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**Protocol Title**

Phase II Trial of Dovitinib in BCG-Refractory Urothelial Carcinoma Patients with Tumor FGFR3 Mutations or Over-expression: Hoosier Cancer Research Network GU12-157


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# PROTOCOL SIGNATURE PAGE

Protocol title: **Phase II Trial of Dovitinib in BCG-Refractory Urothelial Carcinoma Patients with Tumor FGFR3 Mutations or Over-expression: Hoosier Cancer Research Network GU12-157**

**VERSION DATE: 09JUL2014**

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to Hoosier Cancer Research Network and keep a record for your files.

_____ _____

Signature of Investigator Date

_____

Investigator Name (printed)

_____

Investigator Title

_____

Name of Facility

_____

Location of Facility (City and State)

_____ ❑ Not Submitting to IRB

Expected IRB Approval Date

**PLEASE COMPLETE AND EMAIL COPY TO HOOSIER CANCER RESEARCH NETWORK**

## STUDY SYNOPSIS

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| **TITLE** | Phase II Trial of Dovitinib in BCG-Refractory Urothelial Carcinoma Patients with Tumor FGFR3 Mutations or Over-expression |
| **STUDY PHASE** | Phase II |
| **OBJECTIVES** | **Primary Objective:**<br>• To determine the 6-month complete response rate in BCG-refractory UC patients with FGFR3 mutant or over-expressing tumors treated with dovitinib.<br><br>**Secondary Objectives:**<br>• To determine the 1-year relapse free survival (RFS) rate in BCG-refractory UC patients treated with dovitinib.<br>• To determine the rate of progression to muscle-invasive stage (i.e. T2-T4).<br>• To determine 3- and 6-month partial response rate defined as a reduction in T-stage on post-therapy TURBT (i.e. T1 ≥ Ta; T1+Tis ≥ Tis)<br>• To characterize treatment related toxicity rates assessed by CTCAE v4.0<br>**Exploratory Objectives:**<br>• To characterize concordance rates between UC patient detected tumor, urine, and circulating free plasma FGFR3 mutations.<br>• To characterize associations between pre-treatment germline (as assessed by PBMC extracted DNA) FGFR SNPs and post-treatment 6-month complete response rate and 1-year relapse free survival rate in patients treated with dovitinib.<br>• To characterize associations between pre-treatment germline (as assessed by PBMC extracted DNA) VEGFR SNPs and post-treatment 6-month complete response rate and 1-year relapse free survival rate in patients treated with dovitinib.<br>• To characterize VEGFR over-expression status within tumor tissue<br>• To characterize pre- and post-treatment bladder tumor FGFR and VEGFR pathway phosphorylation changes as assessed by bladder tumor tissue immunohistochemistry.<br>• To characterize post-treatment bladder tissue dovitinib concentrations.<br>• To characterize associations between post-treatment hypertension, 6-month complete response rate and 1-year relapse free survival rate in patients treated with dovitinib. |
| **STUDY DESIGN** | This trial will be a single-arm, multi-center, phase II study conducted through Hoosier Cancer Research Network assessing the 6-month complete response rate and toxicity profile of oral dovitinib therapy in BCG-refractory urothelial carcinoma patients with tumors with FGFR3 mutations or over-expression who are ineligible for or refusing cystectomy. |

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| **NUMBER OF PATIENTS** | Screen 50 for 20 evaluable patients |
| **ELIGIBILITY** | Inclusion<br>1. Histologically confirmed non-muscle invasive urothelial carcinoma of the bladder (NMIBC) defined as Ta, T1, or Tis stage. Tumor staging must be confirmed by TURBT performed within 42 days prior to registration.<br>2. Presence of either an FGFR3 mutation or FGFR3 over-expression within bladder tumor tissue. FGFR3 mutations (see Table 1-2) in exons 7, 10, and 15 will be assessed by massively parallel sequencing analysis utilizing the Ion Torrent Personal Genome Machine (PGM) in the CLIA-certified Molecular Pathology and Translational Research Laboratory at the Dartmouth Hitchcock Medical Center . FGFR3 over-expression will be assessed by standard IHC analysis performed within the Indiana University Simon Cancer Center Immunohistochemistry (IHC) Core Lab.<br>NOTE: Patients will initially be allowed to enroll if their tumors demonstrate either an FGFR3 mutation or FGFR3 over-expression. However, a minimum of 10 FGFR3 mutation positive patients will be enrolled at study completion. If 10 patients with tumors that are FGFR3 over-expressors but FGFR3 mutation negative are accrued prior to enrolling 10 FGFR3 mutation positive patients, subsequent enrollment will be restricted to patients with tumors that are FGFR3 mutation positive.<br>3. Documented BCG-refractory disease defined as failure to achieve a tumor free state after at least 2 prior intravesical treatment courses, one of which must have been intravesical BCG therapy.<br>NOTE: There is no maximum limit on the number of prior BCG therapy courses. In addition, there is no maximum limit on the number of prior non-BCG intravesical therapy courses (i.e. gemcitabine, valrubicin, interferon, mitomycin C, etc.).<br>4. Medically unfit to undergo cystectomy or electively choosing to forego cystectomy<br>5. ECOG (WHO) performance status 0 or 1 or 2<br>6. Age ≥ 18 years old<br>7. Patients must have the following laboratory values:<br>• White blood cell count (WBC) > 3.0 K/mm3<br>• Absolute neutrophil count (ANC) ≥ 1.5 K/mm3<br>• Platelets ≥ 100 K/mm3<br>• Hemoglobin (Hgb) ≥ 9 g/dL<br>• Serum total bilirubin: ≤ 1.5 x ULN<br>• ALT and AST ≤ 3.0 x ULN<br>• Serum creatinine ≤ 1.5 x ULN or serum creatinine > 1.5 – 3 x ULN if calculated creatinine clearance (CrCl) is ≥ 30 mL/min using the Cockcroft-Gault equation, see formula below:<br>CrCl = [140-age (years)] x weight (kg) / [72 x serum Cr (mg/dL)]<br>(if patient is female multiply the above by 0.85)<br>• Urine dipstick reading: Negative for proteinuria or, if documentation of +1 (+2 for patients with renal cell carcinoma) results for protein on dipstick reading, then total |

urinary protein ≤ 500 mg and measured creatinine clearance ≥ 50 mL/min/1.73m2 from a 24 hour urine collection

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

Exclusion

1. Patients with muscle-invasive (i.e. T2, T3, T4), locally advanced non-resectable, or metastatic urothelial carcinoma as assessed on baseline radiographic imaging obtained within 28 days prior to study registration. The required radiographic imaging includes:
   a. Abdomen/Pelvis – CT scan
   b. Chest – chest x-ray or CT scan
2. Patients with concurrent upper urinary tract (i.e. ureter, renal pelvis) non-invasive urothelial carcinoma.
3. Patients with another primary malignancy within 3 years prior to starting study drug, with the exception of adequately treated in-situ carcinoma of the uterine cervix, clinically localized prostate cancer, biochemically relapsed non-metastatic prostate cancer (i.e. PSA only disease), or skin cancer (such as basal cell carcinoma, squamous cell carcinoma, or non-melanomatous skin cancer)
4. Patients who have received the last administration of an anti-cancer therapy including chemotherapy, immunotherapy, and monoclonal antibodies ≤ 4 weeks prior to starting study drug, or who have not recovered from the side effects of such therapy
5. Patients who have received prior VEGFR-targeted or FGFR-targeted agents (i.e. sunitinib, pazopanib, sorafenib, bevacizumab, axitinib, etc.).
6. Patients who have had radiotherapy ≤ 4 weeks prior to starting study drug, or who have not recovered from radiotherapy toxicities
7. Patients who have undergone major surgery (e.g. intra-thoracic, intra-abdominal or intra-pelvic), open biopsy or significant traumatic injury ≤ 4 weeks prior to starting study drug, or patients who have had minor procedures (i.e. TURBT), percutaneous biopsies or placement of vascular access device ≤ 1 week prior to starting study drug, or who have not recovered from side effects of such procedure or injury
8. Patients with any of the following concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study:

- Impaired cardiac function or clinically significant cardiac diseases, including any of the following:

a. History or presence of serious uncontrolled ventricular arrhythmias
b. Clinically significant resting bradycardia
c. LVEF assessed by 2-D echocardiogram (ECHO) < 50% or lower limit of normal (whichever is higher) or multiple gated acquisition scan (MUGA), < 45% or lower limit of normal (whichever is higher)
d. Any of the following within 6 months prior to starting study drug: myocardial infarction (MI), severe/unstable angina, Coronary Artery Bypass Graft (CABG), Congestive Heart Failure (CHF), Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA), Pulmonary Embolism (PE)
e. Uncontrolled hypertension defined by a SBP ≥ 160 mm Hg and/or DBP ≥ 100 mm

Hg, with or without anti-hypertensive medication(s)

- Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of dovitinib (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
- Cirrhosis, chronic active hepatitis or chronic persistent hepatitis
- Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory)
- Patients who are currently receiving anti-coagulation treatment with therapeutic doses of warfarin. Full-dose anti-coagulation with low molecular weight heparin is permitted.
- Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection, uncontrolled diabetes) that could cause unacceptable safety risks or compromise compliance with the protocol

9. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
10. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception (defined below). Highly effective contraception must be used by both sexes (female patients and their *male partners) during study treatment and for 30 days after the last dose of study medication.*

    Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Combination of the following (a+b):

      a. Placement of an intrauterine device (IUD) or intrauterine system (IUS)

      b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

    Oral, implantable, or injectable hormone contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study

    Women of child-bearing potential (sexually mature women) who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months), must have a negative serum pregnancy test ≤ 14 days prior to starting study drug.
11. Fertile males not willing to use contraception. Fertile males must use condom with spermicide. Highly effective contraception, as defined above, must be used by both sexes (male patients and their female partners) during study treatment and for 90

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| | days after the last dose of study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.<br>12. Patients unwilling or unable to comply with the protocol |
| **EVALUATION CRITERIA** | Primary Objective:<br>• The 6-month complete response rate is defined as the proportion of patients treated with dovitinib with no evidence of any remaining urothelial carcinoma tumors of any T-stage (including Tis) present within the bladder as assessed by standard of care cystoscopic examination with TURBT and urine cytology performed at 6 months after initiation of study therapy.<br>Endpoints for Secondary Objectives:<br>• The 1-year relapse free survival rate is defined as the proportion of patients treated with dovitinib with no evidence of any remaining urothelial carcinoma tumors at 12 months of follow-up.<br>• The rate of progression to muscle-invasive stage for dovitinib is defined as the proportion of patients with clinical or pathologic progression to muscle-invasive stages (i.e. T2-T4) at any time point on study.<br>• The 3- and 6-month partial response rates are defined as the proportion of patients treated with persistent but reduced T-stage tumors on post-therapy TURBT (i.e. T1 ≥ Ta; T1+Tis ≥ T1).<br>• Treatment related toxicity rates will be assessed by CTCAE v4.0.<br>NOTE: Patients with residual non-invasive UC tumors with no component of carcinoma in situ (i.e. Ta, T1) at 3-month cystoscopy and TURBT are not considered relapses and will be permitted to continue on dovitinib therapy. If the subsequent 6-month cystoscopy/TURBT, and urine cytology shows no evidence of any remaining urothelial carcinoma in such patients, they will be considered a complete response. Patients with any component of carcinoma in-situ (CIS) at 3-month cystoscopy/TURBT will be considered relapses and will not continue on dovitinib therapy. Any non-invasive UC tumors (i.e. Ta, T1, Tis) at the 6-month or any subsequent cystoscopy/TURBT is considered relapsed disease. Similarly progression to invasive UC tumors (T2-T4) at any time point is also considered relapsed disease and patients will not continue on dovitinib therapy.<br>Endpoints for Exploratory Objectives<br>• Pre- and post-treatment bladder tumor FGFR pathway phosphorylation changes will be assessed by bladder tumor tissue immunohistochemistry utilizing commercially available antibodies including, but not limited to, the following: FGFR3, pFGFR3, VEGFR2, pVEGFR2, FRS2, pFRS2, ERK, pERK.<br>• Pre-treatment germline FGFR SNPs will be assessed by testing extracted DNA from patient PBMC's (collected prior to initiating dovitinib therapy) with validated commercial probes. |

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| | • Pre- and post-treatment bladder tumor VEGFR pathway phosphorylation changes will be assessed by bladder tumor tissue immunohistochemistry utilizing commercially available antibodies including, but not limited to, the following: FGFR3, pFGFR3, VEGFR2, pVEGFR2, FRS2, pFRS2, ERK, pERK.<br>• Pre-treatment germline VEGFR SNPs will be assessed by testing extracted DNA from patient PBMC's (collected prior to initiating dovitinib therapy) with validated commercial probes.<br>• Presence of VEGFR over-expression within tumor tissue will be assessed and interpreted by standard immunohistochemistry analysis with appropriate controls.<br>• Hypertension will be defined as a systolic blood pressure (SBP) of $\geq$ 140 mmHg or a diastolic blood pressure (DBP) of $\geq$ 90 mm Hg recorded at any time after dovitinib therapy is initiated.<br>• Presence of FGFR3 mutations (see Table 1-2) within patient tumor tissue and urine will be assessed by massively parallel sequencing of exons 7, 10, and 15 utilizing the Ion Torrent PGM instrument.<br>• Presence of FGFR3 mutations within patient free plasma will be assessed by PCR-amplification of the target regions and sequencing.<br>• Post-treatment bladder tissue dovitinib concentrations will be assessed by TURBT fresh frozen tissue obtained at the 3-month cystoscopy |
| **STATISTICAL CONSIDERATIONS** | **General Considerations**<br>Statistical analysis of this study will be the responsibility of the Department of Biostatistics at IUSM. Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima and standard deviations. Categorical variables will be summarized by frequencies and percentages. Missing data are expected to be rare. For patients that start therapy but do not make it to the primary endpoint evaluation, their 6-month status will be treated as not achieving CR. Consequently, our estimate of 6-month CR rate will be conservative. For secondary outcomes, missing data, if any, will not be imputed and complete-case analysis will be adopted. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol.<br>**Primary Objective Statistical Considerations**<br>The 6-month complete response rate will be summarized by frequency and rate. The one-sided 90% confidence interval (CI) of Agresti-Coull type will be calculated for the rate.<br>**Secondary Objectives Statistical Considerations**<br>All secondary objectives are hypothesis generating in nature. One year RFS will be summarized by mean, median and standard deviation. Muscle-invasive progression, 3- |

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| | and 6-month PR, and toxicity rates will be presented as rates and corresponding 90% Agresti-Coull CIs.<br><br>**Sample size justification**<br><br>A one-sided 90% confidence interval (CI) of Agresti-Coull type will be calculated for the 6-month CR rate. With an expected CR rate of $\geq$ 25%, a sample size of 20 subjects will have a power of 0.80 to exclude a lower bound being $\leq$ 10%. |
| **ENROLLMENT PERIOD** | 18 months |
| **FOLLOW-UP PERIOD** | 6 months |

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## List of Abbreviations

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|---|---|
| AE | Adverse Event |
| ALT | Alanine aminotransferase/glutamic pyruvic transaminase/GPT |
| AML | Acute myeloid leukemia |
| ANC | Absolute neutrophil count |
| ASCO | American society of clinical oncology |
| AST | Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT |
| ATC | Anatomical therapeutic chemical classification system |
| AUC | Area under the curve |
| BCG | Bacillus Calmette-Guerin |
| bFGF | Basic fibroblast growth factor |
| b.i.d. | *bis in diem*/twice a day |
| BP | Blood pressure |
| BSC | Best supportive care |
| BUN | Blood urea nitrogen |
| CABG | Coronary artery bypass graft |
| CBC | Complete blood count |
| CHF | Congestive heart failure |
| CI | Confidence interval |
| c-Kit | Cellular kit tyrosine kinase receptor |
| Cmax | Maximum (peak) concentration of drug |
| CML | Chronic myeloid leukemia |
| CNS | Central nervous system |
| CPK | Creatine phosphokinase |
| CK-MB | MB isoenzyme of creatine phosphokinase |
| CR | Complete response |
| CrCl | Creatinine clearance |
| CRF | Case Report/Record Form; the term CRF can be applied to either EDC or Paper |
| CRO | Contract research organization |
| CSF-1R | Colony-stimulating factor-1 receptor |
| CSR | Clinical study report |
| CSR addendum | An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR |
| CT | Computer tomography |
| CTCAE | Common terminology criteria for adverse events |
| CTH | Clinical Trial Head |
| CVA | Cerebrovascular accident |
| CYP | Cytochrome P |
| DBP | Diastolic blood pressure |
| DCE-MRI | Dynamic contrast-enhanced magnetic resonance imaging |
| DCR | Disease control rate |
| DLT | Dose limiting toxicity |
| ECG | Electrocardiogram |

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| ECHO | Echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case record/report form |
| EDC | Electronic data capture |
| EDTA | Ethylenediaminetetraacetic acid |
| EORTC QLQ-C30 | The European Organisation for Research and Treatment Of Cancer Quality of Life Questionnaire QLQ-C30 |
| EOT | End of treatment |
| FAS | Full analysis set |
| FGF | Fibroblast growth factor |
| FGFR | Fibroblast growth factor receptor |
| FKSI-DRS | Functional assessment of cancer therapy Kidney symptom index – Disease related symptoms |
| FLT3 | FMS-like tyrosine kinase 3 |
| GCP | Good clinical practice |
| GI | Gastrointestinal |
| GIST | Gastrointestinal stromal tumor |
| HDL | High density lipoprotein |
| HIV | Human immunodeficiency virus |
| HR | Hazard ratio |
| IB | Investigator's brochure |
| ICH | International Conference on Harmonization |
| IDMC | Independent data monitoring committee |
| IEC | Independent Ethics Committee |
| IHC | Immunohistochemistry |
| IMS | Integrated Medical Safety |
| IN | Investigator notification |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System |
| ITT | Intent-to-treat |
| IV | intravenous(ly) |
| IVRS/IWRS | Interactive voice response system/Interactive web response system |
| LDL | Low density lipoprotein |
| LVEF | Left ventricular ejection fraction |
| MAP | Master Analysis Plan documents project standards in the statistical methods, which will be used within the individual clinical trial RAP documentation. |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Myocardial infarction |
| mRCC | Metastatic renal cell cancer/carcinoma |
| MRI | Magnetic resonance imaging |
| MTD | Maximum tolerated dose |
| mTOR | Mammalian target of rapamycin |
| MUGA | Multiple gated acquisition (scan) |
| NCI | National cancer institute |
| NMIBC | Non-muscle Invasive Bladder Cancer |

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| o.d. | *omnia die*/once a day |
| ORR | Overall response rate |
| OS | Overall survival |
| PD | Progressive disease |
| PD | Pharmacodynamic |
| PDGFRβ | Beta-type platelet-derived growth factor receptor |
| PE | Pulmonary embolism |
| pERK | Phosphorylated extracellular signal-related kinase |
| pFRS2 | Phosphorylated factor receptor substrate-2 |
| PFS | Progression free survival |
| PK | Pharmacokinetic |
| PLGF | Placental growth factor |
| p.o. | *per os*/by mouth/orally |
| PPS | Per protocol set |
| PR | Partial response |
| PRO | Patient-reported outcome |
| QOL | Quality of life |
| RAP | The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses |
| RCC | Renal cell cancer |
| REB | Research Ethics Board |
| RECIST | Response evaluation criteria in solid tumors |
| RTK | Receptor tyrosine kinase |
| SAE | Serious Adverse Event |
| SBP | Systolic blood pressure |
| SCF | Stem cell factor |
| SD | Stable Disease |
| SEC | Study evaluation completion |
| SGOT | Serum glutamic oxaloacetic transaminase/AST |
| SGPT | Serum glutamic pyruvic transaminase/ALT |
| SOP | Standard Operating Procedure |
| SSC | Study steering committee |
| SUSAR | Suspected unexpected serious adverse reaction |
| TIA | Transient ischemic attack |
| TKI | Tyrosine kinase inhibitor |
| TrkA | Tyrosine kinase A receptor |
| TSH | Thyroid stimulating hormone |
| TURBT | transurethral resection of bladder tumor |
| ULN | Upper limit of normal |
| UNE | Upper limit not estimable |
| UPC | Urine protein/creatinine ratio |
| VEGF | Vascular endothelial growth factor |
| VEGFR | Vascular endothelial growth factor receptor |
| WHO | World health organization |

## Glossary of Terms

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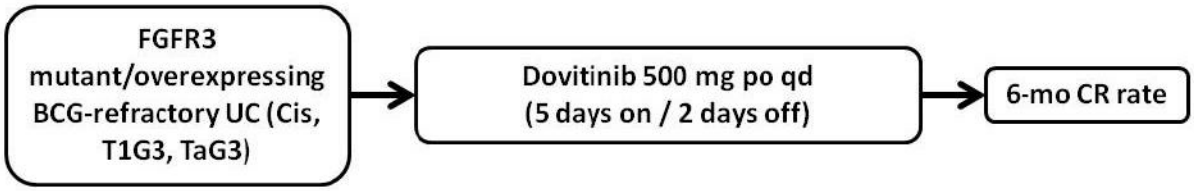
| Assessment | A procedure used to generate data required by the study |
| Control drug | A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug |
| Cycles | Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days) |
| Enrollment | Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol) |
| Investigational drug | The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug." |
| Investigational treatment | Drug whose properties are being testing in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage |
| Other study treatment | Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment |
| Patient number | A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study |
| Period | A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc. |
| Premature patient withdrawal | Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival |
| Randomization number | A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment |
| Stage related to study timeline | A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc. |
| Stage in cancer | The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body |
| Stop study participation | Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later |
| Study drug | Any drug administered to the patient as part of the required study procedures; includes investigational drug and any combination or control drug(s) |
| Study treatment | Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins.<br>In specific examples where it is important to judge study treatment relationship relative to a drug component of a combination treatment, study treatment in this case can refer to a drug component |
| Study drug discontinuation | Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal |
| Variable | Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points |

## SCHEMA

Phase II Trial of Dovitinib in BCG-Refractory Urothelial Carcinoma Patients with Tumor FGFR3 Mutations or Over-expression: Hoosier Cancer Research Network GU12-157




- Assessments
  - SOC Cystoscopy, urine cytology, TURBT q3month
  - CBC, CMP, toxicity assessment qMonth
- Key Stats
  - The 6-month CR rate will be estimated with a one-sided 90% confidence interval of Agresti-Coull type. With an expected CR rate of $\geq 25\%$, a sample size of 20 patients will have a power of 0.80 to exclude a lower bound being $\leq 10\%$.
- Key Eligibility
  - Failure to achieve CR within 6 mo of initial BCG or recurrence within 12 mo of CR from prior BCG
  - FGFR3 mutation accessed by massively parallel sequencing analysis using the Ion Torrent PGM instrument or over-expression by IHC
  - Medically unfit to undergo cystectomy or willing to forego cystectomy
  - ECOG PS 0-2
  - No concurrent upper tract tumors

# 1. Background

## 1.1 Overview of Non-Muscle Invasive Urothelial Carcinoma of the Bladder (NMIBC) and Current Treatment Options for BCG-Refractory Patients

### 1.1.1 Non-Muscle Invasive Urothelial Carcinoma of the Bladder (NMIBC)

Currently, urothelial carcinoma (UC) of the bladder is the fifth most common site of new human cancer diagnoses. In 2012, over 73,000 individuals will be diagnosed with UC, and more than 14,000 patients will die from their disease (Siegel et al., 2012). Most new UC cases (~ 50,000 patients) are non-muscle invasive at diagnosis with disease limited to the mucosal epithelium (Ta/Tis) and immediate connective tissue layer beneath the mucosa (T1) (Ries et al., 2003). The clinical course of non-muscle invasive UC of the bladder (NMIBC) is dominated by frequent recurrences and surveillance testing (cystoscopy, bladder biopsy, urine cytology, etc.). The need for long-term invasive monitoring and treatment has significant cost and morbidity consequences for UC patients. Compared to other malignancies, UC ranks highest in lifetime per patient costs with an average cost from diagnosis to death of $96,500 per patient (Botteman et al., 2003).

High-risk NMIBC affects 25,000 patients each year and is defined by any carcinoma in-situ histology, T1 tumors, grade 3 tumors, tumors > 3 cm in size regardless of grade, greater than three tumors at presentation, and tumors that have recurred within 12 months of prior resection (Holmang et al., 1999, Pow-Sang and Seigne, 2000). Progression to muscle invasive stages requiring complete cystectomy for effective management occurs in 40% of high-risk NMIBC patients. Progression to metastatic disease occurs in 20-30% of these individuals with death due to UC in nearly all of these patients (Cookson et al., 1997, Heney et al., 1983, Kurth et al., 1995, Millan-Rodriguez et al., 2000).

### 1.1.2 Intravesical Bacillus Calmette-Guerin (BCG) for High-risk Non-Muscle Invasive UC of the Bladder (NMIBC)

Standard therapy for high-risk NMIBC patients include transurethral resection of bladder tumor (TURBT) augmented by intravesical administration of Bacillus Calmette-Guerin (BCG). BCG is a bovine mycoplasma derived agent which creates a profound inflammatory reaction in the bladder epithelium, and thereby, reduces tumor recurrences. BCG therapy is typically administered on a weekly basis for six weeks via a urinary catheter which remains in the bladder for 2-3 hours during each administration. The optimal length of BCG therapy beyond the six-week induction phase is unknown. Two meta-analyses of randomized trials of TURBT + BCG versus TURBT alone demonstrated a reduction in 12-month tumor recurrence rate from 56% to 29% ($p<0.001$) and a reduction in progression to muscle-invasive stages from 13.8% to 9.8% ($p=0.001$) in association with BCG therapy. No improvement in overall survival was observed with the use of BCG therapy (Shelley et al., 2000, Sylvester et al., 2002).

### 1.1.3 Clinical Challenges of Post-BCG Tumor Recurrences

While BCG therapy is successful at preventing early tumor recurrences with 12-month post-BCG recurrence free survival rates approaching 70%, most patients do not maintain sustained remissions (Shelley et al., 2000). With 5-year follow-up, recurrent bladder tumors requiring repetitive TURBT and further cystoscopic surveillance are observed in 66% of patients (Herr, 2009). For post-BCG UC tumor recurrences, a second six-week course of BCG may be administered at the discretion of the treating urologist if a significant disease-free

interval was observed between the initial BCG instillation and the tumor recurrence. Ultimately, however, failure of BCG to prevent tumor recurrences presents a significant clinical challenge in the management of NMIBC patients.

Although a consensus definition is not established, UC patients with post-BCG recurrent tumors are generally classified as: 1) *BCG-refractory* – failure to achieve a tumor-free state by 6 months after initial BCG treatment; 2) *BCG-resistant* – persistent tumor noted at 3 months after initial BCG treatment but to a lesser degree/stage/grade which clears by 6 months with additional BCG treatment; 3) *BCG relapsing* – recurrent tumor noted in follow-up after achieving a disease-free state at 6 months after initial BCG treatment; 4) *BCG-intolerant* – recurrent tumor noted after a suboptimal initial BCG treatment which was truncated due to treatment related toxicity. These definitions have important prognostic implications particularly in the BCG-refractory population where 5-year rates of progression to muscle-invasive stage is observed in 58% of patients (Herr, 2009).

### 1.1.4 Non-surgical Approaches to Treating BCG-Refractory UC patients

Given the high-rate of progression to muscle-invasive stages, both the American Urological Association and the European Association of Urology have advocated for cystectomy as a standard option for BCG-refractory UC patients (2007, Babjuk et al., 2008). However, due to the 28% morbidity and 3% mortality rates associated with cystectomy, many patients either have co-morbidities precluding surgical intervention or electively seek nonsurgical alternative therapy options (Stein et al., 2001). Thus, a high interest and need exists to develop non-surgical alternative therapies for BCG-refractory UC patients.

Additional intravesical therapy with non-BCG agents has been extensively evaluated both in the front-line and post-BCG settings. Representative agents include mitomycin C, doxorubicin, gemcitabine, thiotepa, interferon-alpha, docetaxel, and valrubicin. In addition, newer technologies aimed at improving drug delivery such as local microwave hyperthermia and electromotive intravesical mitomycin C have been explored (O'Donnell and Boehle, 2006, Yates and Rouprêt, 2010). Most often, however, trials have enrolled a mixture of BCG-refractory and BCG -relapsing patients making between-study comparisons difficult.

For true BCG-refractory UC patients, gemcitabine and valrubicin are the most thoroughly studied agents. Gemcitabine is a deoxycytidine analogue inhibitor of DNA synthesis with broad clinical activity in UC (El Karak and Flechon, 2007). In a phase I study in BCG-refractory or BCG-intolerant UC patients, Dalbagni et al determined a maximum tolerated dose (MTD) of 2000 mg with intravesical gemcitabine administered twice weekly in 100 ml normal saline solution with a 1-hour bladder dwell time in three week cycles. Treatment was well tolerated. At the MTD, one of six patients had grade 3 thrombocytopenia and neutropenia in the absence of infection. Encouraging clinical activity was observed with 7 of 18 patients (39%) demonstrating a complete response (no tumor on bladder biopsy or urine cytology) (Dalbagni et al., 2002). In a subsequent phase II study of intravesical gemcitabine administered according to the same phase I schedule at the 2000 mg dose and conducted in 30 BCG-refractory or BCG-intolerant patients, Dalbagni et al observed a complete response rate of 50% at the first post-gemcitabine cystoscopic examination with 30% of patients recurrence-free at 6-months. Only 3 patients (10%) maintained a complete remission for 12 months or longer. At 1 year, the cumulative rate of progression to muscle-invasive stages was 3.5%. Treatment continued to be well-tolerated with rare grade 3 toxicities including: dysuria (20%), cellulitis (3%), rash (3%) (Dalbagni et al., 2006).

Valrubicin is an N-trifluoroacetyl, 14-valerate derivative of the anthracycline doxorubicin. Valrubicin inhibits the breaking and resealing of DNA strands by topoisomerase II resulting in cell cycle arrest between S and $G_2$ phases (Onrust and Lamb, 1999). In a phase I study in 32 patients eligible for intravesical therapy, 70% of whom had received prior BCG treatment, Greenberg et al determined an 800 mg intravesical MTD for valrubicin when administered weekly in a six week cycle with a 2-hour bladder dwell time. Urinary symptoms including dysuria (53%), urinary frequency (32%), local urinary burning symptoms (28%), and hematuria

(22%) were the most commonly observed treatment related toxicities. Complete response was observed in 13 patients (41%) (Greenberg et al., 1997). In a larger phase II study of intravesical valrubicin according to the phase I dose and schedule but restricted to a patient population of 90 BCG-refractory carcinoma in-situ UC patients, Steinberg et al observed a complete response rate at six months of 21% (19 patients). Of the patients with complete response at six months, 13 maintained their response 12 months or greater duration for a 12-month recurrence free rate of 14%. Forty-four patients underwent cystectomy with 6 patients (7%) observed to have pathologic T3 or greater disease. A toxicity profile similar to the phase I valrubicin experience was observed with urinary frequency (66%), urinary urgency (63%), and dysuria (60%) as the most commonly reported side effects.(Steinberg et al., 2000) Based on these trial results, valrubicin was originally approved by the FDA for the treatment of BCG-refractory UC carcinoma in-situ patients in 1998 and later re-approved in May 2007 for the same indication after manufacturing quality concerns were addressed (2010b).

Collectively, gemcitabine and valrubicin both demonstrate promising initial complete response rates in BCG-refractory UC patients. However, both agents produce durable remissions of greater than 1 year in only 10-15% of patients. Therefore, a need clearly exists to explore the clinical efficacy of novel agents in this high-risk NMIBC population.

### 1.1.5 Vascular Endothelial Growth Factor (VEGF) as a Therapeutic Target in UC

The critical role of angiogenesis in migration, proliferation, and metastasis of malignant tumors is well established (Folkman, 1971, Folkman, 1975, Folkman, 1986, Folkman, 1995, Kerbel and Folkman, 2002). Vascular endothelial growth factor (VEGF) is a key mediator of angiogenesis. In UC, investigators have demonstrated associations between tumor VEGF expression and prognosis (Fauconnet et al., 2009, Yang et al., 2004). Specifically, increased expression of the VEGF receptor has been associated with more advanced stage and tumor grade in UC patients (Swellam and El-Aal, 2005). In preclinical UC models, the addition of anti-angiogenic agents to platinum-based chemotherapy has shown improved tumor control (Kong et al., 2005, Sonpavde et al., 2009, Zhang et al., 2002). In a phase II study in 77 post-platinum metastatic UC patients treated with the oral VEGF receptor tyrosine kinase inhibitor sunitinib, Gallagher et al observed a partial response rate of 5% (4 patients). However, some tumor regression or stable disease lasting > 12 weeks was achieved in 43% of patients (Gallagher et al., 2010). Similarly, Bellmunt et al examined the activity of sunitinib in 37 chemo-naive platinum-ineligible metastatic UC patients. A partial response rate of 8% was observed with stable disease > 12 weeks in 54% for a clinical benefit rate of 62% (Bellmunt J et al., 2010). In a phase II trial in 43 platinum-eligible front-line metastatic UC patients, Hahn et al observed a 72% response rate (19% complete response, 53% partial response) when the anti-VEGF-A receptor monoclonal antibody bevacizumab was added to standard cisplatin plus gemcitabine chemotherapy (Hahn NM et al., 2010). A promising overall survival of 19.1 months was observed, however, high rates of toxicity were encountered with venous thromboembolic events in 21% of patients and 3 treatment related deaths (1 CNS hemorrhage, 1 aortic dissection, and 1 sudden cardiac death). It is unclear if the toxicity observed in this study is a bevacizumab related phenomenon or a reflection of increased thromboembolic risk in metastatic UC patients undergoing cytotoxic chemotherapy as similar rates have been reported by other investigators in UC patients receiving chemotherapy in the absence of anti-angiogenic therapy (Apolo et al., 2009). Taken together, these studies in advanced poor prognosis UC populations demonstrate promising anti-tumor activity with VEGF directed therapy. Thus, a rationale exists for targeting VEGF in earlier stage UC patients.

### 1.1.6 Fibroblast Growth Factor Receptor as a Therapeutic Target in UC

UC carcinogenesis is a multi-step process that affects multiple cellular genes and signaling pathways. Low-grade NMIBC tumors are characterized by mutations in the fibroblast growth factor receptor-3 (FGFR3) and the Harvey rat sarcoma viral oncogene homologue (HRAS) genes (Mitra et al., 2006, Wu, 2005). FGFR3

mutations or over-expression promote FGFR dimerization and constitutive activation of downstream signaling pathways in the absence of ligand in up to 80% of early-stage UC tumors (Table 1) (Knowles, 2008).

**Table 1-1:** FGFR3 mutation and Over-expression Status According to T-stage

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

While many FGFR3 mutations have been reported, S249C, Y375C, R248C, and G372C account for greater than 95% of all reported mutations (Kompier et al., 2010). These mutations result in a hyperplastic phenotype dominated by frequent tumor recurrences with infrequent progression to muscle-invasive stages. Somatic FGFR3 mutations (see Table 1-2) in exons 7, 10, and 15 will be assessed in FFPE tumor tissues by massively parallel sequencing analysis utilizing the Ion Torrent Personal Genome machine (PGM) and performed in the CLIA-certified Molecular Pathology and Translational Research Laboratory at the Dartmouth Hitchcock Medical Center.

**Table 1-2:** FGFR3 mutations to be analyzed

| **FGFR3 Mutations** |
|---|
| R248C |
| S249C |
| G372C |
| S373C |
| Y375C |
| K562E |
| K562Q |
| K562M |
| K562T |

While FGFR3 mutations are highly associated with low-grade NMIBC, over-expression of FGFR3 has been observed in up to 42% of muscle-invasive UC tumors (Tomlinson et al., 2007). Furthermore, either an FGFR3 mutation or over-expression of the FGFR3 protein in the absence of mutation has been observed in 54% of muscle-invasive UC tumors (Tomlinson et al., 2007). Thus, while FGFR3 mutations likely are an early event in the tumorigenesis of low-grade non-invasive UC tumors, over-expression of FGFR3 may still play a role in the continued proliferation of high-grade muscle-invasive UC tumors. Furthermore, increasing evidence demonstrates that fibroblast growth factor receptor-1 (FGFR1) is a crucial mediator of tumor angiogenesis (Powers et al., 2000). In preclinical tumor models, blockade of the FGF pathway has proven to be an effective method of overcoming resistance to VEGFR inhibitors (Casanovas et al., 2005). Given the previously described importance of VEGF in UC progression, a rationale exists for combined VEGFR and FGFR inhibition in UC patients. A combined VEGFR/FGFR approach may be particularly well suited for early-stage UC patients where both pathways play critical biological roles.

## 1.2 Overview of Dovitinib

Dovitinib is an inhibitor of RTKs: FGFR, VEGFR, PDGFRβ, CSF 1R, c-Kit, RET, TrkA, and FLT3 that mediate tumor cell proliferation and survival.

RTKs are involved in the growth of different types of tumors as well as in the initiation, growth, and maintenance of blood vessels supplying the tumor with blood, oxygen, and nutrients (Arteaga, 2001, Cohen, 2002, Schlessinger, 2000).

Several RTKs are expressed on solid tumors and are involved in cancer cell growth and survival (Collett and Erikson, 1978, Takahashi et al., 1995). In some cases, mutations of these RTKs and their subsequent aberrant signaling are directly linked to the abnormal growth of tumor cells (Deininger et al., 2000, Mizuki et al., 2000). In many other cases, expression and/or over-expression of these RTKs have been demonstrated; however, the exact role of these kinases in tumorigenesis is still unknown. It has been found that some tumors are dependent on a single mutation in a growth factor receptor kinase. These include FLT3 mutations in 20% to 30% of patients with Acute Myeloid Leukemia (AML) (Gilliland and Griffin, 2002); FGFR3 ectopic expression/mutation in 15% to 20% of patients with multiple myeloma (Li et al., 2001, Rasmussen et al., 2003); c-Kit in gastrointestinal stromal tumors (GIST), a rare form of stomach cancer (DeMatteo, 2002), and the Philadelphia chromosome fused gene translocation mutation (Bcr-Abl) in nearly all patients with Chronic Myeloid Leukemia (CML) (Druker et al., 2001a, Druker et al., 2001b).

RTKs such as VEGF receptors, FGF receptors, and PDGF receptors have been shown to play an important role in tumor angiogenesis (Dvorak, 2003). VEGF is produced by both the host and the cancer cells and has a direct effect on endothelial cells, causing their proliferation, migration, invasion, and growth (Nagy et al., 2002). FGFs are potent stimulators of angiogenesis in both normal and pathological tissues, having a direct effect on both vessel assembly and sprouting (Auguste et al., 2003). Blockade of the FGF pathway can overcome resistance to VEGFR inhibitors, emphasizing the importance of FGFR and specifically the need for multi-targeted inhibitors (Casanovas et al., 2005). PDGF receptors are expressed on pericytes - smooth muscle cells that surround the vasculature and provide maintenance and support to the tumor neo-vasculature (Bergers et al., 2003). Inhibition of these three growth factor receptor kinases should provide a powerful and broad inhibition of the angiogenesis process and provide potent anti-tumor effects.

Dovitinib is a broad-targeted-profiled RTK inhibitor active against these three RTKs (VEGF, FGF and PDGF) involved in tumor cell growth. Based on its potency as an inhibitor of these RTKs both in vitro and in vivo, and the compound's oral availability, dovitinib has been investigated as a single agent in metastatic renal cell carcinoma (RCC), metastatic breast cancer (mBC), hepatocellular carcinoma (HCC), endometrial cancer, advanced urothelial cancer (mainly bladder cancer), advanced melanoma, multiple myeloma (MM), acute myeloid leukemia (AML), and other solid tumor studies. It is also being investigated in combination with fulvestrant in a metastic breast cancer study. The maximum tolerated dose (MTD) of dovitinib was 400 mg/day for the continuous once daily dosing regimen and 500 mg/day for the 5 days on/2 days off dosing regimen.

A comprehensive review of dovitinib is contained in the Investigator's Brochure (IB) supplied by the investigational drug supplier, Novartis. This document should be reviewed prior to initiating the study.

### 1.2.1 Mechanism of Action

Dovitinib exhibits a dual mechanism of action: anti-tumor effects via its anti-proliferative activity as well as anti-angiogenic activity. Dovitinib is a potent inhibitor in cells of the VEGFR 1, 2, and 3, FGFR1 (inhibitory concentration 50% (IC50 of 8nM), FGFR2 (IC50 of 40nM) and FGFR3 (IC50 of 9nM), PDGFRβ, c-Kit, RET, TrkA, CSF 1R, and FLT3 with IC50s of less than 40nM. Stem cell factor (SCF) also termed KIT ligand, or steel factor has been shown to modulate tumor angiogenesis (Zhang et al., 2000). In cultured human endothelial cells and c-Kit expressing cancer cells, dovitinib inhibited VEGF- and SCF-stimulated mitogenesis; in a second model of angiogenesis driven by FGF-2, dovitinib potently inhibited neovascularization of Matrigel plugs *in vivo* with an average effective dose (50% inhibition) (ED50) of 3 mg/kg. The effects on endothelial cells suggest that dovitinib may have potent anti-angiogenic activity. PDGFR and FGFR are also believed to play a role in the proliferation of certain tumor cells and supporting stromal cells.

As a result of inhibition of target RTKs by dovitinib, other ligand-stimulated cellular functions are blocked, including activation of downstream signaling molecules, cellular proliferation, and survival. Anti-tumor effects for this agent may therefore be secondary to anti-angiogenesis, anti-proliferative activity against tumor cells, and anti-stromal activity.

### 1.2.2 Clinical Experience

As of 10 September 2013, a total of 2078 patients have been treated across 45 dovitinib clinical trials; including approximately 1693 patients treated in 22 Oncology Clinical Development trials and 385 patients treated in 23 investigator initiated clinical trials.

Adverse events (AEs) and/or laboratory data (hematology and chemistry) were available from 1009 patients as of 10 September 2013. The five most commonly reported non-laboratory AEs were nausea, fatigue, diarrhea, vomiting and decreased appetite for both continuous daily dosing and 5 days on/2 days off dosing regimens**.** Commonly reported AEs were reversible and manageable; most were mild or moderate in severity (CTCAE grade 1 or 2).

The majority of the hematology laboratory abnormalities were grade 1 or 2 events across all dosing regimens. Regarding ANC abnormalities, in the 5 days on/2 days off dosing regimen, there were 20 patients with grade 3 and 5 patients with grade 4 absolute neutrophil count (ANC) decreases out of 455 patients in solid tumor and MM studies. In the Phase III RCC study, there were 5 patients with grade 3 and 2 patients with grade 4 platelet count decreases out of 269 patients evaluable for this parameter. Regarding platelet abnormalities, there were 16 grade 3 and 5 with grade 4 platelet count decrease out of 465 patients in solid tumor and MMstudies . In the Phase III RCC study, there were 3 patients with grade 3 and 3 patients with grade 4 platelet count decrease out of 268.

The most frequent lab test abnormalities observed for biochemistry wereliver function test (LFT) elevations (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, and total bilirubin). In most cases these changes were CTC grade 1 or 2. Below is a brief summary of the grade 3/4 LFT elevations for the 5 days on/2 days off dosing regimen as of 10 September 2013:

- AST: 29 grade 3 and 1 grade 4 were reported out of 784 patients evaluable for this parameter.
- ALT: 24 grade 3 and 2 grade 4 were reported out of 785 patients evaluable for this parameter.
- Total bilirubin: 3 grade 3 and 4 grade 4 were reported out of 782 patients evaluable for this parameter.

As of 30 June 2013, a total of 25 non-HCC patients who received dovitinib treatment had post-baseline LFT elevations defined astotal bilirubin > 2 x ULN and AST and/or ALT > 3 x ULN( including 1 patients whose LFT increase occurred more than 30 days after the last dose of dovitinib). None of the patients qualifies as a

"Hy's Law" case (Reuben, 2004). Please see IB edition 12 Section 5.2.1.5 Hepatic dysfunction as defined by laboratory criteria for more detail.

Two cases of hepatic disorders that were deemed dovitinib-related by the Investigator and resulted in death have been reported as of 10 November 2013. Please see IB edition 12 Section 5.2.1.7Investigator notifications for more detail.

As reported in IB edition 12, baseline and on-study ECG data were available from 854 patients who were treated with TKI258 on the 5 days on / 2 days off schedule across 8 single agent studies, CTKI258A2107, CTKI258A2112, CTKI258A2116, CTKI258A2128, CTKI258A2201, CTKI258A2202, CTKI258A2204, and CTKI258A1101, and one randomized controlled study, CTKI258A2302. Consistent with the September 2009 analyses, outlier analyses did not suggest an effect of dovitinib on the ECG intervals QTcF, PR, or QRS. The proportion of patients with post-baseline QTcF > 480 msec and QTcF > 500 msec were < 1% for each category; the proportion of patients with QTcF change from baseline > 60 msec also was < 1%. Similarly, proportion of patients with notable changes in QRS (increase from baseline > 25% and to a value > 110 msec) and PR (increase from baseline > 25% and to a value > 200 msec) was < 1% for each interval.

As reported in IB edition 12, baseline and on-study cardiac imaging data were available from 527 patients treated with dovitinib across 13 studies: CTKI258A2101, CTKI258A2102, CTKI258A2103, CTKI258A2104, CTKI258A2105, CTKI258A2107, CTKI258A2112, CTKI258A2116, CTKI258A2128, CTKI258A2201, CTKI258A2202, CTKI258A2204, and CTKI258A2302.

Of these 527 patients who had both baseline and on-study data, 20 patients (3.8%) had a post-treatment decrease in ejection fraction (EF) ≥ 20% on ECHO or MUGA. Among these 20 patients, 15 had EF decrease to a value that was below 50% (Table 5-24). The LVEF data and associated clinical data were reviewed by an independent cardiologist consultant. According to his assessment, dovitinib was probably or at least possibly contributory to the decrease in LVEF in 2 cases, based on the available data.

As of the 28 April 2011 cutoff date, the median progression-free survival (95% CI) was 5.45 months (0.03 to 10.68 months) and the median overall survival (95% CI) was 11.79 months (0.95 to 15.57 months) for the 59 advanced RCC patients enrolled into the phase II portion of study CTKI258A2107. In the updated efficacy analysis of the Phase II portion of this study with data cutoff of 30 March 2012, 67 heavily pre-treated patients showed a median progression free survival of 3.7 (CI 3.0-5.6) months. Investigator assessment of median PFS was also 3.7 (CI 3.3-5.5) months with a median OS of 11.8 months. An overall median PFS of 3.7 months is considered to be clinically beneficial in this heavily pretreated population. In phase I clinical pharmacology solid tumor studies (CTKI258A2112 and 2116), the following tumor types have demonstrated clinical benefit (i.e., prolonged disease stabilization for at least 4 months or tumor regression): thyroid cancer, RCC, pancreatic neuroendocrine tumors, colon cancer, adnexal tumor, melanoma, gastrointestinal stromal tumor, prostate cancer, thymoma, and adenoid cystic carcinoma with FGFR1 amplification. In addition, a confirmed partial response has been observed in one patient with advanced ovarian carcinoma (study 2112).

As of September 2012, pharmacokinetic data was available from about 500 patients in phase I and II studies.

Noncompartmental analysis was conducted on full plasma PK profiles of dovitinib. Coefficients of variation in the PK parameters ($C_{max}$ and $AUC_{24}$) ranged from 16 to 111$C_{max}$ was observed at approximately 4-8 hours after dosing, and the concentration of dovitinib declined monoexponentially thereafter. Within the tested dose levels ranging from 50 to 600 mg/day, linear absorption of dovitinib was observed. Dovitinib was extensively distributed to tissues.

Time-dependent PK of dovitinib was observed across all tested dose levels ranging from 50 to 600 mg/day. Following multiple daily administration at doses below 400 mg, the auto-induction of CYP1A1/A2 resulted in lower plasma exposure of dovitinib on day 7 (steady state) than that observed on day 1. However, after increasing the daily dose to 400 - 600 mg, TKI258 plasma concentration on day 7 was found to be similar to or greater than that on day 1, suggesting a more pronounced accumulation of dovitinib at higher doses. In addition, an over-proportional increase in dovitinib plasma exposure was observed with doses from 400 to 600 mg/day. The maximum tolerated dose of dovitinib for the continuous daily dosing schedule was 400 mg (study 2105).

The time-dependent PK and the nonlinear PK resulted in dose-dependent time to reach steady state, as well as dose-dependent accumulation at steady state. To prevent the prolonged and over-proportional accumulation in dovitinib exposure with dose escalation, an intermittent dosing schedule of 5 days on/2 days off was proposed for study 2107. At tested dose levels of 500 mg and 600 mg, no accumulation was observed on day 15 (steady state). The MTD for the 5 days on/2 days off dosing schedule was 500 mg (studies 2107 and 1101).

A human ADME (absorption, distribution, metabolism and excretion) study identified the major metabolites of dovitinib as C-hydroxyl metabolites (in feces) and an N-oxide (in plasma). These metabolites are more than 5-fold less pharmacologically active than the parent drug. The ADME study demonstrated that the majority of the dose administered was recovered from feces, and less than 21% of the dose was recovered in urine. In addition, the oral absorption of dovitinib was ~75% of the dose (2106).

Drug-drug interaction studies are ongoing. Available data from human, as well as *in vitro* studies, demonstrate that dovitinib has low or no inhibition potential for CYP450s. Therefore, dovitinib is not expected to cause inhibitory metabolic drug-drug interactions when co-administered with drugs metabolized by CYP450s. Dovitinib, however, does induce CYP1A2, CYP2C9 and CYP2C19; hence co-administration with substrates of CYP1A2/2C9/2C19 could reduce the exposure of these substrates.

A relative bioavailability (BA) study (2112) was conducted to compare the final market image (FMI) capsule of dovitinib (monohydrate salt) with the clinical service form (CSF) capsule of dovitinib (anhydrate salt). PK data from 16 evaluable patients demonstrated that the FMI capsule and the CSF capsule have comparable bioavailability. Therefore, FMI capsules have replaced CSF capsules to be used in the clinical studies. Similarly, another relative bioavailability study (2116) is being conducted to compare the FMI tablet of dovitinib (monohydrate salt) with the CSF capsule of dovitinib (anhydrate salt). PK data from the first 16 evaluable patients demonstrated that the FMI tablet and CSF capsule have comparable bioavailability. Therefore, FMI tablets are being used in some new clinical studies moving forward.

Tests of food effect (FE) on absorption of dovitinib FMI capsules demonstrated that there was no clinically relevant effect in humans (study 2112). Based on the results of the food effect test, dovitinib FMI capsules can be taken with or without food.

## Summary of potential toxicity in patients

### Gastrointestinal system

Nausea, vomiting, anorexia/decreased appetite, and diarrhea were reported as DLTs in clinical studies with dovitinib. Additionally, they were the top commonly reported AEs for both continuous once daily dosing regimen (N = 155) and 5 days on/2 days off dosing regimen (N = 378 for global, N = 28 for Japan study 1101). Most of these events were mild to moderate (grade 1/2). Grade 3/4 events occurred in less than 10% of patients for both continuous once daily dosing regimen and 5 days on / 2 days off dosing regimen, with an exception of grade 3/4 decreased appetite reported in 14.3% of patients treated in the phase I study in Japan..

Cases of gastrointestinal tract perforation and fistula formation with suspected relationship to the study drug have been reported. Dovitinib inhibits VEGF along with FGFR and PDGF; perforation and fistula formation is a known class effect for VEGF inhibitors.

### Cardiovascular system

Sinus bradycardia and hypertensive crisis were reported as DLTs in clinical studies with dovitinib. Additionally, hypertension was the most commonly reported AE in the 14.3% of patients on 5 days on/2 days off dosing reschedule (N = 378, global studies). Hypertension is a well-known effect of VEGF inhibition. Patients should be monitored for blood pressure as per study protocol. In situations for which hypertension or worsening state is being reported, protocol toxicity management guideline should be followed. When needed, adequate medical care (e.g. anti-hypertensive therapy) should be administered according to the institutional standard practice.

As QT prolongation has been reported in other tyrosine kinase inhibitors, an extensive ECG monitoring schedule has been implemented in 14 clinical studies with dovitinib.

According to the central ECG analysis, available ECG data revealed no effect on cardiac repolarization of dovitinib across days and doses of therapy, nor is there any specific outlier signal observed consistent with the central tendency finding. This conclusion was also supported by a negative result in the exposure-ECG model. ECHO/MUGA evaluation was performed in 14 clinical studies with dovitinib (N = 517). The available data was reviewed by an independent cardiologist consultant, who concluded that, based on the available data; dovitinib probably or at least possibly contributed to a $\geq$ 20% increase in LVEF in 4 patients (0.8%). Nevertheless, please follow study protocol inclusion/exclusion criteria, and adhere to safety monitoring schedule for ECG, cardiac enzymes including troponin, creatine phosphokinase (CK) and MB isoenzyme of creatine phosphokinase (CK-MB), and cardiac imaging (MUGA/ECHO). Toxicity management guideline as provided in the study protocol must be followed when a cardiac abnormality is observed. There is the need for extra caution to patients with history of QT interval prolongation and decreased LVEF.

### Hematologic events

Neutropenia was reported as DLTs from dovitinib clinical studies (continuous once daily dosing regimen) in patients with acute myeloid leukemia or multiple myeloma.

Grade 3 and 4 hematological toxicity is generally not common in patients treated with dovitinib for solid tumors. Grade 3 and 4 decrease in neutrophil values were observed in 3.6% and 1.5% of patients in the global Phase I and II studies, in 1.1% and 0.2% of patients in the global Phase III RCC study, in 3.4% and 0.0% of patients in the global Phase II HCC study and in 10.7% and 3.6% in the Japanese phase I study, respectively. Grade 3 and 4 thrombocytopenia is also uncommon, with grade 3 and 4 decrease in platelet values observed in 3.3% and 0.6% of patients in the global Phase I and II studies, in 0.0% of patients in the global Phase III RCC study, in 8.1% and 1.3% of patients in the global Phase II HCC study, in 1.8% and 1.2% in the Phase I BE study and in 3.6% and 0.0% of patients, respectively in the Japanese phase I study. Additionally, grade 3/4 lymphopenia was reported as an adverse event in 21.4% of patients in the Phase I Japan study (17.9% of grade 3 and 3.6% of grade 4) (Table 5-16).

Investigators are advised to follow protocol provided guidelines for hematologic toxicity management, e.g. dose modification, treatment interruption/discontinuation.

### Hepatic effects

Delayed recovery from AST/ALT elevations and grade 3 liver function disorder were reported as DLTs in dovitinib phase I clinical studies.

Newly occurring or worsening grade 3 and 4 increase in AST values were observed in 5.6% and 0.3% of patients in the global Phase I and II studies, in 0.2% and 0.0% of patients in the global Phase III RCC study, in 26.2% and 1.3% of patients in the global Phase II HCC study, in 1.8% and 0.0% of patients in the Phase I BE study and in 14.3% and 0.0% of patients in the Japanese phase I study, respectively. Newly occurring or worsening grade 3 and 4 increase in ALT values were observed in 5.3% and 0.5% of patients in the global Phase I and II studies, in 0.2% and 0.0% of patients in the global Phase III RCC study, in 15.4% and 1.3% of patients in the global Phase II HCC study, in 0.0% of patients in the Phase I BE study and in 10.7% and 0.0%, respectively in the Japanese phase I study. ALT/AST increased as an adverse event, regardless of study drug relationship, were common in AST and ALT in the global Phase I and II studies; 3.1% and 2.6% of patients for AST and ALT, respectively, in the global Phase III RCC study; 1.8% and 0.6% of patients for AST and ALT, respectively, in the global Phase I BE study; 25.5% and 18.8% of patients for AST and ALT, respectively, in the global Phase II HCC study and 25 - 28.6% of patients in the Japan study) (Table 7-1, Table 7-2, Table 7-3, Table 7-4 and Table 7-5). In addition, grade 3/4 ALT/AST increased, regardless of study drug relationship, were reported in 2.4 - 2.9%, 12.1 - 23.5%, and 3.6% for the 5 days on / 2 days off global Phase I and II studies, Phase II HCC study, and Phase I Japan study, respectively. Of note, no patients treated with dovitinib have experienced hepatotoxicity meeting the criteria for Hy's Law, which is considered predictive of severe drug-related hepatocellular injury.

In addition, a fatal case of hepatotoxicity (cholestatic liver injury) was observed in a patient with metastatic breast cancer after approximately one month of treatment with dovitinib; both the cholestatic liver injury and the death were deemed drug-related by the investigator. A review of the safety database for dovitinib showed that no other serious hepatotoxic event with a similar pattern and severity.

Dovitinib inhibits VEGF, as well as FGFR and PDGF. Hepatotoxicity is a known class effect for VEGF inhibitors. Investigators are reminded to evaluate the pattern of liver function test abnormalities and follow the management paradigm in the study protocols to interrupt or discontinue dovitinib treatment. Dovitinib re-challenge should only be considered if the patient's liver function tests return to grade 1 or baseline.

### Renal system

No DLTs were reported in the renal system in phase I studies. Grade 3 and 4 increase in creatinine values is not common in patients treated with dovitinib (1.6 and 0.8% of patients in the global Phase I and II studies; 0.0 and 0.6% of patients in the Phase I BE study; 0.7 and 0.0% in the HCC study and no grade 3 or 4 creatinine value increase in the Japanese phase I and Phase III RCC studies.

### Other reported toxicities

Increased gamma glutamyltransferase and hypokalemia were the other laboratory DLTs, whereas fatigue/asthenia were the other non-laboratory DLTs reported in. For both dosing schedules (once daily and 5 days on/2 days off), fatigue/asthenia were listed among the commonly reported AEs (≥10% of patients). In addition, fatigue/asthenia had high incidences among all grade 3/4 events.

Other commonly reported adverse events from both dosing schedules, regardless of study drug relationship, include headache, dyspnea, constipation, pyrexia, cough, dyspepsia, and dry mouth. About 3.9% of patients (n = 16) reported for palmar-plantar erythrodysesthesia syndrome (PPES) in the studies using 5 days on/2 days off dosing schedule (N = 378 global studies, and N = 28 Japan study 1101). Among them, 3 grade 3 events were reported and no grade 4 events were observed. PPES has also been reported with the use of other tyrosine kinase inhibitors.

Serum amylase and triglycerides are monitored in the clinical studies with dovitinib, because their abnormal levels were reported in the preclinical toxicology studies. Newly occurring or worsening grade 3/4 increase in triglycerides were reported in patients who have received dovitinib treatment in clinical trials of the 5 days on/2 days off dosing schedule; 88 with grade 3 and 18 with grade 4.

### 1.2.3 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biological processes, pathogenic processes and/or pharmacologic responses to a therapeutic intervention.

In preclinical *in vitro* models in the RT114 and RT4 UC cell lines which over-express FGFR3, significant inhibition of FGFR3 signaling and cell growth was observed in association with dovitinib therapy. Furthermore, in an orthotopic model of FGFR3 S249C activating mutation transformed NIH3T3 fibroblast subcutaneous tumor implants, dovitinib significantly inhibited tumor growth. In addition, dovitinib was well tolerated and demonstrated anti-tumor activity in an orthotopic bladder cancer mouse model in tumors over-expressing FGFR3 (2010a). The relative contributions of FGFR3 over-expression versus specific FGFR3 activating mutations in human urothelial carcinoma have not been fully characterized. Therefore as a secondary objective of this trial we aim to characterize pre- and post-treatment bladder tumor FGFR pathway phosphorylation changes, 6-month CR rates, and 1-year RFS rates according to FGFR3 over-expression versus mutation status.

Biomarkers predictive of clinical efficacy and toxicity are emerging for VEGF directed therapies. In a recent randomized placebo-controlled phase III study (ECOG 2100) of paclitaxel plus bevacizumab (a recombinant humanized monoclonal antibody to VEGF) in the first-line treatment of metastatic breast cancer, patients who received bevacizumab demonstrated a significant prolongation of progression free survival (11.8 vs. 5.9 months, HR=0.60 p=0.001) (Miller et al., 2007). When the entire study population was analyzed (n=772), no significant differences in median overall survival were observed between patients who received bevacizumab and those who received placebo (26.7 months vs. 25.2 months, HR 0.88 p=0.15). In a planned biomarker analysis, the breast cancer tumor genotype frequencies of single nucleotide polymorphisms (SNPs) in seven VEGF and VEGF receptor genes were determined from patient formalin fixed paraffin embedded tissue blocks (FFPE). Patients whose tumors possessed a VEGF (-2578 AA) or a VEGF (-1154 AA) genotype had a marked statistically significant improvement in median overall survival in association with bevacizumab therapy (-2578 AA genotype HR 0.58 p=0.023, -1154 AA genotype HR 0.62 p=0.001) (Schneider et al., 2008). Furthermore, significant associations between hypertension and patients with the VEGF (-634 CC) genotype (p=0.005) and the VEGF (-1498 TT) genotype (p=0.022) were also observed. Confirmation of these observations is planned in a prospective large randomized phase III trial testing the role of bevacizumab in addition to standard chemotherapy for breast cancer patients in the adjuvant setting. Lastly, investigators have also observed associations between the development of treatment related hypertension and favorable clinical outcomes in patients treated with VEGF directed therapies (Bono et al., 2011). To date, no predictors of response to VEGF directed therapy have been examined or reported in bladder cancer. Therefore as additional secondary objectives of this trial we plan to assess associations between improved biologic and clinical outcomes according to VEGFR over-expression, host VEGFR mutation, and treatment related hypertension status.

In addition, the ability to detect circulating tumor cells (CTCs) within the peripheral blood of cancer patients is well established (Yu et al., 2011). While promising, the current FDA approved CellSearch® technology has significant limitations including, but not limited to: 1) the need for real time analysis of specimens within 72 hours of collection; 2) the inability to do full genome profiling of CTC DNA/RNA; and 3) the dependence on tumor cells to express the pan-cytokeratin epithelial marker (EpCAM) on their cell surface and hence an inability to detect cells which have undergone epithelial to mesenchymal transformation (EMT). Accordingly, investigators have begun examining more readily available means to identify, quantify, and characterize tumor genomic content circulating within patients. The study of circulating free DNA/RNA (CFDNA/CFRNA) from peripheral blood and urine demonstrated feasibility in early studies (Gormally et al., 2007). A particular advantage of CFDNA/CFRNA platforms is the ability to analyze banked frozen patients samples. As a purely exploratory objective of this trial, we plan to assess the presence of FGFR3 mutations in patient baseline CFRNA from plasma and CFDNA from urine samples.

Lastly, while dovitinib has demonstrated excellent systemic bioavailability in oral form and the bladder epithelium is well vascularized, confirmation of dovitinib reaching its target will greatly enhance the clinical interpretation of patient outcomes at the completion of the study. As such, a final exploratory objective of this trial will be to measure bladder tissue concentrations of dovitinib at the initial post-treatment biopsy.

# 2 Study Purpose/Rationale

Due to the significant morbidity and quality of life detriments associated with cystectomy, new treatment approaches are clearly needed for BCG-refractory UC patients. Given dovitinib's dual targeting of the VEGFR and FGFR pathways, the preclinical activity of dovitinib in UC cell lines, the convenience of a daily oral administration, and a tolerable side effect profile, a strong rationale exists to test the clinical efficacy of dovitinib in BCG-refractory UC. This is particularly true for patients with tumors harboring FGFR3 mutations or with FGFR3 over-expression.

# 3 Objectives and Endpoints

## 3.1 Primary Objectives

- To determine the 6-month complete response rate in BCG-refractory UC patients with FGFR3 mutant or over-expressing tumors treated with dovitinib.

### 3.1.1 Endpoint for Primary Objectives

- The 6-month complete response rate is defined as the proportion of patients treated with dovitinib with no evidence of any remaining urothelial carcinoma tumors of any T-stage (including Tis) present within the bladder as assessed by standard of care cystoscopic examination with TURBT and urine cytology performed at 6 months after initiation of study therapy.

  NOTE: Patients with residual non-invasive UC tumors with no component of carcinoma in situ (i.e. Ta, T1) at 3-month cystoscopy and TURBT are not considered relapses and will be permitted to continue on dovitinib therapy. If the subsequent 6-month cystoscopy/TURBT, and urine cytology shows no evidence of any remaining urothelial carcinoma in such patients, they will be considered a complete response. Patients with any component of carcinoma in-situ (CIS) at 3-month cystoscopy/TURBT will be considered relapses and will not continue on dovitinib therapy. Any non-invasive UC tumors (i.e. Ta, T1, Tis) at the 6-month or any subsequent cystoscopy/TURBT is

considered relapsed disease. Similarly progression to invasive UC tumors (T2-T4) at any time point is also considered relapsed disease and patients will not continue on dovitinib therapy.

## 3.2 Secondary Objectives

- To determine the 1-year relapse free survival rate in BCG-refractory UC patients treated with dovitinib.
- To determine the rate of progression to muscle-invasive stage (i.e. T2-T4).
- To determine 3- and 6-month partial response rate defined as a reduction in T-stage on post-therapy TURBT (i.e. T1 -> Ta; T1+Tis -> Tis).
- To characterize treatment related toxicity rates assessed by CTCAE v4.0.

### 3.2.1 Endpoint for Secondary Objectives

- The 1-year relapse free survival rate is defined as the proportion of patients treated with dovitinib with no evidence of any remaining urothelial carcinoma tumors at 12 months of follow-up.

  **NOTE:** Patients with residual non-invasive UC tumors with no component of carcinoma in situ (i.e. Ta, T1) at 3-month cystoscopy and TURBT are not considered relapses and will be permitted to continue on dovitinib therapy. If the subsequent 6-month cystoscopy/TURBT, and urine cytology shows no evidence of any remaining urothelial carcinoma in such patients, they will be considered a complete response. Patients with any component of carcinoma in-situ (CIS) at 3-month cystoscopy/TURBT will be considered relapses and will not continue on dovitinib therapy. Any non-invasive UC tumors (i.e. Ta, T1, Tis) at the 6-month or any subsequent cystoscopy/TURBT is considered relapsed disease. Similarly progression to invasive UC tumors (T2-T4) at any time point is also considered relapsed disease and patients will not continue on dovitinib therapy.

- The rate of progression to muscle-invasive stage for dovitinib is defined as the proportion of patients with clinical or pathologic progression to muscle-invasive stages (i.e. T2-T4) at any time point on study. Pathologic progression is assessed by histological finding at TURBT or cystectomy. Clinical progression is assessed by clinician's physical exam and findings on radiologic imaging as ordered per the treating physician's discretion.
  - The 3- and 6-month partial response rates are defined as the proportion of patients treated with persistent but reduced T-stage tumors on post-therapy TURBT (i.e. T1 -> Ta; T1+Tis -> T1).
  - Treatment related toxicity rates will be assessed by CTCAE v4.0.

## 3.3 Exploratory Objectives

- To characterize concordance rates between UC patient detected tumor, urine, and circulating free plasma FGFR3 mutations.
- To characterize associations between pre-treatment germline (as assessed by PBMC extracted DNA) FGFR SNPs and post-treatment 6-month complete response rate and 1-year relapse free survival rate in patients treated with dovitinib.
- To characterize associations between pre-treatment germline (as assessed by PBMC extracted DNA) VEGFR SNPs and post-treatment 6-month complete response rate and 1-year relapse free survival rate in patients treated with dovitinib.

- To characterize VEGFR over-expression status within tumor tissue
- To characterize pre- and post-treatment bladder tumor FGFR and VEGFR pathway phosphorylation changes as assessed by bladder tumor tissue immunohistochemistry.
- To characterize post-treatment bladder tissue dovitinib concentrations.
- To characterize associations between post-treatment hypertension, 6-month complete response rate and 1-year relapse free survival rate in patients treated with dovitinib.

### 3.3.1 Endpoint for Exploratory Objectives

- Presence of FGFR3 mutations (see Table 1-2) in tumor tissue and urine will be assessed by massively parallel sequencing of exons 7, 10, and 15 utilizing the Ion Torrent PGM instrument. Presence of FGFR3 mutations within patient free plasma will be assessed by PCR-amplification of the target regions and sequencing.
- Pre-treatment germline FGFR SNPs will be assessed by testing extracted DNA from patient PBMC's (collected prior to initiating dovitinib therapy) with validated commercial probes.
- Pre-treatment germline VEGFR SNPs will be assessed by testing extracted DNA from patient PBMC's (collected prior to initiating dovitinib therapy) with validated commercial probes.
- Presence of VEGFR over-expression within tumor tissue will be assessed and interpreted by standard immunohistochemistry analysis with appropriate controls.
- Pre- and post-treatment bladder tumor FGFR and VEGFR pathway phosphorylation changes will be assessed by bladder tumor tissue immunohistochemistry utilizing commercially available antibodies including, but not limited to, the following: FGFR3, pFGFR3, VEGFR2, pVEGFR2, FRS2, pFRS2, ERK, pERK.
- Post-treatment bladder tissue dovitinib concentrations will be assessed by TURBT fresh frozen tissue obtained at the 3-month cystoscopy
- Hypertension will be defined as a systolic blood pressure (SBP) of $\geq$ 140 mmHg or a diastolic blood pressure (DBP) of $\geq$ 90 mm Hg recorded at any time after dovitinib therapy is initiated.

Objectives and related endpoints are described in Table 3-1 below.

**Table 3-1 Objectives and related endpoints**

| | Objective | Endpoint | Analysis |
|---|---|---|---|
| Primary | • To determine the 6-month complete response rate in BCG-refractory UC patients with FGFR3 mutant or overexpressing tumors treated with dovitinib | • 6-month complete response rate | Refer to Section 10.5 |
| Key secondary | • To determine the 1-year relapse free survival rate defined in BCG-refractory UC patients treated with dovitinib<br>• To determine the rate of | • 1-year relapse free survival rate | Refer to Section 10.6 |

| | Objective | Endpoint | Analysis |
|---|---|---|---|
| | progression to muscle-invasive stage (i.e. T2-T4) | • Muscle-invasive progression rate | |
| | • To determine 3- and 6-month partial response rate defined as a reduction in T-stage on post-therapy TURBT (i.e. T1 -> Ta; T1+Tis -> Tis) | • 3- and 6-month partial response rate | |
| | • To characterize treatment related toxicity rates assessed by CTCAE v4.0 | • Treatment related toxicity rates | |
| Exploratory | • To characterize pre- and post-treatment bladder tumor FGFR pathway phosphorylation changes | • Pre- and post-treatment bladder tumor FGFR pathway phosphorylation changes will be assessed by bladder tumor tissue immunohistochemistry utilizing commercially available antibodies including, but not limited to, the following: FGFR3, pFGFR3, VEGFR2, pVEGFR2, FRS2, pFRS2, ERK, pERK | Refer to Section 10.7 |
| | • To characterize associations between pre-treatment germline (as assessed by PBMC extracted DNA) FGFR SNPs and post-treatment 6-month complete response rate and 1-year relapse free survival rate in patients treated with dovitinib | • Pre-treatment germline FGFR SNPs will be assessed by testing extracted DNA from patient PBMC's (collected prior to initiating dovitinib therapy) with validated commercial probes | |
| | • To characterize pre- and post-treatment VEGFR pathway phosphorylation changes as assessed by bladder tumor tissue immunohistochemistry | • Pre- and post-treatment bladder tumor VEGFR pathway phosphorylation changes will be assessed by bladder tumor tissue immunohistochemistry utilizing commercially available antibodies including, but not limited to, the following: FGFR3, pFGFR3, VEGFR2, pVEGFR2, FRS2, pFRS2, ERK, pERK | |
| | • To characterize associations between pre-treatment germline (as assessed by PBMC extracted DNA) VEGFR SNPs and post-treatment 6-month complete response rate and 1-year relapse free survival rate in patients treated with dovitinib | • Pre-treatment germline VEGFR SNPs will be assessed by testing extracted DNA from patient PBMC's (collected prior to initiating dovitinib therapy) with validated commercial probes | |
| | • To characterize associations between post-treatment hypertension 6-month | • Hypertension will be defined as a systolic blood pressure (SBP) of $\geq$ 140 mmHg or a | |

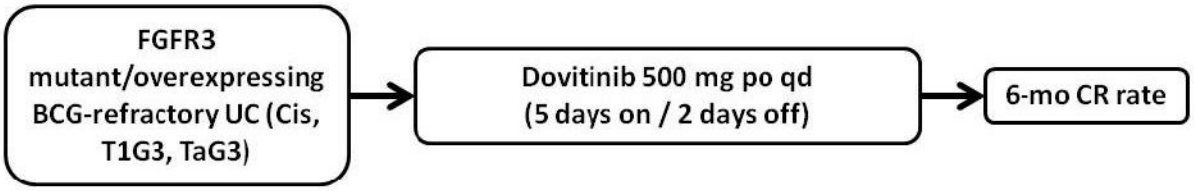
| Objective | Endpoint | Analysis |
|---|---|---|
| complete response rate and 1-year relapse free survival rate in patients treated with dovitinib | diastolic blood pressure (DBP) of ≥ 90 mm Hg recorded at any time after dovitinib therapy is initiated | |
| • To characterize concordance rates between UC patient detected tumor, urine and circulating free plasma FGFR3 mutations | Presence of FGFR3 mutation within patient tumor tissue, urine, will be assessed by massive parallel sequencing analysis of exons 7, 10, and 15 utilizing Ion Torrent PGM instrument. Presence of FGFR3 mutation within patient free plasma will be assessed by PCR-amplification of the target regions and sequencing | |
| • To characterize post-treatment bladder tissue dovitinib concentrations | • Post-treatment bladder tissue obtained at 3-month TURBT will be analyzed by IUSCC Clinical Pharmacology Analytical core according to standard commercial assays | |
| • To characterize VEGFR over-expression status within tumor tissue | • Presence of VEGFR over-expression within tumor tissue will be assessed by standard IHC analysis | |

# 4 Investigational Plan

## 4.1 Study Design

This trial will be a single-arm, non-randomized, multi-center, phase II study conducted through Hoosier Cancer Research Network assessing the 6-month complete response rate and toxicity profile of oral dovitinib therapy in BCG-refractory urothelial carcinoma patients with tumors with FGFR3 mutations or over-expression who are ineligible for or refusing cystectomy. A sample size of 20 evaluable patients receiving dovitinib therapy is expected (up to 50 patients screened). Study design is shown in Figure 4-1. This study will characterize the clinical relevance and viability of FGFR3 and VEGFR as therapeutic targets in this biologically enriched population. Furthermore, due to the routine acquisition of pre- and post-treatment bladder biopsies as standard of care practice, this trial will significantly enhance identification and development of prognostic and predictive dovitinib biomarkers.

**Figure 4-1 Study design**




### 4.1.1 Investigational Treatment, Other Study Treatment, Study Treatment, Supportive Treatment

Investigational treatment in all patients will consist of oral dovitinib 500 mg taken once daily for 5 consecutive days followed by 2 days off repeated every week. Each treatment cycle will be defined as 28 days (4 weeks). In patients not experiencing significant toxicity or relapsed disease, a study-defined maximum number of dovitinib cycles will not be stipulated. Dovitinib will be supplied in the form of 100 mg hard gelatin capsules or film coated tablets.

Standard of care cystoscopy and urine cytology will be performed every 3 months ± 7 days during the first 12 months of follow-up and per the treating urologist's discretion thereafter. Standard of care tumor biopsy and bladder biopsies will be performed every 3 months ± 7 days during the first 6 months of follow-up and per the treating urologist's discretion thereafter.

Anti-emetic medications are permitted at the discretion of the treating physician.

Colony stimulating growth factor (i.e. erythropoietin, darbopoeitin, pegfilgrastim, etc.) support is permitted at the discretion of the treating physician.

**Table 4-1 Study drugs**

| Study drugs | |
|---|---|
| Investigational drug | Dovitinib |
| Standard of Care | Cystoscopy with tumor biopsy, bladder biopsy, urine cytology |
| Physician discretion | Anti-emetic medications |
| Physician discretion | Colony stimulating growth factors |

### 4.1.2 Treatment Arms

This trial is a single-arm non-randomized trial. As such, all patients enrolled will receive dovitinib as outlined in section 4.1.1.

## 4.2 Definition of End of the Study

The study will end when all patients have either: 1) Confirmed relapsed disease OR 2) 12-months of follow-up after discontinuing dovitinib in the absence of relapsed disease.

For early stopping rules for the study see section 10.10 Early Stopping Rules.

## 4.3 Early Study Termination

The study can be terminated at any time for any reason by the Sponsor Investigator or Novartis, the investigational drug supplier. Should this be necessary, the patient should be seen as soon as possible and treated as described in Section 7 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

# 5 Population

The investigator or his/her designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered enrollment in the study.

## 5.1 Inclusion Criteria

Patients eligible for inclusion in this study have to **meet all** of the following criteria:

1. Histologically confirmed non-muscle invasive urothelial carcinoma of the bladder defined as Ta, T1, or Tis stage. Tumor staging must be confirmed by TURBT performed within 42 days prior to registration.
2. Presence of either an FGFR3 mutation or FGFR3 over-expression within bladder tumor tissue. Somatic FGFR3 mutations (see Table 1-2) in exons 7, 10, and 15 will be assessed in FFPE tumor tissues by massively parallel sequencing analysis utilizing the Ion Torrent Personal Genome Machine (PGM) and performed in the CLIA-certified Molecular Pathology and Translational Research Laboratory at the Dartmouth Hitchcock Medical Center. FGFR3 over-expression will be assessed by standard IHC analysis performed within the Indiana University Simon Cancer Center Immunohistochemistry (IHC) Core Lab.

   NOTE: Patients will initially be allowed to enroll if their tumors demonstrate either an FGFR3 mutation or FGFR3 over-expression. However, a minimum of 10 FGFR3

mutation positive patients will be enrolled at study completion. If 10 patients with tumors that are FGFR3 over-expressors but FGFR3 mutation negative are accrued prior to enrolling 10 FGFR3 mutation positive patients, subsequent enrollment will be restricted to patients with tumors that are FGFR3 mutation positive.

3. Documented BCG-refractory disease defined as failure to achieve a tumor free state after at least 2 prior intravesical treatment courses, one of which must have been intravesical BCG therapy.

   **NOTE:** There is no maximum limit on the number of prior BCG therapy courses. In addition, there is no maximum limit on the number of prior non-BCG intravesical therapy courses (i.e. gemcitabine, valrubicin, interferon, mitomycin C, etc.).
4. Medically unfit to undergo cystectomy or electively choosing to forego cystectomy
5. ECOG (WHO) performance status 0 or 1 or 2
6. Age ≥ 18 years old
7. Patients must have the following laboratory values:
   - White blood cell count (WBC) ≥ 3.0 K/mm$^3$
   - Absolute neutrophil count (ANC) ≥ 1.5 K/mm$^3$
   - Platelets ≥ 100 K/mm$^3$
   - Hemoglobin (Hgb) ≥ 9 g/dL
   - Serum total bilirubin: ≤ 1.5 x ULN
   - ALT and AST ≤ 3.0 x ULN
   - Serum creatinine ≤ 1.5 x ULN or serum creatinine >1.5 – 3 x ULN if calculated creatinine clearance (CrCl) is ≥ 30 mL/min using the Cockcroft-Gault equation, see formula below:

     CrCl = [140-age (years)] x weight (kg) / [72 x serum Cr (mg/dL)] (if patient is female multiply the above by 0.85)
   - Urine dipstick reading: Negative for proteinuria or, if documentation of +1 (+2 for patients with renal cell carcinoma) results for protein on dipstick reading, then total urinary protein ≤ 500 mg and measured creatinine clearance ≥ 50 mL/min/1.73m$^2$ from a 24 hour urine collection
8. Patients who give a written informed consent obtained according to local guidelines

## 5.2 Exclusion Criteria

Patients eligible for this study **must not meet any** of the following criteria:

1. Patients with muscle-invasive (i.e. T2, T3, T4), locally advanced non-resectable, or metastatic urothelial carcinoma as assessed on baseline radiographic imaging obtained within 28 days prior to study registration. The required radiographic imaging includes:
   a. Abdomen/Pelvis – CT scan
   b. Chest – chest x-ray or CT scan
2. Patients with concurrent upper urinary tract (i.e. ureter, renal pelvis) non-invasive urothelial carcinoma.

3. Patients with another primary malignancy within 3 years prior to starting study drug, with the exception of adequately treated in-situ carcinoma of the uterine cervix, clinically localized prostate cancer, biochemically relapsed non-metastatic prostate cancer (i.e. PSA only disease), or skin cancer (such as basal cell carcinoma, squamous cell carcinoma, or non-melanomatous skin cancer)
4. Patients who have received the last administration of an anticancer therapy including chemotherapy, immunotherapy, and monoclonal antibodies ≤ 4 weeks prior to starting study drug, or who have not recovered from the side effects of such therapy
5. Patients who have received targeted prior VEGFR or FGFR-targeted agents (i.e. sunitinib, pazopanib, sorafenib, bevacizumab, axitinib, etc.).
6. Patients who have had radiotherapy ≤ 4 weeks prior to starting study drug, or who have not recovered from radiotherapy toxicities
7. Patients who have undergone major surgery (e.g. intra-thoracic, intra-abdominal or intra-pelvic), open biopsy or significant traumatic injury ≤ 4 weeks prior to starting study drug, or patients who have had minor procedures (i.e. TURBT), percutaneous biopsies or placement of vascular access device ≤ 1 week prior to starting study drug, or who have not recovered from side effects of such procedure or injury
8. Patients with any of the following concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study:
    - Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
        a. History or presence of serious uncontrolled ventricular arrhythmias
        b. Clinically significant resting bradycardia
        c. LVEF assessed by 2-D echocardiogram (ECHO) < 50% or lower limit of normal (whichever is higher) or multiple gated acquisition scan (MUGA), < 45% or lower limit of normal (whichever is higher)
        d. Any of the following within 6 months prior to starting study drug: myocardial infarction (MI), severe/unstable angina, Coronary Artery Bypass Graft (CABG), Congestive Heart Failure (CHF), Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA), Pulmonary Embolism (PE)
        e. Uncontrolled hypertension defined by a SBP ≥ 160 mm Hg and/or DBP ≥ 100 mm Hg, with or without anti-hypertensive medication(s)
    - Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of dovitinib (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
    - Cirrhosis, chronic active hepatitis or chronic persistent hepatitis
    - Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory)
    - Patients who are currently receiving anticoagulation treatment with therapeutic doses of warfarin. Full-dose anti-coagulation with low molecular weight heparin is permitted.
    - Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection, uncontrolled diabetes) that could cause unacceptable safety risks or compromise compliance with the protocol

9. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
10. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception (defined below). Highly effective contraception must be used by both sexes (female patients and their *male partners) during study treatment and for 30 days after the last dose of study medication.*

    Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Combination of the following (a+b):

      a. Placement of an intrauterine device (IUD) or intrauterine system (IUS)

      b.Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

    Oral, implantable, or injectable hormone contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study

    Women of child-bearing potential (sexually mature women) who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months), must have a negative serum pregnancy test ≤ 14 days prior to starting study drug.
11. Fertile males not willing to use contraception. Fertile males must use condom with spermicide. Highly effective contraception, as defined above, must be used by both sexes (male patients and their female partners) during study treatment and for 90 days after the last dose of study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
12. Patients unwilling or unable to comply with the protocol

# 6 Treatment

## 6.1 Treating the Patient

The investigator needs to instruct the patient to take the study drug dovitinib as per protocol. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on a drug accountability form (see study procedure manual [SPM] for example) and entered into the EDC system.

### 6.1.1 Administration

Dovitinib will be dosed on a flat scale of 500 mg (i.e. 5 x 100 mg per capsule/tablet) on a 5 days on/2 days off dosing schedule. Dovitinib may be taken with or without food.

- If a patient forgets to take dovitinib at the routinely scheduled time, then the patient can take dovitinib within 6 hours of the routinely scheduled time. If a dose is not taken within this 6 hour window, it should be skipped. If a patient's dose is skipped on a given day, then the patient should resume dovitinib at the routinely scheduled time the next morning, provided it is a scheduled day of dosing.
- If a patient routinely takes his/her dose of dovitinib in the evening, and forgets to take dovitinib as scheduled, then the patient can take dovitinib within 6 hours of the routinely scheduled time. If a dose is not taken within this 6 hour window, it should be skipped. The patient should resume dovitinib at the routinely scheduled time the next evening, provided it is a scheduled day of dosing.

### 6.1.2 Dosing and Treatment Schedule

**Table 6-1 Dosing and treatment schedule**

| Study drugs | Pharmaceutical form and route of administration | Dose | Frequency |
|---|---|---|---|
| Dovitinib | Capsule/tablet for oral use | 500 mg | 5 days on/2 days off |

### 6.1.3 Dose Modification and Dose Delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study drug. The following guidelines need to be applied:

These changes must be recorded in the eCRF.

**Table 6-2 Dose reduction steps for dovitinib**

| | Dose reduction* | | |
|---|---|---|---|
| | Starting dose level - 0 | Dose level - 1 | Dose level - 2 |
| Dovitinib | 500 mg | 400 mg | 300 mg** |
| *Dose reduction should be based on the worst toxicity demonstrated at the last dose.<br>**Dose reduction below 300 mg is not allowed. | | | |

### 6.1.4 Treatment Interruption and Treatment Discontinuation

| Toxicity intensity [a] | Dose modification [b, c] |
|---|---|
| **Cardiovascular** | |
| Hypertension | Treatment-emergent hypertension should be treated as per standard cardiology practice. Recommended agents for the management of blood pressure elevations on dovitinib include angiotensin-converting enzyme inhibitors and calcium channel blockers. |
| SBP < 160 mmHg and/or DBP < 100 mm Hg, with or without anti-hypertensive medication | Maintain dose level |
| SBP ≥160 mmHg and/or DBP ≥ 100 mm Hg, with or without anti-hypertensive medication, but not immediately life-threatening | Delay the study treatment and initiate/intensify antihypertensive therapy.<br>Dovitinib may be restarted in conjunction with standard anti-hypertensive medication if BP is controlled (i.e. BP < 160/100 mmHg).<br>Once BP is controlled after suspending dovitinib, maintain dose level or ↓ 1 dose level at the discretion of the investigator. |
| Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention | Discontinue study treatment permanently |

| Toxicity intensity [a] | Dose modification [b, c] |
|---|---|
| indicated | |
| Left ventricular systolic dysfunction | |
| Left ventricular ejection fraction (LVEF) ≥ 50%/LLN (ECHO), or ≥ 45%/LLN (MUGA) | Maintain dose level |
| LVEF < 50%/LLN (ECHO), or < 45%/LLN (MUGA), or<br>Symptomatic due to drop in ejection fraction responsive to intervention | Delay study treatment until resolved to ≥ 50%/LLN (ECHO) or ≥45%/LLN (MUGA), then ↓ 1 dose level |
| Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support or heart transplant indicated | Discontinue study treatment |
| Other cardiovascular | |
| Grade 1 | Maintain dose level |
| Grade 2 | Maintain dose level<br>If asymptomatic decrease of LVEF by absolute value of 20% and to <LLN, delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level |
| Grade 3 | Delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level |
| Grade 4 | Discontinue study treatment |
| **Gastrointestinal** | |
| Diarrhea | At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated according to institutional standard of care |
| Grade 1 (despite maximal anti-diarrheal medication) | Maintain dose level |
| Grade 2 (despite maximal anti-diarrheal medication) | Delay study treatment, until resolved to ≤ grade 1, then re-start at the current dose level<br>If diarrhea returns as ≥ grade 2, then suspend dose until resolved to ≤ grade 1, then ↓ 1 dose level |
| Grade 3/4 (despite maximal anti-diarrheal medication) | Delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level |
| Nausea | Suspend dose for CTCAE grade 2-3 nausea only if it could not be controlled despite the use of standard anti-emetics. |
| Grade 1 (despite standard anti-emetics) | Maintain dose level |
| Grade 2 (despite standard anti-emetics) | Delay study treatment, until resolved to ≤ grade 1, and then re-start at the current dose level.<br>If nausea returns as ≥ grade 2, then suspend dose until resolved to ≤ grade 1, then ↓ 1 dose level. |
| Grade 3 (despite standard anti-emetics) | Delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level |
| Vomiting | Suspend dose for CTCAE grade 2-4 vomiting only if it could not be controlled despite the use of standard anti-emetics. |
| Grade 1 (despite standard anti-emetics) | Maintain dose level |
| Grade 2 (despite standard anti-emetics) | Delay study treatment, until resolved to ≤ grade 1, and then re-start at the current dose level.<br>If nausea returns as ≥ grade 2, then suspend dose until resolved to ≤ grade 1, then ↓ 1 dose level. |
| Grade 3/4 (despite standard anti-emetics) | Delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level |
| **Hematologic** | |

| Toxicity intensity [a] | Dose modification [b, c] |
|---|---|
| Febrile neutropenia (Grade 3 or 4)<br>(Per protocol) fever of unknown origin without clinically or microbiologically documented infection (ANC <1.0 x $10^9$/L, fever ≥ 38.5°C) | Delay study treatment until resolved, then ↓ 1 dose level |
| ≥ Grade 3 anemia judged to be a hemolytic process secondary to study treatment | Discontinue study treatment. |
| ≥ Grade 3 lymphopenia considered clinically significant | Requires dose interruption until resolved to ≤ grade 1, then ↓ dose level. |
| Neutropenia/Neutrophil count decreased | |
| Grade 1 or 2 | Maintain dose level |
| Grade 3<br>Grade 4 | Delay study treatment until resolved to ≤ grade 2, then:<br>If resolved by ≤ 7 days after suspending dovitinib, maintain dose level<br>If resolved by > 7 days after suspending dovitinib, ↓ 1 dose level |
| Thrombocytopenia/Platelet count decreased | |
| Grade 1 or 2 | Maintain dose level |
| Grade 3 | Delay study treatment until resolved to ≤ grade 1, then:<br>If resolved by ≤ 7 days after suspending dovitinib, maintain dose level<br>If resolved by > 7 days after suspending dovitinib, ↓ 1 dose level |
| Grade 4 | Delay study treatment until resolved to ≤ grade 1, then ↓ 1 dose level |
| **Hepatic** | |
| ≥ grade 3 alkaline phosphatase or GGT | Isolated values of ≥ grade 3 alkaline phosphatase or GGT values will NOT require dose interruption. |
| **ALT or AST** | |
| ≤ 3.0 x ULN | Maintain dose level with LFTs[e] monitored as per protocol. |
| > 3.0 to ≤ 5.0 x ULN,<br>without bilirubin elevation to > 2.0 x ULN | Maintain dose level with weekly monitoring of LFTs[e], or more frequently if clinically indicated, until resolved to ≤ grade 1 or baseline. |
| > 5.0 x ULN | Delay study treatment until resolved to ≤ grade 1 or baseline, then ↓ 1 dose level.<br>Monitor LFTs[e] weekly, or more frequently if clinically indicated, for 8 weeks; then, every 2 weeks for 4 weeks; then, every 4 weeks as per protocol.<br>Following re-introduction of dovitinib, if ALT or AST elevations > 3 x ULN recur as assessed on 2 separate measurements no more than 1 week apart, then study treatment should be permanently discontinued.<br>If study treatment is permanently discontinued, then patients should be monitored weekly (including LFTs[e]), or more frequently if clinically indicated, until AST or ALT have resolved to ≤ grade 1 or stabilization (i.e., no CTCAE grade change over 4 weeks). |
| **Total bilirubin** | |
| ≤ 1.5 x ULN | Maintain dose level with LFTs[e] monitored as per protocol. |
| > 1.5 to 3.0 x ULN<br>with ALT or AST ≤ 3.0 x ULN | Maintain dose level with LFTs[e] monitored as per protocol. |

| Toxicity intensity [a] | Dose modification [b, c] |
|---|---|
| > 3.0 x ULN | Discontinue study treatment permanently.<br>Patients should be monitored weekly (including LFTs[e]), or more frequently if clinically indicated, until total bilirubin has resolved to ≤ grade 1 or stabilization (i.e., no CTCAE grade change over 4 weeks).<br>Note: If grade 3 or grade 4 hyperbilirubinemia is due to the indirect component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator. |
| **ALT or AST, and concurrent Bilirubin elevation** | |
| ALT or AST > 3.0 x ULN<br>AND<br>Total Bilirubin > 2.0 x ULN | Discontinue study treatment permanently.<br>Patients should be monitored weekly (including LFTs[e]), or more frequently if clinically indicated, until ALT/AST and total bilirubin have resolved to ≤ grade 1 or stabilization (i.e., no CTCAE grade change over 4 weeks). |
| **Renal** | |
| Serum creatinine | |
| Grade 1 or 2 | Maintain dose level |
| Grade 3 | Delay study treatment until resolved to ≤ grade 1 or baseline, then ↓ 1 dose level |
| Grade 4 | Discontinue study treatment |
| Amylase and/or lipase elevations | |
| Asymptomatic Grade 1 or 2 | Maintain dose level |
| Asymptomatic Grade 3 or 4 | Patients who develop grade 3 or 4 hyperlipasemia or hyperamylasemia without clinical or other evidence of pancreatitis may continue study medication without interruption |
| **Pancreatitis** | |
| Grade 2 | Maintain dose level |
| Grade 3 or 4 | Discontinue study treatment |
| Hand-foot syndrome | |
| Grade 1 or 2 | Maintain dose level |
| Grade 3 | Delay study treatment until resolved to ≤ grade 1 then ↓ 1 dose level |
| Grade 4 | Discontinue study treatment |
| **Other clinically significant adverse events** | |
| Grade 1 or 2 | Maintain dose level |
| Grade 3 (except hyperlipidemia [d]) | Delay study treatment until resolved to ≤ grade 1 or baseline, then maintain dose level or ↓ 1 dose level at the discretion of the investigator |
| Grade 4 | Delay study treatment until resolved to ≤ grade 1 or baseline, then ↓ 1 dose level or discontinue dovitinib at the discretion of the investigator |
| All dose modifications should be based on the worst preceding toxicity. | |
| [a] Common Terminology Criteria for Adverse Events (CTCAE) v4.03 | |
| [b] Patients are allowed two dose reductions: a dose reduction to 400 mg from 500 mg, and, if necessary, a dose reduction to 300 mg from 400 mg. | |
| [c] If a patient requires a dose interruption of > 14 days starting from the first day a dose was missed, then the patient must be discontinued from the study. Patients who discontinue the study for a study related adverse | |

| Toxicity intensity [a] | Dose modification [b, c] |
|---|---|
| event including an abnormal laboratory value must be followed at least once a week for 4 weeks and subsequently at 4 week intervals until resolution or stabilization of the event, whichever comes first. | |
| [d] Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using standard therapies. Fluvastatin and Rosuvastatin may have potential of drug to drug interactions. If these statins are prescribed, close clinical monitoring including serum lipids is required since dovitinib could reduce the exposure of statins. Statins should be prescribed according to product label/data sheets for HMG-CoA reductase inhibitors. Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Blood tests to monitor hyperlipidemia must be taken in the fasting state. Grade 2 or higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or Grade 2 or higher hypertriglyceridemia (>2.5 x ULN) should be treated with fibrate, or appropriate lipid-lowering medication in addition to diet. | |
| [e] LFTs include albumin, ALT, AST, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated [quantification of isoenzymes], if alkaline phosphatase ≥ Grade 2), and GGT. | |

### 6.1.5 Permitted Concomitant Therapy

Anti-emetic medications are permitted at the treating physician's discretion.

Colony stimulating growth factor (i.e. erythropoietin, darbopoietin, pegfilgrastim) support is permitted at the treating physician discretion.

Full dose anti-coagulation with low molecular weight heparin (i.e. enoxaparin, fondaparinux) is permitted.

The patient needs to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be recorded in the eCRF.

### 6.1.6 Prohibited Concomitant Therapy

Full dose anti-coagulation with warfarin is not permitted.

### 6.1.7 Hormonal Contraception Excluded

Hormonal contraception is not allowed during the study. Women of childbearing potential are required to use two forms of highly effective contraceptives (e.g. male condom with spermicidal; diaphragm with spermicide; intra-uterine device).

## 6.2 Study Drug(s)

### 6.2.1 Packaging and Labeling

Dovitinib will be provided as a gelatin capsule or film coated tablet of 100 mg strength . The capsules/tablets will be provided in either blisters or bottles. Dovitinib medication labels will comply with the legal requirements of each country and be printed in the local language. The inactive ingredients for the dovitinib capsules are pregelatinized starch, colloidal silicon dioxide, microcrystalline cellulose, and magnesium stearate.

### 6.2.2 Supply, Receipt and Storage

The study drug must be stored in a secure area, limited access area. The storage conditions are

described on the medication label. It will be administered only to patients entered into the clinical study, at no cost to the patient, in accordance with the conditions specified in this protocol. The capsules/tablets should be stored according to the label in a secured, limited access area until required.

Investigational pharmacy will maintain accurate records demonstrating dates and amount of study drug shipped, to whom dispensed (patient by patient accounting), and accounts of any study treatment accidentally or deliberately destroyed. At the end of the study, reconciliation must be made between the amount of study drug supplied, dispensed, and subsequently destroyed or returned.

Details are listed in Table 6-3 below.

**Table 6-3 Drug Supply and Storage**

| Study drugs | Supply | Storage |
|---|---|---|
| Dovitinib | Centrally supplied by Novartis | Please see study drug label |

### 6.2.3 Dispensing and Preparation

Capsules/tablets including instructions for administration are dispensed by study personnel on an outpatient basis.

Patients will be provided with adequate supply of study drug for self-administration at home until at least their next scheduled study visit.

### 6.2.4 Drug Compliance and Accountability

#### 6.2.4.1 Drug Compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the drug accountability form (see SPM). This information must be captured in the source document at each patient visit.

#### 6.2.4.2 Drug Accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability form (see SPM). Drug accountability will be documented. Patients will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation.

### 6.2.5 Disposal and Destruction

Any unused study dovitinib will be documented and disposed of according to institutional standards. Documentation of the destruction should be recorded on the drug accountability form (see SPM).

### 6.2.6 Other Concomitant medication

Patients must be instructed not to take additional medications including over-the-counter products and herbal/alternative medications during the study without prior consultation with the

investigator. It is important to avoid concomitant medications that are known to cause hepatotoxicity.

Oral contraceptives are generally metabolized by CYP3A4/2C9, and act also as a moderate inhibitor of CYP1A2, therefore should not be used. Thus, patients who are sexually active and are using oral contraceptives as a method of contraception should change to two highly effective contraceptive methods during the study participation.

Permitted treatments during the study include, but are not limited to the following:

- Pain medication to allow the patient to be as comfortable as possible
- Nutritional support or appetite stimulants (e.g. megestrol)
- Oxygen therapy and blood products or transfusions
- Prophylactic anti-emetics are allowed for patients who, at the discretion of the investigator, have experienced ≥ grade 1 nausea or vomiting.
- Hematopoietic growth factors should be used according to the guidelines established by the American Society of Clinical Oncology (ASCO) or as dictated by local practice. The ASCO guidelines are available [http://jco.ascopubs.org/cgi/content/full/24/19/3187]
- The administration of anticoagulation and antiaggregation agents (e.g. eptifibatide, epoprosterol, prasugrel, dipyridamole, fondaparinux) should be allowed except prasugrel, due to its potential drug-drug interaction with dovitinib. Prasugrel is primarily metabolized by the CYP3A4 and CYP2B6 and to a lesser extent by the CYP2C9 and CYP2C19. In vitro study demonstrated that dovitinib is an inducer of CYP2C9 and CYP2C19, co-administration of dovitinib with prasugrel is likely to reduce the exposure of prasugrel. For oral anticoagulants, the upper limit of INR is < 1.5.
- The administration of androgen deprivation therapy or orchiectomy as part of the definitive treatment for clinically localized prostate cancer or biochemically relapsed non-metastatic (i.e. PSA relapse only) is permitted.

The following concomitant treatments are not allowed during the study:

- Concurrent use of isoniazid, labetalol, trovafloxacin, tolcapone, and felbamate are not permitted, since alternative less hepatotoxic drugs are available to use.
- Concurrent use of other investigational drugs is not permitted.
- The administration of other antineoplastic therapy (e.g. chemotherapy, immunotherapy, targeted therapy, monoclonal antibodies and radiation therapy) is not permitted.
- The administration of anti-androgen therapy (e.g. bicalutamide, flutamide, nilutamide) for the treatment of prostate cancer is not permitted.
- The administration of androgen deprivation therapy or orchiectomy for the treatment of metastatic prostate cancer is not permitted.

### 6.2.7 Pharmacokinetic Interactions

Dovitinib is metabolized mainly by CYP1A1/2 and FMO. FMO is not readily induced or inhibited by any other agents, therefore the drug-drug interactions between dovitinib and FMO inducers/inhibitors are of lesser concern. To a lesser extent, dovitinib could be metabolized by CYP3A4, CYP2C8, and CYP2D6 enzymes.

Though no drug interactions have been studied clinically, drugs that inhibit (ciprofloxacin, clinafloxacin, enoxacin, fluvoxamine, oltipraz, propranolol, rofecoxib, thiabendazole, and zafirlukast) or induce CYP1A1/2 (omeprazole and tobacco) may interact with dovitinib and should be used with caution.

In vitro, dovitinib has a potential to induce CYP1A2 activity 2- to 14-fold, as well as CYP2C9 and CYP2C19 activity to a lesser extent (< 3- to 4-fold). Therefore, CYP1A2, CYP2C9, and CYP2C19 substrates as listed below should also be used with caution:

- **CYP1A2 substrates:** clozapine, cyclobenzaprine, imipramine, mexiletine, naproxen, riluzole, tacrine, and theophylline.
- **CYP2C9 substrates:** losartan, irbesartan, diclofenac, ibuprofen, piroxicam, tolbutamide, glipizide, celecoxib, fluvastatin, naproxen, phenytoin, rosiglitazone, sulfamethoxazole, tamoxifen, tolbutamide, torsemide, and warfarin.
- **CYP2C19 substrates:** diazepam, phenytoin, phenobarbital, lansoprazole, omeprazole, pantoprazole, rabeprazole, amitriptyline, clomipramine, clopidogrel, cyclophosphamide and progesterone.

# 7 Visit schedule and assessments

## 7.1 Study Flow and Visit Schedule

Table 7-1 lists all of the assessments except for laboratory assessments and indicates with an "X" the visits when they are performed. Table 7-2 lists all laboratory assessments. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which data are entered into the database (D) or may remain in source documents only (S) (column category). Assessments that generate data for the EDC system are listed.

Since dovitinib is given in a 5 days on/2 days off dosing schedule, day 12 assessments are intended to be performed on the last dosing day of the 2$^{nd}$ week in cycle 1 and cycle 2 and day 26 assessments are intended to be performed on the last dosing day of the 4$^{th}$ week in cycle 1 and cycle 2.

All assessments have a ±3 days window unless otherwise indicated. In the event of public holidays (e.g. Christmas, New Year's Day), there is a ±5 days window on all assessments. Every effort must be made to follow the schedule of assessments within the windows outlined in the protocol. Additional assessment may be performed as clinically indicated.

**Table 7-1 Visit evaluation schedule**

| | Category | Reference to assessment types | Baseline | Cycle 1 | | | Cycle 2 | | Subsequent cycles | End of study treatment |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit no.** | | | **1** | **2** | **3** | **4** | **5** | **6** | **7+** | |
| **Day of cycle** | | | **-28 to -1** | **1** | **12** | **26** | **12** | **26** | **26 (or 28)** | |
| | | | | | | | | | | |
| **Patient Assessments** | | | | | | | | | | |
| | | | | | | | | | | |
| Obtain Informed Consent | D | | X | | | | | | | |
| Demography | D | 7.10.1 | X | | | | | | | |
| Inclusion / exclusion criteria | S | 5.1, 5.2 | X | | | | | | | |
| Relevant medical history/previous medical conditions | D | | X | | | | | | | |
| Prior/concomitant medications | D | | X | Continuous | | | | | | |
| Adverse events | D | | X | Continuous | | | | | | |
| Registration | D | | X | | | | | | | |
| Diagnosis and extent of cancer | D | 7.10.2 | X | | | | | | | |
| Prior antineoplastic therapy | D | 7.10.3 | X | | | | | | | |
| Vital signs | D | 7.10.4 | X(<14) | | X | X | X | X | X | X |
| Physical examination | D | | X (<14) | | | X | | X | X | X |
| ECOG PS | D | 7.10.5 | X (<14) | | | X | | X | X | X |
| | | | | | | | | | | |
| **Study Treatment** | | | | | | | | | | |
| | | | | | | | | | | |
| Dovitinib dosing[a] | D | | | X | X | X | X | X | X | |
| | | | | | | | | | | |
| **Tumor Assessments** | | | | | | | | | | |
| | | | | | | | | | | |
| FGFR3 mutation / overexpression status | D | 7.10.6 | X[f] | | | | | | | |
| Cystoscopy | D | 7.10.7 | X[b] | | | | | | X[b] | |
| TURBT | D | 7.10.7 | X[c] | | | | | | X[c] | |
| Urine cytology | D | 7.10.7 | X[d] | | | | | | X[d] | |
| | | | | | | | | | | |
| **Radiographic Assessments** | | | | | | | | | | |
| | | | | | | | | | | |
| CT Abdomen/pelvis | D | 7.10.8 | X | | | | | | | |
| Chest x-ray or CT | D | 7.10.8 | X | | | | | | | |

| | Category | Reference to assessment types | Baseline | Cycle 1 | | | Cycle 2 | | Subsequent cycles | End of study treatment |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit no.** | | | **1** | **2** | **3** | **4** | **5** | **6** | **7+** | |
| **Day of cycle** | | | **-28 to -1** | **1** | **12** | **26** | **12** | **26** | **26 (or 28)** | |
| | | | | | | | | | | |
| **Cardiac Assessments** | | | | | | | | | | |
| | | | | | | | | | | |
| 2-D Echo or MUGA | D | 7.10.9 | X | | | | | | X[e] | X |
| ECG | D | 7.10.9 | X | | X | X | | | X[e] | X |
| | | | | | | | | | | |
| **Correlative Studies** | | | | | | | | | | |
| | | | | | | | | | | |
| FGFR1 and FGFR2 mutation status | S | 7.10.6 | | X[g] | | | | | | |
| VEGFR1/2/3 mutation / overexpression status | S | 7.10.6 | | X[g] | | | | | | |
| Plasma FGFR3 mutations | S | 7.10.10 | | X[g] | | | | | | |
| Urine FGFR3 mutations | S | 7.10.10 | | X[g] | | | | | | |
| Tumor dovitinib PK | S | 7.10.10 | | | | | | | X[h] | |
| FGFR & VEGFR Pathway Signaling on TURBT samples | S | 7.10.6.6 | | X[i] | | | | | X[i] | |

a. Dovitinib will be dosed on a flat scale of 500 mg (i.e. 5 x 100 mg per capsule/tablet) on a 5 days on/2 days off dosing schedule. See section 6.1.1 for further detail.

b. Initial baseline cystoscopy must be performed within 42 days of study registration. Subsequent cystoscopic evaluations will be performed every 3 months +/- 7 days (e.g. 3 month, 6 month, 9 month, 12 month) during the first year of follow-up and as clinically indicated per treating physician thereafter. Note: Patients with residual non-invasive UC tumors with no CIS at initial 3-month cystoscopy/TURBT are not considered relapses. Patients with any component of CIS at initial 3-month cystoscopy and TURBT will be considered relapses and will not continue on dovitinib therapy. Any non-invasive UC tumors (i.e. Ta, T1, Tis) at the 6-month or any subsequent cystoscopy/TURBT is considered relapsed disease. Similarly progression to invasive UC tumors (T2-T4) at any time point is also considered relapsed disease and patients will not continue on dovitinib therapy. See section 7.10.11.2 for details.

c. Initial TURBT must be performed within 42 days of study registration. Subsequent TURBT's will be performed every 3 months +/- 7 days (e.g. 3 month, 6 month) during the first 6-months of follow-up and as clinically indicated per treating physician thereafter. Note: Patients with residual non-invasive UC tumors with no CIS at initial 3-month cystoscopy/TURBT are not considered relapses. Patients with any component of CIS at initial 3-month cystoscopy and TURBT will be considered relapses and will not continue on dovitinib therapy. Any non-invasive UC tumors (i.e. Ta, T1, Tis) at the 6-month or any subsequent cystoscopy/TURBT is considered relapsed disease. Similarly progression to invasive UC tumors (T2-T4) at any time point is also considered relapsed disease and patients will not continue on dovitinib therapy. See section 7.10.11.2 for details.

d. Initial urine cytology must be performed within 42 days of study registration. Subsequent urine cytologies will be performed every 3 months +/- 7 days (e.g. 3 month, 6 month, 9 month, 12 month) during the first year of follow-up and as clinically indicated per treating physician thereafter

e. Subsequent on-treatment Echo and ECG testing to be performed only as clinically indicated

f. Mandatory submission of unstained slides from TURBT specimen must be submitted for FGFR3 mutation/overexpression status prior to study registration. Refer to SPM for collection and shipping

guidelines.

g. Archived pre-treatment tissue samples for study correlatives will be collected from enrolled eligible patients. Blood and urine samples for study correlatives will be collected at Cycle 1 Day 1 from enrolled eligible patients. The correlative analyses will be completed in batch groupings at study completion. Refer to SPM for collection, processing and shipping guidelines.

h. Tissue for dovitinib PK analysis will be collected at the initial post-treatment cystoscopy with TURBT performed 3 months +/- 7 days after starting dovitinib therapy. Refer to SPM for collection, processing and shipping guidelines.

i. Unstained slides are to be submitted from the pre-treatment TURBT specimen and from the post-treatment cystoscopy with TURBT performed 3 months +/- 7 days after starting dovitinib therapy. Refer to SPM for collection and shipping guidelines.

**Table 7-2 Laboratory assessment schedule**

| | Test name | Category | Reference to assessment types | Baseline | Cycle 1 | | | Cycle 2 | | Subsequent cycles | End of study treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit no.** | | | | **1** | **2** | **3** | **4** | **5** | **6** | **7+** | |
| **Day of cycle** | | | | **-14 to -1** | **1** | **12** | **26** | **12** | **26** | **26** | |
| **Hematology** | Hemoglobin | D | 7.10.11 | X | X | X | X | X | X | X | X |
| | RBC | D | 7.10.11 | X | X | X | X | X | X | X | X |
| | WBC | D | 7.10.11 | X | X | X | X | X | X | X | X |
| | Platelets | D | 7.10.11 | X | X | X | X | X | X | X | X |
| | Differentials: | | 7.10.11 | X | X | X | X | X | X | X | X |
| | ANC | D | | | | | | | | | |
| | lymphocytes | S | | | | | | | | | |
| | monocyte | S | | | | | | | | | |
| | eosinophil | S | | | | | | | | | |
| | basophil | S | | | | | | | | | |
| **Chemistry** | Urea/BUN | S | 7.10.11 | X | X | X | X | X | X | X | X |
| | Creatinine | D | 7.10.11 | X | X | X | X | X | X | X | X |
| | Total bilirubin | D | 7.10.11 | X | X | X | X | X | X | X | X |
| | ALT | D | 7.10.11 | X | X | X | X | X | X | X | X |
| | AST | D | 7.10.11 | X | X | X | X | X | X | X | X |
| | GGT | D | 7.10.11 | X | X | X | X | X | X | X | X |
| | Alkaline phosphatase | S | 7.10.11 | X | X | X | X | X | X | X | X |
| | Albumin | D | 7.10.11 | X | X | X | X | X | X | X | X |
| | Total protein | S | 7.10.11 | X | X | X | X | X | X | X | X |
| | Calcium | D | 7.10.11 | X | X | X | X | X | X | X | X |
| | Sodium | S | 7.10.11 | X | X | X | X | X | X | X | X |
| | Magnesium | D | 7.10.11 | X | X | X | X | X | X | X | X |
| | Potassium | D | 7.10.11 | X | X | X | X | X | X | X | X |
| | Phosphorous | D | 7.10.11 | X | X | X | X | X | X | X | X |
| | Glucose | S | 7.10.11 | X | X | X | X | X | X | X | X |
| | LDH | D | 7.10.11 | X | X | X | X | X | X | X | X |
| | Amylase | D | 7.10.11 | X | X | X | X | X | X | X | X |
| | Lipase | D | 7.10.11 | X | X | X | X | X | X | X | X |
| **Serum lipid profile** | Total cholesterol, triglycerides, LDL, HDL | S | 7.10.11 | X | | | X | | X | X | X |
| **Coagulation** | PT or INR | S | 7.10.11 | X | | | | | X | X[a] | |
| | PTT | S | 7.10.11 | X | | | | | X | X[a] | |
| | Fibrinogen | S | 7.10.11 | X | | | | | X | X[a] | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Urinalysis** | Dipstick: specific gravity, PH, protein, blood, glucose... | S | 7.10.11 | X[f] | | | X[b] | | X[b] | X[b] | |
| | Microscopic: WBC, RBC, bacteria, casts... | S | 7.10.11 | X | | | X[b] | | X[b] | X[b] | |
| **Thyroid function** | TSH, T3, T4 | D | 7.10.11 | X | | | | | | X[c] | X |
| **Cardiac enzymes** | CPK, CK-MB, troponin T or I | S | 7.10.11 | X | | | X[d] | | X[d] | X[d] | |
| **Pregnancy[e] test** | | S | 7.10.11 | X | | | X | | X | X | |

[a]Additional PT/INR, PTT, and Fibrinogen studies will be performed only as clinically indicated in subsequent treatment cycles.

[b]Additional urine dipstick and microscopic studies will be performed only as clinically indicated in subsequent treatment cycles.

[c]Additional TSH, T3, and T4 studies will be performed (+/- 5 days) on cycle 3 day 26, cycle 6 day 26 and as clinically indicated in subsequent treatment cycles.

[d]Additional CPK, CK-MB, troponin T or I studies will be performed only as clinically indicated in subsequent treatment cycles.

[e]A serum pregnancy test will be assessed in female patients of childbearing potential within 14 days of registration and on day 26 (± 5 days) of all subsequent treatment cycles.

[f]If documentation of +1 (+2 for patients with renal cell carcinoma) results for protein on dipstick reading, a 24 hour urine for protein must be obtained

## 7.2 Biomarkers

All patients will be required to have bladder tumor FGFR3 mutation and over-expression status determined from a TURBT sample obtained within 42 days of registration. All other biomarker analyses will be exploratory in nature and do not need to be performed as part of study screening or eligibility assessments.

## 7.3 Eligibility Screening and Patient Registration

Patient eligibility will be confirmed through the Hoosier Cancer Research Network's secure web-based electronic data capture system. Once eligibility criteria are entered and the patient is confirmed as eligible, the EDC system will assign a unique patient identification number to the patient, and register the patient.

Patients must be registered prior to starting protocol therapy and begin therapy within 5 working days of registration.

**Blinding**
The study treatment is not blinded to the patient or the investigator.

## 7.4 Information Collected on Screen Failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment and eligibility information will be entered in the EDC system.

## 7.5 Patient Demographics and Other Baseline Characteristics

At screening/baseline, the following demographic and screening/baseline characteristic data will be collected from all patients:

- Date of birth
- Sex
- Ethnicity
- Race
- Height
- Weight
- Systolic blood pressure
- Diastolic blood pressure
- ECOG performance status
- Cystectomy eligibility status (if ineligible, record reason)
- White blood cell count
- Absolute neutrophil count

- Hemoglobin
- Platelet count
- Creatinine
- AST
- ALT
- Total bilirubin
- Alkaline phosphatase
- Left ventricular ejection fraction
- Charlson comorbidity index (CCI)

  The CCI for each patient is determined by summation of relative point values for each patient co-morbidity condition according to the following system:

  Conditions assigned 1 point each:

  - Myocardial infarct
  - Congestive heart failure
  - Peripheral vascular disease
  - Dementia
  - Cerebrovascular disease (CVA with mild or no residual effects or TIA)
  - Chronic lung disease
  - Connective tissue disease
  - Peptic ulcer
  - Mild chronic liver disease (i.e. without evidence of portal hypertension, includes chronic hepatitis)
  - Diabetes without end-organ damage (excludes diet-controlled alone)

  Conditions assigned 2 points each:

  - Hemiplegia
  - Moderate or severe kidney disease (GFR $\leq$ 60 ml/min by Cockcroft-Gault formula)
  - Diabetes with end organ damage (i.e. retinopathy, neuropathy, nephropathy)
  - Any cancer (exclude if > 5 years from diagnosis with no active disease)
  - Leukemia (acute or chronic)
  - Lymphoma

  Conditions assigned 3 points each:

- Moderate or severe liver disease (i.e. with evidence of portal hypertension)

Conditions assigned 6 points each:

- Metastatic solid organ cancer
- AIDS

For example, a patient with BCG-refractory urothelial carcinoma (2 pts), type 2 diabetes without end organ damage (1 pt), past history of a non-ST-elevation myocardial infarction (1 pt), with history of chronic obstructive pulmonary disease (1 pt) would have a CCI = 5.

- Bladder tumor stage (Ta, Tis, T1, Ta + Tis, T1 + Tis)
- Number of prior intravesical BCG courses (i.e. BCG x 2 courses → mitomycin C x 1 course → gemcitabine x 1 course = 2 prior BCG courses)
- Number of prior intravesical courses of any type (i.e. BCG x 2 courses → mitomycin C x 1 course → gemcitabine x 1 course = 4 prior intravesical courses)
- Number of prior intravesical agents received (i.e. BCG x 2 courses → mitomycin C x 1 course → gemcitabine = 3 prior agents)
- Date of last intravesical therapy of any kind
- Date of last intravesical BCG therapy
- Tumor FGFR3 mutation status
- Tumor FGFR3 over-expression status

## 7.6 Treatment Period

All patients will be treated until either: 1) relapsed disease is noted; 2) Treatment related toxicity requiring a third dose reduction is encountered; 3) Treatment related toxicity not yet requiring a third dose reduction but per the treating physician's discretion is deemed unsuitable for further dovitinib therapy is encountered; or 4) Patient electively foregoes further dovitinib therapy at any time.

## 7.7 End of Treatment and Premature Withdrawal Visit

Patients who discontinue study drug before completing the study should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. The date and reason for stopping the study treatment will be recorded in the eCRF. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days or 5 half-lives (whichever is longer) following the last dose of study drug.

Patients who discontinue study treatment also should return for tumor assessments per the study calendar and should not be considered withdrawn from the study. If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the date and tumor response status as well as

the date and tumor relapse status. Record the date and tumor response status as well as date and tumor relapse status in the eCRF.

Patients who discontinue study drug should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

If a withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information in the eCRF.

If a patient discontinues study drug, but continues study assessments, the reason for study completion should be recorded in the eCRF.

End of treatment/Premature withdrawal visit is not considered as the end of the study.

### 7.7.1 Criteria for Premature Patient Withdrawal

Patients **may** voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients may be withdrawn from the study if any of the following occur: pregnancy; discovery of patient ineligibility; errors in treatment compliance [study drug, other prescribed or non-prescribed medications]; missed/unscheduled/off-schedule/incomplete/incorrect assessments.

### 7.7.2 Follow-up for Toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. If a patient requires a dose delay of > 14 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study. However, the patient will continue to be followed for toxicity as previously described. All patients will be followed for adverse events and serious adverse events for 30 days following the last dose of dovitinib.

## 7.8 Replacement Policy

Patients prematurely withdrawn within the first 3 months of therapy and prior to the first post-therapy cystoscopy with urine cytology and TURBT will be replaced. Patients prematurely withdrawn after their first post-therapy cystoscopy with urine cytology and TURBT will not be replaced.

## 7.9 Follow up Period

All patients must have safety evaluations for 30 days or 5 half-lives (whichever is longer) after the last dose of study treatment. All patients will be followed for tumor relapse status until tumor relapse is noted or for 12 months beyond last dose of study treatment in patients who stopped dovitinib prior to disease relapse.

Patients lost to follow up should be recorded as such on the eCRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

## 7.10 Assessment Types

### 7.10.1 Demographics

At baseline, demographic and baseline characteristic data will be collected from all patients. See section 7.5 for details.

### 7.10.2 Diagnosis and Extent of Cancer

#### 7.10.2.1 Tumor Stage

Bladder tumor stage will be defined according to the American Joint Commission on Cancer (AJCC) Staging system for bladder tumors (Edge SB et al., 2010). T-stage classifications include:

Tx – Primary tumor cannot be assessed

T0 – no evidence of primary tumor

Ta – Noninvasive papillary carcinoma which does not invade into the lamina propria

Tis – Carcinoma in situ

T1 – Tumor invades into the lamina propria but not into the muscularis propria

T2a – Tumor invades into the inner half of the muscularis propria

T2b – Tumor invades into the outer half of the muscularis propria

T3a – Tumor microscopically invades the perivesical tissue

T3b – Tumor macroscopically invades the perivesical tissue

T4a – Tumor invades the prostatic stroma, uterus, or vagina

T4b – Tumor invades into the pelvic wall, or abdominal wall

#### 7.10.2.2 Lymph Node Stage

Bladder lymph node stage will be defined according to the American Joint Commission on Cancer (AJCC) Staging system for bladder tumors.(Edge SB et al., 2010) N-stage classifications include:

Nx – Lymph nodes cannot be assessed

N0 – no lymph node metastasis

N1 – Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)

N2 – Multiple regional lymph node metastases in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph nodes)

N3 – Lymph node metastases to the common iliac lymph nodes

#### 7.10.2.3 Metastases Stage

Bladder metastasis stage will be defined according to the American Joint Commission on Cancer (AJCC) Staging system for bladder tumors (Edge SB et al., 2010). M-stage classifications include:

M0 – No distant metastasis

M1 – Distant metastasis

### 7.10.3 Prior Anti-neoplastic Therapy

At baseline, the following prior anti-neoplastic therapy characteristic data will be collected from all patients:

- Number of prior intravesical BCG courses (i.e. BCG x 2 courses → mitomycin C x 1 course → gemcitabine x 1 course = 2 prior BCG courses)
- Number of prior intravesical courses of any type (i.e. BCG x 2 courses → mitomycin C x 1 course → gemcitabine x 1 course = 4 prior intravesical courses)
- Number and name of prior intravesical agents received (i.e. BCG x 2 courses → mitomycin C x 1 course → gemcitabine x 1 course = 3 prior agents)
- Date of last intravesical therapy of any kind
- Date of last intravesical BCG therapy

### 7.10.4 Vital Signs

At baseline and subsequent study visits, the following vital signs data will be collected from all patients:

- Temperature ($^{o}$C)
- Heart rate (beats per minute)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Respiratory rate (breaths per minute)
- Height (cm) [only recorded at baseline]
- Weight (kg)

### 7.10.5 ECOG Performance Status

At baseline and subsequent study visits, the Eastern Cooperative Oncology Group (ECOG) performance status (PS) data will be collected from all patients. The ECOG PS values are defined as follows:

- ECOG 0 – Fully active, able to carry on all pre-disease performance without restriction
- ECOG 1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

- ECOG 2 – Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- ECOG 3 – Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- ECOG 4 – Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- ECOG 5 – Dead

### 7.10.6 FGFR1, FGFR2, FGFR3, VEGFR1, VEGFR2, and VEGFR3 Mutation, Over-expression, and Pathway Analyses

#### 7.10.6.1 FGFR3 Mutation Status

Somatic FGFR3 mutations (see Table 1-2) in exons 7, 10, and 15 will be assessed in FFPE tumor tissues by massively parallel sequencing analysis utilizing the Ion Torrent Personal Genome Machine (PGM) and performed in the CLIA-certified Molecular Pathology and Translational Research Laboratory at the Dartmouth Hitchcock Medical Center.

Unstained slides from the patients' TURBT sample that was obtained within 42 days of registration will be submitted to two different laboratories prior to registration to determine FGFR3 mutation status and over-expression status. The laboratories will directly notify the site within 5-7 days, the results of the testing. In cases where multiple biopsies were obtained, the site pathologist is asked to send slides from the biopsy with the highest grade and the greatest volume of tumor present within the biopsy sample. Consider the biopsy results depicted below:

| Biopsy sample | Location | Diagnosis | Tumor volume |
|---|---|---|---|
| #1 | Dome | Ta low-grade UC | Tiny |
| #2 | Rt Lateral wall | T1 high-grade UC + CIS | Moderate |
| #3 | Left Lateral wall | CIS | Small |
| #4 | Posterior wall | T1 high-grade UC + CIS | Large |

In the example above, the site pathologist would be asked to send slides from biopsy #4 from the posterior bladder wall.

Consider the biopsy results below:

| Biopsy sample | Location | Diagnosis | Tumor volume |
|---|---|---|---|
| #1 | Dome | Ta low-grade UC | Tiny |
| #2 | Rt Lateral wall | CIS | Moderate |
| #3 | Left Lateral wall | CIS | Large |
| #4 | Posterior wall | No malignancy | Large |

In the example above, the site pathologist would be asked to send slides from biopsy #3 from the left lateral bladder wall.

Consider the biopsy results below:

| Biopsy sample | Location | Diagnosis | Tumor volume |
|---|---|---|---|
| #1 | Dome | Ta low-grade UC | Tiny |
| #2 | Rt Lateral wall | T1 high-grade UC | Moderate |
| #3 | Left Lateral wall | CIS | Moderate |
| #4 | Posterior wall | No malignancy | Large |

In the example above where there is the presence of both T1 high-grade UC and CIS residing in separate samples, the site pathologist would be asked to send slides from both biopsy #2 from the rt lateral bladder wall and biopsy #3 from the left lateral bladder wall.

Refer to SPM for detailed collection, labeling and shipping guidelines. Upon receipt in the laboratory, each slide will be visually inspected for any signs of damage during shipment. One H&E stained slide will be reviewed under light microscope to assess percent tumor cell content. A minimum of 40% tumor cell content is required in the entire tissue section; otherwise, macrodissection will be performed to ensure maximum tumor cell content.

DNA will be isolated utilizing a standard commercially available extraction kit (i.e. Qiagen PureGene) according to manufacturer specifications. FGFR3 mutational status will be determined by DNA sequencing of all coding exons including exons 7, 10, and 15. Upon completion of testing, the presence/absence of an FGFR3 mutation (see Table 1-2) will be communicated to the treating site via email and /or fascimile.

A whole blood sample will be collected at cycle 1 day 1.

DNA from PBMC's will be extracted using a standard commercially available DNA extraction kit (i.e. Qiagen DNeasy™). FGFR3 single nucleotide polymorphisms (SNPs) in PBMC's will be analyzed by commercially validated probes. Refer to SPM for collection and shipping guidelines.

### 7.10.6.2 FGFR3 Overexpression Status

Presence of FGFR3 over-expression within tumor tissue will be assessed at study entry by the IUSCC's IHC Core. The IHC antibody used to determine FGFR3 over-expression is commercially available from Novus Biologicals.

Refer to SPM for collection, labeling and shipping guidelines.

Presence of FGFR3 over-expression within tumor tissue will be assessed and interpreted by two separate pathologists. Brain, kidney, and testes are the recommended positive controls. Non specific immune serum will be used as the negative control. Staining intensity will be graded 0, +1, +2,+3 and $\geq$ +1 brown staining in the tissues defines positivity. Up to 3 pieces of tissue are to be analyzed at 3 to 5 high power fields if available.

Upon completion of testing, the presence/absence of FGFR3 over-expression will be communicated to the treating site within 5-7 days.

### 7.10.6.3 FGFR1 and FGFR2 Mutation Status

FGFR1 and FGFR2 single nucleotide polymorphisms (SNPs) in PBMC DNA extracted as described in 7.10.6.1 will be analyzed utilizing commercially validated probes. In cases of scant PBMC DNA availability, FGFR3 analyses will take priority over FGFR1 and FGFR2 analyses. Refer to SPM for collection and shipping guidelines.

### 7.10.6.4 VEGFR1, VEGFR2, and VEGFR3 Mutation Status

A whole blood sample will be collected at cycle 1 day 1.

DNA from PBMC's will be extracted using a standard commercially available DNA extraction kit (i.e. Qiagen DNeasy™). VEGFR1, VEGFR2, and VEGFR3 single nucleotide polymorphisms (SNPs) in PBMC's will be analyzed by commercially validated probes. Refer to SPM for collection and shipping guidelines.

### 7.10.6.5 VEGFR Over-expression Status

Presence of VEGFR1, VEGFR2, and VEGFR3 overexpression within tumor tissue will be assessed by the IUSCC's IHC Core.

Presence of VEGFR1, VEGFR2, and VEGFR3 over-expression within tumor tissue will be assessed and interpreted by standard immunohistochemistry analysis with appropriate controls. Refer to SPM for collection and shipping guidelines.

### 7.10.6.6 FGFR and VEGFR Pathway Signaling Analyses

Assessment of the effect of dovitinib on FGFR and VEGFR pathway signaling will be assessed by the IUSCC IHC Core through analysis of pre- and post-treatment TURBT specimens.

All samples will be analyzed for FGFR3, pFGFR3, VEGFR2, pVEGFR2, FRS2, pFRS2, ERK, pERK by standard immunohistochemistry analysis with appropriate controls. Where additional tissue is available, analysis of additional FGFR/VEGFR pathway markers will also be performed. Refer to SPM for collection and shipping guidelines.

## 7.10.7 Cystoscopy, TURBT, and Urine Cytology Evaluations

### 7.10.7.1 Cystoscopy and TURBT

All patients must have an adequate staging cystoscopy and TURBT performed within 42 days prior to study registration. In order to be considered adequate, the muscularis propria portion of the bladder wall must be present within at least one of the TURBT biopsies. All patients will be re-evaluated for response by standard of care cystoscopy every 3 months ± 7 days (e.g. 3 month, 6 month, 9 month, 12 month) during the first year of follow-up. All patients will be re-evaluated for response by standard of care TURBT/biopsy every 3 months (e.g. 3 month, 6 month) ± 7 days during the first 6 months of follow-up. At each of the follow-up TURBT/biopsy evaluations, biopsy tissue should be obtained from each of the following areas to ensure uniform disease evaluation and tissue acquisition:

1. All previously documented baseline tumor sites

2. Bladder dome
3. Anterior bladder wall
4. Left lateral bladder wall
5. Right lateral bladder wall
6. Bladder trigone
7. Any additional new suspicious bladder areas

In the absence of recurrence at 1-year from study registration, cystoscopic surveillance and TURBT/biopsies are at the treating physician's discretion.

**NOTE:** Patients with residual non-invasive UC tumors with no component of carcinoma in situ (i.e. Ta, T1) at 3-month cystoscopy and TURBT are not considered relapses and will be permitted to continue on dovitinib therapy. If the subsequent 6-month cystoscopy, TURBT, and urine cytology shows no evidence of any remaining urothelial carcinoma in such patients, they will be considered a complete response. Patients with any component of carcinoma in situ (CIS) at 3-month cystoscopy/TURBT will be considered relapses and will not continue on dovitinib therapy. Any non-invasive UC tumors (i.e. Ta, T1, Tis) at the 6-month or any subsequent cystoscopy/TURBT is considered relapsed disease. Similarly progression to invasive UC tumors (T2-T4) at any time point is also considered relapsed disease and patients will not continue on dovitinib therapy.

#### 7.10.7.2 Urine Cytology

All patients must have standard of care urine cytology obtained within 42 days prior to study registration. All patients will be re-evaluated for response by standard of care urine cytology obtained every 3 months ± 7 days (e.g. 3 month, 6 month, 9 month, 12 month) during the first year of follow-up. In the absence of recurrence at 1-year from study registration, additional urine cytology assessments are at the treating physician's discretion.

#### 7.10.7.3 Urine Fluorescent In-Situ Hybridization

Testing of urine by fluorescent in-situ hybridization (FISH) for recurrence is not required at any time point as part of this study. The treating urologist may order commercial urine FISH testing (i.e. Urovysion®) at their own discretion.

### 7.10.8 Radiographic Evaluations

#### 7.10.8.1 Abdomen and Pelvis CT scan

All patients will have an abdomen and pelvis CT scan performed within 28 days prior to study registration. Subsequent scans while on study and in follow-up are at the treating physician's discretion.

#### 7.10.8.2 Chest x-ray or Chest CT scan

All patients will have a chest x-ray performed within 28 days prior to study registration. A chest CT may be substituted for the required chest x-ray provided it is also performed within 28 days prior to study registration. Subsequent x-rays and CT scans while on study and in follow-up are at the treating physician's discretion.

### 7.10.9 Cardiac Evaluations

#### 7.10.9.1 Left Ventricular Ejection Fraction

All patients will have left ventricular ejection fraction assessed within 28 days prior to study registration by either a 2-D echocardiogram or MUGA scan. Additional evaluations of left ventricular ejection fraction will be performed, as clinically indicated and at End of Treatment.

#### 7.10.9.2 Electrocardiogram

All patients will have cardiac dysrhythmias and prior ischemic history assessed by 12-lead electrocardiogram within 28 days prior to study registration, at Cycle 1 Day 12 and Day 26, as clinically indicated in subsequent on-treatment cycles, and at End of Treatment.

### 7.10.10 Correlative Studies

#### 7.10.10.1 Plasma FGFR3 Mutation Status

Presence of FGFR3 mutation within circulating plasma will be assessed at baseline by the IUSCC TVC. Peripheral blood for plasma isolation will be obtained at Cycle 1 Day 1.

Plasma free RNA will be isolated utilizing a standard commercially available RNA extraction kit (i.e. QiaAmp™ Circulating Nucleic Acid Purification Kit). As the quantity of circulating free plasma RNA is expected to be low (picogram to nanongram range), FGFR3 mutations within circulating free plasma RNA will be assessed utilizing PCR-amplification of the target regions and sequencing. Refer to SPM for collection and shipping guidelines.

#### 7.10.10.2 Urine FGFR3 Mutation Status

Presence of FGFR3 mutation within exfoliated urine tumor cells will be assessed at Cycle 1 Day 1 by the CLIA-certified Molecular Pathology and Translational Research Laboratory at the Dartmouth Hitchcock Medical Center. A 30 ml urine sample will be obtained from each patient at Cycle 1 Day 1 (this sample is separate from the standard of care urine cytology sample). Presence of FGFR3 mutations (see Table 1-2) within patient urine will be assessed by massively parallel sequencing of exons 7, 10, and 15 utilizing the Ion Torrent PGM instrument.

Refer to SPM for collection, processing and shipping guidelines.

#### 7.10.10.3 Tumor Dovitinib Pharmacokinetic Evaluation

All patients will have a post-therapy dovitinib pharmacokinetic evaluation performed. Bladder biopsy tissue for the dovitinib pharmacokinetic evaluation should be collected on cycle 3 day 26 (± 7 days) at the time of the first post-dovitinib TURBT. The biopsy tissue may be obtained from a bladder tumor region or from normal appearing urothelium.

Dovitinib tissue concentrations will be analyzed by mass spectroscopy and liquid chromatography methodologies developed specifically for this protocol by the IUSCC Clinical Pharmacology Analytical Core (CPAC). Refer to SPM for collection and shipping guidelines.

### 7.10.11 Laboratory Studies

#### 7.10.11.1 Complete blood counts

A complete blood count including Hemoglobin, WBC, platelets, and differential will be obtained from each patient within 14 days of registration, at cycle 1 day 1, cycle 1 day 12, cycle 1 day 26, cycle 2 day 12, cycle 2 day 26, on day 26 of all subsequent cycles, and at the end of study treatment.

#### 7.10.11.2 Chemistry Studies

Serum chemistries including BUN, creatinine, total bilirubin, ALT, AST, GGT, alkaline phosphatase, albumin, total protein, calcium, sodium, magnesium, potassium, phosphorous, glucose, LDH, amylase, and lipase will be assessed in each patient within 14 days of registration, at cycle 1 day 1, cycle 1 day 12, cycle 1 day 26, cycle 2 day 12, cycle 2 day 26, on day 26 of all subsequent cycles, and at the end of study treatment.

#### 7.10.11.3 Lipid Profile Studies

Serum total cholesterol, triglycerides, LDL, and HDL will be assessed in each patient within 14 days of registration, at cycle 1 day 26, cycle 2 day 26, on day 26 of all subsequent cycles, and at the end of study treatment.

#### 7.10.11.4 Coagulation Studies

PT/INR, PTT, and fibrinogen will be assessed in each patient within 14 days of registration, at cycle 2 day 26, and as clinically indicated for all subsequent cycles.

#### 7.10.11.5 Urine Studies

Urine dipstick and urinalysis with specific gravity, pH, protein, blood, glucose, WBC, RBC, bacteria, and casts will be assessed in each patient within 14 days of registration. Urine dipstick must be negative for protein or, if documentation of +1 (+2 for patients with renal cell carcinoma) results for protein on dipstick reading, then total urinary protein $\leq$ 500 mg and measured creatinine clearance $\geq$ 50 mL/min/1.73m$^2$ must be attained from a 24 hour urine collection. Additional urine dipstick and microscopic studies will be performed only as clinically indicated in subsequent treatment cycles.

#### 7.10.11.6 Thyroid Function Studies

TSH, T3, and T4 will be assessed in each patient within 14 days of registration, on cycle 3 day 26 ($\pm$ 5 days), cycle 6 day 26 ($\pm$ 5 days), and at the end of study treatment.

### 7.10.11.7 Cardiac Enzyme Studies

CPK, CK-MB, and troponin (T or I) will be assessed in each patient within 14 days of registration and only as clinically indicated in subsequent treatment cycles.

### 7.10.11.8 Pregnancy Testing Studies

A serum pregnancy test will be assessed in female patients of child-bearing potential within 14 days of registration and on day 26 (± 5 days) of all subsequent treatment cycles.

## 7.10.12 Efficacy

### 7.10.12.1 6-month Complete Response Rate (6-month CR rate)

The 6-month complete response (CR) rate is defined as the proportion of patients treated with dovitinib with no evidence of any remaining urothelial carcinoma tumors of any T-stage (including Tis) present within the bladder as assessed by standard of care cystoscopic examination with TURBT and urine cytology performed at 6 months after initiation of study therapy.

**NOTE:** Patients with residual non-invasive UC tumors with no component of carcinoma in situ (i.e. Ta, T1) at 3-month cystoscopy and TURBT are not considered relapses and will be permitted to continue on dovitinib therapy. If the subsequent 6-month cystoscopy, TURBT, and urine cytology shows no evidence of any remaining urothelial carcinoma in such patients, they will be considered a complete response. Patients with any component of carcinoma in situ (CIS) at 3-month cystoscopy/TURBT will be considered relapses and will not continue on dovitinib therapy. Any non-invasive UC tumors (i.e. Ta, T1, Tis) at the 6-month or any subsequent cystoscopy/TURBT is considered relapsed disease. Similarly progression to invasive UC tumors (T2-T4) at any time point is also considered relapsed disease and patients will not continue on dovitinib therapy.

### 7.10.12.2 Relapse Free Survival (RFS)

Relapse Free Survival (RFS) is defined as the time from study registration until the occurrence of any of the following relapse events:

1. Evidence of any component of CIS at 3-month cystoscopy/TURBT
2. Recurrent tumor $\geq$ T2 at any time point
3. Recurrent tumor of any stage that occurs at or after the 6-month cystoscopy evaluation as assessed by bladder cystoscopy, TURBT, or urine cytology. Note: While not required as part of the study follow-up testing, positive urine FISH test (even if an isolated finding) at or after the 6-month study evaluations will be considered relapsed disease.
4. Documentation of metastatic urothelial carcinoma at any time point

### 7.10.12.3 1-year Relapse Free Survival (1-yr RFS)

1-year RFS is defined as the proportion of patients who do not fulfill any of the relapse definitions in section 7.10.11.2 one year after study registration.

### 7.10.12.4 Complete Response (CR)

Complete response (CR) is defined as disappearance of all bladder tumors (of any T-stage), both grossly and microscopically on urine cytology and post-treatment bladder biopsy.

### 7.10.12.5 Partial Response (PR)

A partial response (PR) is defined as persistently present, but reduced bladder tumor T-stage on post-treatment bladder biopsy/TURBT in the absence of any new bladder tumors of any stage and in the absence of progression to muscle-invasive stage (i.e. $\geq$ T2) of any previously documented bladder tumors. A reduction in the number of bladder tumors but that retains the baseline T-stage does not qualify as a partial response. The following is a list of partial response examples:

T1 → Ta

T1 + Tis → T1

T1 + Tis → Ta

Tis → Ta

### 7.10.12.6 Progression to Muscle-Invasive Disease

Progression to Muscle-Invasive disease is defined as the appearance of any tumor of $\geq$ T2 at any time in follow-up.

### 7.10.12.7 Progressive Disease (PD)

Progressive Disease (PD) is defined as the appearance of any muscle-invasive ($\geq$T2) tumor, lymph node metastases (N1-3), or any metastases (M1) at any time in follow-up.

### 7.10.12.8 Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy is documented.

### 7.10.12.9 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that relapsed or progressive disease is objectively documented.

### 7.10.12.10 Duration of Complete Response

The duration of CR is measured from the time measurement criteria are first met for CR until the first date that relapsed or progressive disease is objectively documented.

### 7.10.13 Safety and Tolerability

Safety will be monitored by assessing the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

# 8 Safety Monitoring and Reporting

## 8.1 Adverse Events

### 8.1.1 Definitions and Reporting

An adverse event for the purposes of this protocol is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s).

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, or grades 1 - 4, will be used. CTCAE grade 5 (death) will not be used in this study; rather, this information will be collected and recorded in the Adverse Events eCRF as end of treatment or survival information.

Adverse events will be recorded from the time of consent and for at least 30 days after treatment discontinuation. All Adverse events considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

Abnormal laboratory values or test results occurring after signing the informed consent form constitute adverse events only if they induce clinical signs or symptoms, or require therapy, (e.g., any hematologic abnormality that requires transfusion or hematological stem cell support) or changes in study medication(s) are considered clinically significant and should be recorded on the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g., cause study discontinuation or constitutes in and of itself a Serious Adverse Event) should be recorded on the Adverse Events eCRF.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE grade 1-4)
2. Causality to the adverse event (reasonable possibility that AE is related to dovitinib): (no, yes)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)

5. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.

**Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements, see Section 8.2.**

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Disease progression should not be regarded or reported as an adverse event itself unless associated with a separate adverse event.

Whenever possible, a diagnosis should be reported instead of underlying signs and symptoms.

### 8.1.2 IND Safety Reports Unrelated to This Trial

IND safety reports not occurring on this trial but involving the study intervention (outside SAEs) received from outside sources will be reviewed by the Sponsor Investigator and will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines.

### 8.1.3 Laboratory Test Abnormalities

#### 8.1.3.1 Definitions and Reporting

Abnormal laboratory values or test results that constitute adverse events or underlying conditions should not be reported separately in addition to the respective adverse events or underlying diagnosis.

Additionally, laboratory abnormalities that are considered clinically significant due to induction of clinical signs or symptoms, or requiring concomitant therapy (e.g. any hematologic abnormality that requires transfusion or cytokine treatment) or changes in study medication(s), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for adverse events should be followed until they have returned to normal or an adequate explanation of the abnormality is found.

Laboratory abnormalities, that do not meet the criteria of clinical significance, as judged by the investigator, should not be reported as adverse events. A grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality

may be required by the protocol in Section 6 and should not contribute to designation of a lab parameter abnormality as a SAE:

## 8.2 Serious Adverse Events

### 8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
    - Any SAEs that are expected due to the condition being treated, including if the SAE is a primary outcome measure, and whether there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere
    - Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

### 8.2.2 Reporting

To ensure patient safety, report every SAE, **regardless of suspected causality**, occurring

- after the patient begins taking study drug and until at least 30 days after the patient has stopped study treatment

Any SAEs experienced after this 30 days period should only be reported if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug), complete the SAE Report Form, and send the completed, signed form to **Hoosier Cancer Research Network (HCRN) within 1 business day of discovery of the event.**

Hoosier Cancer Research Network shall notify Novartis upon learning of the occurrence during the study. Events will be reported to the oncology Novartis Integrated Medical Safety (IMS) department. **All events must be reported, by FAX (**877-778-9739**), to Novartis Pharmaceuticals DS&E Department within 24 hours of learning of its occurrence along with Novartis SAE Report Fax Coversheet.**

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure (new occurrence) and is thought to be related to dovitinib, an oncology Novartis Integrated Medical Safety (IMS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

#### 8.2.2.1 Study Center (Site) Requirements for Reporting SAEs

Investigators and other site personnel must report any SAEs occurring during the course of the study within one business day of discovery of the event. This includes events both related and unrelated to the investigational product.

Related means that there is a reasonable possibility the drug caused the adverse experience.

| | |
|---|---|
| Unrelated | The Adverse Event is *clearly not related* to the investigational agent(s) |
| Unlikely | The Adverse Event is *doubtfully related* to the investigational agent(s) |
| Possible | The Adverse Event *may be related* to the investigational agent(s) |
| Probable | The Adverse Event is *likely related* to the investigational agent(s) |
| Definite | The Adverse Event is *clearly related* to the investigational agent(s) |

**The completed SAE Report Form (see SPM) must be faxed to Hoosier Cancer Research Network within 1 business day of discovery of the event.** The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information will be faxed to Hoosier Cancer Research Network, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

#### 8.2.2.2 Death and Immediately Life-Threatening Events

Any death and immediately life-threatening event from any cause while a patient is receiving trial treatment on this protocol or up to 30 days after the last dose of trial treatment, or any death and immediately life-threatening event occurring more than 30 days after trial treatment has ended but which is felt to be treatment related must be reported **within one business day of discovery of the event**. All deaths must be reported primarily for the purposes of SAE reporting; however, deaths due unequivocally to progression are not SAEs.

Your local IRB should be notified and its reporting procedure followed. The completed SAE Reporting Form should be faxed to Hoosier Cancer Research Network **within one business day of discovery of the event**.

#### 8.2.2.3 HCRN Requirements for Reporting SAEs

Hoosier Cancer Research Network will report any possibly related SAE to Novartis **within one business day** of receipt of the SAE Reporting Form and to regulatory authorities (FDA) per federal requirements.

Hoosier Cancer Research Network will fax a MedWatch to Novartis and will provide follow-up information as reasonably requested.

### 8.3 Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form (see SPM) and reported to Hoosier Cancer Research Network within one business day of learning of its occurrence. Hoosier

Cancer Research Network will report all pregnancies to the oncology Novartis Integrated Medical Safety (IMS) department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

## 8.4 Warnings and Precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

## 8.5 Data and Safety Monitoring Plan

As this is a small phase II trial of only 20 enrolled patients, a formal data and safety monitoring committee will not be employed. However, the Hoosier Cancer Research Network data management team provides patient safety oversight for all Hoosier Cancer Research Network trials. Specific data and safety monitoring tasks conducted by Hoosier Cancer Research Network include:

- Review of clinical trials conducted for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by data quality control review process
- Notification of the Sponsor Investigator and funding company of recommended action
- Notification of sites coordinated by Hoosier Cancer Research Network of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications

In addition, Hoosier Cancer Research Network will compile data summary reports for this trial and submit these reports monthly to the Sponsor Investigator. Hoosier Cancer Research Network will submit data summary reports to a Data Safety Monitoring Committee (DSMC) a minimum of twice per year for review.

# 9 Data Review and Management

## 9.1 Data Confidentiality

Information about study patients will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed patient authorization informing the patient of the following:

- What protected health information (PHI) will be collected from patients in this study

- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the patient is alive) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

## 9.2 Site Monitoring

All study sites will be monitored by Hoosier Cancer Research Network. This includes on-site visits for prior to first study startup for new Hoosier Cancer Research Network sites and annual on-site visits for existing member sites. Sites will be monitored for accuracy, timeliness, and completeness of data collection. Hoosier Cancer Research Network will review source documents for verification of agreement with data submitted via the data collection system. The investigator/ institution guarantee access to source documents by Hoosier Cancer Research Network or its designee and appropriate regulatory agencies. In addition, adherence to protocols through evaluation of study deviations will be analyzed.

The trial site may also be required to participate in a quality assurance audit by Novartis or its designee as well as inspection by appropriate regulatory agencies.

It is important for the investigator and his/her relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

## 9.3 Data Handling and Record Collection

### 9.3.1 Case Report Forms

An electronic case report form (eCRF) is required and must be completed for each included patient. The completed dataset is the sole property of Hoosier Cancer Research Network and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from Hoosier Cancer Research Network.

## 9.4 Database Management and Quality Control

Data will be entered into the study database by investigator/study coordinator for EDC studies.

For studies using eCRFs, Hoosier Cancer Research Network personnel will review the data entered by investigational staff for completeness and accuracy. Detected discrepancies for which the resolution is obvious/self-evident will be corrected by Hoosier Cancer Research Network

Data Management personnel. Electronic data queries are stating the nature of the problem and requesting clarification will be created for all other discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data will be processed centrally and the results will be sent electronically to Hoosier Cancer Research Network.

At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis.

# 10 Statistical Methods and Data Analysis

## 10.1 General Considerations

Statistical analysis of this study will be the responsibility of the Department of Biostatistics at IUSM. Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima and standard deviations. Categorical variables will be summarized by frequencies and percentages. Missing data are expected to be rare. For patients that start therapy but do not make it to the primary endpoint evaluation, their 6-month status will be treated as not achieving CR. Consequently, our estimate of 6-month CR rate will be conservative. For secondary outcomes, missing data, if any, will not be imputed and complete-case analysis will be adopted. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol.

## 10.2 Analysis Sets

### 10.2.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned. Patients will be analyzed according to the treatment they have been assigned to.

### 10.2.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication.

### 10.2.3 Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who do not have significant deviations from the inclusion/exclusion criteria and are compliant with the treatment plan.

### 10.2.4 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PAS) consists of all patients who have evaluable pharmacokinetic (PK) data from post-treatment bladder tissue.

### 10.2.5 Efficacy Set

The efficacy analysis set (EAS) consists of all patients who received at least one dose of study medication and had at least one post-treatment cystoscopy/TURBT and urine cytology performed.

### 10.2.6 Other Analysis Sets

Correlative analysis sets will consist of all patient sets who have evaluable correlative data for each proposed correlative analysis. For instance, the plasma free FGFR3 mutation set will consist of all patients who have baseline plasma evaluable for FGFR3 mutation analysis.

## 10.3 Patient Demographics/Other Baseline Characteristics

Demographic and other baseline data (including disease characteristics and FGFR3 mutation/over-expression status) will be summarized descriptively for all patients for the FAS.

## 10.4 Treatments (Study Drug, Concomitant Therapies, Compliance)

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be summarized for the safety set.

### 10.4.1 Treatment Drug and Compliance

Duration of treatment and compliance status will be tabulated for the safety set.

### 10.4.2 Concomitant Therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be summarized for the safety set.

## 10.5 Primary Objective

The primary objective of the trial is to determine the 6-month complete response rate in BCG-refractory UC patients with FGFR3 mutant or over-expressing tumors treated with dovitinib.

### 10.5.1 Primary Objective Statistical Considerations

The 6-month complete response rate will be summarized by frequency and rate. The one-sided 90% confidence interval (CI) of Agresti-Coull type will be calculated for the rate.

## 10.6 Secondary Objectives

### 10.6.1 Key Secondary Objective(s)

In addition to the study's primary objective, key secondary objectives include:

- To determine the 1-year relapse free survival rate.
- To determine the rate of progression to muscle-invasive stage (i.e. T2-T4).
- To determine 3- and 6-month partial response rate defined as a reduction in T-stage on post-therapy TURBT (i.e. T1 ≥ Ta; T1+Tis ≥ Tis)
- To characterize treatment related toxicity rates assessed by CTCAE v4.0

### 10.6.2 Secondary Objectives Statistical Considerations

All secondary objectives are hypothesis generating in nature. One year RFS muscle-invasive progression, 3- and 6-month PR, and toxicity rates will be presented as rates and corresponding 90% Agresti-Coull CIs.

### 10.6.3 Safety Objectives

#### 10.6.3.1 Analysis Set and Grouping for the Analyses

For all safety analyses, the safety set will be used.

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. post-treatment period: starting at day 31 after last dose of study medication.

#### 10.6.3.2 Adverse Events (AE)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs. However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTC grades), type of adverse event, and relation to the study drug. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

Specific safety event categories (SEC) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s).

For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

#### 10.6.3.3 Laboratory Abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, the study's biostatistical and reporting team will grade laboratory data accordingly.

For laboratory tests covered by CTCAE, a grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

In some cases (e.g. white blood cell differentials), the lower limits of normal ranges used in CTCAE definition may have to be replaced by a clinical meaningful limit expressed in absolute counts.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- frequency table for newly occurring on-treatment grades 1, 2, 3 or 4 (see below for details)
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots will be generated when appropriate.

#### 10.6.3.4 Other Safety Data

**ECG**

- shift table baseline to worst on-treatment result for overall assessments
- lists of ECG evaluations for all patients with at least one abnormality.

**Vital Signs**

- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

## 10.7 Exploratory Objectives

In addition to the study's primary and secondary objectives, key exploratory objectives include:

- To characterize concordance rates between UC patient detected tumor, urine, and circulating free plasma FGFR3 mutations.
- To characterize associations between pre-treatment germline (as assessed by PBMC extracted DNA) FGFR SNPs and post-treatment 6-month complete response rate and 1-year relapse free survival rate in patients treated with dovitinib.

- To characterize associations between pre-treatment germline (as assessed by PBMC extracted DNA) VEGFR SNPs and post-treatment 6-month complete response rate and 1-year relapse free survival rate in patients treated with dovitinib.
- To characterize VEGFR over-expression status within tumor tissue
- To characterize pre- and post-treatment bladder tumor FGFR and VEGFR pathway phosphorylation changes as assessed by bladder tumor tissue immunohistochemistry.
- To characterize post-treatment bladder tissue dovitinib concentrations.
- To characterize associations between post-treatment hypertension, 6-month complete response rate and 1-year relapse free survival rate in patients treated with dovitinib.

### 10.7.1 Exploratory Objectives Statistical Hypothesis, Model, and Method of Analysis

All exploratory objectives are hypothesis generating in nature. Pre- and post- treatment phosphorylation changes in FGFR and VEGFR pathways will be analyzed by paired t-tests. FGFR SNPs, VEGFR SNPs, post-treatment hypertension, and baseline clinical factors of interest (e.g. age, ECOG PS, Charlson Comorbidity Index, gender, T1 vs. CIS, number of prior intravesical therapies, etc.) will be analyzed by univariate logistic regression and Cox regression for significant associations with 6-month CR and 1-year RFS rates, respectively. No multivariate models will be adopted given the small sample size. Concordance rates between tumor, urine, and circulating free plasma FGFR3 mutations will be summarized by Goodman-Kruskal gamma. The post-treatment bladder tissue dovitinib concentrations will be summarized by mean, standard deviation, minimum, median, maximum, and boxplot. Transformations to normality will be considered when necessary.

## 10.8 Sample Size Calculation

The 6-month CR rate will be estimated with a one-sided 90% confidence interval of Agresti-Coull type with the lower bound to be calculated and the upper bound set as 1. With an expected CR rate of $\geq$ 25%, a sample size of 20 patients will have a power of 0.80 to exclude a lower bound being $\leq$ 10%.

Using a conservative estimate of FGFR3 mutation or over-expression present in 40% of BCG-refractory tumors, 50 patients will need to be screened in order to enroll the required 20 patients on dovitinib therapy.

The estimated accrual duration is 12 months and the estimated overall study duration is 2 years.

## 10.9 Early Stopping Rules

Early stopping rules will be performed after the first 10 patients have completed 3-month assessment for progression to T2 or greater stage based on TURBT samples. The study will not be halted while the early stopping rule is being evaluated.

If the probability of the 3-month progression rate being no higher than 20% is lower than 0.1, it will be considered as unacceptable and the study will be closed. Consequently, the trial would be stopped if 3-month progression is observed in 5 or more out of the first 10 patients. Note that the lower bounds of 90% Agresti-Coull confidence interval for 4, 5 and 6 out of 10 patients are 0.19, 0.27, and 0.35, respectively.

# 11 Ethical Considerations and Administrative Procedures

## 11.1 Regulatory and Ethical Compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

## 11.2 Responsibilities of the Investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

## 11.3 Informed Consent Procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent <if applicable: or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form>. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide investigators in a separate document with a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

This study will include requesting patient consent to keep and store any leftover tissue samples in the Hoosier Cancer Research Network already established Biorepository for possible future IRB approved research.

## 11.4 Discontinuation of the Study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.

## 11.5 Publication of Study Protocol and Results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicalstudys.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

## 11.6 Study Documentation, Record Keeping, and Retention of Documents

To enable evaluations and/or audits from Health Authorities/Hoosier Cancer Research Network, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all eCRF's, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

During data entry, range and missing data checks will be performed on-line. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRF's will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

## 11.7 Confidentiality of Study Documents, and Patient Records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

## 11.8 Audits and Inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

### 11.9 Financial Disclosures

Financial disclosures should be provided by study personnel who is directly involved in the treatment or evaluation of patients at the site - prior to study start.

## 12 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

### 12.1 Amendments to the Protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by Hoosier Cancer Research Network and must be approved by each IRB, Novartis, and if applicable, also the local regulatory authority. Local requirements must be followed.

If a protocol amendment requires a change to the Written Informed Consent Form, then the IRB must be notified. Approval of the revised Written Informed Consent Form by the IRB is required before the revised form is used.

The Principal Investigator or his/her designee is responsible for the distribution of the protocol amendment and associated documents to his/her IRB, and to the staff at his/her center. The distribution of these documents to the regulatory authority will be handled by the Principal Investigator or his/her designee according to local practice.

Novartis' willingness to supply study drug is predicated upon the review of the protocol. Hoosier Cancer Research Network agrees to provide written notice to Novartis of any modifications to the protocol or informed consent.

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