Phase 1b Study of Gemcitabine, Nab-paclitaxel, and Ficlatuzumab in Patients with Advanced Pancreatic Cancer

Kimberly Perez, Colin Weekes, James Cleary, Thomas Abrams, Lawrence Blaszkowsky, Peter Enzinger, Marios Giannakis, Lipika Goyal, Jeffrey Meyerhardt, Douglas Rubinson, Matthew Yurgelun, Danielle Stonely, Srivatsan Raghavan, Basil Bakir, Koushik Das, Jason Pitarresi, Andrew Aguirre, Michael Needle, Anil K. Rustgi, Brian Wolpin

Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA ; Department of Medicine, Massachusetts General Hospital, Boston, MA; Harvard Medical School, Boston, MA ; AVEO Oncology, Cambridge, MA; Columbia University Medical Center, New York, NY

BACKGROUND

- Paired-related homeodomain transcription factor 1 (Prrx1) isoforms – Prrx1a and Prrx1b – are involved in pancreatic development, pancreatitis, and carcinogenesis.
- Hepatocyte growth factor (HGF) is a novel transcriptional target of Prrx1b.
- Ficlatuzumab is a potent and selective recombinant humanized HGF inhibitory immunoglobulin G subclass 1 monoclonal antibody which neutralizes HGF/c-Met binding and HGF-induced c-Met phosphorylation, thereby inhibiting the c-Met pathway.
- In preclinical pancreatic adenocarcinoma models, inhibition of Prrx1b-HGF signaling using ficlatuzumab in combination with gemcitabine reduced primary tumor volume and eliminated metastatic disease.

Takano S et al. Genes Dev. 2016;30:233-247; Garcia E, et al. Arch Pathol Lab Med. 2017: 141(6): 751.

OBJECTIVES

Primary objective:
- Identify the maximally tolerated dose in dose-escalation cohort, and safety in an expansion cohort, of ficlatuzumab when administered in combination with gemcitabine and nab-paclitaxel in patients with previously-untreated advanced pancreatic cancer.

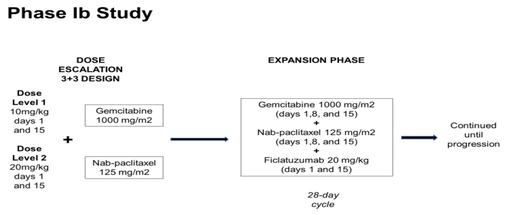
Secondary objective:
- Evaluation of safety, response rate and progression-free survival.

Exploratory objective:
- Evaluate serum and tumor biomarkers of disease response.

ELIGIBILITY

- Cytologically- or histologically- confirmed pancreatic adenocarcinoma or poorly differentiated pancreatic carcinoma that is locally advanced or metastatic to distant sites.
- No prior chemotherapy for metastatic pancreatic cancer.
- Participants are required to have measurable disease, RECIST v1.1.
- Participants enrolled must have disease that is accessible for tumor. biopsy and must agree to a pre-treatment tumor biopsy.
- Adequate hematologic, renal, and liver function.

STUDY SCHEMA



DEMOGRAPHICS

Number of Patients	24
Median Age, years (range)	69 (51-82)
Sex	
Male	12
Female	12
ECOG	
0	9
1	14
2	1
Current Status	
Alive	13
Dead	11

Disease Burden	
Metastatic	24
Median CA 19-9, U/mL (range)	2754 (5-27441)
Median Metastatic Sites (range)	2 (1-5)
Sites of disease	
Liver	19
Lung	8
Lymph nodes	11
Peritoneum	4
other	6

ADVERSE TOXICITY PROFILE ATTRIBUTED TO FICLATUZUMAB

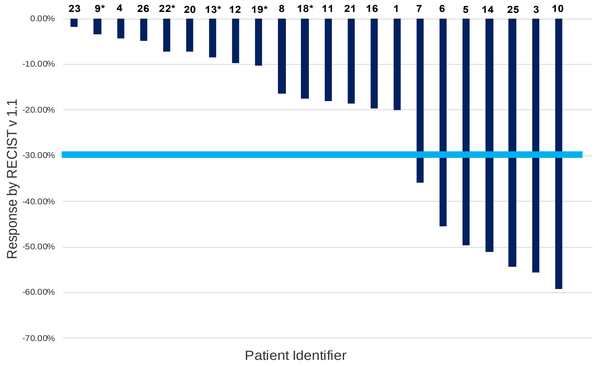
Adverse Event	Number (%) of Patients with Grade 3
Liver	
Elevated bilirubin	1 (4%)
Elevated AST/ALT	1 (4%)
Hypo-albuminemia	3 (12.5%)
General	
Dehydration	2 (8%)
Edema	1 (4%)
Fatigue	1 (4%)
Gastrointestinal	
Nausea/Vomiting	1 (4%)
Electrolyte	
Hyponatremia	1 (4%)
Hypophosphatemia	1 (4%)
Pulmonary	
Pneumonitis	1 (4%)
Dermatologic	
Skin ulceration	1 (4%)
CNS	
Vision changes	1 (4%)
Hematologic	
Neutropenia	4 (16.6%)
Lymphopenia	2 (8%)
Anemia	3 (12.5%)
Thrombocytopenia	1 (4%)

Adverse Event	Number (%) Grade 1	Number (%) Grade 2
Hypo-albuminemia	5 (20.8%)	12 (50%)
Edema lower extremity	7 (29.1%)	5 (20.8%)
Edema upper extremity	3 (12.5%)	4 (16.6%)

Definitions:
Hypoalbuminemia < 3.5 g/dL
Edema >5% discrepancy in volume or circumference at point of greatest visible difference

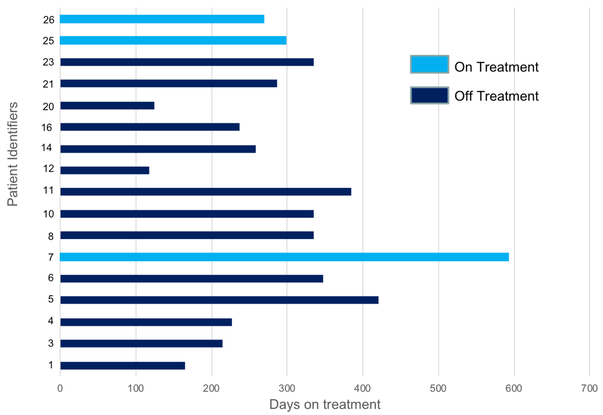
RESULTS

BEST RESPONSE BY RECIST v 1.1



Best Response by RECIST v1.1	Number of patients (%)
Stable Disease	15 (62.5%)
Partial Response	7 (29.2%)
Unevaluable	2 (8.3%)

PROGRESSION FREE SURVIVAL



* Patients 9,13,18,19, and 22 withdrew prior to measured progression

HGF LEVELS AND ASSOCIATED CLINICAL OUTCOMES

Objective: Serial blood samples were collected for circulating HGF measurements.
Procedure: Hepatocyte Growth Factor (HGF) plasma assay (Viracor Eurofins Clinical Diagnostics). Assay was conducted as per manufacturer's specifications.

Cohort Based on Best Response by RECIST v 1.1	Fold change (range) of HGF between Cycle 1 and Cycle 2
Stable Disease and Partial Response	1.48 – 12.75
Stable Disease	2 – 12.75
Partial Response	1.48 - 12

SUMMARY STATUS OF THE TRIAL

- First patient treated 1/31/2018
- Average number of cycles received 7.5 (range 1-15)
- 3 patients remain on active treatment
- 7 patients demonstrated a response per RECIST 1.1

CONCLUSIONS

- The combination of ficlatuzumab with gemcitabine and nab-paclitaxel is associated with durable treatment responses.
- Treatment was associated with significant hypoalbuminemia and edema, and therefore **a follow up safety study is underway with an alternate standard of care cytotoxic regimen.**
- Exploratory correlatives underway include: serum proteomics; tumor IHC analysis; tumor exome and transcriptome sequencing; and tumor derived 3D organoid development and analysis.

Contact: Kimberly Perez, MD; Dana-Farber Cancer Institute **Kimberly_perez@dfci.harvard.edu**