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IKF614/ INSIGHT-005

A new stratum of the explorative, open-labeled, phase I INSIGHT study to evaluate the feasibility and safety, as well as preliminary efficacy, of subcutaneous injections with IMP321 (eftilagimod alpha) in combination with PD-L1 inhibitor (avelumab) for metastatic or unresectable locally advanced urothelial carcinoma (UC)

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Background

Urothelial cancer (UC) is the 6th most common malignancy in the Western world, localized in the upper (5-10%) or the lower (90-95%) urinary tract. Metastatic UC (mUC), which accounts for 5% of all cases, is associated with a dismal prognosis and rapid progression. For more than a decade, 1st line therapy for mUC encompassed platinum-based combination regimens. Immune checkpoint inhibitors (ICIs) have shown significant promise in the treatment of various indications, showcasing noteworthy efficacy and safety profiles in clinical settings. Thus, avelumab was approved for maintenance therapy following progression-free course of chemotherapy for locally advanced (LA) or mUC. Further ICIs (e.g. pembrolizumab, atezolizumab, nivolumab) were registered for treatment of different patient populations with UC. Eftilagimod alpha (efti) is a soluble LAG-3 fusion protein and an MHC class II agonist activating APCs followed by CD8 T-cell activation. The combination of efti with PD-1/PD-L1 blockade is proposed to enhance treatment efficacy of ICIs. Despite ongoing changes in the treatment landscape, based on previous results from the INSIGHT trial, we hypothesize that combining avelumab and efti will display clinically relevant efficacy in unresectable LA UC or mUC subgroups with acceptable toxicity.

Methods

Study Design, Study Treatment and Study Analysis

INSIGHT-005 is a new stratum within the ongoing investigator-initiated INSIGHT phase I platform trial ongoing at multiple sites (n=10) in Germany. Patients with unresectable LA UC or mUC will receive efti in combination with avelumab. 30 patients will be enrolled in 3 subgroups:

I) Previously untreated, eligible for platinum-based therapy, with PD-L1 CPS≥10
II) Previously untreated, not-eligible for platinum-based therapy, irrespective of the PD-L1 status
III) Suffered disease progression after platinum-based chemotherapy for metastatic disease and did not receive avelumab maintenance therapy, irrespective of the PD-L1 status.

Treatment: Enrolled patients will receive avelumab 800 mg i.v. and efti 30 mg s.c. on the same day Q2W for a maximum of 24 cycles. Tumor evaluation will be performed via CT or MRI Q8W.

Primary Endpoint

The primary endpoint of this study is to explore feasibility, safety, and preliminary efficacy of efti when added to avelumab in unresectable LA UC or mUC.

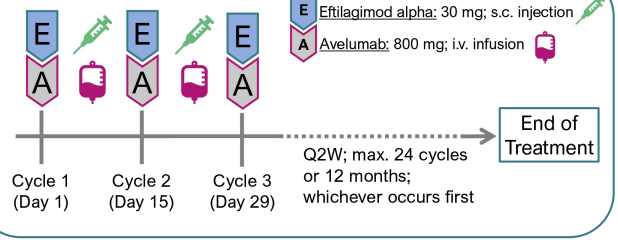
Secondary Endpoints

Secondary endpoints include safety and efficacy parameters as defined by objective response rate, time to response and duration of response as well as PFS according to RECIST 1.1, OS and exploratory biomarker analyses.

Screening

Patients with metastatic or irresectable locally advanced urothelial carcinomas:
Group I) Previously untreated, eligible for platinum-based therapy, with PD-L1 CPS≥10
Group II) Previously untreated, not-eligible for platinum-based therapy, irrespective of their PD-L1 status
Group III) Disease progression after platinum-based chemotherapy for metastatic disease and did not receive avelumab maintenance therapy, irrespective of their PD-L1 status.

Treatment



Tumor assessment
Radiological assessment every 8 weeks during treatment and Follow Up (Q8W)

Biosampling
Tumor biopsy at baseline &
Collection of translational blood samples at baseline, D29, D57, D85, D155 and EOT

Follow Up

Tumor assessment (Q8W) and survival follow-up (Q12W) 18 month after last patient in

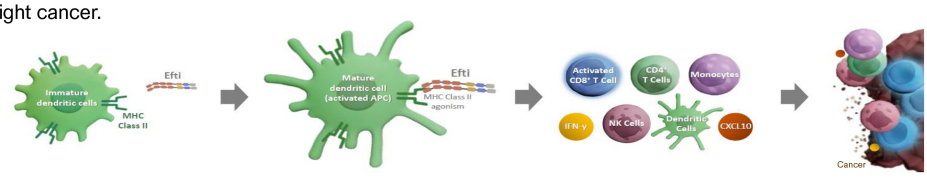
Endpoints

Primary Endpoint:
Feasibility, safety and toxicity of eftilagimod alpha when added to avelumab in metastatic or irresectable locally advanced urothelial carcinomas

Secondary Endpoints:
- **AEs and SAEs (e.g., type, number, frequency)**
- **Assessments of physical examinations, body weight, vital signs, ECOG hematology, biochemistry, coagulation and urinalysis values, ECG and clinically relevant changes of safety relevant cytokines if measured**
- **Objective response rate (ORR) according to RECIST v1.1**
- **Time to and duration of response according to RECIST v1.1**
- **Progression-free survival according to RECIST v1.1**
- **Overall survival**
- **Biomarker analyses and possible links to antitumor activity**

Eftilagimod alpha- Mode of Action

Efti is soluble LAG-3 protein (LAG-3 domains fused to human IgG backbone). Activating Antigen Presenting Cells (APCs) with efti leads to a broader immune response, including increases in activated T cells (CD4/CD8) to fight cancer.



Current status of the trial	
Study Status	Recruiting
FPI	29 November 2023
Study Sites	10 study sites in Germany have ethics approval; further 6 sites in Germany will be added

Study Identifiers	
ClinicalTrials.gov	NCT03252938
EudraCT	2016-002309-20
IKF Study ID	IKF614

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Disclosures
IT: no conflict of interest
TOG: no conflict of interest

Visit INSIGHT at ClinicalTrials.gov