



Open-label, single-arm, Phase II study, evaluating safety and efficacy of INCB054828 (Pemigatinib) as adjuvant therapy for molecularly-selected, high-risk patients with urothelial carcinoma who have received radical surgery. A European Association of Urology Research Foundation Phase II Clinical Trial. Protocol Number: EAU-RF 2018-02. Eudract Number: 2019-001833-14

Overview

The purpose of this clinical trial is to demonstrate the benefit of Pemigatinib, a drug that has indicated promising effects for relapse free survival in molecularly-selected, high-risk patients with urothelial carcinoma who have received radical surgery. Patients will receive Pemigatinib at a once-daily dose on a continuous schedule, continued until 12 months.

Study Objectives

- ◆ *Primary Endpoint:*
Relapse-free survival rate
Defined as the time from the date of start of study treatment until disease relapse or progression by Investigator determination, or death due to any cause, whichever occurs first.
- ◆ *Secondary Endpoints:*
 - Overall Survival
 - Number of treatment-emergent adverse events .

Rationale:

- Patients with invasive disease at radical resection of Urothelial Carcinoma (UC) are at high risk of relapse and may benefit from additional cisplatin-based chemotherapy.
- Patients whose disease progresses on platinum-based chemotherapy or who are ineligible due to inadequate renal function or poor performance status have limited treatment options. In such patients treatments using new agents should be considered.
- Patients who received neo-adjuvant platinum-based chemotherapy who have residual disease at radical resection of UC have a worse prognosis and should be considered with additional treatments using new agents.
- Immune checkpoint inhibitors (ICPIs) have improved outcomes in some patients with platinum-resistant and/or -ineligible metastatic UC; however, benefit may be limited to patients with higher positive tumor and infiltrating immune cell staining for programmed death-ligand-1 (PD-1).
- Fibroblast growth factor (FGF) / FGF receptor (FGFR) genetic alterations are implicated in the pathogenesis of UC, most commonly FGFR3 mutations ($\approx 12\%$) and translocations ($\approx 3-6\%$). FGFR3 genetic alterations are more common in patients with immune desert luminal cluster I subtype UC; these patients are expected to receive less benefit from ICPIs.
- Pemigatinib is a selective, potent, oral inhibitor of FGFR1, 2, and 3, and has shown efficacy in tumors with various FGFR alterations.

The PEGASUS is an open-label, single-arm, Phase II study, evaluating safety and efficacy of INCB054828 (Pemigatinib) as adjuvant therapy for molecularly-selected, high-risk patients with urothelial carcinoma who have received radical surgery.

This trial will evaluate the 2-year relapse-free survival rate (RFS) of high-risk patients previously treated with cisplatin-based chemotherapy or ineligibility to receive adjuvant cisplatin-based chemotherapy. These patients will receive adjuvant Pemigatinib after radical surgery. Improvement of RFS may be regarded as an optimal endpoint for adjuvant therapy trials, given the availability of multiple lines of new therapies in the advanced stages that may affect RFS outcomes in these patients. Secondary objectives are to evaluate safety, tolerability and overall survival.

An explorative objective is to evaluate biomarkers of clinical benefit and prognostic biomarkers. These biomarkers will be evaluated at the time of radical surgery, on the tumor tissue, before the administration of the study drug



Study population

A total of 56 patients with pT3-4 and/or pN1-3 stage UC at radical cystectomy or radical nephroureterectomy with documented FGF/FGFR alterations are to be recruited from urology departments in European hospitals participating in this study.

Key Inclusion Criteria:

- Men and woman, aged 18 years or older with histological evidence of pT3-4 and/or pN1-3 UC of the urinary bladder or upper urinary tract after radical cystectomy/radical nephroureterectomy. Patients with mixed histologies are required to have a dominant (i.e. at least 50%) urothelial cell carcinoma pattern.
- Previous administration of at least 3 cycles of neoadjuvant cisplatin-based chemotherapy OR, if neoadjuvant chemotherapy was not administered, ineligibility to receive cisplatin-based adjuvant chemotherapy based on Galsky's criteria, that include at least one of the following: (1) WHO performance status ≥ 2 and/or (2) creatinine-clearance < 60 ml/min and/or (3) CTCAE Gr ≥ 2 hearing loss and/or (4) CTCAE Gr ≥ 2 neuropathy.
- Evidence of FGFR alterations (mutations or translocations as specified in protocol) as assessed by a centralized Foundation Medicine test (Foundation One).
- Recovered with no evidence of disease confirmed by radiological images, prior to start of adjuvant therapy within 13 weeks after radical surgery.
- Willingness to avoid pregnancy or fathering children.
- Written informed consent.

Please find the full description of the trial on the [Clinical trials.gov](https://clinicaltrials.gov) website.

Protocol writing Committee

- ◆ Dr. Andrea Necchi, Milano
- ◆ Dr. Wim P.J. Witjes, Arnhem

EAU Research Foundation

- ◆ Dr. Wim Witjes, Scientific and Clinical Research Director
- ◆ Dr. Raymond Schipper, Clinical Project Manager
- ◆ Mrs. Xandra Helmonds, Financial Manager

Study Principal Investigator

Dr. Andrea Necchi

Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Nazionale dei Tumori

Milano, Italy

Contact

EAU RF Central Research Office

PO Box 30016, 6803 AA Arnhem, The Netherlands

Email: researchfoundation@uroweb.org, Phone: +31 (0) 26 38 90 677