Phase I Study of Defactinib combined with Pembrolizumab and Gemcitabine in Patients with Advanced Cancer: Experiences of Pancreatic Ductal Adenocarcinoma (PDAC) Patients

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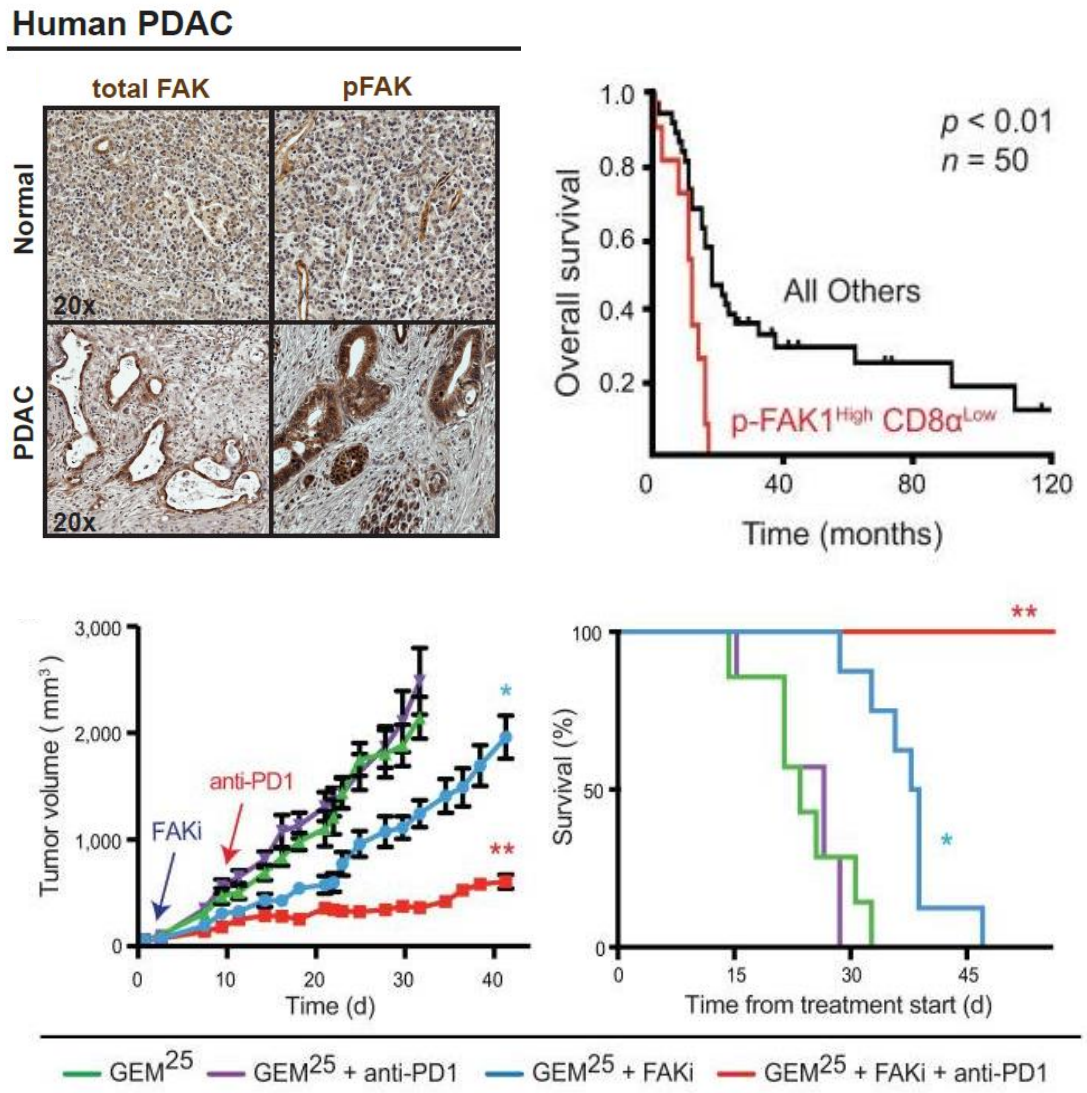
Disclosures

- Dr. Wang-Gillam served as a consultant for Merck, AstraZeneca and Eisai

Background

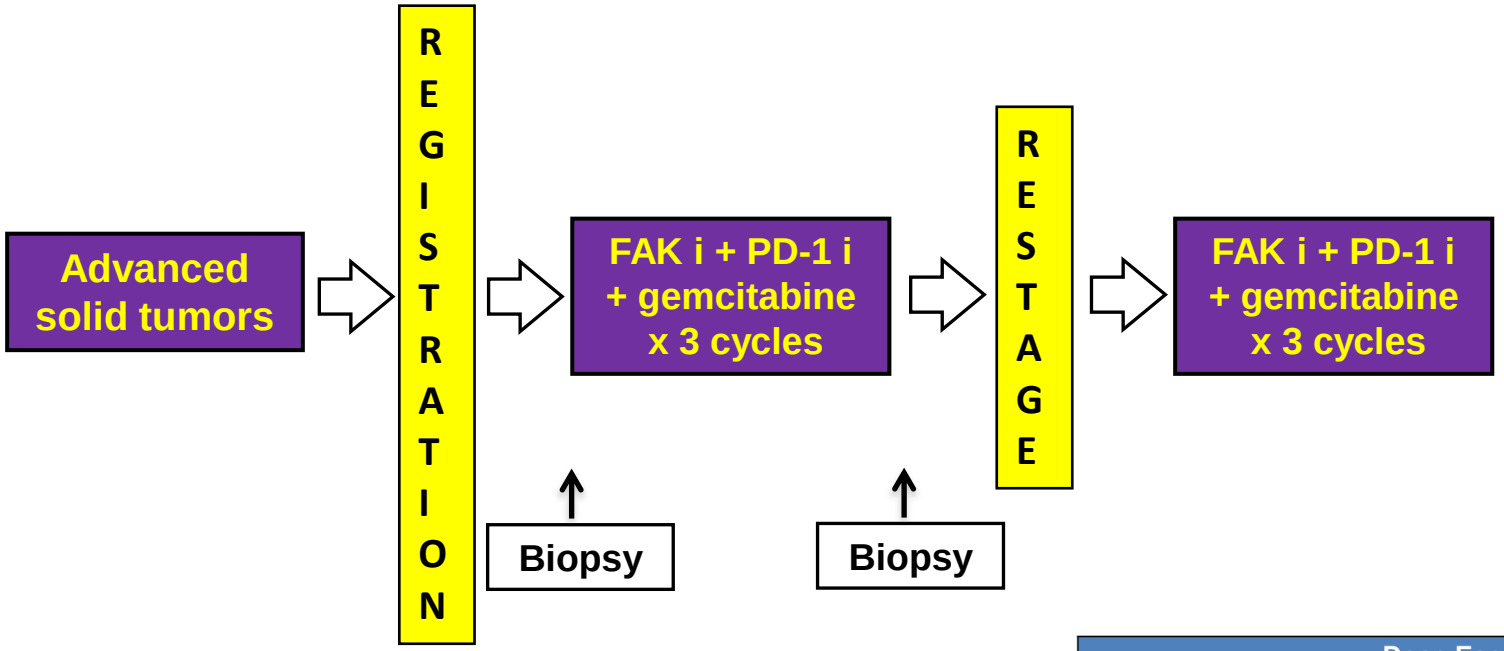
- Focal adhesion kinase (FAK) is a cytoplasmic tyrosine kinase identified in 1990.
- The binding of integrin to extracellular matrix triggers FAK autophosphorylation which activates multiple signaling pathways.[1]
- FAK autophosphorylation is elevated in multiple cancer types,[2] and FAK signaling induces an immunosuppressive microenvironment.[3]
- FAK pathway is consistently hyperactivated in PDAC, and FAK signaling is associated with poor clinical outcome.[3]
- MSS PDAC is known to be resistant to single agent checkpoint blockade,[4] extended survival was seen in FAKi +anti-PD-1 + gemcitabine in PDAC models.[3]
- Defactinib (Verastem, MA) is an orally available, generally well tolerated, potent ATP-competitive FAK inhibitor.[5]



Jiang Hong et al *Nature Medicine 2016:22: 851-60*

1. Lee BY, et al. *Pharmacol Ther* 2015; 38: 199-202
2. Sulzmaier FJ et al. *Nat. Rev. Cancer* 2014; 14: 586-610
3. Jiang H, et al. *Nat Medicine* 2016; (8): 851-60.
4. Foley K, et al. *Cancer Lett* 2016; 381: 244-251
5. Jones SF et al. *Invest New Drugs* 2015; 33: 1100-7

Study Design



- **Dose Escalation cohorts** (3+3 design)
  - Five dose levels
  - Patients with refractory solid tumor with indication for gemcitabine
- **Dose expansion cohorts** (N=10 per group)
  - **mPDAC patients**
  - Maintenance group: front-line gemcitabine and nab-paclitaxel stable at least 4 months
  - Refractory group: second line or beyond

Dose Escalation Schedule
1 cycle = 21 days

Dose Level	Defactinib Dose Days 1-21 (BID)	Pembrolizumab Dose Day 1	Gemcitabine Dose Day 1, 8
Level 1 (Starting Level)	200 mg	200 mg	---
Level 2	400 mg	200 mg	---
Level 3	400 mg	200 mg	500 mg/m^2
Level 4	400 mg	200 mg	750 mg/m^2
Level 5	400 mg	200 mg	1000 mg/m^2

Level 5 dose is the phase II dose

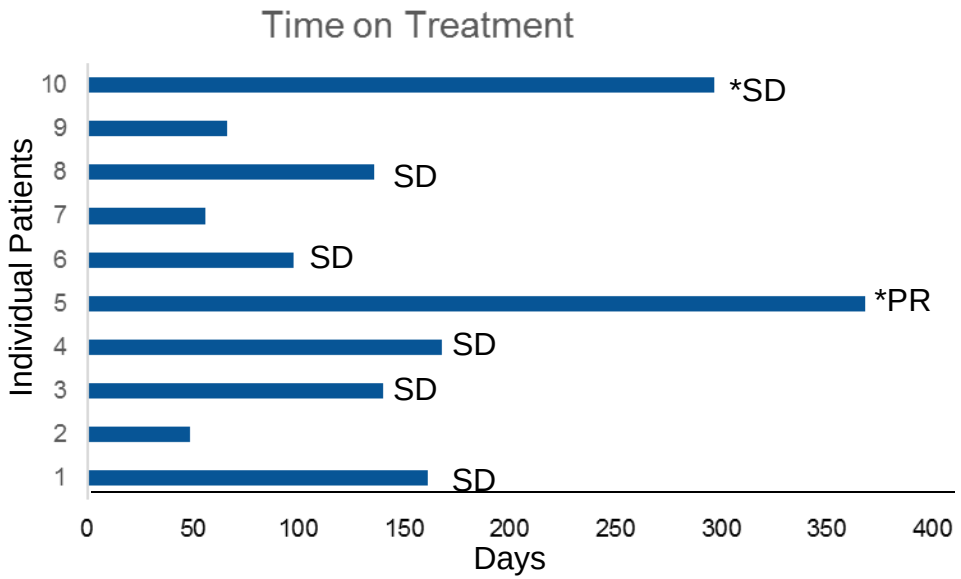
Funded by Precision Medicine Research Program and Barn Jewish Foundation

Results

PDAC Patients

	Dose Escalation (N=8)	Dose Expansion (N=20)	
		Maintenance (N=10)	Refractory (N=10)
CR	0	0	0
PR	1 (13%)	1 (10%)	0
SD	3 (38%)	6 (60%)	5 (50%)
DCR (CR+PR+SD)	4 (50%)	7 (70%)	5 (50%)
PD	4 (50%)	3 (30%)	4 (40%)
Not evaluable			1 (10%)

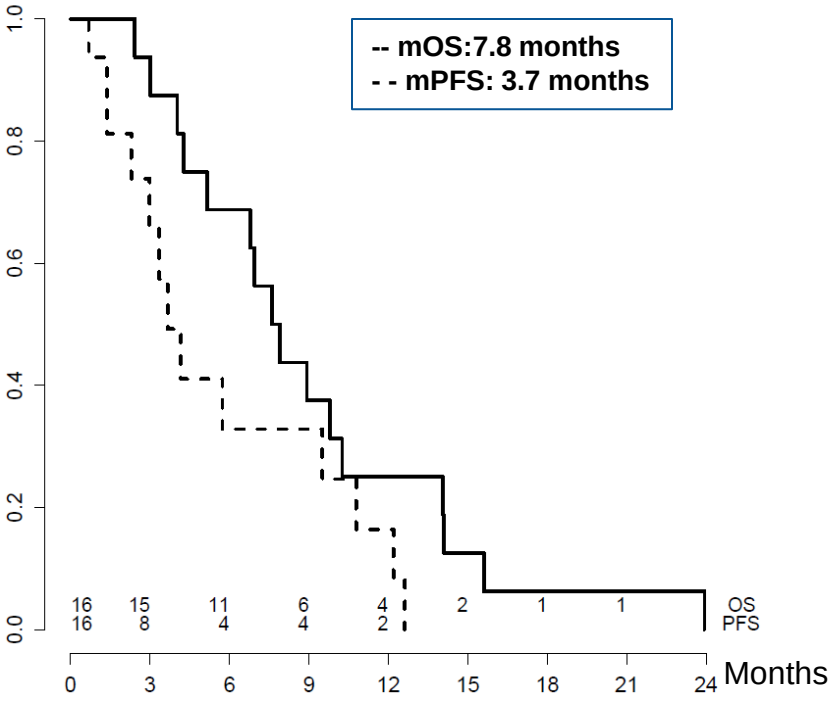
Maintenance Group



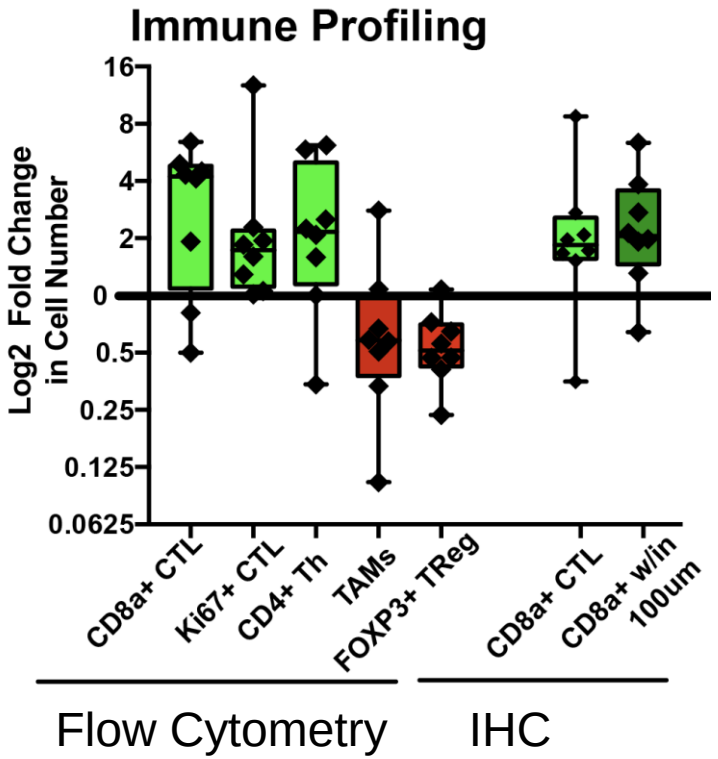
- Two patients (*) were still on the study as of Jan of 2020. The patient with PR has MSS disease.
- One SD patient (#6) was taken off the study due to other medical problems, while others with SD were off the study due to disease progression.
- **Median time on treatment: 4.6 months**

Results

Refractory PDAC



Patients (n=16) include 10 patients from refractory group in the expansion cohort (dose level 5 = phase II dose) and 6 patients from dose escalation cohorts who received triple-drug regimen (level 4 and level 5 dose).



Summary

- The triple drug regimen (Defactinib + Gem+ Pembro) is a well tolerated regimen (reported at 2018 ASCO)
- Encouraging activity was seen in the maintenance group with median time on treatment of 4.6 months.
- Median PFS of 3.7 months and OS of 7.8 months were observed in patients with refractory PDAC, demonstrating early efficacy signal in this recalcitrant disease.
- Two patients with sustained PR in the study have microsatellite stable (MSS) disease.
- Paired biopsies showed treatment-induced T cell and macrophage changes consistent with preclinical observations.
- Further development of a FAKi-based regimen is warranted.

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