IPH4102, THE FIRST-IN-CLASS ANTI-KIR3DL2 MAB, IS SAFE AND CLINICALLY ACTIVE IN ADVANCED CUTANEOUS T-CELL LYMPHOMA (CTCL) PATIENTS: RESULTS FROM THE DOSE-ESCALATION PART OF THE IPH4102-101 PHASE I STUDY

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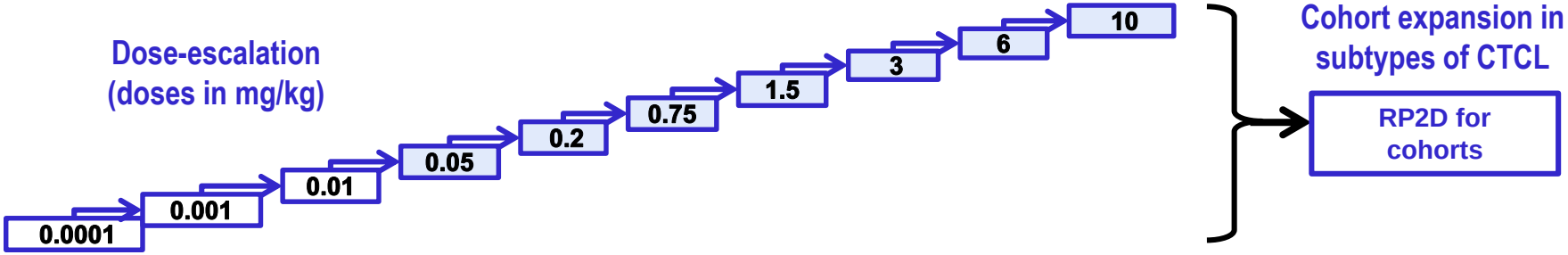
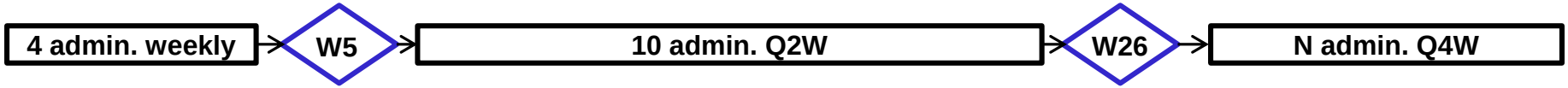
IPH4102-101

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, 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 cells KIR3DL2pos in skin or blood
  - Treatment until progression or unacceptable toxicity
- Intra-patient dose-escalation allowed after W5



BASELINE DISEASE CHARACTERISTICS

	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 at study entry (MF/SS), n (%)	
IB	1 (4)
IIB	3 (12)
IVA1	20 (80)
No. of regimen (systemic) received, **median** (min; max)	**4** (2; 10)

PATIENT EXPOSURE

	All doses N = 25
Duration of exposure, days median (min; max)	 218 (22; 610)
No. of administrations received per patient median (min; max)	 16 (4; 30)
No. of patients receiving increased doses, n (%) No Increased Dose Increased dose ≥ Three times	 6 (24) 19 (76) 10 (40)
No. of patients who received IPH4102, n (%) ≤ 4 times (QW) 5-14 times (QW & Q2W) > 14 times (QW, Q2W & Q4W)	 2 (8) 7 (28) 16 (64)

SUMMARY OF ADVERSE EVENTS (AE)

N = 25	Total	Grade 3	Grade 4
DLT	**0**	-	-
AE	**23 (92%)**	6 (24%)	2 (8%) †
Related AE	**13 (52%)**	2 (8%)	-
SAE	**8 (32%)**	2 (8%)	2 (8%)
Related SAE	**2 (8%) ††**	-	-
AE causing treatment discontinuation	**1 (4%)**	**1 (4%)***	-
Fatal AE	**2 (8%)****		

n is the number of subjects having the given event, or an event in the given category at least once
DLT: Dose limiting Toxicity; (S)AE: (Serious) Adverse Event

† Two patients had grade 4 AE: (i) one 69 year-old patient with grade 4 confusion attributed to viral meningitis, (ii) one other patient with *S. aureus* sepsis before going into CR.

†† Two patients had possibly related SAE: (i) one had grade 2 atrial flutter diagnosed by mandatory ECG without clinical symptoms one hour after end of the first administration. The patient was known for cardiac arrhythmia. She was hospitalized for cardiac work-up, received amiodarone and arrhythmia resolved. The patient received 15 more administrations without reoccurrence of atrial flutter, (ii) one other patient had hepatitis occurring 6 weeks after last administration and treatment discontinuation due to PD. The patient had global PR, received treatment for 1 year, and had normal liver function until 4 weeks after treatment discontinuation. Work-up could not identify a clear cause before death; liver biopsy was suspicious of either viral infection or drug-induced liver injury in presence of HHV-6B in the liver and blood.

* One patient discontinued treatment due to not related general malaise in context of disease progression.

** Two patients had fatal AE: (i) one unrelated death to *S. aureus* sepsis, (ii) one death caused by possibly related SAE of hepatitis (see ††).

ADVERSE EVENTS AT LEAST POSSIBLY RELATED TO DRUG (REPORTED BY ≥2 PATIENTS)

	Related AE (N = 25)		
	All grades* n (%)	Grade 3 n (%)	Grade 4 n (%)
Lymphopenia	4 (16)	2 (8)	0
Asthenia	3 (12)	0	0
Nausea	2 (8)	0	0
Chills	2 (8)	0	0
Pyrexia	2 (8)	0	0
Arthralgia	2 (8)	0	0
Muscle spasm	2 (8)	0	0

n is the number of subjects having the given events, or an event in the given category at least once

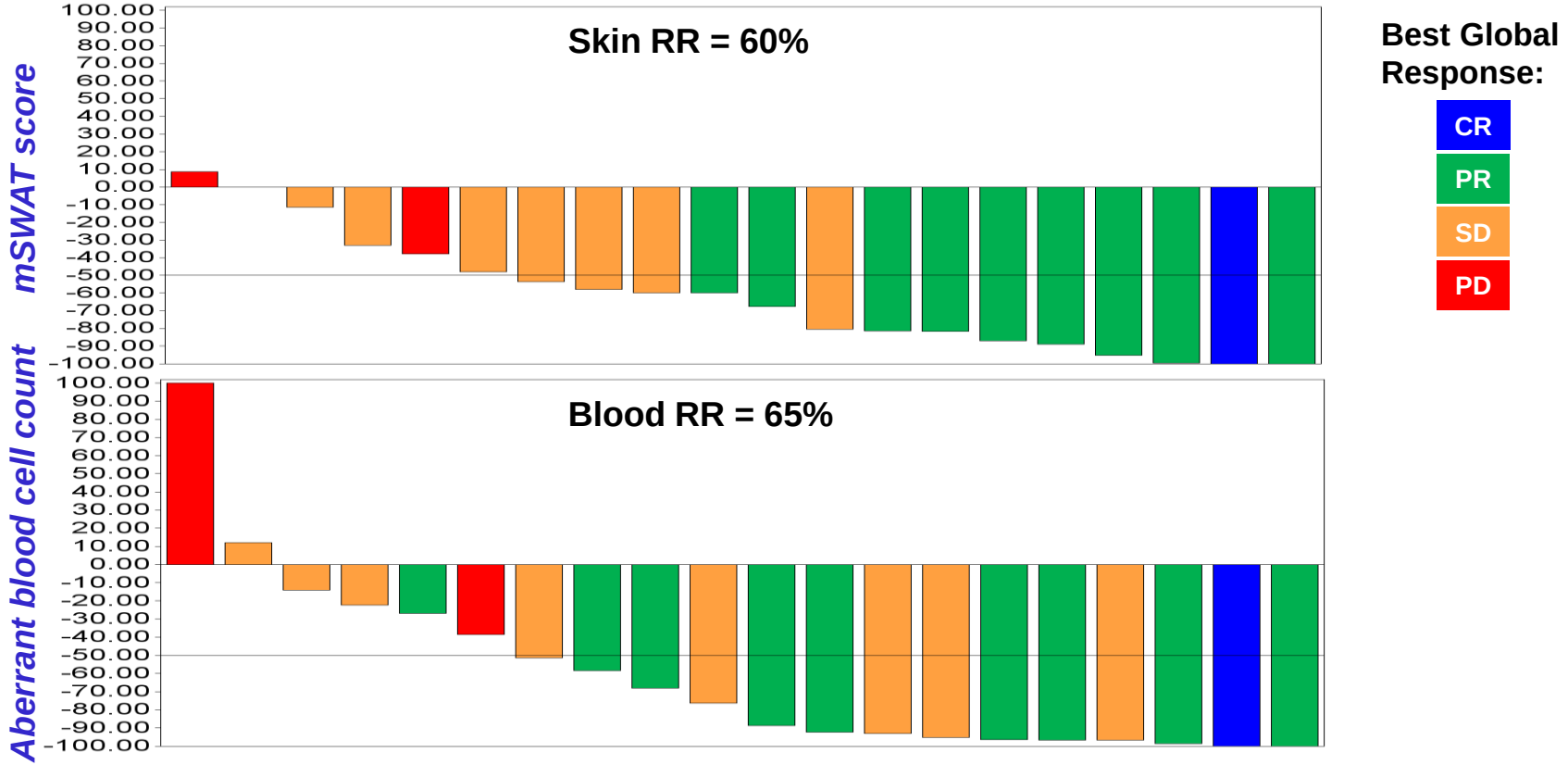
PRELIMINARY CLINICAL RESPONSE RESULTS

	Best Response in all patients Global N=25	Best Response in Sézary Syndrome patients		
		Global n=20	Skin n=20	Blood n=20
Best Response (n)				
CR	**1**	**1**	2	5
PR	**10**	**9**	10	8
SD	**12**	**8**	8	6
PD	**2**	**2**	0	1
ORR	**44 %**	**50 %**	60 %	65 %
ORR4, n (%)	**9 (36%)**	**8 (40%)**		
DOR (days) - median (min – max)	**251 (8.2 months)** (64 – 519+)	**302 (9.9 months)** (64 – 519+)		
PFS (days) - median (min – max)	**299 (9.8 months)** (28 – 610+)	**329 (10.8 months)** (28 – 610+)		

ORR: Overall Response Rate
ORR4: Rate of responses lasting ≥4 mo
PFS: Progression-Free Survival
DOR: Duration of Response

- Results for 25 patients (20 SS) treated with doses ranging from 0.0001 to 10 mg/kg
- All clinical responses are confirmed; 4 responses ongoing (DOR range 104 – 519 days)
- 2 patients reached “near CR” skin response, ie >90% reduction in mSWAT

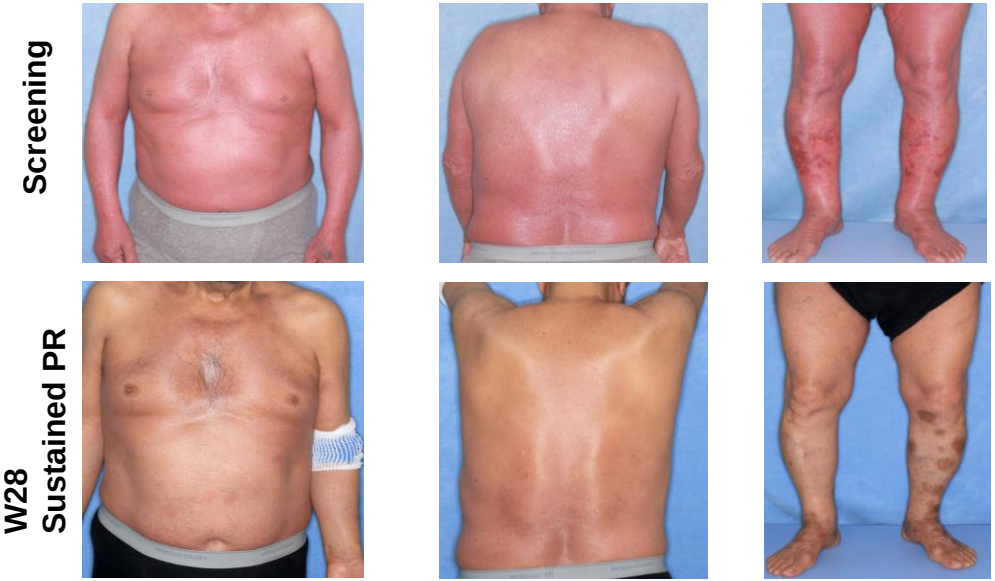
MAXIMUM PERCENT CHANGE IN mSWAT SCORE AND ABERRANT BLOOD CELL COUNTS IN SEZARY PATIENTS

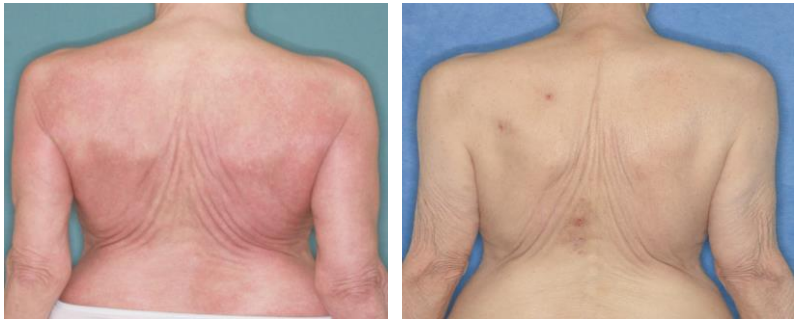


REPRESENTATIVE PICTURES OF RESPONDERS

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

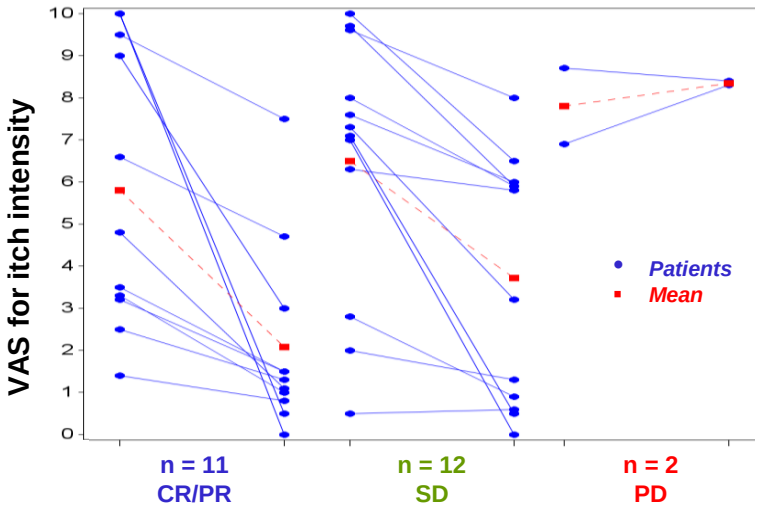
W64 sustained PR

Patient 11-005:

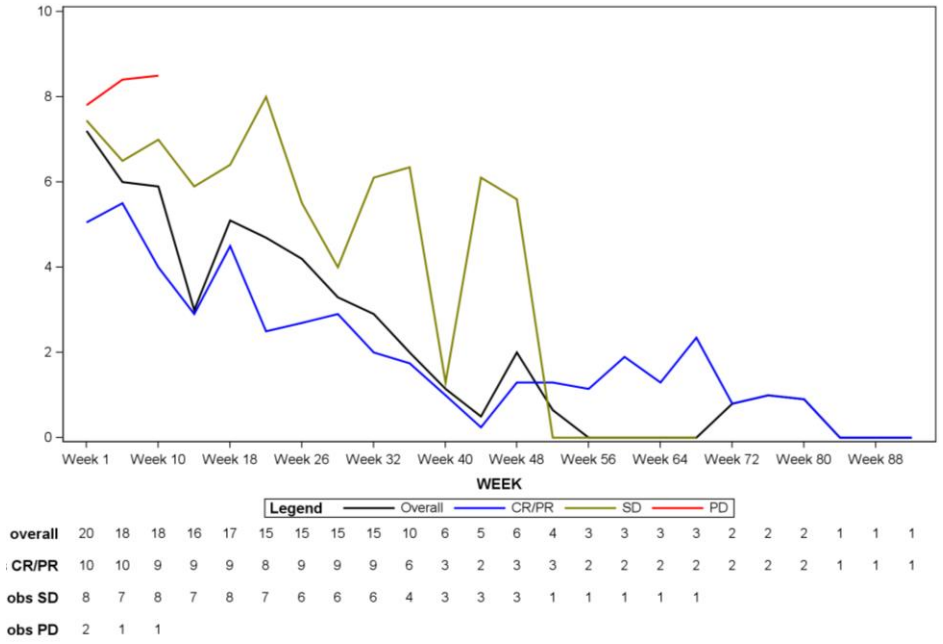
- 77-year old female
- **Sézary Syndrome** diagnosed in NOV 2008
- **6 lines of previous therapies** (incl. ECP + BEX + INFα, MTX, mogamulizumab, ECP + INFα + MTX, romidepsin, BEX+ INFα)
- Started at 0.05 mg/kg on 25JAN16
- Global PR since W10 (0.05 mg/kg)

PRURITUS IMPROVEMENT BY VAS SCORE

Baseline vs Best change in VAS

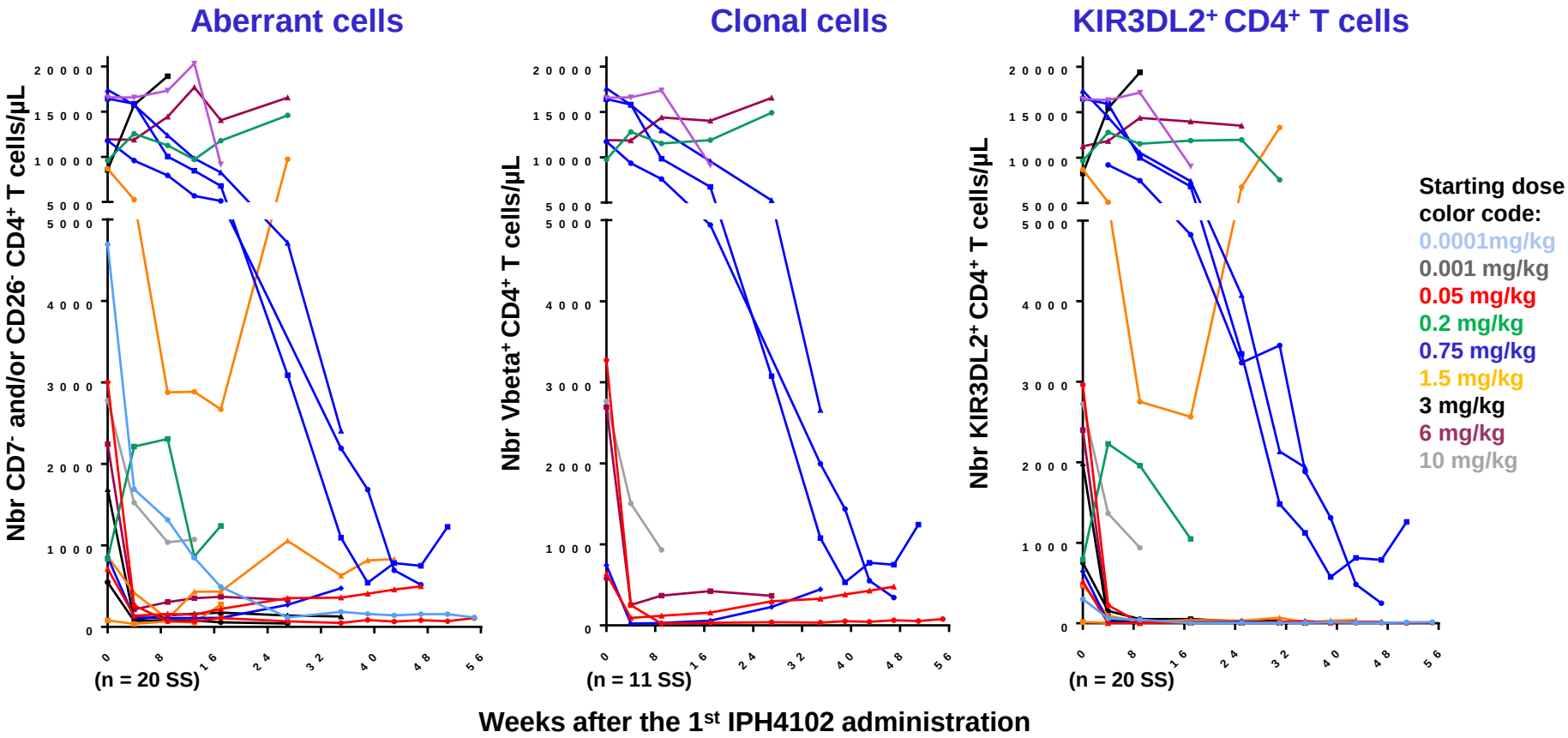


Median VAS change over time



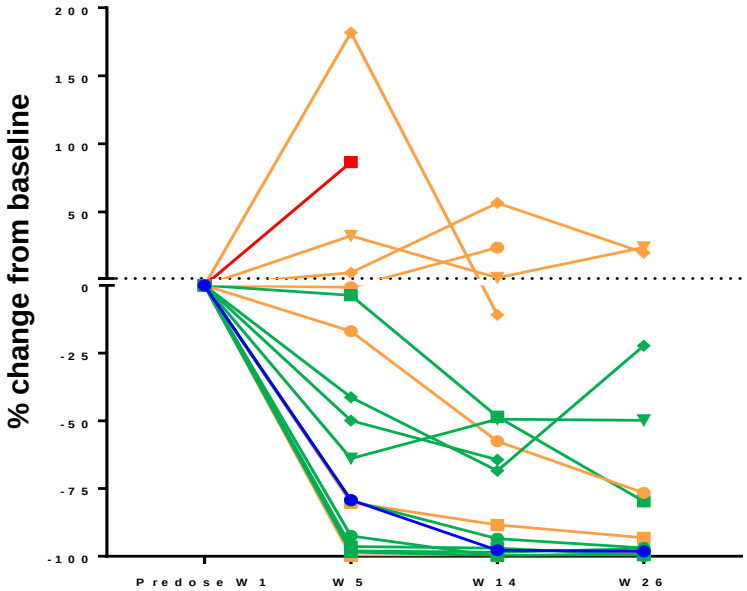
VAS: Visual Analogue Scale

BLOOD ABERRANT, CLONAL AND KIR3DL2^{+} CD4^{+} T CELLS ARE DEPLETED DURING IPH4102 TREATMENT

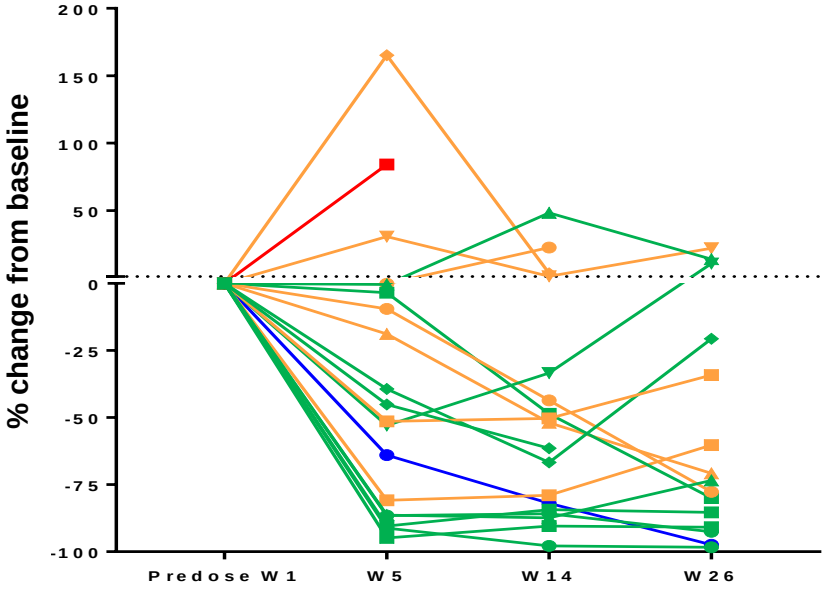


ABERRANT BLOOD CELLS CHANGES FROM BASELINE TEND TO BE RELATED TO GLOBAL CLINICAL RESPONSE

KIR3DL2^{+} CD4^{+} T cells *versus* best Global Response



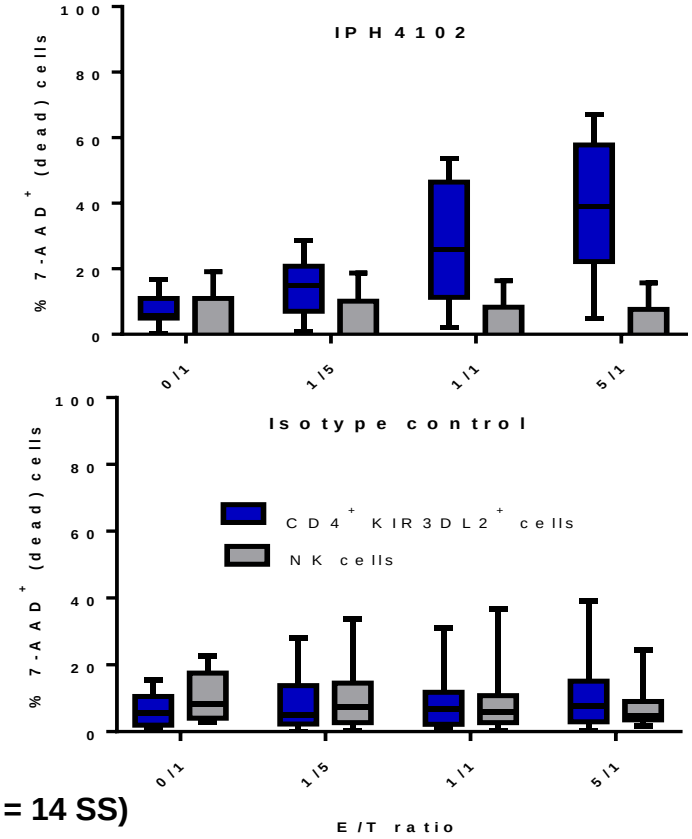
Aberrant CD7^{-} and/or CD26^{-} CD4^{+} T cells *versus* best Global Response



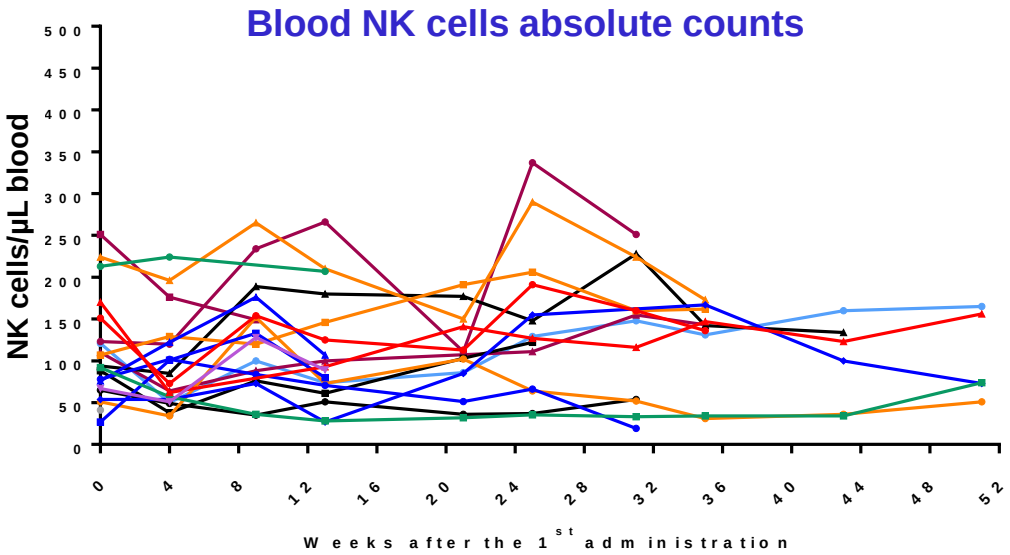
Best global response: CR PR SD PD

(n = 20 SS)

SS PATIENT NK CELLS ARE FUNCTIONAL *EX VIVO* AT BASELINE AND NOT DEPLETED IN BLOOD DURING TREATMENT

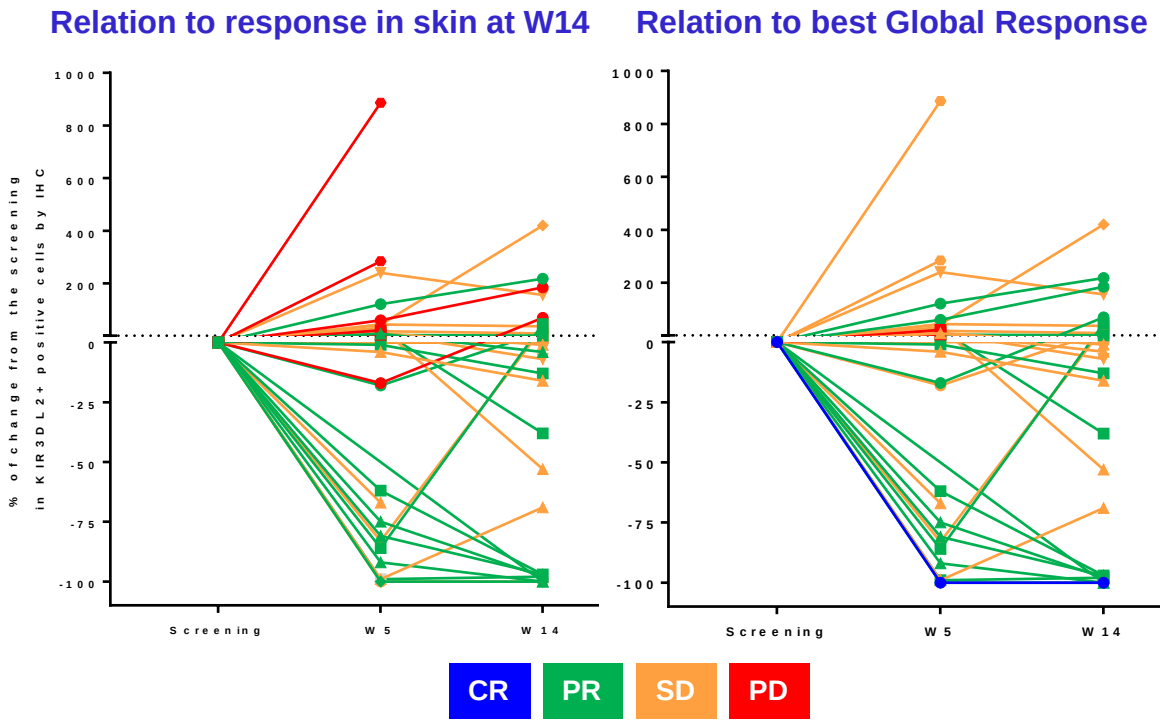


(n = 14 SS)

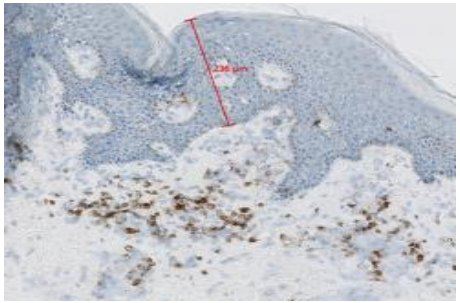


(n = 20 SS)

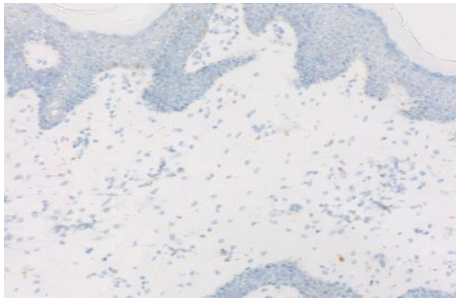
PERCENTAGE OF KIR3DL2⁺ CELLS CHANGES FROM BASELINE IN SKIN BIOPSIES TEND TO BE RELATED TO CLINICAL RESPONSE



SCR: 52% KIR3DL2⁺ cells



Week 14: 0.2%

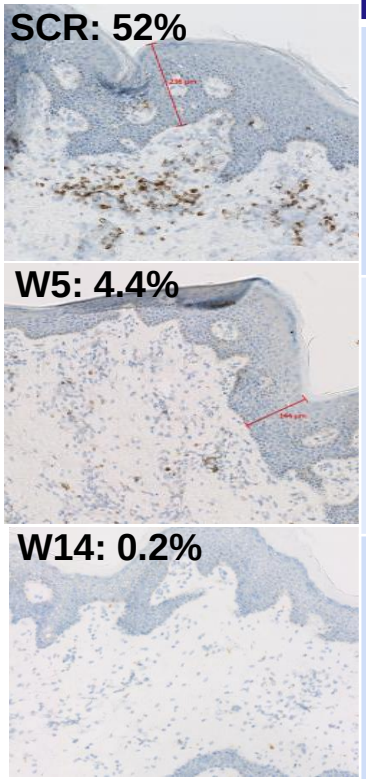


1 plot / biopsy, 1 or 2 biopsies / patient – n = 22 patients - percentage of KIR3DL2⁺ cells among mononuclear cells

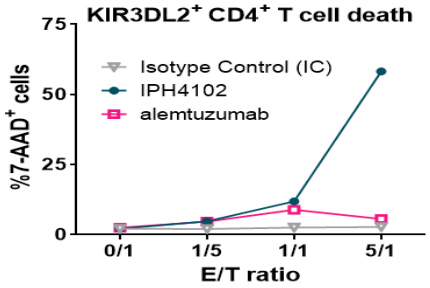
EXPLORATORY/PHARMACODYNAMICS ENDPOINTS SKIN & BLOOD ASSESSMENTS / PT 11-005

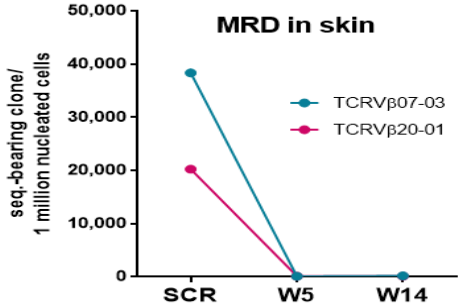
SCR = screening

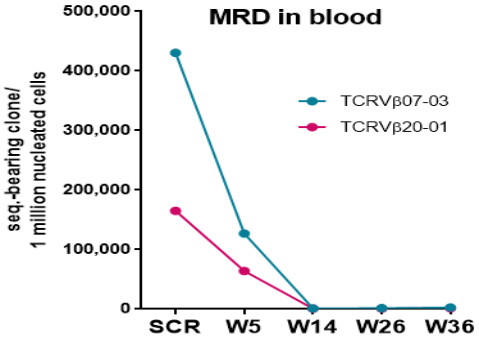
% of KIR3DL2$^+$ cells in skin lesions by IHC

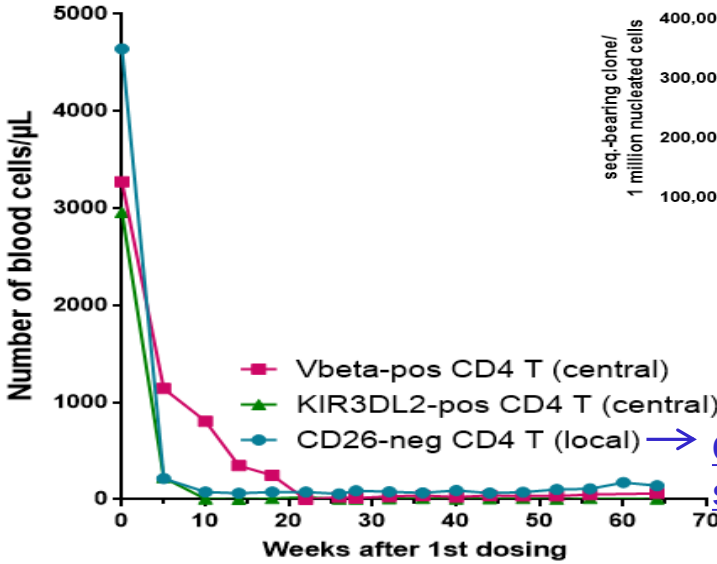


CD4/8 ratio in skin	mSWAT
SCR: 49	SCR: 80.5/1/0
W5: 19	W5: 87/0/0
	W10: 36.5/0/0 PR
W14: 9	W14: 19.3/0/0 PR









CR in blood since W10

IPH4102-101 HIGHLIGHTS
SAFETY, CLINICAL AND BIOLOGICAL ACTIVITY

- IPH4102 MTD was not reached, RP2D is 10 mg/kg
- IPH4102 is safe and well tolerated by heavily pretreated advanced CTCL patients

- Best global ORR is 44% in the overall population and 50% in Sezary patients
- In the Sezary population, median Duration of Response is 9.9 months
- Pruritus is substantially improved in patients having global response or stable disease

- IPH4102 is pharmacologically active at all dose-levels tested:
  - > KIR3DL2^{+} cells are depleted in blood, similarly to aberrant and clonal CD4 T cells
  - > KIR3DL2^{+} cells are depleted in skin lesions

- **Expansion cohort of 15 Sézary patients at the flat dose of 750 mg now completed**

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All our patients and their families…

BACK-UP SLIDES
« FOR MARTINE »

IPH4102-101

PT 01-013: SAE OF POSSIBLY RELATED HEPATITIS

- 75 y o gentleman (172 cm, 79 kg)
- Medical Hx includes Hypertension, hypertrigylceriemia, gout, severe B- and T-lymphopenia
- Initial Dx of Sézary Syndrome: 21 March 2013
- Previous therapies: MTX+Carmustine, CHOP, Targretin, gemcitabine, doxorubicine and ifosphamide+etoposide
- Study entry 27 April 2016 (T4N0M0B2)
- 1st IPH4102 administration 19 March 2016, last administration 17 May 2017,
- Best global response PR, treatment discontinuation on 14 June 2017 due to PD
- On 30 June 2017 grade 4 elevated liver enzymes were detected during assessments for subsequent chemotherapy
- Workup of primary cytolytic hepatitis revealed no clear cause, in particular viral screen was negative except for HHV-6B
- Histopathologic findings are compatible with either DILI or viral infection (HHV-6B)
- Patient died on 12 July 2017

PATIENT DISPOSITION

	Dose-escalation
Screened	34
Screen Failure	9
Safety Population	25
Efficacy Population	25
Replaced Patients	1

- **Reasons for screen failure:**
  - 7 for KIR3DL2 negativity
  - 1 for grade 3 AE during screening
  - 1 for consent withdrawal

BASELINE DISEASE CHARACTERISTICS OF PATIENTS EVALUABLE FOR SAFETY

	All doses N = 25
ANTINEOPLASTIC THERAPY	
Patients who received at least one, n (%)	
Extracorporeal Photophoresis	11 (44)
Medications	25 (100)
Phototherapy	9 (36)
Radiotherapy	7 (28)
MEDICATIONS:	
Treatment setting	
Systemic Treatment	25 (100)
Topical Treatment	13 (52)
Other kinds of Treatment	1 (4)
PHOTOTHERAPY:	
Treatment setting	
Generalized Skin Involvement	8 (32)
Local / Limited Skin Involvement	1 (4)
RADIOTHERAPY:	
Treatment setting	
Generalized Skin Involvement	4 (16)
Local / Limited Skin Involvement	5 (20)

	All doses N = 25
MEDICATIONS RECEIVED, n (%)	
Bexarotene	19 (76)
Methotrexate	17 (68)
Interferon	12 (48)
Mogamulizumab	7 (28)
Doxorubicin	6 (24)
Gemcitabine	6 (24)
Romidepsin	6 (24)
Vorinostat	6 (24)
Nitrogen Mustard	5 (20)
Brentuximab vedotin	3 (12)
Pralatrexate	2 (8)
Corticosteroids	2 (8)
Chlorambucil	1 (4)
Others	17 (68)

SUMMARY OF ADVERSE EVENTS (AE)

N=25	Total
DLT	0
AE **Grade 1** **Grade 2** **Grade 3** **Grade 4**	**23 (92%)** 21 (84%) 17 (68%) 6 (24%) 2 (8%)
Related AE **Grade 1** **Grade 2** **Grade 3** **Grade 4**	**13 (52%)** 12 (48%) 4 (16%) 2 (8%) **-**
Fatal AE	**2 (8%)**
Related fatal AE	**1 (4%)**

N=25	Total
SAE **Grade 1** **Grade 2** **Grade 3** **Grade 4**	**8 (32%)** 3 (12%) 3 (12%) 2 (8%) 2 (8%)
Related SAE **Grade 1** **Grade 2** **Grade 3** **Grade 4**	**2 (8%)** **-** **1 (4%)** **-** **-**
AE causing treatment discontinuation	**1 (4%)**
AE causing treatment delay	**4 (16%)**

N is the number of subjects having the given events, or an event in the given category at least once

(S)AE: (Serious) Adverse Event

AE WITH ONSET AT ANY DOSE OCCURRING IN > 10% PATIENTS IRRESPECTIVELY OF CAUSALITY

	AE (N=25)			
System Organ Class	**All grades n(%)**	**Grade 3 n(%)**	**Grade 4 n(%)**	**Grade 5 n(%)**
Any AE	**23 (92)**	**6 (24)**	**2 (8)**	**2 (8)**
Infections	11 (44)	0	1 (4)	1 (4)
Peripheral oedema	6 (24)	0	0	0
Asthenia	6 (24)	0	0	0
Cough	6 (24)	0	0	0
Headache	6 (24)	0	0	0
Dyspnoea	5 (20)	0	0	0
Pyrexia	5 (20)	0	0	0
Anemia	5 (20)	1 (4)	0	0
Constipation	4 (16)	0	0	0
Lymphopenia	3 (12)	2 (8)	0	0
Fatigue	3 (12)	0	0	0
Malaise	3 (12)	1 (4)	0	0
Diarrhea	3 (12)	0	0	0
Nausea	3 (12)	0	0	0
Arthralgia	3 (12)	0	0	0
Fall	3 (12)	0	0	0

n is the number of subjects having the given events, or an event in the given category at least once

ADVERSE EVENTS AT LEAST POSSIBLY RELATED TO DRUG (REPORTED BY >2 PATIENTS, OR GRADE ≥3)

	Related AE (N = 25)			
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Any related AE	**13 (52)**	**2 (7)**	**0**	**1 (4)**
Lymphopenia	4 (16)	2 (8)	0	0
Asthenia	3 (12)	0	0	0
Nausea	2 (8)	0	0	0
Chills	2 (8)	0	0	0
Pyrexia	2 (8)	0	0	0
Arthralgia	2 (8)	0	0	0
Muscle spasm	2 (8)	0	0	0
Hepatitis	1 (4)	0	0	1 (4)

n is the number of subjects having the given events, or an event in the given category at least once

INFECTIONS

	AE (N = 25)					
	All grades n (%)	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 N (%)**	**Grade 5 N (%)**
Any Infection	**11 (44)**	**7 (28)**	**6 (24)**	**0**	**1 (4)**	**1 (4)**
Upper respiratory tract infection	3 (12)	1 (4)	2 (8)	0	0	0
Lung infection	2 (8)	0	2 (8)	0	0	0
Staph. aureus sepsis	2 (8)	0	0	0	1 (4)	1 (4)
Viral infection	2 (8)	2 (8)	0	0	0	0
Bronchiolitis	1 (4)	1 (4)	0	0	0	0
Bronchitis	1 (4)	0	1 (4)	0	0	0
Catheter site infection	1 (4)	0	1 (4)	0	0	0
Conjunctivitis	1 (4)	0	1 (4)	0	0	0
Cystitis	1 (4)	0	1 (4)	0	0	0
Device related infection	1 (4)	1 (4)	0	0	0	0
Eye infection	1 (4)	0	1 (4)	0	0	0
Gastroenteritris	1 (4)	0	1 (4)	0	0	0
Osophageal candidiasis	1 (4)	0	1 (4)	0	0	0
Otitis externa	1 (4)	0	1 (4)	0	0	0
Paronychia	1 (4)	0	1 (4)	0	0	0
Puncture site infection	1 (4)	1 (4)	0	0	0	0
Rhinitis	1 (4)	1 (4)	0	0	0	0
Sinusitis	1 (4)	1 (4)	0	0	0	0
Skin infection*	1 (4)*	0	1 (4)*	0	0	0
Viral pharyngitis	1 (4)	1 (4)	0	0	0	0

n is the number of subjects having the given events, or an event in the given category at least once

*The only infection reported as related

SAE REGARDLESS OF DOSE AT ONSET

	SAE (N = 25)					
System Organ Class	**All grades n(%)**	**Grade 1 n(%)**	**Grade 2 n(%)**	**Grade 3 n(%)**	**Grade 4 n(%)**	**Grade 5 n(%)**
Any AE	**8 (32)**	**3 (12)**	**3 (12)**	**2 (8)**	**2 (8)**	**2 (8)**
General physical deterioration	2 (8)	1 (4)	1 (4)	0	0	0
Staph. aureus sepsis	2 (8)	0	0	0	1 (4)	1 (4)
Pyrexia	1 (4)	1 (4)	0	0	0	0
Malaise	1 (4)	0	0	1 (4)	0	0
Lung infection	1 (4)	0	1 (4)	0	0	0
Viral infection	1 (4)	1 (4)	0	0	0	0
Confusional state	1 (4)	0	0	0	1 (4)	0
Delirium	1 (4)	0	0	1 (4)	0	0
Asthma	1 (4)	0	1 (4)	0	0	0
Dyspnoea	1 (4)	0	1 (4)	0	0	0
Pulmonary oedema	1 (4)	0	1 (4)	0	0	0
Anemia	1 (4)	0	1 (4)	0	0	0
Atrial flutter	1 (4)	0	1 (4)	0	0	0
Hepatitis	1 (4)	0	0	0	0	1 (4)
Hip fracture	1 (4)	0	0	1 (4)	0	0

n is the number of subjects having the given events, or an event in the given category at least once

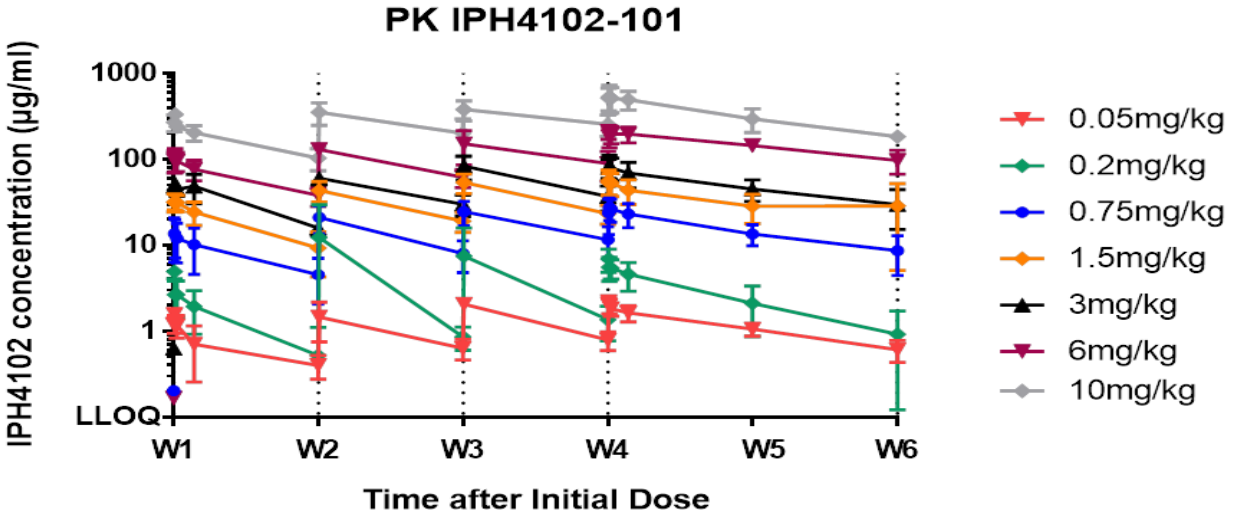
RELATED SAE REGARDLESS OF DOSE AT ONSET

	SAE (N = 25)					
System Organ Class	**All grades n(%)**	**Grade 1 n(%)**	**Grade 2 n(%)**	**Grade 3 n(%)**	**Grade 4 n(%)**	**Grade 5 n(%)**
Atrial flutter	1 (4)	0	1 (4)	0	0	0
Hepatitis	1 (4)	0	0	0	0	1 (4)

n is the number of subjects having the given events, or an event in the given category at least once

- **Atrial flutter grade 2:**
  - Atrial flutter was discovered 1 hour after end of 1st IPH4102 infusion by ECG
  - no symptoms
  - Received Amiodarone and sinus rhythm returned to normal within 4 days
  - Received subsequent IPH4102 administrations without recurrence.
- **Hepatitis**:
  - Grade 4 elevated transaminases were observed 4 weeks after last IPH4102 administration and discontinuation of treatment due to PD
  - A cause could not be definitely identified before the patient died with hepatitis two weeks after
  - Liver biopsy was suspicious of either viral infection or drug induced liver injury
  - The patient was positive for HHV-6B in the liver and in blood.

IPH4102 PK RESULTS



- IPH4102 PK is dose-proportional from 0.75 to 10 mg/kg
- Only slight (and expected) accumulation during the QW regimen (predicted half-life 14-21 days)
- Disease burden can influence exposure: Target-Mediated Drug Disposition (TMDD) was seen in pts with high mSWAT treated at 0.2 mg/kg
- …but no TMDD observed at higher doses in other patients with high disease burden
- Only 1 patient was found positive for Anti-Drug Antibodies (ADA)