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Impact of intensified chemotherapy in metastatic pancreatic ductal adenocarcinoma (PDAC) in clinical routine in Europe

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ABSTRACT

Background: Pancreatic ductal adenocarcinoma (PDAC) is associated with poor prognosis. Gemcitabine is the standard chemotherapy for patients with metastatic pancreatic adenocarcinoma (MPA). Randomized clinical trials evaluating intensified chemotherapies including FOLFIRINOX and nab-paclitaxel plus gemcitabine (NAB+GEM) have shown improvement in survival. Here, we have evaluated the efficacy of intensified chemotherapy versus gemcitabine monotherapy in real-life settings across Europe.

Methods: A retrospective multi-center study including 1056 MPA patients, between 2012 and 2015, from nine centers in UK, Germany, Italy, Hungary and the Swedish registry was performed. Follow-up was at least 12 months. Cox proportional Harzards regression was used for uni- and multivariable evaluation of prognostic factors.

Results: Of 1056 MPA patients, 1030 (98.7%) were assessable for survival analysis. Gemcitabine monotherapy was the most commonly used regimen (41.3%), compared to FOLFIRINOX (n = 204, 19.3%), NAB+GEM (n = 81, 7.7%) and other gemcitabine- or 5-FU-based regimens (n = 335, 31.7%). The median overall survival (OS) was: FOLFIRINOX 9.9 months (95%CI 8.4–12.6), NAB+GEM 7.9 months (95%CI 6.2–10.0), other combinations 8.5 months (95%CI 7.7–9.3) and gemcitabine monotherapy 4.9 months (95% CI 4.4–5.6). Compared to gemcitabine monotherapy, any combination of chemotherapeutics improved the survival with no significant difference between the intensified regimens. Multivariable analysis showed an association between treatment center, male gender, inoperability at diagnosis and performance status (ECOG 1–3) with poor prognosis.

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Conclusion: Gemcitabine monotherapy was predominantly used in 2012–2015. Intensified chemotherapy improved OS in comparison to gemcitabine monotherapy. In real-life settings, the OS rates of different treatment approaches are lower than shown in randomized phase III trials.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies. Most patients present at late clinical stages, either with metastatic or locally advanced disease. PDAC is the fourth leading cause of cancer related mortality, with a 5-year survival rate of 3–7% and a median survival of 6 months after diagnosis [1–3]. Since the incidence is rising and treatment options are limited, PDAC is projected to be the second leading cause of cancer-related death in the United States and Europe by 2030 [4,5]. Only 10–20% of patients qualify for curative surgery due to the extent of local invasion and presence of distant metastasis. Although ongoing trials are evaluating the efficacy of neoadjuvant systemic therapy in patients with locally advanced disease (e.g. CONKO 007 trial, EUDRACT Nr. 2009-014476-21; NEONAX-trial, EUDRACT-Nr. 2013-005559-34; NEOLAP-trial, NCT02125136), palliative chemotherapy is the mainstay of treatment for the majority of patients with advanced PDAC.

Until recently, the nucleoside analogue gemcitabine (GEM) has been the standard-of-care for unresectable PDAC with marginal impact on overall survival (OS) [6]. Despite numerous clinical trials in patients with metastatic pancreatic adenocarcinoma (MPA) [6–9], no significant improvement in patients outcome was made until 2011 [10]. Conroy et al., demonstrated that the gemcitabine-free FOLFIRINOX regimen (folinic acid, fluorouracil, irinotecan and oxaliplatin) showed a significant survival advantage for patients with MPA in a phase III trial, with a median OS of 11.1 months compared to 6.8 months ($P < 0.001$) in the control arm using GEM alone [11]. In 2013, the Metastatic Pancreatic Adenocarcinoma Trial phase III trial with nano-formulated albumin-bound paclitaxel (NAB) in combination with GEM also revealed a significant survival benefit compared to GEM monotherapy, with median OS of 8.5 months for the combination arm compared to 6.7 months for GEM monotherapy, $P < 0.001$)[12]. However, these intensified therapy regimens show a broad spectrum of side effects, and patients need to be carefully selected for the most appropriate protocol [13]. The survival improvements were in addition observed in tightly controlled clinical trial settings. Since circumstances in clinical trials do not reflect the real-life situation, and therapeutic outcomes may vary from study conditions; the efficacy of FOLFIRINOX, NAB+GEM versus GEM-monotherapy and other doublet combinations were investigated in a real-life setting across several European institutions.

Methods

The study cohort includes retrospectively identified patients with MPA receiving palliative chemotherapy from nine European hospitals in UK, Germany, Italy, Hungary and the Swedish quality registry for PDAC. Patients were included during a four-year period, between January 2012 and December 2015. Last follow-up was in December 2016 allowing a minimum follow-up of 12-months for each patient. Patients with histologically proven MPA (including patients who had undergone potentially curative surgery and later relapsed); receiving GEM alone, GEM doublet combinations, FOLFIRINOX, NAB+GEM or 5-FU based combinations, and who completed at least one cycle of chemotherapy were included. Data regarding; age at diagnosis, gender, staging/site of metastasis, first-line chemotherapy and time of death/survival were collected retrospectively from various sources including hospital files, cancer registries, quality registries and census data. Primary endpoint was OS rate at 12-months according to first-line chemotherapy received. Association between patient/tumor characteristics and major palliative chemotherapy regimens was assessed using the Chi-square test. OS was calculated from the date of initiation of first-line palliative chemotherapy to the date of death or last follow-up. Survival curves were drawn using the Kaplan-Meier method. Difference in survival between groups was assessed with the Log-rank test. Univariate and multivariable Cox Proportional Hazards regression was used to assess the association between patient/tumor characteristics and survival. These analyses included center, gender, age, surgery, palliative chemotherapy free interval and different chemotherapy regimens. Analyses were performed with SAS software version 9.3 (Cary, NC). All p-values were 2-sided. P-values <0.05 were considered statistically significant. The statistical analysis was conducted by personnel blinded to the source of the individual dataset. Institutional review board approval was obtained at all participating centers. The study was conducted in agreement with the declaration of Helsinki and guidelines for good scientific practice.

Results

Patient characteristics

We identified 1090 patients from nine individual clinical databases and the Swedish quality registry for PDAC (Fig. 1). After exclusion of patients with incomplete data, 1056 patients were included in the study (1030 in survival analysis). Table 1 summarizes patient demographics. In summary, 450 (42.6%) patients received GEM monotherapy, 81 (7.7%) NAB+GEM, 204 (19.3%) FOLFIRINOX and 321 (30.4%) received other regimens, including GEM or 5-fluoruracil-based combinations. The number of patients recruited from each center are shown in Fig. 1. The mean age was 65.5 ± 9.8 (±std. dev.) years and mean age of the sub-group receiving GEM-monotherapy was significantly higher than those treated with intensified regimens (mean ± std. dev: GEM 69.0 ± 9.4; NAB+GEM 63.9 ± 8.8; FOLFIRINOX 60.3 ± 8.3; $P < 0.0001$). The percentage of patients receiving intensified chemotherapy was highest in those with excellent performance status (ECOG 0; 35.0%) and lowest in those with poor performance status (ECOG 3; 3.8%) at the time of initiation of treatment ($P < 0.0001$). The interval from diagnosis of metastatic disease, to the start of chemotherapy was 3.8 ± 6.6 month (mean ± std. dev) for the entire cohort; however 49.1% received the first cycle of chemotherapy within 3 months. Overall 155 (14.7%) patients had undergone previous curative resection for PDAC and later developed systemic recurrence. Second-line treatment was offered to 42,1% of patients ($n = 446$).

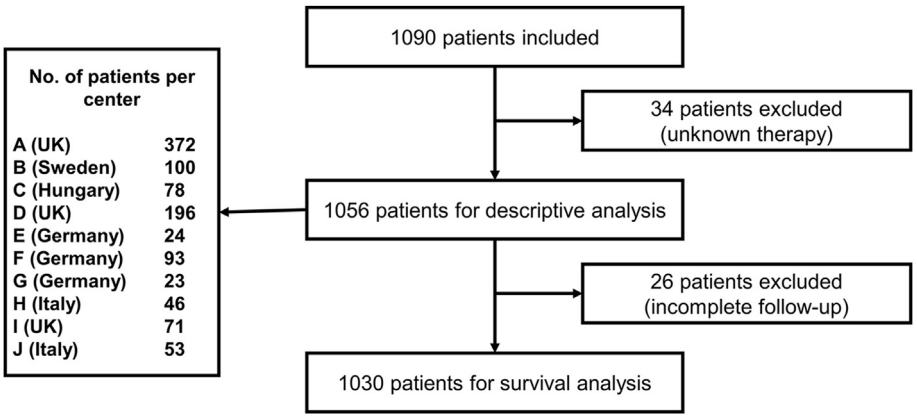


Fig. 1. Flow chart of patients included in the descriptive (N = 1056) and survival (N = 1030) analysis. 34 and 26 patients were excluded for unknown therapy and incomplete follow-up, respectively. The number of patients included by each center and country is depicted for 1056 patients.

Survival analysis

The median OS of the entire cohort (n = 1030) was 6.9 months (95% CI 6.4–7.7) with a 12-month survival rate of 24.5% (Fig. 2). Patients treated with GEM alone reached a median OS of 4.9 months (95% CI 4.3–5.5), NAB+GEM 7.9 months (CI 95% 6.2–10.0) and FOLFIRINOX 9.9 months (95% CI 8.4–12.6). Other combinations such as GEM + capecitabine or platinum-derivatives led to improved median OS varying between 7.7 and 9.3 months (Fig. 3). GEM-monotherapy was inferior to all other therapeutics, NAB+GEM, FOLFIRINOX and other chemotherapy doublets (Log-rank P < 0.0001) (Fig. 4).

Multivariable analysis

On multivariable analysis, previous surgery with curative intent was associated with prolonged survival (HR 0.72; 95% CI 0.58–0.89; P = 0.004), whereas male gender (HR 1.16; 95% CI 1.01–1.34; P = 0.04) and poor performance status (ECOG 1 to 3) were independently associated with shorter survival (Table 2). The treatment center also influenced outcome. When adjusted for age, gender, initial surgical resection, chemotherapy free interval, performance status (ECOG) and treatment center, a significant survival advantage was found for patients treated with NAB+GEM (HR 0.67; 95% CI 0.50–0.90; P = 0.007) and FOLFIRINOX (HR 0.57; 95% CI 0.45–0.74; P < 0.0001) compared to GEM-monotherapy (Table 2). Compared to GEM alone, the use of other combination chemotherapy regimens also led to a significant improvement of survival, when evaluated either as a single group or as individual doublet regimens (Fig. 4). In multivariable analysis; GEM+erlotinib, GEM+capecitabine, GEM+platinum-derivatives and 5-FU-based combinations resulted in HRs similar to those of FOLFIRINOX and NAB+GEM. However, no statistically significant differences for survival times and prognostic factors were identified between any of these GEM-based doublet combinations (Table 2).

Discussion

This is a large multicenter study reporting on the outcome of patients treated for metastatic pancreatic cancer under “real-life” conditions. Data of 1056 patients diagnosed with MPA in six European countries between 2012 and 2015 were retrospectively analyzed and revealed a significant survival benefit for those treated with the combination of NAB+GEM or FOLFIRNOX when compared to GEM. Treatment with other GEM and 5-FU-based combinations were also associated with improved survival compared to GEM alone. Male gender, initial inoperability and an impaired performance status at the time of initiation of treatment were associated with adverse outcome independent of treatment chosen. For the duration of the study, GEM alone was the most commonly administered therapy, followed by the non-homogenous group of a variety of combination therapies. NAB+GEM was only used in 7.7% of the patients, which could be because this treatment option is the latest to be introduced, and that nab-paclitaxel has not gained approval for this indication in all countries at the same time. FOLFIRINOX was most frequently given to patients with excellent or good performance status.

With the exception of the one hundred patients included from the Swedish quality registry for pancreatic cancer, all patients were treated at large academic institutions. This constitutes for selection bias as it has been shown, that high volume centers often choose more aggressive treatments and offer treatment to patients with impaired performance status [15,16], which could be associated with improved survival [17]. Even though these were non-trial patients, the results of this study might overestimate the survival benefits of the investigated drug regimens as it is likely that a more conservative application of drugs occurs on a population based level. The Swedish quality registry is open to any institution medically treating pancreatic cancers, but coverage is still low in terms of systemic treatments reported, with mostly academic institutions contributing.

The given median OS of 6.9 months of all patients is better than for the metastasized subgroup in population based studies from the pre-FOLFIRINOX era [10,18] and when compared to a more recent interim analysis of 2217 patients from the Danish pancreatic cancer database [19], all of which include patients that were not fit for chemotherapy and only received best supportive care. Registry or population-based survival data from patients undergoing active palliative treatment for MPA outside of trials are quite limited. Two single-center studies included patients with palliative treatment in metastatic or locally advanced disease [20,21]. After the introduction of intensified chemotherapy both studies presented a marked improvement of survival outcome, however, in small and heterogenous patient cohorts.

The median OS of 4.9 months (95% CI 4.3–5.5) for patients treated with GEM in our cohort was shorter than the 5.6 months in the original phase III trial that led to its approval [6] and both trials that showed superiority of FOLFIRINOX and NAB+GEM with 6.8 months (95% CI 5.5 to 7.6) and 6.7 months (95% CI 6.01–7.23) respectively [11,12]. This can be explained by the fact, that the study

Table 1
Baseline characteristics of all patients included in the descriptive analysis.

All patients	Total	GEM	NAB+GEM	FOLFIRINOX	Other	P-value
	1056	450 (42.6)	81 (7.7)	204 (19.3)	321 (30.4)	
Center						**<0.0001**
A (United Kingdom)	372	187 (50.3)	30 (8.1)	52 (14.0)	103 (27.7)	
B (Sweden)	100	59 (59.0)	6 (6.0)	5 (5.0)	30 (30.0)	
C (Hungary)	78	28 (35.9)	–	15 (19.2)	35 (44.9)	
D (United Kingdom)	196	100 (51.0)	25 (12.8)	13 (6.6)	58 (29.6)	
E (Germany)	24	3 (12.5)	1 (4.2)	7 (29.2)	13 (54.2)	
F (Germany)	93	10 (10.8)	3 (3.2)	48 (51.6)	32 (34.4)	
G (Germany)	23	–	2 (8.7)	13 (56.5)	8 (34.8)	
H (Italy)	46	10 (21.7)	–	19 (41.3)	17 (37.0)	
I (United Kingdom)	71	31 (43.7)	5 (7.0)	31 (43.7)	4 (5.6)	
J (Italy)	53	22 (41.5)	9 (17.0)	1 (1.9)	21 (39.6)	
Gender						**0.02**
Female	500	236 (47.2)	36 (7.2)	84 (16.8)	144 (28.8)	
Male	556	214 (38.5)	45 (8.1)	120 (21.6)	177 (31.8)	
Age						**<0.0001**
Mean ± Std Dev	65.5 ± 9.8	69.0 ± 9.4	63.9 ± 8.8	60.0 ± 8.3	64.5 ± 9.5	
<50	67	13 (19.4)	5 (7.5)	26 (38.8)	23 (34.3)	
50–59	214	63 (29.4)	20 (9.3)	58 (27.1)	73 (34.1)	
60–69	371	125 (33.7)	30 (8.1)	98 (26.4)	118 (31.8)	
70+	391	245 (62.7)	23 (5.9)	19 (4.9)	104 (26.6)	
Unknown	13	4 (30.8)	3 (23.1)	3 (23.1)	3 (23.1)	
Curative surgery						**0.008**
No	800	345 (43.1)	60 (7.5)	166 (20.8)	229 (28.6)	
Yes	155	45 (29.0)	15 (9.7)	33 (21.3)	62 (40.0)	
Unknown	101	60 (59.4)	6 (5.9)	5 (5.0)	30 (29.7)	
Palliative CTx free interval (months)[a]						**0.001**
Mean ± Std Dev	3.8 ± 6.6	3.3 ± 5.5	4.7 ± 6.5	3.8 ± 5.9	4.6 ± 8.2	
<3 months	519	250 (48.2)	32 (6.2)	86 (16.6)	151 (29.1)	
3–6 months	95	56 (58.9)	5 (5.3)	9 (9.5)	25 (26.3)	
≥6 months	86	24 (27.9)	9 (10.5)	14 (16.3)	39 (45.3)	
Unknown	356	120 (33.7)	35 (9.8)	95 (26.7)	106 (29.8)	
Performance status						**<0.0001**
ECOG - 0	203	45 (22.2)	8 (3.9)	71 (35.0)	79 (38.9)	
ECOG - 1	445	170 (38.2)	47 (10.6)	98 (22.0)	130 (29.2)	
ECOG - 2	158	117 (74.1)	10 (6.3)	6 (3.8)	25 (15.8)	
ECOG - 3	26	18 (69.2)	–	1 (3.8)	7 (26.9)	
Unknown	224	100 (44.6)	16 (7.1)	28 (12.5)	80 (35.7)	
Palliative CTx regimes						
GEM	436	436 (100)				
NAB	14	14 (100)				
GEM + NAB	81		81 (100)			
FOLFIRINOX	191			204 (100)		
GEM + Erl	44				44 (100)	
GEM + Cap	70				79 (100)	
GEM + Other	101				101 (100)	
GEM + Oxa	33				33 (100)	
5-FU + Other	56				44 (100)	
Other regimen	30				30 (100)	

Abbreviations Table 1: CTx, chemotherapy; Gemcitabine, GEM; nab-paclitaxel, NAB; Erlotinib, Erl; Capecitabine, Cap; GEM + Oth, Other (includes any of cisplatin, epirubicin, fluorouracil, carboplatin); Oxaliplatin, Oxa; 5-FU + Other (5-fluorouracil + any of epirubicin, etoposid, ifosfamid, irinitecan, mitomycin C, oxaliplatin); Other regimen (any of capecitabine, cisplatin, epirubicin, etoposid, carboplatin, oxaliplatin, erlotinib).

[a] Interval between date of imaging and date of initiation of palliative CTX.

by Burris et al. [7] also included patients with locally advanced disease without metastasis and that the studies by Conroy et al. [11] and by von Hoff et al. [12] randomized patients with mostly good to excellent performance status (ECOG 0 and 1). In contrast, we found that at least 30% of patients receiving GEM had an ECOG of 2 or less. As shown by others [22–26] and confirmed in the present cohort, excellent performance status is of independent prognostic value, regardless of the choice of chemotherapy. The median OS for FOLFIRINOX and NAB+GEM were also shorter when compared to the original randomized trials, 9.9 months (95% CI 8.4–12.6) vs. 11.1 months (95% CI 9.0–13.1) and 7.9 months (95% CI 6.2–10.0) vs. 8.5 months (95% CI 7.89–9.53), respectively. The attenuated effect could be explained by non-trial conditions with a tendency towards faster de-escalation of treatment [27], dose reductions and co-morbidities, which might have made the patient not-eligible for trial participation. The true effect of dose reduction and protocol modifications on the efficacy for any of the combinations is not well studied. In addition, further variables may impact the outcome data including supportive treatment such as G-CSF (Granulocyte-Colony Stimulating Factor), nutritional support and physical exercise. Despite the slightly decreased OS rates under conditions mimicking clinical routine, both of the recently introduced intensified chemotherapy options led to a clinically and statistically significant improvement. This is the first study to confirm the favorable outcome of patients treated with first line FOLFIRINOX or NAB+GEM for MPA on a larger scale outside of clinical trials. This is important since the “signal to noise ratio” outside tightly controlled trial boundaries is often decreased and small theoretical treatment effects might not be seen when a novel therapeutic tool is introduced into clinical practice. As data on adverse events was poor, it

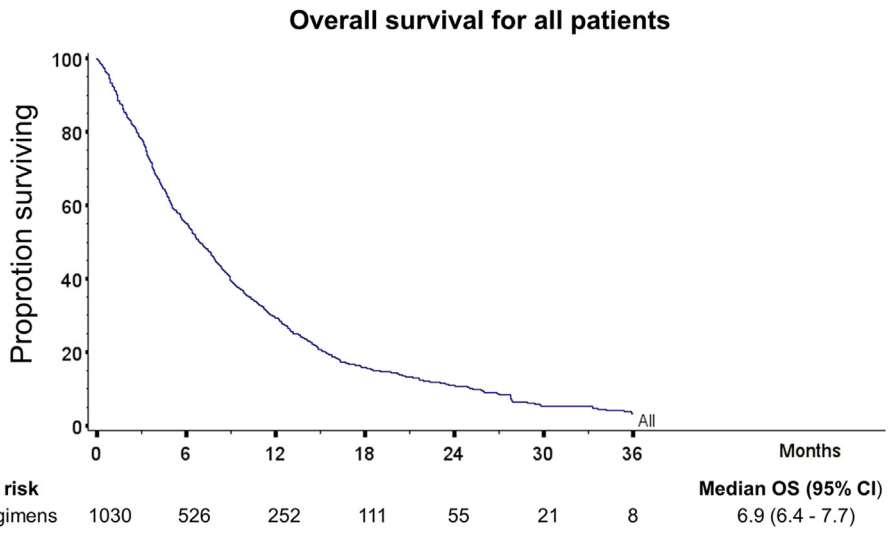
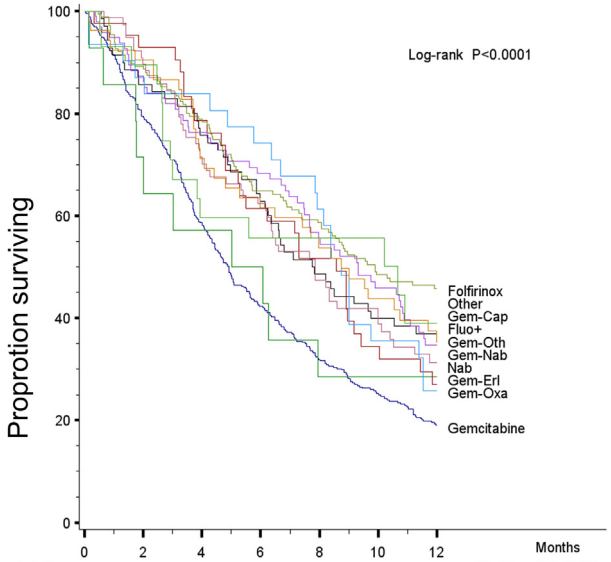


Fig. 2. Kaplan-Meier curves for overall survival (OS) of the entire cohort (N = 1030). Median OS is 6.9 months (95% CI 6.4–7.7).



Patients at risk								Median OS (95% CI)
GEM	429	334	242	170	125	98	72	4.9 (4.3- 5.5)
NAB	14	10	8	7	4	4	3	5.6 (1.7-12.9)
GEM + Erl	43	39	33	25	21	14	11	8.6 (5.2- 9.4)
GEM + Cap	70	60	53	44	34	27	25	7.8 (6.1-10.5)
GEM + Oth	100	81	67	60	48	37	28	9.3 (7.5-10.9)
FOLFIRINOX	195	169	148	115	104	83	71	9.9 (8.4-12.6)
GEM + Oxa	31	27	26	23	19	11	8	8.7 (6.7-11.4)
GEM + Nab	78	39	55	47	34	26	18	7.9 (6.2-10.0)
5-FU + Oth	41	35	27	23	18	14	10	7.7 (4.4-11.7)
Other regimen	30	25	16	13	11	10	7	10.7 (3.0-14.4)

Fig. 3. Kaplan-Meier curves for overall survival (OS) stratified by different chemotherapies applied. Median OS and 95% CI is presented for each treatment. The minimum observation time per protocol was 12 months.
Gemcitabine, GEM; nab-paclitaxel, NAB; Erlotinib, Erl; Capecitabine, Cap; GEM + Oth, Other (includes any of cisplatin, epirubicin, fluorouracil, carboplatin); Oxaliplatin, Oxa; 5-FU + Other (5-fluorouracil + any of epirubicin, etoposid, ifosfamid, irinitecan, mitomycin C, oxaliplatin); Other regimens (any of capecitabine, cisplatin, epirubicin, etoposid, carboplatin, oxaliplatin, erlotinib).

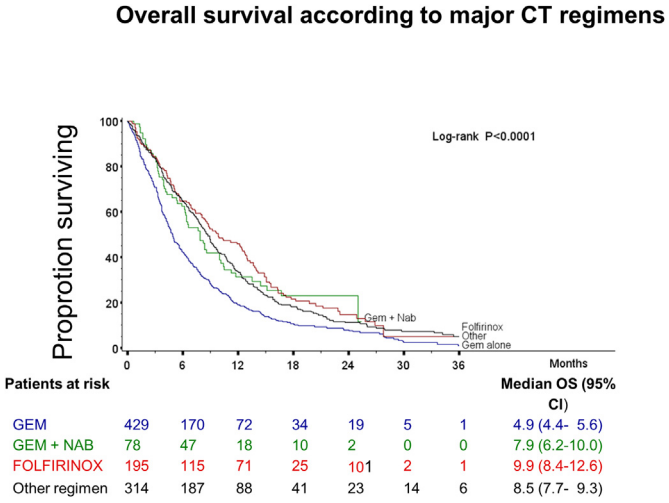


Fig. 4. The approved treatments gemcitabine (GEM), nab-paclitaxel + gemcitabine (NAB+GEM), FOLFIRINOX and other (any other therapy) are presented using Kaplan-Meier curves. Log-rank test was used to discriminate GEM-monotherapy to each of the other therapies revealing inferiority compared to the other therapies. Hazards ratio (HR) and 95% confidence intervals (CI) were obtained from multivariable Cox proportional hazards regression model adjusted for age, sex, curative treatment, palliative chemotherapy (CTx) free interval, performance status (ECOG), and centre.

could not be analyzed as part of this study, thus safety profiles were not evaluated.

Interestingly, we found many of the less aggressive 5-FU or GEM based combinations to be similarly effective in prolonging survival when compared with GEM-monotherapy. Although the heterogeneity and small size of individual treatment cohorts did not allow further analysis, this real-life finding to some extent verifies the findings of recent meta-analyses comparing randomized trials in advanced and metastatic pancreatic cancer, which found survival advantages for GEM based combinations (platinum and capecitabine) [28,29]. In accordance with our study, a systematic review and network meta-analysis by Gresham et al. including 23 randomized studies found no significant difference in terms of OS between FOLFIRINOX or NAB+GEM and other GEM based combinations when compared with GEM monotherapy [29]. In 2007, Moore and colleagues published a phase III study using erlotinib, a small-molecule human EGFR-tyrosine-kinase-inhibitor, together with GEM in a large Canadian cohort of locally advanced or metastatic pancreatic cancer patients, which resulted in a significant, but small improvement of median survival from 5.9 months to 6.4

Table 2
Univariate and multivariable analysis of predictors of overall survival (in 1030 patients with survival data).

Description	Univariate HR (95% CI)		Multivariable HR (95% CI)*	P-value
Center				
A (United Kingdom)	1.00		1.00	
B (Sweden)	**1.45 (1.14–1.84)**	**0.003**	0.37 (0.05–2.83)	0.34
C (Hungary)	0.87 (0.58–1.30)	0.49	1.20 (0.77–1.87)	0.42
D (United Kingdom)	**1.61 (1.33–1.93)**	**<0.0001**	**2.58 (1.74–3.83)**	**<0.0001**
E (Germany)	1.20 (0.79–1.84)	0.40	**1.80 (1.11–2.89)**	**0.02**
F (Germany)	1.05 (0.83–1.34)	0.67	**2.30 (1.48–3.59)**	**0.0002**
G (Germany)	1.10 (0.68–1.78)	0.69	**2.38 (1.33–4.24)**	**0.004**
H (Italy)	**1.77 (1.28–2.46)**	**0.0006**	**3.36 (1.84–6.12)**	**0.0001**
I (United Kingdom)	1.04 (0.79–1.38)	0.76	1.21 (0.91–1.63)	0.20
J (Italy)	0.85 (0.61–1.17)	0.31	1.33 (0.75–2.37)	0.34
Gender				
Female	1.00		1.00	
Male	1.04 (0.91–1.19)	0.60	**1.16 (1.01–1.34)**	**0.03**
Age				
<60	1.00		1.00	
60–69	0.91 (0.77–1.08)	0.29	0.93 (0.78–1.12)	0.45
70+	1.07 (0.91–1.27)	0.40	0.89 (0.74–1.07)	0.22
Unknown	**3.43 (1.10–10.7)**	**0.03**	2.62 (0.82–8.59)	0.11
Curative surgery				
No	1.00		1.00	
Yes	**0.66 (0.54–0.80)**	**<.0001**	**0.72 (0.58–0.89)**	**0.003**
Unknown	1.19 (0.96–1.49)	0.12	5.17 (0.72–37.3)	0.10
Palliative CTX free interval				
(per year)	**0.82 (0.68–0.99)**	**0.04**	0.95 (0.78–1.14)	0.57
Unknown	1.07 (0.92–1.24)	0.38	**0.68 (0.48–0.97)**	**0.03**
Performance status				
ECOG - 0	1.00		1.00	
ECOG - 1	**1.34 (1.10–1.63)**	**0.004**	**1.34 (1.07–1.68)**	**0.01**
ECOG - 2	**1.56 (1.23–1.99)**	**0.0003**	**1.31 (0.99–1.73)**	**0.06**
ECOG - 3	**1.84 (1.15–2.95)**	**0.01**	**2.01 (1.22–3.31)**	**0.006**
Unknown	**1.40 (1.12–1.75)**	**0.003**	0.97 (0.59–1.58)	0.89
Palliative CTx				
GEM	1.00		1.00	
NAB	0.90 (0.50–1.65)	0.74	1.19 (0.64–2.20)	0.58
GEM + Cap	**0.68 (0.53–0.90)**	**0.005**	**0.59 (0.44–0.78)**	**0.0003**
GEM + Erl	**0.67 (0.48–0.94)**	**0.02**	**0.56 (0.37–0.85)**	**0.006**
GEM + Other	**0.68 (0.53–0.87)**	**0.002**	**0.78 (0.60–1.01)**	**0.06**
GEM + NAB	**0.64 (0.48–0.85)**	**0.002**	**0.67 (0.50–0.90)**	**0.007**
GEM + Oxa	**0.68 (0.47–0.98)**	**0.04**	**0.55 (0.36–0.85)**	**0.007**
FOLFIRINOX	**0.58 (0.48–0.70)**	**<.0001**	**0.57 (0.45–0.74)**	**<0.0001**
5-FU + Other	**0.66 (0.46–0.94)**	**0.02**	**0.62 (0.50–01.07)**	**0.10**
Other regimen	**0.59 (0.37–0.92)**	**0.02**	**0.63 (0.39–1.00)**	**0.05**

Abbreviations Table 2: CTx, chemotherapy; Gemcitabine, GEM; nab-paclitaxel, NAB; Erlotinib, Erl; Capecitabine, Cap; GEM + Oth, Other (includes any of cisplatin, epirubicin, fluorouracil, carboplatin); Oxaliplatin, Oxa; 5-FU + Other (5-fluorouracil + any of epirubicin, etoposid, ifosfamid, irinitecan, mitomycin C, oxaliplatin); Other regimens (any of capecitabine, cisplatin, epirubicin, etoposid, carboplatin, oxaliplatin, erlotinib).

months [30]. In our cohort, 44 patients were treated with GEM+erlotinib as first-line chemotherapy and multivariable analysis showed a robust survival advantage over GEM alone with a HR of 0.57 (95% CI 0.37–0.86), which exceeded the effect of FOLFIRINOX, although confidence intervals overlapped. However, the low number of patients treated with GEM+erlotinib suggest a decreasing priority since 2011 and might represent a bias in selecting patients with rash and continued combination therapy compared to patients with no rash and treatment discontinuation. The effectiveness of GEM+capecitabine with a HR 0.58 (95% CI 0.43–0.77) in the palliative setting in this study is of particular interest considering the recently published results from the ESPAC-4 trial, which showed significantly improved OS survival HR 0.79 (0.66–0.96, P = 0.016), but no relapse-free survival benefit for patients treated with GEM+capecitabine compared to GEM-monotherapy in the adjuvant setting [31]. Based on our results, the time interval between initial imaging and start of palliative treatment did not significantly influence survival, a finding consistent with previously published data [32]. A long time interval to initiation of chemotherapy may reflect difficulties in confirmation of diagnosis of metastatic or recurrent disease. This is particularly relevant in cases of peritoneal carcinomatosis, prior supportive therapies, treatment of infectious complications, logistical issues such as waiting lists in the respective participating centers or shortage of treatment slots, which may account for the delays in treatment.

The main limitation of this study is its retrospective and non-controlled design. Due to the lack of comprehensive national or international prospective cancer databases in Europe [14], the use of a retrospective approach was inevitable. This accounts for a number of biases that, to some extent are reflected in this data. Local guidelines, financial implications and availability of certain drugs limit the choices of treatment options. In Italy and Sweden, nab-paclitaxel was approved for MPA only towards the very end of the study period and it is still not routinely available in Hungary. Furthermore, data on dose intensity, dose reductions, treatment discontinuation and average number of cycles per regimen were not completely available and thus not presented. Since our focus was to assess the distribution of first-line regimens we have not looked into second-line options. In part, the heterogeneity of our cohort is also based on the inclusion of patients with prior pancreatic resection and adjuvant treatment. Although this is a

minority, their outcome was significantly better compared to the synchronous metastatic group. The distribution of the chemotherapeutic choice, however, was not influenced in this situation as seen in Table 1. Additionally, the quality of patient records available for analysis varied greatly due to the way patients were managed at different sites and how clinical information was stored. This accounts for the missing data such as previous surgery, imaging dates and side effects. Although this information is not directly linked to chemotherapy, it is important in the understanding of their oncological course. This observation also highlights the need for better documentation in patient records.

On the other hand, we also observed a significant diversity with regards to the use of first-line treatments. A number of centers were using non-conventional chemotherapy combinations, which made statistical analysis challenging due to the number and size of subgroups.

We conclude that the use of novel intensified combination chemotherapy for metastatic pancreatic cancer in clinical routine is variable in Europe. Compared to GEM-monotherapy, intensified treatments such as GEM+NAB and FOLFIRINOX were associated with improved survival, validating the results of randomized trials in a 'real life', multi-center setting. Interestingly, other GEM- and 5-FU-based doublets improved the OS of MPA patients, too. No significant differences amongst intensified therapeutic regimens and doublet combinations were identified within our cohort.

List of where and when the study has been presented in part elsewhere

1. Abstract selected for publication (e15774) at the 2017 annual ASCO meeting, Chicago, June 2017
2. Abstract selected for oral presentation at the 49th annual meeting of the European Pancreatic Club, Budapest, July 2017

Disclaimers

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Author contributions

MAJ, GB, SK study design and coordination, patient recruitment, data analysis and interpretation, manuscript preparation; NL, AV, HW, DP, RDM, AL, RAH, JWV, SA, SC, YTM, LA, GC, MS, MSc patient recruitment; PM statistical analysis; AN, MS manuscript editing and advice. All authors have read and approved the final version of this manuscript.

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