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FOLFIRINOX or gemcitabine/nab-paclitaxel in advanced pancreatic adenocarcinoma: A novel validated prognostic score to facilitate treatment decision-making in real-world

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Abstract

There is no prospective, randomised head-to-head trial comparing first-line FOLFIRINOX and gemcitabine/nab-paclitaxel in advanced pancreatic cancer. We assess real-world effectiveness and quality of life (QoL) of both regimens using a new prognostic score. This analysis includes 1540 patients with advanced pancreatic cancer from the prospective, clinical cohort study Tumour Registry Pancreatic Cancer separated into learning (n = 1027) and validation sample (n = 513). The Pancreatic Cancer Score (PCS) was developed using multivariate Cox regression. We compared overall survival (OS) and time to deterioration (TTD) for longitudinal QoL between first-line FOLFIRINOX (n = 407) and gemcitabine/nab-paclitaxel (n = 655) according to patients'

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; CEA, carcinoembryonic antigen; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; FOLFIRINOX, leucovorin, fluorouracil, irinotecan and oxaliplatin; GEMNAB, gemcitabine combined with nab-paclitaxel; HR, hazard ratio; HRQoL, health-related quality of life; IPTW, inverse probability of treatment weighting; LAPC, locally advanced, unresectable pancreatic cancer; LLN, lower limit of normal; MPC, metastatic pancreatic cancer; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PCS, Pancreatic Cancer Score; PS, propensity score; QoL, quality of life; SMD, standardised mean difference; TPK, Tumour Registry Pancreatic Cancer; TTD, time to deterioration; ULN, upper limit of normal.

prognostic risk, after inverse probability of treatment weighting (IPTW) by propensity score analysis. The PCS includes nine independent prognostic factors for survival: female sex, BMI ≥24/unknown, ECOG performance status ≥1, Charlson comorbidity index ≥1, tumour staging IV/unknown at primary diagnosis, liver metastases, bilirubin >1.5× upper limit of normal (ULN), leukocytes >ULN and neutrophil-to-lymphocyte ratio ≥4. Median OS of the validation sample was 11.4 (95% confidence interval [CI]: 10.4-14.4), 8.5 (95% CI: 6.8-9.6) and 5.9 months (95% CI: 4.0-7.4) for favourable- (0-3 risk factors), intermediate- (4-5 factors) and poor-risk group (6-9 factors), respectively. After IPTW, only poor-risk patients had significantly longer median OS and TTD of overall QoL with FOLFIRINOX (OS: 6.9 months, 95% CI: 3.9-13.3; TTD: 10.6 months, 95% CI: 2.0-14.1) vs gemcitabine/nab-paclitaxel (OS: 4.0 months, 95% CI: 2.8-4.8; TTD: 4.1 months, 95% CI: 2.4-4.5). Our novel PCS may facilitate treatment decisions in clinical routine of advanced pancreatic cancer, since only poor-risk, but not favourable-risk patients, seem to benefit from intensified treatment with FOLFIRINOX.

KEYWORDS
cohort studies, FOLFIRINOX, gemcitabine/nab-paclitaxel, pancreatic carcinoma, prognostic score

What's new?

Prospective, randomised head-to-head trials comparing first-line FOLFIRINOX and gemcitabine/nab-paclitaxel in advanced pancreatic cancer are lacking. Here, real-world data on more than 1000 patients from the prospective German TPK clinical cohort study suggest that only patients stratified as having a poor survival risk by a newly developed prognostic score may benefit from intensified treatment with FOLFIRINOX. Poor-risk patients had significantly longer median overall survival and time-to-deterioration of overall quality of life with FOLFIRINOX vs gemcitabine/nab-paclitaxel, after standardising treatment groups using a propensity score. The novel prognostic score may facilitate treatment decisions in the routine clinical management of advanced pancreatic cancer.

1 | INTRODUCTION

Pancreatic cancer is a highly fatal disease with poor outcomes, increasing incidence and mortality rates.[1] Since more than 80% of tumours are locally advanced, unresectable (LAPC) or metastatic (MPC) at diagnosis, the relative 5-year survival rate is only 10% for all disease stages, both in Germany[2] and the United States.[3,4] Pancreatic cancer is predicted to soon become the second leading cause of cancer-related death in the European Union.[1,5] In Germany, approximately 19 000 new cases and almost as many deaths due to pancreatic cancer were registered in 2018.[2]

To alleviate cancer-related symptoms and prolong life, systemic chemotherapy remains the primary treatment option for LAPC and MPC.[1] Two treatment strategies, FOLFIRINOX (leucovorin, fluorouracil, irinotecan and oxaliplatin) and the combination of nab-paclitaxel and gemcitabine (GEMNAB), have been shown to improve outcomes of patients with MPC.[6-8] Until today, however, there has been no head-to-head phase III randomised trial comparing first-line FOLFIRINOX and GEMNAB and the choice of one regimen over the other is based on clinical parameters.[1,9,10] Real-world data from retrospective studies indicate similar effectiveness of both treatments or a trend towards better survival with FOLFIRINOX.[11-16] However, most studies only focus on patients with MPC, and, even more important, imbalances in patient characteristics were often not considered. Proper patient selection is essential to identify those who will benefit most from a particular treatment.[17] Although several prognostic and predictive factors have been evaluated,[18] to our knowledge, there are no prospectively validated models for risk stratification that help in decision-making for FOLFIRINOX or GEMNAB in routine practice of advanced pancreatic cancer.

Here, we present real-world data on 1540 nonselected patients with LAPC or MPC treated in office-based oncology practices and hospitals in Germany from the prospective clinical cohort study TPK (Tumour Registry Pancreatic Cancer). We developed a prognostic

score for patients with LAPC/MPC, regardless of the type of systemic palliative first-line treatment, and compared OS and time to deterioration (TTD) as a measure of longitudinal health-related quality of life (HRQoL) with FOLFIRINOX or GEMNAB according to patient's prognostic risk. To adjust for confounding factors and to standardise the sample by balanced treatment groups, we used inverse probability of treatment weighting (IPTW) by a propensity score (PS). Our results provide important insights into which patients might benefit most from either treatment and may help to fill the evidence gap, as randomised trials are missing.

2 | PATIENTS AND METHODS

2.1 | Study design

The Tumour Registry Pancreatic Cancer (TPK, AMETHYST) is an open, longitudinal, multicentre, observational, prospective cohort study (NCT02089269). Patients were recruited from February 2014 until July 2018, from October 2019 until August 2020 and from June 2021 until April 2022; follow-up is ongoing. For the present analysis, all those patients who had been recruited until the data cut on 30 June 2020 were included. Patients recruited afterwards will be subject of future interim analyses. Eligible patients were ≥18 years of age with previously untreated LAPC or MPC at start of palliative first-line treatment. Further details on the methodology of the TPK have previously been published.[19]

2.2 | Cohort definition

Until data cut for this interim analysis (30 June 2020), a total of 1978 patients with LAPC/MPC were prospectively recruited into the TPK by 120 office-based oncology practices, hospitals and medical care centres all over Germany. For the present analysis, the study cohort consists of 1540 patients with documented palliative first-line treatment but without any prior (neo)adjuvant systemic treatment (*prognosis score population*; Figure 1). Of these patients, 1062 received FOLFIRINOX or GEMNAB as first-line treatment (*IPTW population*), with 38% of patients (n = 407) treated with FOLFIRINOX and 62% (n = 655) with GEMNAB (Figure 1).

2.3 | Statistical analysis

2.3.1 | Time to event endpoints

All time to event endpoints were estimated using the Kaplan-Meier method.[20] OS was defined as the interval between start of first-line treatment and the date of death from any cause. Patients alive or lost to follow-up at data cut were censored at last contact. Start of first-line treatment was defined as first application of any systemic palliative treatment.

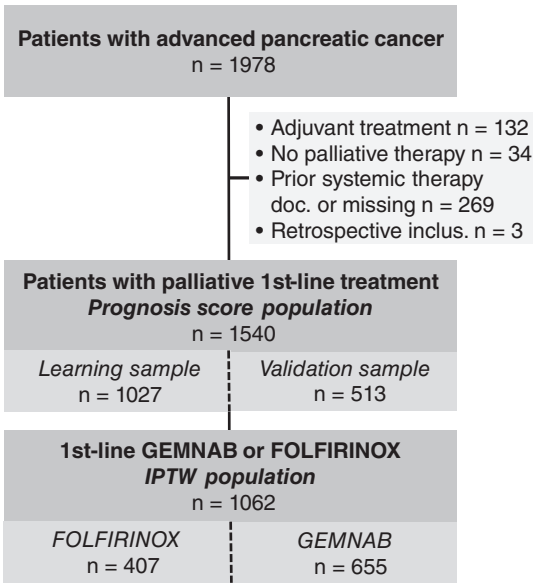

FIGURE 1 Flow chart. Patient flow chart of all patients with advanced pancreatic cancer included in this analysis, starting from the total number of patients recruited into the TPK registry from February 2014 until June 2020. The study cohort consists of all patients with advanced pancreatic cancer and palliative first-line treatment who had not received any prior (neo)adjuvant systemic treatment (n = 1540, *prognosis score population*) including 1062 patients treated with FOLFIRINOX or GEMNAB in first line (*IPTW population*). doc., documented; GEMNAB, gemcitabine plus nab-paclitaxel; inclus., inclusion

2.3.2 | Development of the prognostic Pancreatic Cancer Score (PCS)/real-world

The following 18 variables documented in the TPK were identified as potentially prognostic based on experts' opinion and/or previous publication as a prognostic factor: age, sex, body mass index (BMI), ECOG performance status, any comorbidity, Charlson comorbidity index (CCI), type of health insurance, tumour localisation at primary diagnosis, tumour staging (based on TNM) and grading at primary diagnosis, resection status of primary tumour, presence of liver metastases, number of metastatic sites, bilirubin, haemoglobin below lower limit of normal, thrombocytes higher upper limit of normal (ULN), leukocytes above ULN and neutrophil-to-lymphocyte ratio (NLR; unless otherwise stated, all variables had been documented at start of first-line treatment). The patient sample was randomly split up 2:1 into a learning sample (2/3) and a validation sample (1/3). Prognostic factors were identified in the learning sample by Cox regression with backward elimination,[21] employing a cut-off of $P < .05$. Six factors (sex, localisation of primary tumour, ECOG, BMI, presence of liver metastases and number of metastatic sites) were excluded from variable selection and directly included in the prognostic model. To simplify the score for clinical use, variables were dichotomised before entering the score. The construction of a simple classification rule has been published before.[22]

Based on the prognostic factors identified, a sum score (number of risk factors) was built. For practical reasons, prognostic factors were not weighted and each factor contributed with one unit. This approach was further justified by the fact that hazard ratios (HR) were in a similar range for all identified prognostic factors. Based on the number of prognostic factors, patients were stratified into three risk groups by quartile splitting (lower quartile: favourable, second + third quartile: intermediate, upper quartile: poor risk). The predictive performance of the identified risk groups was tested in the validation sample using log-rank test and Kaplan-Meier method to compare both favourable- vs intermediate-, favourable- vs poor- and intermediate- vs poor-risk groups. Adjustment for multiplicity was done for all three comparisons according to Bonferroni. A similar prognostic score has previously been developed by our group for metastatic colorectal cancer.[22]

2.3.3 | Inverse probability of treatment weighting

To adjust for confounding in the two treatment groups and to standardise the sample by balanced groups, IPTW based on a PS approach was used. For each patient, a PS was estimated using logistic regression containing all 18 variables included for the development of the prognostic score plus T, N and M categories at primary diagnosis, presence of lymphogenic metastases as well as the interaction terms age with ECOG and M category with number of metastatic sites. The logistic regression model was fitted iteratively until sufficient balance for covariates between the two groups was reached. Standardised differences $d < 0.1$ were considered as sufficient balance.[23,24] The IPTW applied for each patient was calculated by taking the inverse of the PS. For the IPTW cohort, the sum of weights refers to the number of patients.

2.3.4 | Quality of life

All patients enrolled in the TPK were asked about their HRQoL at start of treatment and subsequently every 2 months using the validated questionnaires European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL[25] and the pancreatic cancer-specific module EORTC QLQ-PAN26. In the present analysis, we focussed on the EORTC QLQ-C15-PAL questionnaire, consisting of a single item on overall QoL (global health status), two functional scales (physical and emotional function), two symptom scales (fatigue and pain) and five single items (nausea and vomiting, dyspnoea, sleeping difficulties, constipation and loss of appetite). TTD was implemented as a measure of longitudinal HRQoL and defined as the time from start of first-line treatment to the time of first clinically relevant deterioration. Deterioration was considered to be clinically relevant for a given dimension, if a decrease of ≥10 points from baseline (≥10% of the score range) was observed at any time point after baseline.[26,27] According to the Kaplan-Meier method, an event was defined as deterioration of ≥10 points or death; patients without such an event were censored at the time of completion of the last questionnaire. All patients who had completed the baseline and ≥1 further questionnaire were included in the TTD analysis (FOLFIRINOX: n = 272; GEMNAB: n = 288).

All analyses were calculated using SAS software, Version 9.4 of the SAS System for Windows. Copyright © 2002-2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, North Carolina.

3 | RESULTS

3.1 | The Pancreatic Cancer Score

As described in the methods section, the patient sample was randomly split up into learning sample (n = 1027) and validation sample (n = 513). Patients in the validation and learning sample did not substantially differ (Table S1). Eleven variables were identified as promising prognostic factors and thus dichotomised; a multivariate Cox regression model with the resulting binary variables was calculated (Table 1).

Employing a cut-off of $P < .05$, nine variables were identified as independent prognostic factors for survival (marked with an asterisk, Table 1): female sex (HR 1.26, 95% confidence interval [CI]: 1.08-1.47, $P = .003$), BMI ≥24/unknown (HR 1.22, 95% CI: 1.06-1.42, $P = .007$), ECOG ≥1 (HR 1.43, 95% CI: 1.23-1.67, $P < .001$), CCI ≥1 (HR 1.32, 95% CI: 1.13-1.55, $P < .001$), tumour staging IV/unknown at primary diagnosis (HR 1.50, 95% CI: 1.18-1.92, $P = .001$), presence of liver metastases (HR 1.23, 95% CI: 1.04-1.46, $P = .018$), bilirubin >1.5x ULN (HR 1.74, 95% CI: 1.38-2.19, $P < .001$), leukocytes >ULN (HR 1.39, 95% CI: 1. 18-1.64, $P < .001$) and NLR ≥4 (HR 1.57, 95% CI: 1.34-1.83, $P < .001$). Based on these prognostic factors, the PCS was developed, counting each risk factor as one unit. A score of 0-9 was calculated per patient and three risk groups for survival were identified employing a quartile split of the observed risk scores: 0-3 risk factors (favourable risk), 4-5 risk factors (intermediate risk) and 6-9 risk factors (poor risk) [Table S2, questionnaire for the clinical routine use]. About one third of patients were of favourable risk, approximately 50% of intermediate and nearly 20% of poor risk in both learning and validation sample (Table S3).

For each risk group, OS was calculated for the learning sample (Figure 2A). The validity of the PCS was subsequently tested in the validation sample (Figure 2B). Median OS in the validation sample was 11.4 months (95% CI: 10.4-14.4), 8.5 months (95% CI: 6.8-9.6) and 5.9 months (95% CI: 4.0-7.4) for patients with favourable, intermediate or poor risk, respectively. OS differences between favourable- vs intermediate- and favourable- vs poor-risk groups were statistically significant ($P = .009$ and $P < .001$, respectively, adjusted for multiplicity).

3.2 | Patient and tumour characteristics before and after IPTW

Looking at the original population before IPTW, patients with FOLFIRINOX (n = 407) differed from those receiving GEMNAB (n = 655) by several patient characteristics (Table 2). Patients

TABLE 1 Prognostic factors

	Hazard ratio	95% CI	*P*-value
Sex			
Female vs male	1.26	[1.08-1.47]	.003*
Body mass index (BMI)			
≥24/unknown vs <24	1.22	[1.06-1.42]	.007*
ECOG performance status			
≥1 vs 0	1.43	[1.23-1.67]	<.001*
Charlson comorbidity index (CCI)			
≥1 vs 0/unknown	1.32	[1.13-1.55]	<.001*
Localisation of tumour at primary diagnosis			
Pancreas body/tail/unknown vs pancreas head	1.05	[0.90-1.22]	.528
Tumour staging at primary diagnosis			
IV/unknown vs I-III	1.50	[1.18, 1.92]	.001*
Metastases			
Yes vs no/unknown	1.13	[0.89, 1.44]	.322
Liver metastases			
Yes vs no/unknown	1.23	[1.04-1.46]	.018*
Bilirubin			
>1.5× ULN vs ≤1.5× ULN/unknown	1.74	[1.38-2.19]	<.001*
Leukocytes above ULN			
Yes/unknown vs no	1.39	[1.18-1.64]	<.001*
Neutrophil-to-lymphocyte ratio			
≥4 vs <4/unknown	1.57	[1.34-1.83]	<.001*

Note: n = 1027, thereof 286 (27.8%) censored cases. Efron method was used to control for ties. Variables shown had been documented at patients' start of first-line treatment, unless otherwise indicated. The following covariates were not subjected to variable selection: sex, localisation of tumour, liver metastases, metastases, BMI and ECOG Performance Status. The following effects have been removed in backward selection: age at therapy start, any comorbidities, grading at primary diagnosis, haemoglobin below LLN, insurance type, resection status at primary diagnosis, thrombocytes above LLN.
*Significant results ($P < .05$).
Abbreviations: CI, confidence interval; LLN, lower limit of the norm; ULN, upper limit of the norm.

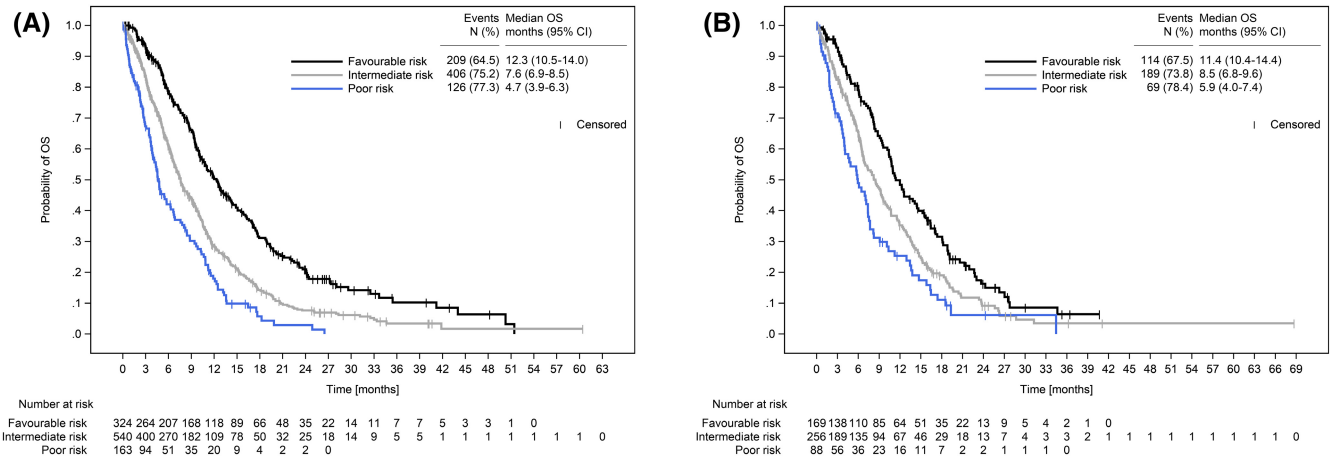

FIGURE 2 Overall survival of learning and validation sample. (A) OS of learning (n = 1027) and (B) validation sample (n = 513) by risk groups according to the PCS. CI, confidence interval; OS, overall survival; PCS, Pancreatic Cancer Score

receiving FOLFIRINOX were younger (median age of 61 vs 71 years; median age of the total cohort: 70 years), more often presented with ECOG 0 (46% vs 34%) and had less often comorbidities (78% vs 85%). After IPTW, the two treatment groups (n = 514.8 for FOLFIRINOX, n = 547.2 for GEMNAB; numbers refer to the sum of weights) were comparable for all characteristics (Table 2).

TABLE 2 Patient and tumour characteristics before and after IPTW

Characteristic at start of first-line treatment	Original cohort			PS-IPTW cohort		
	FOLFIRINOX n = 407	GEMNAB n = 655	SMD	FOLFIRINOX n[a] = 514.8	GEMNAB n[a] = 547.2	SMD
Age (y), mean (±SD)	61.3 (±8.13)	69.2 (±7.87)	−1.072	66.0 (±9.65)	66.2 (±8.63)	−0.028
Sex						
Female	40.5%	45.3%	−0.097	43.2%	44.5%	−0.026
Male	59.5%	54.7%	0.097	56.8%	55.5%	0.026
BMI						
Low (<24)	46.9%	44.7%	0.044	45.6%	46.0%	−0.008
Normal (24-29)	38.6%	36.5%	0.043	36.2%	37.6%	−0.030
High (>29)	14.3%	18.6%	−0.118	18.1%	16.3%	0.050
Missing	0.2%	0.2%	0.021	0.1%	0.1%	0.002
ECOG performance status						
ECOG 0	45.7%	33.7%	0.246	38.5%	38.8%	−0.006
ECOG 1	49.4%	54.8%	−0.109	49.2%	52.3%	−0.062
ECOG 2	4.7%	11.3%	−0.246	12.0%	8.6%	0.125
Any comorbidity						
Yes	77.6%	85.2%	−0.195	81.7%	80.8%	0.025
No	22.1%	14.8%	0.189	18.2%	19.2%	−0.027
Missing	0.2%	0.0%	0.070	0.1%	0.0%	0.028
CCI[b]						
0	76.9%	70.2%	0.152	74.3%	73.3%	0.022
1-2	15.5%	22.6%	−0.182	19.4%	20.3%	−0.024
≥3	7.4%	7.2%	0.008	6.3%	6.4%	−0.004
Missing	0.2%	0.0%	0.070	0.1%	0.0%	0.028
Health insurance						
Not private	88.0%	89.2%	−0.038	88.5%	88.9%	−0.012
Private	10.1%	8.9%	0.042	10.0%	9.4%	0.020
Unknown to site	2.0%	2.0%	−0.001	1.5%	1.7%	−0.014
Localisation of tumour						
Pancreas body	18.7%	23.4%	−0.115	22.2%	21.3%	0.020
Pancreas head	50.4%	49.8%	0.012	48.9%	49.9%	−0.020
Pancreas tail	25.6%	20.5%	0.121	23.2%	21.8%	0.033
Unknown to site	5.4%	6.4%	−0.043	5.7%	6.9%	−0.050
Tumour staging at diagnosis						
I/II	3.4%	4.6%	−0.058	3.6%	4.1%	−0.022
III	5.4%	4.9%	0.024	4.2%	5.2%	−0.046
IV	76.2%	74.4%	0.042	79.5%	74.7%	0.112
Unknown	15.0%	16.2%	−0.033	12.7%	16.1%	−0.093
Tumour grading at diagnosis						
G1	1.2%	1.7%	−0.038	0.9%	1.4%	−0.043
G2	18.2%	21.8%	−0.091	22.0%	20.2%	0.044
G3	20.6%	18.3%	0.059	19.4%	18.5%	0.022
G4	1.2%	1.8%	−0.049	1.7%	1.9%	−0.019
GX	55.5%	55.4%	0.002	54.4%	57.0%	−0.052
Missing	3.2%	0.9%	0.161	1.6%	0.9%	0.052
Resection status of primary tumour						
R0	2.7%	2.6%	0.007	3.1%	3.1%	0.003
R1	2.0%	1.2%	0.059	1.3%	1.4%	−0.006
R2	0.0%	0.3%	−0.078	0.0%	0.2%	−0.048
RX	0.7%	2.9%	−0.162	1.5%	2.1%	−0.041

(Continues)

TABLE 2 (Continued)

Characteristic at start of first-line treatment	Original cohort FOLFIRINOX n = 407	Original cohort GEMNAB n = 655	Original cohort SMD	PS-IPTW cohort FOLFIRINOX n[a] = 514.8	PS-IPTW cohort GEMNAB n[a] = 547.2	PS-IPTW cohort SMD
No resection	94.3%	93.0%	0.056	94.0%	93.3%	0.027
Missing	0.2%	0.0%	0.070	0.1%	0.0%	0.028
Liver metastases						
Yes	59.5%	58.3%	0.023	57.6%	57.2%	0.008
No	24.6%	28.7%	−0.094	28.0%	28.9%	−0.020
Missing	16.0%	13.0%	0.085	14.4%	13.9%	0.015
Lymphogenous metastases						
Yes	21.1%	19.4%	0.043	19.1%	19.8%	−0.016
No	62.9%	67.6%	−0.100	66.5%	66.4%	0.003
Missing	16.0%	13.0%	0.085	14.4%	13.9%	0.015
Metastatic sites						
0	1.7%	2.3%	−0.041	1.8%	1.9%	−0.009
1	17.7%	16.5%	0.032	19.1%	17.8%	0.035
2	37.3%	43.1%	−0.117	36.8%	40.8%	−0.080
≥3	27.3%	25.2%	0.047	27.9%	25.7%	0.050
Missing	16.0%	13.0%	0.085	14.4%	13.9%	0.015
Bilirubin						
≤1.5× ULN	80.8%	75.6%	0.128	76.6%	77.5%	−0.023
1.5-3× ULN	6.9%	7.3%	−0.017	9.2%	7.2%	0.079
>3× ULN	2.7%	4.7%	−0.107	4.5%	3.9%	0.033
Unknown/missing	9.6%	12.4%	−0.089	9.7%	11.4%	−0.055
Haemoglobin <LLN						
Yes	9.8%	9.0%	0.028	8.1%	8.7%	−0.022
No	86.7%	88.5%	−0.055	89.2%	87.9%	0.038
Missing/unknown	3.4%	2.4%	0.059	2.8%	3.4%	−0.036
Thrombocytes >LLN						
Yes	52.6%	54.8%	−0.045	51.5%	52.2%	−0.015
No	43.7%	42.6%	0.023	45.6%	44.3%	0.027
Missing/unknown	3.7%	2.6%	0.063	2.9%	3.5%	−0.033
Leukocytes >ULN						
Yes	22.6%	22.4%	0.004	21.1%	21.1%	−0.001
No	73.5%	75.4%	−0.045	76.0%	75.7%	0.006
Missing/unknown	3.9%	2.1%	0.105	3.0%	3.2%	−0.013
Neutrophil-to-lymphocyte ratio						
<4	47.4%	47.3%	0.002	46.7%	46.0%	0.013
≥4	39.3%	38.2%	0.023	40.3%	38.4%	0.039
Missing	13.3%	14.5%	−0.036	13.0%	15.6%	−0.074

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology Group; GEMNAB, gemcitabine plus nab-paclitaxel; LLN, lower limit of the norm; PS, propensity score; SMD, standardised mean difference; ULN, upper limit of the norm.

[a]For the IPTW cohort, n refers to sum of weights; in order to increase readability, we have refrained from presenting the patient numbers (n) for the given characteristics.

[b]Charlson comorbidity index (CCI) according to Quan et al.[46]

3.3 | Overall survival according to prognostic risk after IPTW

The Kaplan-Meier probability curves for OS after IPTW are shown in Figure 3A to D. IPTW-weighted median OS for favourable-risk patients was quite similar in both treatment groups (12.0 months [95% CI: 9.6-15.1] with FOLFIRINOX vs 10.5 months [95% CI: 9.5-12.6] with GEMNAB, Figure 3B), while in the poor-risk group, median OS with FOLFIRINOX was higher than that with GEMNAB (6.9 months [95% CI: 3.9-13.3] vs 4.0 months [95% CI: 2.8-4.8],

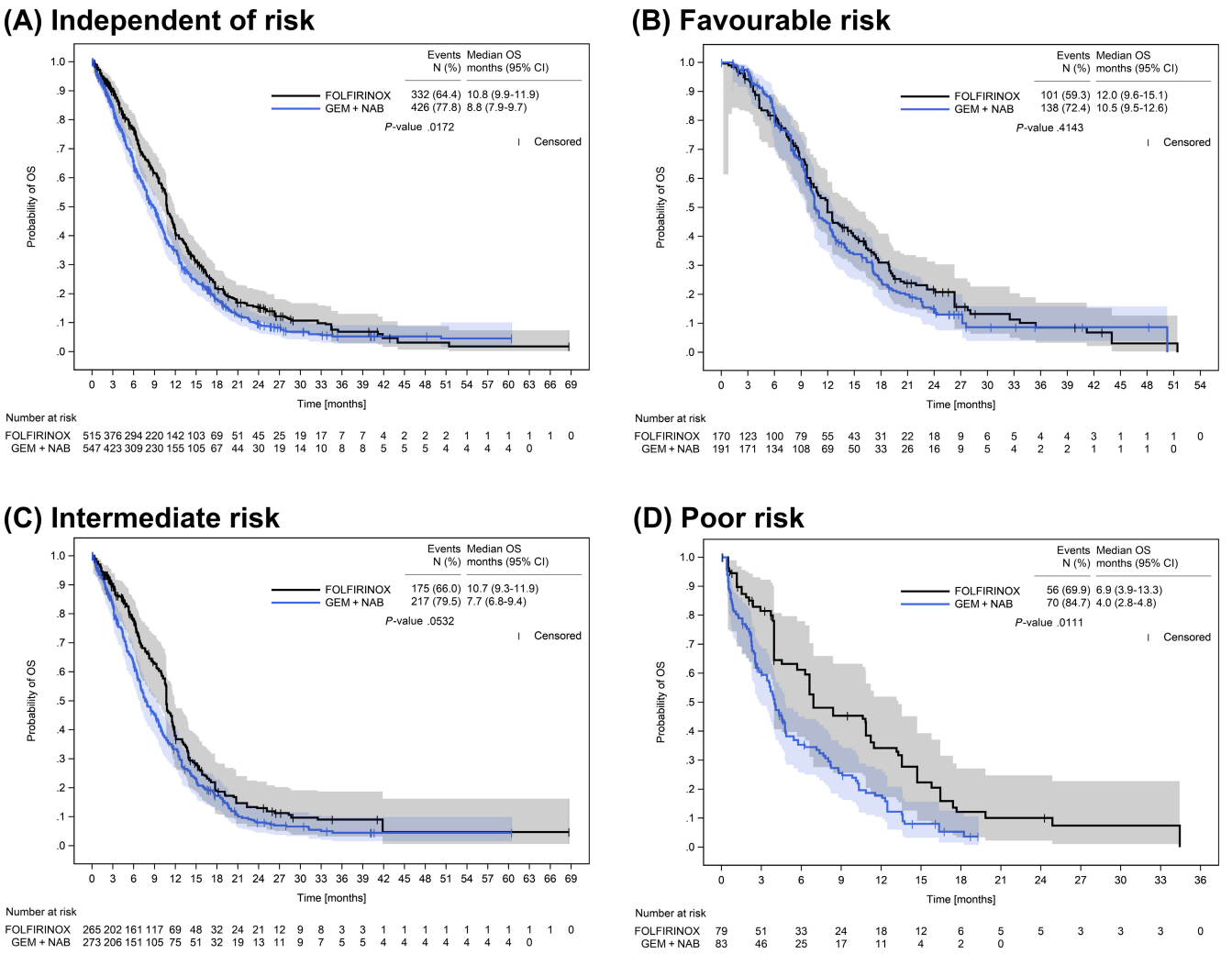

FIGURE 3 Overall survival after IPTW. OS after IPTW in patients receiving first-line treatment with either FOLFIRINOX or GEMNAB independent of prognostic risk (A), by favourable risk (B), intermediate risk (C) and poor risk (D) according to the PCS. Numbers at risk refer to the sum of weights of the respective patients at risk for a given time point. Due to rounding, the weights of the three risk groups do not exactly add up to the sum of weights calculated for the FOLFIRINOX- and the GEMNAB-IPTW cohorts, as shown in (A). *P*-values were calculated with the log-rank test. CI, confidence interval; GEMNAB, gemcitabine plus nab-paclitaxel; OS, overall survival; PCS, Pancreatic Cancer Score

Figure 3D). A trend for a better median OS in patients receiving FOLFIRINOX was already seen in the intermediate-risk group (Figure 3C).

3.4 | Quality of life

For HRQoL, the Kaplan-Meier probability curves for TTD after IPTW are shown in Figure 4A-D. While for patients with favourable risk, median TTD hardly differed by the type of treatment (7.1 months [95% CI: 4.0-8.7] with FOLFIRINOX vs 6.1 months [95% CI: 4.7-8.3] with GEMNAB, Figure 4B), for poor-risk patients, median TTD of overall QoL was more than twice as long with FOLFRINOX as with GEMNAB (10.6 months [95% CI: 2.0-14.1] vs 4.1 months [95% CI: 2.4-4.5], Figure 4D). A trend for a longer median TTD of overall QoL in patients receiving FOLFIRINOX was already seen in the intermediate-risk group (Figure 4C). For the functional scales of the EORTC QLQ-C15-PAL, there was a similar trend of longer median TTD in poor-risk patients receiving FOLFIRINOX (data not shown). Due to low numbers of events, no conclusions can be drawn for the remaining scales.

4 | DISCUSSION

In patients with advanced pancreatic cancer, FOLFIRINOX and GEMNAB are first-line standard of care, however, there are no phase III randomised trials comparing the efficacy of both regimens. To the best of our knowledge, this is the first comparative effectiveness analysis of FOLFIRINOX and GEMNAB in real-world patients with

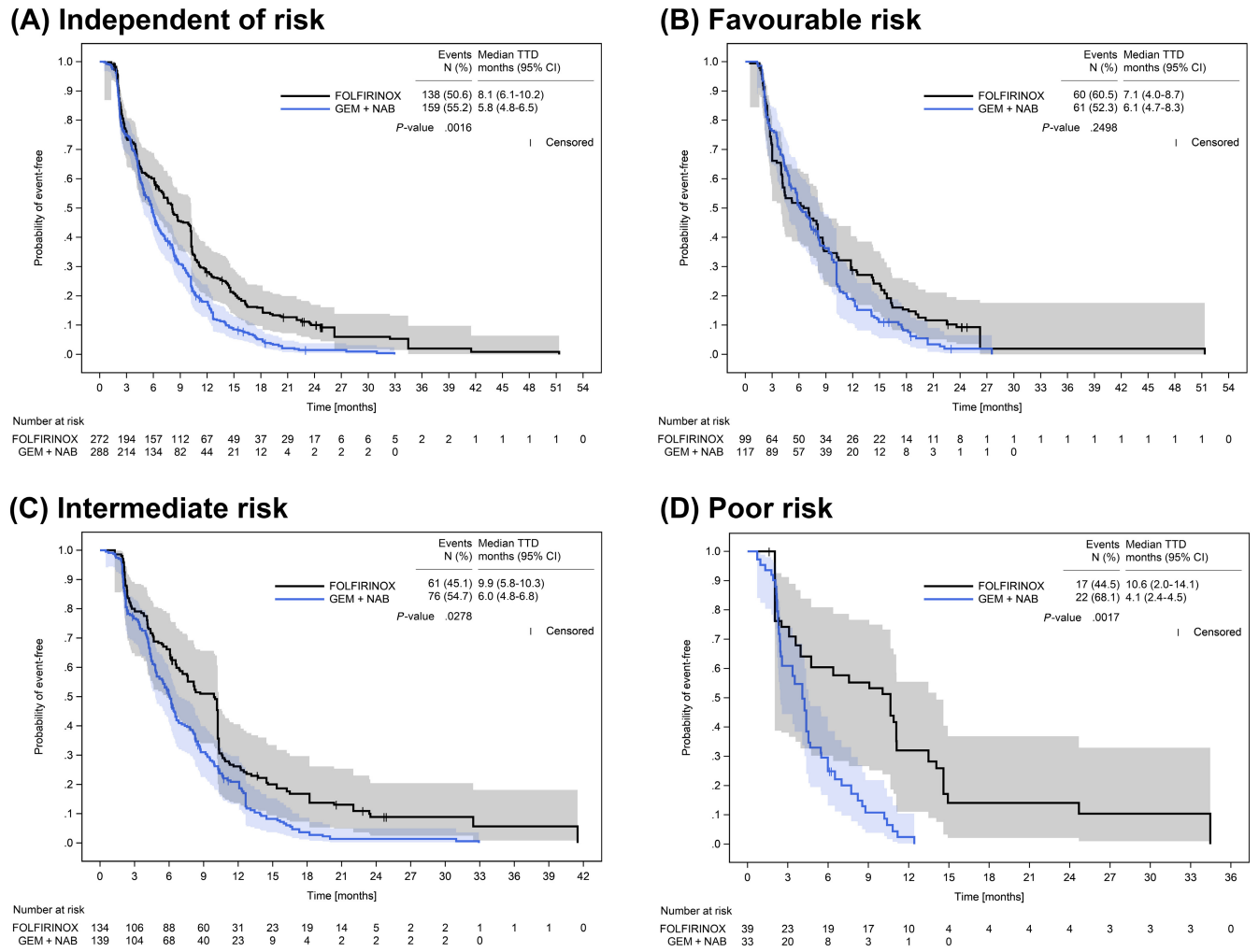

FIGURE 4 Time to deterioration of overall quality of life after IPTW. TTD of overall QoL (global health status) after IPTW in patients receiving first-line treatment with either FOLFIRINOX or GEMNAB independent of prognostic risk (A), by favourable risk (B), intermediate risk (C) and poor risk (D) according to the PCS. Numbers at risk refer to the sum of weights of the respective patients at risk for a given time point. Due to rounding, the weights of the three risk groups do not exactly add up to the sum of weights calculated for the FOLFIRINOX- and the GEMNAB-IPTW cohorts, as shown in (A). *P*-values were calculated with the log-rank test. CI, confidence interval; GEMNAB, gemcitabine plus nab-paclitaxel; PCS, Pancreatic Cancer Score; QoL, quality of life; TTD, time to deterioration

LAPC/MPC according to patients' prognostic risk, after adjustment for baseline imbalances between the two groups.

While several prognostic and predictive factors have been studied over the last decade, in clinical practice, there are neither clear factors, nor prospectively validated prognostic risk scores from large cohort studies that could help choosing the best treatment for the individual pancreatic cancer patient.[17,18] In a smaller retrospective study on 123 relatively nonselected patients with LAPC/MPC, a prognostic score combining BMI >25 and carcinoembryonic antigen (CEA) elevation was developed to identify patients with the highest benefit from aggressive chemotherapy.[17] Inclusion, however, was limited to patients receiving FOLFIRINOX. By combining nine independent prognostic features, which are routinely available prior to start of treatment and as long as whole genome sequencing of pancreatic cancer is not yet standard of care, our new PCS provides an easy-applicable and comprehensive tool that efficiently separates patients into three survival risk groups, regardless of the type of first-line treatment. All factors, that is, patient, tumour and clinical characteristics, have previously been published to be prognostically relevant in (advanced) pancreatic cancer: female sex,[28] BMI,[17] ECOG,[29,30] CCI,[31] tumour stage,[32,33] presence of liver metastases,[30,34] bilirubin level,[30] leukocyte/white blood cell count[35] and NLR.[29,36]

With 70 years in median, the age of our original patient population was representative of that of the average pancreatic cancer cohort, as most patients are a median of 71 years old at diagnosis.[1] In addition, the median age of patients receiving FOLFIRINOX (61 years) and GEMNAB (71 years), respectively, is in line with the age ranges reported for FOLFIRINOX (59-64 years)[11-13,17,37-39] and GEMNAB (68-71 years).[11-13,37-39] Patients receiving FOLFIRINOX more often presented with ECOG 0, whereas patients with GEMNAB were more likely to be ECOG 2, which agrees with other real-word data.[11,13,37] Hence, our results confirm the observation that patients receiving

FOLFIRINOX are rather younger and fitter.[1,14] This is crucial to withstand the toxicities associated with FOLFIRINOX[37] and corresponds to guideline recommendations,[6,9,10,40] but also fits to physicians' preferences in clinical routine.[13,19,41] To overcome these imbalances between treatment groups that could result in an overestimation of the effect for FOLFIRINOX, we used IPTW based on a PS approach. The PS method is a robust alternative for the analysis of nonrandomised intervention trials, with advantages over conventional regression modelling.[42]

Overall effectiveness of FOLFIRINOX and GEMNAB shown by our real-world data was largely comparable, with a slightly longer IPTW-weighted median OS observed for FOLFIRINOX (10.8 vs 8.8 months). Outcome results closely reflect those of the pivotal phase III PRODIGE 4 and MPACT trials reporting a median OS of 11.1 months for FOLFIRINOX[6] and 8.7 months for GEMNAB,[7,8] respectively, even though inclusion was limited to highly selected patients with MPC. Our findings also broadly agree with previous retrospective data: a systemic review of retrospective studies comparing first-line GEMNAB and FOLFIRINOX in MPC or LAPC revealed a slightly longer median OS for FOLFIRINOX (15.9 vs 14.4 months), but the differences, when available, were not statistically significant.[14] In most of these studies, however, differences in patient characteristics may also have confounded results. There are two comparative studies including patients with both LAPC and MPC which used a PS approach by IPTW as well[11,13]: with a IPTW-weighted median OS of 10.1 months for both treatment groups, effectiveness of FOLFIRINOX and GEMNAB was equal in a study on 455 patients (158 FOLFIRINOX, 297 GEMNAB) treated at three academic centres in Austria.[13] In a Canadian study including 1130 patients (632 FOLFIRINOX, 498 GEMNAB) from six cancer centres in British Columbia, crude median OS was 9.6 and 6.1 months for FOLFIRINOX and GEMNAB, respectively (HR 0.60; 95% CI: 0.53-0.69); after IPTW, OS was significantly improved for patients treated with FOLFIRINOX vs GEMNAB (HR 0.77; 95% CI: 0.70-0.85).[11]

As far as we know, this is the first comparative analysis evaluating effectiveness according to patients' prognostic risk. Poor-risk patients as defined by the PCS appear to benefit from aggressive first-line chemotherapy with FOLFIRINOX not only by significantly prolonged survival (median OS of 6.9 vs 4.0 months), but also by better overall HRQoL (median TTD of 10.6 vs 4.1 months). Of note, some phase II/III randomised trials are ongoing to compare the efficacy of modified FOLFIRINOX vs GEMNAB in advanced pancreatic cancer.[43,44] Although not considering patients' prognostic risk, the findings of these trials will be crucial to determine whether our real-world results can be confirmed. Although the safety of FOLFIRINOX was less favourable than gemcitabine in the phase III PRODIGE 4/ACCORD 11 trial, FOLFIRINOX reduced QoL impairment compared to gemcitabine.[45] Since survival can only be prolonged to a limited extent in advanced pancreatic cancer, main goals should focus on alleviation of tumour symptoms and stabilisation of QoL. The identification of patients who will benefit most from either treatment, together with patient's preferences should be the basis for treatment decisions, which may be supported by the PCS.

4.1 | Limitations

A limitation of this analysis is that only those variables were considered as potential prognostic factors which had been documented in the TPK. Furthermore, using weighted prognostic factors could have improved the precision of the PCS, but would have made the score less easy-to-use. Given that HRs did not greatly differ between prognostic factors, the approach of an unweighted score seems appropriate. A further limitation is that validation was performed on a second data set from the same data source and not on a truly independent, external data source. Thus, an additional external validation of our results would further strengthen the generalisability of the PCS. Since the number of poor-risk patients is relatively low, the interpretation of results might be hampered. However, these limitations should be weighed against the strengths of this work which include the prospective, longitudinal design and the analysis of data from a large real-world sample. Combining risk stratification and IPTW to account for imbalances between treatment groups is a major advantage of this work. The inclusion of patients with LAPC is another strength and adds further insights into the effectiveness of FOLFIRINOX and GEMNAB beyond MPC.

5 | CONCLUSIONS

We propose the new PCS combining nine independent prognostic factors, which are usually available prior to start of first-line treatment in patients with LAPC or MPC. The PCS can be of great help in predicting the prognosis of patients with advanced pancreatic cancer and in treatment decision-making. It represents an easy applicable, comprehensive tool, not only for routine clinical use, but possibly also for risk stratification in clinical trials. Assuming balanced treatment groups, our real-world data suggest no general advantage from first-line FOLFIRINOX over GEMNAB. Only poor-risk patients seem to benefit from FOLFIRINOX, whereas for patients with favourable risk, OS and overall QoL appear to be comparable in both treatment groups. Our data warrant further assessment of this newly defined risk scores in future randomised trials.

AUTHOR CONTRIBUTIONS

Norbert Marschner: Conceptualisation, funding acquisition, investigation, resources, supervision, writing—original draft. **Susanna Hegewisch-Becker:** Conceptualisation, investigation, resources, writing—review & editing. **Marcel Reiser:** Investigation, resources, writing—review & editing. **Eyck von der Heyde:** Investigation, resources, writing—review & editing. **Mathias Bertram:** Investigation, resources, writing—review & editing. **Stephan H. Hollerbach:** Investigation, resources, writing—review & editing. **Stephan Kreher:** Investigation, resources, writing—review & editing. **Thomas Wolf:** Investigation, resources, writing—review & editing. **Adrian Binninger:** Conceptualisation, data curation, methodology, project administration, visualisation, writing—original draft. **Marco Chiabudini:** Conceptualisation, data curation, formal analysis, methodology, validation, writing—original

draft. **Anja Kaiser-Osterhues:** Conceptualisation, methodology, visualisation, writing—original draft. **Martina Jänicke:** Conceptualisation, methodology, supervision, visualisation, writing—original draft. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST

Marcel Reiser, Eyck von der Heyde, Mathias Bertram, Stephan H. Hollerbach, Stephan Kreher, Thomas Wolf, Adrian Binninger, Marco Chiabudini, Anja Kaiser-Osterhues and Martina Jänicke declare no conflict of interest concerning the topic of this publication. Outside of the published work, the institutions of Susanna Hegewisch-Becker, Marcel Reiser, Eyck von der Heyde, Mathias Bertram, Stephan H. Hollerbach, Stephan Kreher and Thomas Wolf received remuneration for the documentation of patient data. Norbert Marschner reported receiving honoraria for talks and attendance of conferences from Celgene and Servier; he is Chief executive officer and shareholder of iOMEDICO AG. Susanna Hegewisch-Becker reported a consulting or advisory role for Servier.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The TPK/AMETHYST was approved by the responsible ethics committee and is registered at ClinicalTrials.gov (NCT02089269). Written informed consent was obtained from all patients.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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