Feasibility of eftilagimod alpha (soluble LAG-3 protein) combined with standard-of-care-therapy in advanced non-small-cell lung cancer (NSCLC) adenocarcinomas. Initial results from INSIGHT 003

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Background

Eftilagimod alpha (efti; IMP321) is an MHC II class agonist (soluble LAG-3 protein) which activates antigen-presenting cells followed by T-cell (CD4/CD8) activation (Immutep Ltd.). Data from the TACTI-002 trial (NCT03625323) and INSIGHT-004 of the current multiple-strata INSIGHT phase-I platform-study revealed that the combination of 30 mg efti subcutaneous (s.c.) with anti-PD-(L)1 checkpoint inhibitor is well tolerated with encouraging efficacy especially in NSCLC. Stratum C (INSIGHT-003) of the INSIGHT study aims to evaluate the feasibility and tolerability of s.c. injections with efti combined with Standard-of-Care (SOC) chemo- and immuno-therapy (carboplatin AUC5 / pemetrexed / pembrolizumab) in 1st-line NSCLC-patients.

Figure 1: Study Design

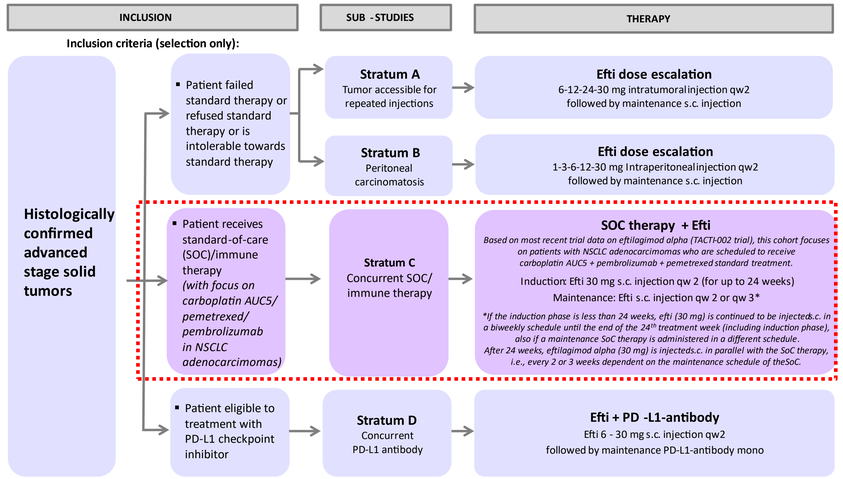

Table 1: Patient overview

Pat-ID	PD-L1 staining - TPS (%)	No of cycles	No of efti injections total	Best response	PFS (months)	OS (months)
001-029	0	17	21	SD	11.9*	12.5*
001-030	30	12	17	PR	7.8	8.8*
001-031	40	17	21	PR	11.0*	11.6*
001-032	0	3	4	PD	1.6	6.1
001-033	0	9	13	PR	8.0	8.0*
001-034	20	11	15	PR	7.7*	7.7*
001-035	5	10	14	PR	6.3*	6.4*
001-036	20	8	11	SD	5.2*	5.4*
001-037	60	8	11	PR	5.7	5.7
001-038	30	8	12	PR	3.9*	5.1*
001-039	60	5	7	PR	3.7*	3.7*

* time to event not yet reached; TPS = tumor proportion score;
SD = stable disease; PD = progressive disease; PR = partial response; response = acc. RECIST 1.1

Methods

In Stratum C, patients with metastatic NSCLC adenocarcinomas are treated with: SOC chemotherapy (carboplatin AUC5 / pemetrexed 500 mg/m^2 q3w for 4 cycles followed by optional pemetrexed 500 mg/m^2 q3w for maintenance) plus pembrolizumab 200 mg q3w combined with s.c. injections of efti (30 mg) (q2w for 24 weeks; thereafter q3w till week 52). Imaging is performed every 8 weeks and assessed locally. The primary endpoint is feasibility (defined by safety and tolerability) while secondary endpoints include objective response acc. to RECIST 1.1 and other efficacy parameters. In total 20 patients will be enrolled.

Results

From 02Aug2021 till data cut off from 14Oct2022, 14 patients with metastatic NSCLC adenocarcinomas have been enrolled. Median age is 66 years and 71.4% are male. Nine (81.8 %) patients had PD-L1 TPS <50% (Table 1). No occurrence of unacceptable toxicities (i.e., causally related to efti AND resulting in permanent discontinuation of combination-treatment before administration of two complete cycles). Five serious adverse events (1 sepsis, grade 5; 1 bronchial infection, grade 3; 1 pancreatitis, grade 3; 1 dyspnea, grade 3; 1 diarrhea, grade 2) were reported. Pancreatitis was possibly related to efti (Table 2), assessed as unexpected and therefore reported as SUSAR. Two patients completed max treatment with 52 weeks.
In total, 154 adverse events (grade 1-2: 88; grade 3: 59; grade 4: 6; grade 5: 1) were documented. The most frequent AEs were neutrophil count decreased in eleven patients (78.6%, grade 1-4), white blood cell decreased in nine patients (64.3%, grade 1-4), platelet-count decreased in eight patients (57.1%, grade 1-3) and anemia in eight patients (57.1%, grade 1-3) (Table 4). One grade 3 AE was considered related to efti (Table 5).

Up to now only the first 11 out of the 14 patients were evaluated for efficacy: Eight (72.2%) partial responses, two (18.2%) stable diseases, one (9.1%) progressive disease as best overall response acc. to RECIST 1.1. (Table 1).

Table 2: Summarized SAEs by patients

SAE	Total n=14 (100%)
Patients with at least one SAE	4 (28.6%)
Patients with at least one SAE with relation to study treatment	1 (7.1%)

First and last author conflicts of interest

AA had no conflict of interest.
TOG had an advisory role for Lilly, MSD Oncology, Bayer, SERVIER, Roche, Novartis, Incyte, Foundation Medicine and BMS, served as speaker for Lilly, and received research funding from Deutsche Forschungsgemeinschaft, Gemeinsamer Bundesausschuss, Deutsche Krebshilfe, Lilly, AstraZeneca and Incyte.

Table 3: Serious adverse events (irrespective of relationship to study drug)

	Total n=14 (100%)				
Serious adverse event	**G1**	**G2**	**G3**	**G4**	**G5**
Dyspnea			1 (7.1%)		
Respiratory infection			1 (7.1%)		
Pancreatitis			1 (7.1%)		
Sepsis					1 (7.1%)
Diarrhea		1 (7.1%)			

Table 4: Most frequent adverse events (irrespective of relationship to study drug)

	Stratum C (n=14 (100%))			
Most common AEs	**G1/G2**	**G3**	**G4**	**G5**
Neutrophil count decreased	3 (21.4%)	4 (28.6%)	4 (28.6%)	
Platelet count decreased	4 (28.6%)	4 (28.6%)		
Anemia	3 (21.4%)	5 (35.7%)		
Aspartate aminotransferase increased	5 (35.7%)			
Chronic kidney disease	2 (14.3%)	1 (7.1%)		
Nausea	2 (14.3%)	1 (7.1%)		
Dyspnea	2 (14.3%)	1 (7.1%)		
Fatigue	1 (7.1%)	1 (7.1%)		
Vomiting	1 (7.1%)	1 (7.1%)		
Alanine aminotransferase increased	2 (14.3%)			
Edema limbs	2 (14.3%)			
Erythroderma	2 (14.3%)			
Fever	2 (14.3%)			
Hypertension	2 (14.3%)			
Hyperthyroidism	2 (14.3%)			
Pain	2 (14.3%)			
Thromboembolic event	2 (14.3%)			
White blood cell decreased	2 (14.3%)	6 (42.9%)	1 (7.1%)	
Platelet count decreased	4 (28.6%)	4 (28.6%)		
Anemia	3 (21.4%)	5 (35.7%)		
Aspartate aminotransferase increased	5 (35.7%)			
Chronic kidney disease	2 (14.3%)	1 (7.1%)		
Nausea	2 (14.3%)	1 (7.1%)		
Dyspnea	2 (14.3%)	1 (7.1%)		
Fatigue	1 (7.1%)	1 (7.1%)		
Vomiting	1 (7.1%)	1 (7.1%)		
Alanine aminotransferase increased	2 (14.3%)			
Edema limbs	2 (14.3%)			
Erythroderma	2 (14.3%)			
Fever	2 (14.3%)			
Hypertension	2 (14.3%)			
Hyperthyroidism	2 (14.3%)			
Pain	2 (14.3%)			
Thromboembolic event	2 (14.3%)			

Table 5: Treatment related irAEs

	Stratum C n=14 (100%)			
	G1/G2	**G3**	**G4**	**G5**
Adverse reaction	**Causality efti**	**Causality efti**	**Causality efti**	**Causality efti**
Alanine aminotransferase increased	1 (7.1%)			
Alkaline phosphatase increased	1 (7.1%)			
Aspartate aminotransferase increased	5 (35.7%)			
Hypertension	1 (7.1%)			
Hyperthyroidism	1 (7.1%)			
Hypothyroidism	2 (14.3%)			
Pancreatitis		1 (7.1%)		
Skin toxicity	4 (28.6%)			

Conclusion

To date, 30 mg efti combined with SOC (carboplatin AUC5 / pemetrexed / pembrolizumab) was well tolerated with only one unexpected SAR (SUSAR) observed. Combination treatment with efti appears to be feasible and safe. First promising signals of therapeutic efficacy with immune checkpoint inhibition (CPI) combination were detectable (disease control rate of 92.9%) which will be further evaluated.

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Study identifiers: EudraCT-No.: 2016-002309-20, Clinicaltrials.gov: NCT03252938

This study is conducted in collaboration with and co-funded by Immutep GmbH.