

Geographic variation in systemic treatment of metastatic pancreatic adenocarcinoma patients in routine clinical practise across Europe

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INTRODUCTION

Pancreatic cancer (PAC) is one of the few cancers with increasing mortality and incidence in both males and females in the EU,¹ and is predicted to become the second leading cause of cancer death by 2018.²
While FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) and gemcitabine-based treatments are considered the regimens of choice for most physicians,³ published data on treatment choices in PAC and real-world outcomes outside clinical trials are scarce, particularly across geographical locations.
This pan-European project aimed to generate data on diagnosis, treatment patterns and outcomes from records of patients who completed first-line metastatic (mPAC) treatment across Europe, focusing on France, Germany, Italy, Spain, and the UK.
In the present analysis, we report data on first-line and second-line mPAC treatment choices, and their geographical variation across the surveyed European countries.

METHODS

Study design

- In this observational chart review, physicians completed a retrospective electronic patient record from initial diagnosis onwards for patients with the following inclusion criteria:
 - ≥ 18 years of age.
 - mPAC diagnosis.
 - Completed first-line treatment for mPAC between 07/2014 and 01/2016 (irrespective of whether patients were currently alive or dead or whether they were receiving active treatment or not).
- Patient numbers per physician were restricted to ensure balanced representation.
- Physicians were encouraged to focus on those receiving treatment in the second line or beyond.
- Data were collected in France, Germany, Italy, Spain, the UK, the Netherlands, Denmark, Norway and Sweden.
- In each country, respondents were recruited across different regions and settings (university and general hospitals, cancer and reference centres, office-based specialists) to ensure a balanced selection.
- Data collected in the patient record included:
 - Initial diagnosis and mPAC diagnosis date, baseline patient and disease characteristics, and symptoms present at diagnosis.
 - All prior therapies received (including resection and radiotherapy) and treatment outcome.
 - All prior chemotherapy doses, dose modifications/discontinuation and associated reasons.
- Data are descriptive and have not been weighted or adjusted.

RESULTS

Patient Characteristics

- A total of 2,565 online patient records were completed by 225 physicians across 9 countries (n=500-504 per country for France, Germany, Italy, Spain and UK).
- All patients had completed first-line mPAC treatment. 208 were waiting to start and 1,666 had started or completed second-line treatment (73.1%).
 - In Italy, 66.0% patients received 2nd-line treatment and the 68.5% were treated in the second line in the UK.
- At diagnosis of metastatic disease, median age was 64 years and the majority of patients were male (Table 1).
 - Median CA19-9 values were lowest at diagnosis in Italy.
 - Median bilirubin was highest in the UK.

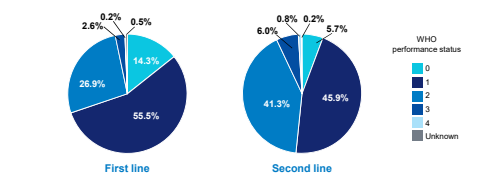
Table 1. Geographic variation of baseline characteristics at diagnosis

	Total (N=2,565)	France (n=504)	Germany (n=504)	Italy (n=500)	Spain (n=504)	UK (n=504)
Age						
≤65 years old, n (%)	1309 (51.0)	214 (42.5)	227 (45.0)	254 (50.8)	297 (58.9)	287 (56.9)
>65 years old, n (%)	1256 (49.0)	290 (57.5)	277 (55.0)	246 (49.2)	207 (41.1)	217 (43.1)
Gender						
Male, n (%)	1479 (57.7)	303 (60.1)	293 (58.1)	278 (55.6)	281 (55.8)	295 (58.5)
Female, n (%)	1086 (42.3)	201 (39.9)	211 (41.9)	222 (44.4)	223 (44.2)	209 (41.5)
Primary Tumour Location						
Head, n (%)	1030 (40.2)	196 (38.9)	212 (42.1)	200 (40.0)	195 (38.7)	207 (41.1)
Body, n (%)	594 (23.2)	114 (22.6)	119 (23.6)	98 (19.6)	115 (22.8)	142 (28.2)
Tail, n (%)	259 (10.1)	55 (10.9)	46 (9.1)	37 (7.4)	67 (13.3)	51 (10.1)
Head/body, n (%)	417 (16.3)	88 (17.5)	75 (14.9)	79 (15.8)	90 (17.9)	71 (14.1)
Body/tail, n (%)	246 (9.6)	46 (9.1)	51 (10.1)	83 (16.6)	35 (6.9)	26 (5.2)
Unknown, n (%)	19 (0.7)	5 (1.0)	1 (0.2)	3 (0.6)	2 (0.4)	7 (1.4)
WHO Performance Status						
0, n (%)	522 (20.4)	71 (14.1)	98 (19.4)	165 (33.0)	71 (14.1)	94 (18.7)
1, n (%)	1432 (55.8)	264 (52.4)	276 (54.8)	260 (52.0)	288 (57.1)	325 (64.5)
2, n (%)	581 (21.9)	151 (30.0)	112 (22.2)	73 (14.6)	140 (27.8)	78 (15.5)
3, n (%)	41 (1.6)	18 (3.6)	16 (3.2)	2 (0.4)	5 (1.0)	0 (0.0)
4, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown, n (%)	9 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.4)
Median CA19-9 (U/mL)	367	478	534	211	425	345
Median albumin (g/dL)	34.0	33.0	37.0	35.0	31.0	32.0
Median bilirubin (mg/dL)	1.8	2.0	2.0	1.8	1.3	2.5

Performance status by line of metastatic therapy

- The majority of patients had WHO performance status 1 at initiation of first-line metastatic treatment.
- At initiation of second-line metastatic treatment, WHO performance status was generally worse than at first-line initiation (PS) (0-1 51.6% vs. 69.8%) (Figure 1).

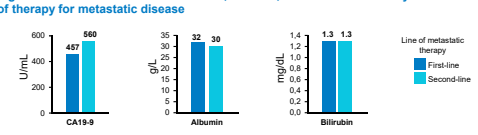
Figure 1. Overall performance status at start of first- and second-line metastatic treatment



Laboratory values by line of therapy for metastatic disease

- At initiation of first-line metastatic therapy, median CA19-9 levels were lower compared with those at initiation of second-line therapy. Median levels of serum albumin and bilirubin were similar at initiation of first- and second-line metastatic therapy (Figure 2).

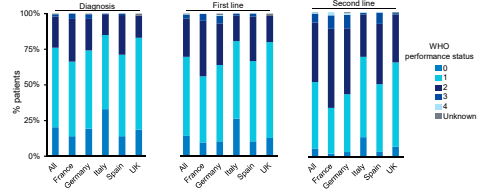
Figure 2. Median CA19-9 tumour marker, albumin, and bilirubin levels by line of therapy for metastatic disease



Geographical variation in patient performance status at diagnosis and initiation

- A greater proportion of patients in Italy had a WHO performance status of 0, whereas more French patients had a performance status of 2 compared with the other countries (Figure 3).

Figure 3. Geographical variation in patient performance status at diagnosis and metastatic treatment initiation across Europe



WHO, World Health Organization.

Overall distribution of first- and second-line metastatic treatments

- FOLFIRINOX was rarely used in the second line. Gemcitabine monotherapy and other gemcitabine- and 5-FU-based combinations were used more frequently in the second than first line (Figure 4).
- Despite French patients having a generally worse performance status, more French patients received FOLFIRINOX as a first line treatment than in the other countries (Figure 5).
 - Full-dose FOLFIRINOX was more widely used in France compared with other countries
 - mFOLFIRINOX was more widely used in the UK than in other countries

Figure 4. Distribution of first- and second-line metastatic therapies

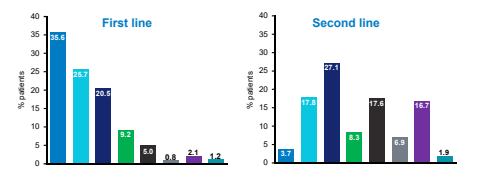


Figure 5. Use of modified and full-dose FOLFIRINOX in first-line treatment of metastatic disease

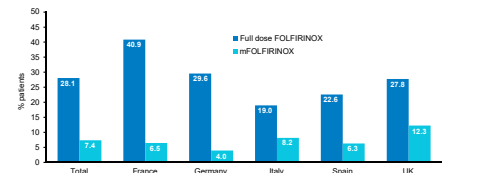


Figure 6. Geographic distribution of first-line treatment regimens used in France, Germany, Italy, Spain and the UK

- First-line treatment choices could be split between 5-FU-based therapies (including FOLFIRINOX, 43.4%) and gemcitabine-based regimens (55.4%) (Table 2).
- The most frequently used first-line regimens were FOLFIRINOX (35.6%), gemcitabine+nab-paclitaxel (25.7%), and gemcitabine-monotherapy (20.5%).
- Treatment was broadly aligned with ESMO guidelines in the surveyed countries.³

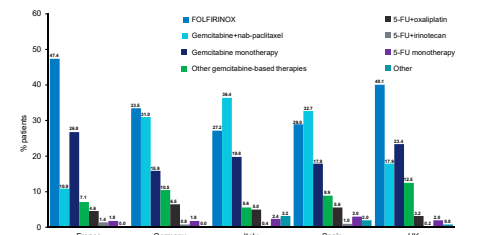
Table 2. Geographic variation in first-line treatment regimen choices

First-line treatment / % patients	Total (N=2,565)	France (n=504)	Germany (n=504)	Italy (n=500)	Spain (n=504)	UK (n=504)
5-FU-based	43.4	55.2	42.7	35.0	38.5	45.4
FOLFIRINOX	35.6	47.4	33.5	27.2	29.0	40.1
Full dose FOLFIRINOX	28.1	40.9	29.0	19.0	22.6	27.8
Modified FOLFIRINOX	7.4	6.5	4.0	8.2	6.3	12.3
Other 5-FU based	7.9	7.7	9.1	7.8	9.5	5.4
5-FU+oxaliplatin	5.0	4.6	6.5	5.0	5.6	3.2
5-FU+irinotecan	0.8	1.4	0.8	0.4	1.0	0.2
5-FU monotherapy	2.1	1.8	1.8	2.4	3.0	2.0
Gemcitabine-based	55.4	44.8	57.3	61.8	59.5	53.8
Gemcitabine+nab-paclitaxel	25.7	10.9	31.0	36.4	32.7	17.9
Gemcitabine monotherapy	20.5	26.8	15.0	19.9	17.9	23.4
Other gemcitabine-combinations	9.2	7.1	10.5	5.6	8.9	12.5
Gemcitabine+erlotinib	1.8	0.0	2.0	0.0	2.8	0.2
Gemcitabine+capecitabine	3.2	0.0	1.2	6.6	3.8	9.3
Gemcitabine+oxaliplatin	3.1	6.7	0.2	4.4	2.2	0.4
Gemcitabine+cisplatin	1.0	0.4	1.2	0.6	0.2	2.6
Other	1.2	0.0	0.0	3.2	2.0	0.8

5-FU, Fluorouracil; FOLFIRINOX, Folic Acid, Fluorouracil, Irinotecan, and Oxaliplatin; mPAC, metastatic pancreatic adenocarcinoma.

- France and the UK used more FOLFIRINOX and less gemcitabine+nab-paclitaxel vs. the other countries (Figure 6).
- Gemcitabine combinations other than nab-paclitaxel were infrequently applied in all countries.

Figure 6. Geographic distribution of first-line treatment choices



Second-line metastatic treatment patterns across France, Germany, Italy, Spain and the UK

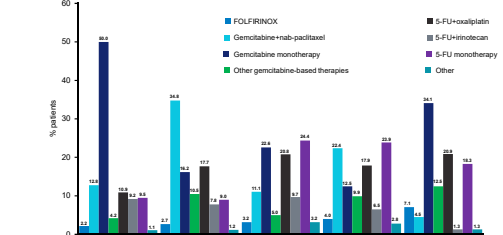
- As with first-line metastatic treatments, second-line metastatic therapies were divided fairly evenly between 5-FU-based therapies (44.9%) and gemcitabine-based (53.2%) treatments with considerable variation between countries (Table 3).
- Distribution of second-line treatments in surveyed countries (Figure 7).
 - France and Germany prescribed fewer 5-FU based regimens.
 - Italy and Spain prescribed fewer gemcitabine-based treatments.
 - Gemcitabine+nab-paclitaxel was most frequently prescribed in Germany and Spain.
 - More gemcitabine monotherapy was used in the UK and France.

Table 3. Geographic variation in second-line treatment regimen choices across Europe

Second-line treatment / % patients	Total (N=1,666)	France (N=338)	Germany (N=332)	Italy (N=279)	Spain (N=352)	UK (N=311)
5-FU-based	44.9	31.8	37.2	58.1	52.3	47.6
FOLFIRINOX	3.7	2.7	2.7	3.2	4.0	7.1
Full dose FOLFIRINOX	2.5	2.0	1.8	2.9	3.1	2.9
Modified FOLFIRINOX	1.3	0.3	0.9	0.4	0.9	4.2
Other 5-FU based	41.2	29.6	34.5	54.8	48.3	40.5
5-FU+oxaliplatin	17.6	10.9	17.7	20.8	17.9	20.9
5-FU+irinotecan	6.9	9.2	7.8	9.7	6.5	1.3
5-FU monotherapy	16.7	9.5	9.0	24.4	23.9	18.3
5-FU intravenous	2.1	4.5	3.0	0.4	1.7	0.6
5-FU oral	14.6	5.0	6.0	24.0	22.2	17.7
Gemcitabine-based	53.2	67.0	61.6	38.7	44.9	51.1
Gemcitabine+nab-paclitaxel	17.8	12.8	34.8	11.1	22.4	4.5
Gemcitabine monotherapy	27.1	50.0	16.2	22.6	12.5	34.1
Other gemcitabine-combinations	8.3	4.2	10.5	5.0	9.9	12.5
Gemcitabine+erlotinib	2.7	0.6	3.4	0.0	4.3	0.0
Gemcitabine+capecitabine	3.2	0.6	0.9	2.5	2.0	10.6
Gemcitabine+oxaliplatin	1.7	3.1	0.3	1.4	3.7	0.0
Gemcitabine+cisplatin	0.7	0.0	6.9	1.1	0.0	1.9
Other	1.9	1.1	1.2	3.2	2.8	1.3

5-FU, Fluorouracil; FOLFIRINOX, Folic Acid, Fluorouracil, Irinotecan, and Oxaliplatin; mPAC, metastatic pancreatic adenocarcinoma.

Figure 7. Geographic distribution of second-line metastatic treatments

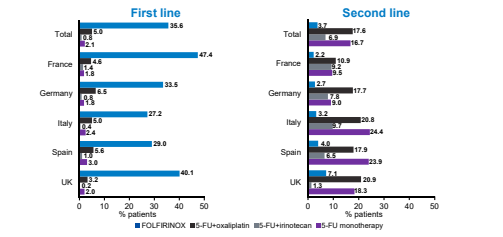


FOLFIRINOX includes full dose and modified FOLFIRINOX; FOLFIRINOX, Folic Acid, Fluorouracil, Irinotecan, and Oxaliplatin.

5-FU-based treatments for metastatic disease in the first and second line

- FOLFIRINOX dominated first-line metastatic treatment choices in the surveyed countries (Figure 6).
- Choice of 5-FU based therapies was highest in Italy and lowest in France for second-line metastatic treatment.
- 5-FU monotherapy and 5-FU+oxaliplatin were chosen equally across Europe for second-line metastatic treatment.
- 5-FU monotherapy use in the second line was higher than 5-FU+oxaliplatin in Italy and Spain; this trend was reversed in Germany.

Figure 8. 5-FU-based treatments for metastatic disease in the first and second line

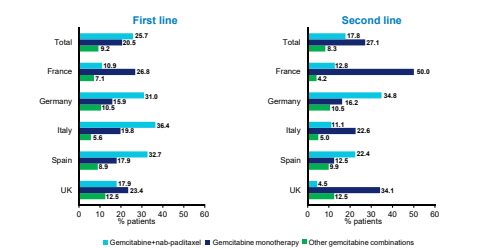


FOLFIRINOX includes full-dose and modified FOLFIRINOX; FOLFIRINOX, Folic Acid, Fluorouracil, Irinotecan, and Oxaliplatin.

Gemcitabine-based treatments in the first and second line

- Gemcitabine monotherapy was more frequently prescribed in France and the UK, while gemcitabine+nab-paclitaxel was more common in other countries (Figure 9).
- Other second-line treatments combined with gemcitabine included oxaliplatin (France, 3.1%), erlotinib (Germany, 8.4%) and capecitabine (UK, 10.6%).⁴

Figure 9. Use of gemcitabine-based regimens in the first and second line



CONCLUSIONS

- First-line treatment choices for mPAC across the surveyed countries are broadly in line with ESMO recommendations.⁴
- The relative proportions of different treatments used varied widely between countries.
- First-line treatment choices for mPAC followed local reimbursement statuses.
 - Country-specific preferences were also observed (e.g. variation in proportions of FOLFIRINOX and gemcitabine+nab-paclitaxel used).
- Second-line treatment also varied widely between countries, showing a lack of standardization, and was mainly guided by choice of first-line treatment and reimbursement policies.
- Over 20 different treatments were reported in this study.
 - During the study period, July 2014 – January 2016, no second-line treatment for mPAC was approved by the regulatory agencies.

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