# PASS-01: Randomized Phase II Trial of Modified FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel and Molecular Correlatives for Previously Untreated Metastatic Pancreatic Cancer

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## ABSTRACT

**PURPOSE** To assess modified folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX; mFFX) versus gemcitabine/nab-paclitaxel (GnP) in de novo metastatic pancreatic ductal adenocarcinoma (PDAC) and explore predictive biomarkers.

**PATIENTS AND METHODS** Patients were randomly assigned 1:1 to mFFX or GnP with exclusion of germline pathogenic variants in *BRCA1/2* or *PALB2*. The primary end point was progression-free survival (PFS) between arms with 0.3 significance. The per-protocol (PP) population included patients who received one dose of chemotherapy. Pretreatment biopsies underwent whole-genome/transcriptome sequencing and patient-derived organoid (PDO) development, providing correlate recommendations at a molecular tumor board and outcomes assessed according to RNA signatures (basal-like *v* classical).

**RESULTS** Of 160 patients randomly assigned (80 mFFX, 80 GnP), 140 patients were in the PP population (71 mFFX, 69 GnP), with median follow-up of 8.3 months. The median PFS was 4.0 months for mFFX versus 5.3 months for GnP (hazard ratio [HR], 1.37 [95% CI, 0.97 to 1.92]; $P = .069$) in intention-to-treat. Median overall survival (OS) was 8.5 months with mFFX and 9.7 months with GnP (HR, 1.57 [95% CI, 1.08 to 2.28]; $P = .017$). Genomic data were generated in 94%, transcriptomes in 74%, and PDOs in 50%. The median PFS for those with basal-like was 3.0 (mFFX) and 5.5 (GnP) months ($P = .17$), and classical PDAC was 6.3 (mFFX) versus 5.4 (GnP) months ($P = .36$). The median OS in basal-like was 7.5 (mFFX) and 8.9 (GnP) months ($P = .75$) versus in classical OS was 9.7 (mFFX) and 13.9 (GnP) months ($P = .047$). Overall, 75 (54%) of patients received second-line treatment, 33/75 (44%) correlate-guided. The median time on second-line treatment was only 2.1 months with a median OS of 5.4 months for a correlate-guided choice versus 4.4 months on a standard chemotherapy approach ($P = .45$).

**CONCLUSION** In the phase II Pancreatic Adenocarcinoma Signature Stratification for Treatment-01 (PASS-01) trial population, PFS was similar between GnP and mFFX; however, OS and safety trends favored GnP. The second-line setting appears inadequate to offer precision choices, given the short survival observed.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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## INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy treated with combination chemotherapy. Modified folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX; mFFX) and gemcitabine/nab-paclitaxel (GnP) are standard treatment options for advanced PDAC.[1-3] Clinician judgment often dictates which

## CONTEXT

**Key Objective**

In a randomized trial comparing survival outcomes between standard chemotherapies in metastatic pancreatic cancer, outcomes by subtype and correlatives were explored to further our understanding of the molecular determinants of response and resistance.

**Knowledge Generated**

In the first-line setting, patients with de novo metastatic cancer (*gBRCA/PALB2* excluded) had longer progression-free survival and overall survival with gemcitabine/nab-paclitaxel over modified FOLFIRINOX where outcomes were worse among basal-like subtypes. Despite extensive molecular profiling, only a few patients were able to benefit from precision choices in the second-line setting.

**Relevance *(A.H. Ko)***

Molecular profiling of metastatic pancreatic cancer not only offers valuable prognostic information, but may even be potentially useful in helping guide selection of chemotherapy if such information can be obtained in a timely fashion.*

*Relevance section written by *JCO* Associate Editor Andrew H. Ko, MD, FASCO.



regimen is offered, as mFFX and GnP have not been prospectively compared in a randomized trial in North America.[4,5] More recent data from the NAPOLI-3 trial favor NALIRIFOX (folinic acid/leucovorin, fluorouracil, liposomal-irinotecan, oxaliplatin) over GnP in unselected patients, offering another first-line option.[6]

PDAC is a genomically heterogenous malignancy. Deleterious *BRCA2* and *PALB2* mutations are found in approximately 10-15% of patients[7] and serve as predictive biomarkers of platinum and PARP inhibitor response, demonstrating that biomarker stratification in PDAC has clinical value. Transcriptomic profiling of PDAC has revealed two broad subtypes, classical and basal-like.[8] In a prospective, biospecimen-based study of patients with PDAC treated in the first-line setting, objective response rates (ORRs) were significantly better in patients with the classical subtype compared with those with basal-like,[9] suggesting the transcriptional subtypes may serve as a predictive biomarker. It has been previously shown that *GATA6* RNA in situ hybridization (ISH)[10] has good concordance with RNA sequencing, a potential surrogate assay with clinical utility. In addition, signatures from patient-derived organoids (PDOs) also suggest biomarkers of sensitivity.[11]

Pancreatic Adenocarcinoma Signature Stratification for Treatment-01 (PASS-01) was a prospective phase II, randomized, multinational clinical trial, comparing mFFX versus GnP in the first-line setting for patients with metastatic PDAC. The study objectives were to compare survival outcomes and to assess outcomes by subtype and molecular correlatives to further our understanding of the molecular determinants of response and resistance.

## PATIENTS AND METHODS

### Study Design and Participants

PASS-01 (ClinicalTrials.gov identifier: NCT04469556) enrolled patients age 18 years or older with metastatic PDAC, measurable disease per RECIST 1.1, and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Eligibility consisted of patients with histologic or radiographic diagnosis of de novo untreated metastatic PDAC at screening with histology subsequently confirmed before random assignment. Patients were required to have a tumor lesion amenable to biopsy with at least four 18-gauge core needle samples. Histologic variants of mucinous adenocarcinoma or adenosquamous carcinoma were permitted. Patients with a known or strongly suspected germline mutation in *BRCA* or *PALB2* were excluded and treated off protocol as per standard of care. Enrollment occurred at six institutions: two in Canada and four in the United States.

Patients were randomly assigned (1:1) to receive mFFX or GnP, dosed as per institutional standard of care. Treatment continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

The final protocol, amendments, and patient informed consent documents were reviewed and approved by the institutional review boards and independent ethics committees at each site. All patients provided written informed consent. This study was conducted in compliance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice Guidelines.

### End Points

The intention-to-treat (ITT) population consisted of all randomly assigned participants and the per-protocol (PP) population of evaluable patients consisted of patients who received at least one dose of assigned chemotherapy. The primary end point of the study was progression-free survival (PFS), defined as the time from random assignment to (first) progression according to RECIST (investigator assessed) or death, whichever earlier, or last follow-up when alive without progression. The secondary efficacy end points were ORR, duration of response (DOR) in the PP population, and overall survival (OS). Disease control rate (DCR) was defined as the rate of complete response (CR), partial response (PR), or stable disease (SD). DOR was defined as the duration from first PR or CR to progression or death, or to last follow-up if the patient was alive without progression at last follow-up. Safety was evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0, of treatment-related serious adverse events (SAEs).

### Biomarkers/Correlative Analysis and Molecular Tumor Board

Several hypotheses for biomarkers of chemotherapy regimens were explored and data discussed at molecular tumor boards (MTB). Biopsies were laser-captured microdissected for whole-genome and transcriptome sequencing (WGTS), and PDOs were derived as previously described.[9,11] Whole genomes reported HRDetect scores available at MTB. Transcriptomic subtype was assessed using a tumor-enriched RNA signature derived by RNA sequencing.[9] This was blinded to physicians at MTB until progression.

Clinical outcomes were analyzed by transcriptional subtype (basal-like or classical) and by *GATA6* expression as secondary end points. *GATA6* ISH expression was assessed on baseline histology slides[10] and levels were dichotomized into high versus low.

Finally, treating with a biomarker-influenced second-line therapy versus an empiric standard of care was recorded by each investigator on the basis of the discussion during MTB focused on each patient. The monthly MTB consisted of all clinical and translational PASS-01 investigators and included presentation of correlative data and a review of existing relevant literature and potential for on-trial or off-label access to therapy. The choice for subsequent lines was the decision of the patient in discussion with the treating investigator, potentially using the information from MTB.

Exploratory end points included CA19-9 response, measured at the early time point of 4 weeks on chemotherapy. Detailed analysis of remaining exploratory end points including whole genome sequencing (WGS), transcriptomics, PDOs, CODEX immunoprofiling, circulating tumor cells, and circulating tumor DNA (ctDNA) is ongoing and will be reported later.

### Statistical Analyses

The sample size justification was based on the primary end point PFS. We estimated a total of 136 patients (68 per group) with a minimum of 112 events will achieve 80% power at a 0.3 significance level to detect a hazard ratio (HR) of 0.7 when the median PFS with mFFX was assumed to be approximately 7 months using two-sided log-rank test. Given the sample size was limited (funding and the clinical setting) and the need to maximize sensitivity/power for detecting a treatment signal, the relaxed two-sided alpha 0.3 (0.15 one side) was chosen to balance the risk of missing a potential efficacy signal for the design. The primary and secondary efficacy end points (PFS/OS) were analyzed on the basis of the ITT principle. The PP analyses were conducted for both primary and other secondary end points and subgroup analysis. The rate of PFS/OS were estimated using the Kaplan-Meier method and compared between the mFFX and GnP arms using log-rank test. HRs were reported with GnP as the reference, HR < 1 indicating mFFX was better, while HR > 1 indicates GnP better. Other secondary end points such as ORR, DOR, and SAEs were compared between two groups using chi-square test for categorical variables and Student t-test or Wilcoxon rank sum test for continuous variables. The association of PFS/OS with *GATA6* and CA19-9 were examined using similar methods. Subgroup analyses were conducted to examine the treatment effect in patient subgroups of interest using Cox proportional-hazard models with interaction term. However, because of the underpowering of these multiple exploratory end points, the focus was on the magnitude of difference in the treatment effect. Data management and all statistical analyses were performed using SAS 9.4 (SAS Institute, Inc, Cary, NC).

## RESULTS

### Patient Characteristics and Enrollment

Between October 2020 and January 2024, 160 patients were enrolled and randomly assigned to receive mFFX (n = 80) or GnP (n = 80; Fig 1). Overall, patients had a median age of 64 years (range, 40-81), 63% were male, and 36% of the patients were non-White (Table 1). Demographic and baseline disease characteristics were generally balanced between groups, although the *KRAS* wildtype (WT) population and ECOG PS 0 was higher in the GnP group (14% *v* 4% and 59% *v* 41%, respectively), and somatic only biallelic *BRCA2* (2), *RAD51C* (2), and one with somatic homologous recombination deficiency (HRD) with no identifiable etiology were higher in the mFFX group (3% *v* 0.6%). However, in a Cox proportional-hazard regression analysis of potential baseline prognostic features, only the absence of liver metastasis appeared significant for better PFS and OS (data not shown). Of the PP population, 71 (89%) in the mFFX group and 69 (86%) in the GnP group were evaluable for PFS and

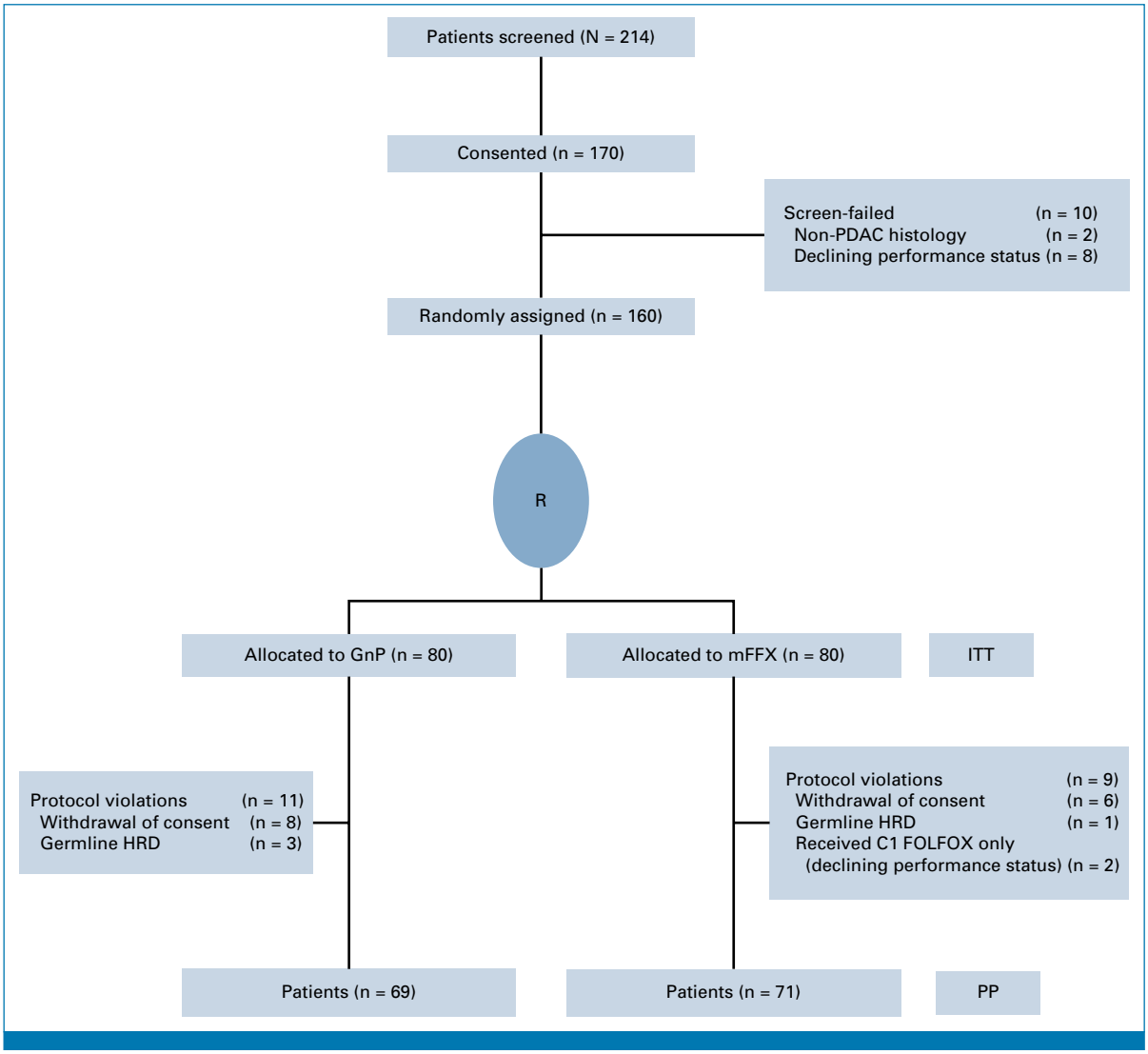



**FIG 1.** CONSORT diagram. FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HRD, homologous recombination deficiency; ITT, intention-to-treat; mFFX, modified FOLFIRINOX; PDAC, pancreatic ductal adenocarcinoma; PP, per-protocol



ORR. At data cutoff, 7 (5%) remained on first-line per arm, and 23 (33%) patients in the GnP group and 14 (20%) in the mFFX group were alive. Median follow-up on the study was 8.3 months as of August 31, 2024 (range, 0.3-37.2 months), with 8.2 months for GnP and 8.4 months for mFFX ($P = .24$). There were 143 PFS events in the ITT population and 130 PFS events among the 140 patients in the PP population.

## Efficacy

For the ITT population, the median PFS was 4.0 months for mFFX and 5.3 months for GnP (HR, 1.37 [95% CI, 0.97 to 1.92]; $P = .069$; Fig 2A). Median OS was 8.5 months for mFFX versus 9.7 months for GnP (HR, 1.57 [95% CI, 1.08 to 2.28]; $P = .017$; Fig 2B). The median duration of PP first-line treatment was 3.7 months for mFFX versus 4.9 months for GnP. Median PFS was 4.2 months for mFFX compared with 5.3 months for GnP (HR, 1.33 [95% CI, 0.93 to 1.90]; $P = .114$). Median OS was 8.7 months for mFFX compared with 10.3 months for GnP (HR, 1.59 [95% CI, 1.07 to 2.36]; $P = .021$; Appendix Figs A1A and A1B, online only). After adjustment for potential confounders (ECOG PS, presence of liver metastasis, and *KRAS* WT status), the HR was reduced to 1.27 and 1.25 for PFS and OS, respectively (Appendix Table A1). There was no statistically significant difference in the treatment effect across baseline features, except better PFS for male gender and OS for absence of liver metastasis when treated with GnP (Appendix Figs A2 and A3).

The ORRs were 30% and 29% for GnP and mFFX, respectively (Figs 3A and 3B). DCR was higher in the GnP group compared with the mFFX group (79.7% *v* 62.9%, $P = .028$). Median time to RECIST response was 3.5 months in both arms. DOR favored GnP at 5.9 versus 4.7 months ($P = .025$). Patients with *KRAS* WT or somatic HRD tended to cluster with deeper responses.

**TABLE 1.** Characteristics of the Patient Population (intention-to-treat)

| | Treatment | | |
|---|---|---|---|
| Patient Characteristic | GnP (n = 80) | mFFX (n = 80) | All (N = 160) |
| Age at random assignment, years, mean (Std. Dev) | 64.6 (7.7) | 62.6 (9.8) | 63.6 (8.8) |
| Range | 44.0-79.0 | 40.0-81.0 | 40.0-81.0 |
| Sex, No. (%) | | | |
| Female | 28 (35.0) | 31 (38.8) | 59 (36.9) |
| Male | 52 (65.0) | 49 (61.3) | 101 (63.1) |
| BMI, median (range) | 26.7 (18.8-44.3) | 25.3 (17.6-42.8) | 26.1 (17.6-44.3) |
| ECOG, No. (%) | | | |
| 0 | 47 (58.8) | 33 (41.3) | 80 (50.0) |
| 1 | 33 (41.3) | 47 (58.8) | 80 (50.0) |
| Race group, No. (%) | | | |
| Asian | 7 (8.8) | 15 (18.8) | 22 (13.8) |
| Black or African American | 10 (12.5) | 5 (6.3) | 15 (9.4) |
| White | 56 (70.0) | 46 (57.5) | 102 (63.8) |
| Other | 3 (3.8) | 8 (10.0) | 11 (6.9) |
| Unknown | 4 | 6 | 10 |
| Region, No. (%) | | | |
| Canada | 37 (46.3) | 35 (43.8) | 72 (45.0) |
| United States | 43 (53.8) | 45 (56.3) | 88 (55.0) |
| Histologic diagnosis | | | |
| Adenocarcinoma | 77 (96.3) | 75 (93.8) | 152 (95.0) |
| Adenosquamous | 0 (0.0) | 1 (1.3) | 1 (0.6) |
| Mucinous adenocarcinoma | 1 (1.3) | 1 (1.25) | 2 (1.3) |
| Poorly differentiated carcinoma | 2 (2.5) | 3 (3.8) | 5 (3.1) |
| CA 19-9 at baseline (U/mL), median (range) | 1,292.0 (1.0-183,038.0) | 1,628.3 (1.0-1,685,985.0) | 1,454.5 (1.0-1,685,985.0) |
| Liver metastasis | | | |
| No | 16 (20.0) | 9 (11.4) | 25 (15.7) |
| Yes | 64 (80.0) | 70 (88.6) | 134 (84.3) |
| NA | 0 | 1 | 1 |
| Lung only metastasis | 0 | 0 | 0 |
| Transcriptional subtype, No. (%) | | | |
| Basal-like | 13 (22.8) | 19 (32.2) | 32 (27.6) |
| Classical | 44 (77.2) | 40 (67.8) | 84 (72.4) |
| NA | 23 | 21 | 44 |
| *KRAS* WT, No. (%) | | | |
| No | 62 (86.1) | 72 (96.0) | 134 (91.2) |
| Yes | 10 (13.9) | 3 (4.0) | 13 (8.8) |
| NA | 8 | 5 | 13 |
| Somatic HRD+, No. (%) | | | |
| No | 79 (98.8) | 76 (95.0) | 155 (96.9) |
| Yes | 1 (1.3) | 4 (5.0) | 5 (3.1) |
| *GATA6* ISH, No. (%) | | | |
| High | 42 (76.4) | 48 (71.6) | 90 (73.8) |
| Low | 13 (23.6) | 19 (28.4) | 32 (26.2) |
| NA | 25 | 13 | 38 |

Abbreviations: FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; HRD, homologous recombination deficiency; ISH, in situ hybridization; mFFX, modified FOLFIRINOX; NA, not available; Std. Dev, standard deviation; WT, wildtype.

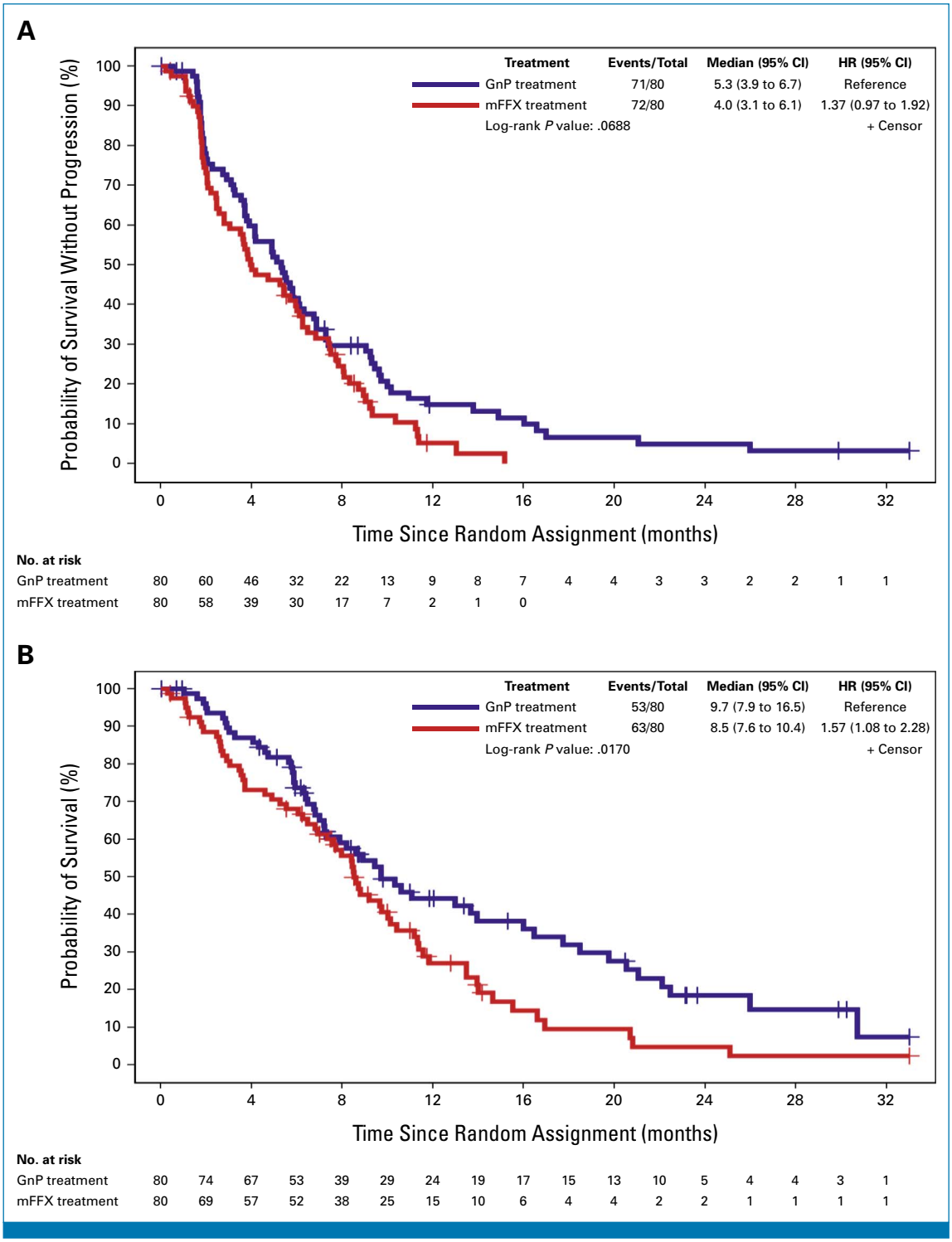
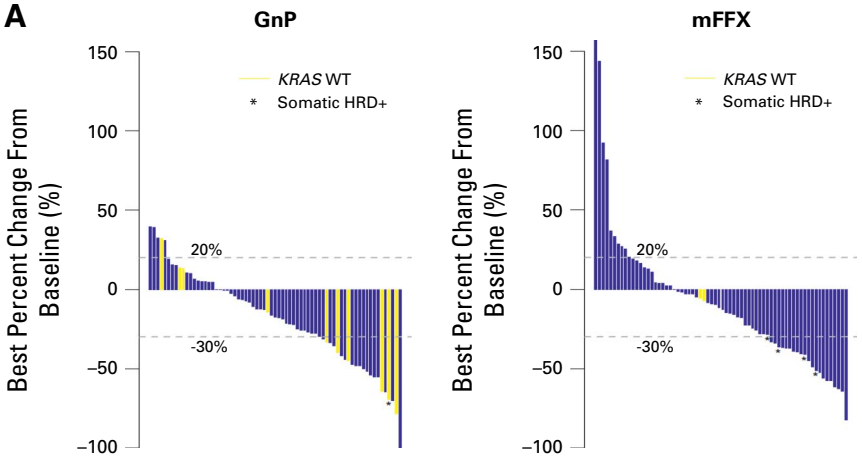



**FIG 2.** Comparison of (A) PFS and (B) OS between two treatment groups: mFFX and GnP treatment for ITT population (160 patients). FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HR, hazard ratio; ITT, intention-to-treat; mFFX, modified FOLFIRINOX; OS, overall survival; PFS, progression-free survival.

## Safety

Given the chemotherapy regimens in this trial were established standards in PDAC with ample published toxicity data, to assess safety, we collected SAEs only. Hospital admissions for clear treatment-related toxicities occurred as unique events in 14/71 (20%) patients on mFFX and 5/69 (7%) patients on GnP. Hospitalizations from mFFX were seven GI-related complications, three febrile neutropenia, and one each of pneumonia, acute renal failure, pulmonary




B

| | Treatment | | |
|---|---|---|---|
| | *GnP (n = 69)* | *mFFX (n = 71)* | *P* |
| CR/PR | 21 (30.4%) | 20 (28.6%) | .07 |
| SD | 34 (49.3%) | 24 (34.3%) | |
| PD | 14 (20.3%) | 26 (37.1%) | |
| Not evaluable | 0 (0.0%) | 1 (1.4%) | |
| DCR (CR/PR/SD) | 55 (79.7%) | 44 (62.9%) | .028 |
| DOR (months), median (range) | 5.9 (1.8-24.1) | 4.7 (1.4-7.6) | .025 |
| TTR (months), median (range) | 3.5 (1.7-19.0) | 3.5 (1.7-7.5) | .30 |

**FIG 3.** Response by chemotherapy. (A) Bar plot of best tumor change on first-line chemotherapy by RECIST 1.1 measurements. (B) Table comparing RECIST 1.1 for first-line response in PP population. CR, complete response; DCR, disease control rate; DOR, duration of response; FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HRD, homologous recombination deficiency; mFFX, modified FOLFIRINOX; PD, progressive disease; PP, per-protocol; PR, partial response; SD, stable disease; TTR, time to response; WT, wildtype.



embolism, and cerebellar stroke. The SAEs requiring admission on GnP included two for severe fatigue, and one each of nausea, cellulitis, and acute renal failure. One patient in 140 had abdominal pain requiring overnight observation from the percutaneous research biopsy (0.6%).

## Outcomes by RNA Subgroup

A total of 74% (103/140) of the PP cohort could be classified into basal-like 26% (27/103) and classical 74% (76/103), with inadequate biopsy sample in the remaining. Median PFS of the basal-like group was 4.0 months versus 5.7 months in the classical group (HR, 1.19 [95% CI, 0.76 to 1.87]; $P = .44$; Fig 4A), while OS was 8.6 months for basal-like versus 10.0 months for classical (HR, 1.24 [95% CI, 0.76 to 2.04]; $P = .39$; Fig 4B). We further assessed whether RNA subtype is a predictive biomarker associated with chemotherapy benefit. Median PFS was similar for classical cases treated with mFFX versus GnP (6.3 versus 5.4 months; HR, 1.26 [95% CI, 0.77 to 2.07]; $P = .36$) but a trend for worse PFS on mFFX for basal-like cases at 3.0 months versus 5.5 months with GnP (HR, 1.76 [95% CI, 0.77 to 4.02]; $P = .17$; Fig 5A and Appendix Table A2). Median OS was worse on mFFX compared to GnP for the classical subtype (9.7 *v* 13.9 months; HR, 1.80 [95% CI, 1.0 to 3.23], $P = .047$), while there was a numerically shorter median OS in the basal-like subtype for mFFX over GnP (7.5 *v* 8.9 months; HR, 1.14 [95% CI, 0.49 to 2.66]; $P = .75$; Fig 5B). Patients with basal-like tumors treated with GnP versus mFFX also showed numerically improved ORR (45% *v* 19%, $P = .20$) and DOR (5.9 *v* 4.8 months, $P = .55$). Patients with classical tumors treated with GnP versus mFFX had ORR of 31% *v* 33% ($P = .55$) and DOR of 6.7 *v* 4.6 months ($P = .01$).

## Subsequent Line Therapy and MTB-Guided Treatments

Of 140 patients, 75 (54%) were able to start second-line therapy. More patients from the GnP arm moved to second-line than from mFFX (61% *vs* 55%, respectively; $P = .48$). The postprogression time-to-event patterns between two arms show no significant difference in OS between the two arms, although there is a trend for better OS for GnP group compared with mFFX (Appendix Fig A4).

RNA subtype was available in 52 second-line patients, showing classical in 38 (73%) and basal-like in 14 (27%). Of second-line treated patients, 42 (56%) received a

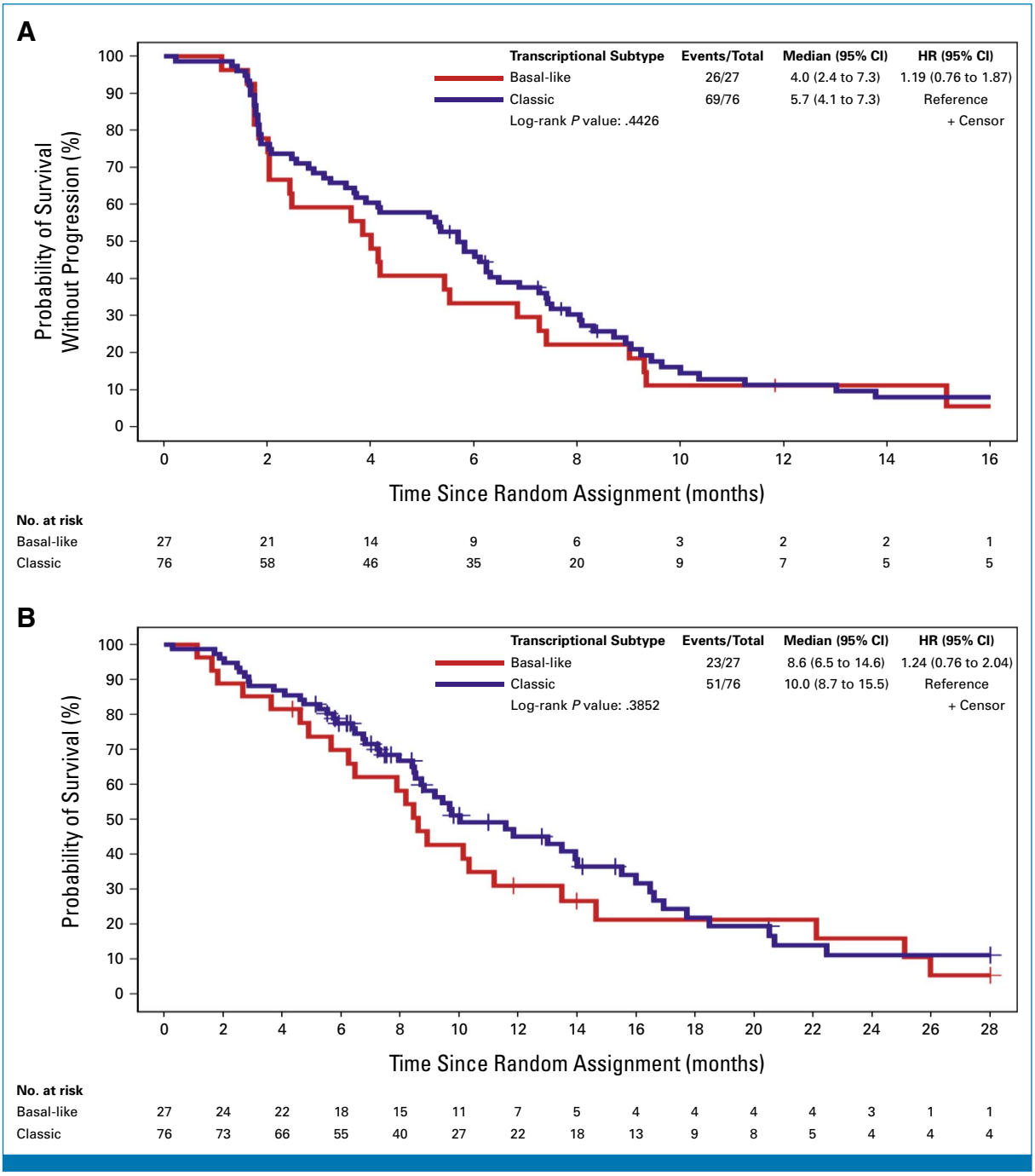



**FIG 4.** Association of PFS/OS with transcriptional subtype. Association of (A) PFS and (B) OS with transcriptional subtype in the 103 patients with subtype data available. HR, hazard ratio; OS, overall survival; PFS, progression-free survival.



routine chemotherapy option and 33 (44%) patients received a correlative-guided therapy on the basis of MTB recommendations.

Specifically, WGS data informed decisions for 18 patients (55%), RNA analysis for five (15%), and PDO drug screening for 10 (30%). Patients in this trial had very limited access to KRAS inhibitor trials (1.4%), resulting in our focus on other rare actionable targets. This included BRAF inhibition, human epidermal growth factor receptor 2–directed therapy, immune checkpoint inhibition for microsatellite instability-high and high tumor mutational burden, and drugs targeting PRMT5 or MAT2A for biallelic *MTAP* deletion. There were 12 patients identified as *KRAS* WT, a subgroup historically associated with better prognosis. Of these, nine received second-line therapy including six correlative-driven therapies guided by MTB recommendations (Table 2). Median time on second-line treatment was 2.2 months for correlative-guided and 1.9 months for routine choices. The median OS from start of second-line treatment was 5.4

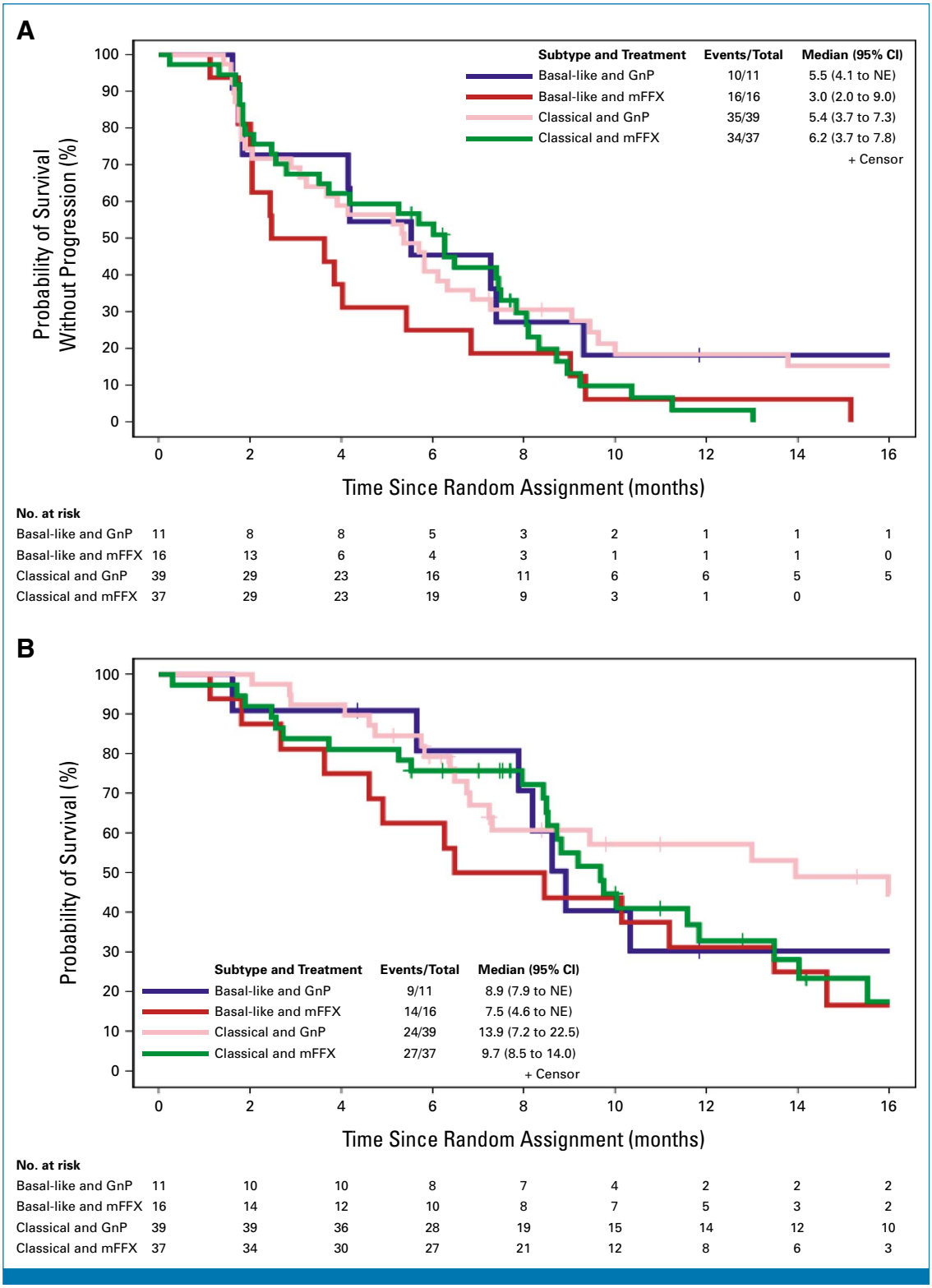



**FIG 5.** PFS and OS by transcriptional subgroup and treatment arm. Association of (A) PFS and (B) OS with transcriptional subtype basal-like or classical randomized to GnP or mFFX of the 103 patients with subtype data available. FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; mFFX, modified FOLFIRINOX; NE, not evaluable; OS, overall survival; PFS, progression-free survival.

**TABLE 2.** Second-Line Correlative-Driven Therapies

| Category | Aberration/Signature | No. of Patients (33) | Treatment Choice |
|---|---|---|---|
| Genomic aberrations (18) | *ERBB2* mutation/amplification (*1 KRAS WT*) | n = 2 | T-DXd/FOLFOX + trastuzumab |
| | *BRAF* mutation/fusion (*all KRAS WT*) | n = 5 | BRAF inhibitor/Mek inhibitor combination/monotherapy |
| | Somatic *BRCA-2*/HRD | n = 2 | Gemcitabine/cisplatin |
| | Tandem duplicator phenotype | n = 2 | mFFX |
| | High TMB | n = 1 | Immunotherapy-based clinical trial |
| | Somatic MSI-H | n = 3 | Pembrolizumab/nivolumab |
| | *KRAS* mutation | n = 2 | KRAS inhibitor trial |
| | *MTAP* deletion | n = 1 | PRMT5 inhibitor clinical trial |
| RNA signatures (5) | *hENT* high | n = 3 | GnP |
| | Basal-like | n = 2 | GnP |
| PDO sensitivities (10) | Chemo-specific sensitivity | n = 7 | 3 = gemcitabine-based<br>3 = platinum-based<br>1 = 5-FU-based |
| | EGFR-pathway sensitivity | n = 3 | EGFR inhibitor–based agents |

Abbreviations: FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; FU, 5-fluorouracil; GnP, gemcitabine/nab-paclitaxel; mFFX, modified FOLFIRINOX; *hENT*, human equilibrative nucleoside transporter[12]; HRD, homologous recombination deficiency; MSI-H, microsatellite instability-high; MTAP, methylthioadenosine phosphorylase; PDO, patient-derived organoid, PRMT5, protein arginine methyltransferase 5; TDXD, trastuzumab deruxtecan, TDP, tandem duplicator phenotype[13]; TMB, tumor mutational burden; WT, wildtype.



versus 4.4 months, respectively ($P$ = .46). Of the 16 patients with basal-like tumors randomly assigned to mFFX in the first-line setting, 66% (6/9) showed a longer time on treatment with second-line gemcitabine-based therapy than first-line therapy, further demonstrating an impact of gemcitabine-based therapies to improve outcomes among the basal-like tumor population (Appendix Fig A5).

### Outcomes by *GATA6* Expression

A secondary objective of this study was to analyze *GATA6* as a potential biomarker of response to mFFX or GnP by evaluating the PFS and OS in each treatment arm according to *GATA6* ISH assay as a surrogate biomarker for classical signature. *GATA6* high by ISH correlates strongly with the classical subtype (correlation coefficient = 0.34, $P$ = .001). In the PP analysis, 110/140 (79%) patients had *GATA6* expression available by ISH. There was a nonsignificant trend toward improved PFS in high expressers (5.7 months) versus low expressers (4.0 months; HR, 0.76 [95% CI, 0.48 to 1.19]; $P$ = .23; Appendix Fig A6). However, there was no significant association of chemotherapy response or PFS with *GATA6* ISH (Appendix Figs A7A and A7B).

### CA 19-9 as an Early Indicator of Chemotherapy Response

Of the 140 patients in the PP population, 29 (20%) were nonexpressors at enrollment (no difference by subtype). Of 95 patients (85%) with CA 19-9 data available at baseline and 4 weeks, a 20% decrease in CA19-9 was associated with better PFS (6.9 [5.7-8.3] months versus 3.7 [2.8-5.0] months, $P$ value .0419). A > 20% increase in CA19-9 at 4 weeks was associated with inferior PFS (6.7 [5.3-7.7] months versus 3.1 [2.1-3.9] months, $P$ < .0001; Figs 6A and 6B). However, 10 of 44 patients with a >20% increase in CA19-9 at 4 weeks, from a baseline CA-19-9 with median of 1,259 (range, 224-22,573), went on to have a radiologic PR or SD for >4 months. Therefore, a >20% increase in CA19-9 at 4 weeks should not be used in isolation to prompt a change in therapy. An intermediate change in CA19-9 (0%-19.9% increase or decrease at 4 weeks) had no significant change on PFS (data not shown).

## DISCUSSION

To our knowledge, PASS-01 is the first randomized trial in Western countries comparing mFFX with GnP. Although PFS favored GnP at the planned 0.3 significance threshold and OS was also significantly better (10.3 *v* 8.7 months in those receiving chemotherapy, $P$ = .021), the differences are small and outcomes remain poor with either treatment. Anticipating these limitations, PASS-01 integrated extensive correlatives and MTB review to inform later-line therapies. We demonstrated the feasibility of coordinating biospecimen collection and molecular analyses across a multicenter study. Initial translational findings highlight the worst outcomes in basal-like PDAC, although PFS, ORR, DOR, and SAEs favored GnP. OS may have been confounded by second-line treatment. Only 54% of patients were able to receive second-line therapies, and despite 44% being guided by correlatives, the benefit was minimal. Overall, PASS-01 confirms the disappointing outcomes with combination chemotherapies for metastatic PDAC, while providing important data to guide first-line therapy selection. It also demonstrated that upfront genomic profiling is

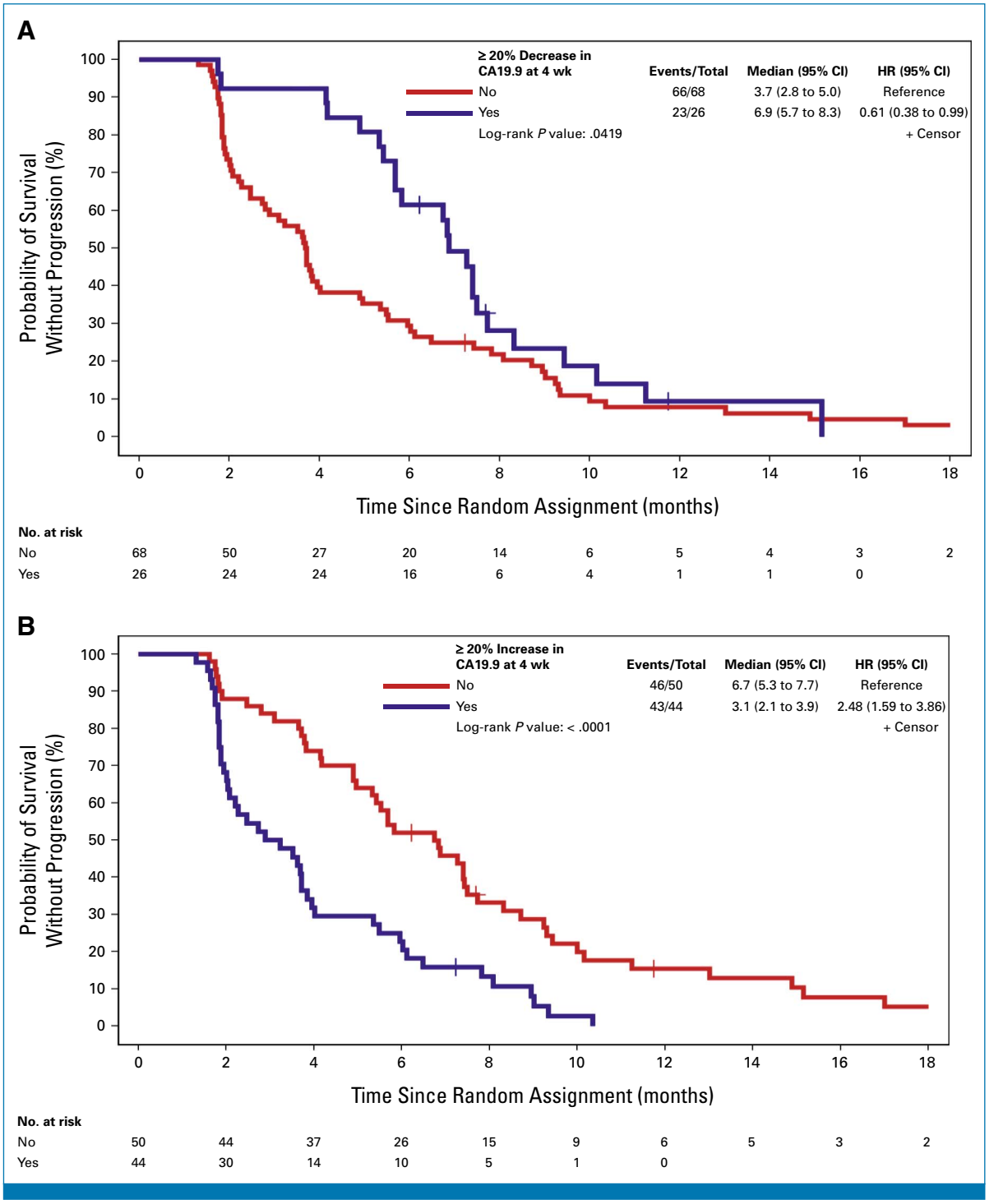



**FIG 6.** PFS by CA-19-9 threshold. CA 19-9 changes from baseline to 4 weeks and progression-free survival. (A) Patients with a >20 decrease in CA 19-9 had a significantly longer PFS (6.9 months [95% CI, 5.7 to 8.3]) compared with those without this decrease (3.7 months [95% CI, 2.8 to 5.0]; $P = .0419$). (B) Conversely, patients with a >20% increase in CA 19-9 had significantly shorter PFS (3.1 months [95% CI, 2.1 to 3.9]) compared with those without this increase (6.7 months [95% CI, 5.3 to 7.7]; $P < .0001$). HR, hazard ratio; PFS, progression-free survival.

feasible and supports prioritizing precision therapy in the first-line setting.

First-line combination chemotherapy has improved OS for patients with metastatic pancreatic cancer, but survival remains modest at under 1 year.[3,6] A systematic review and a phase III meta-analysis show little difference in efficacy outcomes between three regimens, slightly favoring mFFX or NALIRIFOX over GnP.[4,5] A direct mFFX versus NALIRIFOX comparison has not been conducted, and NALIRIFOX was

unavailable during PASS-01 study design. The Japanese GENERATE trial, not included in these reviews, favored GnP over mFFX or S-IROX, with median OS of 17, 14, and 13.6 months, respectively.[14] PASS-01 also favors GnP over mFFX by PFS, OS, response duration, and less chemo-related SAEs. However, these differences are modest, but are practice-informing, and help clinicians guide first-line treatment decisions.

PASS-01's patient population differed from previous trials in ways that may have influenced the results. First, patients with known or suspected germline variants *BRCA1/2* or *PALB2* mutations—recognized biomarkers for better platinum-based chemotherapy—were excluded (approximately 10% of metastatic PDAC cases). A subgroup analysis of *BRCA1/2* or *PALB2* mutations from NAPOLI-3 trial could be informative. Next, to ensure all patients would be chemo-naïve, for PDO pharmacotyping, those with recurrent disease after resection were excluded (generally 7%-10% of first-line trials). Bulky metastases were needed for biopsies and so patients with low volume or lung-only metastasis, known to have better outcomes, were not accrued. All these criteria are potentially selecting for more aggressive presenting disease and higher risk of early symptomatic decline. PASS-01 also enrolled a more diverse population (64% White *v* 83%-87% historically[2,6]), better reflecting North American patients, although the impact of race on outcome remains unclear. Despite these differences, the GnP arm performed as expected, with a median OS close to 10 months, and particularly well in the classical tumor subgroup with a median OS of 14 months. By contrast, the mFFX arm underperformed relative to historical data with a median OS of 8.7 months.

Second-line efficacy was disappointing, despite efforts to use correlative driven selections where available. Second-line therapy was investigator-determined with no protocolized PS criteria, likely contributing to poorer outcomes because of rapid clinical decline. Nevertheless, these data represent real-world experience and align with other trials attempting personalized treatment in PDAC.[15]

Transcriptional subtypes emerge as an important prognostic factor in this randomized data set, with basal-like cases showing numerically worse outcomes, particularly with mFFX. These results build on previous nonrandomized data,[10] highlighting the need for assessment of transcriptional subtype early in treatment selection rather than making a decision agnostic of subtype. Emerging chemotherapy-prediction signatures could be compared blindly on PASS-01 data to build validation and consensus. This has implication for future trials, where basal-like tumors could be prioritized for novel first-line approaches using a GnP backbone for potentially better efficacy with less toxicity (eg, ClinicalTrials.gov identifier: NCT06483555). As RAS inhibitors enter the clinic, understanding the subtype specific on sensitivity may inform combination strategies.[16,17] Our findings on early dynamic changes of CA-19-9 build on previous data[18] and demonstrate very early CA19-9 changes is a strong biomarker and, perhaps if when combined with another marker such as ctDNA, could support early switch strategies in trials, potentially before a clear radiologic or clinical decline.

The main limitation of this trial is the relatively small phase II design, leading to underpowered end points, especially the predictive and exploratory analyses. The more relaxed alpha allowed a better chance of detecting an efficacy signal in either arm and in a more select population than previously tested, but with a higher risk of a false positive. This was an acceptable design recognizing that a larger trial comparing these well-established regimens would have been very difficult to execute. Chance imbalances in patient characteristics between arms may have affected outcomes, although that is not supported by the multivariable analysis, and small differences do not change our conclusions. This smaller study permitted a rich biomarker data set with high rates of biospecimen collection to guide future research. Underpowered subgroups could be combined with other known data sets to refine findings further. The future clinical utility of GATA-6 as a biomarker is likely to be complemented by implementation of a multiplex immunofluorescence pipeline with multiple protein expressions[19] or commercial signatures.

PASS-01 paves the way for upfront profiling and biomarker-driven treatment selection. Advances in profiling technologies now enable rapid genomic stratification that would allow for integral biomarker selection trials. As we enter the era of RAS inhibitors, and other promising strategies expand treatment options, it is important to remember only approximately 50% of patients receive second-line therapy and outcomes remain poor, even with targeted treatments. Optimizing first-line precision approaches is critical for patients with PDAC.



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## CLINICAL TRIAL INFORMATION

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**PASS-01: Randomized Phase II Trial of Modified FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel and Molecular Correlatives for Previously Untreated Metastatic Pancreatic Cancer**

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## APPENDIX

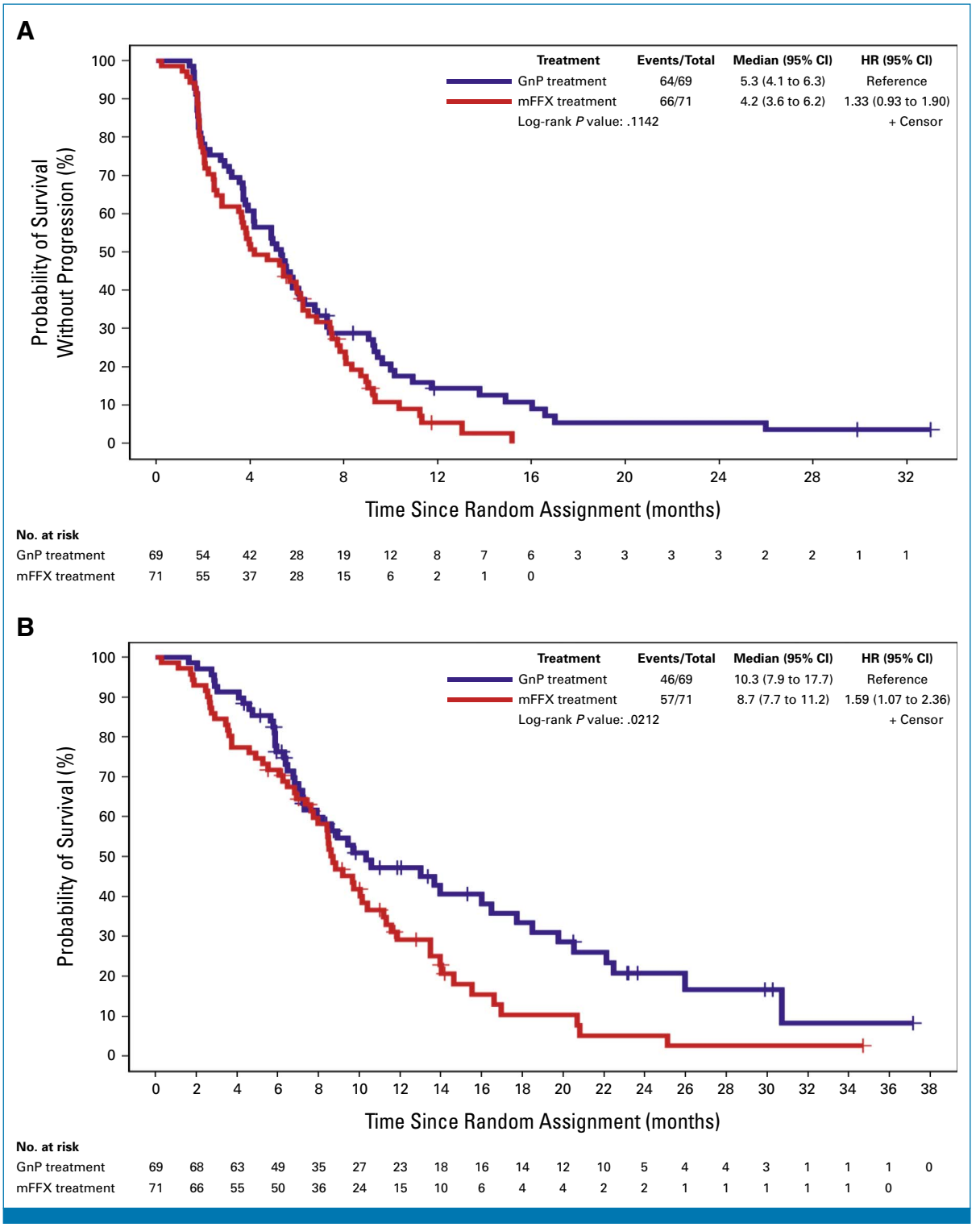


**FIG A1.** Comparison of (A) PFS and (B) OS between two treatment groups: mFFX and GnP treatment for PP population (140 patients). FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HR, hazard ratio; mFFX, modified FOLFIRINOX; OS, overall survival; PFS, progression-free survival; PP, per-protocol.

| Subgroup | GnP (events/total) | mFFX (events/total) | HR (95% CI) (mFFX *v* GnP) | *P* |
|---|---|---|---|---|
| Age | | | | |
| <65 yr | 29/31 | 37/40 | 1.13 (0.86 to 1.95) | .510 |
| ≥65 yr | 36/38 | 28/31 | 1.43 (0.92 to 2.22) | |
| Liver metastasis | | | | |
| No | 13/15 | 7/9 | 1.12 (0.47 to 2.85) | .750 |
| Yes | 51/54 | 59/82 | 1.30 (0.90 to 1.89) | |
| ECOG | | | | |
| 0 | 38/41 | 20/32 | 1.25 (0.76 to 2.04) | .820 |
| 1 | 28/28 | 37/39 | 1.85 (0.80 to 2.11) | |
| Sex | | | | |
| Female | 28/27 | 28/28 | 0.83 (0.47 to 1.47) | .049 |
| Male | 38/42 | 40/43 | 1.75 (1.13 to 2.70) | |
| Race | | | | |
| Other | 21/23 | 27/29 | 1.33 (0.78 to 2.28) | .980 |
| White | 43/48 | 39/42 | 1.32 (0.85 to 2.06) | |
| Primary tumor | | | | |
| Body/tail | 44/48 | 42/48 | 1.34 (0.87 to 2.07) | .880 |
| Head | 19/20 | 22/23 | 1.27 (0.71 to 2.20) | |
| Transcriptional subtype | | | | |
| Basal-like | 10/11 | 18/18 | 1.78 (0.77 to 4.08) | .480 |
| Classical | 35/39 | 34/37 | 1.20 (0.80 to 1.98) | |
| *KRAS* | | | | |
| Mutant | 49/54 | 81/88 | 1.34 (0.92 to 1.95) | .820 |
| WT | 10/10 | 2/2 | 1.21 (0.51 to 2.83) | |
| Somatic HRD+ | | | | |
| No | 83/88 | 82/87 | 1.38 (0.98 to 1.94) | .870 |
| Yes | 1/1 | 4/4 | 1.20 (0.75 to 2.21) | |

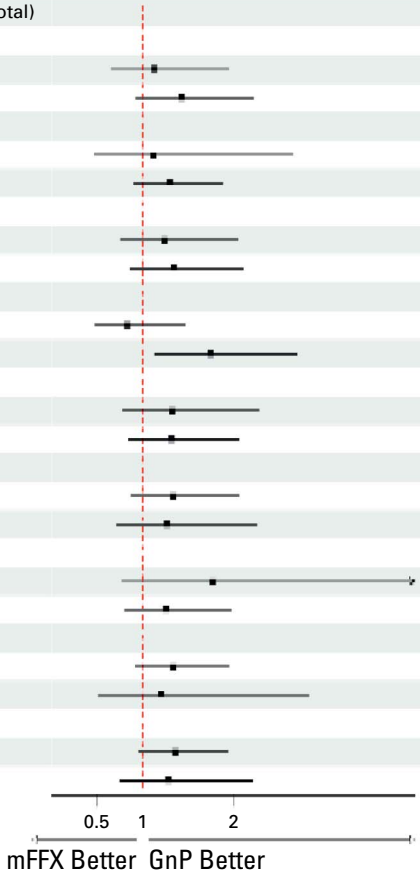


**FIG A2.** Subgroup analysis of PFS. ECOG, Eastern Cooperative Oncology Group; FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HR, hazard ratio; HRD, homologous recombination deficiency; mFFX, modified FOLFIRINOX; PFS, progression-free survival; WT, wildtype.

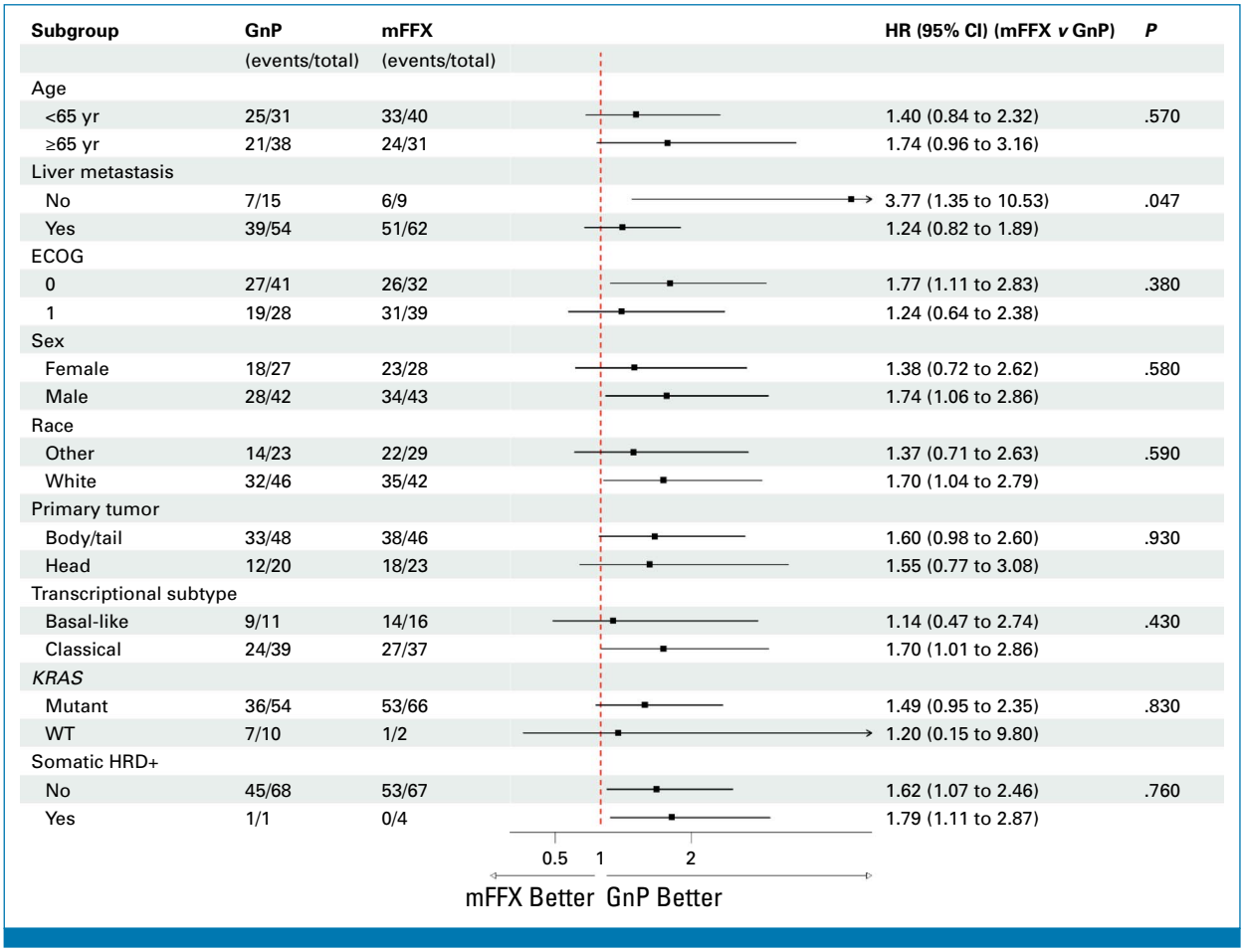


**FIG A3.** Subgroup analysis of OS. ECOG, Eastern Cooperative Oncology Group; FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HR, hazard ratio; HRD, homologous recombination deficiency; mFFX, modified FOLFIRINOX; OS, overall survival; WT, wildtype.

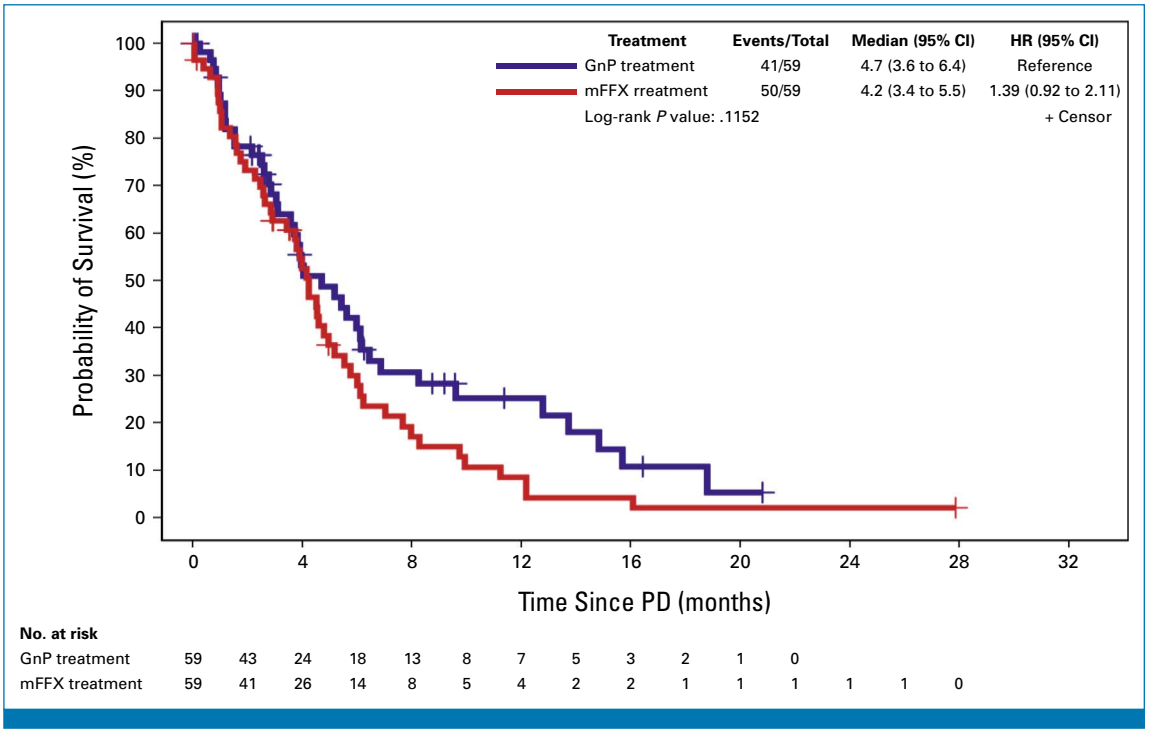


**FIG A4.** Subgroup analysis: comparison of post-PD OS between two treatment groups in those with PD (n = 118) in PP population. FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HR, hazard ratio; mFFX, modified FOLFIRINOX; OS, overall survival; PD, progressive disease; PP, per-protocol.

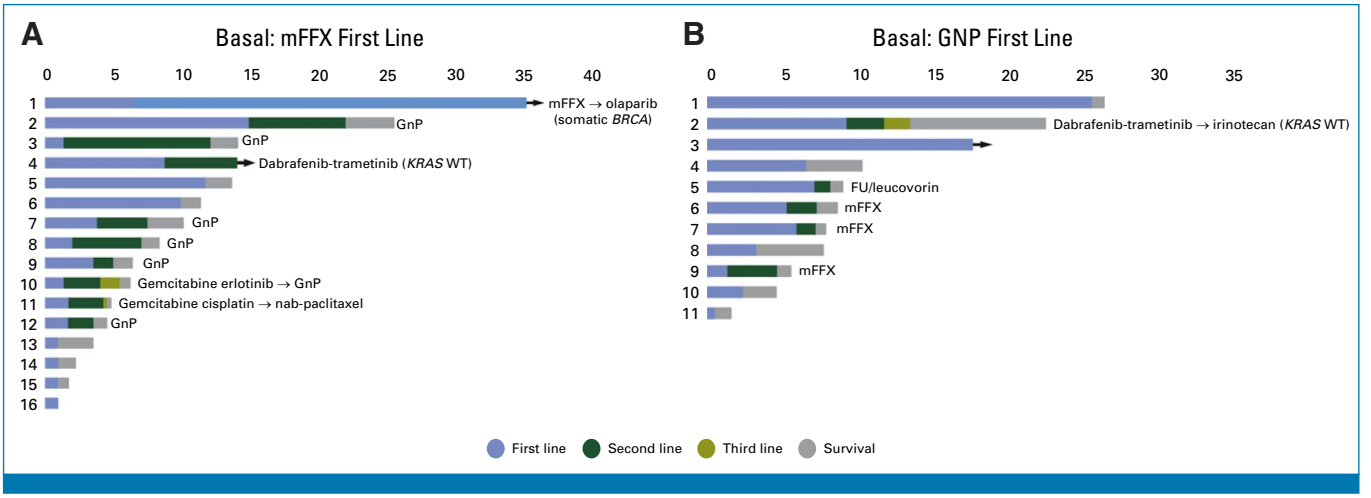


**FIG A5.** Swimmer plot of first-line and subsequent line treatments of basal-like subgroup patients. Each horizontal bar represents a single patient's timeline measured in months: (A) mFFX and (B) GnP. FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; mFFX, modified FOLFIRINOX.

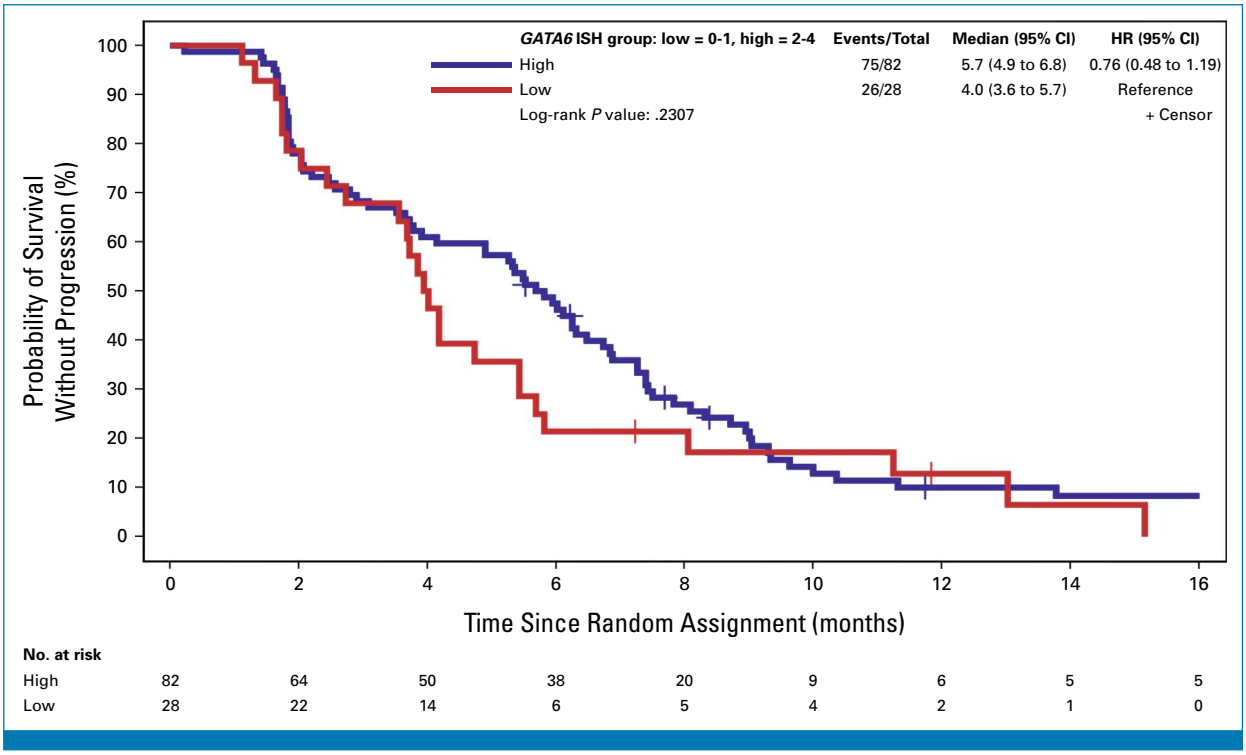


**FIG A6.** Comparisons of PFS between *GATA6* ISH (high *v* low) for all 110 patients with *GATA6* ISH information available. HR, hazard ratio; ISH, in situ hybridization; PFS, progression-free survival.

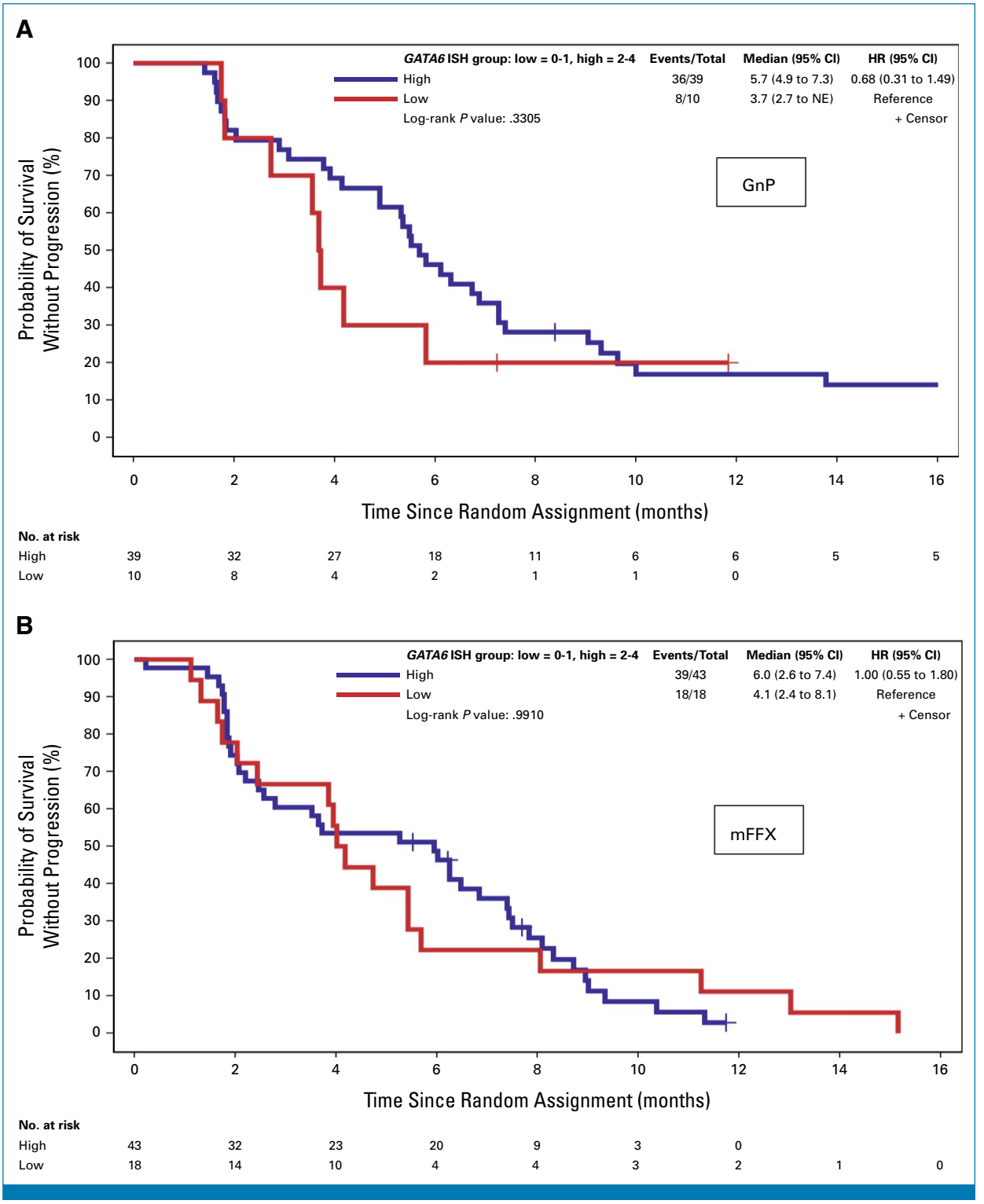


**FIG A7.** PFS by *GATA6* ISH high versus low stratified by treatment arm. (A) Comparison of PFS between *GATA6* ISH groups: high versus low in GnP treatment arm. (B) Comparison of PFS between GATA6 ISH groups: high versus low in mFFX treatment arm. FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HR, hazard ratio; ISH, in situ hybridization; mFFX, modified FOLFIRINOX; NE, not evaluable; PFS, progression-free survival.

**TABLE A1.** Association of Treatment With End Points

| | | Model I | | Model II | |
|---|---|---|---|---|---|
| End Points | Treatment | HR (95% CI) | *P* | HR (95% CI) | *P* |
| PFS | mFFX *v* GnP | 1.33 (0.93 to 1.90) | .12 | 1.27 (0.87 to 1.85) | .21 |
| OS | mFFX *v* GnP | 1.59 (1.07 to 2.36) | .02 | 1.25 (0.81 to 1.93) | .31 |

NOTE: PP analysis: Model I: no adjustment. Model II: adjusted for potential confounders ECOG PS, liver metastasis, and *KRAS* WT.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HR, hazard ratio; mFFX, modified FOLFIRINOX; OS, overall survival; PFS, progression-free survival; PP, per-protocol; WT, wildtype.



**TABLE A2.** Summary of PFS and OS by Transcriptional Subtype and Treatment Arm

| | | PFS | | | OS | | |
|---|---|---|---|---|---|---|---|
| Transcriptional Subtype | Treatment | mPFS (95% CI) | HR (95% CI) | *P* | mOS (95% CI) | HR (95% CI) | *P* |
| Classical | mFFX | 6.3 (3.7 to 7.8) | 1.26 (0.77 to 2.07) | .36 | 9.7 (8.5 to 14.0) | 1.80 (1.0 to 3.23) | .047 |
| | GnP | 5.4 (3.7 to 7.3) | Ref | | 13.9 (7.2 to 22.5) | Ref | |
| Basal-like | mFFX | 3.0 (2.0 to 9.0) | 1.76 (0.77 to 4.02) | .17 | 7.5 (4.6 to NE) | 1.14 (0.49 to 2.66) | .75 |
| | GnP | 5.5 (4.1 to NE) | Ref | | 8.9 (7.9 to NE) | Ref | |

NOTE. The results were based on the KM analysis stratified by subtype.
Abbreviations: FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HR, hazard ratio; mFFX, modified FOLFIRINOX; mOS, median of OS (months); mPFS, median of PFS (months); NE, not evaluable; OS, overall survival; *P*, *P* value on the basis of log-rank test; PFS, progression-free survival; Ref, reference.