A pilot study of pembrolizumab and liver-directed therapy for patients with well-differentiated neuroendocrine tumors and symptomatic and/or progressive liver metastases

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Background:

- Well-differentiated neuroendocrine tumors (WD-NET) have a relatively low tumor mutation burden and do not commonly express the programmed death ligand 1 (PD-L1)
- Preliminary studies suggest that immune check-point inhibitors (CPI) have low response rates for patients with well-differentiated neuroendocrine tumors.
- Intensity of anti-tumor immune response may be enhanced by liver-directed therapies (LDT), including
  - Radiofrequency ablation (RFA)
  - Cryoablation
  - Embolization
  - ^{90}Y Radioembolization
- Abscopal effect is a phenomenon in the treatment of metastatic cancer where localized treatment of a tumor causes not only a shrinking of the treated tumor, but also a shrinking of tumors outside the scope of the localized treatment.
- This pilot study aims to evaluate whether combining pembrolizumab with LDT results in abscopal effects for patients with WD-NET
- (Clinical trial registry number: NCT03457948)

Objectives:

Primary:

- Best observed overall response rate (ORR) in lesion(s) not targeted for liver-directed therapy (abscopal effect) according to RECIST 1.1

Secondary:

- Safety
- Duration of response (DOR), progression-free survival (PFS).

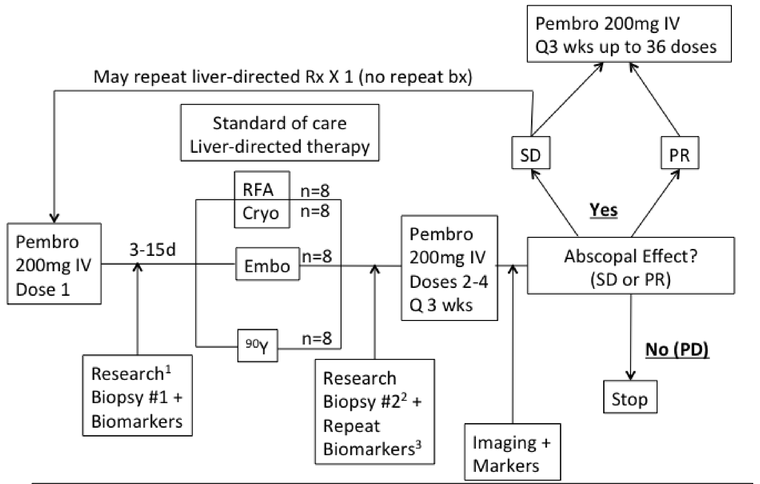
Exploratory:

- T cell receptor (TCR) repertoires change from baseline to post treatment time points
- Immune cell localization within tumor (CD3, DC8, FoxP3)
- Correlate PD-L1 status and Ki67 index with response to therapy

Trial Design:

- Four-arm, open-label non-randomized pilot study for patients with morphologically well-differentiated NET of any grade
- Pembro 200mg IV administered every 21 days up to 36 cycles
- Liver-directed therapy during cycle 1 (and cycle 5)
  - Single lesion RFA: ≤ 6 liver lesions, largest ≤ 4 cm (n = 8)
  - Segmental/subsegmental embolization: ≤ 75% liver replacement by tumor, any number of lesions, largest ≤ 5 cm (n=8)
  - Segmental/subsegmental radioembolization with ^{90}Y glass microspheres: ≤ 75% liver replacement by tumor, any number of lesions, largest > 5 cm (n=8)
  - Single lesion cryoablation: : ≤ 6 liver lesions, largest ≤ 4 cm (n = 8) – enrolment after completion of enrolment into RFA group

Figure 1. Trial Schema



[1]For RFA and Cryo groups, research biopsy and biomarkers will be obtained on the day of the RFA or cryo
[2]Repeat research biopsies will be obtained approximately 5 weeks after liver-directed therapy
[3]Repeat biomarkers will be obtained at screening, on the day of liver-directed treatment, pre-dose on Cycle 2 day 1; approximately 5 weeks after liver-directed therapy, and at treatment discontinuation.

KEY INCLUSION CRITERIA	KEY EXCLUSION CRITERIA
Histologically confirmed morphologically well-differentiated NET of any grade (1-3)	Prior percutaneous thermal ablation, embolotherapy or external beam radiation
At least one symptomatic or enlarging liver lesion over 12 months	> 75% liver parenchyma replacement by tumor
Radiographic, clinical, or biochemical evidence of progression at extrahepatic sites over 12 months	Active untreated CNS metastases
Prior surgical resection/ablation and peptide receptor radionuclide therapy (PRRT) allowed	History of immunodeficiency
Biomarker “unselected”	Active autoimmune disease requiring systemic treatment in the past 2 years
≥ 1 measurable lesion	Baseline liver dysfunction
Presence of at least one biopsiable lesion	History of (non-infectious) pneumonitis (interstitial lung disease) requiring steroids or current pneumonitis
Subjects must consent to baseline tumor biopsy (if risk is acceptable)	History of biliary tract instrumentation (drains, stents, surgical biliary anastomosis)
Adequate end-organ function	

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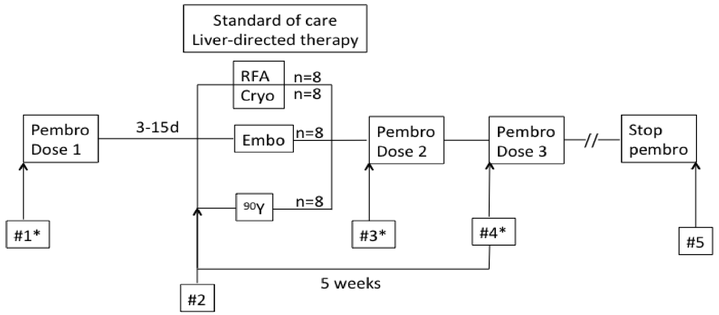
Figure 2. Blood Sampling Schedule



Blood sampling for biomarkers.
* Delineates time points when T-cell receptor sequencing will be analyzed

Analysis plan:

- The point estimate and 90% confidence interval of overall response rate will be obtained for each of the 4 liver-directed therapy groups separately.
- Assuming abscopal overall response rate is 25% for each patient group, with 8 patients in each group, there is 80% power to detect partial response rate significantly different from 1% at alpha of 0.1 by a directional binomial test

Stopping rule for safety:

- Any liver-directed therapy group may be closed due to unacceptable treatment-related toxicity (any grade 4 toxicity, recurrent grade 3 toxicity, or any grade 3 toxicity persisting more than 4 weeks) observed in 3 patients in one group.
- Safety review will occur after a total of 5 patients have been accrued in a given treatment group

Current Status:

- This study is currently open and enrolling patients at UCSF
- Enrolment by group
  - RFA group: 0 of 8 patients
  - Embolization group: 0 of 8 patients
  - Radioembolization group: 1 of 8 patients
  - Cryoablation group: 0 of 8 patients

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