FIH, OPEN LABEL, MULTICENTER PHASE I STUDY OF IPH4102, FIRST-IN-CLASS HUMANIZED ANTI-KIR3DL2 MAB, IN RELAPSED/REFRACTORY CTCL: PRELIMINARY RESULTS OF EXPLORATORY BIOMARKERS

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Abstract

KIR3DL2 is expressed irrespectively of disease stage in all subtypes of CTCL, with the highest prevalence in Sézary Syndrome (SS) and transformed Mycosis Fungoides (MF), two subsets with high unmet need. KIR3DL2 belongs to the killer immunoglobulin-like receptor (KIRs) family found on minor populations of NK and T cells. IPH4102 is a first-in-class anti-KIR3DL2 mAb. It selectively depletes KIR3DL2$^+$ cells and has shown potent efficacy in preclinical models.

IPH4102-101 (NCT02593045) is a first-in-Human phase I study evaluating IPH4102 in relapsed/refractory CTCL patients (pts). The primary objective is to assess the safety and tolerability of IPH4102 by characterizing DLT and AE. Secondary objectives include PK, immunogenicity and signals of anti-neoplastic clinical activity. Exploratory biomarkers aim to characterize and monitor KIR3DL2-expressing and non-expressing cells in involved organs along IPH4102 treatment. Exploratory assessments include SS pts' NK cell function ex vivo. Study design and patient status are presented on poster O-03.

Enrollment started in Nov. 2015. Dose levels 1-7 have been completed without DLT, with 16 pts treated and evaluable for safety and clinical activity. They comprise 13 SS, 2 MF and 1 CD4$^+$, NOS CTCL. Preliminary safety and clinical activity results from pts treated up to dose-level 7 are discussed in poster O-03. Preliminary results for PK and pharmacodynamics in skin and blood, are presented here.

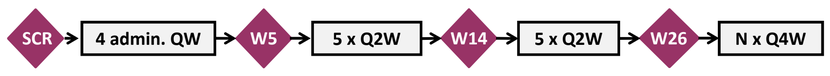
Study objectives

Primary objective: to assess safety & tolerability 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 & macrophage infiltration in lesions
- To assess MRD (TCR-Vβ chain rearrangement)
- To assess cytokine release
- To explore NK cell function pre-dose

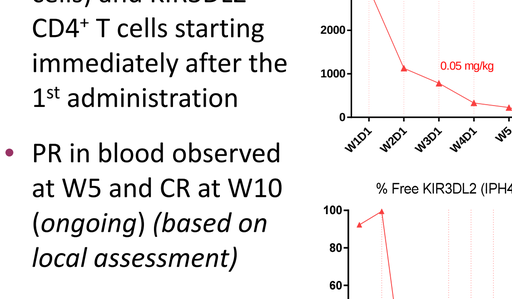
Study design & biomarker time points



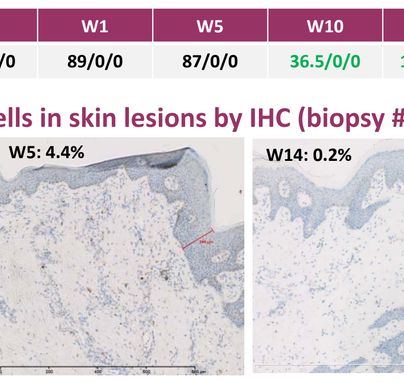
- Ten dose-levels from 0.0001 to 10 mg/kg, with repeated admin.
- Treatment until progression or unacceptable toxicity
- Intra-patient dose-escalation allowed after W5 (if upper next dose-level declared safe by the safety committee)
- Immuno-monitoring of blood cells: screening, weekly for 5 weeks and then every 4 weeks after W10 (pre-dose, but also +2h and +24h after admin. #1 and #4*).
- IPH4102 PK is assessed pre-dose and also, for admin. #1 and #4**, at the end of the injection, and +1h, +2h, +4h and +24h.

	SCR	W1	W2	W3	W4	W5	W10	Q2W	W14	Q2W	W26	Q4W
Ex vivo ADCC assay		X										
Blood Immuno-monitoring	X	X*	X	X	X*	X	X		X		X	X
PK		X**	X	X	X**			X	X	X	X	X
Skin biopsy - IHC	X					X			X			

Preliminary PK results



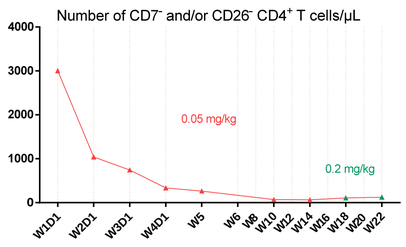
- No unexpected accumulation following injections 4 weekly injections at the doses investigated so far
- In all patients, at all doses analyzed so far, between the 1st and the 2nd administrations, maximal concentration (C_{max}), Area Under the Curve (AUC_{day1-8}) and concentration before re-administration (C_{trough}) are dose-dependent
- Above dose 0.75 mg/kg, PK seems roughly linear, suggesting target saturation in the periphery and in the tissues

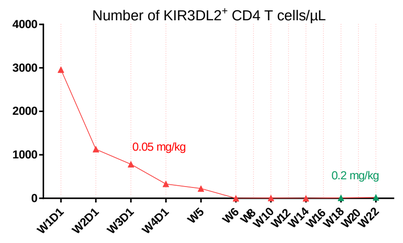


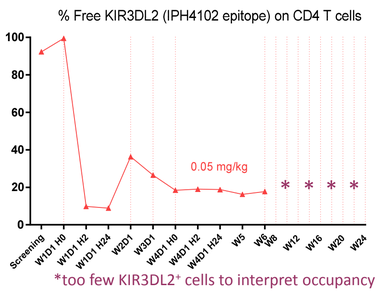
Individual patients' correlative results

➢ **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). $T_4N_XM_0B_2$ at study entry. Started at 0.05 mg/kg IPH4102 on 25JAN16. **"Medium" blood tumor and KIR3DL2 burdens: ~1,300 KIR3DL2/CD4 cell – ~4,600 aberrant cells/µL blood (88% among lymphos).**

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







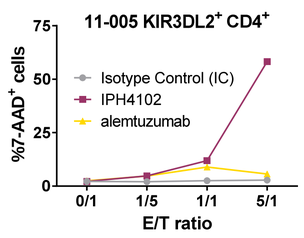
*too few KIR3DL2$^+$ cells to interpret occupancy

- Regular 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 tumor CD4$^+$ T cells

Ex vivo ADCC assay

Autologous NK-mediated death of KIR3DL2$^+$CD4$^+$ tumor cells induced by alemtuzumab, IPH4102 & IC

- NK cells from Sézary patient 11-005 mediate potent ADCC with IPH4102 against primary autologous tumor cells



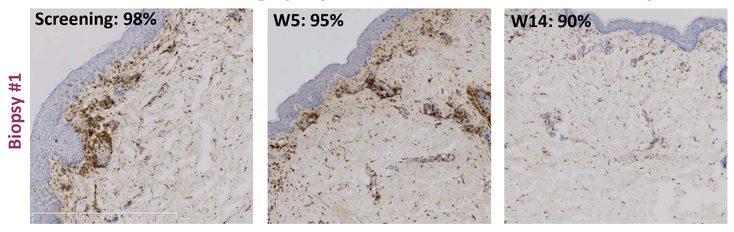
mSWAT results before (SCR and W1) and after IPH4102 admin.

	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

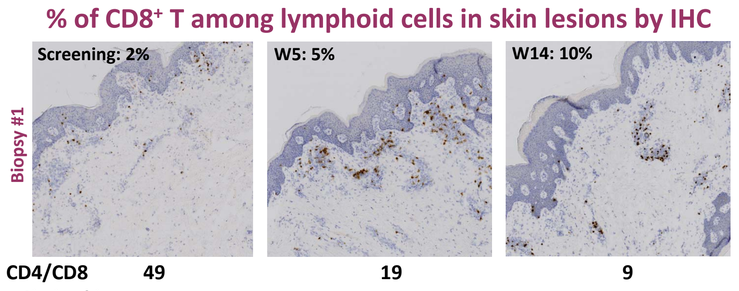
% of KIR3DL2$^+$ cells in skin lesions by IHC (biopsy #1)

- "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 CD4$^+$ T among lymphoid cells in skin lesions by IHC



% of CD8$^+$ T among lymphoid cells in skin lesions by IHC

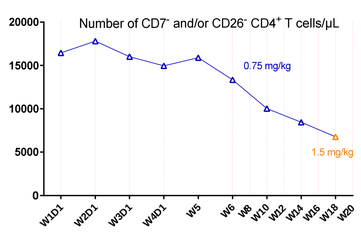


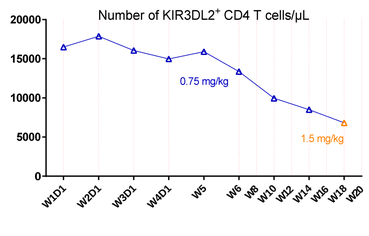
CD4/CD8 ratio in skin	49	19	9

- Skin lesions show decreased CD4 staining and parallel increase in CD8 T cells over time
- Both parameters confirm the actual depletion of skin-resident tumor cells and potential restoration of a normal immune system in skin lesions

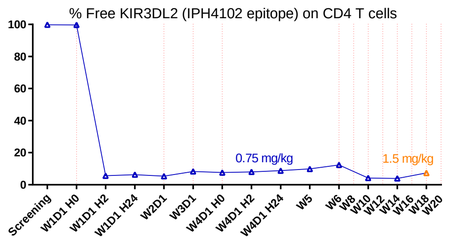
➢ **Patient 01-013:** 74-year old male with SS diagnosed in MAR 2013. Eight lines of previous therapies. $T_4N_0M_0B_2$ at study entry. Started at 0.75 mg/kg IPH4102 on 19MAY16. **"High" blood tumor and KIR3DL2 burdens: ~2,500 KIR3DL2/CD4 cell – ~5,200 aberrant cells/µL blood (99.6% among lymphos).**

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

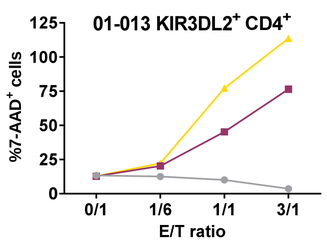




- Delayed onset of blood PR *(local assessment)*, achieved at W14 (*ongoing*), matching decrease in blood tumor cell counts
- Full occupancy of KIR3DL2 on CD4$^+$ T cells achieved rapidly and sustained



Ex vivo ADCC assay

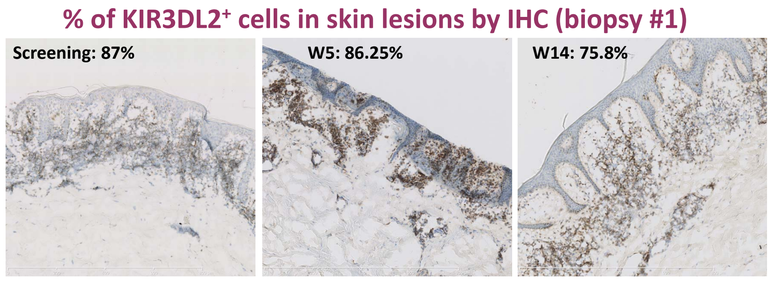


- NK cells from Sézary patient 01-013 mediate potent ADCC with IPH4102 against primary autologous tumor cells (same legend as above)

mSWAT results before (SCR and W1) and after IPH4102 admin.

	SCR	W1	W5	W10
Weighted mSWAT	36/18/0	29/26/0	16/8/0	9/8/0

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



- PR in skin started at W5, improved at W10 (*ongoing*) and is consistent with slight decrease of KIR3DL2 in skin lesions, despite high tumor infiltrate pre-dose

Conclusions on preliminary results of biomarkers

- Preliminary results (up to 1.5 mg/kg) show IPH4102 PK is linear, C_{max} increases in a dose-dependent fashion and there is no unexpected accumulation following QW administrations
- In blood, irrespective of circulating tumor burden, 0.75 mg/kg QW seems to fully saturate KIR3DL2 on tumor cells
- Clinical responses in blood are in agreement with centrally-performed immuno-monitoring results
- Changes in KIR3DL2 staining in skin lesions tend to be associated with changes in weighted mSWAT and objective clinical response in skin
- Follow-up of CD4$^+$ T cells in skin lesions tends to confirm that tumor cells are actually depleted and normal immune system restored in lesions (decrease in skin-resident CD4/CD8 ratio)
- So far, for all SS patients tested, *ex vivo* ADCC assay shows potent NK function pre-dose against autologous blood tumor cells.
- Three more dose-levels remain to be evaluated to confirm these preliminary findings (3, 6 and 10 mg/kg)