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A Pilot Study of Pembrolizumab and Peptide Receptor Radionuclide Therapy for Patients with Well-Differentiated Neuroendocrine Tumors and Symptomatic and/or Progressive Metastases

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BACKGROUND

Expected progression free survival (PFS) for patients with grade 3 well-differentiated neuroendocrine tumors treated with peptide receptor radionuclide therapy (PRRT) is approximately 9 months, and objective response rate (ORR) is 35%. Response rate to single agent immune checkpoint inhibitors for patients with G1-3 NET is <15%. Delivery of targeted radiation using PRRT may potentiate the anti-tumor immune response. The purpose of this study is to evaluate safety and efficacy of the combination of PRRT and PD1 inhibitor pembrolizumab in high-risk NET.

METHODS

In a single arm prospective pilot study, adult patients with WHO grade 2 or 3 (Ki-67 index > 10%) metastatic NET of any primary site received concurrent pembrolizumab 200mg every 3 weeks up to 35 doses and up to 4 doses of ^{177}Lu-DOTATATE PRRT (200mCi) at 8-week intervals. Treatment was terminated in the event of disease progression, performance status deterioration, and/or intolerable toxicity. Primary endpoint was best observed objective response rate (ORR) by RECIST v.1.1. Secondary endpoints were PFS and safety.

RESULTS

A total of 26 patients were enrolled: 15 men, median age 60 years, median Ki-67 index 30% (range 11-70%), 6 patients with grade 2, 20 patients with grade 3 NET. Primary site: 15/26 pancreas, 6/26 small bowel, 3/26 lung, 2/26 other. As of August 15, 2024, 22/26 patients (84.6%) have been on study for at least 24 weeks, and 5/26 (19.2%) are still receiving pembrolizumab. Median follow-up was 13.7 mo. Grade 3 and 4 adverse events include anemia (n=2, 7.7%), neutropenia (n=2, 7.7%), and thrombocytopenia (n=1, 3.8%) related to PRRT, and diabetes mellitus (n=2, 7.7%) and hyponatremia (n=3, 11.5%) attributable to pembrolizumab. In terms of best radiographic response, 9/26 patients (34.6%) demonstrated partial response, 16/26 (61.5%) had stable disease, and 2/26 (7.7%) had disease progression, with 23/26 (88.5%) patients having achieved some shrinkage of their disease (median 24.2%, range 4.3-84.1%). Median PFS was 11.2 months (95% CI 8.6, 14.4 months). Overall, 21 patients discontinued participation due to disease progression (n=17), performance status deterioration (n=2), or completion of planned two years of pembrolizumab treatment (n=2). Updated safety, PFS, and ORR analyses will be reported.

CONCLUSIONS

In this pilot study of patients with well differentiated NET with Ki67>10%, combination treatment with ^{177}Lu-DOTATATE PRRT and pembrolizumab was well tolerated and associated with ORR 34.6% and mPFS 11.2 months. Additional research is needed to identify the patients most likely to benefit from combination therapy and to determine the incremental benefit of each component.

ABSTRACT ID 28609