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Phase II Randomized, Double-Blind Study of mFOLFIRINOX plus Ramucirumab versus mFOLFIRINOX plus placebo in Advanced Pancreatic Cancer Patients

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Beihang University

2018

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Abstract

Phase II Randomized, Double-Blind Study of mFOLFIRINOX plus Ramucirumab versus mFOLFIRINOX plus placebo in Advanced Pancreatic Cancer Patients

By Yusi Liu

Background - Pancreatic cancer is a kind of highly lethal cancer. The prognosis of pancreas adenocarcinoma, known as PCA made little progress in the last decade. However, FOLFIRINOX, a combination of PCA drugs, which works on Vascular Endothelial Growth Factor (VEGF) and VEGF receptor is an exception. This study is an interim study of a phase II randomized, multi-center and double-blinded study designed to compare the efficacy and safety of mFOLFIRINOX plus Ramucirumab (Arm A) versus mFOLFIRINOX plus placebo (Arm B) in patients with recurrent or metastatic pancreatic cancer (PCA). The primary endpoint is progression free survival (PFS) and secondary endpoints are overall survival and disease response.

Method and Result - The study summarized the interim analysis after total 65 subjects were enrolled (33 in Arm A and 32 in Arm B). Patients had been followed up for at least 9 months. Based on KM curve analysis, no significant difference for PFS was observed between Arm A and Arm B (p-value = 0.747). The median PFS time was 5.3 months for Arm A [95% CI (2.1, 7.7)] vs 3.6 months for Arm B [95% CI (2.1, 9.5)] and the 9-month PFS rate between the two arms are also comparable (20.7% [95% CI (15.8%,54.2%)] for Arm A vs 33.9% [95% CI (15.5%,53.3%)] for Arm B). For the secondary endpoints, the median OS between the two arms were comparable (10.5 months for Arm A [95% CI (4.3, 13)] vs 9.5 months for Arm B [95% CI (3.6, 25.1)]). For disease response, Arm B have obviously better disease (19.05% CR/PR) than Arm A (4.55%). However, this difference did not reach to the significant level yet.

Conclusion - The interim analysis result suggested that Arm B may have better PFS and OS as well as disease response than Arm A in a long run. However, at this time point, no evidence shows significant difference between Arm A and Arm B for both primary point and secondary points. Hence, we suggest that the trail should continue to enroll more subjects until reach the targeted sample size.

Keywords: Phase II randomized clinical trials, Pancreatic Cancer, Progression free survival, Overall survival, Disease response

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Contents

I. Introduction

Pancreatic cancer, which is known as one of the most highly lethal cancers [1], usually causes patients to die within 1 year[2]. Though pancreatic cancer ranks the fourth among cancer-related deaths in the United States, the cause is still largely unknown[3]. The prognosis of pancreas adenocarcinoma, known as PCA, made little progress in the last few years with the exception of FOLFIRINOX, which successfully changed the median overall survival to 11.1 months at best.[3, 4] FOLFIRINOX is successful because of its use of Vascular Endothelial Growth Factor (VEGF). VEGF plays a key role in regulating physiological angiogenesis during embryogenesis, skeletal growth and reproductive functions. VEGF is also related to tumors, intraocular neovascular disorders and other conditions' pathological angiogenesis. [5] VEGF and the VEGF receptor called (VEGFR)-mediate significantly contribute to the pathogenesis and progression of PCA.[1, 6]. VEGFR-2 leads to the invasion and metastasis of PCA cells.[7, 8] A previous study suggests that the expression of receptors is a significant signal of prediction and prognostic factor in PCA treatment[9].

Results from previous studies about anti-angiogenic agents applied in the study of PCA fails to improve the primary outcomes, including overall survival (OS), significantly. An AViTA Trail evaluated the use of bevacizumab and reported a negative primary outcome (decreased OS).[10] Another phase III trial with gemcitabine plus bevacizumab versus gemcitabine suggested the same results (p= 0.95) [11]. Axitinib, a treatment of advanced renal cell carcinoma after the failure of one prior systemic therapy, plus gemcitabine compared with gemcitabine alone showed no significant difference in OS in a phase III trial.

Anti-angiogenic therapy in PCA may be influenced by the choice of chemotherapeutic backbone. Though the above studies fail to improve the primary outcomes, other previous studies illustrate the possibility of building more intensive chemotherapy backbones especially those including a fluoropyrimidine. Anti-tumor activity of Fluoropyrimidine can be enhanced significantly by anti-angiogenic agents which blocks VEGF. Findings from single agent backbone studies suggest the combination and fluoropyrimidine (5FU or capecitabine) with bevacizumab reached their primary

endpoints in two separate single arm phase II trials [12]. Another pooled analysis about gemcitabine-based doublets with bevacizumab has shown some advantage related to survival comparing to historical controls. [13].

Comparing to gemcitabine alone, FOLFIRINOX, a combination of a fluoropyrimidine, oxaliplatin and irinotecan, shows significant advantage of survival in treatment of PCA[1].These studies are why we chose FOLFIRINOX as the chemotherapeutic backbone in our study.

Ramucirumab (RAM) (IMC-1121B, trade name Cyramza), which was approved by the FDA in 2014, is a fully human monoclonal antibody (IgGI). RAM works by blocking the binding of VEGFR ligands, which prevents VEGFR-2 from entering the cell. Hence, RAM plays an important role in inhibiting ligand-stimulated activity of VEGFR-2, which causes a negative effect on multiplication, proliferation and metastasis of human endothelial cells [14]. RAM was used as monotherapy in the treatment of subjects with advanced or metastatic gastric cancer as well as gastro-esophageal junction (GEJ) adenocarcinoma. In the RAINBOW trail, in which RAM was combined with paclitaxel for the therapy of advanced/metastatic gastric and GEJ adenocarcinoma in the second line setting, shows significant advantage of OS[14, 15]. In a RAISE trail, the advantage of using ramucirumab in the treatment of metastatic colorectal cancer has been illustrated. RAM plus FOLFIRI and placebo plus FOLFIRI has been compared in the second line setting for metastatic colorectal carcinoma patients in this trail. Arm with RAM plus FOLFIRI shows significant improvement of OS with manageable side effects[16].

This study is a phase II, multicenter, double-blinded, randomized, 2-arm trial. In this study, 85 subjects with advanced PCA were recruited and separated into two arms (43 in treatment group and 42 in control group). PFS of mFOLFIRINOX plus RAM and mFOLFIRINOX plus placebo of the two groups has been compared and estimated. We also estimate and compare the median overall survival (mOS), response rate (RR) and toxicities in each group.

II. Statistical Method

2.1 Study Design and Subject Registration

This is a phase II, multicenter, double-blinded, randomized, 2-arm trial evaluating the efficacy and safety of mFOLFIRINOX plus RAM (Arm A) vs. mFOLFIRINOX plus placebo (Arm B) in 85 subjects with advanced PCA, not amenable to curative treatment. The estimated enrollment period for this study is 36 months and the estimated study duration is 45 months. The inclusion, exclusion criteria, drug regimen and consent information are available in the initial protocol version dated March 31, 2016.

The interim analysis used the intention-to-treat (ITT) analysis dataset that included all subjects who meet the eligibility criteria and were registered onto the study irrespective of their compliance to the planned course of treatment. A total of 65 subjects were available (33 in Arm A and 32 in Arm B). The intention-to-treat principle asserts that the effect of a treatment policy can be best assessed by evaluating based on the intention to treat a subject (i.e. the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed and analyzed as members of that group irrespective of their compliance to the planned course of treatment. The safety analysis dataset included all subjects who are randomized and received at least one dose of study treatment (on either arm). Subjects would be analyzed for safety according to the treatment received. The safety data was not available for this analysis. All data was collected from subjects who registered through HCRN electronic data capture (EDC) system.

If a subject decides to withdraw from the study for whatever reasons, all efforts should be made to completed and the off-study reason and off-treatment reason should be recorded. A complete final evaluation at the time of the subject's study withdrawal should be made. If the reason of removing subject from the study is an adverse event, it will be recorded on electronic case report form (eCRF).

2.2 Statistical Analysis

2.2.1 Descriptive Analysis

Descriptive statistics for demographic variables as well as p-values for test of difference between the two arms were calculated by chi-square test for categorical variables (Gender, Race) and Anova for continuous variables (age). Contingency analysis was conducted for disease response, off-study reason and off-treatment reason.

2.2.2 Survival Analysis

2.2.2.1 Kaplan-Meier Method and Two-sided log-rank test

Progression-free survival (PFS) and overall survival was estimated for each arm by Kaplan-Meier method. Registration date, off study date, progression free survival date, death date as well as the censor statuas at the end points of study were recorded. 9 months PFS and OS were reported with a 95% confidence interval by Kaplan-Meier estimation and Greenwood's formula for standard error. Kaplan-Meier Method provided survival curve, and KM estimator is:

$$\hat{S}_{KM}(t) = \prod_{k:t_{(k)} \le t} (1 - \frac{d_k}{n_k})$$

$where\ n_k = size\ of\ the\ risk\ set\ R_k\ at\ time\ t_{(k)},$

$d_k = size\ of\ failures\ at\ time\ t_{(k)}$

Greenwood's formula gives the standard error for a KM estimator:

$$var(\hat{K}) \approx K^2 \sum \frac{1 - \hat{P}_t}{N_t \hat{P}_t} \approx \hat{K}^2 \sum \frac{1 - \hat{P}_t}{N_t \hat{P}_t}$$

$N_t\ is\ the\ number\ of\ subject\ on\ test\ at\ time\ t-,$

$P_t\ is\ estimated\ by\ \frac{X_t}{N_t}, where\ X_t\ is\ the\ number\ who\ survive\ from\ t-\ to\ t+.$

$where\ n_k = size\ of\ the\ risk\ set\ R_k\ at\ time\ t_{(k)},\ d_k = size\ of\ failures\ at\ time\ t_{(k)}$

According to the above formulas, 95% confidence intervals calculated by KM estimation for PFS and OS can be reported as:

$$\hat{\hat{S}}_{KM}(t) \pm 1.96 * \sqrt{var(\hat{\hat{K}})}$$

Two-sided log-rank test were used for testing the difference between PFS and OS between arm A and arm B. Suppose that:

$$H_0: S_1(.) = S_2(.)$$

Under H_0, test statistics is:

$$Z = \frac{(O-E)}{\sqrt{(V)}} \sim \mathrm{N}(0,1)$$

$where\ O = observed\ number\ of\ failure$

$E = excepted\ number\ of\ failure$

$V = variance\ calculated\ by\ Greenwood\ fomula$

2.2.2.2 Cox Proportional Hazard Model

In addition to the above analyses, cox proportional hazard models were built for finding univariate association of each demographic variable with PFS and OS. Multivariable models adjusted by gender, race and age were estimated by using the same Cox-PH model. Because Cox Proportional Hazard model should be built under proportional hazard assumption, hence KM curves were used to check the proportional hazard assumption in this study.

The hazard function at each time T for a subject expressed by:

$$h(t|z) = h_0(t) * e^{\beta^T Z}$$

And when Z = 0, the hazard function $h_0(t)$ is the baseline hazard. Hazard ratio between Z1 and Z can be expressed as:

$$\frac{h(t|Z_1)}{h(t|Z)} = h_0(t) * \frac{e^{\beta^T Z_1}}{e^{\beta^T Z}}$$

which is independent of time T.

2.2.3 Interim analysis and O'Brien-Fleming approach

2.2.3.1 Interim analysis in clinical trials

Interim analysis is an analysis of data which is conducted before data collection has been completed in clinical trials studies. We introduce the chance of falsely rejecting the null hypothesis when we go through the data and consider stopping. Type I error α will be introduced to these hypothesis tests every time. However, repeated test with the accumulating data will increase type I error each time. As a result, if the null hypothesis is true, repeatedly testing the same hypothesis at the same significance level using accumulating data will increase the chance of identifying significance result. Hence, in interim analysis, by whatever approach, hypothesis test will start with a very small significant level.[17] The primary aim of this interim analysis was to estimated differences for PFS and OS between the two arms and 0.0013 is used for this study according to O'Brien-Fleming approach

2.2.3.2 O'Brien-Fleming approach.

O'Brien and Fleming proposed a useful multiple testing procedure for comparing two treatment in clinical trials where subject responses were dichotomous and immediate in 1979.[18] According to O'Brien and Fleming, the total number of interim analyses must be fixed at the start (5 in this study). Significance level changes with the number of interim analysis. For example, 4 interim analyses and one final analysis were planned in this study, this analysis was the second interim analysis so we choose 0.0013 as the significance level according to O'Brien-Fleming approach significance level form[18]. Otherwise the trail will continue until the assigned sample size has been completed. The above analysis was all conducted by SAS 9.4 software.

III. Result

3.1 Descriptive Analysis

3.1.1 Summary of baseline demographic

P-values for the relationships between race, gender and age with treatment groups were 0.708,0.958, 0.612 respectively, suggesting there was no difference between Arm A and Arm B for race, gender and age. Hence, balance of factors can be indicated. (**Table 1.**).

Table 1: *Descriptive Statistics- Summary of Baseline demographic differences between study arms*

			Arms		
Covariate	**Statistics**	**Level**	**Arm A N=33**	**Arm B N=32**	**P-Value**
Race	N (Col %)	White	28 (84.85)	27 (84.38)	0.708
	N (Col %)	Non-White	5 (15.15)	5 (15.63)	
Gender	N (Col %)	Female	16 (48.48)	17 (53.13)	0.958
	N (Col %)	Male	17 (51.52)	15 (46.88)	
Age	N		33	32	0.612
	Mean		61.58	62.53	
	Median		62	66	

3.1.2 Distribution of disease response base on study arms

P-value for testing difference in the disease response between two arms by fisher exact test was 0.564 which indicated there was no difference between two arms for disease response. Only one patient in

arm B (4.67%) was complete response. 14 (64.64%) patients and 11 (52.38%) patients experienced disease progression in Arm A and Arm B respectively. 1 (4.55%) and 3 (14.29%) patients received partial response in Arm A and Arm B respectively. 7 (31.82%) patients in Arm A and 6 (28.57%) patients in Arm B remain stable disease. (**Table 2**).

Table 2: *Distribution of Disease Response based on study arms*

Covariate	Statistics	Level	Arms		P-value
			Arm A N=33	Arm B N=32	
Disease Response	N (Col %)	Complete Response	0 (0)	1 (4.76)	0.564
	N (Col %)	Progressive Disease	14 (63.64)	11 (52.38)	
	N (Col %)	Partial Response	1 (4.55)	3 (14.29)	
	N (Col %)	Stable Disease	7 (31.82)	6 (28.57)	

There were 12 (60%) patients in Arm A and 10 (58.82%) patients in Arm B left study due to death related to progressive disease (**Table 3**). There were 11 (44%) patients in Arm A and 9 (37.5%) patients in Arm B off treatment due to the same reason (disease progression) (**Table 4**). Hence, disease progression contributed to off-study reason and off treatment reason most.

In a conclusion, Arm B had obviously better disease response (19.05% Complete Response plus Partial Response) the arm A (4.55%). However, it didn't reach to the significance level yet.

Table 3: *Distribution of Off Study Reason based on study arms*

Covariate	Statistics	Level	Arms		P-value
			Arm A N=33	Arm B N=32	
Off Study Reason	N (Col %)	Patient Reused Follow-up	6 (30)	2 (11.76)	0.308
	N (Col %)	Symptomatic Deterioration	0 (0)	1 (5.88)	
	N (Col %)	Death Related to Progressive Disease	12 (60)	10 (58.82)	
	N (Col %)	Death Due to Other Causes	1 (5)	3 (17.65)	
	N (Col %)	Screen Failure	0 (0)	1 (5.88)	
	N (Col %)	Other	1 (5)	0 (0)	

Table 4: *Distribution of Off Treatment Reason based on study arms*

Covariate	Statistics	Level	Arms		P-value
			Arm A N=33	Arm B N=32	
Off Treatment Reason	N (Col %)	Patient Non-Compliance	1 (4)	0 (0)	0.665
	N (Col %)	Alternative Antineoplastic Therapy	0 (0)	1 (4.17)	
	N (Col %)	Disease Progression	11 (44)	9 (37.5)	
	N (Col %)	AE / Side Effects / Complications	6 (24)	7 (29.17)	
	N (Col %)	Death on Study (During Treatment)	0 (0)	1 (4.17)	
	N (Col %)	Patient Withdrawal After Therapy Start	4 (16)	3 (12.5)	

Covariate	Statistics	Level	Arms		P-value
			Arm A N=33	Arm B N=32	
	N (Col %)	Patient Withdrawal Before Therapy Start	1 (4)	0 (0)	
	N (Col %)	Other Complicating Disease	1 (4)	0 (0)	
	N (Col %)	Symptomatic Deterioration	1 (4)	2 (8.33)	
	N (Col %)	Screen Failure Before Therapy Start	0 (0)	1 (4.17)	

**Note: Complete response is the disappearance of all signs of cancer in response to treatment. Partial response is the disappearance of some signs of cancer in response to treatment but not all.*

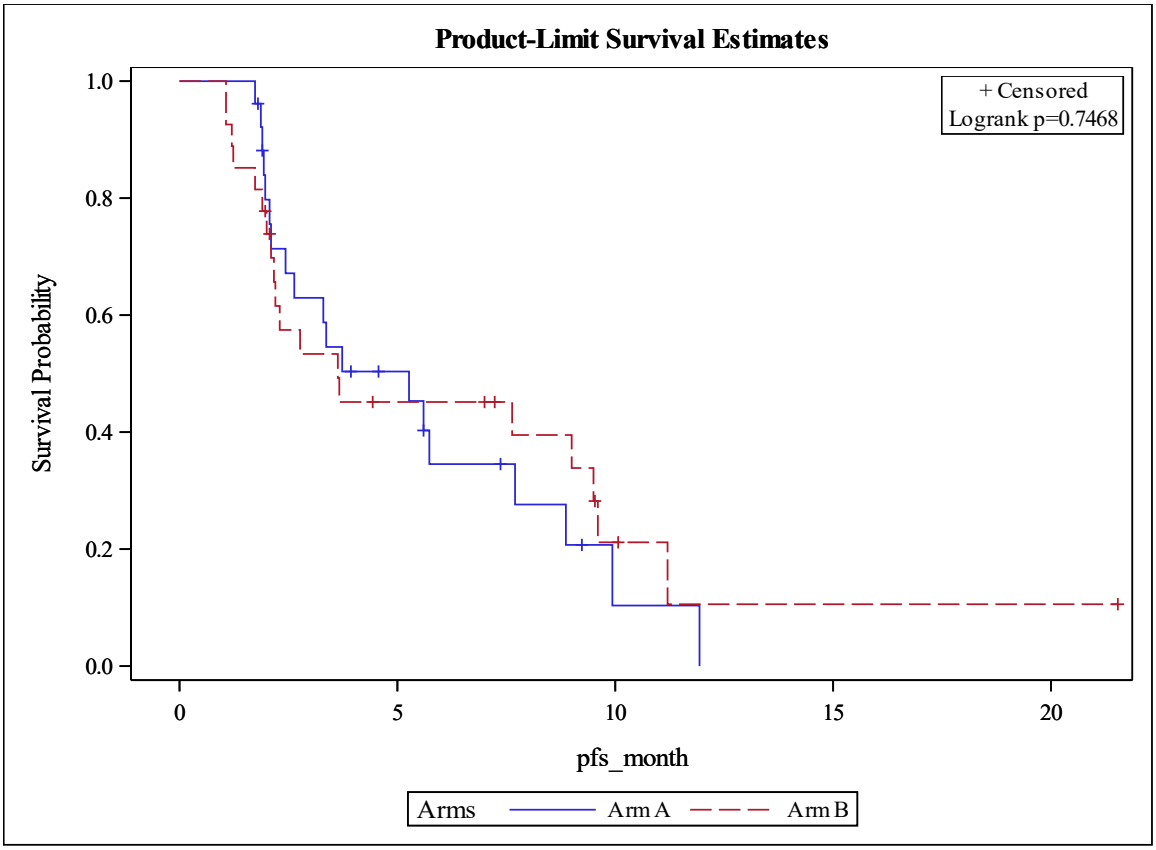
3.2 Survival Analysis

3.2.1 Progression-Free Survival Analysis

The maximum time to progression was 21.53 months. Median PFS was 5.3 (2.1,7.7) months for patients in Arm A and 3.6 (2.1, 9.5) months for patients in Arm B. At the first 3 months, PFS for patients in Arm A and Arm B are 63.0 % (40.8%, 78.8%) and 53.4% (32.6%,70.4%) respectively. PFS rates for Arm A was higher than it for Arm B. However, Arm A patients showed lower PFS rate at 9 months (the endpoint). PFS rates for Arm A patients and Arm B patients are 20.7% (15.8%,54.2%) and 33.9% (15.5%, 53.3%) respectively at 9 months (**Figure 1)**.

Log-rank test showed no significant difference between Arm A and Arm B in PFS (P= 0.747). But lower PFS rate at start with higher PFS rate in the end indicated treatment group (Arm B) may have better PFS than control group (Arm A) at significant level in a long run.

Figure 1: *KM survival curves for PFS for Arm A and Arm B*



Arms	No. of Subject	Event	Censored	Median Survival (95% CI)	3 Mo Survival	6 Mo Survival	9 Mo Survival	12 Mo Survival	18 Mo Survival
Arm A	26	19 (73%)	7 (27%)	5.3 (2.1, 7.7)	63.0% (40.8%, 78.8%)	34.5% (15.8%, 54.2%)	20.7% (5.9%, 41.7%)	0.0% (0.0%, 0.0%)	0.0% (0.0%, 0.0%)
Arm B	27	19 (70%)	8 (30%)	3.6 (2.1, 9.5)	53.4% (32.6%, 70.4%)	45.2% (25.4%, 63.0%)	33.9% (15.5%, 53.3%)	10.6% (0.9%, 34.0%)	10.6% (0.9%, 34.0%)

For univariate analysis, the hazard ratio of Arm A vs. Arm B was 1.11 (0.58, 2.11). Though the hazard of being in control group are 1.11 times that of being in treatment group, this relationship between arms and disease progression was not significant (p=0.747). Additionally, none of other covariates (gender, race, age) was predictor of PFS. After adjusting for gender, race and age, the hazard of being in Arm A is 1.09 (0.57,2.08) times of being in Arm B. The association still remained not significant (p= 0.787) (**Table 5**)

Table 5: *Univariate and multivariate analysis for association PFS*

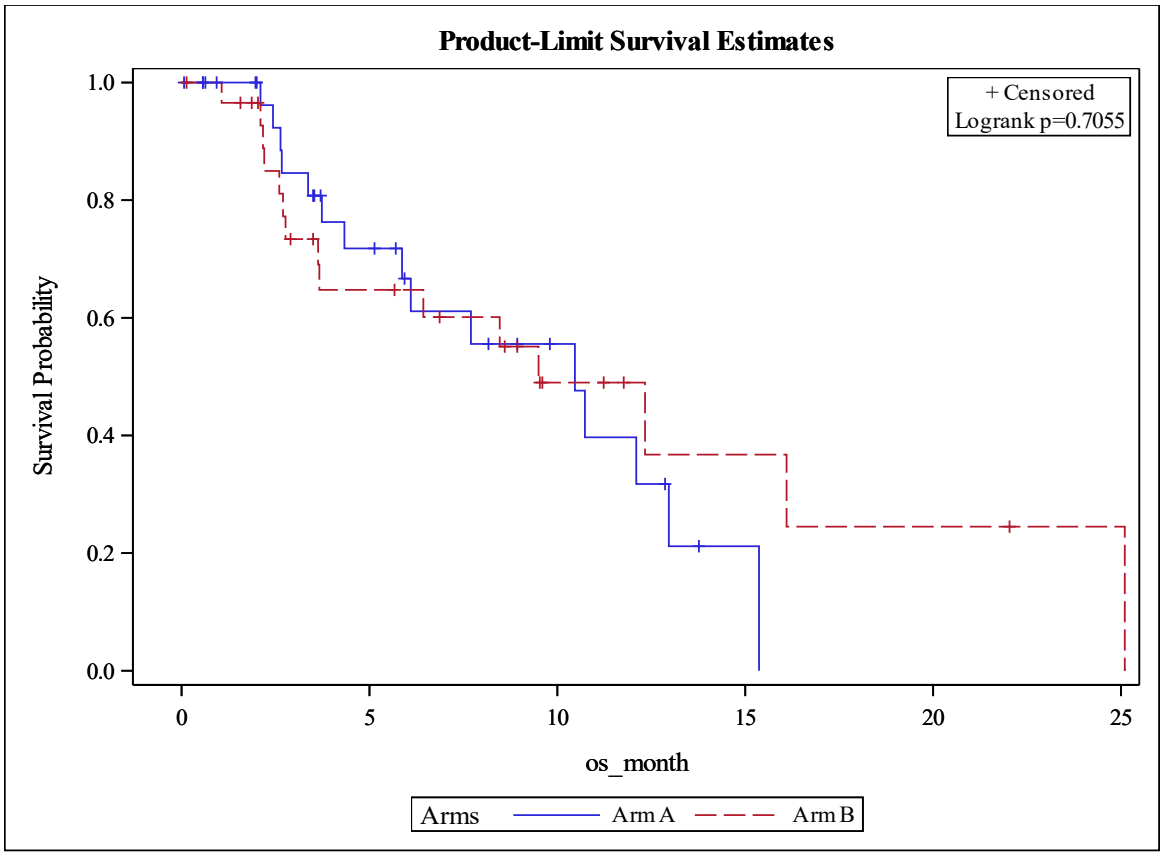
Demographic Variable	Level	N	Univariate Analysis HR (95% CI)	P-value	Multivariate Analysis HR (95% CI)	P-value
Gender	Male	26	1.22 (0.64-2.32)	0.543	0.81 (0.40-1.61)	0.541
	Female	27	-	-	-	-
Race	White	44	0.91 (0.38-2.20)	0.832	0.67 (0.25-1.82)	0.437
	Non-White	9	-	-	-	-
Arms	Arm A	26	1.11 (0.58-2.11)	0.747	1.09 (0.57-2.08)	0.787
	Arm B	27	-	-		
Age		53	1.03 (0.98-1.07)	0.276	1.03 (0.98-1.08)	0.238

3.2.2 Overall Survival Analysis

Similarly, the maximum time to overall death was 21.53 months. Median OS was 10.5 (4.3,13) months for patients in Arm A and 9.5 (3.6, 25.1) months for patients in Arm B. At the first 3 months, OS rates for patients in Arm A and Arm B were 84.6% (64.0%, 93.9%) and 73.4% (52.1%, 86.3%) respectively. OS rates for Arm A was higher than it for Arm B. However, similar to PSF rate, Arm A patients showed lower OS rate at 9 months (the endpoint). OS rates for Arm A patients and Arm B patients were 55.6% (32.4%,73.6%) and 55.1% (33.3%,72.4%) respectively at 9 months (**Figure 2)**.

Log-rank test showed no significant difference between Arm A and Arm B in OS (P= 0.7055). However, also similar to PFS, lower OS rate at start but higher OS rate in the end indicated treatment group (Arm B) may have better OS than control group (Arm A) at significant level in a long run.

Figure 2: *KM survival curves for OS for Arm A and Arm B*



Arms	No. of Subject	Event	Censored	Median Survival (95% CI)	3 Mo Survival	6 Mo Survival	9 Mo Survival	12 Mo Survival	18 Mo Survival
Arm A	33	15 (45%)	18 (55%)	10.5 (4.3, 13)	84.6% (64.0%, 93.9%)	66.7% (43.8%, 81.9%)	55.6% (32.4%, 73.6%)	39.7% (16.9%, 61.9%)	0.0% (0.0%, 0.0%)
Arm B	30	15 (50%)	15 (50%)	9.5 (3.6, 25.1)	73.4% (52.1%, 86.3%)	64.7% (43.0%, 80.0%)	55.1% (33.3%, 72.4%)	49.0% (27.0%, 67.8%)	24.5% (4.9%, 51.8%)

For univariate analysis, the hazard ratio of Arm A vs. Arm B was 1.15 (0.55, 2.44) for OS. Though the hazard of being in control group were 1.15 times that of being in treatment group, this relationship between arms and disease progression is not significant (p=0.706). Additionally, none of other covariates (gender, race, age) was predictor of OS. For multivariate analysis, after adjusting for gender, race and age, the hazard of being in Arm A was 1.14 (0.54,2.41) times of being in Arm B. The association still remained not significant (p= 0.732) (**Table 6**.)

Table 6: *Univariate and multivariate analysis for association OS*

Demographic Variable	Level	N	Univariate Analysis HR (95% CI)	P-value	Multivariate Analysis HR (95% CI)	P-value
Gender	Male	31	1.20 (0.57-2.51)	0.630	0.91 (0.42-1.97)	0.814
	Female	32	-	-	-	-
Race	White	53	1.07 (0.32-3.63)	0.909	0.70 (0.19-2.58)	0.594
	Non-White	10	-	-	-	-
Arms	Arm A	33	1.15 (0.55-2.44)	0.706	1.14 (0.54-2.41)	0.732
	Arm B	30	-	-	-	
Age		63	1.05 (1.00-1.12)	0.076	1.06 (0.99-1.12)	0.074

Proportional hazard assumption was checked by KM curves. From the above plot **(Figure 1 and Figure 2**). KM curves for Arm A and Arm B are not parallel, so proportional hazard assumption is false in this situation.

IV. Discussion

This interim analysis aimed to evaluate the effect of treatment in Arm A and Arm B for the primary endpoint, PFS. In our PFS analysis, patient with sequence number 198-1018 (from Gettysburg Cancer Center) had been excluded because of the unreasonable PFS survival time (smaller than 1). In addition, patients with sequence number 198-1026 (from Indiana University Melvin and Bren Simon Cancer

Center) and 198-1065 (University Medical Center, Inc.; DBA University of Louisville Hospital/James Graham Brown Cancer Center) had also been excluded because of the unreasonable OS survival time (smaller than 1). For easy interpretation, Asian (n=1) patient, African American (n = 6) patients and Unknown race patients (n=3) were combined into one single race group (Others) for the analysis.

Two arms seemed to be comparable with no difference between the demographic variables. Result from summary table (Table 1.) indicated that for the both two arms, race, gender and age are random assigned in each group without any selection bias. Percentage of each level of race and gender was roughly equal which indicated balance in each group and each level for the variables.

Most patients showed signs of progressive disease based on the disease response, off-study reason and off-treatment reason. However, the difference of percent of progressive disease did not reach significant level yet at this time point.

P-value for univariate analysis between disease response and the two arms showed no significant relationship between each other. Arm B had obviously better disease response (19.05 % CR/PR) than arm A (4.55%) but not reach to the significance level yet (**Table 2.**). Similarity, p-values for univariate analyses between off-study reason, off treatment reason gave the same result. (**Table 3., Table 4.**)

Among those 65 patients enrolled in this interim analysis, 7 patients in Arm A and 6 patients in Arm B showed stable disease without progression for positive response, so they were excluded for PFS analysis. As a result, 26 patients in Arm A and 27 patients in Arm B remained for further analysis of PFS.

According to the KM curve analysis, there is no significant difference for PFS between Arm A and Arm B (log-rank p-value = 0.747) suggesting that these two arms were not different based on the significance level of 0.0013 according to the O'Brien-Fleming approach. The median PFS (5.3 months for Arm A [95% CI (2.1, 7.7)] vs 3.6 months for Arm B [95% CI (2.1, 9.5)]) and 9-month PFS (20.7% [95% CI (15.8%,54.2%)] for Arm A vs 33.9% [95% CI (15.5%,53.3%)] for Arm B) rate between the two groups are comparable. However, result of monthly survival rate analysis as well as KM curves of

the two groups shows PFS survival of Arm A is higher than it of Arm B at 3 months but lower at 9 months, (**Figure 1.**) suggesting positive effect of treatment may occur in a long run. Univariate Cox-models based on proportional hazard assumption indicated none of the covariate (Gender, Race, Arms, Age) was predictor of PFS at this end point (9 months).

After removed the two patients with unreasonable OS time, 33 patients in Arm A and 30 patients in Arm B remained for the following data analysis. Similarly, for OS, the treatment arms are not significantly different (log-rank p-value = 0.706) suggesting no evidence showed significant difference on OS between Arm A and Arm B. The median survival and the 9-month survival rate between the two arms are comparable (55.6% [95% CI (32.4%,73.6%))] vs 55.1% [95% CI (33.3%,72.4%)] for Arms A and B, respectively). Different with PFS, Arm A's 9-month OS is still higher than it in Arm B, so no further indication can draw at this point (9 months). According to longer followed time OS analysis, the cross of two KM curves occurred between 9 months and 12 months which indicated that treatment may have positive effect on PCA after at least 9 months. Base on the above conclusion, treatment, mFOLFIRINOX plus RAM, is more effective on PFS than OS.

This analysis had some limitations. First of all, the mean age of these PCA patients is 61.58 and 62.53 for Arm A and Arm B respectively. As a result, conclusions can only be drawn for the old instead of the whole age group of PCA patients. Categorize age into relatively young and relatively old groups can be applied in the future analysis. Secondly, univariate Cox models for these patients didn't fit the proportional hazard assumption, so the result was just a robust relationship.

V. Conclusion

This interim study indicated that Arm B may have better PFS as well as OS and disease response performance in the later phase. However, there was still not enough evidence shows significant difference between the two groups on PFS and OS or disease response at this time point. Therefore, we suggest that the trial should continue to accrue subjects until the targeted sample size has been achieved.

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