FOLFIRINOX with Glycogen Synthase Kinase-3 Beta (GSK-3β) Inhibitor Elraglusib and Transforming Growth Factor- β (TGFβ) Inhibitor Losartan in Untreated Metastatic Pancreatic Ductal Adenocarcinoma(PDAC): Interim analysis of safety cohort.

*Priyadarshini Pathak[1], *Eric Lin[2], Ildiko Philips[2], Daniel Schmitt[3], Andrew Mazar[3],Elizabeth Walsh[1], Amaya Pankaj[2], Michael Raabe[2], Yuhui Song[2], Bidish Patel[2], Katherine Xu[2], Joshua Kocher[2], Linda Nieman[2],Lawrence Blaszkowsky[1], Martin Aryee[2], #David Ting[2], #Colin Weekes[1]

Mass General Brigham

[1]Division of Hematology Oncology, Massachusetts General Hospital, Boston, MA 02114, USA, [2]Mass General Cancer Centre, Charlestown, MA, 02129, USA, Actuate Therapeutics Inc., [3]Fort Worth, TX 76107

*Authors contributed equally. #Authors jointly supervised this work

Harvard Medical School

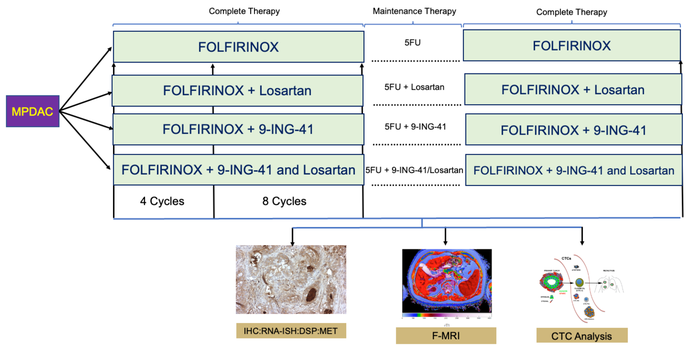
Introduction

- Epithelial to mesenchymal transition (EMT) is one of the key drivers of aggressive biology in metastatic PDAC.
- The COMPASS trial has shown better survival outcomes with chemotherapy in the Epithelial (E) subtype compared to Quasi mesenchymal (QM) subtype.
- Exposure to FOLFIRINOX induces tumor cell plasticity leading to chemoresistance via EMT from E to QM subtype.
- GSK-3β and TGFβ are known pathways promoting tumor cell plasticity with EMT. Inhibiting GSK-3β and TGFβ could thereby delay acquired resistance to FOLFIRINOX.
- Here we show using pre-clinical models that pharmacologic GSK-3β inhibition with elraglusib is able to convert QM PDAC cells into an E state synergizing with FOLFIRINOX therapy. We also present early data clinical from NCT05077800 highlighting the potential efficacy of this therapeutic strategy in metastatic PDAC.

Objectives

- Determine safety and tolerability of FOLFIRINOX in combination with elraglusib and losartan.
- Determine the Progression Free Survival of FOLFIRINOX with elraglusib and losartan in metastatic PDAC

Study Design



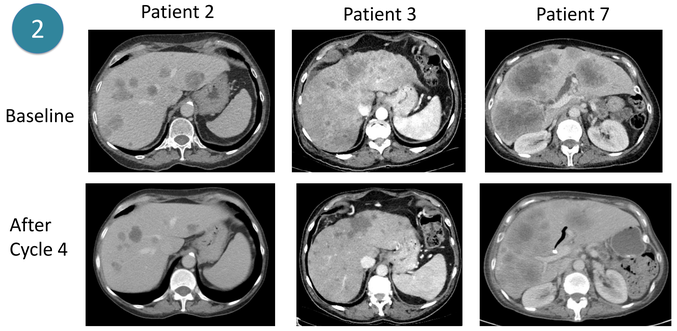
Results

1

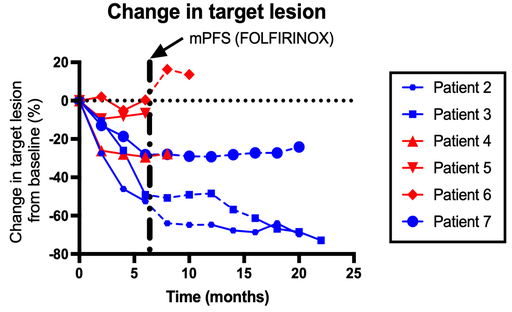
Table 2: Adverse events

Event	FOLFIRINOX + elraglusib + losartan	
	Grade 1 or 2	Grade 3 or 4
	No of patients/total no (%)	*No of patients/total no (%)*
Hematologic		
Neutropenia	1/6 (16.66%)	0 (0%)
Febrile Neutropenia	0/6 (0%)	0 (0%)
Thrombocytopenia	5/6 (83.33%)	0 (0%)
Anemia	6/6 (100%)	0 (0%)
Nonhematologic		
Fatigue	6/6 (100%)	0 (0%)
Vomiting	4/6 (66.66%)	0 (0%)
Diarrhea	5/6 (83.33%)	0 (0%)
Neuropathy	5/6 (83.33%)	0 (0%)
Transaminitis	6/6 (100%)	0 (0%)
Thromboembolism	1/6 (16.66%)	1 (0%)
Vision changes	6/6 (100%)	0 (0%)
Hypotension	3/6 (50%)	0 (0%)

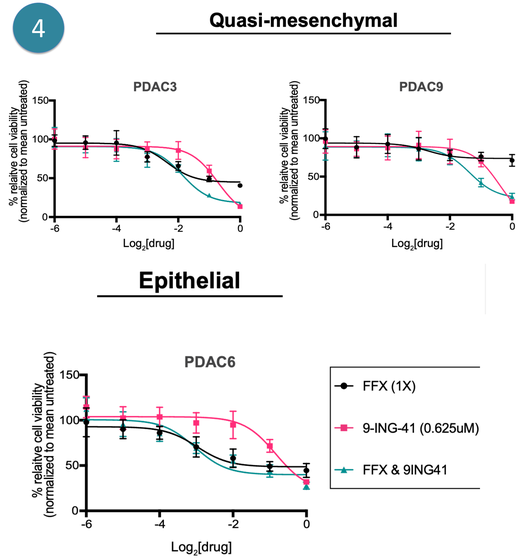
2



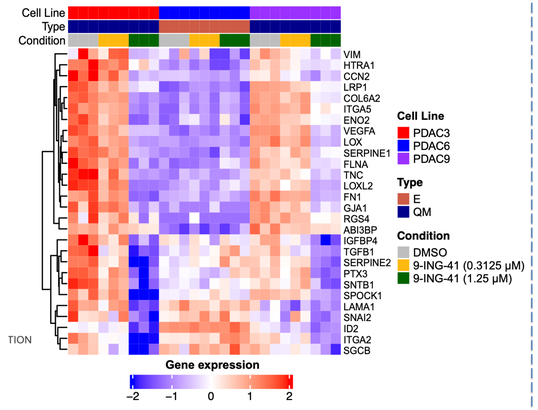
3



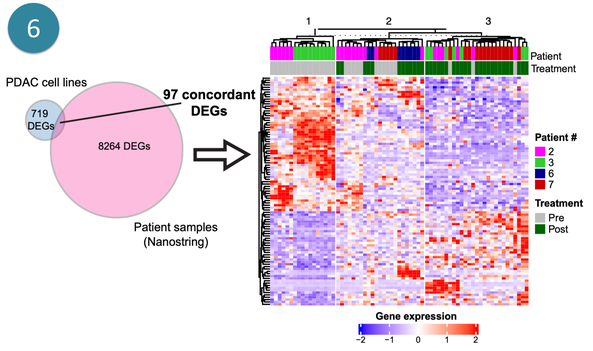
4



5



6



Conclusions

- The combination was well tolerated in the safety cohort.
- There is initial evidence of clinical activity.
- Gene expression analysis of cell lines and patient tumors treated with FOLFIRINOX and elraglusib demonstrate a phenotypic shift from QM to E state.
- NCT05077800 is currently enrolling and final results are eagerly awaited.

Acknowledgements

ACTUATE THERAPEUTICS

LUSTGARTEN Pancreatic Cancer Research