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Dual Src and EGFR Inhibition in Combination with Gemcitabine in Advanced Pancreatic Cancer: Phase I Results

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Abstract

Pancreatic adenocarcinoma remains a major therapeutic challenge, as the poor (<8%) 5-year survival rate has not improved over the last three decades. Our previous preclinical data showed

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Conflicts of interest

DBC has served as an advisory board consultant for Merrimack and Raphael Pharmaceuticals and has institutional research funding from Synta, Incyte, Celgene, Hoffman-LaRoxhe, EMD-Serono, and Oncolytics Biotech. LWG has served as a consultant for Celgene and has institutional research funding from Astellas Pharma, Pfizer, Onxy, SunPharma, Lilly, and Bristol-Myers Squibb. EC has served on advisory boards for Castle Biosciences, Taiho, EMD-Serono, Amgen, Lilly, Advaxis, Bayer and Merrimack. EC is currently employed at Amgen and owns Amgen stock; however, this work was done while at Vanderbilt-Ingram Cancer Center prior to her employment with Amgen. JB has served as a consultant for Celgene, Genentech, Aduro, Boston Biomedical, Janssen, Cornerstone, Symphogen, and Bayer and has institutional research funding from Genentech, Abbvie, Taiho, Bayer, 5Prime, Phoenix, Incyte, and Vertex. For the remaining authors, none were declared.

COMPLIANCE WITH ETHICAL STANDARDS

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained for all individual participants included in the study.

cooperative attenuation of pancreatic tumor growth when dasatinib (Src inhibitor) was added to erlotinib (EGFR inhibitor) and gemcitabine. Thus, this study was designed to determine the maximum-tolerated dose of the triplet combination. Standard 3+3 dose escalation was used, starting with daily oral doses of 70 mg dasatinib and 100 mg erlotinib with gemcitabine on days 1, 8, and 15 (800 mg/m²) of a 28-day cycle (L₀). Nineteen patients were enrolled, yet 18 evaluable for dose-limiting toxicities (DLTs). One DLT observed at L₀, however dasatinib was reduced to 50 mg (L₋₁) given side effects observed in the first two patients. At L₋₁, a DLT occurred in 1/6 patients and dose was re-escalated to L₀, where zero DLTs reported in next four patients. Dasatinib was escalated to 100 mg (L₁) where 1/6 patients experienced a DLT. Although L₁ was tolerable, dose escalation was stopped as investigators felt L₁ was within the optimal therapeutic window. Most frequent toxicities were anemia (89%), elevated aspartate aminotransferase (79%), fatigue (79%), nausea (79%), elevated alanine aminotransferase (74%), lymphopenia (74%), leukopenia (74%), neutropenia (63%), and thrombocytopenia (63%), most Grade 1/2. Stable disease as best response was observed in 69% (9/13). Median progression-free and overall survival was 3.6 and 8 months, respectively. Dasatinib, erlotinib, and gemcitabine was safe with manageable side effects, and with encouraging preliminary clinical activity in advanced pancreatic cancer.

Keywords

dasatinib; erlotinib; dual Src and EGFR inhibition; pancreatic cancer

INTRODUCTION

Pancreatic adenocarcinoma is a major therapeutic challenge, as the overall five-year survival rate of 8% has remained relatively unchanged for the past three decades [1]. Until recently, gemcitabine-based therapies were the standard treatment option for patients with advanced or metastatic disease and remain standard for patients with a poor performance status. These regimens, however, result in minimal responses [2–4]. The addition of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor erlotinib to gemcitabine showed a modest but significant improvement in overall survival leading to FDA approval for patients with advanced disease [4]. However, a significant difference in tumor responses was not observed between treatment arms emphasizing the need for developing novel treatment strategies to improve clinical outcomes.

Src, a non-receptor tyrosine kinase encoded by the proto-oncogene c-Src, participates in numerous signaling pathways, including EGFR-mediated signaling networks [5]. The expression and activity of Src has been associated with malignant transformation and cancer progression in a variety of human cancers, including pancreatic cancer [6–9]. We have previously shown a stepwise increase in cytoplasmic and membranous staining of Src from normal pancreas to chronic pancreatitis to advancing tumor grade of pancreatic adenocarcinoma, suggesting that Src expression increases with pancreatic neoplasia progression [10]. Studies from multiple laboratories [8,11,12], including ours [10], have previously established a mechanistic rationale for targeting Src in pancreatic carcinoma. We have shown that pharmacologic inhibition of Src with dasatinib resulted in attenuation of cell proliferation and induced cell cycle arrest and apoptosis in pancreatic cancer cell lines

[10]. This outcome was recapitulated in pancreatic tumor xenografts as dasatinib significantly inhibited tumor growth. Despite the observed antitumor activity, dasatinib had no effect on the phosphorylation of specific proteins in cell survival and angiogenic pathways (e.g., STAT3 and MAPK), suggesting possible resistance mechanisms to dasatinib [10].

A recent global genomic analysis observed that pancreatic tumors are highly heterogeneous with genetic alterations in multiple, overlapping pathways, which provided rationale that treatment strategies towards the disease should target multiple signaling pathways rather than just the products of one gene [13]. Thus, we sought to characterize the underlying mechanisms of targeting two tyrosine kinases, EGFR and Src, in combination with gemcitabine, with the hypothesis that targeting multiple tumor-associated pathways would enhance effect and potentially minimizing inherent and acquired resistance. Indeed, the combination of dasatinib with erlotinib and gemcitabine resulted in synergistic inhibition of proliferation and viability in pancreatic cancer cell lines, as well as xenograft tumor growth compared to individual or two drug combinations of these agents [14]. Furthermore, only the three drug combination was shown to overcome constitutive activation of STAT3-mediated signaling [14]. This latter observation is especially important given our previous preclinical data that provided compelling evidence to suggest that STAT3 is a key mediator of chemoresistance in pancreatic carcinoma [10,14]. Based on this preclinical data, we designed this phase I study to evaluate safety and tolerability of dasatinib, erlotinib, and gemcitabine in patients with advanced pancreatic cancer. Secondary objectives included assessing antitumor activity and correlating changes in CA19-9 with tumor response. We also explored the feasibility (and potential utility) of performing serial diffusion-weighted imaging (DWI).

MATERIALS AND METHODS

Patient Selection

This investigator-initiated, single institution phase I study (NCT01660971) of dasatinib, erlotinib, and gemcitabine was conducted in patients with locally advanced or metastatic pancreatic carcinoma. The study was approved by the institutional review board. Informed consent was obtained from all individual participants included in the study. Eligible patients had pathologically confirmed pancreatic adenocarcinoma (excluding islet cell or ampullary tumors) that was metastatic or locally advanced and unresectable, had measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [15], no prior gemcitabine treatment for advanced disease, adequate organ function (hematologic, renal, and hepatic), and were ≥ 18 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1. Patients who received prior adjuvant therapy including gemcitabine were eligible if their last dose of gemcitabine was greater than six months prior to enrollment and they had fully recovered from side effects. Additional inclusion criteria and patient exclusion criteria are listed in the clinical trial protocol included in the Supplement.

Study Treatment

This is a phase I study that investigated the standard dose of erlotinib with escalating doses of dasatinib and gemcitabine (Table 1). Dose escalation began with 70 mg of dasatinib once daily, 100 mg of erlotinib once daily, and 800 mg/m² gemcitabine infusion over 30 minutes administered weekly for three weeks of each four-week cycle. Starting doses for dasatinib and gemcitabine were chosen based on results from previous studies. A phase I/II study by Haura, *et al.* investigated dasatinib in combination with erlotinib in advanced non-small cell lung cancer, and found 150 mg once daily of erlotinib and 70 mg twice daily of dasatinib was tolerated [16]. A phase I study by Uronis and colleagues found 1000 mg/m² gemcitabine administered weekly for three weeks of each four-week cycle plus 50 mg twice daily dosing of dasatinib to be tolerable [17]. Since this study evaluated the triplet combination, the investigators felt a safe starting dose for gemcitabine and dasatinib would be one step lower than that of the Uronis trial in combination with the standard dose of erlotinib in pancreatic cancer.

Dose escalation was planned for groups of three patients until the maximum tolerated dose (MTD) was established in a standard 3+3 design. No intra-patient dose escalation was allowed. Dose limiting toxicity (DLT) was defined as any treatment-related, first cycle (28 days): Grade 3 nonhematologic toxicity, except nausea, vomiting, and hypertension. Nausea and vomiting were considered dose-limiting if hospitalization or repeated hydration was required despite the use of antiemetic agents; Grade 4 neutropenia lasting > seven days or Grade 4 neutropenia of any duration associated with fever >38.5°C; Grade 4 thrombocytopenia for seven consecutive days, bleeding in the face of Grade 3–4 thrombocytopenia, or Grade 3 fatigue of three days. Additionally, any treatment-related toxicity that required holding treatment for >14 days or the inability to administer 75% of the planned total dose of any one of the three agents (due to toxicity) during the first treatment cycle was also dose-limiting. Patients continued on study until unacceptable toxicity, disease progression, patient withdrawal, or specific changes in patient's condition that in the judgment of the investigator rendered the patient unacceptable for further treatment. Patients were followed for adverse events for 30 days or until treatment-related adverse events resolved, whichever was greater. All patients were followed for survival until death.

Study Assessments

Toxicity assessments were performed at each cycle and graded according to the NCI Common Toxicity Criteria, Version 4.0. All patients who received at least one treatment were evaluable for safety. Patients that were removed from the study during the first four weeks of treatment for reasons other than progressive disease or drug-related adverse events were not considered evaluable for DLT and were replaced. Disease assessments were performed at baseline and every eight weeks using RECIST v1.1. Only those patients who received at least one cycle of therapy and had a post baseline disease assessment were considered evaluable for response. Patients were followed for survival endpoints until death. Tumor marker CA19-9 was measured at baseline and every four weeks (\pm seven days) during therapy.

Diffusion-Weighted MRI

DWI is an emerging MRI technique that is sensitive to the microscopic, thermally-induced self-diffusion of water molecules within a system [18]. DWI returns estimates of the apparent diffusion coefficient (*ADC*), and in well-controlled situations, the *ADC* has been shown to correlate inversely with tissue cellularity.[19] Multiple preclinical and clinical studies have shown that chemotherapy and radiation therapy lead to measurable changes in *ADC* that are associated with tumor response [20–23]. Therefore, it is reasonable to hypothesize that a relationship would exist between changes in *ADC* and tumor response to dasatinib, erlotinib, and gemcitabine.

As a pilot study, we collected pre- and post-treatment (i.e., week 4 of Cycle 1) DWI data on three patients. DWI examinations were performed on a Philips 3T Achieva scanner with a 16-channel torso coil (Philips Healthcare, Best, The Netherlands), and data were collected using a respiratory-gated, single-shot echo planar sequence in three orthogonal diffusion encoding directions with two *b*-values (200 and 750 s/mm²) and the following parameters: repetition time = 1650 ms; echo time = 75 ms; diffusion time = 36.5 ms; diffusion gradient duration = 19.2 ms; number of signals averaged = 4 for *b* = 200 s/mm² and 8 for *b* = 750 s/mm²; acquisition matrix = 120×103×13 sections and a reconstructed voxel size = 1.25×1.25×5 mm³. *ADC* values were computed for each voxel *via*: $ADC = \ln[S_1/S_2]/(b_2 - b_1)$, where *S*₁ is the signal acquired at *b*₁ and *S*₂ is the signal acquired at *b*₂. T₂-weighted anatomical images were also collected for tumor localization and region of interest (ROI) delineation. The mean *ADC* value was collected from each tumor ROI.

Statistical Analysis

Due to the nature of this study, descriptive statistics were used to summarize demographics, adverse events, and tumor response. Confidence intervals were estimated using the Wilson method, and survival functions were estimated using the Kaplan-Meier method. Summary statistics were used to describe the changes in CA19-9 and *ADC*. Linear and Cox (proportional hazards) regression models were used to evaluate the relationship between tumor response and CA19-9; *p*<0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Between July 2012 and October 2015, 19 patients were enrolled and three dose levels were investigated. Baseline patient characteristics are listed in Table 2. One patient exhibited disease progression prior to completing the DLT observation window, and thus was replaced in the dose escalation cohort. Median age was 61 years (range, 48–77), 53% were male, and 74% of patients had metastatic disease. A majority (95%) of patients were either treatment naïve or had one prior therapy for advanced disease, and six (32%) patients received prior adjuvant therapy containing gemcitabine. Nine patients came off study due to unacceptable toxicity, three of which came off study during the first treatment cycle; two patients withdrew consent after starting treatment, and one patient each withdrew due to a protocol non-compliance or exhibited a poor performance status. The other six patients came off study due to disease progression.

Treatment and Toxicities

Dose escalation proceeded according to Table 1. At a dose of 70 mg dasatinib, 100 mg erlotinib, and 800 mg/m² gemcitabine (Level 0), one of two patients experienced two DLTs (Grade 3 nausea and vomiting with hospitalization). The second patient did well but experienced fatigue she deemed unacceptable, yet was not dose limiting. Additionally, both patients experienced Grade 3 neutropenia once during the first two cycles. Thus, based on the side effects observed in the first two patients at Level 0, dasatinib was de-escalated to 50 mg. At this dose, one of six patients experienced a DLT (Grade 3 dyspnea). Dasatinib was re-escalated to the starting dose, and four additional patients were evaluated. Among those patients, no DLTs were observed and thus dasatinib was escalated to 100 mg (Level 1). At this dose, one DLT (Grade 3 elevated aspartate aminotransferase) was observed in the next six patients enrolled. Although Level 1 was tolerable, dose escalation was stopped as the investigators felt the next dose level, which only escalated gemcitabine to 1000 mg/m², would increase toxicity, especially hematological toxicities, without improving benefit.

The most common treatment-related toxicities were anemia (89%), elevated aspartate aminotransferase (79%), fatigue (79%), nausea (79%), elevated alanine aminotransferase (74%), lymphocytopenia (74%), leukopenia (74%), neutropenia (63%), diarrhea (58%), and hypophosphatemia (58%); a majority of these were Grade 1–2. Other frequently observed (20%) adverse events are listed in Table 3. Fifteen patients experienced at least one Grade 3 adverse event, with the most common being neutropenia (32%), lymphocytopenia (26%), and leukopenia (21%). Grade 4 neutropenia and lymphocytopenia occurred in three patients and one patient, respectively. All Grade 3–4 adverse events are listed in Table 3.

Antitumor Activity

Six patients did not undergo a post baseline disease assessment and therefore were not evaluable for response. Of the 13 evaluable patients, no responses were observed, however, nine patients exhibited a best response of stable disease for a disease control rate (DCR) of 69%. Eight patients exhibited some form of tumor regression while on treatment (Figure 2A), and the median duration of stable disease was 5.5 months (95% Confidence Interval [CI], 3.8 to NA). The overall median progression-free survival (PFS) was 3.6 months (Figure 2B; 95% CI, 2.0 to 9.9), while the median overall survival (OS) was 8.0 months (Figure 2B; 95% CI, 4.4 to 17). Additionally, the 12-month OS rate was 32%.

CA19-9 Correlative Analysis

Twelve patients had both CA19-9 measurements at baseline and four weeks, as well as a disease response assessment at eight weeks. A moderate but significant positive correlation (Figure 1 in the Supplement; Pearson Correlation; 0.65, $p=0.023$) was observed between changes in CA19-9 levels at four weeks and tumor size at eight weeks. The reduction in percent change between baseline and 4-week CA19-9 levels was significantly ($p<0.001$) different between patients that achieved a best response of stable disease versus those who progressed. Additionally, an increase in CA19-9 over time was significantly associated with an increased hazard of death (hazard ratio=1.26; $p=0.017$).

DWI Correlative Studies

Pre- and post-treatment tumor *ADC* maps along with mean *ADC* and percent change from baseline are presented in Figure 3. Corresponding baseline and 8-week tumor RECIST measurements and percent change are also included. The expected inverse relationship between changes in tumor size and *ADC* (i.e., increase in *ADC* and decrease in tumor size) was observed for all three patients (Figure 3).

DISCUSSION

Although a greater understanding of the genomic landscape and molecular pathways of tumorigenesis have led to improvements in survival for some cancers, the use of individual targeted therapies have not yet provided a meaningful impact on clinical outcome in pancreatic cancer. Based on our preclinical data that suggested simultaneous inhibition of Src and EGFR in combination with gemcitabine had a synergistic anti-tumor effect in PDAC [14], we designed this phase I study to evaluate the safety of combining dasatinib, erlotinib, and gemcitabine in patients with locally advanced or metastatic pancreatic cancer.

Overall, dasatinib and erlotinib administered with gemcitabine was safe with manageable side effects. The MTD was not officially reached, and the RP2D was determined to be 100 mg dasatinib, 100 mg erlotinib, and 800 mg gemcitabine (Level 1) as the investigators thought the next dose level (Level 2) would only increase toxicities without improving benefit. Although the AEs were manageable, the addition of dasatinib to gemcitabine and erlotinib increased the frequency of multiple toxicities compared to the previous Phase III Canadian study that investigated gemcitabine and erlotinib. Of note, the frequency of severe (Grade 3) neutropenia was higher at 47% versus 24% [4]. Severe rash was not observed at all whereas the Phase III study reported 6% of patients had Grade 3 rash, and the frequency of mild (Grade 2) rash in the current study was slightly less at 47% versus 66% [4]. We note, however, that the dosage and treatment scheme of gemcitabine and erlotinib in the previous study was different thus limiting a direct comparison with the current study. Additionally, caution should be taken when interpreting the observed clinical activity due to the small number of patients evaluated in this study.

The combination of dasatinib, erlotinib, and gemcitabine exhibited clinical activity in patients with advanced pancreatic cancer as evidenced by a 69% DCR. Additionally, eight (62%) patients experienced tumor regression at the time of best response with a median duration of stable disease of 5.5 months. The Phase III Canadian study observed a significant improvement in median OS of 6.2 months compared to 5.9 months with gemcitabine monotherapy, which led to FDA approval for patients with locally advanced, unresectable or metastatic disease [4]. Our study observed a median OS of 8 months, as well as a higher DCR (69% versus 58%), suggesting that adding dasatinib to erlotinib and gemcitabine could represent a viable treatment option to improve disease stabilization and survival.

Current recommended first-line regimens to treat patients with locally advanced or metastatic pancreatic cancer are FOLFIRINOX or gemcitabine plus nab-paclitaxel based on randomized studies that observed significant clinical benefits compared to gemcitabine

monotherapy. FOLFIRINOX improved the median OS compared to gemcitabine (11.1 months versus 6.8 months) [2]. Adding nab-paclitaxel to gemcitabine also improved median OS (8.5 months versus 6.7 months) [3]. However, these improvements in survival came at a cost of increased toxicities and therefore these regimens are only recommended for patients with a good performance status. Single-agent gemcitabine or best supportive care is recommended for patients with a poor performance status. Given the inferior clinical activity of gemcitabine monotherapy, the results from the current study provide motivation for further investigation of dasatinib, erlotinib, and gemcitabine in patients with a poor performance status.

The development of blood-based assays and noninvasive imaging techniques that can provide surrogate biomarkers of response is an active area of research. As a secondary objective, we explored the utility of CA19-9 to assess early tumor response and observed a significant ($p=0.022$) correlation between levels of CA19-9 at four weeks with tumor size at eight weeks. Furthermore, a time dependent covariate analysis resulted in a significant ($p=0.017$) association between temporal changes in CA19-9 and death, suggesting that CA19-9 could represent a viable biomarker for survival in this setting.

In a pilot study, we explored the feasibility (and potential utility) of performing serial DWI assessments of disease response. Image data from all three patients were collected and analyzed successfully without complications. Additionally, the expected relationship between change in *ADC* and tumor size was observed. Of special interest, the RECIST measurement after two cycles of treatment indicated stable disease, whereas a measureable change in *ADC* was observed after one treatment cycle. Unfortunately, due to the small sample size, no formal statistical associations between *ADC* and response could be performed. Nonetheless, our preliminary results suggest that early changes in *ADC* could be representative of later changes in tumor size, and perhaps predictive of tumor response. Further optimization is ongoing to improve the robustness, and consequently the reliability, of this imaging technique in serial assessments of disease response.

CONCLUSIONS

Our results suggest that dasatinib in combination with erlotinib and gemcitabine was tolerable, and that this combination exhibited some clinical activity in patients with locally advanced and metastatic pancreatic cancer. Although a direct comparison cannot be made, the improved survival benefit of the current study compared to the erlotinib and gemcitabine combination should not be overlooked, and could represent a viable treatment option for patients with a poor performance status who are not candidates for other, more effective therapies. Additionally, our results provide evidence that further investigation of *ADC* as a surrogate biomarker of tumor response is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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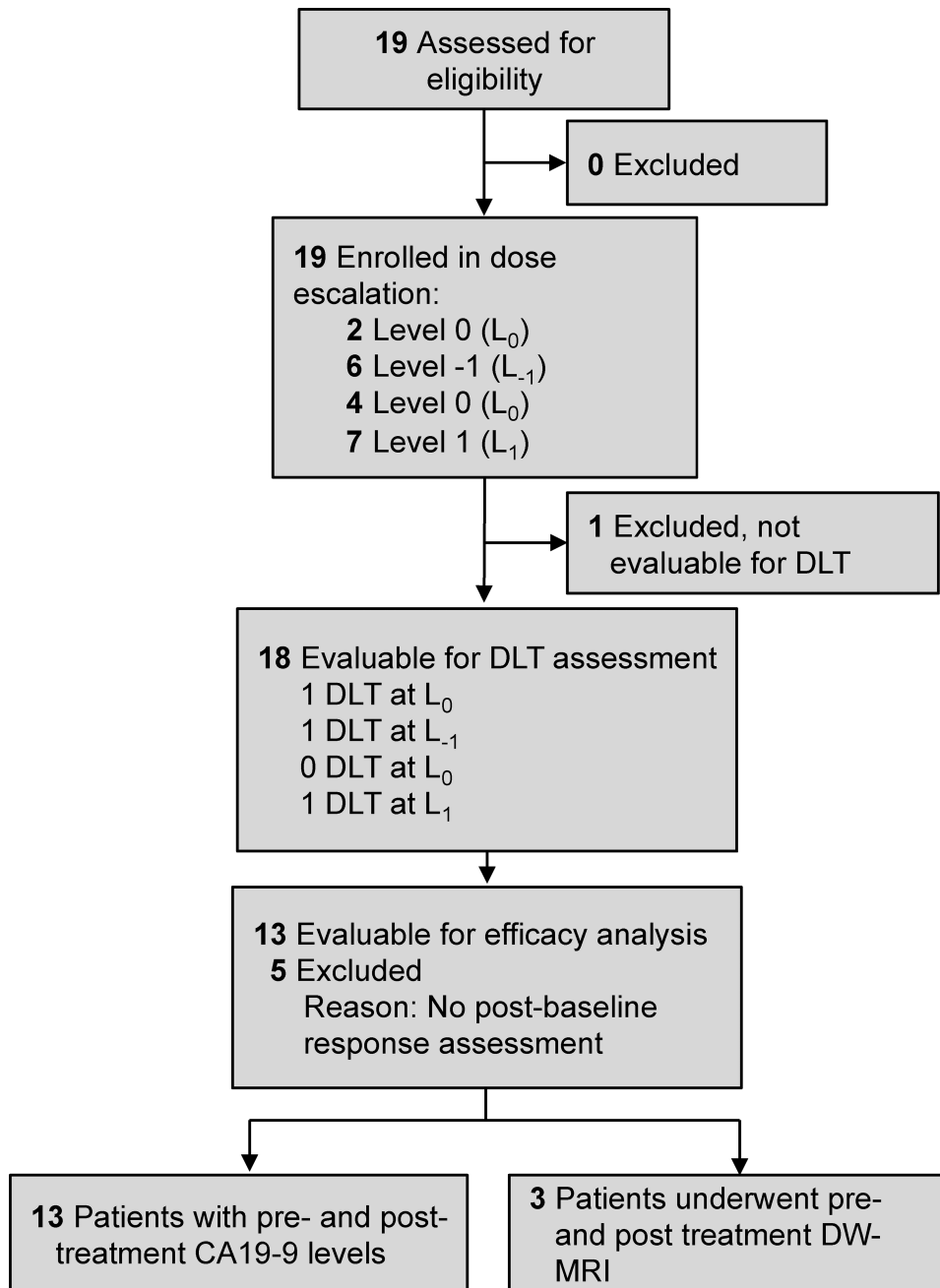


Figure 1. Consolidated Standards of Reporting Trials Diagram

Study diagram listing number of eligible subjects enrolled onto the study, and numbers of patients in the safety, efficacy, and biomarker correlate analyses.

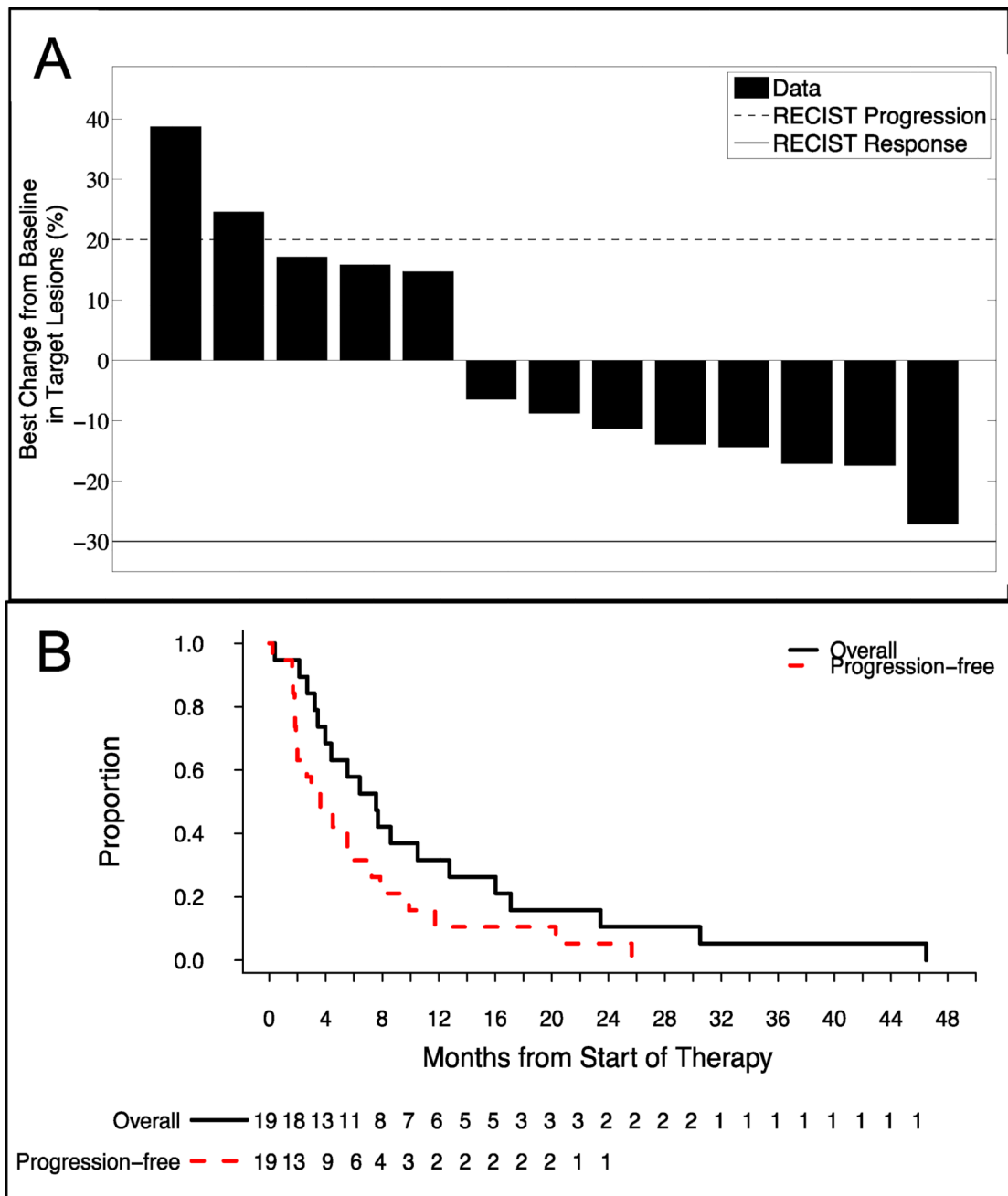


Figure 2. Antitumor Activity

(A) Best percentage change from baseline in the sum of all target lesions is presented for each efficacy evaluable patient on study. Solid and dashed lines represent the RECIST v1.1 definition for partial response and progressive disease, respectively. Although no responses were observed, eight (62%) of patients had reductions in tumor size suggesting the triplet combination has some antitumor activity in patients with advanced pancreatic carcinoma. (B) Kaplan-Meier analysis of progression-free survival (dashed red line) and overall survival (block solid line). The overall median progression-free survival was 3.6 months whereas the median overall survival was 8.0 months.

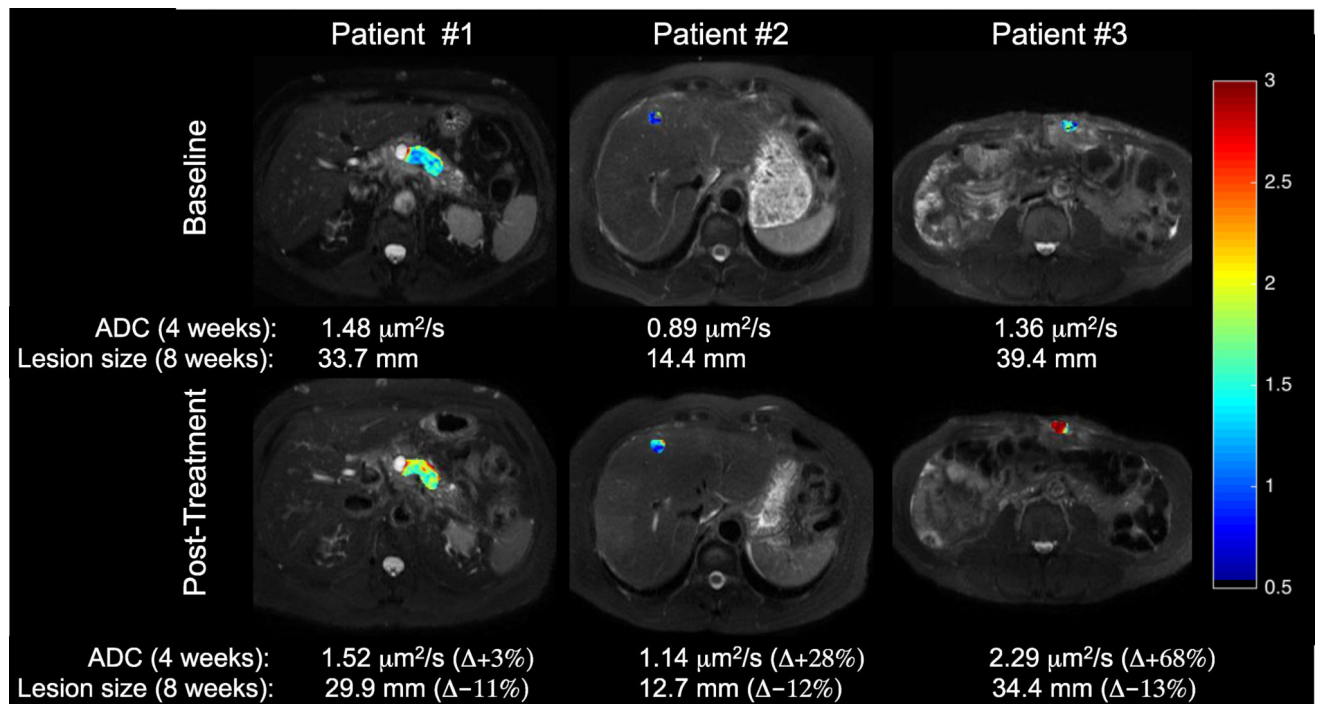


Figure 3. Preliminary DW-MRI results

ADC maps overlaid onto T_2 -weighted anatomical images. The baseline and post-treatment mean *ADC* values and percent change from baseline are presented for each patient. The corresponding baseline and 8-week RECIST measurement, as well as percent change in tumor size is also presented. The expected inverse relationship between changes in *ADC* and tumor size is observed in all three patients. Notably, a measurable change in *ADC* for all three patients is detected after one treatment cycle, which corresponds to later changes in tumor size.

Table 1

Dose Escalation Schedule (standard 3+3 design) with Dose Limiting Toxicities

Dose Level	Gemcitabine (mg/m ²)	Erlotinib (mg QD)	Dasatinib (mg QD)	Cycle 1 (28-days) Toxicity
Level -1	800	100	50	6 patients; 1/6 with DLT ^a
Level 0 (starting)	800	100	70	6 patients; 1/6 with DLT ^b
Level 1	800	100	100	7 patients (6 evaluable); 1/6 with DLT ^c
Level 2	1000	100	100	Not Evaluated
Level 3	1000	100	140	Not Evaluated

^aGrade 3 dyspnea;^bGrade 3 nausea and vomiting;^cGrade 3 elevated AST

QD: once daily; AST: aspartate aminotransferase

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Table 2

Patient Characteristics (N = 19)

Data	Results
Gender -No. (%)	
Male	10 (53)
Female	9 (47)
Median age -No. (range)	61 (48–77)
Race -No. (%)	
White	19 (100)
Ethnicity -No. (%)	
Non-hispanic	19 (100)
Disease Status -No. (%)	
Locally Advanced	5 (26)
Metastatic	14 (74)
Baseline Median CA 19-9 Level -No. (quartile)	318 (62-9470)
PS (ECOG) -No. (%)	
0	3 (16)
1	16 (84)
Number of Patients Receiving Adjuvant Gemcitabine -No. (%)	6 (32)
Number of Previous Lines of Therapy for Advanced Disease -No. (%)	
0	15 (79)
1	3 (16)
2	1 (5)

PS: performance status; ECOG: Eastern Cooperative Oncology Group

Table 3

Most common (frequency 20%) treatment-related adverse events categorized by highest grade experienced per patient (N = 19)

	All Grades	Grade 1	Grade 2	Grade 3 ^a	Grade 4
Non-Hematological					
Elevated AST	15 (79%)	10	2	3	0
Fatigue	15 (79%)	2	11	2	0
Nausea	14 (74%)	8	5	2	0
Elevated ALT	14 (74%)	10	2	2	0
Diarrhea	11 (58%)	9	2	0	0
Dysgeusia	9 (47%)	3	6	0	0
Rash	9 (47%)	9	0	0	0
Anorexia	8 (42%)	2	6	0	0
Oral Mucositis	7 (37%)	5	1	1	0
Vomiting	6 (32%)	3	1	2	0
Peripheral Edema	6 (32%)	3	3	0	0
Elevated Alkaline Phosphatase	5 (26%)	3	2	0	0
Fever	4 (21%)	4	0	0	0
Hematological					
Anemia	17 (89%)	3	11	3	0
Lymphocytopenia	14 (74%)	2	6	5	1
Leukopenia	14 (74%)	2	8	4	0
Neutropenia	12 (63%)	0	3	6	3
Thrombocytopenia	12 (63%)	7	3	2	0
Hypophosphatemia	11 (58%)	1	10	0	0

AST: aspartate aminotransferase; ALT: alanine aminotransferase

^a Additional Grade 3 dyspnea observed by one patient