Open-label, single-arm, Phase II study, evaluating safety and efficacy of INCB054828 (Pemigatinib) as adjuvant therapy for molecularly-selected, high-risk patients with urothelial carcinoma who have received radical surgery. A European Association of Urology Research Foundation Phase II Clinical Trial

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Sponsor and Central Study-Management:	EAU Research Foundation Mr. E.N. van Kleffensstraat 5 NL 6842 CV Arnhem PO Box 30016 6803 AA Arnhem The Netherlands Tel: + 31 26 389 0677 Fax +31 26 389 0679 E-mail: researchfoundation@uroweb.org www.uroweb.org
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Acronym:	PEGASUS
Principal Investigator:	Andrea Necchi, MD IRCCS San Raffaele Hospital and Scientific Institute Via Olgettina 60, 20132 Milano, Italy; Telephone : +39 (02) 23902402 Fax : +39 (02) 76010185 Email : necchi.andrea@hsr.it
Protocol writing committee:	Andrea Necchi, Milano Wim P.J. Witjes, Arnhem

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List of Abbreviations and Relevant Definitions

AC	Adjuvant Chemotherapy
AE	Adverse Event: any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
ALT	Alanin-aminotransferase
AR	Adverse Reaction: all untoward and unintended responses to an investigational medicinal product related to any dose administered.
AST	Aspartate-aminotranferase
CI	Confidence Interval
CIS	Carcinoma In Situ
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSUR	Drug Safety Update Report
EAU (RF)	European Association of Urology (Research Foundation)

ECG	ElectroCardioGram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOT	End Of Treatment
EudraCT	European drug regulatory affairs Clinical Trials
FGF(R)	Fibroblast Grow Factor (Receptor)
FSH	Follicle Stimulating Hormone
GC	Combination of gemcitabine and cisplatin
GCP	ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 5, adopted by CPMP July 1996. European Directives 2001/20/EC and 2005/28/EC and the most recent "REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC".
GDPR	General Data Protection Regulation
gLOH	Genome-wide Loss Of Heterozygosity
HIV	Human Immunodeficiency Virus
HRT	Hormonal Replacement Therapy
IB	Investigators Drug Brochure
ICF	Informed Consent Form
IRB/IEC	Institutional Review Board / Institutional Ethics Committee
ICPIs	Immune Checkpoint Inhibitors
ITT	Intention To Treat
LDH	Lactate Dehydrogenase
MIBC	Muscle Invasive Bladder Cancer
MRI	Magnetic Resonance Imaging
MVAC	Combination of methotrexate, vinblastine, adriamycin, and cisplatin
NAC	Neo-adjuvant Chemotherapy
NYHA	New York Heart Association
OS	Overall Survival
PD-1	Programmed Death Ligand 1
PI	Principal Investigator
QD	Once Daily
RC	Radical Cystectomy
RFS	Relapse Free Survival

RNU	Radical Nephro Ureterectomy
SAE	Serious Adverse Event: A serious adverse event is any untoward medical occurrence that at any dose: results in death; is life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalization; results in persistent or significant disability or incapacity or is a congenital anomaly/birth defect.
SUSAR	Suspected Unexpected Serious Adverse Reaction: A serious adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. summary of product characteristics for an authorised product.
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
TMB	Tumor Mutational Burden
UC	Urothelial Carcinoma
ULN	Upper Limit of Normal
US	United States of America
WBC	White Blood Cells
WHO	World Health Organisation
WOCBP	Women Of Child Bearing Potential

Confidentiality Statement

1. STUDY SYNOPSIS

Study Title and number	Open-label, single-arm, Phase II study, evaluating safety and efficacy of INCB054828 (Pemigatinib) as adjuvant therapy for molecularly-selected, high-risk patients with urothelial carcinoma who have received radical surgery. A European Association of Urology Research Foundation Phase II Clinical Trial. EAU RF number: 2018-02.
Rationale	• Patients with invasive disease at radical resection of Urothelial Carcinoma (UC) are at high risk of relapse and may benefit from additional cisplatin-based chemotherapy. • Patients whose disease progresses on platinum-based chemotherapy or who are ineligible due to inadequate renal function or poor performance status have limited treatment options. In such patients treatments using new agents should be considered. • Patients who received neo-adjuvant platinum-based chemotherapy who have residual disease at radical resection of UC have a worse prognosis and should be considered with additional treatments using new agents. • Immune checkpoint inhibitors (ICPIs) have improved outcomes in some patients with platinum-resistant and/or -ineligible metastatic UC; however, benefit may be limited to patients with higher positive tumor and infiltrating immune cell staining for programmed death-ligand-1 (PD-1). • Fibroblast growth factor (FGF) / FGF receptor (FGFR) genetic alterations are implicated in the pathogenesis of UC, most commonly FGFR3 mutations(≈ 12%) and translocations (≈ 3-6%). FGFR3 genetic alterations are more common in patients with immune desert luminal cluster I subtype UC; these patients are expected to receive less benefit from ICPIs. • Pemigatinib is a selective, potent, oral inhibitor of FGFR1, 2, and 3, and has shown efficacy in tumors with various FGFR alterations.
Objectives	• The primary objective of this study is to evaluate 2-year relapse free survival rate of high-risk patients previously treated with cisplatin-based chemotherapy or ineligibility to receive cisplatin-based adjuvant chemotherapy. These patients will receive adjuvant Pemigatinib after radical surgery of their urothelial carcinoma. • Secondary objectives are to evaluate safety, tolerability and overall survival. • An explorative objective is to evaluate biomarkers of clinical benefit and prognostic biomarkers. These biomarkers will be evaluated at the time of radical surgery, on the residual post-chemotherapy tumor tissue, before the administration of the study drug.
Study Design & Intervention	This is an open-label, single-arm, phase 2 study. Patients will receive Pemigatinib at a once-daily (QD) dose of 13.5 mg on a continuous schedule. Treatment will be continued until 12 months, or until the evidence of disease relapse or onset of unacceptable toxicity. Hyperphosphatemia can be managed with diet modification, phosphate binders, or dose modification. Since mineralization of the cornea and retinal changes consisting of serous retinal detachment have been reported in humans, ophthalmic exams are done at baseline and once every 12 weeks during treatment and should include a visual acuity test, slit-lamp examination and fundoscopy. Additional assessments (eg. Orbital CT) should be done if clinically relevant retinal findings are observed on ophthalmologic exams and

	in participants with reported visual AEs or change in visual acuity, if the events or changes are suspected to be of retinal origin.
Study Population	A total of 56 patients with pT3-4 and/or pN1-3 stage UC at radical cystectomy or radical nephroureterectomy with documented FGF/FGFR alterations. **Key Inclusion Criteria:** • Men and woman, aged 18 years or older with histological evidence of pT3-4 and/or pN1-3 UC of the urinary bladder or upper urinary tract after radical cystectomy / radical nephroureterectomy. Patients with mixed histologies are required to have a dominant (i.e. at least 50%) urothelial cell carcinoma pattern. • Previous administration of at least 2-3 cycles of neoadjuvant cisplatin-based chemotherapy OR, if neoadjuvant chemotherapy was not administered, ineligibility to receive cisplatin-based adjuvant chemotherapy based on Galsky's criteria, that include at least one of the following: (1) WHO performance status ≥ 2 and/or (2) creatinine-clearance < 60 ml/min and/or (3) CTCAE Gr ≥ 2 hearing loss and/or (4) CTCAE Gr ≥ 2 neuropathy. • Evidence of FGFR3 alterations (mutations or gene fusions as specified in protocol) as assessed by a centralized Foundation Medicine test (Foundation One CDx assay). • Recovered with no evidence of disease confirmed by radiological images, prior to start of adjuvant therapy within 13 weeks after radical surgery. • Willingness to avoid pregnancy or fathering children. • Written informed consent for screening of tumor tissue and if evidence of FGFR alterations written informed consent for the start of the complete study. **Key Exclusion Criteria:** • Any previous receipt of a selective FGFR inhibitor. • Presence of primary CIS only. • Presence of another malignancy in the 3 years before enrolment except for basal cell carcinoma or squamous cell carcinoma of the skin, cis of cervix, localised prostate cancer in active surveillance or other non invasive or other indolent malignancy that has undergone potentially curative therapy. • Presence of pregnancy or lactation or not willing to avoid pregnancy or fathering children. • Distant metastases (M1 disease) or presence of radiological evidence of disease at baseline. • Treatment with other investigational drugs, receipt of anticancer medications (except for neoadjuvant cisplatin-based chemotherapy, see second inclusion criterion) or radiotherapy of the bladder or upper urinary tract prior to - or after radical surgery. • Use of any potent CYP3A4 inhibitors or inducers within 14 days or 5 half lives (whichever is longer) before the first dose of study treatment. • Abnormal laboratory parameters: o Total bilirubin ≥ 1.5 × upper limit of normal (ULN; ≥ 2.5 × ULN if Gilbert syndrome). o AST and/or ALT > 2.5 × ULN o Creatinine clearance ≤ 30 mL/min based on Cockroft-Gault. o Serum phosphate > institutional ULN.

	○ Serum calcium outside of the institutional normal range or serum albumin-corrected calcium outside of the institutional normal range when serum albumin is outside of the institutional normal range. • History of human immunodeficiency virus infection or active tuberculosis infection. • Diagnosis of immunodeficiency or receiving chronic systemic steroid therapy (exceeding > 10 mg daily of prednison equivalent; inhalation steroids are permitted). • Evidence of hepatitis B virus or hepatitis C virus active infection or risk of reactivation. • Severe hepatic impairment. • Known prior severe hypersensitivity to investigational product or its excipients. • History of clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months of enrolment, New York Heart Association Class III or IV (Appendix 4). • Current evidence of corneal disorder/keratopathy (including but not limited to bullous/band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjunctivitis, etc) or retinal disorder (including but not limited to, central serous retinopathy, macular/retinal degeneration, diabetic retinopathy, retinal detachment, etc) as confirmed by ophthalmologic examination. • Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending the required study visits.
Main study Endpoints	• Primary endpoint: 2-year relapse free survival rate. • Secondary endpoints: Overall survival and incidence and severity of side effects, biomarkers evaluation. • Safety aspects: changes in laboratory values.
Nature and extent of the burden and risks associated with participation and risk-benefit	This is a phase II study with a drug that has indicated promising effects for relapse free survival in this high-risk group of patients. On the other hand, there are side effects that should be managed with dose reduction or stop; frequent laboratory checks or other supportive measures in consultation with a medical oncologist. Further, at relapse or progression, subjects will be asked to sign a consent to allow a biopsy of the relapse or metastases and tumor tissue to be sent to the sponsor's central laboratory (Foundation Medicine) for genetic sequencing. Based on the current available information of Pemigatinib, the risks related to the expected treatment outcome, quality and quantity of side effects of the study medication can be considered as acceptable.
Timing	The study includes a 2-year recruitment phase, followed by a 1-year treatment and subsequent follow-up phase. • Protocol ready: June 2019 • Start EC submission procedure: September 2019 • Start Initiation of the centers: April 2020 • Last patient follow up: April 2024 • Study Closure: 2024.

2. INTRODUCTION AND RATIONALE

About 1.7 million new cases of cancer have been diagnosed in 2018 in the US with urothelial carcinoma located in the urinary bladder being the 4th most common cancer in males [1]. Amongst them, 20% are non-metastatic muscle invasive bladder cancers (stage pT2-4N0M0) for which radical cystectomy can provide optimal local control. Most urothelial tumors originate in the urinary bladder (90%) or upper urinary tract (~10% in renal pelvis/ureter). Invasive tumors in the upper urinary tract are typically managed with radical resection alone (radical nephroureterectomy (RNU) or radical ureterectomy (RU)). Standard of care treatment for muscle invasive bladder cancer (MIBC) is cisplatin based neo-adjuvant chemotherapy followed by radical cystectomy (RC)[2]. However, surgery often remains insufficient for cure and up to 30% of the patients will eventually develop recurrence, either local pelvic or distant metastases within 2 years [3]. Therefore, effective systemic treatment must be initiated to treat metastases that are not visible at the time of surgery. Cisplatin-based regimens are effective and, in a neoadjuvant setting, they improve the absolute overall survival by 5% and the specific survival by 9% [4]. Various combinations have been assessed and the most efficient so far are either the combination of methotrexate, vinblastine, adriamycin, and cisplatin (MVAC), or the less toxic combination of gemcitabine and cisplatin (GC). Both are considered equally effective. In a meta-analysis of 17 studies, the average complete response rate on bladder specimen (pT0) following neoadjuvant cisplatin (NAC) was between 10 and 46% [5-8] Complete response rate after NAC can be used as a surrogate marker of specific survival with a 5 year specific survival rate of 80% [9]. However despite NAC, 19% of patients are found to have lymph node- positive disease on postoperative pathological analysis [9,10]. The presence of lymph node metastatic disease is a well known independent prognostic factor of overall survival in patients with MIBC [3,9]. Multi-institutional case series report a 70% 5-year survival rate in patients with no lymph node disease compared with < 40% in those positive for lymph node metastases [3]. In a study including 150 patients who had node-positive disease despite RC and NAC, Kassouf et al reported a significant recurrence-free survival advantage (HR, 0.29; 95% CI, 0.10-0.81, p=0.02) with a trend towards significance in prolonged overall survival (HR, 044; 95% CI, 0.18-1.11, p=0.08) in 37 patients treated with Adjuvant Chemotherapy (AC) [11]. A possible implication of such data is that patients with positive nodes on histopathology might benefit from adjuvant, second-line chemotherapy. A recent meta-analysis by Leow et al. and a study by Millikan do concur with this [12, 13]. However, there is little evidence on how bladder cancer patients with positive lymph nodes after radical cystectomy and NAC should be managed and currently, no treatment is approved as second-line chemotherapy for a progressive disease despite RC and NAC. Patients with invasive disease at radical resection of Urothelial Carcinoma (UC) are at high risk of recurrence and may benefit from additional cisplatin-based chemotherapy [3,13]. In current daily practice, patients who have invasive residual disease at radical resection and have not received neo-adjuvant cisplatin may go on to receive adjuvant cisplatin based chemotherapy [2] which, despite not having shown definitive clinical benefit, is used in 22% of patients undergoing radical cystectomy in the US [12.] . Up to 60% of patients who undergo radical cystectomy are not candidates for adjuvant cisplatin based chemotherapy because they received neoadjuvant chemotherapy or they are cisplatin ineligible or they experienced post-operative problems such as decreased performance status or deterioration of renal function [14] This population has a significant unmet need as there are no treatment options available to help reduce the risk of

recurrence and improve survival. The checkpoint inhibition approach is attractive in this setting considering the lack of effective, available treatment options and the positive preliminary results with PD-1/PD-L1 blockade in advanced bladder cancer. [15]. However benefit may be limited to patients with higher positive tumor and infiltrating immune cell staining for programmed death-1 ligand-1 (PD-1). Multiple clinical trials are currently exploring the efficacy of immune checkpoint inhibitors in this setting [16]

Alterations in fibroblast growth factor receptor (*FGFR*) gene (eg, mutations or fusions) are common; in stage ≥ T2 bladder cancer, 5%-20% of patients have point mutations in *FGFR3*, and 40% have upregulated expression of FGFR3 protein. Alterations in *FGFR* type 3 (*FGFR3*) are particularly frequent in patients with immunologically "cold" luminal I subtype UC [17,18]. Aberrant signaling through FGFR resulting from gene amplification or mutation, chromosomal translocation, and ligand-dependent activation of the receptors has been demonstrated in multiple types of human cancers, including urothelial cancers. FGFR signaling contributes to the development of malignancies by promoting tumor cell proliferation, survival, migration, and angiogenesis [19].

Pemigatinib is an inhibitor of the FGFR family of receptor tyrosine kinases that is proposed for the treatment of advanced malignancies [20].

Fibroblast Growth Factor Receptor Inhibitor in Oncology and Hematology Trial (fight)-201 is a phase 2, open-label, multicenter study to evaluate the efficacy and safety of Pemigatinib in patients with metastatic or surgically unresectable UC harboring *FGFR3* mutations and translocations (cohort A) and other *FGF/FGFR* genetic alterations (cohort B) (NCT02872714). Interim results of the (fight)-201 trial have been recently presented (Necchi A; et al. ESMO 2018 annual meeting). Patients with *FGFR3* mutations/fusions (cohort A) or other *FGF/FGFR* genetic alterations (cohort B) were enrolled and received Pemigatinib 13.5 mg orally once daily (QD) on a 21-day cycle (2 weeks on/1 week off) until disease progression or unacceptable toxicity. At data cutoff (July 6, 2018), 108 patients were enrolled. The efficacy-evaluable population consisted of 103 patients, and the safety-evaluable population consisted of 108 patients (5 patients did not have *FGF/FGFR* alterations confirmed through the sponsor's central laboratory). Among 103 patients, 61 were enrolled in cohort A and 42 in cohort B. Of 61 patients in cohort A, 49 discontinued treatment and 12 had treatment ongoing.
The objective response rate (ORR) in cohort A was 21% (95% CI, 12%-34%) and included 13 confirmed partial responses (PRs). A total of 22 patients had stable disease (SD), including 1 unconfirmed PR in an ongoing patient who had not yet had a confirmatory scan. In cohort B, 1 patient had a confirmed PR; 1 patient with *FGF10* amplification had an unconfirmed PR. Median duration of response (DOR) in cohort A was 6 months, and median PFS was 4 months (95% CI, 3.0-5.6 months). The 3-month PFS in cohort A was 63% (95% CI, 49.4%-73.9%).
Most common treatment-related adverse events (TRAE) included hyperphosphatemia, diarrhea, alopecia, constipation, and stomatitis. As a more intense treatment regimen may increase the efficacy of Pemigatinib, the protocol has been amended to enroll patients with *FGFR3* mutations/fusions on a continuous dosing schedule, with the starting dose of 13.5 mg.

EAU RF is proposing to study Pemigatinib for the treatment of high risk patients after radical

surgery with fibroblast growth factor (FGF)/FGFR genetic alterations [21].

3. STUDY OBJECTIVES & ENDPOINTS

The primary objective of this study is to evaluate the 2-year relapse-free survival rate (RFS) of high-risk patients previously treated with cisplatin-based chemotherapy or ineligibility to receive adjuvant cisplatin-based chemotherapy. These patients will receive adjuvant Pemigatinib after radical surgery of their urothelial carcinoma.
Secondary objectives are to evaluate safety, tolerability and overall survival.
An explorative objective is to evaluate biomarkers of clinical benefit and prognostic biomarkers. These biomarkers will be evaluated at the time of radical surgery, on the tumor tissue, before the administration of the study drug.

3.1 Rationale for 2-year relapse-free Survival Endpoint

Improvement of RFS may be regarded as an optimal endpoint for adjuvant therapy trials, given the availability of multiple lines of new therapies in the advanced stages that may affect RFS outcomes in these patients.

3.2 Biomarker Research

The aim of biomarker research is to evaluate biomarkers of clinical benefit and prognostic biomarkers in patients receiving adjuvant treatment with pan-FGFR inhibitor Pemigatinib. These biomarkers will be evaluated at the time of radical surgery, on the tumor tissue, before the administration of the study drug. The biomarkes will be evaluated on paraffin-embedded tumor tissue from radical surgery, and will rely on next-generation sequencing technology. Tumor samples will be centralized to Foundation Medicine for molecular evaluation, Address: Central Laboratory Foundation Medicine GmbH, Nonnenwald 2, 82377 Penzberg, Germany.
In case of neo-adjuvant chemotherapy, the proposed setting will be ideal to access tumor tissue that can be representative of a chemo-resistant disease assessed immediately before starting the study drug.
Tumor specimens will be used to analyze biomarkers. Comprehensive genomic profiling (CGP) will be performed with a hybrid capture-based next-generation sequencing assay (FoundationONE-CDx).
CGP will be performed on hybridization-captured, adaptor ligation-based libraries to a median coverage depth of 743× for 395 cancer-related genes plus select introns from 31 genes frequently rearranged in cancer. Results will be analyzed for base substitutions, short insertions/deletions (indels), rearrangements, and copy number alterations (amplification and homozygous deletion). Custom filtering will be applied to remove benign germline events as described. Reportable Genomic Alterations will be called as known if the specific variant is present in the Catologue Of Somatic Mutations In Cancer database, if the variant has been characterized as pathogenic, or if the variant has likely functional status (disruptive alterations in tumor suppressor genes); all other variants will be classified as variants of unknown significance.

To determine microsatellite status, 114 intronic homopolymer repeat loci on the FoundationOne-CDx panel will be analyzed for length variability and compiled into an overall Micro Satellelite Instability score via principal components analysis. Tumor mutational burden (TMB) will be calculated as the number of somatic base substitutions or indels per megabase (Mb) of the coding region target territory of the test (1.1 Mb) after filtering to remove known somatic and deleterious mutations and extrapolating that value to the exome or genome as a whole. TMB will be categorized as low (<6 mutation [mut]/Mb), intermediate (6–20 mut/Mb), or high (≥20 mut/Mb). Germline and somatic status for mutations will be determined without matched normal tissue as described. Percent genome-wide loss of heterozygosity (gLOH) will be used as a marker of homologous recombination deficiency and calculated as described and a gLOH score of ≥14% was defined as gLOH-High.

4. STUDY DESIGN and PROCEDURES

This is an open-label, single-arm, phase 2 study. Patients will receive Pemigatinib at a once-daily (QD) starting dose of 13.5 mg on a continuous dose regimen. Treatment will be continued until 12 months, or until the evidence of disease relapse or onset of unacceptable toxicity. The study includes a 2-year recruitment phase, followed by a 1-year treatment and subsequent follow-up phase.

A radiological assessment of disease status will be performed at screening (after radical surgery). Subsequently, disease status will be assessed according to daily urological practice until the start of new anticancer therapy, disease relapse, death or end of study. Follow-up imaging scans are usually based on the recurrence possibility (timing, probability, site, and potential treatment) and functional aspects. In spite of low level of evidence, a suggested oncologic follow-up schedule includes CT scans every 4 months during the first year and every 6 months until the third year [22]. During the investigators meeting at the occasion of the annual EAU meeting in Barcelona, on March 17th, 2019, the investigators proposed and agreed to use a 12 weeks interval (+/- 1 week) for imaging procedures in this high risk group of patients. Relapse free survival will be assessed starting from date of first dose and then every 12 weeks until disease relapse or death. Final assessment of the 2-year relapse free survival rate will be done at 2 years. Overall survival will be assessed from the first dose until death (every 12 weeks from disease relapse to death or termination of the study). (See Appendix 6)

4.1 Study Periods

4.1.1 Molecular Pre-screening:

Prescreening will be performed on tumor samples from the RC/RNU specimens. Potential subjects will give their consent for testing of their tumor tissue, whereafter they can be screened/enrolled based on local genomic sequencing outcome at the sponsor's central laboratory. The timing of pre-screening consent can be prior to,- or after RC/RNU.

4.1.2 Screening and Treatment Period:

After signing the informed consent form for the complete study, the screening period will then take place in the period after surgery until week 13 after surgery. At Day 1, prior to the start of treatment, results from screening visit evaluations should be reviewed to determine whether the subject continues to meet the eligibility requirements. Subsequent visits during the treatment phase will take place at Day 8, Day 15 and Day 21 and subsequently at 3 week intervals. Timing of subsequent visits can be prolonged to max. 9 week intervals if no problems exist during the first 12 weeks of therapy. Dates for subsequent study visits will be determined based on Day 1, the start of treatment, and should occur within 3 days (±) of the scheduled date unless delayed for safety reasons.

Subjects will self-administer study drug using an oral QD regimen in a continuous dosing schedule. Each dose of Pemigatinib should be taken first thing in the morning upon waking or after a 2-hour fast; subjects should then fast for an additional 1 hour after taking study drug. The starting dose is 13.5 mg Pemigatinib. Study treatment will continue until 12 months, or until the evidence of disease relapse or onset of unacceptable toxicity.

If a dose is missed by more than 4 hours, the subject should skip the dose and take the next scheduled dose at the usual time. Any missed doses reported by the subject should be recorded in the subject's source documents.

4.1.3 End of Treatment

When the subject permanently discontinues study drug, the end of treatment (EOT) visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The subject should be encouraged to return for the follow-up visit.

4.1.4 Safety Follow-up:

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 to 35 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported until at least 30 days after the last dose of study drug; or until toxicities resolve, return to baseline, or are deemed irreversible; death; or initiation of a new anticancer treatment, whichever occurs first. Reasonable efforts should be made to have the subject return for the follow-up visit and report any AEs that may occur during this period.
If a subject is scheduled to begin a new anticancer therapy before the end of the 30-day safety follow-up period, the safety follow-up visit should be performed before new anticancer therapy is started. Once new anticancer therapy has been initiated, the subject will move into the survival follow-up period.

4.1.5 Disease Status Follow-up:

Subjects who discontinue study treatment for a reason other than disease relapse or progression will move into the disease status follow-up period and should be assessed every 12 weeks by radiologic

imaging to monitor disease status. Every effort should be made to collect information regarding disease status until:

- The start of new antineoplastic therapy.
- Disease relapse or progression.
- Death.
- The end of the study.

At disease relapse or progression, a biopsy and subsequent genomic sequencing at the sponsors central laboratory is recommended after written informed consent of the patient.

4.1.6 Survival Follow-up:

Once a subject has confirmed disease relapse or progression, or starts a new anticancer therapy, the subject moves into the survival follow-up period and should be contacted by telephone, email, or visit at least every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. The investigator or qualified representative can also use continuing subject records to report data on subsequent treatment regimens,and overall survival in the eCRF.

4.1.7 End of Study:

The end of the study may be designated as the timepoint when all subjects have discontinued the study after 2 years of follow-up or when the sponsor terminates the study.

4.2 Pre-Treatment Tests

4.2.1 Informed Consent Forms and Prescreening Molecular Tests

Subjects must have confirmation of an FGF/FGFR alteration to be considered for the study. Therefore, subjects will be asked to sign a pre-screening consent to allow tumor tissue to be sent to the sponsor's central laboratory (Foundation Medicine) for genetic sequencing. The timing of pre-screening consent can be prior to,- or after RC/RNU. The process of genetic sequencing will take approximately 14 days. Once genetic sequencing has confirmed an FGF/FGFR alteration, a valid informed consent for enrollment in the complete study must be obtained from the study subject before conducting any study-specific procedures.
The Investigator must obtain documented consent from each potential participant prior to participating in a clinical trial. Consent must be documented by the participant’s dated signature or by the participant’s legally acceptable representative’s dated signature on a consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent forms should be given to the participant after signature.
Similarly at relapse or progression, subjects will be asked to sign a consent to allow a biopsy and subsequent tumor tissue to be sent to the sponsor's central laboratory (Foundation Medicine) for genetic sequencing.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/IEC’s approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant’s willingness to continue participation in the trial. The communication of this

information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature. The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements. The informed consent process for each subject must be documented in writing within the subject source documentation.

4.2.2 Inclusion and Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

4.2.3 Demographic Data and Medical History

Demographic data such as sex and age will be assessed and recorded by the investigator or a qualified designee. A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the participant has been enrolled in this study will be recorded separately and not listed as medical history.

4.2.4 Prior Medications Review

The investigator or qualified designee will review prior medication use, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant has been enrolled in this study will be recorded separately and not listed as a prior medication.

4.2.5 Disease Details and Treatments

The investigator or qualified designee will obtain prior and current details regarding disease status and all prior cancer treatments including systemic treatments, radiation and surgeries.

4.2.6 Unique Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures. Each participant will be assigned only one screening number.

4.2.7 Other Pre-treatment Examinations

The investigator or qualified designee will obtain results of molecular pre-screening, physical examination (length, weight, pulse, blood pressure), WHO performance status, New York Heart Association (NYHA) status, ECG, laboratory and radiological tests as described in the flowchart (Appendix 6). A comprehensive eye-examination should be performed by a qualified ophthalmologist at screening, once every 12 weeks (± 7 days), at EOT if abnormalities were shown at the previous, latest examination, and as clinically indicated. The eye-examination should include a visual acuity test, slit-lamp examination, and funduscopy with digital imaging. Additional assessments (eg, Orbital CT) should be done if clinically relevant retinal findings are observed on ophthalmologic exams and in participants with reported visual AEs or change in visual acuity, if the events or changes are suspected to be of retinal origin. Every effort should be made to ensure that all subsequent examinations are performed by the same ophthalmologist.

4.2.8 Registration Procedure

If the patient satisfies all selection criteria, registration of enrollment of a patient in the complete study will be done by the investigator or a qualified representative in the eCRF. For registration the following information will be needed:

- Institutions name
- Name of investigator
- Date of informed consent of the complete study

At registration, a number will be allocated to the patient (patient study inclusion number). This number identifies the patient and must be reported on all eCRF's and other relevant documents. This patient sequential identification number identifies the patient for the Sponsor. The local investigator and his personnel maintain a list which identifies the patients' sequential identification number with the patients source data. This list is safeguarded by the local investigator and his personnel.

4.3 Study Treatment

The investigator 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.

4.3.1 Supply, Packaging, and Labeling

Study drug will be supplied as 2 mg and 4.5 mg tablets. Pemigatinib tablets will be packaged in high-density polyethylene bottles. No preparation is required.
All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country.

4.3.2 Storage

Pemigatinib drug product should be stored as detailed on the investigational product labeling.

4.3.3 Instruction to Subjects for Handling Study Drug (Pemigatinib)

The subject must be instructed in the handling of study drug as follows:

- To store the study drug at room temperature.
- To only remove from the study drug bottle the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- To make every effort to take doses on schedule.
- To report any missed doses.
- To take study drug immediately upon rising or after a 2-hour fast with a glass of water; the subject should refrain from eating 1 hour after taking study drug.
- If the subject vomits after taking study drug, the subject should not take another dose.
- To keep study drug in a safe place and out of reach of children.
- To bring all used and unused study drug bottles to the site at each visit.

- If a dose of Pemigatinib is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be administered at the usual time.

4.3.4 Treatment Compliance

Compliance with all study-related treatments should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with Pemigatinib will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). Subjects will be instructed to bring all study drugs with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

4.3.5 Adverse Events

The most common treatment-emergent adverse events in more than 20% of the patients receiving continuous dose Pemigatinib monotherapy for advanced malignancies were hyperphosphataemia (70%), stomatitis (48%), diarrhea (39%), hair loss (38%), dry mouth (37%), dysgeusia (36%), fatigue (29%), constipation (33%), decreased appetite (27%), nausea (26%), dry eyes (22%), anaemia (21%), asthenia (21%) and palmar-plantar erythrodysaesthesia syndrome (21%) (21). Hyperphosphatemia can lead to symptoms such as muscle cramps and contractions, numbness or tingling in the mouth. A hyperphosphatemia can be managed with diet modification, phosphate binding drugs or dose modification.

Other common adverse events observed in 10-20% of the patients were abdominal pain, vomiting, backpain, epistaxis, dry skin, increased blood creatinine level, joint pain, decrease of weight, oedema, nail problems, hypercalcaemia, urinary tract infection, pain in extremity and low sodium blood levels (21).

Less common adverse events observed in less than 10% of the patients are pyrexia, dehydration and hypophosphatemia.

Ophthalmic exams are done at baseline and at least once every 12 weeks during treatment. Additional assessments will be done in participants with reported changes in vision.

4.3.6 Treatment Interruptions and Adjustments

Dose interruptions and modifications may occur for individual study subjects. The occurrence of toxicities (related or unrelated to study drug) will guide decisions for treatment interruptions and discontinuation for individual subjects. Treatment with Pemigatinib may be interrupted up to 14 days to allow for resolution of toxicity. Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. The treating investigator should contact a representative of the sponsor to discuss the case of any subject whose treatment has been delayed for more than 14 days before restarting treatment with Pemigatinib.
Because subjects may enter the study with extensive pretreatment toxicities, these dose reduction rules are provided as guidelines. Individual decisions regarding dose reduction should be made

using clinical judgment and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the study drug and the subject's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules. In case of occurrence of toxicities the investigator should, if needed, treat/follow up the patient until the toxicity has been resolved.
In cases where study drug should be restarted at a next lower dose, the new dose can be 9 mg on a continuous schedule, and then 6.5 mg, since these were dose cohorts in the INCB 54828-101 study. However, individual decisions regarding dose reduction and new dose level should be made using clinical judgment, utilizing the tablet doses available (4.5 mg and 2 mg) and in consultation with the representative of the study sponsor.

Table. Guidelines for Interruption and Restarting of study drug:

ADVERSE EVENT	ACTION TAKEN
Chemistry	
• AST and/or ALT > 5.0 ULN Note: in subjects with bone metastases-related elevation at baseline, contact the study sponsor to discuss clinical management and possible dose-reductions.	**Step 1**: interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 except by approval of the medical monitor **Step 2**: If assessed as related to study drug, restart study drug at next lower dose; monitor as clinically indicated.
Other toxicities	
Any Grade 1 or Grade 2 toxicity	Continue study drug treatment and treat the toxicity; monitor as clinically indicated
Any Grade 3 toxicity, if clinically significant and not manageable by supportive care	**Step 1**: interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 except by approval of the medical monitor **Step 2**: If assessed as related to study drug, restart study drug at next lower dose; monitor as clinically indicated.
Any recurrent Grade 3 toxicity after 2 dose reductions	Discontinue study drug administration.
Any Grade 4 toxicity	Discontinue study drug administration.

4.3.7 Management of Hyperphosphatemia and Serous Retinal Detachment

Table: Recommended Approach for Hyperphosphatemia management:

Serum Phosphate Level	Supportive Care	Guidance for Interruption/Discontinuation of INCB054828	Guidance for Restarting INCB054828
> 5.5 mg/dL and ≤ 7 mg/dL	Initiate a low-phosphate diet.	No action.	Not applicable.
> 7 mg/dL and ≤ 10 mg/dL	Initiate/continue a low-phosphate diet and initiate phosphate-binding therapy once serum phosphate level is > 7 mg/dL. Monitor serum phosphate at least twice a week and adjust the dose of binders as needed; continue to monitor serum phosphate at least twice a week until return to normal range.	If serum phosphate level continues to be > 7 mg/dL and ≤ 10 mg/dL with concomitant phosphate-binding therapy for 2 weeks, or if there is recurrence of serum phosphate level in this range, *interrupt* INCB054828 for up to 2 weeks (not including the planned dose interruption per treatment cycle).	Restart at the same dose when serum phosphate is < 7 mg/dL. If serum phosphate level recurs at > 7 mg/dL, restart INCB054828 with dose reduction.
> 10 mg/dL	Continue to maintain a low-phosphate diet, adjust phosphate-binding therapy, and start/continue phosphaturic agent. Continue to monitor serum phosphate at least twice a week until return to normal range.	If serum phosphate level is > 10 mg/dL for 1 week following phosphate-binding therapy and low phosphate diet, *interrupt* INCB054828. If there is recurrence of serum phosphate level in this range following 2 dose reductions, *permanently discontinue* INCB054828.	Restart INCB054828 at reduced dose with phosphate binders when serum phosphate is < 7 mg/dL.

Table: Recommended Approach for Serous Retinal Detachment*

RETINAL DETACHMENT	ACTION TAKEN
Mild and moderate	Monitor with ophthalmology examination
Mild and moderate with Worsening Vision	Interrupt study drug administration until the toxicity has resolved or vision improved
Worsening	Interrupt study drug administration until the toxicity has resolved to mild/moderate
Severe (Grade 3)	Interrupt study drug administration until the toxicity has resolved to mild/moderate

*participants should be monitored for signs and symptoms of serous retinal detachment, and the retina should be assessed with optical coherence tomography

4.3.8 Criteria for permanent discontinuation of study drug

The occurrence of unacceptable toxicity not caused by the underlying malignancy will be presumed to be related to study drug treatment and will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to be not in the subject's best interest.
- An AE requiring more than 2 dose reductions, if below the minimal biologically active dose of

Pemigatinib.

- Persistent AE requiring a interruption of therapy for more than 21 days unless a greater period of interruption has been approved by the sponsor.
- Increase in QT/QTc to > 500 milliseconds or to > 60 milliseconds over baseline.

4.4 During Treatment- & Follow-Up Procedures

4.4.1 Concomitant Medication

Concomitant medication has to be documented during the treatment phase. In case of existing possible treatment related adverse events after the treatment phase concomitant medication documentation has to be continued. During the study, other treatments or the administration of other drugs for the treatment of MIBC are not permitted. Any other non-experimental drug(s) in treatment for other indications are permitted if they are not prohibited (as indicated below), provided they are recorded in the eCRF.

Restricted medications:

The use of mild or moderate CYP3A4 inhibitors or inducers should involve careful monitoring. The pH level of stomach acid impacts the absorption of Pemigatinib. As a result, limited use of proton pump inhibitors or antacids while on study is recommended. Use of calcium-based phosphate-binding medications while on study is cautioned due to a concern for soft tissue mineralization.
Close clinical surveillance is recommended when pemigatinib is administered with medicinal products containing P-gp or OCT2 / MATE1 substrates.

Prohibited medications:

The following medications and measures are prohibited:

- The concomitant administration of potent CYP3A4 inhibitors and inducers (Appendix 5) is prohibited. Based on the low overall bioavailability of topical ketoconazole, there are no restrictions in its use.
- Any concomitant use of a selective FGFR inhibitor is prohibited.
- Investigational study drug for any indication is prohibited.
- Use of any anticancer medications other than the study medication from 21 days before Day 1 is prohibited.

4.4.2 Other During Treatment Examinations

The investigator or qualified designee will obtain results of WHO performance status, ECG, opthalmological-, laboratory- and radiological tests as described in the flowchart (Appendix 6).

4.4.3 Relapse or Progression

All types of relapse will be included i.e. local, regional and distant metastasis as well as second primary tumor of the upper urinary tract. In addition, all deaths occurring without prior documentation of tumor relapse will be considered as an event. Any new primary cancer will not be considered as relapse and should be reported as SAE. All relapses must be documented by radiological evidence or biopsy, as determined by the investigator. Suspicion of relapse based on physical examination findings or laboratory signs must be confirmed by radiological examination

and/or biopsy. Equivocal findings on standard radiological imaging should be confirmed by repeated examinations or cytology/histology or other imaging techniques. The date of relapse or progression as indicated by the date of radiology or biopsy as confirmed by the investigator, will be used as the timepoint of relapse or progression. At disease relapse or progression, a biopsy and subsequent genomic sequencing at the sponsors central laboratory is recommended after written informed consent of the patient.

4.4.4 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

4.4.5 Adverse Events

The investigator or qualified designee will report all adverse events and serious adverse events as indicated in chapter 6.

4.5 Pregnancy

Patients or partners of patients who become pregnant during the study treatment phase must not receive additional doses of study treatment but may continue other study procedures at the discretion of the investigator.
The investigator, or his/her designee, will collect pregnancy information on any patient or partner of the patient who becomes pregnant while participating in this study i.e. from signature of informed consent till 3 months after the last study treatment.The investigator, or his/her designee, will record pregnancy information on the Pregnancy Report Form and submit it to the Sponsor within 24 hours of learning of a patient's or partner of patient's pregnancy. The pregnancy will be followed to determine the outcome. At the end of the pregnancy, whether that be full-term or prematurely, information on the status of the mother and child will be forwarded to the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.
While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded and followed as an AE or a SAE, as described in Section 6.1 and 6.2.
A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 6.2. Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered reasonably related in time to the investigational product by the investigator, will be reported to the Sponsor as described in Section 6.3. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

4.6 Premature Termination of the Study

For reasonable cause, the Sponsor, may terminate this study provided a written notice is submitted at a reasonable time in advance of intended termination.

5. PATIENT SELECTION & WITHDRAWAL CRITERIA

5.1 Study Population

A total of 56 patients with FGFR alterations as assessed by a centralized Foundation Medicine test (Foundation One) will be eligible to start Pemigatinib after providing their informed consent if they meet all of the following inclusion criteria.

5.2 Inclusion Criteria

1. Men and woman, aged 18 years or older with histological evidence of pT3-4 and/or pN1-3 urothelial cancer (UC) of the urinary bladder or upper urinary tract after radical cystectomy / radical nephroureterectomy. Patients with mixed histologies are required to have a dominant (i.e. at least 50%) urothelial cell carcinoma pattern.
2. Previous administration of at least 2-3 cycles of neoadjuvant cisplatin-based chemotherapy OR, if neoadjuvant chemotherapy was not administered, ineligibility to receive cisplatin-based adjuvant chemotherapy based on Galsky's criteria, that include at least one of the following: (1) WHO performance status ≥ 2 and/or (2) creatinine-clearance < 60 ml/min and/or (3) CTCAE Gr ≥ 2 hearing loss and/or (4) CTCAE Gr ≥ 2 neuropathy [23].
3. Evidence of FGFR3 alterations (mutations or gene fusions as specified in protocol) as assessed by a centralized Foundation Medicine test (Foundation One CDx assay).
   A list of the allowed FGFR alterations is provided below.

GENE	ALTERATION
FGFR3	R248C
FGFR3	S249C
FGFR3	G370C
FGFR3	S371C
FGFR3	Y373C
FGFR3	G380R
FGFR3	G380E
FGFR3	A391E
FGFR3	R399C
FGFR3	S433C
FGFR3	D641N
FGFR3	K650M
FGFR3	K650E
FGFR3	K650Q
FGFR3	K650T
FGFR3	K650N
FGFR3	Novel FGFR3 fusion (with partner specified)
FGFR3	FGFR3-BAIAP2L1
FGFR3	FGFR3-IGH
FGFR3	FGFR3-TACC3
FGFR3	FGFR3-WHSC1

4. Recovered with no evidence of disease confirmed by radiological images, prior to start of adjuvant therapy within 13 weeks after radical surgery.
5. WHO performance status of 0, 1 or 2.

6. Willingness to avoid pregnancy or fathering children. If the patient is male, he must use a condom during sexual intercourse during the treatment period and 240 days thereafter (120 days to eliminate study treatment and 120 days spermatogenesis cycle) **plus** partner use of a contraceptive method with a failure rate of <1% per year (See Appendix 1). If the patient is female, and of childbearing potential, she must practice adequate contraception (Appendix 1) for 30 days prior to administration of study treatment, have a negative pregnancy test and continue such precautions during the study treatment period and for 150 days after the last study treatment (120 days to eliminate study treatment and 30 days menstruation cycle) (See Appendix 1 for standards of adequate contraceptive methods).
7. Written informed consent for screening of tumor tissue and if evidence of FGFR alterations written informed consent for the start of the complete study.

5.3 Exclusion Criteria

Patients with <u>any of the following exclusion criteria</u> will NOT be eligible for the study:

1. Any previous receipt of a selective FGFR inhibitor.
2. Presence of primary CIS only.
3. Presence of another malignancy in the 3 years before enrolment except for basal cell carcinoma or squamous cell carcinoma of the skin, cis of cervix, localised prostate cancer in active surveillance or other non invasive or other indolent malignancy that has undergone potentially curative therapy.
4. Presence of pregnancy or lactation or not willing to avoid pregnancy or fathering children.
5. Distant metastases (M1 disease) or presence of radiological evidence of disease at baseline.
6. Treatment with other investigational drugs, receipt of anticancer medications (except for neoadjuvant cisplatin-based chemotherapy, see second inclusion criterion) or radiotherapy of the bladder or upper urinary tract prior to- or after radical surgery.
7. Use of any potent CYP3A4 inhibitors or inducers within 14 days or 5 half lives (whichever is longer) before the first dose of study Tx.
8. Abnormal laboratory parameters:
    i. Total bilirubin ≥ 1.5 × upper limit of normal (ULN; ≥ 2.5 × ULN if Gilbert syndrome).
    ii. AST and/or ALT > 2.5 × ULN
    iii. Creatinine clearance ≤ 30 mL/min based on Cockroft-Gault.
    iv. Serum phosphate > institutional ULN.
    v. Serum calcium outside of the institutional normal range or serum albumin-corrected calcium outside of the institutional normal range when serum albumin is outside of the institutional normal range.
9. History of human immunodeficiency virus infection or active tuberculosis infection.
10. Diagnosis of immunodeficiency or receiving chronic systemic steroid therapy (exceeding > 10 mg daily of prednison equivalent; inhalation steroids are permitted).
11. Evidence of hepatitis B virus or hepatitis C virus active infection or risk of reactivation.
12. Severe hepatic impairment .
13. Known prior severe hypersensitivity to investigational product or its excipients.

14. History of clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months from enrollment, NYHA Class III or IV (Appendix 4).
15. Current evidence of corneal disorder/keratopathy (including but not limited to bullous/band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjunctivitis, etc) or retinal disorder (including but not limited to, central serous retinopathy, macular/retinal degeneration, diabetic retino-pathy, retinal detachment, etc) as confirmed by ophthalmologic examination.
16. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending the required study visits.

5.4 Patient Withdrawal and Early Dropouts (off study)

In the patient informed consent form the patients will be informed that they have the right to withdraw from the study at any time without affecting their subsequent care and may be withdrawn at the investigator's discretion at any time. In the event that the patient drops out, the investigator will, if possible, indicate the reason for withdrawal. Reasonable effort will be made to contact any patient lost to follow up during the course of the study in order to complete assessments and retrieve any outstanding data. Patients withdrawn from the trial will not be replaced.

Off study criteria:

- When the investigator considers it in the best interest of the patient that he/she will be withdrawn
- Patient or legal representative request withdrawal of informed consent
- Lost to follow up or administrative reasons
- Non-compliance with study treatment or procedure requirements.
- Study termination by ethical- or health authorities or the Sponsor.
- Others, only applicable after consultation with the sponsors study monitor.

Participants who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant discontinues/withdraws from participation in the trial, if possible, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in chapter 6 - Adverse Events.
If the patient discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, patients will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments.

Notes:

- Patients who experience unacceptable study drug related adverse events should stop treatment with the study drug. These patients continue follow up for disease status and survival.

- Patients who develop a relapse or metastases of disease stop study drug treatment and they are asked to consent with biopsy and subsequent genomic sequencing after relapse or metastases, whereafter follow up for survival only is continued.
- Patients who become pregnant should stop study drug treatment and should be followed for the outcome of pregnancy and survival.

6. REPORTING ADVERSE EVENTS

6.1 Adverse Events (AE's)

An adverse event is any undesirable clinical occurrence in a patient whether it is considered to be drug related or not. The observed or volunteered adverse events regardless of suspected causal relationship to the study treatment will be recorded on the adverse event page of the eCRF. An adverse event is classified by the investigator as mild (1), moderate (2), severe (3) life threatening (4) or death (5) according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (CTCAE, Appendix 2).
Events involving adverse treatment reactions, illness with onset during the study, or exacerbations of pre-existing illness should be recorded. Objective test finding (e.g. laboratory results) that need treatment should also be recorded.
Note that the following examples of adverse events do not need to be recorded:
• Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE.
• Hospitalisation for elective treatment of a pre-existing condition (known/diagnosed prior to informed consent signature) that did not worsen from baseline.
• Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
• The disease/disorder being studied, or expected relapse, progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.

An example of events which are to be recorded in the medical history section of the eCRF and not as an AE is eg. pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e. prior to the first study product administration).
The investigator should also provide information on the duration (start and stop date), relation to study treatment, start of concomitant therapy and outcome of the adverse event. Follow up of the adverse event after therapy discontinuation, is required if the adverse event or its sequelae persist. Follow up is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator. Adverse event information will be collected from the start of drug treatment up to the visit 30-35 days after stop of drug treatment or longer if drug related adverse events have not resolved or not returned to baseline, whichever is longest. A representative of the Sponsor shall consider all adverse events and, if required, shall report them to the appropriate authorities.

6.2 Serious Adverse Events (SAE's)

A serious adverse event is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalization (except for elective hospitalization for a pre-existing condition that did not worsen from baseline; See 6.1)
- results in persistent or significant disability / incapacity or
- is a congenital anomaly/birth defect.

If, as a result of an adverse event during a clinical investigation, a patient has to be hospitalised, or their hospitalisation is unduly prolonged because of potential disability or danger to life or because an intervention has been necessitated or the event is terminal, the adverse event is regarded as serious. For example, if – according to the investigator - an adverse event causes foetal distress, foetal death or a congenital anomaly or malignancy results from the use of the drug during a clinical investigation, this would be processed as a serious adverse event.
All serious adverse events which occur from the start of study treatment up to the Safety follow up visit 30-35 days after EOT visit whether or not considered related to the treatment, must be reported immediately (within one day of the investigator becoming aware of the adverse event) by sending a completed Serious Adverse Event Report Form by e-mail or fax to EAU RF representatives: ClinicalTrial@phast.it with a copy to the recipient at EAU RF: RFsafety@uroweb.org. Serious adverse events **related to either study participation or related to study treatment** should be reported throughout the entire study period.
An event which is part of the natural course of the disease under study (i.e., disease relapse or progression) is captured as an efficacy measure; therefore it does not need to be reported as a SAE. Progression/relapse of the tumor will be recorded in the clinical assessments in the eCRF. Death due to a progressive disease is to be recorded on a specific form in the eCRF but not as a SAE.
However, if relapse or progression of the underlying disease is more severe than what would normally be expected for the patient, or if the investigator considers that there was a causal relationship between study drug treatment or protocol design/procedures and the disease progression/relapse, then this must be reported as a SAE. Any new cancer (non-related to the cancer under study) must be reported as an SAE.
A representative of the Sponsor will report SAE's to the IRB/IEC that approved the protocol and to the regulatory authorities via the annual general progress report or development safety update reports (DSURs). (See also 8.4)

6.3 Suspected Unexpected Serious Adverse Reactions (SUSAR's)

Suspected unexpected adverse reactions are SAE's considered to be related to study treatment, of which the nature, or severity, is not consistent with the information in the Investigators drug Brochure (IB).
A representative of the Sponsor will report (expedited) all SUSARs to the investigators, competent authorities and IEC's. The expedited reporting will occur within the per law defined time intervals which is currently not later than 15 days after the Sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term is currently a maximum of 7 days for a preliminary report, with another 8 days for completion of the report.

7. STATISTICAL CONSIDERATIONS

7.1 Patient Accrual, Study Duration and Calculation of Patient Numbers

The recruitment period will be 2 years and patients will be followed for an additional 2 years or until relapse or progression. 2-Year relapse-free survival (RFS) rate is the primary endpoint. No interim analyses are planned. Patients will be consecutively molecularly screened and enrolled into the study. It is expected that about 35% of the total screened patients will be eligible and will be enrolled in this study to receive Pemigatinib treatment. Treatment will be continued for a maximum period of 12 months or until the evidence of disease relapse or unacceptable toxicity development. The assumption is that treatment with Pemigatinib will result in a significant higher 2-year RFS rate at 2 years of 45% RFS compared to the reported 30% RFS at 2 years in bladder cancer patients [3].

Statistical Power Calculations:
In an exact single-stage phase II design [24] with power: 0.80; one-sided alpha: 0.10; H0: 2-year RFS: 30%; H1: 2-year RFS: 45% and follow-up duration of 2 years, the total number of eligible and treated patients needed to be enrolled is 50. Patients who withdraw from the study before completing the study period of 2 years, cannot be included in the calculation of the 2-year RFS rate. We estimate that ~15% of the patients will be withdrawn. Therefore, we need a total of 56 patients enrolled. Cut-off to reject the alternative hypothesis H1 is a total of 20 or more patients who experience relapse or progression at or before 2 years of study follow up.

A total of 56 patients needed in this phase II trial is corresponding to approximately 150 patients needed for molecular pre-screening. The primary analysis includes the planned analysis of the primary endpoint 2-year RFS rate which will be analyzed at the 2-years follow-up time point. RFS is defined as the time from the date of start of treatment until disease relapse or progression by investigator determination, or death due to any cause, whichever occurs first. See also 4.4.3.

7.2 Efficacy Analysis Population

The intention to treat (ITT) population will serve as the population for the primary and key secondary efficacy analyses. For the secondary efficacy analyses, all enrolled and eligible patients who will receive at least one dose of the study drug will be included.

7.3 Safety Analysis Population

The safety analysis population will be represented by all patients included in this study, including bladder cancer patients and upper tract tumor patients, and will be used for the analysis of safety data in this study. The population consists of all randomized participants who received at least 1 dose of study treatment.

7.4 Statistical Analysis

7.4.1 Demographics, Safety and Tolerability and Biomarkers Analysis

Missing data will not be replaced. Descriptive statistics, e.g. mean, standard deviation, median, range, frequency distributions will be used to characterize patient characteristics, demographics and

baseline measurements of the patient population. For each patient enrolled, the reason for discontinuation (e.g. patient decision, urologists decision, lack of efficacy, adverse events) should be clarified. The description of the reasons for discontinuation will be performed. Descriptive statistics and frequency distributions as appropriate will be presented to summarize the toxicity profile. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, SUSARs and laboratory tests as described above. The incidence and severity of all serious and non-serious adverse events will be tabulated as well as the treatment related toxicity > grade 2. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.
A summary of tumor-specific gene alterations and gene expression profiles and their correlation to RFS and OS with Pemigatinib treatment will also be prepared.

7.4.2 Relapse Free Survival Analysis and 2 year RFS rate

Relapse free survival is defined as the time from the date of start of study treatment until disease relapse or progression by Investigator determination, or death due to any cause, whichever occurs first. Relapse free survival will be analyzed and graphically presented by the Kaplan-Meier method. The percentage of patients with relapse free survival at 2 years will be calculated with its 95% Confidence Interval.

7.4.3 Overall Survival Analysis

Overall Survival (OS) is defined as the time from the date of start of study treatment to death due to any cause. Participants without documented death at the time of analysis will be censored at the date of the last follow-up. Overall survival will be analyzed and graphically presented by the Kaplan-Meier method. The percentage of patients who survive at 2 years will be calculated with its 95% Confidence Interval.

8. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS; PUBLICATION

8.1 Ethical and Regulatory Considerations

This study will be performed in accordance with ethical principles that originate in the Declaration of Helsinki (see for the most recent version: www.wma.net) and conducted in adherence to the study Protocol; GCP; and local regulatory requirements as applicable to the study locations.

Prior to the start of the study, approval from the IRB/IEC in accordance with applicable country-specific regulatory requirements will be obtained. The processing of the personal data of patients taking part in this study, and in particular regarding data related to consent, shall comply with the local law on the privacy and, for the European Union, with the General Data Protection Regulation (GDPR) as of May 2018.

The genomic sequencing tests are provided by Roche Italy and Roche Germany in collaboration with Foundation Medicine. Roche and Foundation Medicine located in Germany will receive the pseudonomized patient details and tissue samples will be send to Foundation Medicine GmbH by

clinicians and/or pathologists of the participating hospitals for genomic sequencing. The resulting data will subsequently be made accessible (always pseudonomized) to Foundation Medicine Inc. in USA for the analysis of the acquired genomic data, the correspondence and the drafting of the report that will be returned to the clinician and/or pathologists of the participating hospitals..
Patients will explicitly have to give consent to the transfer of their pseudonymised data to the US. Roche and Foundation Medicine will retain the personal pseudonomised data and destroy these data after a period of 10 years. Foundation Medicine will return any unused tissue samples to the hospitals pathologists. Patients can withdraw their consent and obtain cancellation of personal data shared with the aforementioned companies. However, Foundation Medicine Inc, USA has the possibility to treat and use some data in a completely anonymous form, even if the consent is withdrawn by the patient.
Eligible patients will be fully informed by the Principal Investigator (PI), the local investigator and/or the local research coordinator and his research staff, whatever is applicable, about the study and asked to participate. The patient will receive a patient information sheet and will have ample opportunity to ask any questions he/she might have. He/she will have sufficient time to consider the study's implications before deciding to participate in the study. Patient's consent will be noted on an informed consent form (ICF).

If during the study the patient for whatever reason no longer wishes to participate he/she can withdraw his/her consent at any time. Study medication will then be stopped and further treatment will be initiated at the discretion of the treating physician.
Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
It is the responsibility of the investigator to verify adherence to the protocol, the protection of the rights of the patient, the completeness, accuracy and consistency of the data to be entered in the eCRF and adherence to local regulations.

8.2 Study Organisation & Management

For this multicentre study, an initiating investigators meeting at a central location will be held to standardise data management procedures and resolve questions regarding protocol conduct. At the initiation meeting, the investigator and eventual other site study personnel will be instructed how to conduct the study- and data management procedures. In addition, the sites will be provided with the required materials by the EAU RF representatives. EAU RF's representatives may conduct field data review periodically. It is the responsibility of EAU RF's representatives to verify adherence to the protocol and the completeness, accuracy and consistency of the data. The investigator or a qualified employee will enter all relevant data into eCRF's, in accordance with the instructions provided.

8.3 Handling and Storage of Data and Documents

Data management will be performed in a validated database via an Electronic Data Capture (EDC) system. The investigator and other involved site personnel will be trained in the proper use of the EDC system after which they will be provided with access to the EDC system so that an eCRF can be completed for each subject. Entries made in the eCRF must be verifiable against source

documents; if updates to the database are not possible, any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and eCRF entries, and will sign and date the designated forms in each subject's eCRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all query responses.

The investigator will guarantee that all team members and other persons involved in his centre will respect the confidentiality of any information related to the study patients. All parties involved in this study will maintain strict confidentiality to assure that the patients privacy is not violated. Likewise, the appropriate measures shall be taken to avoid access of the study data by non-authorised persons. Patient data will be pseudonymized before entering in the database and extracts of the data will be available for statistical analyses and reporting.

Qualified representatives of the sponsor or its designees, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and subject records at each monitoring visit.
Original subject records (e.g., hospital charts, clinical records, pathology reports, laboratory printouts) should be available at each study site for source document review by the sponsor or its designees. Source document review is the cross checking of information recorded on eCRF's with that recorded in the original subject records. It is not the purpose of source document review to ensure that all information in the eCRF is also recorded elsewhere in the subject's records; the purpose is to help ensure that the eCRF accurately reflects information generated during the study. In this study, source document review of specific types of information will be conducted in all patients enrolled. The sponsor and/or its designee ensure the privacy of the patient data by only collecting the patient data without the patient details that could identify the individual patient. The investigator should give the monitor access to all relevant patient data. Queries to be issued to the investigator will consist of questions to clarify for instance missing data, inconsistencies, illegible data, illegal values and items that are not clearly corrected.

When all patient and visit data are received at the sponsor or its designee, all data problems have been resolved, all data checks and quality control checks have been performed, the study database is considered to be clean and can be locked. In addition, the study centre may be audited in depth for study quality assurance by the sponsor or its designee, and/or inspected by a national regulatory authority. This audit may include review of all source documents, drug records, original clinic case-notes, some or all of the facilities used in the trial, etc. Patient confidentiality will be maintained at all times and consent for this will be obtained prior to entry of the patient into the clinical trial.

8.4 Amendments

Amendments are changes made to the study protocol, after an initial favourable opinion by the IRB/IEC has been given. Amendments will be notified or submitted for approval to the IRB/IEC as required according to local law.

8.5 General Progress Report

According to local requirements, the sponsor / principal investigator (PI) will submit a summary of the progress of the study to the IRB/IEC once a year. Information will be provided on the date of

inclusion of the first patient, numbers of patients included and numbers of patients that have completed the study, Serious Adverse Events / Suspected Serious Adverse Reactions (SUSARs), other issues, and amendments.

8.6 End of Study Report

According to local requirements, the sponsor/PI will notify the IRB/IEC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. In case the study is ended prematurely, the sponsor / PI will notify the IRB/IEC within 15 days, indicating the reasons for the premature termination.

Within one year after the end of the study, the sponsor / PI will submit a final study report with the results of the study, including any publications/abstracts of the study, to the IRB/IEC.

8.7 Steering Committee

A Steering Committee will be assembled, consisting of urologist / medical oncologists key opinion leaders in the field of genito-urinary surgery and oncology and physicians/scientists with clinical and methodological expertise. The Steering Committee is responsible for the assignment of National Coordinators. Each participating country has one National Coordinator who has been selected by the Steering Committee. The Steering Committee will convene once or twice a year during recruitment phase of the study. Meeting frequency may decrease during the follow-up phase of the study.

8.8 Public Disclosure and Publication Policy

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the participating investigator(s) and the Steering Committee. Guidelines on authorship will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE).

The first publication will be based on data from all centers, analyzed as stipulated in the protocol by statisticians/epidemiologists acting on behalf of the sponsor. The investigators agree that they can present data collected at one center or a small group of centers before the full, initial publication, after obtaining written agreement of the sponsor on behalf of the Steering Committee.
The sponsor must receive copies of any intended communication in advance of submission for publication. In order to ensure that the sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the sponsor for review at least ninety (90) days prior to submission for publication, public dissemination, or review by a publication committee.

Parties who wish to present or publish any data from this study can submit a formal request to the sponsor or the Steering Committee. After formal agreement by the sponsor the procedure as described above for any intended communication will need to be followed.

8.9 Financing and insurance

There are no special incentives or financial compensations that patients will receive through participation in the study. The Sponsor or its representatives will arrange a liability insurance /clinical trial insurance which is in accordance with GCP and local legal requirements.

8.10 Risk analysis

This is a phase II study with a drug that has indicated promising effects for relapse free survival in this high-risk group of patients who need a cystectomy or nephroureterectomy for treatment of their urothelial carcinoma. On the other hand, there are side effects that should be managed with dose reduction or stop; frequent laboratory checks or other supportive measures in consultation with a medical oncologist. Further, at relapse or progression, subjects will be asked to sign a consent to allow a biopsy of the relapse or metastases and tumor tissue to be sent to the sponsor's central laboratory (Foundation Medicine) for genetic sequencing. Based on the current available information of Pemigatinib, the risks related to the expected treatment outcome, quality and quantity of side effects of the study medication can be considered as acceptable.
Benefit for the patient is that the patient is followed according to the latest standards and guidelines of treatment of MIBC and the patient has a chance on early detection of relapse of disease.

Privacy risks are covered as much as possible by following well established procedures such as pseudonymization of the data which are entered in the web based eCRF. For accidents where the confidentiality of privacy may be at risk, the EAU-RF has taken a privacy insurance for the entire duration of the study.

Another risk is that, although a feasibility questionnaire that was performed amongst the potential participants prior to the finalisation of the study protocol indicated that the number of 56 patients can be reached within the specified timeframe of 2 years, the recruitment can stay behind expectations. To avoid such a risk, the recruitment will be closely monitored. If recruitment is clearly behind expectations, the Steering Committee in mutual agreement with the sponsor may decide to ask more European centres interested to participate in this study or prolong the recruitment period.

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Appendix 1 Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:
Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the treatment phase and 240 days thereafter:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in table below when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

  Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly for 30 days prior to administration of study treatment, continue contraception during the study treatment period and for 150 days after the last study treatment (120 days to eliminate study treatment and 30 days menstruation cycles).

Table: Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of < 1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system [b] ● Intrauterine device ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) Acceptable hormonal contraceptives are limited to those which inhibit ovulation. c) Hormonal contraception may be susceptible to interaction with Pemigatinib, which may reduce the efficacy of the contraception method.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected, after the last dose of study treatment, and as required locally.

Appendix 2 Common Terminology Criteria for Adverse Events v 4.0 (CTCAE)

The descriptions and grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting.

http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf

Appendix 3 Investigator Protocol Signature Sheet

Investigator Signature:

I have read and agree to the 'Open-label, single-arm, Phase II study, evaluating safety and efficacy of Pemigatinib as adjuvant therapy for molecularly-selected, high-risk patients with urothelial carcinoma who have received radical surgery.
A European Association of Urology Research Foundation Phase II Clinical Trial.
EAU RF number: 2018-02. Final Version 2.0 dated 29 June 2021.

I agree to conduct this study in accordance with the protocol and in accordance with the Declaration of Helsinki and (inter)national regulations (as applicable) and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME:

TITLE: INVESTIGATOR: SIGNATURE: _____

DATE: _____

PLACE:

Full investigational site contact details, including telephone numbers, will be documented in the Trial Master File.

Principal Investigator:

NAME: Prof. Andrea Necchi

SIGNATURE: _____

DATE: _____

MILANO, ITALY

Sponsors Medical Expert and Epidemiologist:

NAME: Dr. Wim PJ Witjes

SIGNATURE: _____

DATE: _____

ARNHEM, THE NETHERLANDS

Appendix 4 WHO Performance Score & NYHA Classification of Heart Failure

WHO Performance Score

The WHO score (published by Oken *et al* in 1982 [25], also called the ECOG or Zubrod score (after C. Gordon Zubrod), runs from 0 to 5, with 0 denoting perfect health and 5 death:

0. Asymptomatic
1. Symptomatic but completely ambulatory
2. Symptomatic, <50% in bed during the day
3. Symptomatic, >50% in bed, but not bedbound
4. Bedbound
5. Death

Classes of Heart Failure

Doctors usually classify patients' heart failure according to the severity of their symptoms. The table below describes the most commonly used classification system, the **New York Heart Association Functional Classification**[1] (NYHA). It places patients in one of four categories based on how much they are limited during physical activity.

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

[1] *Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.*

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Appendix 5 CYP3A Inhibitors and Inducers

Source: University of Washington School of Pharmaceutics: Drug Interaction Database Program. 2002. http://www.druginteractioninfo.org. Accessed May 2015. *Highlighted row indicates recent additions to the lists at the time the database search was performed.*

Inhibitor	Therapeutic Class	Inhibitor dosing (oral)
		Potent CYP3A Inhibitors (yielding substrate AUCr > 5)
indinavir /RIT	Protease Inhibitors	800/100 mg BID (1 day)
tipranavir/RIT	Protease Inhibitors	500/200 mg BID (2 days)
ritonavir	Protease Inhibitors	3 doses of 100 mg over 24 h
cobicistat (GS-9350)	None	200 mg QD (14 days)
indinavir	Protease Inhibitors	800 mg TID (7 days)
ketoconazole	Antifungals	400 mg QD (4 days)
troleandomycin	Antibiotics	500 mg single dose
telaprevir	Antivirals	750 mg TID (16 days)
danoprevir / RIT	Antivirals	200/100 mg QD (14 days)
elvitegravir / RIT	Treatments of AIDS	150/100 mg QD (10 days)
saquinavir / RIT	Protease Inhibitors	1000/100 mg BID (14 days)
lopinavir / RIT	Protease Inhibitors	400/100 mg BID (2 days)
itraconazole	Antifungals	200 mg QD (4 days)
voriconazole	Antifungals	200 mg BID (9 days)
mibefradil	Calcium Channel Blockers	100 mg single dose
LCL161	Cancer Treatments	600 mg single dose
clarithromycin	Antibiotics	500 mg BID (7 days)
posaconazole	Antifungals	400 mg BID (7 days)
telithromycin	Antibiotics	800 mg QD (6 days)
grapefruit juice DS[2]	Food Products	240 mL TID (2 days) and 90 min, 60 min, 30 min prior to midazolam
conivaptan	Diuretics	40 mg BID (5 days)
nefazodone	Antidepressants	100-200 mg BID (12 days)
nelfinavir	Protease Inhibitors	1250 mg BID (14 days)
saquinavir	Protease Inhibitors	1200 mg TID (5 days)
idelalisib	Kinase Inhibitors	150 mg BID (8 days)
boceprevir	Antivirals	800 mg TID (6 days)

Inducers	Therapeutic class	Object (oral, unless otherwise specified)	% ↓ AUC	% ↑ oral CL	Precipitant Dose (oral)
		Potent Inducers (AUC decreased by ≥ 80% or CL increased by more than 5 fold (400%))			
rifampin	Antibiotics	budesonide	**99.7**	**36904.5**	600 mg QD (7 days)
mitotane	Other Antineoplastics	midazolam	**94.5**	Not Provided	maximum of 3.5 g TID (chronic therapy)
avasimibe	Other Antilipemics	midazolam	**93.5**	Not Provided	750 mg/day (7 days)
phenytoin	Anticonvulsants	nisoldipine	**89.5**	Not Provided	200-450 mg/day (chronic treatment)
carbamazepine	Anticonvulsants	quetiapine	**86.6**	**643.1**	200 mg TID (26 days)
enzalutamide	Antiandrogens	midazolam	**85.9**	Not Provided	160 mg QD (85±3 days)
St John's Wort	Herbal Medications	midazolam	**80.0**	Not Provided	300 mg TID (14 days)
rifabutin	Antibiotics	delavirdine	Not Provided	**458.0**	300 mg QD (14 days)
phenobarbital	Anticonvulsants	verapamil	**76.6**	**400.9**	100 mg QD (21 days)

Appendix 6 Flowchart and Laboratory Evaluations.

	Pre-sur-gery	Sur-gery	Screening	Treatment period 12 months					Follow up after treatment 12 months		
			Week 0 up to week 13 after surgery	First 3 weeks after start of treatment			Q 3 weeks*	End of Treatment (EOT)	Safety	Disease status	Survival status
				Day 1 enrollment	Day 8 (± 3 days)	Day 15 (± 3 days)	Day 21 (± 3 days), etc		EOT + 30-35 days	Every 12 weeks	Every 12 weeks
Inf.Consent	X		X								
Selection criteria	X		X	X							
Tumor Tissue for genomic profiling			X								
Demographics & Med. History			X								
Phys. Exam. & NYHA status			X								
WHO PS			X	X			X	X		X	
ECG			X				X q12 wks	Prev. Abn.	Prev. Abn.		
Hematology & Biochemistry			X	Repeated only if done > 14 days prior to day 1	X	X	X q3 wks*	Prev. Abn.	Prev. Abn.		
Urine / Serum Pregnancy test (females of childbearing potential)			X	X	Only in case of susp. preg-nancy	Only in case of susp. preg-nancy	Only in case of susp. preg-nancy	Only in case of susp. preg-nancy	Only in case of susp. preg-nancy	Only in case of susp. preg-nancy	
Urinalysis, Coagulation, Lipid and Endocrine Panels			X				X ***	Prev. Abn.	Prev. Abn.		
CT / MRI chest/abdomen/pelvis Q 12 weeks**			X				X q12 wks			X	
Ophthalmological investigations every12 weeks			X				X q12 wks	Prev. Abn.			
Study drug dispensing and accountability				X			X	X			
Concomitant medication			X	X	X	X	X	X	X		
Adverse events (CTCAE v4.0)					X	X	X	X	X	X only study or drug related SAEs	X only study or drug related SAEs
Survival data											X

Prev. Abn.: Only in case of abnormalities at previous, latest test or examination.
* Timing of subsequent visits and laboratory examinations can be prolonged to max. 9 weeks intervals if no problems exist during the first 12 weeks of therapy.
** CT / MRI every 12 weeks +/- 1 week. At disease relapse or progression, a biopsy and subsequent genomic evaluation is recommended.
*** Urinalysis, Coagulation panel, Lipid panel and Endocrine panel (next page): repeat at 3 weeks and only in case of (persistent) abnormalities repeat q3 weekly; EOT and Safety EOT + 30 days only in case of previous, latest test abnormalities.

Laboratory test to be performed in the local laboratory at each hospital. Other than hematology and chemistry lab tests: Hepatitis screening only at screening, if not done already before radical surgery.
Urinalysis, Coagulation panel, Lipid panel and Endocrine panel: repeat at 3 weeks and only in case of (persistent) abnormalities repeat q3 weekly; EOT and Safety EOT + 30 days only in case of previous, latest test abnormalities.

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Total protein	Occult Blood	Hepatitis serology
Hemoglobin	Albumin	Glucose	
Platelet count	Alkaline phosphatase	Protein	
WBC (total and differential)	Alanine aminotransferase (ALT)	PH and Specific gravity	
Red Blood Cell Count	Aspartate aminotransferase (AST)	Bilirubin	
Absolute Neutrophil Count	Lactate dehydrogenase (LDH)	Urobilinogen	**COAGULATION PANEL**
Absolute Lymphocyte Count	Total Bilirubin	Ketones	PT (INR)
	Direct Bilirubin (If total bilirubin is elevated above the upper limit of normal)	Leukocytes	Activated Partial Thromboplastine Time (aPTT)
	Uric Acid	Nitrite	
	Creatinine / Creatinine clearance according to Cockroft-Gault formula.		**LIPID PANEL**
	Blood Urea Nitrogen	*Urine pregnancy test and/or serum β-human chorionic gonadotropin† (β-hCG) †*	Total cholesterol
	Calcium		Triglycerides
	Chloride		Low-density lipoprotein
	Glucose		High-density lipoprotein
	Phosphate		
	Potassium		**ENDOCRINE PANEL**
	Sodium		Parathyroid hormone (PTH)
	Vitamin D (25-hydroxyvitamin D and 1,25-dihidroxyvitamin D)		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.