# C-14

## Cabozantinib as salvage therapy for well differentiated grade 3 neuroendocrine tumors (G3 NETs)

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### BACKGROUND

G3 NETs are a recently recognized entity and although the treatment recommendations largely follow those for grade 1 and 2 NETs, the outcomes of therapy are inferior. Little is known about the optimal therapy sequencing but small studies have suggested a benefit of multikinase inhibitors. Somatostatin analogs, PRRT and chemotherapy have all been reported to have activity but later lines of therapy are needed. In this study, we sought to evaluate the activity of cabozantinib in patients with heavily pretreated G3 NETs.

### METHODS

Using the Mayo Clinic electronic medical record, we searched for patients with G3 NET who received cabozantinib focusing on patients who were either heavily pretreated or had a very high nuclear grade as measured by Ki-67. Information on baseline patient and tumor characteristics, tolerability and efficacy were extracted.

### RESULTS

Five patients (3 women, 2 men) met inclusion criteria. Four had pancreatic primary tumor and one had a NET of unknown primary. The median Ki-67 was 10 (range: 10-55) on the initial biopsy and 56 (range: 29-77) on repeat biopsy prior to starting cabozantinib. All patients had grade progression on repeat biopsy, 3 with Ki67 > 50 on repeat biopsy. All patients had genomic studies and 2 had TMB > 200 m/Mb, presumably temozolomide-induced hypermutation. Four patients had prior somatostatin analogs, and all had PRRT and CAPTEM prior to cabozantinib. Three patients had other chemotherapy prior to cabozantinib (all had irinotecan and oxaliplatin regimens). One patient had everolimus and one patient (with high TMB) had immunotherapy without response. Four patients had a substantial response, but one has not had follow-up imaging. Two have progressed (after 4 and 9 months) and three are still receiving cabozantinib (after 1, 7 and 10 months) with sustained response in 2 patients. Four patients needed dose reduction for toxicity including the patients who have had response for 7 and 10 months).

### CONCLUSIONS

Cabozantinib seems to have substantial antitumor activity in this small cohort of extensively pretreated mostly pancreatic G3 NET patients. Despite very high Ki-67 and multiple lines of prior therapy, including chemotherapy and PRRT, responses have been profound and in 2 cases durable. While no patient had to discontinue cabozantinib for toxicity, 4 needed a dose reduction. Cabozantinib may be a viable option for patients with advanced and heavily pretreated G3 NETs and further studies are warranted.

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