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Real-World Clinical Practice of Intensified Chemotherapies for Metastatic Pancreatic Cancer: Results from a Pan-European Questionnaire Study

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Key Words
Pancreatic cancer · Palliative chemotherapy · FOLFIRINOX · Nab-paclitaxel

Abstract
Introduction: Recently, FOLFIRINOX and gemcitabine + nab-paclitaxel have been introduced as a novel intensified chemotherapy regimen for patients with metastasized pancreatic cancer. This study aims to analyze the real-world clinical practice with FOLFIRINOX and gemcitabine + nab-paclitaxel across Europe. ***Methods:*** Invitations to participate in an anonymous web-based questionnaire were sent via e-mail to 5,420 doctors in 19 European countries through the network of national gastroenterological, oncological, surgical and pancreatic societies as well as the European Pancreatic Club. The questionnaire consisted of 20 questions, 14 regarding the use of intensified chemotherapy, 4 regarding demographics of the participants, and 1 to verify the active involvement in the management of metastatic pancreatic cancer. ***Results:*** Two hundred and thirteen responses were received and 153 entries were valid for analysis. Of those, 63.4% came from an academic institution, 51% were oncologists, and 52% treated more than 25 cases per year. A majority of responses (71%) were from Italy (40%), Germany (23%), and Spain (8%). As first-line therapy, 11% used gemcitabine +/– erlotinib, 42% used FOLFIRINOX, and 47% used gemcitabine + nab-paclitaxel. Of the intensified regimens, both were applied to equal parts, but the likelihood of protocol deviation was higher when using FOLFIRINOX ($p < 0.01$). FOLFIRINOX was considered more toxic than gemcitabine + nab-paclitaxel (neutropenia 88 vs. 68%; polyneuropathy 42 vs. 41%; rapid deterioration 42 vs. 31%). FOLFIRINOX was rated to achieve longer survival with an acceptable quality of life (52 vs. 44%). Moreover, 57% of participants thought that gemcitabine + nab-paclitaxel should be the backbone for further clinical trials in pancreatic cancer. ***Conclusion:*** Inten-

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sified chemotherapy is widely used in pancreatic cancer patients in Europe following its recent clinical approval. Interestingly, nab-paclitaxel and FOLFIRINOX were used at comparable frequency although the latter had to be de-escalated more often.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a major cause of cancer-related mortality in Europe and the United States. By 2030, PDAC is projected to become the second leading cause of cancer-related deaths next to lung cancer in the United States [1]. Eighty percent of patients never qualify for potentially curative surgery and approximately half of the patients present with distant metastasis at the time of diagnosis. The overall 5-year survival rate is less than 5%, accounting for a number of 85,300 predicted deaths in Europe in 2015 with rising incidence [2]; this kind of a situation is considered a medical emergency [3]. For metastatic pancreatic cancer, which makes up for approximately half of all newly diagnosed cases, there are currently 3 chemotherapeutic regimens available which, by international consensus, are considered first-line treatment options [4]. Gemcitabine is a nucleoside analogue that was approved almost 20 years ago and it exerts a moderate survival benefit over untreated patients and was mostly used for its clinical benefit [5, 6]. In the mid-2000 period, the addition of erlotinib, an epidermal growth factor receptor inhibitor, was shown to mediate a significant but clinically irrelevant survival benefit of approximately 2 weeks [7]. However, a small subgroup of patients with severe rash (grade ≥2) benefited most (10.5 months) from the addition of erlotinib [8, 9]. FOLFIRINOX, a gemcitabine-free combination protocol utilizing 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin was the first so-called intensified chemotherapy regimen that showed a clinically relevant increase in survival when compared to gemcitabine monotherapy (11.1 vs. 6.8 months; hazard ratio for death, 0.57; 95% CI 0.45–0.73; $p < 0.001$) [10, 11]. The almost doubling of survival time can be considered a hallmark in oncology and has since been introduced in daily clinical practice. However, due to its higher toxicity profile in studies, it is unclear which subgroup of patients truly benefits from this regimen. The latest innovation in the treatment of palliative pancreatic cancer patients was the successful clinical introduction of nab-paclitaxel, a nanoparticle-sized albumin-bound paclitaxel, in combination with gemcitabine. The combination resulted in a significant increase in survival when compared to gemcitabine alone (8.5 vs. 6.7 months, hazard ratio for death, 0.72; 95% CI 0.62–0.83; $p < 0.001$) [12, 13]. Although not directly comparable due to methodological differences of the phase III trials, gemcitabine + nab-paclitaxel appeared to be less toxic than FOLFIRINOX. Therefore, healthcare providers have oftentimes the difficult task of choosing one of 3 regimens, which are all considered first-line options. This questionnaire study aims to investigate the current practice and decision-making process of physicians who are treating patients with metastatic pancreatic cancer in Europe for the first time.

Methods

This is a web-based questionnaire study that aimed to understand the current practice in the use of intensified chemotherapy for treatment of metastatic pancreatic cancer under real-life conditions in Europe. The questionnaire was written in English and was available online from June 1st 2015 through November 30th 2015. Invitations where sent via e-mail through the network of national gastroenterological, oncological, surgical, and pancreatic societies of 20 European countries as well as the European Pancreatic Club. In total, 5,420 individual emails were sent. In October 2015, a reminding e-mail was sent to the same list of recipients. At the beginning of the questionnaire, participants were asked whether they were actively involved in treating metastatic pancreatic cancer and if the answer was no, those responders were not asked any further questions. The questionnaire contained 4 demographic questions regarding the country of practice, specialty, healthcare setting, and disease-specific case load of the responders, followed by 14 questions regarding their current practice in using intensified chemotherapy for metastatic pancreatic cancer. All questions could be answered by choosing from a dropdown menu or by clicking on predefined options, there was no need to enter text. In 5 cases, however, open fields for alternative answers were provided. In some cases, multiple answers were accepted. The name and institution of the participants were not recorded. The analysis was conducted using Microsoft Excel 2016 and Prism 5. The full questionnaire can be viewed online (online suppl. Fig. 1, see www.karger.com/doi/10.1159/000453257).

Results

Frequency of Intensified Chemotherapy Use across Europe

A total of 213 individuals responded by filling in the questionnaire sent to them via e-mail and this resulted in an overall response rate of 3.9%. Out of those, 55 answered that they were not actively treating patients with

metastatic pancreatic cancer and another 5 gave invalid answers in terms of their country of origin; therefore, they were excluded, leaving 153 questionnaires for further analysis. The distribution by country, specialty, hospital setting, and annual case load is shown in Tables 1, 2 and Figure 1a. As first-line therapy, 11% of participants currently used gemcitabine +/– erlotinib, 42% used FOLFIRINOX, and 47% used gemcitabine + nab-paclitaxel (Fig. 1b). While 45% responded that they would use intensified chemotherapy (FOLFIRINOX or gemcitabine + nab-paclitaxel) in more than half of their patients, 37% said that they would use intensified chemotherapy in 25–50% and 18% said that they would use it in less than 25% of cases. The 3 most frequently mentioned criteria for choosing one of the 2 intensified regimens over gemcitabine +/– erlotinib were the patients' performance status (34%), personal experience (23%), and current guidelines (22%). Interestingly, when asked which of the 2 regimens were preferred, 50% responded in favor of FOLFIRINOX ($n = 76$) and the other half in favor of gemcitabine + nab-paclitaxel ($n = 77$). The 3 most frequently given reasons for choosing one intensified regimen over the other were expected longer survival rates (47%), a more favorable toxicity profile (44%), and restrictions due to the patients' performance status (42%), the latter leading to the administration of gemcitabine + nab-paclitaxel.

National Preferences for Choosing Intensified Chemotherapy

We found some differences in the answers with respect to the country of origin, specialty, and hospital setting of the responders. From a geographical perspective, only countries with 5 or more answers were considered including Italy ($n = 61$), Germany ($n = 35$), Spain ($n = 12$), the United Kingdom ($n = 9$), Sweden ($n = 7$), and France ($n = 6$). Whereas a majority of physicians from Italy ($n =$ 38 out of 61), Spain ($n = 8/12$), and the United Kingdom ($n = 5/9$) used gemcitabine + nab-paclitaxel as first-line therapy, FOLFIRINOX was predominantly used in Germany ($n = 20/35$) and France ($n = 4/6$; Fig. 1c). In Sweden, gemcitabine +/– erlotinib is still the most frequently applied palliative treatment ($n = 3/7$). The frequency of using intensified regimens was the highest in Spain (>50% of cases; $n = 9/12$) and the lowest in Sweden (>50% of cases; $n = 1/7$). The favored intensified regimen differed by country with Italian, Spanish, and Swedish physicians preferring gemcitabine + nab-paclitaxel and German, French, and British doctors use FOLFIRINOX more frequently (Fig. 1d).

Table 1. Distribution of responses by country

Country	Number (%)
Italy	61 (39.9)
Germany	35 (22.9)
Spain	12 (7.8)
UK	9 (5.9)
Sweden	7 (4.6)
France	6 (3.9)
Hungary	5 (3.3)
Netherlands	3 (2.0)
Czech	2 (1.3)
Finland	2 (1.3)
Romania	2 (1.3)
Russia	2 (1.3)
Belarus	1 (0.7)
Belgium	1 (0.7)
Latvia	1 (0.7)
Norway	1 (0.7)
Portugal	1 (0.7)
Turkey	1 (0.7)
Ukraine	1 (0.7)
Total	153

Table 2. Distribution of responses by hospital setting specialty and annual case load

Hospital setting	Number (%)
Academic	97 (63.4)
Non-academic tertiary center	25 (16.3)
District hospital	24 (15.7)
Outpatient setting	3 (2.0)
Other	4 (2.6)
Specialty	
Oncology	78 (51.0)
Surgery	31 (20.3)
Gastroenterology	42 (27.5)
Other	2 (1.3)
Annual case load	
<25	73 (47.7)
25–50	54 (35.3)
>50	26 (17.0)

Estimated Toxicity Profile

Based on the participants' experience, the toxicity profile of intensified chemotherapy was reported to be similar for either regimen, with neutropenia being the most common adverse event (88% FOLFIRINOX, 68% gemcitabine + nab-paclitaxel), followed by polyneuropathy (42% FOLFIRINOX, 41% gemcitabine + nab-paclitaxel) and rapid deterioration of performance (42% FOLFIRINOX, 31% gemcitabine + nab-paclitaxel). Over-

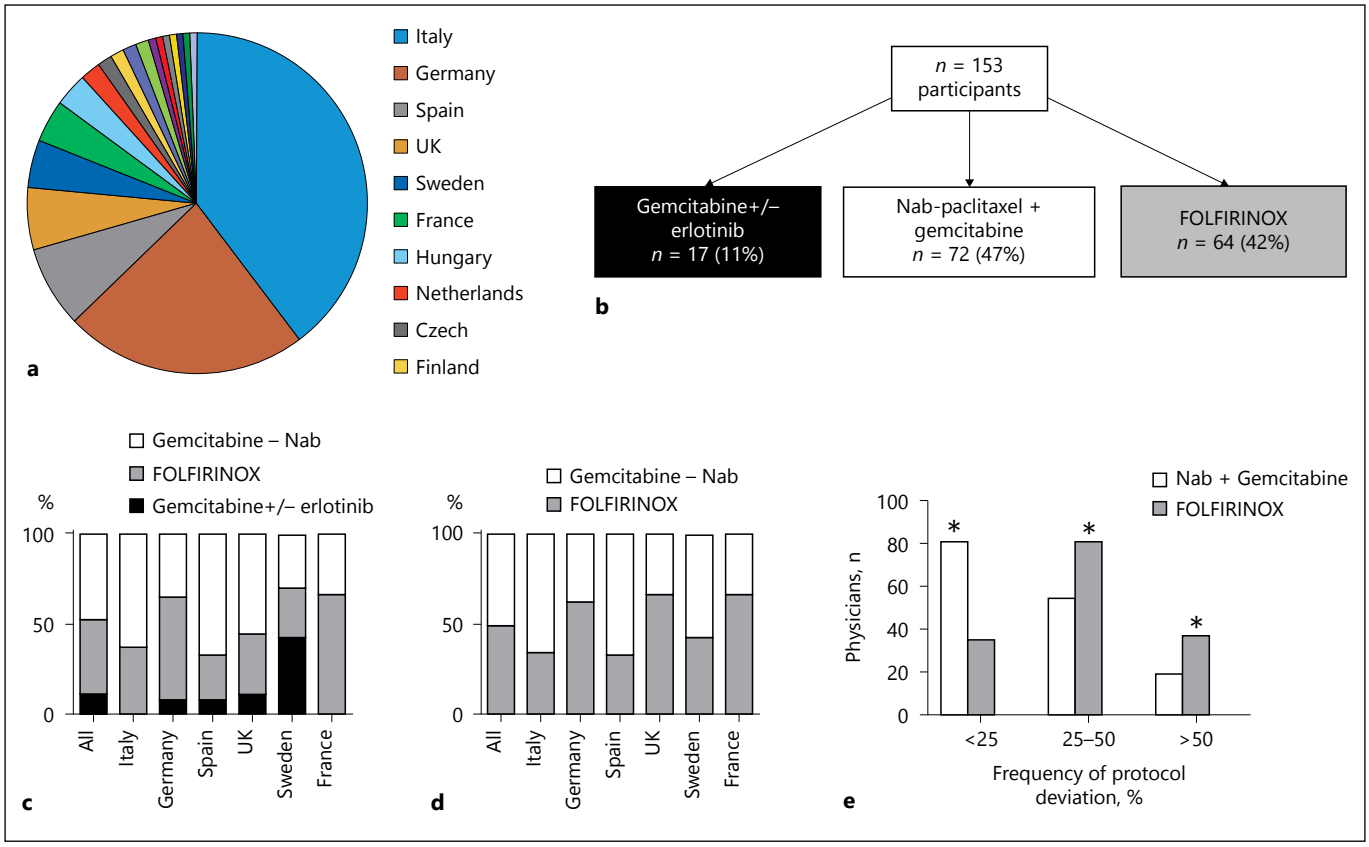

Fig. 1. a–e Distribution of participating countries (%). All participants answering question 6: What is current first-line chemotherapy regimen of choice for treating patients with metastatic pancreatic cancer in your center? Answers to question 6 according to country: What is current first-line chemotherapy regimen of choice for treating patients with metastatic pancreatic cancer in your center? Answers to question 9 according to country: Which is the favored chemotherapeutic regimen among the combination protocols? Answers to question 11: rate of deviation from the original treatment protocol due to complications or toxicity when using intensified chemotherapy in metastatic pancreatic cancer in case of FOLFIRINOX or gemcitabine + nab-paclitaxel. * $p < 0.01$ using unpaired t test.

all, the likelihood of deviating from the original protocol by adjusting, interrupting, or deescalating treatment was higher when using FOLFIRINOX compared to nab-paclitaxel (Fig. 1e, $p < 0.01$).

Second-Line Treatment

Notably, the choice of second-line treatment in need of de-escalation varied, according to which intensified regimen was used as first line. In case of FOLFIRINOX, 39% would switch to gemcitabine + nab-paclitaxel, 25% to gemcitabine +/– erlotinib, and 11% to FOLFOX or FOLFIRI respectively (Fig. 2a). If gemcitabine + nab-paclitaxel was used as first line, 37% would switch to 5-FU or Capecitabine, 33% choose gemcitabine +/– erlotinib, and only 23% considered FOLFIRINOX a suitable alternative (Fig. 2b). When asked about their overall experience with intensified chemotherapy in the treatment of metastatic pancreatic cancer, responders agreed that patients survived longer with acceptable quality of life in 52% of cases when using FOLFIRINOX versus 44% for gemcitabine + nab-paclitaxel. In contrast, 33% replied that patients had longer overall survival but significantly increased toxicity, thereby impairing the overall quality of life with FOLFIRINOX versus 12% with gemcitabine + nab-paclitaxel. In contrast, 11% of responders stated that there is no difference in survival using gemcitabine + nab-paclitaxel versus 5% with FOLFIRINOX, but acceptable quality of life.

Preferences According to Specialty and Institution

If analyzed according to the respondent's specialty, it appeared as if oncologists ($n = 78$) preferred gemcitabine + nab-paclitaxel over FOLFIRINOX (61 vs. 34%) as first-line therapy, whereas gastroenterologists ($n = 42$) saw it the opposite way (28 vs. 57%). Surgeons ($n = 31$) did not

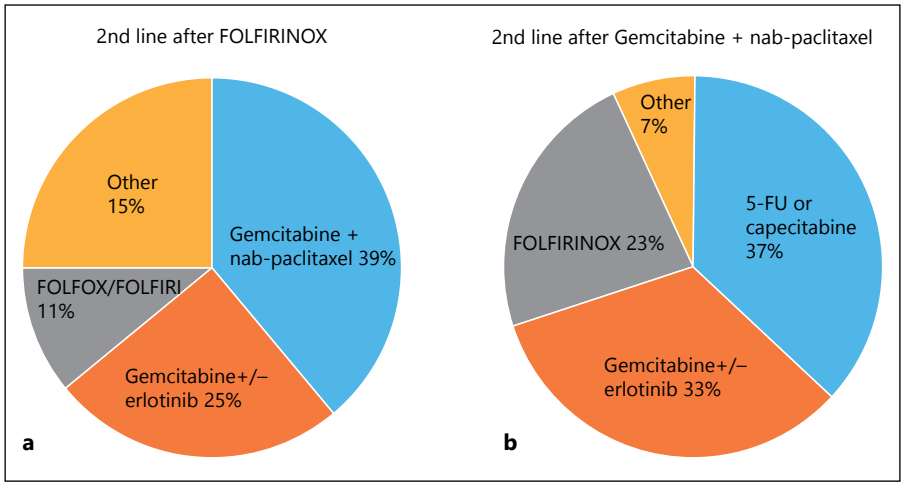

Fig. 2. a, **b** Answers to question 13: What is your second-line treatment of choice after de-escalating following FOLFIRINOX first-line therapy and gemcitabine + nab-paclitaxel first-line therapy.

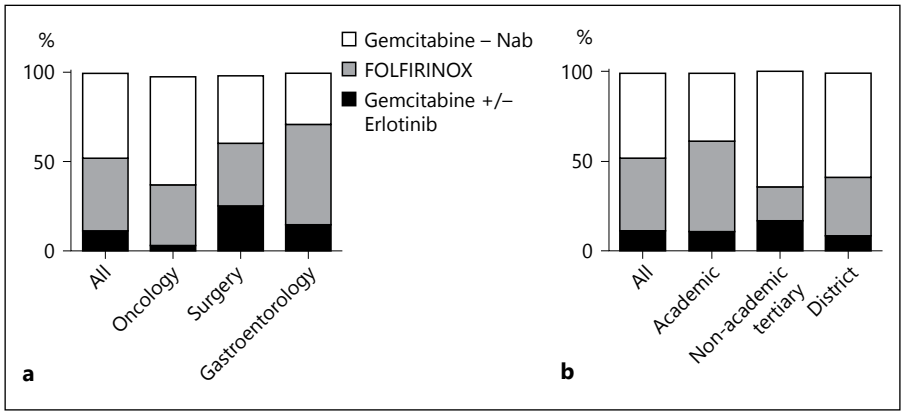

Fig. 3. a, **b** Answers to question 6 according to specialty: What is current first-line chemotherapy regimen of choice for treating patients with metastatic pancreatic cancer at your center? Answers to question 6 according to hospital setting: What is the current first-line chemotherapy regimen of choice for treating patients with metastatic pancreatic cancer in your center?

state a preference (38 vs. 35%; Fig. 3a). Similar results were obtained when physicians were asked for their favored intensified regimen. The specialty also influenced the frequency with which intensified regimens were used. Oncologists said they use intensified chemotherapy in more than half of their patients in 55%. In contrast, only 29% of surgeons and 38% of gastroenterologists used those therapies in more than half their patients.

Interestingly, the use of palliative chemotherapy in patients with pancreatic cancer was influenced by the institutional set up. The most frequently used first-line therapy in academic centers ($n = 97$) was FOLFIRINOX (51%), whereas gemcitabine + nab-paclitaxel was the preferred option at non-academic tertiary ($n = 25$) or district hospitals ($n = 24$; 64 and 58%; Fig. 3b). The percentage of doctors using intensified chemotherapy in more than half of their patients was the lowest at non-academic tertiary hospitals (12%) and similar at academic and district hospitals (49 and 58%).

Nutritional Support and Future Clinical Trials

Overall, 73% of responders said that nutritional support was part of the standard protocol treatment when FOLFIRINOX is used, whereas 64% said so when using gemcitabine + nab-paclitaxel. A majority of participants (57%) thought that gemcitabine + nab-paclitaxel should be used as the backbone for further clinical trials in patients with metastatic pancreatic cancer.

Discussion

This is an open questionnaire study conducted in 19 European countries, which aims to understand the current practice and decision-making process of physicians treating patients with metastatic pancreatic cancer. It is, to the best of our knowledge, the first study to explore physicians' experiences and preferences

with the newly available intensified chemotherapeutic options for metastatic pancreatic cancer in daily routine.

The results from published randomized trials seemed to reflect the day-to-day experience of many participants in this survey. The criteria for choosing one intensified regimen over the other were patients' performance status and expected toxicity versus the potential longer life expectancy. Based on the experience of the participants of this questionnaire, FOLFIRINOX was more toxic and associated with a higher burden of adverse events as reflected in the estimated higher likelihood of protocol deviation and higher rates of neutropenia, polyneuropathy, worsening performance status, and need for nutritional support. In the original phase III trial by Conroy et al, which led to the approval of FOLFIRINOX, rates of grade 3 or 4 neutropenia, neuropathy, and diarrhea were reported to be as high as 45, 9.1, and 12.7% [11], whereas the administration of gemcitabine + nab-paclitaxel in the MPACT trial caused less neutropenia and diarrhea (38 and 6%) but more frequently neuropathy (17%) [12]. Accordingly, 39% of the survey participants answered that they considered gemcitabine + nab-paclitaxel a suitable de-escalation regimen after FOLFIRINOX first-line therapy, but only 23% would do it vice versa. This finding is particularly interesting as it indicates that by switching between intensified regimens, many participants do not follow current international guidelines [14, 15]. Whether administering intensified regimens as second-line treatment really qualifies as de-escalation remains a matter of ongoing debate.

Despite the higher toxicity, participants rated FOLFIRINOX over gemcitabine + nab-paclitaxel in achieving longer survival with acceptable quality of life. This finding is supported by previously reported data where the quality of life impairment had been found to be reduced in patients treated with FOLFIRINOX compared to gemcitabine alone as part of the original phase II/III study [11, 16]. The effect of nab-paclitaxel in combination with gemcitabine on overall quality of life has not been investigated so far. However, it has also been demonstrated from a registry-based retrospective study that simply meeting the eligibility criteria for either of the 2 intensified regimens as set in the phase III trials will be associated with longer survival, even without receiving the drug [17]. The results from this questionnaire thus also reflect a clinical dilemma. Since the FOLFIRINOX trial excluded patients with an ECOG of less than 1 or age greater 75 years, a comparison of the 2 intensified regimens is difficult to make. Based on these data most clinicians and most guidelines will restrict the use of FOLFIRINOX to patients with good to excellent performance status [18, 19], without knowing whether patients who do less well, but still qualify for nab-paclitaxel, would in fact also benefit from FOLFIRINOX. Interestingly, a recent analysis by the National Institute for Health and Care Excellence in England concluded that there was not enough evidence available supporting that patients with a Karnofsky performance status of 70 or 80 would truly benefit from nab-paclitaxel + gemcitabine as compared to gemcitabine alone and questioned the usefulness of performance status to allocate patients to different lines of treatment. In the same analysis, a direct comparison of the 2 study cohorts from the Conroy and von Hoff trials showed that apart from age, there were no significant differences in non-subjective patient characteristics [20].

A by-country-analysis of answers showed some regional differences reflecting differing national guidelines and preferences. This observation may be affected by the fact that the FOLFIRINOX trial was conducted in France, whereas the MPACT trial was a multinational trial. The finding that more than half of the responders from the United Kingdom used gemcitabine + nab-paclitaxel as first-line therapy, but preferred FOLFIRINOX over gemcitabine + nab-paclitaxel if asked for their favored combination protocol, can to some extent be explained by sampling error, caused by the low number of responses from Britain ($n = 9$). The fact that oncologists where more likely to apply gemcitabine + nab-paclitaxel and gastroenterologists preferred FOLFIRINOX is intriguing and may be influenced by the respective specialty, which is predominantly involved in the care of pancreatic cancer patients. In Italy, where nab-paclitaxel is widely used as first-line, oncologists are the predominant specialty treating metastatic pancreatic cancer. On the other hand, in Germany, where FOLFIRINOX is widely applied, next to hemato-oncologists, gastroenterologists are involved to a large extent in the care for pancreatic cancer patients. The reason why FOLFIRINOX was more widely applied at academic centers compared to non-academic institution remains unclear. One could speculate that such institutions would have more experience in treating pancreatic cancer patients due to their higher case load and might therefore be willing to treat them more aggressively. A similar tendency was found in a survey conducted in 2007 among German doctors who were medically treating patients with pancreatic cancer in the palliative intent [21], which showed that high-volume centers treating more than 30 patients per year were more likely to apply a combination regimen in patients with good performance sta-

tus as compared to low-volume centers treating less than 5 patients annually (61 vs. 44%) Vice versa those low-volume centers tended to always apply monotherapy as compared to high-volume centers (39 vs. 18%). The same trend was observed when comparing academic centers to private practice settings. By that time, the most commonly applied combinations were gemcitabine with oxaliplatin or erlotinib and gemcitabine alone for monotherapy [21].

One obvious limitation of our study was the fact that the overall response rate was poor and greatly differed by country, accounting for almost two-thirds of valid answers originating from only 2 countries and despite our efforts, some large European countries are not represented at all. In order to balance this uneven distribution, we conducted a second call for participation via e-mail; however, the overall response rate remained poor. Therefore, our results regarding national preferences of intensified chemotherapies must be interpreted with great care and cannot be generalized. In spite of this limitation, we believe this study provides a general overview and outlook, thereby creating the needed opportunity to conduct further studies and discussion on the real world use of intensified palliative chemotherapy for pancreatic cancer. Other potential biases include the overrepresentation of academic physicians, as this might not reflect the common practice in many places. Further, the responders were not blinded to the results of the clinical trials discussed above; thus, despite asking for personal experience, answers could have been influenced by the respondents' perception of the published trial data with regards to efficacy and toxicity of the respective regimen as well as bias by recall.

We conclude that shortly after the introduction of intensified chemotherapies as first-line treatment for metastatic pancreatic cancer in Europe, both FOLFIRINOX and gemcitabine + nab-paclitaxel are widely available throughout Europe and used at almost the same frequency. A majority of the participants in this European questionnaire study believe that future clinical trials should be based on the use of gemcitabine + nab-paclitaxel.

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Statement of Ethics

This is a web-based questionnaire study that evaluates personal experiences of physicians across Europe. No individual patient data are evaluated, therefore, no ethical approval was obtained.

Disclosure Statement

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