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First-in-Human, Multicenter Phase I Study of IPH4102, First-in-Class Humanized Anti-KIR3DL2 Monoclonal Antibody, in Relapsed/Refractory Cutaneous T-Cell Lymphomas: Preliminary Safety, Exploratory and Clinical Activity Results

M. Bagot[1,7], P. Porcu[3], C. Ram-Wolff[1,7], M. Khodadoust[2], M. Battistella[1], A. Marie-Cardine[1,7], S. Mathieu[1], M. Vermeer[4], M. Duvic[5], S. Whittaker[6], A. Bensussan[1,7], C. Paturel[8], C. Bonnafous[8], N. Thonnart[7], A. Widemann[8], C. Bonin[8], H. Sicard[8], C. Paiva[8], K. Pilz[8] and **Y. H. Kim[2]**

1 Hôpital Saint Louis – 75475 Paris, France | 2 Stanford Cancer Institute - Palo Alto, CA , USA | 3 Ohio State University – Columbus, OH, USA | 4 LUMC - Leiden, the Netherlands | 5 MD Anderson Cancer Center – Houston, TX, USA | 6 Guy's and St Thomas' Hospital – London, UK | 7 INSERM U976, 75475 Paris, France | 8 INNATE PHARMA - 13009 Marseille, France

Abstract

KIR3DL2 is expressed in all subtypes of CTCL, irrespective of clinical stage, with the highest prevalence in Sézary syndrome (SS) and transformed mycosis fungoides (MF), two subsets with a high unmet need. KIR3DL2 belongs to the killer immunoglobulin-like receptor (KIRs) family found on minor populations of normal NK and T cells.

IPH4102 is a first-in-class anti-KIR3DL2 mAb: it depletes selectively KIR3DL2$^+$ cells by recruiting immune effectors and has shown potent efficacy in preclinical models.

IPH4102 is currently being investigated in a first-in-human phase 1 study (NCT02593045) evaluating repeated administrations of single-agent IPH4102 in relapsed/refractory CTCL. The primary objective is to assess safety and tolerability of increasing doses of IPH4102. Secondary objectives include PK, immunogenicity and signals of anti-tumor activity. Exploratory biomarkers aim to characterize KIR3DL2$^+$ cells in involved tissue/disease compartments and monitor changes during treatment. Minimal residual disease (MRD) is measured in the skin, blood and/or lymph nodes. *Ex vivo* NK-mediated killing of autologous tumor cells is assessed pre-dose on SS patients (pts) samples.

The dose-escalation part has a 3+3 design with accelerated titration and aims to determine the maximal tolerated dose (MTD) or recommended phase 2 dose (RP2D). Pts receive IPH4102 administrations until progression or unacceptable toxicity. Intra-patient dose-escalation is allowed, only past the first complete clinical assessment at week 5 and provided the upper next dose-level is declared safe by the safety committee.

Enrollment into study started in November 2015 and is ongoing. Data cut-off date is September 10, 2016. A total of 16 pts have been treated at the first 7 dose-levels and are evaluable for safety and clinical activity. They comprise 13 SS, 2 MF and 1 "NOS" CD4$^+$ pts.

Study objectives

Primary objective: to assess safety & tolerability of repeated administrations of IPH4102 by:
- Characterizing the DLT and (S)AEs
- Identifying the MTD or RP2D

Secondary objectives:
- To explore antitumor activity
- To assess PK and immunogenicity

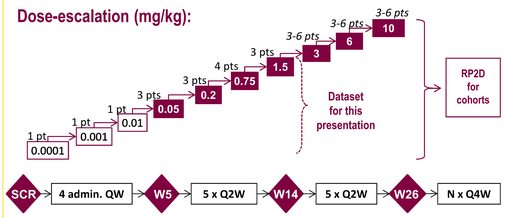
Translational objectives, biomarker exploration:
- To monitor KIR3DL2$^+$ cells in skin, blood and LN
- To monitor immune cell activation in blood
- To explore NK and macrophage infiltration in skin lesions
- To assess MRD (Molecular Residual Disease) clonal TCR-Vβ chain rearrangement)
- To explore NK cell function pre-dose

Key eligibility criteria

- Patients with relapsed/refractory CTCL who have received ≥ 2 previous systemic therapies
- For MF/SS patients: clinical stage ≥ IB
- Centrally-assessed KIR3DL2 expression (> 5%) on malignant cells in blood (flow cytometry) or in at least 1 skin lesion (immunohistochemistry, IHC)

Study design

Dose-escalation (mg/kg):



- Accelerated 3+3 design (0.0001 to 10 mg/kg)
- Regular safety and clinical activity assessments to decide on treatment extension and intra-patient dose-escalation
- Clinical response criteria assessed according to E. Olsen *et al*, JCO 2011
- Immuno-monitoring of blood cells: screening, weekly for 5 weeks and then Q4W after W10 (pre-dose, but also +2h and +24h after admin. #1 and #4)
- Skin biopsies taken at SCR, W5, W14 and End of Tx visit

Baseline characteristics

Patients (N)	N = 16
CTCL Subtype	
MF	2
SS	13
CD4$^+$ CTCL, NOS	1

Patients (N)	N = 16
Stage at screening	
IB	1
IIB	1
IVA	13
NA	1

- Data cut-off date
- 19 pts screened - 3 screen failures for KIR3DL2-negativity (none for other causes)
- 16 pts evaluable for safety and clinical activity
- 15 pts with ECOG performance status ≤ 1

Patients (N)	N = 16
Systemic tx received	
2	2
3	3
4-5	4
6-7	4
≥8	3

Preliminary safety results

Total Pts n = 16	AEs Pt # (%)	Related AEs Pt # (%)
Any	**14 (88%)**	**6 (38%)**
Grade 1	12 (75%)	6 (38%)
Grade 2	9 (56%)	3 (19%)
Grade 3	1 (6%)	0
Grade 4	1 (6%)	0
Grade 5	1 (6%)	0
Grade UNK	3 (19%)	0
Serious	**4 (25%) – 8**	**1 (6%)**
Grade 1		0
Grade 2		1 (6%)
Grade 3		0
Grade 4		0
Grade 5		0
DLT	**0**	**0**

- No AE led to treatment discontinuation
- 1 death reported so far (unrelated SAE of sepsis)
- Related SAE in 1 pt: asymptomatic atrial flutter occurred 1 h after end of the 1st IPH4102 infusion. After appropriate medication, sinus rhythm returned to normal within 4 days. Pt received subsequent IPH4102 administrations without recurrence
- One gr. 2 infusion-related reaction was observed

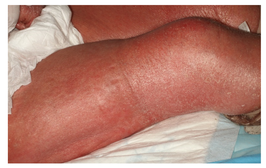
Preliminary clinical activity results

	All pts Best Global Response n=16	Sézary Syndrome pts Best Global Response n=13	Best Response in Skin n=13	Best Response in Blood n=13	Best Response in LN n=9
Best Response (n)					
CR	**0**	0	2	3	0
PR	**6**	5	4	5	1
SD	**10**	8	7	5	5
PD	**0**	0	0	0	0
NA	**0**	0	0	0	1
Missing	**0**	0	0	0	2
ORR	**38 %**	38 %	46 %	62 %	11 %

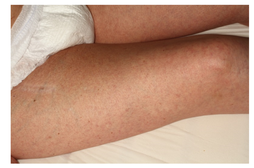
- 12 pts were still on treatment at data cut-off, including all responders

➢ **Patient 01-001:** 80-year old female. SS diagnosed in DEC 2013. Two lines of previous therapies (methotrexate and bexarotene). T4NxM0B2 at study entry. Started at 0.0001 mg/kg on 18NOV15 then dose-escalated to all doses.

06JAN2016 (W8, 0.0001 mg/kg – mSWAT (W10) = 55/2/0)



20JUL2016 (W36, 0.2 mg/kg – mSWAT = 0/0/0)



Individual patient's correlative results

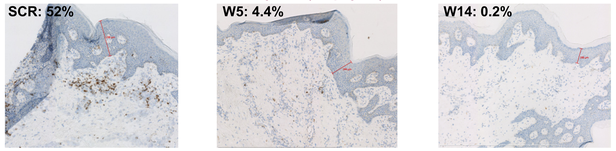
➢ **Patient 11-005:** 77-year old female with SS diagnosed in NOV 2008. Six lines of previous therapies (incl. ECP + bexarotene + INFα, methotrexate, mogamulizumab, ECP + INFα + methotrexate, romidepsin, bex. + INFα). T4NxM0B2 at study entry. Started at 0.05 mg/kg IPH4102 on 25JAN16.

mSWAT results before (SCR and W1) and after IPH4102 administration

	SCR	W1	W5	W10	W14
Weighted mSWAT	80.5/1/0	89/0/0	87/0/0	36.5/0/0	19.25/0/0

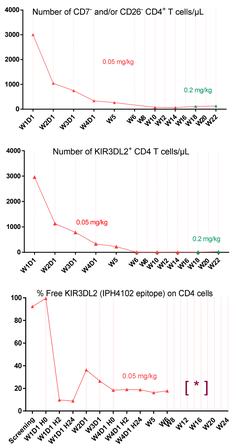
- "Long lasting" (>167 days, ongoing) global clinical PR and progressive decrease in mSWAT are consistent with almost complete loss of KIR3DL2 staining in IHC

% of KIR3DL2$^+$ cells in skin lesions by IHC (biopsy #1)



Immuno-monitoring of blood cells
(Centrally assessed, flow cytometry)

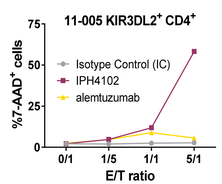
- Decrease in blood tumor cells (CD26$^-$/CD7$^-$ CD4$^+$ T cells) and KIR3DL2$^+$ CD4$^+$ T cells starting immediately after the 1st administration
- PR in blood observed at W5 and CR at W10 (ongoing) (based on local assessment)
- Full occupancy of KIR3DL2 on CD4 T cells achieved rapidly



*Since W10, too few KIR3DL2$^+$ cells to interpret occupancy

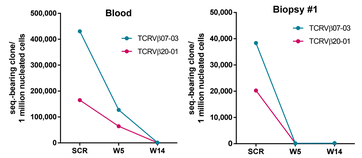
Ex vivo ADCC assay
Autologous NK-mediated death of KIR3DL2$^+$CD4$^+$ tumor cells induced by IPH4102

- NK cells from SS pt 11-005 mediate potent ADCC with IPH4102 against primary autologous tumor cells



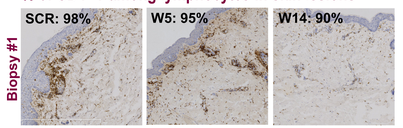
MRD in skin (biopsy #1) & blood

- 2 dominant clones found pre-dose in skin and blood
- Both substantially decrease by W5 and W14 in skin biopsies and blood (still above detection limit)

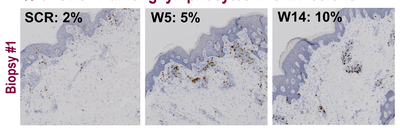


- Skin lesions show decreased CD4 and parallel increase in CD8 staining over time
- Altogether, IHC results show the actual depletion of skin-resident tumor cells and potential normalization of the immune system of the tumor environment in skin

% of CD4$^+$ T among lymphocytes in skin lesions



% of CD8$^+$ T among lymphocytes in skin lesions



CD4/CD8 ratio in skin	49	19	9

Conclusions & perspectives

- Seven dose-levels were completed (0.0001 to 1.5 mg/kg) with 16 patients evaluable for safety and efficacy, including 13 SS, 2 MF and 1 CD4$^+$ TCL NOS
- IPH4102 is well tolerated in an heavily pretreated patient population: no DLT was reported and the majority of AE is low grade and typical for CTCL
- Preliminary global ORR is 38% in the evaluable population and 38% in SS patients: responses are still ongoing at the time of this presentation
- Changes in weighted mSWAT and objective clinical response in skin and blood tend to be associated with changes in KIR3DL2 staining, as well as changes in MRD
- Responders show decrease in CD4/CD8 ratio in skin lesions and in blood
- So far, for all SS pts tested, *ex vivo* ADCC assay shows potent NK function pre-dose against autologous blood tumor cells
- Dose-level 3 mg/kg has been completed without DLT occurrence
- The last two dose-levels remain to be evaluated (6 and 10 mg/kg)

ASH 2016

Disclosures: H. Sicard, C. Paturel, A. Widemann, C. Bonnafous, C. Paiva, C. Bonin and K. Pilz are employees/consultants of Innate Pharma. All authors are equity owners (Innate Pharma).