UPDATE ON LIVER CANCER TRIALS IN HAWAII

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DISCLOSURE

- Research funding from GSK

- Hepatocellular cancer (HCC) is not a common cancer in the US, **however**
  - Hawaii has the second highest incidence of HCC in the US
  - HCC is a leading cause of cancer death despite not being a common cancer

Mortality Average Number & Percent of Deaths Per Year			
Male		Female	
No. Deaths	Percent	No. Deaths	Percent
Lung & Bronchus		Lung & Bronchus	
314	24.1%	230	21.1%
Prostate		Breast	
125	9.6%	155	14.2%
Colon & Rectum		Pancreas	
118	9.1%	101	9.3%
Liver & Intrahepatic Bile Duct		Colon & Rectum	
103	7.9%	98	9.0%
Pancreas		Liver & Intrahepatic Bile Duct	
100	7.7%	49	4.5%

Hawaii Cancer at a Glance 2014-2018

- TSR-022 (Anti-TIM-3 Antibody) and TSR-042 (Anti-PD-1 Antibody) in Patients With Liver Cancer
  PI: Acoba

- Evaluation of Treatment Predictors Reflecting Beta-catenin Activation in Hepatocellular Carcinoma (ExTRACT-HCC)
  PI: Kwee

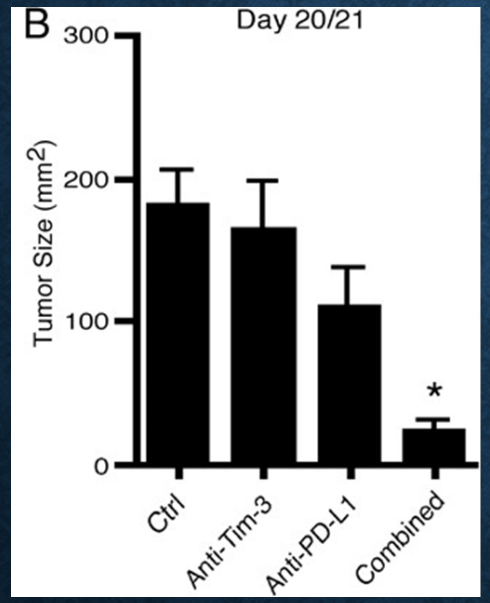
TSR-022 (ANTI-TIM-3 ANTIBODY) AND TSR-042 (ANTI-PD-1 ANTIBODY) IN PATIENTS WITH LIVER CANCER

SYSTEMIC THERAPY FOR HCC

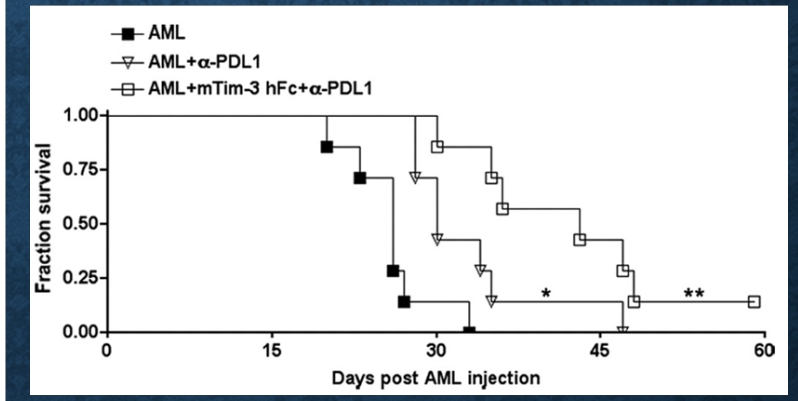
Drug(s)	Response	Survival
Sorafenib	2%	10.7 mo
Lenvatinib	19%	13.6 mo
Nivolumab	15%	16.4 mo
Atezolizumab + Bevacizumab	27%	19.2 mo
Durvalumab + Tremelimumab	20%	16.4 mo

TARGETING TIM-3 AND PD-1

- Targeting TIM-3 might have additive or synergistic effects with those induced by anti-PD-1 antibodies



5 × 105 CT26 cells were implanted into wild-type BALB/c mice. Mice were then treated with anti-Tim-3, anti-PD-L1, anti-Tim-3 + anti-PD-L1, or control immunoglobulins



B6 mice (10 mice/group) were injected iv with 1 × 106 C1498FFDsR cells. Ten days after AML injection, mice were treated with mTim-3 hFc (100 μg/dose), anti-PD-L1 (200 μg/dose) or combination of both every other day for total of 5 doses.

RATIONALE FOR ANTI-TIM-3 AND ANTI-PD-1

- UHCC Bioinformatics Team used tissue collected for an HCC PET study and TCGA data to develop a 4-gene signature that had prognostic value in HCC and included TIM-3

- TSR-022 (cobolimab, anti-TIM-3) + TSR-042 (dostarlimab, anti-PD-1) well tolerated, most side effects were Grade 1-2:
  - Fatigue (19%), rash (7%), nausea (7%)
  - Grade ≥3 – total 11.7%; lipase (1.9%), rash (1.4%)

OBJECTIVES

- **Primary objective**: response rate
- **Secondary objectives**:
  - Progression free survival
  - Overall survival
  - Alpha-fetoprotein response
  - Safety

KEY ELIGIBILITY CRITERIA

- ≥18 years of age
- Histologically or cytologically confirmed hepatocellular cancer
- BCLC stage B or C
- Child-Pugh class A or B7 (limited to 6 patients)
- Adequate hematologic and renal function
- Performance status ECOG 0 or 1
- Measurable disease
- No prior systemic therapy for HCC
  - Prior local therapy is allowed

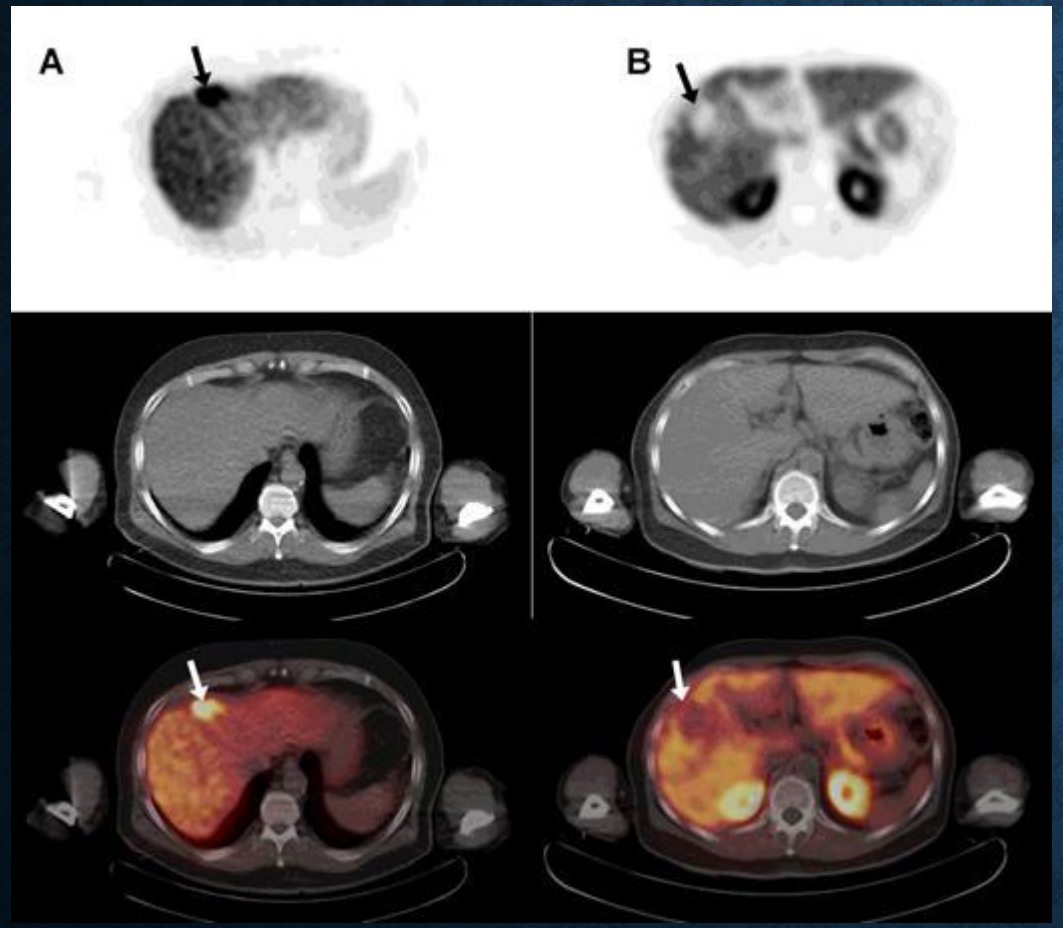
STUDY DESIGN

- Phase II open-labeled single-arm study
- Cobolimab and dostarlimab administered every 3 weeks
- Study treatment will be stopped upon progression, unacceptable toxicity, patient choice
- Imaging every 9 weeks
- Sample size = 40 pts to show in increase in response rate from 20% to 35%

INTERIM ANALYSIS

- 16 patients consented and received at least one cycle
- 5 White, 5 Native Hawaiian, 4 Asian, 2 other
- 13 evaluable patients
  - 1 CR, 5 PR (ORR 46%)
  - 3 Stable disease (Disease control rate 67%)
  - 4 Progression (31%)
- 1 grade 4 treatment related AE (neutropenia)
- Grade 1/2 AEs included pruritus, rash, fatigue, hypothyroidism, hypophysitis, and elevated AST and ALT

EVALUATION OF TREATMENT PREDICTORS REFLECTING BETA-CATENIN ACTIVATION IN HEPATOCELLULAR CARCINOMA (EXTRACT-HCC)



FCH high FCH low

- Fluorocholine PET/CT approved for HCC in the European Union
- 18F-fluorocholine (FCH) PET/CT detects HCC with ~ 95% sensitivity, but there are two imaging phenotypes (FCH low vs. FCH high).

RATIONALE AND OBJECTIVES

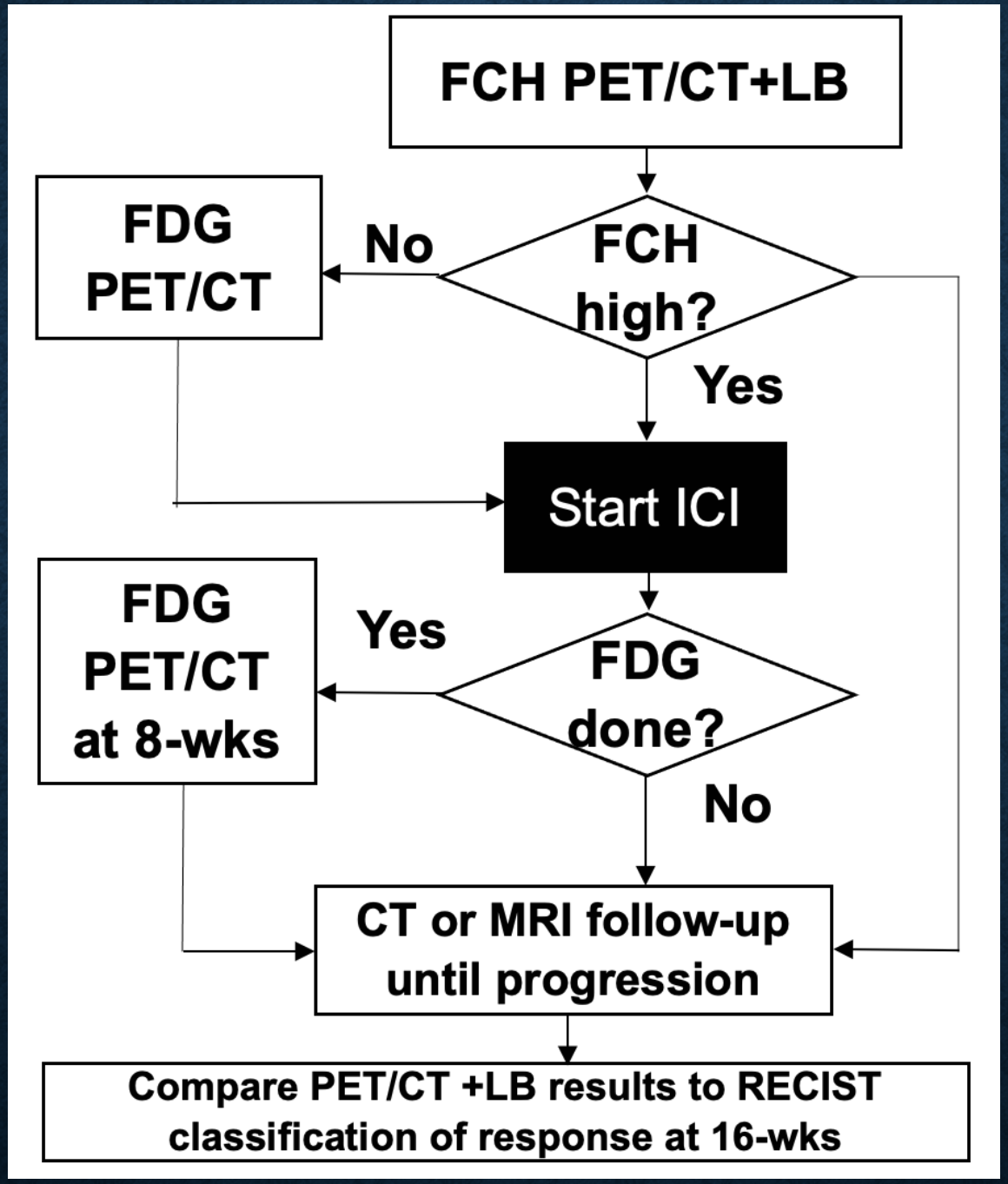
- High uptake of FCH is associated with activation of the WNT/β–catenin pathway
- Activation of the WNT/b-catenin pathway alters immune cell infiltration into the tumor microenvironment
  - Associated with resistance to immune checkpoint inhibitor
- FCH low tumors are often FDG avid and associated with inflammatory gene signatures
- FCH high tumors may be resistant to immunotherapy, FCH low and FDG avid tumors may be sensitive to immunotherapy

OBJECTIVES

- **Primary objective**: Association between FCH-PET and response to immunotherapy
- **Secondary objective**: Association between FDG-PET, ctDNA and response

KEY ELIGIBILITY CRITERIA

- Age 18 years or older (no upper limit of age)
- Hepatocellular carcinoma diagnosed histologically or radiographically
- BCLC Stage B or C
- Measurable disease defined as at least one tumor lesion that can be accurately measured by RECIST v1.1
- Eligible for treatment with an immune checkpoint inhibitor agent
- Child-Pugh score of 7 or less
- Adequate hepatic and renal function


FCH PET/CT+LB
FCH high?
No
FDG PET/CT
Yes
Start ICI
FDG done?
Yes
FDG PET/CT at 8-wks
No
CT or MRI follow-up until progression
Compare PET/CT +LB results to RECIST classification of response at 16-wks

QUESTIONS?