European Journal of Cancer 151 (2021) 3–13

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Gemcitabine/nab-Paclitaxel versus FOLFIRINOX for palliative first-line treatment of advanced pancreatic cancer: A propensity score analysis

Jakob M. Riedl [a], Florian Posch [a], Lena Horvath [b], Antonia Gantschnigg [c], Felix Renneberg [d], Esther Schwarzenbacher [a], Florian Moik [e], Dominik A. Barth [a], Christopher H. Rossmann [a], Michael Stotz [a], Renate Schaberl-Moser [a], Martin Pichler [a], Herbert Stöger [a], Richard Greil [d], Angela Djanani [f], Konstantin Schlick [d], Armin Gerger [g,*]

[a] *Division of Clinical Oncology, Department of Internal Medicine, Medical University of Graz, Graz, Austria*
[b] *Department of Internal Medicine V: Hematology and Oncology, Medical University of Innsbruck, Innsbruck, Austria*
[c] *Department of Surgery, Paracelsus Medical University, Salzburg, Austria*
[d] *IIIrd Medical Department of Hematology, Medical Oncology, Hemostaseology, Rheumatology and Infectious Disease, Salzburg Cancer Research Institute, Paracelsus Medical University, Salzburg, Austria*
[e] *Clinical Division of Hematology and Hemostaseology, Department of Medicine I, Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria*
[f] *Department of Internal Medicine I: Gastroenterology and Hepatology, Medical University of Innsbruck, Innsbruck, Austria*
[g] *Division of Clinical Oncology, Department of Internal Medicine, Medical University of Graz, Graz, Austria*

Received 17 January 2021; received in revised form 13 March 2021; accepted 24 March 2021
Available online 2 May 2021

KEYWORDS
Pancreatic cancer;
FOLFIRINOX;
Gemcitabine/nab-paclitaxel;
First-line treatment;
Real-world;
Propensity score

Abstract ***Background:*** Gemcitabine/nab-paclitaxel (GN) and FOLFIRINOX are standard first-line treatment options for advanced pancreatic ductal adenocarcinoma (aPDAC), but currently no prospective randomised head-to-head comparison between these treatments has yet been performed.
Methods: We conducted a comparative propensity score (PS) analysis of overall (OS) and progression-free survival (PFS) in a tri-centre cohort of patients with aPDAC undergoing palliative first-line treatment with either GN or FOLFIRINOX.
Results: In unadjusted analysis, OS and PFS were highly similar between patients treated with GN (n = 297) and FOLFIRINOX (n = 158). In detail, median, 1- and 2-year OS estimates were 10.1 months, 42% and 18% in the GN group, as compared to 11.2 months, 45% and

* *Corresponding author*: Division of Clinical Oncology, Department of Internal Medicine, Medical University of Graz, Auenbruggerplatz 15, Graz, 8036, Austria. Fax: +43 316/385 13355.
E-mail address: armin.gerger@medunigraz.at (A. Gerger).

https://doi.org/10.1016/j.ejca.2021.03.040

12% in the FOLFIRINOX group, respectively (log-rank p = 0.783). Accordingly, median (4.6 versus 4.8 months), 6-month (40% versus 43%) and 1-year (9% versus 9%) PFS estimates did not significantly differ (log-rank p = 0.717). However, patients treated with FOLFIRINOX were significantly younger, had fewer comorbidities, and a better Eastern Cooperative Oncology Group performance status. These imbalances were accounted for by weighting the data with the PS. In PS analysis of survival outcomes, OS and PFS remained comparable between the two treatment groups. In detail, PS-weighted median, 1- and 2-year OS estimates were 10.1 months, 42% and 18% in the GN group, as compared to 10.1 months, 40% and 13% in the FOLFIRINOX group (PS-weighted log-rank p = 0.449). PS-weighted PFS estimates again did not differ (PS-weighted log-rank p = 0.329).

Conclusion: This real-world comparative effectiveness study indicates that FOLFIRINOX and GN have similar effectiveness in the palliative first-line treatment of aPDAC.

1. Introduction

Accounting for around 50,000 annual deaths in Europe and the United States of America (USA) each, pancreatic cancer (PC) ranks third in cancer-related mortality in the western world [1,2]. With a median 5-year relative survival rate of 37% for localised, 13% for regional and 3% for distant cancer stage, PC has the lowest survival rate of all cancers. Together with rising incidence rates of PC, this poses a major public health burden globally [2]. Complete surgical tumour resection represents the only potentially curative therapeutic option. However, the vast majority of patients with PC either present with primary metastatic or locally advanced inoperable cancers or develop local or distant recurrence during the course of their disease [3,4]. Until recently, treatment options for advanced pancreatic ductal adenocarcinoma (aPDAC) have been very limited. In 1997, gemcitabine monotherapy became the standard of care for the palliative first-line treatment of aPDAC, although only a modest but statistically significant overall survival (OS) benefit of 5.6 versus 4.4 months was demonstrated when compared with fluorouracil [5]. Thereafter, numerous chemotherapy combination and targeted agents have been tested against gemcitabine but failed to improve patient outcomes. In 2011, the French PRODIGE trial reported promising findings of a statistically significant and clinically meaningful survival benefit of 11.1 versus 6.8 months with the chemotherapy triplet FOLFIRINOX (Leucovorin, Fluorouracil (5-FU), Irinotecan, Oxaliplatin), as compared with gemcitabine in patients with metastatic PC and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 [6]. Two years later, the MPACT trial, which included patients with metastatic PC and a Karnofsky performance index greater than 70, compared gemcitabine/nab-paclitaxel (GN) to gemcitabine alone and demonstrated a significantly increased OS for the combination treatment (8.5 months in the GN group compared with 6.7 months in the Gemcitabine group) [7]. Today, GN and FOLFIRINOX or dose-modified FOLFIRINOX without bolus 5-FU are recommended as standard of care in palliative first-line treatment for patients with aPDAC and good performance status [8,9]. However, as no randomised comparative head-to-head trial between these two chemotherapy regimens has been conducted yet, the question regarding equal effectiveness remains unresolved.

To address this issue, we have conducted a tri-centre retrospective study including all consecutive patients treated with GN or FOLFIRINOX at three academic centres in Austria. We implemented a propensity score (PS) analysis using inverse-probability-of-treatment-weight (IPTW) to rigorously account for non-random treatment assignment. To the best of our knowledge, this is the largest study reporting PS-adjusted efficacy data comparing FOLFIRNOX and GN as palliative first-line treatment in aPDAC.

2. Methods

2.1. Study design

We conducted a tri-centre, retrospective cohort study, including all consecutive patients with histologically confirmed aPDAC who were initiated on palliative first-line treatment with either full dose or dose-modified FOLFIRINOX or GN at three academic centres (Medical University of Graz, Paracelsus Medical University Salzburg and Medical University of Innsbruck) in Austria between August 2010 and October 2019 (n = 455). Patients were identified using the respective in-house electronic healthcare databases as well as the in-house pharmacy prescriptions program, thus obtaining 100% local coverage. All eligible patients were aged 18 years or older, had histologically confirmed pancreatic ductal adenocarcinoma, radiologically confirmed advanced disease and received at least one cycle of the mentioned palliative first-line regimens between August 2010 and October 2019. The advanced disease stage was

defined as a composite of locally advanced inoperable tumours and/or tumours with distant metastatic spread. Patients who were treated with FOLFIRINOX or GN as induction or neoadjuvant treatment for locally advanced resectable or borderline resectable tumours were excluded from this study. Baseline and outcome data were retrospectively collected from the respective in-house electronic healthcare databases as well as from the central registry of the Austrian Social Security Providers Association (for all-cause death). The study was approved by the institutional review board of the leading centre (Ethics Committee of the Medical University of Graz, Austria; document number 31-035 ex 18/19). All methods were performed by following the relevant local and national guidelines and regulations.

2.2. Study outcomes

The primary end-point of the analysis was OS, defined as the time from the first day of first-line chemotherapy until death from any cause or censoring alive. Secondary end-points were (1) progression-free survival (PFS), defined as the time from the first day of first-line chemotherapy until radiological progression of disease, death from any cause, or censoring alive, whichever came first; (2) investigator-assessed objective response rate (ORR), that is, the composite of complete or partial remission; and (3) disease control rate (DCR), that is, the composite of complete or partial remission or stable disease. Radiological therapy response was assessed by treating physicians in analogy to the Response Evaluation Criteria in Solid Tumours, version 1.1 (CITE). Central radiology review was not performed.

2.3. Statistical methods

All statistical analyses were performed using Stata 15.0 (Stata Corp., Houston, TX, USA). Continuous variables were reported as medians (25th–75th percentile) and count data as absolute frequencies (%). Rank-sum, χ^2 and Fisher's exact tests were used to study associations between variables, as appropriate. The magnitude of potential differences in baseline variables between patients in the GN group and the FOLFIRINOX group was quantified with standardised mean differences (SMDs), considering SMDs $\geq$0.2 to indicate a relevant covariate imbalance between the two study groups [10]. A PS model was developed by backward selection from a multivariable logistic regression model of treatment group assignment, including all baseline variables as explanatory variables that were differently distributed between the GN group and the FOLFIRINOX group at either a p-value of association $\leq$0.10 and/or an SMD $\geq$0.2, respectively. Backward elimination continued until all variables in the model were multivariably associated with group assignment at a Wald test p-value of $\leq$0.20. The PS, defined as the probability of a patient to be in the FOLFIRINOX group conditional on the included baseline variables, was obtained from this final PS model and transformed into the IPTW, defined as the inverse of the probability of receiving the treatment that the patient actually received. Owing to a patient with a strongly outlying IPTW, we used a 'trimmed' IPTW according to best-practice recommendations, using only the patients with an IPTW $>$ the 1st and $<$ the 99th percentile of its distribution. Next, PS balance diagnostics were performed by qualitatively examining the change in SMD upon weighting the data with the IPTW [10]. Median follow-up was estimated with the reverse Kaplan–Meier estimator [11]. For subsequent outcome analyses, we performed a complete case analysis of all patients with an observed 'trimmed' IPTW (n = 412). Moreover, follow-up was truncated at 24 months. OS and PFS were estimated with Kaplan–Meier estimators, which were subsequently weighed with the IPTW. Schoenfeld tests revealed strong evidence for a violation of the proportional hazards assumption according to treatment group in the OS analysis. We therefore used flexible parametric regression models (Stata routine `stpm2`, directly modelling on the log-cumulative hazard scale), allowing for a time-varying association of treatment assignment with OS (3 degrees of freedom for the main effect and 2 degrees of freedom for the time-varying effect) [12]. In these models, we also fitted interactions between treatment group and selected covariables to perform hypothesis-generating subgroup analyses (with interaction p-values $<$0.10 considered indicative of a potential subgroup 'effect') [13].

3. Results

3.1. Cohort description and crude outcome rates

A total of 455 patients were included in the analysis, of whom 297 (65.3%) received GN and 158 (34.7%) were treated with FOLFIRINOX (Table 1). The median age of the cohort was 67 years (25th–75th percentile: 59–72) and 41% were women (n = 187). Most patients had a good to moderate performance status (ECOG 0-1 points: n = 409, 91%) and presented with some comorbidity (median Charlson Comorbidity Index: 9 [8–10], with 6 points allocated to metastatic cancer).

At a median follow-up of 26.2 months (25th–75th percentile: 14–44), we observed 349 deaths and 377 PFS outcome events. Median, 1- and 2-year OS estimates were 10.1 months (95% confidence interval [CI]: 9.3–11.4), 42% (95% CI: 37–47) and 15% (95% CI: 11–19), respectively. The corresponding PFS estimates were 4.6 months (95% CI: 4.2–5.3), 9% (95% CI: 7–13) and 0% (95% CI: 0–2), respectively (Supplementary Fig. 1). Investigator-assessed ORR and DCR estimates were 33% (95% CI: 28–38) and 61% (95% CI: 56–66), respectively. As compared to metastatic aPDAC, OS was significantly better in patients with locally advanced inoperable aPDAC (log-rank p = 0.0145). In detail,

Table 1
Baseline characteristics of the study cohort. Distribution is overall and by treatment group (n = 455).

Variable	n (% miss.)	Overall (n = 455)	GN (n = 297)	FOLFIRINOX (n = 158)	p	SMD	SMD_{IPTW}
Demographics & comorbidity							
Center: Graz, Austria	455 (0%)	140 (31%)	107 (36%)	33 (21%)	**<0.0001**	0.34	0.03
– Innsbruck, Austria	/	90 (20%)	78 (26%)	12 (8%)		0.51	0.33
– Salzburg, Austria	/	225 (49%)	112 (38%)	113 (72%)		0.72	0.26
Age (years)	455 (0%)	67 [59–72]	70 [62–74]	63 [53–67]	**<0.0001**	0.72	0.32
Female gender	455 (0%)	187 (41%)	123 (41%)	64 (41%)	0.851	0.02	0.15
BMI (kg/m^2)	447 (2%)	24 [21–26]	24 [21–26]	23 [21–27]	0.835	0.02	0.03
Charlson comorbidity index	446 (2%)	9 [8–10]	9 [8–10]	8 [7–9]	**<0.0001**	0.38	0.16
History of myocardial infarction	450 (1%)	27 (6%)	23 (8%)	4 (3%)	**0.035**	0.23	0.06
Chronic heart failure	450 (1%)	17 (4%)	15 (5%)	2 (1%)	0.065	0.21	0.14
Diabetes mellitus	454 (0%)	128 (28%)	90 (30%)	38 (24%)	0.152	0.14	0.03
ECOG							
0 point	447 (2%)	186 (42%)	87 (30%)	99 (63%)	**<0.0001**	0.71	0.12
1 point	/	223 (50%)	170 (58%)	53 (34%)		0.50	0.14
2+ points	/	38 (9%)	34 (12%)	4 (3%)		0.36	0.05
Tumour variables							
Tumor location: Pancreatic head	436 (4%)	249 (57%)	175 (61%)	74 (50%)	**0.024**	0.22	0.21
– Corpus of pancreas	/	95 (22%)	57 (20%)	38 (26%)		0.14	0.05
– Tail of pancreas	/	71 (16%)	39 (14%)	32 (22%)		0.21	0.24
– Other	/	21 (5%)	17 (6%)	4 (3%)		0.16	0.04
Grading: G3	283 (38%)	109 (39%)	73 (37%)	36 (43%)	0.330	0.13	0.45
Primary palliative setting	454 (0%)	382 (84%)	242 (81%)	140 (89%)	**0.033**	0.22	0.05
Surgery of primary tumour	455 (0%)	83 (18%)	65 (22%)	18 (11%)	**0.006**	0.28	0.11
Prior adjuvant chemotherapy	451 (1%)	58 (13%)	44 (15%)	14 (9%)	0.085	0.18	0.02
Tumor extent: Locally advanced	448 (2%)	96 (21%)	61 (21%)	35 (22%)	0.282	0.04	0.09
– Metastatic (one organ)	/	233 (52%)	161 (55%)	72 (46%)		0.18	0.28
– Metastatic (two organs)	/	88 (20%)	52 (18%)	36 (23%)		0.13	0.20
– Metastatic (three + organs)	/	13 (8%)	18 (6%)	13 (8%)		0.08	0.09
Laboratory parametersy							
Haemoglobin (g/dL)	442 (3%)	12.7 [11.2–13.6]	12.5 [11.1–13.6]	13.0 [11.4–13.8]	**0.042**	0.15	0.01
Leukocyte count (G/L)	441 (3%)	8.1 [6.2–10.3]	8.0 [6.0–10.3]	8.1 [6.8–10.0]	0.228	0.09	0.32
Neutrophil count (G/L)	406 (11%)	5.6 [4.0–7.5]	5.4 [3.9–7.5]	5.8 [4.4–7.6]	0.200	0.08	0.35
Lymphocyte count (G/L)	404 (11%)	1.4 [1.0–1.8]	1.4 [1.0–1.9]	1.4 [1.1–1.8]	0.999	0.02	0.04
Platelet count (G/L)	444 (2%)	251 [195–320]	251 [195–320]	251 [199–327]	0.286	0.12	0.03
C-reactive protein (mg/L)	383 (16%)	3 [1–10]	3 [1–10]	4 [1–0]	0.572	0.08	0.22
Alkalic phosphatase (units/L)	426 (6%)	123 [82–234]	120 [83–218]	125 [82–247]	0.859	0.04	0.04
LDH (units/L)	421 (7%)	203 [170–260]	204 [174–259]	193 [163–265]	0.152	0.02	0.01
Creatinine (mg/dL)	428 (6%)	0.8 [0.7–0.9]	0.8 [0.7–1.0]	0.8 [0.7–0.9]	0.215	0.16	0.09
Albumin (g/dL)	199 (56%)	4.0 [3.5–4.3]	3.9 [3.5–4.2]	4.1 [3.7–4.4]	0.079	0.24	0.22
CEA (ng/mL)	344 (24%)	7 [3–25]	6 [3–21]	9 [3–29]	0.248	0.10	0.19
CA 19-9 (U/mL)	442 (3%)	1086 [94–8647]	959 [74–6390]	1555 [135–12,278]	0.117	0.11	0.11

Data are reported as medians [25th–75th percentile] for continuous variables, and absolute frequencies (column %) for count data. n (% miss.) reports the number of patients with fully observed data for the respective variable (% missing). p-values are from rank-sum, X^2 and Fisher's exact tests, as appropriate. p values < 0.05 are highlighted in bold.
SMD, standardised mean difference; SMD IPTW, SMD weighted by the inverse-probability-of-treatment-weight; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; GN, gemcitabine/nab-paclitaxel.

median OS estimates were 13.6 and 9.8 months in patients with locally advanced and metastatic disease, and the respective 1-year OS estimates were 59% and 39% (Supplementary Fig. 2).

3.2. First-line chemotherapy description

Patients in the GN group received a median of three chemotherapy cycles (2–6) for a median treatment duration of 2.9 months (1.6–5.5), as compared to five cycles (2–7) and a median treatment duration of 3.4 months (1.5–6.4) in the FOLFIRINOX group. Both dose modifications and treatment discontinuations due to toxicity were slightly more frequent in the GN group (69% and 21% of patients) than in the FOLFIRINOX group (53% and 14% of patients), respectively (p = 0.001 and p = 0.049). In terms of safety, the proportion of patients who developed febrile neutropenia and diarrhoea was significantly higher in the FOLFIRINOX group, whereas risks of any neuropathy, any

Table 2
Adverse events in advanced pancreatic cancer according to treatment with GN or FOLFIRINOX (n = 455).

Toxicities	n (% miss.)	Overall (n = 455)	GN (n = 297)	FOLFIRINOX (n = 158)	p
Any grade neuropathy	452 (1%)	153 (34%)	92 (31%)	61 (39%)	0.101
Any grade neutropenia	452 (1%)	112 (25%)	77 (26%)	35 (22%)	0.372
Febrile Neutropenia	452 (1%)	24 (5%)	11 (4%)	13 (8%)	**0.040**
Cholangitis	452 (1%)	27 (6%)	21 (7%)	6 (4%)	0.159
Diarrhoea	452 (1%)	120 (27%)	65 (22%)	55 (35%)	**0.003**
Fatigue	452 (1%)	192 (42%)	118 (40%)	74 (47%)	0.144

Data are reported as absolute frequencies (column %) for count data. n (% miss.) reports the number of patients with fully observed data for the respective variable (% missing). p-values are from rank-sum, X^2 and Fisher's exact tests, as appropriate. p values < 0.05 are highlighted in bold. GN, gemcitabine/nab-paclitaxel.

neutropenia, cholangitis and fatigue were similar between the two treatment groups (Table 2).

3.3. Outcome according to treatment-unadjusted analysis

OS was highly similar in patients treated with GN and FOLFIRINOX. In detail, median-, 1- and 2-year OS estimates were 10.1 months, 42% and 18% in the GN group, as compared to 11.2 months, 45% and 12% in the FOLFIRINOX group, respectively (log-rank p = 0.783; Fig. 1A). The proportional hazards assumption appeared to be violated upon visual inspection of survival curves ('crossing curves' in Fig. 1A, Schoenfeld test p = 0.012); therefore, we performed a flexible parametric OS regression in which the relative hazard of death from any cause did not significantly favour either therapy (hazard ratio [HR] for OS for FOLFIRINOX = 0.82, 95% CI: 0.61–1.11, p = 0.199). In terms of PFS, median (4.6 versus 4.8 months), 6-month (40% versus 43%) and 1-year (9% versus 9%) estimates were also highly comparable between the two treatment groups (log-rank p = 0.717, HR for PFS for FOLFIRINOX = 0.96, 95% CI: 0.77–1.20, p = 0.718; Fig. 2A).

3.4. Development of a propensity score

Patients in the GN group significantly differed from patients in the FOLFIRINOX group according to several important baseline characteristics (Table 1). In detail, patients in the FOLFIRINOX group were significantly younger, had a lower number of comorbidities, lower prevalence of a history of myocardial infarction and better ECOG performance status. To address this major source of confounding for comparing GN and FOLFIRINOX, we developed a 'trimmed' IPTW from a PS model including the variables centre, age, Charlson Comorbidity Index, prior history of myocardial infarction, ECOG performance status, and tumours located in the pancreatic corpus (Supplementary Table 1). The PS covered the whole probability range (Supplementary Fig. 2A) and the 'trimmed' IPTW (Supplementary Fig. 2B) achieved sufficient balance on baseline covariables, as indicated by pertinent reductions in SMDs (Table 1). For example, SMDs were reduced from 0.72 to 0.32 for age, 0.38 to 0.16 for the Charlson Comorbidity Index, 0.23 to 0.06 for the history of myocardial infarction, and ≤0.71 to ≤0.14 for ECOG performance status.

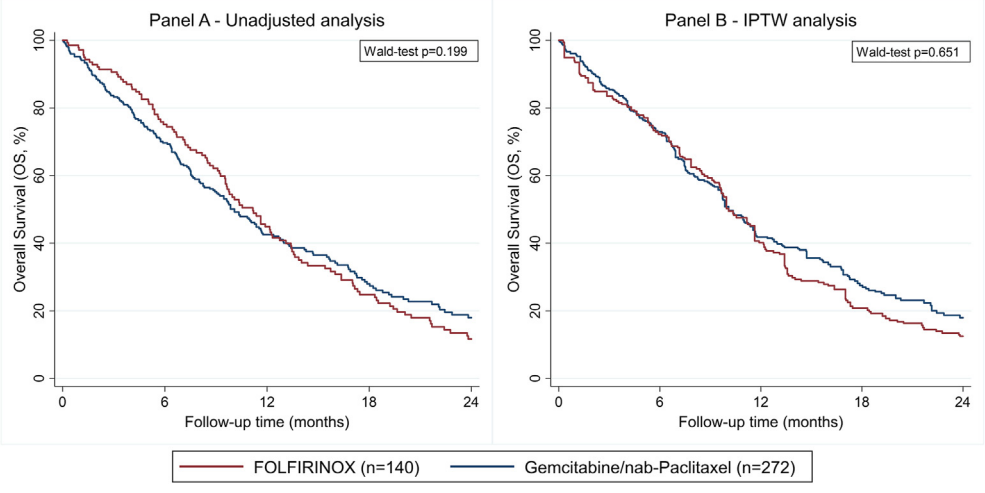

Fig. 1. **Overall survival in advanced pancreatic cancer according to treatment with gemcitabine/nab-paclitaxel (GN) or FOLFIRINOX (n = 412)**. Panel A—unadjusted Kaplan–Meier estimator and Panel B—IPTW Kaplan–Meier estimator (propensity score analysis). Wald-test p-values are from a flexible parametric regression model accounting for non-proportional hazards (crossing curves). IPTW, inverse probability of treatment weight.

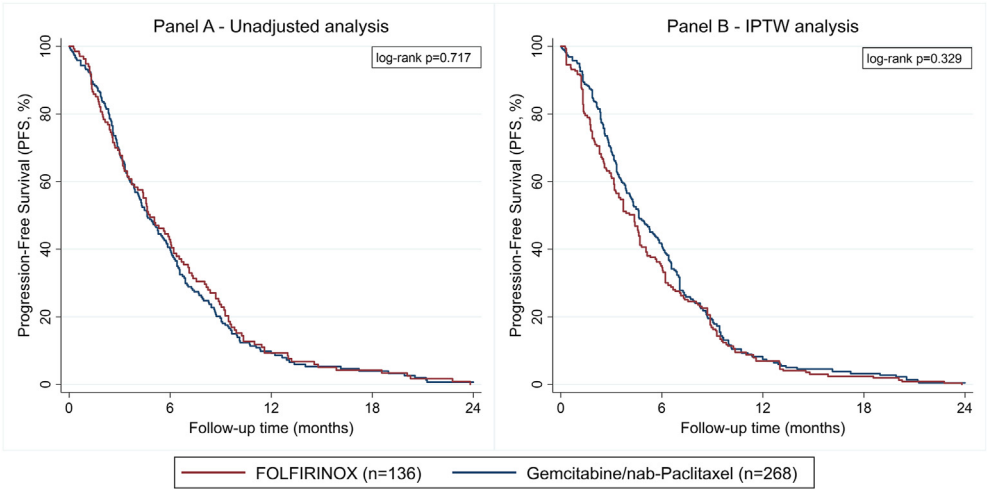

Fig. 2. **Progression-free survival in advanced pancreatic cancer according to treatment with GN or FOLFIRINOX (n = 404)**. Panel A—unadjusted Kaplan–Meier estimator and Panel B—IPTW Kaplan–Meier estimator (propensity score analysis).

3.5. Propensity score analysis

Upon weighting the data with the IPTW, OS remained comparable between the two treatment groups. In detail, IPTW-weighted median, 1- and 2-year OS estimates were 10.1 months, 42% and 18% in the GN group, as compared to 10.1 months, 40% and 13% in the FOLFIRINOX group, respectively (IPTW-weighted log-rank p = 0.449, IPTW-weighted HR for OS for FOLFIRINOX [flexible parametric regression model] = 1.11, 95% CI: 0.71–1.73, p = 0.651; Fig. 1B). IPTW-weighted median (4.6 versus 4.4 months), 6-month (41% versus 35%) and 1-year (7% vs. 7%) PFS estimates were again similar between the two treatment groups (IPTW-weighted log-rank p = 0.329, IPTW-weighted HR for PFS for FOLFIRINOX = 1.13, 95% CI: 0.88–1.46, p = 0.329; Fig. 2B).

3.6. Exploratory, hypothesis-generating subgroup analyses

With the exception of sex, the relative efficacy of the two treatments was not statistically significantly different across several subgroups, such as locally advanced PDAC (Fig. 3).

3.7. Exploratory analyses—1st-line response rate and 2nd-line chemotherapy

In the 1st-line therapy, the investigator-assessed ORR and DCR were 31% and 58% in the GN group, and 36% and 65% in the FOLFIRINOX group, respectively (both p > 0.18). No evidence regarding a higher 1st-line response rate with one of the two treatments was observed both in unadjusted analysis (odds ratio [OR] for objective response with FOLFIRINOX = 1.20, 95% CI: 0.76–1.89, p = 0.431) and IPTW-adjusted analysis (OR = 0.82, 95% CI: 0.47–1.42, p = 0.482), respectively. Significantly more patients underwent 2nd-line chemotherapy after first-line treatment with FOLFIRINOX (120 of 158 patients, 76%) compared to GN (145 of 297 patients, 49%). The two most frequent 2nd-line treatment regimens were GN (n = 76, 63%) and gemcitabine monotherapy (n = 20, 17%) after first-line therapy with FOLFIRINOX, and nanoliposomal irinotecan with 5-FU (n = 52, 36%) and OFF (leucovorin, 5-FU and oxaliplatin) (n = 32, 22%) after GN first-line therapy, respectively.

4. Discussion

To date, no randomised controlled trial comparing the two recommended standard first-line chemotherapy regimens GN and FOLFIRINOX in advanced PC has been published. In the present study, we aimed to overcome this lack of comparative data by performing a propensity score–matched comparative effectiveness analysis of real-world outcomes from 455 patients treated with either FOLFIRINOX or GN. In unadjusted analysis, FOLFIRINOX was associated with a slight but not significantly increased OS, PFS and ORR. However, patients treated with FOLFIRINOX had a significantly higher rate of favourable prognostic baseline characteristics. To minimise potential bias and to rigorously account for non-random treatment assignment, a PS model using IPTW was implemented. In propensity score–adjusted analysis, survival outcomes were highly comparable between the two treatment groups.

Median OS as well as treatment response rate were numerically higher with FOLFIRINOX in the PRODIGE trial when compared to GN in the MPACT trial. In contrast, FOLFIRINOX was associated with a higher rate of severe neutropenia and sensory neuropathy [6,7]. However, baseline characteristics of the two

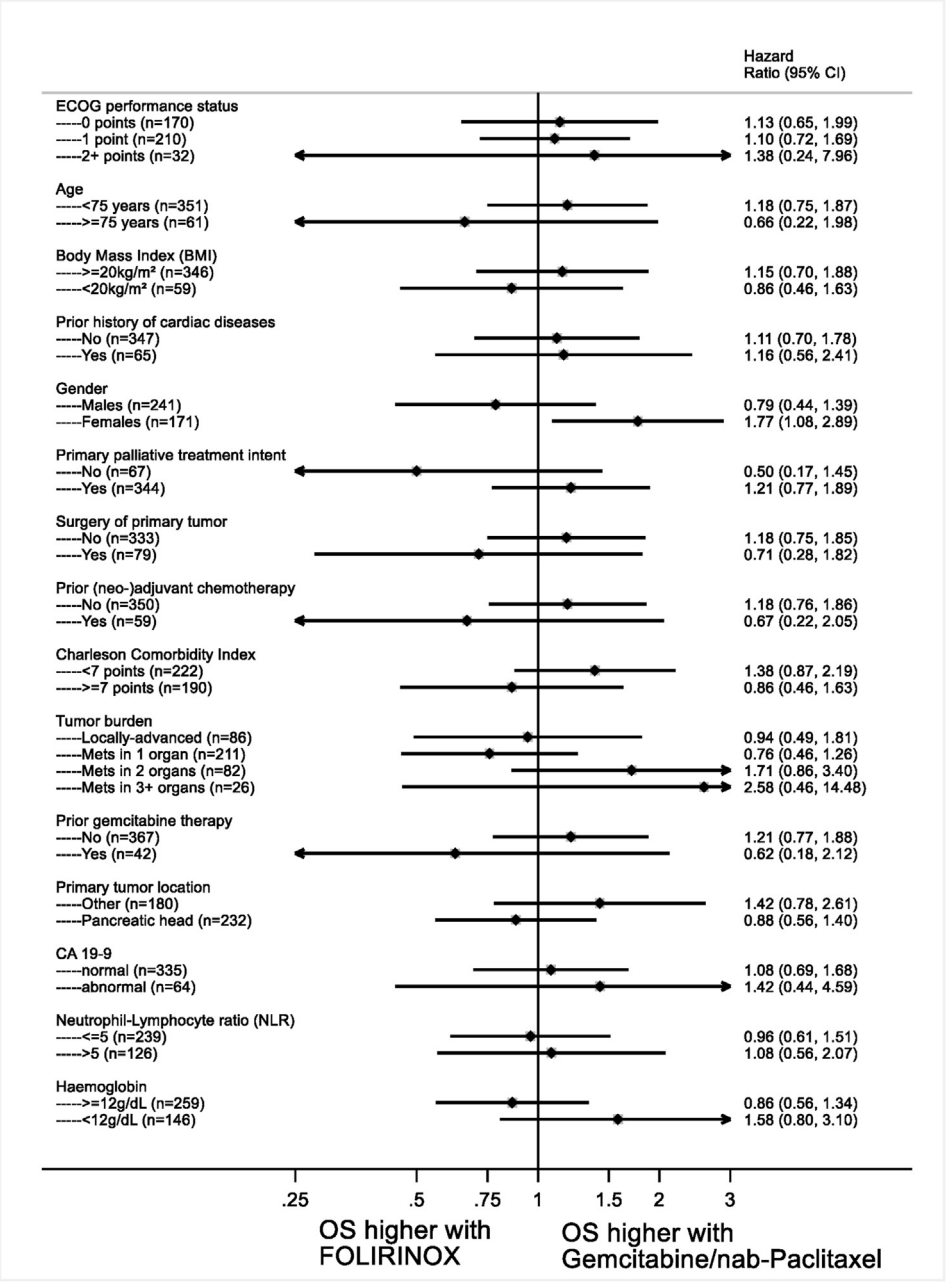

Fig. 3. **Exploratory subgroup analyses for the comparative efficacy of GN and FOLFIRINOX towards overall survival.** Coefficients were estimated with an IPTW flexible parametric regression model by fitting interactions between the treatment group and the respective variable. IPTW, inverse probability of treatment weight; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; CI, confidence interval; CA 19-9, carbohydrate antigen 19-9.

study cohorts did significantly differ in terms of several well-established prognostic indicators such as age, performance, status and site of metastasis, which hampers a cross-trial treatment comparison. Still, in clinical practice, physicians tend to prefer FOLFIRINOX in younger and fitter patients, as pointed out in several studies reporting real-world data on treatment patterns in aPDAC in the USA and Germany [14,15]. In the absence of a randomised controlled trial, several retrospective studies have presented real-world comparative efficacy data on FOLFIRINOX versus GN in aPDAC. However, results are conflicting and most of these studies were either limited by small sample size and/or lack of adjustment for significant imbalances between treatment cohorts [16–18]. One large retrospective chart review study conducted by Kim *et al.*, which included PC patients with metastatic disease treated at oncology practices in the USA, found no difference in outcomes between the two treatment regimens [15]. Most recently, Chiorean *et al.* performed

a thorough systematic review and meta-analysis of pooled observational outcome data of almost 7000 patients with advanced or metastatic PC treated with either FOLFIRINOX or GN as palliative first-line treatment [19]. Overall, a slight but statistically insignificant OS and PFS benefit was found for the treatment with FOLFIRINOX. Still, these results should be interpreted with caution as patients treated with FOLFIRINOX had lower median age and were more likely to have good performance status. These potential confounders might have significantly affected comparative outcomes. Accordingly, in our present study, we found that patients treated with FOLFIRINOX were significantly younger, had better ECOG performance status, fewer comorbidities and a lower prevalence of a history of myocardial infarction. Ignoring these imbalances might lead to an overestimation of the treatment effect for FOLFIRINOX. In the naive survival analysis, we found slight but insignificant favourable survival outcomes and treatment response rates for FOLFIRINOX compared to GN. The respective median OS of 10.1 months for GN and 11.2 for FOLFIRINOX is in line with other large-scale retrospective studies reporting real-world outcome data, such as by Hegewisch-Becker *et al.* (9.1 versus 11.3 months) [14], Kim *et al.* (12.1 versus 13.8) [15], Cartwright *et al.* (9.8 versus 11.4) [17] and Kang *et al.* (11.4 versus 9.6) [18] that alongside other studies confirm the real-world effectiveness of the two treatment regimens [20]. To elucidate potential differences in effectiveness between the respective treatments, a rigorous adjustment for baseline imbalances of patient covariables is necessary to account for the large amount of selection bias likely affecting such analysis. IPTW using a PS is a powerful statistical method for reducing the effect of baseline confounding in observational studies that can mimic randomization, given that the statistical assumptions underlying this approach are met [10]. In the IPTW-adjusted analysis in which a sufficient balancing between the two treatment cohorts could be achieved, the minor differences in terms of treatment efficiency diminished and median OS and PFS estimates were highly similar for GN and FOLFIRINOX. These results indicate that GN and FOLFIRINOX are equally effective in the first-line treatment of aPDAC. Interestingly, Williet *et al.* used a similar statistical approach by propensity score matching and found a non-significant trend towards better survival for FOLFIRINOX [21]. However, in this study, only patients with metastatic PC were included and the PS-matched analysis was limited by its relatively small sample size ($n = 98$), which might have led to an over- or underestimation of the real treatment effect.

Several important insights could be obtained from this study. First, investigator-assessed response rates were similar with GN and FOLFIRINOX, suggesting that both are acceptable treatment options for patients who have a high need for response, such as patients with imminent biliary obstruction. Second, our main finding of comparable efficacy with GN and FOLFIRINOX has global relevance, as a large community of PC patients in developing nations often have limited access to expensive antineoplastic agents such as nab-paclitaxel, and therefore FOLFIRINOX may be regarded as an effective and financially accessible treatment for aPDAC. In terms of safety, treatment with GN was associated with a higher rate of toxicity−related treatment discontinuation and dose reduction. This stands in contrast to a study by Wang *et al.* that reported higher discontinuation rates for FOLFIRINOX [22]. Importantly, when interpreting these results, the higher prevalence of adverse prognostic baseline characteristics in the GN treatment group of our cohort must be considered, which may impact rates of adverse events. In detail, rates of febrile neutropenia and diarrhoea were higher in the FOLFIRINOX group, whereas other toxicities including any grade neuropathy, fatigue and cholangitis were balanced between the two treatment groups, which is consistent with other studies [15,18,23]. Notably, rates of any grade neutropenia were significantly lower in our study compared to toxicity data from the MPACT and the ACCORD12 trial, which might be attributed to an underreporting of adverse events because of the retrospective study design.

To determine whether the treatment effect was dependent on a particular patient's characteristics, we performed an exploratory IPTW-adjusted subgroup analysis. In line with the treatment comparison in the overall cohort, we found that the observed treatment effect was consistent across all patient subgroups except for women, in which a statistically significant association for abetter outcome with GN was shown. As we were not able to derive a plausible biological rationale for this, this finding is intriguing and may be caused by residual confounding. However, potential metabolic influences of sex on chemotherapy efficacy and toxicity, as pointed out previously in other cancer entities, cannot be fully excluded in this setting and should be considered in future studies. Otherwise, relative treatment effectiveness was highly similar among all relevant patient subgroups, with only non-significant trends being observed, such as for metastatic burden. Here, the subgroup analysis indicated that patients with a higher number of metastatic lesions derived a greater OS benefit when treated with GN compared to FOLFIRINOX. Importantly, treatment efficacy appeared to be similar in the subgroup of 96 patients with locally advanced inoperable aPDAC, of whom two-thirds were treated with GN (i.e. outside the existing label for this therapy) and one-third with FOLFIRINOX. The investigator-assessed response rate in our cohort of locally advanced inoperable aPDAC patients was similar to the recently published LAPACT trial, although OS of our subcohort was slightly worse than

the LAPACT cohort, most likely due to our stringent exclusion criterion of only considering locally advanced aPDAC patients who were 'truly' inoperable [24]. Our exploratory finding of a similar relative efficacy of GN and FOLFIRINOX in patients with locally advanced aPDAC also aligns well with a recently published retrospective cohort study of Perri *et al.* showing comparable OS for patients with LAPC treated with FOLFIRINOX or GN [25]. Further support for an overall similar efficacy between the two chemotherapy regimens comes from a preliminary report of the randomised phase II SWOG1505 trial that showed comparable OS estimates in patients with resectable PDAC undergoing perioperative chemotherapy with mFOLFIRINOX or GN [26].

Recent advances in the second-line treatment of aPDAC have expanded the arsenal of therapeutic options, resulting in further improvement of disease outcome [27]. After gemcitabine-based first-line treatment, the best evidence exists for a combination of nanoliposomal irinotecan plus 5-FU and leucovorin, which demonstrated superior OS as compared to 5-FU and leucovorin in the NAPOLI-1 trial [28]. Other treatment options in this setting are chemotherapy protocols consisting of oxaliplatin and fluorouracil, which, however, have led to conflicting outcome data [29,30]. After failure of FOLFIRINOX as first-line treatment, GN is the preferred second-line option for patients who retain a good performance status. Yet, to date, no randomised controlled trial has proven the efficacy of GN in this setting. In our study, approximately 60% of the overall study cohort received a 2nd-line treatment with a significantly higher proportion of patients in the FOLFIRINOX treatment group. These findings are consistent with previous reports and again might likely be attributed to the higher proportion of young and relatively fit patients in the FOLFIRINOX treatment group [15,18,19,21]. As anticipated, the most frequently administered second-line treatment regimens were GN after FOLFIRINOX and nanoliposomal irinotecan with 5-FU after GN, which is in line with current guideline recommendations from the European Society for Medical Oncology and the National Comprehensive Cancer Network [8,31]. Interestingly, we observed separating OS curves after a median follow-up of 12 months with a non-significant trend towards better survival for GN. Given that most patients have ended first-line treatment at this point, improved outcomes in respective second-line treatment might provide a speculative explanation for this finding. However, our study was not designed to determine the optimal treatment sequence, which warrants investigation in a prospective randomised controlled trial.

The following limitations of this study need to be discussed. First, owing to the retrospective design of this study, a potential risk regarding selection and information bias should be considered. We aimed to minimise the chance of bias by including a large cohort of patients consecutively treated at three different academic centres. We thus believe that this study accurately reflects outcomes of real-world palliative first-line treatment of patients with aPDAC. Second, although an IPTW-weighted PS analysis was performed to rigorously account for imbalances of patient baseline characteristics between the two treatment cohorts, a residual risk for confounding might have affected the treatment effect and cannot be fully excluded. Importantly, as indicated by a significant reduction of SMDs, the IPTW-adjusted model achieved a sufficient balancing of several known prognostic indicators, such as age, ECOG performance status and comorbidities. Third, no information regarding rates of primary dose modifications was available. Fourth, accurate classification of adverse events according to common terminology criteria could not be sufficiently performed and selected adverse events might be underreported because of the retrospective nature of this study. This should be kept in mind when interpreting our safety data, which were a secondary end-point of the study.

5. Conclusion

In this real-world comparative effectiveness study, FOLFIRINOX and GN demonstrated similar effectiveness in the palliative first-line treatment of aPDAC and both chemotherapy regimens represent valid treatment options in this setting. Treatment decisions should be based on the respective toxicity profiles as well as on the individual patient's preferences.

Ethics approval and consent to participate

The study was approved by the IRB of the Medical University of Graz, Austria; document number 31-035 ex 18/19. Written informed consent was not obtained from individual patients, as this is not mandated in Austria and Germany for retrospective database studies approved by an ethics committee.

Patient involvement

Patients were neither involved in the design nor conduct of this study, nor in the writing of this manuscript.

Transparency declaration

The lead authors (JMR and AG) affirm that the manuscript is an honest, accurate and transparent account of the study being reported and that no important aspects of the study have been omitted.

Availability of data and materials

All data generated or analysed during this study are included in this published article (and its supplementary information files). Statistical analysis code is available on request from FP. The data set analysed during the present study cannot be shared under the current protocol and ethics committee approval.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution

JMR, FP, AD, KS and AG conceived and designed the study; FP interpreted the results; JMR, FP and AG contributed to the writing of the manuscript; all authors collected data and contributed patients, performed all statistical analyses, wrote the first draft of the manuscript, agree with the manuscript's results and conclusions and ICMJE criteria for authorship read and met.

Conflict of interest statement

RG, AD and AG have received honoraria from Celgene and have been members of the consulting or advisory role for Celgene. The other authors declare no conflict of interest.

Acknowledgements

We thank Samantha O. Hasenleithner (Diagnostic and Research Institute of Human Genetics, Diagnostic and Research Center for Molecular BioMedicine, Medical University of Graz, Graz, Austria) for proofreading the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.03.040.

References

[1] Carioli G, Bertuccio P, Boffetta P, Levi F, La Vecchia C, Negri E, et al. European cancer mortality predictions for the year 2020 with a focus on prostate cancer. Ann Oncol 2020;31(5):650–8.
[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA A Cancer J Clin 2020;70(1):7–30.
[3] Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul J-L, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med 2018;379(25):2395–406.
[4] Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroenterol 2016;22(44):9694–705.
[5] Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15(6):2403–13.
[6] Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364(19):1817–25.
[7] Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369(18):1691–703.
[8] Margaret AT, Mokenge PM, Chiorean EG, Brian C, Courtney S, Amol KN, et al. NCCN guidelines insights: pancreatic adenocarcinoma, version 1.2019. J Nat Comprehensive Cancer Network J Natl Compr Canc Netw 2019;17(3):202–10.
[9] Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol 2015;26:v56–68.
[10] Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34(28):3661–79.
[11] Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Contr Clin Trials 1996;17(4):343–6.
[12] Ng R, Kornas K, Sutradhar R, Wodchis WP, Rosella LC. The current application of the Royston-Parmar model for prognostic modeling in health research: a scoping review. Diagnostic and Prognostic Research 2018;2(1):4.
[13] Moik F, Riedl JM, Winder T, Terbuch A, Rossmann CH, Szkandera J, et al. Benefit of second-line systemic chemotherapy for advanced biliary tract cancer: a propensity score analysis. Sci Rep 2019;9(1):5548.
[14] Hegewisch-Becker S, Aldaoud A, Wolf T, Krammer-Steiner B, Linde H, Scheiner-Sparna R, et al. Results from the prospective German TPK clinical cohort study: treatment algorithms and survival of 1,174 patients with locally advanced, inoperable, or metastatic pancreatic ductal adenocarcinoma. Int J Canc 2019;144(5):981–90.
[15] Kim S, Signorovitch JE, Yang H, Patterson-Lomba O, Xiang CQ, Ung B, et al. Comparative effectiveness of nab-paclitaxel plus gemcitabine vs FOLFIRINOX in metastatic pancreatic cancer: a retrospective nationwide chart review in the United States. Adv Ther 2018;35(10):1564–77.
[16] Cho IR, Kang H, Jo JH, Lee HS, Chung MJ, Park JY, et al. FOLFIRINOX vs gemcitabine/nab-paclitaxel for treatment of metastatic pancreatic cancer: single-center cohort study. World J Gastrointest Oncol 2020;12(2):182–94.
[17] Cartwright TH, Parisi M, Espirito JL, Wilson TW, Pelletier C, Patel M, et al. Clinical outcomes with first-line chemotherapy in a large retrospective study of patients with metastatic pancreatic cancer treated in a US community oncology setting. Drugs Real World Outcomes 2018;5(3):149–59.
[18] Kang J, Hwang I, Yoo C, Kim K-p, Jeong JH, Chang H-M, et al. Nab-paclitaxel plus gemcitabine versus FOLFIRINOX as the first-line chemotherapy for patients with metastatic pancreatic cancer: retrospective analysis. Invest N Drugs 2018;36(4):732–41.
[19] Chiorean EG, Cheung WY, Giordano G, Kim G, Al-Batran SE. Real-world comparative effectiveness of nab-paclitaxel plus gemcitabine versus FOLFIRINOX in advanced pancreatic cancer: a systematic review. Ther Adv Med Oncol 2019;11:1758835919850367.
[20] Riedl JM, Posch F, Prager G, Eisterer W, Oehler L, Sliwa T, et al. The AST/ALT (De Ritis) ratio predicts clinical outcome in patients with

pancreatic cancer treated with first-line nab-paclitaxel and gemcitabine: post hoc analysis of an Austrian multicenter, noninterventional study. Ther Adv Med Oncol 2020;12:1758835919900872.

[21] Williet N, Saint A, Pointet AL, Tougeron D, Pernot S, Pozet A, et al. Folfirinox versus gemcitabine/nab-paclitaxel as first-line therapy in patients with metastatic pancreatic cancer: a comparative propensity score study. Therap Adv Gastroenterol 2019;12:1756284819878660.

[22] Wang Y, Camateros P, Cheung WY. A real-world comparison of FOLFIRINOX, gemcitabine plus nab-paclitaxel, and gemcitabine in advanced pancreatic cancers. J Gastrointest Canc 2019;50(1):62–8.

[23] Muranaka T, Kuwatani M, Komatsu Y, Sawada K, Nakatsumi H, Kawamoto Y, et al. Comparison of efficacy and toxicity of FOLFIRINOX and gemcitabine with nab-paclitaxel in unresectable pancreatic cancer. J Gastrointest Oncol 2017;8(3):566–71.

[24] Philip PA, Lacy J, Portales F, Sobrero A, Pazo-Cid R, Manzano Mozo JL, et al. Nab-paclitaxel plus gemcitabine in patients with locally advanced pancreatic cancer (LAPACT): a multicentre, open-label phase 2 study. Lancet Gastroenterol Hepatol 2020;5(3):285–94.

[25] Perri G, Prakash L, Qiao W, Varadhachary GR, Wolff R, Fogelman D, et al. Response and survival associated with first-line FOLFIRINOX vs gemcitabine and nab-paclitaxel chemotherapy for localized pancreatic ductal adenocarcinoma. JAMA Surgery 2020;155(9):832–9.

[26] Sohal D, Duong MT, Ahmad SA, Gandhi N, Beg MS, Wang-Gillam A, et al. SWOG S1505: results of perioperative chemotherapy (peri-op CTx) with mfolfirinox versus gemcitabine/nab-paclitaxel (Gem/nabP) for resectable pancreatic ductal adenocarcinoma (PDA). J Clin Oncol 2020;38(15_suppl):4504.

[27] Kieler M, Unseld M, Bianconi D, Schindl M, Kornek GV, Scheithauer W, et al. Impact of new chemotherapy regimens on the treatment landscape and survival of locally advanced and metastatic pancreatic cancer patients. J Clin Med 2020;9(3):648.

[28] Wang-Gillam A, Li CP, Bodoky G, Dean A, Shan YS, Jameson 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(10018):545–57.

[29] Oettle H, Riess H, Stieler JM, Heil G, Schwaner I, Seraphin J, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. J Clin Oncol 2014;32(23):2423–9.

[30] Gill S, Ko Y-J, Cripps C, Beaudoin A, Dhesy-Thind S, Zulfiqar M, et al. PANCREOX: a randomized phase III study of fluorouracil/leucovorin with or without oxaliplatin for second-line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy. J Clin Oncol 2016;34(32):3914–20.

[31] Appendix 6: cancer of the pancreas: MCBS eUpdate published online 20 June 2017. Ann Oncol 2017;28:iv157. www.esmo.org/Guidelines/Gastrointestinal-Cancers.