively small, indicating that only 56% of the nal-iri+5-FU/LV arm (66/117 patients) and 60% of the 5-FU/LV arm (71/117) received treatment for at least 6 weeks and did not violate any inclusion/exclusion criteria nor significantly deviate from the protocol. Nevertheless, the findings of the analysis using the PP population were in accordance with the analyses using the ITT and safety populations in that they demonstrated a beneficial effect of nal-iri+5-FU/LV in comparison to 5-FU/LV in terms of median OS.

Table 11 Sensitivity analyses of overall survival in the NAPOLI-1 trial

Sensitivity analysis	Nal-iri+5-FU/LV	5-FU/LV
Stratified analysis on ITT population		
N	117	119
Median OS, months (95% CI)	6.1 (4.76 to 8.87)	4.2 (3.29 to 5.32)
HR (95% CI; p-value)[¶]	0.57 (0.41 to 0.80; p=0.0009)	
Safety population		
N	117	105
Median OS, months (95% CI)	6.2 (4.86 to 8.87)	4.2 (3.29 to 5.29)
HR (95% CI; p-value)	0.66 (0.48 to 0.91; p=0.0108)	
PP population		
N	66	71
Median OS, months (95% CI)	8.9 (6.44 to 10.5)	5.1 (3.98 to 7.16)
HR (95% CI; p-value)	0.57 (0.37 to 0.88; p=0.0106)	
ITT population (censoring at change in therapy)		
N	117	119
Median OS, months (95% CI)	6.1 (4.70 to 12.68)	4.0 (3.06 to 5.88)
HR (95% CI; p-value)	0.5665 (0.39 to 0.83; p=0.0033)	

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; OS=overall survival; PP=per protocol
[¶]For the stratified analysis on the ITT population, the p-values are derived from the two-sided stratified log-rank test, incorporating randomisation strata; HRs are derived using the stratified Cox proportional hazards model with treatment as the independent variable.
Source: CS, Table 17 and company response to the ERG clarification letter, Table 10

During the clarification process, the ERG requested a breakdown of reasons why patients from the ITT population of the NAPOLI-1 trial were not included in the PP analysis; the company's response is provided in Table 12. The information in Table 12 highlights that by far the most common reason for exclusion from the ITT population was "insufficient dosing" of study treatment in the nal-iri+5-FU/LV arm and a combination of insufficient dosing or not receiving the dose at all in the 5-FU/LV arm. As noted in Table 8 of this ERG report, the PP population was modified to require a minimum exposure threshold during the first 6 weeks of treatment of at least 80% of the planned dose and therefore insufficient dosing is presumed by the ERG to relate to patients who did not receive 80% of the planned dose. The company notes that requiring patients to receive doses as planned through 6 weeks removed patients who could not tolerate treatment early on, as well as patients who failed treatment (progressed or died) before adequate dosing during the first 6 weeks could be completed. However, given median OS was considerably longer for both treatment groups in the PP population than in the ITT population (2.8 months OS gain in the nal-iri+5-FU/LV arm and 0.9 months OS gain in the 5-FU/LV arm), patients in the NAPOLI-1 trial may have experienced considerably more treatment benefit had they been able to tolerate at least 80% of the planned dosing.

Table 12 Reasons for excluding patients from the PP population for overall survival in the NAPOLI-1 trial

	Nal-iri+5-FU/LV (N=117)	5-FU/LV (N=119)
Patients excluded from the ITT population, n (%)	51 (43.6)	48 (40.3)
Reason, n (%)		
Did not meet eligibility criteria: adequate hepatic function	1 (0.9)	1 (0.8)
Enrolled with Vater-Papilla tumour	0	1 (0.8)
Insufficient dosing	47 (40.2)	31 (26.1)
Insufficient evidence of distal metastases	1 (0.9)	1 (0.8)
Not dosed	2 (1.7)	13 (10.9)
Randomised to 5-FU/LV, treated with nal-iri+5-FU/LV	0	1 (0.8)

ITT=intent-to-treat; PP=per protocol
Source: company response to the ERG clarification letter, Table 6

Finally, as part of the clarification process, the ERG requested the results of several sensitivity analyses that were pre-specified in the TSAP. The company provided these results (see Appendices to this ERG report, Section 11.5). The results of the sensitivity analyses suggested that nal-iri+5-FU/LV statistically significantly improved OS in comparison to 5-FU/LV alone.

Subgroup analyses of the primary efficacy outcome

The company performed subgroup analyses for OS in order to examine the robustness of the overall treatment effect across pre-specified subgroups of prognostic factors. The subgroups for which analyses were conducted are reported in Table 13.

The results of these subgroup analyses are provided in the CSR (pages 123-124). They suggest that the treatment effect [redacted] nal-iri+5-FU/LV [redacted] 5-FU/LV [redacted]. However, the ERG notes that the number of patients in each of these [redacted] and the study was not [redacted] effects and therefore the results of these analyses [redacted]. The ERG does not consider any of the results of the subgroup analysis to suggest that there any obvious subgroups of patients who shouldn't be given nal-iri+5-FU/LV. However, clinical advice to the ERG is that patients who had received prior irinotecan are unlikely to be considered for nal-iri+5-FU/LV since they have already been exposed to non-liposomal irinotecan.

Table 13 Pre-planned subgroups for overall survival sensitivity analyses in the NAPOLI-1 trial

Factor	Subgroup Levels
[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]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Source: CSR, Table 7-17

Progression-free survival

The results of the primary analysis of PFS for the ITT population performed at the data cut-off point of 14 February 2014 are provided in Table 14. Median PFS was longer for patients treated with nal-iri+5-FU/LV than for patients treated with 5-FU/LV (3.1 months versus 1.5 months). The company states that the difference in median PFS between treatment groups is statistically significant. However, as explained in Section 4.2.4 of this ERG report, the PH assumption is invalid for PFS data and, therefore, it is not appropriate to use the results of the log-rank test to assess statistical significance in terms of median PFS.

Table 14 Progression-free survival) in the NAPOLI-1 trial – ITT population

	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Median PFS, months[†] (95% CI)	3.1 (2.69 to 4.17)	1.5 (1.41 to 1.84)
HR (95% CI; p-value)[§]	0.56 (0.41 to 0.75; p=0.0001)	
Progressed n (%)	65 (55.6)	59 (58.0)
Died n (%)	18 (15.4)	23 (19.3)
Reason for censoring n (%)		
Clinical deterioration	3 (2.6)	2 (1.7)
Last non-PD assessment within 12 weeks of cut-off date	15 (12.8)	7 (5.9)
Not treated and no post-baseline tumour assessment	1 (0.9)	10 (8.4)
Other	15 (12.8)	8 (6.7)

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; PD=progressive disease; PFS=progression-free survival
[†]Median PFS is the K-M estimate of the median PFS time. [§]HRs are derived from the un-stratified Cox proportional hazards model with treatment as the independent variable. P-values are derived from the two-sided un-stratified log-rank test
Source: CS, Table 18 and company response to the ERG clarification letter, Table 8

Interim results with a data cut-off of 25th May 2015 were in accordance with the results from the primary efficacy analysis, median PFS was found to be 3.1 months (95% CI: 2.7 to 4.2) for nal-iri+5-FU/LV compared with 1.5 months (95% CI: 1.4 to 1.8) for 5-FU/LV. The company also presents median PFS results from the final data cut (March 2016); these results are [redacted] to the interim results presented in the CS.

Sensitivity analyses: progression-free survival

The results of the sensitivity analyses of PFS are provided in Table 15. Median PFS was longer for patients in the nal-iri+5-FU/LV arm than in the 5-FU/LV arm for all analyses. Median PFS time was considerably longer for nal-iri+5-FU/LV in the PP population in comparison to the ITT population (1.2 months PFS gain). As with OS, this demonstrates the extent of benefit that patients receiving nal-iri+5-FU/LV can experience if they are able to tolerate the study drug for 6 weeks at ≥80% of the planned dose.

Table 15 Sensitivity analyses of progression-free survival in the NAPOLI-1 trial

Sensitivity analysis	Nal-iri+5-FU/LV	5-FU/LV
Stratified analysis on ITT population		
N	117	119
Median PFS, months (95% CI)	3.1 (2.69 to 4.17)	1.5 (1.41 to 1.84)
HR (95% CI; p-value)[¶]	0.51 (0.37 to 0.70; p<0.0001)	
PP population		
N	66	71
Median PFS, months (95% CI)	4.3 (3.06 to 5.72)	1.6 (1.41 to 2.60)
HR (95% CI; p-value)	0.46 (0.31 to 0.67; p<0.0001)	
Evaluable population		
N	104	92
Median PFS, months (95% CI)	3.1 (2.66 to 4.21)	1.4 (1.41 to 1.81)
HR (95% CI; p-value)	0.53 (0.39 to 0.72; p<0.0001)	
ITT population (early discontinuation)		
N	117	119
Median PFS, months (95% CI)	3.1 (2.66 to 4.14)	1.4 (1.41 to 1.68)
HR (95% CI; p-value)	0.55 (0.41 to 0.74; p<0.0001)	
ITT population (missing data)		
N	117	119
Median PFS, months (95% CI)	3.1 (2.69 to 4.17)	1.5 (1.41 to 1.84)
HR (95% CI; p-value)	0.56 (0.41 to 0.75; p=0.0001)	
ITT population (progression directly derived from lesion data)		
N	117	119
Median PFS, months (95% CI)	3.3 (2.66 to 4.21)	1.4 (1.41 to 1.84)
HR (95% CI; p-value)	0.56 (0.41 to 0.76; p=0.0001)	

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; PFS=progression-free survival; PP=per protocol
[¶]For the stratified analysis on the ITT population, the p-values are derived from the two-sided stratified log-rank test, incorporating randomisation strata; HRs are derived using the stratified Cox proportional hazards model with treatment as the independent variable
Source: CS, Table 19 and company response to the ERG clarification letter, Table 10

Time to treatment failure

The results of the analysis of TTF for the ITT population are provided in Table 16. Median TTF was longer for nal-iri+5-FU/LV patients in comparison to 5-FU/LV patients (2.3 months versus 1.4 months).

Table 16 Time to treatment failure in the NAPOLI-1 trial – ITT population

	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Median TTF, months (95% CI)	2.3 (1.58 to 2.79)	1.4 (1.31 to 1.41)
HR (95% CI; p-value)	0.60 (0.45 to 0.78; p=0.0002)	
Progressed, n (%)	61 (52.1)	65 (54.6)
Died, n (%)	1 (0.9)	5 (4.2)
Other reason for treatment termination (n (%))	41 (35.0)	43 (36.1)

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; TTF=time to treatment failure
Source: CS, Table 20 and company response to the ERG clarification letter, Table 8

Sensitivity analyses: time to treatment failure

The results of the sensitivity analyses of TTF are provided in Table 17. The results of the sensitivity analyses were in accordance with the results of the primary analysis of TTF; median TTF was longer for patients in the nal-iri+5-FU/LV arm than for patients in the 5-FU/LV arm for both sets of sensitivity analyses.

Table 17 Sensitivity analyses of time to treatment failure in the NAPOLI-1 trial

Sensitivity analysis	Nal-iri+5-FU/LV	5-FU/LV
PP population		
N	66	71
Median TTF, months (95% CI)	4.1 (2.79 to 5.53)	1.4 (1.41 to 2.43)
HR (95% CI; p-value)	0.49 (0.34 to 0.71; p=0.0001)	
Evaluable population		
N	104	92
Median TTF, months (95% CI)	2.5 (1.68 to 2.89)	1.4 (1.35 to 1.45)
HR (95% CI; p-value)	0.58 (0.43 to 0.78; p=0.0004)	

CI=confidence interval; HR=hazard ratio; PP=per protocol; TTF=time to treatment failure
Source: CS, Table 21 and company response to the ERG clarification letter, Table 10

Objective response

The results for objective response for the ITT population are provided in Table 18. The ORR was found to be statistically significantly higher for patients in the nal-iri+5-FU/LV arm in comparison to patients in the 5-FU/LV arm.

Table 18 Objective response in the NAPOLI-1 trial – ITT population

	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Best overall response, n (%)		
Partial response	9 (7.7)	1 (0.8)
Stable disease[†]	47 (40.2)	26 (21.8)
Non-complete response/non-progressive disease	3 (2.6)	2 (1.7)
Progressive disease	35 (29.9)	56 (47.1)
Not evaluable[¶]	23 (19.7)	34 (28.6)
Objective response rate[¶]		
N	9	1
Rate, % (95% CI)	7.69 (2.86 to 12.52)	0.84 (0.0 to 2.48)
Rate difference (95% CI)	6.85 (1.75 to 11.95)	
p-value[§]	0.0097	

CI=confidence interval; ITT=intent-to-treat; RECIST= response evaluation criteria in solid tumours
[†]Designation of stable disease required at least one assessment of stable disease according to RECIST v1.1 criteria at least 6 weeks after starting treatment
[¶]Subjects with insufficient data for response classification were classified as not evaluable for best overall response, and as a non-responder for objective response in the ITT population.
[§]Two-sided p-values from pairwise Fisher's exact test
Source: CS, Table 22

4.3 Approach to identifying and assessing the quality of evidence to include in an ITC

4.3.1 Company's approach to deriving an ITC

As noted in Section 4.2.1, the company identified 13 RCTs (16 publications) for inclusion into its systematic review. To determine whether it was possible to compare nal-iri+5-FU/LV with a comparator that is more relevant to NHS clinical practice than 5-FU/LV, the company undertook a NMA feasibility assessment; this assessment is described in the clinical effectiveness text of the CS (Section 4.10.1). The company considered the network of evidence formed by 12 of these RCTs (as in one trial[34] not all patients had received gemcitabine previously) and presented network diagrams summarising the identified evidence in the CS (Figure 6). The company considered that evidence from three trials (NAPOLI-1, CONKO-003 and PANCREOX) could, theoretically, be included in an ITC to generate evidence for the effectiveness of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV. The network of evidence used in the ITC is shown in Figure 1.

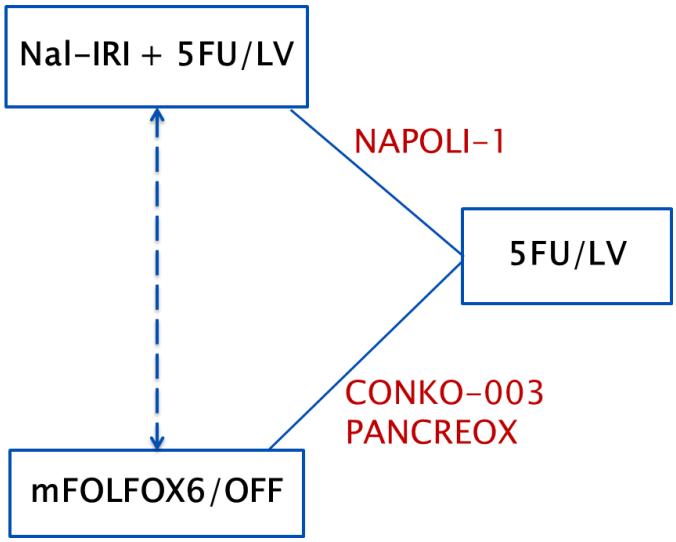

Figure 1 ITC network: Combining NAPOLI-1, CONKO-003 and PANCREOX

Source: CS, Figure 14

The company provides several reasons why the trials are not homogeneous, and therefore why it is inappropriate to include these trials in an ITC. These reasons are presented, along with ERG comments, in Table 19. The company concludes that the conduct of an ITC was considered "unfeasible".

Advice to the company from a panel of three KOLS considered that it was difficult to determine if trials were similar because:

- potentially relevant information is not consistently provided for all three trials
- it is difficult to identify treatment effect modifying variables due to the severity of disease and the complexity of treatment regimens.

The KOLS concluded that combining data from the three trials in an ITC might be considered flawed and "naïve". Thus the company states that an ITC was not conducted because a NMA was deemed "unfeasible".

However, the company considered that results from an ITC were necessary to allow the cost effectiveness of nal-iri+5-FU/LV to be compared with oxaliplatin+5-FU/LV (NHS standard of care), and thus an ITC was undertaken. The Bucher adjusted indirect comparison method[35] was used to undertake the ITC. Results from the ITC are provided, in the form of PFS and OS HRs, in the cost effectiveness section of the CS (CS, Table 39, p104).

Importantly, the company highlights that, upon inspection of the K-M curves:

- the NAPOLI-1 trial OS K-M curves cross and therefore the PH assumption for OS is not likely to hold
- the PFS K-M curves cross in both the CONKO-003 trial and in the PANCREOX trial, meaning that the PH assumption for PFS is not likely to hold within/between trials.

Table 19 Company assessment of comparability of trials included in the ITC

Parameter	Issue	ERG comment
Trial characteristics		
Study location	Not comparable: • NAPOLI-1 – multinational • CONKO-003 – Germany • PANCREOX – Canada	The ERG agrees. Trial location is a possible source of heterogeneity within the network
Follow-up	Follow-up duration not reported for the NAPOLI-1 and PANCREOX trials	The ERG notes that in the poster that reports the PANCREOX trial, follow-up duration is reported to be 4 months. Follow-up duration remains unknown for NAPOLI-1, which the ERG considers to be unlikely as the company conducted this trial and ought to have access to this information Nevertheless, the ERG notes that follow-up durations differ considerably between PANCREOX (4 months) and CONKO-003 trial (54.1 months), and that this introduces heterogeneity into the network
5-FU/LV treatment	Inconsistent reporting of treatment details means that it is difficult to comment on the comparability of dosing	The ERG disagrees. The treatment regimens are adequately reported, although information relating to the PANCREOX trial is only available online from the ClinicalTrials.gov trial register website Although there are differences between trials in terms of the oxaliplatin+5-FU/LV regimens and the 5-FU/LV monotherapy regimens, the ERG does not consider there is any evidence to suggest that these differences in regimens lead to differences in efficacy. The ERG therefore, considers that the

Parameter	Issue	ERG comment
		different regimens of oxaliplatin+5-FU/LV may be considered to be of similar efficacy, and similarly, the different regimens of 5-FU/LV may be considered to be equally efficacious
Prior treatment	Inconsistent prior treatments: • NAPOLI-1 – any prior gemcitabine combination therapy • CONKO-003 – prior gemcitabine monotherapy • PANCREOX – prior gemcitabine therapy (unclear whether monotherapy or in combination)	The ERG agrees that prior treatment is a possible source of heterogeneity within the network
Patient characteristics		
Patient age	Median age of patients was 62 years in the CONKO-003 and NAPOLI-1 trials, and 65 years in the PANCREOX trial	The ERG disagrees this is a source of heterogeneity and considers median age is sufficiently similar across trials (range: 61 in 5-FU/LV arm of the CONKO-003 trial to 67 in PANCREOX trial).
Other patient characteristics	Inconsistent reporting of ECOG PS, CA19-9 levels and number of metastatic sites	The ERG agrees that due to inconsistent reporting, it is not possible to assess whether there is heterogeneity with regards to these patient characteristics
Outcomes		
PFS	PH assumption is not likely to hold within the CONKO-003 and PANCREOX trials	The ERG agrees that the PH assumption is violated for the CONKO-003 and PANCREOX trials. ERG analyses indicate that PH is also violated for NAPOLI-1 PFS data See Section 4.3.2 of this ERG report for ERG assessment of PH issues
OS	PH assumption is not likely to hold in the NAPOLI-1 trial	Results of analyses conducted by the ERG indicate that the PH assumption is violated for the NAPOLI-1, CONKO-003 and PANCREOX trials. See Section 4.3.2 of this ERG report for ERG assessment of PH issues
Response rate	NAPOLI-1 was the only trial to report both the objective response rate and CA19-9 response	The ERG agrees with the company.

ECOG=Eastern Co-operative Oncology Group; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; PS=performance status
Source: CS, pages 72 to 73

4.3.2 ERG's critique of the company's ITC

The ERG considers that the company's systematic review to identify trials that could be used as sources of evidence for an ITC was appropriately undertaken and that the most relevant trials were identified. The ERG also broadly agrees with the company's assessment of bias in these trials (see Appendices to this ERG report, Section 11.4). In addition, the ERG is in general agreement with the company about the limitations of the clinical effectiveness evidence used in the network, namely trial heterogeneity and violation of PH assumptions.

The ERG has carried out additional work to assess the validity of the PH assumptions that need to hold for the results of the ITC to be reliable. The PH assumption within trials is best assessed by considering H-H plots. This type of plot shows the relationship between the

cumulative hazard for each trial event at common time points in two trial arms. These plots were created to assess the proportionality of patient OS and PFS experience using K-M data from the nal-iri+5-FU/LV and 5-FU/LV arms of the NAPOLI-1 trial and by digitising published K-M data from the two arms of the CONKO-003 and PANCREOX trials. For an assumption of PH to be valid, two criteria must be met:

- the data should follow a straight line trend, with individual data points randomly distributed close to, and on either side, of a trend line
- the linear trend line should pass through the graph origin (zero value on both axes), i.e. the intercept component of the linear regression model should be zero.

Results from the ERG's analyses are summarised in Table 20.

Table 20 Summary of findings of analyses undertaken by the ERG to assess proportional hazards

Trial	OS		PFS	
	Linear trend?	Intercept value	Linear trend?	Intercept value
NAPOLI-1 trial	No	N/A	No, except for later stages when proportionality appears reasonable	-0.121 (95% CI: -0.189 to -0.052, p<0.001)
CONKO-003 trial	Only appears supported after about 7.5 months	-0.141 (95% CI: -0.187 to -0.096, p<0.0001)	No	N/A
PANCREOX trial	Appears reasonable	+0.073 (95 %CI: 0.039 to 0.106, p<0.0001)	No	N/A

In addition, for results from the ITC to be reliable, PFS and OS data for 5-FU/LV within the three trials (NAPOLI-1, CONKO-003 and PANCREOX) should be equivalent (i.e. can be assumed to exhibit a HR of 1.0). An examination of data from the three trials shows that this assumption is not valid.

Full details of the analyses conducted by the ERG to investigate PH in the ITC are presented in the Appendices to this ERG report (Section 11.3.2).

4.3.3 ERG's conclusions on the credibility of results of the company's ITC

The ERG considers that the findings from the ITC are not reliable, due to the heterogeneity of the trials and because the necessary PH assumptions (OS and PFS) are not met. It is therefore not possible to derive a credible estimate of clinical or cost effectiveness for nal-iri+5-FU/LV compared with oxaliplatin+5-FU/LV.

4.4 Safety

Safety data for nal-iri+5-FU/LV and 5-FU/LV are reported for the NAPOLI-1 trial safety population. Safety data from the NAPOLI-1 trial for nal-iri monotherapy are also presented in the CS (but not examined in detail in this ERG report). The CS does not include any comparison of AE data between nal-iri+5-FU/LV and oxaliplatin+5-FU/LV, oxaliplatin+capecitabine or capecitabine monotherapy; however, in Appendix 4.3 of the CS the company presents some AE data for oxaliplatin+5-FU/LV from the CONKO-003 and PANCREOX trials. The ERG has compared AEs across these two trials, two other RCTs which include treatment with oxaliplatin+5-FU/LV (the SWOG S1115 trial[36] of mFOLFOX6 without bolus 5-FU and the Yoo trial[17] of mFOLFOX) and the NAPOLI-1 trial in Section 4.7. A comparison of AEs reported for nal-iri monotherapy between the NAPOLI-1 trial and NCT00813163 is presented by the ERG in Appendices to this ERG report (Section 11.8).

4.4.1 Adverse events reported in NAPOLI-1

A summary of the incidence of aggregated AEs is provided in Table 21. While the proportion of treatment emergent AEs (TEAEs) was similar across both arms (nearly all patients experienced a TEAE in the trial), all other types of AEs were reported less frequently in the 5-FU/LV arm than in the nal-iri+5-FU/LV arm. The majority of AEs in all arms were treatment-related, particularly in the nal-iri+5-FU/LV arm where approximately 90% of all TEAEs were treatment-related, compared with approximately 70% for patients treated with 5-FU/LV.

The company highlights that the primary reasons for dose delay with nal-iri+5-FU/LV arm were myelosuppression, particularly neutropenia, and decreased neutrophil count. The ERG observes that another notable AE resulting in dose delay in the nal-iri+5-FU/LV arm was a [redacted] (see Appendices to this ERG report, Section 11.6.1). Myelosuppression was also cited as the main reason for dose reduction for patients receiving nal-iri+5-FU/LV, alongside gastrointestinal disorders (see Appendices to this ERG report, Section 11.6.2). Gastrointestinal disorders and infections and infestations were the primary reasons cited by the company for discontinuation of treatment with nal-iri+5-FU/LV (Appendices to this ERG report, Section 11.6.3).

Table 21 Summary of adverse events in the NAPOLI-1 trial – safety population

Adverse event n (%)	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=134)
≥1 TEAE	116 (99.1)	132 (98.5)
≥1 TR-TEAE	107 (91.5)	93 (69.4)
≥1 CTCAE grade 3 or higher TEAE	90 (76.9)	75 (56.0)
≥1 CTCAE grade 3 or higher treatment-related TEAE	63 (53.8)	24 (17.9)
≥1 serious TEAE	56 (47.9)	60 (44.8)
≥1 TEAE leading to any dose modification	83 (70.9)	48 (35.8)
• ≥1 TEAEs resulting in dose delay	72 (61.5)	43 (32.1)
• ≥1 TEAE leading to dose reduction	39 (33.3)	5 (3.7)
• ≥1 TEAE leading to dose discontinuation	13 (11.1)	10 (7.5)
≥1 TR-TEAE leading to any dose modification		
• ≥1 TR-TEAE resulting in dose delay	59 (50.4)	19 (14.2)
• ≥1 TR-TEAE leading to dose reduction	35 (29.9)	3 (2.2)
• ≥1 TR-TEAE leading to dose discontinuation	5 (4.3)	2 (1.5)

CTCAE=common terminology criteria for adverse events; TEAE=treatment-emergent adverse event; TR-TEAE=treatment-related treatment-emergent adverse event
Source: CS, adapted from Table 30 and company response to ERG clarification letter, Table 17

TEAEs that were very common (≥10%) are summarised in Appendices to this ERG report (Section 11.7, Table 73). AEs that were very common (≥10%) in patients treated with nal-iri+5-FU/LV and occurred at a higher frequency (≥5%) than in the 5-FU/LV arm were as follows: diarrhoea (59.0% versus 26.1%), vomiting (52.1% versus 26.1%), nausea (51.3% versus 34.3%), decreased appetite (44.4% versus 32.1%), fatigue (40.2% versus 27.6%), anaemia (37.6% versus 23.1%), pyrexia (23.1% versus 11.2%), neutropenia (23.1% versus 3.0%), weight decreased (17.1% versus 6.7%), neutrophil count decreased (14.5% versus 1.5%), white blood cell count decreased (14.5% versus 1.5%), alopecia (13.7% versus 4.5%), stomatitis (13.7% versus 6.0%), mucosal inflammation (10.3% versus 3.7%) and platelet count decreased (10.3% versus 2.2%).

Serious TEAEs are summarised by the company in Appendix 6, Table 8, of the CS. The most common (>3%) serious TEAEs for patients treated with nal-iri+5-FU/LV were vomiting (11.9%), diarrhoea (6.0%), abdominal pain (4.3%), nausea (3.4%) and sepsis (3.4%); the most common serious TEAE (>3%) for patients treated with 5-FU/LV was abdominal pain (4.5%).

Treatment-emergent deaths that were attributed to AEs were similar in the nal-iri+5-FU/LV arm (2.6%) and the 5-FU/LV arm (2.2%). One death (0.9%) was assessed as being related to treatment in the nal-iri+5-FU/LV arm with no deaths assessed as being attributable to treatment in the 5-FU/LV arm.

A safety comparison with patients heterozygous for *UGT1A1*28* was difficult to perform because of the small number of patients in this subgroup ([redacted]

[redacted]). However, the company reports that no large differences in the frequency or severity of TEAEs were detected. Nonetheless, the ERG observes that the draft summary of product characteristics (SmPC) highlights that individuals who are homozygous for *UGT1A1*28* are at [redacted].

Although not presented in the CS, the ERG also notes from the draft SmPC that [redacted] have been described. [redacted] However, the incidence of [redacted] among [redacted] compared to [redacted] was reported in [redacted] compared to [redacted]. It is noted in the SmPC that this is consistent with [redacted] that showed a [redacted].

4.4.2 Overall comment on safety with nal-iri+5-FU/LV

The company states that, overall, the safety profile of nal-iri+5-FU/LV is consistent with prior experience with nal-iri, and with the safety profiles of irinotecan and 5-FU/LV. Despite some apparent differences in the incidences of some AEs for nal-iri monotherapy in the NAPOLI-1 trial compared with the incidences of some AEs for nal-iri monotherapy NCT00813163, the ERG agrees with this assessment.

It is further noted by the company that despite a higher incidence of neutropenia overall with nal-iri+5-FU/LV than with nal-iri monotherapy, more frequent and severe gastrointestinal AEs were observed in the nal-iri monotherapy arm. This, it is argued, suggests that the more frequent administration of nal-iri, with a lower dose, results in fewer and less severe gastrointestinal AEs.

4.5 Health related quality of life

In the CS, HRQoL data are reported for the nal-iri+5-FU/LV and 5-FU/LV arms of the NAPOLI-1 trial.

4.5.1 Primary evidence for health related quality of life

The evaluation of HRQoL was conducted using data from the NAPOLI-1 trial PRO population, which only included ITT patients who had completed the EORTC-QLC-C30 questionnaire at baseline and on at least one subsequent occasion: nal-iri+5-FU, [redacted]; 5-

FU: [redacted]; (CSR, Table 7-2). The EORTC QLQ-C30 questionnaire consists of 15 subscales in three independent domains: Global Health Status; Functional Scale Score (physical, role, emotional, cognitive, and social functioning); and Symptom Scale Score (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).

Patients were required to complete the EORTC-QLQ-C30 questionnaire at the start of treatment, every 6 weeks thereafter and at 30 days post follow-up. On days that the patient received the study drug, the questionnaire was completed prior to study drug administration.

Baseline EORTC-QLQ-C30 scores were similar between treatment arms for all domains: for Global Health Status, scores were above the midpoint of the scale; for Functional Scale, the scores were high (≥75) indicating a high/healthy level for functioning; and for Symptom Scale, the scores were noted to be between 0 and 33 for all symptoms, indicating low levels of symptomatology. Findings over time were reported at 6 weeks and 12 weeks. No appreciable changes in Global Health Status or Functional Scale were reported, suggesting there were no negative effects on HRQoL from treatment, as measured by these scales. A similar finding was reported for most of the subscales within the Symptom Scale, with the exception of nausea and vomiting, and diarrhoea. For both arms, the baseline score on the nausea and vomiting subscale was 0 (indicating no symptomology). This score [redacted] in the nal-iri+5-FU+LV arm but [redacted] at 6 weeks and was [redacted] at 12 weeks. The diarrhoea scale also had a baseline score of 0 in both arms, [redacted] in the nal-iri+5-FU/LV arm [redacted] in the 5-FU/LV arm at 6 weeks [redacted] in the nal-iri+5-FU/LV [redacted] at 12 weeks.

4.5.2 Q-TWiST analysis

As supportive evidence, the company also undertook a quality adjusted time without symptoms or toxicity (Q-TWiST) analysis as described by Revicki 2006 (page 412).[37] This involved partitioning total survival in the ITT population over 12 months into: time with AE grade ≥3 toxicity (TOX); time in relapse after disease progression (REL); and time without symptoms or AE grade ≥3 toxicity (TWiST). Mean Q-TWiST was then calculated by multiplying the time spent in each health state by its respective utility (0.5 for TOX, 0.5 for REL and 1.0 for TWiST).

The results from the Q-TWiST are summarised in Table 22. Time in TOX favoured 5-FU/LV over nal-iri+5-FU/LV by 0.7 months, there was little difference between arms for time in REL (marginally favouring 5-FU/LV) and TWiST favoured nal-iri+5-FU/LV by 1.0 months. The company reported the TWiST gain to be statistically significant. Overall, nal-iri+5-FU/LV

patients had a 1.3 months (95% CI: 0.4 to 2.1) greater Q-TWiST (range threshold analyses: 0.9 to 1.6 months), with a relative Q-TWiST gain of 24% (range threshold analyses: 17% to 31%).

Table 22 Results from the Q-TWiST analysis in the NAPOLI-1 trial – ITT population

Health state	Utility	Nal-iri+5-FU/LV (n=117)		5-FU/LV (n=119)	
		Months	Score	Months	Score
TOX: Time with AE grade ≥3 toxicity	0.5	1	0.5	0.3	0.15
REL: Time in relapse after disease progression	0.5	2.5	1.25	2.7	1.35
TWiST: Time without symptoms or AE grade ≥3 toxicity	1	3.4	3.4	2.4	2.4
Total (Q-TWiST)			5.1		3.9

Source: CS, Section 4.7.2.6

The company also conducted a scenario analysis using data from the PP population. The results of this analysis support the results generated using ITT data. In the PP population, Q-TWiST was also reported to be significantly superior in nal-iri+5-FU/LV patients (Q-TWiST gain=1.8 months; 95% CI: 0.7 to 3.0); this gain is reported by the company to be clinically and statistically significant.

4.5.3 Overall comment on health related quality of life

Whilst, theoretically, HRQoL data are useful, the ERG questions whether, given the relatively small number of patient responses (Table 23), the EORTC-QLQ-C30 results generated from the data collected as part of the NAPOLI-1 trial can be considered robust.

Table 23 Proportions of patients in the NAPOLI-1 trial ITT population who compled the EORTC-QLC-C30 questionnaire

Assessment	nal-iri+5-FU/LV	5-FU/LV
Baseline	[redacted]	[redacted]
12 weeks	[redacted]	[redacted]
30 days post follow-up	[redacted]	

Source: CSR, adapted from Table 7-2 and Table 7-16

The company states that the results from the Q-TWiST analysis show that treatment with nal-iri+5-FU/LV results in statistically significant and clinically important gains in quality-adjusted survival compared with treatment with 5-FU/LV. The ERG notes that although some differences in Q-TWiST scores are described as being statistically significant, no p-values are reported in the CS although confidence intervals, presented for these estimates at ASCO 2016 by Pelzer (and reported by the ERG in Section 4.5.2), appear to show statistical significance. In addition, it is noted that the authors of the Revicki 2006 study[37] suggest that a difference in Q-TWiST scores of 10% to 15% is clinically important; in the PRO population of the NAPOLI-1 trial, a Q-TWIST score of 24% is reported (range threshold analyses: 17%

to 31%), suggesting that the results are clinically important. However, the ERG notes that the results of the Q-TWiST analyses are not presented in the CSR and so appear to be a post-hoc exploratory analysis; the findings should therefore be treated with caution.

4.6 Efficacy evidence from non-randomised study (NCT00813163)

The ERG considers that the efficacy findings from the NCT00813163 study are of limited relevance to the decision problem. However, as noted in Section 4.2.3, the ERG has noted that the proportion of patients treated with gemcitabine monotherapy and combination therapy may have some impact on efficacy if the choice of prior therapy also reflects patient fitness especially if a greater proportion of patients receiving prior combination therapy reflects a fitter patient population. It is interesting to note, therefore, that in the NCT00813163 study, there was a greater proportion of patients with worse PS (25% with KPS ≤70) compared with patients in the NAPOLI-1 trial (~9%) despite a higher proportion of patients having been previously treated with combination therapy (77.5% compared with ~55%). However, median OS and PFS for patients treated with nal-iri monotherapy in the NCT00813163 study (5.2 and 2.4 months respectively) was similar to that reported in the nal-iri monotherapy arm of the NAPOLI-1 trial (4.9 and 2.7 months respectively). More information on the NCT00813163 study is described in Appendices to this ERG report (Section 11.8).

4.7 Additional work on clinical effectiveness undertaken by the ERG

As highlighted previously (Sections 2.2.2 and 3.3 of this ERG report), oxaliplatin+5-FU/LV regimens are the most common regimens used for treating patients with metastatic pancreatic cancer previously treated with gemcitabine. Oxaliplatin+5-FU/LV is, therefore, considered by the ERG to be the standard of care, and the most appropriate comparator to nal-iri+5-FU/LV. As methodological issues precluded the conduct of an ITC, and since the company did not present safety data for oxaliplatin+5-FU/LV, the ERG presents a narrative summary of the efficacy and safety of nal-iri+5-FU/LV alongside that of oxaliplatin+5-FU/LV. The ERG's approach is pragmatic and enables crude comparisons across RCTs to be undertaken to determine if results obtained in the NAPOLI-1 trial differ markedly to results obtained in other RCTs. The obvious limitation of the approach is that it is impossible to reach reliable conclusions about relative effectiveness, particularly as trial populations may differ. It is not possible to derive a quantitative estimate but it is possible to explore (qualitatively) the similarity and differences of trial results, and the extent to which these may be attributed to differences in trial and patient characteristics.

4.7.1 Trial characteristics

Trial characteristics are summarised in Table 24. Alongside nal-iri+5-FU/LV, different types of oxaliplatin+5-FU/LV regimens are considered: OFF in CONKO-003, mFOLFOX6 in the PANCREOX trial, mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial and mFOLFOX in the trial conducted by Yoo. The NAPOLI-1 trial is the only multinational trial, the other trials were conducted in Germany, Canada, US and South Korea respectively. The NAPOLI-1 trial is also the largest trial (n=266) and the Yoo trial of mFOLFOX is the smallest (n=61). In all of the trials, patients had received prior gemcitabine but the extent to which this was monotherapy and/or combination therapy varied widely; only 9.8% of patients received monotherapy in the trial of mFOLFOX reported by Yoo, compared to 100% of patients receiving OFF in the CONKO-003 trial. Trial follow-up periods differed considerably across trials (where reported) from a planned follow-up of 4 months in the PANCREOX trial of mFOLFOX6 to a median follow-up of 54.1 months in the CONKO-003 trial of OFF. The dates of recruitment spanned 11 years from 2004 to 2015. The earliest of the trials to be completed was the CONKO-003 trial of OFF (2007) and the most recent trial to be completed was the phase II SWOG S1115 trial of mFOLFOX6 without bolus 5-FU (2015).

Table 24 Characteristics of randomised controlled trials which investigated nal-iri+5-FU/LV or oxaliplatin+5-FU/LV

Characteristic	NAPOLI-1	CONKO-003	PANCREOX	SWOG S1115	Yoo
Design	Phase III, open-label RCT	Phase III, open-label RCT	Phase III, open-label RCT	Phase II, open-label RCT	Phase II, open-label RCT
Recruited, n (dates)	n=266* (2012 to 2013)	n=168 (2004 to 2007)	n=108 (2010 to 2013)	n=120 (2012 to 2015)	n=61 (2007 to 2008)
Follow-up	Not known	54.1 months (median)	4 months (reported in methods)	Every 6 months for up to 3 years (reported in methods)	5.6 months (median)
Country	Multi-centre, multinational trial: North America (20 sites), Europe (30 sites), Asia (12 sites), South America (8 sites) and Oceania (6 sites)	Germany, 16 centres	Canada, 15 centres	US, 534 centres	Asian Medical Center, Seoul, Korea
Intervention	Nal-iri + 5-FU/LV, every 2 weeks: 80 mg/m^2 nal-iri, 400 mg/m^2 LV over 30 minutes, followed by 2400 mg/m^2 5-FU over 46 hours on Day 1	OFF every 4 weeks:† 85 mg/m^2 oxaliplatin on Days 8 and 22, 200 mg/m^2 LV on Days 1, 8, 15 and 22, 5-FU 2,000 mg/m^2 over 24 hours on Days 1, 8, 15 and 22 2 week of rest before next cycle of treatment	mFOLFOX6, every 2 weeks: 85 mg/m^2 oxaliplatin (given as a 2-hour infusion), 400 mg/m^2 LV (given as a 2-hour infusion simultaneous to oxaliplatin), 400 mg/m^2 dose of 5-FU given as bolus followed by 2400 mg/m^2 continuous infusion over 46 hours on Day 1	mFOLFOX6 (without bolus 5-FU) every 2 weeks: 85 mg/m^2 oxaliplatin (given as a 2-hour infusion) and continuous 5-FU over 46hours on Day 1 (no detail about 5-FU dose or administration of LV given)	mFOLFOX every 2 weeks: 85 mg/m^2 oxaliplatin (given as a 2-hour infusion), 400 mg/m^2 LV and 2,000 mg/m^2 5-FU IV over 46hours on Days 1
Comparator	5-FU + LV (6 weekly cycle): LV at a dose of 200 mg/m^2 over 30 minutes followed by 2,000 mg/m^2 5-FU over 24 hours administered on Days 1, 8, 15 and 22 2 week of rest before next cycle of treatment	5-FU + LV (6 weekly cycle):† 200 mg/m^2 LV followed by 2,000 mg/m^2 5-FU over 24 hours on Days 1, 8, 15 and 22 2 week of rest before next cycle of treatment	5-FU + LV (6 weekly cycle): 400 mg/m^2 LV (given as a 2-hour infusion) and 400 mg/m^2 dose of 5-FU given as bolus followed by 2400 mg/m^2 continuous infusion over 46 hours on Day 1	Selumetinib (AZD-6244) + the Akt inhibitor MK-2206: 100 mg AZD-6244 daily on days 1 to 28 plus MK2206 daily on Days 1 to 28 .	mFOLFIRI.3 every 2 weeks: 70 mg/m^2 irinotecan (over 1 hour), 400 mg/m^2 (over 2 hours) and 2000 mg/m^2 5-FU (over 46 h) from Day 1 and another 70 mg/m^2 irinotecan (over 1 hour) at the end of the 5-FU infusion
Previous treatment	Gemcitabine therapy (monotherapy: 45.8% or combination: 54.2%)	First-line gemcitabine monotherapy (100%)	Gemcitabine therapy	Gemcitabine therapy (1-line but no more than 1-line)	Gemcitabine-based1st-line therapy (monotherapy 9.8% or combination 91.2%)

IV=intravenous; KPS=Karnofsky Performance Status; RCT=randomised controlled trial
* NAPOLI-1 was a three-armed trial comparing nal-iri+5-FU/LV with 5-FU/LV and nal-iri monotherapy with 5-FU/LV. Data reported here are for patients in the former comparison
† Included best supportive care according to current palliative care guidelines, i.e. including anti-infective treatment, psychological counselling as needed, biliary stenting or drainage (if indicated), nutritional advice, pain management, and nutritional supplementation

4.7.2 Patient characteristics

Patient characteristics are summarised in Table 25. Across the trials, with the exception of the trial of mFOLFOX reported by Yoo in which the median age of patients was 55, the median age was relatively similar across the trial arms of interest (ranging from 62 years in the OFF arm of CONKO-003 to 65 years in the mFOLFOX6 arm of PANCREOX). A similar proportion of patients had previously had curative surgery with nal-iri+5-FU/LV in the NAPOLI-1 trial (36.1%) as with mFOLFOX in the Yoo trial (36.7%) but more patients treated with OFF in the CONKO-003 trial had had curative surgery (44.7%). At least 88% of patients had metastatic disease in any given trial, and relatively similar proportions of patients treated with nal-iri+5-FU/LV in the NAPOLI-1 trial had liver metastasis (64.1%) as those treated with mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial (62.9%); in the Yoo trial, the proportion of patients with liver metastasis treated with mFOLFOX was slightly greater (70.0%). Body mass index was also similar in the two trials that reported this measure (the NAPOLI-1 trial of nal-iri+5-FU and the PANCREOX trial of mFOLFOX6), being approximately 23 kg/m^2. A comparison of the duration of previous gemcitabine therapy was difficult because not all of the trials reported this measure and where they did, it was not reported consistently. However, the median duration of previous gemcitabine therapy was much higher in the NAPOLI-1 trial for nal-iri+5-FU arm (22.1 months) than in the OFF arm of the CONKO-003 trial (4.6 months).

The most notable difference across trials appeared to relate to baseline PS. In particular, 59.0% of patients treated with nal-iri+5-FU/LV in the NAPOLI-1 trial, 53.9% of patients treated with OFF in the CONKO-003 trial and 45.0% of patients treated with mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial had KPS ≥90 or ECOG PS 0, whereas the proportions of patients with ECOG PS 0 treated with mFOLFOX6 in PANCREOX and with mFOLFOX in Yoo were 13.0% and 16.7% respectively. The mFOLFOX6 arm of the PANCREOX trial and mFOLFOX arm of the Yoo trial also included patients with ECOG PS 2: 11.1% and 3.3% respectively.

Table 25 Participant characteristics of randomised controlled trials which investigated nal-iri+5-FU/LV or oxaliplatin+5-FU/LV

Characteristic	NAPOLI-1		CONKO-003		PANCREOX		SWOG S1115		Yoo	
Regimen	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=119)	OFF (n=76)	5-FU/LV (n=84)	mFOLFOX6 (n=54)	5-FU/LV (n=54)	mFOLFOX6 (n=62)	AZD-6244 + MK-2206 (n=58)	mFOLFOX (n=30)	mFOLFORI.3 (n=31)
Age, median (Range) years	63 (41, 81)	62 (34, 80)	62 (37, 83)	61 (43, 78)	65 (38, 82)	67 (48, 78)	66 (34, 83)	69 (54, 88)	55 (35, 69)	55 (37, 73)
Sex (% male)	59.0	56.3	52.6	57.1	57.4	55.6	35.5	60.3	66.7	77.4
% Metastatic	100	100	88.2	88.1	92.6	94.4	100	100	--	--
% Liver metastases	64.1	69.7	--	--	--	--	62.9	74.1	70.0	61.3
Duration of advanced disease, median months	6.9	6.2	--	--	7.9	5.7	--	--	--	--
% Performance status	KPS ≥90: 59.0 80: 32.5 ≤70: 8.6	KPS ≥90: 47.9 80: 42.9 ≤70: 8.4 Missing: 0.8	KPS ≥90: 53.9 ≤80: 46.1	KPS ≥90: 47.6 ≤80: 52.4	ECOG 0: 13.0 1: 75.9 2: 11.1	ECOG 0: 18.9 1: 75.5 2: 5.7	ECOG* 0: 45.0 1: 55.0	ECOG* 0: 41.5 1: 58.5	ECOG 0: 16.7 1: 80.0 2: 3.3	ECOG 0: 16.1 1: 83.9 2: 0
Albumin, g/dL, mean	3.97 (0.46)	3.98 (0.51)	--	--	--	--	≥3 (eligibility criteria)		>3 (eligibility criteria)	
BMI, median (range), kg/m^2	Mean (SD): 23.33 (4.13) Min, max 16.0, 43.5	Mean (SD): 23.57 (5.05) Min, max 16.7, 42.9	--	--	23.7 (18.1, 37.7)	24.3 (16.5, 53.9)	--	--	--	--
% Curative surgery	34.2	36.1	44.7	32.1	--	--	--	--	36.7	32.3
Duration of previous gemcitabine, median (range), months	22.1 (0.1, 129.3)	21.4 (2.1, 147.9)	4.6 [95% CI: 3.8 to 6.0]†	5.3 [95% CI: 4.4 to 6.0]†	--	--	≤ 4 months: 37.1%	≤ 4 months: 37.9%	--	--

-- Not reported; BMI=body mass index; ECOG= Eastern Cooperative Oncology Group; KPS=Karnofsky performance Status; SD=standard deviation
*Results for PS only reported in poster presentation which included 115 patients (mFOLFOX6, n=60, AZD-6244 + MK-2206, n=55)
† CONKO-003 also reports data < 3months (27.6% versus 25.0%), 3 to 6 months (32.9% versus 38.1%) and >6months (39.5% versus 36.9%)

4.7.3 Efficacy outcomes

Key efficacy findings are summarised in Table 26.

Three of the RCTs investigating oxaliplatin+5-FU/LV (the CONKO-003 trial, the PANCREOX trial and the SWOG S1115 trial) report an OS of between 5.9 months and 6.7 months. These results are similar to those reported for nal-iri+5-FU/LV in the NAPOLI-1 trial (6.1 months). The trial reported by Yoo, however, reports a less impressive OS for mFOLFOX of only 3.4 months.

RCTs investigating oxaliplatin+5-FU/LV report a PFS of 2.9 months for OFF in the CONKO-003 trial and between 2.0 months and 3.1 months for mFOLFOX6 (without and with bolus in the SWOG S1115 trial and PANCREOX trial respectively). These results are similar to those reported for nal-iri+5-FU/LV in the NAPOLI-1 trial (3.1 months). The trial reported by Yoo, however, reports a less impressive PFS for mFOLFOX of only 1.4 months.

Response rates appeared to be generally similar in two of the trials of oxaliplatin+5-FU/LV (the SWOG S1115 trial of mFOLFOX6 without bolus 5-FU and the Yoo trial of mFOLFOX) of approximately 7%, which compare to 9% for patients treated with nal-iri+5-FU/LV in the NAPOLI-1 trial. In all three of these trials, the best response was a partial response. In the PANCREOX trial of mFOLFOX6, response rates in both arms appeared to be much higher than any other trial, ranging from 8.8% for patients treated with 5-FU/LV to 13.2% for patients treated with mFOLFOX6. However, it is not stated how many responses were complete responses (if indeed any).

The proportion of patients who received subsequent treatment on disease progression could also impact on OS, although it should be noted that there are currently no proven third-line treatment options available. Nonetheless, it is noticeable that, from a comparison of the 5-FU/LV arms, the higher the proportion of patients who received subsequent therapy, the higher the median OS reported. A similar picture emerged for oxaliplatin+5-FU/LV with the exception of the mFOLFOX6 arm of the PANCREOX trial, which had much fewer patients who received subsequent therapy than in any other trial.

Alternatively, a higher proportion of patients receiving subsequent treatment can be indicative of a higher proportion of patients who are fitter at that point in time and, therefore, more likely to receive additional treatment. There does not appear to be any apparent relationship between the proportion who received subsequent treatment and the proportion of patients with ‘better’ PS at baseline (KPS ≥90 or ECOG PS 0).

Table 26 Key efficacy findings reported from randomised controlled trials of patients with metastatic pancreatic cancer treated with nal-iri+5-FU or oxaliplatin+5-FU/LV and who were all previously treated with gemcitabine

Endpoint	NAPOLI-1		CONKO-003		PANCREOX		SWOG S1115		Yoo	
	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=119)	OFF (n=76)	5-FU/LV (n=84)	mFOLFOX6 (n=54)	5-FU/LV (n=54)	mFOLFOX6 (n=62)	AZD-6244 + MK-2206 (n=58)	mFOLFOX (n=30)	mFOLFORI.3 (n=31)
OS, months	6.1 (4.76, 8.87)	4.2 (3.29, 5.32)	5.9	3.3	6.1	9.9	6.7 (6.0, 8.3)	3.9 (3.5, 4.6)	3.4 *	3.8 *
HR (95% CI)	0.67 (0.49 to 0.92)		0.66 (0.48 to 0.91)		1.78 (1.08 to 2.93)		--		--	
12-month OS, n (%)	-- (26)	-- (16)	15 (19.7)	11 (13.1)	--	--	--	--	--	--
PFS, months	3.1 (2.69 to 4.17)	1.5 (1.41 to 1.84)	2.9*	2.0*	3.1	2.9	2.0 (1.8, 2.9)	1.9 (1.8, 2.1)	1.4 *	1.9 *
HR (95% CI)	0.56 (0.41 to 0.75)		0.68 (0.50 to 0.94)*		1.00 (0.66 to 1.53)		--		--	
ORR (%)	7.7	0.8	--	--	13.2	8.5	6.5	0	7	0 †
Additional therapy on progression (%)	37.1	42.0	28.9 ‡	21.4 ‡	Chemo-therapy: 6.8	Chemo-therapy: 23.1	53 ¥	35 ¥	Crossover: 23.3 §	Crossover: 38.7 §

CI=confidence interval; HR=hazard ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

-- Not reported

Note: 12-month OS reported in appendices to CS and taken from K-M curve in CONKO-003 (figure 3), rate for NAPOLI-1 is only given in the text of the summary to the CS

* Data reported in weeks in published paper

† The trial authors state that objective response could not be ascertained in the mFOLFIRI.3 arm

¥ Based on population of patients reported in the conference poster (n=60 and n=55)

§ After disease progression to a stage at which a salvage regimen was required, a crossover to the alternate protocol was undertaken by 12 patients (39%) in the mFOLFIRI.3 arm and by 7 (23%) in the mFOLFOX arm. The median time to crossover to the alternate treatment was 8.3 weeks (range 3.3 to 18.1 weeks) in the mFOLFIRI.3 arm, and 15 weeks (range 7.0 to 32.6 weeks) in the mFOLFOX arm

‡ Paper reports: Of these, seven patients (32%) in the OFF arm were treated with taxanes, and 13 patients (72%) in the 5-FU/LV arm received oxaliplatin-based chemotherapy

Note data for NAPOLI-1 reported above are from initial analysis, 14 February 2014 (consistent with all data for clinical effectiveness reported in the clinical effectiveness sections of the CS and this ERG report)

4.7.4 Safety findings

Key AEs reported across trials are summarised in Table 27. The reporting of AEs was not consistent. It is unclear if the AEs reported in the CONKO-003 trial and PANCREOX trial were TEAEs or treatment-related and so are assumed by the ERG to be TEAEs. For the NAPOLI-1 trial, the AEs presented in Table 27 are TEAEs. As highlighted in Section 4.4, the majority of AEs in this trial were treatment-related. In the SWOG S1115 trial and in Yoo, all AEs were reported to be treatment-related.

The incidence of treatment-related neutropenia with mFOLFOX in Yoo, both all-grade (48.2%) and grade ≥3 (20.7%), was much higher than the proportion of TEAEs reported with nal-iri+5-FU/LV in NAPOLI-1 (23.1% and 14.5% respectively; treatment-related neutropenia is not reported in the CS but from Table 14.3.1.6 of the CSR, it is evident that [redacted] cases of [redacted] associated with nal-iri+5-FU/LV [redacted]). There was also a much greater proportion of patients with grade 3 to 4 neutropenia reported with mFOLFOX6 in the PANCREOX trial (32.7%) than with nal-iri+5-FU/LV (14.5%) in the NAPOLI-1 trial. Interestingly, the SWOG S1115 trial reported no cases of treatment-related neutropenia with mFOLFOX6 without bolus 5-FU.

Diarrhoea appeared to be more common with nal-iri+5-FU/LV than with all oxaliplatin+5-FU/LV regimens. All-grade diarrhoea was 50.0% with nal-iri+5-FU/LV in the NAPOLI-1 trial compared with no more than 21.1% reported with OFF in the CONKO-003 trial. Grade ≥3 diarrhoea was 12.8% with nal-iri+5-FU/LV in the NAPOLI-1 trial, compared with no more than 6.5% with mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial. However, rates of vomiting appeared to be relatively similar between nal-iri+5-FU/LV and all oxaliplatin+5-FU/LV regimens. All-grade rates of vomiting were either slightly greater with OFF in the CONKO-003 trial (59.2%) or slightly lower with mFOLFOX in the Yoo trial (48.2%) than with nal-iri+5-FU/LV in the NAPOLI-1 trial (52.1%); grade ≥3 vomiting was 11.1% with nal-iri+5-FU/LV in the NAPOLI-1 trial, compared with no more than 10.3% with mFOLFOX in the Yoo trial.

Other AEs of note identified by the company were anaemia and fatigue. The incidence of all-grade anaemia appeared to be lower with nal-iri+5-FU/LV in the NAPOLI-1 trial (37.6%) than with oxaliplatin+5-FU/LV regimens (55.2% in the Yoo trial of mFOLFOX to 60.5% in the CONKO-003 trial of OFF). However, the incidence of grade ≥3 anaemia appeared to be higher with nal-iri+5-FU/LV in the NAPOLI-1 trial (9.4%) compared with between 2.0% with mFOLFOX6 in the PANCREOX trial to 3.9% with OFF in the CONKO-003 trial. The

incidence of grade ≥3 fatigue appeared to be similar with nal-iri+5-FU/LV in the NAPOLI-1 trial (13.7%) than with oxaliplatin+5-FU/LV regimens (12.9% to 14.2%).

In the CS, the company highlights that peripheral neuropathy, a common type of neurotoxicity, is a frequent treatment-related AE for oxaliplatin-containing chemotherapy regimens. The company argues that, based on a review of colorectal cancer,[38] grade ≥2 neuropathy occurs in approximately 40% to 50% of patients. In the RCTs of oxaliplatin+5-FU/LV regimens in metastatic pancreatic cancer, the incidences of all-grade neurotoxicity and treatment-related neurotoxicity were similar (OFF in the CONKO-003 trial was 42.1% and mFOLFOX in the Yoo trial was 44.8%) to those in the aforementioned review. Grade 3 neuropathy was reported to occur in 10% to 20% of patients treated with oxaliplatin-containing chemotherapy in the aforementioned review of colorectal cancer.[38] However, grade ≥3 peripheral neuropathy was reported to be at most 4.1% mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial and grade ≥3 neurotoxicity was reported by 3.9% of patients treated with OFF in the CONKO-003 trial; no incidence of grade ≥3 neurotoxicity was reported for patients treated with mFOLFOX. Clinical advice received by the ERG is that neurotoxicity generally correlates with duration of treatment so will tend to be higher for patients with colorectal cancer who are likely to stay on treatment for longer periods than patients with pancreatic cancer. When grade 2 neurotoxicity occurs, dose reductions/omissions are usually instigated to prevent worsening. In patients treated with nal-iri+5-FU/LV in the NAPOLI-1 trial, peripheral neuropathy was much less common (all grade: 1.7% and grade ≥3: 0) than reported with oxaliplatin+5-FU/LV.

In addition to data summarised in Table 27, there appear to be a similar amount of AEs leading to treatment discontinuation with nal-iri+5-FU/LV (11.1% in the NAPOLI-1 trial) as with mFOLFOX6 with or without bolus 5-FU (9.7% in the PANCREOX trial and 16.3% in the SWOG S1115 trial respectively). AEs leading to treatment discontinuation were not reported for OFF in the CONKO-003 trial or mFOLFOX in the Yoo trial. However, it is noted that in the CONKO-003 trial, a dose reduction to 75% was required in 10% of OFF administrations; 9% of planned OFF administrations were not given, and 81% of OFF administrations were full doses.

Compared with 0.9% of treatment-related deaths with nal-iri+5-FU/LV in the NAPOLI-1 trial, there were no treatment-related deaths from AEs with mFOLFOX6 in PANCREOX and 3.4% with mFOLFOX in the Yoo trial. It is not reported if there were any treatment-related deaths in the CONKO-003 trial of OFF or the SWOG S1115 trial of mFOLFOX6 without bolus 5-FU.

Table 27 Key safety findings reported from randomised controlled trials of patients with metastatic pancreatic cancer treated with nal-iri+5-FU or oxaliplatin+5-FU/LV and who were all previously treated with gemcitabine

Adverse event	NAPOLI-1		CONKO-003		PANCREOX		SWOG S1115		Yoo	
	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=134)	OFF (n=76)	5-FU/LV (n=84)	mFOLFOX6 (n=54)	5-FU/LV (n=54)	mFOLFOX6 (n=62)	AZD-6244 + MK-2206 (n=57)	mFOLFOX (n=29)	mFOLFORI.3 (n=29)
Neutropenia, All grades, n (%)	27 (23.1)	4 (3.0)	--	--	--	--	--	--	14 (48.2)	13 (44.8)
Grade 3 to 4, n (%)	17 (14.5)	1 (0.7)	--	--	16 (32.7)	2 (3.8)	0	0	6 (20.7)	7 (24.1)
Febrile neutropenia, All grades, n (%)	[redacted]	[redacted]	--	--	--	--	--	--	0	1 (3.4)
Grade 3 to 4, n (%)	2 (1.7)	0	--	--	2 (4.1)	0	0	0	0	1 (3.4)
Diarrhoea, All grades, n (%)	69 (59.0)	35 (26.1)	16 (21.1)	19 (22.6)	--	--	--	--	5 (17.2)	12 (41.4)
Grade 3 to 4, n (%)	15 (12.8)	6 (4.5)	1 (1.3)	0	1 (2.0)	0	4 (6.5)	4 (7.0)	0	2 (6.9)
Vomiting, All grades, n (%)	61 (52.1)	35 (26.1)	45 (59.2) †	39 (46.4) †	--	--	--	--	14 (48.2)	9 (31.0)
Grade 3 to 4, n (%)	13 (11.1)	4 (3.0)	1 (1.3) †	3 (3.6) †	2 (4.1)	0	3 (4.8)	1 (1.8)	3 (10.3)	3 (10.3)
Anaemia, All grades, n (%)	44 (37.6)	31 (23.1)	46 (60.5)	54 (64.3)	--	--	--	--	16 (55.2)	15 (51.7)
Grade 3 to 4, n (%)	11 (9.4)	9 (6.7)	3 (3.9)	2 (2.4)	1 (2.0)	0	2 (3.2)	3 (5.3)	1 (3.4)	1 (3.4)
Fatigue, All grades, n (%)	47 (40.2)	37 (27.6)	--	--	--	--	--	--	--	--
Grade 3 to 4, n (%)	16 (13.7)	5 (3.7)	--	--	7 (14.2)	1 (1.9)	8 (12.9)	7 (12.3)	--	--
Neurotoxicity, All grades, n (%)	[redacted]	[redacted]	32 (42.1)	6 (7.1)	--	--	--	--	13 (44.8)	1 (3.4)
Grade 3 to 4, n (%)	[redacted]	[redacted]	N: 3 (3.9)	N: 0	PN: 2 (4.1)	PN: 0	0	0	0	0

-- Not reported; N=neuropathy; PN=peripheral neuropathy
† CONKO-003 reports nausea/emesis (vomiting) together
Note: AEs reported by Yoo were described as treatment-related AEs as were grade 3 to 5 AEs reported in SWOG S1115 while treatment-related AEs were also reported for the NAPOLI-1 trial, data here are presented for treatment emergent AE; it is unclear whether AEs reported for other trials are treatment-emergent or treatment-related but are assumed to be treatment-emergent
Data marked as CiC extracted from CSR, Table 14.3.2.7.3

4.7.5 ERG comment on efficacy and safety findings from the ERG's narrative summary of additional trial data

Overall, the trial evidence suggests that, for patients treated with nal-iri+5-FU/LV or oxaliplatin+5-FU/LV, OS is expected to be approximately 6 months and PFS approximately 2 to 3 months. The findings from the trial by Yoo suggest a lower OS and PFS but survival with oxaliplatin+5-FU/LV appears to be similar to the irinotecan regimen, FOLFORI.3. It is unclear why the findings in this trial differ so markedly to those from the other trials but this phenomenon may be related to differences in trial and baseline characteristics, namely the fact that this was the only trial conducted in a predominantly Asian population, a much larger proportion of patients who had received gemcitabine combination (as opposed to monotherapy) therapy in the past, a younger patient population, and a greater proportion of patients with ECOG PS 1. The Yoo trial is also a relatively small trial (nearly half the size of the next smallest PANCREOX trial) which may have been a contributory factor.

The ERG notes the median OS of 9.9 months reported in the 5-FU/LV arm of the PANCREOX trial, is much longer than median OS reported in the other four trials (Table 26). Without access to a fully published paper, the ERG can only speculate possible reasons for this. These include imbalances in the mFOLFOX6 arm versus the 5-FU/LV arm, namely fewer patients with ECOG PS 0 (13.0% versus 18.9%) but more with ECOG PS 2 (11.1% versus 5.7%), the greater duration of advanced disease in the mFOLFOX6 arm (7.9 months versus 5.7 months) and much fewer patients treated with mFOLFOX6 than treated with 5-FU/LV receiving subsequent chemotherapy on disease progression (6.8% versus 23.1%).

As expected, neurotoxicity, including peripheral neuropathy, was more common in patients treated with oxaliplatin+5-FU/LV than in patients treated with nal-iri+5-FU/LV. Although neutropenia is recognised as a very common AE in the population treated with nal-iri+5-FU/LV, it appears to be even more common in two trials of oxaliplatin+5-FU/LV (the PANCREOX trial of mFOLFOX6 and the Yoo trial of mFOLFOX); perhaps surprisingly, there were no cases of neutropenia reported in the SWOG S1115 trial of mFOLFOX6 without bolus 5-FU. Diarrhoea, on the other hand, does appear to be more common with nal-iri+5-FU/LV than oxaliplatin+5-FU/LV, as does anaemia.

The ERG urges caution in interpreting the findings from these crude comparisons. The results may be unreliable because of potentially important differences in trial characteristics and in patient populations and, as also noted in the CS, unreported additional potentially relevant information.

4.8 Conclusions of the clinical effectiveness section

The only trial which assesses the effectiveness of nal-iri+5-FU/LV is the NAPOLI-1 trial. This is a phase III, multi-centre, multinational, RCT comparing the intervention with 5-FU/LV. Overall, the NAPOLI-1 trial appears to be of reasonable quality; the ERG considers that there is some risk of bias from the fact that it was an open-label trial.

The patient population recruited to the NAPOLI-1 trial is, in many respects, representative of patients who would be treated for metastatic pancreatic cancer after progressing on treatment with gemcitabine in routine clinical practice in England. It is however noticeable that a greater proportion of patients had received prior gemcitabine combination therapy and fewer patients had received gemcitabine monotherapy than would be seen in NHS clinical practice in England. Furthermore, as is common with all clinical trials, the patient population was on average younger and fitter than would be seen in clinical practice, and this may explain why a relatively large proportion of patients received study treatment in the third-line (or later) setting.

Results from the trial show that, for a range of efficacy measures, including OS and PFS, nal-iri+5-FU/LV is superior to 5-FU/LV. The increase in median OS of 1.9 months reported in the NAPOLI-1 trial compared with those receiving 5-FU/LV represents a significant improvement in OS (a 45% increase in median OS compared with the median OS in the 5-FU/LV arm), likely to be of great value to both the patient and their family. Furthermore, despite an increase in TEAEs compared with 5-FU/LV, particularly in relation to myelosuppression and gastrointestinal disorders, there was no apparent deterioration in HRQoL with nal-iri+5-FU/LV.

However, in the NHS, 5-FU/LV is rarely used to treat patients with metastatic pancreatic cancer who have progressed following treatment with gemcitabine. The most common regimen currently used to treat these patients, despite the lack of a reliable evidence base to support it, is oxaliplatin+5-FU/LV (considered by the ERG to be the most common treatment in approximately 75% of cases). Capecitabine monotherapy is considered by the ERG to be the next most commonly used comparator (in 25% of cases) although differences by geographical region exist and so some clinicians also use oxaliplatin+capecitabine in a minority of cases. The company concluded that it was not feasible to conduct an ITC to compare nal-iri+5-FU with any of the comparators used in the NHS or specified in the NICE scope, although an ITC comparing nal-iri+5-FU/LV with oxaliplatin+5-FU/LV was conducted for the purposes of generating evidence to inform the company's economic evaluation. The ERG considers that the results from the ITC lack reliability as the PH assumptions required

to conduct a credible comparison were not met and there was also some evidence of heterogeneity across trials in terms of trial location, patient characteristics, prior treatment with gemcitabine (monotherapy versus combination therapy) and length of trial follow-up. Therefore, it is not possible to generate a reliable quantitative measure of the relative efficacy of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV.

Taking a pragmatic approach to comparing the effectiveness of nal-iri+5-FU/LV with oxaliplatin+5-FU/LV, the ERG undertook a crude comparison of findings across RCTs. The ERG concluded that the PFS and OS outcomes for patients treated with oxaliplatin+5-FU/LV reported in these trials are similar in magnitude to the PFS and OS outcomes of patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial. The ERG also compared AEs across the trials and while it is likely that treatment with nal-iri+5-FU results in more cases of diarrhoea in patients than treatment with oxaliplatin+5-FU/LV, it is likely to result in fewer cases of neutropenia or neurotoxicity. However, these findings can only be considered exploratory.

In summary, it appears that treatment with nal-iri+5-FU/LV is of greater efficacy than 5-FU/LV for patients with metastatic pancreatic cancer who have progressed on treatment with gemcitabine. Despite an increase in AEs (mostly myelosuppression and gastrointestinal disorder), there appears to be no appreciable deterioration in HRQoL for patients treated with nal-iri+5-FU compared with 5-FU/LV. However, 5-FU/LV is rarely used to treat such patients and it is impossible to say whether nal-iri+5-FU/LV is more or less clinically effective than oxaliplatin+5-FU/LV, oxaliplatin+capecitabine or capecitabine monotherapy in the population of interest.

5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company in support of prescribing nal-iri in combination with 5-FU/LV for the treatment of metastatic adenocarcinoma of the pancreas in adult patients who have progressed following gemcitabine based therapy.

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 an electronic copy of their economic model, which was developed in Microsoft Excel.

5.1 The company's review of cost effectiveness evidence

5.1.1 Objective of the cost effectiveness review

A systematic review was conducted to summarise findings from published cost effectiveness studies that are relevant to the decision problem. The searches were conducted on 19 January 2016. The databases searched, along with date limits, and sources that were hand searched, are listed in Table 28. Details of the search strategies employed by the company are provided in Appendix 7 of the CS.

Table 28 Data sources for economic systematic review

Search strategy component	Sources	Date limits
Electronic database searches via the OVID platform	MEDLINE® MEDLINE® In-Process & Other Non-Indexed Citations	1946 to present
	Excerpta Medical Database (Embase®)	1980 to 201, 6 week 3
	Econlit	1886 to December 2015
	The Cochrane® Library, including: Central Register of Controlled Trials (CENTRAL) Cochrane Database of systematic Reviews Database of Abstracts of Reviews of Effects (DARE) Health Technology Assessment (HTA) NHS Economic Evaluation Database (EED)	 December 2015 2005 to 13 January 2016 2nd quarter 2015 4th quarter 2015 2nd quarter 2015
Hand searching	Reference lists of included studies and relevant systematic reviews	NA
	Cost effectiveness Analysis (CEA) Registry	NR
	Research Papers in Economics (RePEc)	NR
	Conference proceedings, including: American Society of Clinical Oncology (ASCO) European Society for Medical Oncology (ESMO) International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	2013 to 2016
	Previous HTA submissions/appraisals	

HTA=health technology assessment; NA=not applicable; NR=not reported
Source: CS, p92 and CS, Appendices 7.1 and 7.4

5.1.2 Eligibility criteria used in study selection

The inclusion/exclusion criteria used to facilitate study selection are presented in Table 29.

Table 29 Eligibility criteria used in economics search strategy

	Inclusion criteria	Exclusion criteria
Population	Patients with advanced or metastatic (stage IV) pancreatic cancer who have been previously treated with gemcitabine-containing treatment at any line of therapy (including gemcitabine in non-adjuvant/adjuvant/locally advanced patients who are now diagnosed with metastatic disease)	Studies in which it is unclear whether the population meets the eligibility criteria
Interventions	Pegylated liposomal irinotecan hydrochloride trihydrate (nal-iri) in combination with 5-FU and LV	-
Comparators	Oxaliplatin in combination with 5-FU and LV (FOLFOX or OFF regimens) Capecitabine in combination with oxaliplatin Fluoropyrimidine monotherapy, including capecitabine, 5-FU† and S-1	-
Outcomes	Model perspective, time horizon and discounting Description of model or cost assumptions Summary health outcomes (e.g. QALYs, LYG) ICERs	-
Study design	CUAs Other forms of CEA will be tagged (and included if no CUAs are identified)	-
Language restrictions	English language. English language abstracts of non-English language publications will also be included	-
Date of publication	Not restricted by date	-

CEA=cost effectiveness analysis; CUA=cost utility analysis; ICER=incremental cost effectiveness ratio; LYG=life years gained; QALY=quality adjusted life years
†Including in combination with LV
Source: CS, Appendix 7, Table 10

5.1.3 Included and excluded studies

The company identified 253 papers through the electronic searches and removed 37 duplicate papers, leaving 216 titles and abstracts to be reviewed. Seven records were ordered for full paper review and all seven were excluded: four on the basis of patient population (no prior treatment) and one each for reasons of language (Japanese), intervention (none of interest) and paper type (review). The publications excluded on the basis of the full text review are detailed in Appendix 7.7 of the CS (Table 11). No publications meeting the eligibility criteria were identified via hand searches.

No relevant studies were identified by the company.

5.1.4 Findings from cost effectiveness review

The company's review identified no evidence to support the use of nal-iri in combination with 5-FU/LV for the treatment of patients with advanced or metastatic (stage IV) pancreatic cancer who have been previously treated with gemcitabine based therapy (any line), including gemcitabine in non-adjuvant/adjuvant/locally advanced patients who are now diagnosed with metastatic disease.

5.2 ERG critique of the company's literature review

The ERG is satisfied with the company's search strategy and is confident that there are no cost effectiveness studies that fully meet the company's inclusion criteria. The databases searched and search terms used appear to be reasonable.

The company also reports the methods and results for searches carried out to identify HRQoL data relevant to the decision problem. Further detail on these searches are given in Section 5.3.5 of this ERG report, and in the CS (Section 5.4.3 and Appendix 9). The ERG considers these details to be helpful.

5.3 Summary of the company's submitted economic evaluation

The company has developed a de novo economic model to allow the comparison of three treatment regimens: nal-iri+5-FU/LV, oxaliplatin+5-FU/LV and 5-FU/LV monotherapy.

The company model is a partitioned survival model which comprises four mutually exclusive health states: pre-progression on treatment, pre-progression off treatment, post-progression treatment (including patients receiving second-line therapy and those receiving palliative care) and death. All patients enter the model in the pre-progression on treatment health state. At the beginning of each time period patients can either remain in the same health state or progress to a worse health state. For example, patients in the pre-progression on treatment health state can move to the pre-progression off treatment health state, the post-progression treatment state or the death state, whilst patients in the post-progression treatment state can only move to the death state. A schematic of the company model is reproduced in Figure 2. The ERG has added two blue arrows to Figure 2 as, in the company model, patients may move directly from either of the pre-progression treatment states (pre-progression on treatment and pre-progression off treatment) to the death state.

Estimates of OS, PFS and TTF for patients treated with nal-iri+5-FU/LV and 5-FU/LV are based on K-M data from the NAPOLI-1 trial. Estimates of OS, PFS and TTF for patients treated with oxaliplatin+5-FU/LV are based on data from an ITC combined with various assumptions. The proportion of patients in the pre-progression on treatment health state is estimated as the difference between PFS and TTF. The proportion of patients in the post-progression treatment state is estimated as the difference between OS and PFS.

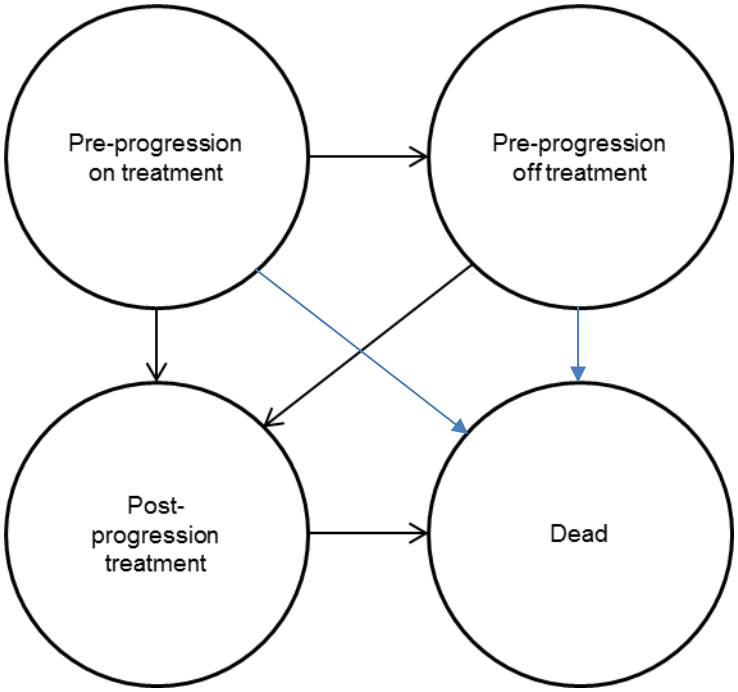

Figure 2 Company model structure

Source: CS, adapted from Figure 8 (Blue lines added by the ERG)

5.3.1 Population

The population reflected in the company model is adult patients with metastatic adenocarcinoma of the pancreas who have progressed following gemcitabine based therapy, as per the NICE scope and the NAPOLI-1 trial.

Based on the results of a study of the average body surface area (BSA) of adult cancer patients in the UK,[39] the company has assumed that population BSA is 1.79m^2. The company notes that this BSA value is similar to the BSA of the NAPOLI-1 trial ITT population (1.75m^2). Age and sex are not variables in the model.

5.3.2 Interventions and comparators

Pre-progression treatment

The company model allows the cost effectiveness of nal-iri+5-FU/LV to be compared with oxaliplatin+5-FU/LV (NHS standard of care) and 5-FU/LV (a comparator in the NAPOLI-1 trial). Dosing schedules and dosing levels differ between the intervention and each comparator. Dosing schedules used in the company model are displayed in Table 30.

Table 30 Dosing schedules

Treatment	Nal-iri+5-FU/LV (Intervention)	Oxaliplatin+5-FU/LV (NHS standard of care)	5-FU/LV (NAPOLI-1 trial comparator)
Nal-iri dose	80mg/m^2	--	--
Oxaliplatin dose	--	85mg/m^2	--
LV dose	400mg/m^2	200mg/m^2	200mg/m^2
5-FU dose	2400mg/m^2	1000mg/m^2	2000mg/m^2
5-FU delivery time	46hrs	46hrs	24hrs
Dosing frequency	Every 2 weeks	Every 2 weeks	Days 1, 8, 15 and 22 followed by 2 weeks rest in a 6 week cycle

-- not applicable
Source: CS, p123

Post-progression treatment

Based on the experience of patients included in the NAPOLI-1 trial, the company has assumed that 38% of patients receiving treatment with nal-iri+5-FU/LV and 31% of patients receiving treatment with 5-FU/LV monotherapy receive anti-cancer treatment post-progression. The company also assumes that the proportion of patients receiving oxaliplatin+5-FU/LV who go on to receive anti-cancer treatment post-progression is the same as the estimate used for the nal-iri+5-FU/LV cohort (38%). The company does not provide details of the post-progression treatments. It is not clear to the ERG whether these proportions relate to all patients or only those whose progression event was not fatal. The ERG also notes that within the company's clarification response figures from the NAPOLI trial show that the proportions of patients in the nal-iri+5-FU/LV and 5-FU/LV arms who received anti-cancer treatment post-progression were 35.9% and 42.0% in the respectively.

5.3.3 Perspective, time horizon and discounting

The economic evaluation is undertaken from the perspective of the NHS. The time horizon is set at 10 years and both costs and outcomes are discounted at a rate of 3.5% per annum.

5.3.4 Treatment effectiveness and extrapolation

Nal-iri+5-FU/LV and 5-FU/LV

The primary data source for the economic model was patient-level data from the final data cut of the NAPOLI-1 trial (March 2016). At this point all patients were dead. The company modelled survival and TTF using parametric distributions fitted to K-M data taken from the NAPOLI-1 trial.

The company compared six standard parametric models (exponential, Weibull, Gompertz, log-logistic, log-normal and gamma). The most appropriate distribution was chosen based on how well the distribution fitted K-M data from the NAPOLI-1 trial (assessed using Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC] statistics) and the

clinical and biological plausibility of the distribution. This approach resulted in log-normal distributions being selected to model OS, PFS and TTF in the base case. Log-logistic distributions were used to model these parameters in a scenario analysis. Key survival and TTF parameter values from the NAPOLI-1 trial and the company model are displayed in Table 31. The NAPOLI-1 trial OS and PFS K-M data used in the company model are shown in Figure 3 and Figure 4 respectively.

Table 31 Key NAPOLI-1 trial and model survival and time to treatment failure parameter values

	Figures used in company model		Figures in CS, where different from company model	
Parameter values	**Nal-iri+5-FU/LV**	**5-FU/LV**	**Nal-iri+5-FU/LV**	**5-FU/LV**
PFS				
NAPOLI-1 trial median, months	3.1	1.5	-	-
Company model median, months	3.49*	2.09	3.47	-
Company model mean, months	5.47*	2.81	5.45	-
OS				
NAPOLI-1 trial median, months	6.2	4.2	-	-
Company model median, months	6.75*	4.66*	6.24	4.67
Company model mean, months	10.20*	7.69*	10.18	7.66
TTF				
NAPOLI-1 trial median, months	1.6	0.76	-	-
Company model median, months	1.7	1.10	-	-
Company model mean, months	4.6	2.0	-	-

CS=company submission; OS=overall survival; PFS=progression-free survival; TTF=time to treatment failure
Source: CS, Table 37 and company model

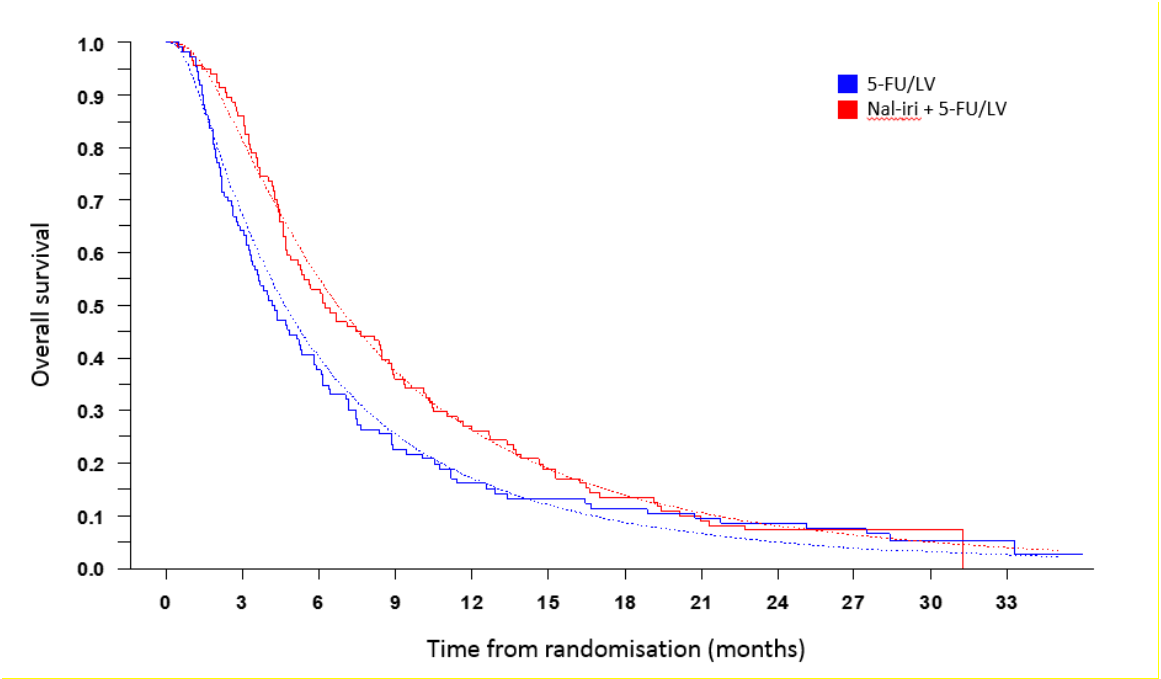

Figure 3 Base case (log-normal) model fit to overall survival

Source: CS, Figure 10

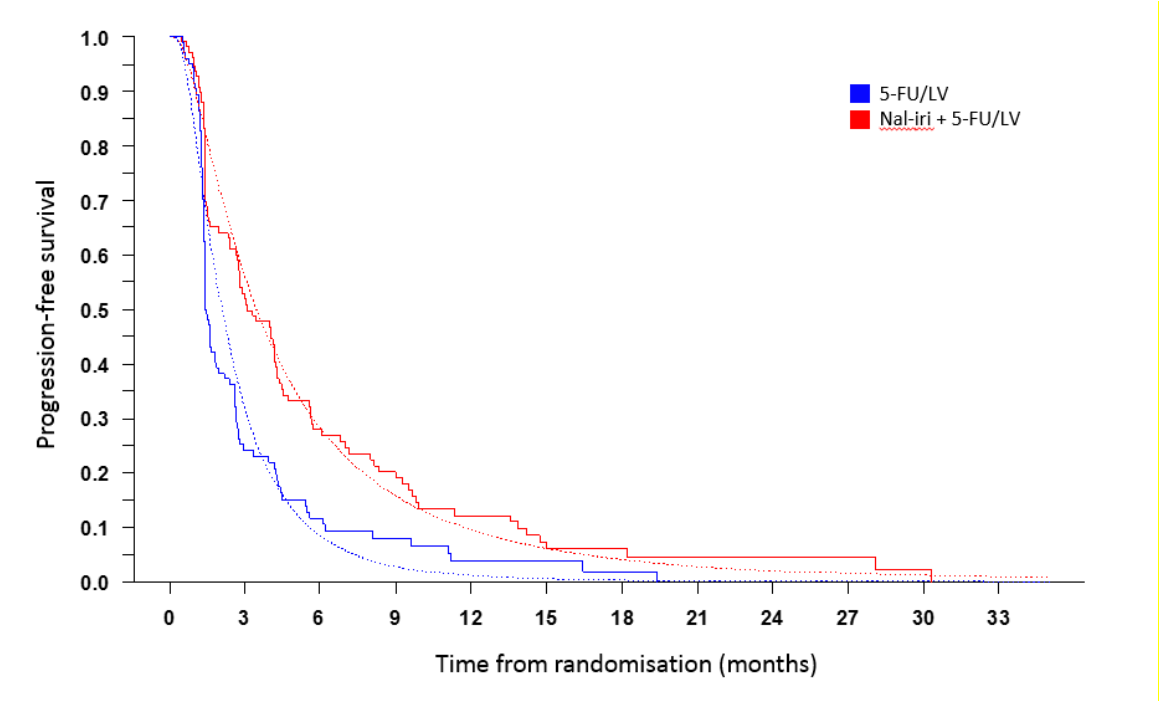

Figure 4 Base case (log-normal) model fit to progression-free survival

Source: CS, Figure 11

Oxaliplatin+5-FU/LV

The company performed an ITC (using the Bucher adjusted ITC method[35]) to generate estimates for the effectiveness of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV using data from the CONKO-003 and PANCREOX clinical trials. The resultant PFS and OS HRs were used to adjust the 5-FU/LV base case PFS and OS models to generate survival estimates for patients treated with oxaliplatin+5-FU/LV.

The company notes the limitations of two key assumptions that underpin the ITC methodology. First, the survival estimates for oxaliplatin+5-FU/LV from the ITC rely on the assumption that the dosing regimens for oxaliplatin+5-FU/LV used in the CONKO-003 and PANCREOX trials (OFF and FOLFOX6, respectively) are equivalent. Second, the application of survival estimates from the ITC relies on the assumption of PH between the nal-iri+5-FU/LV and 5-FU/LV arms of the NAPOLI-1 trial, which the company states do not hold for OS.

A critique of the ITC may be found in Section 4.3 of this ERG report.

5.3.5 Health related quality of life

The cancer-specific EORTC-QLQ-C30 questionnaire was used during the NAPOLI-1 trial to collect HRQoL data. The company states that they did not map between EORTIC-QLC-30 and EuroQol-5 dimension (EQ-5D) utility values because:

- a substantial amount of HRQoL data were missing, with the majority of the missing data being due to discontinuation of treatment because of disease progression, adverse events or death (i.e. not random)
- although one potential mapping algorithm was identified,[40] this was an ASCO abstract and no algorithm was available.

The company conducted a systematic review to identify HRQoL studies relevant to the decision problem. Studies reporting health state utility values relating to patients with metastatic pancreatic cancer were considered eligible for inclusion. Full details of the company's search are included in Appendix 9 of the CS. Six studies met the inclusion criteria for the review.

Utility values from a US study, adjusted first to reflect the values of the UK population and then further adjusted to include disutility associated with AEs, are used in the company model. The US utility values, adjusted to reflect the values of the UK population but without AE associated disutility adjustments, have previously been used by the ERG[41] during the

NICE appraisal of nab-paclitaxel in combination with gemcitabine for previously untreated metastatic pancreatic cancer (TA360).[13]

A summary of the utility values employed in the model is included in Table 32.

Table 32 Summary of utility values for cost effectiveness analysis

	Utility value	95% CI	Reference	Justification
5-FU/LV				
Baseline utility value				
Pre-progression	0.742	NR	TA360 ERG report[41]	Utility data from NAPOLI-1 trial could not be used
Post-progression	0.671*	NR		
Nal-iri+5-FU/LV				
Baseline utility value				
Pre-progression	0.742	NR	TA360 ERG report[41]*	Utility data from NAPOLI-1 trial could not be used
Post-progression	0.671*	NR		
Oxaliplatin+5-FU/LV				
Baseline utility value				
Pre-progression	0.742	NR	TA360 ERG report[41]	Assumed to be equivalent to nal-iri + 5-FU/LV
Post-progression	0.671*	NR		
Adverse events (utility decrements)				
Abdominal pain	–0.069	-0.093 to -0.045†	Doyle, 2008[42]	
Anaemia	–0.204	-0.156 to -0.252	-	Assumed equivalent to fatigue
Diarrhoea	–0.204	-0.156 to -0.252	-	
Fatigue	–0.204	-0.156 to -0.252	Swinburn, 2010[43]	
Nausea	–0.048	-0.079 to -0.016	Nafees, 2008[44]	
Neutropenia	–0.090	-0.122 to -0.058	Nafees, 2008[44]	
Vomiting	–0.048	–0.079 to –0.016	-	Assumed equivalent to nausea

AE=adverse event; ERG=Evidence Review Group; NR=not reported
*Indicates value amended during clarification process (0.672 in original submission)
Source: CS, Table 42

5.3.6 Resources and costs

Drug costs

Table 33 shows the unit costs of drugs included in the company model.

Table 33 Drug unit costs

Items	Vial size	Cost per vial	Cost per unit	Reference
Nal-iri	50mg	[redacted]	[redacted]	CS
5-FU bolus injection	500mg	£12.80	£0.0128*	BNF 2016[45]
5-FU infusion	500mg	£64.00	£0.0128*	
LV	50mg	£100.00	£0.375	
Oxaliplatin	50mg	£311.00	£3.11*	

BNF=British National Formulary
*Indicates values that differ between the CS and the company model. Where there is a discrepancy, values from the company model are presented
Source: CS, Table 45 and company model

The company calculates average drug costs from the average number of vials used per patient. The average number of vials used for each drug is based on the probability of needing a given number of vials based on a normal distribution of the dose per patient. The average number of vials used also takes into account the recommended dose per m^2 and assumes that 5-FU comes in 500mg vials and all other drugs come in 50mg vials. The average dose per patient is calculated based on mean BSA and the recommended dose of the drug, and is then adjusted using a dose intensity multiplier to allow treatment costs to be adjusted for missed and reduced doses. The values of these multipliers are provided in Table 34.

Table 34 Mean dose intensity multipliers used in the company model

Treatment	Mean dose intensity multiplier	Reference
Nal-iri+5-FU/LV	85%	NAPOLI-1 trial
Oxaliplating+5-FU/LV	85%	Assumption
5-FU-LV	95%	NAPOLI-1 trial

Source: Company model

Administration costs

The company has used NHS Reference Costs as the source of administration costs for each treatment. The first drug administered in any regimen is costed as simple parental chemotherapy (£239.12) and subsequent drugs are assumed to require 30 minutes of nurse time (£18.00) to remove the initial infusion and to set up the next infusion. Because of the long infusion time associated with 5-FU treatment, an additional cost of £97.14 (non-consultant outpatient attendance, medical oncology) is applied to account for resource use associated with the patient's return to hospital to have the infusion pump removed as an outpatient. The costs of administering each treatment are displayed in Table 35.

Table 35 Administration costs for nal-iri+5-FU/LV, 5-FU/LV and oxaliplatin+5-FU/LV

	Nal-iri+5-FU/LV			Oxaliplatin+5-FU/LV			5-FU/LV	
	Nal-iri	5-FU	LV	Oxaliplatin	5-FU	LV	5-FU	LV
Administration cost	£239.12	£115.14	£18.00	£239.12	£115.14	£18.00	£115.14	£239.12
Total cost per treatment	£372.26			£372.26			£354.26	
Cost per week	£186.13			£186.13			£236.17	

Source: Company model

Treatment-related monitoring costs

The company has assumed that patients will be monitored until the termination of active anti-cancer treatments. Monitoring costs are split into two: initial monitoring costs prior to the start of therapy, and monitoring costs during the treatment period. Initial monitoring costs include laboratory tests in preparation for the initiation of treatment and are only applied to the first cycle of the model. After the initiation of treatment, patients are monitored with follow-up visits and laboratory tests for as long as they remain on active treatments. Treatment-related monitoring costs used in the model are shown in Table 36 and Table 37.

Table 36 Initial monitoring and laboratory test costs

Visit and tests	Unit cost	Reference	Proportion of patients	Cost per week
Outpatient visit (consultant)	£170.85	NHS Reference Costs 2014-15[46]	100%	£170.85
CT scan	£108.71		100%	£108.71
Radiographic/MRI scan	£181.76		10%	£18.18
Full blood count	£3.01		100%	£3.01
Liver function test	£6.89		100%	£6.89
Ultrasound	£53.74		5%	£2.69

CT=computed tomography; MRI=magnetic resonance imaging
Source: CS, Table 48

Table 37 Monitoring costs during treatment

Visit and test	Unit costs	Reference	Number	Frequency	Proportion of patients	Cost per week
Community visit (nurse)	£44.00	Curtis 2015[47]	1	Every 4 weeks	60%*	£6.60
Outpatient visit (consultant)	£170.85	NHS Reference Costs 2014-15[46]	1	Every 4 weeks	100%	£42.71
Outpatient visit (non-consultant)	£97.14		1	Every 4 weeks	50%	£12.14
CT scan	£108.71		1	Every 12 weeks	100%	£9.06
Full blood count	£3.01		3	Every 4 weeks	100%	£2.26
Liver function test	£6.89		3	Every 4 weeks	100%	£5.17
Tumour Marker CA19-9 test	£1.38		6	Every 4 weeks	100%**	£2.07

CT=computed tomography
* 50% in CS but 60% used in model
** 5% in CS but 100% used in model
Source: CS, Table 49 and company model

Adverse event costs

The company has included costs associated with grade 3+ TEAEs reported by ≥5% of patients in the model. Costs of managing each AE are listed in Table 38. The expected number of each AE per patient for each treatment was estimated based on data from the NAPOLI-1 trial, with costs associated with AEs for patients treated with oxaliplatin+5-FU/LV assumed to be equal to those for patients treated with nal-iri+5-FU/LV.

Table 38 Summary of weekly costs included in the cost effectiveness model

Adverse events	Value	HRG code	Reference
Anaemia	£528.15	SA04L	NHS Reference Costs 2014-15[46]
Neutropenia	£127.70	XD25Z	
Abdominal pain	£387.25	FZ90A – FZ90B	
Diarrhoea	£319.34	FZ49D - FZ49H	
Nausea	£319.34	NA	Assumed to be the same as diarrhoea
Vomiting	£319.34	NA	
Fatigue	£44.00	NA	1 nurse visit per day for the duration of the adverse event[47]

HRG=Healthcare Resource Group; NA=not applicable
Source: CS, Table 50

Post-progression treatment costs

Patients in the NAPOLI-1 trial were eligible to receive other anti-cancer therapies following progression. However, the company notes that no details about the costs of these subsequent therapies were collected during that trial. The company has assumed that the average weekly cost of post-progression treatment is equal to the weekly drug cost for nal-iri+5-FU/LV ([redacted]). Patients who receive anti-cancer therapy post-progression continue

to receive treatment until death. The weekly costs for post-progression treatment are summarised in Table 39.

Table 39 Costs of post-progression treatment

	Nal-iri+ 5-FU/LV	Oxaliplatin+ 5-FU/LV	5-FU/LV	Reference
Cost of post-progression treatments	[redacted]	[redacted]	[redacted]	Assumed equal to nal-iri
Percent of patients**	31%†	Assumed equal to nal-iri+5-FU/LV, i.e. 31%	38%†	NAPOLI-1 trial
Average cost per week	[redacted]	[redacted]	[redacted]	

*This is the figure used in the model; however, the figure reported in the CS is [redacted]
**It is not clear to the ERG whether these proportions relate to all patients or only those whose progression event was not fatal.
†These are the figures used in the model and reported in the CS; however, the figures quoted in the clarification response are 35.9% and 42.0% for the nal-iri+5-FU/LV and 5-FU/LV arms respectively
Source: CS, Table 53, company model and clarification response

Palliative- and terminal-care costs

The company assumes that patients who do not go on to receive anti-cancer therapy post-progression receive palliative care, which amounts to one home care visit by a nurse every week until death. The percentage of patients who receive palliative care in the model is based on the percentage of patients who did not switch to another anti-cancer therapy following disease progression in the NAPOLI-1 trial: 69% in the nal-iri+5-FU/LV arm and 62% in the 5-FU/LV arm. The company assumes that the percentage of patients receiving oxaliplatin+5-FU/LV who receive palliative care is equal to the percentage of patients treated with nal-iri+5-FU/LV who receive palliative care.

In line with the model submitted as part of the NICE TA360[13] appraisal, the company assumes that terminal care is provided to patients in the 4 weeks prior death. The company accounts for terminal care costs in the model by assuming that, 4 weeks before death, 50% of patients receive more frequent home visits by a nurse and 50% of patients are moved to hospice care. Terminal care costs are included in addition to ongoing palliative care costs.

The palliative- and terminal-care costs included in the company model are provided in Table 40 and Table 41 respectively.

Table 40 Palliative care costs

Item	NAl-iri+ 5-FU/LV	Oxaliplatin+ 5-FU/LV	5-FU/LV	Reference
Nurse home care visit per week	1			Advisory board
Costs per nurse home care visit	£44.00			NHS Reference Costs 2014-15[46]
Percent of patients	69%†	Assumed equal to nal-iri+5-FU/LV	62%†	NAPOLI-1 trial*
Average cost per week	£30.36	£30.36	£27.28	

NHS=National Health Service.
*Percentages are for patients who did not switch to anti-cancer therapy following disease progression
†Indicates values that differ between the company clarification response and the company model. Where there is a discrepancy, values from the company model are presented
Source: CS, Table 51

Table 41 Terminal care costs incurred in the 4 weeks before death

Items	No.	Frequency	% of patients	Unit cost	Source	Cost per week
Nurse home care	3	Every week	50%	£44.00	Curtis 2015 [47]	£66.00
Hospice centre/ palliative care unit	7	Every week	50%	£103.01	NHS Reference Costs, 2014-15	£360.54
Total						£426.54

Source: CS, Table 52

5.3.7 Cost effectiveness results

Base case results

Base case incremental cost effectiveness results for treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV and versus 5-FU/LV are shown in Table 42. Pairwise cost effectiveness results for the comparison of treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV and of nal-iri+5-FU/LV versus 5-FU/LV are shown in Table 43 and Table 44 respectively.

In the base case, nal-iri+5-FU/LV generates 0.20 additional quality adjusted life years (QALYs) and 0.31 additional life years compared with oxaliplatin+5-FU/LV and, compared with 5-FU/LV, generates an additional 0.13 QALYs and an additional 0.21 life years. Patients treated with nal-iri+5-FU/LV-are estimated to have higher total lifetime costs than patients receiving either of the other two treatments. The incremental cost effectiveness ratio (ICER) for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV is £[redacted] per QALY gained and the ICER for the comparison of nal-iri+5-FU/LV versus 5-FU/LV is £[redacted] per QALY gained.

Table 42 Base case model results (incremental)

Technologies	Total		Incremental		ICER (Cost/QALY)
	Costs	QALYs	Costs	QALYs	
5-FU/LV	£13,338.32	0.4294			
Oxaliplatin+5-FU/LV	£13,974.83	0.3621	£636.51	-0.0673	[redacted]
Nal-iri+5-FU/LV	[redacted]	0.5635	[redacted]	0.1341	[redacted]

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: CS, Table 55 (costs and QALYs) and ERG calculations (incremental results)

Table 43 Base case cost effectiveness results (nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV)

Technologies	Total		Incremental		ICER (Cost/QALY)
	Costs	QALYs	Costs	QALYs	
Nal-iri+5-FU/LV	[redacted]	0.5635	-	-	-
Oxaliplatin+5-FU/LV	£13,974.83	0.3621	[redacted]	0.2013	[redacted]

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: CS, Table 55

Table 44 Base case cost effectiveness results (nal-iri+5-FU/LV versus 5-FU/LV)

Technologies	Total		Incremental		ICER (Cost/QALY)
	Costs	QALYs	Costs	QALYs	
Nal-iri+5-FU/LV	[redacted]	0.5635	-	-	-
5-FU/LV	£13,338.32	0.4294	[redacted]	0.1341	[redacted]

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: CS, Table 55

Disaggregated cost estimates for treatment with nal-iri+5-FU/LV, oxaliplatin+5-FU/LV and 5-FU are shown in Table 45 and Table 46. Disaggregated QALY estimates for treatment with nal-iri+5-FU/LV, oxaliplatin+5-FU/LV and 5-FU/LV are shown in Table 47 and Table 48.

Table 45 Disaggregated cost estimates (nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV)

Health state	Nal-iri+ 5-FU/LV	Oxaliplatin+ 5-FU/LV	Increment	Absolute increment	% absolute increment
Drug	[redacted]	£4,450*	[redacted]	[redacted]	[redacted]
Admin	£3,174	£2,655	£518	£518	[redacted]
AE	£242	£202	£39	£39	[redacted]
Monitoring	£1,675	£1,452	£223	£223	[redacted]
Palliative	£2,492	£2,098	£394	£394	[redacted]
Pre-progression	£25,507	£6,407	£14,621	£14,621	[redacted]
Post-progression	£5,578	£3,117	£2,461	£2,461	[redacted]
Total	[redacted]	£19,975*	[redacted]	[redacted]	100%

AE=adverse event
*Indicates values that differ between the CS and the company model. Where there is a discrepancy, values from the company model are presented
Source: CS, Table 60 and company model

Table 46 Disaggregated cost estimates (nal-iri+5-FU/LV versus 5-FU/LV)

Health state	Nal-iri+ 5-FU/LV	5-FU/LV	Increment	Absolute increment	% absolute increment
Drug	[redacted]	£971	[redacted]	[redacted]	[redacted]
Admin	£3,174	£1,874	£1,300	£1,300	[redacted]
AE	£242	£74	£168	£168	[redacted]
Monitoring	£1,675	£945	£730	£730	[redacted]
Palliative	£2,492	£2,372	£120	£120	[redacted]
Pre-progression	£25,507	£6,236	£18,885	£18,885	[redacted]
Post-progression	£5,578	£7,103	-£1,525	£1,525	[redacted]
Total	[redacted]	£13,338	[redacted]	[redacted]	100%

AE=adverse event
Source: CS, Table 59

Table 47 Summary of QALY gain by health state for nal-iri+5-FU/LV versus 5-FU/LV

Health state	Nal-iri+ 5-FU/LV	5-FU/LV	Increment	Absolute increment	% total absolute increment
Pre-progression	0.3279	0.1724	0.1555	0.1555	116%
Post-progression	0.2355	0.2569	-0.0214	0.0214	-16%
Total	0.5635	0.4294	0.1341	0.1341	100%

QALY=quality adjusted life year
Source: Company model

Table 48 Summary of QALY gain by health state for nal-iri+5-FU/LV versus oxaliplatin+5 FU/LV

Health state	Nal-iri+ 5-FU/LV	Oxaliplatin+ 5-FU/LV	Increment	Absolute increment	% absolute increment
Pre-progression	0.3279	0.2305	0.0974	0.0974	48%
Post-progression	0.2355	0.1316	0.1039	0.1039	52%
Total	0.5635	0.3621	0.2013	0.2013	100%

QALY=quality adjusted life year.
Source: Company model

5.3.8 Sensitivity analyses

Deterministic sensitivity analysis

The company did not provide any deterministic sensitivity analyses for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV.

One-way sensitivity analyses were conducted for the comparison of nal-iri+5-FU/LV versus 5-FU/LV. The sensitivity analyses involved varying 44 cost, resource use and utility parameter values (see CS, Table 62). The base case ICER per QALY gained was most sensitive to varying the pre-progression utility values. The results were also sensitive to the cost of nal-iri and to mean BSA. All other variables had minimal impact on the size of the ICER per QALY gained. The tornado diagram in Figure 5 shows the ten parameters with the biggest impact on the ICER per QALY gained for the comparison of nal-iri+5-FU/LV versus 5-FU/LV.

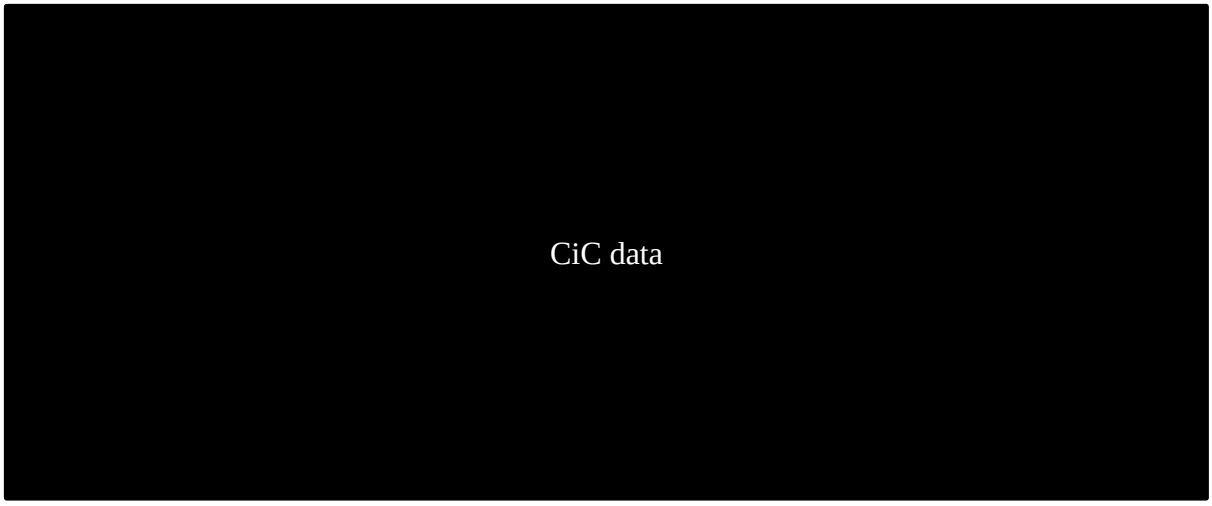

Figure 5 Tornado diagram of deterministic sensitivity analysis ICERs for the comparison of nal-iri+5-FU/LV versus 5-FU/LV

Admin=administer; BSA=body surface area; chemo=chemotherapy
Source: CS, Figure 21

Scenario analyses

Three scenario analyses were undertaken by the company, namely:

1. using data from the February 2014 data cut from the NAPOLI-1 trial instead of from the March 2016 data cut
2. omitting utility decrements associated with AEs and
3. using a log-logistic instead of log-normal distribution for PFS, OS and TTF for nal-iri+5-FU/LV versus 5-FU/LV.

The results of these scenario analyses are shown in Table 49.

Table 49 Scenario analyses results

Scenario	ICER per QALY gained	
	Nal-iri+5-FU/LV versus 5-FU/LV	Nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV
Base case	[redacted]	[redacted]
February 2014 data cut from NAPOLI-1 trial using log-normal distribution	[redacted]	[redacted]
AE utility decrements omitted	[redacted]	[redacted]
Log-logistic distribution for PFS, OS and TTF for nal-iri+5-FU/LV versus 5-FU/LV	[redacted]	–

AE=adverse event; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; TTF=time to treatment failure
*Indicates values that differ between the CS and the company model. Where there is a discrepancy, values from the company model are presented
Source: CS, Table 63 and company model

Probabilistic Sensitivity Analysis

The company undertook probabilistic sensitivity analyses (PSA) to derive the mean ICERs per QALY gained for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV and for nal-iri+5-FU/LV versus 5-FU/LV. The PSAs were run for 1000 iterations. The ERG has recalculated these ICERs following identification of a calculation error. The company and ERG results are shown in Table 50.

The probabilistic ICER for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV is £85,525 per QALY gained, which is comparable to the deterministic ICER per QALY gained (Table 50). At a cost effectiveness threshold of £50,000 per QALY gained, treatment with nal-iri+5-FU/LV has a 0% probability of being cost effective compared with treatment with oxaliplatin+5-FU/LV. The cost effectiveness plane and cost effectiveness acceptability curve (CEAC) for this comparison are shown in Figure 6 and Figure 7 respectively.

Table 50 Deterministic and probabilistic ICER results

Treatment	Incremental costs	Incremental QALYs	ICER per QALY gained	
			CS	ERG calculation*
Deterministic results				
Nal-iri+5-FU/LV				
Oxaliplatin+5-FU/LV	[redacted]	0.2013	[redacted]	-
5-FU/LV	[redacted]	0.1341	[redacted]	-
Probabilistic sensitivity analysis results				
Nal-iri+5-FU/LV				
Oxaliplatin+5-FU/LV, model (CS)	[redacted]	0.1348	[redacted]	[redacted]
5-FU/LV, model (CS)	[redacted]	0.2035	[redacted]	[redacted]

CS=company submission; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
*ERG re estimated probabilistic ICERs as the company's calculations were incorrect
Source: CS and company model

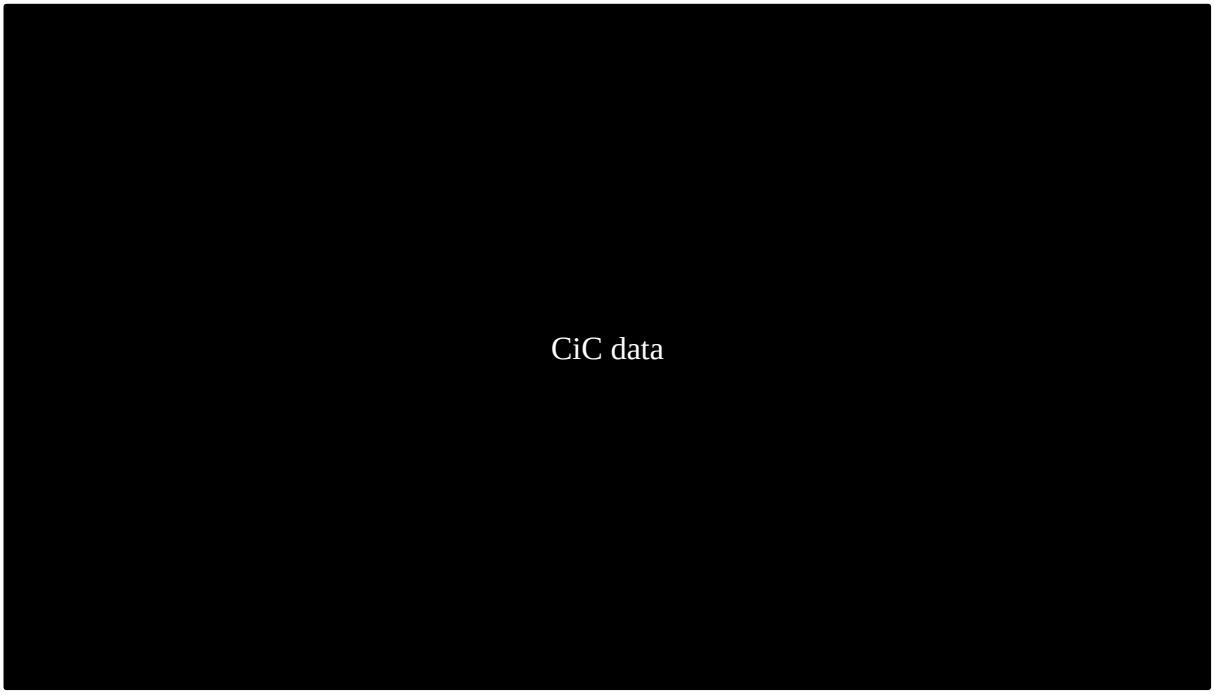

Figure 6 Cost effectiveness plane for nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV

QALY=quality adjusted life year
Source: CS, Figure 19

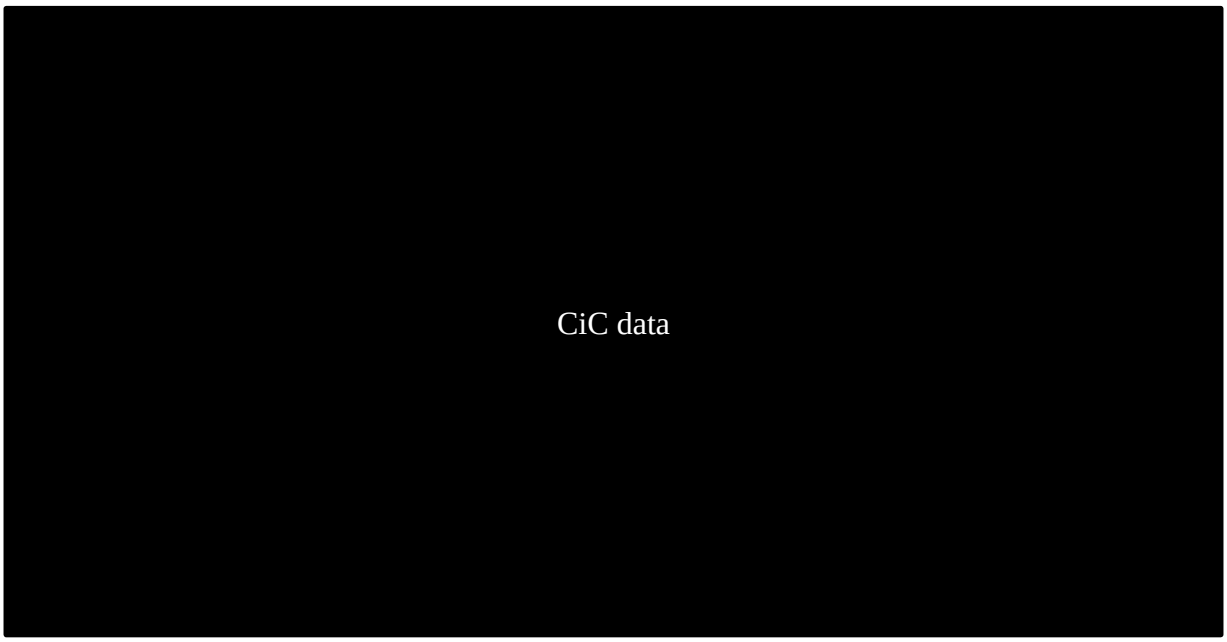

Figure 7 Cost effectiveness acceptability curve for nal-iri+5-FU/LV versus oxaliplatin+5 FU/LV

QALY=quality adjusted life year
Source: CS, Figure 20

The probabilistic ICER for the comparison of nal-iri+5-FU/LV versus 5-FU/LV is £ per QALY gained, which is also comparable to the deterministic ICER per QALY gained (Table 50), but is more variable than the probabilistic ICER per QALY gained for the comparison of

nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV. This is because the company assumes that many of the parameters in the estimate of the ICER per QALY gained for oxaliplatin+5-FU/LV are equal to those for nal-iri+5-FU/LV, which reduces the uncertainty in the probabilistic analysis. There are few assumptions of parameter equality in the calculation of the probabilistic ICER per QALY gained for nal-iri+5-FU/LV versus 5-FU/LV, which means there is likely to be more uncertainty in this PSA ICER per QALY gained than there is in the PSA ICER per QALY gained for nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV. At a cost effectiveness threshold of £50,000 per QALY gained, treatment with nal-iri+5-FU/LV has a [redacted]% probability of being cost effective compared with treatment with 5-FU/LV. The cost effectiveness plane and CEAC for this comparison are shown in Figure 8 and Figure 9 respectively.

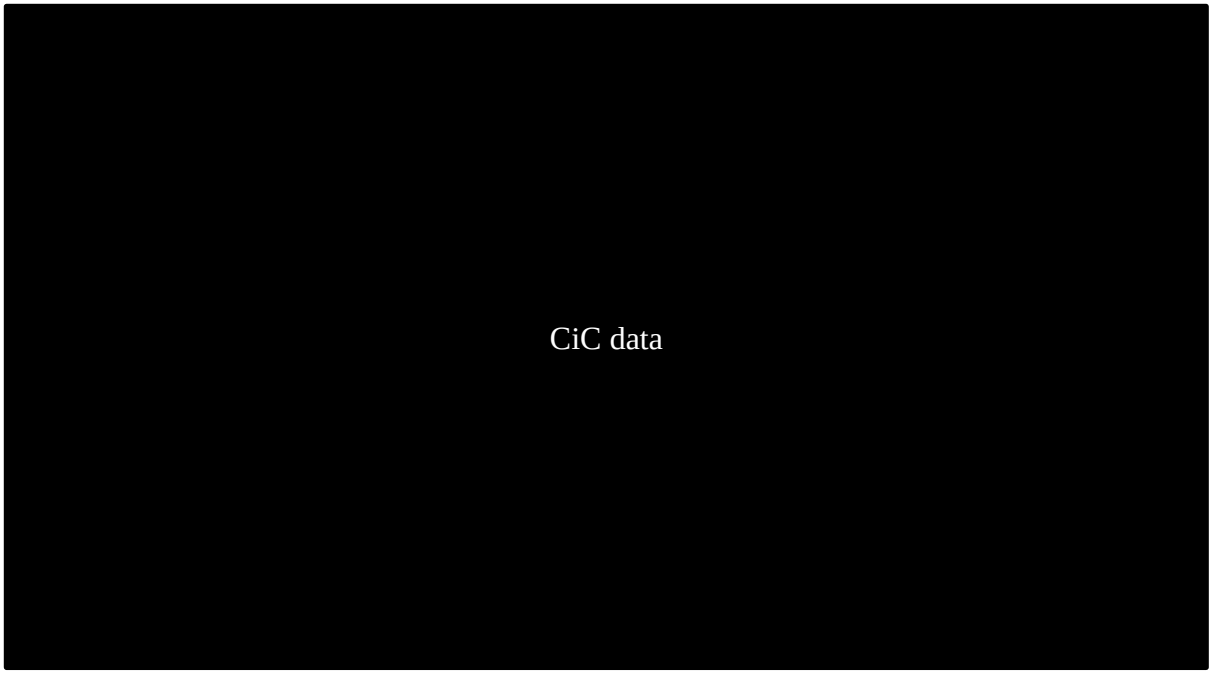

Figure 8 Cost effectiveness plane for nal-iri+5-FU/LV versus 5-FU/LV

QALY=quality adjusted life year
Source: CS, Figure 17

Figure 9 Cost effectiveness acceptability curve for nal-iri+5-FU/LV versus 5-FU/LV

QALY=quality adjusted life year
Source: CS, Figure 18

5.3.9 Model validation and face validity check

The company states that their model was validated through a multi-step process to verify the structure and underlying modelling and economic assumptions, which was followed by verification of all numerical data included in the model and mark-up of the reference publication. The model development team was supported by a quality control team that was not involved in model development. A model verification checklist was followed.

5.4 Completed model checklists

5.4.1 NICE reference case checklist

Table 51 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 NICE	Partial -amended to specify the combination of nal-iri with 5-FU in line with the revised indication in the SmPC
Comparator(s)	As listed in the scope developed by NICE	Partial - oxaliplatin in combination with capecitabine was excluded due to lack of published data. Fluoropyrimidine (5-fluorouracil) was included in combination with leucovorin (5-FU/LV). FOLFOX6 was included as oxaliplatin+5-FU/LV
Perspective costs	NHS and PSS	Partial - the model only includes NHS costs. Personal Social Service costs have not been considered
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Partial - patient related direct health effects are considered. No impact on carers has been considered in the model
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 10 year time horizon
Synthesis of evidence on outcomes	Based on systematic review	Survival and time on treatment data associated with treatment with nal-iri+5-FU/LV with 5-FU/LV have been taken from the NAPOLI-1 trial The company carried out a systematic review to identify evidence to use in an ITC to allow a comparison of effectiveness between treatment with nal-iri+5-FU versus oxaliplatin+5-FU/LV. However, results from the company's ITC were considered unreliable (by both the company and the ERG)
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects are expressed in QALYs
Health states for QALY	Reported directly by patients and/or carers	The company derived utility estimates using figures published in multiple sources
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes - NHS costs, valued at relevant prices, have been used. PSS costs are not included in the model
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Yes - benefits and costs have been discounted at the 3.5% rate
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes - all QALYs estimated by the economic model have the same weight

ERG=Evidence Review Group; EQ-5D=EuroQol-5 dimension; HRQoL=Health related quality of life; ITC=indirect treatment comparison; NICE=National Institute for Health and Care Excellence; PSS=personal social services QALY=quality adjusted life year; SmPC=summary of product characteristics;

5.4.2 Drummond checklist

Table 52 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?	Partial	Appropriate data available for nal-iri+5FU/LV and 5-FU/LV. Comparative effectiveness of nal-iri+5-FU/LV and oxaliplatin+5-FU/LV was not established
Were all the important and relevant costs and consequences for each alternative identified?	Yes	Key costs and outcomes were identified
Were costs and consequences measured accurately in appropriate physical units?	Yes	-
Were the cost and consequences valued credibly?	Partially	The ERG considers that the company's survival projections lack clinical credibility for both comparators. In addition, some of the unit costs were incorrectly calculated
Were costs and consequences adjusted for differential timing?	Yes	Discount rate of 3.5% per annum
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICER calculated correctly
Was allowance made for uncertainty in the estimates of costs and consequences?	Partially	Deterministic, scenario and probabilistic sensitivity analyses were undertaken for the nal-iri+5-FU/LV versus 5-FU/LV comparison. However, only scenario and probabilistic sensitivity analysis were undertaken for the comparison with oxaliplatin+5-FU/LV
Did the presentation and discussion of study results include all issues of concern to users?	Yes	The results are presented and discussed in detail and an end of life treatment case has been proposed by the company

ERG=evidence review group; ICER=incremental cost effectiveness ratio

5.5 ERG critique of company model and exploratory and sensitivity analyses

5.5.1 Introduction

The company's de novo economic model is constructed according to conventional modelling practice. The ERG considers that this structure captures the treatment and progression pathway for patients with metastatic pancreatic cancer and that it is appropriate to use model outputs to inform cost effectiveness decision-making. On clinical advice, the ERG considers oxaliplatin+5-FU/LV to be the main comparator to nal-iri+5-FU/LV as this is the current standard of care in the NHS. However, the ERG also considers this comparison to be flawed as the clinical effectiveness data used by the company to estimate the effectiveness of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV are unreliable and thus any cost effectiveness results relating to this comparison should be viewed with caution. The ERG does not consider 5-FU/LV to be a relevant comparator.

Sections 5.5.2 to 5.5.6 of this ERG report include details of the ERG's main concerns relating to the submitted model, namely the use of parametric distributions to represent and project mature time-to-event data, the use of unreliable data to represent the effectiveness of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, the choice of health state utility values and the methods employed to cost drugs. The ERG has addressed additional minor concerns in Section 5.5.7. The ERG's preferred approach to modelling these elements is also presented in the relevant sections. Unless otherwise stated, all of the data from the NAPOLI-1 trial that have been used by the ERG originate from the published paper,[6] the CS or from the company's clarification response.

5.5.2 Indirect treatment comparison: nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV

Due to the absence of direct head-to-head clinical trial data, the company performed an ITC to obtain an estimate of the clinical effectiveness of treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV; the latter is the current standard of care in the UK. Despite the company indicating that an ITC was not credible due to violation of PH assumptions and heterogeneity between trials, the company considered that results from the ITC were necessary to allow a comparison of cost effectiveness to be undertaken. The ERG considers the HRs used to facilitate the company's ITC are unreliable. A full critique of the company's ITC may be found in Section 4.2 and Appendices to this ERG report (Section 11.3). The ERG highlights the fact that the PH assumption is not compatible with log-normal parametric models since these are accelerated time failure (AFT) models and do not produce a single HR.[48] Furthermore, the ERG determined that a time ratio (TR) adjustment could not be

performed due to the AFT assumption also being violated when examining NAPOLI-1 trial data.

Results from crude analyses carried out by the ERG suggest that, overall, the PFS and OS outcomes for patients treated with oxaliplatin+5-FU/LV reported in published trials are similar in magnitude to the PFS and OS outcomes of patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial (see Section 4.7 of this ERG report for further details). To aid the decision-making process, the ERG has performed a number of sensitivity analyses exploring the effect of altering key model effectiveness outcomes for oxaliplatin+5-FU/LV (Section 6, Table 60). Total QALY gains were altered to determine the uncertainty surrounding the clinical effectiveness of oxaliplatin+5-FU/LV.

5.5.3 Time-to-event data

Projection of time-to-event data: nal-iri+5-FU/LV versus 5-FU/LV

To capture survival benefits over time, the company fitted separate parametric models to K-M data from the nal-iri+5-FU/LV and 5-FU/LV treatment arms of the NAPOLI-1 trial. The parametric models were used to estimate OS, PFS, post progression survival (PPS) and pre-progression on-treatment (time on treatment).

The primary purpose of curve fitting is to anticipate what is likely to happen to patients remaining on treatment or at risk subsequent to a data cut. However, in the NAPOLI-1 trial almost all the trial data are complete so that in only one instance is there any need to extrapolate beyond the reported data (involving a single patient still at risk at data cut-off). Thus there is little or no value in fitting parametric survival functions to these data, as the original trial observations must take precedence over any theoretical mathematical construct. Furthermore, the company has not provided any biological rationale or justification for their selection of log-normal distributions to project survival. Log-normal models are invariably problematic, generally leading to overestimates of survival due to their distinctively long tails. The ERG considers that the model should make maximum use of the best available clinical effectiveness evidence (i.e. the mature survival data from the NAPOLI-1 trial) rather than replacing these data with fitted parametric models which serve only to increase uncertainty by concealing the underlying disease dynamic. During the clarification process, the ERG requested K-M data for the nal-iri+5-FU/LV and 5-FU/LV treatment arms of the NAPOLI-1 trial. The ERG has replaced the company projections with complete trial K-M data to estimate OS, PFS and time on treatment for patients treated with nal-iri+5-FU/LV, and PFS and time on treatment for patients treated with 5-FU/LV (Figure 10 to Figure 13).

Progression-free survival

Comparison of the company's log-normal curves and the K-M data from the NAPOLI-1 trial for PFS are presented in Figure 10. The company's log-normal curve overstates the PFS in both the nal-iri+5-FU/LV and 5-FU/LV treatment arms for the first 4 months of PFS, and then understates PFS from 6 months onwards, especially in the comparator arm.

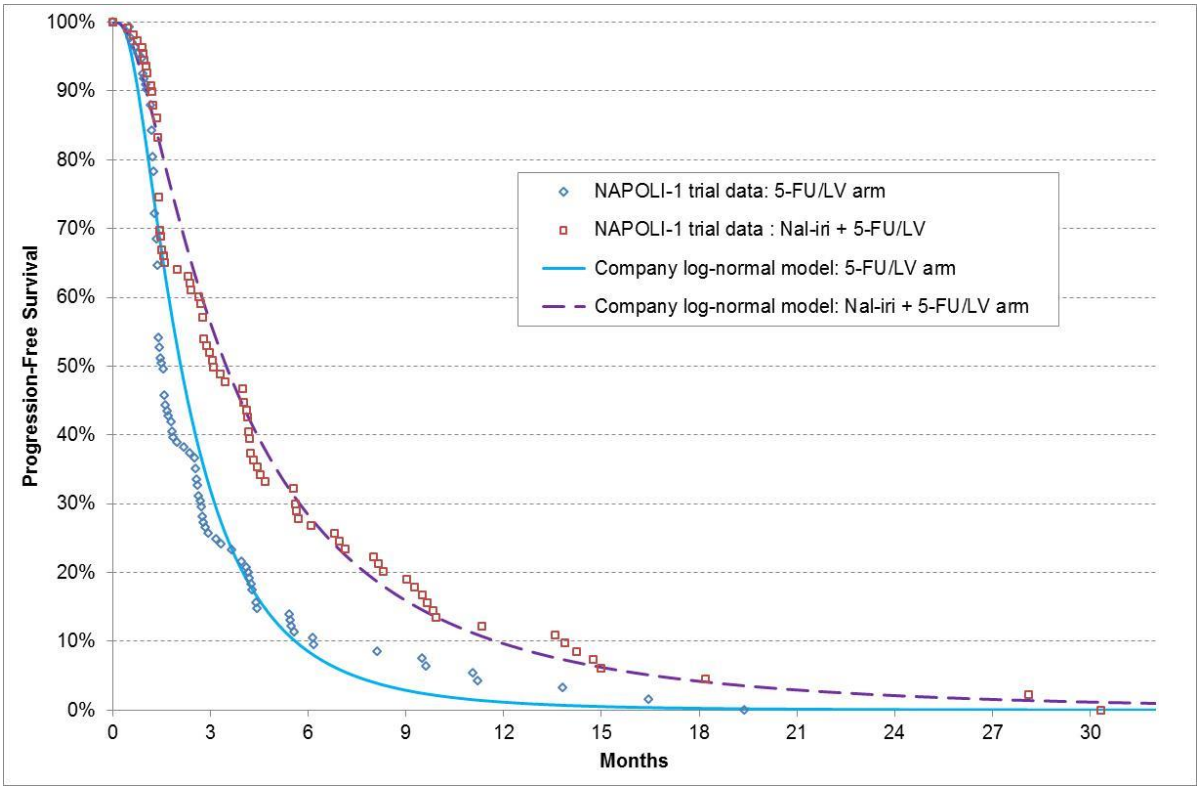

Figure 10 PFS company projections versus K-M data

The company model estimates a gain in mean PFS attributable to treatment with nal-iri+5-FU/LV of 2.657 months (5.472 versus 2.815) which is 4.8% greater than the accurate gain calculated by the K-M analysis of 2.535 months (5.677 versus 3.142).

Post-progression survival

The company model does not use PPS data from the NAPOLI-1 trial directly, but estimates PPS as the difference between estimated OS and PFS. This approach combines trial data which are complete with some which are not, and suggests that the mean PPS for nal-iri+5-FU/LV treated patients is 0.154 months less than that for patients in the comparator arm. In order to assess whether this model estimate of PPS gain is reliable, it is important to consider the PPS trial data directly (Figure 11).

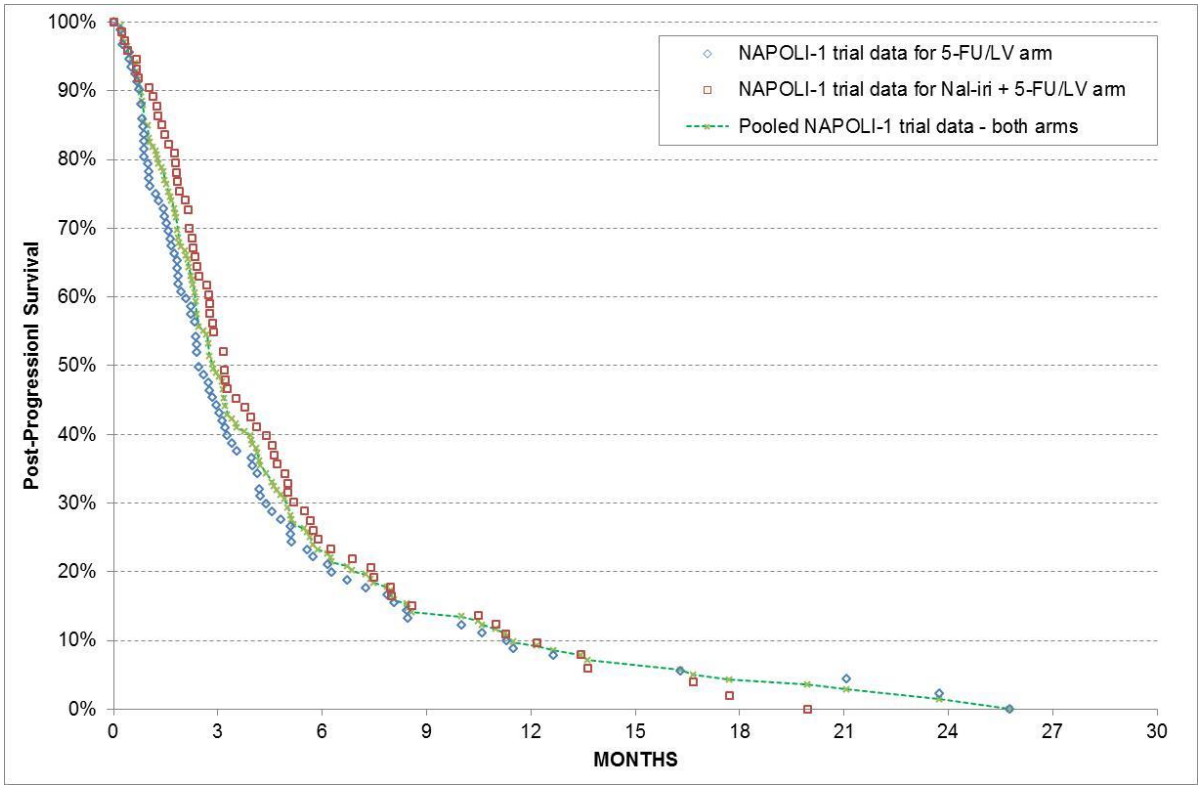

Figure 11 NAPOLI-1 PPS K-M data

The K-M analysis indicates that following disease progression there is no evidence that PPS differs by treatment arm (Log-rank test p=0.535). Therefore, the ERG has reanalysed the data, pooling patients from both arms of the NAPOLI-1 trial. Results from this analysis indicate that any patient surviving a progression event can expect a mean additional survival time of 4.897 months (the shape of the survival curve is also suggestive that patients entering the PPS state are not homogeneous, with about 30% subject to a better PPS than other patients).

However, the equivalent PPS survival time of individual patients does not mean that there is no difference in overall mean PPS between trial arms. This is because PFS is a compound variable (indicating either death or disease progression can have occurred); differences between trial arms can occur so that different proportions of PFS patients who die prior to confirmation of disease progression may affect the balance between the trial arms in the number of patients entering the post-progression state.

Examination of the NAPOLI-1 trial data show that such a difference is present: [redacted] of progression events in the 5-FU/LV arm are deaths compared with [redacted] in the nal-iri+5-FU/LV arm, indicating that more patients in the latter arm will survive to enter the PPS health state. Applying these proportions to the trial arms separately results in estimates for PPS of 3.604 months for patients treated with 5-FU/LV versus 3.815 months for patients treated with

nal-iri+5-FU/LV, an advantage of 0.210 months in favour of patients treated with nal-iri+5-FU/LV.

This finding suggests that the method used in the company model to estimate survival trends, namely by log-normal parametric models, and then assuming that PPS can be reliably calculated as the simple difference between OS and PFS, is flawed and unreliable in this case.

Overall survival

There are three approaches that may be followed to estimate the mean OS benefit which may be expected from treatment with nal-iri+5-FU/LV compared to 5-FU/LV:

1) Simple K-M calculation of the estimated mean survival in each trial arm without recourse to any modelling or extrapolation. This is potentially unbalanced as the trial data are complete for the nal-iri+5-FU/LV arm but exhibit a single patient still alive and at risk in the 5-FU/LV arm

2) Use K-M OS data directly in both trial arms, but model the likely survival experience of the final patient in the 5-FU/LV arm by extrapolation

3) Apply the method described above of estimating OS by addition of survival in the PFS and PPS states, extrapolating PFS for the single surviving pre-progression patient in the 5-FU/LV arm, and taking account of the differential in death rates included within the recorded progression events.

The differences between the results obtained by these three methods, and the company model serve to illustrate the extent of uncertainty associated with estimating trial-based OS estimates.

Method 1: Simple K-M OS calculation

The K-M estimated means for the recorded OS data from the NAPOLI-1 trial, are 7.178 months for patients treated with 5-FU/LV and 9.391 months for patients treated with nal-iri+5-FU/LV, giving a net OS gain of **+2.212 months** (95% CI 0.173 to 4.251). This may be compared with the base case company model estimated mean gain of 2.503 months.

Method 2: K-M OS data with extrapolation for the final patient in the nal-iri+5-FU/LV arm

The K-M estimated mean for the recorded OS data from the NAPOLI-1 trial for patients treated with nal-iri+5-FU/LV is 9.391 months. Figure 12 shows trial OS data together with the

ERG long-term exponential survival trend applied to the 5-FU/LV arm from 28.4 months. This yields an estimated mean OS for patients treated with 5-FU/LV of 7.584 months and a net mean OS gain of **+1.807 months** attributable to treatment with nal-iri+5-FU/LV. Details of the ERG's exponential extrapolation are outlined in Appendix 11.9.

Method 3: Addition of estimates of PFS and PPS, adjusting for differential death rates, and extrapolating PFS for the final patient in the nal-iri+5-FU-LV arm

This method involves using the K-M estimates of mean PFS for each trial arm (which are each based on complete trial data), to which is added the estimated time in the post-progression state based on the pooled K-M data analysis (Figure 11) adjusted for the proportion of patients experiencing a non-fatal progression event as described above.

For the 5-FU/LV arm, this yields mean estimates for PFS (3.142 months), PPS (3.604 months) and OS (6.746 months). Similarly, in the nal-iri+5-FU/LV arm mean estimates are PFS (5.677 months), PPS (3.815 months) and OS (9.491 months), so that the net mean OS gain is +**2.745 months** attributable to treatment with nal-iri+5-FU/LV.

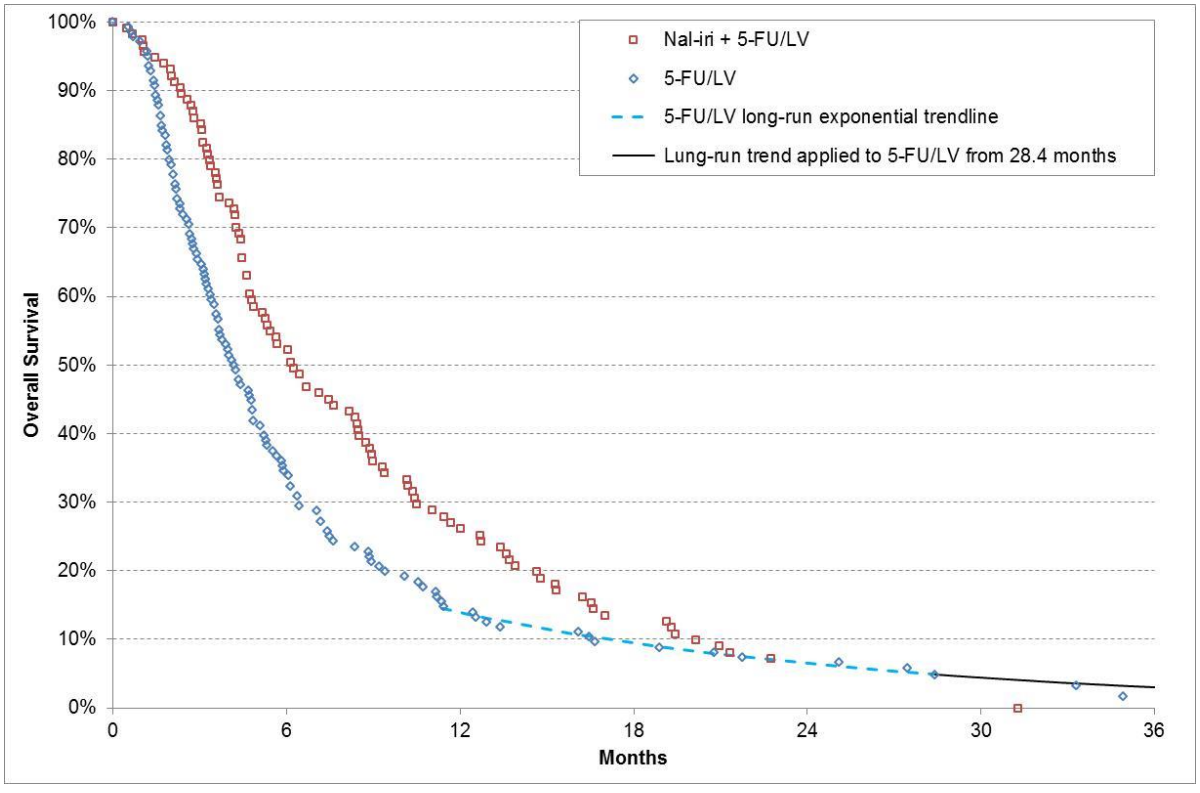

Figure 12 NAPOLI-1 OS K-M data, with ERG long-term extrapolation for patients treated with 5-FU/LV

Summary: The ERG has employed three different methods to estimate the mean survival gain shown in the NAPOLI-1 trial arising from treatment with nal-iri+5-FU/LV rather than 5-

FU/LV. The estimates range from 1.807 months (Method 2) to 2.212 months (Method 1) and 2.745 months (Method 3); these can be compared to the company's log-normal models yielding a mean OS gain of +2.503 months. Though each of the ERG methods has some merit, the ERG prefers Method 2, on the grounds that Method 1 is easily biased by non-equivalent cut-off points for estimating partial 'area under curve' totals, and Method 3, though technically valid, has been found sometimes to be liable to greater sensitivity to parameter uncertainty.

A summary of OS estimates disaggregated by PFS and PPS estimates generated using the company model, and the ERG's preferred approach is presented in Table 53. In all cases, the implementation of the ERG's preferred approach to modelling survival results in less optimistic predictions than those generated using the company's approach. The PPS estimates for both nal-iri+5-FU/LV and 5-FU/LV using ERG assumptions are reduced considerably, and the net mean difference in PPS is more in favour of 5-FU/LV compared to the company model.

However, it must be noted that in both the company model and the ERG's preferred approach the estimates of PPS are anomalous and inconsistent with the finding that each patient entering the post-progression state has an equal prospect of additional survival time prior to death. In addition, the observed difference in the proportion of patients suffering a fatal progression event would be expected to generate a survival gain (not a loss) as a consequence of having previously been treated with nal-iri+5-FU/LV. Nonetheless, it can be concluded that the survival benefit associated with nal-iri+5-FU/LV arises predominantly prior to disease progression, which is consistent with the observation that PPS K-M data indicate that there is no additional benefit following progression.

Table 53 Company and ERG mean survival estimates

Treatment	PFS (months)	PPS (months)[#]	OS (months)
Company approach			
Nal-iri+5-FU/LV	5.472	4.697	10.169
5-FU/LV	2.815	4.851	7.666
Difference	**+2.657**	**-0.154**	**+2.503**
ERG preferred approach			
Nal-iri+5-FU/LV	5.677	3.714[#]	9.391
5-FU/LV	3.142	4.442[#]	7.584
Difference	**+2.535**	**-0.728**[#]	**+1.807**

PFS=progression-free survival; PPS=post-progression survival; OS=overall survival; # for consistency, ERG PPS figures are calculated as the difference between OS and PFS estimates.
Source: Company model and ERG calculations

Time on treatment

The company's approach to modelling the time on treatment trial data systematically under-estimates overall time on treatment for patients in both arms of the NAPOLI-1 trial, especially during the first 15 months from randomisation (Figure 13). Additionally, the fitted models continue to accrue additional treatment time long after the last patient in the trial had ceased treatment (after 29 months for nal-iri+5-FU/LV and 16 months for 5-FU/LV), due to the long tails of the log-normal distribution. Overall, the company models underestimate time on treatment in the 5-FU/LV arm by 15%, and in the nal-iri+5-FU/LV arm by 1.4%.

Since the trial data for this outcome are complete, there can be no justification for extrapolating beyond the trial duration, nor indeed for modelling this variable at all.

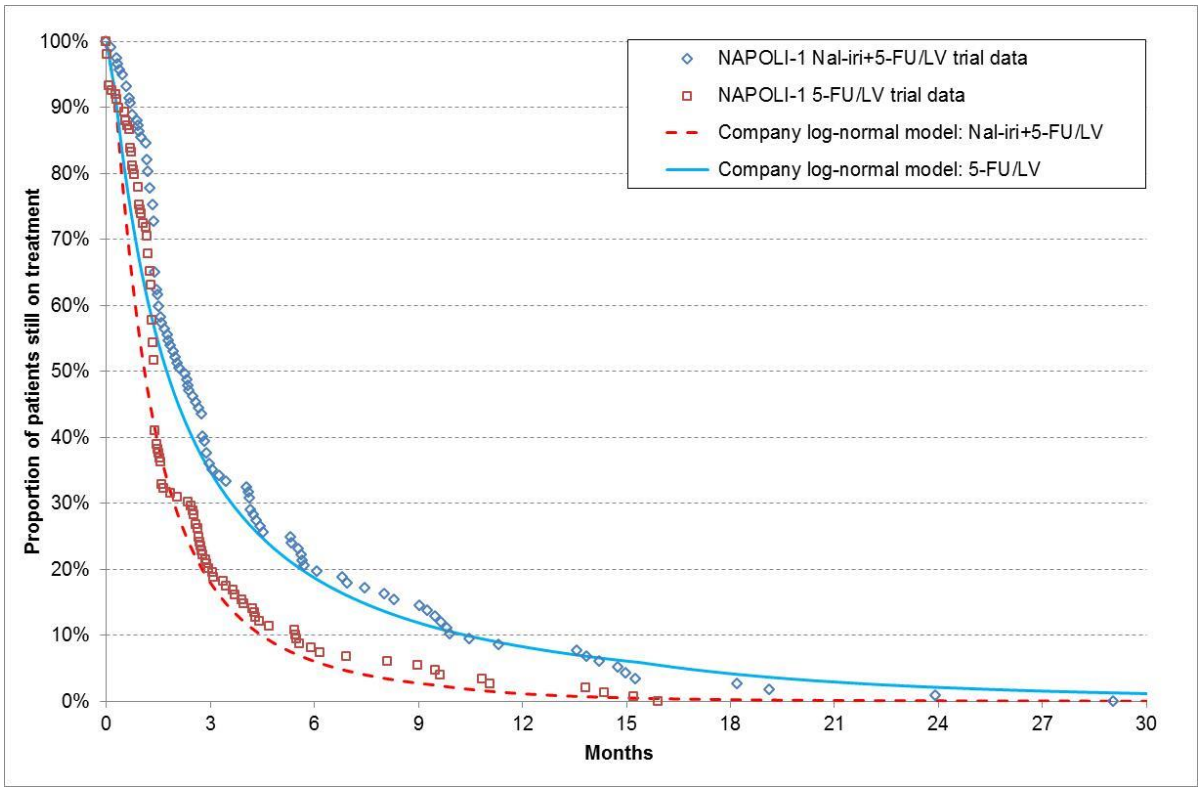

Figure 13 Patients on treatment: company projections and K-M data

For the comparison of treatment with nal-iri+5-FU/LV versus 5-FU/LV, the application of time to treatment data from the NAPOLI-1 trial increases the company's base case ICER per QALY gained by nearly £2,000 per QALY gained (see Table 59).

Time on treatment: oxaliplatin+5-FU/LV

To represent PFS and OS for patients treated with oxaliplatin+5-FU/LV, the company adjusted the parametric curves used to model PFS and OS for patients treated with nal-iri+5-FU/LV, using HRs generated by their ITC. However, to model time on treatment, the company assumed that patients treated with oxaliplatin+5-FU/LV remained on treatment for the same length of time as patients treated with nal-iri+5-FU/LV in the NAPOLI-1 trial (CS page 129). No rationale was provided for this assumption.

Thus, the company model uses the same log-normal curve to model pre-progression treatment for patients treated with nal-iri+5-FU/LV and for patients treated with oxaliplatin+5-FU/LV. This results in the proportion of patients receiving oxalipatin+5-FU/LV, who are in the 'pre-progression on treatment' state at 22 weeks, exceeding the proportion of patients in the PFS state. The company uses a model correction to resolve this issue by over-riding the trial time on treatment data with PFS data when it appears that there are more patients on treatment than remain alive in PFS. **The need for the company to apply an arbitrary model correction highlights that, for the population of patients receiving oxaliplatin+5-FU/LV, either the method used to represent PFS or the method used to represent pre-progression on treatment must be incorrect.** The ERG considers that the company's assumption that the duration of exposure to treatment is the same for patients treated with nal-iri+5-FU/LV as for patients treated with oxaliplatin+5-FU/LV is erroneous. The ERG examined the effect of using the company's pre-progression on treatment curve for patients receiving 5-FU/LV to model the time on treatment for patients receiving oxaliplatin+5-FU/LV to assess the impact of such a change on the ICER estimate.

For the comparison of treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, when the time on treatment of oxaliplatin+5-FU/LV is assumed equal to that of 5-FU/LV, this increases the company's base case ICER per QALY gained by £17,692.

5.5.4 Costs of treatments

Dose intensity reductions

In the NAPOLI-1 trial, in cases where treatment resulted in toxicity, some patients missed doses or received reduced doses. In the company model, it is assumed that, as a result of reduced doses or dose omissions, there is a corresponding reduction in drug acquisition costs. Based on data from the NAPOLI-1 trial, the company estimated that, on average, patients prescribed nal-iri+5-FU/LV and 5-FU/LV would receive 85% and 95% respectively of the anticipated licensed dose. The company has assumed that dose reductions for patients receiving oxaliplatin+5-FU/LV are the same as the dose reductions for patients receiving nal-

iri+5-FU/LV (i.e. 85%). In clinical practice, savings from reduced doses of chemotherapy only materialise if each change from the normal dose is known sufficiently in advance to allow the pharmacy department to alter the parenteral formulation. Due to the nature of the administration process, doctors typically see patients on the same day that the parenteral treatment is prepared by the pharmacy department. The ERG considers that although planned treatment alterations can vary between treatment administration sessions, this variation is difficult to anticipate in routine clinical practice, especially in NHS centres treating small numbers of patients. It is important to note that following examination of the CSR and the company's clarification response, the ERG concludes that there are no reductions in LV dosing in any of the NAPOLI-1 trial arms; however, the company's dose intensity reduction in the model is inclusive of LV for all of the treatments.

The ERG considers the case for pro-rata reductions in drug costs to be questionable in an NHS setting and that full costing should be used in the base case analysis to take into account possible wastage. For the comparison of treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, use of the full dose increases the company's base case ICER per QALY gained by £10,263 to £95,320 and, for the comparison of nal-iri+5-FU/LV versus 5-FU/LV, the effect is to increase the company's base case ICER per QALY gained by £16,355 to £148,701.

Body surface area and acquisition of generic drugs

In the company model, a mean BSA value of 1.79 per m^2 was taken from the study by Sacco et al[39] for adult cancer patients in the UK. The Sacco study[39] presents data for different tumour types and allows gender differences in BSA to be taken into account. The value selected by the company was undifferentiated by tumour type or site and did not take into account the male: female balance of patients participating in the NAPOLI-1 trial. Using the same publication, the ERG identified specific mean BSA values for patients with upper gastrointestinal cancer[39] (1.898 for males and 1.654 for females) and used these to generate weighted acquisition costs for all drugs dosed by BSA. Use of the more relevant BSA value results in increased drug costs for all patients in the company model.

All drugs used in the company model, except nal-iri, are available as generic formulations and so may be sourced relatively cheaply by the NHS. However, the company model substantially overestimates the acquisition cost of the generic drugs by using prices sourced from the BNF[45] and by failing to take advantage of the economic efficiencies that are achievable by using a mixture of different vial sizes.

The Department of Health's electronic market information tool (eMit) provides details of the average prices paid by NHS hospitals in England for generic drugs.[49] These unit costs are thus more reflective of the actual cost of drugs to the NHS than those given in the BNF.[45]

To calculate average drug acquisition costs, the company has estimated the proportion of patients requiring anything from one to 20 vials of each drug in each treatment combination using a normal distribution. The mean number of vials used in the calculation of the normal distribution was derived from the required dose per m^2, mean BSA and the relevant dose intensity modifier. The company has assumed that only one vial size is available for each generic drug: 500mg for 5-FU, 50mg for oxaliplatin and 50mg for LV. In fact, information provided in the eMit[49] database indicates that there are multiple vial sizes available for each of these generic drugs and, as a general rule (although not in every case), the larger the size of the vial, the lower the cost per mg of the drug. The company has chosen the smallest available vial sizes to calculate the cost of the generic drugs and, therefore, ignores the potential savings that can be gained by combining different vial sizes to achieve the required dose. The acquisition cost of nal-iri is based on 50mg vials in the company model and the ERG has not seen any evidence that this drug will be available in any other size vial.

The ERG has re-calculated the average cost per dose of the intervention and the comparators using prices from the eMit[49] database. To take into account the range of vial sizes available for each of the generic drugs, the ERG first used a normal distribution for BSA to estimate the proportion of patients requiring a given dose. The optimum combination of vial sizes for that dose was then determined according to the price per mg of each available vial size. The ERG's revised average cost per dose is the sum of the cost of each dose (optimised by available vial sizes) weighted by the proportion of patients expected to receive each dose.

The price of drugs, and range of available vial sizes according to information in the eMit[49] database, are shown in Table 54. The results of the ERG's re-calculations of average drug costs are shown in Table 55.

Table 54 Drug costs used in the company model: company model versus ERG

Drug name	Vial size	Company model	ERG
		Cost per mg	
Nal-iri	50mg	[redacted]	-
Oxaliplatin	50mg	£3.140	£0.212
	100mg	-	£0.155
5-FU	500mg	£0.012	£0.002
	1000mg	-	£0.001
	2500mg	-	£0.002
	5000mg	-	£0.001
LV (as calcium folinate)	50mg	£0.375	£0.025
	100mg	-	£0.030
	300mg	-	£0.015

ERG=Evidence Review Group; mg=milligram
Source: Company model, eMit, ERG calculations

Table 55 Weekly average treatment costs per patient used in the model: company versus ERG drug acquisition costs using revised BSA value

Item	Company model			ERG (revised BSA)		
Nal-iri+5-FU/LV	Nal-iri	5-FU	LV	Nal-iri	5-FU	LV
Weekly drug cost	[redacted]	£24.97	£118.80	[redacted]	£2.24	£5.19
Weekly treatment cost	[redacted]			[redacted]		
Oxaliplatin+5-FU/LV	Oxaliplatin	5-FU	LV	Oxaliplatin	5-FU	LV
Weekly drug cost	£238.84	£11.35	£61.74	£13.14	£1.19	£2.72
Weekly treatment cost	£311.93			£17.04		
5-FU/LV	5-FU		LV	5-FU		LV
Weekly drug cost	£31.16		£91.27	£2.94		£4.19
Weekly treatment cost	£122.43			£7.12		

BSA=body surface area; ERG=Evidence Review Group
Source: Company model and ERG calculations

Combining the ERG's preferred BSA values and preferred drug acquisition costs in the company model yields an increase in the ICER of nearly £[redacted] per QALY gained for treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, and a decrease of more than £[redacted] per QALY gained for nal-iri+5-FU/LV versus 5-FU/LV (£[redacted] and £[redacted] per QALY gained respectively).

Post-progression treatment costs

On page 127 of the CS, it is stated that the company has assumed that the average weekly cost per patient of post-progression treatment is equivalent to the weekly cost of treatment with nal-iri+5-FU/LV. In the company model, the weekly cost of post-progression treatments is equivalent to the acquisition cost of nal-iri ([redacted]) – a price that does not include the cost of 5-FU/LV. Moreover, the cost used in the company model does not include any administration or monitoring costs.

Clinical advice to the ERG is that, in the NHS following failure of second-line therapy patients are unlikely to receive further chemotherapy. In addition, there is no evidence to suggest that the provision of conventional chemotherapy would have any significant impact on survival. The ERG considers that it is more appropriate to assume that, after progression all patients receive best supportive care (BSC) in the form of palliative therapy.

For the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, use of palliative care rather than the company's post-progression treatment costs decreases the company's base case ICER per QALY gained by more than £[redacted], and for the comparison of nal-iri+5-FU/LV versus 5-FU/LV the effect is to increase the size of the company's base case ICER per QALY gained by £[redacted]. The decrease in the size of the ICER versus oxaliplatin+5-FU/LV is explained by the greater reduction in total costs in the nal-iri+5-FU/LV arm as a result of a longer time spent in PPS compared to the oxaliplatin+5-FU/LV arm.

Adverse event costs

As part of the clarification process, the ERG requested NAPOLI-1 trial grade 3 or higher treatment related AEs reported by ≥5% of patients. Table 44 of the CS includes details of the costs associated with treating AEs that are used in the company model. The ERG has concerns about the choice of Healthcare Resource Groups (HRG) codes used to cost AEs. The approach taken to determine the cost of treating a patient with grade 3 to 4 diarrhoea was calculated using a weighted average of day case HRG codes, whilst the definition of grade 3 or higher AEs is that they require hospital admission.[50] The ERG considers that the use of the weighted average of costs for all types of admission is more reflective of the costs to the NHS. Using the ERG's revised unit costs per AE (see Table 56), the ICER per QALY gained for treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV increases by nearly £[redacted], and for treatment with nal-iri+5-FU/LV versus 5-FU/LV the ICER increases by nearly £[redacted] per QALY.

Table 56 Unit cost of AEs: company model and ERG amendments

Adverse Event	Unit cost per AE		HRG code	Admission type	
	Company model	ERG		Company model	ERG
Anaemia	£528.15	£405.47	SA04L, Iron Deficiency Anaemia with CC score 0-1	Non-elective short stay	Weighted over all admissions
Neutropenia	£127.70	£127.70	XD25Z Neutropenia drugs band 1, NHS Trusts High Cost Drugs	n/a	n/a
Abdominal pain	£387.25	£752.10	FZ90A - FZ90B. Weighted average of Abdominal Pain with Interventions and without Interventions	Regular Day or Night Admissions	Weighted over all admissions
Diarrhoea	£319.34	£2,739.90	FZ49D - FZ49H. Weighted average of Nutritional Disorders with and without Interventions	Day case	Weighted over all admissions
Nausea	£319.34	£2,739.90	Assumed same as diarrhoea	Day case	Weighted over all admissions
Vomiting	£319.34	£2,739.90	Assumed same as diarrhoea	Day case	Weighted over all admissions
Fatigue	£44.00	£1,848.00	1 nurse visit per day (£44) for duration of event	1 day	42 days*

AEs=adverse events; ERG=Evidence Review Group; HRG=healthcare resource groups
* Mean duration from company clarification response, Table 22

5.5.5 Health state utility values

The health state utility values used in the company model are based on those presented in a US study by Romanus et al[51] (0.8 for progression-free survival and 0.75 for post-progression survival). Previously, these values have been used in the company model submitted during the appraisal of nab-paclitaxel in combination with gemcitabine for previously untreated metastatic pancreatic cancer (TA360).[13] These values were amended (by the ERG involved in that appraisal) to make them more relevant for use in a UK patient population; the amended values were 0.742 and 0.671 for the progression-free health state and for the progressed health state respectively.[41]

The Romanus study[51] was conducted in first-line patients with advanced pancreatic cancer. Patients in this study[51] had an ECOG PS of 0 to 2 and received gemcitabine plus placebo or gemcitabine plus bevacizumab as a first-line treatment. The ERG considers that utility values derived from a first-line patient population are likely to overstate patient quality of life when applied to a second-line patient population. Furthermore, there is considerable uncertainty regarding the appropriateness of using Romanus[51] based utility values as the values for patients with stable disease were similar to those for the age-matched US general population.

The ERG considers that the pre-progression and post-progression health state utility values of 0.742 and 0.671 used in the company model overestimate patient HRQoL. Moreover, the utility values derived from the Romanus study[51] accounted for treatment related AEs arising

from active chemotherapy. The separate addition, by the company, of disutility values associated with AEs results in double counting of treatment related disutility.

The ERG considers the use of the progressed disease health state utility value used in the ERG TA360 report[41] (0.671) to be a more accurate reflection of the quality of life of patients in the population of interest who are in the progression-free state than the value used by the company (0.742). The ERG considers that a value of 0.6 should be used to represent quality of life for patients in the post-progression health state. This value was presented in a study reporting results from the phase III RAINBOW trial,[52] and was derived from patients with locally advanced or metastatic gastric cancer receiving second-line combination chemotherapy. It is important to note that this value was obtained from patients upon progression/end of treatment and does not take into account further deterioration in health following progression. Patients in the RAINBOW trial[52] had similar demographic characteristics to those in the NAPOLI-1 trial. In that trial,[52] EQ-5D index scores were elicited using the time-trade off (TTO) method and were calculated using UK population-based preference weights from the study by Dolan.[53] The various utility value options are presented in Table 57.

For the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, the use of the ERG's preferred health state utility values, increases the company's base case ICER per QALY gained by more than £10,000, and for the comparison of nal-iri+5-FU/LV versus 5-FU/LV the effect is to increase the size of the company's base case ICER per QALY gained by nearly £16,000.

Table 57 Utility value options

Source	PFS	PPS
Romanus study[51] - US values	0.80	0.75
ERG report for the appraisal of nab-paclitaxel in combination with gemcitabine for previously untreated metastatic pancreatic cancer (TA360)[41] & company submission	0.742	0.671
ERG's preferred values	0.671	0.60

PFS=progression-free survival; PPS=post-progression survival

5.5.6 Terminal disutility

The company model does not include the effects of terminal disutility on patient quality of life. The ERG has estimated the mean EQ-5D utility during the 4 weeks before death to be 0.146 using results from the study by Van den Hout et al.[54] This study involved collecting utility values from patients receiving palliative care for advanced lung cancer, observing rapid declines in in average EQ-5D utility in the weeks leading up to death. The ERG

recognises that these utility values relate to patients with lung cancer but, to the ERG's knowledge, this is the only study available presenting utility data derived from patients who are only receiving palliative care for advanced cancer.

For the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, the application of the terminal disutility, increases the company's base case ICER per QALY gained by about £[redacted] and the effect on the comparison of nal-iri+5-FU/LV versus 5-FU/LV decreases the size of the ICER per QALY gained by about £[redacted].

5.5.7 Minor issues of concern

The ERG has identified a further seven areas of concern with regards to the company's cost effectiveness evaluation. The impact of ERG changes to rectify these concerns has not been included in the ERG's cost effectiveness results tables (Section 6, Table 58 and Table 59) as their impact on the size of any of the estimated ICERs per QALY gained is minimal.

5-FU dose in oxaliplatin+5-FU/LV treatment arm

The company assume that the dose of 5-FU in the oxaliplatin+5-FU/LV treatment arm to be 1000mg/m^2 every 2 weeks. This dose for 5-FU was not provided with any justification. According to the company clarification response and clinical advice received by the ERG, in current UK clinical practice, the most common dose of 5-FU in combination with oxaliplatin and LV is 2400mg/m^2 (mFOLFOX6). Implementing the dose change in the company model results in a decrease of £[redacted] to the ICER (£[redacted] per QALY gained) for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV.

Terminal care cost

The submitted company model includes terminal care costs for the final 4 weeks before patient death. The ERG considers these costs to be an underestimate of the true costs incurred during routine clinical practice in the NHS. In the model, it is assumed that 50% of patients receive three home visits by a nurse every week and 50% receive daily care at a hospice/palliative care unit. The company's assumptions do not take into account the additional costs incurred by patients who die in hospital/hospice nor do they include the costs of intensive community palliative nursing, additional drugs and equipment. The ERG has estimated terminal care costs to be £4,103 per patient or £1,026 per week. These costs were derived using mean hospital stay data for malignant gastrointestinal tract disorders[46] and terminal care resource use data from the study by Taylor et al.[55] Costs include in-patient costs for terminal care in hospital, costs for death in hospital and costs for death at home (including GP home visits, community nurse visits, Macmillan nurse visits and additional

drugs and equipment). Implementing this amendment in the company model had no impact on the size of the estimated ICERs per QALY gained as they occur equally to all patients in both treatment arms.

Treatment administration: pharmacist costs

Although a pharmacist cost for each infusion is included in the parameters worksheet in the company model and in the CS (page 125), this cost is not incorporated in the calculation of treatment administration costs. The cost of 15 minutes of pharmacist time required for the preparation of infusion based chemotherapies is in line with the parameters already defined in the company model and those used in the appraisal of nab-paclitaxel in combination with gemcitabine for previously untreated metastatic pancreatic cancer (TA360).[13] Including the cost of pharmacist time results in an increase of £11 per infusion to treatment administration cost.

For the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, the inclusion of pharmacist costs, increases the company's base case ICER per QALY gained by £[redacted] and the effect on the ICER per QALY gained for the comparison of nal-iri+5-FU/LV versus 5-FU/LV is to increase it by £[redacted].

Treatment administration: infusion disconnection costs

It is stated in the CS (page 124) that, because of the long infusion time required to deliver 5-FU, an additional cost of £97.14[46] has been applied to account for resource use associated with the patient's return to hospital for removal of the cannula and that this cost is independent of infusion time. On clinical advice, the ERG has estimated that approximately 90% of patients would receive a home visit from a community nurse to disconnect this type of infusion pump, and that this visit would take about an hour of nurse time, including travel. This means that only 10% of patients would be likely to attend an outpatient clinic to have their infusion pump removed. Substituting nurse home visits for 90% of patients results in an average total cost of £49.31 per patient for infusion removal.

For the comparisons of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV and versus 5-FU/LV, applying this adjustment in the company model results in reducing the company's base case ICERs per QALY gained by £[redacted] and £[redacted] respectively.

Adverse event disutility

The company has included the effects of selected grade 3+ AEs on HRQoL in their model, namely anaemia, neutropenia, abdominal pain, diarrhoea, nausea, vomiting and fatigue. Disutility values have been obtained from studies by Doyle et al[42] and Nafees et al[44] (both

studies relate to patients with lung cancer) and from Swinburne et al[43] who elicited health state utilities from patients with renal cell carcinoma. The Doyle[42] and Swinburne[43] studies included patients with a mean age that is less than 45 years and did not include patients with metastatic pancreatic cancer. The inclusion of disutility estimates from different patient populations and varying treatment contexts results in an unpredictable bias. The ERG is not able to assess the potential size of this problem due to lack of data.

UGT1A1*28 allele testing

*UGT1A1*28* allele testing is not currently provided as standard care in NHS clinical practice. On clinical advice, it is expected that 5% of patients would receive *UGT1A1*28* allele testing in an NHS setting and such testing is likely to incur additional resource use and training costs; however, the ERG does not consider that these costs would have a substantial impact on the size of the estimated ICERs per QALY gained.

Probabilistic sensitivity analysis

The company's PSA has misrepresented the uncertainty in the submitted model in two ways: by assuming that all parameters are independent of one another and by incorrectly calculating the PSA ICERs per QALY gained.

Parameter values

The company has taken the simplest approach to performing a PSA, which is to assume that all parameters are independent and so vary randomly according to their own distributions without relying on the value of any other parameter. The ERG considers that it is unlikely that all of the parameters are independent, and that it is possible to account for at least some of the parameter dependencies. For instance, the ERG considers it implausible for post-progression utility values to be higher than pre-progression utility values. If pre-progression utility values are already known, then it is also known that post-progression utility values will, at the very least, not be greater than pre-progression values. So, if pre-progression utility values are known, some of the uncertainty in the post-progression utility values can be removed by building this logical relationship into the model. Another way to reduce uncertainty would be to use the Cholesky decomposition, which takes takes into account correlation between the elements in a regression equation used to derive the parameters of a parametric survival curve.

Calculation of ICERs

The company has overestimated the probabilistic ICERs per QALY gained by taking an average of all ICERs produced by the PSA (a 'mean of ICERs') instead of using the mean of incremental costs and mean of incremental QALYs taken over all iterations to derive a single ratio (an 'ICER of means'). Using an ICER of means approach, the company's PSA ICER per QALY gained is reduced from £[redacted] to £[redacted] for the comparison of treatment with nal-iri+5-FU/LV versus 5-FU/LV and from £[redacted] to £[redacted] for the comparison of treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV. Compared with the mean of ICERs method, the ICER of means method yields probabilistic ICERs per QALY gained for both comparisons that are closer to the company's deterministic ICERs per QALY gained. This indicates that there is less uncertainty in the model (based on the parameters the company has chosen to vary) than is actually suggested by the PSA ICERs reported in the CS.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG identified an error in the value used in the company model to represent baseline utility during the post-progression survival state of the model (0.672 was used instead of 0.671). All of the ICER per QALY gained estimates generated by the ERG have been calculated using the value of the company base case that results following correction of this error.

Table 58 and Table 59 show the effects of the various ERG amendments, both individually and simultaneously, on the size of the company's base case ICERs per QALY gained for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV and nal-iri+5-FU/LV versus 5-FU/LV respectively. The ERG has only implemented changes that have a major impact on the size of the ICERs per QALY gained and has not included changes relating to minor issues (i.e. those described in Section 5.5.8).

The ERG considers that the results (HRs) from the ITC used by the company to facilitate a comparison of the cost effectiveness of treatment with nal-iri+5-FU/LV versus oxaliplatin+5FU/LV are unreliable. The ERG cautions that the ICERs per QALY gained for this comparison are also unreliable and should not be used to inform decision-making. However, to aid decision making, the ERG has generated a range of cost effectiveness results for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV based on assumptions that treatment with oxaliplatin+5-FU/LV results in 10% more, 10% fewer or an equal number of QALYs to treatment with nal-iri+5-FU/LV. These results are presented in Table 60.

Details of the Microsoft Excel revisions made by the ERG to the company model are presented in the Appendices to this ERG report (Section 11.10) and are also included in the ERG amended cost effectiveness model.

Table 58 Cost effectiveness results (nal-iri+5-FU/LV vs oxaliplatin+5-FU/LV): ERG revisions to company base case comparison

Model scenario ERG revision	Nal-iri+5-FU/LV			Oxaliplatin+5-FU/LV			Incremental			ICER	
	Cost	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**£/QALY**	**Change**
****Original CS base case***	[redacted]	***0.564***	***0.847***	***£13,975***	***0.362***	***0.535***	[redacted]	***+0.201***	***+0.312***	[redacted]	--
A. Company base case**	[redacted]	***0.563***	***0.847***	***£13,975***	***0.362***	***0.535***	[redacted]	***+0.201***	***+0.312***	[redacted]	--
R1. 5-FU/LV pre-progression time on treatment curve for oxaliplatin+5-FU/LV	[redacted]	0.563	0.847	£10,416	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
R2. Full dose intensity	[redacted]	0.563	0.847	£15,082	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
R3. ERG BSA & drug acquisition costs	[redacted]	0.563	0.847	£9,773	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
R4. ERG post-progression treatment costs	[redacted]	0.563	0.847	£11,034	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
R5. ERG AE costs	[redacted]	0.563	0.847	£14,957	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
R6. ERG health state utilities	[redacted]	0.504	0.847	£13,975	0.324	0.535	[redacted]	+0.180	+0.312	[redacted]	[redacted]
R7. ERG terminal disutility	[redacted]	0.552	0.847	£13,975	0.356	0.535	[redacted]	+0.196	+0.312	[redacted]	[redacted]
R8. ERG OS	[redacted]	0.527	0.782	£13,975	0.362	0.535	[redacted]	+0.165	+0.247	[redacted]	[redacted]
R9. ERG PFS	[redacted]	0.565	0.847	£13,975	0.362	0.535	[redacted]	+0.203	+0.312	[redacted]	[redacted]
R10. ERG Time on treatment	[redacted]	0.563	0.847	£13,975	0.362	0.535	[redacted]	+0.201	+0.312	[redacted]	[redacted]
B. R1:R10	[redacted]	**0.465**	**0.782**	**£5,809**	**0.318**	**0.535**	[redacted]	**+0.147**	**+0.247**	[redacted]	[redacted]
C. R2:R10	[redacted]	**0.465**	**0.782**	**£7,838**	**0.318**	**0.535**	[redacted]	**+0.147**	**+0.247**	[redacted]	[redacted]

Costs and QALYs discounted; life years undiscounted
BSA=body surface area; CS=company submission; ERG=Evidence Review Group; QALYs=quality adjusted life years
*Original base case estimate with error **This is the company base case ICER estimate following correction of an error in post progression utility value in company model

Table 59 Cost effectiveness results (nal-iri+5-FU/LV vs 5-FU/LV): ERG revisions to company base case comparison

Model scenario ERG revision	**Nal-iri+5-FU/LV**			**5-FU/LV**			**Incremental**			**ICER**	
	Cost	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**£/QALY**	**Change**
****Original CS base case***	[redacted]	***0.564***	***0.847***	***£13,338***	***0.429***	***0.639***	[redacted]	***0.134***	***+0.209***	[redacted]	--
A. Company base case**	[redacted]	***0.563***	***0.847***	***£13,338***	***0.429***	***0.639***	[redacted]	***0.134***	***+0.209***	[redacted]	--
R1. ERG OS, PFS, time on treatment	[redacted]	0.529	0.782	£13,655	0.429	0.637	[redacted]	+0.100	+0.145	[redacted]	[redacted]
R1a. ERG OS	[redacted]	0.527	0.782	£13,261	0.426	0.637	[redacted]	+0.101	+0.145	[redacted]	[redacted]
R1b. ERG PFS	[redacted]	0.565	0.847	£12,891	0.431	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R1c. ERG time on treatment	[redacted]	0.563	0.847	£14,212	0.429	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R2. Full dose intensity	[redacted]	0.563	0.847	£14,317	0.429	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R3. ERG BSA & drug acquisition costs	[redacted]	0.563	0.847	£12,436	0.429	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R4. ERG post-progression treatment costs	[redacted]	0.563	0.847	£6,643	0.429	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R5. ERG AE costs	[redacted]	0.563	0.847	£13,597	0.429	0.639	[redacted]	+0.134	+0.209	[redacted]	[redacted]
R6. ERG health state utilities	[redacted]	0.504	0.847	£13,338	0.384	0.639	[redacted]	+0.120	+0.209	[redacted]	[redacted]
R7. ERG terminal disutility	[redacted]	0.552	0.847	£13,338	0.418	0.639	[redacted]	+0.135	+0.209	[redacted]	[redacted]
B. R1:R7	[redacted]	**0.465**	**0.782**	**£6,648**	**0.374**	**0.637**	[redacted]	**+0.091**	**+0.145**	[redacted]	[redacted]

Costs and QALYs discounted; life years undiscounted
BSA=body surface area; ERG=Evidence Review Group; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; TTF=time to treatment failure
*original base case estimate with error **This is the new company base case ICER estimate due to an error in post progression utility value in company model

Table 60 Alternative ICER estimates for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV

Scenario	ICER per QALY gained
Base case	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	[redacted]
ERG scenario B	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	[redacted]
ERG scenario C	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	[redacted]

ERG=Evidence Review Group; QALY=quality adjusted life year; ICER=incremental cost effectiveness ratio

6.1 Conclusions of the ERGs cost effectiveness review

The company's model was constructed according to conventional practice. However, the ERG has concerns about the validity of a number of the model inputs used by the company. The main areas of concern that affect all cost effectiveness comparisons relate to the replacement of complete trial data with parametric survival curves (an approach that adds uncertainty to projections), errors in the methods used to calculate drug costs and use of inappropriate utility values.

In addition, the ERG considers that the company's base case cost effectiveness results for the comparison of nal-iri+5-FU/LV versus oxaliplatin-5FU/LV should be interpreted with extreme caution. Firstly, the lack of effectiveness evidence led the company to use HR results from an ITC to adjust survival projections for patients treated with nal-iri+5-FU/LV to reflect the experience of patients treated with oxaliplatin+5-FU/LV. These HRs are considered by the company and by the ERG to be unreliable. Secondly, as log-normal curves, which are accelerated failure time models, were used to project survival and pre-progression on treatment for patients treated with nal-iri+5-FU/LV, these distributions are not compatible with the proportional hazards assumption and an alternative TR adjustment should have been considered.

The cost effectiveness results that are generated following the application of the ERG's preferred input values are all considerably higher than the range normally considered acceptable by NICE.

7 END OF LIFE

The company puts forward the case (CS, Section 4.13.2.3) that nal-iri+5-FU/LV should be considered under the NICE End of Life criteria, even though it recognises that the gain in median OS reported in the NAPOLI-1 trial does not exceed 3 months which is normally the minimum amount of survival gain required by NICE.[56] The company's reasoning with ERG comment is summarised in Table 61.

Table 61 End-of-life criteria

Criterion	Company statement in support of criteria	ERG comment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	A systematic review of real-world, peer reviewed, observational European studies [by Carrato 2015[57]] (n=91) found that the median life expectancy at diagnosis was 4.6 months in patients with pancreatic cancer irrespective of stage of diagnosis, and the median survival for patients with metastatic disease was 2.8 to 5.7 months	The ERG concurs that patients with metastatic pancreatic cancer have a life expectancy of less than 24 months
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	Median OS was 6.1 months in the nal-iri+5-FU/LV group compared with 4.2 months in the 5-FU/LV group. While the increased survival of 1.9 months is below the 3 months specified in the end-of-life criteria, it represents a 45% increase that would be of substantial benefit to these patients, given the very short life expectancy at diagnosis	The results from the company's economic model suggest that the mean OS gain associated with treatment with nal-iri+5-FU/LV versus 5-FU/LV is 2.5 months. In the ERG amended model the mean survival gain for nal-iri+5-FU/LV versus 5-FU/LV is 1.67 months. The ERG cautions that the OS gain with nal-iri+5-FU/LV compared with 5-FU/LV represents an increase with a treatment that is not commonly used to treat patients with metastatic pancreatic cancer who have progressed following treatment with gemcitabine; a more appropriate comparison would be with oxaliplatin+5-FU/LV. It has not been possible to produce a reliable estimate of the difference in OS between nal-iri+5-FU/LV and oxaliplatin+5-FU/LV. However, the ERG notes that in three RCTs[36,58,59] of oxaliplatin+5-FU/LV, the median OS in the oxaliplatin+5-FU/LV was approximately 6 months, which is similar to that reported in NAPOLI-1 for nal-iri+5-FU/LV. In another RCT of oxaliplatin+5-FU/LV,[17] median OS was lower (3.4 months). It is unclear why the findings in this trial differ so markedly to those from the other trials but this phenomenon may be related to differences in trial and baseline characteristics. **Overall, the OS outcomes for patients treated with oxaliplatin+5-FU/LV reported in these trials are similar in magnitude to the OS outcomes of patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial**
The treatment is licensed or otherwise indicated for small patient populations	The 10-year prevalence of pancreatic cancer in the UK in 2006 was 4349[60]. In 2012 the 5-year prevalence in the UK[61] was 3522	The ERG considers that the anticipated licenced population will be small

OS=overall survival
Source: CS, adapted from Table 34

8 KEY POINTS FOR DECISION MAKERS

8.1 Background

Pancreatic cancer is a condition associated with a particularly high burden of illness since the vast majority of patients present with advanced disease. The outlook for patients with pancreatic cancer has not improved since the 1970s.[62] The median life expectancy at diagnosis is only 4.6 months.[57] Figures published by Cancer Research UK show that there were 7,887 new cases of pancreatic cancer in England in 2013.[5]

Compared with many other types of cancer, there have been relatively few developments in new treatments for patients with metastatic pancreatic cancer. The fluoropyrimidine chemotherapy treatment, 5-FU, has been the mainstay of treatment since the 1950s. Following the approval of gemcitabine for treating metastatic pancreatic cancer in the 1990s, 5-FU became increasingly used as second-line treatment option. More recently it has been used in combination with irinotecan and oxaliplatin (FOLFIRINOX) in the first-line setting and with oxaliplatin (FOLFOX and OFF regimens) as a second-line treatment option following treatment with gemcitabine. FOLFIRINOX, FOLFOX and OFF are not licensed treatments. FOLFOX regimens (mFOLFOX4 or mFOLFOX6) are the most common regimens used in England (~75%). Another treatment option that has emerged for the treatment of second-line metastatic pancreatic cancer and is used in England is capecitabine (~25%), either as a monotherapy or in combination with oxaliplatin.

This appraisal considers the clinical and cost effectiveness nal-iri for use within its anticipated marketing authorisation (CHMP positive opinion is expected circa 21 July 2016), i.e. nal-iri+5-FU/LV for the treatment of metastatic adenocarcinoma of the pancreas, in adult patients who have progressed following gemcitabine-based therapy. The comparators are oxaliplatin+5-FU/LV (e.g. FOLFOX), fluoropyrimidine monotherapy (e.g. 5-FU) and oxaliplatin+capecitabine.

8.2 Clinical effectiveness evidence

Nal-iri+5-FU/LV versus 5-FU/LV

- Direct evidence is only available for the comparison of the effectiveness of nal-iri+5-FU/LV versus 5-FU/LV from the NAPOLI-1 trial; this shows nal-iri+5-FU to be superior in terms of OS and PFS but with a greater number of AEs, notably myelosuppression and gastrointestinal disorders
- Although patients did receive additional treatment on disease progression which may have confounded OS results, the type of treatment received was similar in each arm and there was no treatment crossover from 5-FU/LV to nal-iri+5-FU/LV
- The ERG considers that:
    - except for the usual caveat that goes with nearly all clinical trials that patients tend to younger and fitter than seen in clinical practice, the patient population recruited to the NAPOLI-1 trial is broadly representative of patients with metastatic pancreatic cancer previously received treatment with gemcitabine in clinical practice in England; however, the proportion of patents who received gemcitabine combination therapy was greater than expected in clinical practice in England
    - the trial was generally well designed and conducted with the main potential source of bias being the open-label design
    - the company's OS and PFS HR results are unreliable due to the fact that the approach taken to calculate these values is only valid if the relevant K-M data are proportional to one another; neither the OS nor the PFS K-M data are proportional
    - 5-FU/LV is rarely given to patients who have previously received treatment with gemcitabine.

Nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV

- There is no evidence to allow a direct comparison of the efficacy of nal-iri+5-FU/LV with oxaliplatin+5-FU/LV (the most commonly used regimen in NHS practice for the population of interest)
- The company considered an ITC to be "unfeasible" due to the violation of the PH assumption and trial heterogeneity (in terms of trial location, patient characteristics, prior treatment with gemcitabine [monotherapy versus combination therapy] and length of trial follow-up)
- However, the company considered that results from an ITC were necessary to allow the cost effectiveness of nal-iri+5-FU/LV to be compared with oxaliplatin+5-FU/LV
- The ERG does not consider the results from the ITC to be reliable and so undertook a crude comparison of efficacy and safety data across key RCTs and concluded that, overall, the PFS and OS outcomes for patients treated with oxaliplatin+5-FU/LV reported in these trials are similar in magnitude to the PFS and OS outcomes of patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial.

Other comparators detailed in the final scope issued by NICE

- The company has not provided any evidence to demonstrate the relative effectiveness (or cost effectiveness) of nal-iri+5-FU/LV with oxaliplatin+capecitabine or capecitabine monotherapy.

8.3 Cost effectiveness evidence

Issues relating to the company model

The ERG considers that the structure of the company model (which is constructed according to conventional modelling practice) is appropriate for use in NHS decision-making. However, the ERG has a number of concerns relating to the parameter values used within the model.

Modelling survival

- The company uses log-normal distributions to reflect patient experience (in terms of OS, PFS and TTF) during and beyond the NAPOLI-1 trial period for patients receiving nal-iri+5-FU/LV and those receiving 5-FU/LV. The ERG considers that:
    - trial data, rather than a parametric distribution, should have been used - the company's fitted curves (which are not supported by any biological rationale) only serve to increase uncertainty and may conceal the underlying disease dynamic
    - there is no need for any projection (except for OS for one patient in the 5-FU/LV arm) since the NAPOLI-1 trial was not an ongoing trial but complete
    - the projections made by the company are overly optimistic.
- The company has assumed that the weekly proportion of patients receiving treatment with oxaliplatin+5-FU/LV is the same as that observed for patients in the nal-iri+5-FU/LV arm of the NAPOLI-1 trial. However, at 22 weeks, the proportion of patients receiving oxalipatin+5-FU/LV exceeds the proportion in the PFS state. The company, therefore, incorporated a correction to ensure that the proportion on treatment and the proportion in the PFS were equal from 22 weeks onwards. The ERG considers that:
    - the necessity of employing an amendment suggests that the modelling approach employed by the company is flawed (either in terms of PFS or time on treatment).

Costs

- The NAPOLI-1 trial protocol required that, in cases where treatment resulted in toxicity, patients received reduced doses. In the company model, it is assumed that, as a result of reduced doses, there is a corresponding reduction in drug acquisition costs. The ERG considers that:
    - the case for pro-rata reductions in drug costs to be questionable in an NHS setting and that full costing should be used in the base case analysis.
- In terms of drug costs, the ERG considers that:
    - the company model substantially overestimates the acquisition cost of the generic drugs (oxaliplatin and 5-FU/LV) by using BNF rather than eMiT prices

and by failing to take advantage of the economic efficiencies that are achievable by using a mixture of different vial sizes

- a BSA specific to patients with gastrointestinal cancer, rather than one relating to a more general population of adult patients with cancer, should have been employed to estimate drug costs
- The use of a post-progression treatment cost of £907.43 per week is an overestimate and that it would be more appropriate to assume that patients simply receive BSC.

- The ERG considers that:
  - the terminal care costs used in the company model underestimate the true costs incurred during routine clinical practice in the NHS
  - the utility values used in the company model are overestimates
  - the decrement in quality of life experienced by patients during the final 4 weeks of their life is not captured in the company model.
- The ERG considers that
  - the costs of treating adverse events in the company model underestimate the true costs incurred during routine clinical practice in the NHS
  - the utility values used in the company model are overestimates
  - the decrement in quality of life experienced by patients during the final 4 weeks of their life is not captured in the company model

Other minor issues

- Other minor issues (which have no substantial impact on cost effectiveness results) relate to terminal care costs, treatment administration (pharmacy costs, infusion pump disconnection costs), costs of treating AEs, disutility associated with AEs, *UGT1A1*28* allele testing and the methods used to undertake PSA.

Cost effectiveness of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV

On clinical advice, the ERG considers oxaliplatin+5-FU/LV to be the main comparator in the cost effectiveness evaluation as this treatment is the current standard of care in the NHS. However, the ERG considers results for this comparison to be erroneous due to the lack of reliable clinical effectiveness data. As well as applying ERG's preferred modelling approaches to the company model, the ERG has also explored relative cost effectiveness by generating cost effectiveness results for this comparison by varying the total QALY estimate for the oxaliplatin+5-FU/LV treatment arm.

Cost effectiveness results

The company has submitted a Patient Access Scheme (PAS) application. This is currently undergoing consideration by the PAS Liaison Unit.

For nal-iri+5-FU/LV versus 5-FU/LV, the company's base case ICER increases to £[redacted] per QALY gained following the implementation of all of the ERG's preferred model revisions.

End of life

The treatment is indicated for patients with a life expectancy of less than 24 months and the anticipated licence is for a small population. However, neither the median estimates of OS from the NAPOLI-1 trial nor the estimates of mean life expectancy generated by the company's model or the ERG amended model suggest that treatment with nal-ir+5-FU/LV will lead to an extension of life of an additional 3 months when compared with 5-FU/LV (a comparator that is rarely used in clinical practice). The weight of evidence from the ERG's admittedly exploratory crude comparisons suggests that OS for patients treated with oxaliplatin+5-FU/LV reported in these trials is very similar in magnitude to OS for patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial.

9 OVERALL CONCLUSIONS

Treatment with nal-iri+5-FU/LV appears to be of greater efficacy than 5-FU/LV for patients with metastatic pancreatic cancer who have progressed on treatment with gemcitabine in the NAPOLI-1 trial. Despite an increase in AEs (mostly myelosuppression and gastrointestinal disorder), there appears to be no appreciable deterioration in HRQoL for patients treated with nal-iri+5-FU compared with 5-FU/LV.

The patient population recruited to the NAPOLI-1 trial is, in many respects, representative of patients who would be treated for metastatic pancreatic cancer who progress on treatment with gemcitabine in routine clinical practice in England. It is however noticeable that a greater proportion of patients had received prior gemcitabine combination therapy and fewer patients had received gemcitabine monotherapy than would be seen NHS clinical practice in England. Furthermore, as is common with all clinical trials, the patient population was on average younger and fitter than would be seen in clinical practice, which may explain why a relatively large proportion of patients were receiving study treatment in the third-line (or later) setting.

However, 5-FU/LV is rarely used to treat patients with metastatic pancreatic cancer who have progressed on treatment with gemcitabine. Overall, the PFS and OS outcomes for patients treated with oxaliplatin+5-FU/LV reported in these trials are similar in magnitude to the PFS and OS outcomes of patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial.

The ERG considers that the company's ICERs per QALY gained for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV and 5-FU/LV are underestimated. The ERG identified a number of common issues affecting both comparisons and these are related to the costing methodologies adopted and the estimation of health state utilities as described in the CS. For the oxaliplatin+5-FU/LV comparison, the ERG considers the main issue of concern to be the company's ITC, thus the (corrected) estimated ICER per QALY gained (£[redacted]) is judged to be unreliable. The ERG urges caution when interpreting the cost effectiveness estimates for the nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV comparison. For this comparison, the ERG's revised model estimated ICERs per QALY gained are £[redacted] and £[redacted] for Scenarios B and C, respectively. The ERG performed additional analyses in order to aid decision making in the absence of a reliable ITC effectiveness results.

With regards to nal-iri+5-FU/LV versus 5-FU/LV, the ERG did not consider the company's approach to modelling survival to be appropriate. The ERG disagrees with the use of log-

normal parametric curves instead of mature RCT data from the NAPOLI-1 trial. The ERG amendments to the nal-iri+5-FU/LV versus 5-FU/LV comparison resulted in an ICER of £ [redacted], an increase of more than £[redacted] from the company base case estimate. The ERG does not regard treatment with 5-FU/LV to be a relevant comparator to current UK clinical practice.

9.1 Implications for research

One major limitation is the lack of head-to-head evidence for treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV. Results from a trial that compares these two treatments could, therefore, help clinical decision making. A trial that compares evidence of the effectiveness of nal-iri+5-FU/LV with either non-liposomal irinotecan monotherapy or in combination with 5-FU/LV (i.e. FOLFIRI) may also be informative.

The reporting of key trial outcome measures for comparator drugs are generally reported in the form of HRs. The fundamental assumption supporting the mathematics used to generate hazard ratios is that hazards remain proportional over time. Examination of the K-M data from the NAPOLI-1 trial indicates that this assumption does not hold for OS or PFS (except in the later stages) data. This renders the HR figures for these two outcome measures as meaningless. Furthermore, the mathematics used in an ITC to generate measures of relative efficacy relies on hazards for each outcome measure being proportional, both within and between, included trials. Again, within the company's ITC not all of these PH assumptions held. The ERG suggests that further statistical research is required to develop methods that can be used:

- to provide a general measure of comparative efficacy in cases where trial outcome data are not proportional
- in the absence of head-to-head trial data, to generate comparative effectiveness results in situations where the PH assumption does not hold.

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11 APPENDICES

11.1 Additional secondary analyses in the NAPOLI-1 trial

Additional analyses were conducted and reported by the company in the CS, as summarised in Table 62. These were secondary outcomes not specified in the NICE scope.

Table 62 Analysis strategy for additional efficacy endpoints in the NAPOLI-1 trial

Endpoint	Definition	Statistical method	Population used for analysis
Tumour marker response	Evaluated by the change in CA19-9 serum levels, which was assessed at treatment start, every 6 weeks thereafter, and at 30 days post follow-up. Response was defined as a decrease of ≥50% of CA19-9 in relation to the baseline level at least once during the treatment period	Tumour marker response rates were pairwise compared using Fisher's exact tests. Time to first tumour marker response was summarised using KM methods	TMRE
CBR rate	CBR is a composite parameter based on four characteristic features of pancreatic cancer: Primary measures of clinical benefit: • Change in pain intensity • Change in analgesic consumption • Change in performance status Secondary measure of clinical benefit: • Change in weight	Objective CBR rates were compared using Fisher's exact tests. Contingency tables for pain classification (analgesic consumption by pain intensity), primary measures of classification (KPS), and overall CBR (primary measures by weight) were presented for each treatment group. Median time to CBR and median duration of CBR were computed using data from patients with CBR	CBRE

CA19-9=Cancer antigen 19-9; CBR=clinical benefit response; CBRE=clinical benefit response evaluable; KM=Kaplan-Meier; TMRE=tumour marker response evaluable
Source: CS Sections 4.3.4, 4.4.3 and 4.4.4

Tumour marker response

The results for tumour marker response for the tumour marker response evaluable (TMRE) population are provided in Table 63. Patients in the nal-iri+5-FU/LV arm were statistically significantly more likely to have reductions of ≥50% from baseline in CA19-9 levels than patients treated with 5-FU/LV alone.

Table 63 Tumour marker (CA19-9) response in the NAPOLI-1 trial – TMRE population

	Nal-iri+5-FU/LV (n=97)	5-FU/LV (n=81)
Tumour marker response, n (%)	28 (28.9)	7 (8.6)
p-value†	p=0.0006	
Median time to first tumour marker response¶, months (95% CI)	4.3 (2.92 to NR)	NR (3.91 to NR)
Log-rank p-value§	p=0.0392	
Wilcoxon p-value§	p=0.0180	

CA19-9=Cancer antigen 19-9; CI=confidence interval; NR=not reached; TMRE=tumour marker response evaluable
†Two-sided p-values from pairwise comparisons of tumour marker response rates using Fisher's exact test.
¶Median time to first tumour response is Kaplan-Meier estimate of the median time to first tumour marker response, in months.
§Two-sided p-values from pairwise comparisons of time to first tumour marker response
Source: CS, Table 23, and company response to ERG clarification letter, question A15

Effect of baseline CA19-9 level on overall survival

An additional analysis was performed to investigate the effect of baseline CA19-9 level on OS. Patients who received study medication and had a recorded baseline CA19-9 measurement were categorised according to baseline CA19-9 measurement, and HRs and corresponding 95% CI were calculated for each quartile. The results, presented in Figure 14, suggest that, compared with 5-FU/LV, nal-iri+5-FU/LV has a greater treatment effect on OS amongst patients with higher CA19-9 levels.

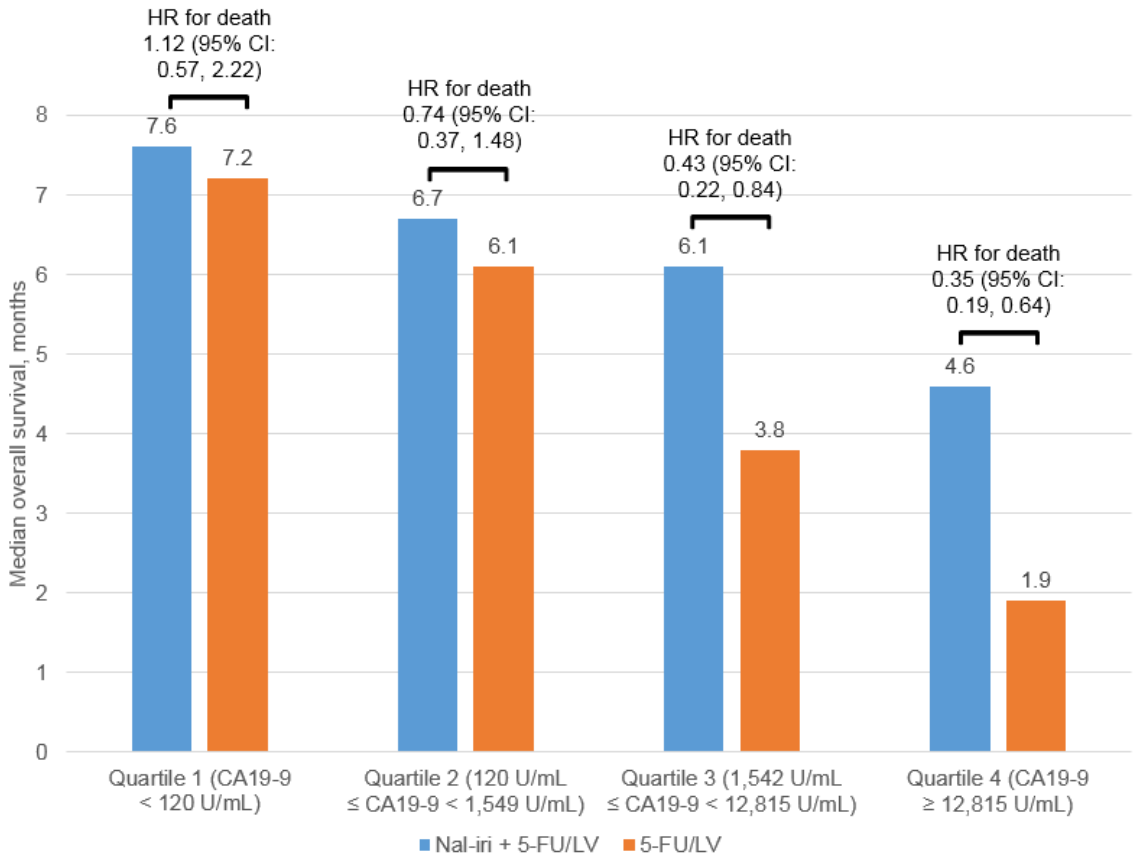


Figure 14 Effect of baseline CA19-9 level on overall survival in the NAPOLI-1 trial – TMRE population

CA19-9=carbohydrate antigen 19-9; HR=hazard ratio

Source: CS, Figure 5

Clinical benefit response

The results of the assessment of Clinical benefit response (CBR) rate are shown in Table 64. The nal-iri+5-FU/LV arm showed a CBR rate of 14.1% compared with 11.7% in the 5-FU/LV arm.

Table 64 Clinical benefit response in the NAPOLI-1 trial – CBRE population

	Nal-iri+5-FU/LV (n=78)			**5-FU/LV (n=60)**		
Analgesic consumption						
Pain intensity, n (%)	Positive	Stable	Negative	Positive	Stable	Negative
Positive	6 (7.69)	3 (3.85)	3 (3.85)	0	3 (5.00)	2 (3.33)
Stable	2 (2.56)	31 (39.74)	10 (12.82)	2 (3.33)	21 (35.00)	8 (13.33)
Negative	0	5 (6.41)	18 (23.08)	0	7 (11.67)	17 (28.33)
Performance status						
Pain classification, n (%)	Positive	Stable	Negative	Positive	Stable	Negative
Positive	1 (1.28)	9 (11.54)	1 (1.28)	0	4 (6.67)	1 (1.67)
Stable	0	27 (34.62)	4 (5.13)	0	16 (26.67)	5 (8.33)
Negative	0	24 (30.77)	12 (15.38)	0	15 (25.00)	19 (31.67)
Primary measure						
Weight, n (%)	Response	Stable	Non-response	Response	Stable	Non-response
Positive	1 (1.28)	1 (1.28)	0	0	3 (5.00)	0
Non-positive	9 (11.54)	26 (33.33)	41 (52.56)	4 (6.67)	13 (21.67)	40 (66.67)
CBR, n (%)			11 (14.10)			7 (11.67)
p-value						p=0.8007

CBR=clinical benefit response; CBRE=clinical benefit response evaluable
Source: CS, Table 24

The company notes some limitations of the evaluation of CBR, namely that:

- the pain component of the CBR assessment was based on patient-reported daily diary data and diary compliance was low (60% of ITT patients were in the CBRE population); this resulted in a dataset that was highly variable in quality
- the CBR classification rules (CS, Section 4.3.4.2) required observed maintenance of 4 consecutive weeks with robust criteria in each category for classification of improvement, while classification of negative CBR was less robust due to the categorisation of 'any worsening' as negative for pain.

Therefore, the company states that the CBR assessment may detect gross improvements in CBR, but conclusions regarding negative classification should be interpreted with caution.

11.2 Results of company tests for proportional hazards for overall survival in the NAPOLI-1 trial

The results of the tests for PH for the OS endpoint using various analysis populations are provided in Table 65.The results of the performed tests indicated a violation of the PH assumption for all cases, with the exception of the tests using the stratified, ITT population (p=0.1712), and using the ITT population with censoring at change in therapy (p=0.0951).

Table 65 Overall survival: assessments of proportional hazard assumptions in the NAPOLI-1

	Comparison of nal-iri+5-FU/LV versus 5-FU/LV
Unstratified, ITT population	p=0.0169
Unstratified, safety population	p=0.0111
Unstratified, PP population	p=0.0034
Stratified, ITT population	p=0.1712
Censoring at change in therapy, ITT population	p=0.0951
Post-baseline therapy as time-dependent covariate, ITT population	p=0.0162

ITT=intent-to-treat; PP=per protocol
Source: Company response to the ERG clarification letter

11.3 ERG testing of proportional hazards

11.3.1 Proportional hazards testing for NAPOLI-1 trial data

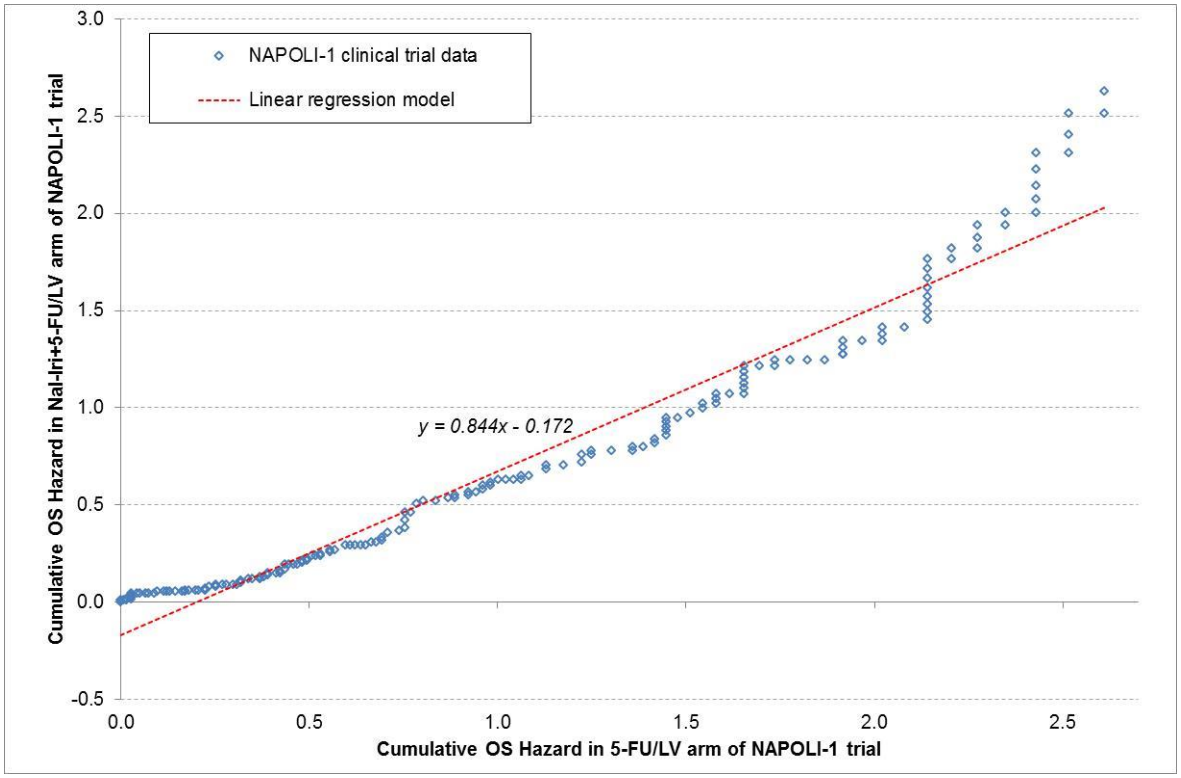
The validity of the PH assumption within the trial is best assessed by considering the H-H plot which shows the relationship between the cumulative hazard for each trial event at common time points in the two trial arms (OS, Figure 15; PFS; Figure 16; TTF, Figure 17). For the PH assumption to be valid, two criteria must be met:

- the data should follow a straight line trend, with individual data points randomly distributed close to and on either side of the trend line
- the linear trend line should pass through the graph origin (zero value on both axes).

Overall survival

Visual inspection of Figure 15 indicates that the NAPOLI-1 results do not support a simple interpretation of the relationship between mortality patterns in the two trial arms. Fitting a simple linear regression model does not generate a reliable representation of the trial data; the model under-estimates mortality hazard in the intervention arm in the early and late phases of the trial, and systematically over-estimates mortality hazard in the intervention arm in the main period of the trial (2.6 – 14 months). It is also noticeable that the linear model estimates a statistically significant deviation from the origin of -0.172 (95% CI: -0.209 to -0.130, $p<0.0001$).

Thus the NAPOLI-1 OS results violate the PH assumption on two grounds: the data show that the HR changes in a non-linear fashion over time, and attempting to estimate a single constant HR results in a relationship which does not conform to the requirement for the trend line to pass through the origin.

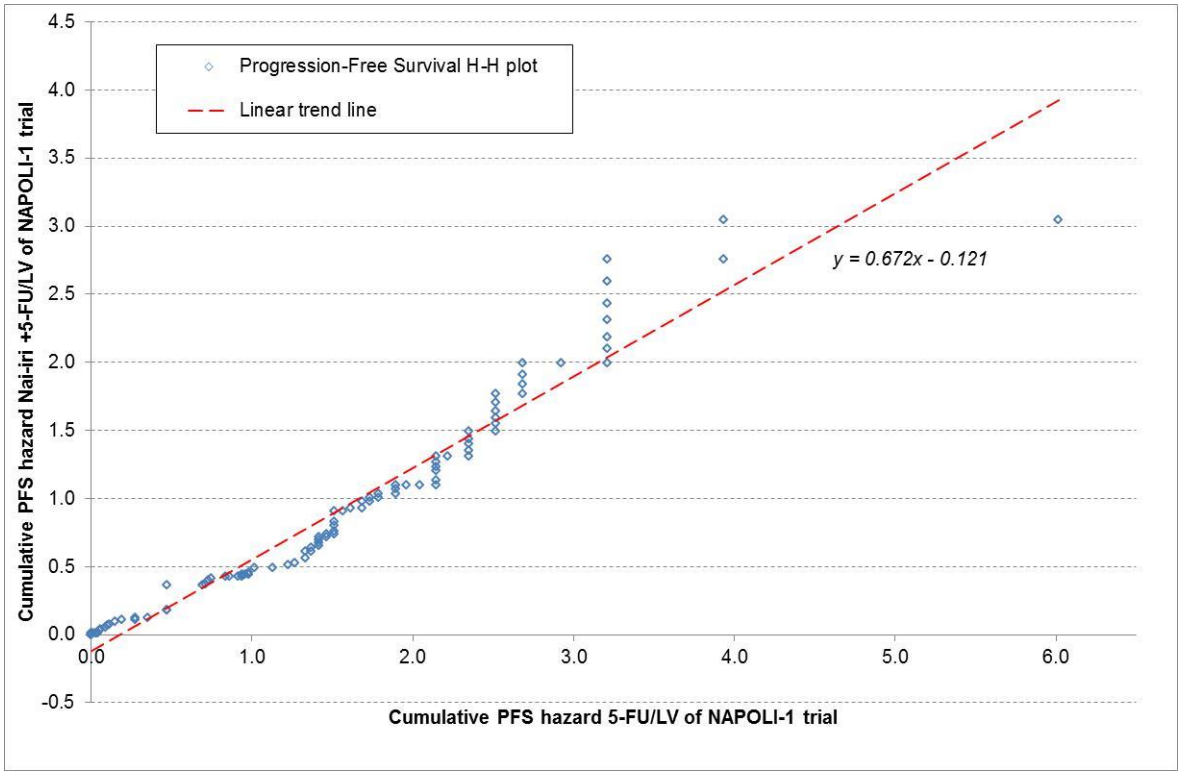


HR=hazard ratio; OS=overall survival

Figure 15 Comparison of alternate trend models for overall survival hazard ratio in the NAPOLI-1 trial

Progression-free survival

Similarly, visual inspection of Figure 16 indicates that the PH assumption is also violated for the PFS data for NAPOLI-1. The linear model under-estimates disease progression hazard in the intervention arm in the early and late phases of the trial, and systematically over-estimates disease progression hazard in the intervention arm in the main period of the trial (1.5 – 8 months). It is also noticeable that the linear model estimates a statistically significant deviation from the origin of -0.121 (95% CI: -0.189 to -0.052, p<0.001).

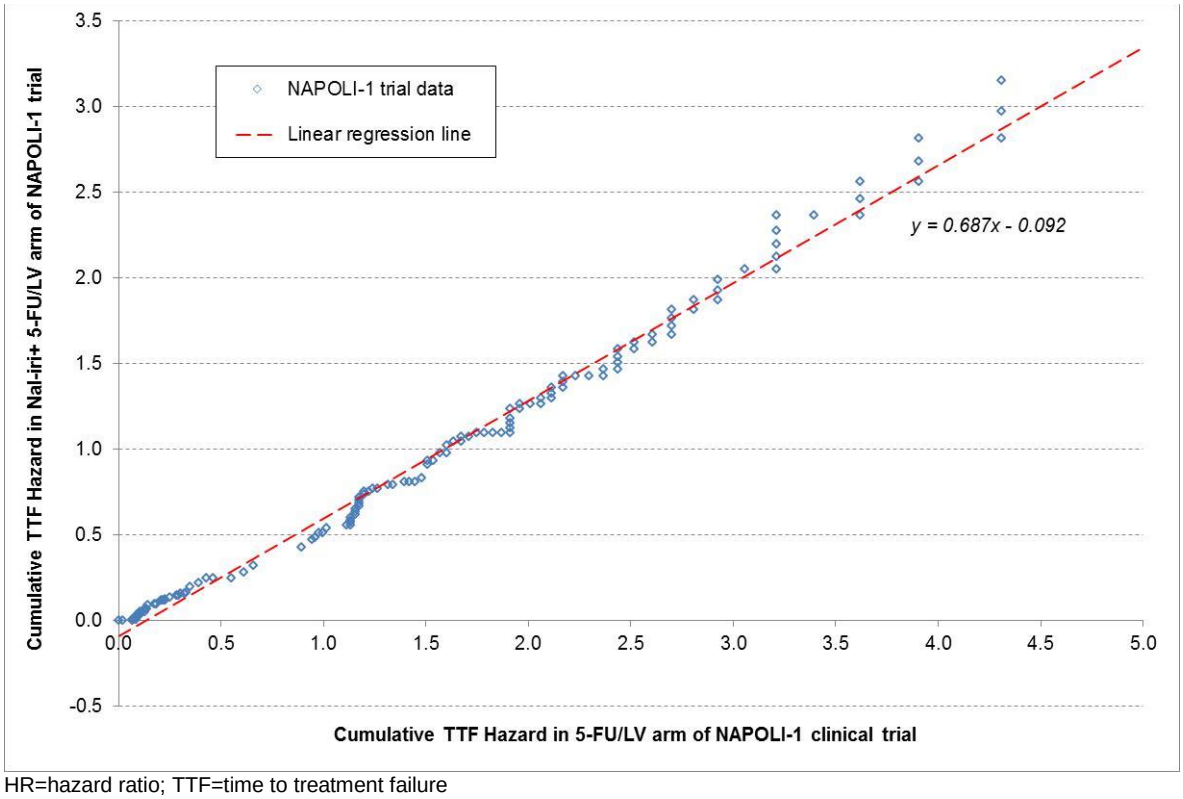


HR=hazard ratio; PFS=progression-free survival

Figure 16 Comparison of alternate trend models for progression-free survival hazard ratio in the NAPOLI-1 trial

Time to treatment failure

Visual inspection of Figure 17 suggests that the PH assumption may be valid for TTF data. However, closer inspection indicates a shallower trend during the first 1.5 months in the intervention arm of the NAPOLI-1 trial, before the long-term linear relationship becomes established. This is confirmed by the small but statistically significant deviation from the origin of -0.092 (95% CI: -0.114 to -0.070, p<0.0001). Thus a simple single HR will tend to progressively understate estimated cumulative treatment failure hazard in the long-term and the PH assumption does not hold.



HR=hazard ratio; TTF=time to treatment failure

Figure 17 Comparison of alternate trend models for time to treatment failure hazard ratio in the NAPOLI-1 trial

11.3.2 Proportional hazards testing for the indirect treatment comparison of nal-iri+5-FU/LV (NAPOLI-1) versus OFF (CONKO-003) and mFOLFOX6 (PANCREOX)

To conduct its cost effectiveness analysis, the company carried out an ITC to compare the effectiveness of treatment with nal-iri+5-FU/LV and treatment with oxaliplatin+5-FU/LV.

The NAPOLI-1 trial: nal-iri+5-FU/LV versus 5-FU/LV

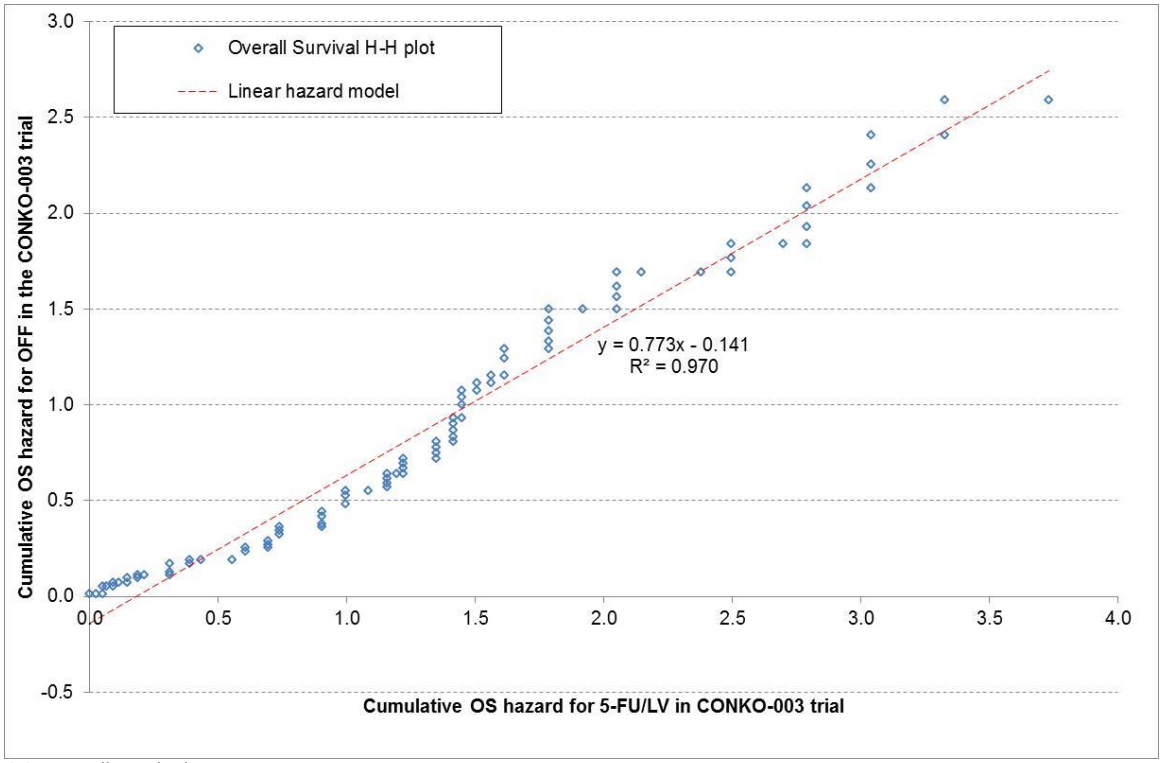
An ITC comparing the effectiveness of nal-iri+5-FU/LV with oxaliplatin+5-FU/LV depends critically on the validity of the PH assumption of treatment nal-iri+5-FU/LV versus 5-FU/LV within the NAPOLI-1 trial. As described in Section 11.3.1, the NAPOLI-1 trial OS and PFS data violate the PH assumption.

The CONKO-003 trial: oxaliplatin+5-FU/LV (OFF) versus 5-FU/LV

In addition, an ITC comparing the effectiveness of treatment with nal-iri+5-FU/LV with oxaliplatin+5-FU/LV depends on the validity of the PH assumption of OFF versus 5-FU/LV within the CONKO-003 trial. Figure 18 indicates that for OS, overall, the linearity assumption is only supportable after about 7.5 months. Prior to this there is a sustained deviation from proportionality. The requirement for the trend line to pass through the origin is not supported by the trial data which indicate a statistically significant negative estimated regression constant of -0.141 (95% CI: -0.187 to -0.096, $p<0.0001$).

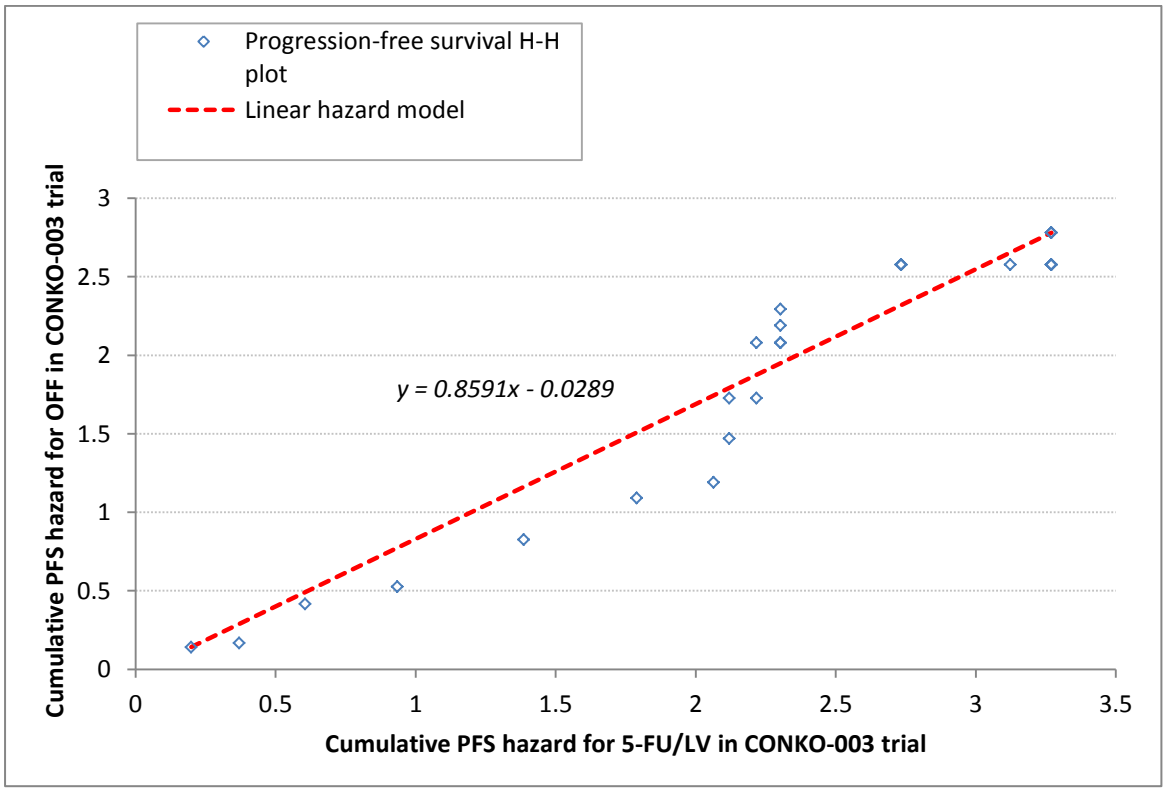
Thus the CONKO-003 trial OS results violate the PH assumption on two grounds: the data show that the HR changes in a non-linear fashion over time, and attempting to estimate a single constant HR results in a relationship which does not conform to the requirement that the trend line should pass through the origin.

Similarly, Figure 19 shows that for PFS, PH is violated as there is sustained deviation from proportionality, indicating that the HR changes in a non-linear fashion over time.



OS=overall survival

Figure 18 Comparison of trial data and a linear trend model for overall survival hazards in the CONKO-003 trial



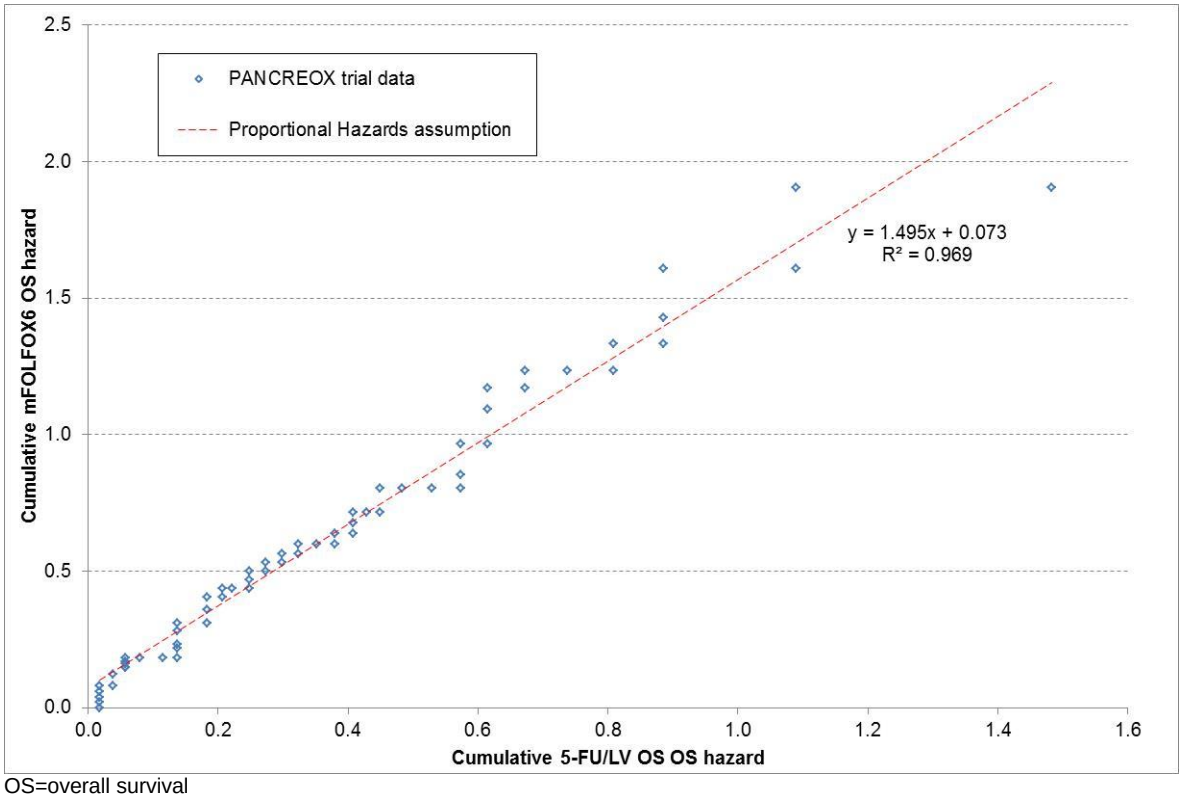
PFS=progression-free survival

Figure 19 Comparison of trial data and a linear trend model for progression-free survival hazards in the CONKO-003 trial

The PANCREOX trial: oxaliplatin+5-FU/LV (mFOLFOX6) versus 5-FU/LV

Figure 20 indicates that overall the linearity assumption may be reasonable in the PANCREOX trial. However, the requirement for the trend line to pass through the origin is not supported by the trial data which indicate a statistically significant positive estimated regression constant of +0.073 (95 %CI: 0.039 to 0.106, p<0.0001). Though this may appear to represent only a minor violation of the PH assumption, it has the potential to propagate a substantial long-term discrepancy when used to generate extrapolated OS estimates in the decision model.

Figure 21 shows that for PFS, the PH assumption is likely to be violated. PFS data deviate substantially from proportionality, indicating that the HR changes in a non-linear fashion over time.



OS=overall survival

Figure 20 Comparison of trial data and a linear trend model for overall survival hazards in the PANCREOX trial

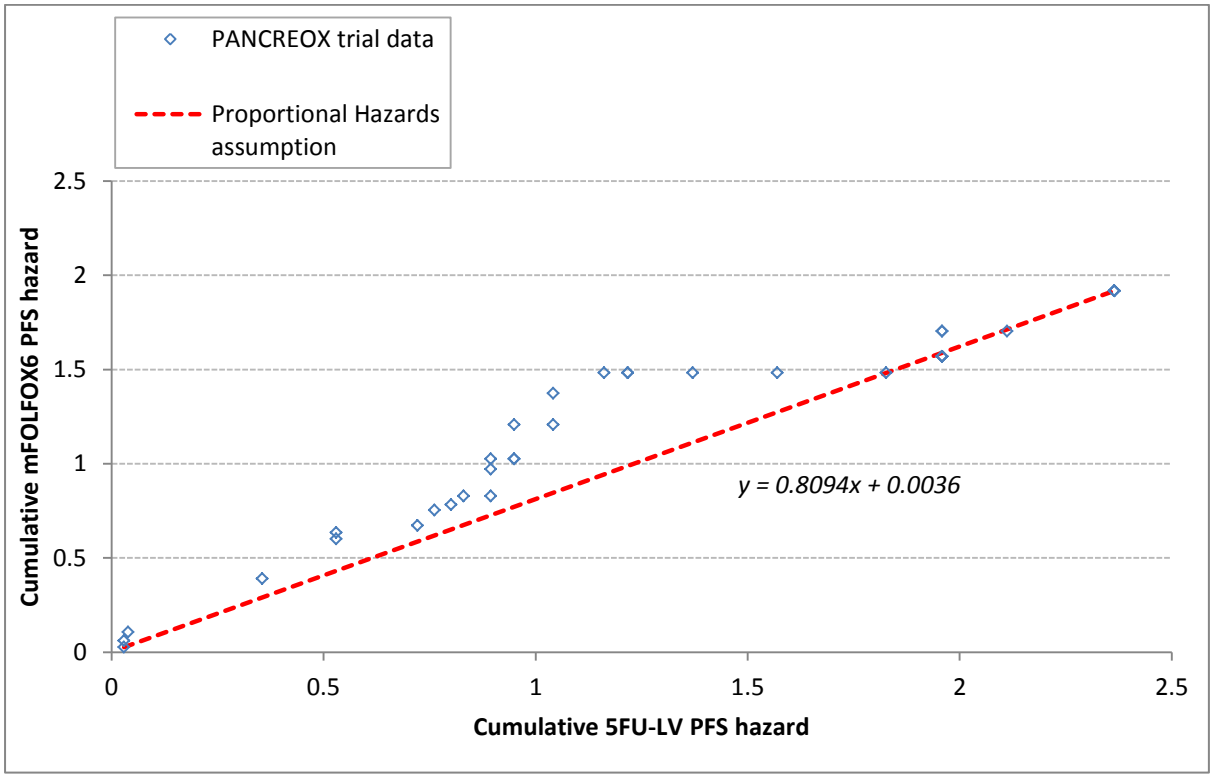


Figure 21 Comparison of trial data and a linear trend model for progression-free survival hazards in the PANCREOX trial

Conclusion

Within each of the three networked trials (NAPOLI-1, CONKO-003 and PANCREOX) the PH assumption is violated for mortality hazards comparing 5-FU/LV with each of the 'active' treatments for both OS and PFS.

In addition, the ITC proposed by the company involve the further assumption that the trial OS data for the common comparator (5-FU/LV) in the three clinical trials are equivalent (i.e. can be assumed to exhibit a HR of 1.0). An examination of the trial data from these three trials indicates that the PH assumption is not valid for these inter-trial comparisons.

The ERG has concluded that the available OS and PFS trial data do not support the use of the PH assumption in estimating HRs. Such HRs cannot be considered reliable and should not be used in populating a decision model comparing nal-iri+5-FU/LV with any of the other treatments in the proposed evidence network.

11.4 Quality assessment of randomised controlled trials included in the company submission

The company's assessment of study quality, i.e. an assessment of risk of bias, is reproduced in Table 66 with ERG comment.

Table 66 Company's quality assessment of the CONKO-003, PANCREOX and NAPOLI-1 trials with ERG comment

Study question	NAPOLI-1	CONKO-003	PANCREOX
Was randomisation carried out appropriately?	Yes. Patients were randomised 1:1 in the nal-iri+5-FU/LV and 5-FU/LV arms by IWRS after all screening assessments were completed and *UGT1A1*28* results were available.	Yes – Patients were randomly assigned to treatment groups using computer-generated random numbers at the study coordination centre.	Unclear – patients were randomised with stratification factors: Age (<70; ≥70 years); Sex ECOG performance score (0; 1; 2); Liver metastases However, the method of randomisation was not described.
ERG comment	Agree	Agree	Agree
Was the concealment of treatment allocation adequate?	Open-label study. Blinding of study treatment was not feasible due to different dosing schedules in the different arms. Using a double-dummy design would result in an unacceptable number of infusions lasting up to 46 hours.	N/A – Open-label trial.	N/A – open-label trial.
ERG comment	Agree	Agree	Agree

Study question	NAPOLI-1	CONKO-003	PANCREOX
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes. Patient demographics in both groups were well balanced in terms of sex, race, age and BMI. The nal-iri+ 5-FU/LV and 5-FU/LV groups were also comparable for all baseline disease characteristics, including KPS, albumin level, number and anatomical location of metastatic lesions, measurable metastatic lesions, previous anti-cancer treatment, best response to prior therapy, prior radiotherapy, prior surgery, prior Whipple procedure, has biliary stent, and number and type of concomitant medical conditions (including anaemia, gastrointestinal disorders, fatigue, type 2 diabetes, hypertension, and psychiatric disorders).	The OFF treatment arm had a slightly higher percentage of patients with a better KPS than the FF arm (53.9% with a KPS of 90–100 in the OFF arm versus 47.6% in the FF arm), despite KPS being a stratification criteria prior to randomisation. Median duration of first-line treatment with gemcitabine monotherapy was 4.6 months (95% CI: 3.8 to 6.0) with OFF and 5.3 months (95% CI: 4.4 to 6.0) with FF; hazard ratio 1.03 (95% CI: 0.75 to 1.41). Mean times to start of treatment after random assignment were not significantly different between treatment arms (5.5 days with OFF versus 4.1 days with FF; p=0.10).	Patients in the mFOLFOX6 arm had a longer duration of advanced disease (7.9 months) than patients in the 5-FU/LV arm (5.7 months). In addition, a higher percentage of patients had an ECOG performance score of 2 in the mFOLFOX6 arm (11.1% versus 5.7%), and a lower percentage had ECOG performance score of 0 (13.0% versus 18.9%). A similar proportion of patients had ECOG performance score of 1 in each treatment arm (75.9% in the mFOLFOX6 arm) and 75.5% in the 5-FU/LV arm).
ERG comment	The ERG notes slight imbalances in KPS score and proportion of patients with “other” metastatic lesions between arms. Taken together, the greater proportion of patients with “other” metastatic lesions and patients with KPS 90 in the 5-FU/LV arm could suggest patients were less fit than those in the nal-iri+5-FU/LV arm although the ERG recognises there is a large degree of subjectivity in determining PS. Furthermore, it is noted that the proportion of patients with KPS ≤70 (i.e. the least fit) were similar between arms (8.6% versus 8.4%)	Agree	Agree

Study question	NAPOLI-1	CONKO-003	PANCREOX
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Open-label trial. However, sponsor personnel did not have access to the randomisation code for treatment assignment. In the course of data cleaning and statistical programming development, limited sponsor clinical and biometrics personnel had access to data for individual patients that could be unblinded due to the uniqueness of the visit schedules for each arm. Access to the data in the electronic data capture system was controlled and limited only to authorised personnel for specified data review.	The trial was open-label, but it was not clear whether the outcome assessors were blind to treatment allocation.	The trial was open-label, but it was not clear whether the outcome assessors were blind to treatment allocation.
ERG comment	Agree. The ERG notes that following a protocol amendment, as a result of the new RECIST 1.1 guidelines, [33] central independent confirmation of objective tumour response was no longer required in the trial	Study end points and serious adverse events were centrally evaluated	Agree

Study question	NAPOLI-1	CONKO-003	PANCREOX
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There was a lower rate of discontinuation with nal-iri+5-FU/LV (88.0%) than with 5-FU/LV (95.0%). This is mainly due to a lower percentage of patients discontinuing due to progressive disease (48.7% versus 53.8%). Other differences were higher discontinuation due to an adverse event (9.4% versus 5.9%), lower discontinuation due to death (1.7% versus 4.2%), and lower discontinuation due to subject decision (12.0% versus 16.0%).	Drop-outs after first treatment administration were not reported.	The withdrawal rate due to an adverse event was 16.3% in the mFOLFOX6 arm and 1.9% in the 5-FU/LV arm. Other drop-outs and adjustments were not reported.
ERG comment	The ERG notes that a greater proportion of patients enrolled in the 5-FU/LV arm (10.9%) never received the treatment they were allocated compared with the nal-iri+5-FU/LV arm (1.7%)	Information on lost to follow-up is reported in Fig 1. There are no unexpected imbalances or drop-outs. The ERG concurs that information on drop-outs after first treatment administration are not reported	The abstract for this paper states that more patients withdrew due to adverse events in the mFOLFOX6 arm (20.4%) than the 5-FU/LV arm (1.9%) and more patients withdrew due to progression in the 5-FU/LV arm (74.1%) than the mFOLFOX6 arm (50.0%). The ERG concurs that other drop-outs and adjustments were not reported. The ERG also notes that a greater proportion of patients received subsequent chemotherapy on disease progression in the 5-FU/LV arm (23.1% than the mFOLFOX6 arm (6.8%)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No.	No.
ERG comment	Agree. However the company explain that not all exploratory analyses are reported in its submission (i.e. biomarker analyses)	Agree.	Agree

Study question	NAPOLI-1	CONKO-003	PANCREOX
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The ITT population was used for the analyses for the primary endpoint (overall survival) and secondary endpoints including progression-free survival. The ITT population was the most appropriate population for these endpoints as it included all randomised patients. The evaluation of tumour marker response used the tumour marker response evaluable population, which only included patients who had elevated CA19-9 level (>30 U/mL) at baseline. The evaluation of clinical benefit response used the clinical benefit response evaluable population, which only included patients who had at least one of: baseline pain intensity ≥20 (out of 100); baseline morphine consumption ≥10 mg/day oral morphine equivalents; baseline KPS of 70–90 points. The evaluation of quality of life used the patient-reported outcome population, which only included ITT patients that provided baseline and at least one subsequent assessment on the EORTC-QLQ-C30 instrument.	The analysis was only performed on the patients that received treatment – 8 patients underwent random assignment but were excluded from analysis before first treatment administration by the steering committee because of withdrawal of informed consent (n=2), lack of progressive disease at baseline (n=1), major GI bleeding that resulted in contraindication of further chemotherapy (n=1), and death before the study started (n=4).	Unclear – it is not reported which population the analyses were performed on.
ERG comment	Agree	Agree but the ERG notes that once a patient had received their first treatment administration, patients who were subsequently lost to follow-up (intervention, n=4, control, n=1) or had a complete response (n=1 in both arms) were included in the analysis	Agree. The ERG however notes that for baseline characteristics, n=54 for both arms and for the analysis of OS, n=54 for both arms

CA19-9=Cancer antigen 19-9; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30= European Organisation for Research and Treatment of Cancer; GI=gastrointestinal; ITT=intention-to-treat; KPS=Karnofsky Performance Status; N/A=not applicable; PS=performance status

11.5 Additional sensitivity analyses of overall survival in the NAPOLI-1 trial

As part of the clarification letter to the company, the ERG requested the results of several sensitivity analyses of OS which were pre-specified in the TSAP. The result of the Wilcoxon test for OS is provided in Table 67.

Table 67 Wilcoxon test result for overall survival in the NAPOLI-1 trial – ITT population

Wilcoxon pairwise comparison of treatments	Two-sided p-value from Wilcoxon test: nal-iri+5-FU/LV versus 5-FU/LV
OS	0.0009

OS=overall survival
Source: Company response to the ERG clarification letter, Table 11

The results for the OS Cox regression model with a time-dependent covariate to account for post-baseline therapy for nal-iri+5-FU/LV versus 5-FU/LV are provided in Table 68.

Table 68 Overall survival Cox regression model with a time-dependent covariate to account for post-baseline therapy in the NAPOLI-1 trial – ITT population

	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Patients with change in therapy, n (%)	36 (30.77)	45 (37.82)
Died	22 (18.80)	27 (22.69)
Censored	14 (11.97)	18 (15.13)
Alive	14 (11.97)	17 (14.29)
Lost to follow-up	0	1 (0.84)
Subject withdrew consent from follow-up	0	0
Patients with no change in therapy, n (%)	81 (69.23)	74 (62.18)
Died	53 (45.30)	53 (44.54)
Censored	28 (23.93)	21 (17.65)
Alive	23 (19.66)	10 (8.40)
Lost to follow-up	1 (0.85)	0
Subject withdrew consent from follow-up	4 (3.42)	11 (9.24)
HR for study treatment (95% CI)	0.6802 (0.4921 to 0.9402)	
Two-sided p-value	0.0196	
Hazard ratio for change in therapy (95% CI)	1.0872 (0.7515 to 1.5728)	
Two-sided p-value	0.6574	

CI=confidence interval; HR=hazard ratio; OS=overall survival
Source: Company response to the ERG clarification letter, Table 12

Results from the Cox regression model with stepwise selection of covariates (p-value to enter <0.25, p-value to remain <0.15).are provided in Table 69 for OS.

Table 69 Overall survival Cox regression model including covariates in the NAPOLI-1 trial – ITT population

	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Excluded from analysis, n (%)	5 (4.27)	10 (8.40)
Died, n (%)	73 (62.39)	78 (65.55)
Censored, n (%)	39 (33.33)	31 (26.05)
HR (p-value) for other model selected terms		
Treatment group: nal-iri + 5-FU/LV	0.580 (0.0012)	
Baseline KPS ≥90	0.639 (0.0089)	
Baseline albumin ≥4 g/dL	0.697 (0.0305)	
Stage 4 at diagnosis	2.042 (0.0003)	
Time since last anti-cancer therapy >1.3 months	0.737 (0.0724)	
Presence of liver metastases	1.873 (0.0012)	
Baseline CA19-9 ≥40 U/mL	1.925 (0.0038)	
Age >65 years	1.338 (0.0781)	

HR=hazard ratio; KPS=Karnofsky performance score; OS=overall survival
Source: Company response to the ERG clarification letter, Table 13

11.6 Type of adverse events leading to dose modification in the NAPOLI-1 trial

11.6.1 Dose delay

The company highlights that the primary reasons for dose delay in the nal-iri+5-FU/LV arm were neutropenia and neutrophil count decreased (i.e. myelosuppression). From the company's CSR (Table 14.3.2.4.3), the ERG notes that neutropenia resulted in dose delay for [redacted] of patients in the nal-iri+5-FU/LV arm compared with [redacted] in the 5-FU/LV arm. Neutrophil count decreased resulted in dose delay for [redacted] and [redacted] respectively. Another notable AE resulting in dose delay in the nal-iri+5-FU/LV arm was [redacted] ([redacted] compared with [redacted] in the 5-FU/LV arm).

11.6.2 Dose reduction

Myelosuppression was also cited as the main reason for dose reduction with nal-iri+5-FU/LV, alongside gastrointestinal disorders. From the company's CSR (Table 14.3.2.4.1), most commonly (≥5%) [redacted] was a reason for [redacted] of cases in the nal-iri+5-FU/LV arm followed by [redacted].

11.6.3 Dose discontinuation

Gastrointestinal disorders and infections and infestations were the primary reasons cited by the company for discontinuation of treatment with nal-iri+5-FU/LV. As reported in Table 14.3.2.5.1 of the CSR, the proportions in the nal-iri+5-FU/LV arm for infections and infestations were [redacted] and [redacted] respectively.

11.7 Very common AEs reported in the NAPOLI-1 trial

The AEs that were very common (≥10%) in the NAPOLI-1 trial are summarised in Table 70.

Table 70 Summary of adverse events occurring in ≥10% of patients in any treatment group in the NAPOLI-1 trial – safety population

Adverse event, n (%)	Nal-iri (n=147)	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=134)
Any treatment emergent adverse event	145 (98.6)	116 (99.1)	132 (98.5)
Diarrhoea	103 (70.1)	69 (59.0)	35 (26.1)
Vomiting	80 (54.4)	61 (52.1)	35 (26.1)
Nausea	89 (60.5)	60 (51.3)	46 (34.3)
Decreased appetite	72 (49.0)	52 (44.4)	43 (32.1)
Fatigue	54 (36.7)	47 (40.2)	37 (27.6)
Anaemia	48 (32.7)	44 (37.6)	31 (23.1)
Abdominal pain	50 (34.0)	27 (23.1)	42 (31.3)
Pyrexia	29 (19.7)	27 (23.1)	15 (11.2)
Neutropenia	22 (15.0)	27 (23.1)	4 (3.0)
Constipation	26 (17.7)	26 (22.2)	32 (23.9)
Asthenia	35 (23.8)	24 (20.5)	22 (16.4)
Weight decreased	29 (19.7)	20 (17.1)	9 (6.7)
Neutrophil count decreased	15 (10.2)	17 (14.5)	2 (1.5)
White blood cell count decreased	10 (6.8)	17 (14.5)	2 (1.5)
Alopecia	32 (21.8)	16 (13.7)	6 (4.5)
Stomatitis	5 (3.4)	16 (13.7)	8 (6.0)
Dizziness	17 (11.6)	15 (12.8)	13 (9.7)
Back pain	12 (8.2)	15 (12.8)	16 (11.9)
Hypokalaemia	32 (21.8)	14 (12.0)	12 (9.0)
Oedema peripheral	28 (19.0)	13 (11.1)	20 (14.9)
Mucosal inflammation	8 (5.4)	12 (10.3)	5 (3.7)
Leukopenia	6 (4.1)	12 (10.3)	1 (0.7)
Platelet count decreased	3 (2.0)	12 (10.3)	3 (2.2)
Abdominal pain upper	17 (11.6)	11 (9.4)	10 (7.5)
Dehydration	15 (10.2)	9 (7.7)	9 (6.7)
Hypomagnesaemia	20 (13.6)	7 (6.0)	5 (3.7)
Hypoalbuminemia	19 (12.9)	7 (6.0)	8 (6.0)

Source: CS, adapted from Table 31

11.8 Non-randomised study of nal-iri monotherapy (NCT00813163)

The company also presents evidence in the CS from a multinational, single-arm phase 2 study of 40 patients treated with nal-iri monotherapy, referred to by its ClinicalTrials.Gov identifier, NCT00813163. This study was excluded from the company's systematic review since it did not include the intervention of interest, nal-iri+5-FU/LV.

Eligibility criteria for entry into the NCT00813163 study were not dissimilar to the NAPOLI-1 trial, the main exceptions being there was no specific stipulation that patients must have adequate renal function and patients were excluded if they had not been previously treated with irinotecan. Patients entered into the NCT00813163 study were also not permitted to have received prior irinotecan, whereas this was permitted in the NAPOLI-1 trial (under protocol version 2 or later), however the numbers of such patients were small ([redacted] patients in the nal-iri monotherapy arm and [redacted] patients in the nal-iri+5-FU/LV arm).

The nal-iri monotherapy dose and scheduling in the NCT00813163 study was the same as in the nal-iri monotherapy arm of the NAPOLI-1 trial. However, unlike the NAPOLI-1 trial, patients were not initially tested for the *UGT1A1*28* allele in the NCT00813163 study and so no initial dose reductions were made based on the results of any pharmacogenetic test in NCT00813163.

A descriptive critical appraisal of the only included non-randomised study was undertaken using a tool developed by Chambers 2009.[63] This includes eight items and for a study to be considered 'good' quality, all eight criteria must be met. The NCT00813163 study met five of the criteria including one or more of the criteria deemed by Chambers 2009 to classify the study as 'satisfactory' quality. The ERG considers that this checklist for assessing the quality of the non-randomised study appears to be an appropriate tool but the ERG notes that while it has been used in a modified format in three systematic reviews,[64-66] it has not been validated as a tool. Indeed, one of the future research recommendations of Chambers 2009 was to focus on focus on validating quality criteria.

Some notable baseline differences between the NCT00813163 study and the NAPOLI-1 trial were differences in the proportion of Asian patients, male patients, baseline KPS and patients previously treated with gemcitabine monotherapy or combination therapy as summarised in Table 71.

Table 71 Notable differences in baseline characteristics between the NCT00813163 study and nal-iri arms of the NAPOLI-1 trial*

Baseline characteristic	NCT00813163	NAPOLI-1	
	Nal-iri (n=40)	Nal-iri (n=151)	Nal-iri + 5-FU/LV (n=117)
Male, n (%)	19 (47.5)	87 (57.6)	69 (59.0)
Asian	25 (62.5)	52 (34.4)	34 (29.1)
KPS ≤70	10 (25.0)	15 (9.9)	10 (8.5)
Previously treated with gemcitabine monotherapy	9 (22.5)	67 (44.3)	53 (45.3)
Previously treated with gemcitabine combination	31 (77.5)	84 (55.6)	64 (54.7)

*For the NAPOLI-1 trial, data are for ITT population
Source: CS, adapted from Tables 14 and 28 and Wang-Gillam 2015 paper

In the NCT00813163 study, the primary endpoint was OS rate at 3-months with additional secondary endpoints including (but not limited to) PFS and ORR. Overall, key efficacy results appear to be similar to those reported in the NAPOLI-1 trial (Table 72).

Table 72 Key findings from the NCT00813163 study and NAPOLI-1 trial*

Outcome	NCT00813163	NAPOLI-1	
	Nal-iri (n=40)	Nal-iri (n=151)	Nal-iri+5-FU/LV (n=117)
Median OS (95% confidence interval)	5.2 (--, --)	4.9 (4.2, 5.6)	6.1 (4.76, 8.87)
Proportion of patients alive at:			
• 3 months, n (%)	30 (75.0)	--	--
• 6 months, n (%)	17 (42.5)	--	--
• 12 months, n (%)	10 (25.0)	--	30 (25.6)
Median PFS (95% confidence interval)	2.4 (--, --)	2.7 (2.1, 2.9)	3.1 (2.69, 4.17)
Objective response rate, n (%)	3 (7.5)	9 (6.0)	9 (7.7)

OS=overall survival; PFS=progression-free survival
-- Not reported
*For the NAPOLI-1 trial, analyses are for ITT population, median OS and median PFS are the Kaplan-Meier estimate of the median PFS time
Source: CS, executive summary and adapted from Tables 16, 18, 22 and 29 and Wang-Gillam 2015 paper

Safety data, in particular, from this study does however add supporting evidence for toxicity associated with nal-iri. A total of 27 patients (67.5%) were able to maintain a dose of 120 mg/m^2 throughout their entire treatment course in the NCT00813163 study, and the majority of patients (75.0%) discontinued due to disease progression rather than toxicity. In the NAPOLI-1 trial, the company noted that certain gastrointestinal AEs and alopecia, hypoalbuminemia, hypomagnesaemia, hypokalaemia and asthenia were more commonly reported in the nal-iri monotherapy arm, while myelosuppression and stomatitis were more common in the nal-iri+5-FU/LV arm. The frequency of severe TEAEs (Grade 3 or higher) was generally also higher in the nal-iri monotherapy arm than nal-iri + 5-FU arm (with the exception of neutropenia, white cell count decreased, neutrophil count decreased, and fatigue). This, the company argues, suggests that the more frequent administration of nal-iri

(every 2 weeks compared with every 3 weeks) with a lower dose, as in the nal-iri+5-FU/LV combination arm compared with the nal-iri monotherapy arm, results in fewer and less severe gastrointestinal AEs. Clinical advice to the ERG is that a similar pattern is observed with treatment with non-liposomal irinotecan monotherapy and FOFIRI.

There were notable differences in the incidence of AEs in the NCT00813163 study and the NAPOLI-1 trial when only the nal-iri monotherapy arms were compared. In particular, in the NCT00813163 study there was an increase in the incidence of the following AEs when compared with AE data from the nal-iri monotherapy arm of NAPOLI-1 trial (Table 73): leukopenia (+33.1%), fatigue (+26.2%), neutropenia (+25.0%), alopecia (+20.3%) and 'weight decreased' (+18.8%). There was an increase in the incidence of the following grade ≥3 AEs when compared with AE data from the nal-iri monotherapy arm of NAPOLI-1 trial (Table 74): neutropenia (+24.6%) and leukopaenia (+22.3%). Possible explanations for these differences between studies include differences in the baseline characteristics, particularly the greater proportion of Asians, patients with KPS ≤70 and previous use of gemcitabine combination therapy in the NCT00813163 study than in the NAPOLI-1 trial. The fact that patients were not tested for *UGT1A1*28* prior to receiving treatment in NCT00813163 may also have been a factor although the authors of the non-randomised study note there was no correlation between *UGT1A1* polymorphisms with either haematologic AEs (myelosuppression) or non-haematologic AEs (including gastrointestinal disorders). The sample size of the NCT00813163 study was also relatively small and this could also explain why some AEs appear to be more common in this study than in the NAPOLI-1 trial.

Table 73 Adverse events occurring in ≥10% of subjects in NCT00813163 and a comparison of the incidence of the same adverse events in the NAPOLI-1 trial*

Adverse Event n (%)	NCT00813163	NAPOLI-1	
	Nal-iri (n=40)	Nal-iri (n=147)	Nal-iri + 5-FU/LV (n=117)
Diarrhoea	30 (75.0)	103 (70.1)	69 (59.0)
Fatigue	25 (62.5)	54 (36.7)	47 (40.2)
Nausea	24 (60.0)	89 (60.5)	60 (51.3)
Vomiting	23 (57.5)	80 (54.4)	61 (52.1)
Anorexia / decreased appetite†	23 (57.5)	72 (49.0)	52 (44.4)
Alopecia	17 (42.5)	32 (21.8)	16 (13.7)
Neutropenia	16 (40.0)	22 (15.0)	27 (23.1)
Abdominal pain	15 (37.5)	50 (34.0)	27 (23.1)
Weight decreased	15 (37.5)	29 (19.7)	20 (17.1)
Leukopenia	15 (37.5)	6 (4.1)	12 (10.3)
Anaemia	13 (32.5)	48 (32.7)	44 (37.6)

*For the NAPOLI-1 trial, analyses are for the safety population
† Reported as anorexia in the NCT00813163 study and decreased appetite in the NAPOLI-1 trial
Source: CS, Table 31 and Table 32

Table 74 Adverse events of grade 3 or higher occurring in ≥10% of subjects in the NCT00813163 study and the NAPOLI-1 trial*

Adverse Event n (%)	NCT00813163	NAPOLI-1	
	Nal-iri (n=40)	Nal-iri (n=147)	Nal-iri + 5-FU/LV (n=117)
Any treatment-emergent adverse event ≥grade 3	26 (65.0)	112 (76.2)	90 (76.9)
Neutropenia	12 (30.0)	8 (5.4)	17 (14.5)
Leukopenia	10 (25.0)	4 (2.7)	1 (0.9)
Fatigue/asthenia†	8 (20.0)	19 (12.9)	28 (23.9)
Diarrhoea	6 (15.0)	31 (21.1)	15 (12.8)
Anaemia	6 (15.0)	16 (10.9)	11 (9.4)
Abdominal pain	6 (15.0)	12 (8.2)	8 (6.8)
Hyponatraemia	6 (15.0)	9 (6.1)	3 (2.6)
Gamma-glutamyl transferase elevated	5 (12.5)	--	--
Nausea	4 (10.0)	20 (13.6)	13 (11.1)
Anorexia	4 (10.0)	--	--

*For the NAPOLI-1 trial, analyses are for the safety population
†Data reported for fatigue/asthenia combined in the NCT00813163 study but reported separately for the NAPOLI-1 trial; hence for the NAPOLI-1 trial the data have been combined by adding the two categories together in this table

11.9 Survival modelling: ERG survival extrapolation

Overall survival in the 5-FU/LV arm of the NAPOLI-1 trial was extrapolated using a simple 2-parameter exponential model fitted to the K-M events occurring between 11.3 and 34 months. The last event at 34.9 months was excluded as too unstable (95% confidence interval includes zero).

The following exponential function was applied to the 5-FU/LV arm from 28.4 months onwards:

OS = EXP(-(0.063822 * months + 1.2008081))

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11.10 ERG changes to submitted company model

All revisions are activated by a logic switch with 0 = unchanged, 1 = apply ERG modification

Logic switches are indicated by range variables Mod_n = 1 – 13

A menu of revisions/Mod numbers appears on the 'CEA' worksheet together with summary results as used to transfer to the ERG report.

Model Revision	Binary Switch	Sheet	Implementation Instructions
Table 25-R1. 5-FU/LV Pre-progression time on treatment curve for oxaliplatin+5-FU/V dosing curve	Mod_11	Log-normal	Replace formula in cell AB12 by =IF(Mod_12=0,(MIN(1-NORM.S.DIST((LN($Q12*84/365.25)-P_3231)/P_3232, TRUE),AD12)),(MIN(1-NORM.S.DIST((LN($Q12*84/365.25)-P_3131)/P_3132, TRUE),T12))) copy formula in cell AB12 to range AB13:AB533
Table 27-R1. ERG OS naliri+5-FUV/LV	Mod_2	Log-normal	Replace formula in cell Z12 by =IF(Mod_2=0,(1-NORM.S.DIST((LN($Q12*84/365.25)-P_3221)/P_3222, TRUE)),'ERG OS'!W5) copy formula in cell Z12 to range Z13:Z533
Table 27-R1. ERG PFS naliri+5-FUV/LV	Mod_2	Log-normal	Replace formula in cell Y12 by =IF(Mod_2=0,(1-NORM.S.DIST((LN($Q12*84/365.25)-P_3211)/P_3212, TRUE)),'ERG OS'!AC5) copy formula in cell Y12 to range Y13:Y533
Table 27-R1. ERG pre-progression on treatment nal-iri+5-FUV/LV	Mod_2	Log-normal	Replace formula in cell W12 by =IF(Mod_2=0,(MIN(1-NORM.S.DIST((LN($Q12*84/365.25)-P_3231)/P_3232, TRUE),Y12)),'ERG OS'!AF5) copy formula in cell W12 to range W13:W533
Table 27-R1. ERG OS 5-FUV/LV	Mod_2	Log-normal	Replace formula in cell U12 by =IF(Mod_2=0,(1-NORM.S.DIST((LN($Q12*84/365.25)-P_3121)/P_3122, TRUE)),'ERG OS'!AA5) copy formula in cell U12 to range U13:U533
Table 27-R1. ERG PFS 5-FUV/LV	Mod_2	Log-normal	Replace formula in cell T12 by =IF(Mod_2=0,(1-NORM.S.DIST((LN($Q12*84/365.25)-P_3111)/P_3112, TRUE)),'ERG OS'!AD5) copy formula in cell T12 to range T13:T533
Table 27-R1. ERG pre-progression on treatment 5-FUV/LV	Mod_2	Log-normal	Replace formula in cell R12 by =IF(Mod_2=0,(MIN(1-NORM.S.DIST((LN($Q12*84/365.25)-P_3131)/P_3132, TRUE),T12)),'ERG OS'!AG5) copy formula in cell R12 to range R13:R533
R2. Full dose intensity 5-FU/LV	Mod_3	Control	Replace formula in cell I18 by =IF(Mod_3=0,95%,100%) Replace formula in cell J18 by =IF(Mod_3=0,95%,100%)
R2. Full dose intensity Nal-iri+5-FU/LV	Mod_3	Control	Replace formula in cell C18 by =IF(Mod_3=0,85%,100%) Replace formula in cell D18 by =IF(Mod_3=0,85%,100%) Replace formula in cell E18 by =IF(Mod_3=0,85%,100%)
R2. Full dose	Mod_3	Control	Replace formula in cell F18 by =IF(Mod_3=0,85%,100%)

Model Revision	Binary Switch	Sheet	Implementation Instructions
intensity Oxaliplatin+ 5-FU/LV			Replace formula in cell G18 by =IF(Mod_3=0,85%,100%) Replace formula in cell H18 by =IF(Mod_3=0,85%,100%)
R2. Full dose intensity 5-FU/LV	Mod_3	Input - Cost	Replace formula in cell E9 by =Control!I18 Replace formula in cell F9 by =Control!J18
R2. Full dose intensity Nal-iri+5-FU/LV	Mod_3	Input - Cost	Replace formula in cell H9 by =Control!C18 Replace formula in cell I9 by =Control!D18 Replace formula in cell J9 by =Control!E18
R2. Full dose intensity Oxaliplatin+ 5-FU/LV	Mod_3	Input - Cost	Replace formula in cell L9 by =Control!F18 Replace formula in cell M9 by =Control!G18 Replace formula in cell N9 by =Control!H18
R3. ERG BSA	Mod_5	Control	Replace formula in cell C8 by =IF(Mod_5=0,1.79,1.795)
R3. ERG BSA	Mod_5	Control	Replace formula in cell D8 by =IF(Mod_5=0,1.79,1.795)
R3. ERG BSA	Mod_5	Parameters	Replace formula in cell D10 by =Control!C8 OR Replace formula in cell D10 by =Control!D8
R4. ERG drug acquisition costs 5-FU/LV	Mod_4	Input – Cost	Replace formula in cell E19 by =IF(AND(Mod_4=0,Mod_3=1),E18+F8,0)+(IF(AND(Mod_4=1,Mod_3=1),Control!X16,0)+ IF(AND(Mod_4=1,Mod_3=0),Control!X16,0)+IF(AND(Mod_4=0,Mod_3=0),E18+F18,0))
R4. ERG drug acquisition costs nal-iri+5-FU/LV	Mod_4	Input – Cost	Replace formula in cell H19 by =IF(AND(Mod_4=0,Mod_3=1),H18+I18+J18,0)+(IF(AND(Mod_4=1,Mod_3=1),Control!R16,0)+ IF(AND(Mod_4=1,Mod_3=0),Control!R16,0)+IF(AND(Mod_4=0,Mod_3=0),H18+I18+J18,0))
R4. ERG drug acquisition costs oxaliplatin+5-FU/LV	Mod_4	Input – Cost	Replace formula in cell L19 by =IF(AND(Mod_4=0,Mod_3=1),L18+M18+N18,0)+(IF(AND(Mod_4=1,Mod_3=1),Control!U16,0)+ IF(AND(Mod_4=1,Mod_3=0),Control!U16,0)+IF(AND(Mod_4=0,Mod_3=0),L18+M18+N18,0))
R5. ERG Post progression	Mod_6	Input - Cost	Replace formula in cell BV9 by =IF(Mod_6=0,62%,100%)

Model Revision	Binary Switch	Sheet	Implementation Instructions
costs 5-FU/LV			
R5. ERG Post progression costs nal-iri+5-FU/LV and oxaliplatin+5-FU/LV	Mod_6	Input - Cost	Replace formula in cell BW9 by =IF(Mod_6=0,69%,100%)
R5. ERG Post progression costs 5-FU/LV	Mod_6	Input - Cost	Replace formula in cell CL9 by =IF(Mod_6=0,CL7*CL8,0)
R5. ERG Post progression costs nal-iri+5-FU/LV	Mod_6	Input - Cost	Replace formula in cell CM9 by =IF(Mod_6=0,CM7*CM8,0)
R5. ERG Post progression costs oxaliplatin+5-FU/LV	Mod_6	Input - Cost	Replace formula in cell CN9 by =IF(Mod_6=0,CN7*CN8,0)
R6. ERG health state utilities (pre-progression)	Mod_1	Parameters	Replace formula in cell D110 by =IF(Mod_1=0,0.742,0.671)
R6. ERG health state utilities (post-progression)	Mod_1	Parameters	Replace formula in cell D111 by =IF(Mod_1=0,0.671,0.6)
R7. ERG terminal disutility 5-FU/LV	Mod_10	Input – Utility	Replace formula in cell C12 by =IF(Mod_10=0,Parameters!$D$111,Parameters!$D$111-J20)
R7. ERG terminal disutility nal-iri+5-FU/LV	Mod_10	Input – Utility	Replace formula in cell D12 by =IF(Mod_10=0,Parameters!$D$111,Parameters!$D$111-J20)
R7. ERG terminal disutility oxiplatin+5-FU/LV	Mod_10	Input – Utility	Replace formula in cell E12 by =IF(Mod_10=0,Parameters!$D$111,Parameters!$D$111-J20)
Minor Issues	**Binary Switch**	**Sheet**	**Implementation Instructions**
ERG 5-FU dose	Mod_13	Input – Cost	Replace formula in cell M8 by =IF(Mod_13=0,1000,2400)
ERG 5-FU dose	Mod_13	Control	Replace formula in cell G16 by =IF(Mod_13=0,1000,2400)
Terminal Care Costs	Mod_7	Input - Cost	Replace formula in cell CH9 by =IF(Mod_7=0,(CH7+CH8),terminalcostERG)
Pharmacist costs	Mod_8	Input – Cost	Replace formula in cell E13 by =IF(Mod_8=0,E7*E11*E12,E7*E11*E12+11) Replace formula in cell I13 by =IF(Mod_8=0,I7*I11*I12,I7*I11*I12+11)

Model Revision	Binary Switch	Sheet	Implementation Instructions
			Replace formula in cell M13 by =IF(Mod_8=0,M7*M11*M12,M7*M11*M12+11)
Pharmacist costs	Mod_8	Control	Replace formula in cell S9 by =IF(Mod_8=0,admincost_n5L_5FU,admincost_n5L_5FU+11) Replace formula in cell V9 by =IF(Mod_8=0,admincost_o5L_5FU,admincost_o5L_5FU+11) Replace formula in cell X9 by =IF(Mod_8=0,admincost_5L_5FU,admincost_5L_5FU+11)
Infusion disconnection costs (Nurse visit)	Mod_9	Input - Cost	Replace formula in cell AD8 by =IF(Mod_9=1,Parameters!$D$42*0.5+nurse90,Parameters!$D$42*0.5+Parameters!$D$43) Replace formula in cell AG8 by =IF(Mod_9=1,Parameters!$D$42*0.5+nurse90,Parameters!$D$42*0.5+Parameters!$D$43) Replace formula in cell AJ8 by =IF(Mod_9=1,Parameters!$D$42*0.5+nurse90,Parameters!$D$42*0.5+Parameters!$D$43)
ERG Adverse event costs	Mod_12	Input – Cost	Replace formula in cell A07 by =IF(Mod_12=0,Anaemia,405.47) Replace formula in cell AO9 by =IF(Mod_12=0,AbdominalPain,752.1) Replace formula in cell AO10 by =IF(Mod_12=0,Diarrhoea,2739.9) Replace formula in cell AO11 by =IF(Mod_12=0,Nausea,2739.9) Replace formula in cell AO12 by =IF(Mod_12=0,Vomiting,2739.9) Replace formula in cell AO13 by =IF(Mod_12=0,Fatigue,1848)

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Pegylated liposomal irinotecan hydrochloride trihydrate for treating pancreatic cancer after gemcitabine

You are asked to check the ERG report from Liverpool Reviews and Implementation Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Friday 8 July 2016** 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 Health State Utility Values

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.5.5 Health State Utility values, Pages 112 – 113 The health state utility values in the company model are the same as the ones that were preferred by the ERG in the appraisal of nab-paclitaxel for first line pancreatic cancer (TA360). The ERG considers that utility values derived from a first-line patient population are likely to overstate patient quality of life when applied to a second-line patient population. The ERG failed to recognise that the patient population that would be considered for second line chemotherapy and therefore nal-iri, **would only be those patients considered fit enough for further treatmen**t (<40% of patients who have progressed following gemcitabine –based therapy according to KOL opinion). The ERG failed to take account of the evidence that the baseline Karnofsky performance status scores (KPS) of patients in NAPOLI-1 (Table 14 of CS) are in line with those of first line pancreatic cancer patients in study	Take out section "5.5.5 Health state utility values" of the ERG report and revise the ERG cost-effectiveness model so it reverts to the health state utility values of the CS. Revise the ERG cost-effectiveness results to reflect this change (Tables 58 and Table 59). Other sections of the ERG report that refer to these changes should be revised accordingly.	The ERG amendment of the health state utility values does not take into account the characteristics of adult patients who have progressed following gemcitabine-based therapy who would be considered fit enough for further chemotherapy treatment and it does not take into account the evidence base on the performance status of this population	This is not a factual inaccuracy. The ERG considers the health state utility values presented by the company to overestimate the HRQoL for second-line patients with pancreatic cancer. The ERG considers the use of the progressed disease health state utility value used in the appraisal of nab-paclitaxel (TA360) to be a more suitable reflection of the progression-free state in second-line patients. The value for progressed disease (0.6) was obtained from the RAINBOW trial. Patients in the RAINBOW trial had ECOG scores ranging from 0 to 1, these scores are reflective of patients with KPS scores of 70 or greater (97% of patients in the NAPOLI-1 trial had KPS ≥70). Patients in the RAINBOW trial also had very similar sociodemographic characteristics to patients in the NAPOLI-1 trial. In the RAINBOW study, health state utility values were elicited from respondents using the EQ-5D time-trade off method.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
CA046 in TA360. The inclusion criteria of both of these studies is KPS≥70. The proportion of subjects with baseline KPS of 70, 80, 90 and 100 were 7%, 32%, 44% and 16% respectively in CA046 (TA360). In NAPOLI-1, which the ERG considers to include the relevant patient population for the decision problem of this appraisal, the baseline KPS of 70, 80, 90 and 100 were 6%, 32%, 44% and 15% respectively in the Nal-IRI + 5-FU/LV arm and 8%, 43%, 34% and 14% in the 5-FU/LV arm. Given the performance status of these two populations match so closely it is not unreasonable to assume that the quality of life of these two populations would be very similar.			

Issue 2 Dose intensity reductions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.5.4 Cost of Treatments, Dose Intensity Reductions, Pages 107 – 108 In the company model, it is assumed that, as a result of reduced doses or dose omissions, there is a corresponding reduction in drug acquisition costs. Based on data from the NAPOLI-1 trial, the company estimated that, on average, patients prescribed nal-iri+5-FU/LV and 5-FU/LV would receive 85% and 95% respectively of the anticipated licensed dose. The revised ERG model assumes there would be absolutely no reductions in acquisition costs as a result of these dose reductions due to the inability of NHS centres to be able to plan for these dose changes. The ERG provides **no evidence** as to why it would not be possible for NHS centres to realise **any** savings as a result of pro-rata reductions in drug costs in these circumstances.	Amend section "5.5.4 Cost of Treatments, Dose Intensity Reductions" of the ERG report and revise the ERG cost-effectiveness model so that it takes into account the reduced dosing of nal-iri that reflects the actual dosing in NAPOLI-1.	The ERG do not provide any evidence to support their amendment of the economic model.	This is not a factual inaccuracy. Upon receiving clinical advice, the ERG did not consider the pro-rata reductions in dosing intensity and reductions in subsequent costing for all treatment groups to be representative of clinical practice in an NHS setting. The company does not provide any evidence from UK clinical practice to support their dose reduction assumptions. Furthermore, the company applies a cost reduction to reflect the reduction in dosing intensity to LV across all treatment groups. There is no evidence in the clinical trial protocol or company clarification response to suggest that LV doses had been reduced in the NAPOLI-1 trial.

Issue 3 Body surface area and acquisition of generic drugs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.5.4 Cost of Treatments, Body surface area (BSA) and acquisition of generic drugs, Pages 108 – 109 In their revised economic model the ERG takes into account the range of vial sizes available for each of the generic drugs, the ERG first used a normal distribution for BSA to estimate the proportion of patients requiring a given dose. The **optimum** combination of vial sizes for that dose was then determined according to the price per mg of each available vial size. The ERG's revised average cost per dose is the sum of the cost of each dose (**optimised** by available vial sizes) weighted by the proportion of patients expected to receive each dose. The ERG seems to be assuming that there would be the **optimal** combination of vial sizes in **all patients** so as to minimise the acquisition cost of each dose. The ERG provides no evidence that this does happen in clinical practice.	Amend "5.5.4 Cost of Treatments, Body surface area and acquisition of generic drugs" of the ERG report and revise the ERG cost-effectiveness model to reflect that fact that it is very unlikely that there would **always** be the optimal combination of vial sizes in UK clinical practice.	The ERG do not provide any evidence to support their amendment of the economic model.	This is not a factual inaccuracy. The ERG does not consider the use of the smallest available vial sizes for all drugs (as used by the company in its model) to be representative of clinical practice in an NHS setting. In clinical practice, it is likely that technicians or pharmacists preparing infusions would use different vial sizes to obtain the required dose for administration.

Issue 4 Description of incidence of adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, page 11, paragraph 2 The following wording is misleading given the evidence: "Safety results are reported in the CS for the safety population (n=251), i.e. patients who received at least one dose (including partial dose) of study medication. In the nal-iri arm, the incidence of AEs was higher than in the 5-FU/LV arm."	Replace text with: "Safety results are reported in the CS for the safety population (n=251), i.e. patients who received at least one dose (including partial dose) of study medication. In the nal-iri arm, the incidence of AEs was comparable with that in the 5-FU/LV arm."	This current wording is misleading, as the incidence of TEAEs is 99.1% for nal-iri + 5-FU/LV and 98.5% with 5-FU/LV	The ERG concurs this is misleading. Text modified to: "Safety results are reported in the CS for the safety population (n=251), i.e. patients who received at least one dose (including partial dose) of study medication. In the nal-iri arm, the incidence of all treatment emergent AEs was similar between arms but treatment-related AEs, grade ≥3 AEs, serious AEs and dose modifications were higher than in the 5-FU/LV arm."

Issue 5 ERG data reporting errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.3, second paragraph Error in following section: "This may explain why a greater proportion of patients withdrew from the 5-FU/LV arm (10.9%) before treatment than from the nal-iri+5-FU/LV arm (1.7%)."	Replace with: "This may explain why a greater proportion of patients withdrew from the 5-FU/LV arm (11.8%) before treatment than from the nal-iri+5-FU/LV arm (1.7%)."	Error	This is not a factual inaccuracy. In the company's clarification response (A5, Table 4) the number (%) of patients who withdrew before being treated is stated to be 13/119 (10.9).
Section 1.3, page 13, first paragraph Error in following section: "in the PP population was relatively small, indicating that only 56% of the nal-iri+5-FU/LV arm (66/117 patients) and 60% of the 5-FU/LV arm (71/117) received treatment for at least 6 weeks"	Replace with: "in the PP population was relatively small, indicating that only 56% of the nal-iri+5-FU/LV arm (66/117 patients) and 60% of the 5-FU/LV arm (71/119) received treatment for at least 6 weeks"	Error	"71/117" for the 5-FU/LV arm is a typographical error by the ERG. Text amended as proposed by the company.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.2.2, sixth paragraph Error in following section: "The most commonly used second-line treatments (not necessarily post-gemcitabine) for patients with metastatic pancreatic cancer were capecitabine monotherapy (27.6%), oxaliplatin + capecitabine (24.1%) and gemcitabine (10.3%)."	Replace with: "The most commonly used second-line treatments (not necessarily post-gemcitabine) for patients with metastatic pancreatic cancer were capecitabine monotherapy (27.6%), oxaliplatin + 5-FU/LV (24.1%) and gemcitabine (10.3%)."	Error	"Oxaliplatin+capecitabine" is a typographical error by the ERG. Text amended as proposed by the company.
Section 3.1. Error in following section: "In the NAPOLI-1 trial, patients were allowed to have received previous gemcitabine therapy in any setting, i.e. in the adjuvant or neoadjuvant setting (12.2%) first-line (56.1%) or second- line or later (31.7%) treatment for metastatic pancreatic cancer."	Replace with: "In the NAPOLI-1 trial, patients were allowed to have received previous gemcitabine therapy in any setting, i.e. in the adjuvant or neoadjuvant setting ([redacted]%) first-line ([redacted] %) or second- line or later ([redacted] %) treatment for metastatic pancreatic cancer."	Error	The proportions cited by the ERG are all calculation errors. Text amended as proposed by the company. The ERG also amended the proportions on page 38
Section 4.2.4, Trial population table, box 3, fourth bullet Error in following section: "patients who ml inclusion/exclusion criteria"	Replace with: "patients who met all inclusion/exclusion criteria"	Error	"ml" is a typographical error by the ERG. Text amended as proposed by the company.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 7, page 41 OS row reads “ITT” in the rightmost cell	In the OS row, the last cell on the right should read “ITT, PP, and other sensitivity analyses”	Error	The ERG only stated “ITT” since the populations for the sensitivity analyses are reported in Table 11 but for completeness and clarity, reference to “PP, and other sensitivity analyses” can also be added to Table 7. Text amended as proposed by the company.
Section 4.2.5, first paragraph Error in following section: “This may explain why a much larger proportion of patients withdrew from the 5-FU/LV arm (13/119, 10.9%) before being treated than from the”	Replace with: “This may explain why a much larger proportion of patients withdrew from the 5-FU/LV arm (14/119, 11.8%) before being treated than from the”	Error	This is not a factual inaccuracy. In the company’s clarification response (A5, Table 4) the number (%) of patients who withdrew before being treated is stated to be 13 (10.9).
Section 4.2.6., page 46, second paragraph Error in following section: “was relatively small, indicating that only 56% of the nal-iri+5-FU/LV arm (66/117 patients) and 60% of the 5-FU/LV arm (71/117) received treatment for at least 6 weeks and did not violate”	Replace with “was relatively small, indicating that only 56% of the nal-iri+5-FU/LV arm (66/117 patients) and 61% of the 5-FU/LV arm (71/117) received treatment for at least 6 weeks and did not violate”	Error	n=117 in the 5-FU/LV arm is a typographical error by the ERG (and should read “119”). Text amended partially as proposed by the company. The proportion of patients is however 60% (71/119) as stated by the ERG and not 61% as stated by the company.

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr><td>Section 4.4.1, page 58, second paragraph

Error in following section:

“common (>3%) serious TEAEs for patients treated with nal-iri+5-FU/LV were vomiting (11.9%), diarrhoea (6.0%), abdominal pain (4.3%),”</td><td>Replace with:

“common (>3%) serious TEAEs for patients treated with nal-iri+5-FU/LV were vomiting (9.4%), diarrhoea (6.0%), abdominal pain (4.3%),”</td><td>Error</td><td>“11.9%” is a transcription error by the ERG. Text amended as proposed by the company.</td></tr>
<tr><td>Error in Table 23
<table><tr><th>Assessment</th><th>nal-iri+5-FU/LV</th><th>5-FU/LV</th></tr><tr><td>Baseline</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>12 weeks</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>30 days post follow-up</td><td></td><td>[redacted]</td></tr></table></td><td>Replace with
<table><tr><th>Assessment</th><th>nal-iri+5-FU/LV</th><th>5-FU/LV</th></tr><tr><td>Baseline</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>12 weeks</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>30 days post follow-up</td><td></td><td>[redacted]</td></tr></table></td><td>Error</td><td>The ERG took the baseline total from Table 7-2 of the CSR which does not tally with the baseline totals in Table 7-16 of the CSR. The ERG has amended this table using only data from Table 7-16 of the CSR (and which match the data proposed by the company).</td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.7.1, first paragraph Error in following section: “The NAPOLI-1 trial is also the largest trial (n=266) and the Yoo trial of mFOLFOX is the smallest (n=61). In all of the trials, patients had received prior gemcitabine but the extent to which this was monotherapy and/or combination therapy varied widely; only 9.8% of patients received monotherapy in the trial of mFOLFOX reported by Yoo, compared to 100% of patients receiving OFF in the CONKO-003 trial.”	Replace with: “The NAPOLI-1 trial is also the largest trial (n=417, and n=236 for the trial arms considered) and the Yoo trial of mFOLFOX is the smallest (n=61). In all of the trials, patients had received prior gemcitabine but the extent to which this was monotherapy and/or combination therapy varied widely; only 9.8% of patients received monotherapy in the trial of mFOLFOX (6.7% in the mFOLFOX arm of the trial) reported by Yoo, compared to 100% of patients receiving OFF in the CONKO-003 trial.”	Error and more specific data added	“n=266” is a typographical error by the ERG. Text amended as proposed by the company.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.7.2, first paragraph Error in following section: "of patients had previously had curative surgery with nal-iri+5-FU/LV in the NAPOLI-1 trial (36.1%) as with mFOLFOX in the Yoo trial (36.7%) but more patients treated with OFF in the CONKO-003 trial had had curative surgery (44.7%). At least 88% of patients had metastatic disease in any given trial, and relatively similar proportions of patients treated with nal-iri+5-FU/LV in the NAPOLI-1 trial had liver metastasis (64.1%) as those treated with mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial (62.9%);"	Replace with: "of patients had previously had curative surgery with nal-iri+5-FU/LV in the NAPOLI-1 trial (34.2%) as with mFOLFOX in the Yoo trial (36.7%) but more patients treated with OFF in the CONKO-003 trial had had curative surgery (44.7%). At least 88% of patients had metastatic disease in any given trial, and relatively similar proportions of patients treated with nal-iri+5-FU/LV in the NAPOLI-1 trial had liver metastasis (64.1%) as those treated with mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial (65.0%);"	Error	"36.1%" is a transcription error by the ERG. Text amended as proposed by the company. For SWOG S1115 the proportion is taken from the Clinical.Trials.gov website (https://clinicaltrials.gov/ct2/show/NCT01658943), 39/62 = 62.9% as stated by the ERG in its report. Table 25 footnote amended for clarity.
Section 4.7.2, first paragraph Error in following section: "However, the median duration of previous gemcitabine therapy was much higher in the NAPOLI-1 trial for nal-iri+5-FU arm (22.1 months) than in the OFF arm of the CONKO-003 trial (4.6 months)."	Replace with: "However, the median duration of previous gemcitabine therapy was higher in the NAPOLI-1 trial for nal-iri+5-FU arm (5.1 months) than in the OFF arm of the CONKO-003 trial (4.6 months)."	Error. It was 22.1 weeks, not months, which equals 5.1 months and therefore not 'much' higher.	"22.1 months" is a transcription error by the ERG. Text amended as proposed by the company. Text also amended in Table 25 of ERG report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Appendix section 11.4 Quality assessment of randomised controlled trials included in the company submission – table Error in following section: "The ERG notes that a greater proportion of patients enrolled in the 5-FU/LV arm (10.9%) never received the treatment they were allocated compared with the nal-iri+5-FU/LV arm (1.7%)"	Replace with: "The ERG notes that a greater proportion of patients enrolled in the 5-FU/LV arm (11.8%) never received the treatment they were allocated compared with the nal-iri+5-FU/LV arm (1.7%)"	Transcription error	This is not a transcription error. In the company's clarification response (A5, Table 4) the number (%) of patients who withdrew before being treated is stated to be 13 (10.9).
Appendix section 11.6.dose discontinuation Error in following section: "As reported in Table 14.3.2.5.1 of the CSR, the proportions in the nal-iri+5-FU/LV arm for infections and infestations were 5.1% and 4.3% respectively."	Replace with: "As reported in Table 14.3.2.5.1 of the CSR, the proportions in the nal-iri+5-FU/LV arm for gastrointestinal disorders, infections and infestations were 5.1% and 4.3% respectively."	Omission of dose discontinuation reason.	"gastrointestinal disorders" omitted in error by the ERG. Text amended as proposed by the company.

Issue 6 AE reporting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, fourth paragraph The following sentence is misleading given the evidence: "In the nal-iri arm, the incidence of AEs was higher than in the 5-FU/LV arm."	Remove sentence.	TEAEs were reported by 99.1% of patients with nal-iri + 5-FU/LV and 98.5% of patients with 5-FU/LV, which is almost identical.	See response to Issue 4.
Section 4.8, third paragraph The following sentence is misleading given the evidence: "Furthermore, despite an increase in TEAEs compared with 5-FU/LV, particularly in relation to myelosuppression and gastrointestinal disorders, there was no apparent deterioration in HRQoL with nal-iri + 5-FU/LV."	Replace sentence with: "Furthermore, despite an increase in myelosuppression and gastrointestinal disorders, there was no apparent deterioration in HRQoL with nal-iri + 5-FU/LV."	TEAEs were reported by 99.1% of patients with nal-iri + 5-FU/LV and 98.5% of patients with 5-FU/LV, which is almost identical.	The ERG concurs this is misleading. Text amended as proposed by the company.

Issue 7 Quality of life reporting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.2, fifth paragraph The following statement is confusing: "Comparative EORTC-QLC-30 data after 12 weeks were not reported"	Remove this part of the sentence	These data are reported in the CSR, which has been used multiple times throughout the ERG report.	This is a typographical error. The text should read: "Comparative EORTC-QLC-30 data at 30 days post follow-up were not reported" Text also added to end of Section 4.5.1 The ERG could not locate the data at 30 days post follow-up in the CSR

Issue 8 Risk of bias of open-label trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.3, second paragraph There is no explanation of the reason for an open label design in the following: "There is a risk of bias arising from the fact that it was an open-label trial."	Replace with: "There is a risk of bias arising from the fact that it was an open-label trial; however, blinding of study treatment was not feasible due to different dosing schedules in the different arms, and using a double-dummy design would result in an unacceptable number of infusions lasting up to 46 hours."	Nowhere in the report is it reflected that the open-label design of the trial was a necessity.	The ERG concurs with the company. Text amended as proposed by the company.
Section 1.3, second paragraph The following sentence does not consider all the possible effects of the trial design: "The open-label nature of the trial, combined with a lack of independent assessment of disease progression, favouring nal-iri + 5-FU/LV over 5-FU/LV."	Replace with: "The open-label nature of the trial, combined with a lack of independent assessment of disease progression, may also have introduced bias into the assessment of disease progression."	These factors may not favour nal-iri + 5-FU/LV over 5-FU/LV, and could favour 5-FU/LV over nal-iri + 5-FU/LV.	The ERG concurs with the company. Text amended as proposed by the company.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.5 first paragraph There is no explanation of the reason for an open label design in the following: "The ERG considers that the greatest risks of bias occur from the fact that the NAPOLI-1 trial was an open-label trial."	Replace with: "The ERG considers that the greatest risks of bias occur from the fact that the NAPOLI-1 trial was an open-label trial. However, blinding of study treatment was not feasible due to different dosing schedules in the different arms, and using a double-dummy design would result in an unacceptable number of infusions lasting up to 46 hours."	Nowhere in the report is it reflected that the open-label design of the trial was a necessity.	The ERG did state in its report: "The company highlights that blinding of study treatment was not feasible due to different dosing schedules in the different arms" Additional text added after this sentence as follows: "In addition, using a double-dummy design would result in an unacceptable number of infusions lasting up to 46 hours."
Section 4.2.5, first paragraph The following sentence does not consider all the possible effects of the trial design: "The open-label nature of the NAPOLI-1 trial may also have introduced bias into the assessment of disease progression, favouring nal-iri + 5-FU/LV over 5-FU/LV."	Replace with: "The open-label nature of the NAPOLI-1 trial may also have introduced bias into the assessment of disease progression."	These factors may not favour nal-iri + 5-FU/LV over 5-FU/LV, and could favour 5-FU/LV over nal-iri + 5-FU/LV.	The ERG concurs with the company. Text amended as proposed by the company.

Issue 9 Meaning unclear

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.2.2, sixth paragraph The following paragraph is unclear: "Clinical advice received by the ERG is that gemcitabine is most commonly used for patients previously treated with FOLFIRINOX. It is not commonly used for patients who have previously been treated with gemcitabine but may be used again in some instances where patients have been disease-free after completing treatment with gemcitabine for a relatively long time (e.g. 12 months)."	Remove or revise	The meaning is unclear, as clinical advice to the company was that gemcitabine would not be used on patients previously treated with gemcitabine.	Clinical advice to the ERG was that gemcitabine may be used in the adjuvant or neoadjuvant setting and used again if patients had been disease-free for a relatively long period of time. Nevertheless, the ERG has removed "It is not commonly used for patients who have previously been treated with gemcitabine but may be used again in some instances where patients have been disease-free after completing treatment with gemcitabine for a relatively long time (e.g. 12 months)" since "Clinical advice received by the ERG is that gemcitabine is most commonly used for patients previously treated with FOLFIRINOX" suffices to convey the point being made.

Issue 10 Omission of facts/opinions from the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.2, first paragraph The following statement suggests that it was the company's decision to consider 5-FU/LV as a comparator in the company submission whereas the company considered 5-FU/LV as a comparator because it was included in the NICE scope for this appraisal: "The company considered 5-FU/LV to be a relevant comparator (but, as explained in Section 3.3 of this ERG report, this decision is disputed by the ERG)."	Replace with: "The company compared nal-iri + 5-FU/LV with 5-FU/LV as it was the only head-to-head data available and was also included in the NICE scope. The company highlighted that oxaliplatin + 5-FU/LV was a more relevant comparator as it is much more widely used in clinical practice, and the ERG agree with this."	The reason that 5-FU/LV was included as a comparator was because it was in the NICE scope and there was head-to-head evidence available.	It was assumed by the ERG that the company considered 5-FU/LV to be a relevant comparator since it was the comparator in the NAPOLI-1 trial and evidence for clinical and cost effectiveness was presented for this comparison. The company has not presented an argument in its submission that this is not a relevant comparator although, as recognised in the ERG report, the ERG notes the company considers oxaliplatin+5-FU/LV to be a more relevant comparator. Nevertheless, the ERG has altered the text to the following: "The company's literature search led to the identification of one RCT that was considered to be directly relevant to the decision problem (the NAPOLI-1 trial). This trial compared treatment with nal-iri+5-FU/LV with 5-FU/LV. The company highlighted that oxaliplatin+5-FU/LV was a more relevant comparator as it is much more widely used in clinical practice, and the ERG agrees with this."

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.1.2, second paragraph The following statement does not provide the reason for the exclusion of a study from the systematic review: "The ERG notes that this study was excluded from the company's systematic review."	Replace with: "The ERG notes that this study was excluded from the company's systematic review, because it included nal-iri monotherapy only and was therefore not directly relevant to the decision problem."	This is listed as a reason for exclusion in the company submission in Section 4.1.2 of the main submission document, as well as 2.6 of the appendices. Not including the reason for exclusion implies that it was overlooked in the systematic review.	In Section 11.8 of the ERG report, the ERG states: "This study was excluded from the company's systematic review since it did not include the intervention of interest, nal-iri+5-FU/LV." However, the ERG accepts that, for clarity, it should also have stated this in Section 4.1.2. Text amended as proposed by the company.

Issue 11 Site of metastatic lesions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.3 sixth paragraph The following statement is misleading: "Patients in the 5-FU/LV arm were more likely to have metastatic lesions in sites other than the pancreas compared with patients in the nal-iri + 5-FU/LV arm."	Replace with: "Patients in the 5-FU/LV arm were slightly more likely to have metastatic lesions in sites other than the pancreas compared with patients in the nal-iri + 5-FU/LV arm."	There was a higher proportion of patients with liver (69.7% vs 64.1%), peritoneal (26.9% vs 23.9%) and other (32.8% vs 23.1%) metastases in the 5-FU/LV arm than in the nal-iri + 5-FU/LV arm. There was a higher proportion of patients with distant lymph node (27.4% vs 26.1%) and lung (30.8% vs 30.3%) metastases in the nal-iri + 5-FU/LV arm than in the 5-FU/LV arm.	This is not a factual inaccuracy but the text could have been better worded by the ERG in its original report. Text now reads: "There was a notably higher proportion of patients with "other" metastases in the 5-FU/LV arm than in the nal-iri+5-FU/LV arm (32.8% versus 23.1%); also marginally higher were incidences of liver metastases (69.7% versus 64.1%) and peritoneal metastases (26.9% versus 23.9%) while metastatic lesions of the pancreas were higher in the nal-iri+5-FU/LV arm than in the 5-FU/LV arm (64.1% versus 60.5%)."

Issue 12 Hazard ratios

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.4, eighth paragraph (third paragraph in the Cox proportional hazard modelling section) The following statement requires further clarification: "Consequently, the ERG is of the opinion that HRs are not an appropriate measure of survival benefit for nal-iri + 5-FU/LV versus 5-FU/LV."	Replace with: "Consequently, the ERG is of the opinion that HRs are not an appropriate measure of survival benefit for nal-iri + 5-FU/LV versus 5-FU/LV. However, as in all clinical trials, the statistical methods were pre-specified, and it could not have been predicted that the proportional hazards assumption would be violated."	Clarification	Although the use of Cox proportional hazards was pre-specified, the ERG considers that when designing a trial plans for testing the proportional hazards assumption, and how to analyse data if the assumption is not valid, should also be outlined. The ERG recognises that there are however mixed feelings in the statistical community about this. Some statisticians are of the opinion that after seeing the data, no changes to the planned statistical analyses should be made at all. Therefore, text amended to: "Consequently, the ERG is of the opinion that HRs are not an appropriate measure of survival benefit for nal-iri + 5-FU/LV versus 5-FU/LV. Although the use of Cox PH modelling was pre-specified in the TSAP, and while recognising that one view is that statistical methods should remain unaltered once the data has been seen, the ERG considers that when designing a trial, methods for testing the PH assumption and how to analyse data if the assumption is not valid should also be outlined."

Issue 13 Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.7 Further clarification required	After last sentence add: "Only the arms of relevance from the five trials are discussed in this section (i.e. the nal-iri + 5-FU/LV arm in NAPOLI-1, the OFF arm in CONKO-003, the mFOLFOX6 in PANCREOX, the mFOLFOX6 arm in SWOG S1115, and the mFOLFOX arm in Yoo)."	Clarification	Text added as proposed by the company.

Issue 14 Efficacy outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.7.3, third paragraph Suggest revised groupings of PFS study results for following statement: "RCTs investigating oxaliplatin + 5-FU/LV report a PFS of 2.9 months for OFF in the CONKO-003 trial and between 2.0 months and 3.1 months for mFOLFOX6 (without and with bolus in the SWOG S1115 trial and PANCREOX trial respectively). These results are similar to those reported for nal-iri + 5-FU/LV in the NAPOLI-1 trial (3.1 months). The trial reported by Yoo, however, reports a less impressive PFS for mFOLFOX of only 1.4 months."	Replace with: "RCTs investigating oxaliplatin + 5-FU/LV report a PFS of 2.9 months for OFF in the CONKO-003 trial and 3.1 months for mFOLFOX6 in the PANCREOX trial. These results are similar to those reported for nal-iri + 5-FU/LV in the NAPOLI-1 trial (3.1 months). The SWOG S1115 trial and the trial reported by Yoo, however, report a less impressive PFS for mFOLFOX6 without bolus 5-FU and mFOLFOX, respectively, of only 2.0 months and 1.4 months, respectively."	We believe that 2.0 months for the SWOG S1115 trial is not similar to 3.1 months reported in NAPOLI-1, and should be included with the Yoo trial in reporting a less impressive PFS.	Given the relatively short survival times associated with pancreatic cancer, the ERG concurs the results can also be interpreted as suggested by the company. Text amended as proposed.

Issue 15 Body surface area and acquisition of generic drugs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.5.4 Cost of Treatments, Body surface area (BSA) and acquisition of generic drugs, Page 107 In their revised economic model the ERG uses the specific mean BSA value for patients with gastrointestinal cancer, without providing a rationale for why this value is applicable to pancreatic cancer.	The ERG need to provide a clear evidence based rationale for this amendment or revert back to the method used in the company submission.	The ERG do not provide a rationale or evidence to support their amendment of the economic model.	This is not a factual inaccuracy. The ERG considers pancreatic cancer to be a form of gastrointestinal cancer.

Issue 16 Time on treatment with oxaliplatin+5-FU/LV

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.5.3 Time-to-event data, Time on treatment: oxaliplatin+5-FU/LV, Page 106 The company submission assumes that the time on treatment for patients receiving oxaliplatin+5-FU/LV is equivalent to patients receiving nal-iri+5-FU/LV. The ERG state that this assumption is erroneous but give no rationale as to why. In their revised economic model the ERG assumes that the time on treatment for patients receiving oxaliplatin+5-FU/LV is equivalent to patients receiving 5-FU/LV, however no rationale is provided. It is unlikely that a treatment with an additional agent, oxaliplatin, would have the same time on treatment as 5-FU/LV alone.	Amend "5.5.3 Time-to-event data, Time on treatment: oxaliplatin+5-FU/LV" of the ERG report and revise the ERG cost-effectiveness model to reflect that fact that it is very unlikely that the time on treatment for patients receiving oxaliplatin+5-FU/LV would be equivalent to 5-FU/LV.	The ERG do not provide any evidence to support their amendment of the economic model and it is unlikely that a treatment with an additional agent, oxaliplatin, would have the same time on treatment as 5-FU/LV alone.	This is not a factual inaccuracy. The ERG considers the company's use of the nal-iri+5-FU/LV time on treatment curve to represent time on treatment for oxaliplatin+5-FU/LV to be flawed as it requires a model correction to prevent the proportion of patients receiving oxaliplatin+5-FU/LV to exceed the number of patients in the PFS state. The ERG presents an alternative assumption which does not require an arbitrary model correction to further inform the decision making process.

Issue 17 Errors in Table 24

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Several data errors in Table 24	Please see changes and comments in the table below.	Error	The ERG notes and welcomes suggested changes to the text in the table made by the company (but has not noted any comments). The following changes have been accepted since these were transcription errors / omissions in the ERG report: For NAPOLI-1, n=236 (not n=266) and nal-iri administered over 90 minutes. For CONKO-003, OFF is every 6 weeks (not every 4 weeks). For SWOG S1115, the dose for 5-FU is 2400 mg/m^2 continuously for 46 to 48 hours (not just 46 hours) and for MK2206 the dose is 135mg and this is weekly (not daily). The following change has been rejected: For SWOG S1115, the primary source of data is Clinical.Trials.gov website (https://clinicaltrials.gov/ct2/show/NCT01658943) and here n=120

Characteristic	NAPOLI-1	CONKO-003	PANCREOX	SWOG S1115	Yoo
Design	Phase III, open-label RCT	Phase III, open-label RCT	Phase III, open-label RCT	Phase II, open-label RCT	Phase II, open-label RCT
Recruited, n (dates)	n=236* (2012 to 2013)	n=168 (2004 to 2007)	n=108 (2010 to 2013)	n=113 (2012 to 2015)	n=61 (2007 to 2008)
Follow-up	Not known	54.1 months (median)	4 months (reported in methods)	Every 6 months for up to 3 years (reported in methods)	5.6 months (median)
Country	Multi-centre, multinational trial: North America (20 sites), Europe (30 sites), Asia (12 sites), South America (8 sites) and Oceania (6 sites)	Germany, 16 centres	Canada, 15 centres	US, 534 centres	Asian Medical Center, Seoul, Korea
Intervention	Nal-iri + 5-FU/LV, every 2 weeks: 80 mg/m^2 nal-iri (over 90 min), 400 mg/m^2 LV over 30 minutes, followed by 2400 mg/m^2 5-FU over 46 hours on Day 1	OFF every 6 weeks:† 85 mg/m^2 oxaliplatin on Days 8 and 22, 200 mg/m^2 LV on Days 1, 8, 15 and 22, 5-FU 2,000 mg/m^2 over 24 hours on Days 1, 8, 15 and 22 2 week of rest before next cycle of treatment	mFOLFOX6, every 2 weeks: 85 mg/m^2 oxaliplatin (given as a 2-hour infusion), 400 mg/m^2 LV (given as a 2-hour infusion simultaneous to oxaliplatin), 400 mg/m^2 dose of 5-FU given as bolus followed by 2400 mg/m^2 continuous infusion over 46 hours on Day 1	mFOLFOX6 (without bolus 5-FU) every 2 weeks: 85 mg/m^2 oxaliplatin (given as a 2-hour infusion) and continuous 5-FU (2400 mg/m^2) over 46 hours on Day 1 (no detail about 5-FU dose or administration of LV given)	mFOLFOX every 2 weeks: 85 mg/m^2 oxaliplatin (given as a 2-hour infusion), 400 mg/m^2 LV and 2,000 mg/m^2 5-FU IV over 46hours on Days 1
Comparator	5-FU + LV (6 weekly cycle): LV at a dose of 200 mg/m^2 over 30 minutes followed by 2,000 mg/m^2 5-FU over 24 hours administered on Days 1, 8, 15 and 22 2 week of rest before next cycle of treatment	5-FU + LV (6 weekly cycle):† 200 mg/m^2 LV followed by 2,000 mg/m^2 5-FU over 24 hours on Days 1, 8, 15 and 22 2 week of rest before next cycle of treatment	5-FU + LV (2 weekly cycle): 400 mg/m^2 LV (given as a 2-hour infusion) and 400 mg/m^2 dose of 5-FU given as bolus followed by 2400 mg/m^2 continuous infusion over 46 hours on Day 1	Selumetinib (AZD-6244) + the Akt inhibitor MK-2206: 100 mg AZD-6244 daily on days 1 to 28 plus 135 mg MK2206 weekly on Days 1 to 28 .	mFOLFIRI.3 every 2 weeks: 70 mg/m^2 irinotecan (over 1 hour), 400 mg/m^2 (over 2 hours) and 2000 mg/m^2 5-FU (over 46 h) from Day 1 and another 70 mg/m^2 irinotecan (over 1 hour) at the end of the 5-FU infusion
Previous treatment	Gemcitabine therapy (monotherapy: 45.8% or combination: 54.2%)	First-line gemcitabine monotherapy (100%)	Gemcitabine therapy	Gemcitabine therapy (1-line but no more than 1-line)	Gemcitabine-based1st-line therapy (monotherapy 9.8% or combination 91.2%)

IV=intravenous; KPS=Karnofsky Performance Status; RCT=randomised controlled trial

* NAPOLI-1 was a three-armed trial comparing nal-iri+5-FU/LV with 5-FU/LV and nal-iri monotherapy with 5-FU/LV. Data reported here are for patients in the former comparison

† Included best supportive care according to current palliative care guidelines, i.e. including anti-infective treatment, psychological counselling as needed, biliary stenting or drainage (if indicated), nutritional advice, pain management, and nutritional supplementation

Issue 18 Errors in Table 25

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Several data errors in Table 25	Please see changes and comments in the table below.	Error	The ERG notes and welcomes suggested changes to the text in the table made by the company. The following changes have been accepted since these were transcription errors / omissions in the ERG report: NAPOLI-1, in the nal-iri+5-FU/LV arm, KPS ≤70: 8.5 (not 8.6) and notes the duration of previous gemcitabine therapy it reported was weeks, not months, and has therefore accepted the change for median duration in the nal-iri+5-FU/LV arm and further amended the range and all data for 5-FU/LV arm. The company's comments highlight that the data for SWOG S1115 reported in the abstract do not always match that in the poster. For this reason, the ERG has taken all its data from Clinical.Trials.gov website (https://clinicaltrials.gov/ct2/show/NCT01658943) and here n=120 and so all of the ERG's original percentages reported are correct; all suggested changes by the company for this trial have therefore been rejected.

Characteristic	NAPOLI-1		CONKO-003		PANCREOX		SWOG S1115		Yoo	
Regimen	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=119)	OFF (n=76)	5-FU/LV (n=84)	mFOLFOX6 (n=54)	5-FU/LV (n=54)	mFOLFOX6 (n=62)	AZD-6244 + MK-2206 (n=58)	mFOLFOX (n=30)	mFOLFORI.3 (n=31)
Age, median (Range) years	63 (41, 81)	62 (34, 80)	62 (37, 83)	61 (43, 78)	65 (38, 82)	67 (48, 78)	66 (34, 83)	69 (54, 88)	55 (35, 69)	55 (37, 73)
Sex (% male)	59.0	56.3	52.6	57.1	57.4	55.6	35.0	57.0	66.7	77.4
% Metastatic	100	100	88.2	88.1	92.6	94.4	100	100	--	--
% Liver metastases	64.1	69.7	--	--	--	--	65.0	74.1	70.0	61.3
Duration of advanced disease, median months	6.9	6.2	--	--	7.9	5.7	--	--	--	--
% Performance status	KPS ≥90: 59.0 80: 32.5 ≤70: 8.5	KPS ≥90: 47.9 80: 42.9 ≤70: 8.4 Missing: 0.8	KPS ≥90: 53.9 ≤80: 46.1	KPS ≥90: 47.6 ≤80: 52.4	ECOG 0: 13.0 1: 75.9 2: 11.1	ECOG 0: 18.9 1: 75.5 2: 5.7	ECOG* 0: 45.0 1: 55.0	ECOG* 0: 41.5 1: 58.5	ECOG 0: 16.7 1: 80.0 2: 3.3	ECOG 0: 16.1 1: 83.9 2: 0
Albumin, g/dL, mean	3.97 (0.46)	3.98 (0.51)	--	--	--	--	≥3 (eligibility criteria)		>3 (eligibility criteria)	
BMI, median (range), kg/m^2	Mean (SD): 23.33 (4.13) Min, max 16.0, 43.5	Mean (SD): 23.57 (5.05) Min, max 16.7, 42.9	--	--	23.7 (18.1, 37.7)	24.3 (16.5, 53.9)	--	--	--	--
% Curative surgery	34.2	36.1	44.7	32.1	--	--	--	--	36.7	32.3
Duration of previous gemcitabine, median (range), months	5.1 (0.1, 129.3)	21.4 (2.1, 147.9)	4.6 [95% CI: 3.8 to 6.0]†	5.3 [95% CI: 4.4 to 6.0]†	--	--	≤ 4 months: 36.7%	≤ 4 months: 37.9%	--	--

Issue 19 Errors in Table 27

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Several data errors in Table 27	Please see changes in the table below.	Error	The ERG notes and welcomes suggested changes to the text in the table made by the company. The following changes have been accepted since these were transcription errors / omissions in the ERG report: CONKO-003, neurotoxicity may more accurately be classified as paresthesia. PANCREOX, n=49 and n=53 for mFOLFOX6 and 5-FU/LV respectively. All suggested changes for SWOG S1115 have been rejected. This is because the company appears to have derived its data from a different source to the ERG. The ERG has extracted data from Clinical.Trials.gov website (https://clinicaltrials.gov/ct2/show/NCT01658943) which appears to be a more up to date analysis than either the poster or abstract for this trial.

Adverse event	NAPOLI-1		CONKO-003		PANCREOX		SWOG S1115		Yoo	
	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=134)	OFF (n=76)	5-FU/LV (n=84)	mFOLFOX6 (n=49)	5-FU/LV (n=53)	mFOLFOX6 (n=60)	AZD-6244 + MK-2206 (n=55)	mFOLFOX (n=29)	mFOLFORI.3 (n=29)
Neutropenia, All grades, n (%)	27 (23.1)	4 (3.0)	--	--	--	--	--	--	14 (48.2)	13 (44.8)
Grade 3 to 4, n (%)	17 (14.5)	1 (0.7)	--	--	16 (32.7)	2 (3.8)	--	--	6 (20.7)	7 (24.1)
Febrile neutropenia, All grades, n (%)	[redacted]	[redacted]	--	--	--	--	--	--	0	1 (3.4)
Grade 3 to 4, n (%)	2 (1.7)	0	--	--	2 (4.1)	0	--	--	0	1 (3.4)
Diarrhoea, All grades, n (%)	69 (59.0)	35 (26.1)	16 (21.1)	19 (22.6)	--	--	16 (26.7)	11 (22.0)	5 (17.2)	12 (41.4)
Grade 3 to 4, n (%)	15 (12.8)	6 (4.5)	1 (1.3)	0	1 (2.0)	0	**4 (6.7)**	**4 (7.3)**	0	2 (6.9)
Vomiting, All grades, n (%)	61 (52.1)	35 (26.1)	45 (59.2) †	39 (46.4) †	--	--	**16 (26.7**	16 (29.0)	14 (48.2)	9 (31.0)
Grade 3 to 4, n (%)	13 (11.1)	4 (3.0)	1 (1.3) †	3 (3.6) †	2 (4.1)	0	**3 (5.0)**	1 (1.8)	3 (10.3)	3 (10.3)
Anaemia, All grades, n (%)	44 (37.6)	31 (23.1)	46 (60.5)	54 (64.3)	--	--	18 (30.0)	4 (7.3)	16 (55.2)	15 (51.7)
Grade 3 to 4, n (%)	11 (9.4)	9 (6.7)	3 (3.9)	2 (2.4)	1 (2.0)	0	**2 (3.3)**	**3 (5.5)**	1 (3.4)	1 (3.4)
Fatigue, All grades, n (%)	47 (40.2)	37 (27.6)	--	--	--	--	26 (43.3)	15 (27.3)	--	--
Grade 3 to 4, n (%)	16 (13.7)	5 (3.7)	--	--	7 (14.2)	1 (1.9)	**8 (13.3)**	6 (10.9)	--	--
Neurotoxicity, All grades, n (%)	[redacted]	[redacted]	P: 32 (42.1)	P: 6 (7.1)	--	--	P: 7 (11.7)	P: 0	13 (44.8)	1 (3.4)
Grade 3 to 4, n (%)	[redacted]	[redacted]	P: 3 (3.9)	P: 0	PN: 2 (4.1)	PN: 0	P: 0	P: 0	0	0

-- Not reported; N=neuropathy; P=paresthesia; PN=peripheral neuropathy
† CONKO-003 reports nausea/emesis (vomiting) together
Note: AEs reported by Yoo were described as treatment-related AEs as were grade 3 to 5 AEs reported in SWOG S1115 while treatment-related AEs were also reported for the NAPOLI-1 trial, data here are presented for treatment emergent AE; it is unclear whether AEs reported for other trials are treatment-emergent or treatment-related but are assumed to be treatment-emergent
Data marked as CiC extracted from CSR, Table 14.3.2.7.3

Issue 20 Errors in Table 54 Drug costs used in the company model: company model versus ERG

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Several data errors in Table 54	Please see changes in yellow in the table below.	Error	Data in Table 54 of the ERG report were copied from Table 45 of the company submission. Table 45 provides the wrong values and so data have now been amended in the ERG report to match the table below.

Drug name	Vial size	Company model	ERG
		Cost per mg	
Nal-iri	50mg	[redacted]	-
Oxaliplatin	50mg	£3.11	£0.212
	100mg	-	£0.155
5-FU	500mg	£0.013	£0.002
	1000mg	-	£0.001
	2500mg	-	£0.002
	5000mg	-	£0.001
LV (as calcium folinate)	50mg	£0.375	£0.025
	100mg	-	£0.030
	300mg	-	£0.015

Issue 21 Description of incidence of adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 9 overall conclusion: The following sentence is misleading: "Despite an increase in AEs (mostly myelosuppression and gastrointestinal disorder), there appears to be no appreciable deterioration in HRQoL for patients treated with nal-iri+5-FU compared with 5-FU/LV."	Removal of sentence	This overall statement is misleading as the incidence of TEAEs is 99.1% for nal-iri + 5-FU/LV and 98.5% with 5-FU/LV, as reported in CS. (please refer to issue 4 as well)	Text amended to state: "Despite an increase in myelosuppression and gastrointestinal disorders, treatment-related AEs, grade ≥3 AEs, serious AEs and dose modifications arising from AEs, there was no apparent deterioration in HRQoL with nal-iri+5-FU/LV compared with 5-FU/LV." See also response to Issue 4 and Issue 6

Issue 22 Eligibility criteria for NCT00813163

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 11.8 Non-randomised study of nal-iri monotherapy (NCT00813163): Error in following sentence: "Eligibility criteria for entry into the NCT00813163 study were not dissimilar to the NAPOLI-1 trial, the main exceptions being there was no specific stipulation that patients must have adequate renal function and patients were excluded if they had not been previously treated with irinotecan."	Removal of the word "not" and change into: "Eligibility criteria for entry into the NCT00813163 study were not dissimilar to the NAPOLI-1 trial, the main exceptions being there was no specific stipulation that patients must have adequate renal function and patients were excluded if they had been previously treated with irinotecan."	Error	"not been previously treated" was a typographical error. Text amended as proposed by the company

Issue 23 Differences between NCT00813163 study and the NAPOLI-1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 11.8 Non-randomised study of nal-iri monotherapy (NCT00813163), last paragraph. Rephrasing of following sentence required: "Some notable baseline differences between the NCT00813163 study and the NAPOLI-1 trial were differences in the proportion of Asian patients, male patients, baseline KPS and patients previously treated with gemcitabine monotherapy or combination therapy as summarised in Table 71.been previously treated with irinotecan."	Rephrasing of the KPS element within this sentence or provision of detailed breakdown in the adjacent table 71.	The wording is misleading as the KPS (KPS = 100 and KPS = 90) are similar between these trials, but there is a higher proportion of patients with KPS = 80 in NAPOLI-1 and a lower percentage with KPS = 70. ERG fails to present a breakdown of this.	Table 71 amended for clarity.

Issue 24 Errors in Table 72 Key findings from the NCT00813163 study and NAPOLI-1 trial*

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Several data errors in Table 72	Please see changes in yellow in the table below.	Error	This is not a factual inaccuracy. The data reported by the ERG for median OS and PFS and ORR were copied from the published paper by Wang-Gillam et al 2015. For OS and PFS these data were only reported to 1 decimal place in the published paper. The ERG welcomes the more detailed data provided by the company and has amended the OS and PFS data in Table 72 accordingly. However, the company's reported ORR for nal-iri monotherapy below differs to that in the published paper. ORR reported in Table 72 of the ERG report therefore remains unaltered.

Outcome	NCT00813163	NAPOLI-1	
	Nal-iri (n=40)	Nal-iri (n=151)	Nal-iri+5-FU/LV (n=117)
Median OS (95% confidence interval)	5.2 (--, --)	4.9 (4.23, 5.62)	6.1 (4.76, 8.87)
Proportion of patients alive at:			
• 3 months, n (%)	30 (75.0)	--	--
• 6 months, n (%)	17 (42.5)	--	--
• 12 months, n (%)	10 (25.0)	--	30 (25.6)
Median PFS (95% confidence interval)	2.4 (--, --)	2.7 (2.13, 2.89)	3.1 (2.69, 4.17)
Objective response rate, n (%)	3 (7.5)	5 (3.3)	9 (7.7)

Issue 25 Errors in Table 74 Adverse events of grade 3 or higher occurring in ≥10% of subjects in the NCT00813163 study and the NAPOLI-1 trial*

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Several data errors in Table 74	Please see changes in yellow in the table below.	Error	All proposed changes have been accepted since these were transcription errors / omissions in the ERG report.

Adverse Event n (%)	NCT00813163	NAPOLI-1	
	Nal-iri (n=40)	Nal-iri (n=147)	Nal-iri + 5-FU/LV (n=117)
Any treatment-emergent adverse event ≥grade 3	26 (65.0)	112 (76.2)	90 (76.9)
Neutropenia	12 (30.0)	8 (5.4)	17 (14.5)
Leukopenia	10 (25.0)	4 (2.7)	1 (0.9)
Fatigue/asthenia†	8 (20.0)	19 (12.9)	25 (21.4)
Diarrhoea	6 (15.0)	31 (21.1)	15 (12.8)
Anaemia	6 (15.0)	16 (10.9)	11 (9.4)
Abdominal pain	6 (15.0)	12 (8.2)	8 (6.8)
Hyponatraemia	6 (15.0)	9 (6.1)	3 (2.6)
Gamma-glutamyl transferase elevated	5 (12.5)	4 (2.7)	2 (1.7)
Nausea	4 (10.0)	8 (5.4)	5 (4.3)
Decreased appetite	4 (10.0)	13 (8.8)	5 (4.3)

STA ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pegylated liposomal irinotecan hydrochloride trihydrate for treating pancreatic cancer after gemcitabine [ID778]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/121/02

Erratum completed 15th July 2016

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 25 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 report affected are presented here. Please note:

- New text added by the ERG is in *italics and underlined*.
- Text deleted completely (as opposed to being re-worded) is struck out.
- Unaltered text which is considered to be of relevant context to that added, amended or deleted (such as headings or sentences preceding or following the added, amended or deleted text) is presented in its original font.
- All other unaltered text is greyed out.

6 weeks and did not violate any inclusion/exclusion criteria nor significantly deviate from the protocol, including significant deviations in study drug administration. The company also presented median OS and median PFS results for the ITT population generated from analyses of final data cut (March 2016) data; these results are [redacted] to the interim results presented in the CS.

Safety results are reported in the CS for the safety population (n=251), i.e. patients who received at least one dose (including partial dose) of study medication. In the nal-iri arm, the incidence of *all treatment emergent AEs was similar between arms but treatment-related AEs, grade ≥3 AEs, serious AEs and dose modifications were* higher than in the 5-FU/LV arm. For patients treated with nal-iri+5-FU/LV the primary reason for dose delay was myelosuppression (e.g. neutropenia), the main reasons for dose reductions were myelosuppression and gastrointestinal disorders and the primary reasons for discontinuation of treatment were gastrointestinal disorders, and infections and infestations.

The primary health related quality of life evidence was derived from the patient-reported outcomes (PRO) population, which only included ITT patients who had completed the EORTC-QLC-C30 questionnaire at baseline and on at least one subsequent occasion ([redacted]). No statistically significant differences were reported between arms in scores at 6 or 12 weeks; comparative EORTC-QLC-C30 data *at 30 days post follow-up* were not reported. The company also undertook a quality adjusted time without symptoms or toxicity (Q-TWiST) analysis for the ITT population (n=236). The company states that the results from the Q-TWiST analysis (relative Q-TWiST gain of 24%) show that treatment with nal-iri+5-FU/LV results in statistically significant and clinically important gains in quality-adjusted survival compared with treatment with 5-FU/LV. The company reported that a sensitivity analysis conducted in the PP population supported this finding.

The company explored the feasibility of conducting a network meta-analysis (NMA) or ITC to compare nal-iri+5-FU/LV with other relevant comparators (e.g. oxaliplatin+5-FU/LV). The company considered a network of evidence formed by 12 of the 13 RCTs included in its systematic review and presented network diagrams summarising the identified evidence. Three trials could be linked by a common comparator (5-FU/LV): the NAPOLI-1 trial, CONKO-003 trial and PANCREOX trial. The company stated that the proportional hazards (PH) assumptions necessary to generate reliable results were violated for both OS and PFS. In addition, the company considered that trials were too heterogeneous in terms of trial location, patient characteristics, prior treatment with gemcitabine (monotherapy versus combination therapy) and length of trial follow-up for results to be used in an ITC. These limitations led the company to conclude that an ITC was “unfeasible”. Advice, sought by the

company, from a panel of three UK key opinion leaders (KOLS) was that it was difficult to compare the key trials and combining data from them in an ITC might be considered flawed and "naïve".

Evidence from one phase II non-RCT (NCT00813163) is also presented in the CS, including safety data. This non-randomised study was not included in the company's systematic review because it only investigated the effectiveness of nal-iri monotherapy. The company states that results from this study show that, overall, the safety profiles of nal-iri+5-FU/LV and nal-iri monotherapy in the NAPOLI-1 trial were consistent with prior experience (i.e. consistent with the results of this study (NCT00813163).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG is not aware of any additional RCTs or non-randomised studies that the company should have included as part of the evidence base.

Overall, the ERG agrees with the company that the NAPOLI-1 trial is of reasonable quality, although there is a risk of bias arising from the fact that it was an open-label trial*; however, blinding of study treatment was not feasible due to different dosing schedules in the different arms, and using a double-dummy design would result in an unacceptable number of infusions lasting up to 46 hours*. This may explain why a greater proportion of patients withdrew from the 5-FU/LV arm (10.9%) before treatment than from the nal-iri+5-FU/LV arm (1.7%). *The open-label nature of the trial, combined with a lack of independent assessment of disease progression, may also have introduced bias into the assessment of disease progression.*

Despite slight differences in some baseline characteristics, the ERG is satisfied that the treatment groups in the NAPOLI-1 trial were relatively well balanced. The patient population in the NAPOLI-1 trial was generally similar to the population that is likely to be considered for treatment with nal-iri+5-FU/LV in NHS clinical practice in England, aside from the usual caveat that only suitably fit patients are recruited to clinical trials which means the trial population may be slightly younger and fitter than the population seen in clinical practice.

The ERG is generally satisfied with the statistical approach employed by the company to analyse the data from the NAPOLI-1 trial, with the exception that the results of formal testing of PH for OS, PFS and TTF were not presented in the CS. The ERG's own analyses show that the assumptions of PH for OS, PFS and TTF in the nal-iri+5-FU/LV and 5-FU/LV arms are not supported and, therefore, the log-rank test results that the company uses to demonstrate statistical significance in terms of median OS, PFS and TTF are not valid.

While the company states that the results of the sensitivity analyses support the primary analyses, the ERG notes that the analyses of data from the PP population generated median OS and PFS results that were longer (in both treatment arms) than those for the ITT population (OS: 8.9 versus 5.1 months; PFS: 4.3 versus 1.6 months). However, the number of patients in the PP population was relatively small, indicating that only 56% of the nal-iri+5-FU/LV arm (66/117 patients) and 60% of the 5-FU/LV arm (*71/119*) received treatment for at least 6 weeks and did not violate any inclusion/exclusion criteria nor significantly deviate from the protocol. The most common reason for exclusion from the PP population was "insufficient dosing" or receiving no dose of the study drug. Thus patients in the NAPOLI-1 trial may have experienced considerably more treatment benefit had they been able to receive at least 80% of the planned dose throughout the duration of the study, particularly in the nal-iri+5-FU/LV arm.

Whilst, theoretically, HRQoL data from the NAPOLI-1 trial is useful, the ERG questions whether the EORTC-QLQ-C30 questionnaire results can be considered robust, given the relatively small number of patient responses. The ERG agrees that the Q-TWiST score of 24% suggests a clinically important result. However, the ERG cautions that the Q-TWiST analysis was not presented in the Clinical Study Report (CSR) of the NAPOLI-1 trial and so appears to be a post-hoc exploratory analysis; the findings should therefore be treated with caution.

Despite some apparent differences in the incidence rates of some AEs for patients treated with nal-iri monotherapy in the NAPOLI-1 trial compared with those in the NCT00813163 study, the ERG generally agrees with the company's overall assessment that the safety profiles of nal-iri+5-FU/LV and nal-iri monotherapy are consistent with prior experience with nal-iri, non-liposomal irinotecan and 5-FU.

Regarding the feasibility of conducting an ITC to allow the efficacy of nal-iri+5-FU/LV to be compared with that of other relevant comparators, the ERG agrees with the company that trial heterogeneity is a limitation. However, the ERG's primary reason for rejecting the validity of the results from the ITC relate to the PH assumptions being violated both within and between the arms of the three trials included in the ITC (i.e. the NAPOLI-1, CONKO-003 and PANCREOX trials) for both OS and PFS data. Thus the ERG considers that it is not possible to derive a credible estimate of clinical or cost effectiveness for nal-iri+5-FU/LV compared with oxaliplatin+5-FU/LV.

To enable a crude comparison of efficacy and safety data across key RCTs, the ERG extracted relevant data from RCTs of oxaliplatin+5-FU/LV that were identified in the

company's systematic review (i.e. the CONKO-003, PANCREOX, SWOG S1115 and Yoo

oxaliplatin+capecitabine (24.1%) and gemcitabine (10.3%). Clinical advice received by the ERG is that gemcitabine is most commonly used for patients previously treated with FOLFIRINOX. ~~It is not commonly used for patients who have previously been treated with gemcitabine but may be used again in some instances where patients have been disease-free after completing treatment with gemcitabine for a relatively long time (e.g. 12 months).~~

2.2.3 Third-line treatment for metastatic pancreatic cancer

The ERG notes that very few patients with metastatic pancreatic cancer live long enough to receive third-line treatment. In the aforementioned Smyth 2015[11] study only 1 (0.5%) out of 191 patients in the UK sample received a third-line treatment. The specific regimen received by the patient is not known.

2.2.4 Pegylated liposomal irinotecan hydrochloride trihydrate

Pegylated liposomal irinotecan hydrochloride trihydrate (nal-iri) does not currently have a marketing authorisation from the Committee for Human Medicinal Products (CHMP). CHMP positive opinion is expected circa 21 July 2016. If approved, it is anticipated that it will be provided in combination with 5-fluorouracil (5-FU) and folinic acid (also known as leucovorin [LV]) for the treatment of metastatic adenocarcinoma of the pancreas, in adult patients who have progressed following gemcitabine-based therapy, i.e. after previous treatment with gemcitabine in any setting: adjuvant, neoadjuvant, first-line metastatic, second-line metastatic or even later.

Nal-iri is a nanoliposomal formulation of the anti-cancer drug irinotecan. Irinotecan is a derivative of camptothecin, which inhibits the DNA enzyme topoisomerase I. It is converted by non-specific carboxylesterases present in the liver, blood and macrophages[14] into its metabolite SN-38, which is 100- to 1000-fold more active than irinotecan. Whilst non-liposomal irinotecan is sometimes used as a component drug of the FOLFIRINOX regimen (i.e. in combination with oxaliplatin+5-FU/LV) as a first-line treatment for metastatic pancreatic cancer, it is rarely used as a second-line or later treatment. It has, however, been studied in combination with 5-FU/LV (but not with oxaliplatin) as part of a regimen known as FOLFIRI (folinic acid [LV], 5-FU, irinotecan).[12,15-17]

The rationale for developing a nanoliposomal formulation of irinotecan is that nanoliposomes are expected to accumulate within the tumour and release irinotecan slowly over time. This should yield a higher concentration of chemotherapeutic agent in the tumour, decrease the rate at which it is removed from the body and result in better tumour shrinkage or slower

3.1 Population

The company has provided evidence for the population for which it expects the intervention to be licensed (since nal-iri does not currently have a marketing authorisation; CHMP positive opinion is expected circa 21 July 2016), i.e. treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) in adult patients who have progressed following gemcitabine-based therapy. The company highlights that patients who have progressed following gemcitabine-based therapy can include patients previously treated with monotherapy or combination therapy. The ERG notes that the licence, if granted, will be largely based on the clinical results from the NAPOLI-1 trial. In the NAPOLI-1 trial, patients were allowed to have received previous gemcitabine therapy in any setting, i.e. in the adjuvant or neoadjuvant setting (*12.8%*) first-line (*54.7%*) or second- line or later (*32.6%*) treatment for metastatic pancreatic cancer.

3.2 Intervention

The intervention is pegylated liposomal irinotecan hydrochloride trihydrate (nal-iri) in combination with 5-FU and folinic acid (also known as leucovorin [LV]). As noted above, the intervention is not currently licensed.

The recommended dose and regimen of nal-iri is 80 mg/m^2 administered intravenously over 90 minutes, diluted prior to administration with 5% glucose solution or 0.9% sodium chloride solution for injection to a final volume of 500 mL; it must not be administered as a bolus injection or an undiluted solution. Nal-iri is then followed by LV 400 mg/m^2 administered intravenously over 30 minutes, followed by 5-FU 2400 mg/m^2 administered intravenously over 46 hours. Nal-iri+5-FU/LV is administered every 2 weeks.

A reduced starting dose of nal-iri of 60 mg/m^2 should be considered for patients known to be homozygous for the *UGT1A1*28* allele (since patients homozygous for this allele have been found to be at increased risk of developing haematological (e.g. neutropenia) and/or digestive toxicities).[18] A dose increase of nal-iri to 80 mg/m^2 should be considered if tolerated in subsequent cycles. The ERG notes that testing for *UGT1A1*28* is not routinely conducted in NHS clinical practice. Therefore, if nal-iri+5-FU/LV was to be used in clinical practice without prior testing, this may mean that some AEs reported in the NAPOLI-1 trial would occur more often in clinical practice, resulting in more dose reductions which would likely be required as a result. The ERG also notes that in healthy individuals, it has been estimated that the proportion of people homozygous for *UGT1A1*28* is higher in people with varying degrees of African ancestry (18.1%) than Caucasians of European ancestry (11.3%) or Asians of Chinese and Japanese descent (2.1%).[19]

4.1.2 Evidence synthesis

The company's literature search led to the identification of one RCT that was considered to be directly relevant to the decision problem (the NAPOLI-1 trial). This trial compared treatment with nal-iri+5-FU/LV with 5-FU/LV. *The company highlighted that oxaliplatin+5-FU/LV was a more relevant comparator as it is much more widely used in clinical practice, and the ERG agrees with this.* With the inclusion of only one relevant study, it was not possible for the company to carry out a meta-analysis.

The methods and results from a non-randomised study (NCT00813163[27]) that was designed to assess the effectiveness of nal-iri monotherapy, was reported in the CS and was described as 'supporting evidence'. (The ERG notes that this study was excluded from the company's systematic review *because it included nal-iri monotherapy only and was therefore not directly relevant to the decision problem*).

To compare the effectiveness of nal-iri+5-FU/LV with other comparators, a "best-case evidence network scenario" was constructed (reproduced in this ERG report in Section 4.3, Figure 1). This network showed that an ITC allowing the comparison of the effectiveness of nal-iri+5-FU/LV with oxaliplatin+5-FU/LV (but no other relevant comparators) might, theoretically, be possible. However, the company states that it was not feasible to conduct an ITC due to the PH assumptions being violated for both OS and PFS data and also due to heterogeneity between trials and limited reporting. This view was supported by the panel of three KOLS who were consulted by the company. No clinical efficacy results are presented in the clinical effectiveness section of the CS for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV (although, results from an ITC conducted by the company are used in the company's cost effectiveness model). The clinical effectiveness section of the CS comprises narrative descriptions and findings from the NAPOLI-1 trial and the non-randomised NCT00813163.

The ERG considers that the company's approach to evidence synthesis is appropriate. The ERG is satisfied that appropriate steps were taken to compare nal-iri+5-FU/LV with relevant comparators and agrees that there were methodological issues precluding the conduct of an ITC which could produce credible results (detailed further in Section 4.3 of this ERG report). However, the ERG considers that it would have been useful if the company had presented results tables describing the efficacy and safety of relevant comparators, in particular for oxaliplatin+5-FU/LV. Therefore, to facilitate a crude comparison of nal-iri+5-FU/LV with other relevant comparators (in particular, oxaliplatin+5-FU/LV) the ERG has extracted efficacy and safety data from the key trials identified by the company's systematic review and presented these data in Section 4.7.

gemcitabine monotherapy compared with 54.2% of patients who received combination therapy. Thus, in this respect, the patient population appears to differ to that expected to be seen in NHS clinical practice in England although it should be noted that [redacted]% of patients in the NAPOLI-1 trial only received gemcitabine as an adjuvant or neo-adjuvant treatment. Clinical advice to the ERG is that gemcitabine monotherapy is more commonly used in the adjuvant setting and gemcitabine combination therapy is more commonly used in the neo-adjuvant setting.

Previous use of gemcitabine monotherapy versus combination therapy could reflect performance status (PS) to some extent. In the NHS, patients offered combination therapy are likely to have a good PS. As a KPS of ≥70 was required for trial entry, this could in part explain why there was a greater proportion of patients treated with gemcitabine combination therapy than with monotherapy. It could also be a reason why [redacted]% of patients in the NAPOLI-1 trial received the study drug as a third-line or later treatment, this is a higher proportion than would be expected to be treated in NHS clinical practice.

The higher proportion of patients treated with gemcitabine combination therapy than monotherapy in NAPOLI-1 could simply be a result of different treatment practices in the countries involved in the trial. In particular, it is noted that nab-paclitaxel in combination with gemcitabine is now commonly used outside of England but is not recommended by NICE for treating patients with metastatic pancreatic cancer in England.

The company states that, overall, the baseline patient characteristics were similar across treatment arms. The ERG agrees with this assessment but notes slight imbalances between treatment groups with regards to the site of metastatic lesions and KPS.

There was a notably higher proportion of patients with "other" metastases in the 5-FU/LV arm than in the nal-iri+5-FU/LV arm (32.8% versus 23.1%); also marginally higher were incidences of liver metastases (69.7% versus 64.1%) and peritoneal metastases (26.9% versus 23.9%) while metastatic lesions of the pancreas were higher in the nal-iri+5-FU/LV arm than in the 5-FU/LV arm (64.1% versus 60.5%). The proportion of patients with a baseline KPS 90 was higher in the nal-iri+5-FU/LV arm than in the 5-FU/LV arm, but the opposite was the case in terms of KPS 80 (KPS 90, 43.6% versus 33.6%; KPS 80, 32.5% versus 42.9%). Taken together, the differences in the site of the lesion and the greater proportion of patients with KPS 90 in the 5-FU/LV arm could suggest patients were less fit than those in the nal-iri+5-FU/LV arm although the ERG recognises there is a large degree of subjectivity in determining PS. Furthermore, it is noted that the proportion of patients with KPS ≤70 (i.e. the least fit) were similar between arms (8.6% versus 8.4%).

4.2.4 Statistical approach adopted for the conduct and analysis of NAPOLI-1

In this section, the ERG provides a description and critique of the statistical approach adopted to analyse data collected during the NAPOLI-1 trial in relation to the outcomes stipulated in the NICE scope. Information relevant to the statistical approach taken by the company has been extracted from the CSR,[29] the trial statistical analysis plan (TSAP),[30] the trial protocol (version 2.2)[31] and the CS.

Trial population

The various trial populations used to analyse efficacy and safety outcomes are defined in Box 3.

Box 3 Definitions of trial populations in the NAPOLI-1 trial

- **Intent-to-treat (ITT) population**: all randomised patients, as defined by the confirmation of a successful allocation of a randomisation number through interactive web response system (IWRS). This population was the primary population for all efficacy parameters unless otherwise stated
- **Safety population**: patients that received at least one dose (including partial dose) of study medication. All safety analyses were performed on this population
- **Per protocol (PP) population**: patients who received treatment for at least 6 weeks and did not violate any inclusion/exclusion criteria nor significantly deviate from the protocol, including significant deviations in study drug administration
- **Evaluable patient (EP) population for tumour response**: all randomised and treated patients who *met all* inclusion/exclusion criteria, had measurable disease at baseline and were evaluable for response, i.e. patients with at least one tumour evaluation while on treatment and those with early (≤12 weeks) disease progression, including symptomatic deterioration and death
- **Tumour marker response evaluable (TMRE) population**: patients who had CA19-9 >30 U/mL at baseline
- **Clinical benefit response evaluable (CBRE) population**: patients who met at least one of the following criteria: baseline pain intensity ≥20 (out of 100); baseline morphine consumption ≥10 mg/day oral morphine equivalents; baseline KPS of 70–90 points
- **Patient-reported outcomes (PRO) population**: all ITT patients that provided baseline and at least one subsequent assessment on the EORTC-QLQ-C30 instrument
- **Pharmacokinetic (PK) population**: all treated patients with at least one PK assessment

Efficacy outcomes

The definitions and methods of analysis for the primary and secondary efficacy outcomes from the NAPOLI-1 trial are listed in Table 7. For OS, PFS, TTF and ORR, the company presents results for the ITT population and results are fully reported for the PP and EP populations for PFS, TTF and ORR in the CS and CSR. The ERG is satisfied that all

outcomes were pre-specified in the TSAP and that all outcomes were fully reported in the CSR.

In addition to the outcomes reported in Table 7 the company also reported on tumour marker response and clinical benefit rate. Additional information on these outcomes is reported in the Appendices of this ERG report in Section 11.1.

Table 7 Analysis strategy for NAPOLI-1 trial efficacy end points specified in the NICE scope

Endpoint	Definition	Statistical method	Population used for analysis
Primary outcome			
OS	Defined as the time from the date of patient randomisation to the date of death or the date last known alive	OS was compared using un-stratified log-rank tests. KM analyses were performed for each arm to obtain non-parametric estimates of the OS function and median OS. 95% CIs were computed using the log-log method. Un-stratified Cox PH regressions were used to estimate HRs and 95% CIs	*ITT, PP, and other sensitivity analyses*
Secondary outcomes			
PFS	Time from the date of patient randomisation to the date of death or disease progression, whichever occurred earlier. PFS was based on tumour and disease progression assessments per investigator according to RECIST guidelines v1.1	PFS was compared using un-stratified log-rank tests. KM analyses were performed for each arm to obtain non-parametric estimates of the PFS function and median PFS. 95% CIs were computed using the log-log method. Un-stratified Cox PH regressions were used to estimate HRs and 95% Cis	ITT, PP, EP
TTF	Defined as the time to discontinuation of treatment for any reason, including disease progression, toxicity, and death	TTF was compared using un-stratified log-rank tests. KM analyses were performed for each arm to obtain non-parametric estimates of the TTF function and median TTF. 95% CIs were computed using the log-log method. Cox PH regressions were used to estimate HRs and 95% CIs	ITT, PP, EP
ORR	Defined by the percentage of patients with a best overall response of CR or PR as assessed by the investigator from randomisation until progression or end of study, and as defined by RECIST guidelines v1.1	The 95% CI for the proportion experiencing objective response was calculated based on the normal approximation. ORRs were pairwise compared using Fisher's exact tests	ITT, PP, EP

CI=confidence interval; CR=complete response; EP=evaluable patient for tumour response; HR=hazard ratio; ITT=intent-to-treat; KM=Kaplan-Meier; KPS=Karnofsky performance score; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; PP=per protocol; PR=partial response; RECIST=response evaluation criteria in solid tumours; TTF=time to treatment failure
Source: CS Sections 4.3.4, 4.4.3 and 4.4.4

Outline of analyses

It was planned that the primary analysis would take place once 305 deaths had occurred. The efficacy and safety data presented in the CS are from this primary analysis, which was performed using a data cut-off point of 14 February 2014.

The company highlights that there have also been some updated results for OS, PFS and ORR presented as a poster and abstract with a data cut-off date of 25 May 2015 after 378 OS events.[32]

In March 2016, a final analysis of the NAPOLI-1 trial data set was performed as all patients included in the trial had died by this time. The March 2016 results for OS and PFS were used to inform the company's cost effectiveness analysis (see Section 5.3.4).

Cox proportional hazard modelling

The analyses carried out by the company to generate OS, PFS, and TTF hazard ratios (HRs) were conducted using Cox PH modelling. The validity of this method relies on the hazards of the two comparative drugs being proportional. The company mentions in the CS (Section 4.10.1.1) that the K-M curves for the NAPOLI-1 trial OS data cross, indicating that the PH assumption is unlikely to hold. This potential violation of PH casts doubt on the validity of the generated HRs for OS.

As part of the clarification process, the ERG requested details of any testing of the PH assumption that was carried out by the company. In response, the company tested the PH assumption for the NAPOLI-1 trial OS data and provided results of the test for various analysis populations (see Appendices to this ERG report, Section 11.2). For the ITT population (analysed using un-stratified log-rank tests), the test rejected the null hypothesis that the PH assumption is valid (p=0.0169). The results of the ERG's own analyses of the OS data are in agreement with those of the company.

As the company did not report any test of the PH assumption for PFS or TTF, the ERG carried out its own testing of the PFS and TTF data from the NAPOLI-1 trial (see Appendices to this ERG report, Section 11.3.1) and found the PH assumption to be violated for both outcomes. Consequently, the ERG is of the opinion that HRs are not an appropriate measure of survival benefit for nal+iri+5-FU/LV versus 5-FU/LV. *Although the use of Cox PH modelling was pre-specified in the TSAP, and while recognising that one view is that statistical methods should remain unaltered once the data has been seen, the ERG considers that when designing a trial, methods for testing the PH assumption and how to analyse data if the assumption is not valid should also be outlined.*

ERG assessment of statistical approach

A summary of the checks made by the ERG in relation to the statistical approach adopted by the company to analyse data from the NAPOLI-1 trial is provided in Table 8. Having carried out these checks, the ERG is satisfied with the statistical approach employed by the company, with the exception of the violation of the PH assumption for OS, and the lack of testing of PH for PFS and TTF.

4.2.5 Assessment of risk of bias of the NAPOLI-1 trial

The company's assessments of risk of bias presented in the CS (Table 15) are reproduced, along with ERG comments, in the Appendices to this ERG report (Section 11.4, Table 66). Overall, the ERG agrees with the company's assessments and considers that the trial was of reasonable quality. The ERG considers that the greatest risks of bias occur from the fact that the NAPOLI-1 trial was an open-label trial. This may explain why a much larger proportion of patients withdrew from the 5-FU/LV arm (13/119, 10.9%) before being treated than from the nal-iri+5-FU/LV arm (2/117, 1.7%). It is possible that patients recruited to the 5-FU/LV arm may have withdrawn from the trial upon being told that they had been randomised to receive the control treatment. Indeed, the reason for withdrawal given for 11 of the 14 (78.6%) patients in the 5-FU/LV arm who did not receive any study treatment was "subject decision". *The open-label nature of the NAPOLI-1 trial may also have introduced bias into the assessment of disease progression.* There is no independent assessment of disease progression. The company highlights that blinding of study treatment was not feasible due to different dosing schedules in the different arms. *In addition, using a double-dummy design would result in an unacceptable number of infusions lasting up to 46 hours.* The ERG recognises the company's assertion that, as a result of the new RECIST 1.1 guidelines,33 central independent confirmation of objective tumour response is no longer required for RCTs that do not have tumour response as their primary endpoint since it is considered that the control arm serves as an appropriate means to interpret data.

As highlighted in Section 3.3 of this report, the dosing schedule for 5-FU/LV in the nal-iri+5-FU/LV arm was different to that used in the 5-FU/LV arm. However, as argued by the company, the ERG considers it is highly unlikely that this created a bias in favour of the nal-iri+5-FU/LV arm, since the planned and recorded dose intensities of 5-FU were higher in the control arm.

4.2.6 Results from the NAPOLI-1 trial

As reported in Section 4.2.4, both the company and the ERG agree that the PH assumption is violated for the OS data. The ERG's calculations indicated that the PH assumption is also violated for PFS and TTF (Appendices to this ERG report, Section 11.3.1). For this reason, the ERG has not interpreted the HRs that are presented for these outcomes in the CS, as the HRs were calculated assuming that the PH assumption is valid.

Primary efficacy outcome

The results of the primary analysis of OS for the ITT population performed using a data cut-off point of 14 February 2014 are provided in Table 9. Median OS was longer for nal-iri+5-FU/LV patients in comparison to 5-FU/LV patients (6.1 months versus 4.2 months). The

The details of subsequent treatments received by patients in each arm are shown in Table 10.

Table 10: Post-treatment anti-cancer therapy in the NAPOLI-1 trial

	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=119)
Received post-treatment anti-cancer therapy, n (%)*	42 (35.9)	50 (42.0)
Gemcitabine-based	11 (9.4)	14 (11.8)
5-FU-based	28 (23.9)	35 (29.4)
Irinotecan-based	10 (8.5)	12 (10.1)
Platinum-based	24 (20.5)	24 (20.2)
Other non-investigational agents	14 (12.0)	12 (10.1)
Investigational	5 (4.3)	4 (3.4)
No record of post-treatment anti-cancer therapy, n (%)	75 (64.1)	69 (58.0)

*Subjects who received therapy in combination are counted in more than one therapy category.
Source: Company response to the ERG clarification letter, adapted from Table 26

Sensitivity analyses of the primary efficacy outcome

The results of the sensitivity analyses of OS are provided in Table 11. Median OS was longer for patients in the nal-iri+5-FU/LV arm than patients in the 5-FU/LV arm for all analyses. The ERG notes that in the safety population, results were almost identical to those presented for the ITT population. Therefore, it seems that despite the fact a larger percentage of patients in the 5-FU/LV arm did not receive any study treatment in comparison to the nal-iri+5-FU/LV arm, bias has not been introduced.

Median OS times were considerably longer for both treatment groups in the PP population in comparison to the ITT population (2.8 months OS gain in the nal-iri+5-FU/LV arm and 0.9 months OS gain in the 5-FU/LV arm). However, the number of patients in the PP population was relatively small, indicating that only 56% of the nal-iri+5-FU/LV arm (66/117 patients) and 60% of the 5-FU/LV arm (*71/119*) received treatment for at least 6 weeks and did not violate any inclusion/exclusion criteria nor significantly deviate from the protocol. Nevertheless, the findings of the analysis using the PP population were in accordance with the analyses using the ITT and safety populations in that they demonstrated a beneficial effect of nal-iri+5-FU/LV in comparison to 5-FU/LV in terms of median OS.

Table 21 Summary of adverse events in the NAPOLI-1 trial – safety population

Adverse event n (%)	Nal-iri+5-FU/LV (n=117)	5-FU/LV (n=134)
≥1 TEAE	116 (99.1)	132 (98.5)
≥1 TR-TEAE	107 (91.5)	93 (69.4)
≥1 CTCAE grade 3 or higher TEAE	90 (76.9)	75 (56.0)
≥1 CTCAE grade 3 or higher treatment-related TEAE	63 (53.8)	24 (17.9)
≥1 serious TEAE	56 (47.9)	60 (44.8)
≥1 TEAE leading to any dose modification	83 (70.9)	48 (35.8)
• ≥1 TEAEs resulting in dose delay	72 (61.5)	43 (32.1)
• ≥1 TEAE leading to dose reduction	39 (33.3)	5 (3.7)
• ≥1 TEAE leading to dose discontinuation	13 (11.1)	10 (7.5)
≥1 TR-TEAE leading to any dose modification		
• ≥1 TR-TEAE resulting in dose delay	59 (50.4)	19 (14.2)
• ≥1 TR-TEAE leading to dose reduction	35 (29.9)	3 (2.2)
• ≥1 TR-TEAE leading to dose discontinuation	5 (4.3)	2 (1.5)

CTCAE=common terminology criteria for adverse events; TEAE=treatment-emergent adverse event; TR-TEAE=treatment-related treatment-emergent adverse event
Source: CS, adapted from Table 30 and company response to ERG clarification letter, Table 17

TEAEs that were very common (≥10%) are summarised in Appendices to this ERG report (Section 11.7, Table 73). AEs that were very common (≥10%) in patients treated with nal-iri+5-FU/LV and occurred at a higher frequency (≥5%) than in the 5-FU/LV arm were as follows: diarrhoea (59.0% versus 26.1%), vomiting (52.1% versus 26.1%), nausea (51.3% versus 34.3%), decreased appetite (44.4% versus 32.1%), fatigue (40.2% versus 27.6%), anaemia (37.6% versus 23.1%), pyrexia (23.1% versus 11.2%), neutropenia (23.1% versus 3.0%), weight decreased (17.1% versus 6.7%), neutrophil count decreased (14.5% versus 1.5%), white blood cell count decreased (14.5% versus 1.5%), alopecia (13.7% versus 4.5%), stomatitis (13.7% versus 6.0%), mucosal inflammation (10.3% versus 3.7%) and platelet count decreased (10.3% versus 2.2%).

Serious TEAEs are summarised by the company in Appendix 6, Table 8, of the CS. The most common (>3%) serious TEAEs for patients treated with nal-iri+5-FU/LV were vomiting (*9.4%*), diarrhoea (6.0%), abdominal pain (4.3%), nausea (3.4%) and sepsis (3.4%); the most common serious TEAE (>3%) for patients treated with 5-FU/LV was abdominal pain (4.5%).

Treatment-emergent deaths that were attributed to AEs were similar in the nal-iri+5-FU/LV arm (2.6%) and the 5-FU/LV arm (2.2%). One death (0.9%) was assessed as being related to treatment in the nal-iri+5-FU/LV arm with no deaths assessed as being attributable to treatment in the 5-FU/LV arm.

A safety comparison with patients heterozygous for *UGT1A1*28* was difficult to perform because of the small number of patients in this subgroup ([redacted]

FU: [redacted]; (CSR, Table 7-2). The EORTC QLQ-C30 questionnaire consists of 15 subscales in three independent domains: Global Health Status; Functional Scale Score (physical, role, emotional, cognitive, and social functioning); and Symptom Scale Score (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).

Patients were required to complete the EORTC-QLQ-C30 questionnaire at the start of treatment, every 6 weeks thereafter and at 30 days post follow-up. On days that the patient received the study drug, the questionnaire was completed prior to study drug administration.

Baseline EORTC-QLQ-C30 scores were similar between treatment arms for all domains: for Global Health Status, scores were above the midpoint of the scale; for Functional Scale, the scores were high (≥75) indicating a high/healthy level for functioning; and for Symptom Scale, the scores were noted to be between 0 and 33 for all symptoms, indicating low levels of symptomatology. Findings over time were reported at 6 weeks and 12 weeks. No appreciable changes in Global Health Status or Functional Scale were reported, suggesting there were no negative effects on HRQoL from treatment, as measured by these scales. A similar finding was reported for most of the subscales within the Symptom Scale, with the exception of nausea and vomiting, and diarrhoea. For both arms, the baseline score on the nausea and vomiting subscale was 0 (indicating no symptomology). This score [redacted] in the nal-iri+5-FU+LV arm [redacted] in the 5-FU/LV arm at 6 weeks and was [redacted] at 12 weeks. The diarrhoea scale also had a baseline score of 0 in both arms, [redacted] in the nal-iri+5-FU/LV arm [redacted] in the 5-FU/LV arm at 6 weeks [redacted] in the nal-iri+5-FU/LV [redacted] 0 in the 5-FU/LV arm) at 12 weeks. *Comparative EORTC-QLC-30 data at 30 days post follow-up were not reported.*

4.5.2 Q-TWiST analysis

As supportive evidence, the company also undertook a quality adjusted time without symptoms or toxicity (Q-TWiST) analysis as described by Revicki 2006 (page 412).[37] This involved partitioning total survival in the ITT population over 12 months into: time with AE grade ≥3 toxicity (TOX); time in relapse after disease progression (REL); and time without symptoms or AE grade ≥3 toxicity (TWiST). Mean Q-TWiST was then calculated by multiplying the time spent in each health state by its respective utility (0.5 for TOX, 0.5 for REL and 1.0 for TWiST).

The results from the Q-TWiST are summarised in Table 22 Time in TOX favoured 5-FU/LV over nal-iri+5-FU/LV by 0.7 months, there was little difference between arms for time in REL (marginally favouring 5-FU/LV) and TWiST favoured nal-iri+5-FU/LV by 1.0 months. The

company reported the TWiST gain to be statistically significant. Overall, nal-iri+5-FU/LV patients had a 1.3 months (95% CI: 0.4 to 2.1) greater Q-TWiST (range threshold analyses: 0.9 to 1.6 months), with a relative Q-TWiST gain of 24% (range threshold analyses: 17% to 31%).

Table 22 Results from the Q-TWiST analysis in the NAPOLI-1 trial – ITT population

Health state	Utility	Nal-iri+5-FU/LV (n=117)		5-FU/LV (n=119)	
		Months	Score	Months	Score
TOX: Time with AE grade ≥3 toxicity	0.5	1	0.5	0.3	0.15
REL: Time in relapse after disease progression	0.5	2.5	1.25	2.7	1.35
TWiST: Time without symptoms or AE grade ≥3 toxicity	1	3.4	3.4	2.4	2.4
Total (Q-TWiST)			5.1		3.9

Source: CS, Section 4.7.2.6

The company also conducted a scenario analysis using data from the PP population. The results of this analysis support the results generated using ITT data. In the PP population, Q-TWiST was also reported to be significantly superior in nal-iri+5-FU/LV patients (Q-TWiST gain=1.8 months; 95% CI: 0.7 to 3.0); this gain is reported by the company to be clinically and statistically significant.

4.5.3 Overall comment on health related quality of life

Whilst, theoretically, HRQoL data are useful, the ERG questions whether, given the relatively small number of patient responses (Table 23), the EORTC-QLQ-C30 results generated from the data collected as part of the NAPOLI-1 trial can be considered robust.

Table 23 *Patients in the NAPOLI-1 trial ITT population who completed* the EORTC-QLC-C30 questionnaire

Assessment	nal-iri+5-FU/LV *(n=117)*	5-FU/LV *(n=119)*
Baseline, *n (%)*	*71 (60.5)*	*56 (47.1)*
12 weeks, *n (%)*	*49 (41.9)*	*44 (37.0)*
30 days post follow-up, *n (%)*		Not reported

Source: CSR, *adapted from Table 7-16*

The company states that the results from the Q-TWiST analysis show that treatment with nal-iri+5-FU/LV results in statistically significant and clinically important gains in quality-adjusted survival compared with treatment with 5-FU/LV. The ERG notes that although some differences in Q-TWiST scores are described as being statistically significant, no p-values are reported in the CS although confidence intervals, presented for these estimates at ASCO 2016 by Pelzer (and reported by the ERG in Section 4.5.2), appear to show statistical significance. In addition, it is noted that the authors of the Revicki 2006 study[37] suggest that a difference in Q-TWiST scores of 10% to 15% is clinically important; in the PRO population of the NAPOLI-1 trial, a Q-TWIST score of 24% is reported (range threshold analyses: 17% to 31%), suggesting that the results are clinically important. However, the ERG notes that

the results of the Q-TWiST analyses are not presented in the CSR and so appear to be a post-hoc exploratory analysis; the findings should therefore be treated with caution.

4.6 Efficacy evidence from non-randomised study (NCT00813163)

The ERG considers that the efficacy findings from the NCT00813163 study are of limited relevance to the decision problem. However, as noted in Section 4.2.3, the ERG has noted that the proportion of patients treated with gemcitabine monotherapy and combination therapy may have some impact on efficacy if the choice of prior therapy also reflects patient fitness especially if a greater proportion of patients receiving prior combination therapy reflects a fitter patient population. It is interesting to note, therefore, that in the NCT00813163 study, there was a greater proportion of patients with worse PS (25% with KPS ≤70) compared with patients in the NAPOLI-1 trial (~9%) despite a higher proportion of patients having been previously treated with combination therapy (77.5% compared with ~55%). However, median OS and PFS for patients treated with nal-iri monotherapy in the NCT00813163 study (5.2 and 2.4 months respectively) was similar to that reported in the nal-iri monotherapy arm of the NAPOLI-1 trial (4.9 and 2.7 months respectively). More information on the NCT00813163 study is described in Appendices to this ERG report (Section 11.8).

4.7 Additional work on clinical effectiveness undertaken by the ERG

As highlighted previously (Sections 2,2,2 and 3.3 of this ERG report), oxaliplatin+5-FU/LV regimens are the most common regimens used for treating patients with metastatic pancreatic cancer previously treated with gemcitabine. Oxaliplatin+5-FU/LV is, therefore, considered by the ERG to be the standard of care, and the most appropriate comparator to nal-iri+5-FU/LV. As methodological issues precluded the conduct of an ITC, and since the company did not present safety data for oxaliplatin+5-FU/LV, the ERG presents a narrative summary of the efficacy and safety of nal-iri+5-FU/LV alongside that of oxaliplatin+5-FU/LV. The ERG's approach is pragmatic and enables crude comparisons across RCTs to be undertaken to determine if results obtained in the NAPOLI-1 trial differ markedly to results obtained in other RCTs. The obvious limitation of the approach is that it is impossible to reach reliable conclusions about relative effectiveness, particularly as trial populations may differ. It is not possible to derive a quantitative estimate but it is possible to explore (qualitatively) the similarity and differences of trial results, and the extent to which these may be attributed to differences in trial and patient characteristics. *Only the arms of relevance from the five trials are discussed in this section (i.e. the nal-iri + 5-FU/LV arm in NAPOLI-1,*

the OFF arm in CONKO-003, the mFOLFOX6 in PANCREOX, the mFOLFOX6 arm in SWOG S1115, and the mFOLFOX arm in Yoo).

4.7.1 Trial characteristics

Trial characteristics are summarised in Table 24. Alongside nal-iri+5-FU/LV, different types of oxaliplatin+5-FU/LV regimens are considered: OFF in CONKO-003, mFOLFOX6 in the PANCREOX trial, mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial and mFOLFOX in the trial conducted by Yoo. The NAPOLI-1 trial is the only multinational trial, the other trials were conducted in Germany, Canada, US and South Korea respectively. The NAPOLI-1 trial is also the largest trial (*n=417, and n=236 for the trial arms considered*) and the Yoo trial of mFOLFOX is the smallest (n=61). In all of the trials, patients had received prior gemcitabine but the extent to which this was monotherapy and/or combination therapy varied widely; only 9.8% of patients received monotherapy in the trial of mFOLFOX reported by Yoo, compared to 100% of patients receiving OFF in the CONKO-003 trial. Trial follow-up periods differed considerably across trials (where reported) from a planned follow-up of 4 months in the PANCREOX trial of mFOLFOX6 to a median follow-up of 54.1 months in the CONKO-003 trial of OFF. The dates of recruitment spanned 11 years from 2004 to 2015. The earliest of the trials to be completed was the CONKO-003 trial of OFF (2007) and the most recent trial to be completed was the phase II SWOG S1115 trial of mFOLFOX6 without bolus 5-FU (2015).

Table 24 Characteristics of randomised controlled trials which investigated nal-iri+5-FU/LV or oxaliplatin+5-FU/LV

Characteristic	NAPOLI-1	CONKO-003	PANCREOX	SWOG S1115*	Yoo
Design	Phase III, open-label RCT	Phase III, open-label RCT	Phase III, open-label RCT	Phase II, open-label RCT	Phase II, open-label RCT
Recruited, n (dates)	n=236 § (2012 to 2013)	n=168 (2004 to 2007)	n=108 (2010 to 2013)	n=120 (2012 to 2015)	n=61 (2007 to 2008)
Follow-up	Not known	54.1 months (median)	4 months (reported in methods)	Every 6 months for up to 3 years (reported in methods)	5.6 months (median)
Country	Multi-centre, multinational trial: North America (20 sites), Europe (30 sites), Asia (12 sites), South America (8 sites) and Oceania (6 sites)	Germany, 16 centres	Canada, 15 centres	US, 534 centres	Asian Medical Center, Seoul, Korea
Intervention	Nal-iri + 5-FU/LV, every 2 weeks: 80 mg/m^2 nal-iri over 90 minutes, 400 mg/m^2 LV over 30 minutes, followed by 2400 mg/m^2 5-FU over 46 hours on Day 1	OFF every 6 weeks:† 85 mg/m^2 oxaliplatin on Days 8 and 22, 200 mg/m^2 LV on Days 1, 8, 15 and 22, 5-FU 2,000 mg/m^2 over 24 hours on Days 1, 8, 15 and 22 2 week of rest before next cycle of treatment	mFOLFOX6, every 2 weeks: 85 mg/m^2 oxaliplatin (given as a 2-hour infusion), 400 mg/m^2 LV (given as a 2-hour infusion simultaneous to oxaliplatin), 400 mg/m^2 dose of 5-FU given as bolus followed by 2400 mg/m^2 continuous infusion over 46 hours on Day 1	mFOLFOX6 (without bolus 5-FU) every 2 weeks: 85 mg/m^2 oxaliplatin (given as a 2-hour infusion) and continuous 5-FU (2,400mg/m^2) over 46 to 48 hours on Day 1 (no detail about administration of LV given)	mFOLFOX every 2 weeks: 85 mg/m^2 oxaliplatin (given as a 2-hour infusion), 400 mg/m^2 LV and 2,000 mg/m^2 5-FU IV over 46hours on Days 1
Comparator	5-FU + LV (6 weekly cycle): LV at a dose of 200 mg/m^2 over 30 minutes followed by 2,000 mg/m^2 5-FU over 24 hours administered on Days 1, 8, 15 and 22 2 week of rest before next cycle of treatment	5-FU + LV (6 weekly cycle):† 200 mg/m^2 LV followed by 2,000 mg/m^2 5-FU over 24 hours on Days 1, 8, 15 and 22 2 week of rest before next cycle of treatment	5-FU + LV (6 weekly cycle): 400 mg/m^2 LV (given as a 2-hour infusion) and 400 mg/m^2 dose of 5-FU given as bolus followed by 2400 mg/m^2 continuous infusion over 46 hours on Day 1	Selumetinib (AZD-6244) + the Akt inhibitor MK-2206: 100 mg AZD-6244 daily on days 1 to 28 plus 135mg MK2206 weekly on Days 1 to 28 .	mFOLFIRI.3 every 2 weeks: 70 mg/m^2 irinotecan (over 1 hour), 400 mg/m^2 (over 2 hours) and 2000 mg/m^2 5-FU (over 46 h) from Day 1 and another 70 mg/m^2 irinotecan (over 1 hour) at the end of the 5-FU infusion
Previous treatment	Gemcitabine therapy (monotherapy: 45.8% or combination: 54.2%)	First-line gemcitabine monotherapy (100%)	Gemcitabine therapy	Gemcitabine therapy (1-line but no more than 1-line)	Gemcitabine-based1st-line therapy (monotherapy 9.8% or combination 91.2%)

IV=intravenous; KPS=Karnofsky Performance Status; RCT=randomised controlled trial

** Data for SWOG S1115 taken from the Clinical.Trials.gov website (https://clinicaltrials.gov/ct2/show/NCT01658943)*

§ NAPOLI-1 was a three-armed trial comparing nal-iri+5-FU/LV with 5-FU/LV and nal-iri monotherapy with 5-FU/LV. Data reported here are for patients in the former comparison

† Included best supportive care according to current palliative care guidelines, i.e. including anti-infective treatment, psychological counselling as needed, biliary stenting or drainage (if indicated), nutritional advice, pain management, and nutritional supplementation

4.7.2 Patient characteristics

Patient characteristics are summarised in Table 25. Across the trials, with the exception of the trial of mFOLFOX reported by Yoo in which the median age of patients was 55, the median age was relatively similar across the trial arms of interest (ranging from 62 years in the OFF arm of CONKO-003 to 65 years in the mFOLFOX6 arm of PANCREOX). A similar proportion of patients had previously had curative surgery with nal-iri+5-FU/LV in the NAPOLI-1 trial (36.1%) as with mFOLFOX in the Yoo trial (36.7%) but more patients treated with OFF in the CONKO-003 trial had had curative surgery (44.7%). At least 88% of patients had metastatic disease in any given trial, and relatively similar proportions of patients treated with nal-iri+5-FU/LV in the NAPOLI-1 trial had liver metastasis (64.1%) as those treated with mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial (62.9%); in the Yoo trial, the proportion of patients with liver metastasis treated with mFOLFOX was slightly greater (70.0%). Body mass index was also similar in the two trials that reported this measure (the NAPOLI-1 trial of nal-iri+5-FU and the PANCREOX trial of mFOLFOX6), being approximately 23 kg/m^2. A comparison of the duration of previous gemcitabine therapy was difficult because not all of the trials reported this measure and where they did, it was not reported consistently. However, the median duration of previous gemcitabine therapy was ~~much~~ higher in the NAPOLI-1 trial for nal-iri+5-FU arm (*5.1* months) than in the OFF arm of the CONKO-003 trial (4.6 months).

The most notable difference across trials appeared to relate to baseline PS. In particular, 59.0% of patients treated with nal-iri+5-FU/LV in the NAPOLI-1 trial, 53.9% of patients treated with OFF in the CONKO-003 trial and 45.0% of patients treated with mFOLFOX6 without bolus 5-FU in the SWOG S1115 trial had KPS ≥90 or ECOG PS 0, whereas the proportions of patients with ECOG PS 0 treated with mFOLFOX6 in PANCREOX and with mFOLFOX in Yoo were 13.0% and 16.7% respectively. The mFOLFOX6 arm of the PANCREOX trial and mFOLFOX arm of the Yoo trial also included patients with ECOG PS 2: 11.1% and 3.3% respectively.

Table 25 Participant characteristics of randomised controlled trials which investigated nal-iri+5-FU/LV or oxaliplatin+5-FU/LV

Characteristic	NAPOLI-1		CONKO-003		PANCREOX		SWOG S1115*		Yoo	
Regimen	Nal-iri + 5-FU/LV (n=117)	5-FU/LV (n=119)	OFF (n=76)	5-FU/LV (n=84)	mFOLFOX6 (n=54)	5-FU/LV (n=54)	mFOLFOX6 (n=62)	AZD-6244 + MK-2206 (n=58)	mFOLFOX (n=30)	mFOLFORI.3 (n=31)
Age, median (Range) years	63 (41, 81)	62 (34, 80)	62 (37, 83)	61 (43, 78)	65 (38, 82)	67 (48, 78)	66 (34, 83)	69 (54, 88)	55 (35, 69)	55 (37, 73)
Sex (% male)	59.0	56.3	52.6	57.1	57.4	55.6	35.5	60.3	66.7	77.4
% Metastatic	100	100	88.2	88.1	92.6	94.4	100	100	--	--
% Liver metastases	64.1	69.7	--	--	--	--	62.9	74.1	70.0	61.3
Duration of advanced disease, median months	6.9	6.2	--	--	7.9	5.7	--	--	--	--
% Performance status	KPS ≥90: 59.0 80: 32.5 ≤70: 8.5	KPS ≥90: 47.9 80: 42.9 ≤70: 8.4 Missing: 0.8	KPS ≥90: 53.9 ≤80: 46.1	KPS ≥90: 47.6 ≤80: 52.4	ECOG 0: 13.0 1: 75.9 2: 11.1	ECOG 0: 18.9 1: 75.5 2: 5.7	ECOG* 0: 45.0 1: 55.0	ECOG* 0: 41.5 1: 58.5	ECOG 0: 16.7 1: 80.0 2: 3.3	ECOG 0: 16.1 1: 83.9 2: 0
Albumin, g/dL, mean	3.97 (0.46)	3.98 (0.51)	--	--	--	--	≥3 (eligibility criteria)		>3 (eligibility criteria)	
BMI, median (range), kg/m^2	Mean (SD): 23.33 (4.13) Min, max 16.0, 43.5	Mean (SD): 23.57 (5.05) Min, max 16.7, 42.9	--	--	23.7 (18.1, 37.7)	24.3 (16.5, 53.9)	--	--	--	--
% Curative surgery	34.2	36.1	44.7	32.1	--	--	--	--	36.7	32.3
Duration of previous gemcitabine, median (range), months	5.1 (0.02, 29.8) §	4.9 (0.5, 34.1) §	4.6 [95% CI: 3.8 to 6.0] †	5.3 [95% CI: 4.4 to 6.0] †	--	--	≤ 4 months: 37.1%	≤ 4 months: 37.9%	--	--

-- Not reported; BMI=body mass index; ECOG= Eastern Cooperative Oncology Group; KPS=Karnofsky performance Status; SD=standard deviation

*Data for SWOG S1115 taken from the Clinical.Trials.gov website (https://clinicaltrials.gov/ct2/show/NCT01658943). Results for PS only reported in poster presentation which included 115 patients (mFOLFOX6, n=60, AZD-6244 + MK-2206, n=55)

§ Data reported in weeks in and company response to the ERG clarification letter, Table 7

† CONKO-003 also reports data < 3months (27.6% versus 25.0%), 3 to 6 months (32.9% versus 38.1%) and >6months (39.5% versus 36.9%)

4.7.3 Efficacy outcomes

Key efficacy findings are summarised in Table 26.

Three of the RCTs investigating oxaliplatin+5-FU/LV (the CONKO-003 trial, the PANCREOX trial and the SWOG S1115 trial) report an OS of between 5.9 months and 6.7 months. These results are similar to those reported for nal-iri+5-FU/LV in the NAPOLI-1 trial (6.1 months). The trial reported by Yoo, however, reports a less impressive OS for mFOLFOX of only 3.4 months.

RCTs investigating oxaliplatin + 5-FU/LV report a PFS of 2.9 months for OFF in the CONKO-003 trial and 3.1 months for mFOLFOX6 in the PANCREOX trial. These results are similar to those reported for nal-iri + 5-FU/LV in the NAPOLI-1 trial (3.1 months). The SWOG S1115 trial and the trial reported by Yoo, however, report a less impressive PFS for mFOLFOX6 without bolus 5-FU and mFOLFOX, respectively, of only 2.0 months and 1.4 months, respectively.

Response rates appeared to be generally similar in two of the trials of oxaliplatin+5-FU/LV (the SWOG S1115 trial of mFOLFOX6 without bolus 5-FU and the Yoo trial of mFOLFOX) of approximately 7%, which compare to 9% for patients treated with nal-iri+5-FU/LV in the NAPOLI-1 trial. In all three of these trials, the best response was a partial response. In the PANCREOX trial of mFOLFOX6, response rates in both arms appeared to be much higher than any other trial, ranging from 8.8% for patients treated with 5-FU/LV to 13.2% for patients treated with mFOLFOX6. However, it is not stated how many responses were complete responses (if indeed any).

The proportion of patients who received subsequent treatment on disease progression could also impact on OS, although it should be noted that there are currently no proven third-line treatment options available. Nonetheless, it is noticeable that, from a comparison of the 5-FU/LV arms, the higher the proportion of patients who received subsequent therapy, the higher the median OS reported. A similar picture emerged for oxaliplatin+5-FU/LV with the exception of the mFOLFOX6 arm of the PANCREOX trial, which had much fewer patients who received subsequent therapy than in any other trial.

Alternatively, a higher proportion of patients receiving subsequent treatment can be indicative of a higher proportion of patients who are fitter at that point in time and, therefore, more likely to receive additional treatment. There does not appear to be any apparent relationship between the proportion who received subsequent treatment and the proportion of patients with 'better' PS at baseline (KPS ≥90 or ECOG PS 0).

Table 26 Key efficacy findings reported from randomised controlled trials of patients with metastatic pancreatic cancer treated with nal-iri+5-FU or oxaliplatin+5-FU/LV and who were all previously treated with gemcitabine

							SWOG S1115			
							mFOLFOX6 (n=62)	AZD-6244 + MK-2206 (n=58)		
OS, months	6.1 (4.76, 8.87)	4.2 (3.29, 5.32)	5.9	3.3	6.1	9.9	6.7 (6.0, 8.3)	3.9 (3.5, 4.6)	3.4 *	3.8 *
HR (95% CI)	0.67 (0.49 to 0.92)		0.66 (0.48 to 0.91)		1.78 (1.08 to 2.93)		--		--	
12-month OS, n (%)	-- (26)	-- (16)	15 (19.7)	11 (13.1)	--	--	--	--	--	--
PFS, months	3.1 (2.69 to 4.17)	1.5 (1.41 to 1.84)	2.9*	2.0*	3.1	2.9	2.0 (1.8, 2.9)	1.9 (1.8, 2.1)	1.4 *	1.9 *
HR (95% CI)	0.56 (0.41 to 0.75)		0.68 (0.50 to 0.94)*		1.00 (0.66 to 1.53)		--		--	
ORR (%)	7.7	0.8	--	--	13.2	8.5	6.5	0	7	0 †
Additional therapy on progression (%)	37.1	42.0	28.9 ‡	21.4 ‡	Chemo-therapy: 6.8	Chemo-therapy: 23.1	53 ¥	35 ¥	Crossover: 23.3 §	Crossover: 38.7 §

CI=confidence interval; HR=hazard ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival
-- Not reported
Note: 12-month OS reported in appendices to CS and taken from K-M curve in CONKO-003 (figure 3), rate for NAPOLI-1 is only given in the text of the summary to the CS
* Data reported in weeks in published paper
† The trial authors state that objective response could not be ascertained in the mFOLFIRI.3 arm
¥ Based on population of patients reported in the conference poster (n=60 and n=55), *all other data taken from the Clinical.Trials.gov website (https://clinicaltrials.gov/ct2/show/NCT01658943)*
§ After disease progression to a stage at which a salvage regimen was required, a crossover to the alternate protocol was undertaken by 12 patients (39%) in the mFOLFIRI.3 arm and by 7 (23%) in the mFOLFOX arm. The median time to crossover to the alternate treatment was 8.3 weeks (range 3.3 to 18.1 weeks) in the mFOLFIRI.3 arm, and 15 weeks (range 7.0 to 32.6 weeks) in the mFOLFOX arm
‡ Paper reports: Of these, seven patients (32%) in the OFF arm were treated with taxanes, and 13 patients (72%) in the 5-FU/LV arm received oxaliplatin-based chemotherapy
Note data for NAPOLI-1 reported above are from initial analysis, 14 February 2014 (consistent with all data for clinical effectiveness reported in the clinical effectiveness sections of the CS and this ERG report)

Table 27 Key safety findings reported from randomised controlled trials of patients with metastatic pancreatic cancer treated with nal-iri+5-FU or oxaliplatin+5-FU/LV and who were all previously treated with gemcitabine

			CONKO-003		PANCREOX		SWOG S1115			
			OFF (n=76)	5-FU/LV (n=84)	mFOLFOX6 (n=49)	5-FU/LV (n=53)	mFOLFOX6 (n=62)	AZD-6244 + MK-2206 (n=57)		
Neutropenia, All grades, n (%)	27 (23.1)	4 (3.0)	--	--	--	--	--	--	14 (48.2)	13 (44.8)
Grade 3 to 4, n (%)	17 (14.5)	1 (0.7)	--	--	16 (32.7)	2 (3.8)	0	0	6 (20.7)	7 (24.1)
Febrile neutropenia, All grades, n (%)	[redacted]	[redacted]	--	--	--	--	--	--	0	1 (3.4)
Grade 3 to 4, n (%)	2 (1.7)	0	--	--	2 (4.1)	0	0	0	0	1 (3.4)
Diarrhoea, All grades, n (%)	69 (59.0)	35 (26.1)	16 (21.1)	19 (22.6)	--	--	--	--	5 (17.2)	12 (41.4)
Grade 3 to 4, n (%)	15 (12.8)	6 (4.5)	1 (1.3)	0	1 (2.0)	0	4 (6.5)	4 (7.0)	0	2 (6.9)
Vomiting, All grades, n (%)	61 (52.1)	35 (26.1)	45 (59.2) †	39 (46.4) †	--	--	--	--	14 (48.2)	9 (31.0)
Grade 3 to 4, n (%)	13 (11.1)	4 (3.0)	1 (1.3) †	3 (3.6) †	2 (4.1)	0	3 (4.8)	1 (1.8)	3 (10.3)	3 (10.3)
Anaemia, All grades, n (%)	44 (37.6)	31 (23.1)	46 (60.5)	54 (64.3)	--	--	--	--	16 (55.2)	15 (51.7)
Grade 3 to 4, n (%)	11 (9.4)	9 (6.7)	3 (3.9)	2 (2.4)	1 (2.0)	0	2 (3.2)	3 (5.3)	1 (3.4)	1 (3.4)
Fatigue, All grades, n (%)	47 (40.2)	37 (27.6)	--	--	--	--	--	--	--	--
Grade 3 to 4, n (%)	16 (13.7)	5 (3.7)	--	--	7 (14.2)	1 (1.9)	8 (12.9)	7 (12.3)	--	--
Neurotoxicity, All grades, n (%)	[redacted]	[redacted]	P: 32 (42.1)	P: 6 (7.1)	--	--	--	--	13 (44.8)	1 (3.4)
Grade 3 to 4, n (%)	[redacted]	[redacted]	P: 3 (3.9)	P: 0	PN: 2 (4.1)	PN: 0	0	0	0	0

-- Not reported; P=paresthesia; PN=peripheral neuropathy

† CONKO-003 reports nausea/emesis (vomiting) together

Note: AEs reported by Yoo were described as treatment-related AEs as were grade 3 to 5 AEs reported in SWOG S1115 (reported on the Clinical.Trials.gov website at https://clinicaltrials.gov/ct2/show/NCT01658943) while treatment-related AEs were also reported for the NAPOLI-1 trial, data herare presented for treatment emergent AE; it is unclear whether AEs reported for other trials are treatment-emergent or treatment-related but are assumed to be treatment-emergent

Data marked as CiC extracted from CSR, Table 14.3.2.7.

4.8 Conclusions of the clinical effectiveness section

The only trial which assesses the effectiveness of nal-iri+5-FU/LV is the NAPOLI-1 trial. This is a phase III, multi-centre, multinational, RCT comparing the intervention with 5-FU/LV. Overall, the NAPOLI-1 trial appears to be of reasonable quality; the ERG considers that there is some risk of bias from the fact that it was an open-label trial.

The patient population recruited to the NAPOLI-1 trial is, in many respects, representative of patients who would be treated for metastatic pancreatic cancer after progressing on treatment with gemcitabine in routine clinical practice in England. It is however noticeable that a greater proportion of patients had received prior gemcitabine combination therapy and fewer patients had received gemcitabine monotherapy than would be seen in NHS clinical practice in England. Furthermore, as is common with all clinical trials, the patient population was on average younger and fitter than would be seen in clinical practice, and this may explain why a relatively large proportion of patients received study treatment in the third-line (or later) setting.

Results from the trial show that, for a range of efficacy measures, including OS and PFS, nal-iri+5-FU/LV is superior to 5-FU/LV. The increase in median OS of 1.9 months reported in the NAPOLI-1 trial compared with those receiving 5-FU/LV represents a significant improvement in OS (a 45% increase in median OS compared with the median OS in the 5-FU/LV arm), likely to be of great value to both the patient and their family. Furthermore, *despite an increase in myelosuppression and gastrointestinal disorders compared with 5-FU/LV,* there was no apparent deterioration in HRQoL with nal-iri+5-FU/LV.

However, in the NHS, 5-FU/LV is rarely used to treat patients with metastatic pancreatic cancer who have progressed following treatment with gemcitabine. The most common regimen currently used to treat these patients, despite the lack of a reliable evidence base to support it, is oxaliplatin+5-FU/LV (considered by the ERG to be the most common treatment in approximately 75% of cases). Capecitabine monotherapy is considered by the ERG to be the next most commonly used comparator (in 25% of cases) although differences by geographical region exist and so some clinicians also use oxaliplatin+capecitabine in a minority of cases. The company concluded that it was not feasible to conduct an ITC to compare nal-iri+5-FU with any of the comparators used in the NHS or specified in the NICE scope, although an ITC comparing nal-iri+5-FU/LV with oxaliplatin+5-FU/LV was conducted for the purposes of generating evidence to inform the company's economic evaluation. The ERG considers that the results from the ITC lack reliability as the PH assumptions required to conduct a credible comparison were not met and there was also some evidence of

heterogeneity across trials in terms of trial location, patient characteristics, prior treatment

Table 54 Drug costs used in the company model: company model versus ERG

Drug name	Vial size	Company model	ERG
		Cost per mg	
Nal-iri	50mg	[redacted]	-
Oxaliplatin	50mg	*£3.11*	£0.212
	100mg	-	£0.155
5-FU	500mg	*£0.013*	£0.002
	1000mg	-	£0.001
	2500mg	-	£0.002
	5000mg	-	£0.001
LV (as calcium folinate)	50mg	£0.375	£0.025
	100mg	-	£0.030
	300mg	-	£0.015

ERG=Evidence Review Group; mg=milligram
Source: Company model, eMit, ERG calculations

Table 55 Weekly average treatment costs per patient used in the model: company versus ERG drug acquisition costs using revised BSA value

Item	Company model			ERG (revised BSA)		
Nal-iri+5-FU/LV	Nal-iri	5-FU	LV	Nal-iri	5-FU	LV
Weekly drug cost	[redacted]	£24.97	£118.80	[redacted]	£2.24	£5.19
Weekly treatment cost	[redacted]			[redacted]		
Oxaliplatin+5-FU/LV	Oxaliplatin	5-FU	LV	Oxaliplatin	5-FU	LV
Weekly drug cost	£238.84	£11.35	£61.74	£13.14	£1.19	£2.72
Weekly treatment cost	£311.93			£17.04		
5-FU/LV	5-FU	LV		5-FU	LV	
Weekly drug cost	£31.16	£91.27		£2.94	£4.19	
Weekly treatment cost	£122.43			£7.12		

BSA=body surface area; ERG=Evidence Review Group
Source: Company model and ERG calculations

Combining the ERG's preferred BSA values and preferred drug acquisition costs in the company model yields an increase in the ICER of nearly £10,000 per QALY gained for treatment with nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, and a decrease of more than £10,000 per QALY gained for nal-iri+5-FU/LV versus 5-FU/LV (£94,608 and £122,066 per QALY gained respectively).

Post-progression treatment costs

On page 127 of the CS, it is stated that the company has assumed that the average weekly cost per patient of post-progression treatment is equivalent to the weekly cost of treatment with nal-iri+5-FU/LV. In the company model, the weekly cost of post-progression treatments is equivalent to the acquisition cost of nal-iri ([redacted]) – a price that does not include the cost of 5-FU/LV. Moreover, the cost used in the company model does not include any administration or monitoring costs.

9 OVERALL CONCLUSIONS

Treatment with nal-iri+5-FU/LV appears to be of greater efficacy than 5-FU/LV for patients with metastatic pancreatic cancer who have progressed on treatment with gemcitabine in the NAPOLI-1 trial. *Despite an increase in myelosuppression and gastrointestinal disorders, treatment-related AEs, grade ≥3 AEs, serious AEs and dose modifications arising from AEs, there was no apparent deterioration in HRQoL with nal-iri+5-FU/LV compared with 5-FU/LV.*

The patient population recruited to the NAPOLI-1 trial is, in many respects, representative of patients who would be treated for metastatic pancreatic cancer who progress on treatment with gemcitabine in routine clinical practice in England. It is however noticeable that a greater proportion of patients had received prior gemcitabine combination therapy and fewer patients had received gemcitabine monotherapy than would be seen NHS clinical practice in England. Furthermore, as is common with all clinical trials, the patient population was on average younger and fitter than would be seen in clinical practice, which may explain why a relatively large proportion of patients were receiving study treatment in the third-line (or later) setting.

However, 5-FU/LV is rarely used to treat patients with metastatic pancreatic cancer who have progressed on treatment with gemcitabine. Overall, the PFS and OS outcomes for patients treated with oxaliplatin+5-FU/LV reported in these trials are similar in magnitude to the PFS and OS outcomes of patients who were treated with nal-iri+5-FU/LV in the NAPOLI-1 trial.

The ERG considers that the company's ICERs per QALY gained for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV and 5-FU/LV are underestimated. The ERG identified a number of common issues affecting both comparisons and these are related to the costing methodologies adopted and the estimation of health state utilities as described in the CS. For the oxaliplatin+5-FU/LV comparison, the ERG considers the main issue of concern to be the company's ITC, thus the (corrected) estimated ICER per QALY gained (£[redacted]) is judged to be unreliable. The ERG urges caution when interpreting the cost effectiveness estimates for the nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV comparison. For this comparison, the ERG's revised model estimated ICERs per QALY gained are £[redacted] and £[redacted] for Scenarios B and C, respectively. The ERG performed additional analyses in order to aid decision making in the absence of a reliable ITC effectiveness results.

With regards to nal-iri+5-FU/LV versus 5-FU/LV, the ERG did not consider the company's approach to modelling survival to be appropriate. The ERG disagrees with the use of log-

11.6 Type of adverse events leading to dose modification in the NAPOLI-1 trial

11.6.1 Dose delay

The company highlights that the primary reasons for dose delay in the nal-iri+5-FU/LV arm were neutropenia and neutrophil count decreased (i.e. myelosuppression). From the company's CSR (Table 14.3.2.4.3), the ERG notes that neutropenia resulted in dose delay for [redacted] of patients in the nal-iri+5-FU/LV arm compared with [redacted] in the 5-FU/LV arm. Neutrophil count decreased resulted in dose delay for [redacted] and [redacted] respectively. Another notable AE resulting in dose delay in the nal-iri+5-FU/LV arm was [redacted] ([redacted] compared with [redacted] in the 5-FU/LV arm).

11.6.2 Dose reduction

Myelosuppression was also cited as the main reason for dose reduction with nal-iri+5-FU/LV, alongside gastrointestinal disorders. From the company's CSR (Table 14.3.2.4.1), most commonly (≥5%) [redacted] was a reason for [redacted]% of cases in the nal-iri+5-FU/LV arm followed by [redacted].

11.6.3 Dose discontinuation

Gastrointestinal disorders and infections and infestations were the primary reasons cited by the company for discontinuation of treatment with nal-iri+5-FU/LV. As reported in Table 14.3.2.5.1 of the CSR, the proportions in the nal-iri+5-FU/LV arm for *gastrointestinal disorders,* infections and infestations were [redacted] and [redacted] respectively.

11.8 Non-randomised study of nal-iri monotherapy (NCT00813163)

The company also presents evidence in the CS from a multinational, single-arm phase 2 study of 40 patients treated with nal-iri monotherapy, referred to by its ClinicalTrials.Gov identifier, NCT00813163. This study was excluded from the company's systematic review since it did not include the intervention of interest, nal-iri+5-FU/LV.

Eligibility criteria for entry into the NCT00813163 study were not dissimilar to the NAPOLI-1 trial, the main exceptions being there was no specific stipulation that patients must have adequate renal function and patients were excluded if they had been previously treated with irinotecan. Prior treatment with irinotecan was permitted in the NAPOLI-1 trial (under protocol version 2 or later), however the numbers of such patients were small ([redacted] patients in the nal-iri monotherapy arm and [redacted]. patients in the nal-iri+5-FU/LV arm).

The nal-iri monotherapy dose and scheduling in the NCT00813163 study was the same as in the nal-iri monotherapy arm of the NAPOLI-1 trial. However, unlike the NAPOLI-1 trial, patients were not initially tested for the *UGT1A1*28* allele in the NCT00813163 study and so no initial dose reductions were made based on the results of any pharmacogenetic test in NCT00813163.

A descriptive critical appraisal of the only included non-randomised study was undertaken using a tool developed by Chambers 2009.[63] This includes eight items and for a study to be considered 'good' quality, all eight criteria must be met. The NCT00813163 study met five of the criteria including one or more of the criteria deemed by Chambers 2009 to classify the study as 'satisfactory' quality. The ERG considers that this checklist for assessing the quality of the non-randomised study appears to be an appropriate tool but the ERG notes that while it has been used in a modified format in three systematic reviews,[64-66] it has not been validated as a tool. Indeed, one of the future research recommendations of Chambers 2009 was to focus on focus on validating quality criteria.

Some notable baseline differences between the NCT00813163 study and the NAPOLI-1 trial were differences in the proportion of Asian patients, male patients, baseline KPS and patients previously treated with gemcitabine monotherapy or combination therapy as summarised in Table 71.

Table 71 Notable differences in baseline characteristics between the NCT00813163 study and nal-iri arms of the NAPOLI-1 trial*

Baseline characteristic	NCT00813163	NAPOLI-1	
	Nal-iri (n=40)	Nal-iri (n=151)	Nal-iri + 5-FU/LV (n=117)
Male, n (%)	19 (47.5)	87 (57.6)	69 (59.0)
Asian	25 (62.5)	52 (34.4)	34 (29.1)
KPS = 100	7 (17.5)	22 (14.6)	18 (15.4)
KPS = 90	17 (42.5)	64 (42.4)	51 (43.6)
KPS = 80	6 (15.0)	50 (33.1)	38 (32.5)
KPS ≤70	10 (25.0)	15 (9.9)	10 (8.5)
Previously treated with gemcitabine monotherapy	9 (22.5)	67 (44.3)	53 (45.3)
Previously treated with gemcitabine combination	31 (77.5)	84 (55.6)	64 (54.7)

*For the NAPOLI-1 trial, data are for ITT population
Source: CS, adapted from Tables 14 and 28 and Wang-Gillam 2015 paper, Table 1

In the NCT00813163 study, the primary endpoint was OS rate at 3-months with additional secondary endpoints including (but not limited to) PFS and ORR. Overall, key efficacy results appear to be similar to those reported in the NAPOLI-1 trial (Table 72).

Table 72 Key findings from the NCT00813163 study and NAPOLI-1 trial*

Outcome	NCT00813163	NAPOLI-1	
	Nal-iri (n=40)	Nal-iri (n=151)	Nal-iri+5-FU/LV (n=117)
Median OS (95% confidence interval)	5.2 (--, --)	4.9 (4.23, 5.62)	6.1 (4.76, 8.87)
Proportion of patients alive at:			
• 3 months, n (%)	30 (75.0)	--	--
• 6 months, n (%)	17 (42.5)	--	--
• 12 months, n (%)	10 (25.0)	--	30 (25.6)
Median PFS (95% confidence interval)	2.4 (--, --)	2.7 (2.13, 2.89)	3.1 (2.69, 4.17)
Objective response rate, n (%)	3 (7.5)	9 (6.0)	9 (7.7)

OS=overall survival; PFS=progression-free survival
-- Not reported
*For the NAPOLI-1 trial, analyses are for ITT population, median OS and median PFS are the Kaplan-Meier estimate of the median PFS time
Source: CS, executive summary and adapted from Tables 16, 18, 22 and 29 and Wang-Gillam 2015 paper

Safety data, in particular, from this study does however add supporting evidence for toxicity associated with nal-iri. A total of 27 patients (67.5%) were able to maintain a dose of 120 mg/m^2 throughout their entire treatment course in the NCT00813163 study, and the majority of patients (75.0%) discontinued due to disease progression rather than toxicity. In the NAPOLI-1 trial, the company noted that certain gastrointestinal AEs and alopecia, hypoalbuminemia, hypomagnesaemia, hypokalaemia and asthenia were more commonly reported in the nal-iri monotherapy arm, while myelosuppression and stomatitis were more common in the nal-iri+5-FU/LV arm. The frequency of severe TEAEs (Grade 3 or higher) was generally also higher in the nal-iri monotherapy arm than nal-iri + 5-FU arm (with the exception of neutropenia, white cell count decreased, neutrophil count decreased, and fatigue). This, the company argues, suggests that the more frequent administration of nal-iri

(every 2 weeks compared with every 3 weeks) with a lower dose, as in the nal-iri+5-FU/LV combination arm compared with the nal-iri monotherapy arm, results in fewer and less severe gastrointestinal AEs. Clinical advice to the ERG is that a similar pattern is observed with treatment with non-liposomal irinotecan monotherapy and FOFIRI.

There were notable differences in the incidence of AEs in the NCT00813163 study and the NAPOLI-1 trial when only the nal-iri monotherapy arms were compared. In particular, in the NCT00813163 study there was an increase in the incidence of the following AEs when compared with AE data from the nal-iri monotherapy arm of NAPOLI-1 trial (Table 73): leukopenia (+33.1%), fatigue (+26.2%), neutropenia (+25.0%), alopecia (+20.3%) and 'weight decreased' (+18.8%). There was an increase in the incidence of the following grade ≥3 AEs when compared with AE data from the nal-iri monotherapy arm of NAPOLI-1 trial (Table 74): neutropenia (+24.6%) and leukopaenia (+22.3%). Possible explanations for these differences between studies include differences in the baseline characteristics, particularly the greater proportion of Asians, patients with KPS ≤70 and previous use of gemcitabine combination therapy in the NCT00813163 study than in the NAPOLI-1 trial. The fact that patients were not tested for *UGT1A1*28* prior to receiving treatment in NCT00813163 may also have been a factor although the authors of the non-randomised study note there was no correlation between *UGT1A1* polymorphisms with either haematologic AEs (myelosuppression) or non-haematologic AEs (including gastrointestinal disorders). The sample size of the NCT00813163 study was also relatively small and this could also explain why some AEs appear to be more common in this study than in the NAPOLI-1 trial.

Table 73Adverse events occurring in ≥10% of subjects in NCT00813163 and a comparison of the incidence of the same adverse events in the NAPOLI-1 trial*

	NCT00813163	NAPOLI-1	
Adverse Event n (%)	Nal-iri (n=40)	Nal-iri (n=147)	Nal-iri + 5-FU/LV (n=117)
Diarrhoea	30 (75.0)	103 (70.1)	69 (59.0)
Fatigue	25 (62.5)	54 (36.7)	47 (40.2)
Nausea	24 (60.0)	89 (60.5)	60 (51.3)
Vomiting	23 (57.5)	80 (54.4)	61 (52.1)
Anorexia / decreased appetite†	23 (57.5)	72 (49.0)	52 (44.4)
Alopecia	17 (42.5)	32 (21.8)	16 (13.7)
Neutropenia	16 (40.0)	22 (15.0)	27 (23.1)
Abdominal pain	15 (37.5)	50 (34.0)	27 (23.1)
Weight decreased	15 (37.5)	29 (19.7)	20 (17.1)
Leukopenia	15 (37.5)	6 (4.1)	12 (10.3)
Anaemia	13 (32.5)	48 (32.7)	44 (37.6)

*For the NAPOLI-1 trial, analyses are for the safety population
† Reported as anorexia in the NCT00813163 study and decreased appetite in the NAPOLI-1 trial
Source: CS, Table 31 and Table 32

Table 74 Adverse events of grade 3 or higher occurring in ≥10% of subjects in the NCT00813163 study and the NAPOLI-1 trial*

	NCT00813163	NAPOLI-1	
Adverse Event n (%)	**Nal-iri (n=40)**	**Nal-iri (n=147)**	**Nal-iri + 5-FU/LV (n=117)**
Any treatment-emergent adverse event ≥grade 3	26 (65.0)	112 (76.2)	90 (76.9)
Neutropenia	12 (30.0)	8 (5.4)	17 (14.5)
Leukopenia	10 (25.0)	4 (2.7)	1 (0.9)
Fatigue/asthenia†	8 (20.0)	19 (12.9)	*25 (21.4)*
Diarrhoea	6 (15.0)	31 (21.1)	15 (12.8)
Anaemia	6 (15.0)	16 (10.9)	11 (9.4)
Abdominal pain	6 (15.0)	12 (8.2)	8 (6.8)
Hyponatraemia	6 (15.0)	9 (6.1)	3 (2.6)
Gamma-glutamyl transferase elevated	5 (12.5)	*4 (2.7)*	*2 (1.7)*
Nausea	4 (10.0)	*8 (5.4)*	*9 (7.7)*
Decreased appetite	4 (10.0)	*13 (8.8)*	*5 (4.3)*

*For the NAPOLI-1 trial, analyses are for the safety population
†Data reported for fatigue/asthenia combined in the NCT00813163 study but reported separately for the NAPOLI-1 trial; hence for the NAPOLI-1 trial the data have been combined by adding the two categories together in this table *(Note: data for nal-iri+5-FU/LV arm provided by the company following company's check for factual inaccuracies)*
Source: CS, Table 31 and Table 32

ADDENDUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pegylated liposomal irinotecan hydrochloride trihydrate for treating pancreatic cancer after gemcitabine [ID778]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/121/02

21 July 2016

UNIVERSITY OF LIVERPOOL
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Correction to Table 60

The Evidence Review Group (ERG) would like to notify the appraisal committee of an amendment in its report for the appraisal of pegylated liposomal irinotecan hydrochloride trihydrate (nal-iri) in combination with 5-fluorouracil (5-FU) and folinic acid (LV) for the treatment of metastatic adenocarcinoma of the pancreas, in adult patients who have progressed following gemcitabine-based therapy. The alternative ICER estimates for Scenario B and C in Table 60 of the ERG report were reported incorrectly (the ICER estimates for Scenario B were reported as Scenario C and vice versa). Please find the corrected table below.

Table 60 Alternative ICER estimates for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV

Scenario	ICER per QALY gained
Base case	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	[redacted]
ERG scenario B	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	[redacted]
ERG scenario C	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	[redacted]
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	[redacted]

ERG=Evidence Review Group; QALY=quality adjusted life year; ICER=incremental cost effectiveness ratio

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

Pegylated liposmal irinotecan for the treatment of metastatic adenocarcinoma of the pancreas, in adult patients who have progressed following gemcitabine-based therapy (ID778)

July 2016

File name	Version	Contains confidential information	Date submitted
		YES	11.07.2016

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Pegylated liposmal irinotecan (Onivyde ®) for the treatment of metastatic adenocarcinoma of the pancreas in adult patients who have progressed following gemcitabine-based therapy. In this form the name nal-IRI will be used for this technology.

3.2 Please outline the rationale for developing the patient access scheme.

The simple discount PAS is a mechanism through which the NHS will be able to procure nal-IRI at net prices lower than the current list prices. This discount results in a price that is cost-effective versus current treatment alternatives.

The proposed patient access scheme is a simple discount to the nal-IRI list price. The discounts will apply at the point of invoicing nal-IRI. The scheme for nal-IRI will only be implemented upon publication of positive NICE guidance.

Should the list price for nal-IRI change, the percentage discount will change accordingly to maintain a fixed net price

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

Financially-based scheme: simple discount to list price. The amount of discount and net price will remain commercial in confidence.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?

- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The scheme applies to the entire population for whom nal-IRI has been licensed, namely metastatic adenocarcinoma of the pancreas patients who have progressed following gemcitabine-based therapy.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

Following positive NICE guidance for nal-IRI under the current NICE appraisal, the PAS will apply to all supplies and preparations of nal-IRI and is applicable to all current and future indications. No additional criteria will need to be met.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

The scheme is applicable to 100% of the population treated with nal-IRI in the NHS in England and Wales.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

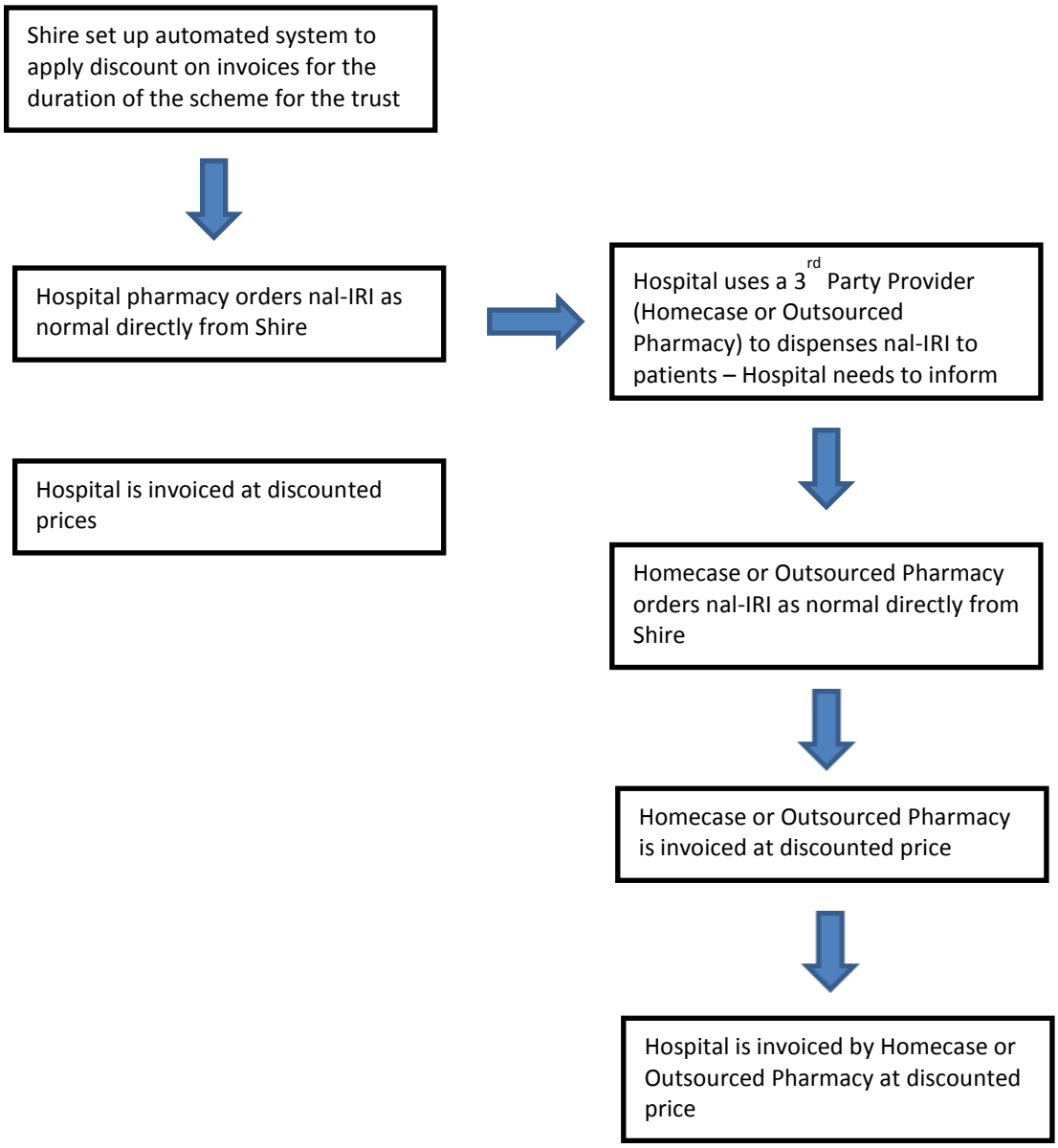
The discount will be applied at the point of invoicing for purchases of nal-IRI packs made by NHS Providers on behalf of NHS patients. The proposed discount will be reflected in the invoice. The amount of discount and net price will remain commercial in confidence.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

There will be no need to collect any additional information.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

The scheme will not require any additional NHS resource to access the PAS net price as hospital pharmacy will operate the standard NHS pharmacy procurement procedure to order nal-IRI directly from Shire.


Shire set up automated system to apply discount on invoices for the duration of the scheme for the trust
Hospital pharmacy orders nal-IRI as normal directly from Shire
Hospital is invoiced at discounted prices
Hospital uses a 3rd Party Provider (Homecase or Outsourced Pharmacy) to dispenses nal-IRI to patients – Hospital needs to inform
Homecase or Outsourced Pharmacy orders nal-IRI as normal directly from Shire
Homecase or Outsourced Pharmacy is invoiced at discounted price
Hospital is invoiced by Homecase or Outsourced Pharmacy at discounted price

3.10 Please provide details of the duration of the scheme.

Subject to positive NICE guidance for nal-IRI under the current NICE appraisal, the proposed scheme will be in place until NICE review of the guidance, subject to the usual NICE review process

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues relating to this scheme.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

The discount will apply automatically and will not require any additional documentation.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

N/A, the scheme proposed is a financial scheme (simple discount at the point of invoice).

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

The population to whom the scheme applies has been presented in the main submission of evidence

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Not applicable

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

In the economic model the simple discount has been incorporated by decreasing the list price per package of nal-IRI from £[redacted] per 50 mg vial to £[redacted] per 50mg vial (a [redacted]% decrease in the list price). The discount was

incorporated in the model in the sheet “Parameters” by changing cell D14, the cost per mg of nal-IRI, from £[redacted] to £[redacted].

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The clinical effectiveness data submitted for the current NICE appraisal of nal-IRI are not affected by the simple PAS offered on the nal-IRI list price.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the ‘Specification for manufacturer/sponsor submission of evidence’.

The proposed scheme consists of a simple discount, and therefore there will be no additional costs associated with its implementation and operation in NHS England and Wales.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Implementation of this scheme will not incur additional treatment-related costs. Treatment costs for the NHS in England and Wales will in fact be reduced whilst all other elements of the treatment pathway will remain unchanged.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

Table 3 Base-case cost-effectiveness results without PAS

	Nal-IRI+5-FU/LV	5-FU/LV	Oxaliplatin+5-FU/LV
Intervention cost (£)	[redacted]	£971	£4,450
Other costs (£)	£13,160	£12,367	£9,525
Total costs (£)	[redacted]	£13,338	£13,975
Difference in total costs (£)	N/A	[redacted]	[redacted]
LYG	0.8474	0.6388	0.5351
LYG difference	N/A	0.2086	0.3123
QALYs	0.5631	0.4290	0.3619
QALY difference	N/A	0.1341	0.2012
ICER (£)	N/A	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 4 Base-case cost-effectiveness results with PAS

	Nal-IRI+5-FU/LV	5-FU/LV	Oxaliplatin+5-FU/LV
Intervention cost (£)	£12,540	£971	£4,450
Other costs (£)	£11,243	£9,925	8,453
Total costs (£)	£23,848	£10,897	£12.903
Difference in total costs (£)	N/A	£12,952	£10,945
LYG	0.8474	0.6388	0.5351
LYG difference	N/A	0.2086	0.3123
QALYs	0.5631	0.4290	0.3619
QALY difference	N/A	0.1341	0.2012
ICER (£)	N/A	£96,591	£54,412

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 5 Base-case incremental results without PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
5-FU/LV	£13,338	0.6388	0.4290	N/A	N/A	N/A	N/A	N/A
Oxaliplatin+5-FU/LV	£13,975	0.5351	0.3619	£637	-0.1037	-0.0671	£9,491 (NW quadrant)	£9,491 (NW quadrant)
Nal-IRI+5-FU/LV	[redacted]	0.8474	0.5631	[redacted]	0.2086	0.1341	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 6 Base-case incremental results with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
5-FU/LV	£10,897	0.6388	0.4290	N/A	N/A	N/A	N/A	N/A
Oxaliplatin+5-FU/LV	£12,903	0.5351	0.3619	£2,007	-0.1037	-0.0671	£29,921 (NW quadrant)	£29,921 (NW quadrant)
Nal-IRI+5-FU/LV	£23,848	0.8474	0.5631	£12,952	0.2086	0.1341	£96,591	£54,412

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Figure 1 Deterministic sensitivity analysis vs 5-FU/LV without PAS

[redacted]

Figure 2 Deterministic sensitivity analysis vs 5-FU/LV with PAS

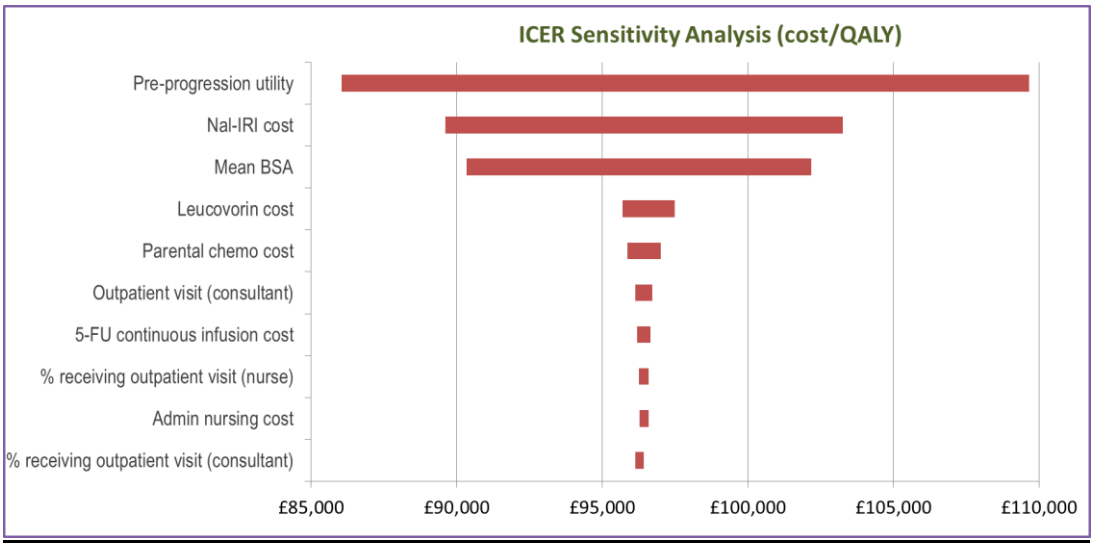
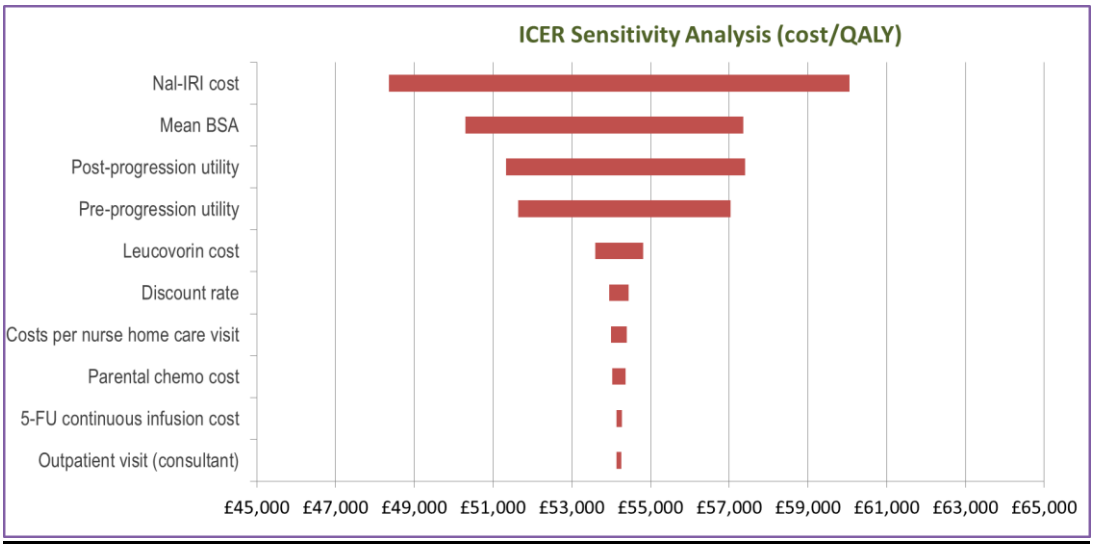


Figure 3 Deterministic sensitivity analysis vs oxaliplatin+5-FU/LV without PAS

[redacted]

Figure 4 Deterministic sensitivity analysis vs oxaliplatin+5-FU/LV with PAS



4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Figure 5 Probabilistic sensitivity analysis vs 5-FU/LV without PAS

[redacted]

Figure 6 Probabilistic sensitivity analysis vs 5-FU/LV with PAS

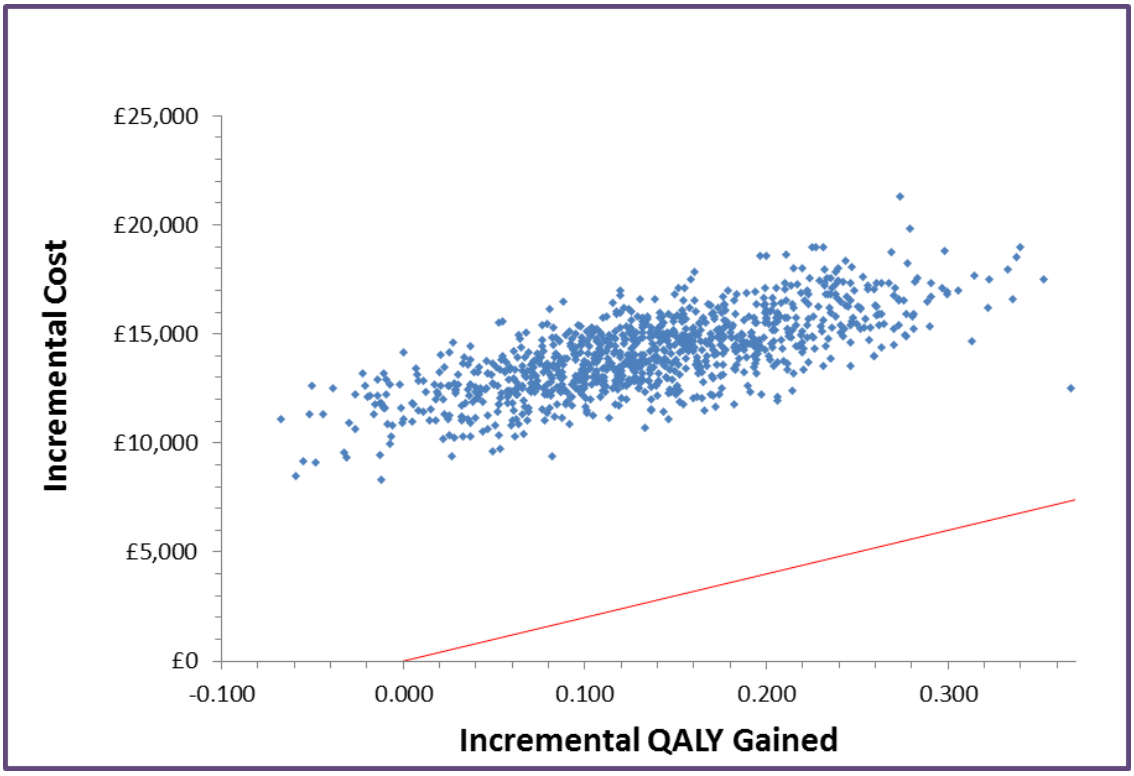
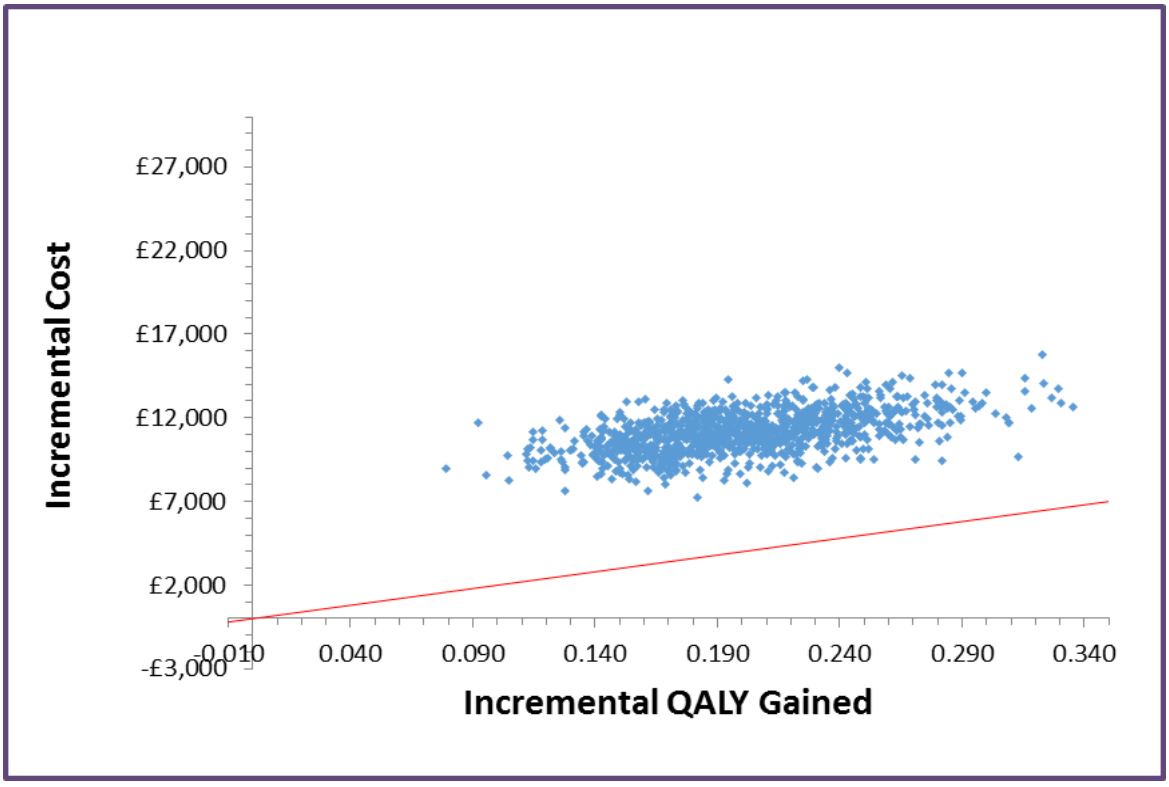


Figure 7 Probabilistic sensitivity analysis vs oxaliplatin+5-FU/LV without PAS

[redacted]

Figure 8 Probabilistic sensitivity analysis vs oxaliplatin+5-FU/LV with PAS



4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Response

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 5 Results showing the impact of patient access scheme on ICERs

	ICER for intervention versus:				
	Comparator 1		**Comparator 2**		**…**
	Without PAS	**With PAS**	**Without PAS**	**With PAS**	
Scenario 1 (base-case)					
Scenario 2					
Scenario 3					
Scenario 4					
…					

PAS: patient access scheme.

5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

These documents are currently being finalised with PASLU and DH. Shire will share them with NICE as soon as they become available.

5.2 Appendix B: Details of outcome-based schemes

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

N/A

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

N/A

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

N/A

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

N/A

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

N/A

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

N/A

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

N/A

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

STA Report

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pegylated liposomal irinotecan hydrochloride trihydrate for treating pancreatic cancer after gemcitabine [ID778]

Confidential appendix including nal-iri discount:

1. nal-iri+5-FU/LV versus oxaliplatin+5-FULV

2. nal-iri+5-FU/LV versus 5-FU/LV

This report was commissioned by the NIHR HTA Programme as project number 15/121/02

18 July 2016

CONTAINS CIC DATA

ALL TABLES AND FIGURES IN THIS APPENDIX ARE CONFIDENTIAL

1 INTRODUCTION

As part of the National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) process to consider the clinical and cost effectiveness of pegylated liposomal irinotecan hydrochloride trihydrate (nal-iri) in combination with 5-fluorouracil (5-FU) and folinic acid (LV) for the treatment of metastatic adenocarcinoma of the pancreas in adult patients who have progressed following gemcitabine-based therapy, Baxalta (the company) developed an economic model using MS Excel.

In the company submission (CS), cost effectiveness results are presented for comparisons between nal-iri+5-FU/LV versus 5-FU/LV monotherapy, and nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV using list prices only. The Evidence Review Group (ERG) report for this appraisal summarises the cost effectiveness results presented in the CS. In addition, the ERG report includes results generated after applying a number of ERG amendments to the company model. Again, the results presented in the ERG report have been generated using list prices for all drugs.

The amendments made by the ERG to the company model for the two base case comparisons are outlined below:

Nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV

- Use of 5-FU/LV pre-progression time on treatment curve for oxaliplatin+5-FU/LV (R1)
- Full dose intensity (R2)
- Use of ERG preferred body surface area (BSA) and drug acquisition costs (R3)
- Use of ERG preferred post-progression treatment costs (R4)
- Use of ERG adverse event (AE) costs (R5)
- Use of ERG preferred health state utility values (R6)
- Application of ERG terminal disutility estimates (R7)
- ERG OS for nal-iri+5-FU/LV (R8)
- ERG PFS for nal-iri+5-FU/LV (R9)
- ERG time on treatment for nal-iri+5-FU/LV (R10).

Nal-iri+5-FU/LV versus 5-FU/LV

- ERG OS, PFS and time on treatment (R1)
- Full dose intensity (R2)
- Use of ERG preferred BSA and drug acquisition costs (R3)
- Use of ERG preferred post-progression treatment costs (R4)
- Use of ERG AE costs (R5)
- Use of ERG preferred health state utility values (R6)
- Application of ERG terminal disutility estimates (R7).

This confidential appendix includes the deterministic cost effectiveness results generated by the company model when the confidential patient access scheme (PAS) discount is applied to nal-iri drug costs in the comparisons between nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV combination therapy, and nal-iri+5-FU/LV versus 5-FU/LV monotherapy.

2 DETERMINISTIC RESULTS

Cost effectiveness results (using PAS prices for nal-iri) for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV combination therapy and nal-iri+5-FU/LV versus 5-FU/LV monotherapy following ERG amendments are displayed in Table 1 and Table 2, respectively. Alternative incremental cost effectiveness ratios (ICERs) examining a selection of clinical effectiveness assumptions on the base case, Scenario B and Scenario C, for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV are presented in Table 3.

It is important to note that when the PAS is applied in the company model, the costs of the oxaliplatin+5-FU/LV and 5-FU/LV regimens change due to the company's post-progression treatment costing assumptions; which assume a proportion of patients in the post-progression health state receive treatments after progression where the weekly costs are equivalent to the weekly drug costs of nal-iri+5-FU/LV. For clarity, the effect of removing this inappropriate relationship (R4) is incorporated into the corrected company base case scenario (A) in Table 1 and Table 2. This allows the effect of the other ERG model amendments to be compared without interference from R4.

The results show that, once the relevant PAS discount is applied to nal-iri, nal-iri+5-FU/LV remains more expensive than both of the base case comparators in the company model, and when all of the ERG's suggested amendments have been implemented.

CONFIDENTIAL APPENDIX

The ERG's revised base case ICER per QALY gained for nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV, when all its preferred revisions are combined and using the PAS price for nal-iri is above £90,000 for scenarios B and C. The ICERs for nal-iri+5-FU/LV versus 5-FU/LV do not fall within a threshold that NICE would consider to be cost effective.

Table 1 Cost effectiveness results (nal-iri+5-FU/LV vs oxaliplatin+5-FU/LV) ERG revisions with PAS included for nal-iri (discount=[redacted] %)

Model scenario ERG revision	Nal-iri+5-FU/LV			Oxaliplatin+5-FU/LV			Incremental			ICER
	Cost	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**£/QALY**
**Original CS base case*	[redacted]	0.564	0.847	£12,903	0.362	0.535	[redacted]	+0.201	+0.312	£54,366
*Corrected Company base case***	[redacted]	*0.563*	*0.847*	*£12,903*	*0.362*	*0.535*	[redacted]	*+0.201*	*+0.312*	*£54,412*
*A. Corrected** company base case + R4 ERG post-progression treatment costs*	[redacted]	0.563	0.847	£11,034	0.362	0.535	[redacted]	+0.201	+0.312	£47,264
R1. 5-FU/LV pre-progression time on treatment curve for oxaliplatin+5-FU/LV	[redacted]	0.563	0.847	£7,561	0.362	0.535	[redacted]	+0.201	+0.312	£64,526
R2. Full dose intensity	[redacted]	0.563	0.847	£11,732	0.362	0.535	[redacted]	+0.201	+0.312	£52,458
R3. ERG BSA & drug acquisition costs	[redacted]	0.563	0.847	£6,827	0.362	0.535	[redacted]	+0.201	+0.312	£56,733
R5. ERG AE costs	[redacted]	0.563	0.847	£12,015	0.362	0.535	[redacted]	+0.201	+0.312	£48,216
R6. ERG health state utilities	[redacted]	0.504	0.847	£11,034	0.324	0.535	[redacted]	+0.180	+0.312	£52,903
R7. ERG terminal disutility	[redacted]	0.552	0.847	£11,034	0.356	0.535	[redacted]	+0.196	+0.312	£48,413
R8. ERG OS	[redacted]	0.527	0.782	£11,034	0.362	0.535	[redacted]	+0.165	+0.247	£56,758
R9. ERG PFS	[redacted]	0.565	0.847	£11,034	0.362	0.535	[redacted]	+0.203	+0.312	£46,035
R10. ERG Time on treatment	[redacted]	0.563	0.847	£11,034	0.362	0.535	[redacted]	+0.201	+0.312	£51,408
B. R1:R10	[redacted]	0.465	0.782	£5,809	0.318	0.535	[redacted]	+0.147	+0.247	£106,898
C. R2:R10	[redacted]	0.465	0.782	£7,838	0.318	0.535	[redacted]	+0.147	+0.247	£93,098

Costs and QALYs discounted; life years undiscounted
BSA=body surface area; CS=company submission; ERG=Evidence Review Group; QALYs=quality adjusted life years
*Original base case estimate with error ** The corrected base case ICER estimate removes an error in the post progression utility value in company model

Table 2 Cost effectiveness results (nal-iri+5-FU/LV vs 5-FU/LV): ERG revisions with PAS included for nal-iri (discount=[redacted] %)

Model scenario ERG revision	Nal-iri+5-FU/LV			5-FU/LV			Incremental			ICER
	Cost	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**£/QALY**
****Original CS base case***	[redacted]	**0.564**	**0.847**	**£10,897**	**0.429**	**0.639**	[redacted]	**0.134**	**+0.209**	**£96,601**
Corrected Company base case**	[redacted]	***0.563***	***0.847***	***£10,897***	***0.429***	***0.639***	[redacted]	***0.134***	***+0.209***	***£96,591***
A. Corrected** company base case + R4 ERG post-progression treatment costs	[redacted]	**0.563**	**0.847**	**£6,643**	**0.429**	**0.639**	[redacted]	**0.134**	**+0.209**	**£103,647**
R1. ERG OS, PFS, time on treatment	[redacted]	0.529	0.782	£7,473	0.429	0.637	[redacted]	+0.100	+0.145	**£137,354**
R1a. ERG OS	[redacted]	0.527	0.782	£6,634	0.426	0.637	[redacted]	+0.101	+0.145	**£136,807**
R1b. ERG PFS	[redacted]	0.565	0.847	£6,673	0.431	0.639	[redacted]	+0.134	+0.209	**£102,546**
R1c. ERG time on treatment	[redacted]	0.563	0.847	£7,482	0.429	0.639	[redacted]	+0.134	+0.209	**£103,610**
R2. Full dose intensity	[redacted]	0.563	0.847	£6,691	0.429	0.639	[redacted]	+0.134	+0.209	**£116,295**
R3. ERG BSA & drug acquisition costs	[redacted]	0.563	0.847	£5,728	0.429	0.639	[redacted]	+0.134	+0.209	**£93,300**
R5. ERG AE costs	[redacted]	0.563	0.847	£6,901	0.429	0.639	[redacted]	+0.134	+0.209	**£110,472**
R6. ERG health state utilities	[redacted]	0.504	0.847	£6,643	0.384	0.639	[redacted]	+0.120	+0.209	**£116,147**
R7. ERG terminal disutility	[redacted]	0.552	0.847	£6,643	0.418	0.639	[redacted]	+0.135	+0.209	**£103,322**
B. R1:R7	[redacted]	**0.465**	**0.782**	**£6,648**	**0.374**	**0.637**	[redacted]	**+0.091**	**+0.145**	**£162,887**

Costs and QALYs discounted; life years undiscounted
BSA=body surface area; ERG=Evidence Review Group; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; TTF=time to treatment failure

*original base case estimate with error **The corrected base case ICER estimate removes an error in the post progression utility value in company model

Table 3 Alternative ICER estimates for the comparison of nal-iri+5-FU/LV versus oxaliplatin+5-FU/LV with PAS included for nal-iri (discount= [redacted] %)

Scenario	ICER per QALY gained
Base case	**£54,412**
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	£129,162
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	Nal-iri+5-FU/LV DOMINATED
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	Nal-iri+5-FU/LV additional cost = £10,945
ERG scenario B	**£106,898**
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	£201,019
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	Nal-iri+5-FU/LV DOMINATED
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	Nal-iri+5-FU/LV additional cost = £15,720
ERG scenario C	**£93,098**
Oxaliplatin+5-FU/LV total QALYs 10% less than nal-iri+5-FU/LV	£175,067
Oxaliplatin+5-FU/LV total QALYs 10% more than nal-iri+5-FU/LV	Nal-iri+5-FU/LV DOMINATED
Oxaliplatin+5-FU/LV total QALYs equal to nal-iri+5-FU/LV	Nal-iri+5-FU/LV additional cost = £13,691

ERG=Evidence Review Group; QALY=quality adjusted life year; ICER=incremental cost effectiveness ratio