CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Irinotecan Liposome (Onivyde) for Metastatic Pancreatic Cancer

January 5, 2018

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The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding irinotecan liposome [nanoliposomal irinotecan](Onivyde) for metastatic pancreatic cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance Report is based on: a systematic review of the literature regarding irinotecan liposome for metastatic pancreatic cancer conducted by the Gastrointestinal Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from registered clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on irinotecan liposome (Onivyde) for metastatic pancreatic cancer, a summary of submitted Provincial Advisory Group Input on irinotecan liposome (Onivyde) for metastatic pancreatic cancer and a summary of submitted registered clinician Input on irinotecan liposome (Onivyde) for metastatic pancreatic cancer and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the effectiveness and safety of irinotecan liposome (Onivyde) injection for the treatment of metastatic adenocarcinoma of the pancreas in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in adult patients who have been previously treated with gemcitabine-based therapy.The Health Canada market authorization indication is for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-FU and LV, in adult patients who have disease progression following gemcitabine-based therapy.[1]

The Health Canada product monograph indicates that irinotecan liposome (Onivyde) is administered by intravenous infusion 70 mg/m^2 over 90 minutes, followed by LV 400 mg/m^2 IV over 30 minutes, followed by 5-FU 2400 mg/m^2 IV over 46 hours, every 2 weeks. One vial contains 43mg of irinotecan base which is equivalent to 50mg irinotecan liposome.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one randomized, open-label, multi-arm, phase III trial (NAPOLI-1, N =417).[2] The trial was designed to compare nanoliposomal irinotecan monotherapy to 5-fluorouracil and leucovorin (5-FU/LV) and nanoliposomal irinotecan plus 5-FU/LV to 5-FU/LV in patients with metastatic pancreatic ductal adenocarcinoma after treatment with gemcitabine-based therapy.[2] Patients were eligible to participate in the NAPOLI-1 trial if they had histologically or cytologically confirmed adenocarcinoma of the exocrine pancreas; metastatic disease; documented disease progression after prior gemcitabine based therapy; Karnofsky performance status (KPS) of ≥ 70; and adequate bone marrow, hepatic and renal function.

Patients were initially randomized (1:1) to receive either nanoliposomal irinotecan monotherapy (120 mg/m^2 every 3 weeks) or 5-FU/LV (2000 mg/m^2 and 200 mg/m^2 every weeks for the first 4 weeks of a 6 week cycle) (Protocol version 1).[3] However, after a protocol amendment, a third arm was added to the trial, nanoliposomal irinotecan (80 mg/m^2) plus 5-FU/LV (2400 mg/m^2 and 400 mg/m^2) every 2 weeks (Protocol version 2).[3] Henceforth, patients were randomized on a 1:1:1 ratio, which was stratified by baseline albumin, KPS and ethnic origin. Patients continued to be treated until disease progression (radiological or clinical deterioration), intolerable toxic effects or other withdrawal criteria.[3]

The primary outcome in NAPOLI-1 was overall survival. The trial was designed to have at least 98% power to detect a hazard ratio (HR) of 0.5 for death with nanoliposomal irinotecan plus 5-FU/LV relative to 5-FU/LV, and at least 85% power to detect a HR of 0.67 for death with nanoliposomal irinotecan relative to 5-FU/LV.[3] The key secondary outcomes were progression-free survival (PFS), objective response rate (ORR), time to treatment failure (TTF), carbohydrate antigen 19-9 (CA19-9) tumour marker response, clinical benefit response (CBR), quality of life and safety.

In total, there were 417 patients enrolled in the trial and included in the ITT population.[2] Patients were randomized to either nanoliposomal irinotecan plus 5-FU/LV (N = 117), nanoliposomal irinotecan monotherapy (N = 151) or 5-FU/LV (N = 149). Sixty-three patients in the trial were enrolled under Protocol version 1 (nanoliposomal irinotecan monotherapy [N = 33] or 5-FU/LV [N = 30]) and 354 were enrolled under Protocol version 2 (nanoliposomal irinotecan combination [N = 117], nanoliposomal irinotecan monotherapy [N = 118] and 5-FU/LV [N=119]).[2] Nineteen patients were not treated with their assigned therapies ($N^{combination}$ = 2, $N^{monotherapy}$ = 3, $N^{control}$ = 14). At the 14-Feb-2014 cut-off date, the majority of patients had discontinued from their assigned therapies.[2] The most common reasons for termination, regardless of randomization status, was progressive disease (52%) and clinical deterioration (12%).[4]

Efficacy

At the 14-Feb-2014 cut-off date, 64% of patients (N=75/117) in the nanoliposomal irinotecan plus 5-FU/LV group and 67% of patients (N=80/119) in the 5-FU/LV group died. Median overall survival was 6.1 months (95% CI: 4.1 to 6.9) for patients treated with nanoliposomal irinotecan plus 5-FU/LV and 4.2 months (95% CI: 3.3 to 5.3) for patients treated with 5-FU/LV (Table 1).[2] Treatment with nanoliposomal irinotecan plus 5-FU/LV was associated with a statistically significant longer overall survival as compared to 5-FU/LV in patients with metastatic pancreatic ductal adenocarcinoma after treatment with gemcitabine-based therapy (HR: 0.67; 95% CI: 0.49 to 0.92; P = 0.012).[2] In contrast, 85% of patients (N = 129/151) treated with nanoliposomal irinotecan and 73% of patients (N = 109/149) treated with 5-FU/LV had died.[2] There was no statistical difference between the nanoliposomal irinotecan monotherapy and 5-FU/LV on overall survival (HR: 0.99, 95% CI: 0.77 to 1.28; P=0.94) . Similar results for both treatment group comparisons were observed at the 16-Nov-2015 cut-off date.[5]

PFS was a key secondary outcome in the NAPOLI-1 trial. Assessments of disease progression were made by the study investigator using the RECIST 1.1 criteria using computed tomography or magnetic resonance imaging at the treatment start, and then every 6 weeks thereafter, as well as 30 days post follow-up.[6]At the 14-Feb-2014 cut-off, more patients in the 5-FU/LV group (77.3%) had disease progression as compared to the nanoliposomal irinotecan combination group (70.9%) (Table 1).[7]The median PFS for the combination group was 3.1 months (95% CI: 2.7 to 4.2) and 1.5 months (95% CI: 1.4 to 1.8) in the control group.[2] Nanoliposomal irinotecan combination therapy was associated with a prolonged PFS as compared to the control therapy (HR: 0.56, 95% CI: 0.41 to 0.75; p-value = 0.0001).[2] In contrast, there was no significant difference between nanoliposomal irinotecan and 5-FU/LV (HR: 0.81, 95% CI: 0.63 to 1.04; P = 0.10).

ORR was another secondary outcome in the trial. The authors first performed an unconfirmed analysis, which was performed by the study investigator using RECIST v1.1 criteria. The ORR for patients treated with nanoliposomal irinotecan combination therapy was 16% (95% CI: 9.56 to 22.92; N = 16/117) while it was 1% (95% CI: 0.0 to 2.48; N = 1/119) for those treated with the control therapy.[2]. In contrast, the confirmed analysis required a confirmation of complete or partial response for at least 4 weeks after the initial assessment.[8] Here, the ORR was 7.7% (95% CI: 2.86 to 12.52; N = 9/117) for patients treated with the combination therapy and it was 0.84% (95% CI: 0 to 2.48; N = 1/119) for patients treated with the control therapy.[7]Additionally, the ORR was 3.31% (95% CI: 0.46 to 6.17; N = 5/151) in the nanoliposomal irinotecan group and 0.67% (95% CI: 0.00 to 1.98) in the control group.[7] The rate difference was not significant between these two treatment groups (P = 0.214).[7]

TTF was defined as the time from randomization to treatment discontinuation for any reason, including: disease progression, treatment toxicity or death.[9] Patients treated with combination therapy had a significantly longer TTF as compared to those treated with the control therapy (HR: 0.60, 95% CI: 0.45 to 0.78; P = 0.0002).[2] However, TTF was not significantly different for nanoliposomal irinotecan monotherapy and 5-FU/LV (HR: 0.82, 95% CI: 0.65 to 1.03; P= 0.10).[2]

Wang-Gillam et al (2016) reported that more patients treated with nanoliposomal irinotecan plus 5-FU/LV (29%) achieved a CA19-9 response (≥50% decrease from abnormal baseline) as compared to patients treated with 5-FU/LV (9%) (P=0.0006).[2] Furthermore, more patients treated with nanoliposomal irinotecan achieved a CA19-9 response (24%) than those treated with 5-FU/LV (11.4%) (P = 0.024).[2]

Quality of Life

Health-related quality of life (HRQoL) was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30). Patient-reportedoutcomes (PROs) were measured at baseline and then every 6 weeks until disease discontinuation. At week 6 and week 12, there were no appreciable changes in the proportion of patients who demonstrated improvements or deterioration between the nanoliposomal irinotecan plus 5-FU/LV and the 5-FU/LV arm.[2] This is most likely due to a high degree of missing data.

Harms

There were 398 patients included in the safety analysis.[2] Patients who received treatment with nanoliposomal irinotecan, regardless of arm, had more grade 3 or higher TEAEs than those treated with 5-FU/LV. For instance, 92% of patients in the combination therapy group and 87% in the monotherapy group had an AE related to the study drug as compared to 69% in the control group.[4]

Limitations

The NAPOLI-1 trial was an open-label RCT design. This design was used because double-blinding would have been difficult to implement owing to the dosing and administration of the study interventions. Although the trial was open-label, objective outcomes (i.e. PFS and ORR) were assessed by the study investigator, which greatly increased the risk of detection bias because patients and the study investigators were aware of treatment status.

It is difficult to interpret the results of the PROs because of high attrition rates for the EORTC-QLQ C30. Although the manufacturer provided a quality-adjusted time without symptoms and toxicity (Q-TWiST)[10], this was a post-hoc analysis and these findings should be interpreted with caution.

NAPOLI-1 assessed the effect of nanoliposomal irinotecan, alone and in combination with 5-FU and LV, compared with 5-FU and LV. Other potentially relevant comparators were not assessed in this

study (i.e. irinotecan [free base] + 5-FU + LV (FOLFIRI), mFOLFOX (oxaliplatin +5-FU + LV) or oxaliplatin + 5-FU + LV (OFF). Of note, the submitter has included a network meta-analysis which includes other comparators (such as 5-FU/LV plus oxaliplatin, a modified FOLFIRI regimen (5-FU/LV + non-liposomal irinotecan, every 2 weeks) and best supportive care) which was critically appraised and assessed by the Clinical Guidance Panel.[11] See Section 7 for more information.

Table 1: Highlights of key outcomes in the NAPOLI-1 trial

Efficacy Outcome	**Combination therapy comparison**		**Monotherapy comparison**	
	Nanoliposomal irinotecan plus 5-FU/LV (N=117)	5-FU/LV (N=119*^)	Nanoliposomal irinotecan (N=151)	5-FU/LV (N=149^)
Primary Outcome				
Median OS, months (95% CI)	6.1 (4.8–8.9)	4.2 (3.3–5.3)	4.9 (4.2–5.6)	4.2 (3.6–4.9)
Hazard Ratio †	0.67 (0.49–0.92), p=0.012		0.99 (0.77–1.28), p=0.94	
Secondary Outcomes ‡				
Median PFS, months (95% CI)	3.1 (2.7–4.2)	1.5 (1.4–1.8)	2.7 (2.1–2.9)	1.6 (1.4–1.8)
Hazard Ratio †	0.56 (95% CI 0.41–0.75), p=0.0001		0.81, (95% CI 0.63–1.04), p=0.10	
Median TTF, months (95% CI)	2.3 (1.6–2.8)	1.4 (1.3–1.4)	1.7 (1.5–2.7)	1.4 (1.3–1.4),
Hazard Ratio †	0.60 (0.45–0.78), p=0.0002		0.82 (0.65–1.03), p=0.10	
EORTC-QLQ-C30	See text for details		See text for details	

Abbreviations: 5-FU = 5-fluorouracil; LV = leucovorin; CI = confidence interval, EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality-of-Life Core Questionnaire; OS = overall survival; PFS = progression-free survival; TTF = time to treatment failure
Notes: Data cut-off date: February 14, 2014
* 5-FU and LV combination control group based on protocol version 2.
^ The 119 and 149 pts who received control treatment were not distinct patients—there is overlap in this group.
† HR < 1 does not favour 5-FU and LV [monotherapy or combination control]
‡ Selected secondary outcomes; for full list of secondary outcome results, refer to Study Publication[2]

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and registered clinician input, respectively.

Patient Advocacy Group Input

From a patient perspective, a common challenge identified by patient and caregiver respondents was late stage diagnosis for patients with pancreatic cancer. This is often because there are few symptoms in early stages or the patient may be misdiagnosed. Late diagnosis could in turn lead to more challenges, including a lack of treatment options, because the cancer has already progressed. The majority of pancreatic cancer respondents were in later stages, and therefore, respondents reported a very high degree of distress due to symptoms of cancer, which included nausea and vomiting, and pain. Patient input submits that treatment options are often limited for metastatic pancreatic cancer. Respondents reported receiving the following treatments: surgery, radiation, gemcitabine, FOLFIRINOX, 5-fluorouracil alone, nab-paclitaxel and capecitabine. Patient input reported that despite a limited effectiveness with the drug therapies as reported by the respondents, there appears to be a high tolerance for drug therapies. Furthermore, patient input identified elements that respondents valued in terms of drug therapy for metastatic pancreatic cancer included: improving quality of life, a willingness to try new therapies and to be given this option, and balancing benefits and risks of drug therapy where it does not compromise quality of life entirely.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of liposomal irinotecan for pancreatic cancer:

Clinical factors:

- Lack of direct comparison data with irinotecan/5-fluorouracil/leucovorin (FOLFIRI) and with oxaliplatin/5-fluorouracil/leucovorin (as FOLFOX or OFF regimens)

Economic factors:

- The high cost of irinotecan liposome compared to regular irinotecan (free base)
- Treatment of adverse events associated with irinotecan liposome but not seen with regular irinotecan

Registered Clinician Input

Four clinician inputs were provided: three inputs from three individual oncologists and one joint input from three oncologists. The clinicians providing input identified that there is a need for a second-line treatment option for patients with metastatic pancreatic cancer who have been treated with gemcitabine based chemotherapy in the first line as there is currently no standard of care.

Summary of Supplemental Questions

One supplemental question was identified during the review as relevant to the pCODR review of irinotecan liposome plus 5-FU/LV and is discussed as supporting information:

- Critical appraisal of a manufacturer-submitted network meta-analysis (NMA) of the relative efficacy and safety of irinotecan liposome plus 5-FU/LV versus active therapies in adult patients with metastatic adenocarcinoma of the pancreas who have been previously treated with gemcitabine-based therapy.

See section 7.1 for more information.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

[Table 2]: Assessment of generalizability of evidence for nanolipomal irinotecan (Onivyde) for metastatic pancreatic cancer.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence (NAPOLI-1)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>Stage of disease</td><td>Stage of disease was not reported.</td><td>Does stage limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>The study limited the enrolment of patients to those with documented measurable or nonmeasurable metastatic disease which by definition is stage IV. This would be an appropriate patient population in Canada. Although the study did not include locally advanced pancreatic cancer (LAPC) patients, it is acceptable clinical practice to extend the clinical benefit observed with new regimens in the metastatic setting to the locally advanced setting.</td></tr>
<tr><td></td><td>Performance Status</td><td>Patient could be included if they had a Karnofsky Performance Status (KPS) > 70.
<table>
<tr><th>Baseline</th><th>Nanoliposomal irinotecan plus 5-FU with LV (n=117)</th><th>5-FU with LV (n=119)</th><th>Nanoliposomal irinotecan (n=151)</th><th>5-FU with LV (n=149)</th></tr>
<tr><td>100</td><td>18 (15%)</td><td>17 (14%)</td><td>22 (15%)</td><td>22 (15%)</td></tr>
<tr><td>90</td><td>51 (44%)</td><td>40 (34%)</td><td>64 (42%)</td><td>54 (36%)</td></tr>
<tr><td>80</td><td>38 (32%)</td><td>51 (43%)</td><td>50 (33%)</td><td>61 (41%)</td></tr>
<tr><td>70</td><td>7 (6%)</td><td>10 (8%)</td><td>15 (10%)</td><td>11 (7%)</td></tr>
<tr><td>50-60</td><td>3 (3%)</td><td>0</td><td>0</td><td>0</td></tr>
</table>
Data source: Wang-Gillam et al (2016)[2]</td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>Although the study allowed those with KPS of 70% or higher, the majority of enrolled patients had a KPS of 90 or 100%. In clinical practice, pancreatic cancer patients are more likely to have a worse performance status at this stage of their disease. Consequently, the use of liposomal nanoliposomal irinotecan should be limited to those whose KPS is at least 70%.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(NAPOLI-1)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>Subgroup analysis
<table><tr><th>KPS</th><th>Nanoliposomal irinotecan plus 5-FU with LV (n=117)</th><th>5-FU with LV (n=119)</th><th>HR (95% CI)</th></tr><tr><td>90-100</td><td>39/66</td><td>37/67</td><td>0.79 (0·50-1.24)</td></tr><tr><td>70-80</td><td>36/51</td><td>43/52</td><td>0.54 (0.35-0.85)</td></tr></table>Data source: Wang-Gillam et al (2016)[2]</td><td></td><td></td></tr>
<tr><td></td><td>Age</td><td>Patients could be enrolled if they were older than 18 years of age
<table><tr><th>Baseline</th><th>Nanoliposomal irinotecan plus 5-FU with LV (n=117)</th><th>5-FU with LV (n=119)</th><th>Nanoliposomal irinotecan (n=151)</th><th>5-FU with LV (n=149)</th></tr><tr><td>Age, median (range)</td><td>63 (57-70)</td><td>62 (55-69)</td><td>65 (58-70)</td><td>63 (55-69)</td></tr></table>Data source: Wang-Gillam et al (2016)[2]
Subgroup analysis
<table><tr><th>Age</th><th>Nanoliposomal irinotecan plus 5-FU with LV (n=117)</th><th>5-FU with LV (n=119)</th><th>HR (95% CI)</th></tr><tr><td>>65</td><td>35/52</td><td>31/38</td><td>0.73 (0.45-1.19)</td></tr><tr><td>< 65</td><td>40/65</td><td>49/81</td><td>0.61 (0.40-0.93)</td></tr></table>Data source: Wang-Gillam et al (2016)[2]</td><td>Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?</td><td>Pancreatic cancer is a disease of the elderly and the age restriction of the trial should not limit the interpretation and generalizability of the results.</td></tr>
</table>

Domain	Factor	Evidence (NAPOLI-1)	Generalizability Question	CGP Assessment of Generalizability
	Organ dysfunction	Not excluded based on organ dysfunction.	Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	Patients enrolled on the trial had to have adequate end of organ function including a normal bilirubin level. In the real world setting, a proportion of patients will have an abnormal bilirubin, most commonly due to biliary obstruction and metastasis. Biliary decompression may be effective in this setting. The CGP supports the use of liposomal irinotecan per the trial eligibility criteria of a normal bilirubin but acknowledges that there may be clinical circumstances where use with a modestly abnormal bilirubin may still be a reasonable consideration and should be based on clinical judgement.
	Metastatic Sites	Patients were excluded if they had active CNS metastases (indicated by clinical symptoms, cerebral edema, steroid requirement, or progressive disease); patient should have been off steroids for at least 28 days prior to starting study therapy	Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	CNS metastasis is rare in pancreatic cancer patients. The sites of metastasis of enrolled patients is similar to those seen in Canadian clinical practice.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence (NAPOLI-1)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>Ethnicity or Demographics</td><td>
<table>
<tr><th>Ethnicity</th><th>nanoliposomal irinotecan plus 5-FU with LV (n=117)</th><th>5-FU with LV (n=119)</th><th>nanoliposomal irinotecan (n=151)</th><th>5-FU with LV (n=149)</th></tr>
<tr><td>White</td><td>72 (62%)</td><td>76 (64%)</td><td>89 (59%)</td><td>92 (62%)</td></tr>
<tr><td>East Asia</td><td>34 (29%)</td><td>36 (30%)</td><td>52 (34%)</td><td>50 (34%)</td></tr>
<tr><td>Black or African American</td><td>4 (3%)</td><td>3 (3%)</td><td>3 (2%)</td><td>3 (2%)</td></tr>
<tr><td>Other</td><td>7 (6%)</td><td>4 (3%)</td><td>7 (5%)</td><td>4 (3%)</td></tr>
</table>
Data source: Wang-Gillam et al (2016)[2]

Subgroup analysis
<table>
<tr><th>Ethnicity</th><th>Nanoliposomal irinotecan plus 5-FU with LV (n=117)</th><th>5-FU with LV (n=119)</th><th>HR (95% CI)</th></tr>
<tr><td>White</td><td>45/75</td><td>53/75</td><td>0.62 (0·41-0·92)</td></tr>
<tr><td>East Asia</td><td>23/34</td><td>25/36</td><td>0.49 (0·27-0·90)</td></tr>
<tr><td>Other</td><td>7/8</td><td>2/8</td><td>3.27 (0.67-15.84)</td></tr>
</table>
Data source: Wang-Gillam et al (2016)[2]
</td><td>If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting? Also, if the demographics of the study countries differ from Canada, the average treatment effect in the trial might not be representative of a Canadian setting.</td><td>The natural history of pancreatic cancer and the effectiveness of available therapies is generally not dependent on ethinicity or gender.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(NAPOLI-1)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>Biomarkers</td><td>CA19-9 was assessed in the trial.

<table><tr><td>CA19-9</td><td>Nanoliposomal irinotecan (n=123)</td><td>5-FU with LV (n=105)</td><td>Nanoliposomal irinotecan plus 5-FU with LV (n=97)</td><td>5-FU with LV (n=81)</td></tr><tr><td>Tumor Marker Response Eval, n (%)</td><td>29 (23.6)</td><td>12 (11.4)</td><td>28 (28.9)</td><td>7 (8.6)</td></tr><tr><td>p-value[1]</td><td>0.0238</td><td></td><td>0.0006</td><td></td></tr><tr><td colspan="5">1. Two-sided p-values from pairwise comparisons of Tumor Marker Response rates using Fisher's exact test.</td></tr></table>Data source: Wang-Gillam et al (2016)[2]</td><td>Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)? Are the results of the trial applicable to all subgroups equally? Is there a substantial group of patients excluded from the trial to whom the results could be generalized?</td><td>CA19.9 is not known to be an effect modifier. The results should be generalizable to patients with and without an elevated CA19.9 level.</td></tr>
<tr><td></td><td>Genotype</td><td>Taken directly from the Clinical Summary: "Seven patients in each nal-IRI-containing arm were homozygous for UGT1A1*28 allele. In the nal-IRI+5-FU/LV combination arm, 3 out of the 7 patients were able to dose escalate nal-IRI to 80 mg/m^2 without the need for further dose reduction. One patient dose escalated but required dose reduction back to 60 mg/m^2, while in 2 patients the initial dose was not changed; and in 1 patient, the dose was reduced to 40 mg/m^2. In the nal-IRI+5-FU/LV arm, 1 patient discontinued treatment due to an adverse event and 1 due to patient's decision; 3 others discontinued due to progressive disease and 2 were still on treatment at the time of initial data cutoff."</td><td></td><td>Although all patients were genotyped for the UGT1A1*28 allele, it is not standard practice to do so in cancer patients. This test is not generally available across Canada. It is reassuring that this particular genotype is not common in the study population and that those with the 1A1*28 allele were able to tolerate the medication without significant toxicity. The only rare exception would be for those patients who have a BRCA related pancreatic cancer. The NAPOLI trial did not report the proportion of patients who were BRCA carriers and thus, the generalizability of the results to this population remains unknown.</td></tr>
</table>

Domain	Factor	Evidence (NAPOLI-1)	Generalizability Question	CGP Assessment of Generalizability
Intervention	Treatment Intent	Palliative.	Are the results of the treatment generalizable to an alternative treatment intent? (i.e., if the trial is palliative in intent, could the therapy also be used in the adjuvant setting or vice versa?)	Given that the study drug was given in previously treated advanced pancreatic cancer patients, it is highly unlikely that the drug would be used in any setting but in the palliative group of patients.
	Line of therapy	The manufacturer stated that the patients who participated in NAPOLI-1 were heavily pre-treated, with experience of ≥2 lines of prior treatment in about 1/3 of patients (34% of patients treated with nal-IRI+5-FU/LV, 31% of patients treated with 5-FU/LV). Consequently, the place in therapy of ONIVYDE® is not restricted to second-line use, but is an evidence-based approach to the treatment of metastatic pancreatic adenocarcinoma in any line of therapy after prior exposure to a gemcitabine-containing therapy in the advanced or metastatic disease setting. Prior exposure to gemcitabine-based therapy could therefore have been in neoadjuvant, adjuvant, front-line or subsequent lines of treatment.	Are the results of the trial generalizable to other lines of therapy?	The current study examined the efficacy of nanoliposmal irinotecan in patients previously treated with gemcitabine or gemcitabine-based combinations given in the neoadjuvant, adjuvant or advanced settings. These results are not generalizable to those who have been treated with FOLFIRINOX in a similar setting. This can also be considered to be in the 2nd line setting after exposure to gem-based therapy in the 1st line setting (as defined by gem-based chemo in the metastatic setting and within 6 months of finishing gemcitabine in the neoadjuvnt or adjuvant settings).

Domain	Factor	Evidence (NAPOLI-1)	Generalizability Question	CGP Assessment of Generalizability
	Administration of intervention	All interventions require intravenous administration.	Are the results of the trial generalizable to a different dose or administration schedule?	Given that this is the initial trial of this regimen, the results should be limited to the reported dose and schedule until other studies of alternate dose or schedules are reported.
Comparator	Standard of Care	The control used in the trial was 5-FU/LV and this was considered a relevant comparator in Canada.	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	There is no widely acceptable standard of care in this patient population in Canada. Although the drugs used in the comparator arm are available across the country, the specific dose of 5-FU/LV is not commonly used. The dose and schedule used in the combination arm is more typical of Canadian practice. Despite this difference, the CGP considers the outcomes between the two different schedules of 5-FU/LV to be clinically comparable.

	Dose and Schedule	• *Nanoliposomal irinotecan plus 5-FU with LV*
		  ○ Nanoliposomal irinotecan over 90 min at a dose of 80 mg/m^2 IV (equivalent to 70 mg/m^2 of irinotecan free base), followed by LV 400 mg/m^2 IV over 30 min and then 5-FU 2400 mg/m^2 IV over 46 hrs, every 2 weeks.
		  ○ An initial dose of 60 mg/m^2 IV nanoliposomal irinotecan was provided to homozygous allele carriers of *UGT1A1*28* for the first-cycle. In the absence of any drug related toxicity, the dose was increased to its standard dose.
		• *Nanoliposomal irinotecan monotherapy*
		  ○ Nanoliposomal irinotecan at a dose of 120 mg/m^2 IV (equivalent to 100 mg/m^2 of irinotecan free base), every 3 weeks.
		  ○ An initial dose of 80 mg/m^2 IV nanoliposomal irinotecan was provided to homozygous allele
			If the dose and/or schedule is not standard, are the results of the trial relevant in the Canadian setting?	As UGT1A1*28 testing is not routinely available in Canada, clinicians may consider using an initial dose of 60mg/m^2, in those patients suspected of having Gilbert's syndrome (UGT1A1*28).

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence (NAPOLI-1)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>carriers of UGT1A1*28 for the first-cycle. In the absence of any drug related toxicity, the dose was increased by 20 mg/m^2 increments to a maximum of 120 mg/m^2.
• 5-FU with LV
○ LV 200 mg/m^2 IV over 30 min followed by 5-FU 2000 mg/m^2 IV over 24 h, every week for the first 4 weeks of each 6-week cycle</td><td></td><td></td></tr>
<tr><td rowspan="2">Outcomes</td><td>Appropriateness of Primary and Secondary Outcomes</td><td>Primary
• OS

Seconday
• PFS
• ORR
• TTR
• CBR</td><td></td><td>Given that the study was conducted in a palliative setting, the outcomes examined in the study are appropriate to guide the use in a clinical setting.</td></tr>
<tr><td>Assessment of Key Outcomes</td><td>There was no difference in how the outcomes were assessed in the trial and in clinical practice.</td><td>If the trial used a different method of assessment than that used in Canadian clinical practice, are the results of the trial applicable to the Canadian setting?</td><td>The frequency of disease assessements with cross-sectional imaging in the study was every 6 weeks. In practice, it is more typical to conduct these tests every 8-12 weeks. Access to such frequent imaging may be limited at many centres across Canada.</td></tr>
<tr><td>Setting</td><td>Countries participating in the Trial</td><td>The trial was conducted in different countries: 76 sites in 14 countries, including North America (20 sites), Europe (30 sites), Asia (12 sites), South America (8 sites), and Oceania (6 sites).

<table><tr><th>Baseline</th><th>Nanoliposomal irinotecan plus 5-FU with LV (n=117)</th><th>5-FU with LV (n=119)</th><th>Nanoliposomal irinotecan (n=151)</th><th>5-FU with LV (n=149)</th></tr></table></td><td>If the trial was conducted in other countries, is there any known difference in the practice pattern between those</td><td>There are some country and region specific practices which will affect the generalizability to the Canadian setting. Specifically, 10-36% of patients on the trial received irinotecan or platinum agents in combination which is generally unlikely in the Canadian</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence (NAPOLI-1)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Europe</td><td>47 (40%)</td><td>49 (41%)</td><td>54 (36%)</td><td>55 (37%)</td></tr>
<tr><td>Asia</td><td>34 (29%)</td><td>35 (29%)</td><td>50 (33%)</td><td>48 (32%)</td></tr>
<tr><td>North America</td><td>19 (16%)</td><td>19 (16%)</td><td>26 (17%)</td><td>25 (17%)</td></tr>
<tr><td>Other</td><td>17 (15%)</td><td>16 (13%)</td><td>21 (14%)</td><td>21 (14%)</td></tr>
</table>
Data Source: EPAR Report[7]

Subgroup analysis
<table>
<tr><th>Region</th><th>Nanoliposomal irinotecan plus 5-FU with LV (n=117)</th><th>5-FU with LV (n=119)</th><th>HR (95% CI)</th></tr>
<tr><td>North America</td><td>14/19</td><td>11/19</td><td>0·79 (0·36-0·75)</td></tr>
<tr><td>Asia</td><td>23/34</td><td>24/35</td><td>0·51 (0·28-0·93)</td></tr>
<tr><td>Europe</td><td>28/47</td><td>34/49</td><td>0·69 (0·42-1·14)</td></tr>
<tr><td>Other</td><td>10/17</td><td>11/16</td><td>0·58 (0·24-1·38)</td></tr>
</table>
Data Source: EPAR Report[7]
</td><td>countries and Canada? Differences in the patterns of care might impact the clinical outcomes or the resources used to achieve the outcomes.</td><td>environment. However, given the lack of difference in efficacy in the subgroup analysis, this is not expected to have a significant impact on the generalizability of the results.</td></tr>
<tr><td></td><td>Location of the participating centres</td><td>The locations of participating centres are unknown.</td><td>If the trial was conducted only in academic centres are the results applicable in the community setting?</td><td>Although community centres were not included in the study, this should not affect generalizability to a broader Canadian population given that the study procedures are available at all centres (except for genotype testing).</td></tr>
</table>

1.2.4 Interpretation

Irinotecan liposome, interchanably called irinotecan liposome,s is comprised of irinotecan free base encapsulated in liposome nanoparticles. Irinotecan is converted into its active metabolite (SN-38) and the liposome is designed to keep irinotecan in circulation longer than free base irinotecan, increasing intratumoral levels of both the parent drug and its metabolite, SN-38.

NAPOLI-1 Trial

The pCODR systematic review identified one randomized, open-label, multi-arm, phase III study of irinotecan liposome in pancreatic cancer. In the study reported in the Lancet, 417 patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy were randomized initially to receive either nano-liposomal irinotecan monotherapy or 5-FU/LV weekly. The study was subsequently amended and a third arm of irinotecan liposome plus 5-FU/LV was added (protocol 2). The primary outcome was overall survival with at least 98% power to detect a hazard ratio of 0.5 for death with the combination relative to 5-FU/LV. In the control arm, the dose of 5-FU/LV was given weekly for 4 weeks every 6 weeks whereas in the combination arm 5-FU/LV was given every other week. Under protocol 2, 354 of the 417 patients were randomized. Efficacy analysis was conducted after the February 14, 2014 data cut-off date at which time 313 patients had died. The study arms were well balanced in terms of baseline clinical characteristics and patient demographics. The majority of patients had previously received gemcitabine-based therapy for metastatic disease rather than in the neoadjuvant or adjuvant settings. Although this trial was limited to only patients with metastatic disease, it is acceptable practice to use the same systemic therapy regimens to those patients with locally advanced,unresectable pancreatic cancer who would otherwise be candidates to receive chemotherapy.

Effectiveness

Analysis of the primary outcome of NAPOLI-1 demonstrated an improvement in median overall survival from 4.2 months in the 5-FU/LV group to 6.1 months in the irinotecan liposome plus 5-FU/LV group (HR: 0.67; 95% CI: 0.49 to 0.92, p=.012). However, there was no statistical difference between the irinotecan liposome monotherapy over 5-FU/LV on overall survival. As for secondary outcomes, median progression free survival also favoured the combination arm over the 5-FU/LV arm (3.1 months versus 1.5 months, HR: 0.56, 95% CI: 0.41 to 0.75, p=.0001) as did the ORR ((7.7% versus 0.84%). In contrast, there was no statistically significant difference between the monotherapy arm versus control in PFS or ORR. It is important to highlight that the radiologic assessments were investigator reported and that the study was non-blinded.

Health-related quality of life (HRQoL) was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30). Although there was no significant difference observed in HRQoL amongst the 3 arms, a substantial degree of missing data likely affected this analysis.

Safety

In terms of toxicity, grade 3 or higher treatment emergent adverse events were observed in the two groups receiving irinotecan liposome. The most commonly reported toxicities were diarrhea, vomiting and nausea. The most common labororatory toxicities were neutropenia, anemia and hypokalemia. Febrile neutropenia was seen in 3% and 4% of patients in the irinotecan liposome combination and monotherapy arms respectively. It is

important to note that 17% and 12% in the irinotecan liposome combination and monotherapy arms received growth factor support. The use of growth factor support in the palliative setting in Canada is not common practice. Adverse events lead to the discontinuation of the study drug in 11% and 12% of patients in the combination and monotherapy arms as compared to 7% in the control arm.

Comparators

The submitter provided a network meta-analysis that compared irinotecan liposome plus 5-FU/LV to 5-FU/LV, OFF, mFOLFOX, mFOLFIRI3 and BSC in patients with metastatic pancreatic cancer.

The results of the NMA indicated that treatment with mFOLFOX was associated with a statistically significant detrimental effect on PFS (HR: 1.95, 95% CI: 1.02 to 3.67) and on (overall survival HR: 2.35, 95% CI: 1.20 to 4.46) as compared to irinotecan liposome plus 5-FU/LV. Similar results were also reported for 5-FU/LV as compared to irinotecan liposome plus 5-FU/LV (PFS [HR: 2.07, 95% CI: 1.48 to 2.91] and overall survival [HR: 1.45, 95% CI: 1.03 to 2.08]). However, the overall conclusions of the NMA are limited because of substantial heterogeneity in the studies and patient characteristics among the included studies. Given these limitations, the comparative efficacy of irinotecan liposomeplus 5-FU/LV to other anticancer agents is uncertain.

Need and Burden of Illness

Although the palliative treatment of advanced pancreatic cancer has significantly improved in the past several years with median survival now exceeding 8 months, long-term survival remains elusive for most pancreatic cancer patients with fewer than 20% of patients being alive at 18 months. Clinicians now have a choice between FOLFIRINOX, gemcitabine with nab-paclitaxel and gemcitabine alone for the first-line treatment of locally advanced and metastatic pancreatic cancer patients who are well enough for systemic therapy. To date, no drug or drug combination has been approved for previously treated patients post-progression. As many as 40% of patients on the PRODIGE ACCORD and MPACT studies went onto to subsequent therapy suggesting that, despite the lack of widely accepted standard, clinicians are proceeding to treat patients with a variety of existing chemotherapeutic agents. There is presently no standard of care therapy in this setting. In Canada, most patients who progress on gemcitabine-based therapy may be considered for a second-line fluoropyrimidine. This post-progression setting represents a current unmet need in the management of advanced pancreatic cancer.

1.3 Conclusions

The pCODR Clinical Guidance Panel concluded that there is a net clinical benefit to irinotecan liposome when given in combination with 5-FU/LV compared to 5-FU/LV in patients who have been previously treated with gemcitabine-based therapy. Although the dose and schedule of 5-FU/LV in the control arm was different than that given in the combination arm, the CGP feels that the clinical efficacy and toxicity profiles of the two 5-FU schedules is similar. The basis of this conclusion is based on one randomized study, the NAPOLI-1 trial. This trial demonstrated a statistically significant and clinically meaningful improvement in overall survival by 1.9 months when compared to 5-FU/LV given weekly.

In reaching this conclusion, the Clinical Guidance Panel considered the following:

- Secondary endpoints including progression-free survival, overall response rate, CA19.9 response, and time to treatment failure all favoured the irinotecan liposome combination arm. However, it is important to note that toxicities including gastrointestinal toxicity and neutropenia were significantly higher in the irinotecan liposome combination arm.
- Currently, no data supports the use of irinotecan liposome in those previously treated with irinotecan containing regimens.
- Furthermore, there is no data to support the substitution of irinotecan liposome in combinations such as FOLFIRINOX.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Gastrointestinal Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Pancreatic cancer is the 10th most common cancer in Canada with 5,200 new cases in 2016 (Canadian Cancer Statistics) with an equal distribution between men and women, However, it is the 4th leading cause of cancer death with 4,700 deaths from pancreatic cancer in 2016. Fewer than 1 in 5 patients present with surgically resectable disease and even after surgery and adjuvant therapy, the median overall survival is 28 months. The majority of patients present with either metastatic or locally advanced, unresectable disease for whom the mainstay of treatment is palliative chemotherapy.

2.2 Accepted Clinical Practice

The treatment of both locally advanced and metastatic pancreatic cancer has evolved over the past decade. Gemcitabine monotherapy, although associated with low toxicity and a median overall survival of approximately 5-6 months has been the mainstay of therapy until the efficacy and safety of FOLFIRINOX (5-Fluorouracil , Leucovorin [LV], Irinotecan and Oxaliplatin) was established in 2011 in the ACCORD PRODIGE study.[12] FOLFIRINOX demonstrated that in the metastatic disease setting, median overall survival was improved to 11.1 months (when compared to gemcitabine alone) (when compared to 6.8 months with gemcitabine alone) with a response rate of 31.6%. Two years later, a randomized phase III study (MPACT) compared first-line gemcitabine and nab-paclitaxel to gemcitabine monotherapy and demonstrated a median overall survival of 8.5 months and response rate of 23% in favour of the combination arm.[13] Although both studies included only patients with metastatic disease, since then, both therapies have been funded in most jurisdictions across Canada for treatment of both metastatic and locally advanced pancreatic cancer.

In contrast, progress in second line therapy for advanced pancreatic cancer has been more modest with few randomized trials. In both the FOLFIRINOX and gemcitabine/nab-paclitaxel trials, approximately 40% of patients were treated with second line therapy. Two studies have investigated the role of oxaliplatin based regimens in this setting. Both combined infusional 5-fluorouracil with oxaliplatin (OFF regimen) in previously gemcitabine treated patients.[14,15] An improvement in overall survival from 3.3 to 5.9 months was noted with the addition of oxaliplatin. A Canadian multicentre randomized trial compared a more conventional oxaliplatin-based regimen, modified FOLFOX-6 with infusional 5-FU and leucovorin in a similar patient population.[16] Although the trial was stopped early, there was a statistically significant detrimental effect of oxaliplatin in terms of overall survival (6.1 versus 9.9 months). This was hypothesized to be related to the additional toxicity attributed to oxaliplatin and the imbalance of postprotocol therapy in the two arms.

Currently in most provinces, only gemcitabine monotherapy is currently funded in patients who have progressed after FOLFIRINOX therapy. In patients who have progressed after gemcitabine and nab-paclitaxel, although not funded, infusional 5-FU is often used if no clinical trial is available. For symptomatic local progression, palliative radiation therapy to the primary tumor or local recurrence can be considered.

The phase III NAPOLI study compared the use of irinotecan liposome combined with infusional 5-FU in metastatic pancreatic cancer patients previously treated with gemcitabine-based therapies.[2]

The current NCCN guidelines includes irinotecan liposome with 5-FU in patients previously treated with gemcitabine based therapies.

2.3 Evidence-Based Considerations for a Funding Population

Patients with advanced pancreatic cancer treated with palliative chemotherapy may have primary refractory disease or will develop progressive disease after initial clinical benefit. These patients may have locally advanced or metastatic disease at the time of progression. In the Canadian setting, approximately 50% of advanced pancreatic cancer patients receive first-line gemcitabine and nab-paclitaxel.[17] Approximately, as many as half may still be well enough to receive further therapy. Although the NAPOLI study included only patients with metastatic disease, given that gemcitabine and nab-paclitaxel is funded in both the locally advanced and metastatic disease setting, it is reasonable that both the locally advanced and metastatic patient populations may be considered as appropriate for the treatment with irinotecan liposome.

2.4 Other Patient Populations in Whom the Drug May Be Used

For patients who are initially treated with FOLFIRINOX, there is insufficient evidence that they will benefit from irinotecan liposome with infusional 5-FU at time of progression.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Input on irinotecan liposome (Onivyde) for treatment of Metastatic Pancreatic Cancer (MPC) was provided in a joint submission from Pancreatic Cancer Canada (PCC) and the Canadian Organization for Rare Disorders (CORD). irinotecan liposome is to be used in combination with 5-fluouracil (5-FU) and leucovorin (LV) in adult patients who have been previously treatment with gemcitabine-based therapy. Input provided by PCC and CORD is summarized below.

The information was collected through individual interviews with patients and caregivers as well as a survey. The survey was developed by CORD and distributed through the PCC, and redistributed through Craig's Cause Pancreatic Cancer Society. Six interviews were conducted by CORD in April and May of 2017 including four patients and two caregivers. All patients had metastatic pancreatic cancer and had been treated with gemcitabine-based therapy. The survey was posted on Survey Monkey from April 20th, 2017 to May 7th, 2017. There were 313 respondents in total. About 52% of respondents (n=163) were caregivers for patients who had died and 48% of respondents (n=150) were split almost evenly between patients and caregivers.

PCC and CORD indicated that all pancreatic cancer patients and caregivers were invited to complete this survey. However, because irinotecan liposome is proposed as second or third line therapy, the interview and survey questions were focused more on the perceived value of an additional or "final" drug option.

From a patient perspective, a common challenge identified by patient and caregiver respondents was late stage diagnosis for patients with pancreatic cancer. This is often because there are few symptoms in early stages or the patient may be misdiagnosed. Late diagnosis could in turn lead to more challenges, including a lack of treatment options, because the cancer has already progressed. PCC and CORD found from the survey that the majority of pancreatic cancer respondents were in later stages, and therefore, respondents reported a very high degree of distress due to symptoms of cancer, which included nausea and vomiting, and pain. CORD and PCC submits that treatment options are often limited for metastatic pancreatic cancer. Respondents reported receiving the following treatments: surgery, radiation, gemcitabine, FOLFIRINOX, 5-fluorouracil alone, nab-paclitaxel and capecitabine. In terms of drug therapy, the medication that was rated the poorest was FOLFIRINOX, with about half indicating that they had "serious" or "unmanageable" adverse events or side effects and the other half reporting that that they were "manageable" or "few"; while only a small number of respondents rated the adverse events or side effects of gemcitabine or nab-paclitaxel as "serious" or "unmanageable". CORD and PCC indicated that respondents, including those with experience of FOLFIRINOX compared to those with irinotecan liposome experience, were very strong in their opinion that irinotecan liposome should be available as an option. Because irinotecan liposome is a four-drug combination instead of the more challenging five-drug combination of FOLFIRINOX, respondents who have experience with irinotecan liposome felt that it was absorbed slower, had longer effectiveness, and had less toxic side effects. PCC and CORD also found that despite a limited effectiveness with the drug therapy as reported by the respondents, there appears to be a high tolerance for drug therapies. PCC and CORD identified elements that respondents valued in terms of drug therapy for metastatic pancreatic cancer included: improving quality of life, a willingness to try new therapies and to be given this option, and balancing benefits and risks of drug therapy where it does not compromise quality of life entirely. For the eight respondents who have experience with irinotecan liposome , they felt that it had positive effects, especially in terms of reducing pain and fatigue. In two cases, respondents reported the side effects were less than experienced with the previous therapies. While most respondents felt they could manage the side effects with other medications or strategies;

however, one patient respondent had stopped irinotecan liposome when the nausea became intolerable.

Please see below for a summary of specific input received from CORD and PCC. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Metastatic Pancreatic Cancer

CORD and PCC reported that a diagnosis of pancreatic cancer is characterized as devastating, cataclysmic and "life shattering", as this type of cancer is very rare, with an incidence of 12.5 per 100,000 persons and an annual death rate of 10.9 per 100,000, resulting in a very low prevalence. About 5% are still alive five years after diagnosis, and the average survival is nine months. CORD and PCC noted that there are very few treatment options for this group of patients. In addition, patients are often diagnosed at a very late stage in the disease, and because of this, their disease may not be amenable to treatment.

According to CORD and PCC, the respondents to the survey were representative of the overall pancreatic cancer patient population. The majority of respondents (38%) were between 55 and 65 years old when diagnosed, the second largest cohort (30%) were between 65 and 75 years old, while the remainder were almost equally divided between "over 75" years of age and "under 55" years old.

Of those who are currently alive and who responded to the question about time of diagnosis (n=91 respondents), 36% of the respondents said they had been diagnosed less than 6 months ago, 27% of respondents said their diagnosis was 6 to 12 months ago, 20% of respondents had been diagnosed for 1 to 2 years, and 11% of respondents were diagnosed between 2 and 5 years ago. Only 5% of respondents had survived more than five years since diagnosis. In brief, about two-thirds who are surviving have been diagnosed for less than one year.

Of the 210 responses to a question about cancer stage, only 20% of respondents said that that their cancer was resectable (stage 1 or 2) when diagnosed, while 37% of respondents said that their cancer was locally advanced but unresectable (stage 2 or 3) upon diagnosis. Almost 40% of respondents said that they were diagnosed with metastatic stage 4 cancer, and the remainder said they did not know.

When asked about the current status of their cancer, about 52% (n=163) of the caregiver respondents reported that the person was deceased. Of the remaining 150 respondents, about 10% (n=15) of the respondents said they no longer had active cancer (i.e., surgically removed or successful treatment). Another 38% (n=57) of respondents reported that the cancer was localized but less than half of these respondents (n=26) said that it was resectable. About one-third of the 150 respondents (n=50) said the cancer had metastasized to other organs, and the remaining 19% of respondents (n=28) provided a more complex description of their status (resected but returned or the cancer had spread).

Respondents reported a very high degree of distress due to symptoms of cancer. The two most problematic symptoms reported were stomach problems, including nausea and vomiting, and pain. Each of these symptoms was stated as "very" difficult by 45% of the respondents and difficult by about 20% of respondents. Approximately 68% of respondents said fatigue was

"much" or "very much" a problem. Other symptoms experienced by more than 55% of respondents as causing "much" or "very much" difficulty were "unexplained weight loss" and jaundice, with more than half being "much" or "very much" bothered by "diarrhea or constipation."

In terms of impact on quality of life, about 75% of respondents said the cancer had "much" or "very much" impacted their home, family or social life. Similarly, about 65% of respondents said their work life had been "much" or "very much" affected. Finally, more than half reported that the tests, treatments, and/or recovery time were experienced as burdensome or very burdensome.

CORD and PCC indicated that the biggest challenge for treatment for many patients is late-stage diagnosis, in part because there are few symptoms in the early stages and the symptoms, when they appear, are often misdiagnosed. This is partly due to the fact that pancreatic cancer is rare and often missed even by specialists until it has metastasized to other areas. By the time the patient is diagnosed, the treatments options that might have been tried were no longer feasible.

The following represent some of the comments that were provided to help illustrate the experiences that respondents have had with metastatic pancreatic cancer and their treatment.

"Bedsores from hospital, difficulty getting correct pain medication prescriptions, difficulty getting medical aid coverage. A nightmare in trying to get correct pain medications to patient on time. Doctors no longer interested; once told to go home to die."

"Diagnosis was delayed due to lack of knowledge of doctors in the ER department. All of the above symptoms were described but overlooked."

"My son was off work with severe back pain which led to his diagnosis for pancreatic cancer. He had a couple of medical/hospital visits but was driven back to the hospital …by the pain. From his first call to me…until his death was just under two weeks."

"No hope. A death sentence. Travel 3.5 hours to surgeon."

"Treated for colon cancer in 2007; unrelated pancreatic cancer in 2012; told 97% failure rate with surgery; followed by aggressive chemo; not supposed to be but I am still here."

3.1.2 Patients' Experiences with Current Therapy for Metastatic Pancreatic Cancer

CORD and PCC submits that treatment options are often limited for metastatic pancreatic patients. About 70% of respondents had received no treatment for their pancreatic cancer; while 27% of respondents had received treatment, and 3% of respondents did not know. Of those who specified a certain type of treatment they received (more than one choice was allowed), 53% of respondents reported receiving surgery and 33% of respondents reported receiving radiation. With respect to the type of medications received, 60% of respondents had received gemcitabine, 29% of respondents had used the combination FOLFIRINOX, 20% of respondents reported 5-Fluorouracil alone, 11% respondents had used nab-paclitaxel, and 2% of respondents had used capecitabine. In addition, 4 of the patient respondents who had been treated reported that they had used irinotecan liposome.

In terms of effectiveness in managing the cancer symptoms and progression, about 60% of those receiving surgery reported that it worked "well" or "very well", while 25% reported that it worked "poorly" or "not at all". In contrast, only 12% of respondents reported that radiation was effective and more than half reported that it was not effective.

For drug therapies, all were rated somewhat similarly, with more respondents reporting that they were ineffective than effective. However, it was noted that the number of respondents who had used each medication or combination was small; therefore, the exact percentages and ratings may not be meaningful. The ranges in percentages of those who rated the drug as effective and ineffective may provide a different perspective. The range (in %) of those who rated the drugs as effective was between 33% to 44%, while the range for those who reported the drugs as ineffective was between 38% to 58%. CORD and PCC indicated that these responses are expected given that patients report that symptoms are very difficult to manage, the diagnosis is often late stage, and experimentation with treatment options is still very limited.

In terms of adverse events and side effects related to all types of therapies, respondents indicated that treatment was mostly manageable and the side effects were tolerable. However, some of the open-ended responses received described a different, and more challenging experience.

The survey question asked patients to rate adverse events and side effects related to therapy on a four option checklist as follows: few, manageable, serious or not manageable. Of the total sample, 54 respondents indicated they had received treatment, 140 respondents had not, and five respondents said they were "not sure"; 114 respondents did not answered the question.

Based on those who reported receiving treatment, CORD and PCC indicated that three-quarter of respondents reported that adverse events or side effects with surgery were "few" or "manageable", and nearly two-thirds of respondents gave the same ratings for radiation. In terms of drug therapy, the medication that was rated the poorest was FOLFIRINOX, with about half indicating that they had "serious" or "unmanageable" adverse events or side effects and the other half reporting that that they were "manageable" or "few". Conversely, only one-fifth to one-fourth of respondents rated the adverse events or side effects of gemcitabine or nab-paclitaxel as "serious" or "unmanageable".

The following represent some of the comments that were provided that describe patient experiences with serious adverse events and side effects due to surgery or drug therapies.

> *"It's hellish how terrible Folfirinox makes the patient feel…. The benefits are so small compared to the costs in terms of quality of life."*
>
> *"Many of the symptoms noted above were experienced largely as a result of the folfirinox chemo he received. He was retired so it didn't impact his work but his quality of life dramatically."*
>
> *"The treatment for my daughter's cancer was horrendous. After a brutal 10 hour surgery… she experienced nausea, vomiting, trouble digesting food and diarrhea…. Complete removal of the tumor was successful so at the time she felt the Chemo would make sure it wouldn't come back. How wrong were we…. The quality of the last 1 1/2 years of her life was terrible. Maybe without the Chemo she might have had a decent chance of living a better quality of life. Such an awful disease."*

Despite their limited effectiveness as reported by many respondents, there appears to be a high tolerance for drug therapies, which bodes well for potential acceptance of additional medications. Below is a quote illustrating this:

> *"My husband lived 26 months with stage 4 pc. His oncologist always kept a balance between treatment and quality of life. It was during his last 3 months, that he lost quality of life."*

3.1.3 Impact of Metastatic Cancer and Current Therapy on Caregivers

PCC and CORD indicated that a diagnosis of pancreatic cancer had a huge impact on the caregiver and the entire family, although the duration of this impact tends to be limited because of the poor post-survival diagnosis, often less than a year. To summarize, caregivers spoke a great deal about their frustration, fear, and concern of how the cancer was affecting their loved one, especially in terms of pain, nausea, and fatigue. These feelings were compounded, in some cases, by misdiagnosis or a delay in diagnosis.

The following represent some of the comments that were provided that describe caregivers experiences of the impact of their loved one having metastatic pancreatic cancer and current therapy.

> *"Treated like his pain and symptoms were in his head and dismissed. I started researching and questioned if it could be pancreas."*
>
> *"Experienced all symptoms to the extreme for 10 months. Was diagnosed finally after 10 months and died 2 months later."*
>
> *"So much time was spent on oncology appointments, treatments, blood tests etc. Twice weekly for many months."*
>
> *"We did not consider test and treatments to be burdensome, as they were critical for treatment plans and diagnosis.*
>
> *"Psychological pressure for a caregiver, not enough or none at all psychological help provided for both: a caregiver and a patient."*
>
> *"Financially Impacted by the disease."*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for irinotecan liposome

PCC and CORD reported that most respondents (89%) were not aware of the new therapy called irinotecan liposome. Only 7% of respondents had heard about the drug but were unaware of how it was used, and 4% of respondents knew about its use in pancreatic cancer. It was noted that there was no difference in awareness among those respondents whose loved ones had died and those who were currently living with cancer.

Respondents were provided a synopsis of the medication, including evidence about the potential benefits, adverse effects and impact on survival, as well as the proposed "place in therapy" following gemcitabine-based therapy. A range of comments were received about patient preferences surrounding the potential adoption of this new drug. The overall message

was that patients and families should be given the option to try the drug if they wished. Other common opinions about the new drug that emerged from the comments included the following themes:

- some patients will do much better than the projected average,
- someone's life may be prolonged until another option was available, and
- access will encourage development of more therapies for pancreatic cancer.

The following are quotes that illustrate these opinions about irinotecan liposome after respondents were provided background information about the drug.

["What we had at the time] was "not very effective but they do provide hope and helps very much to keep going. We need better treatments and more attention to pain management."

"…any effort to fight this terrible cancer is worth the effort. There are so few options for pancreatic cancer and it is such a dreadful one."

"I hope it will provide a viable option for pancreatic cancer treatment and reduce the mortality rate [even for a short time]."

Some key themes were identified as important when discussing expectations of the drug and preferences. These are listed along with quotes supporting them.

1. **Some supported "aggressive treatment" at any cost**

   "It is important that this option is be available to all patients regardless of cost."

   "Give them a fighting chance. Aggressive measures are required until we can get a better understanding of this cancer."

   "I did 6 months of treatment of gemcitabine. I would do almost anything if it would help me to live. My abdominal and high back pain impacts my every day. How to eat and what to eat is something I still struggle with."

   "Where there is life there is hope . All options should be available regardless with no financial stress to patient or family."

   "My husband lived almost two years with chemotherapy treatment so it was worthwhile afor him. If there were something more we would have tried it."

2. **Some are willing to try the drug if it also improved quality of life**

   "The gemcitabine/abraxane combo has been very effective for me. I can manage the side effects but would be happier if I had more energy. I would hope that managing side
   effects would be a big part of new therapies…"

   "I would hope that it can give even a few patients longer lives and maintaining quality of life,"

3. **Some indicated taking a balanced approach in terms of benefits and risks when trying a new therapy**

"As it is used in advanced disease with limited benefits and significant risk of adverse reactions then a very serious patient assessment and personal discussion is necessary so that the patient and family can make an informed decision with the oncologist."

"There is a marginal improvement in survival rate when combined with two other drugs. However do the limited benefits outweigh the side effects ?"

3.2.2 Experiences To Date with Irinotecan liposome

There were eight respondents in total (four surveyed and four interviewed) who had had access to irinotecan liposome. Of this total, four were patient respondents and four were caregiver respondents. Among those surveyed, two patient respondents had died and responses were provided by their caregivers; all of those represented in the interview were still living.

The patient respondents ranged in age from 62 to 75 years. All had been previously treated with gemcitabine; and some respondents included nab-paclitaxel. The time since diagnosis to start of irinotecan liposome varied from two years to almost five years. Most had previously had surgery as well as radiation. All were classified as having stage 4 metastatic cancer. Six respondents felt they had run out of options when they were offered irinotecan liposome; two respondents were not sure whether stopping their gemcitabine (and nab-paclitaxel) was a positive move but acted on the advice of their physician that they may have better response.

Among the survey respondents, 100% of respondents said they felt that irinotecan liposome had had positive effects, especially in terms of reducing pain and fatigue. In two cases, the side effects were less than experienced with the previous therapies. Most felt they could manage the side effects with other medications or strategies; however, one patient respondent had stopped irinotecan liposome when the nausea became intolerable. One caregiver respondent spoke about the tremendous benefit of getting "*two more months*" with her mom. She felt well enough to be able to spend time with her grandchildren and to celebrate the Christmas holidays. Another patient respondent had just had a "family reunion" with all 12 children and 12 grandchildren present. The patient respondent reported that "*Without Onivyde, I would not have had the energy or the presence of mind to enjoy the time together*."

One of the caregivers who had hesitated to switch said the medication was working well and had reduced the pain so that only minor pain medication was required, but she was only concerned as to whether it had been "too early" since there was "no going back" and "no other option."

One patient respondent who had experienced "a lot of ups and downs" with pancreatic cancer and treatments had experienced a "relapse" with her previous treatment (gemcitabine with nab-paclitaxel) to the point where the pain was "atrocious." The patient respondent reported "*I would just sit in the kitchen with tears streaming down; I couldn't stop the pain. And with the pain, I had no appetite, no more hope*." In her words, after the second treatment with irinotecan liposome, she stated: "*the pain was gone; I had hope again. There are some side effects (lacerations in mouth, nausea, diarrhea, and swollen ankles) but I can cope with them and they have gotten less over time. And best of all, my tumour markers are apparently going down. I have hope we can control this disease*."

CORD and PCC indicated that respondents, including those with experience of FOLFIRINOX compared to those with irinotecan liposome experience, were very strong in their opinion that irinotecan liposome should be available as an option. Because nanliposomal liposome is a four-drug combination instead of the more challenging five-drug combination of FOLFIRINOX, respondents who have experience with irinotecan liposome felt that it was absorbed slower, had longer effectiveness, and had less toxic side effects.

3.3 Additional Information

PCC and CORD submits that the pCODR submission template is not ideally suited for rare cancers and definitely not well suited for cancers with a very short life expectancy following diagnosis. A diagnosis of pancreatic cancer signals a crisis situation requiring urgent intervention. Only patient testimonials are capable of conveying the full impact of this devastating diagnosis, horrific symptoms, and almost no hope for survival. Even if pCODR had a pathway for "end-of-life" treatments, PCC and CORD believes that it would not suffice for pancreatic cancer where the life post-diagnosis is so short. An extension of two months is very different if the patient has already survived five or ten or more years, while two months could represent an additional 25% of time with loved ones.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of liposomal irinotecan for pancreatic cancer:

Clinical factors:

- Lack of direct comparison data with irinotecan/5-fluorouracil/leucovorin (FOLFIRI) and with oxaliplatin/5-fluorouracil/leucovorin (as FOLFOX or OFF regimens)

Economic factors:

- The high cost of liposomal irinotecan compared to regular irinotecan (free base)
- Treatment of adverse events associated with liposomal irinotecan but not seen with regular irinotecan

Please see below for more details.

4.1 Factors Related to Comparators

The NAPOLI trial compared liposomal irinotecan with 5-fluorouracil/leucovorin (5-FU/LV) to 5-FU/LV. PAG noted that funded treatments after gemcitabine varies amongst the provinces and options may include capecitabine, 5-FU/LV, FOLFIRI, FOLFOX, and OFF. PAG noted that the standard of care for first-line treatment of locally advanced or metastatic disease is FOLFIRNOX in patients with good performance status or Abraxane-Gemcitabine. PAG is seeking data on irinotecan liposome /5-FU/LV compared to these other regimens used after gemcitabine.

4.2 Factors Related to Patient Population

As treatment with regular irinotecan is already available, PAG indicated that irinotecan liposome /5-FU/LV would be a replacement for FOLFIRI in provinces that fund FOLFIRI for pancreatic cancer. irinotecan liposome/5-FU/LV would be a treatment option in provinces where irinotecan or oxaliplatin-based chemotherapies are not funded for second-line treatment of pancreatic cancer.

The NAPOLI trial enrolled patients treated with gemcitabine based chemotherapy in the first-line setting. PAG is seeking guidance on the use of irinotecan liposome/5-FU/LV in patients who were treated in the first-line setting with chemotherapies such as irinotecan-containing regimens (FOLFIRINOX) as it was noted that patients previously treated with irinotecan were excluded from the trial.

4.3 Factors Related to Dosing

PAG noted that the dosing frequency of every two weeks for irinotecan liposome/5-FU/LV is same as the every two weeks of FOLFIRI. However, the dose of irinotecan liposome is different than regular irinotecan and PAG has some concerns that there may be drug and dose confusion.

4.4 Factors Related to Implementation Costs

PAG noted that drug wastage would be an issue as only one vial size is available and vial sharing may be unlikely given the small number of patients with pancreatic cancer on second-line treatment.

PAG noted that regular irinotecan is available as generic products and is relatively low cost. PAG identified that the modest incremental benefit of irinotecan liposome may not justify its higher price.

4.5 Factors Related to Health System

PAG noted there is an additional chair time for the 90 minute infusion is required when compared to 5-FU/LV but is similar to the infusion time of regular irinotecan.

4.6 Factors Related to Manufacturer

PAG noted that the product monograph indicates that the dose is 70mg/m^2 based on free irinotecan and that the NAPOLI trial indicates that irinotecan liposome 80 mg/m^2 is equivalent to 70 mg/m^2 of irinotecan base. Clear labelling of dose and packaging will help minimize the potential for confusion and error with regular irinotecan.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Four clinician inputs were provided: three inputs from three individual oncologists and one joint input from three oncologists.

The clinicians providing input identified that there is a need for a second-line treatment option for patients with metastatic pancreatic cancer who have been treated with gemcitabine based chemotherapy in the first line as there is currently no standard of care.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for this Type of Cancer

The clinicians providing input indicated that there is no standard of care in second line treatments of metastatic pancreatic cancer previously treated with gemcitabine. In some provinces, oxaliplatin with 5-fluorouracil, 5-fluorouracil alone, or capecitabine are options but the clinicians providing input noted that there is no high level date to support the usage.

5.2 Eligible Patient Population

The clinicians providing input identified that there is an unmet need for second line treatment after gemcitabine based chemotherapy. However, they noted that often patients have poor performance status in this setting and many do not have an acceptable performance status to receive second line therapy. They estimated that about one-quarter to one-third of all patients who received gemcitabine (with or without nab-paclitaxel) would be fit enough for treatment described in the NAPOLI trial.

One clinician providing input noted that cancer of the pancreas is forecasted to be the second leading cause of cancer death in the USA in a decade.

5.3 Identify Key Benefits and Harms with liposomal irinotecan

The clinicians providing input noted that there is no current standard of care in second line palliative care after gemcitabine based chemotherapy. They noted that there is overall survival benefit when Irinotecan liposome plus 5-fluorouracil/leucovorin is compared to 5-fluorouracil/leucovorin. One clinician providing input noted that the control arm in the trial published in the Lancet (the NAPOLI-1 study) may be only slightly better than placebo but best supportive care may not have been a viable control arm.

The product under review is a new delivery method of an old drug and clinicians have experience with managing the side effects associated with irinotecan. It was noted that the toxicity profile of irinotecan liposome appears similar to irinotecan base plus 5-fluorouracil/leucovorin (FOLFIRI).

5.4 Advantages of liposomal irinotecan Over Current Treatments

The clinicians providing input identified that there is an unmet need for second-line treatment in patients previously treated with gemcitabine or gemcitabine/nab-paclitaxel. There is currently no standard second-line therapy after gemcitabine based chemotherapy nor is there any high level evidence for this group of patients.

5.5 Sequencing and Priority of Treatments with liposomal irinotecan

The clinicians providing input identified that irinotecan liposome should be used according to the

NAPOLI trial: second-line with 5-FU/LV (dose as described in trial) after first-line gemcitabine (with or without nab-paclitaxel) in patients with good performance status. They noted that there is no support for use after other first line treatments (e.g. FOLFIRINOX).

One clinician providing input noted that this would be a new treatment option, not replacing an existing option as patients who are going down a less aggressive treatment pathway, supportive care would be considered but they have irinotecan liposome /5-FU/LV as a treatment option available.

Input from clinicians in Ontario has noted that more patients may be treated with gemcitabine/nab-paclitaxel in first line, if the irinotecan liposome with 5-FU/LV is approved for second-line. As the sequence of first-line FOLFIRINOX followed by gemcitabine plus nab-paclitaxel second-line is not funded in Ontario, there is already a high rate of first-line gemcitabine/nab-paclitaxel usage. Over time, second-line irinotecan liposome will have little impact on first-line gemcitabine/nab-paclitaxel usage.

5.6 Companion Diagnostic Testing

Not applicable.

5.7 Additional Information

None identified.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of nanoliposomal irinotecan [irinotecan liposome] in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in adult patients with metastatic adenocarcinoma of the pancreas who have been previously treated with gemcitabine-based therapy.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 3: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of nanoliposomal irinotecan plus 5-FU with LV should be included.	Patients with metastatic pancreatic ductal adenocarcinoma after treatment with gemcitabine-based therapy Subgroups: • Age (< 65 years vs. ≥65 years) • KPS (900-100 vs. 70-80) • Stage at diagnosis (Stage IV vs. other) • Pancreatic tumor location (head vs. other) • Liver metastases • CA19-9 levels • Albumin (≥ 40 g/L vs. < 40 g/L) • Number of previous therapies • Measurable metastatic sites • Previous therapies or procedures	Nanoliposomal irinotecan plus 5-FU with LV	**2nd line setting or beyond** • FOLFIRI (5-FU + LV + Irinotecan) • OFF (Oxaliplatin + 5-FU+ LV) • 5-FU + LV • mFOLFOX-6 (oxaliplatin with 5-FU and LV) • Capecitabine • XELOX	Primary • **OS** • **PFS** • **HRQoL** Secondary • ORR • DOR • DCR Safety • AEs • SAEs • WDAEs

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
	○ Radiotherapy ○ Whipple procedure ○ Biliary stent • Previous anticancer therapy ○ Gemcitabine vs. Gemcitabine combination*			
Abbreviations: 5-FU = 5-fluorouracil; LV = leucovorin; HRQoL=Health related quality of life; RCT=randomized controlled trial; SAE=serious adverse events; AE=adverse events; WDAE=withdrawals due to adverse events; DCR=disease control rate; ORR=objective response rate; DOR=duration of response; ORR = overall response rate; KPS = Karnofsky performance status;				

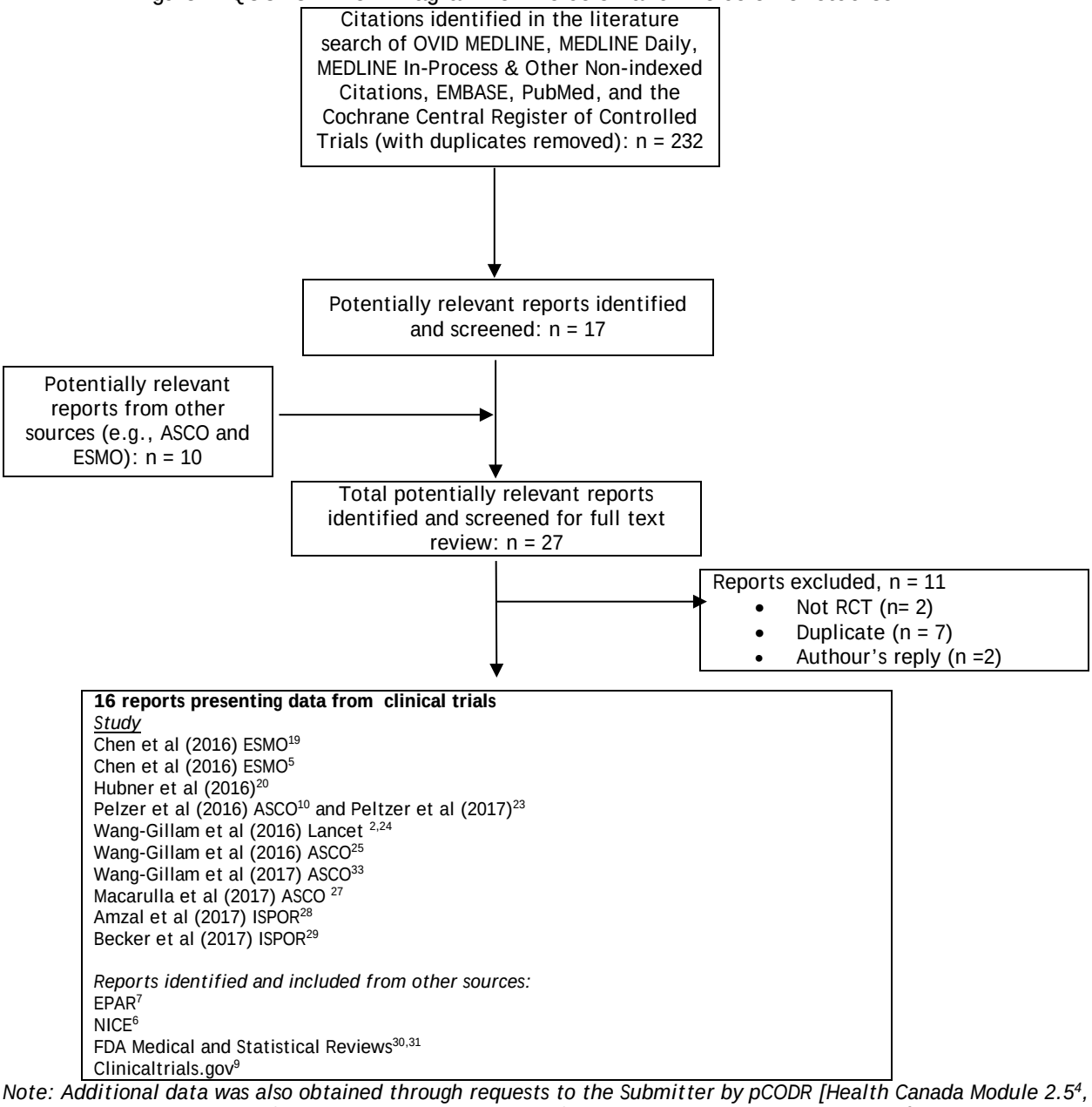
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 232 potentially relevant reports identified, one study (NAPOLI-1) reported in 17 citations was included in the pCODR systematic review.[5,6,10,18-31] Eleven reports were excluded because two were not randomized controlled trials, seven were duplicate reports and two were authour's replies. Additional reports related to the NAPOLI-1 study were obtained from the Submitter.[3,4,8,32]

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data was also obtained through requests to the Submitter by pCODR [Health Canada Module 2.5[4], Health Canada Module 2.7.3[4], Health Canada Module 2.7.4[4], NAPOLI-1 Clinical Summary Report[8], NAPOLI-1 Clinical Study Report[32] and NAPOLI-1 study protocol[3]]

6.3.2 Summary of Included Studies

The pCODR systematic review included one phase 3 RCT that assessed the safety and efficacy of nanoliposomal irinotecan plus 5-FU with LV (5-FU/LV) in patients with metastatic pancreatic ductal adenocarcinoma who have been previously treated with gemcitabine based therapy (NAPOLI-1; N = 417).

6.3.2.1 Detailed Trial Characteristics

a) Trial

NAPOLI-1 was a global, multi-centre, open-label, three-arm randomized phase 3 trial (Table 4 and Table 5).[2] The objective of the trial was to compare the treatment effects of nanoliposomal irinotecan, nanoliposomal irinotecan plus 5-FU/LV and 5-FU/LV in patients with metastatic pancreatic ductal adenocarcinoma who have been previously treated with gemcitabine based therapy. The trial was funded by Merrimack Pharmaceuticals and it was conducted in 14 countries within 76 sites, including Canada.

Table 4: Summary of trial characteristics of the NAPOLI-1 trial

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
NAPOLI-1 **Other identifiers** NCT01494506 **Characteristics** global, multicentre, three-arm, open-label, phase 3 study **Sample size** Randomized: 417 Treated: 396 **Locations** 76 sites in 14 countries, including North America (20 sites), Europe (30 sites), Asia (12 sites), South America (8 sites), and Oceania (6 sites). **Start date:** 01/2012 **Primary data cut-off:** 02/2014 **Final data-cut off:** 11/2015 **Sponsor:** Merrimack Pharmaceuticals	**Key Inclusion Criteria** • Histologically or cytologically confirmed adenocarcinoma of the exocrine pancreas • Metastatic disease • Documented disease progression after prior gemcitabine based therapy • KPS >/= 70 • Adequate bone marrow function • Adequate hepatic function • Adequate renal function **Key Exclusion Criteria** • Active CNS metastasis • Clinically significant GI disorders • Severe arterial thromboembolic events less than 6 months before inclusion • NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure • Active infection or uncontrolled fever • Pregnant or breast feeding patients	**Arm A** Nanoliposomal irinotecan (120 mg/m^2 every 3 weeks) **Arm B** Nanoliposomal irinotecan (80 mg/m^2) plus 5-FU (2400 mg/m^2) with LV (400 mg/m^2) every 2 weeks **Arm C** 5-FU (2000 mg/m^2) with LV (200 mg/m^2) every week for the first 4 weeks of a 6-week cycle	**Primary** **OS** **Secondary** **PFS** ORR TTF CA19-9 response CBR **QoL**
Abbreviations - **KPS:** Karnofsky performance status; **CNS:** central nervous system; **GI:** gastrointestinal; **NYHA:** New York Heart Association; **LV:** leucovorin; **5-FU:** 5-fluorouracil; **OS:** overall survival; **PFS:** progression-free survival; **ORR:** objective response rate; **CA19-9:** carbohydrate antigen 19-9; **CBR:** clinical benefit response ; **QoL:** quality of life			

Table 5: Select quality characteristics of the NAPOLI-1 trial

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
NAPOLI-1	Nanoliposomal irinotecan plus 5-FU with LV vs. 5-FU with LV AND Nanoliposomal irinotecan vs. 5-FU with LV	OS	405[A]	417	IVRS, stratified[B]	Yes	Open-label[C]	Yes	Yes[D]	No	Yes

[A] 405 patients were required to have at least 98% power to detect a hazard ratio (HR) of 0.5 for death with nanoliposomal irinotecan plus 5-FU/LV relative to 5-FU/LV, and at least 85% power to detect a HR of 0.67 for death with nanoliposomal irinotecan relative to 5-FU/LV.

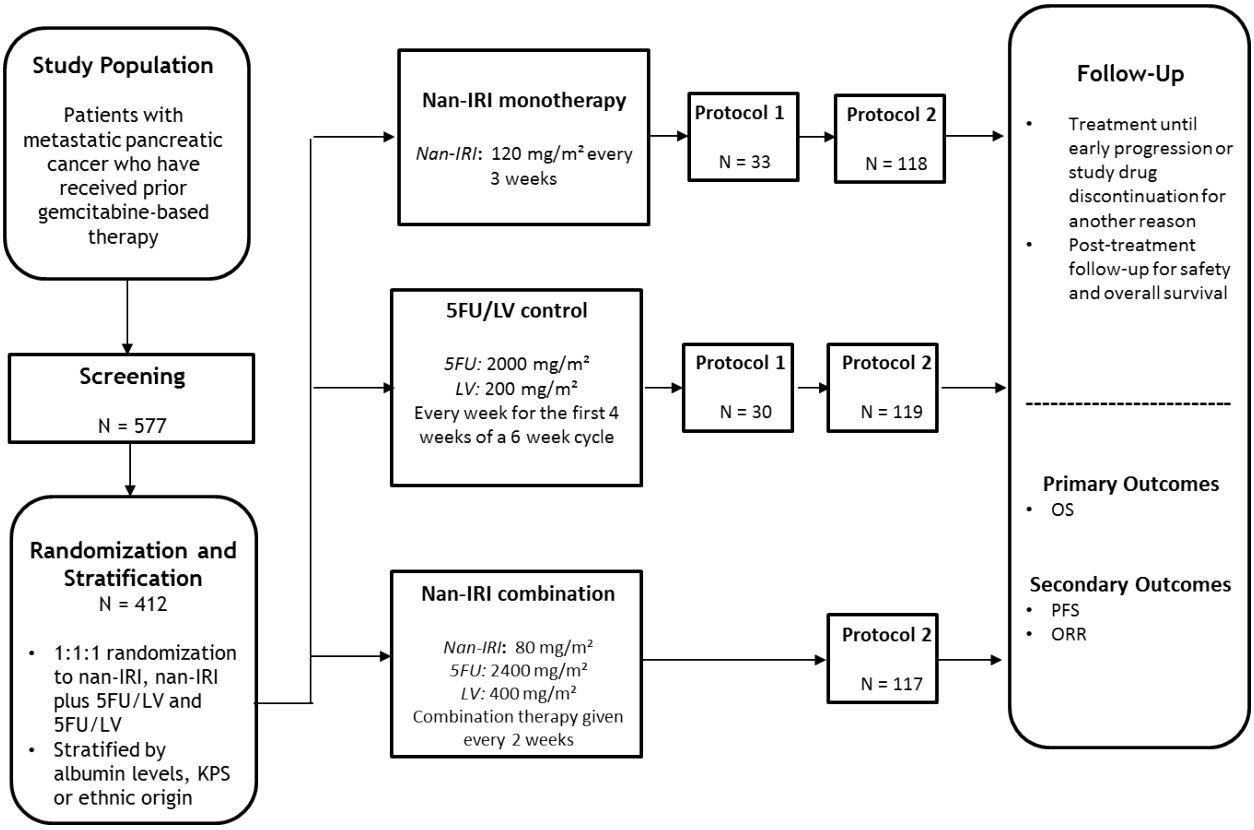
[B] Randomization was stratified by baseline albumin levels (≥40 g/L versus <40 g/L), Karnofsky performance status (70 and 80 versus ≥90), an ethnic origin (White versus East Asian versus all others).

[C] Investigators and patients were not blinded to treatment assignment. Disease progression was assessed by the Study Investigator.

[D] The primary analysis was planned after 305 deaths had occurred and it was conducted on 14-Feb-2014. The trial was considered to be complete once all patients were off the study treatment and at least 90% of all possible events had happened. The final analysis was performed on 16-Nov-2015.

The inclusion criteria for NAPOLI-1 consisted of adult patients who had histologically or cytologically confirmed pancreatic ductal adenocarcinoma and documented measurable or non-measurable distant metastatic disease using RECIST 1.1 criteria.[3] Patients must also have documented disease progression after receiving gemcitabine or gemcitabine containing therapy in the locally advanced or metastatic setting. Examples of the permitted therapies were: single agent gemcitabine; any one gemcitabine-based regimen with or without maintenance gemcitabine; single agent gemcitabine followed by a subsequent platinum agent (i.e. fluoropyrimidine or erlotinib); or gemcitabine administered in the adjuvant setting if the disease recurrence occurred within 6 months of completing the adjuvant therapy.[3] Other key inclusion criteria were a Karnofsky performance status score (KPS) of 70 or more, and adequate haematological, hepatic, and renal function. Patients who had been previously treated with irinotecan or 5-FU, or both were also eligible for enrollment.

Figure 2: Study design of NAPOLI-1



Abbreviations: **nan-IRI** = nanoliposomal irinotecan; **5-FU** = 5-fluorouracil; **LV** = leucovorin; **KPS**:=Karnofsky performance status; **OS=** overall survival; **PFS =** progression-free survival; **ORR =** objective response rate
*NAPOLI-1 was amended to add the nan-IRI combination arm after safety data on the nanoliposomal plus 5-FU/LV became available. Only the patients who were enrolled in the 5-FU/LV arm after the amendment (N=119) were used as the control for the nan-IRI combination arm.

Figure 2 represents the study design of NAPOLI-1. NAPOLI-1 was initially designed to randomize patients on a 1:1 ratio to receive nanoliposomal irinotecan monotherapy or 5-FU/LV (Protocol version 1).[3] However, the trial protocol was amended to include a third arm, nanoliposomal irinotecan plus 5-FU/LV, after safety data on the combination became available (Protocol version 2).[3] Patients continued to be enrolled under Protocol version 1 until Protocol version 2 had been approved.

The NAPOLI-1 trial consisted of two phases, the treatment phase and the follow-up phase.[3] These phases will be described in more detail, more specifically:

Treatment Phase[3]

- Eligible patients were randomized a using a computerized interactive web response system
- Patients were randomized on a 1:1:1 ratio to receive either nanoliposomal irinotecan monotherapy, 5-FU/LV or nanoliposomal irinotecan with 5-FU/LV
- Randomization was stratified by baseline albumin levels (≥40 g/L versus <40 g/L), KPS (70 and 80 versus ≥90) and ethnic origin (white versus East Asian versus all others)
- Treatment continued until disease progression (clinical or radiological) or intolerable toxic effect. Discontinuation occurred under the following circumstances[3]:
  - Patient had evidence of disease progression based on RECIST v1.1 criteria by CT or MRI

- Patient showed symptomatic deterioration
- Patient experienced intolerable toxicity, or had an adverse event which required:
    - A third dose reduction
    - Treatment to be withheld for more than 21 days from the start of next cycle, unless, in the opinion of the investigator, the patient is receiving benefit from study treatment
- Patient was significantly non-compliant with study procedures per PI assessment
- The patient or patient's attending physician requested that the patient be withdrawn from the 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 Guidelines and local regulations, stopped the study or stopped the patient's participation in the study

- Patients that discontinued study treatment for reasons other than objective disease progression continued to have radiological disease assessment every six weeks until objective disease progression or until the patient received another anti-neoplastic therapy

Follow-up Phase[3]

- There was no restriction placed on the use of subsequent treatments and patients could have received more than one therapeutic agent[34]
- Overall survival data was collected after the patient completed the 30 day follow-up visit and every month until death or the study closed
- Other post-discontinuation information was also documented, such as: date of disease progression, documentation of any subsequent anti-cancer and the date of death

The primary efficacy endpoint assessed in the NAPOLI-1 trial was overall survival. Secondary endpoints included: progression-free survival (PFS), time to treatment failure (TTF), objective response rate (ORR), tumour marker response, clinical benefit response (CBR), quality of life (QoL), and safety.

A modified intention-to-treat (ITT) analysis was used when the treatment effect of nanoliposomal irinotecan plus 5-FU/LV was compared to 5-FU/LV (i.e. all randomised patients in Protocol version 2). Wang-Gillam et al (2016) stated that this method was chosen because patients enrolled in the nanoliposomal combination arm were recruited under Protocol version 2 (Refer to Figure 2).[2] In contrast, an ITT analysis was used when the treatment effect of nanoliposomal irinotecan monotherapy were compared to 5-FU/LV (i.e. all randomised patients). No interim analyses were planned for this study.

Under Protocol version 1, the NAPOLI-1 trial was initially required to have a sample size of 270 patients, representing 220 deaths, to have 85% power to detect a hazard ratio (HR) of 0.67 using a two-sided level of 0.05.[3] However, due to the addition of the third arm under Protocol version 2 (i.e. nanoliposomal irinotecan plus 5-FU/LV) the trial also required an amendment to the sample size. It was reported in the NICE Report that the amended power calculation took into account the 63 patients who were enrolled under Protocol version 1.[6] Thus the trial has at least 98% power to detect a hazard ratio (HR) of 0.5 for death with nanoliposomal irinotecan plus 5-FU/LV relative to 5-FU/LV, and at least 85% power to detect a HR of 0.67 for death with nanoliposomal irinotecan relative to 5-FU/LV.[2] Additionally, Wang-Gillam et al (2016) performed two pair-wise comparisons of overall survival and applied a Bonferroni-Holm adjustment to control the family-wise Type 1 error using a two-sided level of 0.05.[3] It was estimated that 305 deaths would be required for the primary overall survival analysis, and thus, the estimated sample size was 405 patients.[3]

As previously mentioned, there were two major protocol amendments made to the NAPOLI-1 trial. The first amendment was made on 14-June-2012 and it instituted the following changes[3] :

- Addition of a third treatment arm (nanoliposomal irinotecan with 5-FU/LV);
- Increase the sample size to 405 patients in order to observe a total of 305 deaths among the three arms;
- Removal of a formal interim statistical comparison for safety;
- Allow patients who were previously treated with irinotecan to enroll;
- Dose modifications for *UGT1A1*28* allele carriers who were randomized to the nanoliposomal irinotecan combination arm; and
- Confirmation of a PR or CR was no longer required in order to align with RECIST 1.1 response assessment.

A second was also made on 19-Oct-2012, which made the following changes[3]:

- Clarification that the comparison between nanoliposomal irinotecan to 5-FU/LV would include patients that were randomized under Protocol Version 1 and Protocol Version 2. In contrast, the comparison between nanoliposomal irinotecan plus 5-FU/LV to 5-FU/LV would include patients who were only randomized under Protocol Version 2.

b) Populations

Baseline characteristics for patients enrolled in NAPOLI-1 are presented in Table 6. The baseline characteristics appeared to be balanced across all treatment groups. Overall, the median age of all patients was 63.0 years (range: 31 to 87) and the majority of patients were male (56.8%), white (60.7%) and had a KPS score of 90 (40.5%) or 80 (35.7%). [7] In addition, patients were more likely to have a tumour in the head of the pancreas (57.3%) and have two measurable metastatic sites (44.1%).[7] Additionally, 44.6% of patients had previously received gemcitabine-alone and 55.4% had received gemcitabine in combination with another anti-cancer therapy. [7] Wang-Gillam et al (2016) reported that 12% of patients had received gemcitabine-based therapy in the adjuvant, neoadjuvant, or locally advanced setting but had not had previous treatment for metastatic disease, 56% had received one previous line of metastatic treatment and 32% had previously received two or more lines of metastatic treatment.[2]

Table 6: Baseline characteristics of patients in NAPOLI-1

	Nanoliposomal irinotecan plus fluorouracil and folinic acid combination therapy (n=117)	Fluorouracil and folinic acid combination therapy control (n=119*)	Nanoliposomal irinotecan monotherapy (n=151)	Fluorouracil and folinic acid monotherapy control (n=149)
Men	69 (59%)	67 (56%)	87 (58%)	81 (54%)
Women	48 (41%)	52 (44%)	64 (42%)	68 (46%)
Age (years)	63 (57–70)	62 (55–69)	65 (58–70)	63 (55–69)
Ethnic origin				
East Asian	34 (29%)	36 (30%)	52 (34%)	50 (34%)
Black or African American	4 (3%)	3 (3%)	3 (2%)	3 (2%)
White	72 (62%)	76 (64%)	89 (59%)	92 (62%)
Other	7 (6%)	4 (3%)	7 (5%)	4 (3%)
Region				
Asia	34 (29%)	35 (29%)	50 (33%)	48 (32%)
Europe	47 (40%)	49 (41%)	54 (36%)	55 (37%)
North America	19 (16%)	19 (16%)	26 (17%)	25 (17%)
Other	17 (15%)	16 (13%)	21 (14%)	21 (14%)
Karnofsky performance status score†				
100	18 (15%)	17 (14%)	22 (15%)	22 (15%)
90	51 (44%)	40 (34%)	64 (42%)	54 (36%)
80	38 (32%)	51 (43%)	50 (33%)	61 (41%)
70	7 (6%)	10 (8%)	15 (10%)	11 (7%)
50–60	3 (3%)	0	0	0
Pancreatic tumour location				
Head	76 (65%)	69 (58%)	99 (66%)	81 (54%)
Other	41 (35%)	50 (42%)	52 (34%)	68 (46%)
Amount of CA19-9‡				
≥40 U/mL	92/114 (81%)	91/114 (80%)	125/146 (86%)	116/144 (81%)
<40 U/mL	22/114 (19%)	23/114 (20%)	21/146 (14%)	28/144 (39%)
Site of metastatic lesions§				
Liver	75 (64%)	83 (70%)	101 (67%)	108 (72%)
Lung	36 (31%)	36 (30%)	49 (32%)	44 (30%)
Lymph node, distant	32 (27%)	31 (26%)	44 (29%)	40 (27%)
Lymph node, regional	13 (11%)	14 (12%)	19 (13%)	20 (13%)
Pancreas	75 (64%)	72 (61%)	99 (66%)	97 (65%)
Peritoneum	28 (24%)	32 (27%)	48 (32%)	39 (26%)
Other	27 (23%)	39 (33%)	38 (25%)	48 (32%)

(Table 1 continues on next page)

	Nanoliposomal irinotecan plus fluorouracil and folinic acid combination therapy (n=117)	Fluorouracil and folinic acid combination therapy control (n=119*)	Nanoliposomal irinotecan monotherapy (n=151)	Fluorouracil and folinic acid monotherapy control (n=149)
(Continued from previous page)				
Measurable metastatic sites (n)				
1	19 (16%)	22 (18%)	36 (24%)	26 (17%)
2	49 (42%)	58 (49%)	63 (42%)	72 (48%)
3	22 (19%)	15 (13%)	22 (15%)	21 (14%)
≥4	7 (6%)	8 (7%)	7 (5%)	10 (7%)
Previous therapies or procedures				
Radiotherapy	24 (21%)	27 (23%)	40 (26%)	33 (22%)
Whipple procedure	30 (26%)	33 (28%)	47 (31%)	36 (24%)
Biliary stent	15 (13%)	8 (7%)	13 (9%)	9 (6%)
Previous lines of metastatic therapy				
0¶	15 (13%)	15 (13%)	17 (11%)	19 (13%)
1	62 (53%)	67 (56%)	86 (57%)	86 (58%)
≥2	40 (34%)	37 (31%)	48 (32%)	44 (30%)
Previous anticancer therapy||				
Gemcitabine alone	53 (45%)	55 (46%)	67 (44%)	66 (44%)
Gemcitabine combination	64 (55%)	64 (54%)	84 (56%)	83 (56%)
Fluorouracil based	50 (43%)	52 (44%)	70 (46%)	63 (42%)
Irinotecan based	12 (10%)	17 (14%)	17 (11%)	17 (11%)
Platinum based	38 (32%)	41 (34%)	54 (36%)	45 (30%)

Data are number of patients (%) or median (IQR). CA19-9=carbohydrate antigen 19-9. *Fluorouracil and folinic acid combination control group based on protocol version 2. †Baseline Karnofsky performance status score was missing for one patient in the fluorouracil and folinic acid group (enrolled under protocol 2) who was subsequently stratified as having a score ≥90. ‡Data were missing for three patients in the nanoliposomal irinotecan plus fluorouracil and folinic acid group and in five patients each in the nanoliposomal irinotecan monotherapy and fluorouracil and folinic acid groups (enrolled under protocol 2). §Investigator-reported with review by the funder's medical team. Some patients had multiple metastatic sites and are listed in more than one group. ¶Patients received neoadjuvant, adjuvant, or locally advanced treatment, but no previous therapy for metastatic disease. ||Columns add up to greater than 100% because some patients received more than one line of therapy and are listed in more than one group, and regimens might include multiple drug classes, but at least one gemcitabine based.

Table 1: **Baseline characteristics**

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c) Interventions

Treatment Dosing Schedule

The dosing schedule for the three treatment arms in the NAPOLI-1 trial are presented below[3]:

- *Nanoliposomal irinotecan plus 5-FU with LV*
  - Nanoliposomal irinotecan over 90 min at a dose of 80 mg/m² IV (equivalent to 70 mg/m² of irinotecan free base), followed by LV 400 mg/m² IV over 30 min and then 5-FU 2400 mg/m² IV over 46 hrs, every 2 weeks.
  - An initial dose of 60 mg/m² IV nanoliposomal irinotecan was provided to homozygous allele carriers of *UGT1A1*28* for the first-cycle. In the absence of any drug related toxicity, the dose was increased to its standard dose.
- *Nanoliposomal irinotecan monotherapy*
  - Nanoliposomal irinotecan at a dose of 120 mg/m² IV (equivalent to 100 mg/m² of irinotecan free base), every 3 weeks.

    - An initial dose of 80 mg/m^2 IV nanoliposomal irinotecan was provided to homozygous allele carriers of *UGT1A1*28* for the first-cycle. In the absence of any drug related toxicity, the dose was increased by 20 mg/m^2 increments to a maximum of 120 mg/m^2.
- *5-FU with LV*
    - LV at a dose of 200 mg/m² IV over 30 min followed by 5-FU at a dose of 2000 mg/m² IV over 24 h, every week for the first 4 weeks of each 6-week cycle

Different doses of nanoliposomal irinotecan were provided to patients in the nanoliposomal irinotecan plus 5-FU/LV treatment group and the nanoliposomal irinotecan monotherapy treatment group (80 mg/m^2 vs. 120 mg/m^2, respectively).[2] However, nanoliposomal irinotecan in the combination arm was administered every 2 weeks while it was administered every three weeks in the monotherapy arm. Thus, these patients received the same amount of total doses (i.e. 240 mg/m^2) over the course of 6 weeks.[8] In contrast, different doses of 5-FU and LV were given to patients in the nanoliposomal irinotecan combination arm and in the 5-FU/LV arm. Wang-Gillam et al (2016) stated that the rationale for providing different doses of 5-FU and LV across was based on evidence from the CONKO-003 trial.[15]

Dose delays, reductions or modifications

In the NAPOLI-1 trial, doses could be delayed for up to three weeks to allow patients to recover from study drug toxicities.[3] Patients who exceeded this three week period could discontinue from their assigned treatment, or they could continue treatment if they were still receiving a benefit from the drug.[3] Dose re-escalations were not permitted during the trial. Patients who required more than two dose reductions and who had an adverse event that required a third dose reduction were discontinued from the trial.[3]

Dose modifications were permitted for those treated with nanoliposomal irinotecan and the details are provided below[3]:

- *Nanoliposomal irinotecan monotherapy*
    - Patients who have their dose increased by both increments of 20 mg/m^2, to the maximum dose (120 mg/m^2) should have their dose reduced in the same way as patients who are not homozygous for *UGT1A1**28. Patients who have had their dose increased by only one increment of 20 mg/m^2, to a final dose of 100 mg/m^2, should have their dose reduced to the starting dose (i.e. 80 mg/m^2) after having a toxicity that warrants a dose reduction. Future toxicities should be handled as per the guidelines for patients homozygous for *UGT1A1**28.
- *Nanoliposomal irinotecan plus 5-FU/LV*
    - Patients who have had their dose increased to the maximum dose for the arm (80 mg/m^2) should have their dose reduced in the same way as patients who are not homozygous for *UGT1A1**28. If the dosing of either nanoliposomal irinotecan or 5-FU/LV needs to be withheld, then the other drug in the combination should not be administered.

No dose modifications were permitted for LV. However, dose modifications for 5-FU were allowed following hematological toxicities or non-hematological toxicities[3].

*UTG121*28 Genotype Status*

Patients who were homozygous carriers of the *UTG1A1*28* allele (rs8175347) were treated with a lower initial dose of nanoliposomal irinotecan because studies have shown that these carriers have an increased risk of grade 3 and 4 haematological toxicity at the initiation of un-capsulated irinotecan therapy[4]. Wang-Gillam et al (2016) reported that there were 27 patients (6.5%) in the

NAPOLI-1 trial who were homogenous for the *UTG1A1*28* allele. Among these patients, seven were in the nanoliposomal irinotecan combination group (6.0%) and seven were in the nanoliposomal irinotecan monotherapy group (4.6%).[4] In the combination group, three patients were able to escalate to the starting dose of 80 mg/m^2, one patient required a dose reduction (40 mg/m^2) and one patient discontinued due to an adverse event.[2] In the monotherapy treatment group, two patients were able to increase their dose (100 mg/m^2 and 120 mg/m^2) and one patient required a dose reduction (40 mg/m^2).[2]

d) Patient Disposition

Patient disposition for the NAPOLI-1 trial is summarized in Figure 3. In total, there were 417 patients enrolled in the trial and included in the ITT population. Patients were randomized to either nanoliposomal irinotecan plus 5-FU/LV (N = 117), nanoliposomal irinotecan monotherapy (N = 151) or 5-FU/LV (N = 149).[2] Sixty-three patients in the trial were enrolled under Protocol 1 (nanoliposomal irinotecan monotherapy [N = 33] or 5-FU/LV [N = 30]) and 354 were enrolled under Protocol 2 (nanoliposomal irinotecan combination [N = 117], nanoliposomal irinotecan monotherapy [N = 118] and 5-FU/LV [N=119]).[2]

Overall, 19 patients were not treated with their assigned therapies ($N^{combination}$ = 2, $N^{monotherapy}$ = 3, $N^{control}$ = 14) (Figure 3).[2] The majority of patients in the 5-FU/LV group were not treated because it was the subject's decision (N = 11/14, 78.6%). Furthermore, one patient in the nanoliposomal irinotecan monotherapy group and one patient in the 5-FU/LV group were treated with nanoliposomal irinotecan plus 5-FU/LV and not with their intended therapy.

At the 14-Feb-2014 cut-off date, most patients had discontinued from their assigned therapies.[2] The most common reasons for termination, regardless of randomization status, was progressive disease (52%) and clinical deterioration (12%).[4] It was also noted that five patients (1.2%) were lost to follow-up.[4]

Figure 3: Patient disposition for the NAPOLI-1 trial

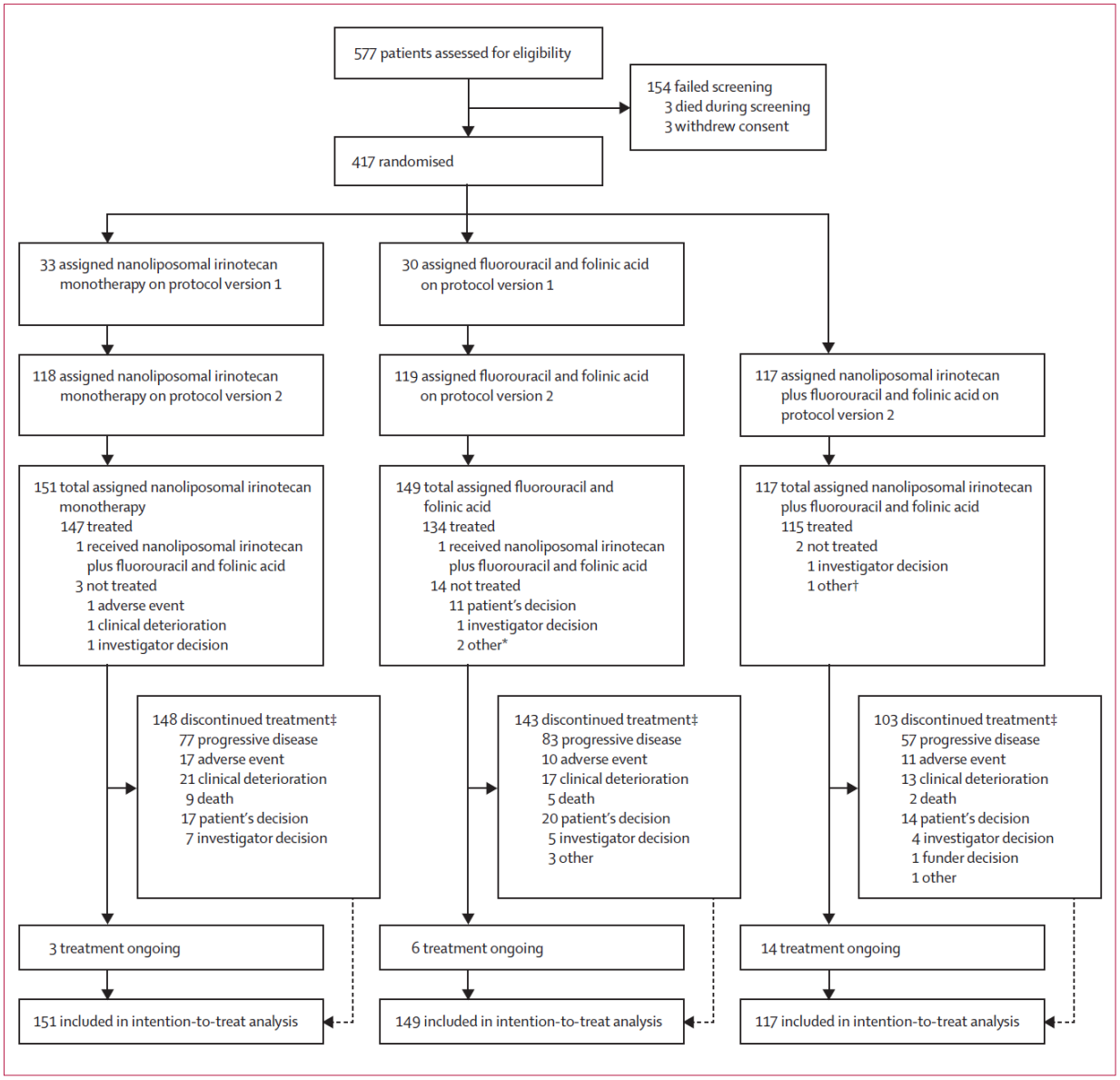

Figure 1: **Trial profile**
*One patient became ineligible after randomisation; one patient had an adverse event that delayed dosing more than 7 days from randomisation. †One patient became ineligible after randomisation. ‡The primary reason for discontinuation was at the discretion of the investigator.

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The Manufacturer reported that 124 protocol deviations occurred during the trial.[32] For patients in the nanoliposomal irinotecan combination arm, 38.5% had a major protocol deviation (N = 45/117) while 26.9% had a deviation in the 5-FU/LV control arm (N = 32/119). The most frequent protocol deviations in the nanoliposomal irinotecan combination and 5-FU/LV control groups resulted from investigational product compliance (32.5% [n = 38/117] and 14.3% [n = 17 / 119], respectively).[32]

Table 7 represents the post-treatment anticancer therapies in the NAPOLI-1 trial. Post-progression anticancer therapy was given to 31% of patients in the nanoliposomal irinotecan combination group (N=36/117) and 38% of patients in the control group (N=45/119).[2] Furthermore, eight patients in the combination group and nine patients in the control group received irinotecan as a post-progression therapy.[2]

Table 7: Post-treatment anticancer therapies

	MM-398+5-FU/LV	5-FU/LV (n=119
Had post-treatment anticancer therapy n(%)	36 (30.8)	45 (37.8)
GEM-based	11 (9.4)	12 (10.1)
5-FU-based	22 (18.8)	30 (25.2)
Irinotecan-based	8 (6.8)	9 (7.6)
Platinum-based	19 (16.2)	22 (18.5)
Other non-investigational agent	13 (11.1)	9 (7.6)
Investigational agent	3 (2.6)	4 (3.4)
No post-treatment anticancer therapy n(%)	81 (69.2)	74 (62.2)

Data source: CSR Table 14.1.1.8. and Submitter Checkpoint Questions[34]

e) Limitations/Sources of Bias

Overall, NAPOLI-1 was well designed phase III, open-label RCT. However, there are a few limitations that should be taken into consideration:

- NAPOLI-1 was an open label study. A double-blinded design would have been very difficult to implement due to the dosing and administration of the study interventions. An open label design has the potential to bias outcomes, including the subjective endpoints, such as progression-free survival, patient reported outcomes and safety.

- The open-label nature of the trial may explain the 10.4% of patients who withdrew from the 5-FU/LV arm as compared to 1.4% in the nanoliposomal irinotecan plus 5-FU/LV arm. The imbalance between the patients who received treatment could bias the assessment of overall survival. However, it is reasonable to believe that this will not bias estimates because the Manufacturer stated that the consistent results demonstrated in the per protocol and safety populations sensitivity analyses support the overall survival benefit reported in the ITT analysis.[8]

- The 25-May-2015 database locks represents a descriptive analysis. It is unclear if the p-value for any subsequent analyses was adjusted for this unplanned analysis. It is critical that the p-value be adjusted because multiple interim analyses will increase the risk of type I error in any subsequent overall survival analysis. Type I error will weaken the final conclusions of the study because they represent false positive results.

- The assessment of PFS, tumour response and disease progression assessments were conducted by the trial investigator. The lack of independent assessment of disease progression may bias the treatment effect in favour of the nanoliposomal irinotecan plus 5-FU/LV arm relative to the 5-FU/LV arm.

- Different doses of 5-FU and LV were given in the combination and control arms. Patients in the combination therapy arm received an intravenous infusion of LV 400 mg/m² over 30

min and 5-FU 2400 mg/m² over 46 h, every 2 weeks, whereas patients in the control arm received 200 mg/m² of LV as a 30-min infusion followed by an infusion of 2000 mg/m² 5-FU over 24 h, every week for the first 4 weeks of each 6-week cycle. Therefore, patients in the combination arm received higher doses of 5-FU and LV compared to the control arm. Although the difference in doses has the potential to bias the treatment effect in either direction, the Clinical Guidance Panel felt that this difference was minimal and would not have a large impact on the overall results.

- In the FDA Statistical Guidance Report, the authors stated that for the Bonferroni-Holm procedure: "…unless both hypotheses of the planned two pair-wise comparisons for the primary endpoints overall survival were rejected, no type I error rate can be transferred from the primary endpoints to the secondary endpoints for either comparison. Since the NAPOLI-1 trial failed to demonstrate a statistically significant difference in overall survival between the MM-398 arm and the 5-FU/LV arm, p-values for the secondary endpoints PFS and ORR are not interpretable for either comparison."[31] Based on this information, the effect estimates representing the comparison of nanoliposomal irinotecan versus 5-FU/LV should be interpreted with caution.

- Wang-Gillam et al (2016) expressed that the results of the CBR analysis should be interpreted with caution. First, the pain assessment was reported using a patient-reported daily dairy and compliance was low (CBRE population = 60% of ITT population). Second, the precision of the CBR classification rules led to a less robust classification of negative CBR relative to a classification of improvement. Thus there may be an increased rate of misclassification of patients as negative response for pain.[24]

- It is difficult to interpret the results of the PROs because of high attrition rates for the EORTC-QLQ C30. Although the Manufacturer provided a quality-adjusted time without symptoms and toxicity (Q-TWiST),[10] this was a post-hoc analysis and these findings should be interpreted with caution.

External validity

- NAPOLI-1 assessed the effect of nanoliposomal irinotecan, alone and in combination with 5-FU and LV, compared with 5-FU and LV. Other potentially relevant comparators were not assessed in this study (i.e. irinotecan (free base) + 5-FU + LV (FOLFIRI), or oxaliplatin + 5-FU + leucovorin (OFF). Of note, the submitter has included a network meta-analysis which includes other comparators (such as 5-FU/LV plus oxaliplatin, a modified FOLFIRI regimen (5-FU/LV + non-liposomal irinotecan, every 2 weeks) and best supportive care), a critical appraisal of which can be found in Section 7 of this report.[35]

- Patients were eligible for the NAPOLI-1 trial if they had a KPS of ≥ 70 and serum albumin levels of ≥ 3.0 g/dL. The inclusion criteria may have selected for healthier patients, which would reduce the generalizability of the trial results.

- Similarly, due to the known toxicity of irinotecan on the liver, and the liver pathology caused by the mechanical impact of pancreatic cancer on liver function (stenting, Whipple procedure, metastases), patients in the NAPOLI-1 study were required to have bilirubin levels within the normal range of their institution. Also, there is no data on patients with renal impairment population. Consequently, the efficacy of MM-398+5- FU/L in patients with impaired renal or hepatic function is not known.[4]

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

The intent of this pCODR review was to evaluate the efficacy and safety of nanoliposomal irinotecan plus 5-FU/LV in adult patients with metastatic adenocarcinoma of the pancreas who have been previously treated with gemcitabine-based therapy. For the efficacy analyses that compare the nanoliposomal irinotecan combination to the control groups, a modified ITT population was used (i.e. all randomised patients in Protocol version 2) because patients in the combination arm were only recruited under Protocol version 2.

Overall survival

The primary outcome in the trial was overall survival and it was defined as the time from randomization to the date of death or the date the patient was last known to be alive.[9] The trial was designed to have at least 98% power to detect a HR of 0.5 for death comparing nanoliposomal irinotecan plus 5-FU/LV relative to 5-FU/LV. The trial was also designed to have least 85% power to detect a HR of 0.67 for death comparing nanoliposomal irinotecan relative to 5-FU/LV. The authors performed a Bonferroni-Holm procedure to control for family wise error among the two pair-wise comparisons of overall survival with a two-sided alpha of 0.05.

The primary analysis for overall survival was conducted on 14-Feb-2014 and it was based on 313 deaths.[2] Wang-Gillam et al (2016) used Kaplan-Meier analyses to obtain the nonparametric estimates of overall survival for each treatment group and 95% confidence intervals (CI) were obtained using a log-log method.[2] The Kaplain-Meier curves for overall survival are presented in Figure 4. Unstratified Cox proportional hazards models were also used to estimate HRs with their corresponding 95% CI.

In the nanoliposomal irinotecan plus 5-FU/LV group, 64% (N=75/117) of patients died while 67% (N=80/119) of patients died in the 5-FU/LV group. Patients treated with the combination therapy had a longer median overall survival (6.1 months [95% CI: 4.76 to 8.87]) as compared to those treated with the control therapy (4.2 months [95% CI: 3.3 to 5.3]) . Nanoliposomal irinotecan plus 5-FU/LV therapy was associated with a significantly prolonged overall survival as compared to 5-FU/LV therapy in patients in metastatic pancreatic cancer (HR: 0.67, 95% CI 0.49 to 0.92; p=0.012).[2]

In contrast, 85% (N = 129/151) of patients treated with nanoliposomal irinotecan and 73% (N = 109/149) of patients treated with 5-FU/LV had died.[2] The median overall survival was similar for both treatment groups (monotherapy: 4.9 months [95% CI: 4.2 to 5.6] and control: 4.2 months [95% CI: 3.6 to 4.9]).[2] There was no statistical difference between nanoliposomal irinotecan and 5-FU/LV on overall survival (HR: 0.99, 95% CI: 0.77 to 1.28; p=0.94).[2]

Figure 4: Efficacy analysis of overall survival and PFS

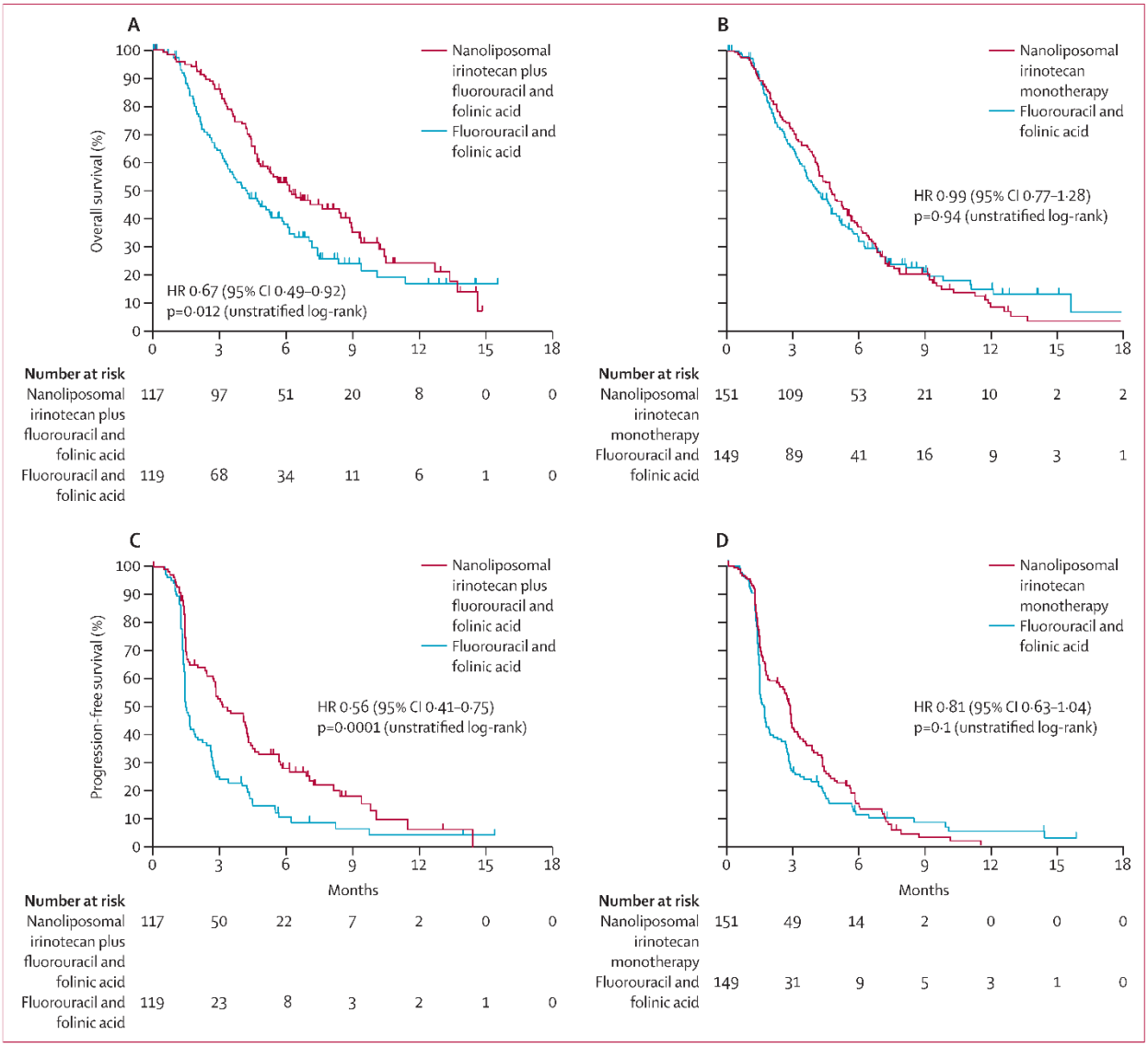

Figure 2: **Kaplan-Meier survival analyses**
HR=hazard ratio. (A) Overall survival with nanoliposomal irinotecan plus fluorouracil and folinic acid versus fluorouracil and folinic acid. (B) Overall survival with nanoliposomal irinotecan monotherapy versus fluorouracil and folinic acid. (C) Progression-free survival with nanoliposomal irinotecan plus fluorouracil and folinic acid versus fluorouracil and folinic acid. (D) Progression-free survival with nanoliposomal irinotecan monotherapy versus fluorouracil and folinic acid.

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Wang-Gilliam et al (2016) also performed pre-specified subgroup analyses.[2] The results of the subgroup analysis showed a consistent protective effect of nanoliposomal irinotecan plus 5-FU/LV relative to 5-FU/LV (Figure 5). However, the trial was not powered to test subgroup effects and these analyses should be considered exploratory.

Figure 5: Subgroup analysis of primary endpoint in NAPOLI-1.

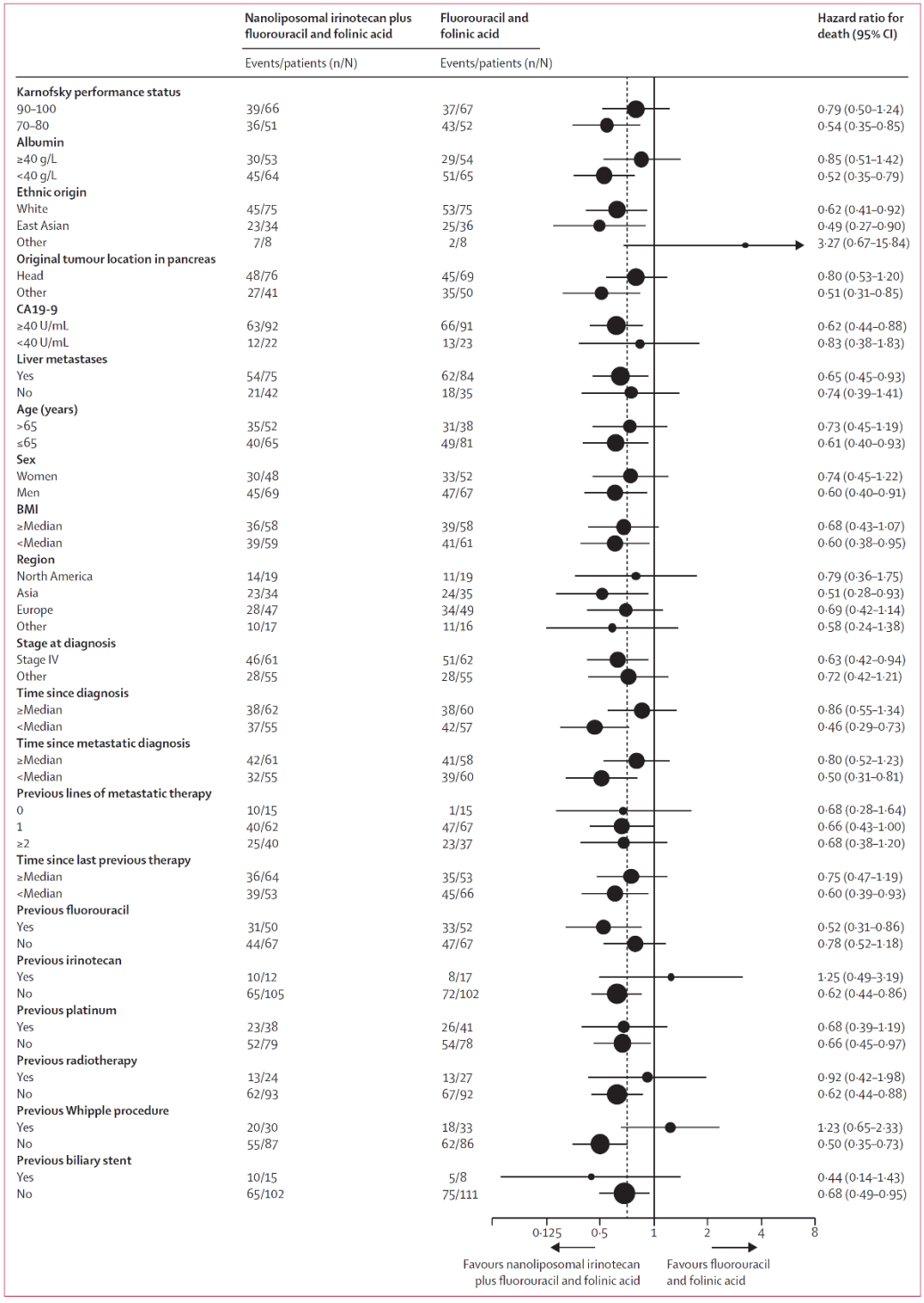

***Figure 3*: Forest plot of treatment effect on survival in prespecified subgroups**
Hazard ratios are depicted by filled circles and 95% CIs by horizontal lines. The size of the circle reflects the size of the subgroup relative to the intention-to-treat population. BMI=body-mass index. CA19-9=carbohydrate antigen 19-9.

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Sensitivity analyses were also performed to test the robustness of the overall survival effect estimates (Table 8). These analyses were conducted in the safety and per protocol populations while one analysis was stratified using the randomization strata (i.e. baseline albumin levels, KPS and ethnic origin).

Table 8: Sensitivity analyses of overall survival in the NAPOLI-1 trial

	Combination therapy comparison		Monotherapy comparison	
	Nanoliposomal irinotecan +5-FU/LV combination, N=117	**5-FU/LV control, N=119**	**Nanoliposomal irinotecan monotherapy, N=151**	**5-FU/LV Mono control, N=149**
Stratified ITT Analysis[A]				
Hazard ratio, p-value	0.57 (0.0009)		0.99 (0.94)	
N	117	119	151	149
Med. OS, Mo. (95%CI)	6.14 (4.76,8.87)	4.24 (3.9, 5.32)	4.86 (4.24,5.62)	4.17 (3.58,4.86)
Safety Population[B]				
Hazard ratio, p-value	0.66 (0.0108)		0.97 (0.84)	
N	117	105	147	134
Med. OS, Mo. (95%CI)	6.2 (4.86, 8.87)	4.2 (3.29, 5.29)	4.90 (4.27, 5.62)	4.17 (3.58, 4.86)
Per Protocol Population[C]				
Hazard ratio, p-value	0.57 (0.106)		1.11 (0.5174)	
N	66	71	116	95
Med. OS, Mo. (95%CI)	8.93 (6.44,10.48)	5.09 (3.98,7.16)	5.40 (4.80,6.28)	4.86 (3.98,5.88)
ITT Population (censoring at change in therapy)				
Hazard ratio, p-value	0.5665 (0.0033)		0.9506 (0.7460)	
N	117	119	151	149
Med. OS, Mo. (95%CI)	6.1 (4.70-12.68)	4.0(3.06-5.88)	4.8 (4.11-5.39)	3.9(3.12-5.22)

A: Randomization strata includes: baseline albumin levels, KPS and ethnic origin.
B: Patients that received at least one dose (including partial dose) of study medication. All safety analyses were performed on this population.
C: 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.
Data Source: NICE Report[6]

Although the results of the sensitivity analyses support the initial analysis of overall survival, it was noted by the Manufacturer that the strict inclusion criteria of the per protocol analysis (i.e. patients who received 80% of planned study drug during the first 6 weeks of treatment and had no major protocol deviations/violations) resulted in a small subgroup of patients.[8] In a response to NICE, the Manufacturer stated that the primary reason patients were excluded from the per protocol analysis was due to insufficient dosing.[6] Regardless, the results of the per protocol analysis demonstrate longer median overall survival for patients in both the nanoliposomal irinotecan combination and control groups (Table 8). This may also indicate that patients who received 80% of planned study drug during the first 6 weeks of treatment could experience more treatment benefit. Additionally, the Manufacturer tested the robustness of the overall survival effect estimates by adjusting for potential differences in post-study drug anticancer therapy.[6]

Here, the Manufacturer censored patients at the time when they received a new anticancer treatment. It was reported that the median overall survival for patients treated with nanoliposomal irinotecan combination therapy was 6.1 months (95% CI: 4.70 to 12.68) and 4.0 months (95% CI: 3.06 to 5.88) for patients treated with the control.[6] The HR for overall survival was 0.57 (95% CI: 0.39 to 0.83).[6]

The final analysis of overall survival was performed on 16-Nov-2015 and it was based on 382 events.[5] Chen et al (2016) reported that the median overall survival for the nanoliposomal irinotecan combination therapy was 6.24 months (95% CI: 4.76 to 8.44) and was 4.24 months (95% CI: 3.29 to 5.32) for the control therapy.[5] Nanoliposomal irinotecan combination therapy was associated with a longer overall survival as compared to the control therapy (HR: 0.75, 95% CI 0.57 to 0.99; P = 0.038). As previously reported, there was no difference between nanoliposomal irinotecan and 5-FU/LV on overall survival (monotherapy median overall survival: 4.86 months [95% CI: 4.24 to 5.62] vs control median overall survival 4.17 months [95% CI: 3.58 to 4.86]; HR: 1.07, 95% CI: 0.84 to 1.36; P = 0.567).[5]

Progression-free survival

PFS was a secondary outcome in the NAPOLI-1 trial. It was defined as the time from randomization to disease progression or death, due to any cause, on or prior to the clinical cut-off date, whichever occurred first.[9] Patients who did not have disease progression and were still alive at the time of the analysis were censored at their last tumour assessment.[9] Tumour and disease progression assessments were made by the study investigator using the RECIST 1.1 criteria.[7] PFS was assessed using computed tomography or magnetic resonance imaging at the treatment start, and then every 6 weeks thereafter, as well as 30 days post follow-up.[6] Wang-Gillam et al (2016) used Kaplan-Meier analyses to obtain the nonparametric estimates of PFS for each treatment group and 95% CI were obtained using a log-log method.[2] In addition, unstratified Cox proportional hazards models were used to estimate the HRs with their corresponding 95% CI.

In the FDA Statistical Guidance Report, it was reported that for the Bonferroni-Holm procedure: "*…unless both hypotheses of the planned two pair-wise comparisons for the primary endpoints overall survival were rejected, no type I error rate can be transferred from the primary endpoints to the secondary endpoints for either comparison. Since the trial NAPOLI-1 failed to demonstrate a statistically significant difference in overall survival between the MM-398 arm and the 5-FU/LV arm, p-values for the secondary endpoints PFS and ORR are not interpretable for either comparison*.".[31] The Manufacturer provided the following response to a query made by the pCODR Review Team: "…Because only one OS comparison was significant (combination), the significance testing for secondary endpoints in the monotherapy arm could not proceed with respect to controlling the experiment-wise error rate."[34]

Table 9. Progression-free survival results in the NAPOLI-1 ITT population.

	Combination therapy comparison		Monotherapy comparison	
	Nanoliposomal irinotecan +5-FU/LV combination, N=117	5-FU/LV control, N=119	Nanoliposomal irinotecan monotherapy, N=151	5-FU/LV Mono control, N=149
Number of events (%)	83 (70.9)	92 (77.3)	127 (84.1)	120 (80.5)
Med. OS, Mo. (95%CI)	3.1 (2.7-4.2)	1.5 (1.4-1.8)	2.7 (2.1-2.9)	1.6 (1.4-1.8)
Hazard ratio, p-value	0.56 (0.41-0.75; p=0.0001)		0.81 (0.63-1.04; p = 0.10)	
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. Data Source: Wang-Gillam et al (2016) Lancet [2] and EPAR Report [7]				

At the 14-Feb-2014 cut-off, more patients in the 5-FU/LV group (77.3%) had disease progression as compared to the nanoliposomal irinotecan combination group (70.9%) (Table 9)[7]. The Kaplain-Meier curves are presented in Figure 4. The median PFS for the combination group was 3.1 months (95% CI: 2.7 to 4.2) and 1.5 months (95% CI: 1.4 to 1.8) in the control group.[2] The authors reported that combination therapy was associated with a prolonged PFS as compared to the control therapy (HR: 0.56, 95% CI: 0.41 to 0.75; p-value = 0.0001).[2] In contrast, Wang-Gillam reported that there was no significant difference between nanoliposomal irinotecan and 5-FU/LV (HR: 0.81, 95% CI: 0.63 to 1.04; P = 0.10).[2]

To test the robustness of the PFS analysis, the Manufacturer conducted several sensitivity analyses using the same patient populations as noted in the overall survival section. The Manufacturer reported that the sensitivity analyses supported the reported effect estimates of PFS using the un-stratified Cox regression model.

The final analysis of the NAPOLI-1 trial was conducted on 16-Nov-2015. Chen et al reported that PFS was prolonged with nanoliposomal irinotecan combination therapy as compared to 5-FU/LV therapy (3.09 months [95% CI: 2.69 to 4.17] vs 1.46 months [95% CI: 1.41 to 1.84]; HR 0.57; 95% CI 0.43 to 0.76; P < 0.001).[5] There was no difference between the nanoliposomal monotherapy and 5-FU/LV treatment groups on PFS (2.73 months [95% CI: 2.14 to 2.89] vs 1.58 months [95% CI: 1.41 to 1.84]; HR 0.81; 95% CI: 0.63 to 1.04; P = 0.111).[5]

Objective Response Rate

ORR was another secondary outcome in the trial and it was defined as the as the proportion of patients with a best overall response of complete response or partial response as assessed by the study investigator using the RECIST 1.1 criteria.[8] Best overall response was measured every 6 weeks after initial response until progression or the end of the study.[9] Patients with insufficient data for response classification were classified as not evaluable for best overall response. ORR effect estimates were compared using the Fisher's exact test for pairwise comparisons.[2]

Wang-Gillam et al (2016) reported the ORR as assessed by the study investigator using RECIST 1.1 criteria.[2] The ORR for patients treated with nanoliposomal irinotecan combination therapy was 16% (N = 19/117) and 1% (N = 1/119) for those treated with the control therapy.[2] The rate difference between the two treatment groups was 15.4% (95% CI: 8.5 to 22.3; P < 0.0001).[2] Furthermore, the ORR was 6% (N = 9/151) in the nanoliposomal irinotecan group and 1% (N=1/149) in the control group.[2] The rate difference between these two treatment groups was also significant (P = 0.02).[2] The Manufacturer reported that sensitivity analyses of ORR using the PPP and PPE were consistent with the reported effect estimates of ORR.[8]

In addition to the unconfirmed analysis, the Manufacturer also provided an unconfirmed analysis (Table 10).[7] This analysis required a confirmation of complete or partial response for at least 4 weeks after the initial assessment.[7] The Manufacturer reported that the ORR was 7.7% (95% CI: 2.86 to 12.52; N = 9/117) for patients in the combination therapy group and 0.84% (95% CI: 0 to 2.48; N = 1/119) for patients in the control therapy group.[7] The rate difference between the two treatment groups was 6.85 (95% CI: 1.75 to 11.95; P = 0.0097).[7] Additionally, the ORR was 3.31% (95% CI: 0.46 to 6.17; N = 5/151) in the nanoliposomal irinotecan group and 0.67% (95% CI: 0.00 to 1.98) in the control group.[7] The rate difference was not significant between these two treatment groups (P = 0.214).[7]

Table 10: Objective response rates in the NAPOLI-1 trial.

	Combination therapy comparison		Monotherapy comparison	
	Nanoliposomal iriontecan+5-FU/LV combination, N=117	5-FU/LV control, N=119	Nanoliposomal irinotecan monotherapy, N=151	5-FU/LV Mono control, N=149
Confirmed (≥ 4 weeks After Investigator Assessment of PR or CR)				
Best Overall Response, n (%)				
Partial Response	9 (7.7)	1 (0.8)	5 (3.3)	1 (0.7)
Stable Disease	47 (40.2)	26 (21.8)	57 (37.7)	35 (23.5)
Non-Complete Response/Non-Progressive Disease	3 (2.6)	2 (1.7)	3 (2.0)	2 (1.3)
Progressive Disease	35 (29.9)	56 (47.1)	51 (33.8)	71 (47.7)
Not Evaluable	23 (19.7)	34 (28.6)	35 (23.2)	40 (26.8)
Objective Response Rate				
N	9	1	5	1
Rate (%)	7.69	0.84	3.31	0.67
95% CI of Rate[1]	2.86, 12.52	0.0, 2.48	0.46, 6.17	(0.0, 1.98)
Rate Difference (95% CI)	6.85 (1.75, 11.95)		2.64 (-0.50, 5.78)	
p-value[2]	0.0097		0.2141	
95% CI is of Overall Response Rate for individual treatment arms and for the rate difference (treatment vs. control) were calculated based on the normal approximation. 2. Two-sided p-values from pairwise Fisher's exact test. Data Source: Wang-Gillam et al (2016) Lancet [2] and EPAR Report[7]				

At the final analysis (16-Nov-2015), Chen et al (2016) stated that the ORR per RECIST 1.1 was higher in the nanoliposomal combination group as relative to the 5-FU/LV control group (17% vs 1%; P < 0.001) as well as for the nanoliposomal monotherapy and control groups (6% vs 1%; P = 0.020).[5]

Time To Treatment Failure

TTF was defined as the time from randomization to treatment discontinuation for any reason, including: disease progression, treatment toxicity or death.[9] The Manufacturer reported that TTF was assessed using pairwise comparisons with unstratified log-rank tests. Kaplain-Meier analyses were performed to obtain nonparametric estimates and the median TTF with the corresponding 95% CI. In addition, Cox proportional hazards were used reported with the corresponding 95% CI.

Wang-Gillam et al (2016) reported that the median TTF was 2.3 months (95% CI: 1.6 to 2.8) for patients allocated to the nanoliposomal irinotecan combination group and 1.4 months (95% CI: 1.3 to 1.4) for patients allocated to the control group.[2] Patients treated with combination therapy had a significantly longer TTF as compared to those treated with the control therapy (HR: 0.60, 95% CI: 0.45 to 0.78; P = 0.0002).[2] Additionally, the median TTF was similar for patients treated with nanoliposomal monotherapy (1.7 months [95% CI: 1.48 to 2.66]) and 5-FU/LV (1.4 months [1.3 to 1.4]).[2] TTF was not significantly different between the two treatment groups (HR: 0.82, 95% Ci: 0.65 to 1.03; P= 0.10).[2]

Tumour Marker Response

Tumour marker response was defined as a 50% decrease in CA19-9 serum levels relative to baseline at least once during the treatment period.[9] Only patients with a baseline CA19-9 value of > 30 U/mL were included in the analysis.[2] Wang-Gillam et al (2016) reported that more patients (29%; N = 97) treated with nanoliposomal irinotecan plus 5-FU/LV achieved a CA19-9 response (≥50% decrease from abnormal baseline) as compared to patients treated with 5-FU/LV (9%; N = 81) (P=0.0006).[2] Furthermore, more patients treated with nanoliposomal irinotecan achieved a CA19-9 response (24%; N = 123) than those treated with 5-FU/LV (11%; N = 105) (P = 0.024).[2]

Clinical Benefit Response

CBR was a composite outcome that measured patient-reported pain, patient-reported pain medication, KPS and weight.[9] Clinical benefit was indicated by:

- An improvement in pain (less pain intensity with stable or decreased pain medication; or less pain medication with stable or decreased pain intensity) with stable or improved KPS; or
- An improvement in KPS with stable or improved pain.

It was noted that if patients had stable KPS and pain, then clinical benefit may be indicated with a positive weight change.[9] CBR was assessed weekly and a patient was classified as having CBR if the clinical benefit was observed and maintained over a 4 week period.[9]

Wang-Gillam et al (2016) reported that the CBR evaluable population included patients who met the following criteria[2]:

- Baseline pain intensity ≥ 20 (out of 100)
- Baseline opioid analgesic consumption ≥ 10 mg/day oral morphine equivalents
- Baseline Karnofsky Performance Scale score of 70 to 90 points

The CBR evaluable population consisted of 78 patients in the nanoliposomal irinotecan combination group (66.7%, N = 117), 92 patients in the nanoliposomal irinotecan monotherapy group (60.9%, N = 151) and 80 in the control group (53.7%, N = 149).[24] The CBR rates for the nanoliposomal irinotecan plus 5-FU/LV and the 5-FU/LV were 14% (N = 11/78) and 12% (N = 7/60), respectively.[24] On the other hand, the CBR rates were 17% in both the nanoliposomal irinotecan (N = 13/92) and 5-FU/LV groups (N = 10/80).[24]

Wang-Gillam et al (2016) stated that these results should be interpreted with caution.[24] First, the pain assessment was reported using a patient-reported daily diary and compliance was low (CBRE population = 60% of ITT population).[24] Second, the precision of the CBR classification rules led to a less robust classification of negative CBR relative to the classification of improvement. Thus, more patients may be misclassified as having a negative response for pain.[24]

Quality of Life

In the NAPOLI-1 Trial, patient-reported outcomes (PROs) were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30). The EORTC-QLQ-C30 consists of three independent domains, and includes: global health-related quality of life (HRQoL), functional scales (cognitive, emotional, physical, role and social functioning), and symptom scales (appetite loss, constipation, diarrhea, dyspnea, fatigue, insomnia, nausea and vomiting, and pain).[9] PROs were measured at baseline and then every 6 weeks until disease discontinuation. The baseline median global HRQoL, functional scales, and symptom scales were similar across all treatment groups.

Wang-Gillam et al (2016) stated that, in terms of the functional and symptom scale scores of the EORTC-QLQ-C30, there were no substantial differences in the proportion of patients who demonstrated improvements or deterioration between the nanoliposomal irinotecan plus 5-FU/LV and the 5-FU/LV arm.[2]

According to the Clinical Study Report, the baseline median Global Health Status scores were similar between the nanoliposomal irinotecan monotherapy and 5-FU/LV control group and the nanoliposomal irinotecan combination and control group.[32] Median scores at Week 6 and Week 12 showed no appreciable changes from baseline and suggested that the effects of the treatments on Global Health Status were negligible.

Similarly, baseline median Functional Scale scores were similar between similar between the nanoliposomal irinotecan monotherapy and 5-FU/LV control group and the nanoliposomal irinotecan combination and control group. Median scores at Week 6 and Week 12 showed no appreciable changes from baseline and suggested that the effects of the treatments on Functional Scale scores were negligible.

As well, baseline median Symptom scores were similar between similar between the nanoliposomal irinotecan monotherapy and 5-FU/LV control group and the nanoliposomal irinotecan combination and control group. Median scores at Week 6 and Week 12 for pain, dyspnea, insomnia, appetite loss, and constipation showed no appreciable changes from baseline and suggested that the effects of the treatments on these symptoms were negligible. Baseline median symptom scores for nausea and diarrhea were 0 (i.e., no symptomatology) showed slight increases post-baseline with scores between 16.7 and 33.3 that indicated low symptomatology among patients whose treatment included nanoliposomal irinotecan. Increases in median scores for fatigue and financial difficulties were low or transient.

It should be noted that the results of the HRQoL should be interpreted with caution because of a low compliance rate, and hence, HRQoL data was only presented for weeks 6 and 12. The NICE Report stated that a "*…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)*".[6]

Pelzer et al (2016) conducted a quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis to identify between-treatment differences in quality-adjusted survival.[10,23] For this analysis, the ITT populations was stratified into three subgroups: 1) time with AE grade ≥ 3 toxicity (TOX), 2) time in relapse after disease progression (REL) and 3) time without symptoms of AE grade ≥ 3 toxicity (TWiST). The mean Q-TWIST was calculated by multiplying time spent in each health state by its respective utility. As compared to patients treated with 5-FU/LV, those who received nanoliposomal irinotecan plus 5-FU/LV had longer mean times in TOX (1.0 vs 0.3 month) and TWiST (mean 3.4 vs 2.4 months).[10,23] Time spent in REL was similar between the two treatment groups. Furthermore, nanoliposomal irinotecan combination therapy was associated with a 1.3 month (95% CI: 0.4 to 2.1) greater Q-TWiST (range threshold analyses: 0.9 to 1.6 months) as well as a higher relative Q-TWiST of 24% (range threshold analyses: 17% to 31%) than the control therapy.[10,23] Although these results demonstrate that nanoliposomal irinotecan plus 5-FU/LV might provide important gains in quality adjusted survival as compared to 5-FU/LV, this was a post-hoc analysis.

Harms Outcomes

A large proportion of patients from the NAPOLI-1 trial were included in the safety analysis population (95%).[2] There were 117 patients in the nanoliposomal irinotecan combination arm, 147 in the monotherapy arm and 134 in the control group. For this analysis, the two 5-FU/LV control groups (Protocol version 1 and 2) were pooled together.

The Manufacturer reported that the median duration of exposure to nanoliposomal irinotecan was 8.7 weeks (IQR: 5.4 to 22.0) for the combination arm and 8.9 weeks (IQR: 6.0 to 16.0) weeks for the monotherapy arm.[2] Patients allocated to the nanoliposomal irinotecan combination group received a greater mean dose of nanoliposomal irinotecan over six weeks (mean: 167.5 mg/m^2 [SD: 44.8]) as compared to those allocated in the monotherapy group (mean: 188.0 mg/m^2 [SD: 52.0]).[2]

Adverse Events

Table 11: Summary of the adverse events that occurred in the NAPOLI-1 safety population

	Nanoliposomal irinotecan monotherapy (N=149)	Nanoliposomal irinotecan+5-FU/LV comb. (N=117)	5-FU/LV control (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 CTCAE grade 3 or higher TEAE	112 (76.2)	90 (76.9)	75 (56.0)
≥1 TEAE related to study drug	128 (87.1)	107 (91.5)	93 (69.4)
≥1 drug related AE of CTCAE grade 3 or higher	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
≥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)

Data Source: Clinial Summary Report [8] and NICE Report[6]

All Grades and Grade 3 or 4 Adverse Events

The majority of patients enrolled in the NAPOLI-1 trial experienced at least one treatment-emergent adverse event (TEAE) (monotherapy: 98.6%, combination: 99.1% and control: 98.5%) (Table 11).[8] Similar patterns were also reported for grade 3 TEAEs (monotherapy: 76.2%, combination: 76.9% and control: 56.0%).[8] The Manufacturer defined TEAEs as "...events that occurred or worsened on or after the day of first dose of the study drug and within 30 days after last administration of study drug.".[4] The Manufacturer also provided an additional definition, which states: "*Treatment-emergent adverse events are not necessarily the result of a treatment's mechanism of action or side effects. Drug-related adverse events are, by definition, related to the drug's biological action.*"[34]

More patients in the nanoliposomal irinotecan combination arm had at least one TEAE related to the study drug (91.5%) versus those treated with monotherapy (87.1%) or control (69.4%).[8] Likewise, more patients in the combination group (53.8%) had at least one drug related Grade 3 or higher TEAE compared to the other treatment groups (monotherapy: 51.7% or control: 17.9%).[8] This was also similar for drug related Grade 4 and Grade 5 TEAE (Table 11).

Table 12: Treatment-emergent adverse events that occurred in ≥ 10% of the NAPOLI-1 safety population

	Nanoliposomal irinotecan monotherapy (N=149)	Nanoliposomal irinotecan+5-FU/LV comb. (N=117)	5-FU/LV control (N=134)
Any TEAEs	145 (98.6)	116 (99.1)	132 (98.5)
Diarrhea	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)
Anemia	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)
Hypokalemia	32 (21.8)	14 (12.0)	12 (9.0)
Edema 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)

Data Source: Clinial Summary Report[8] and NICE Report[6]

Table 12 represents a summary of adverse events that occurred in ≥ 10% of patients.[6,8] The most common TEAEs for all patients were diarrhoea (monotherapy: 70%, combination: 59% and control: 26%); nausea (monotherapy: 61%, combination: 51% and control: 34%); and vomiting (monotherapy: 54%, combination: 52% and control: 26%).

At the final analysis (16-Nov-2015), the most common Grade ≥ 3 TEAE that occurred in ≥ 10% of patients were neutropenia (combination: 28%; monotherapy: 15%, and control: 1%), fatigue (combination: 14%; monotherapy: 6%, and control: 4%), diarrhea (combination: 13%; monotherapy: 21%, and control: 5%), vomiting (combination: 12%; monotherapy:14%, and control: 4%), anemia

(combination: 9%; monotherapy: 11%, and control: 7%) and hypokalemia (combination: 3%; monotherapy:12%, and control: 2%).[5]

Serious Adverse Events

More treatment-emergent SAE occurred in the monotherapy group (61.2%) as compared to the combination (47.9%) or the control groups (44.8%).[4]

Dose modification, reductions, delays or discontinuations

More patients in the combination arm (70.9%) had an adverse event that required at least one dose modification as compared to the monotherapy (55.1%) or the control groups (35.8%) (Table 11).[6] This was also similar for patients who had at least one TEAEs that resulted in a dose delay (combination: 61.5%, monotherapy: 33.3% and control: 32.1%).[6] The frequency of at least one TEAE that led to a dose reduction was similar for the combination and monotherapy groups (33.3% and 31.3%) as compared to the control group (3.7%).[6] This pattern was also observed for those with at least one TEAE leading to a dose discontinuation (combination: 11.1%, monotherapy: 11.6% and control: 7.5%).[6]

Deaths

Wang-Gillam et al (2016) reported that 47 patients died during the treatment period, which were deaths that occurred on or after the day of first dose of the study drug and within 30 days after last administration of study drug.[2] Among these 47 deaths, more deaths occurred in the combination group (15.0%) than in the control (12.7%) or monotherapy group (6.8%).[32] The 47 deaths were attributed to pancreatic cancer (N = 30/47), adverse events (N = 16/47) and the cause of one death was unknown.[2] For the 16 deaths that resulted from an adverse event, five deaths were treatment-related based on the opinion of the investigator. More specifically, four treatment-related grade 5 AE deaths occurred in the monotherapy group [gastrointestinal toxic effect (N =1), infectious enterocolitis (N=1), septic shock (N=1) and disseminated intravascular coagulation with pulmonary embolism (N=1)] and one occurred in the combination arm [septic shock (N=1)].[2]

6.4 Ongoing Trials

Phase II Randomized Study of BAX2398 in Combination With 5-Fluorouracil and Calcium Levofolinate in Japanese Patients With Metastatic Pancreatic Cancer, Which Progressed or Recurred After Prior Gemcitabine-Based Therapy[9]

Study Part 1: To assess the safety and tolerability, and to characterize the pharmacokinetics (PK) of BAX2398 in combination with 5-FU/calcium levofolinate in Japanese patients.

Study Part 2: To compare the efficacy of BAX2398 in combination with 5-FU/calcium levofolinate versus 5-FU/calcium levofolinate as assessed by Progression Free Survival (PFS) using Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1).

Table 13: Ongoing trials of nanoliposomal irinotecan plus 5-FU/LV in patients with metastatic adenocarcinoma of the pancreas who have been previously treated with gemcitabine-based therapy

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study NCT02697058	Key Inclusion Criteria:	Experimental: Part 1: Safety and PK	Primary:

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Characteristics: Phase II Trial **Sample size:** N = 80 **Location:** Japan **Patient Enrolment Dates** Mar-2016 **Data cut-off:** Dec-2017 **Funding** Baxalta US Inc	1. ≥20 years of age at the time of screening. 2. Histologically or cytologically confirmed adenocarcinoma of exocrine pancreas 3. Documented metastatic disease 4. Metastatic disease with at least one measurable lesion as defined by RECIST 1.1 guidelines 5. Documented disease progression after prior gemcitabine or any gemcitabine containing therapy but excluding irinotecan, for locally advanced or metastatic setting. 6. Karnofsky Performance Status (KPS) ≥70 7. Adequate bone marrow reserves, hepatic function and renal function <u>Exclusion Criteria:</u> 1. Active and uncontrolled CNS metastases 2. History of any second malignancy in the last 5 years	BAX2398 in combination with 5-FU/calcium levofolinate Experimental: Part 2: Safety, PK, Efficacy BAX2398 in combination with 5-FU/calcium levofolinate Active Comparator: Part 2: 5-FU/calcium levofolinate alone 5-FU/calcium levofolinate Intervention: Drug: 5-FU/calcium levofolinate	PFS in Part 2 of Study Secondary: PFS in Part 1 of Study OS TTF ORR DCR Tumor marker evaluation QoL
Abbreviations: PFS = Progression free survival; **OS** = Overall survival; **TTF** = Time to treatment failure; **ORR** = Objective response rate; **DCR** = Disease control rate; **QoL** = Quality of life			

7 SUPPLEMENTAL QUESTIONS

7.1 Critical appraisal of the network meta-analysis comparing the efficacy and safety of anti-cancer therapies in advanced stage pancreatic cancer patients with prior exposure to gemcitabine

Background

The pCODR-conducted literature search only identified one RCT that assessed the efficacy and safety of nanoliposomal irinotecan plus 5-FU/LV versus 5-FU/LV in patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine (GEM) based therapies.[2] Thus there is a lack of direct evidence comparing nanoliposomal irinotecan plus 5-FU/LV to other currently funded therapies in Canada. Given the absence of head-to-head trials, the Manufacturer conducted a network meta-analysis (NMA).

Other NMA comparisons have been conducted to compare nanoliposomal irinotecan plus 5-FU/LV to other therapeutic agents. The Manufacturer provided an NMA for NICE.[6]

The objective of this section is to summarize and critically appraise the submitted NMA, which provides evidence of the efficacy of nanoliposomal irinotecan plus 5-FU/LV as compared to other active therapies in patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapies.

Review of manufacturer's ITC

Objectives of manufacturer's NMA

The objectives of the Manufacturers' NMA were to compare nanoliposomal irinotecan plus 5-FU/LV treatment in patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapies to the following therapies:

- **5-FU and LV**
- **Nanoliposomal irinotecan**
- **OFF** (oxaliplatin, 5-FU and LV)
- **mFOLFIRI3** (irinotecan [70 mg/m$^{2;}$ days 1 and 3], LV [400 mg/m$^{2;}$ day 1] and 5-FU [2000 mg/m$^{2;}$ day 1 and 2] every 2 weeks)
- **mFOLFOX** (oxaliplatin [85 mg/m$^{2;}$ day 1], LV [400 mg/m$^{2;}$ day 1] and 5-FU [2000 mg/m$^{2;}$ day 1 and 2] every 2 weeks)
- **mFOLFOX6** (oxaliplatin [85 mg/m$^{2;}$ day 1], LV [400 mg/m$^{2;}$ day 1] and 5-FU [2400 mg/m^{2} over 46 hours] every 2 weeks)
- **XELOX** (oxaliplatin [130 mg/m$^{2;}$ day 1] and capecitabine [1000 mg/m^{2} bid x 14 days])
- **CAP** (capecitabine)
- **Best supportive care** (BSC)

Study Eligibility and Selection Process

The Manufacturer conducted a systematic review to identify eligible studies (criteria in Table 14) for the NMA.[35]

Table 14: Population, interventions, and study design criteria for inclusion of studies

Criteria	Description
Criteria	Description
Population	Adult patients with advanced stage pancreatic cancer receiving treatment in the 2nd line setting
Interventions	The following treatments were considered as the relevant competing interventions of interest: • 5-FU and LV • Nanoliposomal irinotecan • OFF (oxaliplatin, 5-FU and LV) • mFOLFIRI3 (irinotecan [70 mg/m$^{2;}$ days 1 and 3], LV [400 mg/m$^{2;}$ day 1] and 5-FU [2000 mg/m$^{2;}$ day 1 and 2] every 2 weeks) • mFOLFOX (oxaliplatin [85 mg/m$^{2;}$ day 1], LV [400 mg/m$^{2;}$ day 1] and 5-FU [2000 mg/m$^{2;}$ day 1 and 2] every 2 weeks) • mFOLFOX6 (oxaliplatin [85 mg/m$^{2;}$ day 1], LV [400 mg/m$^{2;}$ day 1] and 5-FU [2400 mg/m^2 over 46 hours] every 2 weeks) • XELOX (oxaliplatin [130 mg/m$^{2;}$ day 1] and capecitabine [1000 mg/m^2 bid x 14 days]) • CAP (capecitabine) • Best supportive care
Primary outcomes of interest	Each relevant study reported at least one of the following outcomes: • Progression-free survival (PFS) • Overall survival (OS) • Objective response rate (ORR) • Clinical benefit rate (CBR) • Number of patient withdrawals due to adverse drug reactions • Frequency of all grade III/IV dose limiting toxicity
Study design	Randomized controlled trials and single arm trials (when RCT data was not available)

Data Source: Dranitsaris (2016)[35]

In order to conduct the systematic review, the authours stated that they searched the following databases: PubMed, the Cochrane Library and Google Scholar. The search was performed between 1-Jan-1996 to Aug-2016.[35]

Studies were eligible for inclusion if they used randomized design with at least 30 patients in each group. Furthermore, these studies had to include adult patients aged 18 years of age who were diagnosed with advanced stage pancreatic cancer, had prior exposure to GEM and received at least one prior therapy in the metastatic setting. The authors of the NMA also considered unpublished randomized trials in conference abstracts if they were able to get access to study summary reports.

Once all eligible studies had been identified, the authors extracted the following information: sample size, year of publication, the number and site of metastases, median patient age, performance status, duration of metastatic disease from initial diagnosis, median number of prior therapies, chemotherapy dosage, definition of primary and secondary outcomes, median duration of therapy, patient cross-over and all relevant clinical outcomes (i.e. ORR, CBR, PFS, overall survival, safety). The authors also stated that single arm trials were considered for inclusion

because they wanted to limit the biases that were associated with the use of data from observational studies in the NMAs (vide infra).[35]

The quality of all included studies was assessed using the NICE checklist, which consists of seven questions related to the study quality. The authors noted that if a trial did not meet at least four of the seven quality criteria than the study was excluded from the analysis.[35]

Based on the report submitted by the Manufacturer, it is unclear whether the following actions were performed: screening potential articles in duplicate, screening calibration exercises, and duplicate data extraction.

Network meta-analysis methods

The NMA was performed using a Bayesian three-level hierarchical model. This model allows the authors to incorporate evidence from different trial designs (i.e. single arm and RCTs) by matching baseline characteristics to the treatment arms of the RCT. This matching was done with a "similarity metric", which was defined as the weighted average of the normalized absolute difference in trial-level covariates and it is reported on a scale from 0 to 1.[35] The authors stated that if a study had a similarity metric of ≤ 0.10 then it could be included in the NMA.[35] Single arm studies that were included in the SR were matched using the following criteria: patient age, performance status, sites of metastatic disease, duration of disease and median number of prior therapies.[35]

The authors reported that a range of mixed treatment comparisons were conducted to explore all possible networks using the similarity metric of ≤ 0.10.[35] Each of these analyses provided an estimate of the relative efficacy and its corresponding 95% credible intervals (CrI). The overall comparative effect was expressed as the weighted average of the estimated means using the similarity metrics as weights.[35] The Manufacturer reported using random effect modeling to account for the variability in the trials ensure more conservative estimates.[35] The estimates of ORR and CBR were reported as an odds ratio (OR) while the estimates of PFS and overall survival were reported as hazard ratios (HR) and the estimates of treatment discontinuations and grade III/IV dose limiting toxicity were reported as a relative risk (RR).[35]

Based on the report submitted by the Manufacturer, it is unclear whether the assumptions of NMA were tested. The Manufacturer stated that due to variability in the baseline patient characteristics and missing data they were unable to incorporate non-RCTs into the NMA. The authours commented that they attempted to test whether performing an NMA would be appropriate using data from their included RCTs. However, the authours stated that the some of the included studies "… were small, investigator initiated and not intended for regulatory approval."[34] Thus it was difficult to appropriately apply statistical methods to compare the proportional hazards across trials, minimize bias of potential effect modifiers or explore heterogeneity within their final estimates.

Results

Included studies

The systematic review performed by the Manufacturer identified a total of 1035 citations which retrieved 214 abstracts. In addition, the authors also identified 30 additional records through hand searches. Sixty-seven articles were assessed for eligibility, and from the full-text screening, 23 publications were excluded for patient populations, 26 for study intervention, five for study design and four for a lack of data availability. In total, nine publications were included, which represents nine unique trials. Among the included studies, there were seven RCTs[2,14-16,36-38] and two single arm trials.[39,40] Among the RCTs, five trials contained the regimens of interest [2,14-16,38-40] and two

trials compared CAP to another investigational agent which were not relevant to this NMA.[36,37] On the other hand, the single arm trials assessed the effect of capecitabine and XELOX, respectively.[39,40]

Trial characteristics

Details of the populations, interventions and comparators used in the NMA are reported in Table 15, the NICE checklist for study quality assessment is reported in Table 16 and the direct estimates of ORR, PFS and overall survival are presented in Table 17.

Table 15: PICOS results comparing for trials in the NMA

Trial	Arm	N per arm	Median age	Prior surgery	ECOG PS 0/1 at baseline	Lung mets	Liver mets
Bodoky, 2012	CAP vs	32	62	78%	NR	NR	NR
	Selumitinib	37	63.1	76%	NR	NR	NR
Boeck, 2007	CAP	39	63	31%	NR	23%	79%
Gill, 2014	5-FU/LV vs.	53	67	NR	94.4%	NR	68.5%
	mFOLFOX6	49	65	NR	88.9%	NR	57.4%
Hurwitz, 2015	CAP vs	63	68.0	17.5%	90.5%	44.4%	65.1%
	RUX+CAP	64	66.0	29.7%	75%	45.3%	68.8%
Oettle, 2014	5-FU/F vs.	84	61	NR	NR	NR	NR
	OFF	76	62	NR	NR	NR	NR
Pelzer, 2011	BSC	23	61	NR	NR	NR	NR
	OFF	23	60	NR	NR	NR	NR
Xiong, 2008	XELOX	39	62	41%	71.4%	NR	NR
Yoo, 2009	mFOLFIRI3 vs.	31	55	32%	100%	19%	61%
	mFOLFOX	30	55	37%	97%	17%	70%
Wang-Gillam, 2016	Nal-IRI + FF	117	63	80.2%	NR	31%	64%
	vs. 5-FU/F	119	62	78.2%	NR	30%	70%

Abbreviations: NR = not reported; CAP = capecitabine; mets = metastases; Nal-IRI = nanoliposomal irinotecan

Data Source: Dranitsaris (2016)[35]

Table 16: The NICE checklist for study quality assessment

Citation	Was randomization carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Bodoky, 2012	Yes	No	Yes	No	Yes	No	Yes
Boeck, 2007	Not an RCT	NA	NA	NA	NA	No	Yes
Gill, 2015	Yes	No	Yes	No	Yes	Unsure	Yes
Hurwitz, 2015	Yes	Yes	Yes	Yes	No	No	Yes
Oettle, 2014	Yes	No	Yes	No	No	No	Yes
Pelzer, 2011	Yes	No	Yes	No	No	No	Yes
Xiong, 2008	Not an RCT	NA	NA	No	No	No	Yes
Yoo, 2009	Yes	Yes	Yes	No	No	No	Yes
Wang-Gillam, 2016	Yes	No	Yes	No	No	No	Yes

Abbreviations: ITT = intention to treat, NA = not applicable, RCT = randomized controlled trial
Data Source: Dranitsaris (2016)[35]

Table 17: Clinical outcomes of trials retrieved from the systematic literature review

Trial	Arm	N per arm	Overall Response (95%CI)	Median PFS (mon) (95%CI)	Median OS (mon) (95%CI)
Gill, 2014	5-FU/LV vs.	54	8.5% (1.5 to 17.0%)	2.9	9.9
	mFOLFOX6	54	13.2% (4.0 to 21.9%) p = 0.361	3.1 HR = 1.0 (0.66 to 1.53); p = 0.989	6.1 HR = 1.78 (1.08 to 2.93); p = 0.024
Oettle, 2014	5-FU/LV vs.	84	1.2% (0 to 2.51%)	2.0 (1.6 to 2.3)	3.3 (2.7 to 4.0)
	OFF	76	1.3% (0 to 3.88%) p = 0.94	2.9 (2.4 to 3.2) HR = 0.68 (0.50 to 0.94); p = 0.019	5.9 (4.1 to 7.4) HR = 0.66 (0.48 to 0.91); p = 0.01
Pelzer, 2011	BSC	23	NR	NR	2.3 (1.76 to 2.83)
	OFF	23	NR	NR	4.82 (4.29 to 5.35) HR = 0.45 (0.24 to 0.83); p = 0.008
Yoo, 2009	mFOLFIRI3 vs.	31	0.0% (0 to 10%)	1.9 (1.56 to 2.20)	3.8 (2.86 to 4.71)
	mFOLFOX	30	6.7% (1 to 22%) p = 0.92	1.37 (1.17 to 1.58) HR = NR	3.41 (1.83 to 5.60) HR = NR
Wang-Gillam, 2016	Nal-IRI + FF	117	16.2% (9.56 to 22.9%)	3.1 (2.7 to 4.2)	6.1 (4.8 to 8.9)
	vs. 5-FU/LV	119	0.84% (0 to 2.5%) p < 0.001	1.5 (1.4 to 1.8) HR = 0.56 (0.41 to 0.75); p = 0.0001	4.2 (3.3 to 5.3) HR = 0.67 (0.49 to 0.92); p = 0.012

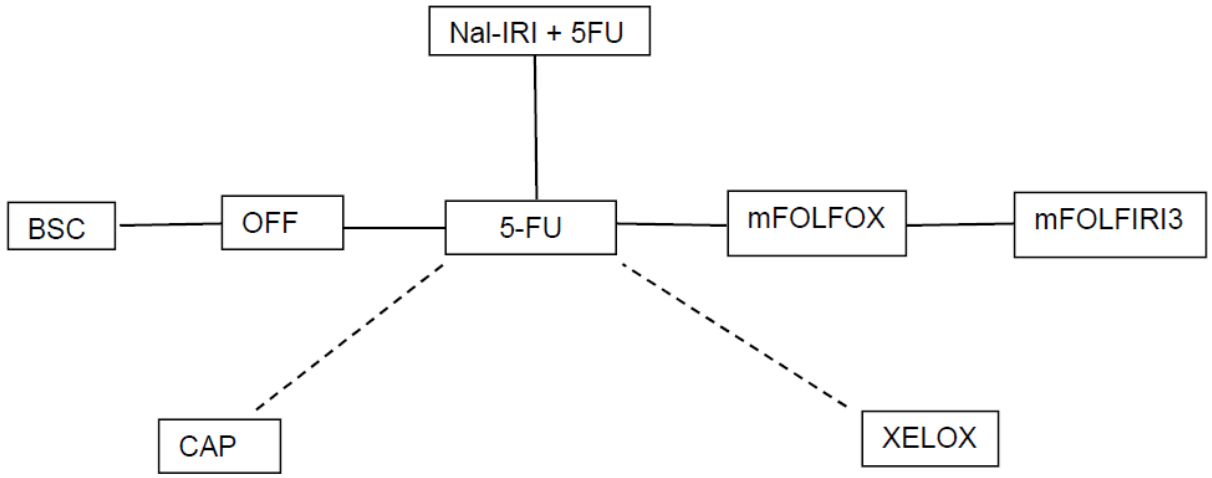
Abbreviations: BSC = best supportive care, OS = overall survival, 5-FU/LV = 5-fluorouracil + leucovorin, 5-FU/F = 5-fluorouracil + folinic acid, mFOLFOX6 = oxaliplatin (100 mg/m^2; day 1), leucovorin (400 mg/m^2; day 1), and then infusional 5-FU (2000 mg/m^2 over 46 hours) every 2 weeks, OFF = oxaliplatin, folinic acid, and 5-fluorouracil, XELOX = oxaliplatin (130 mg/m^2; day 1) and capecitabine (1000 mg/m^2 twice daily for 14 days), mFOLFIRI = irinotecan (70 mg/m^2;days 1 and 3), leucovorin (400 mg/m^2; day 1) and 5-FU (2000 mg/m^2; over 46 hours) every 2 weeks, Nal-IRI + 5-FU = nanoliposomal irinotecan (80 mg/m^2), folinic acid (400 mg/m^2; day 1) and 5-FU (2400 mg/m^2 over 46 hours) every 2 weeks, NR = not reported

Data Source: Dranitsaris (2016)[34,35]

Indirect Treatment Comparison

Figure 6 represents a graphical representation of the NMA used to compare nanoliposomal irinotecan plus 5-FU/LV to 5-FU/LV, OFF, mFOLFOX, mFOLFIRI3 and BSC in patients with metastatic pancreatic cancer.[35]

Figure 6: Network of Evidence Used for the network meta-analysis. Solid lines indicate the availability of randomized trial data, that could be linked to the network. Dashed lines indicate single arm trials. CAP and XELOX could not be added to the final network because the single arms were too dissimilar to the randomized trial arms of the other regimens.



Data Source: Dranitsaris (2016)[35]

Due to differences in patient level characteristics, the Manufacturer did not include any of the single arm trials in the NMA. For the five RCTs included in the NMA, the pCODR Methods Lead inquired about identifying potential systematic differences in patient characteristics across the trials. The Manufacturer stated that the patients, across the five RCTs, were comparable in terms of median age and performance and/or KPS status. However, due to inconsistency in reporting it is diffcilut to determine whether the percentage of patients with prior surgeries, lung metastases, and/or liver metastases were comparable across trials.[34]

The Manufacturer reported that they combined the effect estimates of mFOLFOX and mFOLFOX6 using the Yoo et al (2009)[38] and Gill et al (2004)[16] trials. The Yoo et al (2009) trial assessed the effect if mFOLFOX vs mFOLFIRI in 61 with advanced pancreatic cancer after failure of first-line gemcitabine-based chemotherapy[38]. On the other hand, the Gill et al (2004) trial assessed the effect of mFOLFOX6 vs 5-FU/LV in 108 patients with advanced pancreatic cancer who were previously treated with gemcitabine therapy[16]. The Manufacturer reported that they combined the effect estimates of mFOLFOX and mFOLFOX6 in order to increase the statistical power of the analysis and to include the mFOLFIRI3 into the NMA. Although there are differences in the dosing of 5-FU across the two regimens (i.e. 2400 mg/m^2 vs. 2000 mg/m^2), the pCODR CGP agreed that mFOLFOX and mFOLFOX6 are similar in terms of drugs, doses and administration schedules.[34] Although mFOLFOX and mFOLFOX6 appear to be similar regimens and the patient populations are similar in the Yoo et al (2009)[38] and Gill et al (2004)[16] trials, the two trials used different controls (i.e. mFOLFIRI and 5-FU/LV). Thus, pooling the two estimates together will introduce heterogeneity into the NMA. The pooled estimates of MFOLFOX and mFOLFOX6 were not provide to the Methods Lead.

In addition, the pCODR Methods Lead also asked whether there were systematic differences in other treatment effect modifiers (i.e. lung metastases, KPS, albumin, ethnicity, CA19-9, stage at diagnosis, previous fluorouracil, previous irinotecan, previous platinum, previous radiotherapy, previous whipple procedure and previous biliary stent) and if these effect modifiers have the potential to bias the reported estimates in the analysis. The Manufacturer replied that: *"We agree with pCODR that effect modifiers such as presence of lung metastases, Karnofsky performance status, albumin, ethnicity, CA19-9, previous platinum and stage at diagnosis can affect the findings of the NMA. Unfortunately, four of the five RCTs were small, investigator initiated and not intended for regulatory approval. As a result, the effect modifiers highlighted by pCODR were not consistently reported in the publications. An attempt was made to contact the primary authors for this information, but without success. Therefore, the impact of the effect modifiers on the primary outcomes of the NMA could not be assessed."*[34]

Finally, the pCODR Review Team queried if any formal statistics performed to check for the proportional hazards assumption for OS and PFS for all the treatment comparisons made in the NMA. The Manufacturer stated that they did not perform any additional statistical assessments beyond visual inspection due to the lack of individual patient level data.[34]

The results of the NMA showed that mFOLFOX was associated with a detrimental effect on PFS (HR: 1.95, 95% CI: 1.02 to 3.67) and overall survival (HR: 2.35, 95% CI: 1.20 to 4.46) as compared to nanoliposomal irinotecan plus 5-FU/LV (Table 18).[35] However, these estimates should be considered with caution because the effect estimates of mFOLFOX and mFOLFOX6 were pooled. In addition, 5-FU/LV was associated with a reduced PFS and overall survival relative to nanoliposomal irinotecan plus 5-FU/LV (PFS – HR: 2.07 [95% CI: 1.48 to 2.91] and OS – HR: 1.45 [95% CI: 1.03 to 2.08]).[35] In contrast, the Manufacturer did not observe any significant differences when comparing the treatment effect of nanoliposomal irinotecan plus 5-FU/LV to OFF, mFOLFIRI or BSC (Table 18). Furthermore, the Manufacturer also observed that nanoliposomal irinotecan plus 5-FU/LV was associated with an improvement in ORR as compared to 5-FU/LV, OFF and mFOLFOX (Table 18). Due to missing data, the Manufacturer was unable to assess the effect of treatment-related drug discontinuation for some comparisons in the NMA.[35] However, there were no statistical differences for drug discontinuations for 5-FU/LV and mFOLFOX relative to nanoliposomal irinotecan plus 5-FU/LV (Table 18).

Table 18: Indirect comparison of efficacy and safety relative to Nal-IRI + 5-FU/LV

Regimen (95%CrI)	OR - ORR[1]	HR-PFS[2]	HR-OS[2]	RR-D/C[3]
vs. Nal-IRI + FF				
5-FU/F	0.33	2.07	1.45	0.54
	(0.0 to 0.17)	(1.48 to 2.91)	(1.03 to 2.08)	(0.22 to 1.21)
OFF	0.04	1.42	0.81	Not reported
	(0.0 to 2.24)	(0.82 to 2.45)	(0.47 to 1.45)	
mFOLFOX[4]	0.04	1.95	2.35	6.78
	(0.0 to 0.47)	(1.02 to 3.67)	(1.20 to 4.46)	(0.76 to 130)
mFOLFIRI3	0	1.49	2.18	Not reported
	(0.0 to 0.09)	(0.58 to 3.82)	(0.83 to 5.98)	
BSC	N/A	N/A	1.74	N/A
			(0.64 to 4.67)	

Abbreviations: BSC = best supportive care, 5-FU/F = 5-fluorouracil + folinic acid, mFOLFOX6 = oxaliplatin (85 mg/m^2; day 1), leucovorin (400 mg/m^2; day 1), and then infusional 5-FU (2400 mg/m^2 over 46 hours) every 2 weeks, mFOLFOX = oxaliplatin (85 mg/m^2; day 1), leucovorin (400 mg/m^2; day 1), and then infusional 5-FU (2000 mg/m^2 over 46 hours) every 2 weeks OFF = oxaliplatin, folinic acid, and 5-fluorouracil, mFOLFIRI = irinotecan (70 mg/m^2;days 1 and 3), leucovorin (400 mg/m^2; day 1) and 5-FU (2000 mg/m^2; over 46 hours) every 2 weeks, Nal-IRI + 5-FU = nanoliposomal irinotecan (80 mg/m^2), folinic

acid (400 mg/m^2; day 1) and 5-FU (2400 mg/m^2 over 46 hours) every 2 weeks, CrI = credibility interval, ORR = overall response rate, PFS = progression free survival, OS = overall survival, OR = odds ratio, HR = hazard ratio, RR = relative risk, D/C = treatment discontinuations, N/A = not applicable

[1]An OR less than 1.0 suggests increased benefit with Nal-IRI + 5-FU/LV.
[2]An HR greater than 1.0 suggests increased benefit with Nal-IRI + 5-FU/LV. Stated differently, there would be an increased risk of disease progression or death with the alternative. A significant difference is suggested when the 95%CrI does not cross 1.0.
[3]A RR greater than 1.0 suggests increased risk of treatment discontinuations with Nal-IRI+FF.
[4]Given the minor differences between mFOLFOX and mFOLFOX6, the regimens were treated as comparable in the network. Doing this also allowed mFOLFIRI3 to be added to the network.
Data Source: Dranitsaris (2016)[35]

The results of the NMA on grade III/IV toxicities is presented in Table 19. The authours reported treatment with nanoliposomal irinotecan plus 5-FU/LV was associated with an increased risk of diarrhea (RR: 3.6, 95% CrI: 1.42 to 10.0), fatigue (RR: 4.64, 95% CrI: 1.8 to 14.2) and nausea and vomiting (RR: 3.8, 95% CrI: 1.7 to 9.1).[35] The authors noted that they risk of treatment related death and febrile neutropenia could not be assessed because these adverse events were not reported across most trials.[35] Additionally, the authors also commented that the event rates for many of the toxicities were low, and it turn, introduces uncertainty in the point estimates.

Table 19: Indirect comparison of grade III/IV toxicities relative to Nanoliposomal Irinotecan + 5-FU/LV.

Regimen (95%CrI)[1]	Febrile	Neutropenia	Diarrhea	Anemia	Fatigue	Nausea & Vomiting
vs. Nal-IRI + FF						
5-FU/F	No events reported	27.3 (0.56 to > 100)	3.6 (1.42 to 10.0)	1.76 (0.74 to 4.32)	4.64 (1.8 to 14.2)	3.80 (1.7 to 9.1)
OFF	No events reported	3.3 (0.10 to 66.4)	6.51 (0.85 to 57.8)	0.69 (0.07 to 4.94)	No events reported	5.1 (0.6 to 44)
mFOLFOX[2]	3.13 (0 to > 100)	2.72 (0.29 to 28.8)	0.01 (0.0 to 5.52)	0.0 (0.0 to 1.89)	0.39 (0.02 to 3.5)	0.0 (0.0 to 1.8)
mFOLFIRI3	No events reported	2.08 (0.17 to 27.4)	0.0 (0.0 to 5.52)	0.0 (0.0 to 1.59)	0.96 (0.0 to 17.8)	0.0 (0.0 to 1.8)
BSC	N/A	N/A	N/A	0.68 (0.01 to 40.9)	No events reported	N/A

Abbreviations: BSC = best supportive care, FF = 5-fluorouracil + folinic acid, mFOLFOX6 = oxaliplatin (85 mg/m^2; day 1), leucovorin (400 mg/m^2; day 1), and then infusional 5-FU (2400 mg/m^2 over 46 hours) every 2 weeks, mFOLFOX = oxaliplatin (85 mg/m^2; day 1), leucovorin (400 mg/m^2; day 1), and then infusional 5-FU (2000 mg/m^2 over 46 hours) every 2 weeks OFF = oxaliplatin, folinic acid, and 5-fluorouracil, mFOLFIRI = irinotecan (70 mg/m^2;days 1 and 3), leucovorin (400 mg/m^2; day 1) and 5-FU (2000 mg/m^2; over 46 hours) every 2 weeks, Nal-IRI + 5-FU = nanoliposomal irinotecan (80 mg/m^2), folinic acid (400 mg/m^2; day 1) and 5-FU (2400 mg/m^2 over 46 hours) every 2 weeks, CrI = credible interval, OR = odds ratio, N&V = nausea and vomiting
[1]A RR greater than 1.0 suggests increased risk with Nal-IRI + 5-FU/LV. A significant difference is suggested when the 95%CrI does not cross 1.0.
[2]Given the minor differences between mFOLFOX and mFOLFOX6, the regimens were treated as comparable in the network. Doing this also allowed mFOLFIRI3 to be added to the network.
Data Source: Dranitsaris (2016)[35]

Critical Appraisal of the ITC

The quality of the NMA provided by the Submitter was assessed according to the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[41] Details of the critical appraisal are presented below.

Table 19: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis†

ISPOR Questions	Details and Comments‡
1. Is the population relevant?	**Yes.** The study populations of all the included trials in the NMA matched in review indication, which was to evaluate the efficacy and safety of nanoliposomal irinotecan in combination with 5-FU and LV in adult patients with metastatic adenocarcinoma of the pancreas who have been previously treated with gemcitabine-based therapy.
2. Are any critical interventions missing?	**No.** The Manufacturer included all relative interventions for this patient population in the systematic review.
3. Are any relevant outcomes missing?	**Yes.** The Manufacturer included all relative outcomes for this patient population in the systematic review, which include: ORR, PFS and overall survival. They also included information on the number of patient withdrawals due to adverse drug reactions and the frequency of all grade III/IV dose limiting toxicity. It was noted that HRQoL was not considered in the NMA.
4. Is the context (e.g., settings and circumstances) applicable to your population?	**Yes.** The settings of the three included trials were similar.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes, in part.** The Manufacturer provided a summary of the systematic literature review process used in the NMA.[35] In the summary, the Manufacturer described the information sources they used, their search strategy and their study selection criteria. However, it is unclear whether they performed screening calibration exercises and duplicate data extraction.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**No.** The author used a Bayesian mixed treatment comparison model that used a three-level hierarchical model in order to incorporate evidence from many different types of study designs. There were no closed loops.
7. Is it apparent that poor quality studies were included thereby leading to bias?	**No.** The authors used the NICE checklist to assess the quality of all the trials that met their inclusion criteria (Table 16).
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	**No.** There was no selective reporting of outcomes.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Yes.** The Manufacturer provided a qualitative assessment of heterogeneity (Table 15); however, the Methods team felt that performing a subgroup analysis and a test for difference would have been more informative. The pCODR CGP also identified other potential effect modifiers, which include: lung metastases, KPS, albumin, ethnicity, CA19-9, stage at diagnosis, previous fluorouracil, previous irinotecan, previous platinum, previous radiotherapy, previous whipple procedure and previous biliary stent. Among these potential modifiers, the Manufacturer noted that important covariate data was missing across trials and the impact of these effect modifiers could not be assessed. Regardless, there was still an imbalances in the distribution of these effect modifiers across the studies. Furthermore, additional heterogeneity was introduced by pooling the effect estimates of mFOLFOX and mFOLFOX6.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	**Unclear.** The Manufacturer was unable to assess the impact of treatment effect modifiers due to a lack of missing covariate data.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**Yes.** The Manufacturer used a a three-level hierarchical NMA model that used a "similarity metric" in order to incorporate evidence from non-RCTs and RCTs.

ISPOR Questions	Details and Comments‡
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	**Not applicable.** There was no closed loop.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	**Not applicable.** There was no closed loop.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	**Yes, in part.** Due to the imbalance in baseline characteristics and lack of data, the Manufacturer did not incorporate non-RCTs into the NMA. However, according to the Methods Team, there appeared to be imbalances in the distribution of treatment effect modifiers across the different trials incorporated into the final NMA model. Thus it is unclear whether the Manufacturer attempted to minimize this bias. Furthermore, it is unknown if the Manufacturer attempted to adjust for the treatment effect of the pooled analysis of mFOLFOX and mFOLFOX6.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	**Yes.** The Manufacturer stated that there was some variability across the trials that informed the NMA. Therefore, the Manufacturer used a random effects model to yield more conservative estimates.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Unclear.** It is unclear whether the Manufacturer explored or discussed the assumptions about heterogeneity.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**Unclear.** Subgroup analysis or meta-regression analysis were not performed; however, the Methods Team does recognize that assessment of heterogeneity may have been difficult due to a limited number of studies included in the NMA.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**Yes.** The NMA is presented in Figure 6.
19. Are the individual study results reported?	**Yes.** The submitter provided the baseline characteristics of the trials and the effect estimates of all outcomes used in the NMA.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	**Yes, in part.** The Manufacturer has provided the direct comparisons of PFS, overall survival and OS for all of the trials included in the NMA. The Manfacturer did not provide the pooled effect estimates of mFOLFOX and mFOLFOX-6. However, the Manufacturer did not provide the direct comparisons of the number of patient withdrawals due to adverse drug reactions and the frequency of all grade III/IV dose limiting toxicity.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	**Yes.** The Manufacturer has provided the indirect comparisons of overall survival, PFS, ORR, D/C and grade III/IV toxicities for 5-FU/LV, OFF, mFOLFOX, mFOLFIRI3 and BSC.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**No.**
23. Is the impact of important patient characteristics on treatment effects reported?	**No.**
24. Are the conclusions fair and balanced?	The NMA Report provided by the Manufacturer did not make any strong conclusions in their report. The NMA performed by the Manufacturer showed that mFOLFOX was associated with reduced PFS (HR: 1.95, 95% CI: 1.02 to 3.67) and overall survival (HR: 2.35, 95% CI: 1.20 to 4.46) as compared to

ISPOR Questions	Details and Comments‡
	nanoliposomal irinotecan plus 5-FU/LV. Similar results were also reported for 5-FU/LV as compared to nanoliposomal irinotecan plus 5-FU/LV for PFS (HR: 2.07, 95% CI: 1.48 to 2.91) and overall survival (HR: 1.45, 95% CI: 1.03 to 2.08). However, these claims were weakened due to differences in patient inclusion criteria across the different trials and potential effect modifiers. The Manufacturer also pooled effect estimates of mFOLFOX and mFOLFOX6 across two different trials, which would introduce additional heterogeneity into the NMA. Furthermore, the Manufacturer was unable to assess safety outcomes in their indirect comparison, and therefore, it is difficult to determine the overall benefit of this drug as compared to other relevant comparators.
25. Were there any potential conflicts of interest?	**Not reported.**
26. If yes, were steps taken to address these?	**Not reported.**
ISPOR = International Society For Pharmacoeconomics and Outcomes Research; ORR = objective response rate; PFS = progression-free survival; OS = overall survival; 5-FU = 5-fluorouracil . † Adapted from Jansen et al[41] ‡Bolded comments are considered a weakness of the ITC.	

Conclusion

The Manufacturer submitted an NMA that compared nanoliposomal irinotecan plus 5-FU/LV to 5-FU/LV, OFF, mFOLFOX, mFOLFIRI3 and BSC in patients with metastatic pancreatic cancer. The Manufacturer also sought to compare the effect of nanoliposomal irinotecan plus 5-FU/LV to other anticancer therapies, such as CAP and XELOX, using clinical data from non-RCTs but were unable to do so because of missing patient covariate data and variability in trial level parameters.

The results of the NMA indicated that treatment with mFOLFOX was associated with a statistically significant detrimental effect on PFS (HR: 1.95, 95% CI: 1.02 to 3.67) and on overall survival (HR: 2.35, 95% CI: 1.20 to 4.46) as compared to nanoliposomal irinotecan plus 5-FU/LV. Similar results were also reported for 5-FU/LV as compared to nanoliposomal irinotecan plus 5-FU/LV (PFS [HR: 2.07, 95% CI: 1.48 to 2.91] and overall survival [HR: 1.45, 95% CI: 1.03 to 2.08]). The effect of OFF, mFOLFIRI3 and BSC as compared to nanoliposomal irinotecan plus 5-FU/LV on PFS and overall survival were not statistically significant. However, the overall conclusions of the NMA are limited because of substantial heterogeneity in the studies' designs and the patient characteristics between the included studies. The estimates of mFOLFOX should also be interpreted with caution given the additional heterogeneity that was introduced into the NMA by pooling mFOLFOX and mFOLFOX6. Given these limitations, the comparative efficacy of nanoliposomal irinotecan plus 5-FU/LV and other anticancer agents is uncertain.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Gastrointestinal Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on irinotecan liposome for metastatic pancreatic cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Gastrointestinal Clinical Guidance Panel is comprised of three clinicians.The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** April 2017, **Embase** 1974 to 2017 May 25, **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	(onivyde* or MM398 or "pep 02" or pep02 or HBI 202 or HBI202 or 136572-09-3 or 042LAQ1IIS or 1361317-83-0 or OL741S3N8B).ti,ab,ot,kf,kw,hw,rn,nm.	145
2	MM-398.ti,ab,ot,kf,kw,hw,rn,nm.	1675
3	2 use ppez	22
4	(irinotecan* adj9 (liposome* or liposomal or nanoliposom* or nano)).ti,ab,ot,kf,kw,hw,rn,nm.	514
5	1 or 3 or 4	578
6	5 use ppez	142
7	5 use cctr	23
8	*irinotecan sucrosofate/	54
9	(onivyde* or MM-398 or MM398 or HBI 202 or HBI202 or "pep 02" or pep02).ti,ab,kw.	1703
10	(irinotecan* adj9 (liposome* or liposomal or nanoliposom* or nano)).ti,ab,kw.	314
11	8 or 9 or 10	1904
12	11 use oemezd	209
13	12 and conference abstract.pt.	90
14	limit 13 to english language	90
15	limit 14 to yr="2012 -Current"	73
16	12 not 13	119
17	6 or 7 or 16	284
18	limit 17 to english language	272
19	15 or 18	345

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Add to builder	Query	Items found	Time
#5	Add	Search **(#3) AND #4**	8	09:06:41

Search	Add to builder	Query	Items found	Time
#4	Add	Search **(#1) OR #2**	6258	09:06:34
#3	Add	Search **publisher[sb]**	515391	09:06:09
#2	Add	Search **(irinotecan*[tiab]) AND (liposome*[tiab] OR liposomal[tiab] OR nanoliposom*[tiab] OR nano[tiab])**	144	09:05:59
#1	Add	Search **onivyde*[tiab] OR MM-398[tiab] OR MM398[tiab] OR pep 02[tiab] OR pep02[tiab] OR 136572-09-3[tiab] OR 042LAQ1IIS[tiab] OR 136572-09-3[rn] OR 042LAQ1IIS[rn] OR 1361317-83-0[rn] OR OL741S3N8B[rn] OR OR 1361317-83-0[tiab] OR OL741S3N8B[tiab]**	6205	09:05:46

3. **Cochrane Central Register of Controlled Trials (Central)**
   Searched via Ovid

4. **Grey Literature search via:**

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Onivyde/irinotecan and liposomal

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Onivyde/irinotecan and liposomal

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESMO)
http://oncologypro.esmo.org/Meeting-Resources

Search: Onivyde/irinotecan and liposomal - last 5 years

Detailed Methodology of Literature Review

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (Nov 2016) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Onivyde/irinotecan and liposomal.

No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of Oct 4, 2017.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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