A Pilot Study of Pembrolizumab and Peptide Receptor Radionuclide Therapy for Patients with Metastatic Grade 2/3 Well-Differentiated Neuroendocrine Tumors

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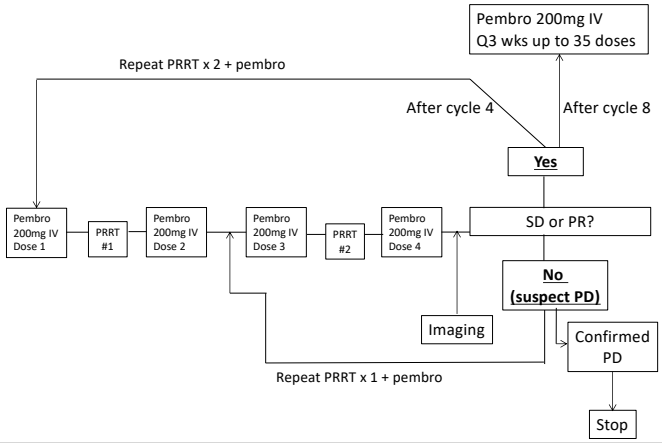
INTRODUCTION

- Well-differentiated neuroendocrine tumors (WD-NET) have low tumor mutation burden and do not commonly express programmed-death ligand 1 (PD-L1).
- Response rate to single agent immune checkpoint inhibitors (CPI) for patients with grade 1-3 WD-NET is ≤ 15% (1,2).
- PRRT for grade 3 NET: median PFS 9 months, PR 31%, DCR 78% at 3 mo (3).
- NETTER-2 PRRT for grade 2-3 NET: median PFS 22.8 mo, PR 43% (4)
- Targeted radiation therapy from ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) may potentiate anti-tumor immune response.

Purpose

To evaluate safety and efficacy of PD-1 inhibitor pembrolizumab in combination with ^{177}Lu-DOTATATE PRRT for patients with grade 2-3 WD-NET.

MATERIALS AND METHODS



Study Therapy

- Pembrolizumab 200mg every 3 weeks for up to 35 doses
- ^{177}Lu-DOTATATE PRRT 200±20mCi every 8 weeks for up to 4 doses

Objectives

- To evaluate the best observed ORR to pembrolizumab plus PRRT according to RECIST 1.1.
- To evaluate safety profile of pembrolizumab in combination with PRRT

Inclusion Criteria

- Adult previously treated patients with WHO grade 2 or 3 WD-NET (Ki-67 index >10%) of any primary site
- Somatostatin receptor expression on DOTA PET
- At least one RECIST-measurable lesion with progression over 1 year
- Adequate bone marrow, renal, and hepatic reserve

Exclusion Criteria

- Prior PRRT
- LDT or external beam radiation within previous 30 days
- Chemotherapy or biologics within previous 14 days
- Prior treatment with immune checkpoint inhibitor
- >75% liver replacement by tumor

Analysis Plan

- Assuming RECIST v 1.1 ORR 25%, 26 patients needed to achieve 99% power at alpha 0.05 by a two-sided binomial test

RESULTS

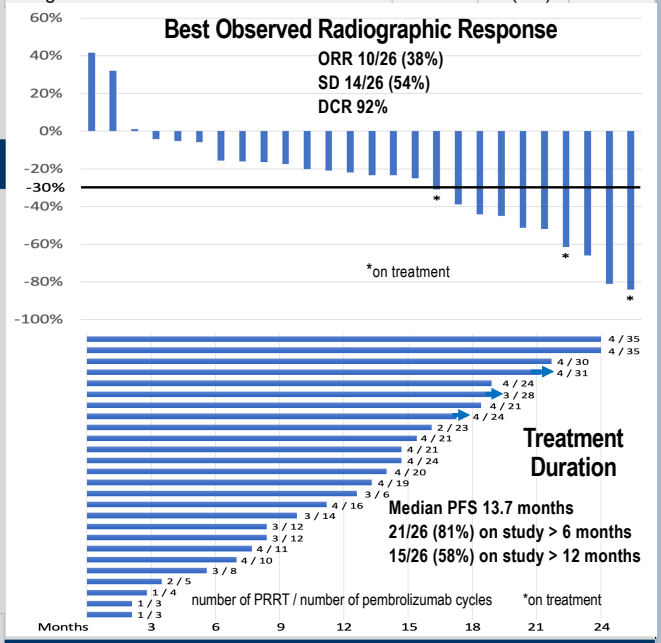
- 26 patients (15 men, 11 women, median age 60 years)
- Primary sites: pancreas (15), ileum (6), lung (3), duodenum (1), rectum (1)
- WHO grade and Ki-67 index
  - Grade 2: 6; Ki-67 index median 16% (range 12-20%)
  - Grade 3: 20; Ki-67 index median 31% (range 21-69%)
- PRRT treatments: one (3), two (2), three (6), four (15)
- Pembrolizumab cycles: median 19, range 3-35
- 21/26 patients (81%) on study longer than 6 months; 15/26 (58%) > 1 year
- Median PFS 13.7 months (range 2-NR months)
- 23/26 patients (88%) discontinued after median 12.6 mo (range 2.1-24 mo) due to
  - Disease progression (n=20)
  - Performance status deterioration (n=2)
  - Treatment completion (n=1)
- 3/26 patients (12%) currently receiving treatment

SAE Attributable to PRRT

NCI CTCAE Grade	3	4
Lymphopenia	2 (8%)	1 (4%)
Neutropenia	1 (4%)	-
Anemia	2 (8%)	-
Thrombocytopenia	1 (4%)	-
Hyponatremia	-	1 (4%)

Immune-Related Adverse Events

NCI CTCAE Grade	1	2	3
Colitis	-	1 (4%)	1 (4%)
Hypothyroidism	2 (8%)	2 (8%)	-
Hyperglycemia (diabetes mellitus)	-	-	2 (8%)
Nephritis	-	1 (4%)	-
Renal tubular acidosis	-	1 (4%)	-
Hepatitis		1 (4%)	
Vitiligo	-	1 (4%)	-



CONCLUSION

Combination treatment with ^{177}Lu-DOTATATE PRRT and pembrolizumab is well tolerated and leads to durable disease control in the majority of patients.

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[1]Strosberg, et al. Clin Cancer Res 2020; 26:2124; [2]Mehnert, et al. Cancer 2020; 126:3021; [3]Zhang J, J Nucl Med 2019; 60:377; [4]Singh, et al. Lancet 2024; 403:2807