Chemotherapy in advanced pancreatic adenosquamous carcinoma: A retrospective multicenter AGEO study

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Chemotherapy in advanced pancreatic adenosquamous carcinoma

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Novelty & Impact:
- First published report evaluating modern regimens of chemotherapy in a large multicenters cohort of patients with advanced pancreatic adenosquamous carcinomas.
- Results highlighted a trend of efficacy favouring modern regimens as FOLFIRINOX or Gemcitabine-Nab paclitaxel versus all other regimens.

Abbreviations
5-FU: 5-fluorouracil
95% CI : 95% confidence intervals
BSC : Best supportive care
CT: Computed tomography
FX : FOLFIRINOX
GN : Gemcitabine-nab paclitaxel
HR: Hazard ratios
OS: Overall survival
PASC: Pancreatic adenosquamous carcinoma
PDAC: Pancreatic ductal adenocarcinoma
PFS: Progression free survival
PS : Performans status
WHO: World Health Organization

Abstract

Pancreatic adenosquamous carcinoma (PASC) account for <5% of pancreatic malignancies. The efficacy of modern chemotherapy regimens in patients with advanced PASC is unknown. Patients with advanced PASC from 2008 to 2021 were consecutively included in this retrospective multicenter study. Overall survival (OS) and progression-free survival (PFS) were evaluated by Kaplan–Meier method. Ninety-four PASC from 16 French centers were included (median age, 67.3 years; males, 56.4%; metastatic disease, 85.1%). The first-line treatment was chemotherapy for 79 patients (84.0%) (37 FOLFIRINOX (FX), 7 Gemcitabine-nab paclitaxel (GN), and 35 for all other regimen) or best supportive care (BSC) alone for 15 patients (16.0%). No significant difference was observed between FX and GN in terms of PFS (p=0.67) or OS (p=0.5). Modern regimens pooled together (FX and GN) as compared to all others chemotherapy regimens showed an improvement of overall response rate (39.5% and 9.7%, p=0.002), PFS (median, 7.8 versus 4.7 months, p=0.02) and OS (median, 12.7 vs 9.2 months, p=0.35). This large study evaluating first-line treatment regimens in advanced PASC suggests that modern regimens as FX or GN may be preferable to all other chemotherapy regimens. These results deserve confirmation in prospective studies.

Introduction

Pancreatic adenosquamous carcinoma (PASC) is a rare histological subtype and accounts for approximately 1 to 4% of all exocrine pancreatic neoplasms (1,2). According to World Health Organization (WHO) classification, PASC is defined by the presence of at least 30% of squamous quota within a contingent of classic adenocarcinoma (3). Several theories attempted to explain the origin of this histological entity, such as the squamous metaplastic differentiation after chronic inflammation (from obstruction), the collision of two independent neoplasms, or its development from pluripotent stem cells (4).

Several national or regional register studies showed that demographic features and tumor stage at diagnosis in patients with PASC were globally similar to those in patients with pancreatic ductal adenocarcinoma (PDAC) (1, 5–10). After surgery for localized pancreatic cancer, disease recurrence seems to be more frequent in PASC than in PDAC (5). In advanced disease, although early studies have suggested that the prognosis of PASC is worse than that of other pancreatic tumors (10–13), more recent cohort studies reported a similar prognosis between PASC and PDAC (1,5,9).

Some data suggest an improvement of clinical outcome of patients with localized PASC with adjuvant chemotherapy or radiotherapy (14–16). By contrast, data regarding efficacy of chemotherapy for PASC in advanced disease are very scarce (only case series) (17,18), and no data are available for modern regimens based on 5-fluorouracil (5FU) (e.g., FOLFIRINOX) or gemcitabine (e.g., gemcitabine in combination with nab-paclitaxel) (19–22).

This prompted us to examine the efficacy of modern chemotherapy regimens and to compare the efficacy of 5FU- and gemcitabine-based regimens in patients with advanced PASC.

Patients and methods

Patients

All consecutive adult over 18 years old patients with locally advanced or metastatic, histologically proven PASC treated from 2008 to 2021 were eligible for this multicenter retrospective study. Patients with borderline PASC were excluded.

The patients' medical records were reviewed to collect relevant demographic and pathological characteristics, treatment regimens received, tumor response, date of disease progression and survival status at the last follow-up.

Outcome measures

Tumor response was assessed among patients with measurable disease on computed tomography (CT) using the RECIST 1.1 criteria. Overall survival (OS) was defined as the time from the diagnosis of advanced disease to death from any reason. Progression-free survival

(PFS) was defined as the time from the diagnosis of advanced disease until disease progression or death, whichever occurred first. Patients who were alive and without disease progression were censored at the date of the last follow-up.

Statistical analyses

Medians (and interquartile and range) and proportions (and percentages) were provided for the description of continuous and categorical variables, respectively. Medians and proportions were compared using the Wilcoxon-Mann-Whitney test and the chi^2-test (or Fisher's exact test, if appropriate), respectively.

OS and PFS were estimated using the Kaplan-Meier method and described using medians or rates at specific time points with their 95% confidence intervals (95% CI). Follow-up was calculated using a reverse Kaplan–Meier estimation. Comparisons were performed using the log-rank test.

The association of survival with clinicopathological factors and first-line chemotherapy regimens was assessed with univariate and multivariate (when appropriate) Cox proportional hazard models, providing hazard ratios (HR) and 95% CI. *P* values <0.05 were considered to indicate statistical significance.

Results

Patients Characteristics

A total of 94 patients with advanced PASC were included in 16 French centers. Main patient characteristics are presented in Table 1. The median age was 67.3 years (range: 34.7-86.8), most patients were males (56.4%), and performance status was 0-1 in 51.1% of patients. Most patients had a metastatic disease (85.1%), and the primary tumor location was preferentially cephalic (43.6%).

Treatment

Among the 94 patients included, 79 (84.0%) patients have received a first-line chemotherapy, while 15 (16.0%) were treated with best supportive care (BSC) alone. First-line chemotherapy protocols were based on 5FU for 57 patients (72.2%), including 37 treated with FOLFIRINOX (FX), and on gemcitabine for 22 patients (27.8%), including seven treated with gemcitabine plus nab-paclitaxel (GN) (Table 1). Thirty-nine patients (49.4%) received a second line of chemotherapy.

Tumor response

Tumor response was assessable in 69 patients with measurable disease (Table 2). There were 2 complete responses (all in the 5FU-based chemotherapy group) and 16 partial

responses (12 in the 5FU-based and 4 in the gemcitabine-based chemotherapy groups). The objective response rate (ORR) was 28.6% and 21.4% for patients treated with 5FU-based and gemcitabine-based chemotherapy, respectively (p=0.58) (Table 2). Modern regimens pooled together (FX and GN) showed a significant increase of ORR as compared to other regimens (39.5% vs 9.7% respectively, p=0.002) (Table 2).

Survival

The median follow-up was 51.9 months (95%CI: 24.3-not reached).

Median PFS for the patients who received first-line chemotherapy was 6.18 months (95%CI: 4.49–8.21) (Figure 1A). PFS was longer in patients treated with 5FU-based chemotherapy than in those treated with gemcitabine-based chemotherapy (median, 7.0 vs 3.96 months; log-rang test, p=0.13) (Figure 1B). Median PFS were 7.8 months and 8.9 months for FX and GN respectively (p=0.67). Modern regimens pooled together (FX and GN) showed a significant increase of median PFS with 7.8 months versus 4.7 months for all others chemotherapy regimens (log rank test, p=0.022) (Figure 1C). Among treated patients, PS (0-1 vs ≥ 2: HR=0.47; 95%CI: 0.26–0.83; p=0.011) and chemotherapy regimen (FX and GN vs other regimens, HR 0.58, IC95 0.36 - 0.93, p= 0.024) were the only factors associated with longer PFS in univariate analysis. Only PS remain significant in multivariate analysis (Table 3).

Median OS was 9.3 months (95% CI, 7.33-12.32) for the entire cohort (Figure 2A), and 10.2 months (95%CI: 9.17–15.44) for patients who received a first-line chemotherapy (Figure 2B). OS was longer in patients treated with 5FU-based chemotherapy than in those treated with gemcitabine-based chemotherapy or with BSC alone (median, 10.3, 7.8, and 3.0 months, respectively; log-rang test, p<0.0001) (Figure 2C). Median OS were 11.8 months and 15.4 months for FX and GN respectively (p=0.5). Modern regimens pooled together (FX and GN) showed a longer OS as compared to those treated with others chemotherapy regimens (median, 12.7 months vs 9.2 months, log-rank test p=0.35) (Figure 2D). In univariate analysis among patients receiving chemotherapy, PS (0-1 vs ≥ 2: HR=0.25; 95%CI: 0.13–0.47; p<0.0001) and metastatic status (synchronous vs metachronous: HR=1.72; 95%CI: 1.01–2.94; p=0.047) were the only factors associated with longer OS (Table 3).

Discussion

To our knowledge, this is the first published report evaluating current systemic chemotherapy in patients with advanced PASC by comparing 5FU-based and gemcitabine-based regimens. Our results show a non-significant PFS and OS benefit with 5FU-based chemotherapy as

compared to gemcitabine-based chemotherapy. However, this may be due to a selection bias, as patients treated with 5FU-based chemotherapy mostly received FOLFIRINOX and therefore might have better PS. As expected, we observed that PS was also significantly associated with PFS and OS in univariate analysis. The proportion of patients in the 5FU-based and gemcitabine-based chemotherapy groups with an ECOG PS of 0-1 was 63.2% and 45.5%, respectively (p=0.15).

FOLFIRINOX and Gemcitabine-nab paclitaxel are both standard first-line treatments in patients with metastatic pancreatic cancer. It showed greater OS with FOLFIRINOX than with Gemcitabine-Nab paclitaxel in patients with metastatic PDAC (23) but real-world comparative effectiveness study indicates that FOLFIRINOX and Gemcitabine-nab paclitaxel have similar effectiveness in the palliative first-line treatment of advanced PDAC (24). Considering this, we showed that modern regimens of FOLFIRINOX and Gemcitabine-nab paclitaxel pooled together allowed a significant longer PFS and a trend of better OS than all other chemotherapy regimens.

Our study has some limitations. Our results should be interpreted with caution owing to the retrospective nature of the study, the small number of patients, and the heterogeneity of our real-life population treated in different centers.

To date, no targeted therapy directed against a specific molecular alteration has shown clinical activity in PASC patients. PASC may harbor more frequently *KRAS* mutations and *TP53* or *CDKN2A* alterations than PDAC (4,25). In a molecular characterization of 23 patients with PASC, Borazanci et al. found potentially targetable cMET (40%) and c-KIT (10%) overexpression (26). The presence in some PASC cased of PD-L1 overexpression or a “hypermutated” tumor profile suggests a potential sensitivity to immune checkpoint inhibitors (27,28).

In conclusion, the low incidence and the lack of knowledge regarding their biological characteristics account for the main unmet need to define the most appropriate therapeutic strategy for patients with advanced PASC. This retrospective, multicenter study, the largest analysis of modern chemotherapy regimens in advanced PASC to date, suggests that modern regimens as FOLFIRINOX or Gemcitabine-nab Paclitaxel may be preferable to all other chemotherapy regimens. Our results should be interpreted with caution due to their retrospective nature and deserve confirmation in prospective studies.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the "CERAPHP Centre" ethics committee (IRB registration number: #00011928).
All participating patients allowed the use of their medical records for clinical research purposes (if alive at the time of data collection).

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon request.

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Author Contributions

Study concept and design: MAK and AZ
Acquisition of data: All authors
Analysis and interpretation of data: MAK, VH, AT, DM, AL, NW, JT, AZ
Drafting of the manuscript: MAK and AZ
Critical revision of the manuscript: All authors
Statistical analysis: MAK
Study supervision: AZ
The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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Conflict of Interest

MAK, VH, VN, PA, AD, MLTM, IT, NW, YT, LM and PH declare no conflict of interest.
CC has received honoraria from Amgen and Servier,and has participated in an advisory board for Servier.
TL has participated in advisory board for AMGEN, Servier, SANOFI, Merck Serono and has received Honoraria from AMGEN, Servier, SANOFI, Pierre FABRE, ASTRA ZENECA, IPSEN
AT: consulting fees from Servier, BMS, MSD, Viatris, Incyte biosciences and Astra Zeneca - travel support form Astra Zeneca.

DM: Consulting fees: Agios, Amgen, Bayer, BMS, HalioDx, Incyte, Merck Serono, MSD, Pierre Fabre Oncologie, Roche, Sanofi, Servier, Viatris. Honoraria for lectures: Amgen, Bayer, BMS, Merck Serono, MSD, Pierre Fabre Oncologie, Roche, Sanofi, Servier, Viatris. Travel expenses: Amgen, Bayer, BMS, Merck Serono, MSD, Pierre Fabre Oncologie, Roche, Sanofi, Servier.

AL has received honoraria for lectures from AAA, Amgen, Astellas, BMS, Esteve, Incyte, Ipsen, Leo-pharma, Mylan, Novartis - honoraria for consulting/advisory relationship from AAA, Astellas, BMS, Incyte, Pierre-Fabre, and Servier - travel support from Bayer, Boehringer, Ipsen, Mylan, MSD, Novartis, Pierre-Fabre - research funding from Bayer, Lilly, Novartis - clinical trials: Astrazeneca (Immunobol-Adj), BMS (Checkmate 577), Incyte (Podium), Lilly (Socrate)

SP has received honoraria for consulting/advisory from Pierre Fabre, Sanofi, Bayer, Servier, Amgen, Merck.

JT received honoraria for speaker or advisory role from: AMGEN, Baxter, BMS, MSD, Merck, Pierre Fabre, Roche, Sanofi, Servier

AZ has participated in consulting and/or advisory boards for Amgen, Lilly, Merck, Roche, Sanofi, Servier, Baxter, MSD, BMS, Pierre Fabre, Havas Life, Alira Health, Zymeworks, Daïchi Sankyo

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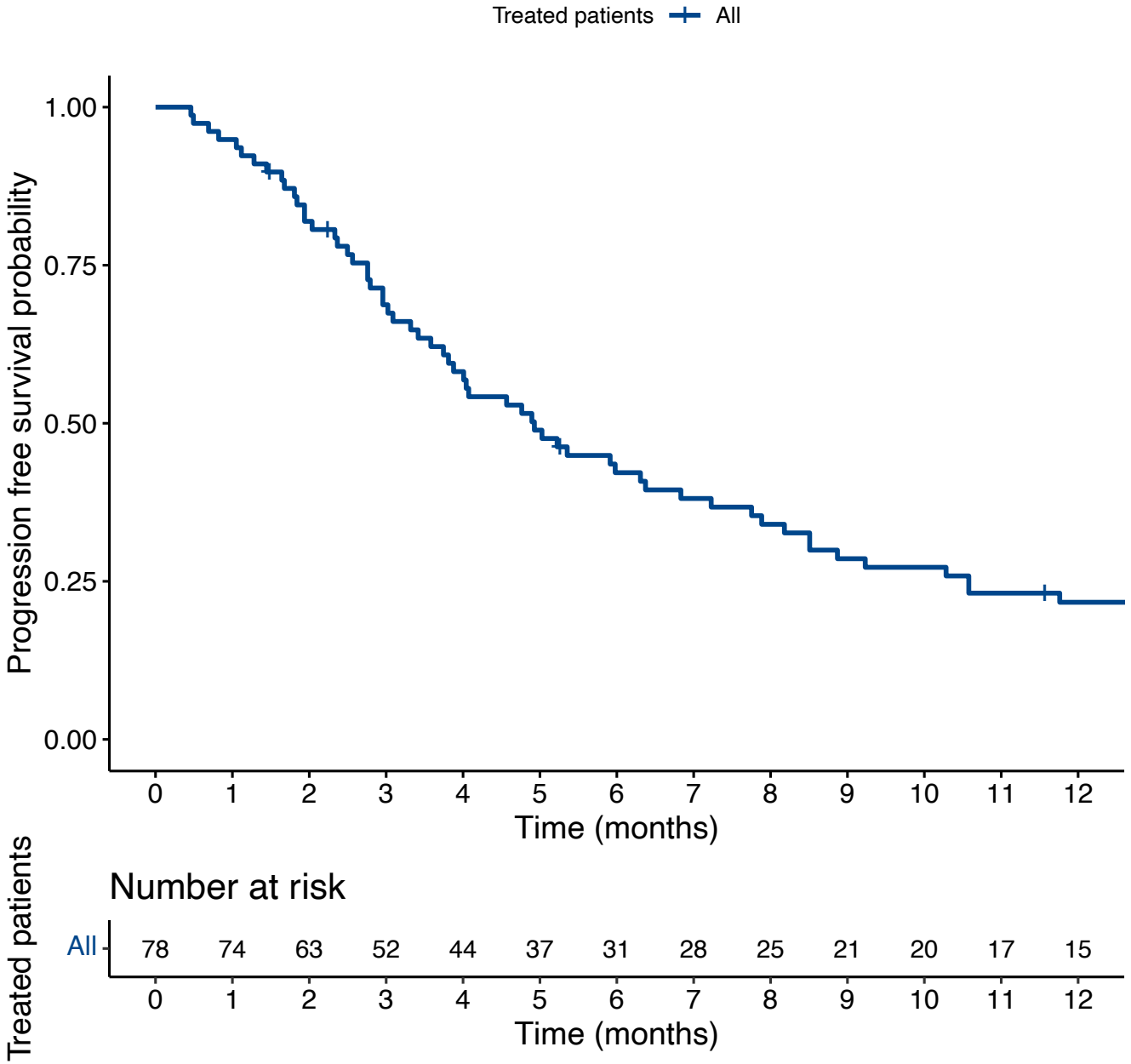
Figure legends

Figure 1. (**A**) Progression free-survival of patients receiving a first line chemotherapy for advanced pancreatic adenosquamous carcinoma; (**B)** Progression-free-survival according to the first-line chemotherapy (5FU-based or Gemcitabine-based) in advanced pancreatic adenosquamous carcinoma; (**C**) Progression-free-survival according to the first-line chemotherapy (FOLFIRINOX and Gemcitabine-Nab Paclitaxel vs others regimens) in advanced pancreatic adenosquamous carcinoma.

Figure 2. (**A**) Overall survival of patients with advanced pancreatic adenosquamous carcinoma (entire cohort); (**B**) Overall survival of patients receiving a first line chemotherapy for advanced pancreatic adenosquamous carcinoma; (**C**) Overall survival of patients with advanced pancreatic adenosquamous carcinoma according to the first line treatment (5FU-based regimens, Gemcitabine-based regimens or best supportive care); (**D**) Overall survival of patients with advanced pancreatic adenosquamous carcinoma according to the first line treatment (FOLFIRINOX and Gemcitabine-Nab Paclitaxel vs others regimens).

(A)



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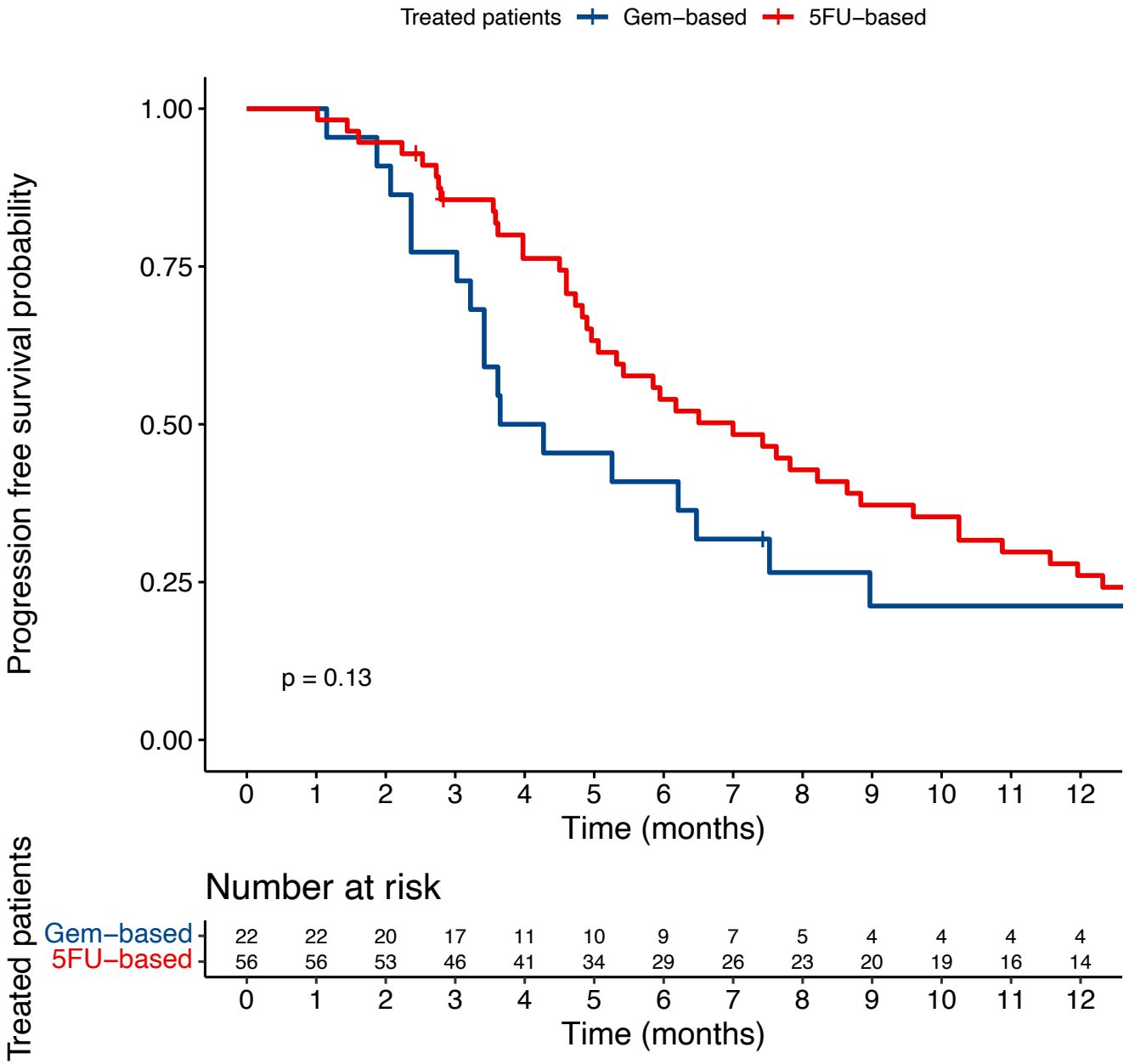

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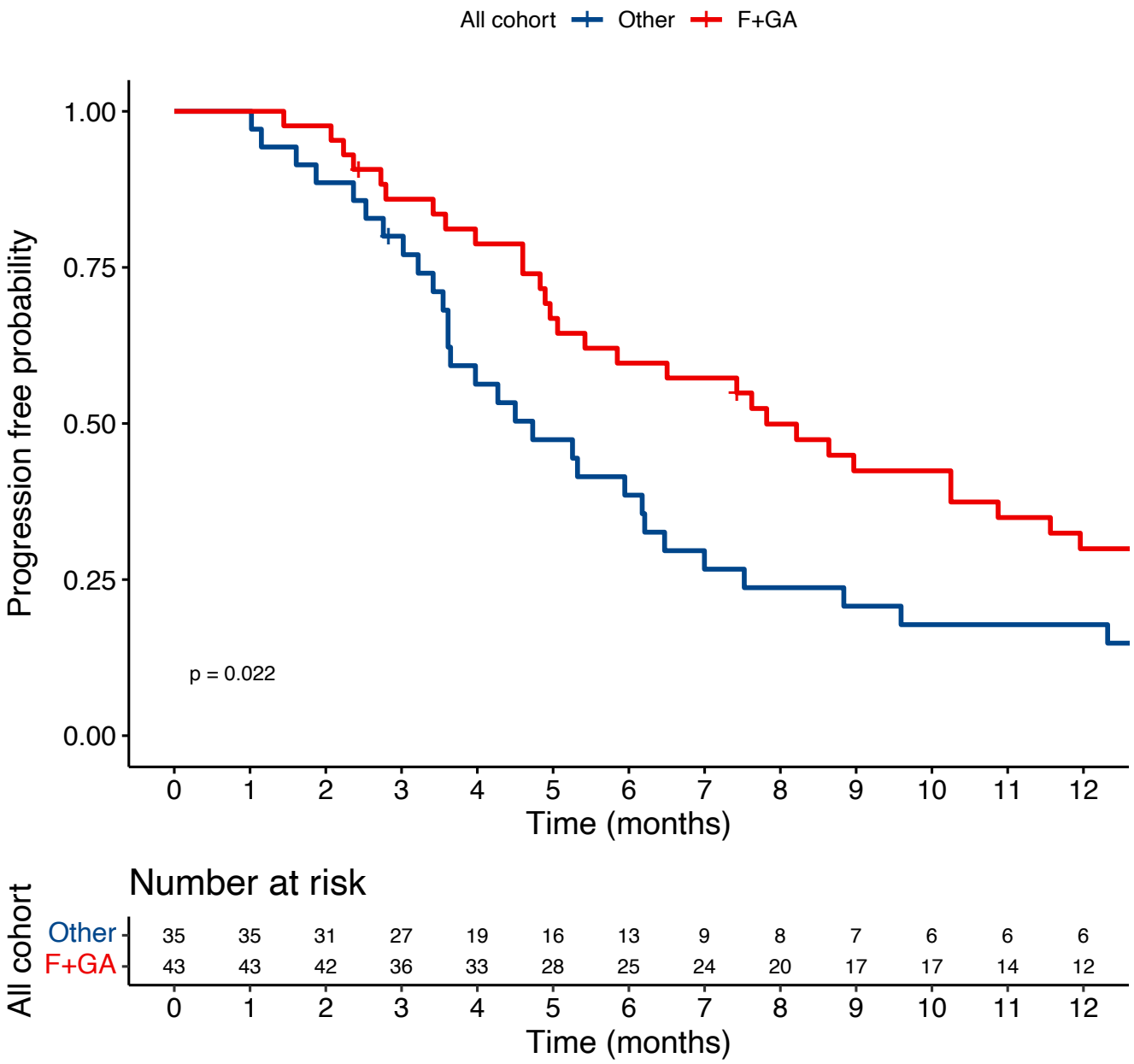
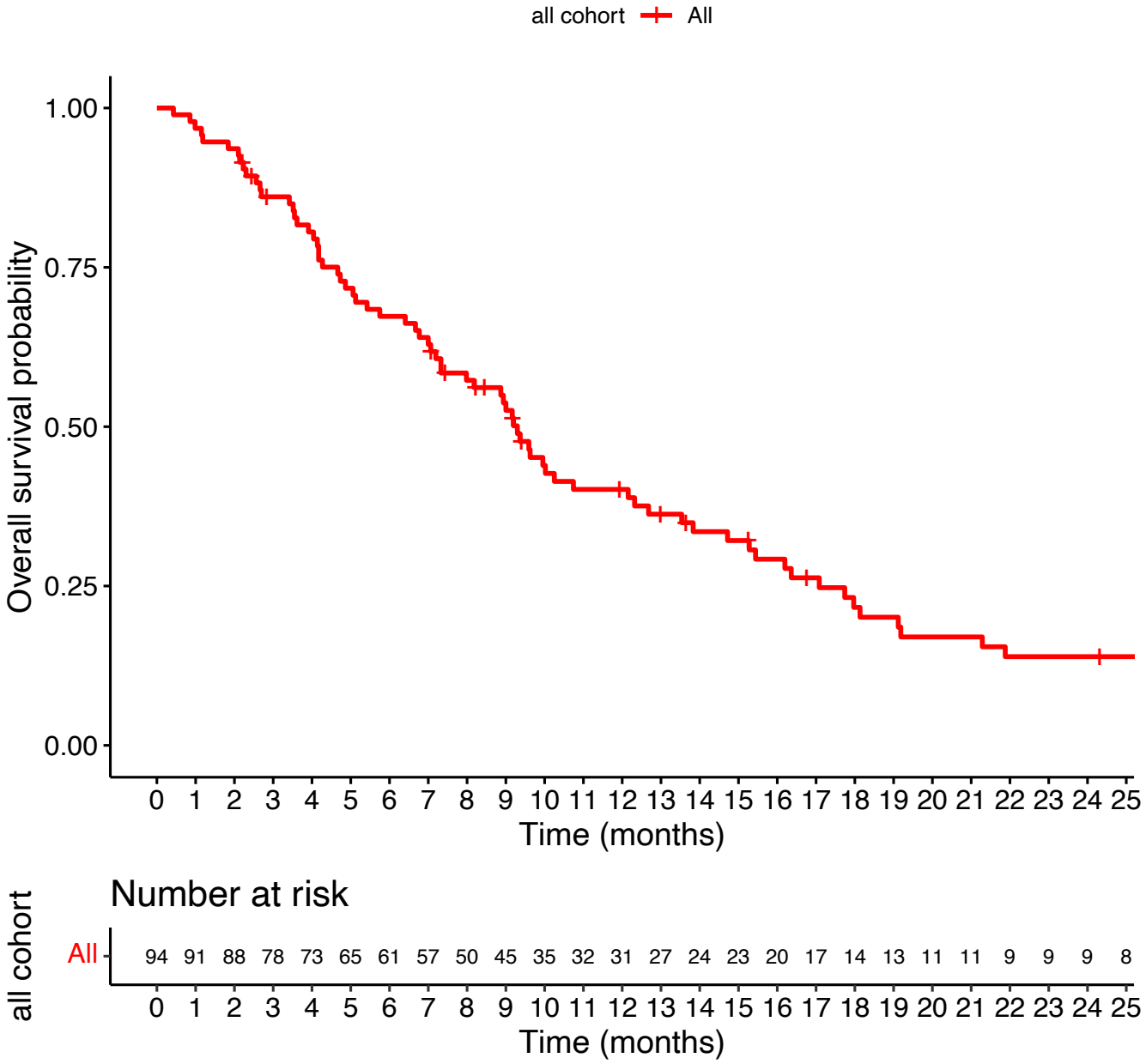
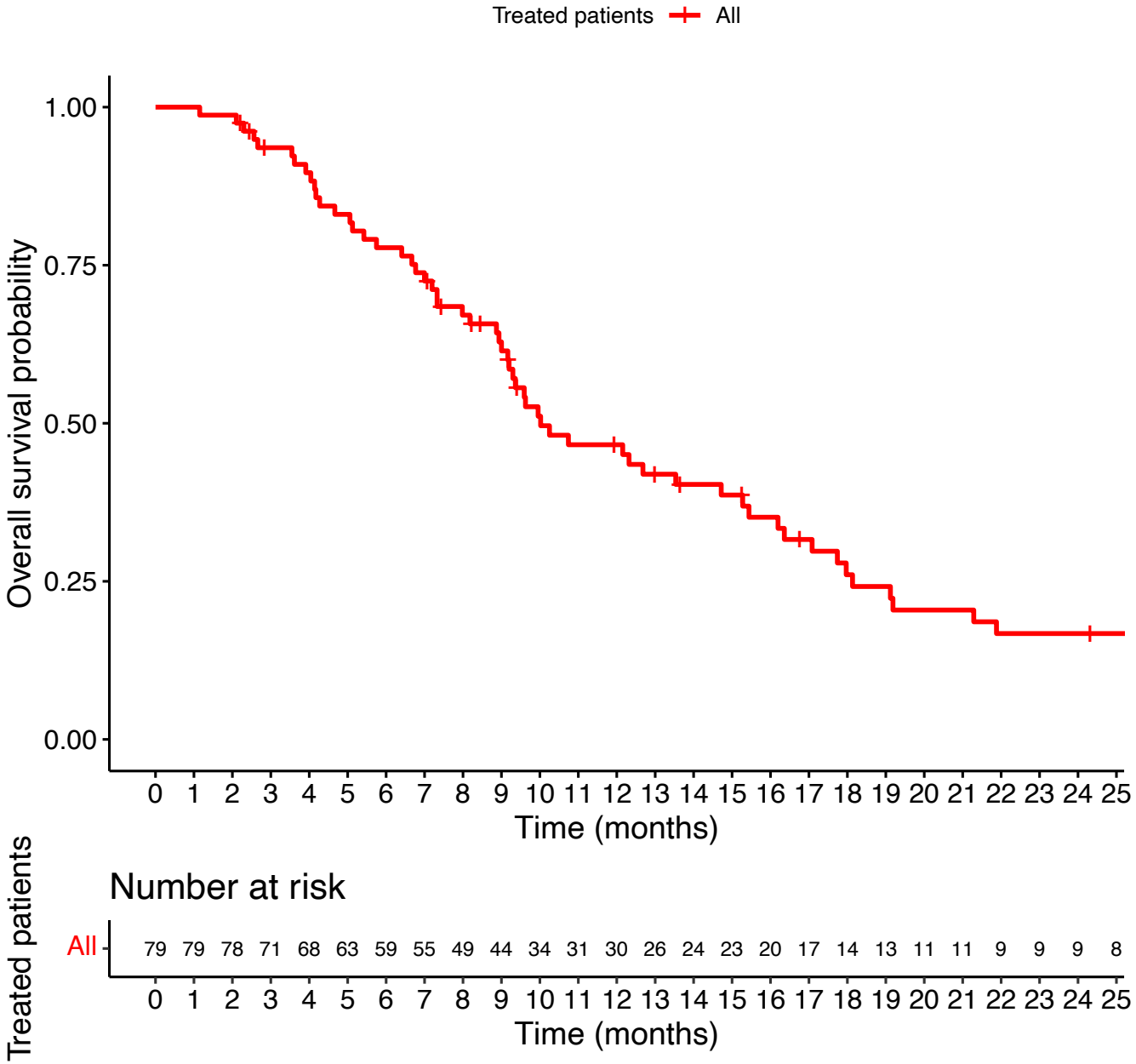


(A)



(B)



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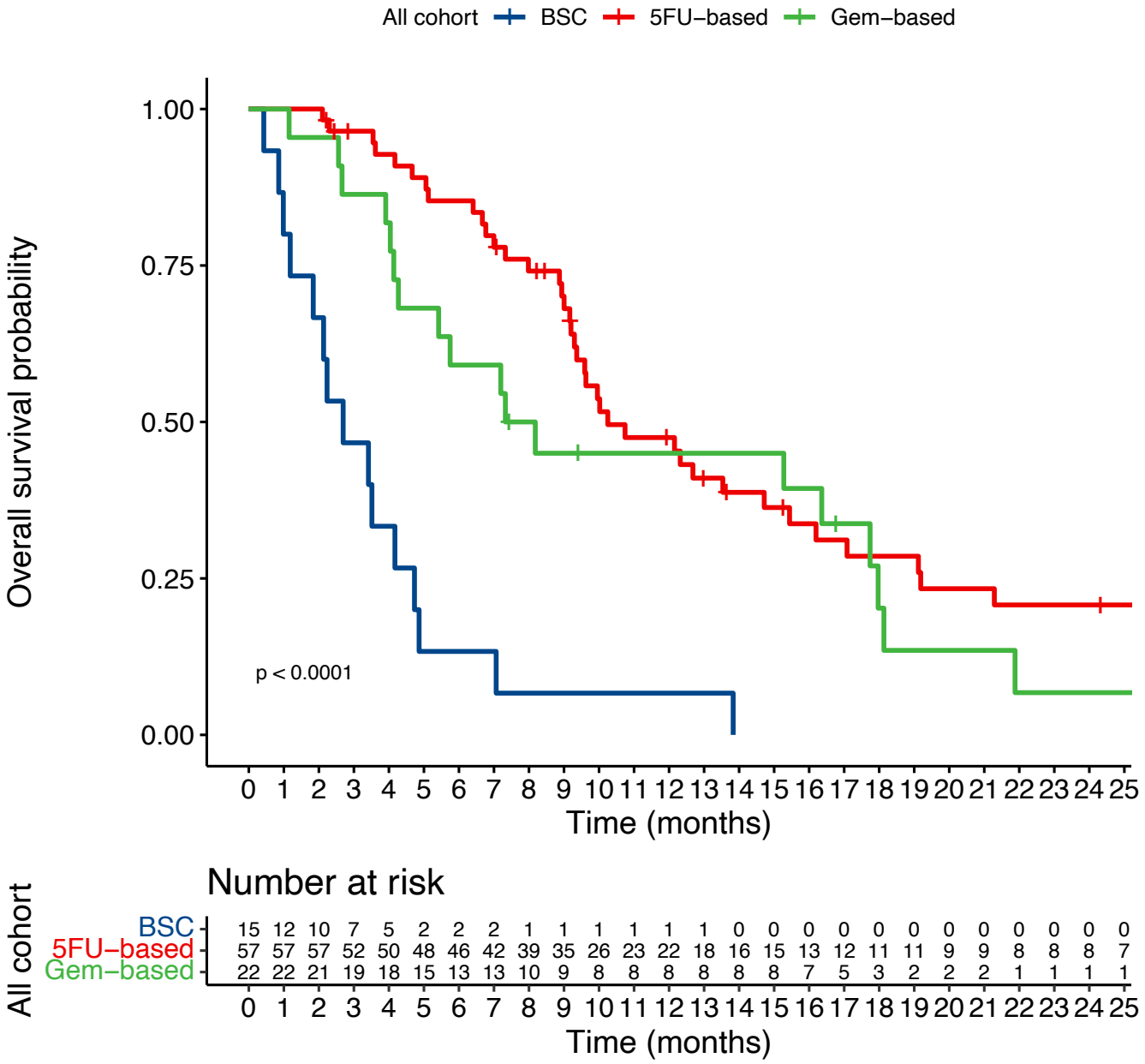

(D)

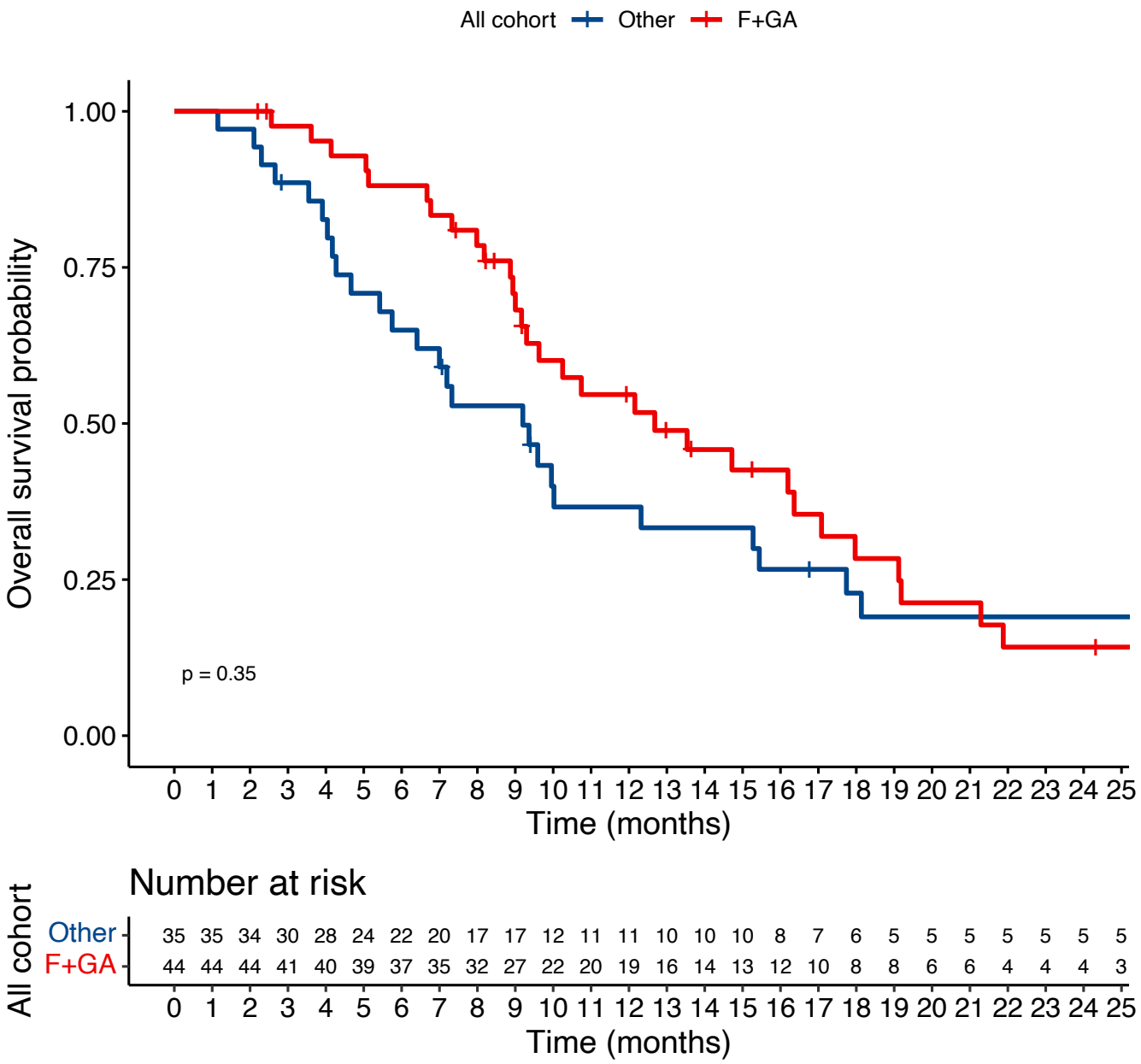

Table 1: Clinical and pathological characteristics

	N=94 patients	%
Age (median - range)	67.3 (34.7 – 86.8)	
>70 years	29	40.4
Gender		
Male	53	56.4
Female	41	43.6
Tumoral site		
Head	41	43.6
Body	21	22.3
Tail	28	29.9
Missing data	4	4.2
Performance Status		
0-1	48	51.1
≥ 2	27	28.7
Missing data	19	20.2
Tumor stage		
Locally advanced	14	14.9
Metastatic	80	85.1
Node	27	33.8
Liver	58	72.5
Peritoneum	16	20
Lung	11	13.8
Number of metastatic sites		
Among metastatic patients, (N=80)*		
1	46	57.5
2	31	38.8
>2	8	10
Missing data	7	8.7
First-line chemotherapy		
No (BSC alone)	15	16.0
Yes	79	84.0
Regimen of first-line chemotherapy		
5FU-based chemotherapy	57	72.2
FOLFIRINOX	37	
FOLFOX	14	
5FU-Cisplatine	3	
FOLFIRI	2	
FOLFOX-Docetaxel	1	
Gemcitabine-based chemotherapy	22	27.8
Gemcitabine	13	
Gemcitabine-Nab paclitaxel	7	
Gemox	1	
Gemcitabine-Erlotinib	1	
Second-line chemotherapy		
Among patients treated in first-line, (N=79)		
Yes	39	49.4
No	31	39.2
Missing data	9	11.4

** Exclusion of 14 patients with locally advanced disease*

Table 2. Tumor response

Regimen of first-line chemotherapy	5FU-based N = 57	Gemcitabine-based N=22	
			P
Evaluable disease	**N = 49**	**N = 20**	
Complete response	2 (4.1%)	0 (0.0%)	
Partial response	12 (24.5%)	4 (21.4%)	
Stable disease	21 (42.8%)	7 (21.4%)	
Progressive disease	14 (28.6%)	9 (57.2%)	
Objective response rate	28.6%	21.4%	***0.58***

Regimen of first-line chemotherapy	FX + GN* N = 44	Other regimens N=35	
			P
Evaluable disease	**N = 38**	**N = 31**	
Complete response	1 (2.6%)	1 (3.2%)	
Partial response	14 (36.9%)	2 (6.5%)	
Stable disease	16 (42.1%)	12 (38.7%)	
Progressive disease	7 (18.4%)	16 (51.6%)	
Objective response rate	39.5%	9.7%	***0.0023***

The *P* values have been determined using the Fisher's exact test

* FX+GN : FOLFIRINOX + Gemcitabine-nab paclitaxel group

Table 3. Univariate and multivariate analysis

Univariate analysis	PFS			OS		
	HR	IC 95%	*P*	HR	IC 95%	*P*
Gender						
Female	1			1		
Male	1.11	0.69 - 1.76	0.67	0.95	0.57 - 1.58	0.84
Age						
≤ 70 years	1			1		
> 70 years	1.01	0.62 - 1.65	0.97	1.11	0.65 - 1.88	0.71
Performance status						
≥2	1			1		
0-1	0.47	0.26 - 0.83	**0.009**	0.25	0.13 - 0.47	**<0.0001**
Tumor stage						
Metastatic	1			1		
Locally advanced	0.81	0.44 - 1.52	0.52	0.78	0.38 - 1.60	0.501
Metastatic status						
Metachronous metastasis	1			1		
Synchronous metastasis	1.50	0.93 - 2.42	0.1	1.72	1.01 - 2.94	**0.047**
According to first-line chemotherapy						
Other regimens	1			1		
FOLFIRINOX or Gemcitabine-Abraxane	0.58	0.36 - 0.93	**0.024**	0.78	0.47 - 1.31	0.35

Multivariate analysis	PFS			OS		
	HR	IC 95%	*P*	HR	IC 95%	*P*
Performance status						
≥2	1					
0-1	0.48	0.27 - 0.85	**0.011**			
According to first-line chemotherapy						
Other regimens	1					
FOLFIRINOX or Gemcitabine-Abraxane	0.59	0.35 - 1.00	0.05			

Abbreviations: PFS: Progression-free survival, OS: Overall survival, PS: Performance Status