Phase 2 Window of Opportunity Study of IPI-549 in Patients with Locally Advanced HPV+ and HPV- Head and Neck Squamous Cell Carcinoma

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PROTOCOL

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

UCSD Principal Investigator / Study Chair

_____
Printed Name

_____ _____
Signature Date

Participating Site Principal Investigator

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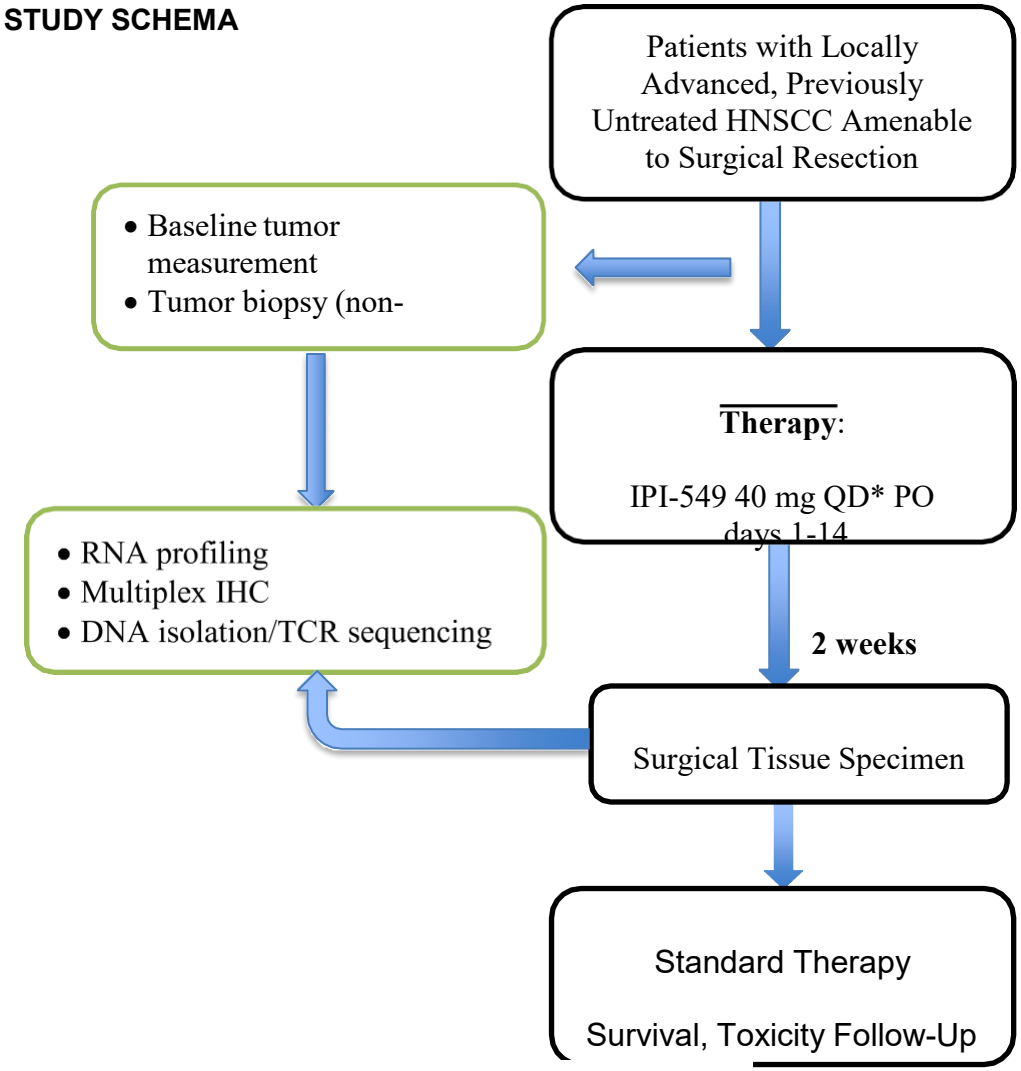
STUDY SCHEMA



*Final dose based on ongoing Phase 1 study

STUDY SUMMARY

Title	Phase 2 Window Study of IPI-549 in Patients with Locally Advanced HPV+ or HPV- Head and Neck Squamous Cell Carcinoma
Short Title	Phase 2 Window Study of IPI-549 in Locally Advanced HNSCC
Phase	2
Methodology	Single arm, unblinded
Study Duration	2 years
Study Center(s)	University of California, San Diego
Objectives	1. To detect a change in the PI3Kgamma regulated gene expression signature of immune suppression. 2. To detect change in myeloid, T cell composition and immune activation markers by IHC as well as TCR sequencing 3. To determine safety and tolerability of IPI-549 and change in tumor size in patients with locally advanced HNSCC.
Number of Subjects	15
Diagnosis and Main Inclusion Criteria	Eligible patients (n=15) with pathologically confirmed locally advanced, previously untreated HNSCC that is amenable to surgical resection.
Study Product(s), Dose, Route, Regimen	IPI-549, 40 mg QD PO* *Final dose based on ongoing Phase 1 study [NCT02637531]
Duration of administration	At least 14 days
Reference therapy	N/A
Statistical Methodology	We anticipate enrolling 15 subjects. Within subject change from the post-treatment to the pre-treatment sample in the immune activation signature will be the primary endpoint. We will test the hypothesis of an increase in this signature using a one sided paired t-test at 5% significance level. With 15 subjects we have 80% power to detect a difference in the mean signature equal to 0.68 standard deviations. A safety stopping rule will halt the study if at any time 3 or more subjects have observed progression prior to surgery.

SCHEDULE OF EVENTS

Procedure	**Screen/ Baseline** (≤ 28 days)	**Window of Opportunity Week 1 Day 1** (±3 days)	**Pre-Surgery**[10] **Week 2 Day 14** (±3 days)	**Follow-up** Approximately 30 days (±7 days)after last dose of study drug
Informed Consent	*Within 28 days*			
Eligibility	X			
Medical History	X			
Demographics	X			
Concomitant Medications Assessment	X	X	X	X[9]
Adverse Event Assessment		X	X	X[9]
Physical Exam[1]	X	X	X	X
Vital Signs and Height	X		X	X
ECOG PS	X		X	X
CBC with Diff[2]	*Within 7 days*	X	X	X
CMP[3]	*Within 7 days*	X	X	X
Pregnancy test[4]	*Within 72 hours*			
HIV (as clinically indicated)	X (*Within 7 days)*			
HEP B & C (as clinically indicated)	*X (Within 7 days)*			
ECG (12-lead)	X			
Tumor tissue collection[5]	X		X[11]	
Blood Collection for Correlative studies[6]	X(*Within 7 days)*		X	
MRI or CT (neck & chest)				X[7]
IPI-549 administration[8]		X		
Safety follow up				X

IPI-549 is 14 days in length with the last administration within 24 hours of surgery.

1. Full physical exam at baseline; targeted physical exam at other time points.
2. CBC with Diff: Complete blood count with differential.
3. CMP: Comprehensive metabolic panel (bicarbonate, calcium, chloride, creatinine, glucose, potassium, sodium BUN, albumin, bilirubin total, alkaline phosphatase, total protein, ALT, AST).
4. Pregnancy test for females of child-bearing potential only.
5. Tumor tissue collection: See Section 6.1.8 for specifications.
6. Blood for correlative studies should be collected at the same time blood is drawn for CBC and CMP if possible. 40 mL blood to be collected at baseline; 30 mL blood to be collected at pre-surgery visits. See Section 6.1.8.
7. Scans will be performed when clinically indicated.
8. IPI-549 administration (Section 5.2): administered PO 40 mg QD until 24 hours prior to date when surgery is performed. Not allowed less than 24 hours of surgery.
9. In Follow-Up period, concomitant medications will be collected at Safety Follow-Up visit (approximately 30 (+7) days after the last dose of study drug) and for SADs. During this period, adverse events will be collected at Safety Follow-Up and SAEs until 90 days after last does of study drug.
10. Surgery is to be performed no later than 48 hours after last dose of therapy. Therapy should continue until the day before surgery.
11. Tumor tissue collection to occur during surgery.

1.0 INTRODUCTION

This protocol proposes to examine the anti-tumor efficacy of IPI-549 in patients with locally advanced HPV+ or HPV- HNSCC. Subjects who are candidates for surgical resection will be enrolled and treated with IPI-549 for 2 weeks prior to surgery. Tumor tissue for research purposes will be obtained by core biopsy prior to treatment and at surgery after 2 weeks of treatment. Tissue will be evaluated by RNA profiling for two PI3Kγ-regulated immune suppression signatures that we previously identified; changes in immune responses will be validated by performing immunohistochemistry to detect myeloid and T cell composition and activation status and by genomic sequencing to detect changes in intra-tumor T cell receptor (TCR) clonality.

2.0 BACKGROUND AND RATIONALE

2.1 Immunotherapy in HNSCC

Immune therapy holds great promise for the treatment of cancer patients, as novel immunotherapeutic agents such as the checkpoint inhibitors pembrolizumab and nivolumab (anti-PD-1) have recently demonstrated potent anti-tumor activity in a subset of cancer patients. Disappointingly, clinical responses to these checkpoint inhibitors occurred in only 20% of patients with head and neck squamous cell carcinoma (HNSCC), a devastating disease that is associated with considerable morbidity and mortality. Improved therapeutic approaches that target the mechanisms of immune escape from checkpoint inhibitors could hold great promise for patients with HNSCC and other cancers. Recent studies from our lab and others show that immune suppressive Tumor Associated Macrophages (TAMs) and Myeloid Derived Suppressor Cells (MDSCs) promote escape from checkpoint inhibitors. Signals from the tumor microenvironment polarize these myeloid cells towards an immunosuppressive phenotype that is characterized by high levels of Arginase, TGFß, IL10 and low levels of MHCII, IL12, iNOS and T cell chemoattractants such as CXCL9 and CXCL10. TAMs and MDSCs then suppress CD8+ T-cell recruitment, survival, and cytotoxic function, thereby inhibiting effective anti-tumor immune responses. Novel immune therapeutics that circumvent resistance to checkpoint inhibitors could provide benefit to numerous cancer patients, including patients with HNSCC.

We recently identified a novel pathway by which TAMs and MDSCs inhibit responsiveness to checkpoint inhibitors [1, 2]. We found that phosphatidylinositol-4,5-bisphosphate 3-kinase gamma (PI3Kγ), a myeloid cell selective isoform of PI3-Kinase, mediates immune suppression in TAMs and MDSCs by inhibiting NFkB activation and promoting mTor, S6K and c/EBPß activation, thereby leading to transcription of immune suppressive factors that inhibit T cell responses to tumors. Our results demonstrated that PI3Kγ, the major PI3K isoform in myeloid cells, promotes resistance to checkpoint inhibitors and stimulates tumor progression as selective inactivation of PI3Kγ suppressed myeloid cell expression of immune suppressive factors and inhibited tumor progression in mouse models of HNSCC, lung, breast, and pancreatic carcinoma, as well as melanoma and glioblastoma. Importantly, PI3Kγ inhibition stimulated responses to checkpoint inhibitors, leading to eradication of tumors and long-term anti-tumor immunological memory in mouse models of HNSCC.

Importantly, we also identified a PI3Kγ-regulated gene expression signature that is associated with outcome in HNSCC and lung cancer patients. Notably, high expression of a PI3Kγ-regulated immune suppression signature was associated with decreased patient survival in these patients. Conversely, low expression of this signature was associated with extended survival in these patients. These results suggested that a PI3Kγ-regulated immune suppression signature could be used to identify cancer patients who are candidates for PI3Kγ inhibitor therapy and to monitor clinical responses to PI3Kγ-inhibitors.

2.2 Study Agent

2.2.1 IPI-549

The PI3K-γ isoform plays important roles in immune cell function and migration, including the immune suppressive tumor microenvironment. IPI-549 is a potent and selective PI3K- γ inhibitor that is being developed by Infinity Pharmaceuticals, Inc. (Infinity) as an orally administered potential therapeutic in multiple cancer indications.

2.2.2 Summary of Pharmacology of IPI-549

Biochemical, cellular, and receptor binding assays showed that IPI-549 is a potent inhibitor of PI3K-γ that is highly selective over other protein and lipid kinases, GPCRs, ion channels, and transporters. Cellular proliferation assays demonstrated that IPI-549 does not have a direct growth inhibitory effect on human solid tumor cells lines. In vitro functional assays demonstrated that IPI-549 blocks bone marrow derived murine myeloid cell polarization to the M2 macrophage phenotype in response to IL-4 and macrophage colony-stimulating factor, and macrophage migration towards CXCL12, but does not inhibit Concanavalin A-induced T cell activation as measured by IFN-γ production. These data indicate the potential for IPI-549 to block immune suppressive macrophage development but not certain T cell activities that are important for the anti-tumor effect mediated by cytotoxic T cells.

The effect of IPI-549 on tumor growth was evaluated in vivo using immune competent, murine syngeneic solid tumor models. Mice treated with IPI-549 demonstrated significant tumor growth inhibition in multiple syngeneic models. Tumor growth inhibition was dose-dependent with dose-proportional plasma and tumor exposure for IPI-549. Studies to elucidate the mechanism of tumor growth inhibition indicated that IPI-549 affects immune-suppressive myeloid cell numbers and/or function, leading to an increase in cytotoxic T cell activity. Studies in both nude and CD8 T cell-depleted mice demonstrated the T-cell-dependence of IPI-549 mediated tumor growth inhibition.

2.2.3 Rationale for IPI-549 as a Potential Therapy for Patients with Cancer

PI3K-γ is expressed in immune cells and has limited, if any, expression in epithelial cancer cells. Furthermore, PI3K-γ is the predominant catalytic isoform found in myeloid cells [2]. In myeloid cells PI3K-γ is activated by GPCRs, the Toll Like Receptors/Interleukin 1 Receptors and RTKs [2]. The role of myeloid cells in promoting tumor growth has been demonstrated in multiple preclinical mouse models [3]. Tumors and their associated stroma secrete chemokines that attract precursor monocytes that differentiate into macrophages. The tumor associated macrophages as well as dendritic cells and granulocytes (collectively known as myeloid derived suppressor cells [MDSC]), actively support the proliferation of the tumor cells while at the same time acting to suppress host antitumor activity [4].

Pre-clinical data from a tumor bearing mouse knockout model of PI3K-γ results in a reduced influx of myeloid cells, and reduced vascularization of the tumor, resulting in reduced tumor growth, suggesting that PI3K-γ inhibition can play a critical role in disrupting the MDSCs [2].

The established role of PI3K-γ in the biology of the tumor microenvironment supports testing IPI-549 in patients with cancer, both as a single agent, and in combination with other drugs. The PI3K-γ isoform plays important roles in immune cell function and migration, including the immune suppressive tumor microenvironment. IPI-549 is a potent and selective PI3K- γ inhibitor that is being developed by Infinity Pharmaceuticals, Inc. (Infinity) as an orally administered potential therapeutic in multiple cancer indications.

2.3 Rationale

HPV+ and HPV- head and neck squamous cell carcinoma (HNSCC) are deadly and disfiguring cancers with limited therapeutic options; while checkpoint inhibitors have promise as new cancer therapeutics, they have demonstrated limited activity in HNSCC. However, we found that inhibitors of PI3Kγ, such as Infinity Pharmaceutical's highly selective inhibitor, IPI-549, repolarized tumor associated macrophages to reverse immune suppression and stimulate anti-tumor immunity in animal models of HNSCC. We identified a signature of immune suppression in mouse models of HPV+ and HPV- HNSCC that was reversed by PI3Kγ inhibition [5]. Using TCGA data, we found that this same signature was associated with poor outcome in HPV+ and HPV- HNSCC patients [5]. Our results suggest that selective PI3Kγ inhibitors might promote anti-tumor immune responses in HNSCC patients. **We hypothesize that treatment with the selective PI3Kγ inhibitor IPI-549 will switch mRNA expression signatures of immune suppression in patient tumors to signatures of immune activation. These signatures could then serve as surrogate biomarkers of IPI-549 efficacy.** Therefore, we propose to establish a Phase II window of opportunity clinical trial to evaluate the effect of IPI-549 on biomarkers of immune suppression. Patients with resectable HNSCC will be treated with the investigational, highly selective PI3Kγ inhibitor IPI-549 for two weeks prior to surgical resection; pre- and post-treatment biopsies will be evaluated for changes in the PI3Kγ-responsive gene expression signature of immune suppression we previously identified. Additionally, we will monitor for changes intratumoral and circulating immune cell populations in collaboration with Dr. Lisa Coussens, OHSU, using multiplex immunohistochemistry. These studies will be useful in identifying biomarkers of response that will allow optimization of future therapeutic strategies for HNSCC.

3.0 STUDY OBJECTIVES

This is a phase 2 window of opportunity trial in patients with locally advanced HNSCC. A key objective is to provide the first proof that macrophage phenotype switching can be accomplished in humans and lay the groundwork for future trials of this novel approach to immune therapy. Subjects who are candidates for surgical resection will be enrolled and treated with 2 weeks of IPI-549, a specific PI3Kγ inhibitor. Tumor tissue for research purposes through core biopsies will be obtained prior to initiation of IPI-549 and at surgery.

3.1 Primary Objectives

1. To detect IPI-549-induced changes in PI3Kγ-regulated signatures of immune suppression.

3.2 Secondary Objectives

1. To measure changes in myeloid and T cell composition and activation status by immunohistochemistry and TCR sequencing.
2. To determine safety and tolerability of IPI-549 and change in tumor size in patients with locally advanced HNSCC.
3. To measure changes in peripheral cytokines and immune cells

3.3 Endpoints

We hypothesize that mRNA signatures of immune response will be increased in IPI-549-treated HNSCC patients. For the efficacy endpoints, RECISTv1.1 will be used.

Primary Endpoints

We hypothesize that the 5-gene mRNA immune response signature from Kaneda et al. [2] will increase with treatment.

Specifically, the signature is: s= *IL12A* + *IL12B* + *IFNG* + *CD8A* – IL6, measured by RNA expression levels from a custom Nanostring Immune Profiling panel.

Secondary Endpoints

1. Adverse events related to IPI-549 (description, grade [CTCAE v5.0], and seriousness).
2. T cell receptor (TCR) sequencing from blood obtained at baseline, surgery, end of treatment or at time of disease progression.
3. Comparison of pre- vs. post-treatment tumor tissue for CD8 expression by immunohistochemistry
4. Comparison of pre- vs. post-treatment peripheral cytokines and immune cells.

We hypothesize that the 42-mRNA signature of PI3Kγ [2] will increase with treatment. Gene expression will be assessed by Nanostring custom panel.

Specifically, the signature is comprised of the sum of 21 immune response and T-cell activation genes, plus the sum of 10 antigen presentation genes, minus the sum of 11 immune suppression genes [2] listed below.

Gene lists for the PI3Kgamma activation signature are:

- *Immune suppression genes: PDGFA PDGFB HBEGF PLAU F3 IFIT1 CD276 IL6 CCL7 CCL4 ID2*
- *Immune response, T cell activation genes: IER3 ADORA2A CCR7 RASGRP1 CXCR3 CX3CR1 IL12B IL12A CD4 CD8A CD8B GZMA GZMK GZMH GZMM IFNG CD28, LAT LAG3 ZBP1 BTLA MALT1*

- *Antigen presentation genes:*
  HLA_DMA HLA_DMB HLA_DRB5 HLA_DOB CIITA 0 *HLA_DQA2 HLA_DRA HLA_DOA HLA_DQB2 CD74.*

Exploratory endpoints

Three IHC panels to assess myeloid and T cell content and activation states, each panel is expected to increase with treatment

- Lymphoid panel: PD-1, CD3, RORgt, CD56, CD8, Tbet, GATA3, FoxP3 PD-L1, CD20, CD45, p16
- Myeloid panel: Tryptase, CD68, CSF1R, DC-SIGN, CD66b, CD83, CD163, MHCII, PD-L1, CD3/20/56, CD45, p16
- T cell activation panel: CD3, CD4, CD8, IDO, Tbet, CD68, PD-1, Eomes, Ki67, Granzyme B, CD45

4.0 PATIENT ELIGIBILITY

4.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study.

1. Patients must have locally advanced, previously untreated HNSCC (unknown primary or any primary site except cutaneous or EBV-related nasopharynx cancer) that is amenable to surgical resection
2. Age 18 years or older
3. Patients must be able to administer IPI-549 by mouth and have no evidence of malabsorption
4. Patients must be able to undergo a core tumor biopsy with tissue available for analytics

5. There must be at least 2 weeks between initiation of IPI-549 and surgical resection
6. ECOG performance status 0-2
7. Patient has adequate organ function as defined below:

Test Name	*Laboratory Value*
Absolute Neutrophil Count	$\geq 1.0 \times 10^9$/L
Platelet count	$\geq 75 \times 10^9$/L (transfusion independent for > 7 days)
Hemoglobin	≥ 8.0 g/dL (may receive transfusions)
Total bilirubin	≤ 1.5 x institution's upper limit of normal (ULN)
AST and ALT	≤ 2.5 X institutional upper limit of normal
Serum creatinine	≤ 1.5 x institution's ULN, or creatinine clearance ≥ 60 ml/min

8. Female patient of childbearing potential has a negative serum or urine pregnancy within 7 days prior to receiving the first dose of study medication.
9. Female patient of childbearing potential agrees to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication.
Note: Females of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

10. Male patient with a partner of childbearing potential agrees to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

4.2 Exclusion Criteria

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation. Subjects are to be excluded from the study if they meet any of the following criteria:

1. Cutaneous squamous cell carcinoma (SCC) or Epstein-Barr virus (EBV) related nasopharynx cancer
2. Severe allergic or anaphylactic reaction to IPI-549.

NOTE: Subjects with a history of anaphylaxis to other agents are eligible for study participation. Subjects who have received alternative therapies, including prior IPI-549, are eligible for study participation

3. Major surgery within 4 weeks prior to initiation of study drug
4. Subjects who have been treated with chemotherapy, biologic therapy, or other investigational agent within < 5 times the half-life of the agent or < 28 days (whichever is shorter) of starting study drug
5. Infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C virus (HCV)
6. Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids
7. Ongoing systemic bacterial, fungal, or viral infections at Screening

NOTE: Subjects on antimicrobial, antifungal, or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met

8. Administration of a live vaccine within 6 weeks of first dose of study drug
9. Administration of any of the following within 2 weeks prior to the administration of study drug:
    a. Strong inhibitors or inducers of CYP3A4, including grapefruit, grapefruit juice and herbal supplements
    b. P-glycoprotien (P-gp) inhibitors
    c. Warfarin, phenytoin, or other substrates of CYP2C8 or CYP2C9 with a narrow therapeutic range
    d. Medications associated with QTc interval prolongation or Torsades de Pointes
10. Baseline QT interval corrected with Fridericia's method (QTcF) > 480 ms (average of triplicate readings)
11. Prior surgery or gastrointestinal dysfunction that may affect drug absorption (e.g. gastric bypass surgery, gastrectomy)
12. Female subjects who are pregnant or breastfeeding
13. Concurrent active malignancy other than nonmelanoma skin cancer, carcinoma in situ of the cervix, or prostate intraepithelial neoplasia
14. History of peptic ulcer and/or gastrointestinal bleed that have not resolved
15. Unstable or severe uncontrolled medical condition (e.g., unstable cardiac function, unstable pulmonary condition including pneumonitis and/or interstitial lung disease, uncontrolled diabetes) or any important

medical illness or abnormal laboratory finding that would, in the Investigator's judgment, increase the risk to the subject associated with his or her participation in the study.

5.0 TREATMENT PLAN

5.1 Study Design

This is a phase 2 window of opportunity trial in patients with locally advanced HNSCC. Subjects who are candidates for surgical resection will be enrolled and treated with 2 weeks of IPI-549, a specific PI3Kγ inhibitor. Tumor tissue for research purposes through core biopsies will be obtained prior to initiation of IPI-549 and at surgery.

5.2 Treatment Dosage and Administration

IPI-549 will be administered 40 mg orally over a 14 day cycle. Dose of IPI-549 will be determined based on observed toxicity in ongoing Infinity clinical trial (NCT02637531). IPI-549 should be self-administered orally (approximately every 24 hours). IPI-549 should be swallowed whole with a glass of water (approximately 8 ounces or 240 mL). Subjects must avoid grapefruit and grapefruit juice while on study drug. Subjects should be advised to avoid food and liquids other than water from 2 hours prior to dosing until 1 hour after dosing.

5.3 Duration of Study Treatment

IPI-549 for 2 weeks prior to surgical resection. Subjects will be monitored continuously for toxicity while on study therapy. Toxicity will be assessed using the NCI-CTCAE, v. 5.0 or higher. There will be no dose modification allowed on study. Missed doses should be recorded on the pill diary. Any grade 3 toxicity will result in discontinuation of IPI-549. If at any time 3 or more subjects have observed progression prior to the start of definitive treatment the study will be halted.

5.4 Duration of Follow Up

All subjects will have a Safety Follow-up visit approximately 30 (+ 7) days after the last dose of study drug. At minimum this visit should include collection of AEs/SAEs and concomitant medications/procedures. This will be a clinic visit. The following activities will be performed during the visit, assessment of concomitant medications, adverse events, physical exam, vital signs and height, ECOG PS, CBC with differential, CMP . MRI or CT scan will be performed if clinically indicated.

5.5 Discontinuation from Study Participation

Patients may be removed from study participation for the following reasons (in addition to those listed for discontinuation of study treatment):

- The patient or legal representative withdraws consent for follow-up;
- The patient is lost to follow-up;
- The patient dies;
- It is the decision of the investigator.

- Severe allergic or anaphylactic reaction to IPI-549
- Disease progression prior to surgery
- Pregnancy
- Severe or life-threatening toxicity

6.0 STUDY PROCEDURES

Refer to the study Schedule of Events for procedures.

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at study treatment completion/early study treatment discontinuation, and during the follow-up period.

6.1 Definitions of Study Assessments

6.1.1 Medical history

A complete medical, surgical and oncology history as well as history of infections are obtained at screening. Any changes from Screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

6.1.2 Review subject eligibility criteria

Review of eligibility criteria as described in Section 3 to ensure subject qualification for study entry.

6.1.3 Concomitant medications

At Screening, concomitant/previous medications and procedures will be assessed including all medications/procedures that have occurred since the last visit.

6.1.4 Physical exam

A full physical exam (PE) will be performed at Screening and will include vital signs (temperature, blood pressure [sitting for 5 minutes], pulse rate, and respiratory rate), height, and weight. If vital signs need to be repeated during a single visit, assessments should be conducted approximately 5 minutes apart. Subsequent exams may be directed as appropriate.

6.1.5 Adverse event assessment

Baseline assessment of subject status for determining adverse events. See Section 7 for Adverse Event monitoring and reporting.

6.1.6 Clinical Laboratory Tests

Blood chemistry, hematology, and βhCG pregnancy tests will be administered throughout the study to monitor safety.

6.1.7 ECG

At the treatment termination visit, a standard 12-lead ECG will be conducted following an approximate 10-minute rest period and obtained in triplicate within approximately a 5-minute time period. QTc measurements will use the Fridericia's correction method (QTcF). ECGs will be read locally by the Investigator. Tumor assessment

6.1.8 Tumor Biopsy and Research Blood Collection

Tumor tissue will be obtained by core biopsy prior to treatment and at surgery after 2 weeks of treatment. The goal of the planned laboratory correlative studies is to further characterize the biology of PI3Kγ inhibition, to gain a better understanding of the impact of IPI-549 on the tumor microenvironment, and explore potential biomarkers. See Section 3 for further details.

6.1.9 Research Sample Collection Guidelines

Specimens should be collected as outlined below and ALL samples should be labeled with the following:

- Protocol number
- Institution
- Patient's de-identified study number
- Date of biopsy or surgery

6.1.9.1 Tumor tissue from initial biopsy

Tumor tissue will be collected from a diagnostic core biopsy preferably performed within 28 days of initiating study treatment.

When possible, 4 core biopsies should be taken for lesions > 1.5 cm, otherwise 2 cores should be taken.

- If 4 cores are obtained, 1 core should be fresh frozen and the rest should be formalin-fixed paraffin embedded (FFPE).

- If < 4 cores are obtained, tissue for research should be FFPE after being divided into the research and diagnostic documentation blocks according to the Pathology staff's specifications.

Ten (10) unstained sections (4-5 micron slices) or one (1) 20 micron roll-ups from FFPE tissue are desired.

Fresh frozen samples should be stored in liquid nitrogen and FFPE samples at room temperature until shipment.

6.1.9.2 Tumor tissue from surgical resection

Tumor tissue for research will be collected from only material in excess of that needed for routine clinical care as determined by a staff pathologist.

Depending on the amount of tissue available, tissue should be collected for research in the following order of preference:

1. Ten (10) unstained sections (4-5 micron slices) and one (1) 20 micron roll-ups from FFPE tissue.
2. 10 unstained sections from fresh frozen tissue.

Fresh frozen samples should be stored in liquid nitrogen and FFPE samples at room temperature until shipment.

6.1.9.3 Peripheral Blood Mononuclear Cells (PBMCs)

Blood for PBMCs will be collected prior to study treatment at screening (may be collected at the same time as blood drawn for routine laboratory tests) and at the time of surgery.

Blood samples will be collected in two heparin green top tubes (approximately 20 ml). Samples should be processed the day of collection according to the PBMC isolation protocol in the Laboratory Manual.

PBMCs should be stored at -80°C.

6.1.9.4 Buffy Coat

Blood samples will be collected in one EDTA purple top tube (approximately 10 ml) prior to study treatment at screening (may be collected at the same time as blood drawn for routine laboratory tests).

Samples should be processed the day of collection according to the buffy coat isolation protocol in the Laboratory Manual.

Samples should be stored at -80°C.

6.1.9.5 Serum Cytokines

Blood samples will be collected in one yellow-gold top serum separation tube (approximately 5 mL) prior to study treatment at screening (may be collected at the same time asblood drawn for routine laboratory tests) and at the time of surgery.

Samples should be processed the day of collection according to the instructions provided below:

1. Fill tube completely. Invert 5-6 times and stand upright for a minimum of 30 minutes to clot.
2. Centrifuge within 2 hours at 1000-1300g for 10 minutes at room temperature.
3. Aliquot into two 2 mL labeled cryovials.
4. Store samples at -65°C to -85°C.
5. Ship samples monthly to The Forsyth Institute:

The Forsyth Institute
c/o Danielle Stephens, MS
The Forsyth Institute
245 First St.
Cambridge, MA 02142

6.1.9.6 Flow Cytometry Analysis

Blood samples will be collected in one purple and black speckled Cyto-Chex tube (approximately 5 mL) prior to study treatment at screening (may be collected at the same time as blood drawn for routine laboratory tests) and at the time of surgery.

Samples should be processed the day of collection according to the instructions provided below:

1. Fill Cyto-Chex tube completely.
2. Immediately after collection, invert gently 10 times to ensure proper mixing.
3. Do **NOT** centrifuge. Do **NOT** open tube.
4. Ship ambient with Gel packs on the day of collection to Primity Bio:

   Primity Bio
   C/O Erika O'donnell
   48383 Fremont Blvd, Suite 118
   Fremont, CA 94538
   USA

5. Email package tracking information to: 0109@primitybio.com

6.1.10 Specimen Handling

Sample handling and storage will be coordinated by

Sharmeela Kaushal
Moores Cancer Center, 3345/3G, GG
3855 Health Sciences Drive
La Jolla, CA 92093-0819
Phone: 858-822-7661

6.1.11 Specimen Banking

Patient samples collected for this study will be retained in the UCSD Moores Cancer Center Biorepository for analysis and future cancer research. Specimens will be stored indefinitely or until they are used up. Samples will be labeled with the protocol number, subject's de-identified study number and collection date. The link between study number and medical record number will be viewed over a password secured encrypted server-client.

The study research coordinator at each local site will review their subject's medical record for demographic and clinical information pertaining to the subject's general medical history, diagnosis, and outcomes of any treatments received. This information will be transmitted to and retained by the Coordinating Site UCSD. Samples and data extracted from the subject's medical record will be coded with a de-identified study number so that the subject's name and identifying information will be removed. A log that links the subject's name and identifiers to the study number will be maintained in a secure database distinct from the secure database into which the subject's clinical information will be entered by study personnel.

Dissemination of specimens for research is at the discretion of the Study Chair, Dr. Cohen. Potential research collaborators outside of UCSD who approach the Moores Cancer Center for clinical specimens will be required to complete an agreement (Material Transfer Agreement or recharge agreement) stating that the specimens will only be released for use in disclosed research,

and any specimen left over from research will either be returned to the Cancer Center or destroyed. Any data obtained from the use of clinical specimen will be the property of UCSD for publication and any licensing agreement will be strictly adhered to. These outside collaborators may include for-profit biotechnology corporations interested in collaborating with UCSD investigators in research diagnostic, prognostic assays and drug development.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UCSD, the investigator or a collaborating researcher or entity.

If patients later decide they do not want their specimens collected to be used for future research, they may tell this to the local site principal investigator, who will inform the Study Chair Dr. Cohen. Dr. Cohen will use his best efforts to stop any additional studies and to destroy the specimens. Samples stored in the Biorepository will be destroyed; for samples that have been disseminated outside of the Biorepository, Dr. Cohen will contact the recipient to notify them of the need to halt further research and destroy specimens.

6.2 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 7 days prior to registration unless otherwise stated. The screening procedures include:

- Written informed consent *(within 28 days)*.
- Review of inclusion and exclusion criteria.
- Complete medical/oncology history.
- Demographics.
- Documentation of concomitant medications.
- Complete physical examination, including vital signs and height.
- Performance status assessment.
- Laboratory tests *(within 7 days; pregnancy test within 72 hours)*.
- Blood collection for correlative studies.
- Documentation of tumor staging.
- Tumor biopsy tissue collection for correlative studies *(within 28 days)*.

7.0 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Progression of the cancer under study or events which are unequivocally due to disease progression should not be reported as an AE during the study (unless it is considered to be drug related by the investigator).

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

As far as possible, each adverse event should be evaluated to determine:

- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

Adverse events monitoring begins at the time of initiating study treatment through ***90 days*** following the last administration of study treatment or study discontinuation/termination, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to IPI-549.

Note: Serious adverse events must be recorded in the case report forms for this 90 day-period; however, non-serious adverse events need only be recorded through 28 days post last study drug administration.

All patients experiencing an adverse event at least possibly related to study treatment will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any clinically significant abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2 Severity

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5.0 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate (grade 2): Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental activities of daily living (ADL). Instrumental ADL

refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
Severe (grade 3): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden
Life-threatening (grade 4): Life-threatening consequences; urgent intervention indicated.
Fatal (grade 5): Death related to AE.

7.3 Seriousness

A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

1. **Results in death.**

2. **Is life-threatening.**
   The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. **Requires in-patient hospitalization or prolongation of existing hospitalization.**
   Note: The following hospitalizations are not considered SAEs:
   - A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event)
   - Elective surgery, planned prior to signing consent
   - Admissions as per protocol for a planned medical/surgical procedure
   - Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
   - Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
   - Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
   - Admission for administration of anticancer therapy in the absence of any other SAEs.

4. **Results in persistent or significant disability or incapacity.**
5. **Is a congenital anomaly/birth defect**
6. **Is an important medical event**
   Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
   For example: allergic bronchospasm requiring intensive treatment in an emergency room

or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.4 Relationship

Attribution categories for adverse events in relationship to protocol therapy are 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.

7.5 Prior experience

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current known adverse events listed in the agent clinical experience section of this protocol or the current Investigator's Brochure.

7.6 Reporting Requirements for Adverse Events

Serious adverse events, or a follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time study treatment initiation through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, requires expedited reporting as described below.

7.6.1 Expedited Reporting

A. The Study Chair and Site Principal Investigator must be notified within 24 hours of learning of any serious adverse events (SAEs) regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.

B. The **UCSD Human Research Protections Program (HRPP)** and **Moores Cancer Center Data and Safety Monitoring Board (DSMB)** must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change

to the risk/benefit ratio for the research.

5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

C. The **FDA** must be notified by the Study Chair according to the following timelines:

- within 7 calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and
- within 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

7.6.2 Routine Reporting Requirements

A. The **UCSD HRPP** must be notified of any adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.

B. The **FDA** must be notified by the Study Chair of all non-serious adverse events annually at the time of the annual report.

8.0 AGENT INFORMATION

8.1 Agent IPI-549

Please refer to Investigator's Brochure for more comprehensive information.

Mechanism of action (or Product description):

IPI-549 drug substance is a freebase, white-to-yellow solid. The IPI-549 drug product is formulated in 2 different capsule strengths (5 mg and 30 mg) for oral delivery with excipients (diluent, disintegrant, and lubricant) that are listed in the FDA Inactive Ingredients Database for approved drug products and/or Generally Regarded as Safe.

Availability: Provided by Infinity Pharmaceuticals Inc.

How supplied: IPI-549 is administered as an oral capsule supplied at the dose specified per subject and/or cohort.

Route of administration for this study: IPI-549 should be self-administered orally (approximately every 24 hours). IPI-549 should be swallowed whole with a glass of water (approximately 8 ounces or 240 mL). Subjects must avoid grapefruit and grapefruit juice while on study drug. Subjects should be advised to avoid food and liquids other than water from 2 hours prior to dosing until 1 hour after dosing.

Side effects:

Adverse Reactions Based on Clinical Data

The following side effects have been observed in 12 people who received IPI-549 according to the results from a Phase 1/1b first-in-human, dose escalation study to evaluate the safety tolerability, pharmacokinetics, and pharmacodynamics of IPI-549 monotherapy and in combination with nivolumab in subjects with advanced solid tumors.

Grade 3 or higher TEAEs occurred in 5 (41.7%) subjects (1 each in the 10,15, and 20mg groups and 2 in the 30mg group.)There was 1 occurrence of each of the following Grade 3 or higher TEAEs: anaemia, haematochezia, small intestinal obstruction, pneumonia, lymphocyte count decreased, and malignant neoplasm progression.

Treatment-emergent SAEs occurred in 5 (41.7%) subjects. Each subject had 1 SAE as follows: malignant neoplasm progression (15mg), haematochezia (20mg), periotonitis (20mg), small intestinal obstruction (30mg), and pneumonia (30mg).

The following side effects have been observed in 56 people who received IPI-549.

Blood and lymphatic system disorders:
Anemia

Gastrointestinal Disorders:
Diarrhea
Nausea
Vomiting
Abdominal pain

General disorders and administration site conditions:
Fatigue
Fever
Local swelling

Metabolism and nutrition Disorders:
Hypomagnesaemia

Nervous system disorders:
Headache

Vascular disorders
Hypertension

Skin and subcutaneous tissue disorders:
Rash
Itchiness
Dermatitis acneiform

Investigations:
Increased liver enzymes
White blood cell count decreased
Blood bilirubin increased

Respiratory, thoracic and mediastinal disorders:
Shortness of breath
Pleuritic pain

9.0 STATISTICAL CONSIDERATIONS

9.1 Study populations

The efficacy population will consist of all subjects who have received 2 weeks of study drug. Any subject who has not received 2 weeks of study drug will be replaced.

The safety population will consist of all subjects who have received any dose of study drug.

9.2 Study Design/Study Endpoints

We anticipate enrolling 15 subjects. The primary analysis will use the efficacy population. Within subject change from the post-treatment to the pre-treatment sample in the immune activation signature will be the primary endpoint. We will test the hypothesis of an increase in this signature using a one sided paired t-test at 5% significance level. With 15 subjects we have 80% power to detect a difference in the mean signature equal to 0.68 standard deviations, which is a modest effect size. Although we lack preliminary data on the magnitude of the standard deviation of within subject changes, effect sizes less than this would be unlikely to be clinically interesting. Also, the differences seen between the poor prognosis and good prognosis groups in Kaneda et al. [2] were greater than this minimal effect size. Thus the study appears to be well-powered to detect meaningful differences.

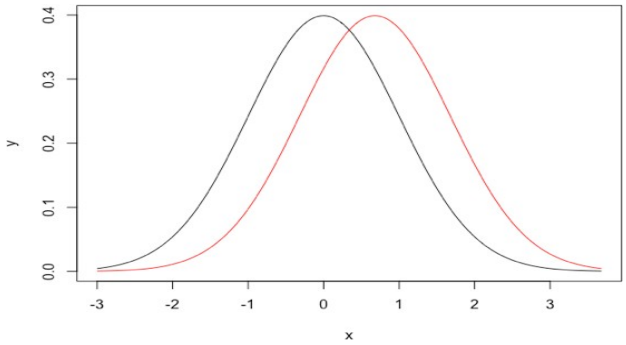


***Figure 1**: Illustration of shift in the signature distribution, which would yield an effect size of 0.68*

9.3 Sample Size and Accrual

We anticipate enrolling 15 subjects. Subjects who do not complete 2 weeks of IPI-549 therapy will be replaced. Thus far, IPI-549 in advanced cancer patients has been well tolerated without serious toxicity. Therefore, we anticipate being able to fully accrue this trial within one year of activation and the administration of IPI-549 will not interfere with planned surgery. If at any time 3 or more subjects have observed progression prior to the start of definitive treatment the study will be halted.

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	2	3
Not Hispanic or Latino	4	8	12
Ethnic Category: Total of all subjects	(A1)	(B1)	(C1)
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	1	2
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	3	8	11
Racial Category: Total of all subjects	(A2)	(B2)	(C2)
	(A1 = A2)	(B1 = B2)	(C1 = C2)

9.4 Safety stopping rule

The study will be stopped early in the event of excessive toxicity leading to delays in definitive surgery. In particular any grade 3 toxicity will result in discontinuation of IPI-549, and any subject who has not received 2 weeks of study drug will be replaced. If at any time 3 or more subjects have observed progression prior to the start of definitive treatment the study will be halted. In addition, if at any time 3 or more subjects have surgery delayed by one week or more because of adverse events at least possibly related to study drug, the study will be halted. These safety stopping rules will be assessed at least bi-annually in a formal safety report.

9.5 Secondary analyses

Safety analysis: The safety analysis will use the safety population**.** Adverse events will be summarized by grade, attribution, and system organ class.

Secondary efficacy analyses: Subjects will have clinical tumor measurement prior to initiating IPI-549 and after 2 weeks administration of IPI-549. Only clinical measurement of disease will be performed. If clinical assessment is not feasible, this will be indicated on the CRF with the reason.

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to UCSD conflict of interest policy.

10.2 Institutional Review Board (IRB) Approval and Consent

In accordance with federal regulations (21 CFR 312.66), an Institutional Review Board (IRB) that complies with regulations in 21 CFR 56 must review and approve this protocol and the informed consent form prior to initiation of the study. The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.
The Principal Investigator or her associate must explain verbally and in writing the nature, duration, and purpose of the study and possible consequences of treatment. Patients must also be informed that they may withdraw from the study at any time and for any reason without jeopardizing their future treatment. In accordance with federal regulations (21 CFR 312), all patients must sign the IRB-approved consent form in the presence of a witness. Prior to the start of the study, a copy of the IRB-approved consent form must be submitted to the Sponsor.

10.3 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

10.4 Data and Safety Monitoring/Auditing

In addition to adverse event monitoring and clinical oversight by the Study Chair and co-investigators, quality assurance of the study will be performed by the UCSD Moores Cancer Center Clinical Trials Office internal monitor. Monitoring intervals will be dependent upon the number of patients enrolled and the complexity of the study.

This study will also use the UCSD Moores Cancer Center Data Safety and Monitoring Board

(DSMB) to provide oversight in the event that this treatment approach leads to unforeseen toxicities. Data from this study will be reported and will include:

1) the protocol title, IRB protocol number, and the activation date of the study.
2) the number of patients enrolled to date
3) the dates of patient enrollment
4) a summary of all adverse events regardless of grade and attribution
5) a response evaluation for evaluable patients when available
6) a summary of any recent literature that may affect the ethics of the study.

10.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, investigators are required to conduct their research according to the plans reviewed and approved by the IRB.

10.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Study Chair. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

10.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and

guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

11.0 Ethical considerations

11.1 Ethical Conduct of Study

This study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practices (GCP) guidelines. The Principal Investigator or qualified designees are responsible for reporting to the authorities and IRB amendments, safety updates and protocol violations that impact subject safety.

11.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

12.0 REFERENCES

1. Kaneda, M.M., et al., *Macrophage PI3Kγ Drives Pancreatic Ductal Adenocarcinoma Progression.* Cancer Discovery, 2016. **6**(8): p. 870.
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3. De Palma, M. and Claire E. Lewis, *Macrophage Regulation of Tumor Responses to Anticancer Therapies.* Cancer Cell, 2013. **23**(3): p. 277-286.
4. Gabrilovich, D.I., S. Ostrand-Rosenberg, and V. Bronte, *Coordinated regulation of myeloid cells by tumours.* Nat Rev Immunol, 2012. **12**(4): p. 253-268.
5. Schmid, M.C., et al., *Receptor tyrosine kinases and TLR/IL1Rs unexpectedly activate myeloid cell PI3Kγ, a single convergent point promoting tumor inflammation and progression.* Cancer cell, 2011. **19**(6): p. 715-727.
6. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1).* European Journal of Cancer, 2009. **45**(2): p. 228-247.

13.0 APPENDICES

Appendix A. Performance Status

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 B: Patient Pill Diary [be sure to bring this diary and pill bottles with you to your next study visit.

Study #: Patient ID:				
Patient name: Patient Signature:			Date:	
Day Number	Day of the week	Date	IPI-549 (mg)	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				

Appendix C: Medications or foods known to inhibit or induce CYP3A

The following list provides medications known to induce or inhibit CYP3A activity. Note that this
is not a comprehensive list of all medications which may modulate CYP3A activity. Additional information can be found at:

- http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf

Note: Subjects receiving IPI-549 are prohibited from concomitant use of medications or foods that are known to be strong inhibitors or inducers of CYP3A.

Classification of In Vivo Inhibitors of CYP3A

Strong Inhibitors([1])	Moderate inhibitors([2])	Weak inhibitors([3])
Boceprevir, clarithromycin, conivaptan, grapefruit juice,([5]) indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil,([6]) nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, ([4]) goldenseal,([4]) isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

1. A strong inhibitor for a specific CYP is defined as an inhibitor that increases the area under the curve (AUC) of a substrate for that CYP by equal or more than 5-fold or > 80% decreasein clearance (CL).
2. A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold or 50%-80% decrease in CL.
3. A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 5-fold or 20%- 50% decrease in CL.
4. Herbal product.
5. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (eg, high- dose, double-strength) or as a “moderate CYP3A inhibitor” when another preparation was used (eg, low-dose, single-strength).
6. Withdrawn from the United States market because of safety reasons.

Protocol IPI-549-01 Infinity Pharmaceuticals, Inc.
IPI-549

Classification of In Vivo Inducers of CYP3A

Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
Avasimibe,(1) carbamazepine, phenytoin, rifampin, St. John's Wort(2)	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodfinanil, Echinacea,(3) pioglitazone, prednisone, rufinamide

1. Not a marked drug.
2. The effect of St. John's Wort varies widely and is preparation-dependent.
3. Herbal product.

Appendix D: Medications associated with prolongation of the QTC and/or with torsades de pointes

Medications that prolong the QT interval and/or have a risk of inducing Torsades de Pointes are listed below. Below, these drugs are divided into two groups based on their known or perceived risk of causing Torsades de Pointes. These lists show examples only, and are not comprehensive.

Medications from Group 1 are prohibited throughout the trial. Medications from Group 2 may be allowed in selected circumstances after consultation with the medical monitor.

Additional information can be found at: http://www.azcert.org/medical-pros/drug-lists/bycategor.cfm

Group 1 Drugs: Generally Accepted to Have a Risk of Causing Torsades de Pointes

Amiodarone	Ibutilide
Arsenic trioxide	Levomethadyl
Bepridil	Mesoridazine Methadone
Chlorpromazine	Moxifloxacin
Chloroquine	Pentamidine Pimozide
Cisapride	Probucol
Disopyramide	Procainamide
Dofetilide	Quinidine
Domperidone	Sotalol
Droperidol	Sparfloxacin
Erythromycin	Thioridazine
Halofantrine	Vandetanib
Haloperidol	

Group 2 Drugs: Drugs That in Some Reports May be Associated with QTc Prolongationand/or Torsades de Pointes, but Lack Substantial Evidence of Causing Torsades dePointes

Alfuzosin	Nicardipine
Amantadine	Nilotinib
Atazanavir	Octreotide
Azithromycin	Ofloxacin
Chloral hydrate	Ondansetron
Clozapine	Oxycodone
Dolasetron	Paliperidone
Dronedarone	Quetiapine
Escitalopram	Ranolazine
Felbamate	Risperidone
Flecainide	Roxithromycin
Foscarnet	Sertindole
Fosphenytoin	Sunitinib
Gatifloxacin	Tacrolimus
Gemifloxacin	Tamoxifen
Granisetron	Telithromycin
Indapamide	Tizanidine
Isradipine	Vardenafil
Lapatinib	Venlafaxine
Levofloxacin	Voriconazole
Lithium	Ziprasidone
Moexipril/HCTZ	

Appendix E: CYP2C8 OR CY2C9 SUBSTRATES

The following lists provide known sensitive CYP2C8 or CYP2C9 substrates.

Medications that are metabolized via CYP2C8 or CYP2C9 should be used with caution. Those with a narrow therapeutic range are prohibited during the trial.

Additional information can be found at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf.

CYP2C8 Substrates	
paclitaxel	cerivastatin
torsemide	rosiglitazone
amodiaquine	repaglinide
	pioglitazone
CYP2C9 Substrates	
celecoxib	Warfarin*
Phenytoin*	glipizide

*Substrates with a narrow therapeutic range are prohibited throughout the trial

Appendix F: P-GP Substrates and medications that are inhibitors of P-GP

The following list provides medications that are substrates or inhibitors of P-gp. Substrates of P-gp should be used with caution during treatment with IPI-549. Inhibitors of P-gp are prohibited during treatment with IPI-549. Note that this is not a comprehensive list of all medications which may be substrates of P-gp or may modulate P-gp activity.

P-gp Substrates	
Amitriptyline	Loperamide
Amiodarone	Losartan
Atorvastatin	Lovastatin
Cefoperazone	Methadone
Chlorpromazine	Methotrexate
Cimetidine	Methylprednisolone
Ciprofloxacin	Morphine
Clarithromycin	Nadolol
Colchicine	Norfloxacin
Cyclosporine	Nortriptyline
Dexamethasone	Ondansetron
Digoxin	Omeprazole
Diltiazem	Pantoprazole
Erythromycin	Phenytoin
Estradiol	Pravastatin
Fentanyl	Propranolol

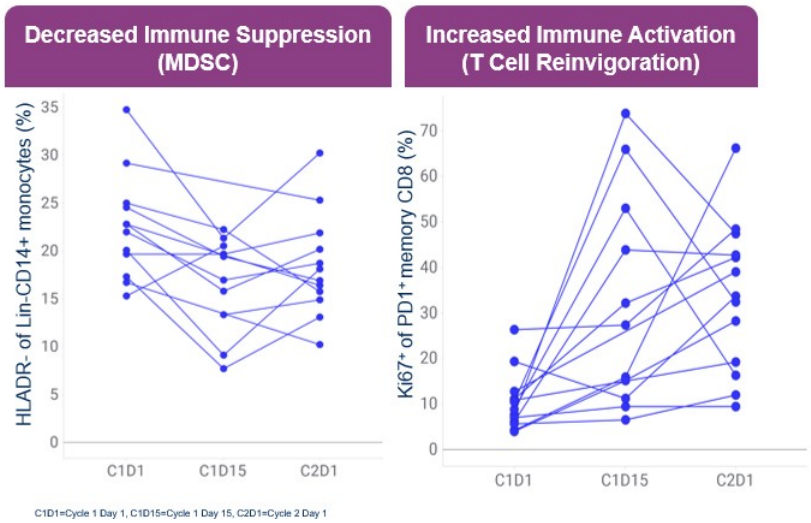
Fexofenadine	Quinidine
Hydrocortisone	Ranitidine
Intraconazole	Sirolimus
Lansoprazole	Tacrolimus
Levofloxacin	Timolol
Lidocaine	Trimethroprim
	Verapamil

P-gp Inhibitors	
Amiodarone	Lovastatin
Amitriptyline	Mefloquine
Carvedilol	Nicardipine
Chlorpromazine	Nifedipine
Clarithromycin	Ofloxacine
Cortisol	Omeprazole
Cyclosporine	Pantoprazole
Desipramine	Progesterone
Diltiazem	Propafenone
Dipyridamole	Propranolol
Doxepin	Quinidine
Erythromycin	Rifampicin (Rifampin)
Felodipine	Saquinavir
Fluphenazine	Simvastatin
Grapfruite juice	Sirolimus
Haloperidol	Tacrolimus
Itraconazole	Testosterone
Ketoconazole	Verapamil

Source: Atkinson AJ et al. Principles of Clinical Pharmacology, 2nd ed. Academic Press, Massachusetts, 2007.

Appendix G: Pharmacodynamic changes observed in peripheral blood of MARIO3 TNBC patients after 15 day treatment with eganelisib in combination with atezolizumab + nab-paclitaxel

PD Effects Observed at Cycle 1 Day 15 in MARIO3 TNBC Cohort



Source: Infinity