Preliminary results of STELLAR-001, a dose escalation phase I study of the anti-C5aR, IPH5401, in combination with durvalumab in advanced solid tumors

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Background

Anaphylatoxin C5a is released in the cancer microenvironment and binds to the C5aR1 receptor, which in turns promotes protumoral inflammation and immune suppression through recruitment and activation of myeloid derived suppressor cells (MDSC) and neutrophils [1].

Overexpression of C5aR1 has been reported in several tumor types and correlates with aggressive tumor features and poor prognosis [2-5].

- High levels of C5aR1 expression are associated with poor prognosis of Non-Small Cell Lung Cancer (NSCLC) after resection and promote tumor metastasis [2].
- Additionally, C5aR1 was found to be upregulated in NSCLC patients in progression after an initial response to an anti-PD-(L)1 therapy (IO). (Table 1)

IPH5401, a fully human anti-C5aR1 antibody, inhibits the C5a mediated effects on MDSC and neutrophils (Figure 1). Our preclinical data suggest that the combined blockade of C5aR1 and anti-PD-1 synergistically reduce tumor growth and delay tumor progression [6].

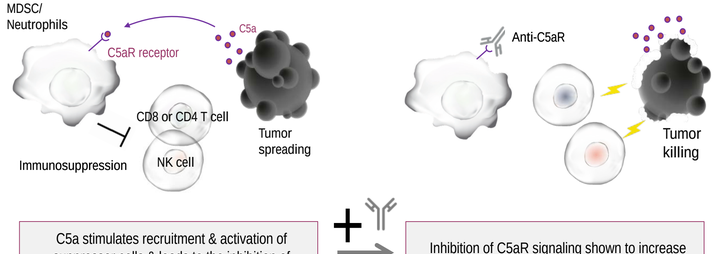
Furthermore in lung cancer mice models, C5a blockade controls the growth of established lung tumors and synergizes with an anti-PD1 [7].

These data suggest that combining IPH5401 with an anti-PD-(L)1 may improve efficacy and overcome secondary resistance to anti-PD-(L)1 therapies.

Table 1: C5 and C5ar1 expression in NSCLC IO-treated patients (Astra Zeneca internal data)

% of NSCLC patients with > 4-fold higher expression compared to IO-naive patients (RNAseq)	IO-Resistant (never responded)	IO-Secondary resistant (responded then progressed)
C5 expression	6/24 (25%)	9/22 (40.9%)
C5aR1 expression	4/24 (16.7%)	7/22 (31.8%)

Figure 1: IPH 5401 – First-In-Class Anti-C5AR mAb



C5a stimulates recruitment & activation of suppressor cells & leads to the inhibition of immune effector cells

+

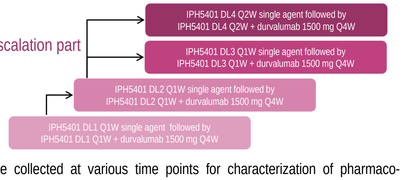
Inhibition of C5aR signaling shown to increase CD8 T cell infiltration & function

Study Design

STELLAR-001 is a multicenter, open-label study of IPH5401 in combination with durvalumab administered to adult subjects with selected advanced solid tumors to evaluate safety, tolerability, pharmacokinetics, immunogenicity, pharmacodynamics, and preliminary antitumor activity.

The study consists of 2 parts: a dose-escalation part and a cohort expansion part. Results from the dose escalation part of the study are presented hereafter.

Figure 2: Dose-escalation part – 4 dose levels



Blood samples were collected at various time points for characterization of pharmaco-kinetics, pharmacodynamics and immunogenicity.

Primary objective

- To evaluate the safety profile, describe the dose-limiting toxicities (DLTs) and determine the maximum tolerated dose (MTD) of IPH5401 in combination with durvalumab

Secondary objectives

- To characterize the pharmacokinetics (PK) of IPH5401 alone during the first 2 weeks and in combination with durvalumab
- To evaluate the preliminary clinical activity of IPH5401 in combination with durvalumab
- To determine the immunogenicity of IPH5401 when administered in combination

Main inclusion criteria for the dose escalation part

- Patients with advanced and/or metastatic histologically-confirmed hepatocellular carcinoma (HCC), urothelial carcinoma (UCC), renal cell carcinoma (RCC) or NSCLC with evidence of active disease, who have been treated with a minimum of one line of systemic therapy in the metastatic setting.
- Patients should have received known standard therapies (including platinum-based chemotherapy in patients with UCC), unless not available or contraindicated.
- ECOG performance status ≤1.
- A minimum life expectancy of 3 months.

Demographic

The 14 treated patients (DL1: 3, DL2: 4, DL3: 3, DL4: 4) were recruited by 4 sites in France and USA, between September 2018 and May 2019.

Table 2: Demographic data at baseline

		NSCLC	HCC	UCC	RCC	Total
Number of patients treated		6	5	2	1	14
Age, year	median (range)	68.5 (48-74)	63 (55-79)	65.5 (58-73)	55 (55-55)	63.5 (48-79)
Gender	Male	4 (67%)	3 (60%)	2 (100%)	1 (100%)	10 (71%)
	Female	2 (33%)	2 (40%)	0 (0%)	0 (0%)	4 (29%)
ECOG	0	2 (33%)	2 (40%)	1 (50%)	0 (0%)	5 (36%)
	1	4 (67%)	3 (60%)	1 (50%)	1 (100%)	9 (64%)
Prior systemic treatment lines	median (range)	3 (1-6)	2 (1-5)	1.5 (1-2)	2 (2-2)	2 (1-6)
Prior IO treatment		6 (100%)	3 (60%)	1 (50%)	1 (100%)	10 (71%)

Table 4: Treatment exposure

		NSCLC	HCC	UCC	RCC	Total
IPH5401 administrations	median (range)	8.5 (2-40)	18 (4-22)	7 (4-10)	13 (13-13)	9.5 (2-40)
Durvalumab administrations	median (range)	3 (1-10)	4 (2-5)	1.5 (1-2)	3 (3-3)	2.5 (1-10)

Efficacy results

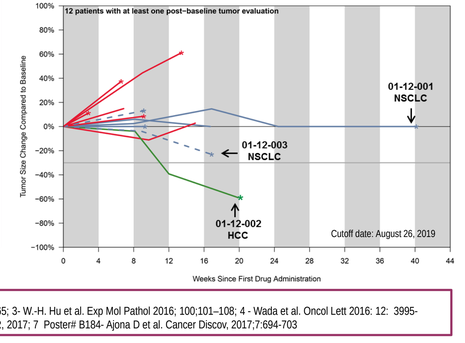
Table 5: Best tumoral response by tumor type (RECIST 1.1)

	NSCLC	HCC	UCC	RCC	Total
Partial Response	0	1	0	0	1
Stable disease	3	1	0	1	5
Progression	2	3	1	0	6
NE*	1	0	1	0	2

* no post-baseline tumor evaluation

- One confirmed PR reported in a HCC patient with prior progression after nivolumab
- One prolonged SD (40 weeks) reported in a NSCLC patient with prior progression after nivolumab
- Clinical benefit rate (CBR), defined as the proportion of patients with CR, PR or SD with at least two consecutive scheduled assessments: 42.9% (95%CI : 21.4--67.4)

Figure 3: Tumor size change



Safety results

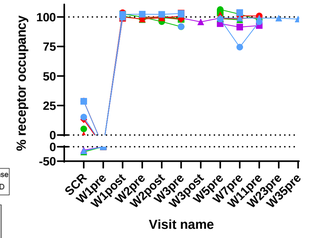
- No treatment-related death was reported. One death related to underlying tumor was reported.
- Study treatment was discontinued in 12 patients, due to tumor progression in 11 patients and due to a treatment-related adverse event (pneumonitis) in 1 patient at DL2.
- There was no DLT reported
- 84 AEs were reported among the 14 patients treated (Table 3) of which 11 were severe (grade 3-4)
- 20 grade 1-2 AE were reported as related to study treatment (3 fatigue and 2 rash as most frequent AE), there was no grade 3-4 related AE and no dose relationship.
- 5 grade 1-2 AE, occurring before the first administration of durvalumab, were reported as related to IPH5401 treatment (2 fatigue, 1 white blood cell count decreased, 1 headache and 1 dry mouth). There was no grade 3-4 IPH5401-related AE and no dose relationship
- One SAE (exacerbation of chronic obstructive pulmonary disease) considered as not related to IPH5401 and durvalumab was reported at DL3.

Table 3: Most frequent (>10%) treatment-emergent AE

	All AEs	gr 3-4 AEs
Total number of reported AEs	84	11
N patients with AE (%)		
• Fatigue	6 (42.9%)	2 (14.3%)
• Headache	4 (28.6%)	0
• Cough	3 (21.4%)	0
• Decrease appetite	3 (21.4%)	0
• Hypertension	3 (21.4%)	0
• Diarrhea	2 (14.3%)	0
• Abdominal pain	2 (14.3%)	0
• Urinary tract infection	2 (14.3%)	0
• Dyspnea	2 (14.3%)	2 (14.3%)
• Muscular weakness	2 (14.3%)	0
• Anemia	2 (14.3%)	0
• Lymphocyte count decreased	2 (14.3%)	1 (7.1%)
• Blood creatinine increased	2 (14.3%)	0
• Rash	2 (14.3%)	0
• Tumor pain	2 (14.3%)	0

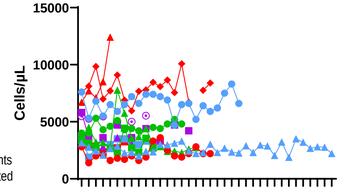
Pharmacodynamic data

Figure 4: C5aR is fully saturated from the first injection of the lowest IPH5401 dose in neutrophils



Each symbol represents a patient at the indicated dose-level.

Figure 5: Neutrophils count is not affected by IPH5401 and durvalumab treatment



Neutrophils counts are obtained from the weekly hematology assessments.

Conclusion

- The combination of IPH5401 and durvalumab was well tolerated, no DLT was reported and no dose relationship could be observed regarding safety.
- Encouraging early efficacy signals were observed in HCC and NSCLC.
- Pharmacodynamic analyses confirmed the full receptor saturation at all dose levels and the absence of impact on neutrophils count.
- STELLAR-001 study is now moving to next step with expansion cohorts in IO-pretreated NSCLC and IO-naive HCC to generate additional safety and efficacy data as well as translational analyses on tumor biopsies.

References

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innate pharma

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