Title: Phase 2 Window of Opportunity Study of Pemigatinib in Non-muscle Invasive Bladder Cancer Patients with Recurrent Low- or Intermediate-Risk Tumors

Johns Hopkins Protocol #: J18158, IRB00194271

Incyte Protocol #: I-54828-17-01

Principal Investigator: Noah M. Hahn MD
Associate Professor of Oncology and Urology
Sidney Kimmel Comprehensive Cancer Center
The James Buchanan Brady Urological Institute
Johns Hopkins University School of Medicine
Director, Bladder Cancer Medical Oncology Program
The Bunting-Blaustein Cancer Research Building 1, Room 1M51
1650 Orleans Street
Baltimore, MD 21287
Office: (443) 287-0553
Fax: (410) 367-2667
Email: nhahn4@jhmi.edu

Incyte Supplied Agents: Pemigatinib

IND: IND 141157

IND Sponsor: Noah Hahn MD

Protocol Type / Version # / Version Date:

Version 1/ September 30, 2018
Version 2/ October 07, 2019
Version 3/ February 25, 2020
Version 4/ March 20, 2020
Version 5/ July 10, 2020
Version 6/ Aug 21, 2020
Version 7/ Jan 24, 2022
Version 8/ February 28, 2022
Version 9/ February 17, 2023

Table of Contents

1. OBJECTIVES 4
   1.1 Primary Objectives 4
   1.2 Secondary Objectives 4
   1.3 Exploratory Objectives 4
   1.4 Study Design 5
2. BACKGROUND 5
   2.1 Non-muscle Invasive Urothelial Carcinoma of the Bladder (NMIBC) 5
   2.2 Fibroblast Growth Factor Receptor as a Therapeutic Target in UC 7
   2.3 Pemigatinib Mechanism of Action and Clinical Pharmacology 9
   2.4 Pemigatinib Clinical Experience in Humans 9
   2.5 Rationale for a Phase 2 Window of Opportunity Trial Design of Pemigatinib in Recurrent NMIBC with a Prior History of Low- or Intermediate-risk NMIBC 10
3. PATIENT SELECTION 12
   3.1 Eligibility Criteria 12
   3.2 Exclusion Criteria 13
   3.3 Inclusion of Women and Minorities 15
4. TREATMENT PLAN 15
   4.1 Agent Administration 15
   4.2 General Concomitant Medication and Supportive Care Guidelines 16
   4.3 Contraception, Use in Pregnancy, Use in Nursing 17
   4.4 Duration of Therapy 17
   4.5 Off Study/Safety Follow-up Visit 17
   4.6 Duration of Follow Up 18
   4.7 Criteria for Removal from Study 18
5. DOSING REDUCTIONS/DOSE DELAYS 18
   5.1 Dose Reductions 18
   5.2 Dose Modifications for Treatment Related Non-Hematologic Toxicity 19
   5.3 Dose Modifications for Treatment Related Hematologic Toxicity 20
6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS 20
   6.1 Definitions 21

6.2 Relationship 23
6.3 Expectedness 23
6.4 Handling of Expedited Safety Reports 24
6.5 Reporting 24
7. PHARMACEUTICAL INFORMATION 27
7.1 Pemigatinib 27
8. CORRELATIVE/SPECIAL STUDIES 30
8.1 Tumor Tissue Studies 30
8.2 Peripheral Blood Mononuclear Cell (PBMC) Studies 33
8.3 Serum, Plasma, and Buffy Coat Studies 34
8.4 Urine Marker Studies 36
9. STUDY CALENDAR 38
10. MEASUREMENT OF EFFECT 41
10.1 Tumor Response 41
10.2 Survival Analyses 44
11. DATA REPORTING / REGULATORY REQUIREMENTS 45
11.1 Data Management 45
11.2 Safety Meetings 45
11.3 Monitoring 45
11.4 Multicenter Guidelines 46
12. STATISTICAL CONSIDERATIONS 47
12.1 Study Design/Endpoints 48
12.2 Sample Size/Accrual Rate 49
12.3 Safety Monitoring and Early Stopping Rules for Safety 49
12.4 Analysis Plans for Primary Objective 50
12.5 Analysis Plans for Secondary and Correlative Objectives 50
13. REFERENCES 52
APPENDIX A: Performance Status Criteria 54
APPENDIX B: Serious Adverse Event Reporting Form 55

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 Assess the complete response rate of pemigatinib therapy in patients with recurrent bladder tumors and a prior history of histologically confirmed low- or intermediate-risk non-muscle invasive urothelial carcinoma of the bladder (NMIBC).

1.2 Secondary Objectives

1.2.1 Characterize the safety profile of pemigatinib therapy in patients with recurrent bladder tumors and a prior history of histologically confirmed low- or intermediate-risk NMIBC.

1.2.2 Assess associations between complete response rate and tumor mutation/fusion status (e.g. FGFR3 specifically, others will also be examined).

1.2.3 Assess associations between complete response rate and baseline NMIBC risk group (low- vs. intermediate-risk).

1.2.4 Assess pemigatinib urothelial tissue concentrations as measured within urothelial tissue sampled at post-treatment TURBT.

1.2.5 Assess 6- 12- and 24-month relapse free survival (RFS) in patients achieving a complete response at initial post-treatment TURBT.

1.3 Exploratory Objectives

1.3.1 Assess associations between complete response rate and tumor intrinsic molecular subtypes (e.g. basal vs. luminal).

1.3.2 Assess associations between complete response rate and tumor baseline CD8+ tumor infiltrating lymphocyte density.

1.3.3 Assess associations between complete response rate and changes in peripheral blood T-cell clonality as measured at baseline and post-treatment.

1.3.4 Assess the post-treatment effects of pemigatinib on tumor gene expression by RNA sequencing among patients with residual tumor present at post-treatment TURBT.

1.3.5 Assess the post-treatment immunomodulatory effects of pemigatinib on the tumor microenvironment as assessed by comparison of pre- and post-treatment

immunohistochemistry (IHC) staining for PD-L1, CD8+, FOXP3, pFGFR3, and other targets of interest where adequate tissue permits.

1.3.6 Assess associations between the development of hyperphosphatemia and complete response rate.

1.4 Study Design

We are proposing a single-arm phase 2 window of opportunity study to assess the antineoplastic activity of pemigatinib in non-muscle invasive bladder cancer (NMIBC) patients with recurrent tumors and a prior history of low- or intermediate-risk NMIBC tumors. Enrolled patients will receive pemigatinib for 4-6 weeks prior to standard of care transurethral resection of bladder tumor (TURBT). The primary endpoint will be complete response rate as determined at TURBT. Secondary endpoints will include safety profile, associations between complete response rate and tumor mutation/fusion status (e.g. FGFR3 specifically, others will also be examined) and NMIBC risk group (low- vs. intermediate-risk), and assessment of pemigatinib post-treatment urothelial tissue concentrations. The study will be conducted at 4-5 high volume bladder cancer institutions within the US and managed through the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center clinical research office.

2. BACKGROUND

2.1 Non-muscle Invasive Urothelial Carcinoma of the Bladder (NMIBC)

Currently, urothelial carcinoma (UC) of the bladder is the sixth most common site of new human cancer diagnoses. In 2018, over 81,000 individuals will be diagnosed with UC, and more than 17,000 patients will die from their disease.[1] Most new UC cases (≈ 60,000 patients) are non-muscle invasive at diagnosis with disease limited to the mucosal epithelium (Ta/Tis) and immediate connective tissue layer beneath the mucosa (T1).[2] The clinical course of non-muscle invasive UC of the bladder (NMIBC) is dominated by frequent recurrences and surveillance testing (cystoscopy, bladder biopsy, urine cytology, etc.). The need for long-term invasive monitoring and treatment has significant cost and morbidity consequences for UC patients. Compared to other malignancies, UC ranks highest in lifetime per patient costs with an average cost from diagnosis to death of $96,500 per patient.[3]

An individual patient's risk for recurrence and progression to muscle-invasive bladder cancer (MIBC) varies according to several clinical factors of the patient's bladder tumor including: size, grade, stage, multi-focality, and frequency of recurrence.[4,5] Clinical criteria defining low-, intermediate-, and high-risk NMIBC patient categories are shown in Table 1.

Risk Group	Characteristics
Low-risk	Initial tumor with all of the following: • Solitary tumor • Ta tumor • Low-grade • < 3 cm • No CIS
Intermediate-Risk	All tumors not defined in the two adjacent categories (between the category of low- and high-risk)
High-risk	Any of the following: • T1 tumor • High-grade • CIS • Multiple and recurrent and large (> 3 cm) Ta low-grade tumors (all conditions must be met for this point on Ta low-grade tumors)

Table 1: Non-muscle Invasive Bladder Cancer Risk Categories

High-risk NIMBC represents approximately 20% of the NMIBC total population.[6] For individuals with high-risk NMIBC, progression to muscle invasive stages (MIBC) requiring complete cystectomy for effective management occurs in up to 40% of patients. Additionally, progression to metastatic disease occurs in 20-30% of these individuals with death due to UC in nearly all of these patients.[7-10] Thus for high-risk NMIBC patients, additional therapies aimed at preventing both tumor progression and recurrence are required. Standard therapy for high-risk NMIBC patients includes transurethral resection of bladder tumor (TURBT) augmented by intravesical administration of Bacillus Calmette-Guerin (BCG). BCG is a bovine mycoplasma derived agent which creates a profound inflammatory reaction in the bladder epithelium, and thereby, reduces tumor recurrences. Two meta-analyses of randomized trials of TURBT + BCG versus TURBT alone demonstrated a reduction in 12-month tumor recurrence rate from 56% to 29% ($p<0.001$) and a reduction in progression to muscle-invasive stages from 13.8% to 9.8% ($p=0.001$) in association with BCG therapy. No improvement in overall survival was observed with the use of BCG therapy.[11,12]

In contrast, for the 80% of NMIBC patients with low- and intermediate-risk disease, progression to MIBC is rare with 1-year rates typically 5% or less and 5-year rates in intermediate-risk patients under 20%. However, tumor recurrence rates remain high with 1-year recurrence rates as high as 24% and 38% and 5-year recurrence rates as high as 46% and 62% in low- and intermediate-risk NMIBC patients respectively.[6] For patients with intermediate-risk NMIBC, intravesical chemotherapy (e.g. mitomycin C) or BCG therapy is recommended.[13] However, the need for intravesical administration, treatment related urinary side effects, and frequent cystoscopic monitoring for recurrence in follow up provide rationale to continue to pursue additional approaches to reduce tumor recurrences in intermediate-risk patients. For low-risk patients, immediate one-time intravesical administration of mitomycin C or other chemotherapy agents at the time of tumor resection has demonstrated a 12% reduction in 1-year tumor recurrence rates.[14] Despite AUA guidelines encouraging

immediate intravesical chemotherapy administration in low-risk NMIBC patients, uptake into clinical practice is poor with less than 1% of patients receiving this treatment.[15] Recent data from the SWOG 0337 randomized phase 3 trial of immediate one-time intravesical administration of gemcitabine versus saline placebo in patients with a suspected low-grade tumor recurrence with no prior history of high-grade NMIBC demonstrated a 34% reduction in time to recurrence (p=0.01) with an estimated 4-year recurrence rate of 36%.[16] Two-thirds of patients in SWOG 0337 had solitary tumors consistent with low-risk disease. Whether intravesical gemcitabine is superior to intravesical mitomycin C and whether clinical usage of intravesical gemcitabine will be more embraced than intravesical mitomycin C is unclear. While studies examining physicians' reasons for non-adherence to clinical guidelines are ongoing, the low rate of immediate peri-procedure intravesical chemotherapy provides an opportunity to develop alternative treatment strategies to reduce tumor recurrences in low- and intermediate-risk NMIBC patients. Taken collectively, improved therapy approaches to prevent recurrent tumors are an urgent need in both low- and intermediate-risk NMIBC patients.

2.2 Fibroblast Growth Factor Receptor as a Therapeutic Target in UC

UC carcinogenesis is a multi-step process that affects multiple cellular genes and signaling pathways. Low-grade NMIBC tumors present in the majority of low- and intermediate-risk NMIBC patients are characterized by mutations in the fibroblast growth factor receptor-3 (FGFR3) and the Harvey rat sarcoma viral oncogene homologue (HRAS) genes.[17,18] FGFR3 mutations promote FGFR dimerization and constitutive activation of downstream signaling pathways in the absence of ligand in up to 67% of early-stage UC tumors (Table 2).[19]

	Ta (%)	T1 (%)	T2 (%)
Mutation	67	42	13
Over-expression	13	15	39
Total	80	57	52

Table 2: FGFR3 mutation and Over-expression Status According to T-stage

Furthermore, when analyzed according to NMIBC risk groupings, activating FGFR3 mutations were observed in 87% and 61% of low- and intermediate-risk tumors respectively compared to only 36% in high-risk tumors.[20]

While many FGFR3 mutations have been reported, S249C, Y375C, R248C, and G372C account for greater than 95% of all reported mutations.[21] These mutations result in a hyperplastic phenotype dominated by frequent tumor recurrences with infrequent progression to muscle-invasive stages. In addition, FGFR3 gene translocations with either transforming acid coil coiled 3 (TACC3) or BAI1-associated protein 2-like 1 (BAIAP2L1) have been described. These translocations are present in approximately 6% of UC tumors and also result in constitutively activated FGFR3

signaling.[22]

In contrast, in MIBC and metastatic UC (mUC), the frequency of FGFR3 mutations decreases substantially. In the UC cohort of The Cancer Genome Atlas (TCGA) project, FGFR3 mutations were reported in only 12% and FGFR3-TACC3 fusions in 2% of patients with MIBC.[23] Despite the lower frequency of FGFR3 activating genomic aberrations, therapeutic approaches targeting inhibition of FGFR3 signaling have shown promising initial results. In phase I trials of mUC patients with FGFR3 mutations or gene fusions who had progressed after standard chemotherapy, the oral FGFR3 tyrosine kinase inhibitors BGJ398, JNJ- 42756493, and AZD4547 have demonstrated reductions in tumor size in 50-60% of patients.[24-26] With this clear signal of anti-tumor activity, registration studies are ongoing in mUC patient populations.

In addition to the direct anti-tumor activity observed in mUC patients with activating FGFR3 alterations, significant preclinical evidence points toward potentially beneficial effects on cells within the tumor microenvironment treated with FGFR inhibitors. In UC and multiple tumor types, the tumor microenvironment is characterized by an intricate growth and signaling balance between tumor cells and surrounding cancer associated fibroblasts (CAFs), vascular endothelial cells, tumor associated macrophages (TAMs), lymphocytes, myeloid derived suppressor cells (MDSCs), antigen presenting cells (APCs), and neutrophils. Fibroblast growth factor receptors (FGFRs) and their ligands (FGFs) mediate the signaling and proliferation of many of these tumor microenvironment cell populations independent of FGFR3 or other FGFR alteration status.[27] For instance, in human dermal fibroblasts TP53 is downregulated in the presence of FGF2. Procopio et. al. have demonstrated the induction of senescence in fibroblasts in response to FGFR inhibitor treatment mediated by upregulation and activation of TP53.[28] Furthermore, cytokine signaling by CAFs plays a critical role in the recruitment and growth of MDSCs within the tumor microenvironment leading to activation of M2-TAMs and regulatory T cells (Tregs) while inhibiting CD8+ T cells and NK cells.[27] All of these influences promote tumor immune evasion. In preclinical breast and lung cancer murine models, investigators have demonstrated reduced MDSC infiltration and treatment mediated effects on CAF cytokine signaling within the tumor microenvironment following treatment with FGFR inhibitor therapy. These pro-immune functional changes resulted in reduced tumor formation and metastases.[29,30] Thus far, the beneficial effects of FGFR inhibition on immune mediators within the tumor microenvironment do not appear restricted to tumors with activating FGFR alterations. Therefore, a strong rationale can be made to study the clinical activity of FGFR3 targeting agents in NMIBC patient populations, particularly the low- and intermediate-risk patients in whom activating FGFR3 genomic aberrations are present in the majority of patients. In addition, study of patients within this population that harbor FGFR3 wild-type tumors is also warranted to confirm that immunomodulatory benefits of FGFR inhibition occur independent of FGFR genomic alteration status. This latter finding could have a transformative effect on the clinical development of FGFR inhibitors across multiple

tumor types including UC.

2.3 Pemigatinib Mechanism of Action and Clinical Pharmacology

Pemigatinib (INCB054828) is an orally bioavailable small molecule inhibitor of tyrosine kinase signaling by FGFR1-3. In phase I human studies, pemigatinib has been studied at doses of 1, 2, 4, 6, 9, 13.5, and 20 mg administered once daily according to a 2 weeks on / 1 week off schedule. In these cohorts, C_{max} concentrations of 103, 147, and 310 nmol/L were observed at the 6, 9, and 13.5 mg doses respectively. Importantly, the C_{min} concentrations observed were 30, 38, and 77 nmol/L, all well above the preclinical IC50 concentration levels necessary for anti-tumor activity. A single 9 mg continuous daily dosing with no treatment interruptions cohort was also examined. The continuous daily dosing produced similar PK profiles as the 2 weeks on / 1 week off schedules with a C_{max} concentration of 183 nmol/L and a C_{min} concentration of 39 nmol/L. Pemigatinib demonstrated peak plasma concentrations 0.5-6 hours after administration. Declines in pemigatinib concentration occurred in a biphasic manner with a mean half-life of 10.9 – 31.2 hours. Pemigatinib is primarily hepatically cleared via P450 by CYP3A4 with 2.3% of pemigatinib excreted intact in the urine. A pharmacodynamic effect, defined as 50% or greater inhibition of pFGFR2 at any timepoint in KATOIII cells spiked into patient plasma samples, was observed in all patients receiving 4 mg pemigatinib doses or higher.[31,32]

2.4 Pemigatinib Clinical Experience in Humans

The safety of pemigatinib (INCB054828) as monotherapy or in combination has been studied in the context of 5 prospective clinical trials including a phase 1/2 monotherapy and combination trial (INCB 54828-101 / NCT02393248), a phase 1 monotherapy trial (INCB 54828-102 / NCT03235570), and 3 phase 2 monotherapy trials in metastatic urothelial carcinoma (INCB 54828-201 / NCT02872714), metastatic cholangiocarcinoma (INCB 54828-202 / NCT02924376), and myeloid/lymphoid neoplasms (INCB 54828-203 / NCT03011372). In total, 249 patients have received at least one dose of pemigatinib monotherapy with 34 patients receiving pemigatinib as part of various combination regimens (cisplatin + gemcitabine + pemigatinib – 7 patients; docetaxel + pemigatinib – 9 patients; pembrolizumab + pemigatinib – 16 patients; trastuzumab + pemigatinib – 4 patients).[31]

In the INCB054828-101 study, 84 patients were treated with monotherapy at doses ranging from 1 to 20 mg on either a 2 weeks on / 1 week off or a continuous dosing schedule. No dose limiting toxicities (DLTs) were observed for the monotherapy cohorts and a maximum tolerated dose (MTD) was not reached. Based on pharmacodynamics, clinical, and side effect profiles, a dose of 13.5 mg on a 2 weeks on / 1 week off schedule was recommended for future studies. Most patients reported at least one treatment emergent adverse event (TEAE), although the vast majority

were low-grade and did not interrupt therapy. Most frequent TEAEs included hyperphosphatemia (69.0%), fatigue (38.1%), dry mouth (35.7%), alopecia (29.8%), stomatitis (26.2%), constipation (25.0%), diarrhea (23.8%), anorexia (22.6%), nausea (21.4%). Of all TEAEs reported, the most frequent ≥ grade 3 TEAEs were fatigue (7.1%), pneumonia (7.1%), and hyponatremia (4.8%). Eight patients (9.5%) discontinued treatment due to TEAEs.[31]

In the INCB054828-201 study in metastatic urothelial carcinoma patients with tumors harboring FGFR3 mutations/fusions or other FGFR genomic alterations, 100 patients have been treated at the 13.5 mg once daily 2 weeks on / 1 week off dosing schedule. Treatment duration has ranged from 4 to 300 days. The majority of patients (89.6%) reported at least 1 TEAE. Most frequent TEAEs included diarrhea (40.0%), alopecia (32.0%), fatigue (29.0%), dry mouth (28.0%), constipation (28.0%), and hyperphosphatemia (27.3%). Most TEAEs were grade 1 or 2 in severity. TEAEs ≥ grade 3 included urinary tract infection (7.0%), fatigue (6.0%), and anemia (5.2%). Serious adverse events (SAEs) considered related to pemigatinib included central serous chorioretinopathy, fatigue, malaise, mucosal dryness, increased creatinine, syncope, and dyspnea (all 1.3% each). TEAEs that led to discontinuation of pemigatinib occurred in 6.5% of patients.[31,33]

As of the most recent data lock in February 2018, 51 mUC patients with tumors harboring FGFR3 mutations/fusions were evaluable for response. Seven confirmed partial responses and 6 unconfirmed ongoing partial responses were observed yielding an objective response rate of 25.5% (95% CI, 14-40%).[33] Radiographic confirmation of initial tumor responses and assessment of response duration is ongoing and will be updated annually within the pemigatinib investigator brochure.

2.5 Rationale for a Phase 2 Window of Opportunity Trial Design of Pemigatinib in Recurrent NMIBC with a Prior History of Low- or Intermediate-risk NMIBC

In summary, a strong rationale exists to study pemigatinib in recurrent NMIBC with a prior history of low- or intermediate-risk NMIBC based upon the following:

1) NMIBC represents a common, sizeable population.

2) Low- and intermediate-risk NMIBC represents the majority of the NMIBC population.

3) While progression to MIBC is rare in low- and intermediate-risk NMIBC patients, tumor recurrences remain frequent and are associated with significant morbidity and expense to patients.

4) Activating FGFR3 genomic alterations are a hallmark of low- and intermediate-risk NMIBC tumors.

5) Clinical activity of FGFR inhibitor therapies (including pemigatinib) has been demonstrated in advanced mUC patient populations harboring FGFR3 genomic alterations.

6) Beyond their anti-tumor activity, FGFR inhibitors may also possess immunomodulatory capacities independent of FGFR3 genomic alteration status which may prove beneficial in future combination UC treatment regimens.

7) Urine cytology and bladder tumor biopsies are easy to obtain in the follow-up care of NMIBC patients. As such, the NMIBC population presents a unique opportunity to assess pre- and post-treatment pharmacodynamic effects of pemigatinib.

Therefore, we propose a proof of concept phase 2 clinical trial of pemigatinib monotherapy at a dose of 9 mg administered on a continuous once daily oral schedule for 4-6 weeks prior to planned TURBT in patients with recurrent tumors with a prior history of low- or intermediate-risk NMIBC. This population is justified for this study due to the high frequency of activating FGFR3 genomic alterations and a relative paucity of other novel therapy approaches within this population. The 9 mg dose is supported by the confirmed pharmacodynamic activity and lower toxicity rate at the 9 mg dose compared to the 13.5 mg dose utilized in metastatic studies.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Prior histologically confirmed low- or intermediate-risk non-muscle invasive urothelial carcinoma of the bladder (NMIBC) defined according to the table below:

Risk Group	Characteristics
Low-risk	Initial tumor with all of the following: • Solitary tumor • Ta tumor • Low-grade • < 3 cm • No CIS
Intermediate-Risk	All tumors not defined in the two adjacent categories (between the category of low- and high-risk)
High-risk	Any of the following: • T1 tumor • High-grade • CIS • Multiple and recurrent and large (> 3 cm) Ta low-grade tumors (all conditions must be met for this point on Ta low-grade tumors)

3.1.2 Documented tumor recurrence as noted in standard of care follow up cystoscopy.

3.1.3 ECOG (WHO) performance status 0-2

3.1.4 Age ≥ 18 years old

3.1.5 Patients must have the following laboratory values:

- White blood cell count (WBC) $\geq$ 3.0 K/mm^3
- Absolute neutrophil count (ANC) ≥ 1.5 K/mm^3
- Platelets ≥ 100 K/mm^3
- Hemoglobin (Hgb) ≥ 9 g/dL
- Serum total bilirubin: ≤ 1.5 x ULN
- ALT and AST ≤ 3.0 x ULN
- Serum calcium $\leq$ ULN
- Serum phosphate $\leq$ ULN
- Serum creatinine ≤ 1.5 x ULN or serum creatinine > 1.5 – 3 x ULN if calculated creatinine clearance (CrCl) is ≥ 30 mL/min using the modified Cockcroft-Gault equation, see formula below:

  CrCl = [140-age (years)] x actual weight (kg) / [72 x serum Cr (mg/dL)]

(if patient is female multiply the above by 0.85)

3.1.6 Patients who give a written informed consent obtained according to local guidelines

3.2 Exclusion Criteria

3.2.1 Patients with concurrent upper urinary tract (i.e. ureter, renal pelvis) high-grade urothelial carcinoma of any T-stage.
NOTE: Patients with histologically confirmed concurrent upper urinary tract non-invasive low-grade urothelial carcinoma may be considered for enrollment after consultation with the study chair.

3.2.2 Patients with high grade urothelial carcinoma on their most recent urine cytology.

3.2.3 Patients with another active second malignancy other than non-melanoma skin cancers and biochemical relapsed prostate cancer. Patients that have completed all necessary therapy and are considered to be at less than 30% risk of relapse are not considered to have an active second malignancy and are eligible for enrollment.

3.2.4 Patients who have received the last administration of an anti-cancer therapy including chemotherapy, immunotherapy, and monoclonal antibodies ≤ 4 weeks prior to starting study drug, or who have not recovered from the side effects of such therapy

3.2.5 Patients who have received prior selective fibroblast growth factor receptor targeting agents (i.e. pemigatinib, dovitinib, BGJ398, AZD4547, JNJ-42756493, etc.).

3.2.6 Patients who have had radiotherapy ≤ 4 weeks prior to starting study drug, or who have not recovered from radiotherapy toxicities

3.2.7 Patients who have undergone major surgery (e.g. intra-thoracic, intra-abdominal or intra-pelvic), open biopsy or significant traumatic injury ≤ 4 weeks prior to starting study drug, or patients who have had minor procedures (i.e. TURBT), percutaneous biopsies or placement of vascular access device ≤ 1 week prior to starting study drug, or who have not recovered from side effects of such procedure or injury

3.2.8 Patients with any of the following concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study:

- Clinically significant cardiac diseases, including any of the following:

a. History or presence of serious uncontrolled ventricular arrhythmias

b. Clinically significant resting bradycardia

c. Any of the following within 6 months prior to starting study drug: myocardial infarction (MI), severe/unstable angina, Coronary Artery Bypass Graft (CABG), Congestive Heart Failure (CHF), Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA), Pulmonary Embolism (PE)

d. Uncontrolled hypertension defined by a SBP ≥ 160 mm Hg and/or DBP ≥ 100 mm Hg, with or without anti-hypertensive medication(s)

- Active impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of pemigatinib (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)

- Cirrhosis, chronic active hepatitis or chronic persistent hepatitis

- Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory)

- Patients who are currently receiving anti-coagulation treatment with therapeutic doses of warfarin. Full-dose anti-coagulation with low molecular weight heparin is permitted.

- Patients with a prior history of significant ocular pathology including but not limited to detached retina, retinal vein/artery occlusion, macular degeneration, or glaucoma. Patients with prior history of cataracts are permitted to enroll.

- Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection, uncontrolled diabetes) that could cause unacceptable safety risks or compromise compliance with the protocol

- History of calcium and phosphate hemostasis disorder or systemic mineral imbalance with ectopic calcification of soft tissues (exception: commonly observed calcifications in soft tissues such as the skin, kidney tendon or vessels due to injury, disease, or aging in the absence of systemic mineral imbalance).

3.2.9 Pregnant or breast-feeding women

3.2.10 Women of child-bearing potential, who are biologically able to conceive, not employing two forms of highly effective contraception. Highly effective contraception must be used throughout the trial and up to 8 weeks after the last dose of study drug (e.g. male condom with spermicidal; diaphragm with spermicide; intra-uterine device). Women of child-bearing potential, defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months), must have a negative serum pregnancy test ≤ 14 days prior to starting study drug.

3.2.11 Fertile males not willing to use contraception, as stated above

3.2.12 Patients unwilling or unable to comply with the protocol

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. TREATMENT PLAN

PHASE 2 STUDY SCHEMA



4.1 Agent Administration

4.1.1 Study Treatment

Pemigatinib treatment will initially consist of two 4.5 mg tablets (total dose = 9 mg) administered once daily by oral administration on days 1-28 of each cycle. Pemigatinib treatment with two 4.5 mg tablets (total dose = 9 mg) administered every other day by oral administration on days 1-28 of each cycle will be utilized in any patients that require a study-specified dose reduction. Ideally, patients should attempt to take pemigatinib at approximately the same time each day,

however, some variability in the timing of each day's dose is acceptable. If a patient misses a planned dose for over 24 hours beyond the prior day's dosing, the missed dose will not be made up. Also, if a patient experiences emesis following a day's dose, that day's dose will not be made up.

Pemigatinib will be administered for at least 1 cycle (4 weeks of pemigatinib therapy) prior to TURBT in all patients. Treatment should continue up until the patient undergoes TURBT. The exact duration of therapy beyond cycle 1 will be dependent upon TURBT scheduling constraints at the local institutions. Patients should remain on treatment up until the patient undergoes TURBT.

4.1.2 Patient Monitoring

Patient vital signs (Temperature, heart rate, respiratory rate, systolic and diastolic blood pressure) should be taken as per institutional standard of care prior to cycle 1 day 1 dosing.

Patients should undergo an ophthalmology examination prior to cycle 1 day 1 dosing as part of their study screening procedures. The exam should include visual acuity test, slit-lamp examination, fundoscopic exams, and optical coherence tomography (OCT). For patients that achieve a complete response at TURBT and remain on pemigatinib post-TURBT, follow-up ophthalmology examinations (same requirements including OCT) should be performed within 14 days of cycle 4 day 1, cycle 7 day 1, cycle 10 day 1 and cycle 13 day 1.

4.1.3 Cycle Length

One cycle is defined as 28 days.

4.2 General Concomitant Medication and Supportive Care Guidelines

4.2.1 Prohibited and/or Restricted Treatments

4.2.1.1 Concurrent administration of any anti-cancer therapies (investigational or approved) are prohibited with the exception of subjects with tumor recurrence noted in the survival follow up period of the study.

4.2.1.2 Any medicinal herbal preparation unless prescribed by the treating physician. All concomitant medications including prescribed medicinal herbal preparations must be documented.

4.2.1.3 Colony stimulating factors (e.g. erythropoietin, darbopoeitin, pegfilgastim) are prohibited.

4.2.1.4 Concurrent potent CYP3A4 inhibitors and inducers are prohibited. The use of moderate CYP3A4 inhibitors or inducers should involve careful monitoring.

4.2.2 Other Restrictions and Precautions

4.2.2.1 Pemigatinib may cause increased serum phosphate. Therefore, a low-phosphate diet and phosphate binding therapy are recommended.

4.2.2.2 Alcohol consumption while on study is strongly discouraged due to the potential to confound interpretation of hepatotoxic events.

4.2.3 Permitted Therapy

4.2.3.1 Subjects are permitted the use of anti-emetic medications at the treating physician's discretion.

4.2.3.2 Subjects are permitted the use of full-dose anti-thrombin targeting anti-coagulants (e.g. enoxaparin, rivaroxaban, etc.) at the treating physician's discretion. However, the use of full-dose warfarin anti-coagulation is not permitted.

4.3 Contraception, Use in Pregnancy, Use in Nursing

See sections 3.2.9 – 3.2.11

4.4 Duration of Therapy

Pemigatinib will be continuously administered once daily on days 1-28 of each 28-day cycle for a minimum of 1 cycle (4 weeks). Patients will continue on pemigatinib up until their TURBT is performed.

In patients achieving a complete response at their post-treatment TURBT evaluation, pemigatinib may continue for a maximum of 13 total cycles with the pre-TURBT cycles included within the 13 cycle total.

4.5 Off Study/Safety Follow-up Visit

Patients should be evaluated for any residual toxicities within 1 month $\pm$7 days of their last study related therapy. For patients achieving a complete response at their post-treatment TURBT, this can coincide with traditional post-op visits. For patients who refuse to return to clinic for an in-person visit, recording of patient reported toxicities by telephone is acceptable.

4.6 Duration of Follow Up

Patients who receive at least one dose of study therapy will be followed for up to 2 years from the date of TURBT. Patients who receive at least one dose of study therapy but who do not undergo TURBT will be followed for up to 2 years from the date of last study therapy administration.

4.7 Criteria for Removal from Study

Patients will be removed from the study for any of the following reasons:

a) Completion of all study therapy and follow up.

b) If the Patient is non-compliant or requests to withdraw from all therapy and follow-up. Any patient who withdraws from therapy, but not follow up, may continue to be followed for study specified secondary endpoints.

c) Pregnancy.

d) Unacceptable toxicity that in the treating physician's discretion places the patient at risk for future significant harm.

e) Intercurrent illness that prevents continuation of therapy or follow up.

5. DOSING REDUCTIONS/DOSE DELAYS

5.1 Dose Reductions

Dose level	Pemigatinib
Starting dose	9 mg po qd d1-28
Dose level -1	9 mg po qod d1-28
Second Dose Reduction	No further study therapy

Table 3: Phase 2 Dose Cohorts

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 will be used to grade adverse events.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study.

Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days after their last study related therapy.

If patients require a second dose reduction, the patient will be removed from the study.

Patients with adverse events meeting criteria for a dose reductions can continue on study with a dose reduction per Table 3 at the discretion of the treating investigator.

5.2 Dose Modifications for Treatment Related Non-Hematologic Toxicity

5.2.1 Grade 1-2 Treatment Related Non-Hematologic Toxicity

No dose interruptions or reductions will be performed for Grade 1 or 2 non-hematologic toxicity.

5.2.2 Grade 3-4 Treatment Related Non-Hematologic Toxicity

If the patient experiences Grade 3-4 drug related toxicity, study therapy must be withheld until the toxicity has resolved to ≤ Grade 1 and the doses must be reduced by one dose level for all subsequent treatment cycles. If the patient takes longer than 21 days for a Grade 3-4 toxicity to subside to Grade 1, further study therapy will not be administered. If the Grade 3-4 toxicity recurs after one dose reduction, further study therapy will not be administered.

5.2.2 Treatment Related Hyperphosphatemia

Data from ongoing clinical studies of selective FGFR inhibitors, including pemigatinib, have demonstrated that hyperphosphatemia is an on-target pharmacologic effect of FGFR inhibition that can typically be managed with low-phosphate diet, phosphate-binding therapy, dose interruptions, and dose reductions.

- If the patient experiences hyperphosphatemia at a level $\leq$ 7.0 mg/dl, no dose modifications are required.

- If the patient experiences hyperphosphatemia at a level > 7.0 mg/dl and $\leq$ 10 mg/dl, phosphate-binder therapy (e.g. sevelamer) should be initiated and study therapy may continue at full dose.

- If hyperphosphatemia at a level > 7.0 mg/dl and $\leq$ 10 mg/dl develops on phosphate-binder therapy or a second hyperphosphatemia level > 7.0 mg/dl

and ≤ 10 mg/dl is noted after phosphate-binder resolution of the initial hyperphosphatemia event, study therapy should be withheld.

- If the phosphate level subsequently improves to a level < 7.0 mg/dl, study therapy may resume with a one dose level reduction. If a third hyperphosphatemia level ≥ 7.0 mg/dl occurs, all further study therapy should be permanently withheld.

- If hyperphosphatemia at a level > 10 mg/dl is noted at any time, phosphate-binder therapy should be initiated (if not already initiated) and study therapy should be withheld.

- If the phosphate level subsequently improves to a level < 7.0 mg/dl, study therapy may resume with a one dose level reduction.

- If a second hyperphosphatemia level ≥ 10 mg/dl occurs, all further study therapy should be permanently withheld.

5.3 Dose Modifications for Treatment Related Hematologic Toxicity

5.3.1 Grade 1-2 Treatment Related Hematologic Toxicity

No dose interruptions or reductions will be performed for Grade 1 or 2 hematologic toxicity.

5.3.2 Grade 3-4 Treatment Related Hematologic Toxicity

If the patient experiences grade 3 or 4 thrombocytopenia/neutropenia (with the exception of anemia), study therapy must be withheld until the toxicity has resolved to ≤ Grade 1 and the doses must be reduced by one dose level for all subsequent treatment cycles.

If the patient takes longer than 21 days for a Grade 3-4 toxicity to subside to Grade 1, further study therapy will not be administered. If Grade 3 or 4 thrombocytopenia/neutropenia recurs after one dose reductions, further study therapy will not be administered. No dose reductions will be performed for grade 3 or 4 anemia. If the patient develops anemia, they may be transfused at the discretion of the investigator.

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

This study will use the descriptions and grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 for adverse event reporting that can be found at

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Information about all AEs, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

All AEs and SAEs experienced by subjects will be collected and reported from the day the informed consent is signed by the patient, throughout the study, and will only be followed for 4 weeks unless related to the investigational agent. All SAEs will be collected for 30 days after subject has completed or discontinued from the study or has taken last dose of pemigatinib. Subjects who have an ongoing AE related to the study procedures and/or medication(s) may continue to be periodically contacted by a member of the study staff until the event is resolved or determined to be irreversible by the investigator.

Subjects who have an ongoing adverse event related to the study procedures and/or medication(s) may continue to be periodically contacted by a member of the study staff until the event is resolved or determined to be irreversible by the investigator.

Laboratory abnormalities: Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, all grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as adverse events. A grade 1 or 2 clinical laboratory abnormality should be reported as an adverse event only if it is considered clinically significant by the investigator.

6.1 Definitions

6.1.1 Adverse Event (AE)

Adverse event is defined as any undesirable sign, symptom or medical condition occurring after starting the study drug (or therapy) even if the event is not considered to be related to the study. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). Medical conditions/diseases present before starting the study treatment are only considered adverse events if they worsen after starting the study treatment (any procedures specified in the protocol). Adverse events occurring before starting the study treatment but after signing the informed consent form will not be recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

6.1.2 Serious Adverse Event (SAE)

A SAE is an undesirable sign, symptom or medical condition which:

- Results in death

- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions) for >24 hours

- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Supplemental Form)

- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

- Is a new cancer (that is not a condition of the study)

- Is associated with an overdose of any kind

- Is a pregnancy or pregnancy outcome of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, or stillbirth.

Events **not** considered to be SAEs are hospitalizations for:

- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a procedure

- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)

- Medical/surgical admission for purpose other than remedying ill health state and was 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 (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

- Admissions for monitoring of treatment-related infusion reactions that do not otherwise meet the criteria for a SAE.

6.2 Relationship

The Principal Investigator must assess whether AEs have a suspected causal relationship to the study drug. A suspected causal relationship is defined as possibly, probably or definitely related:

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial drug
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
Not assessable	There is insufficient or incomplete evidence to make a clinical judgment of the causal relationship.

6.3 Expectedness

Expected adverse events are those which are expected to occur, according to previous clinical experience, and are listed in the Investigator Brochure. The expectedness of an SAE will be assessed by the Principal Investigator.

Unexpected adverse event: An adverse event, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the Investigator's Brochure, package insert or safety reports. Any adverse event that is not included in the informed consent is considered "unexpected".

Expected (known) adverse event: An adverse event, which has been reported in the Investigator's Brochure. An adverse event is considered "expected", only if it is included in the informed consent document as a risk.

6.4 Handling of Expedited Safety Reports

In accordance with local regulations, Incyte and the IND Sponsor will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

Other important findings which may be reported as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from Incyte, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, serious adverse reactions (whether expected or unexpected) shall be reported by Incyte to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

6.5 Reporting

6.5.1 General

All AEs (both expected and unexpected) will be captured on the appropriate study-specific CRFs.

In addition, all SAEs, regardless of causality to study drug, will be reported promptly (within 24 hours of recognition of the AE) to by email and fax to:

1. The IND sponsor: Noah Hahn, MD, nhahn4@jhmi.edu
2. Lead Study Coordinator: Amber Michalik, amichal2@jhmi.edu, 410-

502-0756
3. Incyte: safetyreporting@incyte.com, 866-981-2057

If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

Incyte also needs to be provided a completed SAE form via email. SAE reporting for each subject begins the day the informed consent is signed by the patient and within 30 days after subject has completed or discontinued from the study or has taken last dose of the study drug.

SAEs, occurring using Incyte Study drug, are reported in accordance with the effective protocol. SAEs occurring with any another commercial drug are reported to manufacturer of that drug in accordance with regulations and protocol.

Initial Serious Adverse events (SAEs) and/or subsequent follow-up reports should be reported via email to:

1. SafetyReporting@Incyte.com, fax (+) 1-866-981-2057 and
2. nhahn4@jhmi.edu; amichal2@jhmi.edu, fax: 410-614-7287

SAE reports should be for a single subject with any additional documents (i.e. discharge summary, relevant test results) included for the same subject as individual attachments to the email. One email can have multiple attachments as long as each attachment contains relevant information for the same subject.

Please email your SAE form with a cover sheet and any additional attachments to the following:

1. SafetyReporting@Incyte.com, fax (+) 1-866-981-2057 and
2. nhahn4@jhmi.edu; amichal2@jhmi.edu, fax: 410-614-7287

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the safety department in regards to the subject's condition.

All AE(s) and SAE(s) will be followed until:

- Resolution
- The condition stabilizes
- The event is otherwise explained
- The subject is lost to follow-up

Once the event is resolved, the appropriate AE or SAE report page will be updated. The investigator will also ensure that the follow-up includes any supplemental information that may explain the causality of the event(s). New

or updated information will be recorded on the originally completed AE or SAE report, with all changes signed and dated by the investigator or designee. The updated AE or SAE report will then be signed by the investigator and resubmitted to the IND Sponsor and Incyte.

6.5.1.1 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs.

6.5.1.2 Pregnancy Reporting

An "Initial Pregnancy Report" or equivalent must be completed in full and emailed to SafetyReporting@Incyte.com within 24 hrs of discovery of a pregnancy of a subject who has taken the Incyte product or the pregnancy of a partner for a subject who has taken the Incyte product. The "Follow-up Pregnancy Report Form" or equivalent must be completed and emailed to SafetyReporting@Incyte.com within 30 days after delivery, so that Incyte is provided with information regarding the outcome of the pregnancy. If the pregnancy results in any events which meet the serious criteria (i.e., miscarriage or termination), the SAE reporting process needs to be followed and the timelines associated with an SAE should be followed.

6.5.2 Institutional Review Board (IRB)

All serious adverse events will be reported to the IRB per institutional standards within 3 business days of recognition of the adverse event if the event is related and expected, related and unexpected, or related and fatal or life-threatening due to administration of the investigational product. Follow-up information will be submitted to the IRB as soon as relevant information is available.

6.5.3 Food and Drug Administration (FDA)

All reporting to the FDA will be completed by the Sponsor (Dr. Noah M. Hahn, MD).

6.5.3.1 Expedited IND Safety Reports:

7 Calendar-Day Telephone or Fax Report:
The Sponsor is required to notify the FDA of any fatal or life- threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the investigational agent. Such reports are to

be telephoned or faxed (301-796-9845) to the FDA within 7 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

15 Calendar-Day Written Report:

The Sponsor is required to notify the FDA of any serious adverse event that is unexpected and possibly related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

6.5.3.2 IND Annual Reports

In accordance with the regulation 21 CFR § 312.33, the Sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the adverse events and progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.33 for a list of the elements required for the annual report. All IND annual reports will be submitted to the FDA by the Sponsor-Investigator.

7. PHARMACEUTICAL INFORMATION

7.1 Pemigatinib

7.1.1 Agent Accountability

The IND sponsor or the Sponsor's representative shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

7.1.2 Mode of Action

Pemigatinib is an orally bioavailable small molecule inhibitor of signaling via FGFR1, FGFR2, and FGFR3 tryosine kinases.

7.1.3 Description

The pemigatinib drug product is formulated as immediate release (IR) tablets of 4.5 mg. The tablets of all strengths are round and white to off-white in color and contain the active drug substance along with the excipients microcrystalline cellulose, sodium starch glycolate, and magnesium stearate.

All pemigatinib investigational product required for completion of this study will be supplied by Incyte Corporation and distributed to site pharmacies by Incyte or designee.

7.1.4 Packaging and Labeling Information

Investigational supplies will be affixed with an investigational label in accordance with regulatory requirements. One strength, 4.5mg, tablets will be supplied in 60-count per bottle. Each participating site will receive the drug products after confirmed site activation and the first patient is identified. Shipping and order details are included in the study operations manual.

7.1.5 Storage

Investigational supplies must be stored in a secure, limited-access location. Pemigatinib drug product should be stored at ambient conditions (15° to 30°C, or 59° to 86°F). Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Investigational supplies may not be used for any purpose other than that stated in the protocol.

7.1.6 Route of Administration

Pemigatinib is to be administered as a tablet by oral route.

7.1.7 Returns and Reconciliation

The investigator at each participating site is responsible for keeping accurate records of the clinical supplies received from Incyte or designee, the amount dispensed to, and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Tumor Tissue Studies

8.1.1 Tumor FGFR3 Mutation/fusion Status

The tumor FGFR3 mutation/fusion status of each patient will be determined by analysis of the patient's most recent archived formalin fixed paraffin embedded (FFPE) TURBT sample. Tumor cells will be isolated and enriched from 5 10-micron thickness tumor slides by macro-dissection under the direction of Dr. Alex Baras.

DNA will be extracted and assessed for quality control utilizing standard manufacturer DNA extraction kits and per manufacturer instructions (e.g. DNeasy, Qiagen, N.V.) and per standard spectrophotometric 260nm/280nm methods. Extracted DNA from each sample will be analyzed for functionally activating FGFR3 mutations (e.g. S249C, S373C, G372C, Y375C, G382R, K652E, etc.) or activating FGFR3 gene-gene fusions (e.g. FGFR3:TACC3) on a customized bladder cancer focused next generation sequencing panel.

All DNA sequencing analyses will be performed within Johns Hopkins Greenberg Bladder Cancer Institute under the direction of Drs. David McConkey Ph.D. The data produced from this effort will be made available to Drs. Woonyoung Choi Ph.D. and Dr. Luigi Marchionni Ph.D., for statistical analysis. Additional DNA based investigations on tumor DNA remaining after FGFR3 mutation/fusion analyses may be performed as tumor DNA availability and emerging analysis platforms permit.

8.1.2 Tumor DNA Sequencing

Tumor cells from the patient's most recent archived formalin fixed paraffin embedded (FFPE) TURBT sample and the post-treatment FFPE tumor sample (in non-responding patients) will be isolated and enriched from 5 10-micron thickness tumor slides by macro-dissection under the direction of Dr. Alex Baras. The same slides utilized for the FGFR3 mutation/fusion analysis in section 8.1.1 above may be used for this purpose.

DNA will be extracted and assessed for quality control utilizing standard manufacturer DNA extraction kits and per manufacturer instructions (e.g. DNeasy, Qiagen, N.V.) and per standard spectrophotometric 260nm/280nm methods. Extracted DNA from each sample will be analyzed by whole exome sequencing across the genome for DNA mutations and tumor mutational burden (TMB) on the Ion Torrent platform. Somatic DNA mutations will be determined by parallel analysis of de-identified patient germ-line DNA mutations as described in more detail in section 8.3.4.

All DNA sequencing analyses will be performed within Johns Hopkins Greenberg Bladder Cancer Institute under the direction of Dr. David McConkey Ph.D. The data produced from this effort will be made available to Drs. Woonyoung Choi Ph.D. and Dr. Luigi Marchionni Ph.D., for statistical analysis. Additional DNA based investigations (e.g. whole genome sequencing, whole methylome sequencing) on tumor DNA remaining after the whole exome analysis may be performed as tumor DNA availability and emerging analysis platforms permit.

8.1.3 Tumor Gene Expression and Intrinsic Molecular Subtype Status

Tumor cells from the patient's most recent archived formalin fixed paraffin embedded (FFPE) TURBT sample and the post-treatment FFPE tumor sample (in non-responding patients) will be isolated and enriched from 5 10-micron thickness tumor slides by macro-dissection under the direction of Dr. Alex Baras. RNA will be extracted and assessed for quality control utilizing standard manufacturer RNA extraction kits and per manufacturer instructions (i.e. RNeasy, Qiagen, N.V.) and per standard spectrophotometric 260nm/280nm methods. Extracted RNA from each sample will be analyzed by AmpliSeq RNA gene expression across the whole genome on the Ion Torrent platform. If necessary, manufacturer specific probe primers will be utilized to amplify RNA.

All gene expression analyses will be performed within the Johns Hopkins Greenberg Bladder Cancer Institute under the direction of Dr. David McConkey Ph.D. The data produced from this effort will be made available to Drs. Woonyoung Choi Ph.D. and Dr. Luigi Marchionni Ph.D., for statistical analyses including the determination of each patient's intrinsic molecular subtype (e.g. basal vs. luminal). Additional RNA based investigations on tumor RNA remaining after AmpliSeq RNA gene expression analyses may be performed as tumor RNA availability and emerging analysis platforms permit.

8.1.4 Urothelial Tissue Pemigatinib Pharmacokinetic Analysis

All patients will have a post-therapy pemigatinib pharmacokinetic evaluation performed. According to the study lab manual, bladder biopsy tissue for the pemigatinib pharmacokinetic evaluation should be collected at the time of the first post- pemigatinib TURBT. The biopsy tissue may be obtained from a bladder tumor region or from normal appearing urothelium. Pemigatinib tissue concentrations will be analyzed by mass spectroscopy and liquid chromatography methodologies developed specifically for this protocol by the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center's Analytical Pharmacology Core under the direction of Dr. Michelle Rudek Ph.D., Pharm.D.

8.1.4 Tumor CD8+ T-cell Density Status

The CD8+ T-cell density is defined as the number of CD8+ tumor-infiltrating T-cells per 100 tumor cells within a 400X high power field (hpf). Three representative tumor fields with the greatest gross tumor infiltrating lymphocyte fields will be chosen for measurement by the pathologist with the final CD8+ T-cell density determined as the mean of the CD8+ T-cell density across the three fields.

A 1.0 mm diameter core biopsy will be obtained from representative areas (containing at least 75% tumor) of the patient's most recent archived formalin fixed paraffin embedded (FFPE) TURBT sample and the post-treatment FFPE tumor sample (in non-responding patients). Tissue microarrays for immunohistochemical staining (IHC) analysis will be constructed from unstained spot sections cut from the core biopsies. CD8 IHC on both the pre- and post-treatment TMAs will be performed within the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center's IHC core under the direction of Dr. Alan Meeker Ph.D. with pathology input from Dr. Alex Baras MD Ph.D. CD8 IHC will be performed utilizing the CD8 (RB-9009-P0) antibody (ThermoScientific, Waltham, MA) per manufacturer's instructions. Alternate antibodies may be substituted should improved optimization and validation be observed with newer antibodies during the course of the trial's conduct. Pre- and post-treatment CD8+ staining cells intermixed within surrounding tumor cells will be considered tumor infiltrating CD8+ T-cells. These cells will be counted as will the number of tumor cells within the chosen 400X high power field (hpf). The CD8+ T-cell density will be calculated as:

$$\text{CD8+ T-cell density (CD8+ T-cells per 100 tumor cells)} = \frac{\text{Total \# of CD8+ TILS}}{\text{Total \# of tumor cells per hpf}} \times 100$$

This methodology will be utilized to determine both the pre- and post-treatment tumor infiltrating CD8+ T-cell densities.

In addition to the 1.0 mm diameter core biopsy for TMA construction, up to 35 unstained 5 micron thick sections from both the pre- and post-treatment tumor samples will be cut unto slides for additional correlative investigations. In the event that a patient's TMA section is not suitable for averaging three representative tumor infiltrating lymphocyte regions, whole slides may be used for the CD8+ T-cell density analyses.

8.1.5 PD-L1, CD8+, FOXP3, and Phosphorylated FGFR3 (pFGFR3) Immunohistochemistry

Utilizing the TMAs constructed from the pre-treatment and post-treatment (in non-responding patients) archived tumor specimens, IHC staining for PD-L1,

CD8+, FOXP3, and pFGFR3 will be performed by the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center IHC core under the direction of Dr. Alan Meeker Ph.D. with pathology input from Dr. Alex Baras MD, Ph.D. TMA tumor sections will be stained for PD-L1 utilizing the 28-8 antibody (Dako, Carpinterina, CA), the CD8+ RB-9009-P0 antibody (ThermoScientific, Waltham, MA), the FOXP3 ab22510 antibody (Abcam, Cambridge, MA), and the pFGFR3 ab155960 anti-FGFR3 (phosphor Y724) antibody (Abcam, Cambridge, MA). All IHC staining will be performed per manufacturer's instructions. Alternate antibodies may be substituted should improved optimization and validation be observed with newer antibodies during the course of the trial's conduct. In addition should TMAs not be suitable for this work, whole slides may be used as an alternate tissue source.

8.1.6 Additional Immunohistochemistry Analyses

As tissue availability permits additional IHC staining is planned to further characterize functional immune phenotypes and targets of interest for future drug development. Utilizing the TMAs constructed from the pre- and post-treatment archived tumor specimens, additional IHC stains are planned, but not limited to the following: CD4, CD56, FOXP3, Ki-67, CTLA-4, Hsp27, PTEN, OX40, LAG3, KIR2DL, CSF1R, 4-1BB, IDO, GITR, CD27, CD40L, CD163, pSTAT1, RBP-J, CMAF, LGR4, LGR5, LGR6. The exact list of IHC markers may be modified according to new target identification and emerging translational science. This work will be performed by the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center IHC core under the direction of Dr. Alan Meeker Ph.D. with pathology input from Dr. Alex Baras MD, Ph.D. All IHC staining will be performed per manufacturer's instructions.

8.2 Peripheral Blood Mononuclear Cell (PBMC) Studies

8.2.1 T-cell Receptor Repertoire Analysis

According to the study lab manual, pre- and post-treatment peripheral blood mononuclear cells (PBMCs) will be isolated and enriched from patients at baseline and pre-TURBT in BD Vacutainer® CPT™ (Franklin Lakes, NJ) tubes or an appropriate substitute cell preparation tube. DNA will be extracted and assessed for quality control utilizing standard manufacturer DNA extraction kits and per manufacturer instructions (i.e. DNeasy, Qiagen, N.V.) and per standard spectrophotometric 260nm/280nm methods. Extracted DNA from each sample will be analyzed for T-cell and B-cell receptor mutations by next generation sequencing on the Adaptive Biotechnologies Immunoseq platform. This work will be performed in collaboration with Drs. Kellie Smith, Ph.D and Drew Pardoll, M.D. Ph.D within the Johns Hopkins Bloomberg-Kimmel Institute for Cancer Immunotherapy. The complete source data produced from this effort will be made available to Drs. Woonyoung Choi, Ph.D and Dr. Luigi Marchionni, Ph.D..

for statistical analysis.

8.2.2 Lymphocyte Functional Analysis

According to the study lab manual, pre- and post-treatment peripheral blood mononuclear cells (PBMCs) will be isolated, enriched, and banked for future analyses from patients at baseline and pre-TURBT in BD Vacutainer® CPT™ (Franklin Lakes, NJ) tubes or an appropriate substitute cell preparation tube. Lymphocyte functional analyses will be performed in batch including, but not limited to lymphocyte proliferation assays and interferon-γ ELISA analyses. Alternate lymphocyte functional analyses may be substituted should improved optimization and validation be observed with newer platforms during the course of the trial's conduct. This work will be performed within the Johns Hopkins Bloomberg-Kimmel Institute for Cancer Immunotherapy under the direction of Drs. Kellie Smith, Ph.D. and Drew Pardoll M.D., Ph.D.. The data produced from this effort will be made available to Drs. Woonyoung Choi, Ph.D. and Dr. Luigi Marchionni, Ph.D. for statistical analysis.

8.2.3 Peripheral Blood Lymphocyte Subsets

According to the study lab manual, pre- and post-treatment peripheral blood mononuclear cells (PBMCs) will be isolated, enriched, and banked for future analyses from patients at baseline and pre-TURBT in BD Vacutainer® CPT™ (Franklin Lakes, NJ) tubes or an appropriate substitute cell preparation tube. T-cell subset proportions (%CD4+ T-cells, %CD8+ T-cells, %Treg T-cells, %Myeloid Derived Suppressor Cells, %Natural Killer cells, etc.) will be determined by flow cytometry analysis. This work will be performed within the Johns Hopkins Bloomberg-Kimmel Institute for Cancer Immunotherapy under the direction of Drs. Kellie Smith, Ph.D. and Drew Pardoll M.D., Ph.D.. The data produced from this effort will be made available to Drs. Woonyoung Choi, Ph.D. and Dr. Luigi Marchionni, Ph.D. for statistical analysis.

8.3 Serum, Plasma, and Buffy Coat Studies

8.3.1 Serum Sample Processing

According to the study lab manual, pre- and post-treatment peripheral blood will be collected and banked for future serum sample analyses. Blood for serum should be collected in 2 standard 10 ml red top polypropylene tubes and allowed to clot for 30 minutes at room temperature in a vertical position. The samples should be separated in a centrifuge for 30 minutes at 3500 rpm. Without delay, 1.5 ml serum aliquots should be pipetted into a 2.0 ml snap cap cryovials. After removing the serum, discard the red top tubes. Label each cryovial with the information requested on the pre-printed labels. Freeze the

cryovials immediately at -70°C until time of shipment. DO NOT ALLOW SAMPLES TO THAW. If a -70°C freezer is not available serum samples may be stored at -20°C.

8.3.2 Plasma and Buffy Coat Sample Processing

According to the study lab manual, pre- and post-treatment peripheral blood will be collected and banked for future serum sample analyses. Blood for plasma should be collected in 2 standard 10 ml EDTA lavender top tubes. The samples should be immediately separated in a centrifuge for 10 minutes at 1500 +/- 150g (=1500RCF). Without delay, transfer the resulting supernatant plasma to a fresh 15 ml conical centrifuge tube. After removing the plasma, use the same transfer pipet to carefully aspirate the exposed WBC layer (buffy coat) in a volume of 1 ml or less. Aspirate slowly, using a circular motion, to pull all the visible buffy coat material into the pipet. Some contamination of the WBCs with the underlying RBCs is expected. Expel the buffy coat into one cryovial. Discard the lavender top tubes and the transfer pipet tip. Label each buffy coat cryovial with the information requested on the pre-printed labels. Freeze the cryovials immediately at -70°C until time of shipment. DO NOT ALLOW SAMPLES TO THAW. If a -70°C freezer is not available serum samples may be stored at -20°C.

Run the 15 ml conical centrifuge tube containing the supernatant plasma in a centrifuge for a second time for 10 minutes at 1500 +/- 150g (=1500RCF). Without delay and using a fresh transfer pipet tip, 1.5 ml plasma aliquots of the resulting supernatant should be pipetted into a 2.0 ml snap cap cryovials. Leave a residual volume of about 0.3 ml (~7 mm) on the bottom of the 15 ml conical centrifuge tube to avoid cellular contamination. Label each cryovial with the information requested on the pre-printed labels. Freeze the cryovials immediately at -70°C until time of shipment. DO NOT ALLOW SAMPLES TO THAW. If a -70°C freezer is not available serum samples may be stored at -20°C.

8.3.3 Serum, Plasma, and Buffy Coat Sample Transport

All samples will be transported same day on dry ice or shipped by overnight courier to Dr. David McConkey's laboratory for storage at

ATTN: Drs. Noah Hahn or David McConkey
Johns Hopkins Greenberg Bladder Cancer Institute
Park Building Room 202
600 North Wolfe Street
Baltimore, MD 21287
Phone 410-502-4149
Fax: 410-955-0833

If the timing of the sample collection would result in the sample being received on a weekend or holiday, serum must be frozen immediately at –20 ^{O}C or lower and shipped on the next appropriate business day.

8.3.4 Serum, Plasma, and Buffy Coat Analyses

DNA will be extracted from the buffy coat sample and assessed for quality control utilizing standard manufacturer DNA extraction kits and per manufacturer instructions (e.g. DNeasy, Qiagen, N.V.) and per standard spectrophotometric 260nm/280nm methods. Extracted DNA from each sample will be analyzed by whole exome sequencing across the genome for DNA mutations and tumor mutational burden (TMB) on the Ion Torrent platform. The buffy coat germ-line DNA mutational analyses will be performed in a de-identified manner. As such, the results will not be communicated back to individual study patients. All DNA sequencing analyses will be performed within Johns Hopkins Greenberg Bladder Cancer Institute under the direction of Drs. David McConkey Ph.D. The data produced from this effort will be made available to Drs. Woonyoung Choi Ph.D. and Dr. Luigi Marchionni Ph.D., for statistical analysis. Additional DNA based investigations (e.g. whole genome sequencing) on tumor DNA remaining after the whole exome analysis may be performed as tumor DNA availability and emerging analysis platforms permit.

Additional analyses of the serum and plasma samples may include, but not be limited to pharmacodynamics functional studies of pemigatinib treatment such as assessment of pre- and post-treatment plasma cytokine markers of interest (i.e. IFN-α, TGF-β, IL-10, IL-4, IL-5, IL-13, IFN-γ), circulating tumor free DNA, or Phage Immunoprecipitation sequencing (PhIP-seq). The exact list of analyses will be selected based on assay methodology optimization and validation testing, development of new novel platforms, resources and specimen availability.

8.4 Urine Marker Studies

8.4.1 Urine Sample Processing

A clean catch urine sample will be collected for at baseline, pre-TURBT, and post-TURBT from each patient. Urine should be collected in a standard urinalysis cup and 30 mls aliquotted into two 15 ml screw top conical. The samples should be separated in a centrifuge for 10 minutes at 3500 rpm. Up to 6 mls of supernatant should be transferred to 1.5 ml snap cap cryovials. The cell pellet from each tube should be individually pipetted into a 1.0 ml snap cap cryovial. After removing the cell pellet, the 15 ml cryovials can be discarded. Label each cryovial with the information requested on the pre-printed labels. Freeze the cryovials immediately at -70°C until time of shipment. DO NOT

ALLOW SAMPLES TO THAW. If a -70°C freezer is not available samples may be stored at -20°C.

8.4.2 Urine Marker Analyses

Initially, urine samples will be banked and stored. Future analyses of urinary cytokine changes, urine cell pellet DNA/RNA mutation profiles, T-cell receptor repertoire, and gene methylation analysis are proposed as resources and specimen availability permit. The exact list of urine markers may be modified according to new target identification and emerging translational science.

9. STUDY CALENDAR

Study Day	Screening (0-28 days pre-study)	All Cycles			Post-Treatment TURBT[11]	Safety Follow-up	Long-term Follow-up (every 6 months for up to 2 years)
		Days 1-28	Day 1 +/- 3 days	Day 15 +/- 3 days		30 day post treatment	
REQUIRED ASSESSMENTS							
Medical history	X		X[1,3]				
Physical examination including BP, height and weight	X		X[1,3]				
ECOG performance status	X		X[1,3]			X[3]	
AEs & concomitant medications	X		X[1,3]			X[3]	
Ophthalmology Examination	X[2]		X[2]				
LABORATORY ASSESSMENTS							
CBC w/differential	X[4]		X[5]	X[5]		X[5]	
CMP w/Calcium and Phosphate	X[4]		X[5]	X[5]		X[5]	
Vitamin D3, Parathyroid Hormone	X[4]		X[5]				
Lipid Profile (Total Cholesterol, HDL, LDL) and Triglycerides	X[4]		X[5]				
DISEASE ASSESSMENT							
Cystoscopy	X[6]				X[9]		X[10]
TURBT					X[9]		X[10]
Urine cytology diagnostic sample	X[6]				X[9]		X[10]
TREATMENT							
Pemigatinib		X[8,11]					
CORRELATIVE STUDIES							
Tumor Tissue	X				X[9]		
Bladder Tissue PK sample					X[9]		
PBMC Samples (T-cell Repertoire, lymphocyte functional, lymphocyte subsets)	X[7]				X[12]		
Serum Samples	X[7]				X[12]		
Plasma and Buffy Coat Samples	X[7]				X[12]		
Urine sample	X[7]				X[12]		

[1]Screening medical history, physical examination (including BP, height, and weight), ECOG performance status, AEs, and concomitant medication assessments do not need to be repeated on cycle 1 day 1. These assessments should be repeated on day 1 of each cycle starting with cycle 2 day 1 +/- 3 days.

[2]All ophthalmology examinations should include visual acuity test, slit-lamp examination, fundoscopic exams, and optical coherence tomography (OCT). Baseline exam should initially be performed within 28 days of starting study therapy. For patients that achieve a complete response at TURBT and remain on pemigatinib post-TURBT, follow-up exams (including OCT) should be performed within 14 days of cycle 4 day 1, cycle 7 day 1, cycle 10 day 1 and cycle 13 day 1.

[3]In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in-person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

[4]Baseline complete blood count (white blood cells, hemoglobin, platelets) with differential, complete metabolic profile (including calcium), phosphate, Vitamin D3, parathyroid hormone (PTH), lipid profile (total cholesterol, low density lipid (LDL), high density lipid (HDL)) and triglycerides should be completed within 7 days of starting study therapy.

[5]On-study complete blood count (white blood cells, hemoglobin, platelets) with differential, complete metabolic profile (including calcium), phosphate, Vitamin D3, parathyroid hormone (PTH), lipid profile (total cholesterol, low density lipid (LDL), high density lipid (HDL)) and triglycerides should be completed +/- 3 days of the intended study collection date. Baseline screening labs may be utilized for the cycle 1 day 1 time point. Lipid profile and triglycerides should be obtained in a fasting state. Local laboratories may be utilized for complete blood count, complete metabolic profile (including calcium), phosphate, Vitamin D3, parathyroid hormone (PTH), lipid profile, and triglyceride assessments.

[6]Cystoscopy and urine cytology at baseline should be performed within 28 days of starting study therapy.

[7]Baseline time point PBMC, serum, plasma, buffy coat, and urine correlative samples can be obtained up to 14 days prior to the start of protocol treatment, but must be obtained before the first dose of treatment.

[8]Daily treatment with pemigatinib may continue for a maximum of 13 cycles in patients achieving a complete response at the post-treatment disease evaluation time point.

[9]Cystoscopy, TURBT, correlative tumor tissue sample, bladder tissue PK sample, and urine cytology are required assessments and are to be performed no earlier than 1 cycle (28$\pm$3 days)

after the initiation of pemigatinib. The timing of these study evaluations beyond cycle 1 will be dependent upon the TURBT scheduling requirements at the local institutions. It is strongly encouraged to time the TURBT on the same day as the patient's last pemigatinib dose administration.

[10]Cystoscopy, TURBT, and urine cytology in follow up beyond the initial post-treatment disease assessments are per the discretion of the treating urologist.

[11]Pemigatinib will be continuously administered once daily for a minimum of 1 cycle (4 weeks). If TURBT cannot be done on day 1 of cycle 2 then subject will start cycle 2 and continue on pemigatinib until TURBT can be performed, ideally between 4-6 weeks post initiation of treatment.

[12]Post-treatment PBMC, serum, plasma, buffy coat, and urine correlative samples should be obtained at the time of TURBT or within 3 days prior to the TURBT date. Then post-TURBT urine correlative sample will be collected at the next visit following the TURBT.

10. MEASUREMENT OF EFFECT

For the purposes of this study, patients should be evaluated for tumor response at the post-treatment TURBT time point.

10.1 Tumor Response

10.1.1 Evaluable Population Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first study drug treatment.

Evaluable for tumor response. Only those subjects who have received at least one dose of study therapy, and undergo a restaging TURBT with urine cytology will be considered evaluable for tumor response. These subjects will have their tumor response classified according to the definitions stated below.

NOTE: Subjects who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.

Evaluable for Pathologic Staging. Only those patients who have received at least one dose of study therapy, and undergo post-treatment cystectomy will be considered evaluable for pathologic staging. These patients will have their pathologic staging classified according to the definitions stated below.

10.1.2 Methods for Evaluation of Tumor Response

The post-treatment tumor response will be determined based on the bladder TURBT results and urine cytology results obtained during post-treatment tumor assessments.

NOTE: At time points where bladder TURBTs are not required by the protocol, patients with absence of tumor recurrence on cystoscopy and urine cytology will be classified as T0. Patients with high grade UC on urine cytology but T0 stage on bladder biopsy with no evidence of upper tract UC will be classified as Tis.

These categories are summarized below.

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma which does not invade the lamina propria

Tis	Carcinoma in-situ
T1	Tumor invades into the lamina propria but not into the muscularis propria
T2	Tumor invades into the muscularis propria

Table 4: TURBT T-stage

10.1.3 Methods for Evaluating Pathologic Stage

The post-treatment pathologic stage will be determined in patients who undergo a post-treatment cystectomy and will be determined based on the cystectomy pathology staging results. The staging definitions are summarized below.

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma which does not invade the lamina propria
Tis	Carcinoma in-situ
T1	Tumor invades into the lamina propria but not into the muscularis propria
T2	Tumor invades into the muscularis propria
T2a	Tumor invades into the inner half of the muscularis propria
T2b	Tumor invades into the outer half of the muscularis propria
T3	Tumor invades into the perivesical tissue
T3a	Tumor microscopically invades the perivesical tissue
T3b	Tumor macroscopically invades the perivesical tissue
T4	Tumor invades into adjacent organs
T4a	Tumor invades the prostatic stroma, uterus, or vagina
T4b	Tumor invades into the pelvic wall or abdominal wall

Table 5: Pathologic T-stage

Nx	Lymph nodes cannot be assessed
N0	No lymph node metastases
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2	Multiple regional lymph node metastases in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph nodes)
N3	Lymph node metastases to the common iliac lymph nodes

Table 6: Pathologic N-stage

M0	No distant metastasis
M1	Distant metastasis

Table 7: Pathologic M-stage

10.1.4 Tumor Response Definitions

The post-treatment tumor response will be determined in patients who undergo a post-treatment TURBT and will be determined based on the TURBT pathology staging results. The tumor response definitions are summarized below.

10.1.4.1 Complete Response

Complete response (CR) is defined by an initial post-treatment TURBT tumor stage with the following T-stages: T0. In addition, patients must demonstrate an absence of high grade urothelial carcinoma on urine cytology.

NOTE: Patients with urine cytology samples demonstrating urothelial cell atypia but no definitive high grade urothelial carcinoma with an initial post-treatment TURBT tumor stage of T0 are considered complete responders. Urine cytology diagnoses of “atypical urothelial cells present, cannot exclude high grade urothelial carcinoma (AUC-H)” do not qualify as a relapse event as an isolated finding. However, if such a diagnosis is rendered on a urine cytology at an evaluation time point that does not have a protocol-required TURBT, investigators are strongly encouraged to pursue a TURBT to further workup these high risk cytologic findings.

10.1.4.2 Non-Response

Non-response (NR) is defined by persistent of urothelial carcinoma of any T-stage or grade including isolated carcinoma in-situ (Tis) at the initial post-treatment tumor assessment.

10.1.4.3 Progression to Muscle Invasion

Progression to muscle invasion (pMI) is defined by a post-treatment TURBT with the following T-stages: T2-T4b. For subjects who undergo cystectomy, progression to muscle invasion (pMI) is defined by post-cystectomy tumor stages with the following T-stages: T2-T4b.

10.1.4.4 Progression to Metastatic Stage

Progression to metastatic stage (pMet) is defined by a post-treatment subject with the following M-stages at any time point as assessed pathologically, radiologically, or clinically: M1.

10.1.4.5 Rate of Cystectomy

Rate of cystectomy (CystR) is defined as the proportion of subjects who undergo a post-treatment cystectomy for any reason.

10.1.5 Tumor IHC Staining Intensity Definitions

For validated IHC targets, standardized IHC staining intensity cutoffs will be utilized. For all other IHC targets, IHC staining will be categorized as:

0	< 1% cells stained
1+	1 to < 5% cells stained
2+	5 to < 10% cells stained
3+	$\geq$ 10% cells stained

10.2 Survival Analyses

10.2.1 Relapse-Free Survival (RFS)

RFS is defined as the duration of time from study registration to time of first documented bladder tumor of any stage or grade, progression or death, whichever occurs first.

10.2.1.1 6-month Relapse-Free Survival (6m-RFS)

6m-RFS is defined as the proportion of patients alive and with no evidence of bladder tumors of any stage or grade as assessed by post-treatment tumor assessments performed at least 6 months after study registration.

10.2.1.2 12-month Relapse-Free Survival (6m-RFS)

12m-RFS is defined as the proportion of patients alive and with no evidence of bladder tumors of any stage or grade as assessed by post-treatment tumor assessments performed at least 12 months after study registration.

10.2.1.3 24-month Relapse-Free Survival (6m-RFS)

24m-RFS is defined as the proportion of patients alive and with no evidence of bladder tumors of any stage or grade as assessed by post-treatment tumor assessments performed at least 24 months after study registration.

10.2.2 Overall Survival (OS)

OS is defined as the duration of time from study registration to time of death due to any cause.

10.2.3 Cancer-Specific Survival (CSS)

CSS is defined as the duration of time from study registration to time of death due to bladder cancer.

11. DATA REPORTING / REGULATORY REQUIREMENTS

11.1 Data Management

All information will be collected on study-specific case report forms (CRFs) by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator. Protocol-specified source documents and copies of all study-related documentation will be retained at the site. It is the responsibility of the Principal Investigator to keep all data and essential documentation for a minimum of 5 years after the end of the trial.

To avoid error, the investigator will contact Incyte before the destruction of any records pertaining to the study to ensure they no longer need to be retained.

11.2 Safety Meetings

Scheduled meetings will take place on a regular basis with the frequency dependent on the rate of subject accrual and will include the principal investigator, study coordinator(s), data manager(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

11.3 Monitoring

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring.
Additionally, scheduled meetings will take place monthly and will include the protocol principal investigator, research nurse, data manager, and, when appropriate, the collaborators, subinvestigators, and biostatistician involved with the conduct of the protocol.

During these meetings the investigators will discuss matters related to: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data.

11.4 Multicenter Guidelines

11.4.1 The Protocol Chair

The Protocol Chair, Dr. Noah Hahn, is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments
- Assuring that all participating institutions are using the correct version of the protocol
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study
- Reviewing and ensuring reporting of Serious Adverse Events (SAEs)
- Reviewing data from all sites

11.4.2 The Lead Center

The Lead Center (Johns Hopkins) is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
- Managing central patient registration

- Collecting and compiling data from each site

- Establishing procedures for documentation, reporting and submitting of AE's and SAE's to the Protocol Chair (Dr. Noah Hahn) and all other applicable parties.

- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments

- Assuring that all participating institutions are using the correct version of the protocol

- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study

- Reviewing and ensuring reporting of Serious Adverse Events (SAEs)

- Reviewing data from all sites

11.4.3 Participating Sites

Participating Sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP)

- Submitting data to the Lead Center

- Registering all patients with the Lead Center by submitting patient registration form, and signed informed consent promptly

- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol

- Maintaining regulatory binders on site and providing copies of all required documents to the Lead Center

- Collecting and submitting data according to the schedule specified by the protocol

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

This is a multi-institution, single-arm window of opportunity study to evaluate the impact of pemigatinib on post-treatment tumor complete response rate in non-muscle invasive urothelial carcinoma of the bladder (NMIBC) patients with a prior history of low- or intermediate-risk tumors. Measurement of the primary outcome will occur following at least 4 weeks of pemigatinib therapy. Tumor complete response is defined as the complete absence of any stage bladder tumor on post-treatment TURBT and no evidence of recurrent urothelial carcinoma on post-treatment urine cytology. Our primary hypothesis is that the pemigatinib therapy will result in a complete tumor response rate of50%.

12.1.1 Primary Objective:

Assess the complete response rate of pemigatinib therapy in patients with recurrent bladder tumors and a prior history of histologically confirmed low- or intermediate-risk NMIBC.

12.1.2 Secondary Objectives

12.1.2.1 Characterize the safety profile of pemigatinib therapy in patients with recurrent bladder tumors and a prior history of histologically confirmed low- or intermediate-risk NMIBC.

12.1.2.2 Assess associations between complete response rate and tumor mutation/fusion status (e.g. FGFR3 specifically, others will also be examined).

12.1.2.3 Assess associations between complete response rate and baseline NMIBC risk group (low- vs. intermediate-risk).

12.1.2.4 Assess pemigatinib urothelial tissue concentrations as measured within urothelial tissue sampled at post-treatment TURBT.

12.1.2.5 Assess 6- 12- and 24-month relapse free survival (RFS) in patients achieving a complete response at initial post-treatment TURBT.

12.1.3 Exploratory Objectives

12.1.3.1 Assess associations between complete response rate and tumor intrinsic molecular subtypes (e.g. basal vs. luminal).

12.1.3.2 Assess associations between complete response rate and tumor baseline CD8+ tumor infiltrating lymphocyte density.

12.1.3.3 Assess associations between complete response rate and changes in peripheral blood T-cell clonality as measured at baseline and post-treatment.

12.1.3.4 Assess the post-treatment effects of pemigatinib on tumor gene expression by RNA sequencing among patients with residual tumor present at post-treatment TURBT.

12.1.3.5 Assess the post-treatment immunomodulatory effects of pemigatinib on the tumor microenvironment as assessed by comparison of pre- and post-treatment immunohistochemistry (IHC) staining for PD-L1, CD8+, FOXP3, pFGFR3, and other targets of interest where adequate tissue permits.

12.1.3.6 Assess associations between the development of hyperphosphatemia and complete response rate.

12.2 Sample Size/Accrual Rate

This single-arm non-randomized study will determine the tumor complete response rate in patients with non-muscle invasive urothelial carcinoma of the bladder with a prior history of low- or intermediate-risk tumors who are treated with pemigatinib therapy. The accrual rate is expected to be 3-4 patients per month across 4-5 institutions with accrual completed in 12-18 months. The primary statistical analysis will be an analysis of the observed tumor complete response rate compared to a proposed minimal clinically relevant tumor response rate of 30%, below which further investigation would not be indicated. We hypothesize that pemigatinib therapy will result in a tumor response rate of 50%. Utilizing a one-sided 5% type 1 error allowance and a sample size of 39 patients, this study will have an 80% power to detect a 20% improvement in tumor response rate from 30% (H_0) to 50% (H_1). A Simon 2-stage design will be utilized. With such a design, 19 patients will be accrued in stage 1. If $\geq$ 7 tumor complete responses are observed, the study will proceed to stage 2. Since it will take a month or more to determine if a patient has responded, accrual may be temporarily paused while waiting to determine if there are at least 7 complete responses among the 19 evaluable patients enrolled in stage 1. In stage 2, an additional 20 patients will be accrued. At the completion of the trial if $\geq$ 17 tumor complete responses are observed, pemigatinib will be considered worthy of additional study. This design provides a 67% chance of early stopping should the true tumor complete response rate be less than 30%. Assuming 10% of enrolled patients as unevaluable, a total sample size of 43 patients will be required.

12.3 Safety Monitoring and Early Stopping Rules for Safety

Grade 3 or 4 toxicities directly related to the pemigatinib used in this study will be monitored continuously. The stopping rule for safety is based on the posterior probability that the adverse event (AE) rate is too high. Trial enrollment will be suspended for a safety evaluation if the AE risk convincingly exceeds 30%. This

stopping rule will halt enrollment if the posterior probability of the AE risk exceeding 0.30 is 70% or higher. The prior probability for this toxicity monitoring rule is a Beta distribution with parameters of 1 and 5, assuming a phase 1 study showed 1 DLT out of 6 patients treated at the doses in this study. The estimated probability that a treatment regimen's AE risk exceeds 30% comes from combining this prior distribution with the observed number of patients experiencing an AE to compute the posterior probability distribution of the risk of an AE. If the posterior probability that the risk is too high based on these assumptions is 70% or higher, we should suspend the study to evaluate safety. The following table shows the resulting rules.

Study paused if:	3 AEs	4 AEs	5 AEs	6 AEs	7 AEs	8 AEs
And patients between:	3-4	5-7	8-10	11-13	14-16	17-19

Study paused if:	9 AEs	10 AEs	11 AEs	12 AEs	13 AEs	14 AEs	15 AEs
And patients between:	20-22	23-25	26-28	29-31	32-35	36-38	39

For example, the rule will call for suspending the study if 4 out of the first 5 patients experience AEs. The next table shows the percent of the time that the stopping rule will terminate the study under different hypothetical risks of AEs, along with the average sample size (based on 5000 simulations).

Risk of AE	0.10	0.20	0.25	0.30	0.35	0.40	0.45	0.50
% of Time Study Stops	0.8%	8.7%	21.9%	42.6%	62.7%	82.2%	93.4%	97.9%
Expected Sample Size	38.8	36.6	33.4	28.6	23.7	18.2	13.8	10.6

12.4 Analysis Plans for Primary Objective

The proportion of evaluable patients with a complete tumor response will be reported with an exact binomial 95% confidence interval. The evaluable population includes all subjects who have received at least one dose of study therapy, and undergo a restaging TURBT with urine cytology. Tumor complete response is defined as the complete absence of any stage bladder tumor on post-treatment TURBT and no evidence of recurrent urothelial carcinoma on post-treatment urine cytology.

12.5 Analysis Plans for Secondary and Correlative Objectives

The proportion of toxicities by type and grade according to the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 will be reported with exact binomial 95% confidence intervals for each arm of the study. All patients who receive at least dose of the study drug(s) will be evaluable for toxicity.

To assess the prognostic value of markers of interest measured in this study we plan to evaluate associations between the marker at baseline, changes in the biomarker over time, and the clinical outcome of tumor complete response. Exploratory analyses of

these data will be descriptive and graphical and will take into consideration the nature of the outcome, continuous or categorical, and the technology used. Preference will be to analyze markers as continuous variables with appropriate transformations. Continuous variables will be plotted post-treatment by pre-treatment value, boxplots over time, and boxplots by responder status. Single time point comparisons of continuous variables by response status will be done using two sample t-tests or the non-parametric Mann-Whitney U-test. Comparisons between complete responders and non-responders at baseline and subsequent changes over time will be made using GEE regression analyses or linear mixed effects models. For classes of markers with many variables measured similarly, e.g. flow cytometry data, appropriate transformations and/or preprocessing will be performed and subsequent comparisons between responder categories will be performed using the Benjamini and Hochberg method for controlling the false discovery rate. Principle component analysis may be used for data exploration and visualization. RFS will be summarized descriptively using the Kaplan-Meier method.

13. REFERENCES

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2018. CA: A Cancer Journal for Clinicians:n/a-n/a, 2018
2. Howlader N, Noone AM, Krapcho M, et al: SEER Cancer Statistics Review, 1975-2013. Bethesda, MD, National Cancer Institute, 2016
3. Botteman MF, Pashos CL, Redaelli A, et al: The health economics of bladder cancer: a comprehensive review of the published literature. Pharmacoeconomics 21:1315-30, 2003
4. Babjuk M, Burger M, Zigeuner R, et al: EAU Guidelines on Non–Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2013. European Urology 64:639-653, 2013
5. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al: Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 49:466-5; discussion 475-7, 2006
6. Mostafid H, Bryan RT, Rees J: Diagnosis and treatment of non-muscle-invasive bladder cancer. Trends in Urology & Men's Health 6:23-27, 2015
7. Cookson MS, Herr HW, Zhang ZF, et al: The treated natural history of high risk superficial bladder cancer: 15-year outcome. Journal of Urology 158:62-7, 1997
8. Heney NM, Ahmed S, Flanagan MJ, et al: Superficial bladder cancer: progression and recurrence. Journal of Urology 130:1083-6, 1983
9. Kurth KH, Denis L, Bouffioux C, et al: Factors affecting recurrence and progression in superficial bladder tumours. European Journal of Cancer 31A:1840-6, 1995
10. Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, et al: Primary superficial bladder cancer risk groups according to progression, mortality and recurrence.[see comment]. Journal of Urology 164:680-4, 2000
11. Shelley MD, Court JB, Kynaston H, et al: Intravesical Bacillus Calmette-Guerin in Ta and T1 Bladder Cancer. Cochrane Database of Systematic Reviews:CD001986, 2000
12. Sylvester RJ, van der MA, Lamm DL: Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol 168:1964-70, 2002
13. Chang SS, Boorjian SA, Chou R, et al: Diagnosis and Treatment of Non-muscle Invasive Bladder Cancer: AUA/SUO Guideline, 2016
14. Perlis N, Zlotta AR, Beyene J, et al: Immediate post-transurethral resection of bladder tumor intravesical chemotherapy prevents non-muscle-invasive bladder cancer recurrences: an updated meta-analysis on 2548 patients and quality-of-evidence review. Eur Urol 64:421-30, 2013
15. van Rhijn BWG, Burger M: Bladder cancer: Low adherence to guidelines in non-muscle-invasive disease. Nat Rev Urol 13:570-571, 2016
16. Messing E, Tangen C, Lerner S, et al: PNFLBA-10 A PHASE III BLINDED STUDY OF IMMEDIATE POST-TURBT INSTILLATION OF GEMCITABINE VERSUS SALINE IN PATIENTS WITH NEWLY DIAGNOSED OR OCCASIONALLY RECURRING GRADE I/II NON-MUSCLE INVASIVE BLADDER CANCER: SWOG S0337. The Journal of Urology 197:e914-e915, 2017
17. Mitra AP, Datar RH, Cote RJ: Molecular Pathways in Invasive Bladder Cancer: New Insights Into Mechanisms, Progression, and Target Identification. J Clin Oncol 24:5552-5564, 2006
18. Wu X-R: Urothelial Tumorigenesis: A Tale of Divergent Pathways. Nature Reviews Cancer 5:713-725, 2005
19. Knowles MA: Novel therapeutic targets in bladder cancer: mutation and expression of FGF receptors.(fibroblast growth factor)(Report). Future Oncology 4:71(13), 2008
20. van Rhijn BWG, Zuiverloon TCM, Vis AN, et al: Molecular Grade (FGFR3/MIB-1) and EORTC Risk

Scores Are Predictive in Primary Non–Muscle-Invasive Bladder Cancer. European Urology 58:433-441, 2010

21. Kompier LC, Lurkin I, van der Aa MN, et al: FGFR3, HRAS, KRAS, NRAS and PIK3CA mutations in bladder cancer and their potential as biomarkers for surveillance and therapy. PLoS One 5:e13821, 2010

22. Williams SV, Hurst CD, Knowles MA: Oncogenic FGFR3 gene fusions in bladder cancer. Hum Mol Genet 22:795-803, 2013

23. Powles T, Eder JP, Fine GD, et al: MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 515:558-562, 2014

24. Pal SK, Rosenberg JE, Keam B, et al: Efficacy of BGJ398, a fibroblast growth factor receptor (FGFR) 1-3 inhibitor, in patients (pts) with previously treated advanced/metastatic urothelial carcinoma (mUC) with FGFR3 alterations. J Clin Oncol 34, 2016

25. Rodriguez-Vida A, Saggese M, Hughes S, et al: Complexity of FGFR signalling in metastatic urothelial cancer. Journal of Hematology & Oncology 8:119, 2015

26. Tabernero J, Bahleda R, Dienstmann R, et al: Phase I Dose-Escalation Study of JNJ-42756493, an Oral Pan–Fibroblast Growth Factor Receptor Inhibitor, in Patients With Advanced Solid Tumors. Journal of Clinical Oncology, 2015

27. Katoh M: FGFR inhibitors: Effects on cancer cells, tumor microenvironment and whole-body homeostasis (Review). International Journal of Molecular Medicine 38:3-15, 2016

28. Procopio MG, Laszlo C, Al Labban D, et al: Combined CSL and p53 downregulation promotes cancer-associated fibroblast activation. Nat Cell Biol 17:1193-204, 2015

29. Holdman XB, Welte T, Rajapakshe K, et al: Upregulation of EGFR signaling is correlated with tumor stroma remodeling and tumor recurrence in FGFR1-driven breast cancer. Breast Cancer Res 17:141, 2015

30. Liu L, Ye TH, Han YP, et al: Reductions in myeloid-derived suppressor cells and lung metastases using AZD4547 treatment of a metastatic murine breast tumor model. Cell Physiol Biochem 33:633-45, 2014

31. Incyte: INCB054828 Investigator Brochure, 2018

32. Biopharma P: PRN1371 Investigators Brochure, 2018

33. Necchi A, Pouessel D, Liebowitz-Amit R, et al: Interim results of fight-201, a phase 2, open-label, multicenter study of INCB054828 in patients (pts) with metastatic or surgically unresectable urothelial carcinoma (UC) harboring fibroblast growth factor (FGF)/FGF receptor (FGFR) genetic alterations (GA), European Society for Medical Oncology 2018 Congress Munich, Germany, 2018

APPENDIX A: 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 B: Serious Adverse Event Reporting Form

Please notify: Dr. Noah M. Hahn MD within 24 hours (Fax: 410-614-7287) email: nhahn4@jhmi.edu; amichal2@jhmi.edu
Incyte within 24 hours (fax: 866-981-2057, e-mail: SafetyReporting@Incyte.com)

<table>
<tr><td>Protocol Title:</td><td colspan="3">Phase 2 Window of Opportunity Study of Pemigatinib in Non-muscle Invasive Bladder Cancer Patients with Recurrent Low- or Intermediate-Risk Tumors</td></tr>
<tr><td>Protocol Number:
I-54828-17-01</td><td>Signature of PI:</td><td>Print PI Name:</td><td>Date:</td></tr>
<tr><td>Report Type:
(circle all that apply):

Initial
Follow-up
Final Follow-up
Death Addendum to:</td><td>Serious Criteria
(circle all that apply):

Death
Life-threatening
Hospitalization or Elongation of Existing Hospitalization
Persistent or Significant Disability
Congenital Anomaly
Other Important Medical Event
Cancer
Overdose</td><td>Hospital Admission Date:

Hospital Discharge Date:</td><td>Date Event Discovered:</td></tr>
<tr><td colspan="4">Section A: Subject Information</td></tr>
<tr><td colspan="2">Subject ID:</td><td>Subject Initials:</td><td>Subject Gender:
Male
Female</td></tr>
<tr><td colspan="4">Section B: Event Information</td></tr>
<tr><td rowspan="3">Event diagnosis or symptoms:</td><td>Date of First Dose :</td><td rowspan="3">Action taken with the study drug:
None Interrupted
Discontinued Delayed</td></tr>
<tr><td>Date of Last Dose prior to Event:</td></tr>
<tr><td>Number of Total Doses:</td></tr>
</table>

Event Onset Date:		Event End Date:
Relationship to (check appropriate box):	**Pemigatinib**	**Underlying Disease**
Unrelated		
Probably Unrelated		
Possible Related		
Probably Related		
Definitely Related		

Section C: Brief Description of the Event:

Section D: Relevant Medical History

Section E: Concomitant Drug (Not related to SAE)

Name of the Drug	Start Date	Stop Date	Route	Dose	Frequency

Section F: Comments

Additional Documents: Please specify