Phase II Study of ONC201 in Neuroendocrine Tumors including Pheochromocytoma-Paraganglioma and Desmoplastic Small Round Cell Tumor

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ABSTRACT

Purpose: Tumor dopamine-like DRD2 receptor expression is higher in pheochromocytoma-paraganglioma (PC-PG) compared with other cancers. ONC201 is a bitopic DRD2 antagonist with preclinical ONC201 activity in desmoplastic small round cell tumor (DSRCT).

Patients and Methods: Patients ($N = 30$) with neuroendocrine tumors were treated on this investigator-initiated trial (NCT03034200). ONC201 dose and schedule were 625 mg orally weekly in cohorts A (PC-PG) + B (other neuroendocrine tumors) and 625 mg orally on 2 consecutive days each week in cohort C, which included 5 responding patients. The primary endpoint was radiographic response measured using RECIST. Secondary endpoints included progression-free survival, overall survival, and safety.

Results: In arm A ($n = 10$; all PC-PG), 50% (5/10) exhibited a partial response (PR) and 2 additional patients had stable disease (SD) >3 months. Median duration of therapy for arm A patients was 9 months (range: 1.5–33 months) with 5 patients treated >1 year. In arm B ($n = 12$), there were 1 PR (DSRCT) and 2 SD (DSRCT; neuroblastoma) >3 months. Median duration of therapy in arm A was 18 months (range: 1–33 months) and arm B was 3 months (range: 1.5–33 months). Arm C PC-PG ($N = 8$) showed 1 PR and 7 SD at 3 months, with median duration of therapy >10 months. There was no decline in Karnofsky performance status at week 12 for 28 of 30 patients and no dose modification due to treatment-related adverse events.

Conclusions: Oral ONC201 was well tolerated in patients with metastatic neuroendocrine tumors and associated with clinical benefit, including tumor responses, particularly in some patients with DSRCT and the majority of patients with PC-PG.

See related commentary by Owen and Trikalinos, p. 1748

Introduction

Neuroendocrine tumors are rare cancers derived from endocrine cells with characteristics of neuronal differentiation such as IHC staining with synaptophysin. Patients with neuroendocrine tumors often also have elevated serum markers of neuroendocrine function (e.g., chromogranin, norepinepherine, dopamine, and calcitonin). There are many treatment options for neuroendocrine tumors including local control with surgery, radiation, cryoablation, and radiofrequency ablation as well as systemic therapies of a targeted and non-targeted nature for unresectable or metastatic disease. Because of a variable clinical course from indolent to progressive with "too many to count" metastases, a balance of quality and quantity of life when reviewing indications, risks, and alternatives of therapy is the current clinical approach to these cancers (1–3). A meta-analysis in 2016 showed that no one chemotherapy regimen was significantly better (4). Ongoing efforts of Dr. Karel Pachak at NIH and others have increased genomic knowledge and therapeutic options for targeted treatment of neuroendocrine tumors, particularly pheochromocytoma-paraganglioma (PC-PG; refs. 1, 2, 5–14).

ONC201 is an imipridone heterocyclic small molecule (MW 459) that is a dopamine-like receptor (DRD2) antagonist/caseinolytic protease P (ClpP) agonist with downstream effects involving increased integrated stress response, decreased Ras signaling (decreased ERK/AKT), and TRAIL induction to result in increased cell death signals and decreased cell survival signals in cancer cells (15–25). An analysis of The Cancer Genome Atlas (TCGA) data revealed PC-PG to have the highest expression of all cancers of DRD2, the target of ONC201 (**Fig. 1**; ref. 25), leading us to hypothesize that ONC201 would have antineoplastic activity in these dopamine-associated tumors. Furthermore, ONC201 also had previously demonstrated preclinical efficacy against desmoplastic small round cell tumor (DSRCT), a rare sarcoma of the Ewing sarcoma family with neuroendocrine characteristics (26). There was no TCGA subset data for small cell lung carcinoma, pancreatic neuroendocrine tumors, carcinoids, medullary thyroid carcinoma (MTC), or primitive neuroectodermal tumors including Ewing sarcoma and medulloblastoma. Therefore, we designed a study to test the safety and efficacy of ONC201, a DRD2 antagonist (**Fig. 2**) in PC-PG and other dopamine-associated tumors such as neuroblastoma and cholangiocarcinoma (25, 27) as well as DSRCT for which there was preclinical single-agent efficacy data (26).

Prior studies with ONC201 established therapeutic systemic concentrations with oral dosing and selected a biologically active dose of 625 mg for a once weekly schedule with minimal toxicity (20). Thus, there was enough preclinical evidence and clinical experience in a variety of cancers including brain tumors (23) to design and conduct an investigator-initiated phase II study of weekly oral ONC201 in neuroendocrine tumors [NCT03034200/CASE2716 (IND132665)]. This phase II trial was designed to test feasibility, safety, and potential

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Translational Relevance

Patients with metastatic neuroendocrine cancers need more effective and well-tolerated options. This study translated the single-agent preclinical activity of the first-in-class imipridone, ONC201, against desmoplastic small round cell tumor (DSRCT) and The Cancer Genome Atlas analysis showing exceptionally high dopamine-like receptor (DRD2) expression in pheochromocytoma-paraganglioma (PC-PG) into an investigator-initiated phase II clinical trial with oral ONC201. The mechanism of action for ONC201 involves both specific targeting of DRD2 and mitochondrial caseinolytic protease P with anticancer effects associated with downstream upregulation of TNF-related apoptosis inducing ligand (TRAIL)/DR5, AKT/ERK pathway inhibition, and promotion of an integrated stress response. Not only did a portion of patients with metastatic PC-PG and DSRCT demonstrate responses by RECIST but some were also treated for years—with excellent quality of life. This study demonstrates that targeting a core receptor involved in neuroendocrine function can provide benefit in at least two different types of neuroendocrine cancer.

early efficacy of ONC201 against neuroendocrine tumors, particularly PC-PG and DSRCT.

Patients and Methods

Phase II study of ONC201 in neuroendocrine tumors (NCT03034200/CASE 2716) was an open-label study with design as depicted in **Fig. 3**. This clinical trial had peer review by the Protocol Review and Monitoring Committee of Case Comprehensive Cancer Center. The principal investigator, Peter M. Anderson, held the IND (#132665). The clinical trial and related research procedures including informed consent form (ICF) was approved by Cleveland Clinic IRB in July 2017. The principal investigator and colleagues obtained written informed consent from patients and the study was conducted in accordance recognized ethical guidelines (e.g., Declaration of Helsinki, Belmont Report and U.S. Common Rule). Enrollment ($N = 30$) began in August 2017 and was completed in April 2021. Oncoceutics (acquired by Chimerix) developed ONC201 and provided study drug, Information from other clinical trials evaluating ONC201 that required changes of the list of potential ONC201 drug side effects on the ICF (23, 24). ONC201 study drug was provided by Oncoceutics and dispensed by Cleveland Clinic Investigational Pharmacy. During the COVID-19 pandemic, the study was amended to increase virtual visits and shipping of investigational drug directly to the patient to minimize risk to patients of exposure to the virus.

Patients treated on the study had recurrent and/or metastatic neuroendocrine tumors including PC-PG, DSRCT, and other neuroendocrine tumors with a catecholamine or dopamine biomarker or paracrine dependence on dopamine including MTC, clear cell sarcoma, neuroblastoma, cholangiocarcinoma, and adrenocortical carcinoma (ACC). Subjects also were required to have normal organ function as defined by hemoglobin ≥10 g/dL, leucocytes ≥1,500/mcL, absolute neutrophil count ≥1,000/mcL, platelet count ≥75,000 mcL, total bilirubin within 1.5× institutional upper limit, aspartate aminotransferase ≤5× institutional upper limit, alanine aminotransferase ≤5× institutional upper limit, and serum

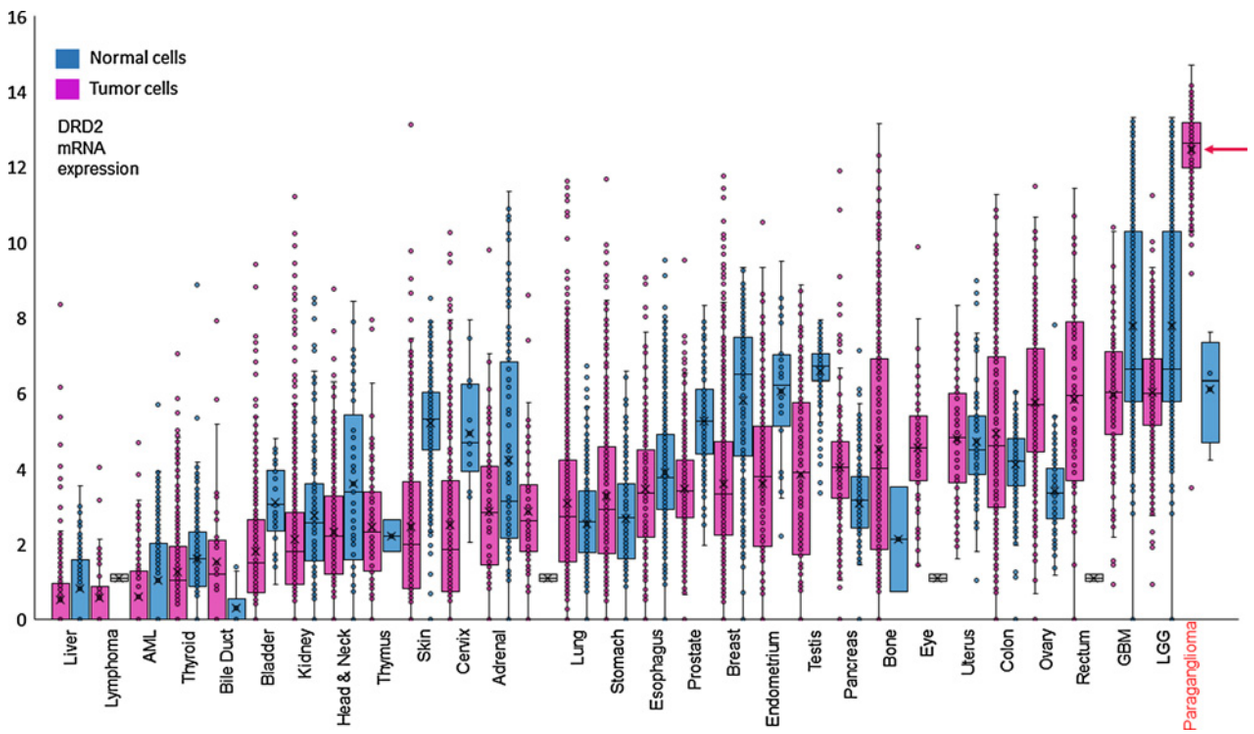

Figure 1.
TCGA analysis of DRD2 mRNA of the dopamine-like DRD2 receptor shows PC-PG to be highly elevated compared with normal cells and is associated with approximately 3–10 × higher expression than all other cancers tested. High DRD2 expression at the protein level has also been confirmed in PC-PG compared with normal adrenal or nerve tissue (25).

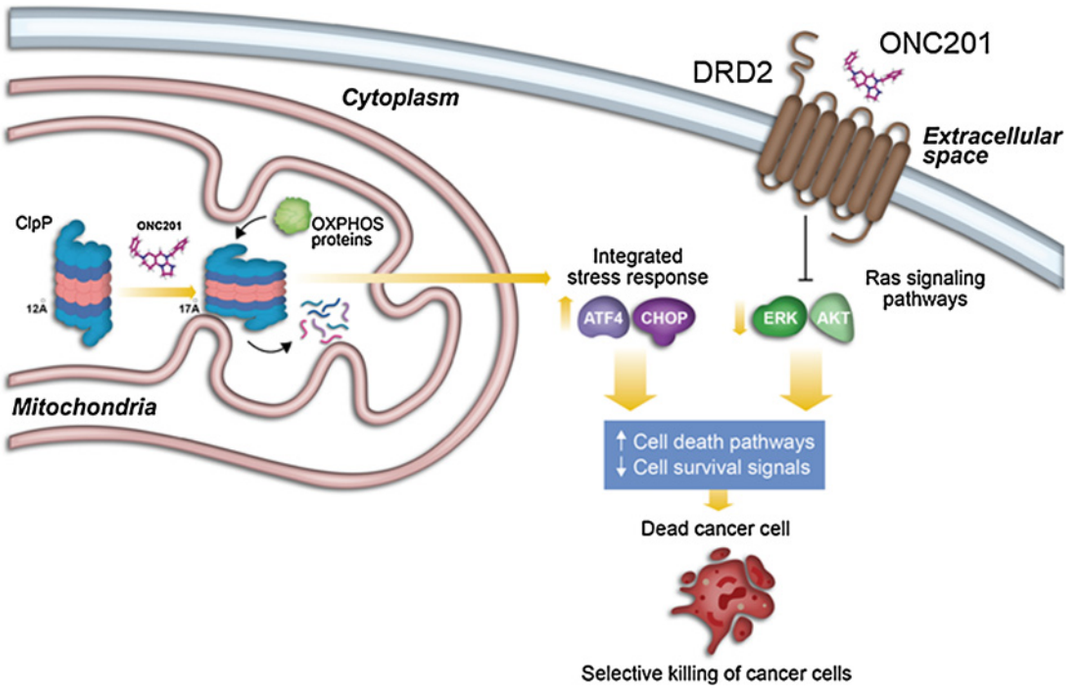

Figure 2.
ONC201 is a DRD2 antagonist and ClpP agonist that causes increased integrated stress response and cell death pathways and decreased cell survival pathways in cancer cells compared with normal cells.

creatinine <3.0 mg/dL. Age was initially ≥ 18 years, but the trial was amended to age ≥14 when additional information about ONC201 in younger patients became available (24). There was no limit on number of prior therapies. Subjects were required to have Karnofsky/Lansky performance status (KPS) of ≥60. At least one measurable lesion on imaging with CT or MRI was required. Exclusion criteria included subjects not able to meet eligibility for organ function, unable to take oral drugs, receiving treatment with other investigational agents or cytotoxic drugs, pregnant or breastfeeding, and psychiatric illness or social situation that would limit compliance with study requirements.

Subjects could not have congestive heart failure, infection or uncontrolled hypertension before study enrollment. All PC-PG subjects initially had alpha and beta blockade and were closely monitored. Arm A had the first dose administered in the Cleveland Clinic Clinical Research Unit (CRU) with blood pressure (bp) monitoring 0, 0.5, 1, 2, and 14 hours after the first dose of ONC201. Initial IND guidance discussions with the FDA recommended patients with small cell lung cancer (SCLC) to be excluded from this study because of expected and common rapid progression of disease and life-threatening symptoms during screening and initial visits in these patients would make conduct of the clinical trial difficult in Cleveland Clinic Children's outpatient oncology clinic that is not used to SCLC clinical care.

After discussion of indications, risks, and alternatives patients signed an ICF and were registered on study in the Case Comprehensive Cancer Center ONCore database. ONC201 was supplied as 625 mg capsules. Dosing of ONC201 was 625 mg orally once weekly for arm A (PC-PG; $N = 10$) and arm B (other neuroendocrine tumors, $N = 12$) and 625 mg orally on 2 consecutive days each week for arm C (PC-PG and other neuroendocrine tumors, $N = 12$).

Timepoints for data collection included prestudy, 6 weeks, 3 months, then every 3 months until disease progression or patient or investigator requested study withdrawal (e.g., for disease progression or other therapy). Data collected included KPS, complete blood counts, serum chemistries, and relevant neuroendocrine serum tumor markers including chromogranin and metanepherines and normetanephrines (PC-PG) and carcinoembryonic antigen and calcitonin (MTC). The primary endpoint was response using tumor measurements on CT or MRI of indicator lesions as defined by RECIST 1.1 (28). Secondary endpoints included progression-free survival, overall survival, clinical benefit, and incidence and severity of treatment-related adverse events (AE). KPS was assessed at each study visit.

Clinical benefit was considered maintenance of performance status with no new metastases in 3 months (SD+PR+CR). After analysis showed a high proportion of PR in arm A and in 1 DSRCT, the study was amended to roll-over responding patients (4 PC-PG +1 DSRCT) and accrue additional neuroendocrine tumor patients on to a more intense dose schedule of ONC201 with study drug administered on 2 consecutive days each week (arm C). Accrual began August 2020 and ended in April 2021. Cutoff for analysis of treatment-related AEs was July 2021. As of November 2021, 7 arm C subjects had stopped study drug and 5 (4 PG-PG and 1 DSRCT) patients on arm C were continuing therapy. For PC-PG on therapy as of 11-2021, 3 were roll-over from arm A and 1 was new. The patient with DSRCT continuing therapy on arm C was not a roll-over.

Genetic analysis of germline and somatic mutations was derived from testing prior to study entry using review of medical records or, if available, from Foundation One, Tempus, or Caris testing of somatic mutations in tumors and germline panels. Study data were entered into a compliant REDCap database. After 3 years from study initiation, the

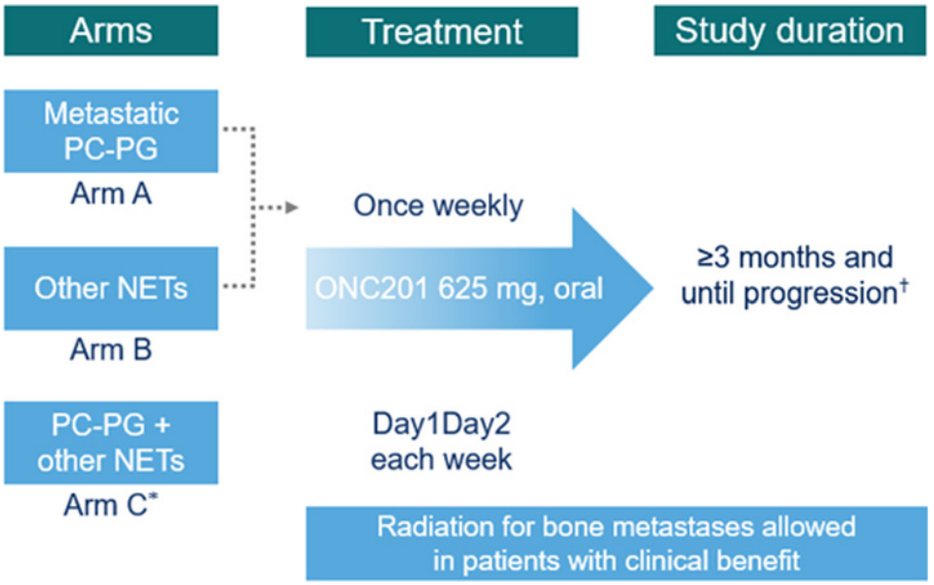

Figure 3.
Phase II study of ONC201 in neuroendocrine tumors was a phase II open-label design. †Progression was as defined by RECIST (28).

database was harmonized with the database of other ongoing ONC201 clinical trials.

Data availability statement

Data were generated by the authors but are not publicly available due to information that could compromise patient privacy or consent but are available upon reasonable request from the corresponding author, Peter M. Anderson (andersp@ccf.org).

Results

Patient characteristics are detailed in **Table 1**. Sites of measurable metastatic disease were more common in lymph nodes in patients with PC-PG and lungs, liver, or abdomen in other neuroendocrine tumors including DSRCT, clear cell sarcoma, MTC, ACC, neuroblastoma, and cholangiocarcinoma. DSRCT is known to have a >4:1 male preponderance; 75% of patients with DSRCT enrolled on this study were male. All patients had new or progressing disease between 3 months prior to study entry and/or at study entry; no patient had indolent disease with similar scans 6 months before study entry.

Germline and somatic mutations of patients are also described in **Table 1**. Although not a predefined endpoint of the study, most patients with PC-PG had information on germline mutation status. SDHB was the most common germline mutation (**Table 1**). Other mutations included SDHA, SDHC, SDHD, RET, and fumarate hydrase. One patient with PC-PG had no germline mutation, but had a NF1 frameshift somatic mutation. One patient with PC-PG had a family history of PC-PG, but declined genetic testing. All patients with DSRCT had the pathognomonic EWS-WT1 gene fusion mutation.

Side effects of ONC201 were mild and infrequent. Almost all patients reported minimal if any difference in activity or function on the day of ONC201 dosing for both once/week and 2 consecutive days/week schedules. One PC-PG patient experienced recurrent, weekly grade 1 encephalopathy (self-described as a mild "fog") in the afternoon and evening of the day of ONC201 dosing that was attributed as definitely related to ONC201. This toxicity did not meet criteria for holding dose or dose interruption because it was a grade 1 self-limited toxicity. This subject has continued on ONC201 therapy for almost 4 years (2.5 years on arm A; >15 months on arm C) and has maintained a KPS 100%.

No ONC201-related grade 3 or 4 treatment-related AE were observed. AEs considered not serious and not-recurring and possibly related to ONC201 across the 30 subjects were seen in 9 subjects and included: grade 1 temporary episodes of dizziness (2), nausea (2), abdominal pain (1), gastroparesis (1), fatigue (2), diarrhea (1), and gastroesophageal reflux (1). Cancer-related side effects before starting ONC201 included grade 1 and 2 pain from bone metastases and anorexia in some patients. ONC201 dosing did not seem to affect appetite. Although arm A patients with PC-PG had bp monitoring in the CRU, no patient with PC-PG experienced transient elevation in bp or subsequent catecholamine crisis on study drug so CRU monitoring of initial dose was discontinued for arm C. Patients with PC-PG self-monitored bp, often using a wireless cuff that transmitted bp data to the electronic medical record. While on ONC201, only a 3 of 14 patients with PC-PG were able to taper completely off long-term alpha and beta blocker antihypertensives because of low bp while on bp medication and ONC201. One patient with PC-PG who had refractory hypertension prior to study entry was able to stabilize bp on ONC201 using combined alpha + beta blockade and improved KPS while on study to 100%. This subject has been able to regularly work >60 hours/week despite a large, but stable disease burden. There was no evidence of cumulative or long-term toxicities.

Responses as determined by RECIST were highest in PC-PG but were also present in DSRCT. **Figure 4** depicts best response by RECIST in PC-PG and the other neuroendocrine tumor cohorts. Significant tumor shrinkage did not continue beyond 9 months in any patient. Best responses by RECIST including partial responses (PR) generally occurred at 3, 6, or 9 months and are depicted in **Fig. 4**. Although there were no complete responses (CR), 7 of 30 patients were stable by RECIST and continued ONC201 therapy for >1 year (**Fig. 5**). As expected in a phase II study with metastatic neuroendocrine tumors including PC-PG and DSRCT, many patients, especially those with larger disease burdens, had progressive disease within 6 weeks to 3 months (**Fig. 5**). Five of 10 patients with PC-PG had SDHB mutation, 3 of whom had a PR, 1 with stable disease and 1 with progression. One patient with ACC appeared to benefit, then developed tumor-

Table 1. Patient characteristics: PC-PG and other neuroendocrine tumors in phase II study of ONC201.

Patient characteristic	PC-PG	Other neuroendocrine tumors
Patients with metastases (%)	14 (100%)	16 (100%)
Age, years, median (range)	57 (18–70)	35.5 (19–65)
Gender, *N* (%)		
Male	3	4
Female	11	12
KPS score, median (range)	90 (70–100)	90 (80–100)
Weight, kg, median (range)	91.2 (72.9–117.9)	81.35 (60.7–108.9)
Height, cm, median (range)	178 (159.3–198.3)	180.7 (160–188)
Time from initial diagnosis, *N* (%)		
<6 months	0 (0)	1 (6.3%)
>6 months to <2 years	2 (14.3%)	1 (6.3%)
>2 years to <5 years	4 (28.6%)	8 (50%)
>5 years to <10 years	2 (14.3%)	5 (31.3%)
>10 years to <20 years	5 (35.7%)	1 (6.3%)
>20 years	1 (7.1%)	0 (0)
Type of neuroendocrine cancer		
PC-PG	14 (100%)	
DSRCT		10 (62.5%)
MTC	1	2 (12.6%)
Cholangiocarcinoma		1 (6.3%)
ACC		1 (6.3%)
Clear cell sarcoma		1 (6.3%)
Neuroblastoma		1 (6.3%)
Prior local treatments, *N*		
Surgery only	2 (14.3%)	1 (6.3%)
Surgery + radiotherapy (RT)	3 (21.4%)	2 (12.5%)
Surgery + chemotherapy	3 (14.3%)	0 (0)
RT + chemotherapy	1 (7.1%)	0 (0)
Surgery + RT + chemotherapy	5 (35.7%)	13 (81.3%)
Sites of metastasis, *N* (%)		
Lymph nodes	11 (78.6%)	12 (75%)
Lung	6 (42.9%)	13 (81.3%)
Liver	2 (14.3%)	8 (50%)
Bone	13 (92.9%)	7 (43.8%)
Other	0	2 (12.5%)
Baseline plasma chromogranin, picogram/mL, median (range)	697 (71–71,760)	N/A
Partial response: % change	−25, −4, −10, +6, +71%	
Stable disease: % change	−60,−36, +2, +7, +1, +73, +313%	
Progression: % change (1 patient not done)	+93%	
Baseline plasma Normetanephrine (median)	284 (65–10,244)	
Partial response: % change	−66, −29, −19, −16, −8%	
Stable disease: % change	−60, −47, −25, −4, −3, 0, +20%	
Progression: % change (1 patient not done)	+113%	
Germline mutations (*N*)	SDHA (2), SDHB (7) SDHC (1), SDHD (1) RET (1)[a] Fumarate hydrase (1)	RET (1)
Somatic mutations (*N*)	NF1 p.F1778 fs ATRX fs +ZFHX3 fs (1)	EWS-WT1(10), EWS-ATF (1), ATRX p. V1557fs +ALKp.R1275 (1) GNAS R201C, KRAS G13D+ PIK3 E542K (1)

[a]Also with PC-PG (MEN2).

associated pain and ascites and withdrew from study prior to 6 weeks study timepoint because the patient and caregivers elected hospice care for unresectable liver metastases. All other patients were evaluated at 6 weeks. Only 2 of 30 patients had study drug discontinued at 6 weeks for symptomatic disease progression. All others went on to be evaluated at 3 months.

Patients with DSRCT often had relatively rapid progression of disease; only 3 of 10 patients with DSRCT had duration of therapy

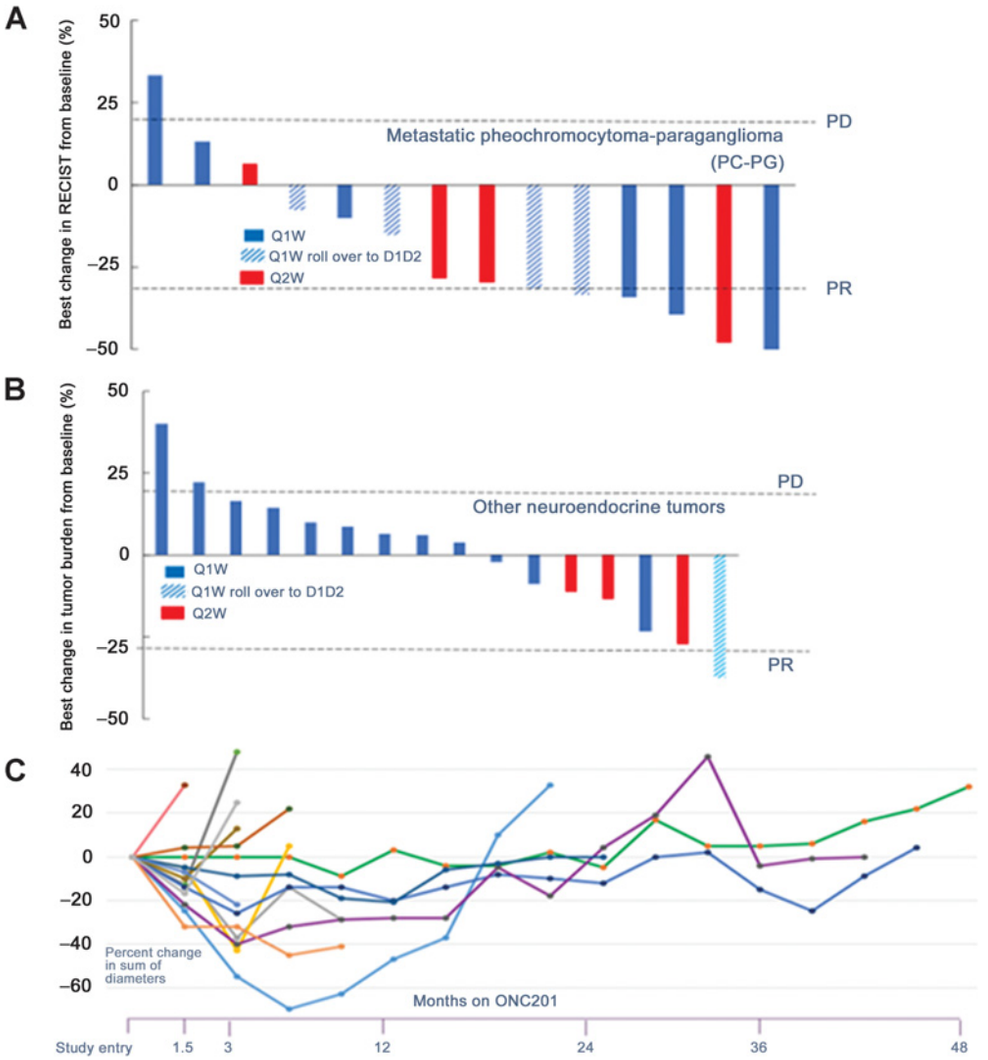

Figure 4.

Best response by RECIST: **A,** PC-PG tumors had responses to both weekly and 2 consecutive days/week dosing. **B,** Other neuroendocrine tumors had a greater proportion with tumor shrinkage using 2 consecutive days/week dosing (red). All responses in roll-over patients (blue hatched) occurred prior to 2 consecutive days/week dosing. **C,** PC-PG tumor responses depicted over time.

≥6 months. However, 2 of 10 (20%) of patients with DSRCT had durations of therapy >12 months and 4 years, respectively. Neither of these outliers had somatic mutations in addition to EWS-WT1. A third patient with metastatic, recurrent DSRCT with limited disease had progression at 3 months and came off study, then had SBRT of the progressing lung metastasis and now remains >3 years off any active therapy without a relapse.

Three case studies are illustrative of clinical benefit of ONC201 in three different neuroendocrine tumors. The youngest patient on study (subject 1015) was 18 years old at study entry and has the SDHA germline mutation. This patient presented with retroperitoneal primary with lymph node and bone metastases 7 years prior to study entry. Despite surgery, therapy with the Y-90 Dotatate radiopharmaceuticals, and chemotherapy, the retroperitoneal mass increased and bone metastases became numerous (>20). Best response by RECIST was at 3 months (−33%, PR). This subject remained on weekly ONC201 for 2.5 years with gradual increase in tumor size, but no side effects. After starting the more intense ONC201 dosing (arm C) disease indicator lesions (1 lung metastasis, retroperitoneal mass, and right caval node) regressed −25% using RECIST after 6 months. After 1 year on arm C, chromogranin has gradually decreased >50% from >1,100 to 560 and normetanepherine also decreased. KPS remains 100% and numerous bone metastases are no longer associated with significant pain. This subject with clinical benefit has remained on ONC201 >3.5 years.

The second case study (patient 1023) is a 50-year-old subject with MEN2 and a germline RET p.C634R gain-of-function mutation. At the age of 16, he presented with neck masses and had multiple surgeries for MTC. Fourteen years later, calcitonin was 871 and plasma normetanephrines became abnormal (2,466). He had bilateral adrenalectomies with two pheochromocytomas on the right and another two on the left. A left neck mass was found 29 years after MTC diagnosis and MTC was

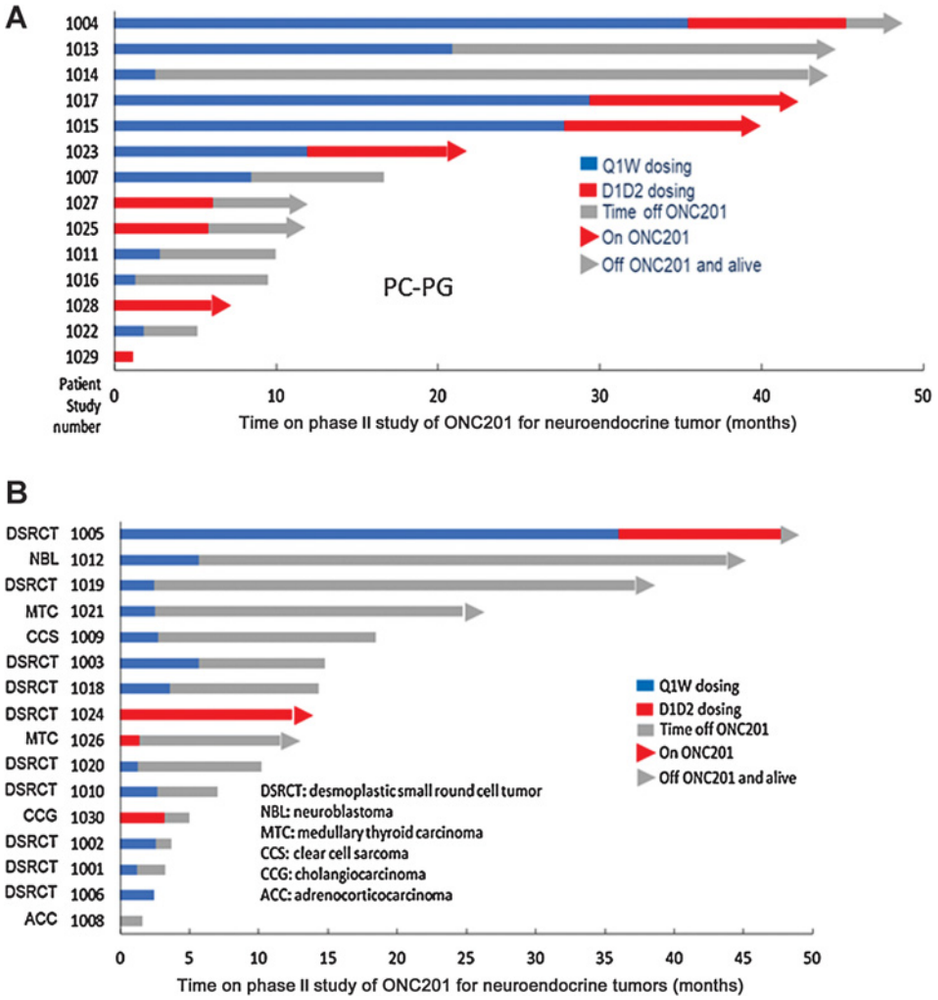

Figure 5.
Duration of ONC201 therapy and overall survival: **A,** $N = 14$ PC-PG 5/14 were treated > 1 year, 4 continue ONC201. Patients without an arrow (5/14) died of tumor progression; 9/14 metastatic PC-PG remain alive. **B,** $N = 16$ other patients with neuroendocrine tumor: 2 patients with DSRCT were treated >1 year; 6/16 other patients with metastatic neuroendocrine tumor are currently alive; 10/16 died of tumor progression.

removed; 2 of 15 lymph nodes were positive. In 2019, the subject presented with a hypertensive crisis and large, extensive abdominal masses near the right kidney, porta hepatis, and retroperitoneum. The patient progressed on lanreotide and continued to require large amounts of antihypertensive medication. Once this patient with two cancers (PC-PG and MTC) started ONC201 weekly, blood pressure became stable. At 3 months, best response by RECIST was −10% (stable disease) with −29% decrease in chromogranin and −25% decrease in normetanepherine. After 1 year, the patient was rolled over to ONC201 arm C with day 1, day 2 weekly ONC201 schedule and had an additional −6% decrease in size of five indicator lesions at 3 months. KPS is 100% >24 months from ONC201 study entry.

The third case study is a 56-year-old with metastatic DSRCT diagnosed 5.5 years prior to ONC201 arm C entry (subject 1024; **Fig. 5**, bottom). He presented with numerous peritoneal and omental tumor nodules and liver metastases and had surgery + hyperthermic intraperitoneal chemotherapy with cisplatin, then systemic doxorubicin+ ifosfamide, then right hepatectomy as initial therapy. Intrahepatic ^{90}Y microspheres were given prior to removal of left side liver metastases and then he had a remission of 9 months. After relapse #1 vincristine +doxorubicin and Ifosfamide were given prior to resection of liver and peritoneal metastases. Adjuvant vincristine + temozolomide + irinotecan was given ×4 months. Remission lasted 1 year before relapse #2 in the liver and peritoneum. Ifosfamide/mesna, carboplatin, and etoposide were given ×4 cycles complicated by cytopenias. Surgery was performed with positive margins and was followed by whole abdominal radiation (1.5 Gy × 20 = 30 Gy with liver and kidney sparing to 20 Gy) + oral temozolomide. Pazopanib was administered 4 months then was discontinued because of gatsrointestinal side effects and fatigue. Doxorubicin liposomes was given at 40 mg/m^2 every 4–6 weeks ×1 year then stopped after with new metastases. On ONC201 best response by RECIST of indicator lesions was a 26% decrease in size at 9 months At 15 months, ONC201 was stopped because of new lung metastases.

Discussion

This exploratory open-label phase II study in rare neuroendocrine tumors was carried out over 4 years. Although SCLC is a neuroendocrine tumor, this group was not included in the study and varieties of indolent neuroendocrine tumors (e.g., carcinoid) were not included as per FDA guidance of this investigator-initiated IND clinical trial; patients with SCLC could be too sick and carcinoid clinical course too indolent to see differences. Patients with the greatest benefit in our study had metastatic PC-PG and DSRCT. Numbers of other neuroendocrine

tumors (e.g., MTC, ACC, cholangiocarcinoma, clear cell sarcoma) were too small to draw meaningful conclusions. Objective responses were observed and peaked 3–9 months after initiation of ONC201, possibly indicating evolution over time by repopulation of resistant clones and/or selection for more actively proliferating cancer cells.

The more intense arm C ONC201 dosing was well tolerated with some reduction in size of indicator lesions in almost all patients. Because no CRs were seen with either once weekly or twice weekly ONC201 schedules in our study, more effective ONC201 use in PC-PG and /or DSRCT could be accomplished with combination therapy or be viewed as an attractive adjuvant option or a useful agent to maintain performance status while having metastatic disease. A more precise estimate of response rates and duration may well require multi-institutional studies or study designs using patients as their own controls due to the rarity of neuroendocrine tumors and heterogeneity of this population.

Limitations of this study in rare cancers are several. First, the study has a small patient population spread across two cohorts including two different dosing strategies. Second, although it appears the more intense 2 consecutive days per week has an excellent safety profile, pharmacokinetic, and pharmacodynamic data comparing AUC in responding versus nonresponding patients on the more intense schedule could have provided insight on impact of getting 2-fold more ONC201 per week. Third, another limitation was lack of correlative studies on tissue to try to discern whether DRD2 antagonism, ClpP agonism or both contribute to responses. Although circulating cell-free DNA (cfDNA) was collected with the hope to provide analysis of minimal residual disease, as of yet we do not have means to analyze cfDNA of numerous different types of EWS-WT1 fusions or rare somatic mutations in addition to germline mutations in PCPG. The major clinical benefit of ONC201 in metastatic PC-PG appeared to be maintenance of performance status with development of few new metastases. Pattern of progression generally was tumor growth and not the development of new lesions, even in patients with large disease burdens. Patients with DSRCT had a much more variable clinical course. Patients with DSRCT with large disease burdens (e.g., too numerous to count visceral and osseous metastases) did not respond. Hence in DSRCT, ONC201 would be better utilized in an adjuvant setting after cytoreduction with chemotherapy and local control measures such as surgery and radiotherapy (29–34). Pazopanib, a tyrosine kinase inhibitor (TKI) with activity against VEGF, has been used for adjuvant therapy of DSRCT (35); ONC201 has preclinical synergy with VEGF inhibition (22). To date no studies of ONC201 with or without pazopanib or other TKI have been done. Another approach that has preclinical data is combining ONC201 with a TRAIL agonist, such as recombinant TRAIL, to convert an anti-proliferative response to ONC201 to an apoptotic response to ONC201 (36).

Patients with metastatic neuroendocrine tumors now have many systemic treatment options (1). These include not only FDA-approved chemotherapy options such as mTOR inhibitors such as everolimus and sunitinib (37–39), but also lanreotide (6, 40), radiopharmaceuticals 131-MIBG, and 177-Lu-DOTATATE (3, 41). Agents to possibly consider for future study could include checkpoint inhibitors (14) and ascorbic acid (42). RET mutations can be drivers in PC-PG, MTC, and other RET-associated cancers (43, 44). Although ONC201 has preclinical activity against MTC, we had a patient with MTC with stable disease at 3 months who elected to go off study to get the RET-selective agent selpercatinib. Another patient with MTC without RET had a minimal response and went off study to try something else. A MEN2 RET germline subject with both PC-PG + MTC and elevated plasma chromogranin, normetanephrines, and calcitonin received ONC201 >24 months with stable disease, KPS 100%, and no grade 1 toxicity. Recently there have been case reports of RET-associated PC-PG responding to selpercatinib (45). The author also has recently seen one additional case of a MEN2 patient with both PC-PG + MTC have both cancers respond to selpercatinib. Another new agent to consider for PC-PG combination therapy will be the hypoxia inducible factor inhibitor, belzutifan, which is FDA approved for von Hippel Lindau–associated renal carcinoma, hemangioblastoma, and other neuroendocrine tumors (46–48).

ONC201 was well tolerated in some subjects with metastatic neuroendocrine tumors for a very long time with no apparent cumulative toxicity. This may be related to relatively cancer-specific mechanisms of action (**Fig. 2**) and/or high therapeutic index. Whether ONC201 is best in class (imipridone) remains to be determined, as other imipridones are in development (16, 17, 49). What was learned in our study is that the engagement of targets by ONC201 seems to result in favorable responses with acceptable toxicity in PC-PG and some DSRCT. Best approaches and populations to define how to use this well-tolerated agent with activity against neuroendocrine tumors will require additional prospective clinical evaluation.

Authors' Disclosures

P.M. Anderson reports grants from Oncoceutics during the conduct of the study. M.M. Trucco reports grants and non-financial support from Oncoceutics during the conduct of the study. S. Thomas reports grants from Oncoceutics during the conduct of the study. V. Prabhu reports personal fees from Oncoceutics and Chimerix during the conduct of the study; in addition, V. Prabhu has a patent for Imipridones for gliomas (US10172862B2) issued and a patent for G protein-coupled receptor modulation by imipridones (US11116771B2) issued. J.E. Allen reports other support from Chimerix and Oncoceutics during the conduct of the study as well as other support from Chimerix and Oncoceutics outside the submitted work; in addition, J.E. Allen has a patent for ONC201 pending, issued, licensed, and with royalties paid from Chimerix/Oncoceutics. No disclosures were reported by the other authors.

Authors' Contributions

P.M. Anderson: Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing, IND132665 and principal investigator. **M.M. Trucco:** Investigation, writing–review and editing. **R.S. Tarapore:** Data curation, formal analysis, visualization, writing–original draft, writing–review and editing. **S. Zahler:** Investigation, writing–review and editing. **S. Thomas:** Investigation. **J. Gortz:** Data curation, investigation. **O. Mian:** Conceptualization, resources. **M. Stoignew:** Funding acquisition, methodology, project administration. **V. Prabhu:** Conceptualization, wrote on DRD2 as ONC201 target and included TCGA data in his CCR paper, which led to concept of a ONC201 trial in PC-PG. **S. Morrow:** Conceptualization, methodology, TCGA analysis (Fig. 1). **J.E. Allen:** Conceptualization, resources, supervision, methodology, writing–review and editing, after trial met initial goals, provided information to expand trial with addition of more intense schedule (arm C).

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