Phase II Study of Ibrutinib in Advanced Carcinoid and Pancreatic Neuroendocrine Tumors

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Ibrutinib

Clinical Trial Protocol …

Phase II Study of ibrutinib in advanced carcinoid and pancreatic neuroendocrine tumors

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5-HIAA	Urinary 5-hydroxyindole acetic acid
AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/SGPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/SGOT
BG	Blood Glucose
CPO	Clinical Pharma Organization
CRF	Case Report/Record Form
CRO	Contract Research Organization
CT	Computer Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DM	Diabetes Mellitus
ECG	Electrocardiogram
GCP	Good Clinical Practices
GEP	Gastroenteropancreatic
GI	Gastrointestinal
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Intramuscular
ITT	Intent to Treat
i.v.	intravenous(ly)
IRB	Institutional Review Board
LAR	Long Acting Release
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
PFS	Progression-Free Survival
PK/PD	Pharmacokinetic/Pharmacodynamic
SAE	Serious Adverse Event
s.c.	Subcutaneous
SSA	Somatostatin Analog
SOP	Standard Operating Procedure
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit Normal

1. Background

1.1 Overview of Neuroendocrine Tumors

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies characterized by a relatively indolent rate of growth and a propensity to produce and secrete a variety of hormones, biogenic amines and other vasoactive peptides. Although they may arise in a variety of organs, NETs predominate within the pancreas (pNETs) and the gastrointestinal (GI) tract (carcinoids), where they originate from the islets of Langerhans and endocrine (enterochromaffin) cells, respectively[1].

Carcinoid tumors have distinct clinical features depending on their site of origin. In fact, based on their embryologic derivation, NETs are often subclassified as foregut (bronchial, stomach, duodenal), midgut (jejunal, ileal, cecal, appendiceal) and hindgut (distal colon and rectal) tumors[2]. While hindgut carcinoid tumors are rarely associated with a hormonal syndrome, metastatic midgut carcinoid tumors usually produce serotonin and other vasoactive substances which give rise to the typical carcinoid syndrome[3]. This syndrome primarily manifests as diarrhea and flushing, a vasomotor phenomenon which causes redness and warmth in the face and upper torso. Carcinoid heart disease, characterized by fibrosis of the tricuspid and pulmonic heart valves, can also occur in patients with severe and prolonged elevation of circulating serotonin. Tumor growth rates also correlate with site of origin. In the metastatic setting, midgut carcinoid tumors tend to behave in the most indolent fashion, whereas NETs originating in the foregut or hindgut regions tend to behave more aggressively once they have metastasized.

pNETs can secrete peptide hormones including insulin, gastrin, glucagon and vasoactive intestinal peptide (VIP). However, most pNETs are unassociated with a hormonal syndrome and are therefore termed “nonfunctioning”[3].

Recent epidemiological data suggest a rising incidence of NETs and increased survival durations over time, but the long-term outcome of patients with advanced-stage disease still remains poor[4-7]. Although historically perceived as similar entities, it is increasingly clear that low- and intermediate-grade pNETs and carcinoid tumors have different biology and respond differently to therapeutic agents. Carcinoid tumors are relatively insensitive to conventional chemotherapy and have no established treatment other than somatostatin analogs (SSAs)[8]. Initially developed to palliate hormonal symptoms, SSAs such as octreotide and lanreotide have been also shown to slow tumor progression in patients with advanced carcinoid tumors. In fact, the randomized phase III PROMID trial evaluated octreotide long-acting repeatable (LAR) versus placebo in patients with metastatic midgut NETs and demonstrated a significant improvement in time-to-progression[9]. More recently, the CLARINET trial randomized patients with hormonally nonfunctioning gastroenteropancreatic NETs to receive depot-lanreotide versus placebo, also demonstrating a statistically significant improvement in progression-free survival (PFS)[10]. pNETs appear to be more sensitive to cytotoxic chemotherapy[11], however there are no placebo-controlled chemotherapy trials and the role of cytotoxic drugs remains controversial. Approved treatment agents for pNETs include everolimus and sunitinib. The mTOR inihibitor everolimus was recently found to significantly prolong PFS in patients with advanced pNETs[12]. A randomized phase III trial of sunitinib, a multitargeted tyrosine kinase inhibitor, in pNETs demonstrated significant improvement in PFS from 5.5 months on the control arm to 11.4

months on the experimental arm[13]. Despite these encouraging results in terms of PFS prolongation, tumor regression is uncommon with targeted agents and no overall survival benefit has been demonstrated[14].

Although impressive progress in the biotherapy field has been made over the last decade, no proven therapeutic options for patients progressing on initial therapy are currently available and response to second line therapies is poorly documented, as demonstrated by lack of recommendations from recent consensus statements[5]. Therefore, there is an urgent need for new and effective agents for both carcinoids and pNETs, and novel cellular and molecular targets needs to be exploited.

1.2 Mast cells as a target for NET therapy

Although often regarded as a host defensive response to the tumor, inflammation has been recently qualified as a collateral consequence of the extensive tissue remodeling that tumor cells mediate within their microenvironment via inflammatory cells such as macrophages, neutrophils, lymphocytes and mast cells[15]. Consistent with this idea, many studies have demonstrated that expansion and maintenance of macroscopic tumors is highly dependent on the actions of inflammatory cells. Recently, chronic activation of Myc in a mouse model of pancreatic β–cell tumorigenesis has been reported to be sufficient to initiate and orchestrate a complex inflammatory and angiogenic response, characterized by a rapid influx of mast cells into the tumor and its adjacent mesenchyma. Furthermore, mast cell recruitment has been described as essential for tumor angiogenesis and macroscopic expansion[16]. Thus, inflammation has been proposed as an "oncogene's weapon" crucial for the development of insulinomas. Mast cells, in particular, have emerged as putative targets for NET therapy.

Reportedly[16], systemic treatment of mice harboring islet–cell tumors with the mast cell inhibitor sodium chromoglycate induces rapid onset of hypoxia and extensive death of tumor and endothelial cells, leading to tumor regression. However in humans, sodium chromoglycate has poor systemic bioavailability. Thus, more systemically effective and tolerable inhibitors of mast cell function should be tested in clinical trials.

1.3 Ibrutinib

Ibrutinib is a novel first-in-class, orally administered, covalent inhibitor of Bruton's tyrosine kinase (Btk). Its chemical name is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and the molecular weight is 440.50 g/mole. Ibrutinib is currently approved for patients with mantle cell lymphoma or chronic lymphoid leukemia (CLL) who have received at least one prior therapy and in patients with CLL with 17p deletion.

1.3.1 Ibrutinib preclinical experience

In preclinical models, ibrutinib has been shown to covalently bind to a cysteine residue (Cys-481) in the Btk active site, thus resulting in a sustained inhibition of the target[17]. Btk is required for B-cell receptor (BCR) signaling[18] but is also critical for mast cell degranulation, acting downstream of the high-affinity IgE receptor FcεRI[19]. Based on preclinical data, blockade of the BCR signaling pathway by ibrutinib has two major effects: 1) direct induction of apoptosis and

2) inhibition of cell homing and migration to inflammatory chemokines and subsequent adhesion to cellular substrates[20,21]. Since the Btk protein is expressed in most hematopoietic cells with the exception of T cells and natural killer (NK) cells[18], a wide range of immunomodulatory effects are expected following ibrutinib administration. Recently, ibrutinib has been found to block the expansion of Myc-driven insulinomas by inhibiting mast cell degranulation. In particular, ibrutinib was shown to trigger collapse of tumor vasculature, thus leading to a dramatic tumor regression[22]. This is consistent with the idea that islet–cell tumorigenesis is causally linked, and continuously dependent on, infiltration of mast cells[16] and that signals from the microenvironment are drivers of disease progression in solid cancers[23]. In addition, ibrutinib has been found to apparently inhibit the proliferation of neoplastic islet-cell, although the mechanisms underlying this unexpected therapeutic benefit remain unclear[22].

1.3.1.1 Pharmacodynamics

Pharmacodynamic assays have been used to demonstrate the on-target effect of ibrutinib. Preclinical, in vitro models have shown the selectivity of the drug in the inhibition of Btk, as compared to other members of the closely related Tec and Src1/Ab1 family kinase (Table 1-3-1-1).

Table 1-3-1-1: Median IC_{50} Values of Ibrutinib Toward Selected Tec and Src/Ab1 Family Kinases

Kinase[a]	Median IC_{50} (nM)	N[b]	Selectivity for BTK[c]	Kinase	Median IC50 (nM)	N	Selectivity for Btk
Btk*	0.39	7	1.0	PAK1	3737	1	9582
ErbB4/HER4*	0.64	2	1.6	mTor/FRAP1	4253	1	10905
Blk*	0.94	2	2.4	TRKB	4472	1	11467
Bmx/Etk*	1.10	2	2.8	MEK2	5003	1	12828
Fgr	2.86	2	7.3	MEKK3	5133	1	13162
Txk*	2.87	1	7.4	Fms	5149	2	13203
Lck	3.49	4	9.0	TRKA	5595	1	14346
Yes/YES1	3.94	2	10	Fer	5635	2	14449
Tec*	5.49	2	14	NEK2	12630	1	32385
Csk	6.17	2	16	CAMK1a	18950	1	48590
EGFR*	7.80	6	20	AKT1	>20000	1	>51282
Brk	10.10	2	26	AMPK(A1/B1/G1)	>20000	1	>51282
Itk*	11.70	3	30	Axl	>20000	1	>51282
Hck	16.98	2	44	c-Met	>20000	1	>51282
ErbB2/HER2*	21.57	2	55	Cdk1/cyclin B	>20000	1	>51282
JAK3*	21.90	3	56	ERK1	>20000	1	>51282

[a] Kinases labeled with an asterisk (*) have a cysteine in the active site representing a possible target for covalent binding with ibrutinib.
[b] N = number of independent assays from which median IC_{50} values were determined.
[c] Selectivity ratios were calculated using non-rounded values.

Moreover, use of a fluorescent probe assay have shown that a single dose of ibrutinib as low as 2.5 mg/kg is sufficient to fully occupy BTK in peripheral blood and tumor tissue for 24 hours in dogs.

1.3.1.2 Pharmacokinetics

After oral administration, ibrutinib exhibited rapid absorption and high plasma clearance in preclinical species. In both rats and dogs, the oral bioavailability was less than 25%. Ibrutinib exposure increased with increasing doses and at dose ≥30 mg/kg was higher in female than in male rats. Gender had no apparent effect on oral exposure in dogs. The mean terminal half-life of ibrutinib after oral administration was less than 5 hours in rodents and 3 to 6 hours in dogs. *In vitro* binding of ibrutinib to plasma protein was high and comparable in mice, rats, dogs, and humans. Ibrutinib was preferentially bound to human serum albumin and less to human α1-acid glycoprotein. The drug is metabolized by CYP3A4/5 and biliary excretion is its major route of elimination in rats.

1.3.1.3 Toxicology

The nonclinical safety profile of ibrutinib has been well characterized through the conduct of single-dose and repeat-dose toxicity studies of up to 13 weeks in duration, and safety pharmacology, genetic toxicity, reproductive and developmental toxicity, immunotoxicity and phototoxicity studies. The primary target organ toxicities were observed in the lymphoid, gastrointestinal and skeletal systems. Ibrutinib was not identified as a mutagen or clastogen. In reproductive studies ibrutinib at 80 mg/kg/day (approximately 14 times the AUC of ibrutinib compared to patients at the dose of 560 mg daily) was associated with increased post-implantation loss, increased visceral malformations (heart and major vessels) and skeletal variations. After immunophenotyping analysis, absolute total B-cell counts were found to be decreased following ibrutinib administration in rats. Minimal phototoxicity potential was identified after evaluation of UV spectrum, photostability, and whole rat distribution data.

1.3.2 Ibrutinib clinical experience

As of 13 December 2013, 24 studies evaluating the safety, efficacy and pharmacokinetics (PK) of ibrutinib have been completed or are ongoing. These include 3 dose-finding Phase 1 studies, 5 studies in healthy volunteers, 7 Phase 2 studies using fixed continuous doses of ibrutinib, 1 Phase 1b study and 1 Phase 2 study combining ibrutinib with chemotherapy or immunotherapy, 5 randomized Phase 3 studies with 3 studies testing single-agent ibrutinib and 2 studies testing ibrutinib in combination, 1 extension study, and 1 extended-treatment rollover safety study for subjects who had participated in previous studies with ibrutinib. Across all studies, malignancies under investigation include chronic lymphocytic leukemia, small lymphocytic lymphoma, mantle-cell lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, multiple myeloma, and Waldenstrom macroglobulinemia. Ibrutinib has never been tested in clinical trials evaluating patients with solid tumors.

1.3.2.1 Pharmacokinetics

The pharmacokinetics (PK) of ibrutinib has been assessed in subjects with B-cell malignancies as well as in healthy subjects. Following oral administration of ibrutinib at doses ranging from 1.25 to 12.5 mg/kg/day as well as fixed dose levels of 420, 560, and 840 mg/day, exposure to

ibrutinib increased as doses increased with substantial intersubject variability. The mean half life (t1/2) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (Tmax) of 2 hours. Administration of 420 mg ibrutinib with a high-fat breakfast in subjects with chronic lymphocytic leukemia (CLL) approximately doubled the mean systemic exposure compared to intake after overnight fasting with median time to Tmax delayed from 2 to 4 hours. Ibrutinib absorption from the GI tract is practically complete, as minimal fecal excretion of unchanged ibrutinib in combination with high levels of oxidative metabolites (liver and gut metabolism) and a lack of reduction products (gut microflora metabolism) was observed. The plasma protein binding of ibrutinib in human plasma is 97.3% and distribution to peripheral tissues is extensive. Ibrutinib is extensively metabolized by CYP3A4 to the dihydrodiol metabolite PCI-45227, a reversible inhibitor of Btk, with approximately 15 times lower inhibitory potency compared to ibrutinib. The metabolite-to-parent AUC ratio ranged from 0.7 to 3.4. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure.

The results of human mass balance study of [14C]-ibrutinib conducted in six healthy male subjects demonstrated that less than 10% of the total dose of [14C]-ibrutinib is renally excreted, whereas approximately 80% is recovered in feces. Subjects with mild and moderate renal insufficiency (creatinine clearance > 30 mL/min) were eligible to enroll in Study PCYC-1102-CA in which pharmacokinetic (PK) assessments were included. No dose adjustment is needed for mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There is no data in patients with severe renal impairment or patients on dialysis. The study of ibrutinib in hepatic impaired subjects is currently in progress.

Significant PK interactions were observed in drug-drug interaction studies in healthy subjects with ketoconazole and rifampin as strong CYP3A4/5 inhibitor and inducer, respectively. On the contrary, *in vitro* data on CYP inhibition and induction do not suggest a clinically relevant effect of ibrutinib or its metabolites on the metabolism of concomitant medications.

1.3.2.2 Ibrutinib in healthy volunteers

In healthy subjects ibrutinib up to 560 mg was generally well tolerated. The most common treatment-emergent adverse events were of grade 1 in severity, with the exception of reported grade 2 headache and rash. Recovery from toxicities was rapid.

1.3.2.3 Ibrutinib in mantle-cell lymphoma

A phase 2 study[25] investigated oral ibrutinib, at a daily dose of 560 mg, in 111 patients with relapsed or refractory mantle-cell lymphoma. Patients were enrolled into two groups: those who had previously received at least 2 cycles of bortezomib therapy and those who had received less than 2 complete cycles of bortezomib or had received no prior bortezomib therapy. The 86% of patients had intermediate-risk or high-risk mantle-cell lymphoma according to clinical prognostic factors. The most common treatment-related adverse events were mild or moderate diarrhea, fatigue, and nausea. Grade 3 or higher hematologic events were infrequent and included

neutropenia (in 16% of patients), thrombocytopenia (in 11%), and anemia (in 10%). A response rate of 68% (75 patients) was observed, with a complete response rate of 21% and a partial response rate of 47%; prior treatment with bortezomib had no effect on the response rate. With an estimated median follow-up of 15.3 months, the estimated median response duration was 17.5 months (95% CI, 15.8 to not reached), the estimated median PFS was 13.9 months (95% CI, 7.0 to not reached), and the median OS was not reached. The estimated rate of overall survival was 58% at 18 months. Based on these data, ibrutinib received FDA approval and should be used at first relapse in patients with mantle-cell lymphoma[26].

1.3.2.4 Ibrutinib in chronic lymphocytic leukemia

Ibrutinib has been tested in a phase 1b-2 multicenter study[27] in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma. A total of 85 patients, the majority of whom were considered to have high-risk disease, received the drug orally once daily; 51 received 420 mg, and 34 received 840 mg. Toxic effects were predominantly grade 1 or 2 and included transient diarrhea, fatigue, and upper respiratory tract infection. The overall response rate was the same in the group that received 420 mg and the group that received 840 mg (71%), and an additional 20% and 15% of patients in the respective groups had a partial response with lymphocytosis. The response was independent of clinical and genomic risk factors present before treatment, including advanced-stage disease, the number of previous therapies, and the 17p13.1 deletion. At 26 months, the estimated PFS rate was 75% and the rate of OS was 83%.

More recently, a multicenter, open-label, phase 3 study[28] has randomized 391 patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma to receive daily ibrutinib or the anti-CD20 antibody ofatumumab. At a median follow-up of 9.4 months, ibrutinib significantly improved PFS; the median duration was not reached in the ibrutinib group (with a rate of PFS of 88% at 6 months), as compared with a median of 8.1 months in the ofatumumab group. At 12 months, the OS rate was 90% in the ibrutinib group and 81% in the ofatumumab group. The overall response rate was significantly higher in the ibrutinib group than in the ofatumumab group (42.6% vs. 4.1%, $P<0.001$). An additional 20% of ibrutinib-treated patients had a partial response with lymphocytosis. Similar effects were observed regardless of whether patients had a chromosome 17p13.1 deletion or resistance to purine analogues. The most frequent nonhematologic adverse events were diarrhea, fatigue, pyrexia, and nausea in the ibrutinib group. Consistent with these results, FDA has granted approval for ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma.

1.3.2.5 Ibrutinib in other hematological malignancies

Phase III trials are underway worldwide to evaluate ibrutinib in the treatment of patients with diffuse large B-cell lymphoma, and the agent is in phase II development for use in follicular lymphoma, multiple myeloma and Waldenstrom macroglobulinemia[29]. Ibrutinib has been investigating as monotherapy or in combination with R-CHOP regimen in patients with diffuse large B-cell lymphoma. Preliminary safety data suggest fatigue, diarrhea, nausea, anemia, and thrombocytopenia as most commonly occurring treatment-emergent adverse events. In myeloma

patients, the most commonly reported toxicities were nausea, diarrhea, arthralgia, muscle spasms and fatigue, anemia, thrombocytopenia, pyrexia and epistaxis. Majority of the adverse events were of Grade 1 or 2 in severity. The most commonly reported Grade 3 adverse events were hypophosphatemia, syncope, and anemia.

1.3.3 Summary of Clinical Safety of ibrutinib

Comment [AT1]: RESPONSE REQUIRED:

Please update Ibrutinib safety language to the following per IB v.9.

Pooled safety data for a total of 1071 subjects treated with ibrutinib monotherapy from 9 studies in B-cell malignancies, which includes subjects from 2 randomized-control studies who crossed over from comparator treatment or placebo to receive ibrutinib monotherapy, are summarized below.

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1071):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Anemia	Hypertension	
Pyrexia	Atrial fibrillation	
Neutropenia		

For more detailed information refer to the current version of the IB.

1.3.3.2 Cytopenias

Treatment-emergent grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib.

1.3.3.3 Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.2).

1.3.3.4. Bleeding-Related Events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis,

and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 5.3 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 5.5 for guidance on ibrutinib management with surgeries or procedures.

1.3.3.5 Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.2).

1.3.3.6 Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity.

1.3.3.7 Second Primary Malignancies

Second primary malignancies, most frequently skin cancers, have occurred in subjects treated with ibrutinib. Second primary malignancies including non-skin carcinomas have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer.

1.3.3.8 Infection

Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib.

1.3.3.9 Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of tumor lysis syndrome are those with comorbidities and/or risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated lactate dehydrogenase (LDH), bulky disease at baseline, and pre-existing kidney abnormalities.

1.4 Study rationale

It is becoming increasingly clear that the microenvironment has a crucial role in the progression of both hematological and solid tumors. In particular, preclinical data suggests that mast cells are recruited within NETs where they remodel the stroma and stimulate angiogenesis, driving macroscopic tumor expansion[16]. Inhibitors of mast cell degranulation have been shown to block this process, driving tumor shrinkage, at least in mouse models[22]. Ibrutinib can affect mast cell degranulation, acting downstream the high affinity IgE receptor FcεRI[19]. Given its favorable risk/benefit ratio for investigation in NETs, we plan to test the hypothesis whether ibrutinib can cause tumor regression in both carcinoid tumors and pNETs.

2. Study objectives

The primary purpose of the study is to determine the objective response rate to ibrutinib therapy in patients with advanced (unresectable or metastatic) low to intermediate grade carcinoid tumors or pNETs.

Secondary objectives are:

- to investigate the progression-free survival (PFS) and overall survival (OS) associated with ibrutinib in patients with advanced carcinoid tumors or pNETs;
- to evaluate the duration of response of carcinoid or pNET patients receiving ibrutinib;
- to assess changes in tumor markers and changes in quality of life (QOL) in NET patients administered with ibrutinib;
- to determine the safety and tolerability of ibrutinib in this patient population.

2.1 Selection of doses

Based on the tolerable side-effect profile of ibrutinib at doses of 560 mg daily in other neoplasms and pharmacokinetic data demonstrating therapeutic drug levels at that level (see section 1.3.2), the dose of ibrutinib in this study will be 560 mg once daily. If tolerability issues occur, the treatment dose may be reduced as described in section 5.2.

3. Endpoints

3.1 Primary endpoints

1. Overall radiographic response rate (ORR), as defined by RECIST v1.1.

3.2 Secondary endpoints

1. Median PFS and PFS rate at 1 year
2. Median OS and OS at 1 year
3. Duration of response
4. Adverse events (AEs)

5. Changes in neuroendocrine tumor markers (such as chromogranin A or pancreatic polypeptide), or hormonal assays (such as urine 5-HIAA, gastrin, glucagon, vasoactive intestinal peptide, etc) if elevated at baseline (> upper limit of normal, ULN);
6. Changes in quality of life (as measured by EORTC questionnaires EORTC QLQ-C30 and QLQ GI.NET21).

3.3 Exploratory endpoint

1. To determine whether the presence and activation of mast cells in the tumor tissue sample predicts for response;
2. To determine whether changes in serum Tryptase-β2 correlate with response.

4. Investigational plan

4.1 Overall study design

This is a prospective phase II open-label trial, stratifying patients equally into two cohorts consisting of carcinoid tumors and pNETs.

4.2 Treatment

The investigational drug used in this study is ibrutinib 560 mg. Ibrutinib will be administered orally once daily and each cycle will be defined as 4 weeks duration. Study treatment should begin within 14 days following enrollment into the study and continue until disease progression, unacceptable toxicity, or withdrawal of consent. Safety and efficacy will be assessed throughout the treatment period.

4.3 Study population

The study population will consist of adult patients with histologically confirmed low to intermediate grade NETs of the GI tract, lungs and unknown primary (carcinoid tumors) or pNETs. All patients must be confirmed to have advanced disease. The study will enroll up to 51 patients in two cohorts (30 carcinoid and 21 pNET patients).

4.4 Inclusion/exclusion criteria

The investigator or his/her designee must ensure that all patients who are offered enrollment in the study meet all of the following inclusion and exclusion criteria:

4.4.1 Inclusion criteria

1. Locally unresectable or metastatic carcinoid or pNET;
2. Measureable disease by RECIST criteria;
3. Tumors must be histologically or cytologically proven and considered low or intermediate grade. Patients with high grade neuroendocrine carcinomas or small cell carcinomas are excluded from the study;
4. Evidence of progressive disease within 12 months of study entry;
5. Allowed prior therapies include:

a) Surgery (major surgery at least more than four weeks prior to baseline assessment);
b) Locoregional therapy such as: chemoembolization, radio-embolization, radiofrequency ablation, radiotherapy as long as there is progressive measurable disease outside the area of locoregional therapy or there is progression in the previously treated areas;
c) Any number of previous lines of systemic therapy. Last treatment before enrollment must have occurred more than 4 weeks for chemotherapy, 6 weeks for antibodies or more than 5 half lives of prior TKIs or small moleculs;

6. Prior or concurrent therapy with somatostatin analogs is permitted for patients with secretory NET;
7. All patients with gastroenteropancreatic NETs must have progressed on (or are intolerant of) prior somatostatin analog;
8. Patients with pancreatic NETs must have have progressed on (or are intolerant of) either everolimus or sunitinib;
9. Age ≥ 18 years;
10. ECOG performance status of 0-2;
11. Life expectancy 12 weeks or more;
12. Adequate bone marrow function as shown by: absolute neutrophil count ≥ 1,000/mm^3, Platelets ≥ 100,000/mm^3, Hb > 10 g/dl;
13. Adequate liver function as shown by: serum bilirubin ≤ 1.5 x ULN, and serum transaminases activity ≤ 2.5 x ULN, with the exception of serum transaminases (< 3 x ULN) if the patient has liver metastases;
14. Adequate renal function as shown by serum creatinine ≤ 2 mg/dl;
15. Women of childbearing potential must have a negative serum pregnancy test within 7 days of the administration of the first study treatment. Women must not be lactating. Both men and women of childbearing potential must be advised of the importance of using effective birth control measures during the course of the study. Childbearing potential for women and men is defined in section 4.4.3;
16. Signed informed consent to participate in the study must be obtained from patients after they have been fully informed of the nature and potential risks by the investigator (or his/her designee) with the aid of written information.

4.4.2 Exclusion criteria

1. High grade NET or small cell neuroendocrine carcinoma;
2. Clinically apparent central nervous system metastases or carcinomatous meningitis;
3. Known positive test for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV);
4. History of stroke or intracranial hemorrhage within 6 months prior to the first dose of study drug;
5. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any class III or IV cardiac disease as defined by the NYHA functional classification;
6. Requirement for anticoagulation with warfarin or similar vitamin K antagonists.

7. Requirement for treatment with a strong cytochrome P450 (CYP) 3A4/5 inhibitor. (See Appendix A)
8. Prior antitumor therapy within 2 weeks of enrollment (with the exception of somatostatin analogs);
9. No other active malignancy within 3 years of enrolment except adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for at least three years;
10. Any medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the patient's safety, interfere with the absorption or metabolism of ibrutinib;
11. Known hypersensitivity to ibrutinib or any component of the ibrutinib formulation;
12. History of noncompliance to medical regimens or unwillingness to comply with the protocol.
13. Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification (see Appendix D)

Comment [AT2]: RESPONSE REQUIRED:

Please include the following exclusion criteria regarding hepatotoxicity.

4.4.3 Definition of childbearing potential

All women are considered of childbearing potential, unless they meet at least one of the following criteria:

a) Females who are menopausal, defined as follows: i) Females who are younger than 55 years old will be considered menopausal if they satisfy all the following three requirements during screening: 1) they are in amenorrhea, defined as absence of menstruation for the previous 12 months; 2) they have a negative urine pregnancy test; and 3) they have a serum FSH level within the laboratory reference range for postmenopausal females; ii) Females who are older than 55 years old: they will be considered menopausal if they are in amenorrhea, defined as absence of menstruation for the previous 12 months before screening.

b) Females who have a documented hysterectomy and/or bilateral oophorectomy and/or tubal ligations.

All men are considered of childbearing potential, unless they meet at least one of the following criteria:

a) Males who have a documented vasectomy more than 6 months prior to the administration of the first study treatment.

b) Female partner/partners who are menopausal (as previously defined) and/or who have a documented hysterectomy and/or bilateral oophorectomy and/or tubal ligations.

5. Study Medication

5.1 Study drug: ibrutinib

The investigational drug used in this study is ibrutinib, available as 140 mg capsules. The inactive ingredients of ibrutinib include: microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate and magnesium stearate.

Pharmacyclics will supply ibrutinib as long as the patient remains on study, shows continuous benefit from treatment, and there are no safety concerns. Ibrutinib should be stored at room temperature (20°C to 25°C, equivalent to 68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F to 86°F).

The starting dose is 560 mg (four 140 mg capsules) taken once daily orally. Doses should be taken approximately the same time each day, without scheduled breaks. Patients who vomit anytime after taking a dose should not "make it up" with extra doses, but instead resume subsequent doses as planned. Any missed dose may be taken as soon as possible on the same day with a return to the normal schedule the following day. If doses are missed or vomited, this must be indicated in the source documents and CRFs. A treatment cycle will be defined as 4 weeks duration. To monitor the correct self-administration of ibrutinib, enrolled patients will be provided with a diary.

Study treatment should begin within 14 days following enrollment onto the study. Patients should be requested to bring their unused medication to the clinic each visit. Compliance should be verified by the investigator's staff through counting the number of capsules consumed between visits. The investigator (or his/her designee) will document dosage administration and all dose changes during the study in the CRF. The dose, amount dispensed, amount received, and amount remaining unused must be recorded.

Patients will be assessed for response after every 3 cycles (12 weeks) of therapy. Patients with evidence of stable disease or response to therapy as defined by RECIST v1.1 will continue protocol therapy. The dose of ibrutinib will be adjusted for toxicity as outlined below. Patients with unacceptable toxicity or progressive disease will discontinue protocol therapy.

5.2 Dose Modification

Ibrutinib should be held or reduced in dose for toxicity or for concomitant use of CYP3A inhibitors (see Appendix A), as described in the sections below. Ibrutinib dosing adjustments are to be made according to the greatest degree of toxicity observed. Doses of ibrutinib which have been reduced for toxicity may not be re-escalated. All interruptions or changes to study drug administration must be recorded. If any patient discontinues study treatment or post-treatment observation, then the reason will be recorded.

Patients experiencing drug-related toxicities that are grade 1 or 2 according to CTCAE criteria should continue ibrutinib without dose modification. However the investigator may reduce the dose by one level if a grade 2 toxicity persists and significantly affects patient quality of life. If a patient experiences a CTCAE grade 3 or higher non-hematological toxicity, a grade 3 or higher neutropenia with infection or fever, or a grade 4 hematological event that is considered drug-related, ibrutinib should be held until resolution of toxicity to ≤ grade 1. Then the drug should be reinitiated at the starting dose. If the toxicity reoccurs, the dose should be reduced by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed as per Table 5-2. If a patient experiences these drug-related toxicities despite two dose reductions, ibrutinib should be discontinued and the patient should be taken off the study. Patients should also be removed from study if off treatment for >3 weeks.

Recommended dose modifications for these toxicities are described below:

Table 5-2: Recommended dose modifications for ibrutinib

Toxicity occurrence	Dispensed As
First	Restart at 560 mg daily
Second	Restart at 420 mg daily
Third	Restart at 280 mg daily
Fourth	Discontinue Ibrutinib

5.2.1 Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant hepatic impairment at the time of screening (Child-Pugh class B or C) are excluded from study participation. For subjects who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib is to a level of 280 mg daily (two capsules). For subjects who develop moderate to severe liver impairment while on study (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule). Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better. Subjects will be monitored for signs of toxicity and follow dose modification guidance as needed (Refer to Appendix D).

Comment [AT3]: RESPONSE REQUIRED:

Please include the following required dose modification language on hepatic impairment.

5.3 Concomitant therapy

- All patients should be maintained on the same medications throughout the study period, as medically feasible;
- The investigator should instruct the patient to notify the study staff about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be recorded;
- Administration of pegfilgrastim or filgrastim following initiation of protocol therapy is at invesigator's discretion for all patients;
- Administration of erythropoietin or darbopoietin is allowed;
- Other concurrent investigational drugs of any type are not allowed in the trial;
- Other concurrent anticancer agents (with the exception of somatostatin analogs) are not allowed in the trial;
- Patients must be instructed not to take any additional medications (including herbal supplements and over-the-counter products) during the trial without prior consultation with the investigator. All medications taken within 30 days of screening should be recorded. If concomitant therapy must be added or changed, the reason and name of the drug/therapy should be recorded;
- In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g. antiemetics or steroids), with the following exceptions:
- CYP3A Inhibitors/Inducers
    - Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

Strong inhibitors of CYP3A (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, or cobicistat) should be avoided

- If a strong CYP3A inhibitor (see Appendix A) must be used, ibrutinib will be reduced to 140 mg or withheldfor the duration of inhibitor use.. Subjects will be monitored more closely for signs of ibrutinib toxicity (at the investigator's discretion). If a moderate CYP3A inhibitor (see Appendix A) must be used, ibrutinib will be reduced to 140 mg (for 840 mg/day dose, reduce to 280mg) for the duration of the inhibitor use. No dose adjustment is required in combination with mild inhibitors.
- Grapefruit and Seville oranges should be avoided during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Appendix A)
- Co-administration of ibrutinib with strong CYP3A inducer, rifampin, in healthy subjects decrease ibrutinib plasma concentrations by approximately 10-fold. Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.
-
- A list of common CYP3A inhibitors and inducers is provided in Appendix A. A comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/ This website is continually revised and should be checked frequently for updates.

- Anti-platelet Agents and Anticoagulants:
  - Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. For guidance on ibrutinib and the use of anticoagulants during procedures/surgeries see Section 5.5.
  - Patients who need to be on anticoagulant therapy during treatment with ibrutinib should be treated with low molecular weight heparin as the preferred therapy. Patients who are on full dose anticoagulation therapy while being treated with ibrutinib and who experience concurrent grade 3 or 4 thrombocytopenia/bleeding despite single ibrutinib dose reduction will permanently discontinue ibrutinib treatment.
  - Subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

5.3.1 Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC50 of 2.15 μg/mL). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available; therefore, co-administration of narrow therapeutic index P-gp substrates (eg, digoxin) with ibrutinib may increase their blood concentration and should be used with caution and monitored closely for toxicity.

5.3.1.1 QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic ECG and electrolyte monitoring should be considered.

5.3.1.2 Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 5.5).

5.4 Interruption or Discontinuation of Treatment

Patients may be removed from study for the following reasons:

- Documented disease progression or symptomatic tumor progression. In the case of symptomatic tumor progression, all efforts should be made to document disease status radiologically prior to removal from study;
- Occurrence of unacceptable toxicity (see table 5-2 regarding dose modifications for toxicity). Patients removed from treatment for intolerable toxicity should still be followed with regular tumor assessments until disease progression or start of a new treatment;
- Patient has been off treatment for >3 weeks;
- The patient chooses to terminate participation in the study;
- At the discretion of the investigator;
- If, at any time, the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event the study chairs should be notified, the reasons for discontinuation should be documented, and the patient should be followed as appropriate per study.

5.5 Guidelines for Ibrutinib Management with Surgeries or Procedure

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for patients who require surgical intervention or an invasive procedure while receiving ibrutinib:

5.5.1. Minor Surgical Procedures
For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure.

5.5.2. Major Surgical Procedures
For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

5.5.3. Emergency Procedures
For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

6. Visit schedule and assessments

6.1 Pretreatment Evaluation
Baseline tumor and patient characteristics including:

- Patient demographics: age, gender and race
- Medical history;
- Medications;
- ECOG performance status;
- Type of neuroendocrine tumor: primary site (if known) vs. unknown;
- Differentiation or grade (if available);
- Known sites of metastases;
- Presence or absence of hormonal syndrome (carcinoid syndrome, gastrinoma syndrome, insulinoma syndrome, etc.);
- Presence or absence of a pathologically elevated hormone or biomarker;
- EORTC QLQ C-30 and EORTC QLQ GI-NET21 questionnaires.

Tests to be performed within 28 ±2 days prior to initiation of therapy (if day 28 falls on a weekend or holiday the deadline may be extended to the next working day):

- Radiologic assessment of tumor burden by CT scan or MRI; In all cases, imaging studies should encompass the abdomen and any other known sites of measurable disease. For small bowel NETs, imaging of the abdomen and pelvis is recommended. For pancreatic NETs, abdominal imaging is sufficient if there are no known extra abdominal sites. For lung NETs, imaging of the thorax and abdomen is recommended.
- Assessment of secretory proteins. All patients will undergo an initial assessment of chromogranin A. Patients with suspected serotonin-producing tumors (and all patients with midgut carcinoid tumors) will have a 24 hour urine 5-HIAA measured at baseline. Other possible neuroendocrine tumor markers/hormones (e.g. pancreatic polypeptide,

gastrin, glucagon, etc.) may be collected at the discretion of the investigator based on clinical symptoms and tumor location.

Tests to be performed within 14 ±2 days prior to initiation of therapy (if day 14 falls on a weekend or holiday the deadline may be extended to the next working day):

- History and physical evaluation including height, weight, vital signs and performance status;
- Baseline hematological and biochemical profiles including CBC with differential and comprehensive metabolic panel (fasting glucose, sodium, potassium, calcium, chloride, bicarbonate, creatinine, blood urea nitrogen, albumin, SGOT (AST) SGPT (ALT) total bilirubin and alkaline phosphatase);
- Serum pregnancy test for women of childbearing potential;
- Correlative laboratory studies with the potential to correlate with response to the treatment (measurement of serum Tryptase-β2).

6.2 Evaluations During Treatment

Beginning of every cycle (defined as 28 ±2 days):

- Physical examination;
- Toxicity assessment;
- Vital signs;
- Weight;
- ECOG performance status;
- CBC with differential;
- Fasting comprehensive metabolic panel;
- Assessment of adverse events.

Data to be obtained every 3 cycles ±1 week of treatment until disease progression, unacceptable toxicity or withdrawal of consent:

- Radiologic assessment of tumor burden by CT scan or MRI;
- Assessment of chromogranin A and/or other tumor markers or hormones if elevated at baseline (see section 6.1);
- EORTC QLQ C-30 and EORTC QLQ GI-NET21 questionnaires;
- Correlative laboratory studies (see section 6.1).

Patients who have an ongoing grade 4 or serious adverse event at the time of discontinuation from study drug treatment will continue to be followed at no less than monthly intervals, until resolution of toxicity to less than grade 2.

6.3 Instructions for processing correlative laboratory studies

Correlative laboratory studies will include the assessment of blood- and tissue-based biomarkers with the potential to correlate with response to treatment.

6.3.1 Blood-based biomarkers

Blood will be collected every three months. Serum measurement of Tryptase-β2 will be performed by ELISA in the Translational Research Core of the Moffitt Cancer Center.

6.3.2 Tissue-based biomarkers:

If available, archival tissue containing a tumor block (preferred) or 10 unstained slides (3-5 micron thick) from patient's primary or metastatic neuroendocrine tumor should be sent to Moffitt Cancer Center for correlative immunohistochemical studies. Specimens should be placed in a secure, airtight container, labeled with the patient name and study number.
Site should contact Moffitt Cancer Center at (813) 745-3275 with expected delivery date.

Shipping address:
Attention Dr. Domenico Coppola
Anatomic Pathology Dept.
H. Lee Moffitt Cancer Center
12902 Magnolia Ave
Tampa, FL 33612

Immunohistochemistry (IHC) will be used to evaluate the expression of c-kit, tryptase and chymase as markers for mast cell presence and activation, respectively. Sections of 3-4 microns in thickness will be cut from the selected formalin-fixed paraffin embedded tissue and subjected to IHC staining protocol using the Dakocytomation Autostainer (DakoCytomation, Carpitenria, Calif). Microwave antigen retrieval with IHC Select EDTA buffer, pH 7.5, will be utilized. Primary antibodies with cross-reactivity against the human subtypes of the above mentioned targets will be diluted and incubated for 60 minutes at room temperature. Using a semiquantitative scoring system, the intensity of IHC staining for c-kit, chymase and tryptase will be scored as either 0 (negative), 1+ (mild positive staining), 2+ (moderate positive) and 3+ (strong positive staining). The correlation between staining patterns and clinical outcomes (response rate or PFS) will be analyzed in a descriptive fashion.

6.4 Evaluation schema

Table 6-5 lists all of the assessments and indicates the visits at which they are to be performed with an "X". All data obtained from these assessments must be supported in the patient's source documentation.

Table 6-5 Visit evaluation schedule

Evaluation	Screening/ Baseline[a]	Each Cycle (day 1 ±2)	Every 3 Cycles ±1 week (until disease progression, unacceptable toxicity or withdrawal of consent)	End[b]
Informed consent	X			
Demographics	X			
Relevant medical	X	X		X

history/ current medical conditions				
Diagnosis and extent of cancer	X			
Physical exam	X	X		X
Vital signs	X	X		X
ECG[c]	X			
ECOG Performace Status	X	X		X
CBC with differential[d]	X	X		X
Glycosylated hemoglobin	X			
Fasting Comprehensive metabolic panel[e]	X	X		X
Pregnancy test and review of contraception[f]	X			
Secretory hormones[g] and serum chromogranin A	X		X	X
Radiologic assessment of tumor burden[h]	X		X	X
Adverse events[i]	X	X		X
Concomitant medications[j]	X	X		X
EORTC QLQ C-30 and EORTC QLQ GI-NET21 questionnaires	X		X	
Correlative laboratory studies[k]	X		X	

[a] Screening includes review of: demography/informed consent, inclusion/exclusion criteria, relevant medical history/concomitant medications, diagnosis and extent of cancer.

[b] Patients who interrupt or permanently discontinue ibrutinib due to an adverse event or abnormal laboratory value must be followed at no less than monthly intervals, until resolution of toxicity to less than grade 2. These patients will be censored, and tumor assessment will be performed off trial at treating physician's discretion.. Patients will be followed for OS each 12 months using their charts or the Social Security Death Index.

[c] ECG should be done at any time when clinically indicated.

[d] Complete blood count must include: hemoglobin, hematocrit, platelets, total while blood cell count and differential.

[e] Comprehensive metabolic panel should include fasting glucose, sodium, potassium, calcium, chloride, bicarbonate, creatinine, blood urea nitrogen, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin and alkaline phosphatase.

[f] For women of child-bearing potential: women of childbearing potential must have a negative serum preganancy test within 14 days of enrollment. Acceptable contraception must be used while on study and for at least 60 days after last dose of ibrutinib.

[g] If patients present with hormonally active tumor, secretory hormone levels corresponding to the syndrome (e.g. urine 5-HIAA, gastrin, glucagon, insulin, etc.) should be measured at baseline, at each restaging cycle and at the end of study treatment.

[h] Baseline radiologic tests (CT or MRI with iv contrast) should include all known sites of metastatic disease. For most midgut carcinoid tumors, a CT or MRI scan of the abdomen and pelvis is indicated. For pancreatic neuroendocrine tumors, a CT or MRI scan of the abdomen may be sufficient. Radiological scans documenting target lesions should be repeated every 3 cycles (12 weeks). The same type of scan should be used at each evaluation.

[i] See section 9.1 for definitions of adverse events.

[j] All concomitant medications, including over the counter drugs, should be documented each visit.

[k] Correlative laboratory studies will include measurement of serum Tryptase β2.

7. Outcome Measures

The primary efficacy endpoint is objective response rate as determined by radiology review.

7.1 RECIST Criteria for response

The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guidelines[30] will be employed in this study. For the purposes of this study, measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; when CT scans have slice thickness >5 mm, the minimum size should be twice the slice thickness).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

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 is recommended to be no greater than 5 mm). At baseline and in follow- up, only the short axis will be measured and followed.
Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable if the soft tissue component meets the definition of measurability described above.
'Cystic lesions' thought to represent cystic metastases can be considered measurable if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Non-measurable lesions: all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques. Blastic bone lesions are non-measurable. Lesions with prior local treatment, such as those situated in a previously irradiated area or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression (by RECIST 1.1) in the lesion.

Target lesions: all measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). 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. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.

Non-target lesions: All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as non-target lesions and be recorded at baseline. Measurements of these lesions are not required and they should be followed as 'present', 'absent' or in rare cases, 'unequivocal progression'.

7.1.1 Evaluation of target lesions

Complete response (CR): complete disappearance of all target lesions, confirmed by repeat assessments at no less than 4 weeks after the criteria for response are first met. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm

Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum longest diameter. This must be confirmed by repeat assessment at no less than 4 weeks after the criteria for response are first met.

Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD): neither sufficient decrease to qualify for partial response nor sufficient increase to qualify for progressive disease.

7.1.2 Special notes on the assessment of target lesions

• Lymph nodes identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. When lymph nodes are included as

target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met since a normal lymph node is defined as having a short axis of <10 mm.

• Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small. However, sometimes lesions or lymph nodes become so faint on a CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure', in which case a default value of 5 mm should be assigned.

• Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

7.1.3 Evaluation of non-target lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR / Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker levels above normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

• When patient has measurable disease. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

• When patient has only non-measurable disease. There is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied is to consider if the increase in overall disease burden based on change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localized to widespread.

7.1.4 New lesions

The appearance of new malignant lesions denotes disease progression.

• The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor, especially when the patient's baseline lesions show partial or complete response).

• If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

• A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and disease progression.

Cytology and Histology: if the measurable disease is restricted to a solitary lesion, its neoplastic nature should ideally be confirmed by cytology or histology. These techniques can be used to differentiate between PR and CR in rare cases.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response, stable disease, and progressive disease.

7.1.5 Evaluation of response

Evaluation of Best Overall Response: the best overall 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). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.
Table 7-1-5 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 7-1-5-1 Evaluation of best overall response in patients with measurable disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Inevaluable	No	PR
PR	Non-PD/or not all evaluated	No	PR
SD	Non-PD/or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD

Any	Any	Yes	PD

Note:
Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

When patients have non-measurable (therefore non-target) disease only, Table 7-1-5-2 is to be used.

Table 7-1-5-2 Evaluation of best overall response in patients with measurable disease

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	Inevaluable
Unequivocal PD	Yes or no	PD
Any	Yes	PD

Inevaluable designation: When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would most likely happen in the case of PD.

7.2 Guidelines for Evaluation of Measurable Disease

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. CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (e.g., for body scans but not for lung). Lesions on a chest X-ray may be considered measurable lesions if they are clearly defined and surrounded by aerated lung. However, CT is preferable. Ultrasound (US) should not be used to measure tumor lesions.
Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal

limit, they must normalize for a patient to be considered in complete response. Cytology and histology can be used in rare cases (e.g., for evaluation of residual masses to differentiate between Partial Response and Complete Response or evaluation of new or enlarging effusions to differentiate between Progressive Disease and Response/Stable Disease). Use of endoscopy and laparoscopy is not advised. However, they can be used to confirm complete pathological response.
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7.3 Confirmation Measurement/Duration of Response

Confirmation: To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks. Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered not to have progressive disease per RECIST 1.1.

Duration of Overall Response: The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression Free Survival (PFS): PFS is defined as the time from the date of first study treatment to the date of the first documented disease progression or death due to any cause. If a patient has not progressed or died at the date of the analysis cut-off or when he/she receives any further anti-cancer therapy, PFS is censored at the time of the last tumor assessment before the cut-off or the anti-cancer therapy date.

Time to Treatment Failure: Time from administration of the initial dose of ibrutinib until study discontinuation for any reason (e.g. disease progression, toxicity, death, withdrawal of consent).

Biochemical marker response will be defined as ≥ 50% reduction in tumor marker from baseline.

8. Statistical Considerations

8.1 Sample size

51 patients (30 patients with carcinoid and 21 patients with pNET).

8.2 Endpoints to be followed

Efficacy Endpoints

- Tumor response rate using RECIST (Primary endpoint);
- OS, determined from the time of drug administration to death from any cause (Secondary endpoint);
- PFS, determined as the time from administration of the initial dose of ibrutinib until objective tumor progression using RECIST, or death (Secondary endpoint);
- Duration of response, defined as time from first observation of an objective response which is subsequently confirmed, to first disease progression or death due to any cause (Secondary endpoint);
- Changes in health-related quality of life, as assessed by EORTC questionnaires EORTC QLQ-C30 and QLQ GI.NET21 (see section 11).

Safety Endpoint

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology and blood chemistry parameters and regular physical examinations. Adverse events will be evaluated continuously throughout the study. Safety and tolerability will be assessed according to the NIH/NCI Common Terminology Criteria for Adverse Events version 4 (CTCAE v4) available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All adverse events will be documented on the adverse event CRF.

Exploratory Analyses (refer to Section 6.3)

As part of this study, we will explore the correlation between early biochemical response and response rates or PFS. Early biochemical responders will be defined as patients with elevated chromogranin A (CgA) who experience a major reduction (>50%) or normalization of their CgA between their baseline (pretreatment) measurement and their follow-up assessment 3 months later.

We also plan to undertake an exploratory analysis of blood- and tissue-based markers that may correlate with the clinical outcomes observed in the study. Exploratory markers will include the measurement of serum Tryptase-β2 and the determination of the presence and activation of mast cells in the tumor tissue samples.

Archival pathology specimens will be reviewed at the study institution (Moffitt Cancer Center) for determination of mitotic rate (number of mitoses per 10 high-powered fields) and Ki-67 index.

This study is not sufficiently powered to establish definitive outcome for the correlative endpoints. These results will be considered hypothesis generating and any comparison with a significant alpha <0.05 will be deemed of sufficient interest to warrant further evaluation.

8.3 Sample-size Calculation

This will be a standard, phase II study, in which two cohorts of patients (carcinoid and pNET) consisting of 30 patients with carcinoid tumors and 21 patients with pNET each will be enrolled.

We have designed the study to test the null hypothesis that ibrutinib has a response rate of 5% or less in this disease. The sample size calculation has been based on the assumption that a true response of greater than 18% (comparable with that seen with agents such as sunitinib in pNET[13] or bevacizumab in carcinoid tumors[31]) would generate interest in a larger randomized study. Taking into account both study feasibility given these relatively rare tumor and the relatively small difference in H1 and H0, with 30 patients in the carcinoid cohort we will be able to test the hypothesis that the true response is 18% versus 5% with a power of 80% and a type 1 error of 6%, while with 21 patients in the pNET cohort we will be able to test the hypothesis that the true response is 20% versus 5% with a power of 80% and a type 1 error of 8%. Patients will be accrued to the protocol according to a Simon's two-stage minimax design. In the carcinoid cohort, 15 subjects will be enrolled into stage-1. If 1 or more response is observed, then another 15 subjects will be enrolled into stage-2. At the completion of the study, if 4 or more responses out of N=30 are observed, significance at 6% is reached. Under this design, and if the true response rate is ≥18%, then the probability of observing ≥1 response in stage-1 is ≥95%. In the pNET cohort, 12 subjects will be enrolled into stage-1. If 1 or more response is observed, another 9 subjects will be enrolled into stage-2. At the completion of the study, if 3 or more responses out of N=21 are observed, significance at 8% is reached. Under this model, and if the true response rate is ≥20%, the probability of observing ≥1 response in stage-1 is 93%. In both cohorts, at least 1 patient must respond in the first stage to proceed to the second stage. At any point when it is realized that this cannot happen, the study will be stopped in the relative cohort, where the therapy will be considered ineffective.

Kaplan-Meier survival analysis will be performed to evaluate OS, PFS and duration of response.

8.4 Replacement of Dropouts

Patients who enroll but do not receive the initial dose of ibrutinib will be considered dropouts and may be replaced. Additionally, patients who drop out before the first scheduled follow-up scan (e.g. completion of the first four cycles of therapy) will be replaced, unless patients drop out due to dose-limiting toxicity or progressive disease. Assuming a 10% drop-out rate, 56 patients will need to be enrolled to reach 51 evaluable patients.

9. Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology and blood chemistry parameters, and regular physical examinations. These assessments should be performed within ±2 days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study. Safety and tolerability will be assessed according to the NIH/NCI CTC version 4.0. Please refer to:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

9.1 Adverse events

Information about all clinically significant adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate. An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring

after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy. Clinically significant laboratory results are those requiring a change in the patient's treatment, further diagnostic testing or specific clinical intervention (i.e., treatment delays or dose modifications, etc). The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- the severity grade (mild, moderate, severe) or (grade 1-4)
- its relationship to the study drug(s) (suspected/not suspected)
- its duration (start and end dates or if continuing at final exam)
- action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
- whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure or will be communicated between Investigator Brochure updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

9.1.1 Attribution

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

- Definite: The AE is clearly related to the study treatment;
- Probable: The AE is likely related to the study treatment;
- Possible: The AE may be related to the study treatment;
- Unlikely: The AE is doubtfully related to the study treatment;
- Unrelated: The AE is clearly not related to the study treatment.

9.2 Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. These events (regardless of seriousness) will be reported to Pharmacyclics Drug Safety per the SAE reporting timelines.

9.2.1 Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher*. Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE vX.X.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.4.6 above.

9.3 Serious adverse events

All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form and sent via email (drugsafety@pcyc.com) or fax (408-215-3500) to Pharmacyclics Drug Safety, or designee, within 24 hours of the event. Pharmacyclics may request follow-up and other additional information from the Sponsor Investigator.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves;
- The event stabilizes;
- The event returns to baseline, if a baseline value/status is available;
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct;
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts).

9.3.1 SAE Definition

An SAE is any adverse event, without regard to causality, that is life-threatening or that results in any of the following outcomes: death; in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity; or a congenital anomaly or birth defect. Any other medical event that, in the medical judgment of the principal investigator, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. A planned medical or surgical procedure is not, in itself, an SAE. Also specifically excluded from this definition of SAE is any event judged by the principal investigator to

represent progression of the malignancy under study, unless it results in death within the SAE Reporting Period.

9.3.2 SAE Reporting Period

The SAEs that are subject to this reporting provision are those that occur from after the first dose of the Study Drug through 30 days after discontinuation of the Study Drug.

9.4 Pregnancy

Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported to Pharmacyclics within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

9.5 Data safety monitoring plan

Data including adverse events will be entered into Oncore. The participating investigator will report all adverse events to the protocol chair and to the IRB according to the local IRB's policies and procedures in reporting adverse events. The protocol chair has the obligation to report all SAE to the FDA and IRB. SAE and AESI will be also reported to Pharmacyclics Drug Safety per the SAE reporting timelines.

10. Data collection

Once eligibility has been established and the participant successfully registered, the participant is assigned a protocol case number. This number is unique to the participant on this trial and must be used for case report form (CRF) completion in Oncore.

Investigators must enter the information required by the protocol onto CRFs.

11. Quality of Life Assessment

Patient quality of life will be measured using the EORTC QLQ-C30 (version 3) and the EORTC QLQ GI.NET21 questionnaires (appendices B and C). The EORTC QLQ-C30 questionnaire is designed to assess the health-related quality of life of cancer patients participating in clinical trials. It is composed of 5 functional scales, three symptom scales, a global health status scale, and six single items. The EORTC QLQ GI.NET21 questionnaire is designed to assess physical and psychological symptoms related to neuroendocrine tumors of the gastrointestinal tract.

Both questionnaires will be scored and handled as recommended in the user manual. Missing items will be imputed with the mean of the non-missing items scored at that assessment time point. Ambiguous items will be considered as missing items. At each assessment time point, summary statistics of the raw score and linear transformation score (on a 0-100 scale) will be provided.

12. Publication of trial results

Publications resulting from this trial may be developed by the investigator who will provide Pharmacyclics an opportunity (within 30 days before submission or other public disclosure) to prospectively review any proposed publication, abstract or other type of disclosure that reports the results of the study.

13. Regulatory considerations

13.1 Protocol review and amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing the study location.

Any change or addition (excluding administrative) to the study protocol or informed consent form protocol must be submitted as amendments and must be reviewed and approved by Pharmacyclics prior to submission to the IRB and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB. Any changes in study conduct must be reported to the IRB. The Principal Investigator will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB approval. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Committees

13.3.1 Scientific Review Committee (SRC)

Each SRC conducts a formal internal peer review of all clinical protocols and general scientific oversight of interventional clinical research. Protocols are reviewed for scientific merit, adequate study design, safety, availability of targeted study population, and feasibility of timely completion of all proposed research projects to be conducted by its assigned programs at the Cancer Center. Each SRC is responsible for evaluation the risk/benefit assessment and corresponding data and safety monitoring plan as part of the scientific review and approval process.

13.3.2 Data Safety Monitoring Committee (DSMC)

The DSMC will meet on a monthly basis and will continually assess for subject safety and recommend changes to protocol and study as required to preserve subject safety and prevent any untoward toxicity.

13.3.3 Protocol monitoring Committee (PMC)

This study will be reviewed by the PMC for data and safety monitoring. The PMC monitors its assigned ongoing research protocol for: adverse event reporting, data and safety monitoring, and internal audit findings. The PMC, upon review of any agenda item, may approve the study for continuation, require revisions, suspend or close a protocol.

13.4 Internal monitoring

The trial will be monitored per Moffitt Cancer Center policy MRI-P.PSO.03, *Monitoring of Investigator Initiated Clinical Research.* Data will be captured in Oncore, Moffitt's Clinical Trials Database, Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/amendments, Good Clinical Practice, and applicable regulatory requirements.

13.5 Ethics and Good Clinical Practice (GCP)

It is the responsibility of the investigator to have prospective approval of the trial protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., advertisements, if applicable, from the IRB/IEC. The trial will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements and laws.

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.6 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request

or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

13.7 Study documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.
Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.8 Retention of records

Retained records will include all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for at least 5 years after the investigation is completed.

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APPENDIX A:

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 5.2 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	Carbamazepine
INDINAVIR	Efavirenz
NELFINAVIR	Nevirapine
RITONAVIR	Barbiturates
CLARITHROMYCIN	Glucocorticoids
ITRACONAZOLE	Modafinil
KETOCONAZOLE	Oxcarbarzepine
NEFAZODONE	Phenobarbital
SAQUINAVIR	Phenytoin
SUBOXONE	Pioglitazone
TELITHROMYCIN	Rifabutin
Moderate inhibitors:	Rifampin
Aprepitant	St. John's Wort
Erythromycin	Troglitazone
diltiazem	
Fluconazole	
grapefruit juice	
Seville orange juice	
Verapamil	
Weak inhibitors:	
Cimetidine	
All other inhibitors:	
Amiodarone	
NOT azithromycin	
Chloramphenicol	
Boceprevir	
Ciprofloxacin	
Delaviridine	
diethyl-dithiocarbamate	
Fluvoxamine	
Gestodene	
Imatinib	
Mibefradil	
Mifepristone	
Norfloxacin	
Norfluoxetine	
star fruit	
Telaprevir	
Troleandomycin	
Voriconazole	

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

Appendix B: EORTC QLQ-C30 (version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix C EORTC QLQ-GLNET21

ENGLISH

EORTC QLQ – GI.NET21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
31. Did you have hot flushes?		1	2	3	4
32. Have you noticed or been told by others that you looked flushed/red?		1	2	3	4
33. Did you have night sweats?		1	2	3	4
34. Did you have abdominal discomfort?		1	2	3	4
35. Did you have a bloated feeling in your abdomen?		1	2	3	4
36. Have you had a problem with passing wind/gas/flatulence?		1	2	3	4
37. Have you had acid indigestion or heartburn?		1	2	3	4
38. Have you had difficulties with eating?		1	2	3	4
39. Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)*	N/A	1	2	3	4
40. Have you had a problem from repeated injections? *(If not having injections please circle N/A)*	N/A	1	2	3	4
41 Were you worried about the tumour recurring in other areas of the body?		1	2	3	4
42. Were you concerned about disruption of home life?		1	2	3	4
43. Have you worried about your health in the future?		1	2	3	4
44. How distressing has your illness or treatment been to those close to you?		1	2	3	4
45. Has weight loss been a problem for you?		1	2	3	4
46. Has weight gain been a problem for you?		1	2	3	4
47. Did you worry about the results of your tests? *(If you have not had tests please circle N/A)*	N/A	1	2	3	4
48. Have you had aches or pains in your muscles or bones?		1	2	3	4
49. Did you have any limitations in your ability to travel?		1	2	3	4
During the past four weeks:					
50. Have you had problems receiving adequate information about your disease and treatment?		1	2	3	4
51. Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)*	N/A	1	2	3	4

Appendix D Child-Pugh Score

Measure	1 point	2 points	3 points
Total bilirubin, μmol/L (mg/dL	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Source:

1. Child CG, Turcotte JG. “Surgery and portal hypertension”. In Child CG. *The liver and portal hypertension.* Philadelphia:Saunders. 1964. pp. 50-64.

Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R . “Transection of te oesophagus for bleeding oesophageal varices”. *The British journal of surgery*, 1973;60: 646-9.