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FG-3019, A Human Monoclonal Antibody to Connective Tissue Growth Factor, Combined with Chemotherapy in Patients with Locally Advanced or Metastatic Pancreatic Ductal Adenocarcinoma

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Abstract

Purpose: Connective tissue growth factor (CTGF) is overexpressed in pancreatic ductal adenocarcinoma (PDAC) and facilitates local desmoplasia, tumor progression and metastasis in animal models. This study evaluated safety and initial efficacy of the anti-CTGF antibody FG-3019 in combination with gemcitabine and erlotinib in patients with previously untreated Stage III or Stage IV PDAC.

Methods: Eight escalating FG-3019 doses/regimens ranging from 3 to 45 mg/kg Q2W and 17.5 and 22.5 mg/kg QW were evaluated. Toxicity, tumor response by CA19.9 and CT scan RECIST criteria, progression-free and overall survival were assessed. FG-3019 day 15 trough plasma levels ($D15C_{min}$), as a measure of exposure, and baseline CTGF levels were correlated with clinical outcomes.

Results: Seventy-five patients were enrolled over 39.6 months. Median and longest treatment duration were 3.3 and 20.9 months, respectively. FG-3019 was well tolerated with no dose-related trends observed in type or incidence of SAEs. No FG-3019- dose-liming toxicity was observed. Median PFS and OS were 3.7 and 7.4 months, respectively. High FG-3019 exposure (D15 $C_{min} \geq 150$ µg/mL), compared to low exposure, was associated with improved median OS (9.0 *vs.* 4.4 months, respectively, p=0.024), 1-year OS rate (34.2% *vs.* 10.8%, respectively, p=0.026), and median PFS (6.0 *vs.* 2.4 months, respectively, p=0.032). Plasma CTGF showed potential as a prognostic biomarker, as low baseline CTGF levels (<10 ng/mL) were associated with improved OS (10.1 *vs.* 4.4 months, p=0.028); and PFS (5.5 *vs.* 2.3 months, p=0.019).

Conclusions: FG-3019 can be safely combined with gemcitabine and erlotinib without incremental toxicity in advanced pancreatic cancer patients. Low baseline CTGF and high FG-3019 exposure were associated with improved survival. Targeting of PDAC by FG-3019 in combination with cytotoxic chemotherapy represents a novel approach to this difficult disease and further trials are warranted.

Keywords: Pancreatic ductal adenocarcinoma; Cancer; CTGF; Desmoplasia

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer death in the United States. Overall 5-year survival according to the most recent SEER data [1] is about 7%, due to many factors, including advanced stage at diagnosis and limited response to currently available therapies [2-4].

PDAC tumors often exhibit a high degree of desmoplasia, characterized by extensive connective tissue stroma and elevated levels of connective tissue growth factor (CTGF) [5,6]. Cancer-stroma interactions affect tumorigenesis, angiogenesis, resistance to therapy and metastatic spread of tumor cells [7]. PDAC cells and stromal stellate cells have been shown to interact with each other to enhance proliferation, reduce apoptosis and increase migration and invasion of cancer cells [5,6,8-11].

CTGF is a 36 kDa glycoprotein of the CCN family [12]. CTGF is a downstream modulator of TGFβ [13,14], interacts with insulin-like

growth factor 1 (IGF-1) [2] and modulates interactions between tumor cells and matrix in many cancers [15,16], including PDAC [7]. Elevated CTGF expression has been detected in many tumor types [5,17] where it has been identified as an invasion-specific gene [18] and is highly expressed within the neoplastic epithelium of PDAC [9]. Wenger et al. showed 59-fold enhancement of CTGF expression in 15 out of 19 samples of pancreatic tumors, compared with only 4.5-fold increase in chronic pancreatitis [5].

It is understood that poor treatment outcomes in pancreatic cancer may be related to the presence of an extensive desmoplastic niche that supports the growth and metastasis of tumors and possibly induces immunosuppression [5-7]. Our hypothesis is that CTGF inhibition would impact stromal remodeling in pancreatic cancer and thereby inhibit tumor growth and metastasis. The use of experimental anti-fibrotic agents such as FG-3019 is a new approach in treatment of desmoplastic tumors and may enhance efficacy of chemotherapeutic agents [19]. Novel combination approaches that target the desmoplastic and cancer cells are needed to improve clinical outcomes in advanced PDAC.

Patients and Methods

Eligible patients were ≥ 18 years old with locally advanced stage III or metastatic stage IV PDAC, with at least one measurable lesion by RECIST criteria, ECOG performance status ≤ 1, and estimated life expectancy of >12 weeks. Anemic (Hb<10.0 g/dL), neutropenic (<1500/mm^3), and/or thrombocytopenic (<100000/mm^3) patients were excluded, as were patients with elevated liver function tests. Prior chemotherapy, except 5-fluorouracil as a radio-sensitizer, was not allowed.

All eligible patients were enrolled to one of the 6 dose cohorts with doses ranging from 3-45 mg/kg of FG-3019 given every 2 weeks (Q2W), or 2 dose cohorts of 17.5 or 22.5 mg/kg every week (QW) after an initial loading dose of 35 or 45 mg/kg, respectively. FG-3019, a human IgG1 monoclonal antibody to CTGF (FibroGen, Inc., San Francisco, CA) was administered by IV infusion. In the first treatment cycle, FG-3019 was administered alone on Day 1 in the Q2W cohorts and on Days 1 and 8 in the QW cohorts. Subsequently, FG-3019 was administered on Days 1 and 15 (Q2W) or Days 1, 8, 15 and 22 (QW) of each 28 day cycle. Treatment with gemcitabine and erlotinib began on Day 15 in the first treatment cycle. Subsequently, Gemcitabine (1000 mg/m^2) was administered on Days 1, 15 and 21 of each cycle and erlotinib (100 mg) was administered orally daily [20]. Growth factor support was allowed at the discretion of the investigator.

The study was registered at clinicaltrials.gov (NCT01181245), the study protocol and informed consent documents were reviewed and approved by the institutional review boards of the participating institutions, and informed consent was obtained from all patients before any study-specified procedures.

Study Design

This was an open label dose-escalation study to evaluate safety and tolerability with secondary assessments of efficacy of FG-3019 with standard doses of gemcitabine and erlotinib (G/E) as chemotherapy in patients with previously untreated locally advanced Stage III and Stage IV PDAC. Eight escalating doses/dose regimens of FG-3019 were tested in sequential cohorts. Patients were treated until disease progression, inability to tolerate study treatment, or termination of therapy due to other reasons as determined by treating physician. After disease progression or treatment termination for any reason, subjects were tracked until their death to obtain information about subsequent treatments and survival.

Assessments

The primary objective of this study was to evaluate safety and tolerability. Secondary endpoints were efficacy and pharmacokinetics (PK) of FG-3019 in combination with G/E. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0. Dose-limiting toxicity was defined as Grade 3 or higher non-hematologic or Grade 4 or higher hematologic toxicity that was related to FG-3019 and could not be managed adequately with medical therapy. Additional laboratory plasma assessments included CA 19.9, baseline CTGF and human anti-human antibodies (HAHA) levels. Plasma was obtained for pharmacokinetic (PK) analyses pre- and post FG-3019 infusions. FG-3019 exposure and plasma CTGF at baseline were correlated with clinical progression and survival outcomes. Assessments of CTGF were limited to baseline values, since subsequent to dosing with FG-3019 plasma CTGF binds to the antibody and apparent plasma levels of CTGF are increased. Day 15 trough levels of FG-3019 ($D15C_{min}$) were used as a surrogate measurement for exposure. Tumor response was assessed by CT every 8 weeks. Disease progression was determined either clinically or radiologically. After discontinuation from the study, 24 subjects received subsequent chemotherapy or chemo-radiation therapy according to investigator choice.

Statistical Analysis and Scoring Rules

The sample size of the study was considered adequate to evaluate initial safety, tolerability pharmacokinetics and preliminary efficacy of FG-3019. In the lower dose cohorts (Cohorts 1-3), the standard 3+3 doses escalation design was used. In each of the higher dose cohorts approximately 12 subjects were enrolled. The increased sample size of 12 subjects in the higher dose cohorts would allow further evaluation of safety events with relatively low incidence. Median time-to-event parameters were estimated with the Kaplan-Meier method using SAS PROC LIFETEST procedure. Overall survival (OS) was defined as the time from the date of the first dose to the date of death from any cause. Progression free-survival (PFS) was defined as the duration from first dose to disease progression (by clinical or radiological criteria) or death for any cause. PFS was determined by time to progression (TTP) if the progression event was observed. If disease progression was not observed, then PFS was determined by the following rules: if death occurred within 4 weeks from the date of last dose of FG-3019, then PFS was equal to OS and recorded as an event. If death occurred more than 4 weeks from the date of last dose of FG-3019, then the PFS date was set to equal the date of last FG-3019 dose and PFS was censored. In exploratory analyses evaluating efficacy parameters by possible prognostic and predictive factors, a log-rank test and Cox regression model were used in time-to-event parameters, and Fisher's exact test was used in categorical parameters. All tests were performed as two-sided at alpha level 0.05.

Results

Patient disposition and demographics

75 patients were enrolled at 7 US sites between 13-Nov-2008 and 29-Feb-2012 (ITT population). Baseline patient characteristics are presented in Table 1. Sixty-six enrolled patients (88%) had metastatic stage IV disease and 9 patients (12%) had stage III locally advanced disease. Patient characteristics such as ECOG performance status, disease stage, age and gender were similar in each dose cohort. The median number of FG-3019 infusions was 9 [range 1 to 83], the median number of gemcitabine infusions was 10 [range 1 to 46], and the median number of erlotinib doses was 54 [range 0 to 564]. Of the ITT population, 8 (10.7%) subjects discontinued treatment due to AE, 49 (65.3%) due to progressive disease, 9 (12.0%) due to death (all causes), 1 (1.3%) due to physician's decision, 7 (9.3%) due to withdrawal of consent, and 1 (1.3%) due to loss to follow up.

Baseline	Total (N=75)
Gender	
Male	41 (55%)
Female	34 (45%)
Age (years), mean [range]	65 [34 – 85]
Race	
White	65 (87%)
Asian	9 (12%)
Other	1 (1%)
ECOG Performance Status	
0	30 (40%)
1	44 (58.7%)
2	1 (1.3%)
Stage	
III	9 (12%)
IV	66 (88%)
Ascites, n (%), obtained from patient records	
Yes	15 (20%)
No	54 (72%)
Unknown	6 (8%)
Sum of Target Lesion (mm), mean (SD)	75.2 (45.8)
Presence of Metastasis, n (%)	
Liver	46 (61%)
Lung	19 (25%)
CA19-9 evaluable (baseline ≥ 70 ng/mL), n (%)	
Yes	54 (72%)
No	21 (28%)

Table 1: Patient Demographics and Characteristics.

Safety

Eight dose/dose regimens of FG-3019 were tested and a maximal tolerated dose (MTD) was not reached. No dose-limiting toxicities (DLT) related to FG-3019 were observed in any treatment cohort. Forty patients (53.3%) experienced at least one SAE (Table 2), including 19 subjects who died within 30 days of the last treatment. The six most frequent SAEs were: disease progression (13.3%), cholangitis (8.0%), pulmonary embolism (8.0%), abdominal pain (4%), bile-duct obstruction (4%) and deep-vein thrombosis (4.0%). Within two weeks after the first FG-3019 dose and before start of chemotherapy, only 8 patients (10.7%) experienced an SAE, with abdominal pain the only type that occurred in ≥ 2 patients. None of the SAEs were considered to be related to FG-3019. In addition, there was no relationship between the dose of FG-3019 and the incidence of SAEs. The most frequently reported primary cause of death for patients who died within 5 weeks of the last dose of combination therapy was disease progression; other primary causes included respiratory arrest, peritonitis, sudden death of unknown etiology, and in one subject a cause was not specified. By study closure on 27 May 2014, all subjects were off study, and overall 73 subjects (97.3%) had died.

Subjects were not pre-medicated to prevent infusion reactions. Ten subjects (13.5%) had [grade 1-2] reactions related to infusion of FG-3019, none of these led to withdrawal from the study and no infusion reactions were observed with subsequent FG-3019 infusions. At the time of long-term follow-up assessment, one subject (from the 22.5 mg/kg QW dose cohort) out of a total of 13 subjects with plasma samples suitable for human anti-human antibody (HAHA) assay had a plasma sample that was deemed to be both reactive and specific, with a titter of 10. This patient also had a reactive but not specific HAHA sample prior to FG-3019 exposure. Otherwise no abnormal laboratory trends regarding HAHA were observed.

FG-3019 pharmacokinetics

Plasma FG-3019 C_{max} increased in direct proportion to the dose administered at a rate of 18.7 μg/mL for every 1 mg/kg of FG-3019 dose. Trough FG-3019 $D15C_{min}$ values were obtained routinely prior to the next dose of FG-3019. Higher FG-3019 doses typically resulted in higher $D15C_{min}$ levels, as shown in Figure 1. The estimated mean half -life (t1/2) following the first dose ranged from 2.5 days at 3 mg/kg to 4.5-9.2 days for doses >10 mg/kg. After repeated dosing on Day 43, the estimated mean half -life (t1/2) ranged from 2.6 days at 3 mg/kg to 6.5-10.8 days for doses >10 mg/kg. There was a trend for t1/2 to increase with dose, however there was no drug accumulation even at the highest dose administered (45 mg/kg). Baseline plasma CTGF levels were measured in each patient to determine if CTGF levels had impact on clinical outcome. The median baseline CTGF level (intact CTGF and N terminal fragment, the principal plasma form of CTGF) was 10.0 ng/ml [range 3.8 to 489.3 ng/mL]. After infusion of FG-3019, plasma free CTGF could not be distinguished from CTGF bound to FG-3019. Circulating FG-3019 binds the N-portion of CTGF and the CTGF ELISA detects both free and antibody-bound CTGF, resulting in elevated values of CTGF due to antibody-bound form.

Preferred Term	Overall		Before G/E Dosing	
	n	(%)	n	(%)
Subjects with at least one TESAE*	**40**	**(53.3)**	**8**	**(10.7)**
Disease progression	10	(13.3)		
Cholangitis	6	(8)		
Pulmonary embolism	6	(8)		
Abdominal pain	3	(4)	2	(2.7)
Bile duct obstruction	3	(4)		
Deep vein thrombosis	3	(4)		
Diarrhoea	2	(2.7)		
Gastrointestinal haemorrhage	2	(2.7)		
Cellulitis	2	(2.7)		
Pneumonia	2	(2.7)		
Sepsis	2	(2.7)		
Dehydration	2	(2.7)		
Renal failure	2	(2.7)		

*TESAE is defined as an SAE that occurred following the first administration of study drug and up to 28 days after the last dose of study drug. In cases where a subject experienced an SAE multiple times, the subject would be counted only once for that SAE.

Table 2: Treatment-Emergent SAEs that Occurred in 2 or More Subjects (ITT Population).

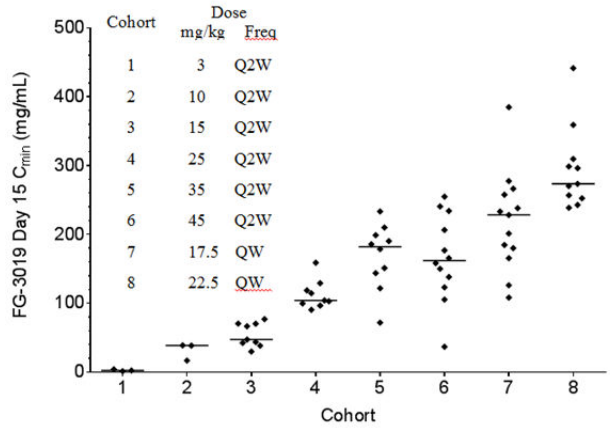

Figure 1: Plasma Trough Levels of FG-3019 on Day 15 ($D15C_{min}$) for each dose level. D15Cmin values for 4 subjects were not available and were imputed from C_{max} values.

Efficacy

Efficacy parameters pre-specified in the protocol included overall survival, progression-free survival, and time to progression, OS, tumor response determined by RECIST and CA19.9 levels. The efficacy analyses were based primarily on the ITT population. CA19.9 response was defined as best response with >50% and >80% reduction from baseline in subjects with values greater than the quantification limit (70 ng/mL).

Response to treatment: Response to treatment was assessed as best response by standard RECIST criteria and changes in CA19.9. In the ITT population, 2 subjects achieved CR (2.7%), 7 patients PR (9.3%) and 34 subjects had stable disease (45.3%) for an overall disease control rate of 57.3%. There was no trend for improved response rate with increasing dose, but response rates were associated with FG-3019 plasma levels above and below 150 ug/mL (p=0.023). In the two cases of the CR, both eventually progressed, with one expiring at 18.9 months after first FG-3019 dose and one alive at study closure on 27 May 2014 at 29.9 months.

Fifty four (72%) of the 75 patients had evaluable levels of plasma CA 19.9 defined as CA 19.9 level ≥ 70 ng/mL (Table 3). Twenty-six subjects (48.1%) had maximal CA 19.9 reduction of >50% and 14 patients (25.9%) had reduction in CA 19.9 of >80%.

	N*	Best CA 19.9 Response#	
		1: Δ >50%, n (%*)	2: Δ >80%, n (%*)
All‡	54	26 (48.1)	14 (25.9)
Stratified by FG-3019 Exposure^			
FG-3019 Day 15 C_{min} ≥ 150 µg/mL	28	16 (57.1)	8 (28.6)
FG-3019 Day 15 C_{min}<150 µg/mL	26	10 (38.5)	6 (23.1)
p-value (Fisher's Exact Test)		0.19	0.76
Stratified by Baseline CTGF Level			
Baseline CTGF <10 ng/mL	23	16 (69.6)	7 (30.4)
Baseline CTGF ≥ 10 ng/mL	31	10 (32.3)	7 (22.6)
p-value†		0.013	0.55

#Best response is defined as the largest reduction from baseline observed during the treatment period.

‡At 8 weeks, 37.1% had Δ >50%, and 14.3% had Δ >80% reductions of CA 19.9.

*Number of patients with quantifiable (≥ 70 ng/mL) levels of plasma CA 19.9 is the denominator for responses.

^with imputation of missing FG-3019 Day 15Cmin data.

†p-value was calculated by 2-sided Fisher Exact Test (missing responses were lumped with 'No' category).

Abbreviations: Δ, maximum reduction from baseline.

Table 3: CA 19.9 Responses (ITT Population).

Progression-free survival: Median PFS in this study was 3.7 (95% CI: 2.1-5.6) months in the ITT population. However, as shown in Figure 2, improved PFS outcomes were associated with higher plasma levels of FG-3019. Median PFS was longer in patients with FG-3019 plasma levels ≥ 150 µg/ml *vs.* patients with levels <150 µg/ml. As can be seen in Figures 2 and 3, 38 patients had plasma levels ≥ 150 µg/ml whereas 37 patients had levels <150 µg/ml. Thus the overall median PFS was influenced by approximately one half of the ITT population with low FG-3019 plasma levels. While patients with low FG-3019 plasma levels (N=37) had a median PFS of 2.4 months, patients with plasma levels ≥ 150 µg/ml (N=38) had a median PFS of 6.0 months (p=0.032). Improved PFS was also observed in patients with baseline plasma CTGF levels <10 ng/ml, compared to patients with FG-3019 plasma levels >10 ng/mL: 5.5 *vs.* 2.3 months (p=0.019) respectively. Multivariate analysis showed FG-3019 exposure and baseline CTGF as independently predictive values for improved overall survival. The combined effect of high FG-3019 and low CTGF levels on PFS showed improved PFS: 6.0 months *vs.* 2.1 months (p=0.006) respectively.

Overall survival: Median OS in the ITT population was 7.4 (95% CI: 5.5-9.1) months and the 1 year OS was 22.7%. Median survival was 10.4 months in 9 subjects with stage 3 disease and 7.2 months in 66 subjects with stage IV disease. However, as with PFS, improved survival was observed with plasma FG-3019 ≥ 150 µg/mL. In patients with plasma FG-3019 ≥ 150 µg/mL (N=38) median survival was 9.0 months and a one year survival rate of 34.2%. In contrast, patients with plasma FG-3019 <150 µg/mL (N=37) had a median OS of 4.4 months (p=0.024) and a one year survival rate of 10.8% (p=0.026) (Figure 3). Certainly expected survival is somewhat longer for stage 3 PDAC than it is for stage 4. Stage 3 patients with plasma FG-3019 ≥ 150 µg/mL (N=4) had median OS of 14.5 months compared to 10.5 months for those with FG-3019 <150 µg/mL (N=5). Stage 4 patients with plasma FG-3019 ≥ 150 µg/mL (N=34) has median OS of 9.0 months compared to 4.1 months for those with FG-3019 <150 µg/mL (N=32). Because the number of stage 3 patients was small, the differences in outcomes for stage 3 and stage 4 patients were not statistically significant.

The potential of baseline CTGF as a prognostic survival biomarker was evaluated. Subjects with baseline CTGF levels <10 ng/mL achieved median OS of 10.1 months compared to OS of 4.4 months in subjects with baseline plasma CTGF ≥ 10 ng/mL (p=0.028). The combined effects of FG-3019 and CTGF levels showed added impact on survival. In the group with FG-3019 levels ≥ 150 µg/ml and low CTGF (<10 ng/mL), median and one year overall survival rates were 11.2 months and 40%, respectively. In contrast, in patients with lower FG-3019 (<150 µg/mL) and higher (>10 ng/mL) CTGF levels, median and one year overall survival rates were 2.6 months and 4.8%, respectively. Multivariate analysis showed that both baseline CTGF and FG-3019 plasma levels were independent predictive factors.

Subjects with ascites (n=15) had median OS of 2.6 months compared to subjects without ascites (n=54) who had median survival of 8.3 months (p=0.012). In general, plasma levels of FG-3019 in subjects with ascites were lower than those in subjects without ascites. For those subjects with ascites who achieved FG-3019 level ≥ 150 ug/mL (N=7), the median survival was 8.7 months compared to 1.9 months for subjects with ascites and FG-3019 level <150 µg/mL (N=8).

Differences in second line chemotherapy did not appear to account for the different survival outcomes for subjects with FG-3019 ≥ 150 ug/mL and for subjects with <150 µg/mL. Thirty percent of subjects with FG-3019 <150 ug/mL (N=11) received second line chemotherapy compared to 34% of subjects with FG-3019 ≥ 150 µg/mL (N=13). The type of chemotherapy agents and regiments was balanced. In these

patients, FG-3019 ≥ 150 ug/mL appeared to provide a non-statistically significant survival advantage.

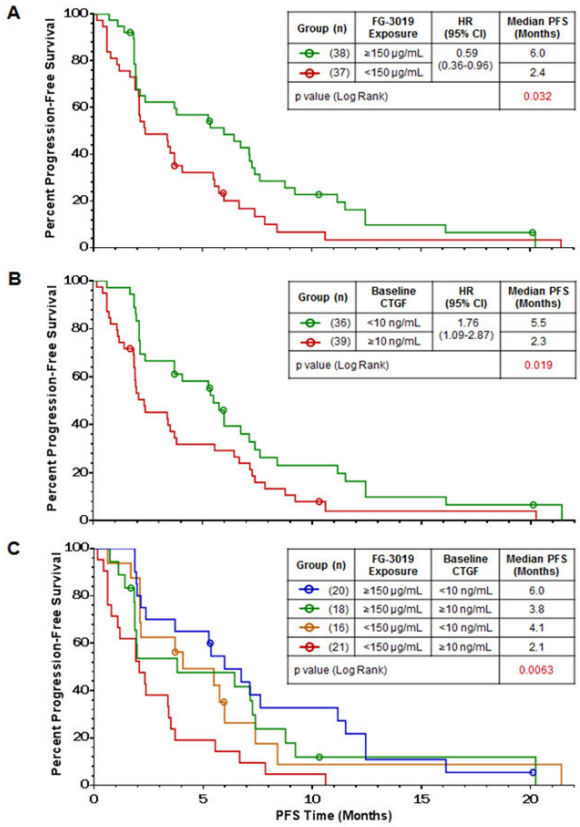

Figure 2: Progression-Free Survival (ITT Population). A: Stratified by median exposure (with imputation of missing D15Cmin data); B: stratified by median BL CTGF: C: bivariate analysis. Open circles represent censored patients. HR: hazard ratio; CI: confidence interval.

Discussion

Pancreatic cancers are highly desmoplastic tumors. CTGF has been defined as an invasion-associated gene in both PDAC [7] and other cancers [18,21] and it was shown to be highly expressed within the neoplastic epithelium of PDAC [5,9]. The pre-clinical proof-of-concept for our study was established in the KPC mouse model of PDAC where targeting CTGF with FG-3019 co-administered with gemcitabine led to a slower tumor progression than with gemcitabine alone [22]. This treatment combination reduced metastases, prolonged survival and increased tumor cell apoptosis associated with down-regulation of the anti-apoptotic X-linked inhibitor of apoptosis protein (XIAP) [22]. In that study, FG-3019 treatment did not appear to affect the penetration of gemcitabine into the tumor. Rather, the results suggest that inhibition of CTGF with FG-3019 enhances anti-tumor effects of chemotherapy.

This clinical study was designed to establish safety and tolerability of FG-3019 in combination with chemotherapy and assess initial efficacy signals in relationship to FG-3019 and CTGF levels. The study was initially designed as a "3+3" trial of three FG-3019 doses. However, with no observation of dose limiting toxicities, the study was expanded to assess a wider range of doses and dose regimens.

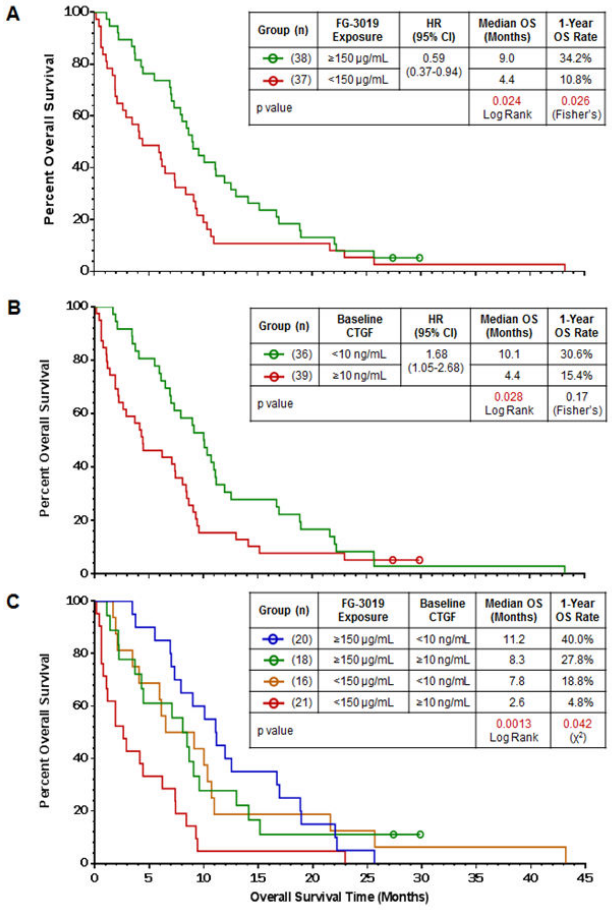

Figure 3: Overall Survival (ITT Population). A: Stratified by median exposure (with imputation of missing D15Cmin data); B: stratified by median BL CTGF: C: bivariate analysis. Open circles represent censored patients. HR: hazard ratio; CI: confidence interval.

A median OS of 6.2 months and 1-year survival rate of 23% were reported by Moore and colleagues [20] in stage 3 and 4 PDAC with G/E alone. In our study with G/E and plasma FG-3019 ≥ 150 µg/mL we observed improved OS of 9.0 months overall (Stage 3 and 4), as well as for those with metastatic disease, suggesting that addition of anti-CTGF therapy to standard chemotherapy may improve survival. The data in this study suggest that a threshold level of circulating FG-3019 is needed to adequately penetrate and block the activity of CTGF in the tumors. As this was an exploratory Phase 1 study, tumor biopsies were not obtained to enable direct measurement of tumor CTGF or FG-3019. Overall survival was greatest (11.2 months) in subjects with lower baseline CTGF levels and increased FG-3019 drug concentrations. These observations support the hypothesis that improved outcomes in PDAC may require targeting of both stroma and tumor cells [22].

This study was initiated in 2008, soon after approval of erlotinib for use in pancreatic ductal adenocarcinoma, and it was assumed that erlotinib would be integrated into the standard of care for PDAC despite its marginal enhancement of gemcitabine efficacy. However, erlotinib has not been broadly incorporated into standard of care. While erlotinib likely added to the quantity and nature of the AEs observed in the study due to its known toxicities, G/E was a reasonable chemotherapeutic backbone on which to assess the safety and activity of FG-3019. During the conduct of this study, FOLFIRINOX was demonstrated to have superior survival efficacy to gemcitabine monotherapy in PDAC, albeit with more severe toxicity [23,24]. Comparing FOLFIRINOX to gemcitabine, median survival was 11.1 months versus 6.8 months, median progression-free survival was 6.4 months versus 3.3 months, and the 12 month survival rate was 48.4% compared to 20.6%.

Since completion of this study, gemcitabine in combination with nab-paclitaxel was demonstrated to have improved efficacy over gemcitabine alone [25]. Comparing the combination to gemcitabine alone, median survival was 8.5 months versus 6.7 months, progression-free survival was 5.5 months versus 3.7 months, one year survival rate was 35% compared to 22%. The results obtained in this pilot study of FG-3019 in combination with G/E are similar to those observed in the phase 3 trial of nab-paclitaxel–gemcitabine. In addition, the OS results with low CTGF and high FG-3019 are similar to FOLFIRINOX (11.2 months *vs.* 11.1 months). The results are also similar to recently reported outcomes in a study of PEGylated recombinant human hyaluronidase in combination with gemcitabine [26].

The results of this study indicate that FG-3019 can be safely combined with gemcitabine and erlotinib without increased toxicity in advanced stage 3 and 4 pancreatic cancer patients. The indications of improved survival with FG-3019 are consistent with previous studies suggesting a role for CTGF in pancreatic cancer and underscore the potential validity of combined treatments that target both stroma and cancer cells in PDAC. Finally, it also indicates potential value of CTGF as prognostic biomarker and supports further evaluation of FG-3019 in combination with chemotherapy in a properly controlled and adequately powered trial comparing standard of care chemotherapy to standard of care plus FG-3019. Based on improved efficacy obtained with FG-3019 plasma levels ≥ 150 μg/mL, future studies will likely be conducted with biweekly doses of 35 mg/kg (or greater) where the majority of patients surpassed that apparent threshold plasma levels.

Authors' Contributions

FibroGen Inc. was the study sponsor that designed the study in consultation with the Principal Investigator (VJP). All authors except those of the sponsor contributed patients to the study. FibroGen was responsible for data collection and analysis. All authors reviewed the manuscript and signed off on its accuracy.

Disclosures

MC, JC, MZ, SH, DL, SP, TBN, EC, and FHV are employees of FibroGen and hold stock and/or stock options in FibroGen. KM is a former employee of FibroGen. There are no other disclosures.

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