NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Shire Pharmaceuticals
   - *Joint response from* Pancreatic Cancer Action and Pancreatic Cancer UK

3. **Comments on the Appraisal Consultation Document received through the NICE website**

The Department of Health submitted a 'no comments' response.
There were no individual comments received from the clinical or patient experts.

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

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Single Technology Appraisal

Pegylated liposomal irinotecan for treating pancreatic cancer after gemcitabine

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Pancreatic Cancer UK	Pancreatic cancer is the fifth leading cause of cancer death in the UK 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% (5.4% in England in 2014) and a ten year survival of less than 1%. Metastatic pancreatic cancer patients have a median survival of between just 2 – 6 months. Pancreatic cancer is not a rare cancer – around 9,400 cases were diagnosed in 2013 - 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, 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.	Comments noted. The patient perspective was acknowledged by the committee, including the value of additional treatment options See FAD section 4.1
Pancreatic Cancer UK	Currently, the only NICE approved treatment for pancreatic cancer is gemcitabine. There is no recognised standard second line treatment option for metastatic pancreatic cancer patients who have previously received gemcitabine-based therapy.	Comments noted. The committee were aware of the treatment options available in clinical practice in England after gemcitabine treatment. See FAD section 4.2

Consultee	Comment [sic]	Response
Pancreatic Cancer UK	Being diagnosed with a disease that has such a poor prognosis and few treatment options 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”. We desperately need promising new treatments to be made available to patients to improve patient choice, give clinicians vital new weapons in their arsenal and ultimately improve survival rates. As such we are disappointed at the appraisal committee’s draft conclusion that Pegylated liposomal irinotecan (Onivyde) - which trial data has shown offers a significant survival benefit over 5FU and LV, as well as a manageable safety profile[i] - should not be recommended for use on the NHS.	Comments noted. The patient perspective was acknowledged by the committee, including the value of additional treatment options See FAD section 4.1
Pancreatic Cancer UK	Are the summaries of clinical and cost effectiveness reasonable given the evidence? Pancreatic Cancer UK, Pancreatic Cancer Action and the APPG on Pancreatic Cancer greatly appreciate the need to ensure value for money, given increasing pressures on precious NHS resources. However, considering the urgent unmet need facing this patient population, for which there has been hardly any improvement in survival over the last 40 years, it is important that promising new treatments are prioritised if we are to see any improvement in these appalling survival rates. We are therefore disappointed that NICE has not determined the drug to be cost or clinically effective at this time.	Comments noted. The committee were aware of the poor prognosis and lack of treatment options for metastatic adenocarcinoma of the pancreas that has progressed after gemcitabine. See FAD section 4.1

Consultee	Comment [sic]	Response
Pancreatic Cancer UK	We welcome that a Patient Access Scheme was put forward by the manufacturer and considered by NICE. We would strongly welcome any further discussions between industry and NICE on price, given the importance of new effective treatments being made available on the NHS to this patient population.	Comments noted.
Pancreatic Cancer UK	The committee concludes that the treatment has a similar clinical effectiveness as FOLFOX. Whilst we largely accept this conclusion, it is worth noting that although the CONKO trial shows an overall survival benefit similar to that shown by Onivyde in the NAPOLI-1 trial, a separate trial, PANCREOX, concluded that there was no benefit to FOLFOX vs 5FU and folinic acid alone .This raises some ambiguity over the clinical effectiveness of FOLFOX.	Comments noted.
Pancreatic Cancer UK	Due to the lack of treatment options and the extremely poor survival rates associated with pancreatic cancer, we regret that the committee has determined the treatment should not be considered under end of life criteria. Although we accept that 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 with marketing authorisation for second line therapy. The committee argues that the treatment cannot be said to offer a survival gain over FOLFOX. Whilst FOLFOX is used in some clinical practice, it is important to bear in mind that there remains no licensed, standard second-line treatment for pancreatic cancer. There are as such limitations to comparing FOLFOX with Onivyde combination therapy.	Comments noted.

Consultee	Comment [sic]	Response
Pancreatic Cancer UK	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? The APPG on Pancreatic Cancer, Pancreatic Cancer UK and Pancreatic Cancer Action are disappointed at the provisional recommendation not to recommend Onivyde for use on the NHS. As previously highlighted, metastatic pancreatic cancer patients face very limited treatment options, meaning it is vital that new effective treatment options are made available to patients as quickly as possible. Whilst such treatment options might only offer incremental survival gains, this is essential to making longer term improvements in overall survival.	Comments noted. The committee recognised the value of additional treatment options. See FAD section 4.1
Pancreatic Cancer UK	The committee compares the effectiveness of Onivyde combination therapy to FOLFOX, which is used as an off-label second-line treatment in clinical practice in the UK where patients are fit enough. However, as already stressed, there is currently no standard second-line treatment option for pancreatic cancer patients who have previously received gemcitabine-based therapy, let alone a licensed option. A NICE approval of Onivyde would therefore be of particular importance, providing an extra option – above and beyond the limited off-label treatments - for patients who have had prior treatment with gemcitabine.	Comments noted. See above response.
Pancreatic Cancer UK	In addition, Onivyde causes significantly less neuropathy in patients than FOLFOX, meaning it could prove more tolerable to some patients. Patients should therefore not be denied this treatment option.	The adverse events associated with pegylated liposomal irinotecan plus 5-FU and LV were discussed by the committee. See FAD section 4.3
Pancreatic Cancer UK	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.	The patient perspective was acknowledged by the committee, including the value of additional treatment options See FAD section 4.1

Consultee	Comment [sic]	Response
Pancreatic Cancer UK	We have heard from patients and carers who are “very disappointed” by the committee’s draft decision: “It’s another step on the path to England becoming a backwater for pancreatic cancer treatment. Compared to other European countries our survival rates are already poor and we’re going to be left further and further behind.” (Patient and carer testimony) This is concerning as it feeds into the sense of nihilism patients, carers and clinicians have all reported when it comes to pancreatic cancer treatments.	Comments noted. The Institute recognises that guidance from other organizations may differ from its own guidance, because of different criteria for making decisions. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company submission and the ERG report.
Pancreatic Cancer UK	It echoes fears we heard from patients following the removal of Abraxane from the Cancer Drugs Fund that: “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) This is of particular concern given that we know that giving patients with advanced disease an extra treatment choice is an advantage in itself, considering the limited number of treatment options currently available.	Comments noted. The committee recognised the value of additional treatment options. See FAD section 4.1
Pancreatic Cancer UK	Patients and carers have previously told 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. 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) We would therefore, urge the committee to reconsider the current ACD decision that Onivyde combination therapy for treating gemcitabine-refractory pancreatic cancer patients should not be recommended for use available for use on the NHS.	Comments noted. See above response.

Consultee	Comment [sic]	Response
Pancreatic Cancer UK	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. It is therefore essential that new effective treatments are made available to pancreatic cancer patients for the kind of improvements in survival we need to be achieved. Clinicians need more weapons in their arsenal and patients want to know that there are more treatment options open to them.	Comments noted. The committee were aware of the poor prognosis and lack of treatment options for metastatic adenocarcinoma of the pancreas that has progressed after gemcitabine. See FAD section 4.1
Pancreatic Cancer UK	Onivyde offers the opportunity for an approved treatment option for patients who have progressed post treatment with gemcitabine.	Comments noted. See above response.
Shire	Shire welcomes the opportunity to comment on the Appraisal Consultation Document (ACD). We understand that NICE welcomes comments on whether all of the relevant evidence has been taken into account, whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and whether the recommendations are sound and a suitable basis for guidance to the NHS. As outlined below, our comments are mainly concerned with whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.	Comments noted. The committee recognised the value of additional treatment options. See FAD section 4.1
Shire	Shire is disappointed with the preliminary decision not to recommend pegylated liposomal irinotecan (hereafter referred to as nal-IRI) in combination with 5-fluorouracil (5 FU) and leucovorin (LV) within its marketing authorisation for treating metastatic adenocarcinoma of the pancreas in adults whose disease has progressed following gemcitabine-based therapy. Gemcitabine is currently the only treatment that is approved by NICE for use in treating pancreatic cancer in England. Before the regulatory approval of nal-IRI, there were no licensed treatments for patients with metastatic pancreatic cancer who have progressed following gemcitabine-based therapy.	Comments noted.

Consultee	Comment [sic]	Response
Shire	Pancreatic cancer is a very severe and life-threatening disease with an exceptionally short life expectancy at diagnosis (median 4.6 months) and a particularly high burden of illness. In a recent systematic review of 91 peer-reviewed observational studies in pancreatic cancer, a median overall survival from diagnosis of 4.6 months was reported (1). The outlook for patients with pancreatic cancer has hardly improved since the 1970s, despite incidence rates rising by 8% in the last decade in the UK (2, 3). This is in contrast to other cancers that have seen significant improvements in overall survival over the last 5 years, and pancreatic cancer has been predicted to become the second leading cause of cancer-related death by 2030 (4). There is a substantial unmet need for new effective treatments to become available for patients.	Comments noted. The committee were aware of the poor prognosis and lack of treatment options for metastatic adenocarcinoma of the pancreas that has progressed after gemcitabine. See FAD section 4.1
Shire	Progression in metastatic disease is inevitable, illustrated by the fact that treatment with gemcitabine has been shown to be associated with a poor response rate (20% or less) and short median progression-free survival (<4 months) in the first-line setting in clinical trials (5, 6). In addition, gemcitabine is increasingly being used as adjuvant treatment (5). For these reasons, patients who fail on gemcitabine-based therapy form a substantial patient pool, yet are currently poorly served, with no licensed or NICE recommended treatments available.	Comments noted.
Shire	There is robust evidence supporting overall survival improvements with nal-IRI+5-FU/LV from NAPOLI-1, which is the largest randomised, controlled, international, multi-centre, Phase 3 trial in patients with pancreatic cancer that have progressed following failure with gemcitabine-based therapy. Results showed that nal IRI+5-FU/LV, compared with 5-FU/LV, had statistically significantly longer: • Overall survival (median 6.1 vs 4.2 months; a 45% relative median survival gain; unstratified hazard ratio 0.67; p=0.0122), • Progression-free survival (median 3.1 vs 1.5 months; hazard ratio 0.56; p=0.0001), and • Time to treatment failure (median 2.3 vs 1.4 months; hazard ratio 0.60; p=0.0002). All of these results are highly clinically meaningful for patients facing such a short life expectancy, as is inevitable with pancreatic cancer.	Comments noted. The committee discussed the overall survival and progression free survival seen in NAPOLI-1. See FAD section 4.3

Consultee	Comment [sic]	Response
Shire	Importantly, nal-IRI was generally well tolerated in most patients, with a predictable toxicity profile and adverse events that are common with irinotecan-based chemotherapy and have management protocols available. In addition, the quality of life results from NAPOLI-1 showed no substantial differences between treatment arms, suggesting that there were no negative effects of adding nal-IRI to 5-FU/LV on health-related quality of life. This is also very important given the improvement seen in overall survival, the potential for tolerability concerns with chemotherapy regimens, and the fact that patients are generally in poor health from the effects of the underlying disease and previous treatments.	The adverse events associated with pegylated liposomal irinotecan plus 5-FU and LV were discussed by the committee. See FAD section 4.3
Shire	Shire believes that patients with pancreatic cancer who have progressed following gemcitabine-based therapy should be able to benefit from access to nal-IRI, a novel and beneficial treatment in an area of high unmet needs. We believe that the summaries of cost-effectiveness contained within the ACD are not reasonable interpretations of the evidence available, and thus the provisional decision not to recommend nal-IRI+5-FU/LV is unsound and will limit the availability of this important therapy for patients with metastatic pancreatic cancer whose disease has progressed following gemcitabine-based therapy. In particular, we would like to comment on the following points: 1. The method of comparison for nal-IRI+5-FU/LV vs oxaliplatin+5-FU/LV 2. The use of parametric modelling vs Kaplan-Meier data 3. Cost savings as a result of nal-IRI dose reductions 4. Chemotherapy cost calculations 5. The innovation of nal-IRI 6. The consideration of nal-IRI+5-FU/LV as an end-of-life medicine. These points are discussed in Sections 1-6, and miscellaneous further points are discussed in Section 7 We sincerely encourage the committee to reconsider its draft guidance in light of our comments.	Comments noted. The committee recognised the value of additional treatment options. See FAD section 4.1

Consultee	Comment [sic]	Response
Shire	1. The method of comparison for nal-IRI+5-FU/LV vs oxaliplatin+5 FU/LV Shire strongly believes that the indirect treatment comparison (ITC) performed by the company, despite its acknowledged limitations, provides a much sounder basis for decision making than the use of a 'crude comparison' by the Evidence Review Group (ERG).	Comments noted. The committee agreed that the ERG was unable to produce a reliable estimate of the difference in overall survival between pegylated liposomal irinotecan plus 5-FU and LV and oxaliplatin plus 5-FU and LV. See FAD section 4.15
Shire	The RCTs (NAPOLI-1, PANCREOX and CONKO-003) included in the submitted ITC all treated patients with pancreatic cancer who had progressed following gemcitabine-based therapy. These trials are the only available trials with a clinically comparable trial design, population, and with a common comparator. Two of the trials identified by the ERG (Yoo et al (5) and SWOG (7)) can only take a single arm that is relevant, since the comparators in these trials are not relevant to current clinical practice or to the comparison between nal IRI+5 FU/LV and oxaliplatin+5-FU/LV. In addition, the trial reported by Yoo et al identified by the ERG was noted as having a notably lower overall survival and progression-free survival with oxaliplatin+5 FU/LV compared with the other identified trials, and therefore was dismissed from the crude comparison. This amounts to a biased selection of the available evidence for inclusion in the crude comparison.	Comments noted. See above response.

Consultee	Comment [sic]	Response
Shire	A crude comparison should not be used for decision making. It is incorrect to simply compare single arms from trials, since this fails to separate the efficacy of the drugs from other effects, e.g. placebo effects, baseline patient characteristics and risks, prior treatment, local practice, and historical context. An illustration of this is that the populations in PANCREOX and CONKO-003 had received, on average, fewer prior treatments and included a lower percentage of patients with metastatic disease than the patients in NAPOLI-1. The effect that these trial/patient characteristics can have on an outcome, and thus the unsuitability of directly comparing single treatment arms from different trials, is highlighted by reported differences in treatment effects between trials, for example the 'anomaly' in overall survival and progression-free survival reported by Yoo et al for oxaliplatin+5-FU/LV, as described above, and the different results for the 5 FU/LV arms in CONKO-003 (median overall survival of 3.3 months (8)) and PANCREOX (median overall survival of 9.9 months (9)). In addition, the European Society for Medical Oncology (ESMO) guidelines (10) specifically refer to the conflicting results found for oxaliplatin for the treatment of pancreatic cancer: "*Second-line therapy of pancreatic cancer has to be considered in terms of risk benefit for the patient. If the general status remains correct, considering the conflicting results on the use of oxaliplatin, MM-398 [nal-IRI] when available in all countries may be the best option for second-line treatment of these patients."*	Comments noted. See above response.
Shire	Using data only from treatment arms of interest is flawed, naïve, biased, and is not methodologically appropriate, based on the ISPOR Task Force on Good Research Practices (11). Indeed, this is reinforced by NICE guidance for the reference case, which states that "it is not acceptable to compare results from single treatment arms from different randomised trials". The clinical opinion provided at the NICE meeting on 27 July 2016 was that the crude comparison performed by the ERG was not viable to compare between treatments. Indeed, the ERG itself acknowledges that caution should be taken in interpreting its crude comparison "due to potential differences in the trial populations and advises that they should be considered, at best, to be exploratory".	Comments noted. See above response.

Consultee	Comment [sic]	Response
Shire	The Bucher adjusted (or anchored) method for indirect comparison (12) is designed to preserve randomisation and compare the magnitude of the treatment effect between two treatments relative to a common comparator (13), thus incorporating possible within-trial placebo effects, baseline patient characteristics and baseline risks. For these reasons, Shire strongly believes that, despite its limitations and underlying uncertainties due to cross-trial heterogeneity, the ITC performed in the original submission provides a more technically sound comparison of nal IRI+5-FU/LV vs oxaliplatin+5-FU/LV than the crude comparison performed by the ERG, which the committee have used for their preliminary ACD decision.	Comments noted. Recognising the uncertainty in the indirect comparison the committee concluded that the company's hazard ratios could not be considered reliable for comparing the relative treatment effect of pegylated liposomal irinotecan plus 5-FU and LV with oxaliplatin plus 5-FU and LV, but the clinical effectiveness of pegylated liposomal irinotecan plus 5-FU and LV could be considered broadly similar to oxaliplatin plus 5-FU and LV. See FAD section 4.5
Shire	2. The use of parametric modelling vs Kaplan-Meier data The committee concluded that Kaplan-Meier data was more appropriate than parametric modelling for use in the comparison of overall survival and progression-free survival between nal-IRI+5 FU/LV and oxaliplatin+5 FU/LV. However, Shire disagrees, and feels that parametric modelling is the most appropriate method since the Kaplan-Meier data were not available for PANCREOX and CONKO-003, and therefore the survival curves needed to be modelled in order to enable the required cost-effectiveness comparison. This meant that it was necessary to use a parametric model for nal-IRI+5 FU/LV so that the hazard ratio for oxaliplatin+5 FU/LV could be applied. Comparing the Kaplan-Meier data for nal-IRI+5 FU/LV to the modelled survival for oxaliplatin+5 FU/LV, which was calculated using the parametric curves for nal-IRI+5 FU/LV, is biased against nal-IRI+5 FU/LV.	The committee concluded that because the data for progression-free survival and time on treatment are complete and virtually complete for overall survival, using the Kaplan–Meier data from NAPOLI-1 was more appropriate than the company's parametric modelling. See FAD section 4.7.

Consultee	Comment [sic]	Response
Shire	In our initial methodology, six parametric models were considered to determine the optimal data fit, with the log-normal, log logistic and gamma curves providing the best fit according to the AIC and BIC for each. The gamma function was found to offer the best fit but was considered inappropriate due to its long tail allowing survival beyond 20 years, which is clinically implausible. Consequently, the log-normal method was selected for the comparison. Shire believes that this is the most appropriate data on which to base the assessment of the cost-effectiveness of nal-IRI+5-FU/LV vs oxaliplatin+5FU/LV as specified in the NICE scoping document.	Comments noted. See above response.
Shire	3. Cost savings as a result of nal-IRI dose reductions The committee concluded that it was not appropriate to assume dose reductions for nal-IRI would always be applicable, and therefore only considered full costing in the economic comparison. However, Shire believes that it is incorrect to assume that there would be no cost savings as a result of nal-IRI dose reductions. The NHS England standard contract for chemotherapy (14) states that “local arrangements should be in place to ensure that as far as practicable high cost items are only reconstituted after patient’s blood results are known”, and that side effects, concerns, toxicities, blood results, weight, BSA and performance status should be discussed and documented before subsequent cycles of chemotherapy	Comments noted. The committee heard from the clinical expert that in clinical practice parenteral treatments are often prepared by the pharmacy department when the patient is seen at the outpatient clinic and not when the patient is treated. Therefore planned treatment variations can be accounted for when treatment is given but are difficult to predict in advance. The committee concluded that it was not appropriate to assume that cost savings from dose reductions would always be accounted for in clinical practice and that full costing should be assumed in the base case. See FAD section 4.9
Shire	In addition, avoidable wastage is high on the agenda with Chemotherapy Governance Groups, and the above pre-requisites help to avoid unnecessary costs. Therefore, it is likely that blood results will be analysed before the pharmacy make up the chemotherapy for it to be administered. For the most efficient cancer centres and units, the patient will have a blood test the day before; however, electronic prescribing means that any drugs prescribed are almost instantaneously transferred, and so can be prepared by the pharmacy on the same day as soon as blood results are received.	Comments noted. See above response.

Consultee	Comment [sic]	Response
Shire	4. Chemotherapy cost calculations The committee concluded that the ERG's method of calculating costs (using the Department of Health's electronic market information tool [eMit]) was more appropriate than the method used in the company submission (BNF). However, there is a great deal of uncertainty regarding prices that requires consideration. For example, the eMIT tool gives the average price of oxaliplatin 100 mg/20 mL solution for infusion as £15.50. The standard deviation of this average price is £14.63, indicating that there is a large variation in price across the English trusts.	The committee noted that the company had assumed that only one vial size is available for each generic drug; 500 mg for 5-FU, 50 mg for oxaliplatin and 50 mg for LV. However, information in the eMit database shows that there are multiple vial sizes for each of these generic drugs and that generally the larger the vial, the lower the cost per mg of the drug. The committee concluded that it was not appropriate to assume use of the smallest sized vials in the company's model and that the ERG's method of calculating costs was more appropriate. See FAD section 4.10

Consultee	Comment [sic]	Response
Shire	5. The innovation of nal-IRI Shire would like the committee to reconsider the innovation of nal-IRI, which, in combination with 5-FU and LV, is the first and only licensed treatment proven to be effective in patients with pancreatic cancer following gemcitabine-based therapy (10, 15), and thus represents a step change in the management of this condition, and is not just an 'extra' treatment option for pancreatic cancer patients, as stated in the ACD. This is supported by the review of orphan designation by the European Medicines Agency (EMA) in September 2016, which stated that pancreatic cancer remains a life-threatening condition that is associated with shortened life expectancy, the claim of a significant benefit of nal IRI+5 FU/LV in pancreatic cancer is justified and nal-IRI+5-FU/LV has significant benefit to patients affected by pancreatic cancer (16). The only treatment for pancreatic cancer currently approved by NICE is gemcitabine, with which there is a poor response rate (20% or less) and a short progression-free survival (<4 months) in the first-line setting in clinical trials (5, 6), and progression with metastatic disease is inevitable. Nal-IRI+5-FU/LV is the only licensed treatment for patients with metastatic pancreatic cancer failing on gemcitabine-based therapy, and its efficacy is based on robust data from a large international, randomised, pivotal Phase 3 trial. This is in contrast to oxaliplatin+5 FU/LV, which is unlicensed in this setting and its available evidence is from conflicting data from single-country investigator-sponsored trials (5, 8, 17).	The committee discussed whether pegylated liposomal irinotecan plus 5-FU and LV was innovative in its potential to make a significant and substantial impact on health-related benefits. See FAD section 4.17

Consultee	Comment [sic]	Response
Shire	There is published evidence showing distinctly modified pharmacokinetic characteristics for nal-IRI compared with non-liposomal irinotecan, including reduced clearance, extended plasma circulation, small volume of distribution, and prolonged terminal half-life (18, 19). 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 (20). In addition, as noted in the ACD, the clinical expert present at the NICE meeting on 27 July 2016 stated that the nanoliposomal particle delivery system has shown better effectiveness than equivalent non-liposomal treatments for treating ovarian cancer, and that this could also apply to nal-IRI compared with irinotecan.	Comments noted.
Shire	The outlook for pancreatic cancer is extremely poor for patients, especially those with metastatic disease and that have failed on gemcitabine-based therapy, and nal-IRI+5-FU/LV has the potential to extend the life of patients without a meaningful detriment to their quality of life where many other development programs for a range of molecules have failed in these patients. Shire believes that nal-IRI+5-FU/LV does indeed represent an innovative treatment option for the treatment of pancreatic cancer.	Comments noted. The committee discussed whether pegylated liposomal irinotecan plus 5-FU and LV was innovative in its potential to make a significant and substantial impact on health-related benefits. See FAD section 4.17
Shire	6. The consideration of nal-IRI+5-FU/LV as an end-of-life medicine The median overall survival from the NAPOLI-1 trial 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 median 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. It is also worth noting that the analysis using the per protocol population, which included patients who received treatment for at least 6 weeks and did not violate any inclusion/exclusion criteria nor significantly deviate from the protocol, showed median overall survival of 8.9 months with nal-IRI+5-FU/LV compared with 5.1 months with 5-FU/LV, which represents an even larger 75% relative increase.	Comments noted. The committee concluded that the criterion for short life expectancy was met. However, pegylated liposomal irinotecan plus 5-FU and LV survival estimates from the trial and model showed that the criterion for extension to life was not met for the comparison with either 5-FU plus LV or oxaliplatin plus 5-FU and LV. See FAD sections 4.14 and 4.15.

Consultee	Comment [sic]	Response
Shire	Another important factor to note is that the duration of therapy is short in pancreatic cancer compared with many other cancers and the population that will be treated is low, and therefore the overall cost of treatment will be low.	Comment noted.
Shire	7. Further points to consider The committee concluded that the patients seen in the NAPOLI-1 trial were fitter than those seen in general practice. Shire acknowledges that while the proportion of patients that have failed on gemcitabine-based therapy are fitter, it is only the fittest patients that will be considered for further treatment. This means that the population in NAPOLI-1 is representative of those that would receive treatment with nal-IRI+5 FU/LV in clinical practice.	Comments noted.
Shire	The committee also highlighted the difference in treatment-emergent serious adverse events between the nal-IRI+5-FU/LV group and the 5-FU/LV group from the NAPOLI-1 trial (47.9% compared with 44.8%). Given the percentages, treatment-emergent serious adverse events were experienced by a similar proportion of patients with nal-IRI+5 FU/LV vs 5 FU/LV. Overall, nal-IRI+5-FU/LV was generally well tolerated in most patients, with a predictable toxicity profile with management protocols available for adverse events. In addition, the percentage of subjects discontinuing due to any treatment-emergent adverse event was similar with nal-IRI+5-FU/LV (11.1%) and 5-FU/LV (7.5%).	Comments noted. The adverse events associated with pegylated liposomal irinotecan plus 5-FU and LV were discussed by the committee. See FAD section 4.3
Shire	The committee also noted the uncertainty in the clinical effectiveness of nal-IRI+5-FU/LV compared with oxaliplatin+5-FU/LV, particularly with the total QALYs for oxaliplatin+5 FU/LV being lower than for 5-FU/LV. They note that the ERG conducted further analyses altering the QALY difference between the two treatments. These crude analyses appeared to use an arbitrary value of ±10%, were not supported by any evidence, and were described by the ERG as exploratory. The ERG stated that they should be used with caution therefore they should not be applied in the ICER calculation given the significant limitations of the comparison and that they are not backed up by the evidence. (References not reported here)	Comments noted.

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Public	Recommendations	UK is lagging behind the rest of the world. We need these drugs as the current scheme is lacking.	Comment noted. The Institute recognises that guidance from other organizations may differ from its own guidance, because of different criteria for making decisions. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company submission and the ERG report.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

ID778 Pegylated liposomal irinotecan for treating pancreatic cancer after gemcitabine

Company response to the Appraisal Consultation Document

6 December 2016

Introduction

Shire welcomes the opportunity to comment on the Appraisal Consultation Document (ACD). We understand that NICE welcomes comments on whether all of the relevant evidence has been taken into account, whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and whether the recommendations are sound and a suitable basis for guidance to the NHS. As outlined below, our comments are mainly concerned with whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.

Shire is disappointed with the preliminary decision not to recommend pegylated liposomal irinotecan (hereafter referred to as nal-IRI) in combination with 5-fluorouracil (5-FU) and leucovorin (LV) within its marketing authorisation for treating metastatic adenocarcinoma of the pancreas in adults whose disease has progressed following gemcitabine-based therapy. Gemcitabine is currently the only treatment that is approved by NICE for use in treating pancreatic cancer in England. Before the regulatory approval of nal-IRI, there were no licensed treatments for patients with metastatic pancreatic cancer who have progressed following gemcitabine-based therapy.

Pancreatic cancer is a very severe and life-threatening disease with an exceptionally short life expectancy at diagnosis (median 4.6 months) and a particularly high burden of illness. In a recent systematic review of 91 peer-reviewed observational studies in pancreatic cancer, a median overall survival from diagnosis of 4.6 months was reported (1). The outlook for patients with pancreatic cancer has hardly improved since the 1970s, despite incidence rates rising by 8% in the last decade in the UK (2, 3). This is in contrast to other cancers that have seen significant improvements in overall survival over the last 5 years, and pancreatic cancer has been predicted to become the second leading cause of cancer-related death by 2030 (4). There is a substantial unmet need for new effective treatments to become available for patients.

Progression in metastatic disease is inevitable, illustrated by the fact that treatment with gemcitabine has been shown to be associated with a poor response rate (20% or less) and short median progression-free survival (<4 months) in the first-line setting in clinical trials (5, 6). In addition, gemcitabine is increasingly being used as adjuvant treatment (5). For these

reasons, patients who fail on gemcitabine-based therapy form a substantial patient pool, yet are currently poorly served, with no licensed or NICE recommended treatments available. There is robust evidence supporting overall survival improvements with nal-IRI+5-FU/LV from NAPOLI-1, which is the largest randomised, controlled, international, multi-centre, Phase 3 trial in patients with pancreatic cancer that have progressed following failure with gemcitabine-based therapy. Results showed that nal-IRI+5-FU/LV, compared with 5-FU/LV, had statistically significantly longer:

- Overall survival (median 6.1 vs 4.2 months; a 45% relative median survival gain; unstratified hazard ratio 0.67; p=0.0122),
- Progression-free survival (median 3.1 vs 1.5 months; hazard ratio 0.56; p=0.0001), and
- Time to treatment failure (median 2.3 vs 1.4 months; hazard ratio 0.60; p=0.0002).

All of these results are highly clinically meaningful for patients facing such a short life expectancy, as is inevitable with pancreatic cancer.

Importantly, nal-IRI was generally well tolerated in most patients, with a predictable toxicity profile and adverse events that are common with irinotecan-based chemotherapy and have management protocols available. In addition, the quality of life results from NAPOLI-1 showed no substantial differences between treatment arms, suggesting that there were no negative effects of adding nal-IRI to 5-FU/LV on health-related quality of life. This is also very important given the improvement seen in overall survival, the potential for tolerability concerns with chemotherapy regimens, and the fact that patients are generally in poor health from the effects of the underlying disease and previous treatments.

Shire believes that patients with pancreatic cancer who have progressed following gemcitabine-based therapy should be able to benefit from access to nal-IRI, a novel and beneficial treatment in an area of high unmet needs. We believe that the summaries of cost-effectiveness contained within the ACD are not reasonable interpretations of the evidence available, and thus the provisional decision not to recommend nal-IRI+5-FU/LV is unsound and will limit the availability of this important therapy for patients with metastatic pancreatic cancer whose disease has progressed following gemcitabine-based therapy. In particular, we would like to comment on the following points:

1. The method of comparison for nal-IRI+5-FU/LV vs oxaliplatin+5-FU/LV
2. The use of parametric modelling vs Kaplan-Meier data
3. Cost savings as a result of nal-IRI dose reductions
4. Chemotherapy cost calculations
5. The innovation of nal-IRI
6. The consideration of nal-IRI+5-FU/LV as an end-of-life medicine.

These points are discussed in Sections 1–6, and miscellaneous further points are discussed in Section 7.

We sincerely encourage the committee to reconsider its draft guidance in light of our comments.

1. The method of comparison for nal-IRI+5-FU/LV vs oxaliplatin+5-FU/LV

Shire strongly believes that the indirect treatment comparison (ITC) performed by the company, despite its acknowledged limitations, provides a much sounder basis for decision making than the use of a 'crude comparison' by the Evidence Review Group (ERG).

The RCTs (NAPOLI-1, PANCREOX and CONKO-003) included in the submitted ITC all treated patients with pancreatic cancer who had progressed following gemcitabine-based therapy. These trials are the only available trials with a clinically comparable trial design, population, and with a common comparator. Two of the trials identified by the ERG (Yoo et al (5) and SWOG (7)) can only take a single arm that is relevant, since the comparators in these trials are not relevant to current clinical practice or to the comparison between nal-IRI+5-FU/LV and oxaliplatin+5-FU/LV. In addition, the trial reported by Yoo et al identified by the ERG was noted as having a notably lower overall survival and progression-free survival with oxaliplatin+5-FU/LV compared with the other identified trials, and therefore was dismissed from the crude comparison. This amounts to a biased selection of the available evidence for inclusion in the crude comparison.

A crude comparison should not be used for decision making. It is incorrect to simply compare single arms from trials, since this fails to separate the efficacy of the drugs from other effects, e.g. placebo effects, baseline patient characteristics and risks, prior treatment, local practice, and historical context. An illustration of this is that the populations in PANCREOX and CONKO-003 had received, on average, fewer prior treatments and included a lower percentage of patients with metastatic disease than the patients in NAPOLI-1. The effect that these trial/patient characteristics can have on an outcome, and thus the unsuitability of directly comparing single treatment arms from different trials, is highlighted by reported differences in treatment effects between trials, for example the 'anomaly' in overall survival and progression-free survival reported by Yoo et al for oxaliplatin+5-FU/LV, as described above, and the different results for the 5-FU/LV arms in CONKO-003 (median overall survival of 3.3 months (8)) and PANCREOX (median overall survival of 9.9 months (9)). In addition, the European Society for Medical Oncology (ESMO) guidelines (10) specifically refer to the conflicting results found for oxaliplatin for the treatment of pancreatic cancer:

"Second-line therapy of pancreatic cancer has to be considered in terms of risk benefit for the patient. If the general status remains correct, considering the conflicting results on the

use of oxaliplatin, MM-398 [nal-IRI] *when available in all countries may be the best option for second-line treatment of these patients."*

Using data only from treatment arms of interest is flawed, naïve, biased, and is not methodologically appropriate, based on the ISPOR Task Force on Good Research Practices (11). Indeed, this is reinforced by NICE guidance for the reference case, which states that "it is not acceptable to compare results from single treatment arms from different randomised trials". The clinical opinion provided at the NICE meeting on 27 July 2016 was that the crude comparison performed by the ERG was not viable to compare between treatments. Indeed, the ERG itself acknowledges that caution should be taken in interpreting its crude comparison "due to potential differences in the trial populations and advises that they should be considered, at best, to be exploratory".

The Bucher adjusted (or anchored) method for indirect comparison (12) is designed to preserve randomisation and compare the magnitude of the treatment effect between two treatments relative to a common comparator (13), thus incorporating possible within-trial placebo effects, baseline patient characteristics and baseline risks. For these reasons, Shire strongly believes that, despite its limitations and underlying uncertainties due to cross-trial heterogeneity, the ITC performed in the original submission provides a more technically sound comparison of nal-IRI+5-FU/LV vs oxaliplatin+5-FU/LV than the crude comparison performed by the ERG, which the committee have used for their preliminary ACD decision.

2. The use of parametric modelling vs Kaplan-Meier data

The committee concluded that Kaplan-Meier data was more appropriate than parametric modelling for use in the comparison of overall survival and progression-free survival between nal-IRI+5-FU/LV and oxaliplatin+5-FU/LV. However, Shire disagrees, and feels that parametric modelling is the most appropriate method since the Kaplan-Meier data were not available for PANCREOX and CONKO-003, and therefore the survival curves needed to be modelled in order to enable the required cost-effectiveness comparison. This meant that it was necessary to use a parametric model for nal-IRI+5-FU/LV so that the hazard ratio for oxaliplatin+5-FU/LV could be applied. Comparing the Kaplan-Meier data for nal-IRI+5-FU/LV to the modelled survival for oxaliplatin+5-FU/LV, which was calculated using the parametric curves for nal-IRI+5-FU/LV, is biased against nal-IRI+5-FU/LV.

In our initial methodology, six parametric models were considered to determine the optimal data fit, with the log-normal, log-logistic and gamma curves providing the best fit according to the AIC and BIC for each. The gamma function was found to offer the best fit but was considered inappropriate due to its long tail allowing survival beyond 20 years, which is clinically implausible. Consequently, the log-normal method was selected for the comparison. Shire believes that this is the most appropriate data on which to base the assessment of the cost-effectiveness of nal-IRI+5-FU/LV vs oxaliplatin+5FU/LV as specified in the NICE scoping document.

3. Cost savings as a result of nal-IRI dose reductions

The committee concluded that it was not appropriate to assume dose reductions for nal-IRI would always be applicable, and therefore only considered full costing in the economic comparison. However, Shire believes that it is incorrect to assume that there would be no cost savings as a result of nal-IRI dose reductions. The NHS England standard contract for chemotherapy (14) states that "local arrangements should be in place to ensure that as far as practicable high cost items are only reconstituted after patient's blood results are known", and that side effects, concerns, toxicities, blood results, weight, BSA and performance status should be discussed and documented before subsequent cycles of chemotherapy. In addition, avoidable wastage is high on the agenda with Chemotherapy Governance Groups, and the above pre-requisites help to avoid unnecessary costs. Therefore, it is likely that blood results will be analysed before the pharmacy make up the chemotherapy for it to be administered. For the most efficient cancer centres and units, the patient will have a blood test the day before; however, electronic prescribing means that any drugs prescribed are almost instantaneously transferred, and so can be prepared by the pharmacy on the same day as soon as blood results are received.

4. Chemotherapy cost calculations

The committee concluded that the ERG's method of calculating costs (using the Department of Health's electronic market information tool [eMit]) was more appropriate than the method used in the company submission (BNF). However, there is a great deal of uncertainty regarding prices that requires consideration. For example, the eMIT tool gives the average price of oxaliplatin 100 mg/20 mL solution for infusion as £15.50. The standard deviation of this average price is £14.63, indicating that there is a large variation in price across the English trusts.

5. The innovation of nal-IRI

Shire would like the committee to reconsider the innovation of nal-IRI, which, in combination with 5-FU and LV, is the first and only licensed treatment proven to be effective in patients with pancreatic cancer following gemcitabine-based therapy (10, 15), and thus represents a step change in the management of this condition, and is not just an 'extra' treatment option for pancreatic cancer patients, as stated in the ACD. This is supported by the review of orphan designation by the European Medicines Agency (EMA) in September 2016, which stated that pancreatic cancer remains a life-threatening condition that is associated with shortened life expectancy, the claim of a significant benefit of nal-IRI+5-FU/LV in pancreatic cancer is justified and nal-IRI+5-FU/LV has significant benefit to patients affected by pancreatic cancer (16). The only treatment for pancreatic cancer currently approved by NICE is gemcitabine, with which there is a poor response rate (20% or

less) and a short progression-free survival (<4 months) in the first-line setting in clinical trials (5, 6), and progression with metastatic disease is inevitable. Nal-IRI+5-FU/LV is the only licensed treatment for patients with metastatic pancreatic cancer failing on gemcitabine-based therapy, and its efficacy is based on robust data from a large international, randomised, pivotal Phase 3 trial. This is in contrast to oxaliplatin+5-FU/LV, which is unlicensed in this setting and its available evidence is from conflicting data from single-country investigator-sponsored trials (5, 8, 17).

There is published evidence showing distinctly modified pharmacokinetic characteristics for nal-IRI compared with non-liposomal irinotecan, including reduced clearance, extended plasma circulation, small volume of distribution, and prolonged terminal half-life (18, 19). 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 (20). In addition, as noted in the ACD, the clinical expert present at the NICE meeting on 27 July 2016 stated that the nanoliposomal particle delivery system has shown better effectiveness than equivalent non-liposomal treatments for treating ovarian cancer, and that this could also apply to nal-IRI compared with irinotecan.

The outlook for pancreatic cancer is extremely poor for patients, especially those with metastatic disease and that have failed on gemcitabine-based therapy, and nal-IRI+5-FU/LV has the potential to extend the life of patients without a meaningful detriment to their quality of life where many other development programs for a range of molecules have failed in these patients. Shire believes that nal-IRI+5-FU/LV does indeed represent an innovative treatment option for the treatment of pancreatic cancer.

6. The consideration of nal-IRI+5-FU/LV as an end-of-life medicine

The median overall survival from the NAPOLI-1 trial 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 median 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. It is also worth noting that the analysis using the per protocol population, which included patients who received treatment for at least 6 weeks and did not violate any inclusion/exclusion criteria nor significantly deviate from the protocol, showed median overall survival of 8.9 months with nal-IRI+5-FU/LV compared with 5.1 months with 5-FU/LV, which represents an even larger 75% relative increase.

Another important factor to note is that the duration of therapy is short in pancreatic cancer compared with many other cancers and the population that will be treated is low, and therefore the overall cost of treatment will be low.

7. Further points to consider

The committee concluded that the patients seen in the NAPOLI-1 trial were fitter than those seen in general practice. Shire acknowledges that while the proportion of patients that have failed on gemcitabine-based therapy are fitter, it is only the fittest patients that will be considered for further treatment. This means that the population in NAPOLI-1 is representative of those that would receive treatment with nal-IRI+5-FU/LV in clinical practice.

The committee also highlighted the difference in treatment-emergent serious adverse events between the nal-IRI+5-FU/LV group and the 5-FU/LV group from the NAPOLI-1 trial (47.9% compared with 44.8%). Given the percentages, treatment-emergent serious adverse events were experienced by a similar proportion of patients with nal-IRI+5-FU/LV vs 5-FU/LV. Overall, nal-IRI+5-FU/LV was generally well tolerated in most patients, with a predictable toxicity profile with management protocols available for adverse events. In addition, the percentage of subjects discontinuing due to any treatment-emergent adverse event was similar with nal-IRI+5-FU/LV (11.1%) and 5-FU/LV (7.5%).

The committee also noted the uncertainty in the clinical effectiveness of nal-IRI+5-FU/LV compared with oxaliplatin+5-FU/LV, particularly with the total QALYs for oxaliplatin+5-FU/LV being lower than for 5-FU/LV. They note that the ERG conducted further analyses altering the QALY difference between the two treatments. These crude analyses appeared to use an arbitrary value of ±10%, were not supported by any evidence, and were described by the ERG as exploratory. The ERG stated that they should be used with caution therefore they should not be applied in the ICER calculation given the significant limitations of the comparison and that they are not backed up by the evidence.

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on Pancreatic Cancer

Pancreatic Cancer UK-Pancreatic Cancer Action Joint response to Appraisal Consultation Document on pegylated liposomal irinotecan for treating pancreatic cancer after gemcitabine

This is a joint response from the All Party Parliamentary Group on Pancreatic Cancer Pancreatic Cancer UK and Pancreatic Cancer Action

Name: [redacted]
Organisation: APPG on Pancreatic Cancer
Position in the organisation: [redacted]

Name: [redacted]
Organisation: Pancreatic Cancer UK
Position in the organisation: [redacted]

Name: [redacted]
Organisation: Pancreatic Cancer Action
Position in the organisation: [redacted]

Brief description of the organisation:

The APPG on Pancreatic Cancer was established in 2012, by a leading group of parliamentarians with an interest in making a difference for pancreatic cancer. The APPG provides an excellent forum for MPs and peers to interact with stakeholders to share ideas about issues impacting pancreatic cancer and to as keeping pancreatic cancer high on the political agenda.

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.

Summary

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.

Currently, the only NICE approved treatment for pancreatic cancer is gemcitabine. There is no recognised standard second line treatment option for metastatic pancreatic cancer patients who have previously received gemcitabine-based therapy.

Being diagnosed with a disease that has such a poor prognosis and few treatment options 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”.

on Pancreatic Cancer

We desperately need promising new treatments to be made available to patients to improve patient choice, give clinicians vital new weapons in their arsenal and ultimately improve survival rates.

As such we are disappointed at the appraisal committee's draft conclusion that Pegylated liposomal irinotecan (Onivyde) - which trial data has shown offers a significant survival benefit over 5FU and LV, as well as a manageable safety profile[viii] - should not be recommended for use on the NHS.

Has all the relevant evidence been taken into account?

The APPG on Pancreatic Cancer, Pancreatic Cancer UK and Pancreatic Cancer Action are satisfied that all relevant evidence has been taken into account.

Are the summaries of clinical and cost effectiveness reasonable given the evidence?

Pancreatic Cancer UK, Pancreatic Cancer Action and the APPG on Pancreatic Cancer greatly appreciate the need to ensure value for money, given increasing pressures on precious NHS resources. However, considering the urgent unmet need facing this patient population, for which there has been hardly any improvement in survival over the last 40 years, it is important that promising new treatments are prioritised if we are to see any improvement in these appalling survival rates. We are therefore disappointed that NICE has not determined the drug to be cost or clinically effective at this time.

We welcome that a Patient Access Scheme was put forward by the manufacturer and considered by NICE. We would strongly welcome any further discussions between industry and NICE on price, given the importance of new effective treatments being made available on the NHS to this patient population.

The committee concludes that the treatment has a similar clinical effectiveness as FOLFOX. Whilst we largely accept this conclusion, it is worth noting that although the CONKO[ix] trial shows an overall survival benefit similar to that shown by Onivyde in the NAPOLI-1 trial, a separate trial, PANCREOX, concluded that there was no benefit to FOLFOX vs 5FU and folinic acid alone[x]. This raises some ambiguity over the clinical effectiveness of FOLFOX.

Due to the lack of treatment options and the extremely poor survival rates associated with pancreatic cancer, we regret that the committee has determined the treatment should not be considered under end of life criteria. Although we accept that 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 with marketing authorisation for second line therapy. The committee argues that the treatment cannot be said to offer a survival gain over FOLFOX. Whilst FOLFOX is used in some clinical practice, it is important to bear in mind that there remains no licensed, standard second-line treatment for pancreatic cancer. There are as such limitations to comparing FOLFOX with Onivyde combination therapy.

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Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

The APPG on Pancreatic Cancer, Pancreatic Cancer UK and Pancreatic Cancer Action are disappointed at the provisional recommendation not to recommend Onivyde for use on the NHS.

As previously highlighted, metastatic pancreatic cancer patients face very limited treatment options, meaning it is vital that new effective treatment options are made available to patients as quickly as possible. Whilst such treatment options might only offer incremental survival gains, this is essential to making longer term improvements in overall survival.

The committee compares the effectiveness of Onivyde combination therapy to FOLFOX, which is used as an off-label second-line treatment in clinical practice in the UK where patients are fit enough. However, as already stressed, there is currently no standard second-line treatment option for pancreatic cancer patients who have previously received gemcitabine-based therapy, let alone a licensed option.

A NICE approval of Onivyde would therefore be of particular importance, providing an extra option – above and beyond the limited off-label treatments - for patients who have had prior treatment with gemcitabine.

In addition, Onivyde causes significantly less neuropathy in patients than FOLFOX, meaning it could prove more tolerable to some patients. Patients should therefore not be denied this treatment option.

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.

We have heard from patients and carers who are “very disappointed” by the committee’s draft decision:

> “It’s another step on the path to England becoming a backwater for pancreatic cancer treatment. Compared to other European countries our survival rates are already poor and we’re going to be left further and further behind.” (Patient and carer testimony)

This is concerning as it feeds into the sense of nihilism patients, carers and clinicians have all reported when it comes to pancreatic cancer treatments.

It echoes fears we heard from patients following the removal of Abraxane from the Cancer Drugs Fund that:

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> "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)

This is of particular concern given that we know that giving patients with advanced disease an extra treatment choice is an advantage in itself, considering the limited number of treatment options currently available.

Patients and carers have previously told 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.

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)

We would therefore, urge the committee to reconsider the current ACD decision that Onivyde combination therapy for treating gemcitabine-refractory pancreatic cancer patients should not be recommended for use available for use on the NHS.

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. It is therefore essential that new effective treatments are made available to pancreatic cancer patients for the kind of improvements in survival we need to be achieved. Clinicians need more weapons in their arsenal and patients want to know that there are more treatment options open to them.

Onivyde offers the opportunity for an approved treatment option for patients who have progressed post treatment with gemcitabine.

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[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

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[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

[viii] 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.

[ix] 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

[x] 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)

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	UK is lagging behind the rest of the world. We need these drugs as the current scheme is lacking.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	