PHASE I OF IPH4102, ANTI-KIR3DL2 MAB, IN RELAPSED/REFRACTORY CUTANEOUS T-CELL LYMPHOMAS (CTCL): **DOSE-ESCALATION SAFETY, BIOMARKER AND CLINICAL ACTIVITY RESULTS**

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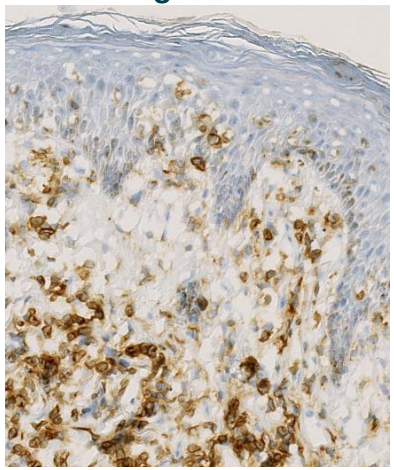
IPH4102-101

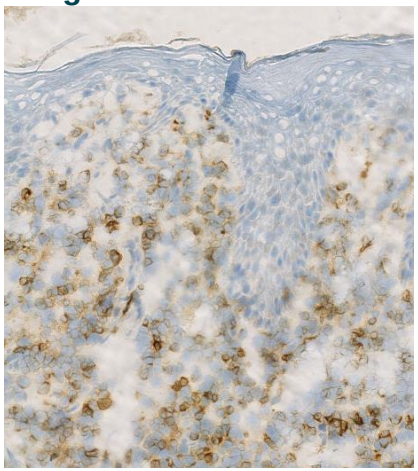
KIR3DL2 IS A THERAPEUTIC TARGET IN CTCL

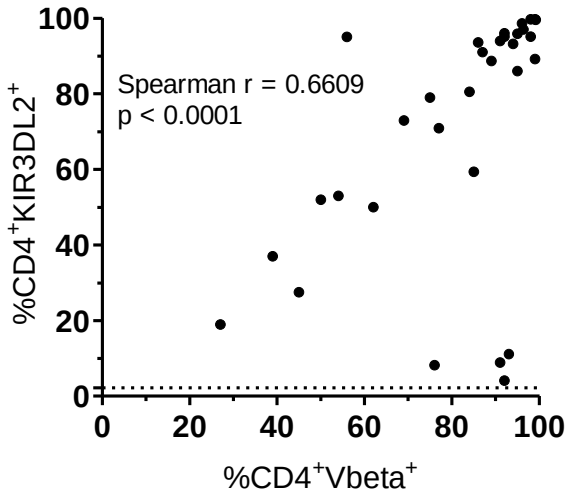
- KIR3DL2 belongs to the Killer Ig-like Receptor family of receptors that modulate NK and T cell activity
- KIR3DL2 is expressed on ~30% of normal NK and <10% normal T cells
- KIR3DL2 is expressed on CTCL cells (skin lesions and blood aberrant cells)
  - > Irrespective of disease clinical stage
  - > With a higher prevalence in Sézary syndrome (SS), $CD30^+$ LPD and Mycosis fungoides with large-cell transformation
  - > KIR3DL2 may have prognostic significance in SS

Stage IIIA SS



Stage IIB transformed MF



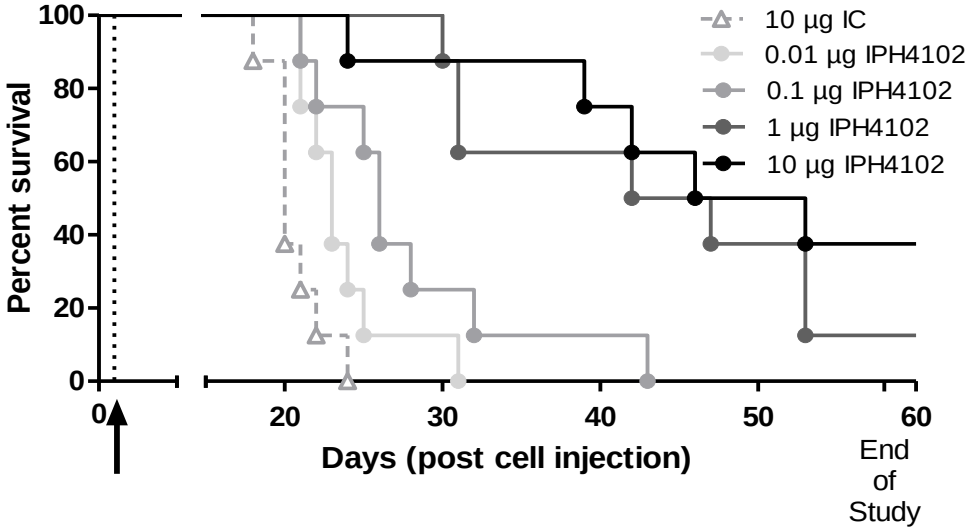


Marie-Cardine *et al*, 2014, Cancer Res. 74(21) - Battistella *et al*, 2016, Br J Dermatol. 175(2) - Hurabielle *et al*, 2017, Clin Cancer Res.

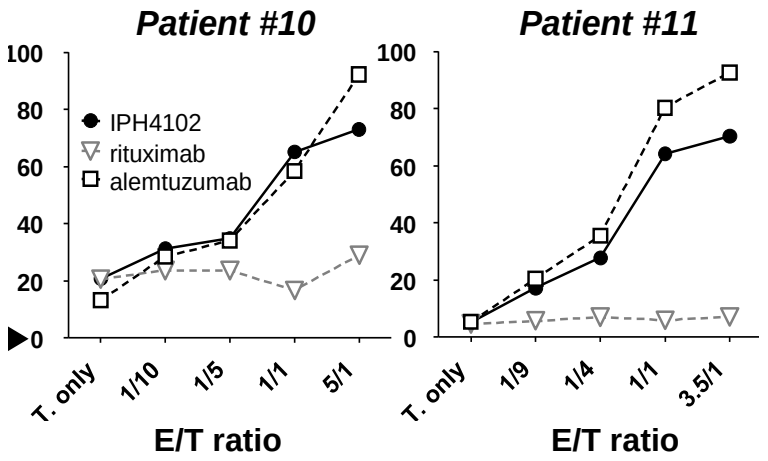
IPH4102, FIRST-IN-CLASS ANTI-KIR3DL2 MAB ATTRIBUTES

- IPH4102 is a humanized antibody that targets and selectively depletes KIR3DL2-positive cells
- Its modes-of-action include ADCC and ADCP (Ab-dependent cell cytotoxicity and phagocytosis)
- IPH4102 has shown potent pre-clinical efficacy:
  - > In mouse models of KIR3DL2-positive tumor cells
  - > In *ex vivo* autologous assays using patient-derived NK and Sézary cells

Mice engrafted iv with KIR3DL2$^+$ tumors

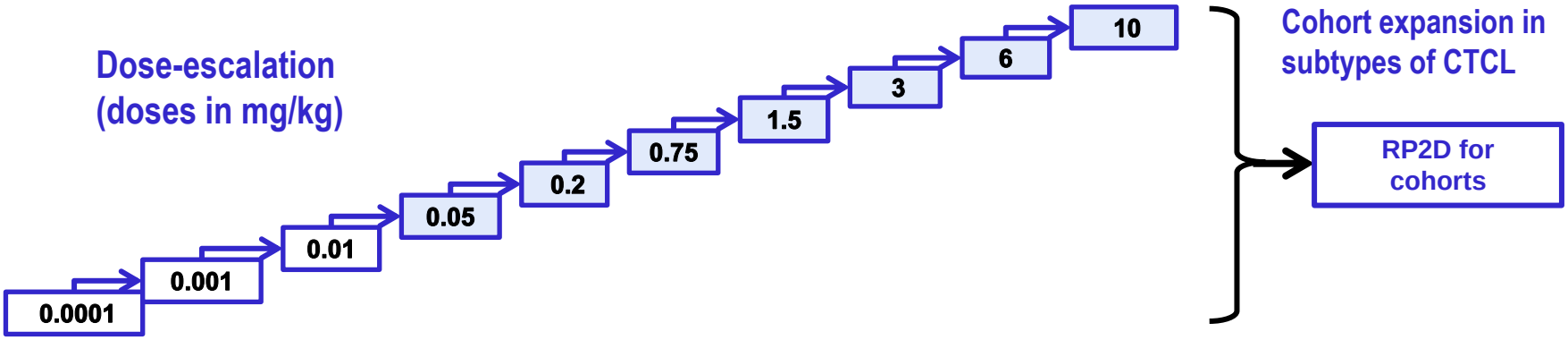


% of 7AAD$^+$ (ie dead) Sézary cells

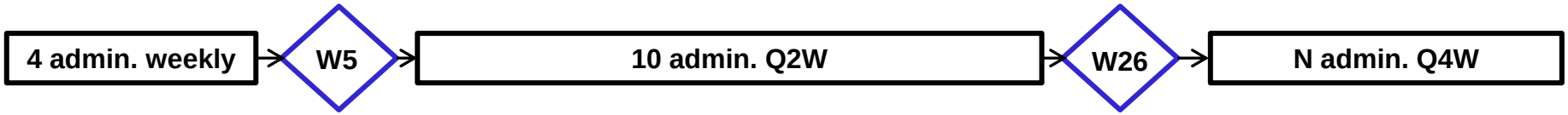


Marie-Cardine *et al*, 2014, Cancer Res. 74(21)

IPH4102-101 PHASE 1 STUDY DESIGN AND OBJECTIVES



- Dose-escalation (10 dose levels – accelerated 3+3 design) followed by cohort expansion
- **Primary objective**: determination of MTD and RP2D, overall safety
- **Secondary objectives**: clinical activity, PK/immunogenicity
- **Exploratory objectives**: changes in KIR3DL2^{+} cells in involved compartments, Molecular Residual Disease (MRD), NK cell function pre-dose
- **Key inclusion criteria**:
  - Any CTCL subtype, $\geq$ 2 prior lines of systemic therapy, if MF/SS stage $\geq$ IB
  - > 5% aberrant lymphocytes express KIR3DL2 in $\geq$ 1 skin lesion or in blood
- Treatment until progression or unacceptable toxicity
- Intra-patient dose-escalation allowed after W5



BASELINE DISEASE CHARACTERISTICS (AS OFF MAY 10, 2017)

	All doses N = 25
Age (years), **median** (min; max)	**71** (42; 90)
MF/SS CTCL type, n (%)	
Mycosis fungoides (MF)	4 (16)
Sézary Syndrome (SS)	20 (80)
Non MF/SS CTCL type, n (%)	
$CD4^+$ T-cell lymphoma, NOS	1 (4)
Clinical stage (MF/SS), n (%)	
IB	1 (4.1)
IIB	3 (12.5)
IVA1	20 (80)
No. of regimen (systemic) received, **median** (min; max)	**4** (2; 10)

- 25 patients treated: 25 evaluable for safety, 24 for clinical activity (1st clinical assessment of the last patient enrolled at 10 mg/kg occurred after data cut-off)
- Seven of screen failures (out of 9/34 pts screened) were due to lack of KIR3DL2 expression
- No dose-cohort had to be expanded for safety reasons

ADVERSE EVENTS POSSIBLY RELATED TO STUDY DRUG (> 5%; > 1 PATIENT)

- **No DLT, MTD not reached**

	Related AE (N = 25)	
	All grades n (%)	Grade 3 n (%)
Any related AE	**13 (52)**	**3 (8)**
Lymphopenia	4 (16)	2 (8)
Asthenia	3 (12)	0
Nausea	2 (8)	0
Hot flush	2 (8)	0
Chills	2 (8)	0
Arthralgia	2 (8)	0
Muscle spasm	2 (8)	0

- No grade 4 or 5 related AEs
- Only 1 related SAE: grade 2 atrial flutter on the day of IPH4102 administration that did not reoccur at subsequent administrations
- One patient developed ADA -> recurrent IRR despite premedication
- N = 10 pts experienced infections, including n = 2 sepsis (including 1 death – *S. aureus*) but all deemed related to underlying disease and not to study drug

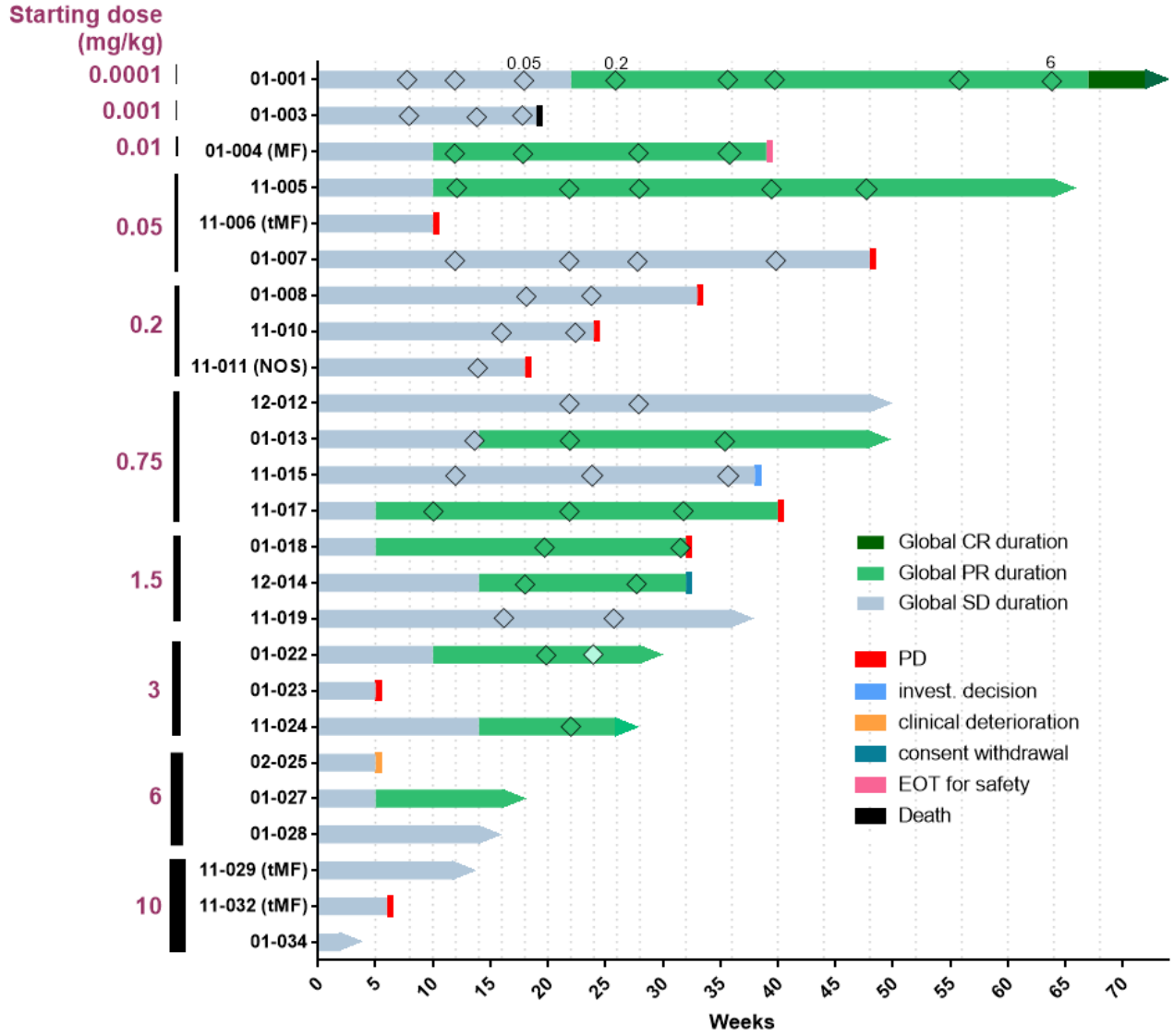
PRELIMINARY CLINICAL RESPONSE RESULTS
(CUT-OFF DATE MAY 10, 2017)

	Best Response in all patients	Best Response in Sézary Syndrome patients		
	Global N=24	Global n=19	Skin n=19	Blood n=19
Best Response (n)				
CR	**1**	**1**	2	5
PR	**9**	**8**	8	7
SD	**12**	**8**	9	5
PD	**2**	**2**	0	1
ORR	**41.7 %**	**47.4 %**	52.6 %	63.2 %
DOR (days) - median (min – max)	**251** (64+ – 379+)	**Not reached** (64+ – 379+)		
PFS (days) - median (min – max)	**274** (28+ – 526+)	**329** (28+ – 526+)		

ORR: Overall Response Rate
PFS: Progression-Free Survival
DOR: Duration of Response

- Median follow-up time is 338 days
- Preliminary results are calculated for 24 patients (19 SS) evaluable for efficacy assessment, treated with doses ranging from 0.0001 to 10 mg/kg
- All clinical responses are confirmed
- 2 patients who were in global PR reached “near CR” skin response, ie >90% reduction in mSWAT
- Pruritus is notably decreased in patients with clinical response

TIME-COURSE OF GLOBAL RESPONSE FOR 24 EVALUABLE PATIENTS



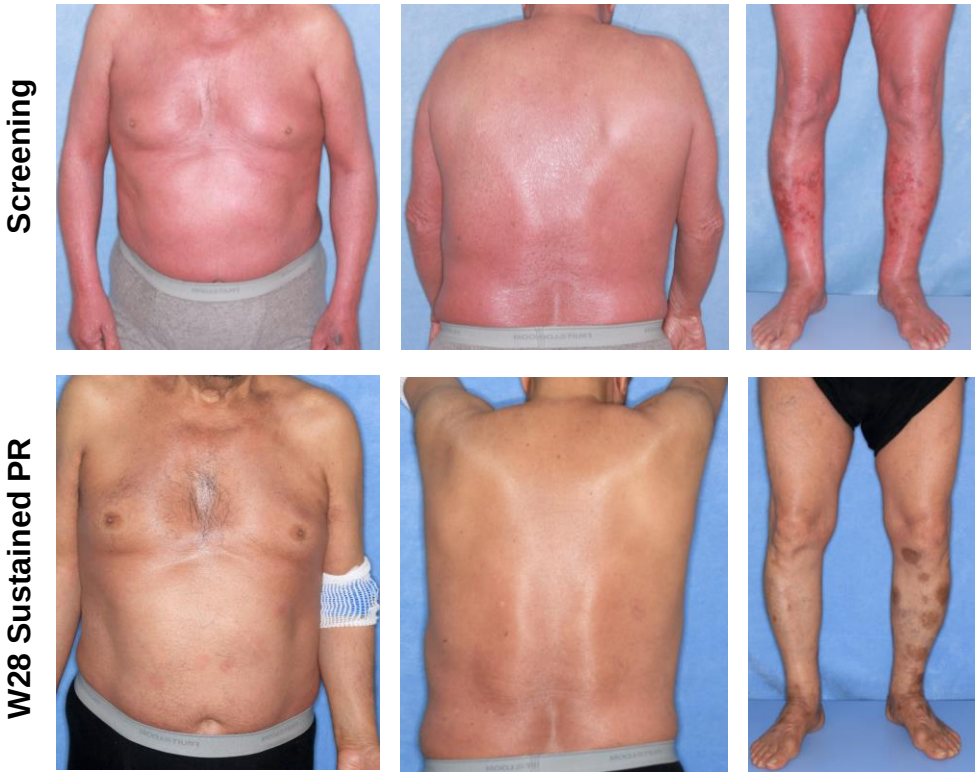
Response evaluation according to International Consensus criteria (Olsen et al, JCO 2011)

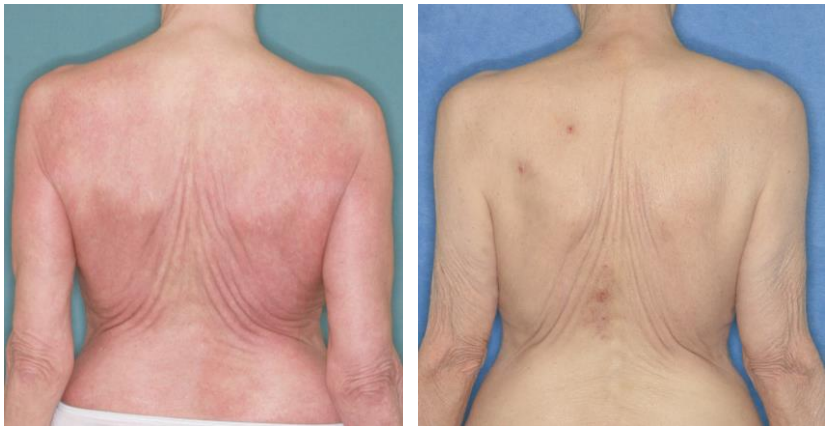
REPRESENTATIVE PICTURES OF RESPONDERS

Patient 11-024:

- 75-year old male
- **Sézary Syndrome** diagnosed in AUG 2011
- **6 lines of previous therapies** (incl. MTX, INFα, vorinostat then mogamulizumab, BEX, pembrolizumab)

- Started at 3 mg/kg on 16OCT16
- Global PR since W14 (3 mg/kg)





Screening **W64 sustained PR**

Patient 11-005:

- 77-year old female
- **Sézary Syndrome** diagnosed in NOV 2008
- **6 lines of previous therapies** (incl. ECP + BEX + INFα, MTX, mogamulizumab, ECP + INFα + MTX, romidepsin, BEX+ INFα)

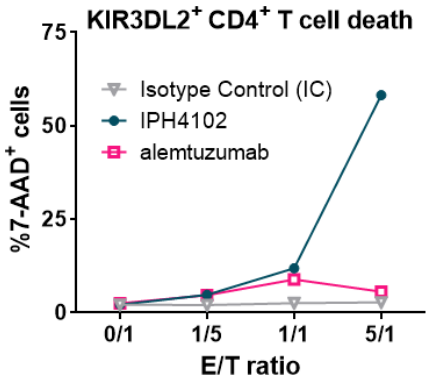
- Started at 0.05 mg/kg on 25JAN16
- Global PR since W10 (0.05 mg/kg)

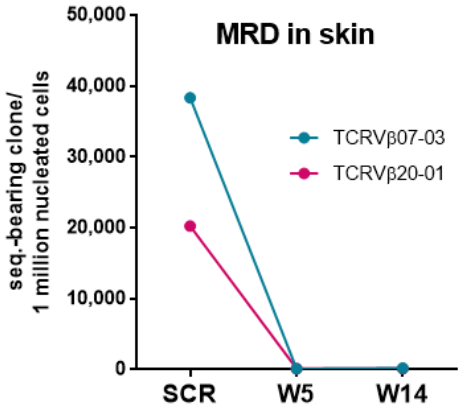
EXPLORATORY/PHARMACODYNAMICS ENDPOINTS
SKIN & BLOOD ASSESSMENTS / PT 11-005

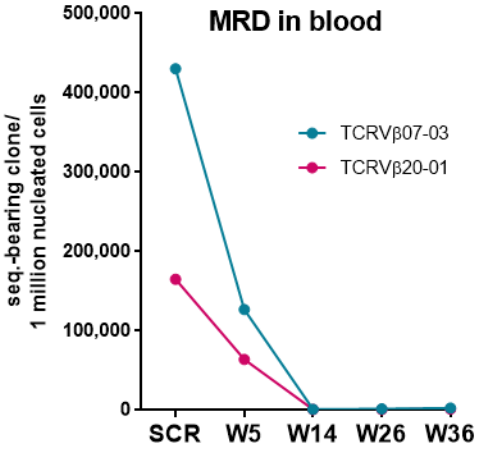
SCR = screening

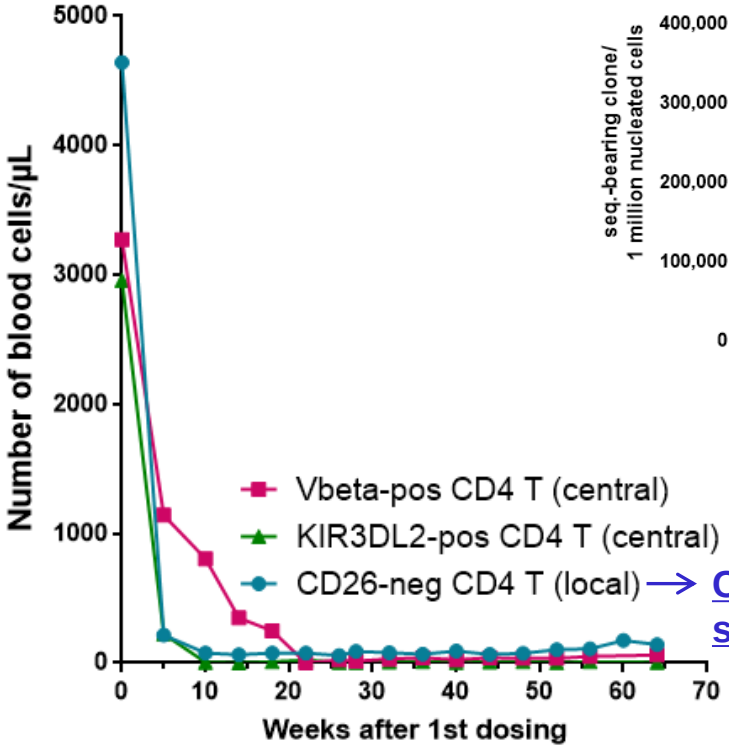
	CD4/8 ratio in skin	mSWAT
SCR: 52%	SCR: 49	SCR: 80.5/1/0
W5: 4.4%	W5: 19	W5: 87/0/0
		W10: 36.5/0/0 PR
W14: 0.2%	W14: 9	W14: 19.3/0/0 PR

% of KIR3DL2$^+$ cells in skin lesions by IHC









CR in blood since W10

IPH4102-101 HIGHLIGHTS
SAFETY, CLINICAL ACTIVITY AND BIOMARKERS

- IPH4102 MTD was not reached: well tolerated in an elderly and heavily pretreated (med. 4 prior lines) patient population
  - > AE are typical for CTCL or reflects low grade infusion-related reactions
  - > Only one related AE of grade 3 or higher occurred (at 0.2 mg/kg)
- Preliminary best global ORR is 41.7% in the evaluable population and 47.4% in SS patients
  - > One global complete response was observed
  - > 2 complete responses in skin and 5 complete responses in blood
  - > Pruritus is substantially improved
- PK is typical for an IgG1 antibody; only 1 patient developed ADA
- Pharmacodynamic endpoints (monitoring of KIR3DL2-positive cells and MRD) are consistent with clinical activity results, confirming drastic elimination of neoplastic cells in skin and in blood, and potential restoration of skin normal immune system
- Patient NK cells pre-dose present robust ADCC activity *ex vivo*

- **Expansion cohorts are planned to start in Q3 2017 at the RP2D, with 30 additional patients, including 15 more SS to confirm preliminary results**

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All our patients and their families…