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Efficacy of Checkpoint Inhibitors in Neuroendocrine Neoplasms: The Mayo Clinic Experience

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BACKGROUND: While immune checkpoint inhibitors (CPI) for low- and intermediate- grade (G1/2) neuroendocrine tumors (NET) have largely been associated with limited efficacy, recent studies have suggested that CPI may represent a promising treatment for high-grade neuroendocrine neoplasms (NEN). However, these trials did not report whether the responses were seen in both well-differentiated and poorly-differentiated tumors.

METHODS: The retrospective cohort study identified all patients older than 18 years of age with a diagnosis of NEN at Mayo Clinic between 2000 and 2020. We cross-referenced this search with patients who were treated with CPIs as monotherapy or combined with other CPIs or cytotoxic chemotherapy. Imaging interpretation and tumor response assessment was performed retrospectively using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria. The primary endpoint was objective response rate (ORR) defined as complete response (CR) and partial response (PR).

RESULTS: We identified 32 patients with NEC who were treated with CPI monotherapy, CPI dual therapy, or CPI with cytotoxic therapy. The median progression free survival (PFS) in all patients with NEC treated with any combination of CPI was 3.5 months compared to patients treated with CPI monotherapy at 2.1 months compared to patients with G3 NET at 2.9 months. The percentage of all patients with NEC treated with CPI who achieved an ORR was 19% compared to all patients with G3 NET at 0% and NEC patients treated with CPI monotherapy at 0%.

CONCLUSION: CPI therapy showed limited antitumor activity in patients with both NEC and G3 NET. Further prospective trials on CPI therapy in NENs should address whether poorly differentiated tumors respond differently than those that are high-grade, yet well-differentiated. CPI therapy therefore remains investigational in patients with G3 NEN and should preferably be offered in the context of a clinical trial.

Response to Treatment for NEC and G3 NET

Response	NEC CPI Monotherapy N = 10	NEC CPI Overall N = 32	G3 NET CPI Monotherapy N = 3
ORR	0	6 (19)	0
DCR	3 (30)	14 (44)	1 (33)
Median PFS, months (95% CI)	2.1 (0.5 – 4.6)	3.5 (1.8 – 4.6)	2.9 (1.4 – 4.2)
Median OS from CPI initiation, months (95% CI)	7.9 (1.1 – 17.9)	7.2 (3.9 – 10.8)	15.4 (13.7 – 17.2)

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