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Systematic or Meta-analysis Studies

# Post-gemcitabine therapy for patients with advanced pancreatic cancer – A comparative review of randomized trials evaluating oxaliplatin- and/or irinotecan-containing regimens

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ABSTRACT

A systematic review and critical evaluation of randomized trial evidence for oxaliplatin- or irinotecan-containing regimens in patients with advanced pancreatic cancer previously treated with gemcitabine has not yet been published. We conducted a comparative systematic review of randomized trials evaluating oxaliplatin- or irinotecan-based therapies in patients with advanced pancreatic cancer previously treated with gemcitabine to assess trial similarity and the feasibility of performing an indirect treatment comparison (ITC). Studies were identified through PubMed and key oncology conference abstracts. The following trials met our criteria: NAPOLI-1 (nanoliposomal irinotecan [nal-IRI] or nal-IRI + 5-fluorouracil [5-FU]/leucovorin [LV] vs 5-FU/LV), CONKO-003 (oxaliplatin + 5-FU/LV [OFF] vs 5-FU/LV), PANCREOX (oxaliplatin + 5-FU/LV [mFOLFOX6] vs 5-FU/LV), and Yoo et al. (2009) (irinotecan + 5-FU/LV [mFOLFIRI3] vs mFOLFOX). Fundamental differences were identified in study design (i.e., number of study sites, number of countries), patient (i.e., locally advanced vs metastatic disease, stratification variables, prior and subsequent treatments) and treatment (i.e., regimens, dose intensity) characteristics, and primary and secondary outcomes (i.e., primary vs secondary outcomes, overall survival [OS], progression-free survival [PFS]) among the 4 included trials. Our comparative review demonstrated significant dissimilarity across trials, which precluded conducting an ITC. In the absence of head-to-head nal-IRI- and/or oxaliplatin-based therapy trials, clinicians are advised to interpret these studies separately within the context of their individual patient population.



## Introduction

Patients with pancreatic cancer have low survival expectancy: a systematic review assessing the burden of pancreatic cancer in Europe reported a median overall survival (OS) of 4.6 months (range, 1.0–6.1 months) [1]. In the European Union, pancreatic cancer is the fourth leading cause of cancer-related deaths; 77,749 pancreatic cancer deaths were reported for the year 2011 and 85,600 are predicted for the year 2016 [2]. Improving treatment options for patients with advanced or metastatic pancreatic cancer is a significant unmet need.

Treatment options for pancreatic ductal adenocarcinoma (e.g., surgery, chemotherapy, radiotherapy) are guided by tumor stage at diagnosis and patient performance status. Targeted therapies are not employed front-line, showing limited clinical efficacy with no clearly defined patient subgroups [3–5]. The most commonly administered first-line therapies in patients with well-preserved

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performance status include FOLFIRINOX (folinic acid [also known as leucovorin (LV)], 5-fluorouracil [5-FU], irinotecan, and oxaliplatin) and gemcitabine/nab-paclitaxel. Gemcitabine alone is an option for elderly or frail patients [6]. Inevitably, all patients will experience disease progression on or following first-line therapy and may be candidates for additional therapy.

Few randomized trials have been conducted in the post-gemcitabine setting, but both oxaliplatin and nanoliposomal irinotecan (nal-IRI) were evaluated in patients with gemcitabine-refractory pancreatic adenocarcinoma. Oxaliplatin is a platinum-based compound typically administered in combination with 5-FU/LV. Nanoliposomal irinotecan, formerly known as MM-398, is an encapsulated irinotecan formulation designed to increase and prolong intratumoral levels of irinotecan and SN-38 (its more active metabolite) [10]. Second-line oxaliplatin-based therapy after previous gemcitabine-based treatment was evaluated in the CONKO-003 [7], PANCREOX [8], and Yoo et al. [9] trials; the NAPOLI-1 trial evaluated nal-IRI in combination with 5-FU/LV.

Head-to-head clinical trials comparing nal-IRI- and oxaliplatin-based therapies in patients with gemcitabine-refractory metastatic pancreatic cancer are lacking. An indirect treatment comparison (ITC) is a type of network meta-analysis that compares treatments in the absence of randomized controlled trial (RCT) data [11]. Results from ITCs are often requested by health technology assessment agencies. Key factors such as study design and patient and treatment characteristics must be similar among trials to avoid inaccurate or biased conclusions. Assessment of trial similarity in an ITC is based on clinical knowledge and expert judgment.

We conducted a comparative systematic review of RCTs evaluating the treatment of advanced pancreatic cancer patients previously treated with gemcitabine-based therapy and critically assessed trial similarity and the feasibility of performing an ITC of oxaliplatin- or irinotecan-based therapies. This review is limited to RCTs with irinotecan- or oxaliplatin-containing regimens as the authors of this analysis felt these were most widely used in clinical practice for patients previously treated with gemcitabine.

## Methods

We performed a PubMed search using the terms "advanced pancreatic cancer AND (oxaliplatin OR irinotecan)" to identify all relevant oxaliplatin or irinotecan systemic treatment studies in patients with advanced pancreatic cancer. Results were limited to RCTs, without time-frame restrictions. Additional studies were identified by reviewing abstracts and posters presented (years 2014–2015) at the American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) annual meetings and the ASCO Gastrointestinal Cancers symposia, and through supplemental searches using the clinicaltrials.gov database.

Identified studies were screened and selected if they met the following criteria: classified as a phase 2 or 3 RCT, enrolled patients with advanced/metastatic pancreatic cancer previously treated with a gemcitabine-based regimen, and randomized patients to an oxaliplatin- and/or irinotecan-containing regimen. Non-randomized and/or first-line advanced pancreatic cancer studies were excluded.

Data were abstracted from the identified studies and assessed for trial similarity. Abstracted data included variables related to patient population, treatment arms, outcomes, and study setting (i.e., the PICOS [Patient, Intervention, Comparator, Outcomes, Setting] framework) [12].

## Results

The conducted literature search yielded 18 citations; 13 citations were excluded for reasons described in Fig. 1. Key features and outcomes from 4 of the 5 trials meeting all inclusion criteria (NAPOLI-1 [10], CONKO-003 [7], PANCREOX [8], and Yoo et al. [9]) are summarized by drug regimen (Table 1), key baseline patient characteristics (Table 2), and study outcomes and characteristics (Table 3). Although the initial CONKO-001 [13] trial met all inclusion criteria of this systematic review, it was not included because the trial was terminated after recruiting less than 50% (46 of 165) of the calculated sample population.

NAPOLI-1 was a multinational, phase 3, open-label RCT comparing nal-IRI ($n = 151$) or nal-IRI plus 5-FU/LV ($n = 117$) with 5-FU/LV ($n = 149$) [10]. The nal-IRI + 5-FU/LV arm was added when safety data for this combination became available. Only patients enrolled in the 5-FU/LV arm following the amendment ($n = 119$) were used as the control arm for the nal-IRI + 5-FU/LV efficacy comparisons. CONKO-003 was a German, phase 3, open-label trial with patients randomized to oxaliplatin plus 5-FU/LV (OFF; $n = 76$) or 5-FU/LV alone ($n = 84$) [7]. PANCREOX was a Canadian, phase 3, open-label trial that randomized 54 patients to mFOLFOX6 (oxaliplatin + 5-FU/LV) and 54 patients to 5-FU/LV [8]. Although this trial was also terminated early, it was included in our analysis because it enrolled more than 80% (108 of 128) of the planned population before termination. Yoo et al. was a South Korean, phase 2,

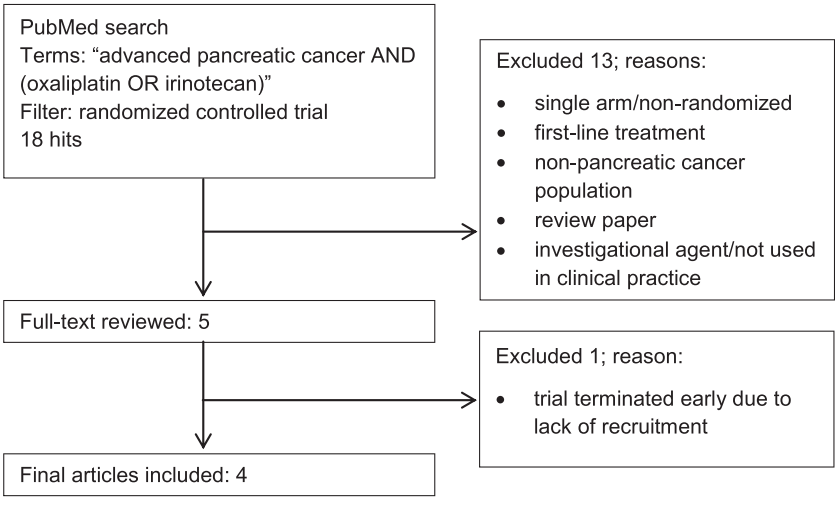


**Fig. 1.** Study selection flowchart.

**Table 1**
Comparison of dosing regimens included in post-gemcitabine randomized clinical trials for advanced pancreatic cancer.

| | Wang-Gillam et al. [10] NAPOLI-1 | | Oettle et al. [7] CONKO-003 | | Gill et al. [8] PANCREOX | | Yoo et al. [9] | |
|---|---|---|---|---|---|---|---|---|
| Arm | Nal-IRI + 5-FU/LV | 5-FU/LV | OFF | 5-FU/LV | mFOLFOX6 | 5-FU/LV | mFOLFIRI.3 | mFOLFOX |
| 5-FU dose, mg/m$^2$ | 2400 | 2000 | 2000 | 2000 | Bolus: 400 Infusion: 2400 | Bolus: 400 Infusion: 2400 | 2000 | 2000 |
| 5-FU infusion time, h | 46 | 24 | 24 | 24 | 46 | 46 | 46 | 46 |
| LV dose, mg/m$^2$ | 400 | 200 | 200 | 200 | 400 | 400 | 400 | 400 |
| LV infusion time, h | 0.5 | 0.5 | NA | NA | 2 (with OX) | 2 (with OX) | 2 | 2 |
| 5-FU/LV frequency | Q 2 wk | Q wk × 4, rest × 2 wk; repeat | Q wk × 4, rest × 3 wk; repeat | Q wk × 4, rest × 3 wk; repeat | Q 2 wk | Q 2 wk | Q 2 wk | Q 2 wk |
| Nal-IRI or IRI dose, mg/m$^2$ | nal-IRI: 80 | NA | NA | NA | NA | NA | IRI: 70 | NA |
| Nal-IRI or IRI infusion time, h | nal-IRI: 1.5 | NA | NA | NA | NA | NA | IRI: 1 | NA |
| Nal-IRI or IRI frequency | Q 2 wk | NA | NA | NA | NA | NA | Q 2 wk | NA |
| OX dose, mg/m$^2$ | NA | NA | 85 | NA | 85 | NA | NA | 85 |
| OX infusion time, h | NA | NA | NA | NA | 2 (with LV) | NA | NA | 2 |
| OX frequency | NA | NA | D8 and D22 of 42-day cycle | NA | Q 2 wk | NA | NA | Q 2 wk |

Abbreviations: 5-FU, 5-fluorouracil; D, day; IRI, irinotecan; LV, leucovorin; mFOLFIRI, 5-FU/LV + irinotecan; mFOLFOX, 5-FU/LV + oxaliplatin; NA, not applicable; nal-IRI, nanoliposomal irinotecan; OFF, oxaliplatin + 5-FU/LV; OX, oxaliplatin; Q, once every; wk, week.

**Table 2**
Comparison of key patient baseline characteristics of included post-gemcitabine randomized clinical trials for advanced pancreatic cancer.

| | Wang-Gillam et al. [10] NAPOLI-1 | | Oettle et al. [7] CONKO-003 | | Gill et al. [8] PANCREOX | | Yoo et al. [9] | |
|---|---|---|---|---|---|---|---|---|
| | Nal-IRI + 5-FU/LV | 5-FU/LV | OFF | 5-FU/LV | mFOLFOX6 | 5FU/LV | mFOLFIRI3 | mFOLFOX |
| No. of ITT patients | 117 | 119 | 76 | 84 | 54 | 54 | 31 | 30 |
| Age, median, y | 63 | 62 | 62 | 61 | 65 | 67 | 55 | 55 |
| Patients aged ⩾ 70 y, % | NR | NR | NR | NR | 37 | 33 | NR | NR |
| Male, % | 59 | 56 | 53 | 57 | 57 | 56 | 77 | 67 |
| ECOG performance status, % | NR | NR | NR | NR | | | | |
| 0 | | | | | 13 | 19 | 16 | 17 |
| 1 | | | | | 76 | 76 | 84 | 80 |
| 2 | | | | | 11 | 6 | 0 | 3 |
| KPS, % | | | | | NR | NR | NR | NR |
| 90–100 | 56 | 56 | 54 | 48 | | | | |
| 70–80 | 44 | 44 | 46 | 52 | | | | |
| Metastatic disease, % | 100 | 100 | 88 | 88 | 93 | 94 | NR | NR |
| Locally advanced disease, % | 0 | 0 | 12 | 12 | 7 | 6 | NR | NR |
| Prior treatment, % | | | | | | | | |
| Gemcitabine alone | 45 | 46 | 100 | 100 | 74.1 | 77.8 | 13 | |
| Gemcitabine combination | 55 | 54 | 0 | 0 | 25.9 | 22.2 | 87 | 93 |
| Any subsequent therapy, % | 31 | 38 | 29 | 21 | 7 | 23 | 39 | 23 |

Abbreviations: 5-FU, 5-fluorouracil; AE, adverse event; ECOG, Eastern Cooperative Oncology Group; IRI, irinotecan; ITT, intent to treat; KPS, Karnofsky Performance Status; LV, leucovorin; mFOLFIRI, 5-FU/LV + irinotecan; mFOLFOX, 5-FU/LV + oxaliplatin; nal-IRI, nanoliposomal irinotecan; NR, not reported; OFF, oxaliplatin + 5-FU/LV; OS, overall survival; PFS, progression-free survival.

**Table 3**
Comparison of key outcomes and study settings in post-gemcitabine randomized clinical trials for advanced pancreatic cancer.

| | Wang-Gillam et al. [10] NAPOLI-1 | | Oettle et al. [7] CONKO-003 | | Gill et al. [8] PANCREOX | | Yoo et al. [9] | |
|---|---|---|---|---|---|---|---|---|
| | Nal-IRI + 5-FU/LV | 5-FU/LV | OFF | 5-FU/LV | mFOLFOX6 | 5-FU/LV | mFOLFIRI3 | mFOLFOX |
| PFS, median, months | 3.1 | 1.5 | 2.9 | 2.0 | 3.1 | 2.9 | 1.9 | 1.4 |
| OS, median, months | 6.1 | 4.2 | 5.9 | 3.3 | 6.1 | 9.9 | 3.8 | 3.4 |
| Withdrawals due to AEs, % | 11.1 | 7.5 | NR | NR | 20 | 1.9 | NR | NR |
| Overall response rate, % | 16 | 1 | NR | NR | 13.2 | 8.5 | NR | 7 |
| Sub-groups presented (variables for initial stratification) | KPS, baseline albumin, ethnicity, tumor location | | Duration of first-line treatment, KPS, M1 status | | Gender, age (< and ⩾70 y), ECOG, liver metastases | | Age (⩽65 vs >65 y), ECOG (0–1 vs 2), earlier best response to gemcitabine[a] | |
| No. of sites (country) | 76 (14 countries)[b] | | 16 (Germany) | | 12 (Canada) | | 1 (South Korea) | |

Abbreviations: 5-FU, 5-fluorouracil; AE, adverse event; ECOG, Eastern Cooperative Oncology Group; IRI, irinotecan; ITT, intent to treat; KPS, Karnofsky Performance Status; LV, leucovorin; mFOLFIRI, 5-FU/LV + irinotecan; mFOLFOX, 5-FU/LV + oxaliplatin; NA, not applicable; nal-IRI, liposomal irinotecan; NR, not reported; OFF, oxaliplatin + 5-FU/LV; OS, overall survival; OX, oxaliplatin; PFS, progression-free survival.

[a] No disease progression vs disease progression on gemcitabine therapy.

[b] Argentina, Australia, Brazil, Canada, Czech Republic, France, Germany, Hungary, Italy, South Korea, Spain, Taiwan, the United Kingdom, and the United States.

single-center study with patients randomized to mFOLFOX ($n = 30$) or mFOLFIRI3 (irinotecan + 5-FU/LV; $n = 31$) [9].

Trial assessment of the 4 identified studies focused on similarities and differences in study design, patient and treatment characteristics, and outcomes (i.e., PICOS criteria).

*Study design characteristics*

The NAPOLI-1, CONKO-003, and PANCREOX studies were phase 3 trials and Yoo et al. [9] was a phase 2 trial. However, study settings and countries varied among the trials. NAPOLI-1 was conducted at 76 sites in 14 countries (Argentina, Australia, Brazil, Canada, Czech Republic, France, Germany, Hungary, Italy, South Korea, Spain, Taiwan, the United Kingdom, and the United States) [10]. CONKO-003 was conducted at 16 institutions in Germany [7]. PANCREOX was conducted at 12 centers in Canada [8]. Yoo et al. was a single-center trial conducted in South Korea [9].

*Patient characteristics*

Consistent with the study inclusion criteria, all trials focused on patients with locally advanced or metastatic pancreatic cancer previously treated with gemcitabine-based therapy. The proportion of patients with metastatic disease varied across studies. NAPOLI-1 enrolled only patients with metastatic disease (100%), whereas 88% of patients in CONKO-003, 93.5% in PANCREOX, and an unknown percentage in Yoo et al. [9] had metastatic disease [7–10].

Variables used to stratify patients at randomization also varied across studies. Karnofsky Performance Status (KPS) was used to stratify patients in NAPOLI-1 and CONKO-003 and Eastern Cooperative Group (ECOG) performance status was used in PANCREOX and Yoo et al. [9]. Age was used to stratify patients in PANCREOX and Yoo et al. [9], but not NAPOLI-1 and CONKO-003. Duration of first-line treatment was used to stratify patients in CONKO-003, whereas patients in Yoo et al. [9] were stratified based on earlier best response to gemcitabine.

Prior treatments and reasons for discontinuing those treatments also varied among the included studies. NAPOLI-1 enrolled patients with disease progression following gemcitabine-based therapy administered in a neoadjuvant, adjuvant, locally advanced, or metastatic setting. NAPOLI-1 patients were heavily pretreated: approximately 45% received prior gemcitabine monotherapy and 55% received prior gemcitabine combination therapy; 33% received 2 or more previous lines of therapy [10]. Patients in CONKO-003 had disease progression on first-line gemcitabine monotherapy [7]. Patients in Yoo et al. received prior first-line gemcitabine-based therapy [9]. In contrast, patients could enroll in PANCREOX following disease progression on or discontinuation of (e.g., for toxicity) a single-agent or combination gemcitabine-based therapy [8].

The percentage of patients receiving subsequent therapy also differed among the trials. In NAPOLI-1, 31% of patients randomized to nal-IRI + 5-FU/LV and 38% to 5-FU/LV received subsequent therapy following trial participation [10]. In CONKO-003, 22 of 76 (29%) patients initially randomized to OFF and 18 of 84 (21%) patients to 5-FU/LV received subsequent therapy [7]. In PANCREOX, significantly more patients randomized to 5-FU/LV than mFOLFOX6 received subsequent therapy (23% vs. 7%; $P = 0.015$) [8]. In Yoo et al., more patients in the mFOLFIRI3 arm (39%) than the mFOLFOX arm (23%) crossed over to the alternate treatment at disease progression [9].

*Treatment characteristics*

We noted several differences in drug doses among the evaluated studies. Although the studies' oxaliplatin-based regimens differed (i.e., OFF, mFOLFOX, mFOLFOX6), they were generally deemed to be representative of oxaliplatin + 5-FU/LV-based chemotherapy regimens and the scheduled oxaliplatin doses were similar (i.e., 85 mg/m$^2$ every 2 weeks). The 5-FU/LV control arms also differed among the studies, with 5-FU/LV dose intensity highest in PANCREOX compared to NAPOLI-1 and CONKO-003. Finally, nal-IRI doses differed within the NAPOLI-1 study: patients randomized to nal-IRI alone received 120 mg/m$^2$ of nal-IRI (equivalent to 100 mg/m$^2$ of irinotecan free base) every 3 weeks whereas patients randomized to nal-IRI + 5FU/LV received 80 mg/m$^2$ of nal-IRI (equivalent to 70 mg/m$^2$ of irinotecan free base) every 2 weeks [10].

A lack of data hindered our ability to assess dose reductions. In NAPOLI-1, median duration of exposure and dose intensity for nal-IRI monotherapy was 8.7 weeks (interquartile range [IQR], 5.4–22.0 weeks) and 167.6 mg/m$^2$ (SD, 44.8 mg/m$^2$) over 6 weeks, compared to 8.9 (6.0–16.0) weeks and 188.0 (52.0) mg/m$^2$ over 6 weeks in combination with 5-FU/LV [10]. For 5-FU, median duration of exposure and dose intensity was 6.0 weeks (IQR, 5.9–12.1 weeks) and 6710.2 mg/m$^2$ (SD, 1719.2 mg/m$^2$) over 6 weeks when administered with LV alone and 8.7 (5.4–22.0) weeks and 5065.0 (1539.1) mg/m$^2$ over 6 weeks in combination with nal-IRI and LV [10]. Adverse events (AEs) resulting in drug discontinuation occurred in 11% of patients treated with nal-IRI + 5FU/LV, 12% of patients treated with nal-IRI, and 7% of patients treated with 5-FU/LV [10]. In CONKO-003, the median oxaliplatin dose administered was 340 mg/m$^2$ (range, 0–4080 mg/m$^2$) [7]. Eighty-one percent of oxaliplatin doses were administered at full dose, 10% were administered at 75% of the full dose, and 9% were not administered [7]. Information on 5-FU dosing was not provided. No information on dose reductions or dose intensity is available for PANCREOX. Eight patients treated with mFOLFOX6 and 1 patient treated with 5-FU/LV withdrew from the study due to an AE [8]. In Yoo et al. , patients treated with mFOLFIRI.3 and mFOLFOX received a median (range) of 3 (1–12) cycles and 3 (1–10) cycles, respectively. No additional information on drug dosing was provided [9].

*Outcomes*

The primary and secondary endpoints evaluated varied across the included studies. Overall survival between the treatment groups was the primary study objective of both NAPOLI-1 and CONKO-003 whereas progression-free survival (PFS) was the primary objective of PANCREOX; 6-month OS was the primary endpoint in Yoo et al. [9]. Secondary objectives also differed: PFS was a secondary objective of NAPOLI-1 and CONKO-003 and OS was a secondary objective of PANCREOX and Yoo et al. [9]. Additional secondary objectives evaluated varied among the studies (e.g., time to treatment failure in NAPOLI-1). All 4 trials evaluated safety or tolerability.

Endpoint results also differed among the studies. In NAPOLI-1, after 313 events, median OS (primary objective; 6.1 vs 4.2 months; unstratified HR, 0.67; 95% CI, 0.49–0.92; $P = 0.012$) and PFS (secondary objective; 3.1 vs 1.5 months; unstratified HR, 0.56; 95% CI, 0.41–0.75; $P = 0.0001$) were longer for patients treated with nal-IRI + 5-FU/LV compared to 5-FU/LV [10]. There was no significant difference in median OS (4.9 vs 4.2 months; unstratified HR, 0.99; 95% CI, 0.77–1.28; $P = 0.94$) or PFS (2.7 vs 1.6 months; HR, 0.81; 95% CI, 0.63–1.04; $P = 0.1001$) for nal-IRI monotherapy compared with 5-FU/LV [10]. In CONKO-003, after a median follow-up of 54.1 months, median OS (primary objective; 5.9 vs 3.3 months; HR, 0.66; 95% CI, 0.48–0.91; log-rank $P = 0.01$) and PFS (2.9 vs 2.0 months; HR, 0.68; $P = 0.019$) were longer for OFF compared with 5-FU/LV [7]. In PANCREOX, median OS (secondary objective; 6.1 vs 9.9 months; HR, 1.78; 95% CI, 1.08–2.93; $P = 0.024$) was significantly longer but PFS (primary objective; 3.1 vs 2.9 months;

HR, 1.00; 95% CI, 0.66–1.53; $P = 0.989$) was similar for mFOLFOX6 compared with 5-FU/LV [8]. Lastly, in Yoo et al. , at a median follow-up of 24.4 weeks, median OS (secondary objective; 16.6 vs 14.9 weeks) and PFS (primary objective; 8.3 vs 6.0 weeks) were similar for mFOLFIRI3 and mFOLFOX [9].

Exploratory analyses of PANCREOX data revealed that for patients younger than 70 years, the median (range) time from diagnosis of advanced disease to study enrollment was 8.2 (0.0–63.0) months for mFOLFOX6 compared to 5.6 (0.2–20.8) months for 5-FU/LV ($P = 0.058$) [8]. In this same subset of patients (< 70 years of age) ECOG performance status also differed, but was not statistically significant ($P = 0.053$). For example, 8.8% and 11.8% of patients randomized to mFOLFOX6 compared to 17.1% and 2.9% of patients randomized to 5-FU/LV had an ECOG performance status of 0 and 2 respectively [8].

Differences in safety evaluations were also noted among the studies, with grade 1 through 4 AEs reported for NAPOLI-1, CONKO-003, and Yoo et al. [9], and grade 3 through 4 AEs reported for PANCREOX. Additionally, different safety terminology was used across the studies. For example, the term "neutropenia" included agranulocytosis, febrile neutropenia, granuloctopenia, neutropenia, neutropenic sepsis, decreased neutrophil count, and pancytopenia in the NAPOLI-1 trial whereas leukopenia alone was reported for the CONKO-003 trial, and neutropenia and febrile neutropenia were reported for PANCREOX and Yoo et al. [9]. Finally, AEs leading to trial withdrawal were only reported for the NAPOLI-1 and PANCREOX trials and treatment-related deaths were only reported for the NAPOLI-1 trial.

Fundamental differences were identified in study design (i.e., number of study sites, number of countries), patient (i.e., locally advanced vs metastatic disease, stratification variables, prior and subsequent treatments) and treatment (i.e., regimens, dose) characteristics, and outcomes (i.e., primary vs secondary outcomes, OS, PFS) among the 4 identified trials. The authors of this review deemed the trials insufficiently similar because of these differences; consequently, we did not perform a formal ITC.

## Discussion

Although several published review articles summarize clinical study results evaluating second-line treatments in patients with advanced pancreatic cancer [14–18], few of these reviews systematically evaluate the available study data to critically assess trial similarity, which is essential for ITCs [16–19]. We performed a comparative review of randomized trial evidence for irinotecan- or oxaliplatin-containing regimens in advanced pancreatic cancer patients with prior gemcitabine-based treatment to determine if the trials were sufficiently similar for an ITC. Similarity of the identified trials was critically assessed by the authors of this review.

We found the studies to be sufficiently different such that an ITC could not be conducted. All studies included in the analysis were phase 2 or 3 trials, but only NAPOLI-1 was a multicenter, multinational trial. Both CONKO-003 and PANCREOX were multicenter, single-nation trials, and Yoo et al. [9] was a single-center study. Differences in study setting can influence trial outcomes due to regional differences in clinical practice.

Analysis of patient characteristics across studies revealed different proportions of enrolled patients with locally advanced pancreatic cancer compared to metastatic disease. These differences are important since median survival differs between these populations. Differences were also noted in previous/subsequent treatments, patient stratification variables, reasons for discontinuing therapy, and time between first- and second-line therapies. These differences can affect trial outcomes and hinder formal trial comparisons.

Treatment regimens varied across the 4 trials included in this comparative review. In typical practice, the schedule variations among the identified studies may not be considered clinically meaningful and these regimens are often used interchangeably. However, dosing can impact tolerability and thereby efficacy, which is particularly important in second-line pancreatic cancer treatment.

Finally, differences in outcomes were found among the studies. Although both CONKO-003 and PANCREOX compared an oxaliplatin-based chemotherapy regimen to 5-FU/LV, the studies reached different conclusions: CONKO-003 reported improved survival for patients randomized to OFF compared to 5-FU/LV [7], but this result was not confirmed in PANCREOX [8]. These discordant findings may be partly attributed to previously described trial differences, but there is uncertainty regarding oxaliplatin in the post-gemcitabine setting. It is worth noting that OS was substantially higher in the 5-FU/LV arm of PANCREOX compared to NAPOLI-1, CONKO-003, and Yoo et al. [9]. Although it is difficult to account for this survival difference with the available data, variables that could explain the PANCREOX results include excellent tolerability of the 5-FU/LV regimen, a higher rate of AE-related treatment withdrawal in the mFOLFOX6 arm, a shorter time since first diagnosis of advanced disease (5.7 vs 7.9 months) in the 5-FU/LV arm, and a greater proportion of post-progression therapy in the 5-FU/LV arm [8]. Differences in post-progression therapy partly explain the OS differences in PANCREOX's mFOLFOX6 and 5-FU/LV arms, but a comparison of 5-FU/LV-treated patients across all 4 studies reveals a similar (CONKO-003) or higher (NAPOLI-1) percentage of patients randomized to 5-FU/LV received post-progression therapy (albeit not necessarily the same treatments).

Additional treatment-related data (e.g., treatment duration, treatment intensity, dose administered) were not available for all studies. For many studies, the recommended starting dose rather than actual administered dose was reported.

Few treatment options exist for patients with advanced/metastatic pancreatic ductal adenocarcinoma. Irinotecan- and/or oxaliplatin-based chemotherapy regimens are options for patients in the second-line setting who progressed on gemcitabine-based chemotherapy regimens. However, as described earlier, results from the CONKO-003 [7] and PANCREOX [8] studies evaluating oxaliplatin-based regimens yielded conflicting results. This, along with the NAPOLI-1 results [10], led the ESMO to conclude that "...considering the conflicting results on the use of oxaliplatin, MM-398 [nal-IRI] ... may be the best option for second-line treatment of these patients" [20].

Ultimately we were unable to fully assess the comparability of the identified studies for several reasons. Many data points were not available for all studies, as evident in Tables 1–3. Second, the studies included in this analysis primarily administered gemcitabine alone or in combination (e.g., with capecitabine, erlotinib, nab-paclitaxel, or cisplatin) as first-line therapy. The role of first-line FOLFIRINOX or nab-paclitaxel/gemcitabine therapy on subsequent treatments in this patient population is not currently known. Third, there were different proportions of patients in the studies with locally advanced and metastatic disease. Last, comparing results and subgroups across different trials with small sample sizes often risks producing unpredictable results as unknown prognostic factors derived from tumor biology may bias comparisons.

## Conclusions

Results from our comparative literature review showed considerable dissimilarities in the evaluated studies, precluding the feasibility of an ITC. A head-to-head trial is required to draw definitive conclusions about nal-IRI- or oxaliplatin-based therapies in the

treatment of patients with advanced pancreatic cancer previously treated with gemcitabine therapy. In the absence of such a trial, clinicians must make treatment decisions by interpreting the studies separately within the context of their individual patient population.

## Conflict of interest

A.V. has received honoraria for advisory boards and talks from Baxalta, Roche, and Celgene. F.C. is in advisory boards for Roche, Merck Serono, Bayer, AstraZeneca, Lilly, Symphogen, and Merrimack. R.A.H. has received honoraria from Celgene. J.F.B. is in a board for Baxalta. A.C. is in advisory boards for Baxalta and Celgene. Y.Y. is an employee of Shire, Cambridge, MA, United States, and holds Shire stocks. D.A.P. and V.E. are employees of Pharmerit International, Bethesda, MD, United States, which received research funding from Shire. F.A.D.J. is an employee of Shire, Zürich, Switzerland, and holds Shire stocks. S.G. is in advisory boards for Baxalta and Celgene and receives research funding from Sanofi Canada and Celgene.

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