A Proof-of-Concept Study for Ilorasertib (ABT-348) Activity in Patients with CDKN2A-Deficient Advanced Solid Cancers: a Phase II Basket Trial

Short Title: Ilorasertib (ABT-348) in Patients with CDKN2A-Deficient Advanced Solid Cancer

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Table of contents

1. Objectives

1.1 Primary objectives

a) In Part I: To evaluate the response rate (partial response, complete response) of Ilorasertib (ABT-348) (Aurora kinase inhibitor) in patients with cancers harboring CDKN2A deletion or mutation as tumor response.
b) In Part I: To identify tumor types for further development.
c) In Part 2 (expanded cohort): To determine the antitumor activity of Ilorasertib (ABT-348) in specific tumor type harboring CDKN2A deletion or mutation.

1.2 Secondary objectives

a) To evaluate the safety and tolerability of Ilorasertib (ABT-348) in this patient population.
b) To assess pharmacodynamics by immunohistochemistry for phospho-Histone H3 (P-HH3).

2. Background

2.1. Outline of research hypotheses

Aurora Kinase

Uncontrolled cell proliferation is a characteristic of tumor cells, and alterations in the genes involved in cell cycle control are frequent in human cancers. Aurora kinases[1] and CDKN2A play a major role in cell cycle checkpoint regulation. Aurora kinases are a family of serine/threonine kinases. Humans have 3 Aurora kinases, Aurora A, B, and C that are expressed in multiple tissues, but only in the G2 and mitotic phases of the cell cycle.[1] Aurora A regulates centrosome function and is required for spindle assembly and the entry of cells into mitosis.[1-3] Aurora B is a chromosomal passenger protein that is an integral part of the spindle assembly checkpoint that ensures proper chromosomal segregation and cytokinesis.[1-3] Aurora C's cellular function is redundant with Aurora B.[1-3] Based on the role of Aurora kinases in centrosome duplication and the proper alignment of chromosomes on mitotic spindles, their abnormal expression is thought to contribute to tumorigenesis by increasing chromosomal instability.[1-3] Inhibition of Aurora kinases causes cells to enter aberrant mitosis resulting in aneuploidy or polyploidy cells, and ultimately leading to death.[1-3]

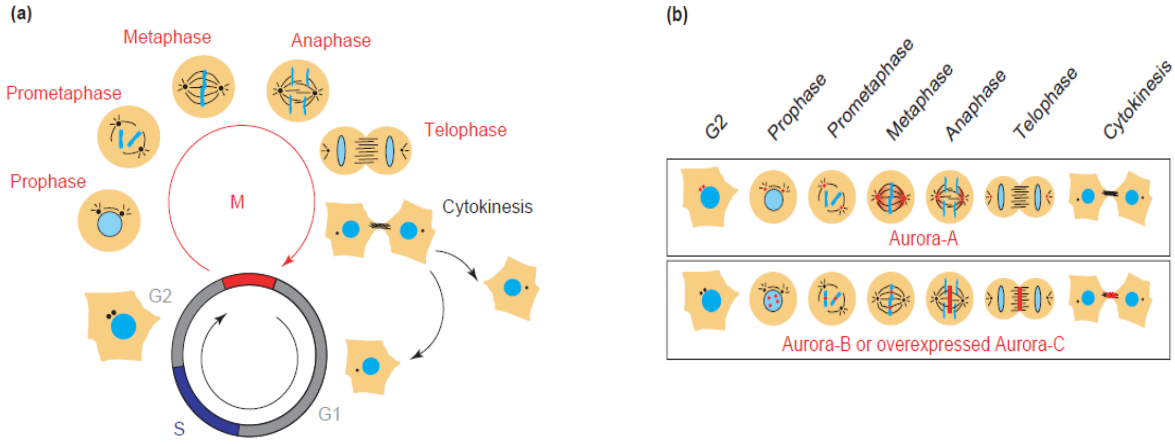

Figure 1. Cell cycle and aurora kinases (Giet et al, Trends in Cell Biology 2005)

CDKN2A

CDKN2A encodes p16INK4A and p19ARF.[4] p16INK4A blocks cell cycle progression by binding CDK4/Cyclin D complex. This leads to accumulation of hypophosphorylated Rb, which plays a major inhibitory role at the G1-S restriction point. p19ARF blocks cell cycle progression by binding p53/Mdm2 complex and preventing p53 degradation at the G1-S and G2-M points.[5, 6] Therefore loss of CDKN2A contributes to tumorigenesis by driving uncontrolled cell cycles.

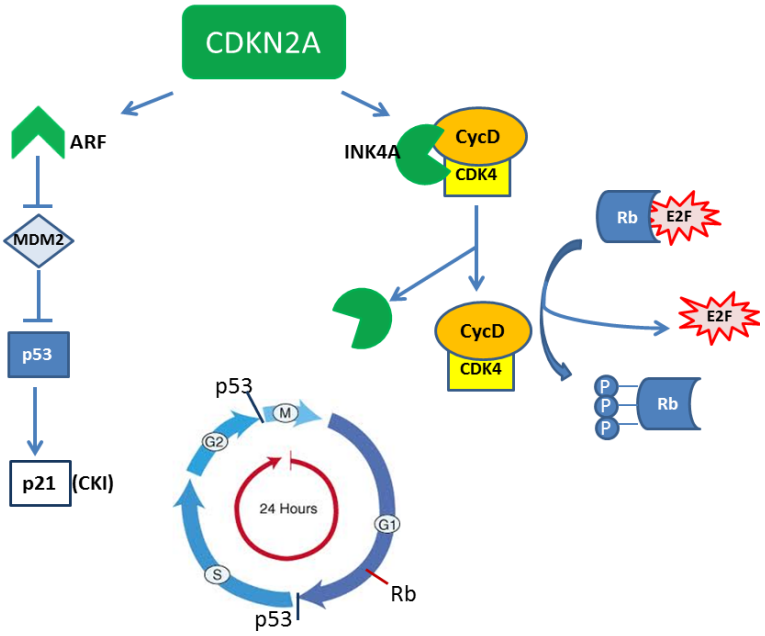

Figure 2. CDKN2A pathway

Many tumor types show CDKN2A deletion more commonly in bladder cancer (43.8%), brain tumor (29.1%), melanoma (27.6%), pancreatic cancer (24.1%), and esophageal cancer (21.3%) from the CGH data with the criteria less than 1.2 copies (Table 1). Germ line mutations in the CDKN2A gene are known to predispose individuals to familial pancreatic cancer and melanoma.[7]

Table 1. CDKN2A Deletion Frequency (<1.2 Copies) from CGH data

General Cancer Type	Frequency	# Deleted	# Tested
Bladder Cancer	43.80%	14	32
Brain and CNS Cancer	29.10%	423	1455
Melanoma	27.60%	32	116
Pancreatic Cancer	24.10%	14	58
Esophageal Cancer	21.30%	13	61
Gastric Cancer	13.80%	31	224
Head and Neck Cancer	9.40%	26	278
Sarcoma	8.40%	19	227
Lung Cancer	6.50%	69	1054
Ovarian Cancer	4.70%	40	859
Leukemia	3.80%	9	239
Breast Cancer	2.90%	26	890
Kidney Cancer	1.90%	12	635
Other Cancer	1.80%	7	399
Liver Cancer	0.80%	2	241
Cervical Cancer	0.80%	1	120
Colorectal Cancer	0.60%	5	849
Myeloma	0.60%	3	530
Prostate Cancer	0.50%	2	365
Normal	0.00%	0	3735

Ilorasertib (ABT-348) activity

Ilorasertib (ABT-348) is a potent, novel, adenosine triphosphate (ATP)-competitive, pan-Aurora kinase inhibitor (IC50 < 120 nM and < 10 nM for Aurora A and Aurora B/C, respectively) with a unique kinase selectivity profile that includes potent activity against the VEGF receptor (VEGFR)/PDGF receptor (PDGFR) family of kinases. Ilorasertib (ABT-348) exhibited sub-micromolar cellular activity against multiple human tumor cell lines derived from broad range of tumor types including colorectal, ovarian, pancreatic as well as lymphoid malignancies. In vivo, Ilorasertib (ABT-348) was broadly efficacious in several established murine xenografts with complete inhibition or regression observed by a once weekly dosing regimen. The inhibition of VEGF signaling was also observed as measured by changes in tumor vascular permeability and contributed to the broad antitumor activity. Based on exposure parameters from nonclinical efficacy studies,

plasma concentrations of Ilorasertib (ABT-348) exhibited low susceptibility to resistance due to poor multidrug resistant (MDR) affinity of Ilorasertib (ABT-348) ranging from 0.5 to 1.0 µg/mL for up to 16 hours are sufficient for robust antitumor activity. Current pharmacokinetic modeling predicts that an oral dose of 400 mg in humans will maintain Ilorasertib (ABT-348) plasma concentrations above the 1.0 µg/ml target for ~17 hours with a projected maximum observed plasma concentration (Cmax) of 2.4 µg/mL.

In two phase I dose escalation studies (solid tumor, hematologic malignancy), 102 patients with advanced solid tumors and 50 with hematologic malignancies were treated with Ilorasertib (ABT-348). In solid tumors, 9 of 102 patients showed response (8 PRs and 1 CR). Two of 9 responders were tested for CDKN2A and these patients were found to be CDKN2A-deleted. In the hematologic study, three of 50 patients responded (2 CRs, 1 PR). Of the 3 patients with response, there were one patient with homozygous deletion and two with wild types for CDKN2A. In terms of estimating the rate of CDKN2A deletion, two of 10 solid tumor patients and one of 11 hematologic patients tested for CDKN2A showed deletion. The results provide potential association between CDKN2A deletion and sensitivity of cancer cells to Ilorasertib (ABT-348).

We hypothesize that CDKN2A deficiency may confer sensitivity to Ilorasertib (ABT-348) (Aurora kinase inhibitor) based on that inhibition of aurora kinases leads polyploid cells induced by CDKN2A deficiency through loss of G1-S checkpoint to mitotic catastrophe, thus increasing cell death.[6] In this phase II trial, we will evaluate the efficacy and safety profile of Ilorasertib (ABT-348) in patients with advanced cancer with CDKN2A deletion or mutation.

2.2. Background drug information: Ilorasertib (ABT-348)

Ilorasertib (ABT-348) [1-(4-(4-amino-7-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)thieno[3,2-c]pyridin-3-yl)phenyl)-3-(3-fluorophenyl)urea] is a novel ATP-competitive multitargeted kinase inhibitor with nanomolar potency (IC50) for inhibiting binding and cellular autophosphorylation of Aurora B, C, and A. It has the molecular formula $C_{25}H_{21}FN_6O_2S$ and molecular weight of 488.54. Ilorasertib (ABT-348) is practically insoluble in water, and sparingly soluble in lipid excipient blends at 25°C (per United States Pharmacopeia criteria). Ilorasertib (ABT-348) has been formulated as either a tablet or a concentrate for infusion solution, 30 mg/vial. In this protocol, only tablet forms will be used

Ilorasertib (ABT-348) is in clinical development. That is, phase I trials have been completed to test monotherapy and combination therapy in solid tumors and hematologic malignancies.

2.2.1. Mechanism of action

Ilorasertib (ABT-348) is a potent, novel, adenosine triphosphate (ATP)-competitive, pan-Aurora kinase inhibitor (IC50 < 120 nM and < 10 nM for Aurora A and Aurora B/C, respectively) with a unique kinase selectivity profile that includes potent activity against the VEGF receptor (VEGFR)/PDGF receptor (PDGFR) family of kinases (Table 2).

Regarding main targets of Ilorasertib (ABT-348), based on the role of Aurora kinases in centrosome duplication and the proper alignment of chromosomes on mitotic spindles, their abnormal expression is thought to contribute to tumorigenesis by increasing chromosomal instability.[1-3]

Evaluation of Ilorasertib (ABT-348) for inhibitory activity across 128 kinases revealed a unique kinome profile "signature."17 In addition to the potent activity against the VEGFR and PDGFR families, Ilorasertib (ABT-348) also potently inhibits the SRC family of cytoplasmic tyrosine kinases. Inhibition of members of the SRC family has translated into therapeutics such as Sprycel® (dasatinib) for the treatment of Gleevec® (imatinib mesylate)-resistant CML.18 Therefore, this unique kinome "signature" inherent to Ilorasertib (ABT-348) has the potential to distinguish it from the other Aurora kinase inhibitors.

Table 2. In vitro potencies of Ilorasertib (ABT-348)

Kinase	Biochemical IC50 (nM)[a]	Cellular PD Marker IC50 (nM)
Aurora A	120	189[b]
Aurora B	7	13[b]
Aurora B (Y156H)c	12	NA
Aurora C	1	13[b]
VEGFR1 (FLT-1)	1	0.3[d]
VEGFR2 (KDR)	2	5[d]
VEGFR3 (FLT-4)	43	2[d]
FLT-3	1	2[d]
CSF-1R	3	3[d]
c-KIT	20	45[d]
PDGFR-α	11	16[d]
PDGFR-β	13	11[d]

NA = not available; PD = pharmacodynamic

a. Enzyme assays were conducted in homogeneous time-resolved fluorescence format using 1 mM ATP.

b. Aurora A, B, and C auto-phosphorylation was performed in nocodazole-arrested HeLa cells by Western analysis using phospho – A, B, and C specific antibodies.

c. Aurora B kinase Y156H mutant.

d. Cellular phosphorylation assays for KDR, CSF-1R, KIT, PDGFR-α, and PDGFR-β are ligand stimulated for 5 to 20 minutes for optimal phosphorylation depending on receptor type. FLT-3 is constitutively phosphorylated in SEM cells; inhibition was determined after 60 minutes of exposure to the compound. FLT-1 activity was determined in BaF3 cells expressing the TEL:FLT1 catalytic domain fusion using proliferation as a surrogate readout.

2.2.2. Preclinical studies
Ilorasertib (ABT-348) exhibited sub-micromolar cellular activity against multiple human tumor cell lines derived from a broad range of tumor types including colorectal, ovarian, pancreatic as well as lymphoid malignancies. In vivo, Ilorasertib (ABT-348) was broadly efficacious in several established murine xenografts with complete inhibition or regression observed by a once weekly dosing regimen. The inhibition of VEGF signaling was also observed as measured by changes in tumor vascular permeability and contributed to the broad antitumor activity.

2.2.3. Clinical experience with Ilorasertib (ABT-348)
Phase 1 clinical trials conducted with Ilorasertib (ABT-348) suggest a possible association of clinical activity and CDKN2A alteration (detailed below) that warrants further investigation.

In two phase I dose escalation studies (solid tumor, hematologic malignancy), 102 patients with advanced solid tumors and 50 with hematologic malignancies were treated with Ilorasertib (ABT-348). In solid tumors, 9 of 102 patients showed response (8 PRs, 1 CR). Two of 9 responders were tested for CDKN2A and these patients were found to be CDKN2A-deleted. In the hematologic study, three of 50 patients responded (2 CRs, 1 PR). Of the 3 patients with response, there were one patient with homozygous deletion and two with wild types for CDKN2A. In terms of estimating the rate of CDKN2A deletion, two of 10 solid tumor patients and one of 11 hematologic patients tested for CDKN2A showed deletion. The results provide potential association between CDKN2A deletion and sensitivity of cancer cells to Ilorasertib (ABT-348).

2.2.4. Pharmacokinetics and pharmacodynamics
Across multiple species > 99% protein binding was observed for Ilorasertib (ABT-348). Therefore, functional aspects of protein binding were evaluated in the histone H3 phosphorylation assay and demonstrated a 100-fold shift in the IC50 value for Ilorasertib (ABT-348) in the presence of mouse plasma (IC50 value of 21 nM without plasma versus 3,300 nM in the presence of 50% mouse plasma). Based on exposure parameters from preclinical efficacy studies, plasma concentrations of Ilorasertib (ABT-348) ranging from 0.5 to 1.0 µg/mL for up to 16 hours are sufficient for robust antitumor activity. Current pharmacokinetic modeling predicts that an oral dose of 400 mg in humans will maintain Ilorasertib (ABT-348) plasma concentrations above the 1 µg/mL target for ~17 hours with a projected Cmax of 2.4 µg/mL. Studies in the GA-10 lymphoma model provided valuable insight into the minimal plasma (threshold) concentration required for antitumor activity. Pharmacokinetic analysis of plasma levels of Ilorasertib (ABT-348) resulting from efficacious doses (6.25 and 12.5 mg/kg) demonstrated a dose-dependent increase in Cmax. These results indicate that in this xenograft a steady-state level of 0.5 µg/ml for 16 hours is sufficient for tumor stasis. Administration of 12.5 mg/kg, a dose that was broadly efficacious in other tumor models, resulted in tumor regression in the GA-10 model (30% cures) at a steady state concentration of 1.0 µg/mL. Based on these results, 0.5 µg/mL is considered to be the threshold concentration required for antitumor activity. This further validates the prediction that an oral dose of 400 mg in humans will maintain efficacious plasma concentrations. Pharmacokinetic studies revealed sustained, reproducible plasma

concentrations of Ilorasertib (ABT-348) in dogs after the compound was dosed orally as a lipid solution. This data also supports oral dosing of Ilorasertib (ABT-348).

2.2.4.1. Absorption

The sum of urinary and biliary excretion following a single 10 mg/kg oral dose of [14C]Ilorasertib (ABT-348) in bile duct-cannulated male Sprague-Dawley rats indicated that at least 37.5% of the dose was absorbed; overall recovery of radioactivity 48 hours postdose was 70.6% of the dose. Approximately 4.1% to 24.9% of radioactivity was recovered in the carcass 48 hours postdose from rats treated PO and IV, indicating incomplete dose recovery in excreta.

2.2.4.2. Distribution

2.2.4.2.1. Plasma protein binding, binding site, red blood cell distribution

Preliminary data revealed that Ilorasertib (ABT-348) (1 µM) has high binding to rat (99.8%), dog (99.9%), monkey (99.6%), and human (99.9%) plasma proteins. Preliminary data suggested [3H]Ilorasertib (ABT-348) distributed preferentially into the plasma compartment, with a blood-to-plasma concentration ratio ranging between 0.75 and 1.08 in human independent of the 0.5 to 5 µM concentration evaluated.

2.2.4.2.2. Tissue distribution studies

Evaluation of tissue distribution in male Long-Evans rats (10 mg/kg, PO) at 3, 6, and 24 hours postdose showed relatively slow uptake of radiolabeled drug and generally low tissue-to-plasma (t/p) ratios (< 1 at 6 hours postdose for heart, lungs, muscle, testes, brain, eyes, skin, pigmented skin, and spinal cord). Radioactivity reached maximum concentrations at 6 hours postdose in all tissues except liver, which showed maximum concentrations at 3 hours postdose. From 6 to 24 hours, the t/p ratio in eye and kidney increased to 2.56 and 1.70, respectively, suggesting potential retention of drug or metabolites in these tissues.

2.2.4.2.3. Placental and lacteal transfer

Placental and lacteal transfer studies have not yet been conducted with Ilorasertib (ABT-348).

2.2.4.3. Metabolism

2.2.4.3.1. In Vitro metabolism

Ilorasertib (ABT-348) showed high microsomal intrinsic clearance (mCLint) in the rat and mouse (97 and 86 µL/min/mg, respectively) and moderate to high mCLint in the human, monkey, and dog (34, 44, and 54 µL/min/mg proteins, respectively). M2 (carboxylic acid) was the only metabolite found in rat liver microsomal incubations and it was also the most significant metabolite in other species, representing 13.7% and 7.1% of the drug-related material in the rat and monkey, but less than 2% in the other species. The M4 metabolite (N-dealkylation on the pyrazole) was detected only by tandem mass spectrometry (i.e., below radiochemical detection limit) and was found in human, dog, monkey, and mouse liver microsomal incubations. Metabolite M2 was also detected in rat, monkey, and mouse hepatocytes. Metabolite M6 (N-acetylglucosamine conjugate) was observed in monkey hepatocytes, but not found in other species. Formation of

metabolites M1, M2, M3, and M4 was catalyzed by recombinant CYP3A isoforms. M1 was formed by CYP1A1; other CYP isoforms did not appear to be involved in Ilorasertib (ABT-348) metabolism.

2.2.4.3.2. In Vivo metabolism

Chromatographic evaluation of the radiochemical profile in bile from rats treated PO showed that approximately 19.3% of the dose was recovered as intact parent drug, indicating biliary clearance was largely by metabolic transformation of [14C]Ilorasertib (ABT-348). M5 (proposed as hydroxylation on benzene ring) and M10 (direct glucuronidation) represented 3.6% and 3.3% of dose, respectively. Other products of metabolism included M1 (hydroxylation on benzene ring), M9 (direct glucuronide conjugate), and M7 and M8 (secondary glucuronide conjugates). In circulation, parent drug represented approximately 69% of plasma radioactivity (oral) and M2, M5, and M11 (hydroxylation on benzene ring) represented approximately 7%, 9%, and 14%, respectively, of plasma radioactivity at 3 hours postdose.

2.2.4.3.3 Elimination

Chromatographic evaluation of the biliary metabolite profile from rats treated IV showed the parent drug represented approximately 19.3% of the dose and the major metabolite M2 (carboxylic acid) represented approximately 35.4%, indicating biliary clearance was largely by metabolic transformation of [14C]Ilorasertib (ABT-348). Mean total recovery in urine was 1.65% for IV administration and 1.0% for oral administration. For rats treated PO, mean2.2.5. Dosage and administration recovery was 33.5% in feces and 28.9% from bile. Approximately 4.1% to 24.9% of radioactivity was recovered in the carcass 48 hours postdose from rats treated PO and IV, indicating incomplete dose recovery in excreta.

2.2.5.1. Recommended dose

The recommended dose of Ilorasertib (ABT-348) is 200mg PO twice a day on D1, 8, and 15.

2.2.5.2. Duration of treatment

It is recommended that patients are treated with Ilorasertib (ABT-348) until disease progression or unacceptable toxicity occurs.

2.2.5.3. Dosage forms and strengths

2.2.5.4. Tablet

1) Dosage Form: Tablets
2) Strength: 50 mg
3) Excipients: Microcrystalline cellulose, povidone, hypromellose 2910, crospovidone, macrogolglycerol hydroxystearate, polysorbate 20, citric acid, colloidal silicon dioxide, magnesium stearate

2.2.6 Study Drug Compliance and Disposal

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Ilorasertib will be dispensed one cycle at a time. The appropriate study personnel will maintain records of study drug receipt and dispensing. The used and expired study drug will be disposed of per MD Anderson Cancer Center policy.

2.2.7. Drug abuse and dependence

No studies on the potential for Ilorasertib (ABT-348) to cause dependence have been performed. However, there is no evidence from the available data that Ilorasertib (ABT-348) treatment can result in dependence.

2.2.8. Adverse reactions/toxicities

Preliminary aggregate data for Ilorasertib (ABT-348) monotherapy are summarized separately for subjects administered the drug PO (Arms A and B in Study M10-943 and Arms A and D in Study M10-944, 96 total subjects) and IV (Arm D of Study M10-943 and Arm E of Study M10-944, 11 total subjects).

Adverse events were reported in 93 of 96 (96.9%) subjects across both studies received Ilorasertib (ABT-348) monotherapy administered PO as shown in Table 3. The most frequently reported treatment-emergent adverse events (> 10%) in subjects treated with Ilorasertib (ABT-348) PO monotherapy are presented in Table 3. As expected based on the mechanism of action of Ilorasertib (ABT-348), gastrointestinal disorders and hypertension were some of the most common adverse events in the study. In addition, thrombocytopenia, fatigue, peripheral edema, pyrexia, decreased appetite, hypokalemia, hypomagnesemia, arthralgia, headache, and proteinuria were also commonly observed among subjects treated with Ilorasertib (ABT-348) monotherapy.

Grade 3 or 4 adverse events were reported by 65 of 96 subjects (67.7%) treated with Ilorasertib (ABT-348) PO monotherapy; the most common of these were hypertension (20 subjects), hypokalemia (8 subjects), anemia (6 subjects), and pneumonia (5 subjects). The most common grade 3 or 4 adverse events considered causally related to ilorasertib by the investigator included hypertension (14 subjects); diarrhea (3 subjects); neutropenia, thrombocytopenia, pancreatitis, fatigue, hyperuricemia, and proteinuria (2 subjects each).

Table 3. Most frequently reported (>10%) treatment-emergent adverse events in all subjects treated with Ilorasertib (ABT-348) PO monotherapy

		Total Subjects (N = 96) n, (%)	
System Organ Class	MedDRA 16.0 Preferred Term	All events	Related[a]
Blood and lymphatic system disorders	Thrombocytopenia	10 (10.4%)	9 (9.4)
Gastrointestinal disorders	Abdominal pain	10 (10.4)	1 (1.0)
	Constipation	12 (12.5)	1 (1.0)
	Diarrhoea	32 (33.3)	17 (17.7)
	Nausea	33 (34.4)	19 (19.8)
	Vomiting	20 (20.8)	9 (9.4)
General disorders and administration site conditions	Fatigue	36 (37.5)	19 (19.8)
	Oedema peripheral	13 (13.5)	1 (1.0)
	Pyrexia	10 (10.4)	0
Metabolism and nutrition disorders	Decreased appetite	23 (24.0)	13 (13.5)
	Hypokalaemia	22 (22.9)	0
	Hypomagnesaemia	14 (14.6)	1 (1.0)
Musculoskeletal and connective tissue disorders	Arthralgia	10 (10.4)	3 (3.1)
Nervous system disorders	Headache	16 (16.7)	5 (5.2)
Renal and urinary disorders	Proteinuria	18 (18.8)	13 (13.5)
Vascular disorders	Hypertension	31 (32.3)	23 (24.0)

a. Events considered possibly or probably related to ilorasertib by the investigator.

A summary of serious adverse events reported in 2 or more subjects treated with Ilorasertib (ABT-348) PO monotherapy is presented in Table 4. Serious adverse events were reported by 56 of 96 subjects (58.3%). The most common serious adverse events were febrile neutropenia, small intestinal obstruction, pneumonia, and acute myeloid leukemia (in 4 subjects each, 4.2%), and fungal pneumonia (in 3 subjects, 3.1%). Pancreatitis (in 2 subjects) was the most common serious adverse event considered causally related to Ilorasertib (ABT-348).

Table 4. Treatment-emergent serious adverse events reported in 2 or more subjects treated with Ilorasertib (ABT-348) PO monotherapy

		Total Subjects (N = 96) n, (%)	
System Organ Class	MedDRA 16.0 Preferred Term	All Events	Related[a]
Blood and lymphatic system disorders	Febrile neutropenia	4 (4.2)	0
Gastrointestinal disorders	Abdominal pain	2 (2.1)	1 (1.0)
	Pancreatitis	2 (2.1)	2 (2.1)
	Small intestinal obstruction	4 (4.2)	0
General disorders and administration site conditions	Fatigue	2 (2.1)	1 (1.0)
	Pyrexia	2 (2.1)	0
Hepatobiliary disorders	Bile duct obstruction	2 (2.1)	0
Infections and infestations	Bronchopulmonary aspergillosis	2 (2.1)	0
	Pneumonia	4 (4.2)	0
	Pneumonia fungal	3 (3.1)	0
	Sepsis	2 (2.1)	0
Metabolism and nutrition disorders	Dehydration	2 (2.1)	1 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute myeloid leukaemia	4 (4.2)	0
Respiratory, thoracic, and mediastinal disorders	Pleural effusion	2 (2.1)	0
	Pulmonary embolism	2 (2.1)	0
Vascular disorders	Hypertension	2 (2.1)	1 (1.0)

a. Events considered possibly or probably related to ilorasertib by the investigator.

2.2.9. Specific safety issues/events (known, potential and unknown risks)

Ilorasertib (ABT-348) is a novel orally bioavailable ATP-competitive inhibitor of Aurora A, Aurora B, and Aurora C. In addition, Ilorasertib (ABT-348) is a potent inhibitor of all members of the VEGF and PDGF family of RTKs. Thus, the safety profile of Ilorasertib (ABT-348) is expected to share some safety profile characteristics of RTK inhibitors, particularly, those inhibiting VEGF and PDGF effects and some safety characteristics associated with antimitotic chemotherapeutic agents. The known and potential risks listed below in the table are considered areas of enhanced focus for surveillance. In addition, single cases and aggregate safety data are reviewed as described below to identify new potential safety issues. Discontinuations, dose reductions or interruptions because of safety issues or AEs also are monitored according to the SRP for each clinical study.

Important identified and potential risks for Ilorasertib (ABT-348) are summarized in the Table 5. These risks were identified on the basis of data from Ilorasertib (ABT-348) clinical studies, and preclinical toxicity studies and other VEGF and PDGF RTK inhibitors and Aurora kinase inhibitors.[8, 9]

Table 5. Identified and potential risks for Ilorasertib (ABT-348)

Risk	Safety Issue	Risk Evaluation and Safety Tools
Known	Hypertension	Vital signs will be monitored according to schedule of assessment in each individual protocol. Frequency and severity of hypertension AEs will be also monitored. Hypertension AEs will be extracted using the SMQ Hypertension (broad). AEs known to be outcomes of hypertension, MI, stroke, LVDF and dose interruptions or discontinuations due to hypertension will be reviewed quarterly. Hypertensive subjects are required to have stable or controlled blood pressure to be enrolled in any study.
Known	Proteinuria	Protein excretion in urine will be monitored in routine urinalysis (Dipstick) per protocol schedule of assessments. Protein/Creatinine ratio will be calculated at protocol prefixed times and used in the assessment of the degree of proteinuria. Excretion of protein in 24 h urine collection will be performed per protocol and ABT-348 administration held in subjects with dipstick proteinuria of $\leq 2+$. The frequency and severity of proteinuria AEs and abnormal urine protein assessments will be monitored quarterly.
Known	Diarrhea and vomiting	Frequency, discontinuations or interruptions of study treatment and outcomes of this adverse event will be monitored in each clinical study quarterly and in real time in SAE assessment.
Potential	Hepatic function abnormal	Hepatic function will be monitored with routine LFTs per schedule of assessment in individual protocols. AEs will be extracted using the SMQ Hepatic disorders (narrow). Review of clinically significant lab changes will be quarterly. LFTs boundaries are included in each protocol for a subject to be enrolled in any ABT-348 study. Categorical analysis of LFTs will be performed quarterly for elevations of ALT/AST ($\geq 3 \times$ ULN) or Bilirubin ($\geq 2 \times$ ULN), and AP ($\geq 2 \times$ ULN).
Potential	Hemorrhagic events	Hemorrhagic events will be extracted using the SMQ haemorrhages (narrow) and they will be reviewed quarterly.
Potential	Gastrointestinal perforation	Cases will be analyzed individually as they occur. Aggregate analysis will be performed quarterly. The AEs will be extracted using the SMQ gastrointestinal perforation (narrow).
Potential	QT prolongation	Inclusion criteria in each protocol will include maximum values for QT. ECG will be taken during the implementation of the studies at prefixed protocol times. Medically significant changes in ECG per investigator assessment will be reported and analyzed on a quarterly basis. The AEs will be extracted using the SMQ (broad) Torsade de pointes/QT prolongation (SMQ).
Potential	LVEF	Inclusion criteria will include minimum values for EF. Ventricular function (decreased LVEF) will be monitored using MUGA at prefixed protocol times during implementation of the studies.
Potential	Neutropenia	Neutropenia will be monitored with routine hematological evaluation. AEs will be retrieved using the SMQ Haematopoietic Cytopenias (broad for all SMQs). The AEs and laboratory results will be analyzed quarterly.
Potential	Skin toxicities	Frequency and severity will be monitored quarterly. Interruptions and discontinuations for these events will be also reviewed quarterly. Hand and foot syndrome CMQ will be used to retrieve the cases.
Potential	Fatigue/Asthenia	Frequency and severity will be monitored quarterly. Interruptions and discontinuations for these events will be reviewed quarterly.
Potential	Hypothyroidism	Frequency and severity of hypothyroidism adverse events will be monitored quarterly. Thyroid stimulating hormone (TSH) will be measured when medically indicated. The hypothyroidism adverse events will be extracted using the SMQ Hypothyroidism (Broad).
Potential	Pancreatitis	Two cases of pancreatitis were reported in the clinical study M10-943. The investigator and the sponsor assessed the causality as probably related in both cases. One of the cases was a DLT. A pancreatic enzyme evaluation will be performed when clinically indicated in subjects with symptoms and/or signs indicative of pancreatitis. The cases of pancreatitis will be extracted from the clinical data base using the Acute pancreatitis SMQ (Narrow).

3. Eligibility Criteria

To be eligible for this trial, patients must meet all of the following criteria.

3.1. Inclusion criteria

1) Patients with histologically confirmed, advanced or metastatic cancer for which standard curative or palliative measures do not exist or are no longer effective.
2) Patients must have CDKN2A-deficient tumor (deletion or mutation). Status will be determined from archived tissue.
   Definition of CDKN2A deficient tumor:
   #1. CDKN2A deletion or mutation by any CLIA-certified sequencing OR
   #2. ≥ 30% of tumor cells with (at least) hemizygous deletion by FISH
3) Patients must have measurable disease by RECIST 1.1.[10]
4) Patients must be ≥18 years of age.
5) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2.
6) Subject has adequate renal function as demonstrated by serum creatinine value of ≤ 1.5 times the upper limit of normal (ULN) and either an estimated creatinine clearance value of ≥ 50 mL/min as determined by the Cockcroft-Gault formula or a creatinine clearance value of ≥ 50 mL/min based on a 24 hour urine collection.
7) Subject has adequate liver function as demonstrated by serum bilirubin </= 2 x ULN and AST and ALT ≤ 2.5 x ULN. For subjects with liver metastasis, adequate liver function is demonstrated by serum bilirubin ≤ 2 x ULN and AST/ALT ≤ 5.0 x ULN.
8) Subject has adequate bone marrow as demonstrated by absolute neutrophil count (ANC) ≥ 1,500/mm^3 (1.5 x 10^9/L); Platelets ≥ 100,000/mm^2 (100 x 10^9/L); Hemoglobin ≥ 9.0 g/dL (1.4 mmol/L).
9) Subject has QTc interval < 500 msec on baseline electrocardiogram.
10) The subject has a documented Left Ventricular Ejection Fraction > 50%.
11) Women of child-bearing potential and men must agree to use adequate contraception (one of the following listed below) prior to the study entry, for the duration of study participation and up to 3 months following completion of therapy. Women of child-bearing potential must have a negative pregnancy test within 7 days prior to initiation of treatment and/or post menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential.
    - Total abstinence from sexual intercourse (minimum one complete menstrual cycle)
    - Vasectomized male subjects or vasectomized partner of female subjects
    - Intrauterine device
    - Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or cream)
    - Additionally, male subjects (including those who are vasectomized) whose partners are pregnant or might be pregnant must agree to use condoms for

the duration of the study and for 3 months following completion of therapy.

12) Ability to understand and willingness to sign informed consent form prior to initiation of the study and any study procedures.
13) Signed informed consent approved by the Institutional Review Board prior to patient entry

3.2. Exclusion criteria

1. Patients with CDKN2A wild type by a CLIA-certified laboratory
2. Subject has known active CNS involvement. The subject has untreated brain or meningeal metastases. CT scans are not required to rule out brain or meningeal metastases unless there is a clinical suspicion of central nervous system disease. Subjects with treated brain metastases that are radiographically or clinically stable for at least 4 weeks after therapy and have no evidence of cavitation or hemorrhage in the brain lesion(s) are eligible, providing that they are asymptomatic, and do not require corticosteroids (must have discontinued steroids at least 1 week prior to study drug administration).
3. Subject has received anti-cancer therapy including chemotherapy, immunotherapy, radiotherapy, hormonal, biologic or any investigational therapy within a period of 21 days or 5 half-lives (whichever is shorter) prior to Study Day 1.
4. Subject has unresolved toxicities from prior anti-cancer therapy, defined as any Common Terminology Criteria for Adverse Events (NCI CTCAE v 4.0) grade 2 or higher clinically significant toxicity (excluding alopecia).
5. Subject has had major surgery within 28 days prior to Study Day 1.
6. Subject currently exhibits symptomatic or persistent, uncontrolled hypertension defined as diastolic blood pressure > 90 mmHg or systolic blood pressure > 140 mmHg. Subjects may be re-screened if blood pressure is shown to be controlled with or without intervention.
7. Subject has proteinuria defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v 4.0) grade > 1 at baseline as measured by a urine dipstick (2+ or greater) and confirmed by a 24 hour urine collection (≥ 1 g/24 hrs). Subjects may be re-screened if proteinuria is shown to be controlled with or without intervention.
8. Subject is receiving therapeutic anticoagulation therapy. Low dose anti-coagulation (e.g., low dose heparin or warfarin) for catheter prophylaxis will be permitted. Use of Aspirin for treatment of Atrial Fibrillation will also be permitted.
9. Patients with another primary malignancy within 3 years prior to starting study treatment with the exception of adequately treated basal cell carcinoma, squamous cell carcinoma or other non-melanomatous skin cancer, or in-situ carcinoma of the uterine cervix.
10. Clinically significant uncontrolled condition(s) including but not limited to:
    - Active uncontrolled infection,
    - Symptomatic congestive heart failure,
    - Unstable angina pectoris or cardiac arrhythmia (subjects with stable atrial fibrillation are not excluded),
    - History of adrenal insufficiency,

11. Psychiatric illness/social situation that would limit compliance with study requirements.
12. Subject has a known infection with HIV, Hepatitis B or Hepatitis C.
13. Subject is known to have poorly controlled diabetes mellitus defined as HbA1c > 7%; subjects with a history of transient glucose intolerance due to corticosteroid administration are allowed in this study if all other inclusion/exclusion criteria are met.
14. Any medical condition which in the opinion of the study investigator places the subject at an unacceptably high risk for toxicities.
15. Subject is unable to swallow or absorb oral tablets normally.
16. Female subject who is lactating or pregnant.
17. Subject takes CYP3A Inhibitors/Inducers (see Appendix I) within 7 days prior to the study drug administration.

4. Treatment Plan

Drug administration will take place as per protocol schedule as shown in Figure 3 unless patient/logistical/medical reasons intervene. A 2-day window is allowed for all assessments. Response evaluation will be performed every 2 cycles between day 43 and day 50.

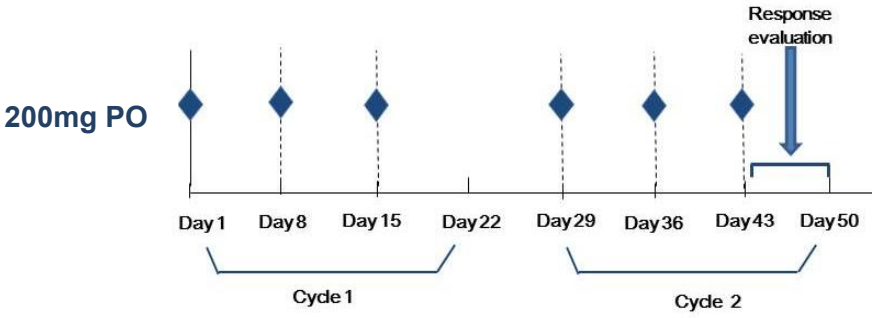

Figure 3. Treatment plan

200 mg ilorasertib will be administered by mouth twice daily on days 1, 8, and 15 of each 28-day cycle. All study visits will take place at MD Anderson Cancer Center. Participants may have labs performed at outside facilities.

Each morning dose of ABT-348 will be taken with 4 ounces of water. Patients should fast for 8 hours before taking this dose. Patients will be allowed to have a light snack 2 hours after the dose, and then may resume normal eating 4 hours after the dose.

4.1. Criteria for removal from the study:

Patients will continue treatment until their disease progresses per RECIST 1.1 or other objective tumor measurements, their side effects become too severe, an inter-current illness that prevents further administration of treatment, patient withdraws consent, or the physician or patient feels it is not in the patient's best interest to continue. Patients will be

treated beyond their disease progression (as described by RECIST 1.1) at the discretion of the PI if they are deriving clinical benefit from the treatment.

4.2. Dose delays and modifications:

If an individual patient experiences any new grade 3 or greater toxicity that is considered to be related to treatment, treatment will be held until recovery to </= grade 1 or to the baseline level. Ilorasertib (ABT-348) will be supplied as 50 mg tablets. Dose may be reduced in increments of 50 mg. All dose delays and reductions are up to physician's discretion. Dose may also be re-escalated based on physician's discretion when toxicities recover to grade 1 or to the baseline level. To stay eligible for the study, treatment can be delayed up to 4 weeks and dose can be reduced down to 50mg BID. For suggested dose reductions, see Appendix III. Patients requiring more than 2 dose reductions during the course of the study will be permanently discontinued.

Patients who experience Grade 4 non-hematologic adverse events will be permanently discontinued form the study unless the patients are experiencing clear clinical benefit and meet the proposed recovery criteria.

4.3. All participants who receive treatment will be considered in the response analysis. In particular, objective response rates will be analyzed in any tumor types with CDKN2A deletion or mutation and subgroup expansion cohort with specific tumor type and CDKN2A deletion or mutation, separately. Response will be evaluated with RECIST 1.1.

4.4. Patient will begin a new cycle if toxicity grade 2 or less; ECOG 2 or less; and no pregnancy.

5. Pretreatment and Treatment Evaluation

- The following treatment evaluations will be conducted as part of this study. If CDKN2A status is not known, tumor tissue will be tested in a CLIA-certified lab prior to initiating treatment.
- Physical examinations including BP measurement at screening and on Day 1, Day 8 and 15 of cycle 1 and 2, then at least once per cycle (28 days).
- Labs should be performed on each dosing day for the first 2 cycles and at least once per cycle (at screening and at Day 1 of subsequent cycles) and on Day 15 of Cycles 1 and 2, including CBC with differential, electrolytes, BUN/creatinine, magnesium, glucose, phosphorus, uric acid, AST, ALT, Alkaline Phosphatase, total bilirubin, albumin, calcium, total protein. PT/PTT at screening only.
- Dipstick urinalysis at screening and Day 1 of every cycle.
- Serum pregnancy test in women of childbearing potential at screening (within 7 days prior to initiating treatment). Serum or urine pregnancy test in women of childbearing potential on Day 1 of Cycle 2 and beyond.
- ECHO/MUGA at screening.

- Skin punch biopsy (optional) of 3mm and hair follicle collection will be collected on Cycle 1 Day 1 at up to 72 hours prior to the first dose and 2−4 hours post the second dose.
- Radiologic evaluations will be obtained at screening and repeated after every 2 cycles of treatment.
- EKGs should be performed at screening, Day 1 of Cycles 2 and 3, followed by every 3 months thereafter or more often as clinically indicated.
- Concomitant medications should be assessed at each visit.

6. Concomitant Medication

All concomitant medications will be documented in the electronic medical record. They will be captured from day 1 (pre-dose) through the safety reporting period.

Premedication: National Comprehensive Cancer Network (NCCN) or American Society of Clinical Oncology (ASCO) approved prophylactic antiemetics may be given as appropriate.

Anti-cancer Agents: No anti-cancer agents or investigational agents may be taken concurrently with Ilorasertib (ABT-348).

Supportive Care: Best supportive care and treatment will be given as appropriate to each subject (antiemetics, antibiotics, transfusions, nutritional support, palliative treatment for pain, etc.).

CYP3A Inhibitors/Inducers: CYP3A inhibitors (strong, moderate and weak) and CYP3A inducers should be used with caution when used concurrently with Ilorasertib (ABT-348) . Subjects will be provided with a list of CYP3A inhibitors/inducers and must bring the list with them to all appointments with any physician or other healthcare provider. Refer to Appendix I for a sample list of medications which should be used with caution.

Substrates of CYP1A2, 2B6, 2C8, 2C9, 2C19, or 2D6: Sensitive substrates of CYP1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 should be used with caution. Refer to package insert of co-administered drug to determine if the drug is a sensitive substrate of CYP1A2, 2B6, 2C8, 2C9, 2C19, or 2D6.

Growth Factors: Biologic response modifiers administered for erythropoiesis (e.g., erythropoietin, darbepoetin alpha) and colony stimulating factors (e.g., G-CSF, GM-CSF, etc.) may be administered according to the ASCO guidelines.

Radiation: Radiation therapy is not allowed during the study. If radiation therapy is needed to treat the symptoms due to underlying cancer, it will be considered clinical progression (as defined in Section 5.4.1).

Surgery: If the subject requires surgery during the study then this needs to be discussed with the Principal Investigator (David Hong, MD).

7. Measurement of Response

The primary objective of this protocol is to determine response rate. Patients will be evaluated every 2 cycles. Confirmatory scans will also be obtained 4 weeks following initial documentation of an objective response.

7.1. Response criteria

Response and progression will be evaluated in this study using the new international criteria proposed by revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. If patients with Gastrointestinal Stromal Tumors (GIST) are included in this study, we will use the Choi criteria[11] as parameters of response.

Evaluation of lesions based on photographs and clinical measurements will also be allowed for Head and Neck Squamous Cell tumors with superficial or skin lesions. These clinical pictures offers difficulties for precise monitoring of lesions based exclusively on CTs.

Patients with bone metastasis will be classified as having classic measurable disease if they met the criteria for on new RECIST 1.1 recommendations.

7.2. Methods of evaluation

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. The following image methods will be accepted as methods to evaluated response:

- Conventional CT (preferred method)
- Magnetic Resonance Image (MRI)
- Chest x-ray
- Bone scan
- PET CT

8. Evaluation of Toxicity

The secondary objective of this protocol is to determine the safety. Toxicities are will be described according to the NCI-CTCAE Version 4.03 (available at http://ctep.cancer.gov/reporting/ctc.html).

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events, and assigning attribution for each event on all subjects enrolled on this study.

Molecular and Clinical Data Integrated Platform (MOCLIP) will be used as the electronic case report form for this protocol and adverse events and protocol specific data will be entered into MOCLIP.

If an adverse experience increases in frequency or severity during a study period, a new record of the experience will be started.

Assessment of Intensity

Maximum intensity should be assigned to an adverse experience. Intensity will be assigned a Grade of 1-5. Final arbitration of intensity in cases of differing assessments by different practitioners will be the attending physician. Day to day fluctuations of intensity may not be recorded but rather the worst grade over the longest time period. Adverse events will be recorded in the Adverse Event log utilizing the recommended AE recording guidelines for Phase II studies, below:

Recommended Adverse Event Recording Guidelines					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

Assessment of Causality

Every effort should be made by the investigator to explain clinically significant adverse experience and to assess its relationship, if any, to the study medication.

Statement of Good Clinical Practices

This trial will be conducted in adherence to the study protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 50, 54 56, 312 and Part 11 as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements. http://www.fda.gov/cder/guidance/index.htm

9. Regulatory and Reporting Requirements

Adverse Event Monitoring and Reporting
The principal investigator is responsible for monitoring the safety of patients who enroll in the study. All drug-related AEs occurring after any administration of the study drug will be followed until resolution, stabilization, death, loss to follow up, or commencement of new therapy. The descriptions and grading scales found in the revised NCI CTCAE version 4.0 will be used for adverse event reporting. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/ctc.html).

Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures

outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last study treatment/intervention, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Adverse Events: Pregnancy

Principal Investigator shall comply with all FDA reporting requirements pursuant to 21 C.F.R. § 312.

In addition to compliance with all FDA reporting requirements pursuant to 21 C.F.R. § 312, the Principal Investigator shall:

a. report all serious adverse events experienced by a study subject receiving an AbbVie product within 24 hours of learning of the event regardless of the relationship of the event to the AbbVie product. Principal Investigator shall make available to AbbVie promptly such records as may be necessary and pertinent to investigate any such event, if specifically requested by AbbVie; and
b. copy AbbVie on the submission to the FDA of events meeting the definition of IND safety reports at the time of submission to the Agency; and

c. notify AbbVie upon any subject receiving an AbbVie Product whose pregnancy has resulted in a negative outcome or untoward event during the course of pregnancy or upon delivery.

AbbVie's contact for reporting serious adverse drug experiences and pregnancy experiences shall be *PPDINDPharmacovigilance@abbvie.com*

Subjects who become pregnant during the study must be discontinued. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. Male subjects should be informed that contraceptive measures should be taken by their female partners. If the subject's partner should become pregnant during the study, this should also be reported and data may be collected. Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to (847) 938-0660 within 24 hours of the site becoming aware of the event.

Data Collection
All patients who meet eligibility criteria and are enrolled in this trial will be registered in Clinical Oncology Research Database at the University of Texas MD Anderson Cancer Center at Houston.

Data Protection and Confidentiality
All patients who meet eligibility criteria and are enrolled in this trial will be registered in Clinical Oncology Research Database (CORe) at the University of Texas MD Anderson Cancer Center at Houston. All protocol participants must be registered in the CORE. The date in the current informed consent document is displayed to ensure only the most current IRB approved version is used. Consent date, registration date, off study date, and evaluability data are required for all registrants.

The principal investigator agrees to keep all information and results concerning the study confidential. The confidentiality obligation applies to all personnel involved with this clinical trial. The Investigator must ensure that each participant's anonymity will be maintained in accordance with applicable laws. The principal investigator should keep a separate log of ID numbers and names. Documents that contain the names associated with these ID numbers (e.g., written consent/assent forms), should be maintained by the Investigator in strict confidence except to the extent necessary to allow auditing by regulatory authorities, auditing or monitoring by the IRB.

The Principal Investigator shall obtain all such permissions and authorizations as may be necessary or desirable to allow the collection and use of information protected under federal privacy laws and state privacy laws, including permission/authorization for monitoring and analysis (including re-analysis in combination with results of other studies), for regulatory submission purposes and for applicable reporting (if any).

10. Statistical Considerations

10.1. Study design and endpoints

This is an open-label, single-center, phase II study exploring the efficacy and safety of Ilorasertib (ABT-348) monotherapy in a diverse population of patients with advanced cancers with CDKN2A deletion or mutation for whom Ilorasertib (ABT-348) is deemed the best treatment option in the opinion of the Investigator.

Primary endpoint is to evaluate the tumor response rate (partial response, complete response) by Response Evaluation Criteria In Solid Tumors, Version 1.1 (RECIST, v1.1) in solid tumors. Secondary endpoints are the safety and tolerability and pharmacodynamics. For safety and tolerability, toxicities will be evaluated according to the NCI-CTCAE Version 4.0 (available at http://ctep.cancer.gov/reporting/ctc.html). For pharmacodynamics, phospho-Histone H3 on biopsied skin tissues will be analyzed with immunohistochemistry.

10.2. Sample size

Sample size calculations are based on single arm, Phase II design with early stopping rules for futility. Early stopping rules will be applied. Accrual in a cohort will stop if >25% overall response rate (ORR) is unlikely. Prior to advancing to the next cohort, an Efficacy/Toxicity Summary will be completed and submitted to the IND Medical Monitor after 10 evaluable patients, and every 10 patients thereafter. The summary will contain aggregating information.

We assume that the targeted level of activity is 25% ORR or greater. ORR is defined as complete response or partial response.

We used the program MultcLeanDesktop Version 2.0.0 to generate an appropriate Bayesian design targeting a clinical benefit rate of 25%. We suppose that: θE = probability of ORR on the experimental arm ~ beta (aE, bE) and θS = probability of ORR for standard treatment in the historical data ~ beta (aS, bS) whereas = 250, bS = 750, aE = 0.5, and bE = 1.5. This specifies an informative prior for the standard with mean 0.25 and a non-informative prior for the experimental arm also with mean 0.25. We stop the trial early if Prob (θS>θE | data) > 0.925. The maximum sample size is set to 40, and we choose to monitor in cohorts of size 10. The stopping boundaries are 0/10, 2/20, 4/30, and 6/40 (where m/n indicates that we stop early if after n patients, we see m or fewer successes). If the true success probability is 5% then the probability of stopping early with these stopping boundaries is 0.99; for 10% it is 0.86; for 15%: 0.59; for 20%: 0.33; for 25%: 0.16; for 30%: 0.07; and for 35%: 0.03.

We will set the maximum sample size to 40 for the cohort in part 1 of the study, not including screen failures. If the observed ORR is 25% with a maximum sample size of N=40, the true ORR from the drug is between 16% and 38%, 90% of the time. Best response will be used for the response evaluation and stable patients will be followed for 6 months before declaring them a non-responder for the sake of analysis. Biomarker-drug combinations that meet these criteria will be recommended for further comparative evaluation in a larger trial. If the lower bound of the 90% posterior credible interval is > 16%, the drug will be recommended for subsequent independent confirmatory study.

10.3. Expansion cohorts

We propose that cohorts be expanded if predetermined sample size and response rate are met in specific tumor types. The objective of expansion cohorts is for patient enrichment by virtue of histology which may show better response. To identify tumor types with sufficiently convincing data to justify expansion to cohorts, we will use a Bayesian approach. We start with a prior distribution on, p, the probability of response, as a beta(1,1) (a uniform distribution). For each cohort, we will compute the posterior probability that p is greater than 0.5 given the data (i.e., Pr(p > 0.5 | data)). We will expand the cohort if this probability exceeds 0.5.

Below is a table of the probabilities that a cohort will be expanded based on the size of the cohort (columns) and the true response probability (rows). The probabilities are computed using standard methods associated with the binomial distribution and Bayesian updating using the beta-binomial distribution. Probabilities > 0.85 are highlighted. These probabilities are computed in the following manner. Suppose we have a cohort of size 3 and a true response rate of 0.8. There are four possibilities: 0 responses, 1 response, 2 responses or 3 responses in these 3 patients. With a true response rate of 0.8 these possibilities will occur with probabilities of 0.008, 0.096, 0.384 and 0.512. The posterior probabilities that p > 0.5 associated with these possibilities are 0.06, 0.31, 0.69, and 0.94. Thus expansion would occur only for 2/3 and 3/3 responses. Since these occur with probabilities 0.384 and 0.512, the overall probability of expansion is 0.384+0.512 = 0.896 (which rounds to 0.90).

	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0.5	0.25	0.50	0.31	0.50	0.34	0.50	0.36	0.50	0.38	0.50	0.61	0.50	0.40	0.50
0.6	0.36	0.65	0.48	0.68	0.54	0.71	0.59	0.73	0.63	0.75	0.84	0.77	0.69	0.79
0.7	0.49	0.78	0.65	0.84	0.74	0.87	0.81	0.90	0.85	0.92	0.96	0.94	0.91	0.95
0.8	0.64	0.90	0.82	0.94	0.90	0.97	0.94	0.98	0.97	0.99	1.00	0.99	0.99	1.00
0.9	0.81	0.97	0.95	0.99	0.98	1.00	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Based on the rule defined above, we will expand eligible tumor subtype cohorts to a total of 25 patients including those patients enrolled in part 1 of the study. With 25 patients, if the observed response probability is 0.7, the 90% credible interval is (0.53, 0.82). This means that the true response probability is between 53% and 82%, 90% of the time. Screen failures will not count against the maximum accrual number. Specific cohorts meeting the response threshold for expansion will be expanded even if part 1 of the study is stopped early for overall futility. Tumor type specific expansion will be triggered after accrual to part 1 of the study is complete: either after all 40 patients have been enrolled, or when part 1 of the study is stopped for overall futility.

An evaluation of safety data will be performed at the time of the first efficacy assessment in this trial (i.e., after 10 patients). If at any point the toxicities are found to be greater than 33% in this safety assessment, enrollment will be stopped for excessive toxicities.

11. Pharmacodynamic Analysis of Skin Biopsy

Aurora kinase inhibition induces several distinct cellular phenotypes including inhibition of histone H3 phosphorylation and the induction of polyploidy. Given the potent inhibition of aurora kinases by Ilorasertib (ABT-348), skin punch biopsy may be analyzed to determine if modulation of these events can be monitored as a surrogate of drug exposure. Analysis may not be limited to histone H3 phosphorylation but may be expanded to testing other events that may be predictive of clinical outcome. Skin punch biopsy of 3mm (optional) will be collected on Cycle 1 Day 1 at up to 72 hours prior to the first dose and 2-4 hours post the second dose on Cycle 1 Day 8. Skin biopsies should be fixed in formalin for between 8 to 24 hours then embedded in paraffin following institutional procedures. The FFPE blocks will be kept in an IHC slide carrier (or equivalent) and stored at 2° to 8°C to maintain the sample integrity until shipment. These samples will be shipped at ambient temperature. Phospho-Histone H3 (P-HH3) will be evaluated by immunohistochemistry (IHC) at the AbbVie laboratory or any CLIA-certified laboratory.

Shipment of Skin Punch Biopsy
Skin punch biopsy FFPE blocks will be placed in an IHC slide carrier (or equivalent) for shipping. Skin punch biopsy blocks slide boxes should be labeled with study drug number, sample matrix (tissue), protocol number, subject number, and collection date. Samples should be packaged using suitable shipping materials and sent at ambient temperature to the following address:

AbbVie
Attention: Peter Ansell, PhD
Cancer Biomarkers
AP10- Room 114
1 North Waukegan Road
North Chicago, IL 60064-6098
PHONE (847)-935-1222

12. Follow-up Period

All subjects will enter the follow-up period upon discontinuation of study treatment for reasons other than withdrawal of consent or death. The subject should be monitored for new and ongoing adverse events until 30 days after the last dose of study treatment. All serious adverse events should be followed until resolution. Patients removed from the study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

13. Confidentiality

All laboratory and clinical data gathered in this protocol will be stored in a password-protected database (MOCLIP/CORe). All patient information will be handled using anonymous identifiers. Linkage to patient identity is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

14. Study Calendar

Table 6. Study Calendar

Assessment Tool*	Baseline (within 2 weeks of C1D1)	Cycle 1 Day				Cycle 2 Day				Cycle 3~X Day			
		1	8	15	22	1	8	15	22	1	8	15	22
History and Physical Exam including BP measurement	X	X	X[8]	X		X	X[8]	X		X			
CDKN2A status	X[6]												
CBC with differential	X	X	X	X	X	X	X	X	X	X			
Sodium, Potassium, Chloride, Bicarbonate, BUN, Creatinine, Glucose, Calcium, Magnesium, Uric Acid, Phosphorus, Total Protein	X	X	X	X		X	X	X		X			

Albumin, Alkaline Phosphatase, Total Bilirubin, AST, ALT	**X**	**X**	**X**	**X**		**X**	**X**	**X**		**X**			
Urinalysis, dipstick	**X**	**X**				**X**				**X**			
PT/PTT	**X**												
Pregnancy Test (in women with childbearing potential)[5]	**X**					**X**				**X**			
12-lead EKG	**X**					**X**				**X**[7]			
ECHO/MUGA	**X**												
Appropriate Radiologic Evaluation	**X**								**X**[4]				
Skin punch biopsy (optional)		**X**[2]	**X**[3]										
Concomitant Medications	At each visit												

* All assessments to be performed within +/- 2 days of the specified date.
1. Urinalysis, dipstick every other cycle
2. Cycle 1 Day 1 at up to 72 hours prior to the first dose.
3. Cycle 1 Day 1 at 2–4 hours post the second dose.
4. Subsequent restaging every 2 cycles. If objective response is observed, a confirmatory scan should be obtained 4 weeks following initial documentation of response.
5. Serum pregnancy test at baseline in women of childbearing potential within 7 days prior to initiating treatment. Serum or urine pregnancy test in women of childbearing potential on Day 1 of Cycle 2 and beyond.
6. If not already performed, CDKN2A status must be determined in a CLIA-certified lab prior to treatment.
7. After Cycle 3, EKG may be performed every 3 months or more often as clinically indicated.
8. Blood pressure measurement only.

15. References

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APPENDIX I- Cautions with Coadministration of Medications

1) **Inhibitors of CYP3A4:**
   - Antibiotics: clarithromycin, erythromycin, troleandomycin, chloramphenicol
   - HIV: anti-retrovirals (delaviridine), protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir)
   - Antifungals: itraconzaole, ketoconazole, voriconazole, fluconazole (>150 mg daily)
   - Antidepressants: nefazodone, fluvoxamine
   - Miscellaneous: Grapefruit or its juice

2) **Inducers of CYP3A4 :**
   - HIV: efavirenz, nevirapine
   - Anticonvulsants, mood stabilizers: carbamazepine, phenytoin, oxcarbamazepine
   - Antibiotics: rifampin (rifampicin), rifabutin, rifapentene
   - Antiretrovirals: efavirenz, nevirapine
   - Miscellaneous: St. John's Wort, modafinil

3) **Drugs with narrow therapeutic window:**
   - Phenytoin
   - Digoxin
   - Wafarin
   - Lithium
   - Aminoglycosides
   - Vancomycin

Avoid St John's Wort

APPENDIX II- Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX III- Management Guidelines for Toxicities

Based upon results from the preclinical safety pharmacology evaluation of Ilorasertib (ABT-348), and experience with other inhibitors of Aurora kinase and VEGF signaling, potential toxicities may include hypertension, proteinuria, gastrointestinal toxicities such as nausea, vomiting and/or diarrhea. For observed toxicities, subjects should be assessed for inter-current illness or other causes and treated as appropriate. While investigator discretion should be used for subject management with regards to these toxicities (i.e., dose interruptions and/or dose reductions), some suggested guidelines are included in the following sections.

Subject Management for Hypertension

Toxicity	Subject Management
Asymptomatic Grade 2 or Grade 3 Hypertension	Initiate antihypertensive therapy and continue Ilorasertib (Ilorasertib (ABT-348)) at same dose level.
Symptomatic Hypertension	Interruption of Ilorasertib (ABT-348) and possible discontinuation of therapy. Once blood pressure is controlled (≤140/90), the subject may resume Ilorasertib (ABT-348) at a dose reduced by 50 mg.
Systolic BP >200 mm Hg or Diastolic BP > 110 mm Hg	Interruption of Ilorasertib (ABT-348) and possible discontinuation of therapy. Once blood pressure is controlled, the subject may resume Ilorasertib (ABT-348) at a dose reduced by 50 mg.

Management of Proteinuria

Subject Management for Proteinuria

Based on the results of routine laboratory analysis:		
Toxicity	Subject Management	Monitoring
Urine dipstick ≥ 2+	Hold until 24 hour urine collection confirms proteinuria < 2 g/24 hrs	Perform the following tests: • 24 hour urine collection for total protein and creatinine Microscopic examination of fresh urine
Based on the results of the 24-hour urine collection:		
Toxicity	Subject Management	Monitoring
Proteinuria < 2.0 g/24 hours	Continue Ilorasertib (ABT-348) planned dose.	Continue urine analysis as routinely scheduled.
Proteinuria ≥ 2.0 g/24 hours	Interrupt Ilorasertib (ABT-348).	Resume Ilorasertib (ABT-348) at same or reduced dose once urine dipstick ≤ 1+ or urinary protein levels decrease to < 2 g/24 hrs.

Management of Gastrointestinal Toxicities

Subject Management for Diarrhea

Diarrhea	Occurrence	Subject Management
Grade 1	2 or more	Subject may continue Ilorasertib (ABT-348) at the same dose. Manage appropriately with an anti-diarrheal agent.
Grade 2	2 or more	Assess and treat as appropriate. If alternative etiology is identified and treatment administered, subject may continue on Ilorasertib (ABT-348) at the same dose. If no other cause has been identified, recommend interruption of Ilorasertib (ABT-348), per investigator discretion. If interruption deemed necessary, once toxicity has resolved to Grade $\leq$ 1, the subject may resume Ilorasertib (ABT-348) at the same dose.
Grade 3	1	Assess and treat as appropriate. If alternative etiology is identified and treatment administered, subject may continue on Ilorasertib (ABT-348) at the same dose. If no other cause has been identified then interrupt Ilorasertib (ABT-348) therapy if diarrhea continues for greater than 72 hours despite maximum supportive care. Once toxicity has resolved to Grade < 2, the subject may resume Ilorasertib (ABT-348) at a dose reduced by 50 mg.
Grade 4	1	Discontinue Ilorasertib (ABT-348).