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ORIGINAL ARTICLE

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Survival of pancreatic cancer patients treated with nab-paclitaxel (nab-P) in clinical practice: analysis of National Health Fund data

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ABSTRACT

Introduction. Despite advances in the last few decades, pancreatic cancer is still characterized by systematically increasing morbidity and high mortality with a low survival rate. The introduction of nab-paclitaxel (nab-P) to the first-line treatment of patients with metastatic pancreatic adenocarcinoma in combination with gemcitabine resulted in improvements in overall survival (OS), progression-free survival (PFS) and objective response rate (ORR).

Material and methods. This study analyzes OS and PFS in pancreatic cancer patients treated with nab-P in the real world setting in Poland, based on data from the National Health Fund (NFZ) database.

Results. Data from 873 patients were found (2014–2019). PFS in the entire population was 169 days (95% CI 147–189) without difference between men and women, but significantly better in younger patients (29–50 years). OS in the entire population was 379 days (95% CI 337–non-assessable), with no difference between men and women. A statistically significant longer PFS and OS was demonstrated in the group of patients diagnosed in 2014–2016.

Conclusion. Nab-paclitaxel, when used in clinical practice, provides treatment results similar to those in clinical trials. Collecting and periodically analyzing demographic and clinical data could help to assess the place of nab-P in the treatment of patients with pancreatic cancer more accurately.

Keywords: advanced pancreatic cancer, nab-paclitaxel, overall survival, progression-free survival
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Introduction

Adenocarcinoma accounts for over 90% of all primary pancreatic neoplasms, and its incidence systematically and significantly increases [1]. Pancreatic cancer is one of the leading causes of cancer-related mortality [2]. Based on data from 2017–2019, it has been estimated that approximately 1.7% of men and women will be diagnosed with pancreatic cancer at some point in their lives [3]. Currently, pancreatic cancer is the 12th most common cancer and the 7th leading cancer death worldwide [4, 5].

During the period from 1990 to 2017, the number of pancreatic cancers doubled worldwide (196 000 *vs.* 441 000). It is believed that the significantly increased incidence results from age structure changes in the world population (the risk of pancreatic cancer increases with age) and the improvement in diagnosis and detection of this disease in developed countries [2].

Europe is ranked second in terms of the incidence of pancreatic cancer after the Western Pacific region (9.3 per 100 000 men and 6.3 per 100 000 women). The highest number of cases is recorded in Germany, France,

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and Italy. Pancreatic cancer is the fourth leading cause of cancer death in Europe (8.8 deaths per 100 000 men and 5.7 per 100 000 women) after lung, colon, and breast cancer [6].

In Poland, 3852 cases were recorded in 2019 (incidence rate of 10.3%), and the number of deaths was 5068 (mortality rate of 13.2%) [7].

The survival rate of patients with pancreatic cancer is still very low, median overall survival (OS) in locally advanced stages does not exceed a year while it is 3–6 months in metastatic disease [8]. Although there has been an increase in the 5-year survival rate in the USA and Europe from less than 5% in the 1990s to 9% in 2019, the global mean rate is only about 3% [2, 9]. Unfavorable results are mainly related to late diagnosis. In most cases, the disease is diagnosed at either a locally advanced or metastatic stage, and only 15–20% of cases are diagnosed at early stages when radical surgery is possible [2].

Chemotherapy is used to treat patients with advanced pancreatic cancer, either as monotherapy or multidrug regimens with gemcitabine, fluoropyrimidine, nab-paclitaxel (nab-P), or irinotecan. The choice of the first-line treatment regimen should be adapted to the patient's general condition. Multidrug regimens (e.g. FOLFIRINOX — oxaliplatin, irinotecan, leucovorin, and fluorouracil) in the first line, and regimens with nanoliposomal irinotecan in the second line are more effective than monotherapy but should only be used in patients with good and very good performance status [10–13].

Nab-paclitaxel (nab-P) is a nanoparticle albumin-bound paclitaxel, showing pharmacological properties different from the conventional form of the drug. It is approved — among other indications — for the first-line treatment of adult patients with metastatic pancreatic adenocarcinoma in combination with gemcitabine [14]. The MPACT study showed that the combination of both drugs compared with gemcitabine alone improves OS, with a median of 8.5 *vs.* 6.7 months, progression-free survival (PFS), with a median of 5.5 *vs.* 3.7 months and objective response rate (23% *vs.* 7%) [13, 15].

The therapeutic value of nab-P in combination with gemcitabine was confirmed by real-world data (RWD), for example, the data from the German pancreatic cancer registry TPK collected prospectively in 104 centers between 2014 and 2017 [16].

Aim of study

This study aims to analyze the results of treatment with nab-P in daily clinical practice in Poland in terms of OS and PFS based on data from the National Health Fund (NHF) database.

Material and methods

The data of pancreatic adenocarcinoma patients treated with nab-paclitaxel (Abraxane®, Bristol-Myers Squibb Pharma EEIG, Ireland) from the NHF database were reviewed. The NHF data were collected after obtaining appropriate approval.

The analyzed data included the demographic characteristics of the patients and the results in terms of OS and PFS.

Overall survival was defined as the time to the last record in the database confirming that the patient was still alive. Progression-free survival was defined as the time to the last record in the database confirming the lack of disease progression in imaging tests and that the patient is still alive.

Statistical analysis

Statistical analysis was performed using survival assesement metods. Overall survival was calculated as the number of days from initiation of treatment to completion of observation or death. Progression-free survival was calculated as the number of days from initiation of treatment to completion of follow-up, disease progression, or death.

The significance of factors influencing OS and PFS was assessed using the log-rank test. The analysis was conducted using the R 4.0.5 software [17].

Results

Data from a total of 873 patients — 447 women (51.2%) and 426 men (48.8%) — treated between 2014 and 2019 were analyzed. The median age was 66 years [range 29–87 years; interquartile range (IQR) 61–70 years] with a predominance of patients over 60 years of age (80.0%).

Most patients were diagnosed in 2018 (n = 373; 42.7%) and 2019 (n = 198; 22.7%), and only 5.2% of patients were diagnosed in 2016 or earlier (n = 45).

Most patients were treated in centers located in the Masovian Provincial Department of the National Health Fund (n = 193; 22.1%), and the least in the Opole Provincial Department of the National Health Fund (n = 13; 1,5%),

The most common causes of treatment discontinuation were disease progression (n = 254; 43.4%) and death (n = 121; 20.7%). In 3 (0.5%) patients, treatment was discontinued due to a change of service provider. Detailed data on the analyzed group available in the NHF database are presented in Table 1.

Progression-free survival in the entire study group was 169 days (95% CI 147–189) (Fig. 1). There was

Table 1. Characteristics of pancreatic adenocarcinoma patients treated with nab-paclitaxel based on data from the National Health Fund database

Feature	Number of pts. n (%)
Sex	
Female	447 (51.2)
Male	426 (48.8)
Median age (years), (range) (IQR)	
66 (29–87) (61–70)	65.3 (8.2)
Age group	
29–50	39 (4.5)
50–60	135 (15.5)
60–70	429 (49.1)
70–87	270 (30.9)
Reason for treatment discontinuation	
Disease progression	254 (43.4)
Change of treatment	22 (3.8)
Patient withdrawal	38 (6.5)
Unacceptable side effects	56 (9.6)
Hypersensitivity to the active substance or excipient	18 (3.1)
Death	121 (20.7)
Another cause	73 (12.5)
Change of service provider	3 (0.5)
Year of diagnosis	
2014–2016	45 (5.2)
2017	257 (29.4)
2018	373 (42.7)
2019	198 (22.7)
Accounting Department of the National Health Fund	
Lower Silesia	40 (4.6)
Kuyavian-Pomeranian	24 (2.7)
Lublin	67 (7.7)
Lubuski	18 (2.1)
Lodzki	19 (2.2)
Lesser Poland	40 (4.6)
Masovian	193 (22.1)
Opole	13 (1.5)
Subcarpathian	49 (5.6)
Podlaski	31 (3.6)
Pomeranian	93 (10.7)
Silesian	107 (12.3)
Świętokrzyski	41 (4.7)
Warmia–Masuria	15 (1.7)
Greater Poland	61 (7.0)
West Pomeranian	62 (7.1)

IQR — interquartile range

no difference in survival between men and women ($p = 0.95$; Fig. 2). On the other side, a statistically significantly longer PFS was demonstrated in younger patients in the 29–50 age group ($p = 0.41$) (Fig. 3). A statistically significant difference ($p < 0.0001$) was demonstrated depending on the year of diagnosis with the highest median in the group patients diagnosed between 2014–2016 (Fig. 4).

Overall survival in the entire study group was 379 days (95% CI 337–not assessable) (Fig. 5). There were no statistically significant differences regarding sex ($p = 0.76$; Fig. 6) and age ($p = 0.65$; Fig. 7). On the other hand, a statistically significant difference ($p = 0.18$) was shown depending on the year of diagnosis with the highest median in the group of patients diagnosed between 2014–2016 (Fig. 8).

Discussion

Pancreatic cancer is still one of the major cancer-related threats to life and health. High mortality is primarily a consequence of the diagnosis at advanced disease stages. There has been some progress in the treatment of advanced disease in recent years, mainly with the introduction of multidrug regimens, but PFS and OS outcomes are still disappointing.

In the phase III PRODIGE 4 study, a statistically significant improvement in median PFS (6.4 *vs.* 3.3 months, $p < 0.001$) and OS (11.1 *vs.* 6.8 months, $p < 0.001$) with the FOLFIRINOX regimen (oxaliplatin, irinotecan, leucovorin, and fluorouracil) use was shown as compared to gemcitabine monotherapy, but the toxicity of the multidrug regimen was significantly greater [12]. In the MPACT study mentioned above, an increase in OS was achieved in patients with metastatic pancreatic cancer with a 28% reduction in the relative risk of death after adding nab-P to gemcitabine compared to gemcitabine alone. Multidrug regimens were moderately toxic with manageable side effects. The combination of nab-P with gemcitabine has become a new standard of systemic therapy in patients with advanced or metastatic pancreatic cancers [13].

In Poland, nab-P in the first-line treatment of patients with metastatic pancreatic adenocarcinoma has been used in combination with gemcitabine since 2017 as part of the Ministry of Health drug program only in patients non-eligible for more intensive chemotherapy according to the FOLFIRINOX regimen. The decision to use nab-P with gemcitabine was in line with the 2014 Polish Society of Clinical Oncology guidelines and the 2015 European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines. No study has ever been conducted to directly compare the results

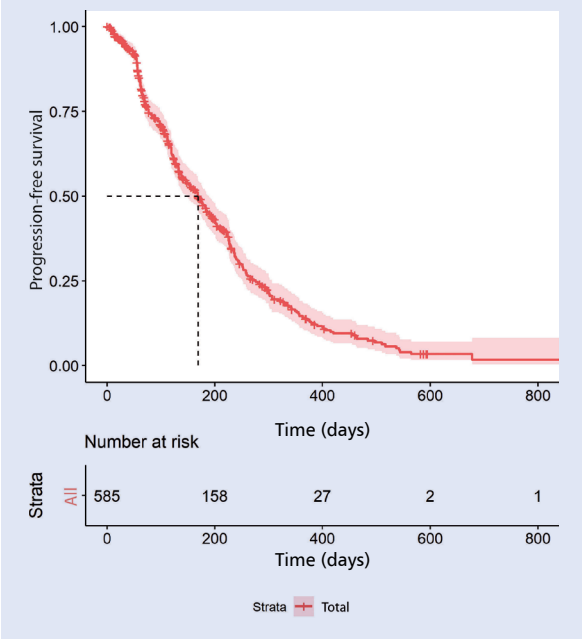

Figure 1. Progression-free survival in the entire group of patients

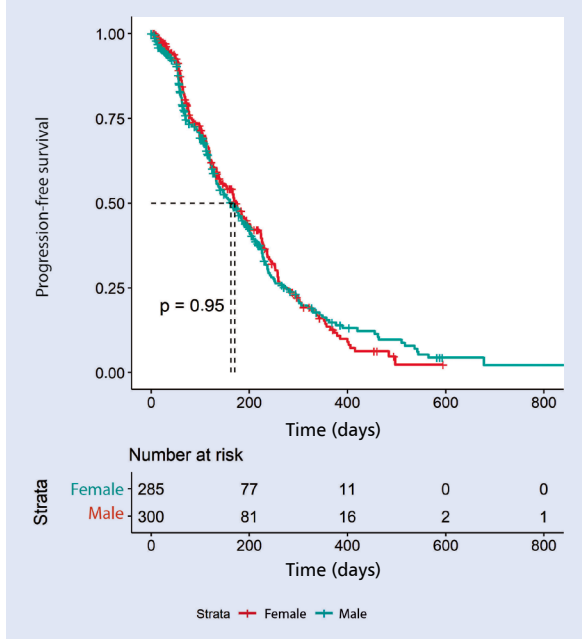

Figure 2. Progression-free survival depending on sex

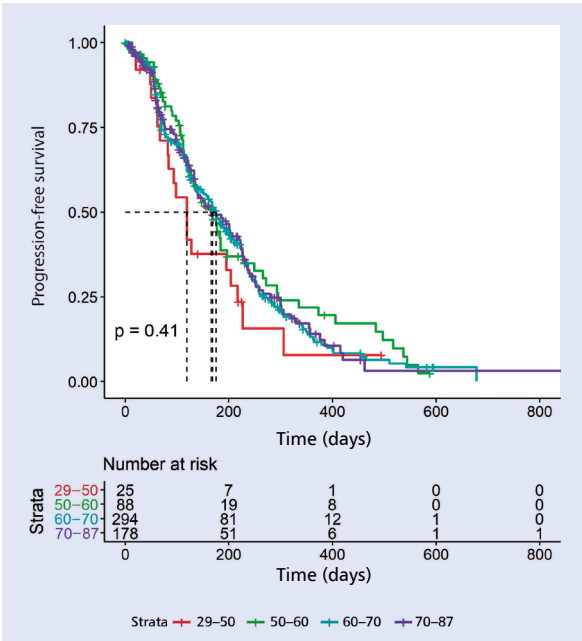

Figure 3. Progression-free survival depending on age

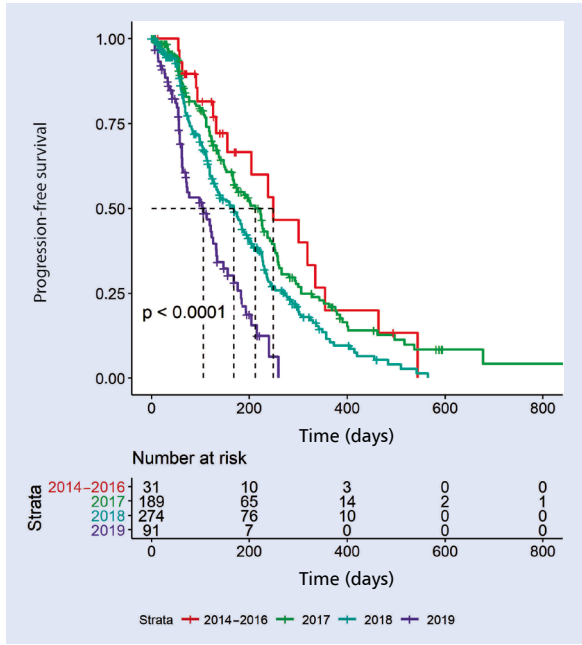

Figure 4. Progression-free survival depending on the year of diagnosis

of chemotherapy with the FOLFIRINOX regimen and the combination of nab-P with gemcitabine, which could help decide on the optimal treatment. However, when analyzing the studies comparing these two regimens with gemcitabine monotherapy (ACCORD 11 with FOLFIRINOX chemotherapy and MPACT with nab-P and gemcitabine) in first-line treatment, it can be noted that both studies included similar patient populations. This is evidenced not only by patient characteristics but also by almost identical results obtained in the control groups. The percentage of patients who received second-line treatment was similar (48% in

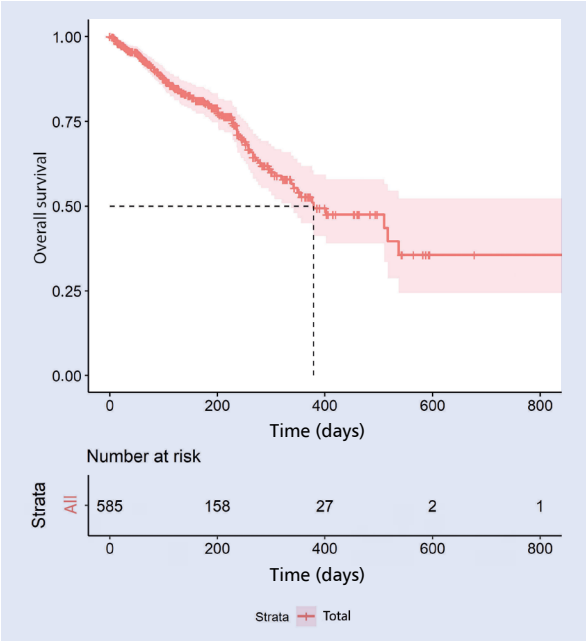

Figure 5. Overall survival in the entire group of patients

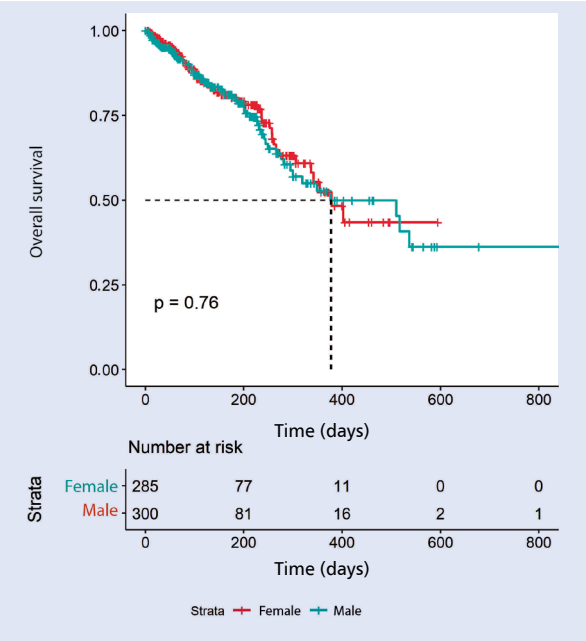

Figure 6. Overall survival depending on sex

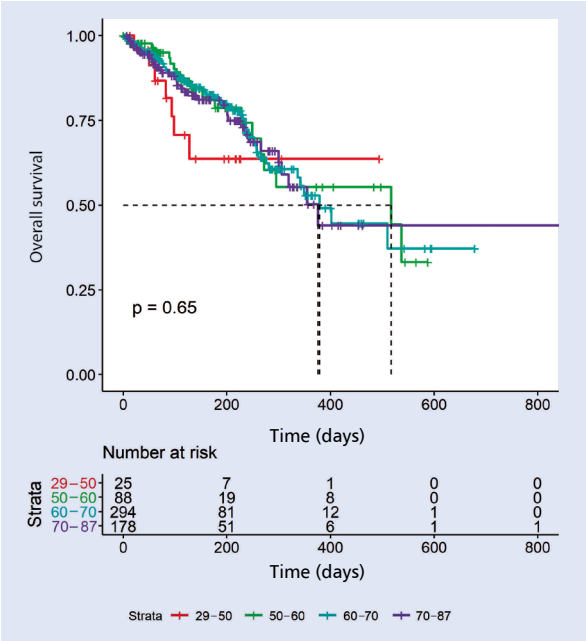

Figure 7. Overall survival depending on age

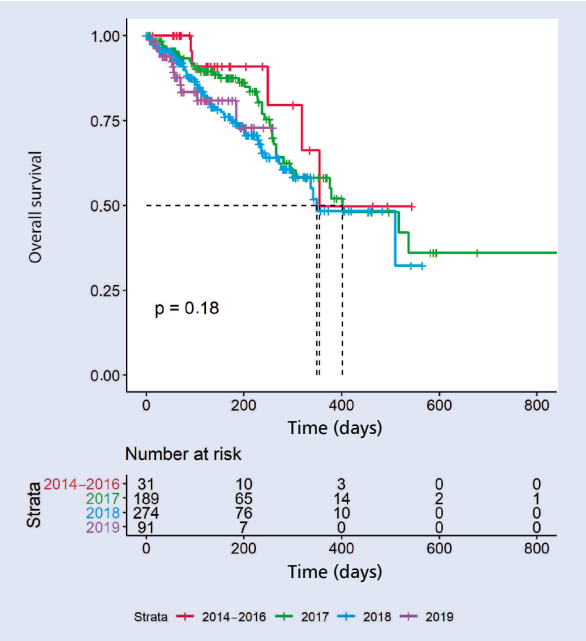

Figure 8. Overall survival depending on the year of diagnosis

ACCORD 11 and 40% in MPACT). Median OS, PFS, and objective response rates (ORR) were numerically better in ACCORD 11 than in the MPACT study (11.1 months, 6.4 months, and 32% *vs.* 8.5 months, 5.5 months, and 23%, respectively) [18]. An indirect comparison of the toxicity of both multidrug regimens indicates a higher incidence of adverse reactions during the FOLFIRINOX regimen, which could favor nab-P with gemcitabine, especially in patients with a worse performance status [19].

The European Society of Medical Oncology (ESMO) recommends the use of multidrug regimens (FOLFIRINOX and nab-P with gemcitabine) in patients with good or very good performance status, which means

scores 1 or 0 according to the Eastern Cooperative Oncology Group (ECOG) classification. Patients with reduced performance status (ECOG 2) should receive gemcitabine monotherapy. ECOG performance status 3-4 and the presence of comorbidities is an indication for the best supportive care [19]. The National Comprehensive Cancer Network (NCCN) guidelines distinguish between patient populations with good and poor performance status. According to the guidelines, combination therapy is recommended in the first group (FOLFIRINOX, nab-P with gemcitabine, and other regimens, e.g. gemcitabine with erlotinib) while monotherapy is recommended in the second group (gemcitabine, capecitabine or fluorouracil) [20].

This article presents the results of treatment with nab-P in the Polish population in daily clinical practice. In terms of sex and age, this population corresponds to patients treated in clinical trials. Unfortunately, the NHF databases do not include complete and detailed information on performance status or other clinical parameters and laboratory test results. This makes it impossible to compare the obtained results to the data from the subgroup analyses presented in individual prospective clinical trials and the current recommendations, taking into account patient performance status in the treatment eligibility criteria.

In the entire analyzed group of 873 patients, PFS was 169 days, and OS was 379 days. In both analyzes, no statistically significant differences were found depending on sex, and in the case of OS, also age. However, in both analyzes, a statistically significant difference was found depending on the year of diagnosis with the greatest benefit in the group of patients diagnosed in 2014–2016. On the one hand, this situation may be the result of the small (lowest!) size of this group, and, on the other hand, the lack of complete data on PFS and OS in the NHF database. The statistically significant improvement in PFS in patients in the youngest age group may be due to similar reasons. Nevertheless, even such a limited analysis shows that the use of nab-P in combination with gemcitabine in the systemic treatment of patients with pancreatic adenocarcinoma allows us to obtain PFS and OS similar to the results of clinical trials.

In 2019, an analysis of data from the pancreatic cancer registry collected prospectively in 104 centers between 2014 and 2017 was conducted in Germany, including a total of 1174 patients with locally advanced, inoperable, or metastatic pancreatic ductal adenocarcinoma. The median age of patients receiving nab-P with gemcitabine was 71 years, and in 64% of patients, ECOG performance status was ≥ 1. The corresponding values for patients receiving gemcitabine monotherapy or the FOLFIRINOX regimen were 78 years and 60 years, and 73% and 52%, respectively. Median PFS after first-line nab-P plus gemcitabine was 5.6 months (95% CI: 5.0–6.2) [for gemcitabine monotherapy and FOLFIRINOX: 4.6 months (95% CI: 3.7–5.2) and 6.3 months (95% CI: 5.5–6.9), respectively], and median OS was 9.1 (95% CI: 8.2–10.1) [for gemcitabine monotherapy and FOLFIRINOX: 6.8 (95% CI: 6.1–9.0) and 11.3 months (95% CI: 10.5–12.5), respectively]. The authors of the study concluded that the 3 most frequently chosen treatment regimens (gemcitabine, nab-P with gemcitabine, and FOLFIRINOX) were used in different patient populations, which confirms that all of them are applicable depending on the clinical situation [16].

In turn, according to the 2018 French guidelines for the diagnosis and treatment of patients with pancreatic cancer, both FOLFIRINOX and gemcitabine in combination with nab-P are the standard for first-line treatment in patients with good performance status [21].

Apart from clinical trials and research conducted in daily clinical practice, registers and databases are valuable sources of knowledge about the actual effectiveness and safety of various technologies. The prerequisite to such usefulness is a systematic, preferably prospective, supply of registers with complete, readable, and reliable data. Only then can the analyzes allow for correct conclusions useful in making therapeutic decisions.

When analyzing the data collected in the National Health Fund, it seems that their poor quality and quantitative value may result from the fact that these registers are used for evaluation, drawing inferences, and decision-making in the area of administration and management of resources rather than for purposes related to clinical practice. The above conditions were the greatest limitation of the presented analysis.

Conclusions

The results of treatment with nab-paclitaxel in daily clinical practice in patients with advanced pancreatic cancer are similar to those known from clinical trials. The drug has an established place in the therapeutic algorithm in the first-line of treatment. Collecting and periodically analyzing demographic and clinical data could further determine the role of nab-P in this still-difficult-to-treat population.

Article Information and Declarations

Conflict of interest

B.R.: advisory/consulting role & travel and accommodation support — Servier, Roche, AstraZeneca, BMS, MSD, Lilly, Pierre Fabre, Novartis.
M.K.: advisory/consulting role & travel and accommodation support — Servier, Roche, AstraZeneca, BMS.
I.R. declares no conflict of interest.

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