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## A phase 2 clinical trial of cabozantinib in patients with unresectable and progressive metastatic pheochromocytoma or paraganglioma: The NATALIE trial

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### BACKGROUND

Metastatic pheochromocytomas and paragangliomas are orphan neuroendocrine tumors. 50% of these tumors are associated with germline mutations of the SDHB gene. SDHB related pheochromocytomas and paragangliomas and many apparently sporadic tumors exhibit abnormal angiogenesis. This trial assessed the efficacy and safety of Cabozantinib, a potent, antiangiogenic, tyrosine kinase inhibitor.

### METHODS

The Natalie trial is a single arm phase 2 clinical trial. Patients older than 18 years of age with progressive metastatic pheochromocytomas and paragangliomas were treated with Cabozantinib 60 mg daily with dose titration down depending on patient's tolerability. The primary endpoint was objective response rate as per RECIST 1.1. Secondary endpoints included progression free survival, overall survival, safety, blood pressure control, and correlations with germline and somatic genotypes and biochemical phenotypes.

### RESULTS

The trial recruited 17 patients. The clinical benefit rate was 94%. The objective response rate was 25%. The medican progression free survival was 16.6 months (95%CI 8.1-34.9 months). Median overal survival was 24.9 months (95%CI lower boundary-23.6 months). 80% of patients exhibited blood pressure improvement. 96% of Cabozantinib related side effects were grade 1-2. Three patients reported grade 3 side effects including hypertension, asymptomatic elevation of pancreatic enzymes, and a rectal fistulae. There were no grade 4 or 5 side effects. Tumors did not have c-met receptor mutations or c-met pathway amplification. Positive responses were reported irrepective of germline genotype.

### CONCLUSIONS

Cabozantinib is an effective systemic therapy for adult patients with metastatic pheochromocytoma and paraganglioma irrespective of the primary tumor origin and genotype.

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