Original Article

Efficacy and tolerability of the combination of nano-liposomal irinotecan and 5-fluorouracil/leucovorin in advanced pancreatic adenocarcinoma: post-approval clinic experience

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Background: Nano-liposomal irinotecan (nal-IRI) plus 5-fluorouracil/leucovorin (5-FU/LV) is the regimen of choice in the 2nd line setting for advanced pancreatic adenocarcinoma (PAC). However, real-world data is limited. Our objectives were to elicit the real-word effectiveness and safety of this combination as an advanced line of therapy in pancreatic cancer patients and analyze the impact of prior lines of therapy on survival outcomes with this regimen.

Methods: We conducted a retrospective cohort study of 58 patients with locally advanced unresectable or metastatic PAC, who were treated with at least one dose of nal-IRI + 5-FU/LV following cancer progression on prior therapies between August 2015 and December 2018 at the Kansas University Medical Center (KUMC) and University of Alabama at Birmingham (UAB).

Results: Median OS was 5.4 (range, 4.2–7) months. Disease control rate (DCR) was highest (84%) for patients given nal-IRI + 5-FU/LV as 2nd line agent after progression on a 1st line gemcitabine-based regimen. However, no significant survival difference was observed between those given nal-IRI + 5-FU/LV after 1st line or beyond the 2nd line (P=0.17). Among those given nal-IRI + 5-FU/LV as 2nd line, use of gemcitabine-inclusive chemotherapy as the 1st line agent did not impact survival (P=0.68). Prior irinotecan exposure and baseline CA 19-9 level did not affect the overall survival (OS) but patients with a higher CA 19-9 level had a significant risk of progression (HR =3.2, P=0.02). Grade 3/4 toxicities were reported in only 19% patients.

Conclusions: Our report suggests that nal-IRI + 5-FU/LV offers a modest survival benefit with a tolerable safety profile as an advanced line of treatment in patients with advanced PAC.

Keywords: Liposomal irinotecan; MM-398; nano-liposomal irinotecan (nal-IRI); pancreatic cancer; 2nd line treatment

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Introduction

Advanced pancreatic adenocarcinoma (PAC) remains an insurmountable challenge and is estimated to cause 47,050 deaths in the US in 2020 with a 5-year survival rate ranging from a mere 2–9% (1-3). Within the past decade, combination therapy with nab-paclitaxel plus gemcitabine (Gem-Abraxane) or FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan and oxaliplatin) has shown survival benefit as compared to gemcitabine monotherapy, leading to a paradigm shift in the treatment of advanced pancreatic cancer (4-6). Despite the use of newer combination chemotherapeutic agents, overall survival (OS) with 1st line treatment remains less than 1 year on an average (4-8). In phase 3 randomized controlled trials, FOLFIRINOX was shown to significantly increase OS from 6.8 to 11.1 months while Gem-Abraxane demonstrated an OS of 8.5 *vs.* 6.7 months (P<0.001) when compared to gemcitabine monotherapy, albeit at the cost of increased risk of myelosuppression and neuropathy with both regimens (5,6). Similarly, progression-free survival (PFS) for the recommended 1st line regimens such as gemcitabine, Gem-Abraxane, and FOLFIRINOX are only 3.4, 5.5, and 6.4 months, respectively (5-7). As such, most patients require 2nd line chemotherapy, but options remain scarce. A promising 2nd line combination of nano-liposomal irinotecan (nal-IRI) with 5-fluorouracil/leucovorin (5-FU/LV) emerged from the NAPOLI-1 trial, the largest global phase 3 trial to date, testing a 2nd line regimen for patients with metastatic pancreatic cancer (9). Patients were randomly assigned to 3 arms: nal-IRI + 5-FU/LV *vs.* nal-IRI alone *vs.* 5-FU/LV alone. The study reported improved OS (6.1 *vs.* 4.2 months, P=0.012) and PFS (3.1 *vs.* 1.5 months, P=0.0001) with nal-IRI + 5-FU/LV when compared to 5-FU/LV alone. The unique formulation of nal-IRI allows for liposomal delivery of irinotecan within the tumor, resulting in >5-fold greater intratumoral accumulation of the active agent as compared to that achieved by free unencapsulated irinotecan resulting in increased efficacy and decreased toxicity (10-12).

Despite the 2015 FDA approval of this combination, there is limited post-approval real-world data regarding its efficacy, safety and optimal sequencing. NAPOLI-1 trial only enrolled patients who failed prior gemcitabine-based therapy, leaving questions about response in patients with prior irinotecan-based therapy unanswered. Therefore, the purpose of this retrospective analysis is to expand on the currently available literature by sharing our institutional experiences regarding the effectiveness and safety of this combination as an advanced line of therapy in patients with advanced PAC irrespective of prior exposures, outside of the controlled environment of a clinical trial.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-338).

Methods

Participants and setting

We designed an observational study involving retrospective analysis of the electronic medical records of patients with advanced PAC (locally advanced unresectable or metastatic disease) who were given nal-IRI and 5-FU/LV following failure of one or more lines of therapy. Patients in this study were treated with nal-IRI + 5-FU/LV from August 2015 to December 2018 at the Kansas University Medical Center (KUMC) and University of Alabama at Birmingham (UAB). All patients (n=58) who were administered even a single cycle of nal-IRI + 5-FU/LV during the study period were included to avoid any potential selection bias. All patients were followed until December 31st, 2019 (cut-off date).

Data collection

Data regarding age, gender, race, functional status [Eastern Cooperative Oncology Group (ECOG) performance status score], baseline CA 19-9 levels, details of prior lines of treatment, specifically prior treatment with irinotecan or Gem-Abraxane was extracted from the electronic medical record. Other variables collected include date of initiation and initial dose strength of nal-IRI + 5-FU/LV, number of dose modifications, dose delays, treatment related side effects, date of progression and date of death.

Outcome measures

The main outcomes of interest in this analysis were effectiveness and tolerability of nal-IRI + 5-FU/LV in cases of advanced PAC after failure of initial lines of therapy. Efficacy of the regimen was defined in terms of OS and PFS. Tolerability of the regimen was determined by the incidence of treatment-associated side effects which were defined in accordance with the National Cancer Institute

Table 1 Baseline patient characteristics

Characteristics	Total enrolled (n=58)
Age (years), median [range]	65.5 [38–82]
Gender, n (%)	
Male	30 (51.72)
Female	28 (48.28)
Race, n (%)	
White	47 (81.03)
Black	10 (17.24)
Other	1 (1.72)
ECOG, n (%)	
0	10 (17.24)
1	44 (75.86)
2	3 (5.17)
3	1 (1.72)
Prior lines of treatment, n (%)	
1	31 (53.45)
2	18 (31.03)
3	9 (15.52)
CA 19-9 levels, n (%)	
High (>200 U/mL)	30 (51.72)
Low (200 U/mL)	28 (48.28)
Prior irinotecan, n (%)	
Yes	27 (46.55)
No	31 (53.45)
Among patients receiving nal-IRI as 2nd line, n (%)	
Prior gemcitabine-based treatment in 1st line	
Yes	24 (77.42)
No	7 (22.58)

ECOG, Eastern Cooperative Oncology Group; nal-IRI, nano-liposomal irinotecan.

Common Terminology Criteria for Adverse Events (NCI-CTCAE V4.0). Exposures of interest also included factors that may have impacted OS; such as prior lines of chemotherapy, previous exposure to irinotecan, prior 1st line therapy with Gem-Abraxane, baseline CA 19-9 levels and ECOG status. Response to nal-IRI + 5-FU/LV was determined by examining periodic CT scans (every 8–12 weeks) and using the RECIST Criteria 1.1 (13).

Statistical analysis

PFS is computed since the initial date of receiving nal-IRI + 5-FU/LV to progression of disease or demise, whatever came first. OS is computed since the initial date of receiving nal-IRI + 5-FU/LV to death. Disease control rate (DCR) is computed by dividing the number of cases who achieved either complete response (CR), partial response (PR) or stable disease (SD) by the total of number of cases. Kaplan-Meier curves for OS, PFS and differences in survival across covariates such as prior irinotecan exposure and prior gemcitabine-based treatment in those receiving nal-IRI + 5-FU/LV in 2nd line setting were created using log-rank test. Using Cox proportional hazard regression analysis, the strength of association between different covariates and risk of mortality or progression were reported. Quantitative variables such as CA 19-9 level and starting dose of nal-IRI were grouped as high *vs.* low (with a cut-off of 200 U/mL) and 70 mg/m^2 *vs.* other doses respectively; and analyzed as categorical variables. There were no missing data or loss to follow-up during the study period.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Research and individual consent waiver were granted due to the retrospective nature of the study, and the study was approved by the Institutional Review Board (STUDY000003970).

Results

Patient characteristics

From August 2015 to December 2018, 58 patients were administered, at the least, a single cycle of nal-IRI + 5-FU/LV. Baseline characteristics are enlisted in *Table 1*.

The median age of the cohort was 65.5 years. The majority (93%) had an ECOG score of 0 or 1. 70.6% had metastatic PAC and the rest (29.4%) had locally advanced unresectable PAC. All patients had been previously treated. Half of the study population only had one prior line of treatment. 46.5% of the patients had received irinotecan as a prior line of therapy. Among patients receiving nal-IRI +

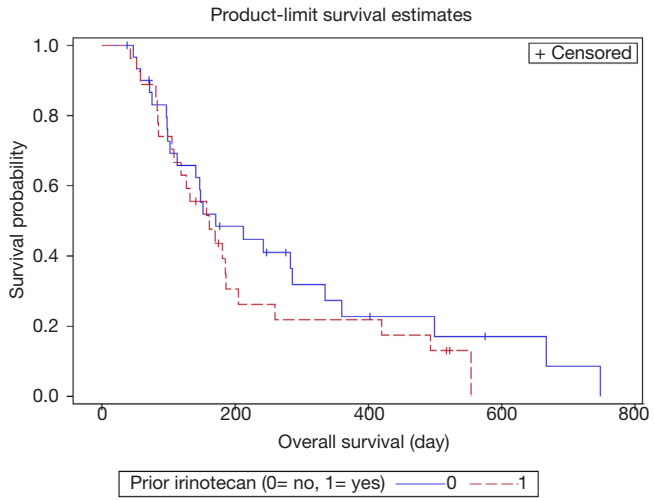

Figure 1 OS for patients with pancreatic cancer treated with nal-IRI + 5-FU/LV and stratified based on history of prior irinotecan treatment. The difference in the OS is not significant (P value =0.3726). OS, overall survival; nal-IRI, nano-liposomal irinotecan; 5-FU/LV, 5-fluorouracil/leucovorin.

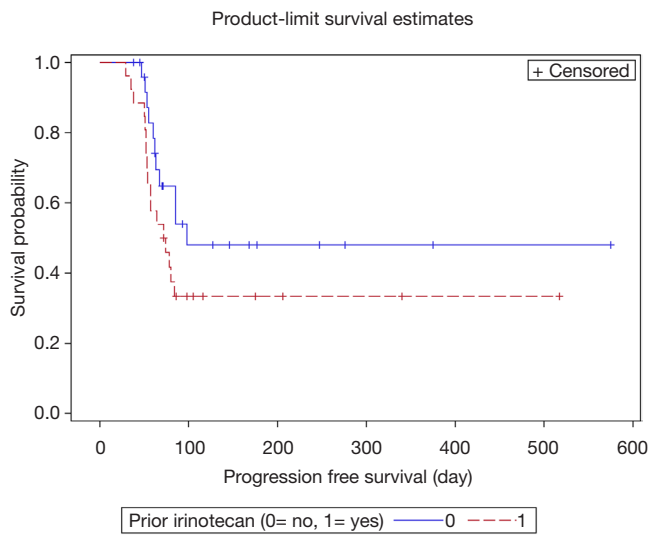

Figure 2 PFS for patients with pancreatic cancer treated with nal-IRI + 5-FU/LV and stratified based on history of prior irinotecan treatment. The difference in the PFS is not significant (P value =0.0590). PFS, progression-free survival; nal-IRI, nano-liposomal irinotecan; 5-FU/LV, 5-fluorouracil/leucovorin.

5-FU/LV directly after 1st line, 77% (24/31) were previously treated with gemcitabine-based regimen as the 1st line therapy. Only about half the study population had a high CA 19-9 level. None of the patients had missing data or any variable of interest.

Dosing schedule and reductions

Doses ranged from 50–70 mg/m^2. Majority of the patients (67%) initiated treatment with the standard 70 mg/m^{2}dose of nal-IRI. About 26% received a lower starting dose of 50 mg/m^2 as per physician discretion based on tolerance to prior therapy and functional status. Seven patients (12%) required 1 dose reduction while only 4 patients (7%) needed 2 dose reductions in the study. Twenty-four (41%) patients had at least one or more dose delays. However, these dose reductions and delays did not affect overall outcomes. Fatigue, anemia and diarrhea were the frequent causes of dose reductions. The cohort was administered a median of 4 doses of nal-IRI until the cut-off date. Among those given nal-IRI as a 2nd line agent, gemcitabine alone and Gem-Abraxane were the 1st line therapies in 6 (20.6%) and 18 (62%) patients, respectively; 4 patients (13.7%) received FOLFIRINOX as the initial therapy whereas one patient was treated with gemcitabine-cisplatin combination. Those given nal-IRI beyond 2nd line had been exposed to variable sequences of gemcitabine or fluoropyrimidine based combination therapies.

Efficacy

The median OS was 5.4 months for our study sample with a median follow up of 6 months. Patients were stratified into those with or without prior irinotecan exposure while patients given nal-IRI + 5-FU/LV as 2nd line were stratified into those who had received a gemcitabine-inclusive combination as 1st line versus others. There were no statistically significant differences in the PFS and OS among these subgroups (*Figures 1,2*, Figures S1,S2) although patients without prior irinotecan exposure trended towards an improved PFS (P value =0.059). Majority of patients had SD (41.38%), with 2 (3.45%) and 4 (6.9%) patients experiencing complete remission and partial remission as per the RECIST 1.1 criteria, respectively (*Table 2*).

Disease progression was reported in 28 patients (48%). The overall DCR was 51.72%. DCR was higher for the subgroup given nal-IRI + 5-FU/LV directly post-1st line treatment (63.33%) as compared to beyond 2nd line (36.67%). Among those given nal-IRI + 5-FU/LV immediately post-1st line, DCR was even better for the

Table 2 Treatment and outcomes of patients treated with nal-IRI + 5-FU/LV

	N (%)
Nal-IRI administration, n (%)	
2nd line	31 (53.45)
>2nd line	27 (46.55)
Starting dose of nal-IRI (mg/m^2), n (%)	
50	15 (25.86)
55	1 (1.72)
60	2 (3.45)
65	1 (1.72)
70	39 (67.24)
Response, n (%)	
CR	2 (3.45)
PR	4 (6.90)
SD	24 (41.38)
PD	28 (48.28)
Patients died at cut-off date, n (%)	
Yes	47 (81.03)
No	11 (18.97)
OS (days), median (95% CI)	161 (127–212)
PFS (days), median (95% CI)	80 (60–no upper limit)
DCR [(CR + PR + SD)/n], %	
Prior irinotecan	37.04
Prior Gem-Abraxane	67.86
Nal-IRI administered as 2nd line	61.29

nal-IRI, nano-liposomal irinotecan; 5-FU/LV, 5-fluorouracil/leucovorin; OS, overall survival; PFS, progression-free survival; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

subset that received gemcitabine-based treatment in 1st line therapy versus those who did not (84.21% *vs.* 15.79%). Baseline CA 19-9 level was not associated with risk of mortality but significantly increased the odds of progression in those with elevated CA 19-9 levels (HR =3.27; 95% CI =1.17, 9.15; P=0.02) compared to those with normal CA 19-9 levels. All the patient and treatment related factors analyzed for association with PFS or OS are enlisted in *Table 3*.

Majority of patients (53%) were given nal-IRI + 5-FU/LV directly following failure of 1st line therapy. There was no significant difference in OS and PFS between patients who received nal-IRI in 2nd line and those receiving it beyond 2nd line (Figures S3,S4). Twenty-two percent of those who progressed after nal-IRI + 5-LU/LV went on to clinical trials, 24 percent received FOLFOX and the rest were transitioned to hospice.

Adverse events

The most frequent treatment-related adverse effects (AEs) included fatigue and anemia. Although the incidence of fatigue and anemia is high, 69% and 65% of these, respectively, were classified as grade 1 in severity. There was only one incidence of grade 4 neutropenia. Other serious side effects were limited to grade 3 toxicity and were relatively few. No drug related mortality or drug discontinuation was reported. All side effects along with grades are listed in *Table 4*.

Discussion

Nearly a decade ago, most patients with advanced PAC were managed with best supportive care (BSC) after progressing on initial therapy. A systematic meta-analysis of 34 clinical studies suggested a survival benefit with 2nd line treatment over BSC alone (median OS of 6.0 *vs.* 2.8 months, P=0.01) (14). In 2015, the National Cancer Care Network (NCCN) guidelines adapted nal-IRI + 5-FU/LV as a 2nd line therapy, post-failure of gemcitabine-inclusive regimens for advanced PAC, based on NAPOLI-1 trial (9). Our analysis is one of the few post-approval, real-world, clinical outcomes assessment with nal-IRI + 5-FU/LV and showed survival benefits similar to that reported in the NAPOL-1 trial with a manageable safety profile. To evaluate the appropriate sequencing for various regimens, we also categorized patients based on prior irinotecan and prior Gem-Abraxane exposure and analyzed their impact on response to nal-IRI + 5-FU/LV.

Our population is comparable to that of the NAPOLI-1 trial in terms of gender distribution, performance status and percentage of patients given nal-IRI + 5-FU/LV as 2nd line agent (53% in both studies) (9). However, our cohort includes a significantly higher percentage of patients who were previously exposed to irinotecan (46.5% *vs.* 10%). We

Table 3 Factors predicting OS and PFS in patients treated with nal-IRI + 5-FU/LV

	HR for mortality (95% CI)	P value	HR for progression at first staging (95% CI)	P value
Prior history of irinotecan	0.52 (0.08, 3.31)	0.4871	0.31 (0.05, 1.90)	0.2078
Prior history of Gem-Abraxane treatment	0.67 (0.10, 4.42)	0.6805	0.27 (0.04, 1.69)	0.1625
ECOG 3 *vs.* 0	26.42 (0.73, 952.03)	0.0734	1.24 (0.05, 28.17)	0.8945
ECOG 2 *vs.* 0	0.48 (0.10, 2.28)	0.3592	0.35 (0.03, 4.04)	0.3966
ECOG 1 *vs.* 0	0.46 (0.20, 1.06)	0.0679	0.44 (0.15, 1.30)	0.1391
Race (African American *vs.* Caucasian)	2.31 (0.82, 6.55)	0.1141	1.18 (0.33, 4.31)	0.7981
Prior lines of treatment (3 *vs.* 1)	1.75 (0.54, 5.68)	0.3533	0.61 (0.14, 2.66)	0.5084
Prior lines of treatment (2 *vs.* 1)	1.28 (0.53, 3.11)	0.5878	1.32 (0.43, 4.05)	0.6245
CA 19-9 (high *vs.* low)	1.71 (0.80, 3.64)	0.1671	3.27 (1.17, 9.15)	0.0243
Nal-IRI as 2nd line of treatment *vs.* beyond 2nd line	0.67 (0.37, 1.20)	0.1735	0.60 (0.29, 1.27)	0.1840
Starting dose =70 mg *vs.* other doses	1.19 (0.52, 2.74)	0.6843	2.96 (0.93, 9.42)	0.0656

OS, overall survival; PFS, progression-free survival; nal-IRI, nano-liposomal irinotecan; 5-FU/LV, 5-fluorouracil/leucovorin; ECOG, Eastern Cooperative Oncology Group.

Table 4 Treatment-related adverse events

Side effect (total n=58)	Any grade, n (%)	Grade 3/4, n (%)
Fatigue	52 (89.7)	1 (1.7)
Diarrhea	24 (41.4)	0
Nausea/vomiting	15 (25.9)	0
Anemia	49 (84.5)	7 (12.1)
Neutropenia	15 (25.9)	1 (1.7)
Thrombocytopenia	24 (41.4)	1 (1.7)
Neuropathy	19 (32.8)	0
Elevated creatinine	9 (15.5)	1 (1.7)
Transaminitis	12 (20.7)	0

share similarity with the cohort reported by Glassman *et al.* in this regard where 59% patients were previously treated with an irinotecan-based regimen (15). They reported a reduced OS and PFS for patients who failed prior irinotecan-based regimens. This finding was attributed in part to the fact that those who progressed after irinotecan-combination regimen were given nal-IRI + 5-FU/LV later in the disease course i.e., median of 3rd line (15). Concerns for resistance to nal-IRI in those previously exposed to irinotecan have also been raised by two recent real-world studies from Korea and US, both demonstrating enhanced survival in patients with no history of irinotecan use (16,17). Contrary to this, we found no significant difference in the OS on subgroup analyses between those with or without prior exposure to irinotecan. However, irinotecan-naïve patients tended towards a better PFS (P value =0.059) although it did not reach statistical significance owing to a small sample size. The NCCN guidelines currently recommend using nal-IRI + 5-FU/LV post fluoropyrimidine-inclusive therapy only if there is no prior exposure to irinotecan (category 1 recommendation) (18). Although the DCR was better for those receiving nal-IRI + 5-FU/LV directly after 1st line versus beyond 2nd line (63.3% *vs.* 36.7%) in our cohort, this did not translate into a significantly improved PFS or OS owing to a small sample size. A trend in the improvement of OS and PFS was observed if nal-IRI + 5-FU/LV was given earlier in the disease course (15,17,19).

Glassman *et al.* reported improved PFS and OS when treated with gemcitabine alone or Gem-Abraxane followed by nal-IRI + 5-FU/LV compared to receiving this in later lines of therapy (15). To assess if the line of therapy is a confounder, we categorized patients treated with nal-IRI + 5-FU/LV in 2nd line into two groups; based on the 1st line therapy received as gemcitabine-inclusive regimen versus non-gemcitabine-based regimens. There was no difference in PFS and OS, however the DCR was higher for those

pre-treated with gemcitabine-based therapies (84.21% *vs.* 15.79%). Kieler *et al* have previously demonstrated a survival benefit in patients with a higher CA 19-9 who receive nal-IRI + 5-FU/LV as opposed to oxaliplatin + 5-FU combination, suggesting a potential role for CA 19-9 as a biomarker for choosing a nal-IRI based regimen (19). The higher baseline CA 19-9 levels did not increase the risk of mortality in our study.

The median OS (5.4 months) reported in our study is comparable to the NAPOLI-1 trial (median OS =6.1 months) as well as other similar real-world studies by Glassman *et al.* (median OS =5.3 months) and Kieler *et al.* (median OS =6.7 months) (9,15,19). Two recent studies conducted in Korean and Taiwanese cohorts have also shown similarly promising real-world survival outcomes (median OS =9.4 and 6.6 months, respectively) (16,20).

As per the NCCN guidelines, additional options for 2nd line use in locally advanced or metastatic PAC include irinotecan-based regimens such as FOLFIRI, FOLFIRINOX or capecitabine with and without oxaliplatin, the OFF regimen (oxaliplatin, folinic acid and 5-fluorouracil) and mFOLFOX-6 (18,21). The OFF regimen demonstrated significantly higher OS and PFS as opposed to 5-FU/LV alone in the CONKO-003 trial (22). However, the subsequent PANCREOX trial yielded discordant results better survival outcomes with 5-FU/LV (23). Hitherto, there have been no randomized phase 3 trials evaluating these as an advanced line of therapy. An Italian phase 2 trial demonstrated a modest response to FOLFIRI (median OS =5 months) albeit with a high toxicity (55% rate of grade 3/4 AEs) (24). A retrospective series looking at 63 patients receiving FOLFIRI post progression of disease on 1–3 lines of gemcitabine ± platinum based regimens reported an encouraging median OS of 6.6 months (25). Role of FOLFIRINOX post-gemcitabine failure has been examined in a small phase 2 study by Kobayashi *et al.* with a promising median OS of 9.8 months although a high rate of neutropenia (66.7%) was noted (26). Xelox i.e., capecitabine and oxaliplatin for gemcitabine resistant disease was examined in two phase 2 studies resulting in similar outcomes with a median OS of 5.7 and 5.3, respectively (27,28). The survival statistics reported by the aforementioned trials evaluating various regimens seem similar to nal-IRI + 5-FU/LV on face value, however, evidence is limited and stems from underpowered phase 2 or retrospective studies and no head to head comparisons exist. Having said that, a 2017 meta-analysis revealed that irinotecan and 5-FU combinations post-gemcitabine failure may confer a greater survival advantage as opposed to 5-FU + oxaliplatin regimens or 5-FU alone although both appeared to improve PFS (29). Kieler *et al.* also demonstrated a better OS and PFS in a matched cohort of patients given nal-IRI + 5-FU/LV versus oxaliplatin plus 5-FU combination for advanced PAC (median OS 9.33 *vs.* 6.18 months, P=0.03) (19). These studies suggest that oxaliplatin based combinations might be less beneficial in advanced settings and randomized clinical trials to prove these findings are needed.

In terms of the safety profile, the NAPOLI 1 trial reported neutropenia (27%), fatigue (14%), diarrhea (13%), vomiting (11%), and anemia (9%) to be the most common grade 3 and 4 treatment-related adverse events (9). Our study cohort reported anemia (12%), neutropenia (<2%), thrombocytopenia (<2%), and fatigue (<2%) to be the most frequent grade ≥3 AEs. The relatively low proportion of serious AEs can be attributed to a one-third of the patients receiving a lower initial dose in our study. Glassman *et al.* also reported lower frequencies of grade 3/4 AEs i.e., anemia (18%), nausea (4%), vomiting (4%), fatigue (2%), diarrhea (2%) and neutropenia (2%), however 70% patients in their cohort were treated with lower than recommended dose of 70 mg/m^2 (15). Dose reductions were not too common in our study and we did not find any significant association between dose reduction and worse outcomes. These findings are comparable to the results of the previous studies (9,15,19). In fact, Glassman *et al.* depicted a positive impact of dose reductions on survival measures (15). Since the NAPOLI-1 trial found no difference in the quality of life (QoL) among the cohorts despite prolonging survival, this comes as an important finding and supports the notion that dose adjustments to improve drug tolerability can empower patients to have a better QoL without compromising the overall drug efficacy. Besides, our drug dosing strategy better mimics actual practice as evidenced by the recent large US database study indicating that 44.5% patients received a lesser than standard nal-IRI dosage (30–65 mg/m^2) in clinical practice (17).

Our study is limited by a retrospective design with a small sample size, which may have led to some false-negative results due to lack of statistical power. However, our study could be more generalizable as it took place across two tertiary level treatment centers in the Midwest and South-Eastern USA, compared to single center studies by Glassman *et al.* and Kieler *et al.* (15,19) Also, to avoid any

potential selection bias, all patients who received even one cycle of nal-IRI + 5-FU/LV were included in the analysis. Our findings support the clinical effectiveness of nal-IRI + 5-FU/LV as an advanced line of therapy post failure of gemcitabine alone or gemcitabine-inclusive combinations and probes into its potential role after irinotecan-based therapies. Future studies may need to investigate the biomarkers in predicting response to nal-IRI.

Conclusions

This report is among the few actual clinical effectiveness and safety analyses of nal-IRI + 5-FU/LV conducted across two cancer centers in the US in a real-world clinical setting. The survival outcome reported in our study is modest (median OS =5.4 months) but encouraging for patients with advanced PAC and limited treatment options. Importantly, we did not find any difference in outcomes in patients given nal-IRI + 5-FU/LV earlier or later (>2nd lines) in the disease course as well as those with or without prior irinotecan exposure. These results call for further validation in randomized controlled trials to broaden the horizon for future clinical applications. Furthermore, our cohort experienced a relatively low incidence of treatment-related serious AEs. This is of utmost priority for patients with aggressive PAC who are debilitated from the underlying disease and any additional therapy-related toxicity can have a drastic detrimental effect on their QoL.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jgo-20-338). Dr. RP is a consultant for Ipsen pharmaceuticals. This has no influence on the data and presentation of this study. No personnel from Ipsen involved or associated with this study either directly or indirectly. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Research and individual consent waiver were granted due to the retrospective nature of the study, and the study was approved by the Institutional Review Board (STUDY000003970).

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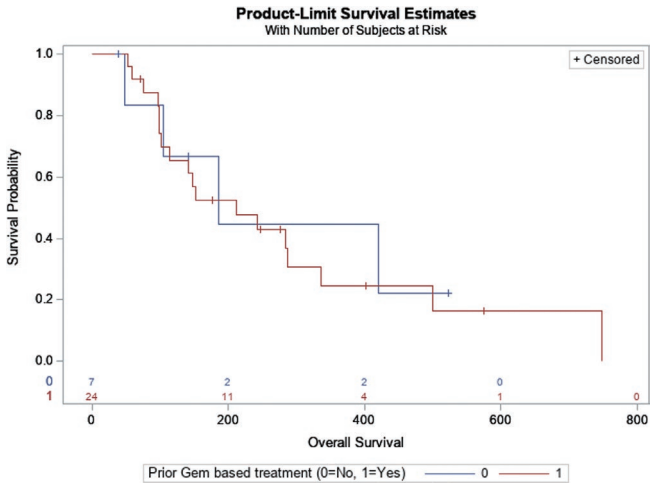

Figure S1 OS for patients with pancreatic cancer treated with nal-IRI + 5-FU/LV in 2nd line setting and after stratification based on history of prior gemcitabine-based treatment in 1st line. The difference in OS is not significant (P value =0.7684). OS, overall survival; nal-IRI, nano-liposomal irinotecan; 5-FU/LV, 5-fluorouracil/leucovorin.

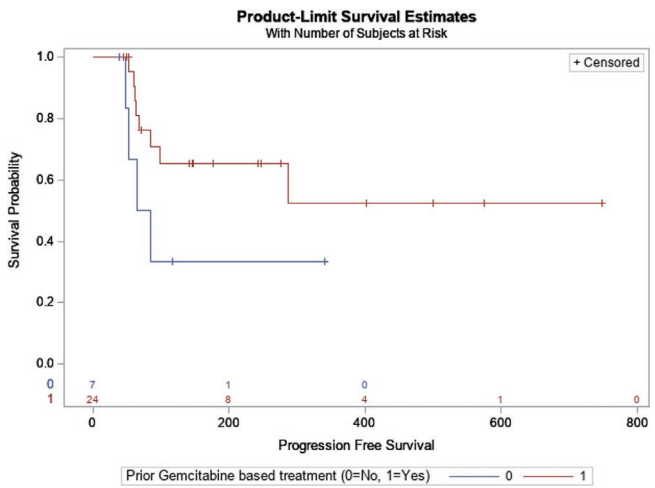

Figure S2 PFS for patients with pancreatic cancer treated with nal-IRI + 5-FU/LV in 2nd line setting and after stratification based on history of prior gemcitabine-based treatment in 1st line setting. The difference in PFS is not significant (P value =0.1341). PFS, progression-free survival; nal-IRI, nano-liposomal irinotecan; 5-FU/LV, 5-fluorouracil/leucovorin.

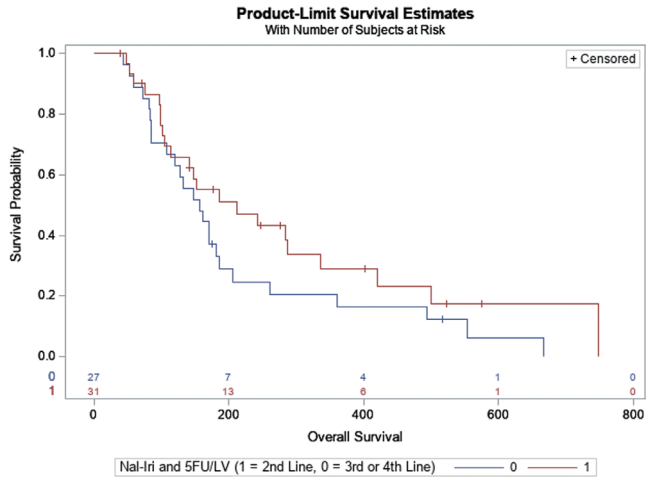

Figure S3 OS of patients with pancreatic cancer treated with nal-IRI + 5-FU/LV in 2nd line setting or beyond 2nd line setting. There is no significant difference in OS between the two groups (P value =0.1704). OS, overall survival; nal-IRI, nano-liposomal irinotecan; 5-FU/LV, 5-fluorouracil/leucovorin.

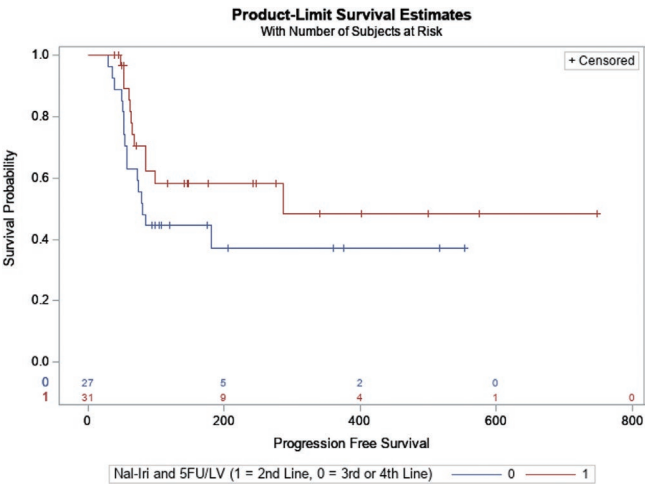

Figure S4 PFS of patients with pancreatic cancer treated with nal-IRI + 5-FU/LV in 2nd line setting or beyond 2nd line setting. There is no significant difference in PFS between the two groups (P value =0.1799). PFS, progression-free survival; nal-IRI, nano-liposomal irinotecan; 5-FU/LV, 5-fluorouracil/leucovorin.

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