STUDY NUMBER: CASE 2716 IRB 17-808

Protocol Date: Amendment #5, November 30, 2020

Phase 2 Study of ONC201 in Neuroendocrine Tumors

PRINCIPAL INVESTIGATOR:
Peter M. Anderson MD, PhD
Pediatric Institute, Hematology/Oncology and Bone Marrow Transplant
[redacted]Cleveland Clinic, 9500 Euclid Ave, Cleveland OH 44195
Cell [redacted] direct 2[redacted]; FAX [redacted]

Co-investigators Cleveland Clinic 9500 Euclid Ave, Cleveland OH 44195

Matteo Trucco MD
Pediatric Oncology [redacted]

Stephanie Thomas MD
Pediatric Oncology [redacted]

Stacey Zahler DO
Pediatric Oncology, [redacted]

Omar Mian MD, PhD
Radiation Oncology, [redacted]

STATISTICIAN: [redacted]

RESEARCH NURSE COORDINATOR
[redacted]

[redacted]

INVESTIGATIONAL PHARMACY

[redacted]

[redacted]

SPONSOR: Case Comprehensive Cancer Center

SUPPORT/FUNDING: Sarcoma Research Fund and Oncoceutics

SUPPLIED AGENT ONC201

IND #: [redacted]

SUMMARY OF CHANGES

Protocol Date	Section	Change
1-15-17	1.2.2	Weekly dosing safety experience updated as per FDA request
	4.1.1	Cohort B inclusion criteria defined as per FDA guidance
	11.2	Study calendar virtual visits for responding patients updated as per FDA
10-11-17	Face page	Change of study personnel
	Summary p6	IRB-17-808 information added; also age 14 and higher
	Table of contents	8.5 RedCap Cloud is database
	1.22	Table 1 is from Jan 2017 (legend) Pediatric experience added
	2.3	bombesin omitted form exploratory objective (SCLC not on this trial)
	4.1.3	Age 14 years and older – same as summary p6
	4.1.7	Performance scale Karnofsky if 16 or older, Lansky if <16
	Page 22	Figure 6 legend updated
	Table 2	Anti-hypertensive instructions to reflect those with normal bp being blocked prior to ONC201 and formulary change of metoprolol preferred to atenolol at Cleveland Clinic
	6.4	Correction # weekly ONC201 doses in 1year is 52
	8.5	IND compliant Data base is REDCap Cloud
	9.0	Parameters of bp to make it easier and more research-subject friendly on the Clinical Research Unit (+/- min or hours for time points instead of exact times)
	11.1	Screening can be done 4 weeks before starting- reflects reality of delays in scheduling CRU and not needing to repeat scans
	Table 5	Omit markers of SCLC since not in this trial; More accurate description of PK/PD ad prolactin time points possible to do in our clinic
	13.0	REDCap Cloud is the database
	14.0	Correction on times being analyzed
	Appendix 1	For PC-PG subjects normotensive on low dose alpha and beta blockade a more realistic MAP
09/13/2018	Footer	Updated version date of protocol
	Staff	Updated staff to reflect current study team
	Study Schema	Removed Study Schema from page 5
		Removed “for a maximum of 1 year (52 doses).” from interventions

Protocol Date	Section	Change
	1.2.2	Added language of additional pediatric experience on this protocol
	2.2.2	Changed method of capturing overall survival
	3.0	Changed study time points to reflect additional treatment past one year
	3.4	Removed 1 year endpoint
	4.0	Added language that allows for an administrative memo to waive inclusion/exclusion of potential patients on a case by case basis. Must be approved by the PI and IRB before treatment can begin
	5.0	RedCap Cloud was named as the IND compliant database being utilized
	6.1	Language added to allow therapy after 1 year
	6.2	Language removed to allow therapy beyond 1 year
	6.4	Language removed to allow therapy beyond 1 year
	6.5	Language changed to reflect new follow-up protocol
	7.0	Language added to mention additional study visits.
	9.0	Changed language in subsequent doses section to allow for additional therapy beyond 1 year and to remove language regarding virtual visits
	10.1.3	Updated PD timing
	11.2	Study calendar revised to allow for therapy beyond 1 year, to remove the virtual visit language and update PD timing.
	Table 8	Updated PD timing
6/10/2020	Face Page	Change of study personnel; address, and phone numbers updates; funding updated
	footer	Updated to 6/1/2020 version
	summary	Brief background/Rationale: Safety paragraph updated to include weekly d1d2 dosing Primary objective: RANO eliminated (no brain tumors on this study)
	summary	Secondary objective: deleted anti-hypertensive medication objective
	summary	Exploratory objective: deleted prolactin and PK
	summary	updated to include an additional 12 patients with d1d2 weekly dosing
	summary	Interventions updated ONC201 dosing on 2 consecutive days weekly
	1.2	Aes and ¼ 2017 typos corrected to AEs and 1/4/2017
	1.2	Weekly dosing section updated to include total of N=25
	1.3	Revised to update current experience in CASE2716 (instead of ongoing other trials in 2017) and summary provided in table 2.
	1.3	ONC201 in Neuroendocrine Tumors at Cleveland Clinic (6/2020): paragraphs and table 3 inserted to summarize experience until 6/2020
	1.4	table numbers revised to tables 4 and 5.

Protocol Date	Section	Change
6/10/2020	1.5	Sentences about possible anti-hypertension effect deleted
	1.5	Secondary objectives revised tocorrespond to protocol summary
	1.5	updated to reflect deletion of table 4 section 6.3
	2.1	Primary objective: update of language to reflect reality of imaging current image scheduling and review with patients is not as easy as in pre-COVID-19 for a variety of reasons including travel, prior authorization and then 2nd read of scans if imaging must be done closer to patient's home by their primary oncologist.
	2.21	RANO deleted
	2.22	Anti-hypertension medication objective deleted [good clinical care for PC-PG patients no longer requires a bp log if well controlled and/or use of a wireless bp cuff that imports data into EPIC via MyChart]
	2.3	biomarker analysis will be only clinically relevant blood tests (as in protocol summary)
	3.0	updated to reflect next 12 patients will have day1day2 weekly dosing of ONC201; Flat dosing of 625mg orally on 2 consecutive days will be used
	3.1	Revised to more inclusive neuroendocrine tumor cohort C
	3.2	Number of subjects amended to an additional 12
	4.1.1	Inclusion criteria for neuroendocrine tumors more specific
	4.2.4	dopamine interaction medication list deleted; others renumbered
	5.0	Addition of research nurse acknowledged
	6.1	amended and simplified for d1d2 weekly dosing. The figure with once weekly dosing is deleted
	6.2	amended to reflect day1d2 schedule and simplified including deletion of CRU admission
	6.3.1	Palliative radiotherapy (e.g. painful non-target bone metastases) allowed at week 6 instead of 12
	6.3.2	RFA changed to thermal ablatio so included cryoablation
	6.3.3	Language inserted to allow drugs for symptom control
	7.0	2x/week schedule is inserted and bolded as follows: **ONC201 (625 mg po) will be administered Day1, Day 2 weekly (start of week +/- 1 day)**
	7.0	Evaluation window specified during COVID-19 pandemic
	8.0	updated according to Investigators Brochure (version 6 11-2019) and IRB 17-808 consent form with inclusion of a revised table 5
	8.4.1	Staff for SAE reporting updated to Research Nurse
	9.0	drug information is amended to reflect d1d2 weekly schedule and permission by sponsor to send ONC201 supplies via express courier with tracking information directly drug to patients.

Protocol Date	Section	Change
6/10/2020	10.0	Prolactin markers and PK /PD have been deleted
	11.1.1	Prolactin deleted
	11.1.2	treatment period labs and imaging windows have been updated
	11.1.2	Since studying d1d2 weekly dosing is a major focus protocol states " Weekly ONC201 study drug dosing +/- 1 day."
	11.1.2	Study calendar: Table 5 renumbered to Table 6; footnotes updated to reflect protocol summary
	12.0	Section on ability to reduce anti-hypertension medication deleted including table 6 in prior version
	12.0	Weeks used instead of dose# used to be consistent with d1d2 weekly schedule
	12.0	References to RANO deleted (no CNS tumors on this study)
	13.0	"An IND compliant database (REDCap) similar to other Oncoceutics ONC201 trials also be used" is now specified
	13.2.1	Written Informed Consent: text inserted to facilitate virtual visits offering timely and more complete discussion of indications, risks, and alternatives before obtaining written informed consent signatures during COVID-19 pandemic. Written informed consent is still required.
	14.0	Paragraph 1 updated to include current age (14) and cohort C as having 2x drug exposure as cohort A+B.
	14.0	RANO text deleted
	14.0	DSRCT and SCLC language deleted concerning subset analysis
	14.0	Statistics Paragraphs revised and updated because (cohorts A+B) met primary endpoints- with reference to table 3, efficacy language for cohort C inserted
	14.0	Hypertension evaluation and analysis deleted
	14.0	paragraph on type 1 and II errors deleted [Since study met endpoints using cohorts A+B]
	14.0	paragraph about effect on hypertension deleted
	14.0	Paragraph on potential catecholamine release and hypertension deleted
	14.0	exploratory objective modified to be consistent with protocol summary
	14.0	Prolactin deleted
	15.0	Appendix section deleted
	16.0	Renumbered to 15.0 References
11/30/2020	8.0	Updated Adverse Events

PROTOCOL SUMMARY

Protocol Number/Title	CASE2716 IRB 17-808 Phase 2 Study of ONC201 in Neuroendocrine Tumors
Study Phase	Phase 2
Brief Background/Rationale	ONC201 is a first-in-class oral drug that was discovered in a phenotypic screen for p53-independent inducers of tumor-selective pro-apoptotic pathways. ONC201 has highly specific binding to a member of the dopamine receptor family of G-coupled protein receptors, DRD2. According to the TCGA database pheochromocytoma-paraganglioma (PC-PG) tumors have been shown to overexpress DRD2 far more than any other cancer. Other neuroendocrine tumors also likely have high DRD2 expression. Because PC-PG have abundant DRD2 receptors and DRD2 inhibition imparts anti-tumor efficacy without killing normal cells via induction of ATF4/CHOP and dual inhibition of Akt and ERK signaling, a phase 2 study of ONC201 in PC-PG and other neuroendocrine tumors will determine whether inhibition of DRD2 is effective in neuroendocrine cancers including PC-PG. ONC201 has demonstrated a favorable safety profile in 24 patients with neuroendocrine tumors. New data shows a dosing on 2 consecutive days per week is safe in other varieties of cancer. This study will collect safety and efficacy data using this schedule.
Primary Objective	Primary Endpoints: PC-PG: To demonstrate objective responses using MRI, CT, PET-CT and/or PET-MRI imaging using RECIST changes in ^{18}FDG uptake
Secondary Objectives	All patients: Determine progression-free survival and overall survival. To document incidence and severity of adverse events that are drug-related.
Exploratory Objective(s)	To determine time course of ONC201 efficacy in PC-PG and other neuroendocrine tumors by measurement blood biomarkers as clinically indicated (for example in PC-PG normetanepherine, metanepherines, and chromogranin A).
Correlative Objective(s)	Correlative Endpoint: Blood samples will be stored for future analysis of ONC201 biomarkers. Samples will be obtained before treatment and at 6 weeks and 3 months.
Sample Size	N=36 (12 PC-PG and 12 other neuroendocrine cancers; an additional 12 patients with d1d2 weekly schedule). Age 14 and older; genders: both; both cohorts to start at same time
Disease sites/Conditions	Recurrent or metastatic neuroendocrine tumors including PC-PG
Interventions	ONC201 625 mg po on 2 consecutive days weekly (N=12)

ABBREVIATIONS

AYA	Adolescents and Young Adults
AE	Adverse Event
CCCC	Case Comprehensive Cancer Center
CCF	Cleveland Clinic Foundation
ccfBio	Biomarker tests done at Cleveland Clinic
ccfDNA	Circulating cell-free DNA
ccfRNA	Circulating cell-free RNA
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
DR4	Death receptor 4 (TRAIL-R1)
DR5	Death receptor 5 (TRAIL-R2)
DRD2	Dopamine-like receptor D2
DSTC	Data Safety and Toxicity Committee
FADD	FAS-associated death domain
FDA	Food and Drug Administration
FDG	18-fluro-deoxy-glucose
GLP	Good Laboratory Practices
ICF	Informed Consent Form
IRB	Institutional Review Board
MR	Mixed Response
MRI	Magnetic Resonance Imaging
MTD	Maximally Tolerated Dose
NCI	National Cancer Institute
ONC201	TC10;7-benzyl-4-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one•2HCl : MW 459
PET	Positron Emission Tomography
PR	Partial Response
PRMC	Protocol Review and Monitoring Committee
RECIST	Response evaluation criteria in solid tumors
RFA	Radiofrequency Ablation
RP2D	Recommended Phase 2 dose
SAE	Serious Adverse Event
SD	Stable Disease
SOC	Standard of Care
TRAIL	Tumor necrosis factor-related apoptosis inducing ligand
TC10	TRAIL inducing compound 10 (ONC201)

TABLE OF CONTENTS

1.0 INTRODUCTION
1.1 Background of neuroendocrine tumors including pheochromocytoma- paraganglioma (PC-PG)
1.2 Name/description of ONC201
1.3 Experience with ONC201 in Neuroendocrine Tumors: (as of June 2020)
1.4 Symptom control in neuroendocrine tumors including PC-PG
1.5 Rationale: TCGA DRD2 data
1.6 Background and rationale of exploratory studies

2.0 OBJECTIVES
2.1 Primary objective: efficacy by imaging
2.2 Secondary objectives: safety + efficacy trends using blood pressure
2.3 Exploratory objective: biomarker trends
2.4 Correlative objective: banking of plasma

3.0 STUDY DESIGN
3.1 Phase 2 study design
3.2 Number of subjects
3.3 Replacement of subjects
3.4 Expected duration of treatment and subject participation

4.0 SUBJECT SELECTION
4.1 Inclusion criteria
4.2 Exclusion criteria
4.3 Inclusion of women and minorities

5.0 REGISTRATION

6.0 TREATMENT PLAN
6.1 Treatment regimen overview
Pre-treatment alpha then beta blockade
6.2 General concomitant medications and supportive care guidelines
6.3 Other therapy allowed while on study
6.4 Criteria for removal from study
6.5 Duration of follow-up

7.0 DOSE DELAYS / DOSE MODIFICATIONS

8.0 ADVERSE EVENTS AND POTENTIAL RISKS
8.1 ONC201 adverse events
8.2 Definitions
8.3 Serious adverse event report form
8.4 Reporting procedures for serious adverse event
8.5 Serious adverse events and OnCore™ and other data base (RedCap Cloud)

8.6 Data Safety Toxicity Committee
8.7 Data and Safety Monitoring Plan

9.0 PHARMACEUTICAL INFORMATION
9.1 Investigational agent(s)
9.2 Commercial agent(s)

10.0 EXPLORATORY/CORRELATIVE
10.1 Exploratory: biomarkers
10.2 Correlative study: banking of plasma

11.0 STUDY PARAMETERS AND CALENDAR
11.1 Study parameters
11.2 Calendar

12.0 MEASUREMENT OF EFFECT

13.0 RECORDS TO BE KEPT/REGULATORY CONSIDERATIONS
13.1 Data reporting
13.2 Regulatory considerations

14.0 STATISTICAL CONSIDERATIONS

15.0 REFERENCES

1.0 Introduction

1.1 Background of pheochromocytoma-paraganglioma (PC-PG)

PC-PG are rare neuroendocrine tumors characterized by neuroendocrine features. Over 50% of patients have either a germline or somatic susceptibility mutation [1-4]. TCA enzyme mutations (e.g. SDHx, FH, and MDH2) are associated with pseudohypoxia and activation of hypoxia inducible signaling pathways involved in transformation, invasiveness, and metastatic potential [5, 6]. Additional germline and somatic mutations have been observed in patients with PC-PG including VHL, EPAS1, RET, NF1, TEMEM127, MAX, H-RAS, HIF 2 alpha, ATRX, PHD1 and PHD2 [1, 7-12] .

Catecholamine production (e.g. normetanepherine, metanepherinine, methoxytyramine [13]), neuroendocrine markers (chromogranin A, synaptophysin), and very high glucose uptake on ^{18}FDG-PET imaging studies [14-17] are common in PC-PG and other neuroendocrine tumors. However, about 10% of PC-PG patients can be "biochemically silent" [6, 15, 18, 19] . About half of therapy-naïve newly diagnosed PC-PG patients will experience progression within 1 year [20]. Despite appearance of metastases, PC-PG can be a chronic and indolent metastatic cancer associated with good performance and excellent quality of life. Nevertheless, many patients require chronic life-long anti-hypertensives to control side-effects of catecholamine excess and about 30% of PC-PG patients had died in the largest series reported to date which involved 132 patients (27 children and 105 adults) seen at NIH in 2000-2014 [6]. Recently the Uppsala group demonstrated that considerable genetic heterogeneity can also exist within and between PC-PG tumor lesions of the same patient [7]. Treatment options for PC-PG patients with metastases remain limited and include local control with surgery, radiofrequency ablation [21], radiotherapy [22], and relatively ineffective chemotherapy regimens which may include VEGF inhibitors [18, 23]. ^{131}I-MIBG (iobenguane I-131, Azedra), a high specific activity beta-emitter that binds dopamine receptors, is being tested to ameliorate hypertension in patients 12 years old and older with PC-PC [24]. The primary endpoint of this clinical trial is reduction of hypertension medications by 50% in 25% of subjects.

1.2 Name and Description of Investigational Agent: ONC201

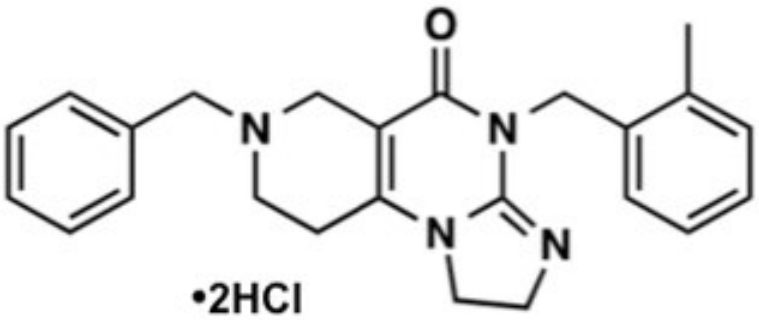


Figure 1 ONC 201

Chemical name: 7-benzyl-4-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo [1,2-a] pyrido [3,4-e]pyrimidine 5(4H) –one.2HCl .(benzyl-benzylmethy-imipridone); MW 459

1.2.1 Preclinical Data: ONC201

Abnormal energy metabolism towards glycolysis, the Warburg effect, [5, 14-17, 25-29] and signals including Akt and ERK contribute towards proliferative, pro-survival, and anti-apoptosis phenotypes of cancer cells including PC-PG [30-39]. Another cancer–specific inhibitor is TNF-related apoptosis inducer ligand (TRAIL) which facilitates tumor-specific suppression in DR4/DR5 death receptor bearing cells [30, 31, 35, 40-80]. TRAIL binds DR4/5 death receptors on cancer cells to cause apoptosis but not in normal cells due to multiple redundant pathways in non-neoplastic tissue [76]. ONC201 was discovered during a screen of over 2000 compounds for activity that would promote apoptosis in cancer cells in a p53 independent manner [30]. This TRAIL + DR5 inducing small molecule was active against hematologic malignancies including lymphoma [81-83], glioblastoma [84], and solid tumors including hepatocellular carcinoma xenografts, chemotherapy–resistant colorectal stem-like cells, and stem cells of desmoplastic small round cell tumor [35, 43, 85, 86].

Experimental profiling predicted ONC201 has specific binding to DRD2, DRD3; weak DRD4, but not to DRD1 or DRD5[87, 88]. The ratio of DRD2/3/4 versus DRD1/DRD5 seems important in the malignant cell proliferation [89] and induction of anti-tumor effects via dopamine receptors [88] [87, 88, 90-92]. In summary, ONC201 is associated with TRAIL induction, an integrated stress response, and apoptosis in hematologic malignancies and solid tumors [30, 35, 41-43, 55, 61, 77, 82-84, 87, 88, 93-95]; (fig 2). Hundreds of cell lines have been tested against ONC201. So far lymphomas and neuroblastomas are among are the most responsive [55, 82]. Of all tumors tested for DRD2 in TCGA, pheochromocytoma-paraganglioma (PC-PG) has the very highest expression (fig. 3)[87]. A possible common theme cancer would be predicted to have DRD2 is neural and neuroendocrine biomarkers as detected by CD56 (neural cell adhesion molecule), chromogranin, and synaptophysin[96, 97], or dopaminergic metabolites such as norepinephrine, metanepherines, vanillylmandelic acid (VMA), or homovanillylmandelic acid (HVA).

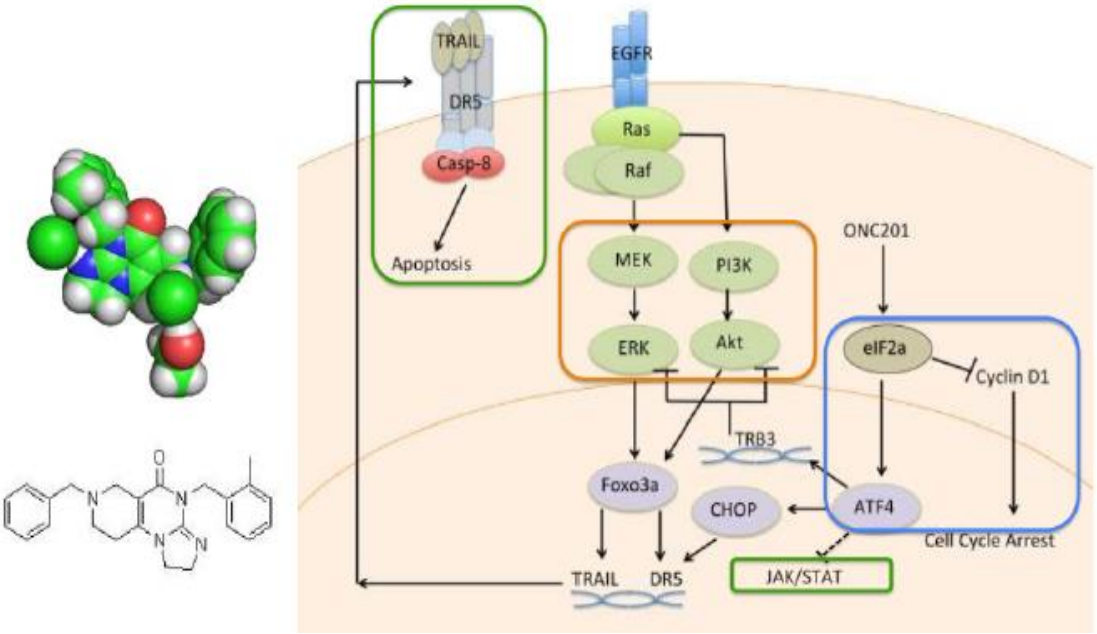


Figure 2. ONC201 is a first-in class small molecule that imparts anti-tumor effects via ATF4>CHOP[81], dual inhibition of Akt and ERK signaling, and subsequent TRAIL induction to induce an integrated stress response[85] and apoptosis [93]. Stereospecific ONC201 binding occurs via the G-coupled protein receptor (GPCR), dopamine-like DRD2 receptor[87].

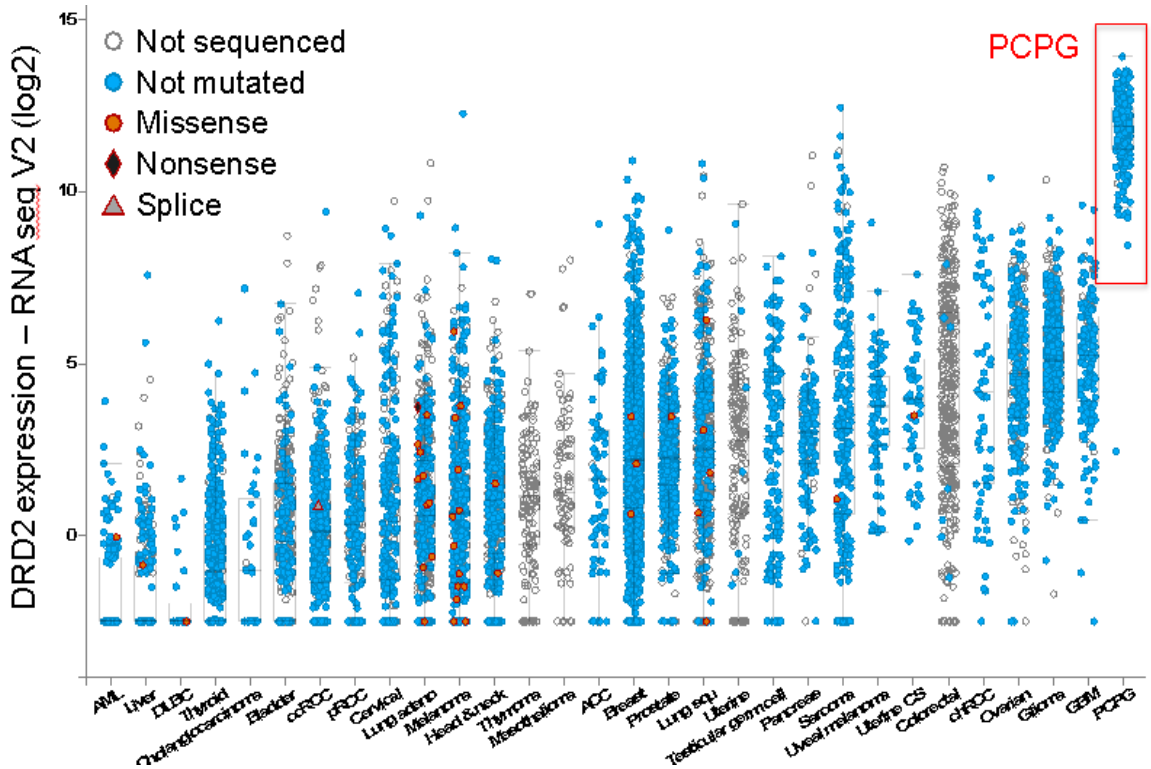


Figure 3. Tumor Expression of DRD2 in TCGA. PC-PG tumors (red bar) have the highest amounts of DRD2 RNA. Also DRD2 receptors were not mutated in PC-PG

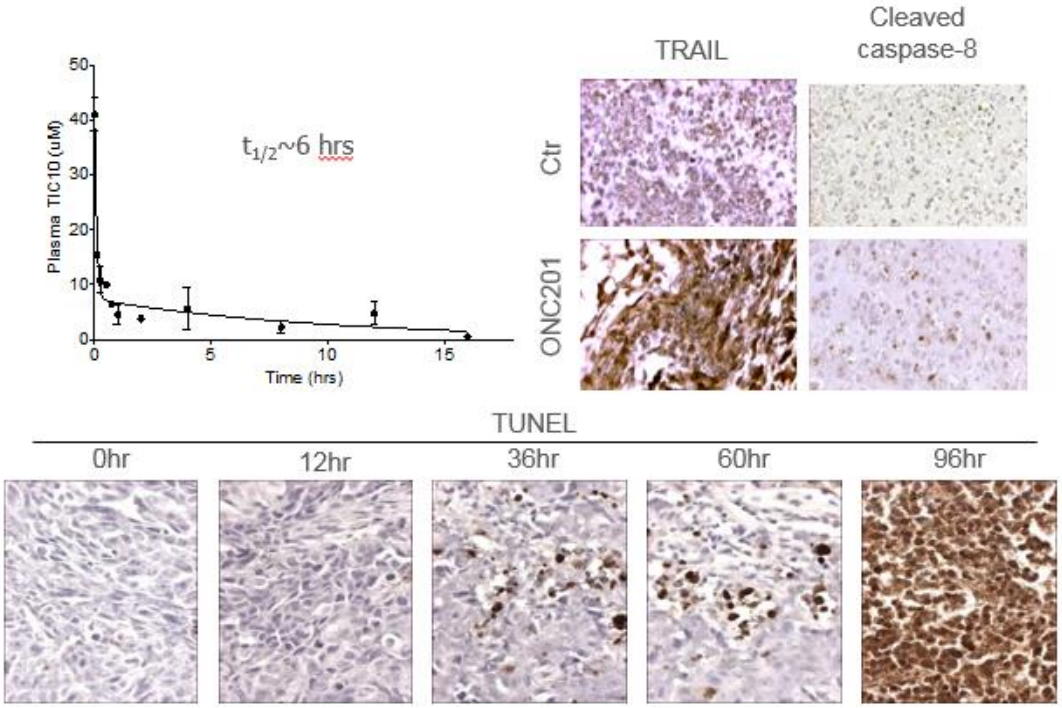


Figure 4. Preclinical ONC201 pharmacokinetics and pharmacodynamics. ONC201 is eliminated from plasma, followed by a delayed and sustained activation of TRAIL and apoptotic cell death of tumor cells (cleaved caspase-8). Data courtesy of Oncoceutics.

Drugs or drug combinations that possess an oncology efficacy profile similar to ONC201 (dual PI3K>Akt *and* Ras>Raf>MEK1/2>.ERK pathway inhibition) are typically very toxic. Nevertheless, the initial safety profile of ONC201 was favorable. Exaggerated dosing in rodents and dogs revealed that ONC201 acute toxicity occurred only at substantially higher than therapeutic doses.

Even at the highest doses tested, the drug did not achieve a maximum tolerated dose (MTD) with oral administration in good laboratory practices GLP studies [98].

1.2.2 Clinical Data

Very few drug-related side effects have been observed with ONC201 in humans [93]. AE were few, there were no AEs greater than grade 1, and a MTD was not reached in the first-in-human phase I trial. Based on preclinical studies [98] and this trial, the recommended phase 2 dose level and schedule of ONC201 in adults is 625 mg (5 tablets) weekly. With this schedule caspase-cleaved cytokeratin-18, a mark of apoptosis, was detected in ONC201-treated patients, which has been shown to correlate with responses against cancer [99-101].

Patients Treated With Weekly Dosing

As of January 4, 2017, a total of 31 cancer patients with various malignancies in late stages and refractory to standard therapies, have been enrolled in 4 independent investigator-initiated clinical trials, and received oral ONC201 on a weekly schedule at various doses up to 625 mg, as summarized in Table 1 below. Individual patients have received up to 21 weekly doses of ONC201.

Table 1. Number of Patients Who Received ONC201 Weekly By Dose and Site (01-2017)

Site	Cancer Institute of New Jersey (CINJ)	Fox Chase Cancer Center (FCCC)	MD Anderson Cancer Center (MDACC)	MD Anderson Cancer Center (MDACC)	**Total Patients**
Tumor Type	Prostate, Endometrial, Colon, GBM	All-comers solid	Non-Hodgkin's Lymphoma	Acute Leukemias	
Clinical Trial #	NCT02324621	NCT02609230	NCT02420795	NCT02392572	
125mg			2	1	**3**
250mg		4*		1	**5**
375mg	3	4 (2 on study)		1	**8**
500mg				2 (on study)	**2**
625mg	12** (3 on study)		1		**13**
Total Patients	**15**	**8**	**3**	**5**	**31**

*Included is one patient was replaced after the first dose of ONC201 due to progressive disease
**Included is one patient was replaced after the first dose of ONC201 due to non-compliance.

Currently, all clinical studies utilizing weekly dosing are being conducted under investigator-initiated INDs; thus, data entry and reporting are being performed under the supervision of the

individual site Investigators. Data reported here represent interim information as provided to Oncoceutics from the individual sites1/4/ 2017. Seven patients remain active in the 4 trials, and these studies continue to accrue patients. Thus, this information does not represent a final clinical database.

Overall ONC201 Safety Experience
In accordance with research agreements, reports of adverse events (AEs) are provided by the investigators to Oncoceutics as requested on a periodic basis, with reports of serious adverse events (SAEs) provided within specified timeframes.

At Cleveland Clinic as of June 2020 a total 25 patients have been treated with weekly ONC201 dosing including N=23 on CASE 2716 (IRB17-808;IND 1[redacted]) and 2 additional patients using single patient IND. To-date, there have been no deaths attributed to study drug. There have been no SAEs assessed by the Investigator as "probably" or "definitely" related to study drug, and no discontinuation of ONC201 due to toxicity has been reported.

Assessing adverse reactions in cancer patients can be challenging relative to underlying disease. Thus far, the most common AEs reported as possibly related to ONC201 were mild/moderate nausea, vomiting, anorexia and fatigue, which are not uncommon in advanced cancer patients.

Safety Experience from Every Three Week ONC201 Dosing
Available clinical safety information from a dosing schedule administering ONC201 every 3 weeks (q3wk) is summarized in the Investigator's Brochure. In brief, data are available from 29 patients treated at CINJ and 17 patients at MGH and DFCI (total of 46 patients). Note that these patients are in addition to the 31 patients described above in the weekly dosing section. Forty-one of these 46 patients received 625 mg doses of ONC201 every 3 weeks and establish a benign safety profile of the study drug. Other than one instance of Grade 3 neutropenia that was attributed as possibly drug related, none of these patients experienced a possibly or probably related >Grade 2 AE.

One report of a non-serious Grade 2 allergic reaction that was probably related to study drug occurred. Two patients with GBM remain on study medication after 14 doses of 625 mg of ONC201, including one patient who continues to exhibit a partial response.

Safety Experience from Weekly ONC201 Dosing
Similar to every 3 week dosing, weekly oral doses of ONC201 ranging from 125 mg to 625 mg have been generally safe and well-tolerated.

Below is a summary of safety information reported to Oncoceutics for each trial where patients have received weekly dosing of ONC201.

Cancer Institute of New Jersey (solid tumor trial)
Database information on AEs from patients receiving weekly dosing is not currently available. No SAE reports have been received to-date.

375mg: 3 patients dosed. Median 21 doses (Range: 18-29 doses).

625mg: 12 patients dosed. Median 11.5 doses (Range 1-21 doses). 3 patients have received 21 doses and are still on protocol.

MD Anderson Cancer Center (NHL trial)

A total of 3 patients have been dosed with ONC201 weekly. No Aes >Grade 2 were attributed as possibly, probably or definitely related to study drug. SAE reports are summarized in the table below, with no SAE attributed to ONC201.

125mg: 2 patients (#5 and #7) dosed. Median 7.5 doses (13 & 2 doses, respectively).

625mg: 1 patient (#9) dosed (5 doses).

Patient #	Patient Description	Dose Level/Schedule	SAE	Grade	PI Attribution To Study Drug
9	57 yr. female	625mg/weekly	Edema – limbs	5	Unlikely Related

MD Anderson Cancer Center (acute leukemia trial)

A total of 5 patients have been dosed with ONC201 weekly, in a dose escalation design ranging from 125mg (1 patient – 7 doses), 250mg (1 patient – 8 doses), 375mg (1 patient – 6 doses) to 500mg (2 patients – 7 and 3 doses, respectively), with the 2 patients receiving 500mg weekly doses of ONC201 remaining on study. No SAEs or Aes of any grade have been reported to Oncoceutics as possibly, probably, or definitely related to study drug.

Fox Chase Cancer Center (solid tumors)

Eight patients with various advanced solid tumors have received ONC201 weekly, ranging from 250mg to 375mg. No SAEs were reported to Oncoceutics as probably or definitely related to study drug. No Aes >Grade 2 were attributed as possibly, probably or definitely related to study drug.

250mg: 4 patients. Median 3 doses (Range: 1-6). SAE reports received are summarized in the table below, with no SAE currently attributed to ONC201.

375mg: 4 patients. Median 3 doses (Range: 2-5). Two patients remain on protocol treatment. No SAEs reported as of January 4th, 2017

Patient #	Patient Description	Dose Level/Schedule	SAE	Grade	PI Attribution To Study Drug
11	36 yr. male	250mg/weekly	Hemorrhage	5	No causality established, currently under review
13	67 yr. female	250mg/weekly	Stroke	4	Unlikely related

Additional evidence the DRD2 engagement by ONC201 was shown by dopamine agonist effects in this early clinical trial: 10/11 patients showed 2-fold induction of prolactin [87].

Pediatric Experience

As of September 8, 2017, 6 pediatric patients from age 3-17 have been treated with ONC201 under compassionate use protocols. No treatment-related adverse events have been reported by investigators to Oncoceutics. Three patients have progressed and 3 patients remain on therapy. One patient, a 26kg 8 year old male who received 375mg ONC201 q1w PO, had limited PK sampling with 9uM plasma concentration of ONC201 at 2 hours following the first dose (approximate Tmax). This result is consistent with the adult PK experience. One Patient was enrolled on this protocol at the age of 17 and has most recently completed the Month 6 study visit at the time of this protocol amendment. Brain tumor patients <18 years old have also been treated (as per Oncoceutics at Society of Neuro-Oncology June 2018) with low toxicity and potential efficacy against K27M midline gliomas.

1.2.3 Clinical Pharmacokinetics

In the first-in human clinical trial, the blood ONC201 level was ~0.1ug/ml at 48 hr. Cmax occurred at an average of 1.8 hr.; half-life was 9.6 hr (SD1.8) hours. ONC201 AUC was 26.3 (SD10.8) h.mg/mL which is consistent with a large distributive volume [93]. ONC201 appeared to saturate absorption at 375mg; drug was detected at approximately 48 hr and none in 7 days (figure 5). There was no evidence of ONC-201 accumulation. Table 1 summarizes ONC201 PK parameters at the recommended phase 2 dose (RP2D) of 625 mg po. Although ONC201 has rapid oral absorption, a large volume of distribution, and detection at 48 hr, anti-cancer activity is associated with TRAIL production beyond 48 hours that is sustained for up to 3 weeks and associated with apoptosis in the M30 assay at 3 weeks [93].

Table 2. ONC201 PK at Recommended Weekly Phase 2 Dose (RP2D; N=6)

Parameter (units)	C_{max} ng/mL	T_{max} hours	AUC_{last} h.ng/mL	$t_{1/2}$ hours	AUC h.ng/mL	V_z/F Liters	CL/F L/hour
Mean	3312	1.8	25515	9.6	26344	381	27.2
SD	2133	1.3	10677	1.8	10763	164	11.0

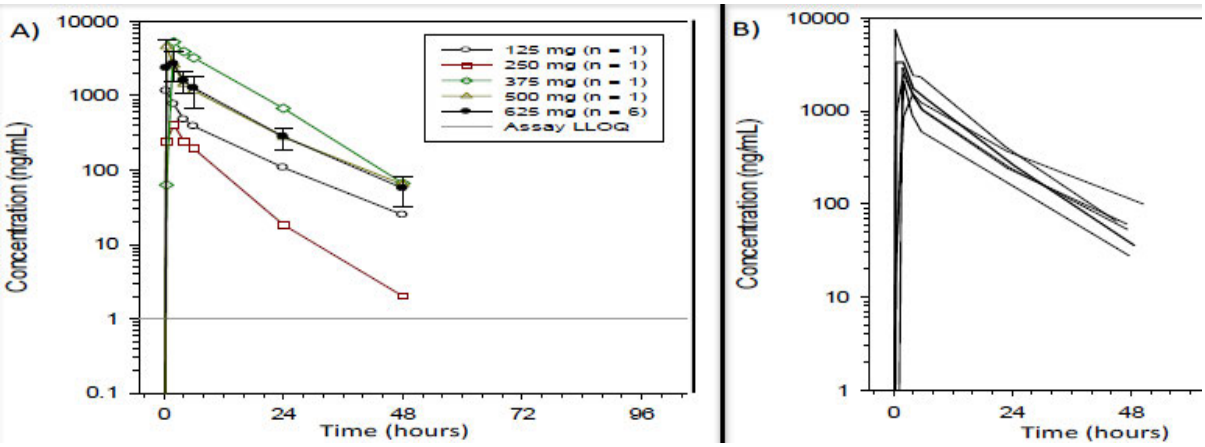


Figure 5. Weekly ONC201 PK for 375, 500 and 625 mg. ref[93] Above-625 mg (N=6)

Twice per week (day 1 and day 2) ONC201 Dosing

PK analysis was performed on twice a week dosing (day 1 and 2) plasma samples from a phase I/II study of oral ONC201 in adult patients with relapsed or refractory acute leukemias and high-risk myelodysplastic syndromes (NCT02392572). Oral doses of ONC201 were given at 125, 250, 375, 500mg and 625mg, 2 days on and 5 days off regimen each week (e.g. Monday and Tuesday of each week). The analysis revealed that 625mg dosed on a 2-day consecutive dosing schedule led to prolonged exposure at concentrations that exceed therapeutic thresholds of ONC201 relative to other dose levels. The 625mg dose resulted in peak plasma levels of ~8,000ng/mL on the day 2 dose and maintained plasma concentrations that exceeded the therapeutic threshold (3uM, 1000ng/ml) for over 72h, whereas lower dose levels on the 2 days on and 5 days off regimen each week schedule hit a maximum plasma concentration of ~4,500ng/mL but fell below the therapeutic threshold by ~30 hours after the first dose (Figure 6).

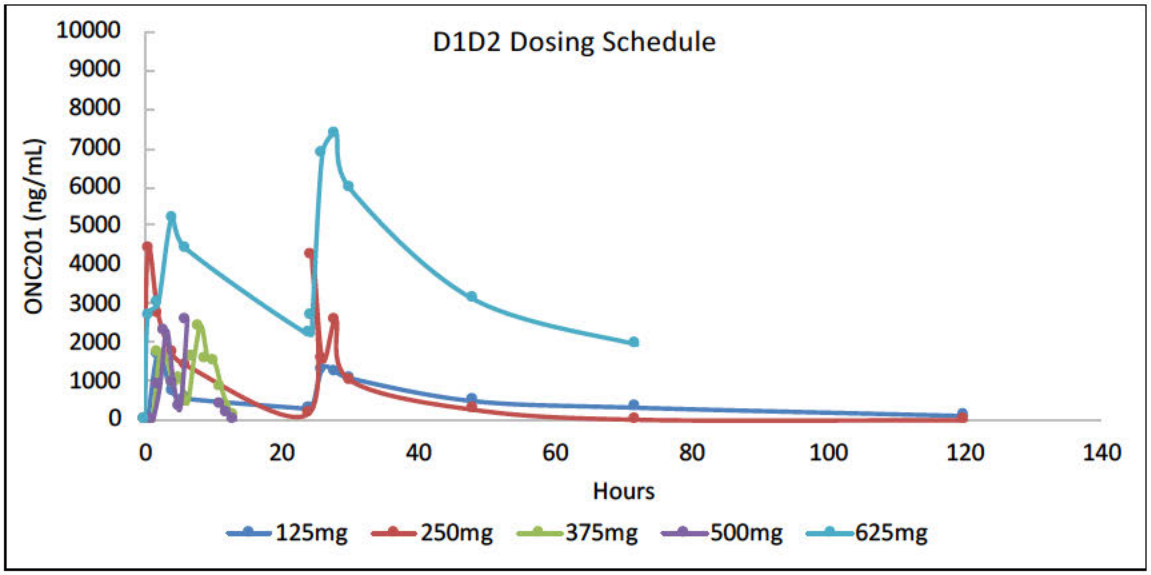


Figure 6. Plasma concentrations of ONC201 from individual patients (refractory acute leukemias and high-risk myelodysplastic syndromes) taking 2 doses on 2 consecutive days. One patient at each dose level (125, 250, 375, 500 and 625 mg). Hour 0 is the baseline right before taking the dose. Blood samples for 375 and 500 mg were only available for day 1.

1.3 Experience with ONC201 in Neuroendocrine Tumors at Cleveland Clinic: (6/2020)

ONC201 dose was 625 mg po/wk. Metastatic PG-PG were enrolled in cohort A. Other neuroendocrine patients were entered in cohort B. Two additional patients had single patient IND. Because hypertension is an issue from catecholamine producing PC-PG, all PC-PG patients had combined alpha + beta blockade and bp was monitored in the clinical research unit after dose #1 ONC201. Additional data was obtained with daily home bp monitoring, often with a wireless cuff which connects into EPIC via MyChart. Labs, scans, and clinic visits were done at week 6, then every 3 months from initial ONC201 dose. Patients with clinical benefit remained on study and could get radiation for bone metastases.

Neuroendocrine tumors were treated with ONC201 included 10 PC-PG, 3 with MTC 13 with other varieties including sarcomas, adrenal cortical carcinoma (ACC), neuroblastoma, and GI

neuroendocrine tumor (NET). ONC201 was exceptionally well tolerated. All patients were able to maintain or improve KPS while on study. No adverse effects on bp were seen including worse hypertension. The only ONC201-related AE was temporary grade 1 neurocognitive dysfunction (N=1) for ~36 hours after weekly ONC201 dosing in 1/10 PC-PG patients and one NET patient had grade 1 fatigue for 2 days after ONC201 but improved GI symptoms (less frequent diarrhea since starting ONC201). PC-PG patients had the most clinical benefit; 4/10 PC-PG patients remain on study at 32, 26, 28, and 8 months with stable or improved KPS. A DSRCT patient achieved a PR at 3 months and has been treated 32 months and continues to have KPS=100%. An ACC patient was initially responsive (PR), but rapidly progressed in liver A patient with high tumor burden of GI NET patient had -10% reduction by RECIST at 3 months and remains on treatment>6 months with improved KPS (80%). MTC may be responsive (1 no response, 2 stable and slightly improved by RECIST at 6 months).

ONC201 given as weekly dosing has been very well tolerated with excellent quality of life and extended clinical benefit against some neuroendocrine tumors. Although ONC201 has some activity against neuroendocrine tumors, especially PC-PG, increased efficacy may be possible with weekly day 1 day 2 dosing.

Table 3. Experience with ONC201 in Neuroendocrine Tumors at Cleveland Clinic

Neuroendocrine tumor types	N	Progression at 3 months	Treatment >3 months	Time on Study >24 months
PC-PG, MTC, NET	13	5/13 (38%)	7/13 (53%)	3/13 (23%)
DSRCT, CSS, ACC, NBL	12	9/12 (75%)	4/12 (25%)	1/12 (8%)
Total	25	14/25(56%)	11/25 (44%)	4/25 (16%)

1.4 Symptom control in neuroendocrine tumors including PC-PG

Common signs and symptoms in patients with PC-PG are related to catecholamine excess. These include (in decreasing order of frequency[1]):

- headache
- sweating
- palpitations,
- hypertension,
- pallor,
- weakness & fatigue,
- nervousness
- nausea,
- hyperglycemia,
- flushing,
- weight loss

Alpha blockade first with doxazosin (or phenoxybenzamine) and then beta blockade (e.g. propranolol or atenolol) are the standard of care for PC-PG patients experiencing symptoms such

as headaches or hypertension and/or requiring surgery or radiation to avoid symptoms associated with catecholamine release [102-104] . Some PC-PG patients are on chronic anti-hypertensives to control symptoms.

Because of potential interaction with dopamine receptors, medications that are dopamine agonists including and some psychotropic medications are relatively contraindicated; see also table 3 section 6.2 [102, 105].

1.5 Rationale

Experimental profiling has determined that ONC201 specifically and directly antagonizes DRD2, DRD3, but not to DRD1, DRD4, or DRD5 [87]. DRD2 is a G protein-coupled receptor (GCPR) that is involved in many functions and is not only present on neural cells binding norepinepherine or epinephrine, but also signaling in lymphocytes and cells involved in hormone signaling [92, 106-113].

Thus, ONC201 is the first anti-cancer drug to bind a GPCR [87, 90-92]. PC-PG have more DRD2 receptors than gastropancreatic neuroendocrine tumors [114]. It would be expected that other tumors with neural or neuroendocrine differentiation and catecholamine biomarkers would have high DRD2 expression [89, 96, 97]. Many subjects with neuroendocrine cancers that release dopamine or are driven in an autocrine manner by dopamine have indolent, but serious disease. This is particularly true for PC-PG. Ability to control symptoms of catecholamine excess in PC-PG is usually done with alpha and beta blockade.

Thus, the primary objective will be to demonstrate objective responses using MRI or CT and also PET-CT or PET-MRI imaging. Secondary objectives will be to determine progression-free survival and overall survival and to determine incidence and severity of AE comparing the well tolerated once weekly schedule with dosing d1d2 weekly schedule.

1.6 Background and rationale of exploratory studies

The finding that DRD2 is a highly specific target of ONC201 led to analysis of DRD2 in cancers using TCGA data [87]. Since PC-PG have the highest DRD2 expression of all cancers in the panel (figure 2), studying ONC201 in PC-PG and similar neuroendocrine tumors may determine whether it is possible to preselect for patients with that would have both high ONC201 binding and excellent surrogate plasma biomarkers including normetanepherine and metanepherines [102], and possibly bombesin (progastrin-releasing peptide; ref [115-119]),

2.0 Objectives

2.1 Primary Objective

To demonstrate objective responses using MRI or CT, PET-CT and/or PET-MRI imaging. The same CT or MRI imaging to assess disease burden at study entry will be compared at week 6 and 3 months. Patients without progression at 3 months will continue treatment and have imaging approximately every 3 months after study entry.

2.2 Secondary Objectives

2.21. Progression – free Survival.
This will be calculated according to RECIST and /or development of new disease

2.2.2 Overall survival:
Overall survival will be by searching for obituaries and/or utilizing the social security death index.

2.3 Exploratory Objective:

All patients To determine time course of ONC201 efficacy by measurement clinically indicated blood biomarkers such as normetanepherine, metanepherines, and/or chromogranin A..

2.4 Correlative Objective(s): NA

Plasma will be collected in BCT tubes, then frozen and stored for future studies of an exploratory nature.

3.0 Study Design: Phase 2 open-label fixed dose study

This study design has been chosen to see whether ONC201 given 2 consecutive days weekly (d1, D2 schedule) has similar safety and better efficacy against neuroendocrine tumors, especially PC-PG. Flat dosing of 625mg orally on 2 consecutive days will be used. The same imaging at study entry will be used at subsequent time points (CT or MRI for week 6, month 3 and every 3 months after that while on therapy; PET-CT or PET-MRI will be at 6 weeks 3 months and 12 months and then yearly while on therapy. Imaging modality choice will be influenced by the quality of prior scans of the subject and will be ordered so clinical comparison is possible.

3.1 Dose escalation / cohorts

There will be one Cohort C with 12 neuroendocrine tumor patients on the day1, day2 weekly schedule

3.2 Number of Subjects

Cohorts A and B will be closed to accrual after patients currently receiving weekly ONC201 roll over to Cohort C. A total of 12 patients receiving twice/week d1d2 ONC201 will be accrued.

3.3 Replacement of Subjects

Subjects will be replaced if enrolled, but not able to get 6week imaging evaluation.

3.4 Expected Duration of Treatment and Subject Participation

Length of treatment will be until progression at two consecutive time points

4.0 Subject Selection

All inclusion and exclusion eligibility criteria in the following sections must be met for a subject to be considered eligible for this study unless an administrative letter is obtained that will allow one or more of the inclusion/exclusion criteria to be waived. This will be done on a case by case basis and will be reviewed by the PI and IRB before treatment can begin.

4.1 Inclusion Criteria

___ 4.1.1 "Subjects must have a unresectable, recurrent, locally advanced, refractory, or metastatic neuroendocrine tumor including pheochromocytoma-paraganglioma (PC-PG), DSRCT, Ewing Sarcoma or PNET, or any neuroendocrine tumor with a catecholamine or dopamine biomarker or autocrine or paracrine dependence on dopamine including cholangiocarcinoma and adrenal cortical carcinoma (ACC). N=12"N=12

___ 4.1.2 There is no limit on number of prior therapies.

___ 4.1.3 Age ≥14 years.

___ 4.1.4 Subjects must have normal organ and marrow function as defined below. Studies should be done within 3 weeks prior to enrollment

- Hemoglobin ≥ 10.0 g/dl
- Leukocytes ≥ 1500/mcL
- Absolute neutrophil count ≥ 1,000/mcL
- Platelet count ≥ 75000/mcL
- Total bilirubin within 1.5 x normal institutional limits
- AST (SGOT) ≤ 5 X institutional upper limit of normal
- ALT (SGPT) ≤ 5 X institutional upper limit of normal
- Serum Creatinine <3.0mg/dL

___ 4.1.5 1 lesion detectable on CT, MRI, ^{18}FDG PET-CT, or PET-MRI

___ 4.1.6 Subjects must have the ability to understand and the willingness to sign a written informed consent document.

___ 4.1.7: Karnofsky or if <16 years old Lansky Play Performance status ≥ 60%

Karnofsky Scale (recipient age ≥ 16 years)		Lansky Scale (recipient age <16 years)	
Able to carry on normal activity; no special care is needed		**Able to carry on normal activity; no special care is needed**	
100	Normal, no complaints, no evidence of disease	100	Fully active
90	Able to carry on normal activity	90	Minor restriction in physically strenuous play
80	Normal activity with effort	80	Restricted in strenuous play, tires more easily, otherwise active
Unable to work, able to live at home cares for most personal needs, a varying amount of assistance is needed		**Mild to moderate restriction**	
70	Cares for self, unable to carry on normal activity or to do active work	70	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance but is able to care for most needs	60	Ambulatory up to 50% of time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	50	Considerable assistance required for any active play, fully able to engage in quiet play
Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly		**Moderate to severe restriction**	
40	Disabled, requires special care and assistance	40	Able to initiate quite activities
30	Severely disabled, hospitalization indicated, although death not imminent	30	Needs considerable assistance for quiet activity
20	Very sick, hospitalization necessary	20	Limited to very passive activity initiated by others (e.g., TV)
10	Moribund, fatal process progressing rapidly	10	Completely disabled, not even passive play

4.2 Exclusion Criteria

The presence of any of the following will exclude a subject from study enrollment.

___ 4.2.1 Subjects not able to take oral drugs

___ 4.2.2 Subjects receiving any other investigational agents.

___ 4.2.3 Subjects receiving cytotoxic chemotherapy

___ 4.2.4 Subjects with uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, severe, uncontrolled hypertension (systolic >150/diastolic>100mmHg) or other symptoms of catecholamine excess after efforts to achieve adequate alpha blockade then beta blockade

___ 4.2.5. Psychiatric illness/social situations that would limit compliance with study requirements including returning for scans, taking oral medication, home monitoring of blood pressure and heart rate, recording side effects in a self-report diary, or becoming pregnant while on study drug

___ 4.2.6. Pregnant and breast-feeding subjects.

___ 4.2.7. Patients with prolactinomas

4.3 Inclusion of Women and Minorities

Men, women, and members of all races and ethnic groups are eligible for this trial.

5.0 Registration

All subjects who have been consented are to be registered in the OnCore™ Database and also an IND compliant database (RedCap Cloud) All subjects will be registered through Cleveland Clinic and will be provided a study number by contacting study coordination [redacted] or research nurse [redacted]

6.0 Treatment Plan

6.1 Treatment Regimen**: 625 mg po d1 d2 weekly (each week can begin +/- 1 day)**

Tumor size and/or metabolic activity will be evaluated at study entry before initial ONC201 at 6 weeks and 3 months. ONC201 will be administered at 625 mg orally day1, day 2 weekly. Patients without progression at 3 months will continue oral ONC201 until progression occurs with imaging and clinical evaluations at approximately 3 month intervals.

6.2 Logistics of ONC201 Dosing

ONC201 dosing will be orally on two consecutive days weekly (each week +/- 1 day) and must start within 3 weeks of registration and study enrollment. PC-PG subjects are to have be on an alpha blocker (e.g. doxazosin) and a beta blocker (e.g. metoprolol or atenolol). These recommendations are adapted from Endocrine Society clinical practice guidelines for pre-surgical Medical preparation of PC-PG patients (table 9 page 1929 ref [102]).

If a subject has nausea or illness causing potential difficulty taking oral drugs, waiting for next day is advised so there is no loss of study drug. If nausea or illness is severe for longer than 2 days, contact study chair. ONC201 will be given until progression as determined appearance of new metastatic disease or lesion progression by RECIST. Patients with clinical benefit may continue to be treated with regular 3 month follow-up..

Dose modifications for ONC201:

If any subject has unacceptable grade 3 or greater drug-related AE or SAE with dose #1 other than hypertension that is controlled with additional medication (e.g. persisting, affecting quality of life, or not ameliorated with medical intervention), the patient will be off study. If 2 or more patients experience the same grade 3 or greater study drug-related AE or study drug related SAE the study will temporarily stop enrollment and will be analyzed for potential means to prevent or ameliorate the side effect and consent form revised.

Oncoceutics will be contacted regarding approaches to drug-related AE and/or SAE including control of episodes of grade 3 or greater hypertension from catecholamine release with additional medications. The consent form will be revised to inform future subjects of anticipated new potential side effects and patients on study will be informed by telephone or email and re-consented at next study visit.

At the present time, no grade ≥ 2 drug-related AEs have been reported in human studies with ONC201. For additional information see also ONC201 Investigators Brochure [98].

.

General Concomitant Medications and Supportive Care Guidelines

Concomitant prescribed medicines will be recorded at study entry and follow-up visits. Any history or current anti-hypertension medication within 3 months of study entry will be recorded.

Supportive care with over-the-counter agents are allowed as clinically indicated (e.g. medicine for pain and headaches, GI side effects such as nausea, diarrhea, and constipation). If used regularly, effort should be made to record such meds as a concomitant medication.

Because of the unknown potential for interaction with ONC201 and dopamine receptor agonist medications decreasing efficacy against PC-PG dopamine agonist psychotropic drugs, L-DOPA, bromocriptine, metoclopramide are prohibited while on study.

Table 3 lists drugs to be avoided in PC-PG patients (and those using an agent such as ONC201 that acts via DRD2 to avoid potential interactions or false elevation of normetanepherine or metanepherines plasma or urine tests) [102].

Table 4. Potential ONC201:DRD2 Medication and Biomarker Test Interactions (Reference [102])

	Adverse	Possible False Elevation[#]	
Drug class/Medication	Reactions	Normetanepherine	Metanepherines
Dopamine D2 agonists [a]	Yes	+	+
Norepinepherine reuptake inhibitors [b]	Yes	++	-
Monoamine Oxidase Inhibitors [c]	Yes	++	++
Serotonin reuptake inhibitors [d]	rare	-	-
Neuromuscular blocker[e]	Yes	-	-
Busipirone	No	-	++
Acetaminophen	No	++	-

[#]False elevation: ++ clear increase; + mild increase; - no increase
[a] examples: metoclopromide, chloropromazine, prochlorperazine, droperidol
[b] tricyclics including amitryptaline, imipramine
[c] examples: tranciproamine, moclobemide, phenelzine
[d]examples paroexetine, fluoxetine
[e]examples: succinylcholine, tubocurarine, atacurium

6.3. Other therapy while on study

6.3.1 Radiotherapy

Radiation oncology consultation is suggested to facilitate treatment of progressive pain and/or neurologic dysfunction in non-target lesions before therapy starts or during treatment. The radiation oncologist should also assist in determining whether AE or SAE are radiation-related, drug-related, prior-treatment-related, or disease-related. To maintain function and quality of life (QOL) all patients will be permitted to have clinically indicated (e.g. pain) radiotherapy of indicator and non-indicator lesions after week 6 and continue ONC201 if there are no new metastases.

6.3.2 Surgery or Thermal Ablation
If major surgery or thermal ablation are done before starting oral ONC201, all side effects should have decreased to grade 2 or less before starting therapy and the surgical specialist or interventional radiologist should also assist in determining whether subsequent AE or SAE are related to prior surgery or thermal ablation , drug-related, or disease-related. Similarly, after week 6 if surgery or ablation of a non-indicator lesion can maintain or improve quality of life, this is allowed.

6.3.3. Chemotherapy

Any investigational agents or commercially available chemotherapy agents other than corticosteroids should not be administered with the intent to treat the subject's malignancy while on ONC201 study drug. Octreotide and zoledronic acid are permitted for treatment of neuroendocrine side effects and bone metastases, respectively. If a patient has persistent and active disease> 6 months after starting d1d2 weekly ONC201 dosing and has clinical benefit, then rational combination therapy on a case-by-case basis after discussion with PI, and written permission from Oncoceutics (study drug supplier), FDA and Cleveland Clinic IRB may be considered. Examples of potential additive or synergy include ONC201 with an mTOR inhibitor, gemcitabine + bavituximab, or NK cellular therapy to allow a patient to get additional ONC201 and additional therapy which may improve efficacy.

6.4 Criteria for Removal from Study

Treatment may continue until one of the following criteria applies:

- Disease progression with documentation of new metastases,
- Intercurrent illness that prevents further administration of treatment,
- The investigator considers it, for safety reasons, to be in the best interest of the subject.
- Unacceptable quality of life or adverse event(s) such as decline in performance from metastatic cancer, seizures, pain, or effects of prior therapy
- Unacceptable treatment related toxicity, NCI CTC AE version 4.0 Grade 3 or 4 that fails to recover to baseline or < Grade 3 in the absence of treatment within 3 weeks
- Any toxicity or other issue that causes a delay of study drug administration by more than 4 weeks (i.e. 7 weeks from last dose)
- Subject decision to withdraw from treatment (partial consent) or from the study (full consent)

- Pregnancy during the course of the study for a child-bearing participant
- Death
- Principal Investigator temporarily suspends or prematurely discontinues study participation. The date and reason for discontinuation must be documented (e.g. non-compliance). Every effort should be made to complete the appropriate assessments.

Principal Investigator and Oncoceutics reserve the right to temporarily suspend or prematurely discontinue this study. The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments.

6.5 Duration of Follow Up

Subjects will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause for a maximum of 3 months. In other words if attribution is "not ONC201 related", follow-up of the AE is not needed indefinitely for study purposes.

Any unexpected SAE that occurs and is considered to be definite, probable, or possibly ONC201 related will be recorded and reported within 3 business days to Cleveland Clinic IRB and Oncoceutics. Serious adverse events (SAE) that are definite, probable, or possibly ONC201 related and still ongoing at the end of the study period will necessitate additional follow-up to determine the final outcome.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

Subjects will be followed for progression-free survival, and b) overall survival. If a subject decides to discontinue ONC201 without progression, contact with subject will be by phone, e-mail, and notes from referring physician every 3 months for year 2 of the study, then yearly for a maximum of 4 years after completion of ONC 201. Overall survival will be captured by searching for obituaries and/or utilizing the social security death index annually.

7.0 Dose Delays/Dose Modifications and evaluation windows

ONC201 (625 mg po) will be administered Day1, Day 2 weekly (start of week +/- 1 day).

If ONC201 cannot be taken orally because of illness, supply problems (for example, lost or damaged pills), a delay up to 3 weeks until restoration of enteral nutrition and/or obtaining new study drug will be considered acceptable.

If patient is still unable to take oral medication(s) after 3 weeks, the study chair should be contacted. If >4week delay, patient will be considered off-study and should get end-of-study evaluations.

Evaluation windows: 6week, 3 month and approximately every 3 months after should be within 10 working days of anticipated date.

8.0 Adverse Events and Potential Risks

8.1 ONC201

The following are potential adverse events as detailed in the ONC201 Investigator's Brochure, version 6 (11-2019).

Table 5. Adverse Events I ONC201 Potential Risks of ONC201 in informed consent form based on IB Version 6 dated November 2019.

Frequent (in 100 people receiving ONC201 20 to 35 may have):

- Fatigue
- Nausea
- Headache
- Vomiting

Occasional (In 100 people receiving ONC201 10 to 20 may have):

- Low white blood cells (Leukopenia)
- Abnormal walking (Gait disturbance)
- Trouble speaking (Dysarthria)
- Insomnia
- High blood sugar (Hyperglycemia)
- Weakness on one side of the body (Hemiparesis)
- Low red blood cells (Anemia)
- Dizziness
- Muscular weakness
- Low phosphorous in the blood (Hypophosphatemia)
- Seizures
- Diarrhea
- High liver enzymes (ALT and AST)

Rare but serious adverse events that were considered related to ONC201(In 100 people receiving ONC201, 3 or fewer may have):

- Encephalopathy
- Lung Infection (Pneumonia)

- Bleeding (Hemorrhage)
- Blood infection (Sepsis)
- Tumor Lysis syndrome, a disease caused by cancer cells dying
- Stroke
- Trouble breathing (Dyspnea)
- Respiratory distress
- Blockage in the intestines (Small bowel obstruction)
- Death

Adverse events that have been observed in previous clinical trials of ONC201 that were attributed by the investigator as possibly-related or probably-related to ONC201 include, but are not limited to fatigue, nausea, headache, vomiting, high blood sugar and low red blood cells.

No induction of cell death in normal tissues has been documented in animal studies with ONC201- even at exaggerated dosing levels. This is consistent at early as well as late observation time points, suggesting that pro-apoptotic signaling in response to ONC201 is highly selective for tumor cells but not normal cells [98]. Clinical pharmacodynamic and preclinical studies in animals show that activity of the study drug outlives its systemic exposure (t ½ about 6 hr in mice and 12 hr in humans (Figures 3 and 4) [87].

The safety margin (ratio of therapeutic dose to lowest dose with a mild adverse event) of ONC201 is at least 10-fold in rats and dogs in GLP toxicology studies[98]. In general, GLP studies with oral ONC201 revealed that adverse events associated with exaggerated doses of ONC201 were mild and reversible. The only findings that were observed in both rats and dogs were decreased activity and decreased food consumption. Weight loss was seen in rats, but not dogs. When (dogs) received very large doses of ONC201 intravenously over 30 minutes (30-50 times the RP2D in humans), some had vomiting and decreased activity. No observed were seen in dogs that were given 25 times the RP2D; no side effects were seen at 50 times the RP2D dose as a 2 hour intravenous infusion. These safety data are consistent with the experience in non-GLP studies as well as in various experiments in mice and also human cells (bone marrow as well as fibroblasts).

Human experience. The first-in man trial of ONC201 was completed in fall 2015 and has been reported in abstract/poster (AACR-EORTC Nov 8, 2015; table 4) [93]. In this trial fever was seen in 1 patient (table 4). There were no grade 2-4 adverse events at the RP2D.There is 1 report of a rash in 2016 in the GBM trial.

8.2 Definitions

8.2.1 Adverse Event

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily

have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

8.2.2 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 24 hours OR
    - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR
    - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

  However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.
- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

8.2.3 Adverse Event Evaluation

The investigator or designee is responsible for ensuring that all adverse events (both serious and non-serious) observed by the clinical team or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's medical records. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant should be reported as an adverse event.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE)
- Description of the event
- Date of onset and resolution
- Expectedness of the toxicity
- Grade of toxicity
- Attribution of relatedness to the investigational agent- (this must be assigned by an investigator, sub-investigator, or treating physician**)**
- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received medication or other intervention, etc.
- Outcome of event

Descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for AE reporting.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

Protocol must specify if attribution is required for individual components of the treatment regimen or the treatment regimen as a whole.

8.3 SAE Report Form

SAEs will be recorded on the FDA Form 3500A (MedWatch) but should only be reported as instructed below. The electronic FDA SAE reporting forms should not be used.

8.4 Reporting Procedures for Serious Adverse Events

For the purposes of safety reporting, all adverse events will be reported that occur through 30 days after the final dose of study drug. Adverse events, both serious and non-serious, and deaths that occur during this period will be recorded in the source documents.

All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization.

8.4.1 SAE Reporting Requirements

Participating investigators must report all grade 2 serious adverse events to the Principal Investigator within **24 hours** of discovery or notification of the event. The participating investigator must also provide follow-up information on the SAE until final resolution.

Peter M. Anderson MD, PhD Principal Investigator
Cleveland Clinic, Pediatric Hematology/Oncology and Bone Marrow Transplant
[redacted]9500 Euclid Ave, Cleveland OH 44195
[redacted]

The Principal Investigator will review the SAE and report the event to the Cleveland Clinic IRB, Oncoceutics, and FDA as applicable. It is the PI responsibility to ensure that grade ≥2 AE and SAE are reported to the Cleveland Clinic IRB according to the local IRB's policies and procedures in reporting adverse events.

Although this is an investigator-initiated IND study, the PI will provide information to Oncoceutics in a timely manner (3-5 working days) which may impact analysis of safety and/or efficacy in other concurrent clinical trials of ONC201.

Institutional Review Board Reporting Requirements:

- The principal investigator or designate will report adverse events to the Cleveland Clinic IRB according to policies and procedures for reporting adverse events.

8.5 SAEs and OnCore

- All SAEs will be entered into OnCore and into an IND compliant database
- A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into OnCore and the IND compliant database (REDCap).

8.6 Data Safety and Toxicity Committee (DSCT)

It is the responsibility of the PI to ensure that ALL SAEs occurring on this trial are reported to the Case Comprehensive Cancer Center's DSCT. This submission is simultaneous with their submission to the sponsor and/or other regulatory bodies.

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

8.7 Data and Safety Monitoring Plan (DSMP)

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

9.0 PHARMACEUTICAL INFORMATION

Investigational Agent: ONC201; Other Name: TIC10

Product description: 125 mg capsules
The investigational drug product is a hydroxypropyl methylcellulose (HPMC) capsule filled with ONC201 dihydrochloride, intended for oral administration. Excipients can include microcrystalline cellulose. Each capsule of drug product contains the equivalent 125mg of anhydrous ONC201 free base. This corresponds to ~150mg of drug substance that corrects for the ONC201 dihydrochloride salt and moisture.

Storage requirements: ONC201 is stable at room temperature as capsules.

Stability: The ONC201 drug product capsules are stored in a multi-dose container. Capsules are packaged in high-density polyethylene (HDPE) white opaque bottles, with an induction seal and capped with a white ribbed SecuRx® polypropylene (PPE) cap.

Route of administration: oral

Drug Procurement: ONC201 will be supplied for this study by Oncoceutics (610-613-4891).

Packaging and labeling: The ONC201 drug product capsules are stored in a multi-dose container. The capsules are packaged in high-density polyethylene (HDPE) white opaque bottles, closed with an induction seal and capped with a white ribbed SecuRx® polypropylene (PPE) cap.

Drug Accountability: The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drugs must be accounted for, including study drug accidentally or deliberately destroyed. Under no circumstances will the

investigator allow the investigational drug to be used other than as directed by the protocol. Cleveland Clinic Investigational Pharmacies will be responsible for drug storage, dispensing ONC201 for study use and compound preparation and dispensing of solution, and drug accountability of patients enrolled at Cleveland Clinic.

Drug Destruction: At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

Other Information:
Drug containers will be labeled "ONC201 Study Drug- for Investigational Use ONLY"

- **Initial supply** of ONC201 will be supplied by Cleveland Clinic investigational pharmacy Doses will be supplied (capsules) and study personnel will provide a calendar with recommended dates of d1, d2 administration until next scheduled follow-up at 6 weeks (60 pills).
- **Subsequent ONC201 doses** Patients with stable disease and responding patients (SD, PR, or CR) will be supplied with 140 pills for 4 cycles of 625 mg (10 capsules weekly with a calendar and drug /symptom diary for a total of 140 capsules before next imaging time point). The additional study drug supplies will be given after review of study radiologic evaluations at study visits and determination of continuing SD, PR or CR status.

Because of interval growth between initial on study scan and 6 weeks, patients with new RECIST progression or new metastases at 6 weeks and are asymptomatic may elect to remain on study. However, interval increase in sum of longest diameters of existing or new lesions between week 6 and 3 months using RECIST will be considered progressive disease. If imaging is stable or PR or CR, continuation supply may be sent to the patient by investigational pharmacy via express courier with tracking information and study personnel will review drug accountability log sent by patient to PI or research nurse with the patient by phone or virtual (video) visit.

10.0 EXPLORATORY STUDY

10.1 Exploratory Study: Neuroendocrine biomarkers and PK/PD

Biomarkers expressed by individual patient's neuroendocrine tumors will be determined at time of study entry.

10.1.2 Rationale for Analysis

Analysis will provide clinical experience, including neuroendocrine biomarkers and efficacy, that may possibly be useful future clinical trials with ONC201.

10.1.3 Collection of Specimens

Most specimens are routine clinical care and are analyzed in Cleveland Clinic Laboratory Medicine facilities (cbc, chemistries, urine VMA/HVA, dopamine, normetanepherine, metanepherines, bombesin, etc.).

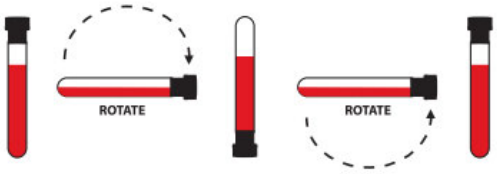
10.1.4 Handling of Specimens
Biomarker specimens are routine clinical care.

10.1.5 Analytical Laboratory:
Biomarker specimens are routine clinical care
.

10.2 Correlative Study: Banking of plasma for future studies
Plasma will be banked for future correlative studies to include potential genetic and epigenetic biomarker analysis, ctDNA analysis, TRAIL, and DR family expression.

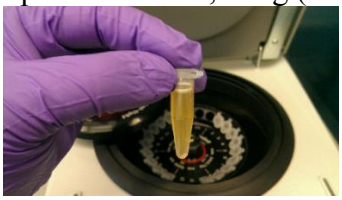
10.2.1 Rationale for Analysis
Analysis to identify novel molecular classifiers and circulating biomarkers to inform future clinical trials with ONC201.

10.2.3 Collection of Specimens
1. Obtain 10 ml venous blood by standard phlebotomy technique from a peripheral access point or from a central line by trained study personnel into BD Vacutainer EDTA tubes, Cat# 366643.
2. Invert tube gently after collection several times after collection.

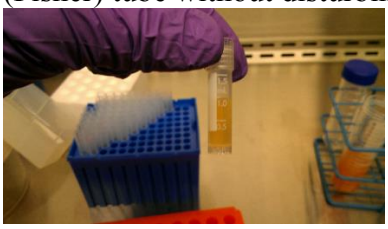


3. Transport the tube immediately to M3-029 (Mian) laboratory. Time between draw and start of laboratory processing should not exceed 1 h. Note: Total processing time not to exceed 3 hours. (if anticipating longer processing, blood should be collected in Streck cfDNA preservative tubes [Cell-Free DNA BCT 6-Tube Pack (RUO) 218961])

10.2.4 Handling and Storage of Specimens
1. Upon arrival in the laboratory, spin tubes at 900 x g for 10 min at room temperature.
2. Transfer supernatant to a 15 ml or 50 ml or tube without disturbing the cellular layer using a 10 ml pipette.
3. An optional second 900 g spin in a new 15 ml conical tube is preferred for removal of residual erythrocytes and mononuclear cells.
4.
5. Aliquot ~1.05 ml plasma form the large tube to a 1.5 ml tubes.
6. Spin tubes at 16,000 g (~13,500 rpm) for 10 min at room temperature.



7. Transfer two times 1 ml of plasma from the 1.5 ml tube to a fresh 1.5-2 ml cryovial (Fisher) tube without disturbing the pellet.



Labeling of tubes
Tubes for plasma collection are labeled as follows:
Patient ID, Tube Number, e.g. 1..n; Date, e.g. Sept 1, 2016;Volume e.g. 1.0 ml
Storage: Plasma vials are stored at -80ºC in a 81 well freezer storage box.

10.2.5 Research and Analytical Laboratory
Translational Hematology and Oncology (THOR) Lab : Omar Y. Mian, MD, PhD
9500 Euclid Ave - [redacted] Cleveland, OH 44195

11.0 STUDY PARAMETERS AND CALENDAR

11.1 Study Parameters.

11.1.1 Screening Evaluation
This will be done by the subject's primary oncologist or principal investigator or co-investigator.

The screening evaluation should be done within 4 weeks of anticipated first dose of ONC201 (if eligible). See Table 5 (next page).

Information to be obtained for eligible patients includes:

- CBC with differential
- LFT (bilirubin, ALT, AST, total alkaline phosphatase)
- BUN and creatinine
- PC-PG: normetanepherine, metanepherines, chromogranin
- Other clinically indicated markers depending on neuroendocrine tumor type (for example urine VMA/HVA, plasma dopamine, or bombesin)
- Measurement of least one detectable lesion (CT or MRI, or PET-CT or PET-MRI)
- Determination of Karnofsky performance status
- Review of prior hypertension medication and eligibility criteria with study coordinator

If there are questions of whether a patient is eligible, the oncologist should discuss with Dr. Peter Anderson ([redacted])

11.1.2 Treatment Period
ONC201 administration should begin within 3 weeks of registration. Labs and imaging windows once enrolled are +/- 2 weeks. Weekly ONC201 study drug dosing +/- 1 day.
On study tumor measurements should be within 3 weeks of registration.

11.2 Study Calendar

Table 6. ++Observations to be Reviewed at Study Entry and Time Points

Study Entry Observation	wk6	3mo	every 3 months	Off therapy
KPS, bp	x	x	x	
*Labs and biomarkers^	x	x	x	
AE# and SAE	x	x	x	x
Imaging Response**	x	x	x	
Symptom + Drug diary	x	x	x	
Clinical benefit assessment	x	x	x	
Survival (PFS and OS)##	x	x	x	x

++face-to-face review is strongly encouraged. However, because COVID-19 causing travel and lodging difficulties, after discussion with PI on a case-by-case basis, written informed consent (see section 13.2.1) , clinical AE, scan measurement review, and lab review can be done using virtual visits and documented in EPIC in prior to study entry and at week 6, 12 and every 3 months prior to ordering ONC201 drug dispensing by investigational pharmacy using express courier with tracking.

*Karnofsky performance status (KPS), blood pressure (bp): if PC-PG, use of wireless cuff to EPIC via MyChart encouraged (order as "connected bp" in EPIC). Labs: cbc with differential, chemistry panel

^biomarkers: as clinically indicated depending on tumor type may include plasma free normetanepherine, metanepherines, chromogranin; if neuroblastoma urine VMA/HVA, dopamine, serotonin, 5-HIAA

BCT tube/plasma for ccfDNA and ccfRNA storage pre, Week 6, and 3 months
#Grade ≥2 AE; any SAE**Tumor measurements (see section 12)
sum of longest axis diameters of solid tumors
sum short axis of involved lymph nodes
sum of products of perpendicular diameters for brain tumors

CT or MRI as per RECIST criteria [120].

PET-CT or PET-MRI: change in SUV on PET.CT or PET-MRI compared to baseline at 6 weeks, months 3,12 months and then yearly.

Clinical benefit: Karnofsky performance status ≥60%, and no new metastases (mixed response continued SD, PR, or CR)

[##] PFS: progression-free survival as per RECIST; OS: overall survival- year 2-5 by phone, email or notes from referring physician.

12.0 MEASUREMENT OF EFFECT

Antitumor Effect – Solid Tumors
For the purposes of this study, subjects should be re-evaluated for imaging response at 6 weeks and every 3 months +/- 2 week (maximum 10 working days).

Imaging responses and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1, ref [120]) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria (table 6).

Definitions
Evaluable for toxicity (Grade ≥2 AE and SAE): All subjects will be evaluable for toxicity from the time of their first treatment with ONC201.

Evaluable for objective response: Only those subjects who have measurable disease present at baseline, have received at least 6 doses of ONC201, and have had their disease evaluated at weeks 6 and 3 months will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. Patients with mixed responses and/or documented progression at week 6 and thereafter will be allowed to stay on study after discussion of indications, risks, and alternatives with their treating oncologist.

Evaluable Non-Target Disease Response: Subjects who have lesions present at baseline that are evaluable, but do not meet the definitions of measurable disease, have received at least 6 doses of ONC201, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters
Measurable Disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter for non-nodal lesions and short axis for nodal lesions to be recorded) as > 20 mm by chest x-ray, as > 10 mm with CT scan, or > 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Bone lesions are considered measurable if there is corresponding 18FDG uptake on PET-CT or PET-MRI with SUV ≥5 and size is ≥10mm. Tumor lesions that are situated in a previously irradiated area are considered to be considered measurable if there is recent change in size of character of the lesion and/or there is 18FDG uptake on PET-CT or PET-MR consistent with active disease (e.g. SUV≥5).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be > 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. Clinical correlation with ^{18}FDG-PET-CT or PET MRI is highly recommended.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) are considered non-measurable disease. Leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis cutis, pneumonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI) are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Target /indicator lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target or indicator lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance, the next largest lesion which can be measured reproducible should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: Other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should may identified as additional non-target lesions and recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted at follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged, but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and > 10 mm diameter as assessed using calipers

(e.g., skin nodules). In the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.
Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable. Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/ assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-holding techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined
PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a
PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if is not routine or serially performed.

Ultrasound: Ultrasound is not reproducibly useful in assessment of lesion size and should not be used a method of measurement. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Tumor markers: Tumor markers trends alone cannot be used to assess response.
FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease and/or appearance of new metastases). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is often evidence of progressive disease (PD) based on a new lesion. If possibly a false positive, biopsy or resection may be required for confirmation of new metastatic disease.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-

PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT or MRI scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FGD-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a complete response (CR) in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. ***Note:*** A 'positive' FDG-PET scan lesion means one which is FDG avid with an initial uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Table 7. Response Criteria and Evaluation of Solid Tumor Target Lesions (RECIST) Measurements: Longest Diameters in Target Lesions* + SUV

Response	Evaluation of Effect in Target Lesion
Complete Response (CR)	Disappearance or fibrosis of all target lesions. Any pathologic lymph nodes must have reduction in short axis to <10mm and have SUV is <4.
Partial Response (PR)	At least 30% decrease in sum of longest diameters of target lesions (compared to initial on study baseline) and any decrease in SUV in ^{18}FDG imaging
Stable disease (SD)	0-29% decrease in sum of longest diameters of target lesions (compared to initial on study baseline) or 0-19% increase in sum of longest diameters of target lesions (compared to initial on study baseline). SUV may increase or decrease
Progressive disease	20% or more increase of sum of longest diameters of target lesions (compared to initial on study baseline). The sum must also be at an increase of at least 5mm or one or more new lesions that are considered metastatic disease (e.g. high SUV) in the setting of rising biomarkers

*At study entry identify 5 or fewer target lesions and sum the longest diameters. This is the number to be used. Lymph nodes: shortest dimension

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

13.0 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The OnCore™ Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore™ is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore™. Access to data through OnCore™ is restricted by user accounts and assigned roles. Once logged into the OnCore™ system with a user ID and password, OnCore™ defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore™ Administrator at OnCore-registration@case.edu.

OnCore™ is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the OnCore™ database. A calendar of events and required forms are available in OnCore™.

An IND compliant database (REDCap) similar to other Oncoceutics ONC201 trials also be used.

13.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided. The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart. The informed consent discussion may be done virtually with the subject and PI having the same version of printed consent form and signing the signature page during the discussion. The PI and subject will exchange electronic versions of the signature page (JPEG or pdf via email) and printed versions of signature pages containing both signatures will be retained for study records. The consent discussion will be documented in EPIC.

13.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.2.3 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

14.0 STATISTICAL CONSIDERATIONS

This study is a phase 2 trial of ONC201 in patients 14years and older who have neuroendocrine tumors. Cohort C will have had 2x drug exposure as the initial cohorts A and B.

The study population will include neuroendocrine cancers including PC-PG because this group has the highest expression or DRD2 of all tumors in the TCGA data set. If DRD2 receptor binding is important we would expect to see clinical benefit (CR + PR + stable disease at 6 weeks and 3 months or longer plus maintenance of Karnofsky performance status $\geq$60). Data will be presented as not only numbers of CR + PR + stable disease at time points, but also duration of lack of progression (clinical benefit). Objective responses will be defined using CT or MRI and RECIST criteria. PET-CT, and/or PET-MRI will be used to assess metabolic responses. Changes in sum of longest diameters and SUV of indicator lesions identified using CT or MRI will be determined. Clinical (therapeutic) benefit is a non-linear quality (yes or no) that requires a) maintenance of performance ($\geq$60% Karnofsky), and b) no new metastases (SD+PR+CR). Because of possibility of responses in subsets of patients, this trial may provide the first positive indication of efficacy in rare tumors but is not powered for subset analysis.

Cohorts A+B have met initial efficacy endpoints for both PC-PG and "other neuroendocrine", respectively; a clinical benefit rate of 25% (3/12 or more CR+PR+SD at 3 months was seen - see table 3 . However additional efficacy with more PR and longer SD are desired. Therefore, because of safety in other trials, the day1d2 weekly dosing of ONC201 is worthy of additional study in neuroendocrine tumor patients including current stable patients with continued metastases as well as additional patients with neuroendocrine tumors.

A secondary goal of the trial is to evaluate the clinical effectiveness of ONC201 in patients with PC-PC and other neuroendocrine tumors by assessing PFS and OS. Results will be depicted in tabular form and as Kaplan-Meier survival curves.

ONC201 Toxicity Monitoring: Stopping Rule Guidelines

Although ONC201 is expected to be safe and tolerable, toxicity will be monitored continuously and the following guidelines will be used to trigger consideration of early closure due to toxicity. If any patient has any grade 3 or greater AE including hypertension or symptoms related to catecholamine excess subsequently controlled with increase of alpha+ beta blockade, the study PI is to be notified and if this is drug-related toxicity the circumstances will investigated and analysis of methods and means to prevent/reduce toxicity will be discussed and implemented.

If 2 or more patients experience unanticipated drug-related grade 3 or greater toxicity except hypertension, Oncoceutics, IRB, and FDA will be notified and consent form changed to reflect potential for this new side effect.

Biomarker exploratory objective: blood biomarkers will include clinically relevant biomarkers. Analysis will be done as a) descriptive tables at pre, week 6, 3 months and subsequent time points b) for biomarkers of 3 or more mean, median and SSD pre vs time points, and most importantly, c) within group comparison (patients as their own control) comparing biomarker change from before treatment as a function of time. Percentage change from pre-therapy will be determined and significance of change pre vs at 6 weeks and 3 months, and longer will be compared as well as patients with both once/week and d1D2 weekly dosing.

Results of objective responses (CR, PR + stable disease), AE/SAE, hypertension medicine tapering, and biomarker trends will be shared as tables with Case Comprehensive Cancer Center Protocol Research Monitoring Committee and Oncoceutics on a quarterly basis and FDA on a yearly basis.

15.0 REFERENCES

1. Pacak, K. and S.J. Wimalawansa, *Pheochromocytoma and paraganglioma.* Endocr Pract, 2015. **21**(4): p. 406-12.
2. Mannelli, M., et al., *15 YEARS OF PARAGANGLIOMA: Metabolism and pheochromocytoma/paraganglioma.* Endocr Relat Cancer, 2015. **22**(4): p. T83-90.
3. Rao, J.U., et al., *Genotype-specific differences in the tumor metabolite profile of pheochromocytoma and paraganglioma using untargeted and targeted metabolomics.* J Clin Endocrinol Metab, 2015. **100**(2): p. E214-22.
4. Lepoutre-Lussey, C., et al., *From Nf1 to Sdhb knockout: Successes and failures in the quest for animal models of pheochromocytoma.* Mol Cell Endocrinol, 2016. **421**: p. 40-8.
5. Jochmanova, I., Z. Zhuang, and K. Pacak, *Pheochromocytoma: Gasping for Air.* Horm Cancer, 2015. **6**(5-6): p. 191-205.
6. Turkova, H., et al., *Characteristics and Outcomes of Metastatic Sdhb and Sporadic Pheochromocytoma/Paraganglioma: An Nih Study.* Endocr Pract, 2015.
7. Crona, J., et al., *Integrative genetic characterization and phenotype correlations in pheochromocytoma and paraganglioma tumours.* PLoS One, 2014. **9**(1): p. e86756.
8. Crona, J., et al., *MAX mutations status in Swedish patients with pheochromocytoma and paraganglioma tumours.* Fam Cancer, 2014. **13**(1): p. 121-5.
9. Yang, C., et al., *Germ-line PHD1 and PHD2 mutations detected in patients with pheochromocytoma/paraganglioma-polycythemia.* J Mol Med (Berl), 2015. **93**(1): p. 93-104.
10. Burnichon, N., et al., *A novel TMEM127 mutation in a patient with familial bilateral pheochromocytoma.* Eur J Endocrinol, 2011. **164**(1): p. 141-5.
11. Buffet, A., et al., *A decade (2001-2010) of genetic testing for pheochromocytoma and paraganglioma.* Horm Metab Res, 2012. **44**(5): p. 359-66.
12. Crona, J., et al., *Next-generation sequencing in the clinical genetic screening of patients with pheochromocytoma and paraganglioma.* Endocr Connect, 2013. **2**(2): p. 104-11.
13. Eisenhofer, G., et al., *Measurements of plasma methoxytyramine, normetanephrine, and metanephrine as discriminators of different hereditary forms of pheochromocytoma.* Clin Chem, 2011. **57**(3): p. 411-20.
14. Zelinka, T., et al., *Role of positron emission tomography and bone scintigraphy in the evaluation of bone involvement in metastatic pheochromocytoma and paraganglioma: specific implications for succinate dehydrogenase enzyme subunit B gene mutations.* Endocr Relat Cancer, 2008. **15**(1): p. 311-23.
15. van Berkel, A., et al., *Correlation between in vivo 18F-FDG PET and immunohistochemical markers of glucose uptake and metabolism in pheochromocytoma and paraganglioma.* J Nucl Med, 2014. **55**(8): p. 1253-9.
16. Timmers, H.J., et al., *Clinical aspects of SDHx-related pheochromocytoma and paraganglioma.* Endocr Relat Cancer, 2009. **16**(2): p. 391-400.
17. Taieb, D., et al., *Renaissance of (18)F-FDG positron emission tomography in the imaging of pheochromocytoma/paraganglioma.* J Clin Endocrinol Metab, 2014. **99**(7): p. 2337-9.

18. Moraitis, A.G., V.L. Martucci, and K. Pacak, *Genetics, diagnosis, and management of medullary thyroid carcinoma and pheochromocytoma/paraganglioma.* Endocr Pract, 2014. **20**(2): p. 176-87.
19. Vicha, A., D. Taieb, and K. Pacak, *Current views on cell metabolism in SDHx-related pheochromocytoma and paraganglioma.* Endocr Relat Cancer, 2014. **21**(3): p. R261-77.
20. Hescot, S., et al., *One-year progression-free survival of therapy-naive patients with malignant pheochromocytoma and paraganglioma.* J Clin Endocrinol Metab, 2013. **98**(10): p. 4006-12.
21. McBride, J.F., et al., *Minimally invasive treatment of metastatic pheochromocytoma and paraganglioma: efficacy and safety of radiofrequency ablation and cryoablation therapy.* J Vasc Interv Radiol, 2011. **22**(9): p. 1263-70.
22. Vogel, J., et al., *External beam radiation therapy in treatment of malignant pheochromocytoma and paraganglioma.* Front Oncol, 2014. **4**: p. 166.
23. Favier, J., et al., *Rationale for anti-angiogenic therapy in pheochromocytoma and paraganglioma.* Endocr Pathol, 2012. **23**(1): p. 34-42.
24. Pharmaceuticals, M.I., *A Study Evaluating Ultratrace Iobenguane I 131 (MIBG) in Patients With Malignant Pheochromocytoma/Paraganglioma.* ClincalTrials.gov, 2016. **NCT00874614**.
25. Dando, I., et al., *The metabolic landscape of cancer stem cells.* IUBMB Life, 2015. **67**(9): p. 687-93.
26. Liberti, M.V. and J.W. Locasale, *The Warburg Effect: How Does it Benefit Cancer Cells?* Trends Biochem Sci, 2016.
27. Bhattacharya, B., M.F. Mohd Omar, and R. Soong, *The Warburg effect and drug resistance.* Br J Pharmacol, 2016.
28. Timmers, H.J., et al., *Staging and functional characterization of pheochromocytoma and paraganglioma by 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography.* J Natl Cancer Inst, 2012. **104**(9): p. 700-8.
29. Pillai, S., et al., *Updates on the genetics and the clinical impacts on phaeochromocytoma and paraganglioma in the new era.* Crit Rev Oncol Hematol, 2016.
30. Allen, J.E., et al., *Dual inactivation of Akt and ERK by TIC10 signals Foxo3a nuclear translocation, TRAIL gene induction, and potent antitumor effects.* Sci Transl Med, 2013. **5**(171): p. 171ra17.
31. Dida, F., et al., *Resistance to TRAIL-induced apoptosis caused by constitutional phosphorylation of Akt and PTEN in acute lymphoblastic leukemia cells.* Exp Hematol, 2008. **36**(10): p. 1343-53.
32. Guenther, M.K., U. Graab, and S. Fulda, *Synthetic lethal interaction between PI3K/Akt/mTOR and Ras/MEK/ERK pathway inhibition in rhabdomyosarcoma.* Cancer Lett, 2013. **337**(2): p. 200-9.
33. Hilton, D.A., N. Ristic, and C.O. Hanemann, *Activation of ERK, AKT and JNK signalling pathways in human schwannomas in situ.* Histopathology, 2009. **55**(6): p. 744-9.
34. Martelli, A.M., et al., *PI3K/AKT/mTORC1 and MEK/ERK signaling in T-cell acute lymphoblastic leukemia: new options for targeted therapy.* Adv Biol Regul, 2012. **52**(1): p. 214-27.
35. Prabhu, V.V., et al., *Small-Molecule ONC201/TIC10 Targets Chemotherapy-Resistant Colorectal Cancer Stem-like Cells in an Akt/Foxo3a/TRAIL-Dependent Manner.* Cancer Res, 2015. **75**(7): p. 1423-32.

36. Qi, X.F., et al., *HMG-CoA reductase inhibitors induce apoptosis of lymphoma cells by promoting ROS generation and regulating Akt, Erk and p38 signals via suppression of mevalonate pathway.* Cell Death Dis, 2013. **4**: p. e518.
37. Qiao, J., et al., *PI3K/AKT and ERK regulate retinoic acid-induced neuroblastoma cellular differentiation.* Biochem Biophys Res Commun, 2012. **424**(3): p. 421-6.
38. Renshaw, J., et al., *Dual blockade of the PI3K/AKT/mTOR (AZD8055) and RAS/MEK/ERK (AZD6244) pathways synergistically inhibits rhabdomyosarcoma cell growth in vitro and in vivo.* Clin Cancer Res, 2013. **19**(21): p. 5940-51.
39. Yang, J.Y., et al., *ERK promotes tumorigenesis by inhibiting FOXO3a via MDM2-mediated degradation.* Nat Cell Biol, 2008. **10**(2): p. 138-48.
40. Abdulghani, J. and W.S. El-Deiry, *TRAIL receptor signaling and therapeutics.* Expert Opin Ther Targets, 2010. **14**(10): p. 1091-108.
41. Allen, J.E. and W.S. El-Deiry, *Regulation of the human TRAIL gene.* Cancer Biol Ther, 2012. **13**(12): p. 1143-51.
42. Allen, J.E., et al., *Identification of TRAIL-inducing compounds highlights small molecule ONC201/TIC10 as a unique anti-cancer agent that activates the TRAIL pathway.* Mol Cancer, 2015. **14**: p. 99.
43. Allen, J.E., et al., *Genetic and Pharmacological Screens Converge in Identifying FLIP, BCL2, and IAP Proteins as Key Regulators of Sensitivity to the TRAIL-Inducing Anticancer Agent ONC201/TIC10.* Cancer Res, 2015. **75**(8): p. 1668-74.
44. Ausserlechner, M.J., et al., *Therapy-resistant acute lymphoblastic leukemia (ALL) cells inactivate FOXO3 to escape apoptosis induction by TRAIL and Noxa.* Oncotarget, 2013. **4**(7): p. 995-1007.
45. Cantarella, G., et al., *TRAIL-related neurotoxicity implies interaction with the Wnt pathway in human neuronal cells in vitro.* J Neurochem, 2008. **105**(5): p. 1915-23.
46. Castro Alves, C., et al., *Leukemia-initiating cells of patient-derived acute lymphoblastic leukemia xenografts are sensitive toward TRAIL.* Blood, 2012. **119**(18): p. 4224-7.
47. Cheong, H.J., et al., *Up-regulation of the DR5 expression by proteasome inhibitor MG132 augments TRAIL-induced apoptosis in soft tissue sarcoma cell lines.* Cancer Res Treat, 2011. **43**(2): p. 124-30.
48. Ding, L., et al., *Cisplatin restores TRAIL apoptotic pathway in glioblastoma-derived stem cells through up-regulation of DR5 and down-regulation of c-FLIP.* Cancer Invest, 2011. **29**(8): p. 511-20.
49. Dorsey, J.F., et al., *Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and paclitaxel have cooperative in vivo effects against glioblastoma multiforme cells.* Mol Cancer Ther, 2009. **8**(12): p. 3285-95.
50. Ehrhardt, H., et al., *Cell cycle-arrested tumor cells exhibit increased sensitivity towards TRAIL-induced apoptosis.* Cell Death Dis, 2013. **4**: p. e661.
51. Gasparini, C., et al., *TRAIL-based therapeutic approaches for the treatment of pediatric malignancies.* Curr Med Chem, 2013. **20**(17): p. 2254-71.
52. Grisendi, G., et al., *Mesenchymal progenitors expressing TRAIL induce apoptosis in sarcomas.* Stem Cells, 2015. **33**(3): p. 859-69.
53. Guiho, R., et al., *TRAIL-based therapy in pediatric bone tumors: how to overcome resistance.* Future Oncol, 2015. **11**(3): p. 535-42.
54. Hori, T., et al., *Ionizing radiation enhances tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis through up-regulations of death receptor 4*

(DR4) and death receptor 5 (DR5) in human osteosarcoma cells. J Orthop Res, 2010. **28**(6): p. 739-45.
55. Ishizawa, J., et al., *ONC201 Exerts p53-Independent Cytotoxicity Through TRAIL and DR5 Induction In Mantle Cell Lymphomas.* Blood, 2013. **122**(21): p. 3822.
56. Ivanov, V.N. and T.K. Hei, *A role for TRAIL/TRAIL-R2 in radiation-induced apoptosis and radiation-induced bystander response of human neural stem cells.* Apoptosis, 2014. **19**(3): p. 399-413.
57. Kim, K., et al., *Molecular determinants of response to TRAIL in killing of normal and cancer cells.* Clin Cancer Res, 2000. **6**(2): p. 335-46.
58. Kim, M., et al., *TRAIL inactivates the mitotic checkpoint and potentiates death induced by microtubule-targeting agents in human cancer cells.* Cancer Res, 2008. **68**(9): p. 3440-9.
59. Kluttermann, K., et al., *TRAIL-induced cytotoxicity in a melphalan-resistant rhabdomyosarcoma cell line via activation of caspase-2.* Anticancer Res, 2006. **26**(1A): p. 351-6.
60. Kontny, H.U., et al., *Sensitivity of Ewing's sarcoma to TRAIL-induced apoptosis.* Cell Death Differ, 2001. **8**(5): p. 506-14.
61. Lim, B., et al., *Targeting TRAIL in the treatment of cancer: new developments.* Expert Opin Ther Targets, 2015. **19**(9): p. 1171-85.
62. Naumann, I., et al., *Bortezomib primes neuroblastoma cells for TRAIL-induced apoptosis by linking the death receptor to the mitochondrial pathway.* Clin Cancer Res, 2011. **17**(10): p. 3204-18.
63. Picarda, G., et al., *Preclinical evidence that use of TRAIL in Ewing's sarcoma and osteosarcoma therapy inhibits tumor growth, prevents osteolysis, and increases animal survival.* Clin Cancer Res, 2010. **16**(8): p. 2363-74.
64. Plasilova, M., et al., *TRAIL (Apo2L) suppresses growth of primary human leukemia and myelodysplasia progenitors.* Leukemia, 2002. **16**(1): p. 67-73.
65. Reuss, D.E., et al., *Sensitivity of malignant peripheral nerve sheath tumor cells to TRAIL is augmented by loss of NF1 through modulation of MYC/MAD and is potentiated by curcumin through induction of ROS.* PLoS One, 2013. **8**(2): p. e57152.
66. Rezacova, M., et al., *The importance of abrogation of G2-phase arrest in combined effect of TRAIL and ionizing radiation.* Acta Biochim Pol, 2005. **52**(4): p. 889-95.
67. Robinson, G.L., et al., *Switching from aerobic glycolysis to oxidative phosphorylation modulates the sensitivity of mantle cell lymphoma cells to TRAIL.* Oncogene, 2012. **31**(48): p. 4996-5006.
68. Sheard, M.A., et al., *Membrane-bound TRAIL supplements natural killer cell cytotoxicity against neuroblastoma cells.* J Immunother, 2013. **36**(5): p. 319-29.
69. Siegelin, M.D., *Utilization of the cellular stress response to sensitize cancer cells to TRAIL-mediated apoptosis.* Expert Opin Ther Targets, 2012. **16**(8): p. 801-17.
70. Snell, V., et al., *Activity of TNF-related apoptosis-inducing ligand (TRAIL) in haematological malignancies.* Br J Haematol, 1997. **99**(3): p. 618-24.
71. Sonnemann, J., et al., *Histone deacetylase inhibitors induce cell death and enhance the apoptosis-inducing activity of TRAIL in Ewing's sarcoma cells.* J Cancer Res Clin Oncol, 2007. **133**(11): p. 847-58.

72. Subbiah, V., et al., *Targeting the apoptotic pathway in chondrosarcoma using recombinant human Apo2L/TRAIL (dulanermin), a dual proapoptotic receptor (DR4/DR5) agonist.* Mol Cancer Ther, 2012. **11**(11): p. 2541-6.
73. Tomek, S., et al., *Trail-induced apoptosis and interaction with cytotoxic agents in soft tissue sarcoma cell lines.* Eur J Cancer, 2003. **39**(9): p. 1318-29.
74. Tsurushima, H., et al., *Radioresponsive tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) gene therapy for malignant brain tumors.* Cancer Gene Ther, 2007. **14**(8): p. 706-16.
75. Unnithan, J. and R.M. Macklis, *TRAIL induction by radiation in lymphoma patients.* Cancer Invest, 2004. **22**(4): p. 522-5.
76. van Dijk, M., et al., *Resistance to TRAIL in non-transformed cells is due to multiple redundant pathways.* Cell Death Dis, 2013. **4**: p. e702.
77. Wagner, J., et al., *The angular structure of ONC201, a TRAIL pathway-inducing compound, determines its potent anti-cancer activity.* Oncotarget, 2014. **5**(24): p. 12728-37.
78. Wang, S. and W.S. El-Deiry, *TRAIL and apoptosis induction by TNF-family death receptors.* Oncogene, 2003. **22**(53): p. 8628-33.
79. Wu, J., et al., *Ether a go-go 1 silencing in combination with TRAIL overexpression has synergistic antitumor effects on osteosarcoma.* Cancer Biother Radiopharm, 2013. **28**(1): p. 65-70.
80. Yoshida, T., et al., *Lipoxygenase inhibitors induce death receptor 5/TRAIL-R2 expression and sensitize malignant tumor cells to TRAIL-induced apoptosis.* Cancer Sci, 2007. **98**(9): p. 1417-23.
81. Ishizawa, J., et al., *ATF4 induction through an atypical integrated stress response to ONC201 triggers p53-independent apoptosis in hematological malignancies.* Sci Signal, 2016. **9**(415): p. ra17.
82. Talekar, M.K., et al., *ONC201 induces cell death in pediatric non-Hodgkin's lymphoma cells.* Cell Cycle, 2015. **14**(15): p. 2422-8.
83. Wang, M., *New Kid on the Block: ONC201 in NHL.* Cell Cycle, 2015: p. 0.
84. Karpel-Massler, G., et al., *TIC10/ONC201 synergizes with Bcl-2/Bcl-xL inhibition in glioblastoma by suppression of Mcl-1 and its binding partners in vitro and in vivo.* Oncotarget, 2015.
85. Kline, C.L., et al., *ONC201 kills solid tumor cells by triggering an integrated stress response dependent on ATF4 activation by specific eIF2alpha kinases.* Sci Signal, 2016. **9**(415): p. ra18.
86. Hayes-Jordan, A., et al., *Death receptor expression and sensitivity targeted in Desmoplastic Small Round Cell Tumor.* Pediatric Blood and Cancer, 2015. **DOI 10.1002**(SIOP Abstracts): p. O-154.
87. Madhukar, N.S., et al., *D2-like dopamine receptor antagonism by ONC201 identified by confluence of computational, receptor binding, and clinical studies.* AACR, 2016.
88. Allen, J.E., *DRD2 (and DRD3 and DRD4) versus DRD1 and DRD5 influence anti-cancer response of dopamine agonists.* personal communication on March 24, 2016, 2016.
89. Cherubini, E., et al., *Genetic and Functional Analysis of Polymorphisms in the Human Dopamine Receptor and Transporter Genes in Small Cell Lung Cancer.* J Cell Physiol, 2016. **231**(2): p. 345-56.

90. Trzaskowski, B., et al., *Action of molecular switches in GPCRs--theoretical and experimental studies.* Curr Med Chem, 2012. **19**(8): p. 1090-109.
91. Gilman, A.G., *G proteins: transducers of receptor-generated signals.* Annu Rev Biochem, 1987. **56**: p. 615-49.
92. Bayliss, A.L. and P.D. Evans, *Characterisation of AmphiAmR11, an amphioxus (Branchiostoma floridae) D2-dopamine-like G protein-coupled receptor.* PLoS One, 2013. **8**(11): p. e80833.
93. Stein, M.N., et al., *First-in-human dose escalation of oral ONC201 in advanced solid tumors.* AACR-EORTC, 2015.
94. Tang, L.H., et al., *Well-Differentiated Neuroendocrine Tumors with a Morphologically Apparent High-Grade Component: A Pathway Distinct from Poorly Differentiated Neuroendocrine Carcinomas.* Clin Cancer Res, 2015.
95. Greer, Y.E. and S. Lipkowitz, *TIC10/ONC201: a bend in the road to clinical development.* Oncoscience, 2015. **2**(2): p. 75-6.
96. Mlika, M., et al., *CD56 antibody: old-fashioned or still trendy in endocrine lung tumors.* J Immunoassay Immunochem, 2015. **36**(4): p. 414-9.
97. Kang, H.J., et al., *EWS-WT1 oncoprotein activates neuronal reprogramming factor ASCL1 and promotes neural differentiation.* Cancer Res, 2014. **74**(16): p. 4526-35.
98. Oncoceutics, I., *Clinical Investigator's Brochure ONC201.* 2015.
99. Krawczyk, N., et al., *Prognostic relevance of induced and spontaneous apoptosis of disseminated tumor cells in primary breast cancer patients.* BMC Cancer, 2014. **14**: p. 394.
100. Tajima, H., et al., *Neoadjuvant chemotherapy with gemcitabine for pancreatic cancer increases in situ expression of the apoptosis marker M30 and stem cell marker CD44.* Oncol Lett, 2012. **3**(6): p. 1186-1190.
101. Olofsson, M.H., et al., *Specific demonstration of drug-induced tumour cell apoptosis in human xenografts models using a plasma biomarker.* Cancer Biomark, 2009. **5**(3): p. 117-25.
102. Lenders, J.W., et al., *Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline.* J Clin Endocrinol Metab, 2014. **99**(6): p. 1915-42.
103. Zuber, S.M., V. Kantorovich, and K. Pacak, *Hypertension in pheochromocytoma: characteristics and treatment.* Endocrinol Metab Clin North Am, 2011. **40**(2): p. 295-311, vii.
104. Pacak, K., *Preoperative management of the pheochromocytoma patient.* J Clin Endocrinol Metab, 2007. **92**(11): p. 4069-79.
105. Martucci, V.L. and K. Pacak, *Pheochromocytoma and paraganglioma: diagnosis, genetics, management, and treatment.* Curr Probl Cancer, 2014. **38**(1): p. 7-41.
106. Lu, J.H., et al., *Dopamine D2 Receptor Is Involved in Alleviation of Type II Collagen-Induced Arthritis in Mice.* Biomed Res Int, 2015. **2015**: p. 496759.
107. Buttarelli, F.R., et al., *The dopaminergic system in peripheral blood lymphocytes: from physiology to pharmacology and potential applications to neuropsychiatric disorders.* Curr Neuropharmacol, 2011. **9**(2): p. 278-88.
108. Huang, X.F., et al., *Dopamine transporter and D2 receptor binding densities in mice prone or resistant to chronic high fat diet-induced obesity.* Behav Brain Res, 2006. **175**(2): p. 415-9.

109. Jensen, R., *Effects of Dopamine D2-Like Receptor Antagonists on Light Responses of Ganglion Cells in Wild-Type and P23H Rat Retinas.* PLoS One, 2015. **10**(12): p. e0146154.
110. Sanchez-Soto, M., et al., *Evidence for Non-Canonical Neurotransmitter Activation: Norepinephrine as a Dopamine D2-like Receptor Agonist.* Mol Pharmacol, 2016.
111. Seeman, P., *All roads to schizophrenia lead to dopamine supersensitivity and elevated dopamine D2(high) receptors.* CNS Neurosci Ther, 2011. **17**(2): p. 118-32.
112. Tolstanova, G., et al., *Role of Dopamine and D2 Dopamine Receptor in the Pathogenesis of Inflammatory Bowel Disease.* Dig Dis Sci, 2015. **60**(10): p. 2963-75.
113. Weiss, D.R., et al., *Conformation guides molecular efficacy in docking screens of activated beta-2 adrenergic G protein coupled receptor.* ACS Chem Biol, 2013. **8**(5): p. 1018-26.
114. Saveanu, A., et al., *Expression of somatostatin receptors, dopamine D(2) receptors, noradrenaline transporters, and vesicular monoamine transporters in 52 pheochromocytomas and paragangliomas.* Endocr Relat Cancer, 2011. **18**(2): p. 287-300.
115. Castellone, M.D., et al., *Cross talk between the bombesin neuropeptide receptor and Sonic hedgehog pathways in small cell lung carcinoma.* Oncogene, 2015. **34**(13): p. 1679-87.
116. Guo, M., X. Qu, and X.Q. Qin, *Bombesin-like peptides and their receptors: recent findings in pharmacology and physiology.* Curr Opin Endocrinol Diabetes Obes, 2015. **22**(1): p. 3-8.
117. Oremek, G.M. and N. Sapoutzis, *Pro-gastrin-releasing peptide (Pro-GRP), a tumor marker for small cell lung cancer.* Anticancer Res, 2003. **23**(2A): p. 895-8.
118. Qin, X.Q. and X. Qu, *Extraintestinal roles of bombesin-like peptides and their receptors: lung.* Curr Opin Endocrinol Diabetes Obes, 2013. **20**(1): p. 22-6.
119. Zhou, J., et al., *Bombesin/gastrin-releasing peptide receptor: a potential target for antibody-mediated therapy of small cell lung cancer.* Clin Cancer Res, 2003. **9**(13): p. 4953-60.
120. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.