Original Article

Second-line and third-line therapy with nanoliposomal irinotecan (nal-IRI) in pancreatic cancer: a single-center experience and review of literature

Christian Möhring[1], Freddy José Frontado Graffe[1], Alexandra Bartels[1], Farsaneh Sadeghlar[1], Taotao Zhou[1], Robert Mahn[1], Milka Marinova[2], Georg Feldmann[3], Peter Brossart[3], Tim R. Glowka[4], Jörg C. Kalff[4], Christian P. Strassburg[1], Maria A. Gonzalez-Carmona[1]^

[1]Department of Internal Medicine I, University Hospital Bonn, Bonn, Germany; [2]Department of Nuclear Medicine, University Hospital Bonn, Bonn, Germany; [3]Department of Internal Medicine III, University Hospital Bonn, Bonn, Germany; [4]Department of Visceral Surgery, University Hospital Bonn, Bonn, Germany

Contributions: (I) Conception and design: C Möhring, MA Gonzalez-Carmona; (II) Administrative support: F Sadeghlar; (III) Provision of study materials or patients: A Bartels, T Zhou, R Mahn, M Marinova, G Feldmann, P Brossart, TR Glowka, JC Kalff, CP Strassburg, MA Gonzalez-Carmona; (IV) Collection and assembly of data: C Möhring, FJ Frontado Graffe, MA Gonzalez-Carmona; (V) Data analysis and interpretation: C Möhring, MA Gonzalez-Carmona; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Maria A. Gonzalez-Carmona. Department of Internal Medicine I, University Hospital Bonn, Venusberg Campus 1, D-53127 Bonn, Germany. Email: maria.gonzalez-carmona@ukbonn.de.

Background: Prognosis of patients with pancreatic cancer is still extremely poor. First-line palliative therapies with FOLFIRINOX or gemcitabine/nab-paclitaxel have been established in the last decade. In the second-line, 5-FU/LV in combination with nanoliposomal irinotecan (nal-IRI) after gemcitabine has been shown to be effective. However, the use of nal-IRI as third-line therapy after FOLFIRINOX and gemcitabine-based chemotherapies is still controversial. In this study, we report about the use of 5-FU/LV + nal-IRI in a daily practice and analyze whether nal-IRI is an option as third-line therapy after FOLFIRINOX and gemcitabine/nab-paclitaxel.

Methods: This is a single center retrospective analysis of patients with irresectable pancreatic cancer who were treated with 5-FU/LV and nal-IRI from 2017 to 2021 as second- or third-line palliative treatment. Overall survival (OS), progression-free survival (PFS) and toxicity were analyzed, and multivariate analysis was used to identify independent prognostic factors.

Results: Twenty-nine patients receiving 5-FU/LV and nal-IRI were included in the analysis. The majority of patients (n=19) received 5-FU/nal-IRI as third-line therapy after pre-exposition to FOLFIRINOX and gemcitabine/nab-paclitaxel. Median OS and PFS were 9.33 months (95% CI: 3.37, 15.30) and 2.90 months (95% CI: 1.64, 4.16), respectively. Furthermore, patients receiving nal-IRI + 5-FU/LV as third-line treatment also showed some benefits, with no OS difference compared to second-line patients (9.33 *vs.* 10.27 months; HR: 1.85; 95% CI: 0.64, 5.41; P=0.253). Adverse effects were similar to reported trials.

Conclusions: In our study, the use of 5-FU/nal-IRI in unselected patients with advanced pancreatic cancer showed similar OS, PFS and tolerance as randomized prospective phase II/III trials. Interestingly, the use of 5-FU/nal-IRI seemed to be beneficial in third-line therapy, despite a pre-exposure to non-liposomal irinotecan.

Keywords: FOLFIRINOX; irinotecan resistance; nal-irinotecan; palliative chemotherapy; pancreatic cancer

^ ORCID: 0000-0003-3956-1457.

Submitted Jul 01, 2022. Accepted for publication Nov 07, 2022. Published online Feb 15, 2023.
doi: 10.21037/jgo-22-632
View this article at: https://dx.doi.org/10.21037/jgo-22-632

Introduction

Pancreatic cancer (PC) is the twelfth most common malignancy globally, and currently the seventh largest cause of cancer mortality. In the western world, PC has an incidence of 8.3/100,000 with an increasing incidence rate worldwide. Besides lifestyle changes, the aging population is the most important factor for the rising burden of PC. By 2030, PC is expected to be the second leading cause of cancer death worldwide (1-3). Mostly, a lack of early symptoms leads to late diagnosis making only 20% of patients with PC suitable for a possibly curative resection and most patients are only eligible for palliative systemic chemotherapy. Thus, PC outcome remains with an extremely poor prognosis and a 5-year-survival-rate of about 6% (4-7).

To date, the accepted possible frontline treatment consists of two combination regimens: the FOLFIRINOX regimen (5-FU/LV, irinotecan and oxaliplatin), which showed a significant survival benefit of 11.1 month compared to 6.8 months for gemcitabine alone in a randomized phase III trial of Conroy *et al.*, and the second established frontline regimen of palliative systemic chemotherapy, the combination of gemcitabine and nano-particle albumin bound paclitaxel (nab-paclitaxel), providing a survival benefit compared to gemcitabine alone of almost two months (8.5 *vs.* 6.7 months) (8,9).

However, progression after front line-therapy is frequent and systemic second-line approaches are limited (10). Nanoliposomal irinotecan (nal-IRI) is a topoisomerase I inhibitor which consists of irinotecan encapsulated by liposome particles. Thus, the conversion to its active metabolite (SN-38) can be extended leading to higher intratumoral levels of SN-38 and more powerful antitumoral effects (11-13).

The randomized phase III NAPOLI-1 trial analyzed the overall survival rate under fluorouracil-based therapies after progression on gemcitabine-based therapies. nal-IRI in combination with fluorouracil/leucovorin (nal-IRI + 5-FU/LV) showed a statistically significant prolonged survival rate compared to 5-FU monotherapy (6.1 *vs.* 4.2 months; P for log rank =0.012) (14). Thus, the combination of nal-IRI + 5-FU/LV represents a valuable option for patients with metastatic PC after gemcitabine-based therapies.

However, clinical experience with the nal-IRI + 5-FU/LV regimen in daily practice setting is limited. Only a few retrospective studies analyzing the clinical efficacy and safety of the use of nal-IRI in combination with 5-FU/LV have been published to date (15-18) and only a small number of studies have been carried out in a real-world setting, with contrary results, describing the clinical experience about the role of nal-IRI + 5-FU/LV as third-line therapy after irinotecan and 5-FU/LV pre-exposure and gemcitabine-based chemotherapy in metastatic PC (15,19-21). Since FOLFIRINOX is taking an increasingly relevant role in PC therapy in both the neoadjuvant/adjuvant and the palliative setting as upfront therapy, more data on the role of nal-IRI after pre-exposure to FOLFIRINOX are of great interest.

Thus, the aim of this study was to analyze the clinical experience with nal-IRI + 5-FU/LV as second-line therapy after a gemcitabine-based regimen, and especially as third-line therapy after a FOLFIRINOX regimen and gemcitabine-based therapy in a real-world cohort of patients with advanced or metastatic PC. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-632/rc).

Methods

Data collection and study design

This is a single-center retrospective study. To avoid selection bias, we included every patient with advanced and metastatic PC who received at least one cycle of nal-IRI + 5-FU/LV after palliative first-line or palliative second-line failure at the University Hospital Bonn, Germany, between January 2017 and May 2021. Twenty-nine patients were included in this study. For analysis, patients were assigned to one of the following two groups: ten patients received standard second-line therapy with nal-IRI, fluorouracil and leucovorin after gemcitabine-based therapy (2L-group) and 19 patients were treated with nal-IRI + 5-FU/LV as third-line therapy after a FOLFIRINOX regimen and gemcitabine-based chemotherapy (3L-group). All previous

systemic therapies were administrated in the setting of advanced disease (at first diagnosis or at recurrence diagnosis). Baseline parameters were registered before therapy onset (*Table 1*). Patients were followed until last patient contact or death. When lost to follow-up, patients were censored at date of last visit. Performance status was determined by an Eastern Cooperative Oncology Group (ECOG). Therapy response was intended to be assessed by computer tomography and/or magnetic resonance imaging (MRI) every 8 weeks. However, this was not possible in all cases, receiving tumor assessment every 8–12 weeks.

According to the RECIST criteria (version 1.1), tumor response was classified as complete or partial remission (CR, PR), stable disease (SD) or progressive disease (PD). Adverse events were recorded according to the common terminology criteria for adverse events (CTCAE, version 5.0). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was reviewed and approved by the Ethics Committee of the Medical Faculty of the University Hospital Bonn (No. 341/17). Because of the retrospective nature of the study, the requirement for informed consent was waived. Datasets were anonymized in compliance with national and international patient's privacy policies.

Patient characteristics and therapy decision

All 29 patients were diagnosed with unresectable locally advanced or metastatic PC. Patients were considered unresectable because of metastatic situation, arterial tumor infiltration or poor performance status and comorbidities. These patients were offered systemic palliative chemotherapy. Before starting systemic chemotherapy, diagnosis was confirmed histologically. Chemotherapy with FOLFIRINOX (oxaliplatin 85 mg/m^2, irinotecan 150 mg/m^2, leucovorin 400 mg/m^2, 5-FU 2,400 mg/m^2 every two weeks) was offered as first-line therapy mostly to younger patients (<75 years) with an ECOG of 0-2 and without relevant comorbidities. Alternatively, gemcitabine in combination with nab-paclitaxel (nab-paclitaxel 125 mg/m^2 followed by gemcitabine 1,000 mg/m^2) or monotherapy with gemcitabine (1,000 mg/m^2) was administered on days 1, 8 and 15 q28d. After progression of disease or increasing toxicity under first-line therapy, all patients with sufficient performance status and organ function received systemic chemotherapy based on the NAPOLI-1 regimen, either as second-line, after gemcitabine-based chemotherapy (2L-group) or as third-line (3L-group), after FOLFIRINOX and gemcitabine-based chemotherapy.

Nanoliposomal irinotecan (nal-IRI; Onivyde®) was administrated intravenously with 80 mg/m^2 (equivalent to 70 mg/m^2 irinotecan base) followed by 2,400 mg/m^2 fluorouracil and 400 mg/m^2 leucovorin every 14 days. Clinical examinations and laboratory controls were done regularly before starting the new cycle.

Statistical analysis

For statistical analysis, patient data were collected by electronic database (AGFA HealthCare ORBIS, NICE) and pseudonymized in a database. Using the Shapiro-Wilk test, continuous variables were tested on normal distribution. The continuous variables are presented as medians with first and third quartiles and differences were determined using Student unpaired *t*-test or non-parametric Mann-Whitney test, as appropriate. Categorial parameters are displayed as absolute frequencies with percentages and Pearson's chi squared test or Fisher's exact test was used for comparison.

Overall survival (OS) and progression-free survival (PFS) were transcribed into Kaplan-Meier curves. OS was defined as the time from application of chemotherapy with nal-IRI + 5-FU/LV until death. PFS was defined as the time from application of nal-IRI + 5-FU/LV until disease progression or death. Log-rank tests were used to compare estimated survival. Univariate and multivariate analyses were performed using Cox regression backward stepwise conditional models. If parameters showed P values ≤0.05 in univariate analysis, they were included in multivariate analysis. P values ≤0.05 were considered statistically significant. SPSS version 22 (IBM Corporation, Armonk, NY, USA) was used for statistical analysis.

Results

Patient characteristics

Between January 2017 and May 2021, 29 patients were included in this study. Of these, ten patients received second-line therapy with nal-IRI + 5-FU/LV after gemcitabine-based therapy (2L-group) and 19 patients were treated with nal-IRI + 5-FU/LV as third-line therapy after FOLFIRINOX and gemcitabine-based chemotherapy regimen in the first- or second-line therapy (3L-group). Baseline parameters are shown in *Table 1*.

Sixteen patients were female (55.2%) and 13 patients

Table 1 Baseline and treatment characteristics

Parameter	All (n=29), n (%)	2L-group (n=10), n (%)	3L-group (n=19), n (%)	P value
Sex				0.433
Female	16 (55.2)	7 (70.0)	9 (47.4)	
Male	13 (44.8)	3 (30.0)	10 (52.6)	
Age (years), median (Q1, Q3)	63.2 (55.0, 72.8)	74.8 (72.2, 78.6)	57.8 (53.4, 63.2)	<0.001
ECOG before nal-IRI + 5-FU/LV				0.310
0	11 (37.9)	3 (30.0)	8 (42.1)	
1	11 (37.9)	6 (60.0)	5 (26.3)	
2	6 (20.7)	1 (10.0)	5 (26.3)	
3	1 (3.4)	0 (0.0)	1 (5.3)	
Pancreatic tumor location				0.863
Head	23 (79.3)	8 (80.0)	15 (78.9)	
Body	3 (10.3)	1 (10.0)	2 (10.5)	
Tail	2 (6.9)	1 (10.0)	1 (5.3)	
Unknown	1 (3.4)	0 (0)	1 (5.3)	
M stage				0.675
M0	9 (31.0)	4 (40.0)	5 (26.3)	
M1	20 (69.0)	6 (60.0)	14 (73.7)	
Site of metastatic lesions				
Liver	12 (41.4)	4 (40.0)	8 (42.1)	1.000
Lung	6 (20.7)	2 (20.0)	4 (21.1)	1.000
Peritoneum	15 (51.7)	5 (50.0)	10 (52.6)	1.000
Other	7 (24.1)	3 (30.0)	4 (21.1)	0.665
Previous surgery				0.090
None	3 (10.3)	1 (10.0)	2 (10.5)	
Explorative	8 (27.6)	5 (50.0)	3 (15.8)	
Curative	11 (37.9)	4 (40.0)	7 (36.8)	
Palliative	7 (24.1)	0 (0)	7 (36.8)	
Systemic chemotherapy				
1L				<0.001
FOLFIRINOX	16 (55.2)	0 (0)	16 (84.2)	
Gemcitabine/nab-paclitaxel	11 (37.9)	8 (80.0)	3 (15.8)	
Gemcitabine alone	0 (0)	0 (0)	0 (0)	
Gemcitabine/capecitabine	2 (6.9)	2 (20.0)	0 (0)	

Table 1 (*continued*)

Table 1 (*continued*)

Parameter	ALL (n=29), n (%)	2L-group (n=10), n (%)	3L-group (n=19), n (%)	P value
2L				<0.001
FOLFIRINOX	3 (10.3)	0 (0)	3 (15.8)	
Gemcitabine/nab-paclitaxel	15 (51.7)	0 (0)	15 (78.9)	
Gemcitabine/erlotinib	1 (3.4)	0 (0)	1 (5.3)	
nal-IRI + 5-FU/LV	10 (34.5)	10 (100.0)	0 (0)	
3L				<0.001
nal-IRI + 5-FU/LV	19 (65.5)	0 (0)	19 (100.0)	
None	10 (34.5)	10 (100.0)	0 (0)	
Reason for discontinuation of nal-IRI + 5-FU/LV				0.306
Therapy is ongoing	2 (6.9)	0 (0)	2 (10.5)	
Death	11 (37.9)	4 (40.0)	7 (36.8)	
Toxicity	1 (3.4)	1 (10.0)	0 (0)	
Progress	12 (41.4)	3 (30.0)	9 (47.4)	
Best supportive care	3 (10.3)	2 (20.0)	1 (5.3)	
Reduced starting dose of nal-IRI + 5-FU/LV	11 (37.9)	6 (60.0)	5 (26.3)	0.114
Dose modification of nal-IRI + 5-FU/LV	16 (55.2)	8 (80.0)	8 (42.1)	0.114
Concomitant local therapy				0.892
None	20 (69.0)	7 (70.0)	13 (68.4)	
HIFU	5 (17.2)	2 (20.0)	3 (15.8)	
Other	4 (13.8)	1 (10.0)	3 (15.8)	
Best response FOLFIRINOX				NA
Partial remission			5 (29.4)	
Stable disease			10 (58.8)	
Progressive disease			2 (11.8)	
Unknown			2 (11.8)	
Bilirubin (mg/dL), median (Q1, Q3)	0.39 (0.28, 0.56)	0.37 (0.27, 0.45)	0.39 (0.28, 1.19)	0.535
CA19-9 (U/L), median (Q1, Q3)	250 (27, 4615)	191 (18, 3427)	449 (41, 5443)	0.582
CEA (µg/L), median (Q1, Q3)	4.5 (2.1, 12.2)	5.3 (3.5, 45.9)	4.1 (1.7, 10.4)	0.341
Time from advanced disease to start nal-IRI, median (Q1, Q3)	56.7 (30.5, 86.4)	37.5 (15.9, 55.9)	81.4 (39.2, 116.9)	0.016

Numerical data are presented as median with under and upper quartile in parentheses. 2L-group, patients who received nal-IRI + 5-FU/LV as second-line chemotherapy; 3L-group, patients who received nal-IRI + 5-FU/LV as third-line chemotherapy. ECOG, Eastern Cooperative Oncology Group; nal-IRI, nanoliposomal irinotecan; 5-FU/LV, 5-fluorouracil in combination with leucovorin; HIFU, high-intensity focused ultrasound; NA, not applicable; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

(44.8%) were male with even distribution between both groups. The majority of patients (96.6%) had an acceptable performance status, presenting an Eastern Cooperative Oncology Group (ECOG) of 0, 1 or 2. Mostly, the pancreatic tumor was located in the head of the pancreas (79.3%). In three patients (10.3%) the pancreatic tumor was located in the corpus and in only two patients (6.9%) in the tail of the pancreas. By the time of diagnosis, 20 patients (69%) presented metastases and nine patients (31%) locally advanced tumors. In the 3L-group, 73.7% of patients were diagnosed with metastasis, while in the 2L-group, 60% of patients (six patients) had metastatic disease. The only statistically significant baseline difference between both groups was the age at the time of the first nal-IRI + 5-FU/LV administration (P<0.001). As expected, in the 3L-group, 14 patients (73.7%) were younger than 65 years, while in the 3L- group all patients were older than 65 years (P<0.001). No further differences in baseline characteristics were observed between both groups.

Therapy

Due to grouping, previous systemic therapies differed significantly between the two groups. In the 2L-group, all patients received gemcitabine-based first-line therapy, whereby 80% were treated with gemcitabine/nab-paclitaxel. In the 3L-group, all patients received FOLFIRINOX, mostly as first-line therapy (84.2%), but also as second-line therapy (15.8%). In the 3L-group, 84.2% of cases received gemcitabine-based therapy as second-line therapy, while the 2L-group was solely treated with nal-IRI + 5-FU/LV. Median therapy duration with nal-IRI + 5-FU/LV was 11.9 weeks.

Eleven patients had prior surgery with curative intention (37.9%) and eight patients (27.6%) had prior explorative surgery. Seven patients (24.1%) received palliative surgery. Only three patients (10.3%) had no surgical therapy before starting second- or third-line therapy. Only one patient of the 2L-group discontinued systemic therapy with nal-IRI + 5-FU/LV because of toxicity.

Most patients (69%) received no other interventions during the systemic therapy, while 13 patients (31%) received concomitant interventions. Of these, five patients (17.2%) were treated once with high-intensity focused ultrasound (HIFU) ablation, four patients (13.8%) needed endoscopic interventional therapy with stenting and four patients (13.8%) were treated otherwise. No difference between the 2L- and the 3L-group was observed.

Efficacy of nal-IRI + 5-FU/LV in second- or third-line therapy

The median overall survival (OS) and the progression-free survival (PFS) were transcribed into Kaplan-Meier diagrams (*Figure 1*). The overall median follow-up was 10.5 months. All patients (n=29) showed a median OS of 9.33 months (95% CI: 3.37, 15.30) (*Figure 1A*). Patients (n=10) receiving nal-IRI + 5-FU/LV as second-line therapy (2L-group) experienced a median OS of 10.27 months (95% CI: 0.0, 23.11) and patients receiving nal-IRI + 5-FU/LV as third-line therapy (3L-group) showed an OS of 9.33 months (95 % CI: 3.39, 15.28) (HR: 1.85; 95% CI: 0.64, 5.41; P=0.253) (*Figure 1B*).

The median PFS was 2.90 months (95% CI: 1.64, 4.16) (*Figure 1C*). In the 2L-group, the median PFS was 3.60 months (95% CI: 2.05, 5.15) while the 3L-group had a median PFS of 2.53 months (95% CI: 2.27, 2.79) (HR: 1.44; 95% CI: 0.60, 3.42; P=0.407) (*Figure 1D*). Although the 3L-group consisted of only 19 patients, we performed a subgroup analysis to investigate the possible influence of irinotecan resistance on therapy efficacy under nal-IRI + 5-FU/LV after FOLFIRINOX. Because one patient had incomplete therapy data concerning FOLFIRINOX therapy, this analysis was done with 18 patients. Patients without progression under FOLFIRINOX (n=4) experienced a median OS of 7.5 months and patients with disease progression under FOLFIRINOX showed a median OS of 5.6 months (P=0.881).

Therapy response under nal-IRI + 5-FU/LV showed no statically significant difference between both therapy lines (*Table 2*). Altogether, no patient experienced a complete response, and four patients (13.8%) experienced a partial response. Furthermore, six patients (20.7%) had a stable condition resulting in a disease control rate of 34.5%.

Additionally, we analyzed the overall survival from the beginning of advanced disease therapy until death or end of observation period. The median survival of the whole cohort was 26.8 months. Interestingly, the 3L-group showed longer median OS (26.9 months; 95% CI: 14.4, 39.4) than the 2L-group (18.2 months; 95% CI: 7.4, 28.9), but this difference was not statistically significant (P=0.739) (*Figure 2*).

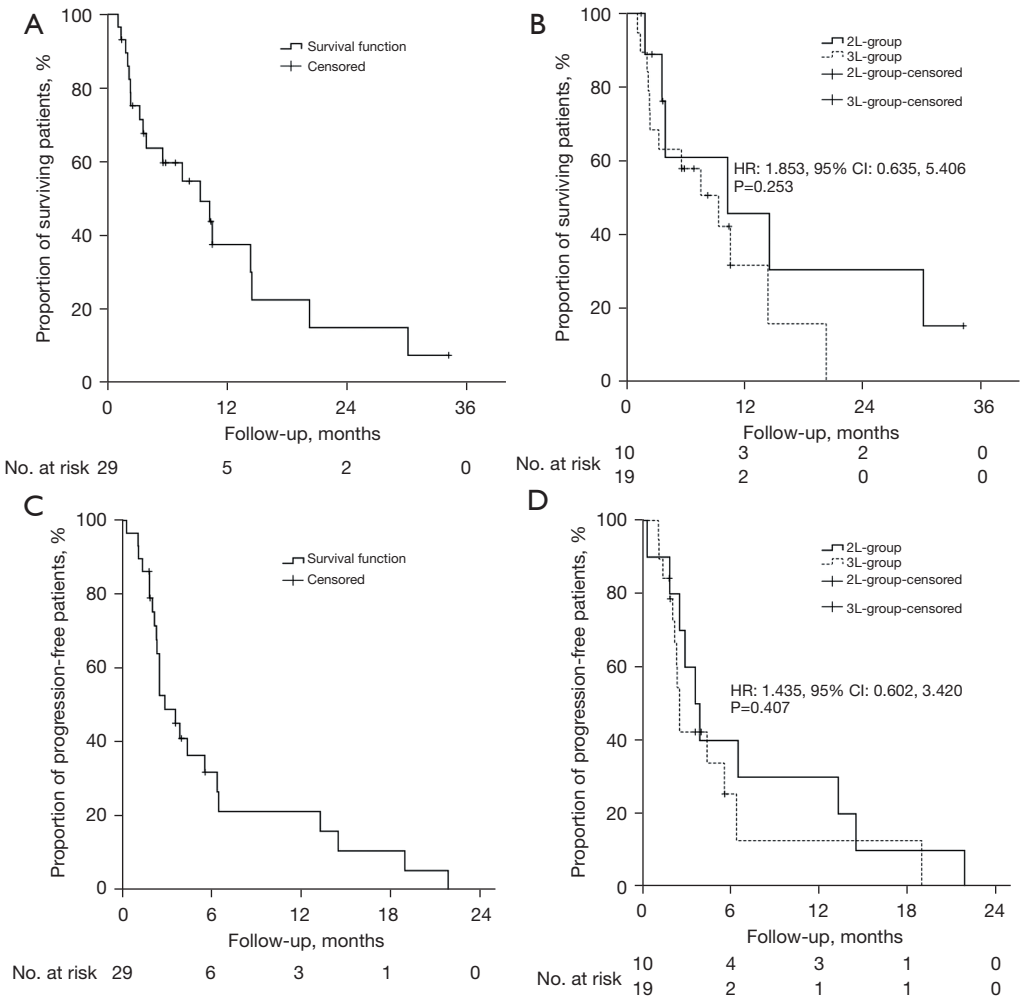

Figure 1 Kaplan-Meier survival analysis. (A) Overall survival total cohort. (B) Overall survival 2L-group *vs.* 3L-group. (C) Progression-free survival total cohort. (D) Progression-free survival 2L-group *vs.* 3L-group. 2L-group, patients who received nal-IRI + 5-FU/LV as second-line chemotherapy; 3L-group, patients who received nal-IRI + 5-FU/LV as third-line chemotherapy; nal-IRI, nanoliposomal irinotecan; 5-FU/LV, 5-fluorouracil in combination with leucovorin.

Factors predicting survival in patients treated with 5-FU/LV + nal-IRI

Predictive parameters affecting OS under nal-IRI + 5-FU/LV are based on univariate and multivariate analysis and are displayed in *Table 3*. The tumor markers CEA (HR: 2.881; 95% CI: 1.023, 8.109) and CA19-9 (HR: 3.319; 95% CI: 1.134, 9.715) as well as metastatic disease (HR: 6.241; 95% CI: 1.417, 27.486), showed significant prognostic value for OS. The type of surgery and metastatic disease (HR: 7.123; 95% CI: 1.548, 32.775) remained independent predictors of survival in the multivariate analysis. Typical oncological baseline values like age (HR: 1.804; 95% CI: 0.689, 4.719) and ECOG (HR for ECOG 1: 1.096; 95% CI: 0.381, 3.151; HR for ECOG 2: 0.620; 95% CI: 0.131, 2.935; HR for ECOG 3: 8.269; 95% CI: 0.803, 85.151) were not statistically significantly linked to OS. The impact of the nal-IRI + 5-FU/LV therapy line (second-line *vs.* third-line) was also analyzed and was due to our study design congruent to FOLFIRINOX preexposure *vs.* FOLFIRINOX naivety. The results showed no influence on OS (HR: 1.853; 95% CI: 0.635, 5.406). Furthermore, dose modifications, such as reduced initial dose (HR: 0.652; 95% CI: 0.233, 1.830) and dose reduction throughout therapy with nal-IRI + 5-FU/LV (HR: 1.292; 95% CI: 0.511, 3.267), had no influence on the survival outcome.

Dosing schedule and toxicity

A distribution of the adverse events grade ≥3 during therapy with nal-IRI + 5-FU/LV is illustrated in *Table 4*. The most common treatment-related adverse events were clinical disorders, such as pain (34.5%), ascites (31%), infection (34.5%) and nausea (31%). Neutropenia occurred in only one patient (3.4%) in the 2L-group and polyneuropathy was reported by two patients in the 3L-group. Interestingly, we observed no statistically significant difference of adverse events between the two groups.

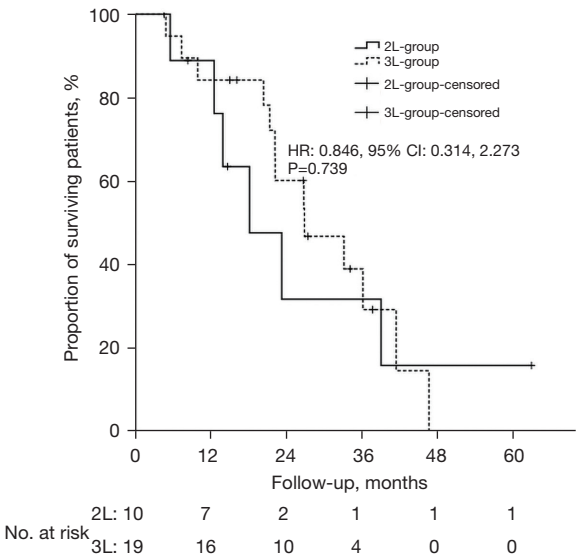

Figure 2 Kaplan-Meier survival analysis from beginning of advanced disease therapy. Overall survival from beginning of advanced disease chemotherapy 2L-group *vs.* 3L-group. 2L-group, patients who received nal-IRI + 5-FU/LV as second-line chemotherapy; 3L-group, patients who received nal-IRI + 5-FU/LV as third-line chemotherapy; nal-IRI, nanoliposomal irinotecan; 5-FU/LV, 5-fluorouracil in combination with leucovorin.

24.1% of patients receiving 5-FU/nal-IRI presented a reduced performance status (ECOG 2-3) before starting the 2nd line/3rd line therapy with 5-FU/nal-IRI. Usually, in these cases and in cases of persistent side effects of previous therapies, such as diarrhea and/or bone marrow suppression, therapy with 5-FU/nal-IRI was started with reduced dose (50% dose) and was augmented to 100% in the second course of therapy, if therapy did not worsened the performance status or side effects. Eleven patients (37.9%) received a reduced starting dose of nal-IRI + 5-FU/LV and 16 patients (55.2%) experienced at least one dose reduction during the nal-IRI + 5-FU/LV regimen, of which 20.7% of patients had reduced the entire regimen of 5-FU/nal-IRI by 50% dose. Both modifications were observed slightly more often in the 2L-group but without statistical significance. Additionally, only one patient (3.4%) needed discontinuation of therapy due to toxicity.

Discussion

In this retrospective analysis, the use of nal-IRI + 5-FU/LV showed similar antitumoral benefits in an unselected cohort of patients with advanced PC as found in randomized prospective phase II/III trials. Interestingly, the use of nal-IRI + 5-FU/LV appears to be beneficial even as a third-line therapy and despite previous exposition to irinotecan during palliative FOLFIRINOX therapy.

PC remains a malignancy with dismissal prognosis of 4.6 months without tumor specific treatment (1). The most efficient first-line regimen with palliative intention

Table 2 Best response to nal-IRI + 5FU/LV

Therapy response nal-IRI + 5-FU/LV	All		2L-group		3L-group		P value
	n=29	%	n=10	%	n=19	%	
CR	0	0.0%	0	0.0%	0	0.0%	NA
PR	4	13.8%	1	10.0%	3	15.8%	0.244
SD	6	20.7%	4	40.0%	2	10.5%	0.143
PD	19	65.5%	5	50.0%	14	73.7%	1.000
DCR (CR + PR + SD)	10	34.5%	5	50.0%	5	26.3%	0.244

2L-group, patients who received nal-IRI + 5-FU/LV as second-line chemotherapy; 3L-group, patients who received nal-IRI + 5-FU/LV as third-line chemotherapy. nal-IRI, nanoliposomal irinotecan; 5-FU/LV, 5-fluorouracil in combination with leucovorin; CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial remission; SD, stable disease; NA, not applicable.

Table 3 Univariate and multivariate time-to-event analysis of baseline and therapy characteristics

Parameter	P value	HR	95% CI	
			Under	Upper
Univariate analysis				
Prior history of gemcitabine/abraxane	0.432	0.603	0.170	2.132
ECOG 0	0.272	Reference		
ECOG 1	0.865	1.096	0.381	3.151
ECOG 2	0.547	0.620	0.131	2.935
ECOG 3	0.076	8.269	0.803	85.151
NAPOLI 2L *vs.* 3L	0.259	1.853	0.635	5.406
CEA <4.5 *vs.* >4.5 µg/L	0.045	2.881	1.023	8.109
CA19-9 <250 *vs.* >250 U/L	0.029	3.319	1.134	9.715
Age <65 *vs.* > 65 years	0.229	1.804	0.689	4.719
Time from advanced disease to start nal-IRI (<50 weeks *vs.* >50 weeks)	0.640	0.803	0.320	2.015
No concomitant local therapy	0.992	Reference		
HIFU	0.922	0.947	0.319	2.810
Other concomitant local therapy	0.928	0.993	0.205	4.236
No surgery	0.009	Ref.		
Explorative surgery	0.002	0.038	0.005	0.304
Curative surgery	0.030	0.175	0.036	0.846
Palliative surgery	0.006	0.060	0.008	0.438
Best response gemcitabine/abraxane PR	0.489	Reference		
Best response gemcitabine/abraxane SD	0.831	1.194	0.235	6.072
Best response gemcitabine/abraxane PD	0.389	2.028	0.407	10.113
Reason for discontinuation of FOLFIRINOX (toxicity *vs.* progress)	0.881	1.108	0.288	4.260
Reduced starting dose	0.417	0.652	0.233	1.830
Dose reduction during therapy	0.588	1.292	0.511	3.267
M0 *vs.* M1	0.015	6.241	1.417	27.486
Multivariate analysis				
No surgery	0.020	Reference		
Explorative surgery	0.004	0.043	0.005	0.364
Curative surgery	0.084	0.249	0.052	1.202
Palliative surgery	0.018	0.093	0.013	0.665
M0 *vs.* M1	0.035	4.080	1.107	15.036

ECOG, Eastern Cooperative Oncology Group performance status; CI, confidence interval; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; nal-IRI, nanoliposomal irinotecan; HIFU, high intensity focused ultrasound; PD, progressive disease; PR, partial remission; SD, stable disease; FOLFIRINOX, 5-FU/LV, irinotecan and oxaliplatin.

Table 4 Adverse events CTCAE ≥3

Parameter	All		2L-group		3L-group		P value
	n=29	%	n=10	%	n=19	%	
Ascites	9	31.0%	2	20.0%	7	36.8%	0.431
Pain	10	34.5%	4	40.0%	6	31.6%	0.698
Fatigue	6	20.7%	1	10.0%	5	26.3%	0.633
Nausea	9	31.0%	2	20.0%	7	36.8%	0.431
Diarrhea	5	17.2%	3	30.0%	2	10.5%	0.306
Neutropenia	1	3.4%	1	10.0%	0	0.0%	0.345
Infection	10	34.5%	4	40.0%	6	31.6%	0.677
Vomiting	3	10.3%	1	10.0%	2	10.5%	1.000
Dyspnea	2	6.9%	0	0.0%	2	10.5%	0.532
Hypertension	1	3.4%	1	10.0%	0	0.0%	0.345
Edema	2	6.9%	2	20.0%	0	0.0%	0.111
Polyneuropathy	2	6.9%	0	0.0%	2	10.5%	0.532

2L-group, patients who received nal-IRI + 5-FU/LV as second-line chemotherapy; 3L-group, patients who received nal-IRI + 5-FU/LV as third-line chemotherapy. CTCAE, common terminology criteria for adverse events; nal-IRI, nanoliposomal irinotecan; 5-FU/LV, 5-fluorouracil in combination with leucovorin.

is the chemotherapy combination of FOLFIRINOX or gemcitabine + nab-paclitaxel (8,9). The pivotal NAPOLI-1 trial generated consensus about systemic second-line treatment using nal-IRI + 5-FU/LV by extending the survival rate of patients with gemcitabine-refractory advanced PC (14).

However, data evaluating the efficacy and tolerability of nal-IRI + 5-FU/LV in a daily practice context in non-selected patients are very heterogenous, especially with the focus on application beyond second-line therapy (15-17,19-23). Moreover, inconsistent data about the benefit of nal-IRI-based therapy after previous irinotecan exposure cause uncertainty about second- or third-line application after FOLFIRINOX, which is evolving to be the most important combined therapy for PC, both in the curative and the palliative setting (15,19-21,23,24). Thus, in this study, the impact on survival of nal-IRI + 5-FU/LV as third-line therapy after previous exposition to FOLFIRINOX and gemcitabine-based therapy was analyzed in our cohort of patients. Of note, all patients in our cohort only received chemotherapy at an advanced stage of disease, with palliative intention.

While the NAPOLI-1 trial showed a median OS of 6.1 months (95% CI: 4.8, 8.9) for nal-IRI + 5-FU/LV, our cohort experienced a slightly longer median OS of 9.33 months (95% CI: 3.37, 15.30). However, our median PFS of 2.90 months (95% CI: 1.64, 4.16) and ORR of 13.8% is in line with PFS (3.1 months; 95% CI: 2.7, 4.2) and ORR (16%) reported in NAPOLI-1 (14). The essential baseline differences between our study cohort and the nal-IRI + 5-FU/LV group of the NAPOLI-1 trial are the significantly lower rate of metastatic disease (69% *vs.* 100%) and the higher portion of pancreatic head tumors (79% *vs.* 65%) in our study. Both parameters were associated with improved survival in the NAPOLI-1 trial and may explain the longer survival in our patient cohort. However, the NAPOLI-1 trial only included 10% of patients with prior non-liposomal irinotecan exposure in the nal-IRI + 5-FU/LV group, whereas our study consisted of 66% non-liposomal irinotecan pre-exposed patients (24). Additionally, the heterogeneity of previous therapy lines in the NAPOLI-1 trial might have affected OS.

Further retrospective analysis of OS rates under nal-IRI + 5-FU/LV after gemcitabine show a range from 4.4 to 9.4 months (15-17,19-23,25). Interestingly, the median PFS reported in the same retrospective studies shows a relatively narrow range of 2.0 to 4.1 months. Our results support the current literature with the above-mentioned OS of 9.33 months and PFS of 2.9 months.

The comparatively wide range of OS may have multiple

origins, such as heterogenous cohorts, but may also be caused by the administration of different therapy lines of nal-IRI + 5-FU/LV. The subgroup analysis of the NAPOLI-1 trial demonstrated significantly improved survival through nal-IRI + 5-FU/LV after 0–1 prior metastatic lines (6.2 *vs.* 4.2 months; P=0.030) but not after ≥2 lines (5.4 months *vs.* 4.3 months; P=0.178) (24). Kasi *et al.* reported real-world data on this topic and could not find any survival difference depending on therapy line of nal-IRI + 5-FU/LV (second-line *vs.* third- or fourth-line: P=0.170) (19). Our results confirm the latter work with no difference between our 2L-group and our 3L-group [10.27 months (95% CI: 0.0, 23.11) *vs.* 9.33 (95 % CI: 3.39, 15.28) (P=0.253)].

Furthermore, of great interest remains the question whether use of nal-IRI after non-liposomal irinotecan exposure is beneficial or not, especially after FOLFIRINOX first-line treatment and in particular after irinotecan resistance.

A post-hoc analysis of the NAPOLI-1 trial as well as the studies by Yoo *et al.* and Barzi *et al.* demonstrated significantly lower survival for patients with prior non-liposomal irinotecan therapy compared to non-liposomal irinotecan naïve patients (6.7 *vs.* 4.6 months; 10.2 *vs.* 4.4 months and 5.6 *vs.* 4.1 months) (15,21,24). Indeed, nal-IRI was capable of overcoming an irinotecan resistance in models of small cell lung cancer, but the clinical relevance of this findings is still unclear (26). Glassman *et al.* and Smith *et al.* took a closer look when they analyzed OS of patients who progressed under non-liposomal irinotecan compared to patients without progression under non-liposomal irinotecan. Both reported significantly shorter OS in patients with tumor progress (Glassman: 3.9 *vs.* 9.0 months, P=0.035; Smith: 4.3 *vs.* 6.1 months, P<0.001) (20,23). Conversely, Kasi *et al.* demonstrated in their retrospective analysis no survival difference between these two groups, thus matching our findings (non-liposomal naïve *vs.* pre-exposed: 10.3 *vs.* 9.3 months) (19). Altogether, the evidence for both scenarios, irinotecan-preexposure or irinotecan-progress remains controversial with stronger data suggesting only a benefit for preexposed but non-progression patients.

One fact contributing to the heterogeneity of the retrospective study landscape is the opacity of earlier therapy lines before nal-IRI/5-FU/LV administration. The majority of studies only display the amount of previous therapy lines and the distribution of previous anti-cancer therapies, but not which chemotherapy was administrated in which line. Moreover, in some studies, the therapy intention (neoadjuvant, adjuvant, palliative) of previous therapy lines remains unclear. Glassman *et al.* showed the therapy sequencing of their cohort and also analyzed the advanced disease OS for every therapy sequence, but not the nal-IRI/5-FU+LV OS for each sequence group (20). Kieler *et al.* demonstrated the therapies received before nal-IRI administration and analyzed the dependence of OS on therapy line, but not on therapy type (22).

A major strength of our study is the analysis of the effect of 5-FU/LV + nal-IRI in palliative third-line therapy after FOLFIRINOX and gemcitabine-based therapy. Few data have been published in this setting to date. Since FOLFIRINOX is the most relevant first-line therapy option for patients with a good performance status and organ function, but also as neoadjuvant/adjuvant therapy, data reporting the efficacy of 5-FU/LV + nal-IRI after FOLFIRINOX and gemcitabine-based therapy for patients with sufficient performance status are most valuable and clinically very relevant (8). Currently, nal-IRI + 5-FU/LV is not recommended for patients with prior exposure to irinotecan. However, in our cohort of patients, we reported on the benefit of nal-IRI + 5-FU/LV after FOLFIRINOX and gemcitabine-based chemotherapy exposure.

Among the various palliative therapy options for advanced and metastatic PC, the optimal sequence of chemotherapy has still to be found. Glassman *et al.* additionally analyzed OS in correlation with the therapy sequence, following diagnosis of advanced disease. The majority of patients received either first-line therapy with gemcitabine + nab-paclitaxel and nal-IRI + 5-FU/LV as second-line treatment (sequence 1) or first-line therapy with FOLFIRINOX and second-line therapy with gemcitabine + nab-paclitaxel followed by third-line treatment with nal-IRI + 5-FU/LV (sequence 2). Both sequences reached an excellent OS, measured from diagnosis of advanced disease until death, of 25.5 months (sequence 1) and 23.0 months (sequence 2) (20). Our results show a similar OS for our 3L-group, which correlates with sequence 2 of Glassman *et al.*, with an OS of 26.9 months (95% CI: 14.4, 39.4) and the 2L-group, which correlates with sequence 1 of Glassman *et al.*, with an OS of 18.2 months (95% CI: 7.4, 28.9), suggesting a trend to prolonged survival in the 3L-group. However, this trend has no statistical significance, probably due to the small sample size of patients in each group (P=0.739) and these results should be interpreted with caution in the light of a possible immortal time bias.

Moreover, our multivariate analysis identified metastatic

disease as a prognostic factor for a worse OS under nal-IRI + 5-FU/LV therapy. The subgroup analysis of the NAPOLI-1 trial demonstrated superior OS in patients with locally advanced disease, compared to metastatic disease (6.3 *vs.* 4.2 months; HR: 0.57; P<0.001) (24). The same study population also experienced better OS with lower baseline CA19-9 values (27). Interestingly, in line with previous results of Glassman *et al.*, the ECOG performance status did not have a significant influence on OS (20). We also checked the influence of a reduced starting dose or dose modification during therapy on OS. Neither therapy adaption appeared to influence OS (for reduced starting dose: HR: 0.652; 95% CI: 0.233, 1.830; P=0.417 and for modification: HR: 1.292; 95% CI: 0.511, 3.267; P=0.588). The prospective NAPOLI-1 trial revealed the same impact of dose modification on OS, which is important information for the treating physicians who must determine the balance between therapy effectiveness and toxicity (28).

The most common adverse events during nal-IRI + 5-FU in our cohort were ascites (31%), pain (34.5%), nausea (31%) and infections (34.5%), which were mostly tumor-related. Only one patient experienced neutropenia grade 3 (3.4%). The NAPOLI1-trial reported a significantly higher rate of neutropenia (27%). The other most common events, fatigue (14%), diarrhea (13%), vomiting (11%) and anemia (9%), showed a similar frequency in our cohort (14). Further retrospective analysis reported lower frequencies of grade ≥3 adverse events, attributing a lower starting dose to the reduced toxicity (19,20). The relatively low frequency of neutropenia might also be caused by the significantly reduced starting dose (37.9%) and dose modifications (55.2%).

Major limitations of this study are its retrospective and monocentric design, and the small patient number with heterogenous baseline characteristics. Thus, a selection bias cannot be excluded. Furthermore, the study is underpowered to compare the both groups of patients. Therefore, lack of significance between both groups of patients could be only related to the low number of patients. Therefore, we cannot perform any statement about the benefit of the use of 5-FU/nal-IRI as third line therapy, and our suggestion that this therapy may be beneficial should be taken with caution. Nevertheless, the retrospective design shows data in a real world setting in patients who are not necessarily eligible for clinical trials in the treatment of palliative pancreatic cancer with 5-FU/nal-IRI in second- and third-line therapy. The strength of the present study is the analysis of the impact on OS, PFS and safety of 5-FU/nal-IRI as third-line therapy after previous exposition to 5-FU and irinotecan, while addressing the important question for the treating physician about the benefit of nal-IRI in this setting for patients with sufficient performance status and progression after FOLFIRINOX and gemcitabine/nab-paclitaxel.

In summary, our study confirms the therapeutic benefits and safety of nal-IRI + 5-FU/LV in a cohort of unselected patients with advanced and metastatic PC. Furthermore, our study reveals a potential survival benefit with nal-IRI + 5-FU/LV as third-line therapy despite pre-exposition to 5-FU/irinotecan (e.g., with FOLFIRINOX), which should be further evaluated.

Acknowledgments

Funding: This work was supported by the following grants awarded to MG: GO 1874/1-2 grant from "Deutsche Forschungsgemeinschaft" (DFG), BONFOR from the University of Bonn, grant number 109255 from "Deutsche Krebshilfe" (German Cancer Aid) and a grant from the Reuthersche endowment fund of the University of Bonn.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-632/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-632/prf

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-632/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-632/coif). MG has contributed to advisory boards for Roche, Eisai, BMS, MSD and AZ. However, these activities have no potential conflicts of interest with the manuscript. This work was supported by the following grants awarded to MG: GO 1874/1-2 grant from "Deutsche Forschungsgemeinschaft" (DFG), BONFOR from the University of Bonn, grant number 109255 from "Deutsche Krebshilfe" (German Cancer Aid) and a grant from the Reuthersche endowment fund of the University of Bonn. TRG serves as an unpaid editorial board of the German Pancreas Club and was elected congress president for 2024 on the annual conference in

2022, not connected to the submitted work. 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).This study was reviewed and approved by the Ethics Committee of the Medical Faculty of the University Hospital Bonn (No. 341/17). Because of the retrospective nature of the study, the requirement for informed consent was waived.

References

1. Carrato A, Falcone A, Ducreux M, et al. A Systematic Review of the Burden of Pancreatic Cancer in Europe: Real-World Impact on Survival, Quality of Life and Costs. J Gastrointest Cancer 2015;46:201-11.
2. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer 2018;103:356-87.
3. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913-21.
4. Malvezzi M, Carioli G, Bertuccio P, et al. European cancer mortality predictions for the year 2017, with focus on lung cancer. Ann Oncol 2017;28:1117-23.
5. Huang J, Lok V, Ngai CH, et al. Worldwide Burden of, Risk Factors for, and Trends in Pancreatic Cancer. Gastroenterology 2021;160:744-54.
6. Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroenterol 2016;22:9694-705.
7. Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an update. Dig Dis 2010;28:645-56.
8. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.
9. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691-703.
10. Walker EJ, Ko AH. Beyond first-line chemotherapy for advanced pancreatic cancer: an expanding array of therapeutic options? World J Gastroenterol 2014;20:2224-36.
11. Kalra AV, Kim J, Klinz SG, et al. Preclinical activity of nanoliposomal irinotecan is governed by tumor deposition and intratumor prodrug conversion. Cancer Res 2014;74:7003-13.
12. Roy AC, Park SR, Cunningham D, et al. A randomized phase II study of PEP02 (MM-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma. Ann Oncol 2013;24:1567-73.
13. Ramanathan RK, Korn RL, Raghunand N, et al. Correlation between Ferumoxytol Uptake in Tumor Lesions by MRI and Response to Nanoliposomal Irinotecan in Patients with Advanced Solid Tumors: A Pilot Study. Clin Cancer Res 2017;23:3638-48.
14. Wang-Gillam A, Li CP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet 2016;387:545-57.
15. Yoo C, Im HS, Kim KP, et al. Real-world efficacy and safety of liposomal irinotecan plus fluorouracil/leucovorin in patients with metastatic pancreatic adenocarcinoma: a study by the Korean Cancer Study Group. Ther Adv Med Oncol 2019;11:1758835919871126.
16. Bang YJ, Li CP, Lee KH, et al. Liposomal irinotecan in metastatic pancreatic adenocarcinoma in Asian patients: Subgroup analysis of the NAPOLI-1 study. Cancer Sci 2020;111:513-27.
17. Su YY, Chiang NJ, Tsai HJ, et al. The Impact of Liposomal Irinotecan on the Treatment of Advanced Pancreatic Adenocarcinoma: Real-World Experience in a Taiwanese Cohort. Sci Rep 2020;10:7420.
18. Barzi A, Miksad R, Surinach A, et al. Real world outcomes of metastatic pancreatic cancer (mPC) patients (pts) treated with liposomal irinotecan (nal-IRI) in the US. J Clin Oncol 2018;36:e16229.
19. Kasi A, McGinnis T, Naik G, et al. Efficacy and tolerability of the combination of nano-liposomal irinotecan

and 5-fluorouracil/leucovorin in advanced pancreatic adenocarcinoma: post-approval clinic experience. J Gastrointest Oncol 2021;12:464-73.
20. Glassman DC, Palmaira RL, Covington CM, et al. Nanoliposomal irinotecan with fluorouracil for the treatment of advanced pancreatic cancer, a single institution experience. BMC Cancer 2018;18:693.
21. Barzi A, Miksad R, Surinach A, et al. Real-World Dosing Patterns and Outcomes of Patients With Metastatic Pancreatic Cancer Treated With a Liposomal Irinotecan Regimen in the United States. Pancreas 2020;49:193-200.
22. Kieler M, Unseld M, Bianconi D, et al. A real-world analysis of second-line treatment options in pancreatic cancer: liposomal-irinotecan plus 5-fluorouracil and folinic acid. Ther Adv Med Oncol 2019;11:1758835919853196.
23. Smith CJ, Bekaii-Saab TS, Cook KD, et al. Nanoliposomal irinotecan (Nal-IRI)-based chemotherapy after irinotecan -based chemotherapy in patients with pancreas cancer. Pancreatology 2021;21:379-83.
24. Macarulla Mercadé T, Chen LT, Li CP, et al. Liposomal Irinotecan + 5-FU/LV in Metastatic Pancreatic Cancer: Subgroup Analyses of Patient, Tumor, and Previous Treatment Characteristics in the Pivotal NAPOLI-1 Trial. Pancreas 2020;49:62-75.
25. Tossey JC, Reardon J, VanDeusen JB, et al. Comparison of conventional versus liposomal irinotecan in combination with fluorouracil for advanced pancreatic cancer: a single-institution experience. Med Oncol 2019;36:87.
26. Leonard SC, Lee H, Gaddy DF, et al. Extended topoisomerase 1 inhibition through liposomal irinotecan results in improved efficacy over topotecan and irinotecan in models of small-cell lung cancer. Anticancer Drugs 2017;28:1086-96.
27. Chen LT, Siveke JT, Wang-Gillam A, et al. Effect of baseline carbohydrate antigen 19-9 (CA19-9) level on overall survival (OS) in NAPOLI-1 trial: A phase III study of MM-398 (nal-IRI), with or without 5-fluorouracil and leucovorin (5-FU/LV), versus 5-FU/LV in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy. J Clin Oncol 2016;34:425.
28. Wang-Gillam A, Hubner R, Mirakhur B, et al. Dose modifications of liposomal irinotecan (nal-IRI) + 5-fluorouracil/leucovorin (5-FU/LV) in NAPOLI-1: Impact on efficacy. J Clin Oncol 2018;36:388.

Cite this article as: Möhring C, Frontado Graffe FJ, Bartels A, Sadeghlar F, Zhou T, Mahn R, Marinova M, Feldmann G, Brossart P, Glowka TR, Kalff JC, Strassburg CP, Gonzalez-Carmona MA. Second-line and third-line therapy with nanoliposomal irinotecan (nal-IRI) in pancreatic cancer: a single-center experience and review of literature. J Gastrointest Oncol 2023;14(1):352-365. doi: 10.21037/jgo-22-632

