#1032P: Safety data from stratum D of the phase I INSIGHT platform trial evaluating feasibility of IMP321 (LAG-3Ig protein, eftilagimod alpha) combined with avelumab in advanced stage solid tumor entities

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Background

Stratum D of the INSIGHT platform trial evaluates s.c. application of eftilagimod alpha (efti, IMP321) combined with avelumab in advanced stage solid tumors. Efti is an MHC class II agonist which activates antigen-presenting cells followed by CD8 T-cell activation. Combination with PD-1/PD-L1 blockade aims at enhanced therapeutic efficacy.

Figure 1: Study Design

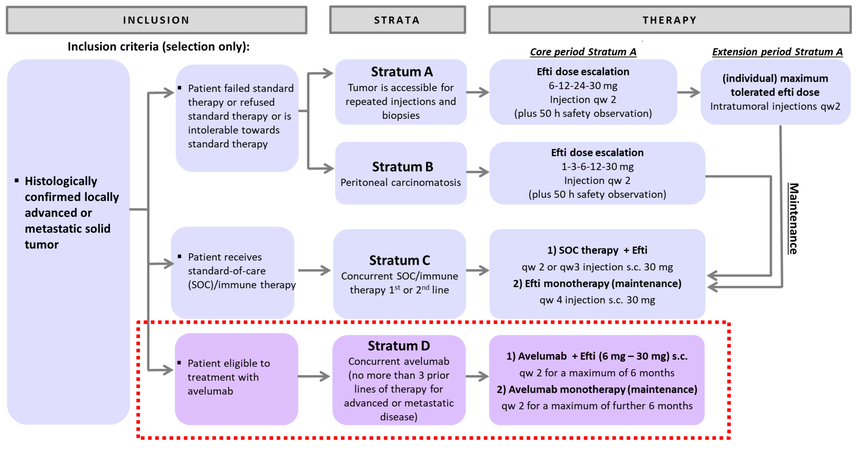

Table 1: Patient overview

Pat-ID	Cohort	Indication	Last prior therapy	PD-L1 staining / MSI / molecular markes	No of cycles	Best response	PFS (months)	OS (months)
001-017	Cohort 1	Adenocarcinoma stomach	1st line FLOT	PD-L1: nk; MSS	5	PD	2	11+
001-018	Cohort 1	Adenocarcinoma gallbladder	Gemcitabine / cisplatin additive	PD-L1: CPS 80%, MSS	3	PD	2	2
001-019	Cohort 1	Adenocarcinoma right colon	3rd line TAS-102	PD-L1: nk; Pan-RAS wt	4	PD	2	6
001-020	Cohort 1	Adenocarcinoma rectum	3rd line TAS-102	PD-L1: nk; Pan-RAS and BRAF wt	4	PD	2	9+
001-021**	Cohort 1	Adenocarcinoma right colon	na	**PD-L1: TPS 1%, CPS 2%; MSI high (Lynch-Syndrome)**	18+	PR	7+	7+
001-022	Cohort 1	Pleural mesothelioma	na	Nk	15+	PR	8+	8+
001-023	Cohort 2	Squamous cell esophageal carcinoma	Def. RCTx carboplatin/ paclitaxel (56 Gy)	PD-L1: CPS 30%	3	SD	2	4+
001-024	Cohort 2	Squamous cell anal carcinoma	Def. RCTx (5-FU+ mitomoycin C)	PD-L1: TPS 50%	7+	PR	4+	4+
001-025	Cohort 2	Adenocarcinoma GEJ Typ III	2nd line paclitaxel / ramucirumab	PD-L1: TPS 30%, CPS 40%	7+	PR	2+	3+
001-026**	Cohort 2	Squamous cell cervical carcinoma	Def. RCTx (cisplatin)	**PD-L1 negative, MSS**	4+	PR	2+	2+
001-027	Cohort 2	Adenocarcinoma GEJ Typ II	2nd line FOLFIRI	PD-L1: CPS 80%, MSS	4	PD	2	2+
001-028**	Cohort 2	Adenocarcinoma rectum	2nd line FOLFIRI	**PD-L1: nk; MSS, RAS and BRAF wt**	2+	nd*		1+

* response assessment not yet performed; + continuing and respective endpoint not yet reached;
** low PD-L1 and MSS stable
nk = not known; SD = stable disease; PD = progressive disease; PR = partial response; response = acc. RECIST 1.1
TPS = tumor proportion score; CPS = combined positivity score

Methods

This investigator-initiated study consists of 4 strata: intratumoral (A) or intraperitoneal efti (B); s.c. efti with SOC (C) or with PD-L1 inhibition (D) (Figure 1). This abstract focuses on preliminary safety data of Stratum D. Patients (pts) receive 800mg avelumab i.v. q2w along with s.c. efti: 6mg efti in cohort 1 (6 pts), 30mg efti in cohort 2 (6 pts). Primary endpoint is safety.

Results

12 pts have been recruited displaying different solid tumor types (cohort 1: gastric, gallbladder, colon cancer, pleural mesothelioma; cohort 2: gastric, gastroesophageal, anal, rectum, cervical cancer) (Table 1).
No dose limiting toxicities (DLTs) occurred. With data cut off from 12-Jun-2020, 1 AE of special interest (AESI) possibly related with avelumab (sarcoidosis grade 1) occurred in cohort 1. 8 serious adverse events (SAEs) were reported, none of them considered causally related (3 SAEs in 2 pts of cohort 1 [1 acute kidney injury grade 5 in 1 pt, 2 preileus grade 3 in 1 pt] and 5 SAEs in 3 pts of cohort 2 [1 anal hemorrhage, 1 gallbladder obstruction, 1 eye pain, 1 surgery to replace the feeding tube, each grade 3, 1 skin infection grade 2] (Table 2; Table 3).
In cohort 1, 42 adverse events (AEs; grade 1-2, 27; grade 3, 13; grade 4, 1; rade 5, 1) occurred in 5 pts. Most common grade 1-2 AEs were pain, nausea in 50%, 33% of the pts. Most common grade 3 AEs were ileus, nausea in 33%, 33% of the pts (Table 4). 1 AE grade 4 (sepsis) and 1 AE grade 5 (acute kidney injury) were reported. All AEs grade 3-5 were considered causally unrelated (Table 5).
In cohort 2, 42 adverse events (AEs; grade 1-2, 20; grade 3, 20; grade 4, 2) occurred in 5 pts. Most common grade 3 AE was pain in 33% (Table 4). 1 AE grade 4 (platelet count decreased) was documented and considered causally unrelated. 1 AE grade 3 (skin infection) was considered possibly related with efti (Table 5). 2 AEs grade 3 (AST increased, ALT increased) were considered possibly related with avelumab (Table 5).
5 pts showed partial response, 1 stable disease, 3 disease progression acc. to RECIST 1.1, 2 clinical progression, 1 have not had tumor assessment yet. Signals of activity were also observed in pre-treated *MSS/PD-L1$_{low}$* patients.

Table 2: Summarized SAEs by patients

SAE	Cohort 1 800mg avelumab + 6mg efti n=6 (%)	Cohort 2 800mg evelumab + 30mg efti n=6 (%)	Total n=12 (%)
Patients with at least one SAE	2 (33%)	3 (50%)	5 (42%)
Patients with at least one SAE with relation to study treatment	0 (0%)	0 (0%)	0 (0%)

First author conflicts of interest

Nothing to declare

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

	Cohort 1 800mg avelumab + 6mg efti n=6 (%)		Cohort 2 800mg avelumab + 30mg efti n=6 (%)		Total n=12 (%)		
Serious adverse event	**G3**	**G5**	**G2**	**G3**	**G2**	**G3**	**G5**
Acute kidney injury		1 (17%)					1 (8%)
Ileus	1 (17%)					1 (8%)	
Anal hemorrhage				1 (17%)		1 (8%)	
Gallbladder obstruction				1 (17%)		1 (8%)	
Eye pain				1 (17%)		1 (8%)	
Surgery to replace the feeding tube				1 (17%)		1 (8%)	
Skin infection			1 (17%)		1 (8%)		

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

	Cohort 1 800mg avelumab + 6mg efti n=6 (%)		Cohort 2 800mg avelumab + 30mg efti n=6 (%)	
Most common AEs	**G1/G2**	**G3**	**G1/G2**	**G3**
Pain	3 (50%)	1 (17%)		2 (33%)
Nausea/Vomiting	2 (33%)	2 (33%)	1 (17%)	
Injection site reaction	1 (17%)		1 (17%)	
Ileus		2 (33%)		
Chills	1 (17%)		1 (17%)	
Fever	1 (17%)		1 (17%)	
Hypokalemia	1 (17%)			1 (17%)

Table 5: Treatment related AEs

	Cohort 1 800mg avelumab + 6mg efti n=6 (%)						Cohort 2 800mg avelumab + 30mg efti n=6 (%)							
	G1/G2			G3	G4	G5	G1/G2			G3			G4	G5
Adverse reaction	**Causality IMP321**	**Causality Avelumab**	**Causality efti and avelumab**				**Causality efti**	**Causality avelumab**	**Causality efti and avelumab**	**Causality efti**	**Causality avelumab**	**Causality efti and avelumab**		
Fever			1 (17%)						1 (17%)					
Lipohypertrophy			1 (17%)											
Injection site reaction	1 (17%)						1 (17%)							
Chills		1 (17%)						1 (17%)						
Dyspnea		1 (17%)												
Nausea		1 (17%)												
Sarcoidosis		1 (17%)												
Skin infection										1 (17%)				
Alanine aminotransferase increased											1 (17%)			
Aspartate aminotransferase increased											1 (17%)			
Hypotension								1 (17%)						
Urinary tract infection								1 (17%)						

Conclusion

Combination treatment with avelumab 800mg and efti 6mg (cohort 1) is feasible and safe. 30 mg efti in cohort 2 appears to be feasible and safe, as well. No unexpected AEs were observed in the combination. In both cohorts, first signals of therapeutic efficacy were detectable which will be further evaluated.

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