Treatment Patterns in US Patients Receiving First-Line and Second-Line Therapy for Metastatic Pancreatic Ductal Adenocarcinoma in the Real World

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ABSTRACT

Introduction: Metastatic pancreatic ductal adenocarcinoma (mPDAC) is a common cancer with poor survival outcomes. Although treatment options are limited, real-world treatment patterns and outcomes are not well understood, particularly beyond first-line treatment. This study described real-world treatment patterns and outcomes for mPDAC in the USA.

Methods: This retrospective analysis used electronic health record-derived de-identified data of patients with mPDAC diagnosed between January 1, 2014 and June 30, 2021. Treatments were classified into six groups: (1) standard combination chemotherapy; (2) nonstandard combination chemotherapy; (3) single-agent chemotherapy; (4) targeted therapy; (5) clinical study drugs; and (6) off-label therapies. Analyses were descriptive in nature. Treatment utilization and switching, and time on treatment and time to discontinuation, were described by first-line (1LOT) and second-line (2LOT) treatment groups. Median overall survival (mOS) from 1LOT and 2LOT was stratified by treatment group, and for 1LOT on the basis of whether patients received further treatment.

Results: 1LOT included 6979 patients, 3241 (46%) of whom received further 2LOT. Standard combination chemotherapy was the most common 1LOT (70%) and 2LOT (46%). Non-standard combination chemotherapy was used more as 2LOT (35%) than 1LOT (11%). First-line time on treatment was generally higher than second-line time on treatment, and time to discontinuation was lower than time on treatment. mOS in days (months) from 1LOT was 271 (8.9), 252 (8.3), 219 (7.2), 170 (5.6), 280 (9.2), and 182 (6.0), and mOS from 2LOT was 202 (6.6), 193 (6.3), 186 (6.1), 193 (6.3), 179 (5.9), and 97 (3.2), for groups 1–6, respectively. Within group 1, mOS from 1LOT was 318 days (10.4 months) for FOLFIRINOX and 241 days (7.9 months) for gemcitabine and nab-paclitaxel.

Conclusion: Most patients with mPDAC received 1LOT in line with clinical practice guidelines, yet mOS remains poor. This study highlights the need for novel therapies to demonstrate improved patient survival compared with therapies in current clinical practice guidelines.

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INTRODUCTION

Pancreatic cancer represents a major global health burden affecting nearly half a million newly diagnosed patients in 2020 [1]. With 466,003 estimated deaths in that year, pancreatic cancer was the seventh most common cause of cancer death [1]. Pancreatic cancer currently is the second leading cause of cancer-related death in the USA and is expected to stay the second leading cause of cancer-related death at least until 2030 [1, 2]. The vast majority of pancreatic tumors are adenocarcinomas arising from the ductal epithelium (PDAC) [3]. Surveillance, Epidemiology, and End Results (SEER) data for 2012–2018 show that 52% of US patients with PDAC are diagnosed with metastatic disease [4], and many patients with a local or regional diagnosis of pancreatic cancer will develop metastases through the course of their disease. Prognosis is poor, with 5-year relative survival rates of 44%, 15%, and 3% for patients diagnosed with localized, regional, or distant disease, respectively [4].

According to clinical practice guidelines established by the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO), patients with advanced unresectable or metastatic pancreatic cancer should be treated with systemic chemotherapy if their performance status and comorbidity profile allow [5, 6]. More specifically, the clinical practice guidelines from the National Comprehensive Cancer Network (NCCN) indicate that first-line treatment options for patients with a good performance score include chemotherapy with (modified) leucovorin, 5-fluorouracil (5-FU), irinotecan, and oxaliplatin (FOLFIRINOX, Eastern Cooperative Oncology Group [ECOG] performance status 0–1), or with gemcitabine and paclitaxel (ECOG performance status 0–2), and single-agent treatment using gemcitabine, capecitabine, or 5-FU are options for those with poor performance status (ECOG performance status 2 or higher) [7]. The ASCO guidelines further distinguish between patients with a good performance status and a favorable comorbidity profile and those with a relatively favorable...
comorbidity profile, where the former are recommended to receive FOLFIRINOX and the latter to receive gemcitabine and nab-paclitaxel as first-line treatment [6]. If the performance score of the patient allows, switching to the alternative type of combination chemotherapy (i.e., fluoropyrimidine- or gemcitabine-based) is typically recommended for those who have progressed on their initial combination therapy [6, 7]. Furthermore, recent years have seen more targeted therapies entering the PDAC treatment landscape, although these are indicated for relatively small subgroups of patients. Olaparib has been approved by the US Food and Drug Administration (FDA) in late 2019 as first-line maintenance therapy for patients with metastatic PDAC harboring germline deleterious mutations in the *BRCA* gene (gBRCAm) [6–8]. In a rare subset of patients with PDAC, immunotherapy with pembrolizumab, an anti-PD-1 checkpoint inhibitor, can be utilized as part of a tissue-agnostic approval for previously treated, microsatellite-instability-high (MSI-H) cancers [6, 7, 9]. Other therapies with a tissue-agnostic approval are larotrectinib or entrectinib for treatment of *NTRK* gene fusion-positive tumors [6, 7, 9].

There is a scarcity of observational studies that describe treatment patterns and corresponding clinical and economic outcomes for advanced (nonresectable or metastatic) pancreatic cancer in routine care, and evidence on second-line treatment utilization and outcomes is lacking. This represents an important evidence gap, because 38% of patients are expected to start second-line systemic treatment after first-line treatment, which is even higher at 43% for patients younger than 70 years [10]. Furthermore, patterns of switching to second-line treatment based on first-line treatments, as well as differences in first-line treatment utilization and outcomes between patients who discontinue treatment overall and those who switch to a second-line treatment, have not been described. Analyzing treatment patterns and outcomes beyond the first line of therapy in routine care is important to understand how patients are being treated and what the corresponding outcomes are. Furthermore, understanding current second-line treatment utilization allows identification of opportunities where emerging treatments have potential to address the unmet need for patients with pancreatic cancer.

To address the identified evidence gap, this study aimed to provide a thorough understanding of real-world treatment patterns and outcomes for patients with metastatic PDAC (mPDAC) in the USA through descriptive analyses of first-line and second-line treatment utilization, as well as switching patterns, time on treatment and time to discontinuation by treatment type, and overall survival.

**METHODS**

**Study Design and Data Source**

This study was a descriptive, retrospective analysis of treatment patterns and outcomes based on data from the nationwide Flatiron Health electronic health record-derived de-identified database between January 1, 2014 and June 30, 2021. The Flatiron Health database is a longitudinal database comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction [11, 12]. During the study period, the de-identified data originated from approximately 280 US cancer clinics.

**Study Population**

Included patients were those with a pathologic diagnosis consistent with adenocarcinoma of the pancreas and diagnosed with stage IV disease on or after January 1, 2014, and up to June 30, 2021, or those who were initially diagnosed with earlier-stage pancreatic cancer and subsequently developed recurrent or progressive disease on or after January 1, 2014 and up to June 30, 2021. This was based on a diagnosis of PDAC (ICD9 code: 157.x [except 157.4]; ICD10 code: C25.x [except C25.4]) with presence of an additional diagnosis for metastases in other organs and with an initiated first-line treatment from January 1, 2014 through latest available date in the data source. Patients had to
be at least 18 years old when initiating first-line treatment (i.e., index therapy) and have at least 1 month of follow-up after starting that therapy. To be included in the analysis of the treatment duration and overall survival for second-line treatments, patients had to have at least 1 month of follow-up after starting the second-line therapy.

Classification of Treatments

Oncologist-defined, rule-based lines of therapy were classified. In synthesizing the results, this study further stratified first- and second-line treatments according to the following mutually exclusive categories based on input from a clinical expert: (1) standard combination chemotherapy (i.e., gemcitabine and nab-paclitaxel, or FOLFIRINOX), (2) nonstandard combination chemotherapy, (3) single-agent chemotherapy, (4) nonchemotherapy targeted therapy, (5) clinical study drugs, and (6) nonchemotherapy off-label drugs. A detailed overview of medications in each of these groups is provided in Supplementary Table S1. Certain treatments were excluded from the analysis on the basis of clinical advice, because these therapies are typically used as maintenance treatment for other concurrent cancers (total number of patients excluded represented less than 1%, see Supplementary Table S2 for a list of these treatments).

Definition of Outcomes

The time on treatment for all patients was measured from the date at which the therapy was started until the date of the last administration of the therapy. The time to discontinuation of treatment was determined on the basis only of those who discontinued treatment for at least 30 days after the last administration date and measured from the date at which the therapy was started until the date of the last administration of the therapy. Patients who died within 30 days (inclusive) of the last administration date or whose observation period ended before 30 days (inclusive) after the last administration date were not considered to be discontinuations. Overall survival was measured as the time from the initiation of the treatment line until the date of death. Given that the mortality data in the database only showed the month and year of death, the middle of the month was used as the date of death in computing the duration of the overall survival time.

Statistical Analysis

All analyses were descriptive in nature and no hypotheses were tested. Treatment utilization in each line of therapy and switching patterns were described by counts and their relative proportions. Descriptive analyses using the median summarized the time on treatment, time to discontinuation, and overall survival, stratified by type of treatment. Overall survival was additionally presented in Kaplan–Meier plots, and overall survival from first-line treatment was further stratified on the basis of whether patients continued to receive second-line treatment (switched) or not (non-switched). The data were prepared for analysis using SAS software version 9.4 (SAS Institute, Cary, NC), and analyzed using SAS, Stata software version 17.0 (Stata Corp, College Station, TX), and R version 4.1.1.

Protection of Patients

The data are de-identified and subject to obligations to prevent re-identification and protect patient confidentiality. Furthermore, as explained in defining the outcomes, the exact date of death was not available in the study data, but the month and year of death were provided, which were handled as described in the “Definition of Outcomes” section. Finally, no individual-level data are presented in this manuscript.

Compliance with Ethics Guidelines

Approval of an ethics committee and informed consent were not required for this study as it concerned the analysis of de-identified data and the reporting of only aggregate results from this
analysis. Institutional Review Board approval of the study protocol for data collection from the real-world cohort was obtained prior to study conduct and included a waiver of informed consent.

RESULTS

Patient Characteristics

The identification of the patient sample from the database is detailed in Fig. 1. Of the 11,410 patients with a PDAC diagnosis in the eligibility period, 8452 adults had identified metastases and started a first-line treatment. Of these patients, 6979 had the required minimum follow-up of 1 month, representing the first-line treatment patient sample used for the analyses. Among the first-line patient sample, 3241 patients started second-line treatment, 2808 of whom had sufficient follow-up and represented the second-line treatment sample used for the analyses.

Table 1 presents the patient demographics and clinical characteristics of the first- and second-line patient samples. The mean age when starting first-line treatment was 67 years and the median duration of follow-up for the first-line treatment sample was 193 days. Patients in the sample (N = 6979) were most often male (n = 3738, 54%) and white (n = 4663, 67%). Most patients (n = 5985, 86%) received care in a community setting. Stage IV disease (i.e., metastatic disease) was the most common (n = 4670, 67%) stage at which patients were initially diagnosed. Overall, patients had a good performance score, with 71% (n = 4973) having a recorded ECOG performance status of 0 or 1. Before the start of first-line treatment (index date), 1373 (20%) patients had undergone a surgical intervention for their disease, with the majority of these patients (76%) undergoing Whipple surgery. A further 72 (1%) received surgery after the index date.

At the start of second-line treatment, patients were on average 67 years old, and the median follow-up was 151 days. Patients in the second-line treatment sample (N = 2808) were most often male (n = 1496, 53%), white (n = 1942, 69%), and more likely to receive care in a community setting (n = 2334, 83%) rather than an academic setting. Those who received second-line treatment had an overall good performance score, with 72% (n = 2033) having an ECOG score of 0 or 1.

Treatment Patterns

As demonstrated in Table 2, the majority of patients received first-line treatment in line with clinical practice guidelines, either standard chemotherapy combinations of gemcitabine and nab-paclitaxel or FOLFIRINOX (n = 4910/6979, 70%) or chemotherapy with a single agent (n = 763, 11%). Furthermore, a substantial proportion of patients received nonstandard combination chemotherapy (n = 766, 11%)—for example with leucovorin, 5-fluorouracil and oxaliplatin (FOLFOX) (n = 251)—or a clinical study drug (n = 432, 6%). Only 1% of patients (n = 66) received a targeted treatment. There was no meaningful difference in the utilization of first-line treatment over time (data not shown).

Overall, 3241 of 6979 (46%) patients who received a first-line treatment continued to have a second line of therapy. Of note, this total number of second-line treatments is higher than the number of patients in the main second-line treatment patient sample because only patients with more than 1 month of follow-up were included in that sample for second-line treatment analyses. More patients received nonstandard combination chemotherapy (n = 992/2808, 35%) compared with first-line treatment (n = 766/6979, 11%). However, patients were still most likely to receive a
Fig. 1  Identification and attrition of the first-line treatment and second-line treatment patient samples from the Flatiron Health electronic health record-derived database. PDAC pancreatic ductal adenocarcinoma
### Table 1 Overview of patient demographics and clinical characteristics

|                          | Patients with first-line treatment | Patients with second-line treatment |
|--------------------------|------------------------------------|-------------------------------------|
| Number of patients       | 6979 (100)                         | 2808 (100)                          |
| Follow-up time, days     | Mean (SD) 281 (279)                | 228 (232)                           |
|                          | Median (min, max) 193 (31, 2692)   | 151 (31, 2505)                      |
| Age, mean (SD)           | Mean (SD) 67 (10)                  | 67 (9)                              |
|                          | Median (min, max) 68 (22, 85)      | 67 (22, 85)                         |
| Age group, years         | 18–25 < 5 (0a)                     | < 5 (0a)                            |
|                          | 26–45 129 (2)                      | 49 (2)                              |
|                          | 46–65 2676 (38)                    | 1171 (42)                           |
|                          | 66–75 2607 (37)                    | 1058 (38)                           |
|                          | 76–85 1566 (22)                    | 529 (19)                            |
|                          | 86 and over < 5 (0a)               | < 5 (0a)                            |
| Gender                   | Female 3241 (46)                   | 1312 (47)                           |
|                          | Male 3738 (54)                     | 1496 (53)                           |
| Race                     | White 4663 (67)                    | 1942 (69)                           |
|                          | Black or African American 612 (9)  | 246 (9)                             |
|                          | Asian 131 (2)                      | 64 (2)                              |
|                          | Hispanic or Latino 17 (0a)         | 7 (0a)                              |
|                          | Other race 943 (14)                | 333 (12)                            |
|                          | Missing 613 (9)                    | 216 (8)                             |
| Ethnicity                | Hispanic or Latino 348 (5)         | 137 (5)                             |
|                          | Missing 6631 (95)                  | 2671 (95)                           |
| Hospice                  | Yes 3614 (52)                      | 1560 (56)                           |
|                          | No/unknown 3365 (48)               | 1248 (44)                           |

### Table 1 continued

|                          | Patients with first-line treatment | Patients with second-line treatment |
|--------------------------|------------------------------------|-------------------------------------|
| BRCA pre-index date      | Positive 117 (2)                   | 90 (3)                              |
|                          | Negative 1661 (24)                 | 954 (34)                            |
|                          | Other value 205 (3)                | 103 (4)                             |
|                          | Missing 4996 (72)                  | 1661 (59)                           |
| Surgery pre-index date   | Whipple 1039 (15)                  | 452 (16)                            |
|                          | Distal pancreatectomy 310 (4)      | 159 (6)                             |
|                          | Total pancreatectomy 9 (0a)        | < 5 (0a)                            |
|                          | Other 15 (0a)                      | < 5 (0a)                            |
| Practice type            | Community 5985 (86)                | 2334 (83)                           |
|                          | Academic 1024 (15)                 | 490 (17)                            |
| Baseline ECOG performance status | ECOG 0–1 4973 (71) | 2033 (72)                           |
|                          | ECOG 2–4 879 (13)                  | 410 (15)                            |
|                          | Unknown 1127 (16)                  | 365 (13)                            |
| Group stage of initial PDAC diagnosis | 1 310 (4) | 100 (4)                             |
|                          | 2 1059 (15)                       | 455 (16)                            |
|                          | 3 506 (7)                         | 186 (7)                             |
|                          | 4 4670 (67)                       | 1909 (68)                           |
|                          | Unknown 434 (6)                   | 158 (6)                             |
| National Cancer Comorbidity Index | Diabetes and diabetes with chronic complications | 1105 (16) | 388 (14) |
|                          | Chronic pulmonary disease 397 (6)  | 153 (5)                             |
standard combination chemotherapy \((n = 1281, \, 46\%\) in the second-line setting. Similar to first-line therapy, some \((n = 141, \, 5\%\) patients received treatment with a drug as part of a clinical study and a similar proportion \((n = 99, \, 4\%\) of patients received a targeted therapy.

Detailed first- to second-line switching patterns are available from Supplementary Table S4 and an illustration of this information is presented in Fig. 2. Those who started with a standard combination chemotherapy and continued to receive second-line treatment \((n = 2341)\) were most likely to continue with a standard combination chemotherapy \((n = 1089, \, 47\%\) or a nonstandard combination therapy \((n = 817, \, 35\%). This pattern was consistent across other first-line treatment groups, with patients being most likely to switch to second-line standard or nonstandard combination chemotherapy.

### Duration of Treatment

The duration of treatment and time to discontinuation for both the first and second lines of therapy, stratified by treatment group, are presented in Table 3. Across all treatment groups, the median time on treatment (minimum, maximum) was 121 (1, 2380) days in the first line and 101 (1, 2031) days in the second line of therapy. Of those receiving a treatment in one of the treatment-classification groups, 56% and 49% discontinued first- and second-line treatment, respectively, whereas the others deceased while receiving therapy or within 30 days of the last therapy administration. The median time to discontinuation was 92 (1, 1135) days for first-line treatment and 70 (1, 792) days for second-line treatment. (Note that the time on treatment and time to discontinuation differ because the former additionally includes patients whose observation period ended, or who died, within 30 days [inclusive] of that last administration date.)

For first-line treatment, patients spent the most time on standard combination chemotherapy at a median of 132 (1, 2380) days, followed by 121 (6, 1057) days for clinical study drugs and 102 (1, 1731) days for nonstandard combination chemotherapy. The median treatment duration for first-line treatment with single-agent chemotherapy was 95 (1, 1763) days. At 61 (15, 289) and 81 (8, 617) days, the shortest time was spent on off-label drugs and targeted therapies, respectively. Time to discontinuation was lower compared with the time on treatment for all treatment groups.

With regards to second-line treatment, most time was spent on standard combination chemotherapy with a median of 119 (6, 1448) days, followed by nonstandard combination chemotherapy with a median of 95 (3, 2031) days.
days. The median time on second-line treatment for single-agent chemotherapy, clinical study drugs, and targeted therapies was similar at 86 (1, 1788), 85 (15, 1100), and 84 (28, 1261) days, respectively. The least time was spent on off-label drugs, at a median of 45 (31, 99) days. Similar to first-line treatment, time to discontinuation was lower compared with the time on treatment for all treatment groups. The duration of treatment prior to switching varied substantially between first- and second-line treatment type (Supplementary Table S4).

![Illustration of treatment switching patterns from first-line treatment to second-line treatment, including the proportion of first-line patients who switched to a second-line treatment in the first-line treatment labels](image)

**Fig. 2** Illustration of treatment switching patterns from first-line treatment to second-line treatment, including the proportion of first-line patients who switched to a second-line treatment in the first-line treatment labels

| Treatment group                        | First-line treatments | Second-line treatments |
|---------------------------------------|-----------------------|------------------------|
|                                       | n^b  | % of total first-line sample (N = 6979) | n^b  | % of total second-line sample (N = 2808) |
| Standard combination chemotherapy     | 4910 | 70                                    | 1281 | 46                                    |
| Nonstandard combination chemotherapy  | 766  | 11                                    | 992  | 35                                    |
| Single-agent chemotherapy             | 763  | 11                                    | 272  | 10                                    |
| Targeted therapy                      | 66   | 1                                     | 99   | 4                                     |
| Clinical study drug                   | 432  | 6                                     | 141  | 5                                     |
| Off-label drug                        | 7    | 0^c                                   | 8    | 0^c                                   |
| Total                                 | 6944 | 100                                   | 2793 | 100                                   |

^aSee Supplementary Table S4 for detailed information on first-line to second-line treatment switching patterns
^bNote that treatments utilized by < 1% of patients were not classified into 1 of the 6 treatment groups (see Supplementary Table S2 for excluded treatments); hence, the total numbers in this table are lower than those reported in Fig. 1 and Table 1
^cNote that percentages may appear as 0% as a result of rounding
Table 3  Duration of treatment in days, stratified by treatment group and line of treatment (time on treatment), and including a subgroup analysis for those patients for whom treatment was discontinued (time to discontinuation)

| Treatment group                  | First-line treatment |                      | Second-line treatment |                      |
|----------------------------------|----------------------|----------------------|------------------------|----------------------|
|                                  |                      |                      |                        |                      |
|                                  | Time on treatment    | Time to discontinuation |                        |                      |
|                                  | \( n \)  | Median days on treatment (min, max) | \( n \)  | Median days to discontinuation (min, max) | \( n \)  | Median days on treatment (min, max) | \( n \)  | Median days to discontinuation (min, max) |
| Standard combination chemotherapy| 4910                | 132 (1, 2380)        | 2762                   | 106 (1, 1065)        | 1281               | 119 (6, 1448) | 617         | 92 (1, 792)                  |
| Nonstandard combination chemotherapy | 766                | 102 (1, 1731)        | 452                    | 71 (1, 1135)         | 992               | 95 (3, 2031) | 484         | 64 (1, 750)                  |
| Single-agent chemotherapy        | 763                 | 95 (1, 1763)         | 375                    | 43 (1, 666)          | 272               | 86 (1, 1788) | 143         | 39 (1, 485)                  |
| Targeted therapy                 | 66                  | 81 (8, 617)          | 30                     | 22 (1, 302)          | 99                | 84 (28, 1261) | 52          | 43 (1, 357)                  |
| Clinical study drug              | 432                 | 121 (6, 1057)        | 233                    | 106 (1, 834)         | 141               | 85 (15, 1100) | 82          | 44 (1, 483)                  |
| Off-label drug                   | 7                   | 61 (15, 289)         | \(< 5\)                | 1 (1, 1)             | 8                 | 45 (31, 99)   | \(< 5\)     | 17 (11, 23)                  |
| Total\(^b\)                     | 6944                | 121 (1, 2380)        | 3800–3900\(^c\)       | 92 (1, 1135)         | 2793              | 101 (1, 2031) | 1300–1400\(^c\) | 70 (1, 792)                  |

\(^a\) Specific medications in each treatment group are specified in Supplementary Table S1

\(^b\) Note that treatments utilized by \(< 1\%\) of patients were not classified into 1 of the 6 treatment groups (see Supplementary Table S2 for excluded treatments): hence, the total numbers in this table are lower than those reported in Fig. 1 and Table 1

\(^c\) Ranges were reported to maintain patient confidentiality
Overall Survival

Outcomes in terms of overall survival from the start of first and second line of therapy for the different treatment groups, as well as subgroup analyses for patients who continued to receive treatment in the second line of therapy (switch) and those who did not receive further treatment (non-switch), are presented in Table 4 and Figs. 3, 4, 5.

Table 4 presents overall survival from start of first-line treatment for the different treatment groups, as well as subgroup analyses for patients who continued to receive treatment in the second line of therapy (switch) and those who did not receive further treatment (non-switch).

| Treatment group               | First-line treatment | Second-line treatment |
|------------------------------|----------------------|-----------------------|
|                              | Median overall       | Median overall        | Median overall         |
|                              | survival (days,     | survival—non-switch  | survival—switch       |
|                              | 95% CI)             | (days, 95% CI)        | (days, 95% CI)        |
| Standard combination         | 271 (261, 282)      | 167 (159, 174)        | 378 (365, 393)        | 202 (188, 216) |
| chemotherapy                 |                      |                      |                      |                  |
| Nonstandard combination      | 252 (233, 271)      | 161 (143, 179)        | 338 (313, 392)        | 193 (177, 208)  |
| chemotherapy                 |                      |                      |                      |                  |
| Single-agent chemotherapy    | 219 (200, 239)      | 142 (128, 165)        | 350 (323, 375)        | 186 (156, 232)  |
| Targeted therapy             | 170 (131, 211)      | 150 (100, 177)        | 320 (168, 408)        | 193 (135, 281)  |
| Clinical study drug          | 280 (242, 310)      | 169 (133, 198)        | 360 (320, 435)        | 179 (162, 219)  |
| Off-label drug               | 182 (93, NR)        | 184 (93, NR)          | 182 (111, NR)         | 97 (33, 117)    |

NR not reached, CI confidence interval

treatment overall (non-switch) compared with those who switched to a second line of therapy are presented in Fig. 4. Median overall survival from first-line treatment was more than twice as high for patients who switched to second-line treatment compared with those who did not, except for patients who received off-label treatment. For example, for standard combination therapy, median survival was 378 (365, 393) days for those who switched compared with 167 (159, 174) days for those who did not receive further treatment.

Overall survival from the start of second-line treatment, stratified by second-line treatment group, is presented in Fig. 5. With the exception of off-label drugs, overall survival across the treatment groups was more comparable than it was based on first-line treatment. Standard combination chemotherapy yielded the highest median overall survival of 202 (188, 216) days, whereas off-label drugs were associated with the lowest overall survival from second-line treatment at 97 (33, 117) days.

Table 5 presents overall survival from start of first-line treatment for different treatment
Fig. 3 Kaplan–Meier plots for overall survival from the initiation of first-line treatment for patients initiating treatment with (a) standard combination chemotherapy, (b) nonstandard combination chemotherapy, (c) single-agent chemotherapy, (d) targeted therapy, (e) a clinical study drug, and (f) off-label drugs. Shaded areas represent 95% Hall–Wellner confidence bands.
Fig. 4 Kaplan–Meier plots for overall survival from the initiation of first-line treatment, stratified on the basis of whether treatment is discontinued or switched, for patients initiating treatment with a standard combination chemotherapy, b nonstandard combination chemotherapy, c single-agent chemotherapy, d targeted therapy, e a clinical study drug, and f off-label drugs. Shaded areas represent 95% Hall–Wellner confidence bands.
Fig. 5 Kaplan–Meier plots for overall survival from the initiation of second-line treatment for patients initiating treatment with 
(a) standard combination chemotherapy, 
(b) nonstandard combination chemotherapy, 
(c) single-agent chemotherapy, 
(d) targeted therapy, 
(e) a clinical study drug, 
and 
(f) off-label drugs. Shaded areas represent 95% Hall–Wellner confidence bands.
sequences. Of the patients who started on FOLFIRINOX (n = 1910), 817 (43%) switched to gemcitabine and nab-paclitaxel, resulting in median overall survival of 372 (353, 392) days. Of the patients who started on gemcitabine and nab-paclitaxel (n = 2990), 251 (8%) switched to FOLFIRINOX, resulting in a slightly lower median overall survival of 347 (311, 379) days compared to the reverse sequence. Following first-line treatment with FOLFIRINOX, 90 (5%) and 69 (4%) patients received second-line non-standard combination chemotherapy or single-agent chemotherapy, yielding an overall survival of 488 (401, 576) days and 486 (333, 581) days, respectively. Conversely, after first-line treatment with gemcitabine and nab-paclitaxel, 726 (24%) and 153 (5%) patients received second-line non-standard combination chemotherapy or single-agent chemotherapy, yielding an overall survival of 375 (355, 413) days and 361 (315, 409) days, respectively.

**DISCUSSION**

We present a comprehensive descriptive analysis of first- and second-line treatment utilization, duration, and outcomes for patients with mPDAC in the USA using real-world data of

| First-line treatment | Median overall survival (days, 95% CI) | Second-line treatment | Median overall survival from first-line treatment (days, 95% CI) |
|----------------------|--------------------------------------|-----------------------|---------------------------------------------------------------|
| FOLFIRINOX           | 318 (302, 333)                       | Gemcitabine and nab-paclitaxel | 372 (353, 392)                                               |
|                      |                                      | Nonstandard combination chemotherapy | 488 (401, 576)                                               |
|                      |                                      | Single-agent chemotherapy | 486 (333, 581)                                               |
|                      |                                      | Targeted therapy | 479 (337, 659)                                               |
|                      |                                      | Clinical study drug | 597 (402, 717)                                               |
|                      |                                      | Off-label drug | < 5 434 (NR, NR)                                              |
| Gemcitabine and nab-paclitaxel | 241 (231, 251) | FOLFIRINOX | 347 (311, 379)                                               |
|                      |                                      | Nonstandard combination chemotherapy | 375 (355, 413)                                               |
|                      |                                      | Single-agent chemotherapy | 361 (315, 409)                                               |
|                      |                                      | Targeted therapy | 337 (239, 527)                                               |
|                      |                                      | Clinical study drug | 347 (312, 416)                                               |
|                      |                                      | Off-label drug | < 5 179 (104, NR)                                             |

*CI confidence interval, NR not reached*
6979 patients from an electronic health record database. With 86% of patients in the data set receiving care in a community setting, the patient sample was representative of routine clinical care. Although the data set included a relatively high proportion of white individuals, the patients’ sex, age, and disease stage at diagnosis were in line with reported national data [4]. Furthermore, 29% of patients in the sample had an ECOG performance score of 2 or higher, or an unknown performance score, and diabetes with or without chronic complications was observed as comorbidity in 16% of patients, which provides a more realistic representation of the real-world patient population compared with clinical studies that typically recruit only fit patients.

The majority of patients received first-line treatment with combination chemotherapy (71%) or single-agent chemotherapy (11%), in line with clinical practice recommendations. Furthermore, only 6% of patients received a clinical study drug as first line of therapy. These findings are in line with previous US studies. DaCosta Byfield et al. found in their 2001–2010 sample that the majority of patients receive treatment with standard chemotherapy (combinations) [13]. Additionally, they found that 13% of patients received targeted treatment. Although this is a higher number compared with our findings, their analysis does not consider clinical study drugs as a separate treatment group, it is unclear what proportion of patients in their sample received treatment in an academic setting, and there may have been changes in clinical practice over time. A study on real-world treatment patterns in the USA by Elias et al. found that first-line treatment differed by patient age, with older patients being more likely to receive monotherapy rather than combination chemotherapy [10]. Although they only provide treatment utilization by age group, they used the same database to identify their 2015–2020 sample and the identified trends were similar to those identified in the current study [10]. In Japan, patients with unresectable and recurrent PDAC diagnosed in 2009 were found to be most likely (62%) to receive gemcitabine as first-line chemotherapy [14].

In comparison with the study by Elias et al. [10], which found that 38% of patients will receive a second line of therapy after their first-line treatment, we found that 46% of treated patients receive more than one line of therapy. However, what treatments are utilized in the second line has not been described by Elias et al. We found that more patients received treatment with a nonstandard combination chemotherapy in the second line (35%) compared with the first line of therapy (11%). This may not be surprising, given that patients’ performance status and organ function may decline after first-line treatment, making them ineligible for standard combination treatment or clinical trials. This may be especially true in situations where patients have progressive disease as their best response on first-line therapy. Similar to the first line of therapy, 4% of patients received targeted therapy and 5% participated in a clinical study as second-line treatment.

In terms of targeted therapies specifically, our results show that only 25% of patients were tested for their BRCA status, which is likely to have contributed to the observation that few patients receive a targeted therapy. Furthermore, although advances have been made in terms of developing therapies for NTRK fusions and the KRAS gene [9], for example, these have not yet resulted in the needed improvement in patient outcomes. This highlights the need not only for more actionable targets with matched treatments but also for increased testing for known targets such as BRCA and NTRK. Therefore, with the current standard of care established a long time ago and without substantial progress in treatment options ever since, this stresses the need for more clinical trials and better patient access to these studies given the poor overall outcomes on existing treatments.

This study is also the first to describe treatment duration for first- and second-line treatment of mPDAC. For the first line of therapy, the median time on treatment varied substantially between treatment groups, being highest for standard combination chemotherapy (132 days) and lowest for off-label drugs (61 days), although the number of patients in this latter group was low. Interestingly, patients
spent a median of 121 days on clinical study drugs, but only 81 days on targeted therapy. The longevity of the treatment duration for standard combination chemotherapy and clinical study drugs may potentially be explained by a relatively good performance status of the patients eligible for these treatments. For the second line of therapy, the median time on treatment was more comparable across treatment groups, but higher for standard combination chemotherapy (119 days) and lower for off-label drugs (45 days) compared with the other groups (range 84–95 days). Median time to discontinuation was lower compared with the time on treatment across both first- and second-line treatment, but trends between treatment groups were similar as for time on treatment. The duration of first-line treatment prior to switching to second-line treatment varied substantially by first- and second-line treatment type. Interpretations of the clinical study drug group are limited, where the relatively high time on treatment for clinical study drugs may be related to the characteristics of the clinical study and may not be reflective of real-world practice. In addition to the findings that a small proportion of patients were tested for their BRCA status and that even fewer patients overall received targeted therapy, the low time spent on these treatments may suggest that these therapies are not prescribed appropriately or that they lack in real-world effectiveness for patients with mPDAC. Additional research is needed to understand the BRCA testing and impact on real-world treatment utilizations.

In terms of median overall survival from first-line treatment, this was highest for patients receiving treatment with a clinical study drug (280 days, 9.2 months). This may be a consequence of selection bias, as discussed for the time on treatment, because it is reflective of patients in a clinical trial setting and not necessarily in the real-world setting. Notably, first-line targeted therapy yielded the lowest median overall survival (170 days, 5.6 months), further suggesting that effective targeted treatment for mPDAC does not exist in a real-world setting. These findings are generally in line with the previously reported age-group-specific first-line survival outcomes as published by Elias et al. [10], demonstrating the overall lack of effective treatment options for patients with mPDAC.

Interestingly, the analysis of overall survival from first-line treatment, stratified on the basis of whether patients switched to a second-line treatment or not, demonstrated substantial differences between these two patient groups. Except for off-label drugs, the results for which were subject to low patient numbers, median overall survival was more than twice as high for patients who switched to a second-line treatment compared with those who did not receive further treatment. This observation can likely be explained by patients who are not able to receive second-line treatment because of either having a poor performance status or having progressed too rapidly to receive further anticancer treatment.

The analysis of overall survival from second-line treatment by treatment group also adds to the existing literature in terms of understanding real-world outcomes for patients with mPDAC. Compared with overall survival from first-line treatment, differences between treatment groups were smaller for survival from initiation of the second line of therapy. Excluding off-label drugs, median overall survival from second-line treatment ranged from 179 days (5.9 months) for clinical study drugs to 202 days (6.6 months) for standard combination chemotherapy. Furthermore, patient demographics and disease characteristics were comparable between first- and second-line treatment. These findings suggest that first-line treatments have a more profound impact on overall survival, highlighting the importance of treatment selection in the first line of therapy.

When we looked into the outcomes by specific first-line standard combination chemotherapy treatment in more detail, fewer patients were found to start on FOLFIRINOX compared with gemcitabine and nab-paclitaxel. However, those who did were more likely to receive gemcitabine and nab-paclitaxel as second-line treatment and had higher overall survival compared with those who started on gemcitabine and nab-paclitaxel and switched to FOLFIRINOX. Given that the NCCN guidelines suggest that FOLFIRINOX should be used in patients with ECOG performance score 0–1 and...
the ASCO guidelines additionally suggest those should have a favorable comorbidity profile [6, 7], the higher overall survival after first-line FOLFIRINOX may be (partly) caused by selection bias of healthier patients. Although those who received FOLFIRINOX as first-line treatment were most likely to switch to gemcitabine and nab-paclitaxel, overall survival was higher for those who switched to nonstandard combination chemotherapy or single-agent chemotherapy. Those who started on gemcitabine and nab-paclitaxel were most likely to switch to nonstandard combination chemotherapy, which was associated with a slightly higher overall survival compared with switching to FOLFIRINOX.

This study has certain limitations arising from the use of real-world data obtained from electronic health records. Data obtained from such records may include missing or miscategorized observations. For example, lines of therapy were determined algorithmically as per prior studies, but the accuracy of this algorithm cannot be confirmed. Furthermore, clinical information recorded as free text was not captured in the electronic health record database and, hence, was not considered in the analyses. Therefore, the clinical interpretation of the identified off-label drug use was limited, for example. Also, treatment that has been provided and captured outside of the Flatiron electronic health records database will not be reflected in the data. Additionally, a lack of more detailed information on the hospital characteristics (e.g., high-volume centers) may have limited interpretation of the results. Finally, given that this was a descriptive analysis, no tests of statistical significance were performed to respect the limitations of real-world data and focus on the clinical interpretation of the results.

CONCLUSIONS

This study highlights most patients receive therapies consistent with clinical guidelines, yet median overall survival remains poor. Over a long period with limited novel therapies, this study provides a comprehensive descriptive analysis of first- and second-line treatment utilization, duration, and outcomes for patients with mPDAC in the USA using real-world data from an electronic health record database. Most patients (81%) received first-line treatment in line with clinical practice guidelines. However, nonstandard combination chemotherapy was more often used as second therapy (35%) than as first-line treatment (11%). Gemcitabine and nab-paclitaxel were more often utilized as first-line standard combination chemotherapy compared with FOLFIRINOX, but patients starting on gemcitabine and nab-paclitaxel were most likely to switch to nonstandard combination chemotherapy whereas those starting on FOLFIRINOX were most likely to switch to gemcitabine and nab-paclitaxel in the second line. The median time on treatment varied between treatment groups and time to discontinuation was lower compared with the time on treatment. Median overall survival for first-line standard chemotherapy and nonstandard combination chemotherapy was 271 days (8.9 months) and 252 days (8.3 months), respectively. Within the first-line standard combination chemotherapy group, patients receiving FOLFIRINOX had higher overall survival compared with gemcitabine and nab-paclitaxel. Among patients who received first-line FOLFIRINOX, overall survival was lowest for those who switched to second-line treatment with gemcitabine and nab-paclitaxel.

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**Data Availability.** No data sharing is applicable given that no data were generated as part of the study.

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