IPH4102-101

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

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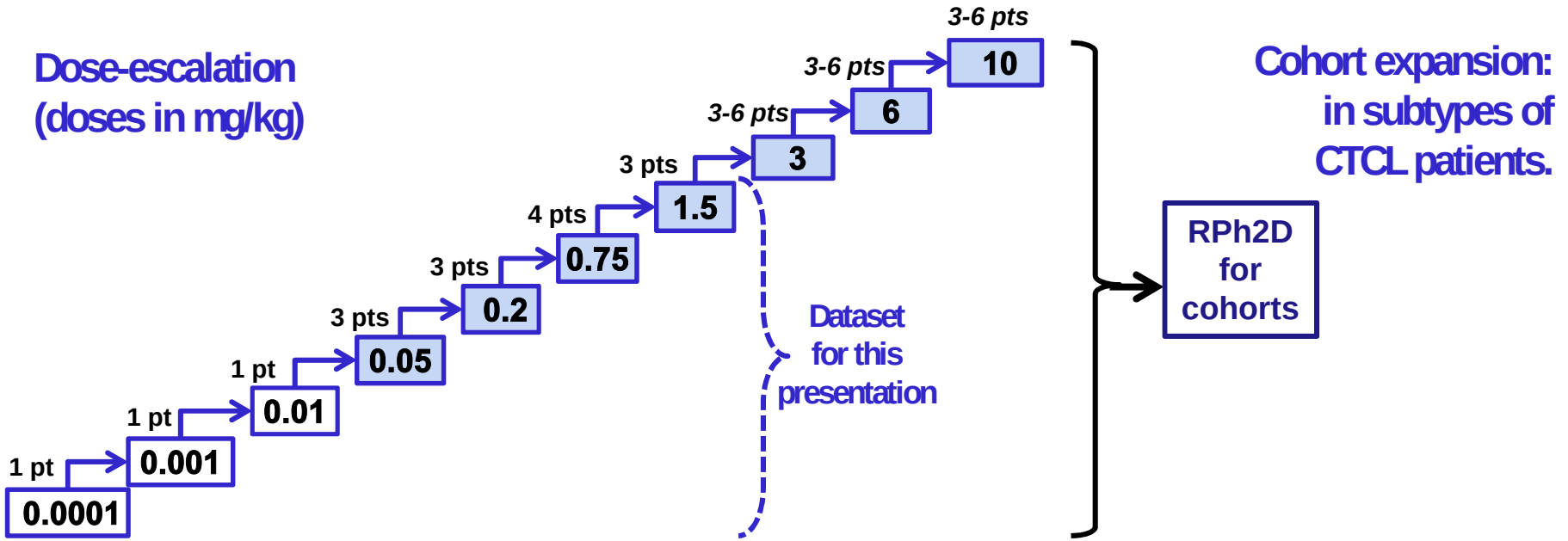
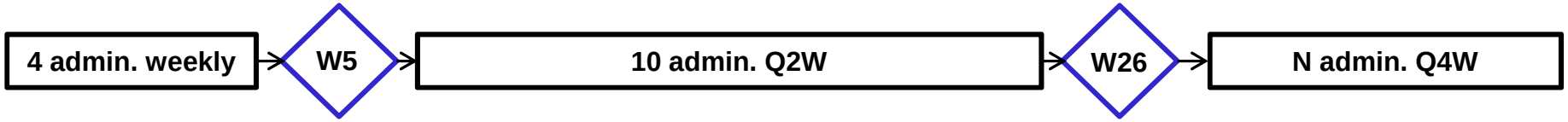
3RD WCCL, NY
OCTOBER 28, 2016

IPH4102-101 STUDY DESIGN
DOSE-ESCALATION & SCHEDULE OF ADMINISTRATION



1st patient treated in Nov 2015; currently exploring dose-level #8 (3 mg/kg)



- Treatment until progression or unacceptable toxicity
- Regular safety and clinical activity assessments to decide on treatment extension
- Intra-patient dose-escalation allowed after at least W5, provided dose level N+1 is considered safe (patient by patient safety committee decision)

STUDY OBJECTIVES

- **Primary objective:** to assess safety & tolerability of increasing IV doses of single agent IPH4102 by:
  - > Characterizing the dose-limiting toxicities (DLT) and (S)AEs
  - > Identifying the MTD or Recommended Phase 2 Dose (RP2D)
- **Secondary objectives**:
  - > To explore antitumor activity (response criteria according to E. Olsen *et al*, JCO 2011, tumor assessments W5, W10 and Q4W)
  - > To assess pharmacokinetics (PK) and immunogenicity
- **Translational objectives, biomarker exploration**:
  - > To monitor the fate of KIR3DL2^{+} cells in skin lesions, blood and lymph nodes (pharmacodynamics)
  - > To monitor immune cell activation in blood
  - > To explore NK cell and macrophage infiltration in skin lesions
  - > To assess Minimal Residual Disease (clonal TCR-Vβ chain rearrangement)
  - > To assess cytokine release
  - > To explore NK cell function pre-dose

KEY ELIGIBILITY CRITERIA (DOSE-ESCALATION PORTION)

- Key inclusion criteria
  - > Patients with relapsed/refractory primary CTCL who have received at least 2 previous systemic antineoplastic therapies
  - > For MF/SS patients: clinical stage ≥ IB
  - > Centrally assessed KIR3DL2 expression (>5%) on malignant cells in blood or in at least 1 skin lesion
- Key exclusion criteria
  - > Limited disease (if MF/SS: stage IA) or CNS disease
  - > Clinical relevant AEs or laboratory results related to previous anti-neoplastic therapy that have not resolved to a NCI-CTCAE grade ≤1
  - > Concomitant corticosteroid use, systemic or topical (WHO class I & II), for skin disease.
  - > Patients who have undergone stem cell transplantation

PATIENT DISPOSITION & DEMOGRAPHICS

- Cut-off date September 10, 2016
- Dose cohorts 1-7 (0.0001 – 1.5 mg/kg) enrolled completely
- Patients who received at least 1 dose are evaluable for safety
- Patients who had a baseline and at least 1 disease assessment (W5) are evaluable for efficacy

	(Doses in mg/kg)							
Patients (n)	**0.0001**	**0.001**	**0.01**	**0.05**	**0.2**	**0.75**	**1.5**	**All Doses**
Screened	1	2	1	3	4	4	4	19
Screen failure		1			1		1	3
Reason for scr. failure: Clinical criteria KIR3DL2 neg		 1			 1		 1	 3
Safety population	1	1	1	3	3	4	3	16
Efficacy population	1	1	1	3	3	4	3	16
Age (y): median [Min;Max]	80	80	56	71 [50;71]	72 [69;88]	74 [68;90]	62 [53;82]	**71** **[50;90]**
Gender: female male	1 0	1 0	0 1	2 1	2 1	2 2	2 1	**10** **6**
Weight (kg): median [Min;Max]	81.8	52.3	77	69.8 [62;124]	80 [56;95]	79 [63;83]	71.4 [68;123]	**76.5** **[52.3;124]**

BASELINE DISEASE CHARACTERISTICS

Patients (N)	0.0001 mg/kg N = 1	0.001 mg/kg N = 1	0.01 mg/kg N = 1	0.05 mg/kg N = 3	0.2 mg/kg N = 3	0.75 mg/kg N = 4	1.5 mg/kg N = 3	All Dose cohorts N = 16
CTCL Subtype								
MF	0	0	1	1	0	0	0	**2**
SS	1	1	0	2	2	4	3	**13**
CD4+ T Cell Lymphoma, NOS	0	0	0	0	1	0	0	**1**
Stage at screening								
IB	0	0	1	0	0	0	0	**1**
IIB	0	0	0	1	0	0	0	**1**
IVA	1	1	0	2	2	4	3	**13**
NA	0	0	0	0	1	0	0	**1**
ECOG PS								
0	0	0	1	2	2	4	0	**9**
1	0	1	0	1	1	0	3	**6**
2	1	0	0	0	0	0	0	**1**
Systemic trt regimens received								
2	1	0	0	0	1	0	0	**2**
3	0	0	0	1	1	0	1	**3**
4-5	0	0	0	0	1	1	2	**4**
6-7	0	0	0	2	0	2	0	**4**
≥8	0	1	1	0	0	1	0	**3**
Received at least one								
Systemic Therapy, other than	1	1	1	3	3	4	3	**16**
Extracorporeal Phototherapy	0	1	0	1	0	3	2	**7**
TSEB*	0	0	1	0	1	1	0	**3**

***TSEB= Total Skin Electron Beam**

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PRELIMINARY SAFETY RESULTS

3RD WCCL, NY

OCTOBER 28, 2016

PATIENT EXPOSURE UP TO SEPT 10TH, 2016

	Number of administrations per level							
Pat ID	0.0001 mg/kg (N=1)	0.001 mg/kg (N=2)	0.01 mg/kg (N=3)	0.05 mg/kg (N=6)	0.2 mg/kg (N=8)	0.75 mg/kg (N=11)	1.5 mg/kg (N=12)	Total
01-001	5	2	3	3	3	1	1	**18**
01-003		5	3	3	1			**12**
01-004			7	3	4	2	1	**17**
11-005				9	4	2	1	**16**
11-006				7				**7**
01-007				7	5	2	1	**15**
01-008					10	3	1	**14**
11-010					9	3	1	**13**
11-011					8	2		**10**
12-012						9	2	**11**
01-013						8	2	**10**
11-015						7	2	**9**
11-017						6	2	**8**
01-018							7	**7**
12-014							5	**5**
11-019							5	**5**
TOTAL	**5**	**7**	**13**	**32**	**44**	**45**	**31**	**177**

SUMMARY OF ADVERSE EVENTS (AE) AS OF SEPTEMBER, 10TH 2016

- 88% of patients have experienced an AE over the duration of treatment
- No related AE of grade 3 or higher were seen
- 1 grade 3 and 1 grade 4 AE
- 1 death (unrelated AE (sepsis))
- No AE led to treatment discontinuation
- 4 patients experienced SAE
- 1 patient experienced related SAE (Atrial Flutter)
- No DLT

TOTAL Patients N = 16	AEs Patient # (%)-Event #	Related AEs Patient # (%)-Event #
Any	**14 (88%) – 87**	**6 (38%) – 20**
Grade 1	12 (75%) – 49	6 (38%) - 13
Grade 2	9 (56%) – 29	3 (19%) - 7
Grade 3	1 (6%) - 1	0
Grade 4	1 (6%) - 1	0
Grade 5	1 (6%) - 1	0
Grade UNK	3 (19%) – 6	0
Serious	**4 (25%) – 8**	**1 (6%) – 1**
Grade 1	1 (6%) - 1	0
Grade 2	2 (13%) - 4	1 (6%) - 1
Grade 3	1 (6%) - 1	0
Grade 4	1 (6%) - 1	0
Grade 5	1 (6%) - 1	0
Grade UNK	0	0
DLT	**0**	**0**

DLT: Dose limiting toxicity
SAE: Serious Adverse Event

SAE DETAILS

Patient ID	AE verbatim	CTCAE Grade	Related	Study day
01-001	SEPSIS STAPH. AUREUS DYSPNEA	4 2	No No	27 270
01-003	FEVER SEPSIS STAPH. AUREUS	1 5	No No	92 138
01-008	ATRIAL FLUTTER PULMONARY ODEMA ASTHMA DECOMPENSATION	2 2 2	Yes No No	1 15 174
11-015	HIP FRACTURE	3	No	6

Pt 01-008:

- 88 y o lady (168 cm, 80 kg)
- Medical Hx includes:
  - Allergic Asthma for ~40 yrs,
  - bilateral pulmonary embolism in 2009
  - diastolic heart failure in 2015
  - Sinus tachycardia known since 2015
- Initial Dx of Sézary Syndrome: 30 January 2015 (T4N2xM0B2), received Targretin (Apr-Jul 2015) and Gemcitabine (Oct 2015- Jan2016)
- Study entry 16 Feb 2016 (T4NxM0B2)
- 1st IPH4102 administration 09 March 2016
- Experiences grade 2 atrial flutter 1 hour after end of 1st IPH4102 infusion; no symptoms (ECG finding);
- Receives Amiodarone and sinus rhythm returns to normal within 4 days
- Received subsequent IPH4102 administrations without recurrence

RELATED ADVERSE EVENTS BY SOC AND GRADE
(IN >1 PATIENT (6%))

All Patients N=16	Related Adverse Events		
System Organ Class	All grades n (%) - event #	Grade 1 n (%) - event #	Grade 2 n (%) - event #
All	6 (38%) - 20	6 (38%) - 13	3 (19%) - 7
Gastrointestinal Disorders	3 (19%) – 4	3 (19%) – 4	
Nausea	2 (13%)	2 (13%)	0
Abdominal pain	1 (6%)	1 (6%)	
Constipation	1 (6%)	1 (6%)	
General Disorders and administration site conditions	3 (19%) – 5	3 (19%) – 5	
Asthenia	1 (6%)	1 (6%)	
Chills	1 (6%)	1 (6%)	0
Fatigue	1 (6%)	1 (6%)	
Malaise	1 (6%)	1 (6%)	
Pain	1 (6%)	1 (6%)	
Musculoskeletal and connective tissue disorders	2 (13%) – 3		2 (13%) – 3
Arthralgia	1 (6%)	0	1 (6%)
Back pain	1 (6%)		1 (6%)
Muscle spasms	1 (6%)		1 (6%)
Respiratory, thoracic and mediastinal disorders	2 (13%) – 2	2 (13%) – 2	
Productive cough	1 (6%)	1 (6%)	0
Dyspnea	1 (6%)	1 (6%)	
Injury, poisoning and procedural complications	1 (6%) – 1		1 (6%) – 1
Infusion related reaction	1 (6%)	0	1 (6%)

- No related AE of grade 3 or higher
- 1 patient experienced infusion related reactions of grade 2

PRELIMINARY SAFETY CONCLUSIONS

In this first in human study of IPH4102:

- 16 patients were enrolled, treated at 7 dose levels (ranging from 0.0001 to 1.5 mg/kg)
- All were evaluable for safety (range of administrations: 5 – 18)
- 12 patients escalated IPH4102 dose at least once
- 15 patients received doses of ≥ 0.2 mg/kg IPH4102
- 12 patients are ongoing, all of whom escalated administration doses to 1.5 mg/kg
- No DLT occurred
- Grade 3 and 4 AE are rare (1 grade 3 and 1 grade 4 AE)
- No related AE of grade 3 or higher occurred

In conclusion:

- IPH4102 is well tolerated in an elderly and heavily pretreated patient population (median age 71 years; 2 – 8 previous lines)
- The majority of AE is typical for CTCL or reflects low grade infusion related reactions

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PRELIMINARY CLINICAL ACTIVITY RESULTS

3RD WCCL, NY

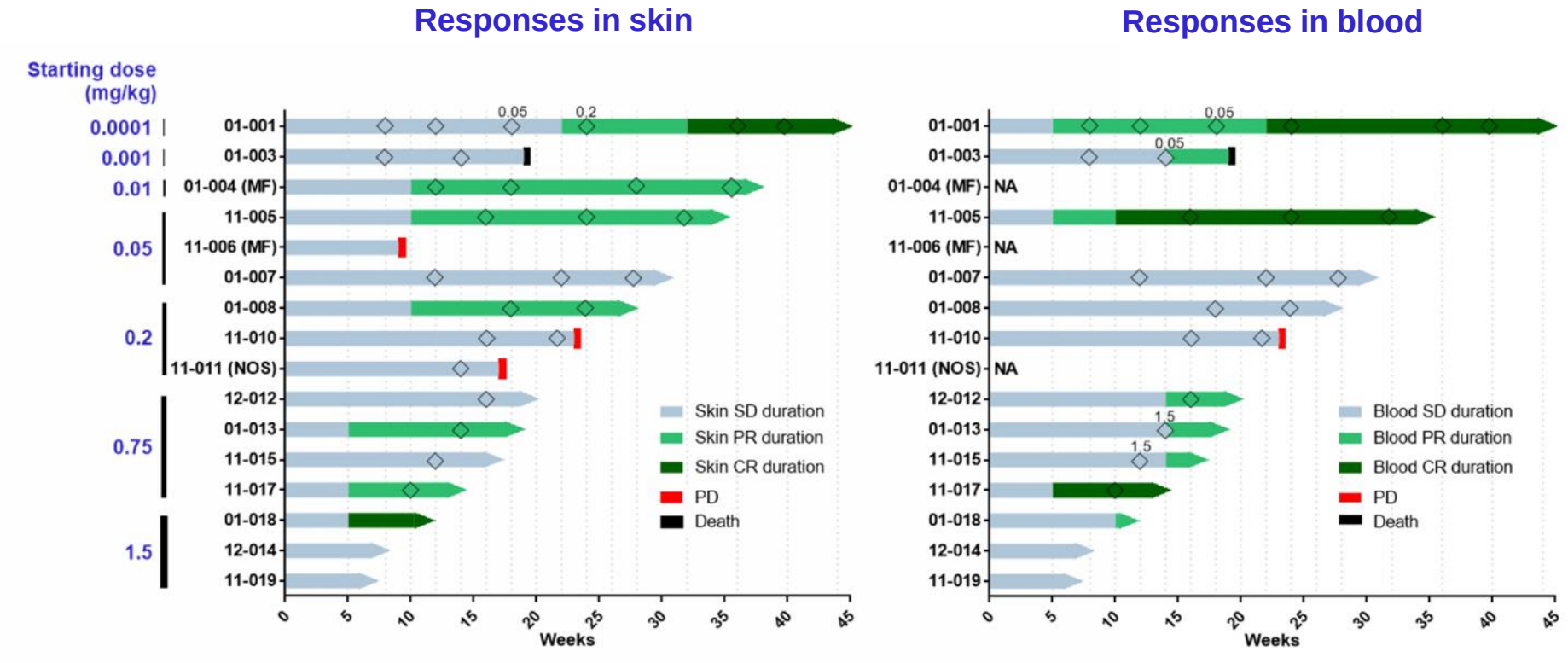
OCTOBER 28, 2016

PRELIMINARY CLINICAL RESPONSE RESULTS (AS OF SEPT 10TH, 2016)

	All Patients Best Global Response N=16	Sézary Syndrome patients			
		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 %
Treatment duration (days)					
Min	**41+**	41+			
Median	**126+**	132+			
Max	**298+**	298+			

Preliminary results calculated for 16 patients evaluable for efficacy assessment, treated with doses ranging from 0.0001 to 1.5 mg/kg

TIMELINE PLOT FOR INDIVIDUAL RESPONSES IN SKIN & BLOOD



There is a trend for dose-response relationship:

- At lower dose-levels, responses seem to appear earlier in blood than responses in skin
- All responses are still ongoing and some responses need to be confirmed with longer follow-up

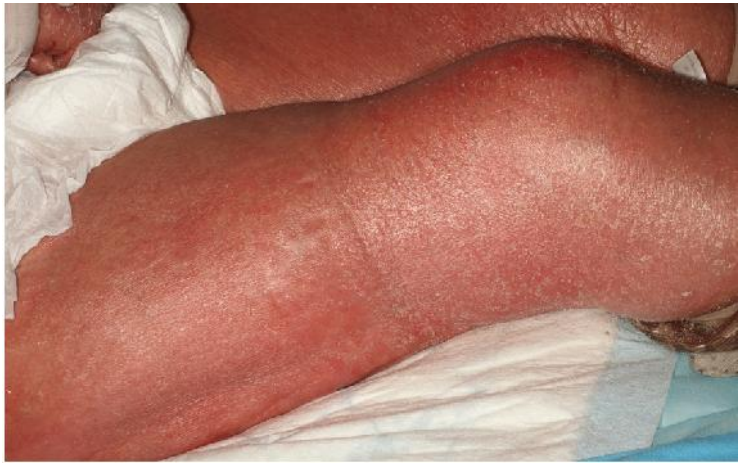
REPRESENTATIVE PICTURES

Patient 01-001:

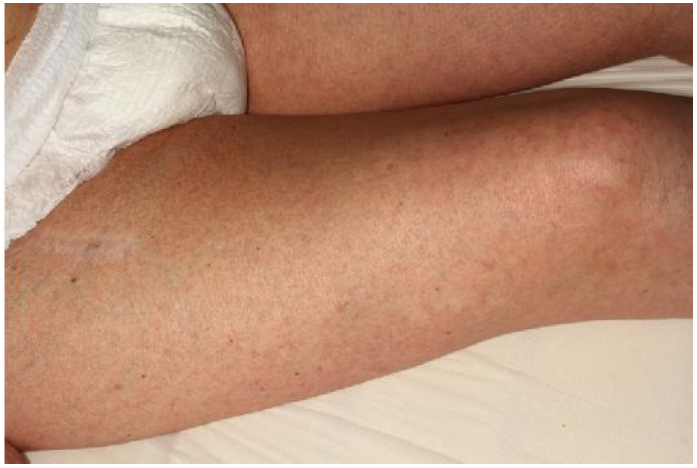
- 80-year old female
- **Sézary Syndrome** diagnosed in DEC 2013
- **2 lines of previous therapies** (methotrexate and bexarotene)

- **$T_4N_xM_0B_2$** at study entry
- Started at 0.0001 mg/kg on 18NOV15 progressively dose-escalated to all doses
- Response in skin: PR at W22 (0.05 mg/kg) then CR at W32 (0.2 mg/kg)

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



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



REPRESENTATIVE PHARMACOLOGY RESULTS

Patient 11-017:

- 69-year old male
- **Sézary Syndrome** diagnosed in APR 2012
- **4 lines of previous therapies** (incl. ECP + bexarotene + INFα, moga., TSEB, methotrexate)

- **$T_4N_2M_0B_2$** at study entry
- Started at 0.75 mg/kg on 20JUN16
- PR in skin at W5 (0.75 mg/kg)

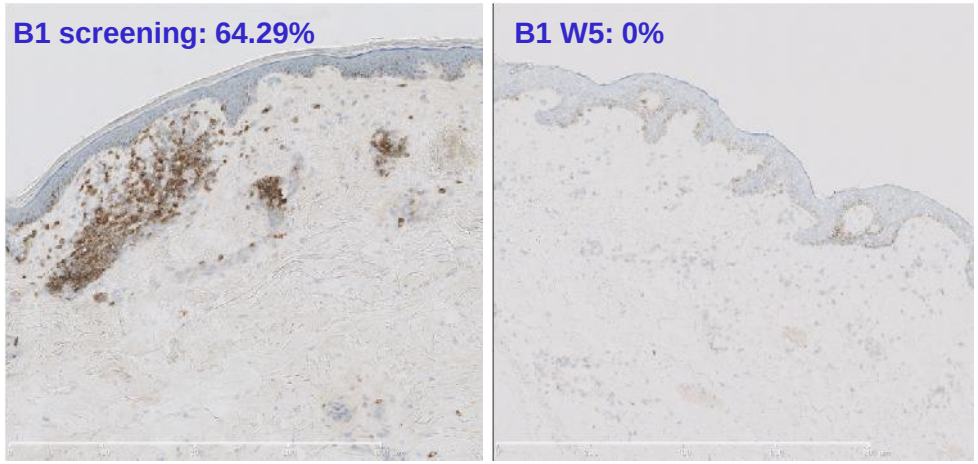
Weighted mSWAT
0.75/0/0 at screening
19/0/0 pre-dose
8/0/0 at W5 (0.75 mg/kg)

Patient 11-005:

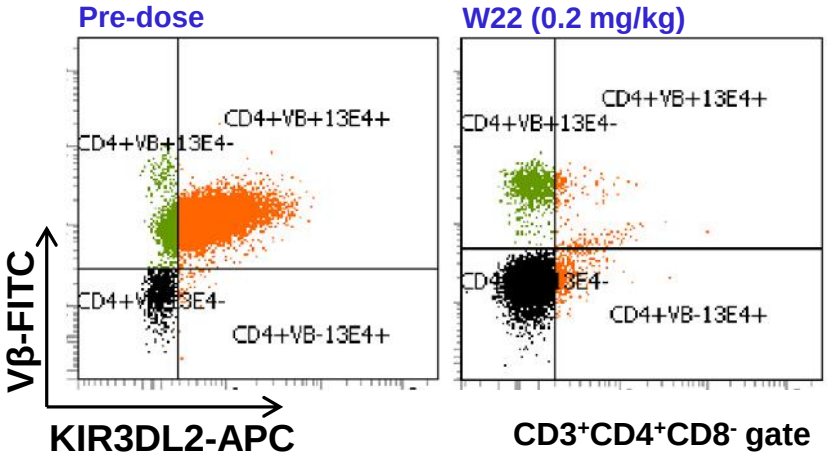
- 77-year old female
- **Sézary Syndrome** diagnosed in NOV 2008
- **6 lines of previous therapies** (incl. ECP + bexarotene + INFα, methotrexate, moga., ECP + INFα + methotrexate, romidepsin, bexarotene + INFα)

- **$T_4N_XM_0B_2$** at study entry
- Started at 0.05 mg/kg on 25JAN16
- PR in blood at W5 (0.05 mg/kg)
- CR in blood at W10 (0.05 mg/kg)

% of KIR3DL2$^+$ cells in skin biopsy #B1

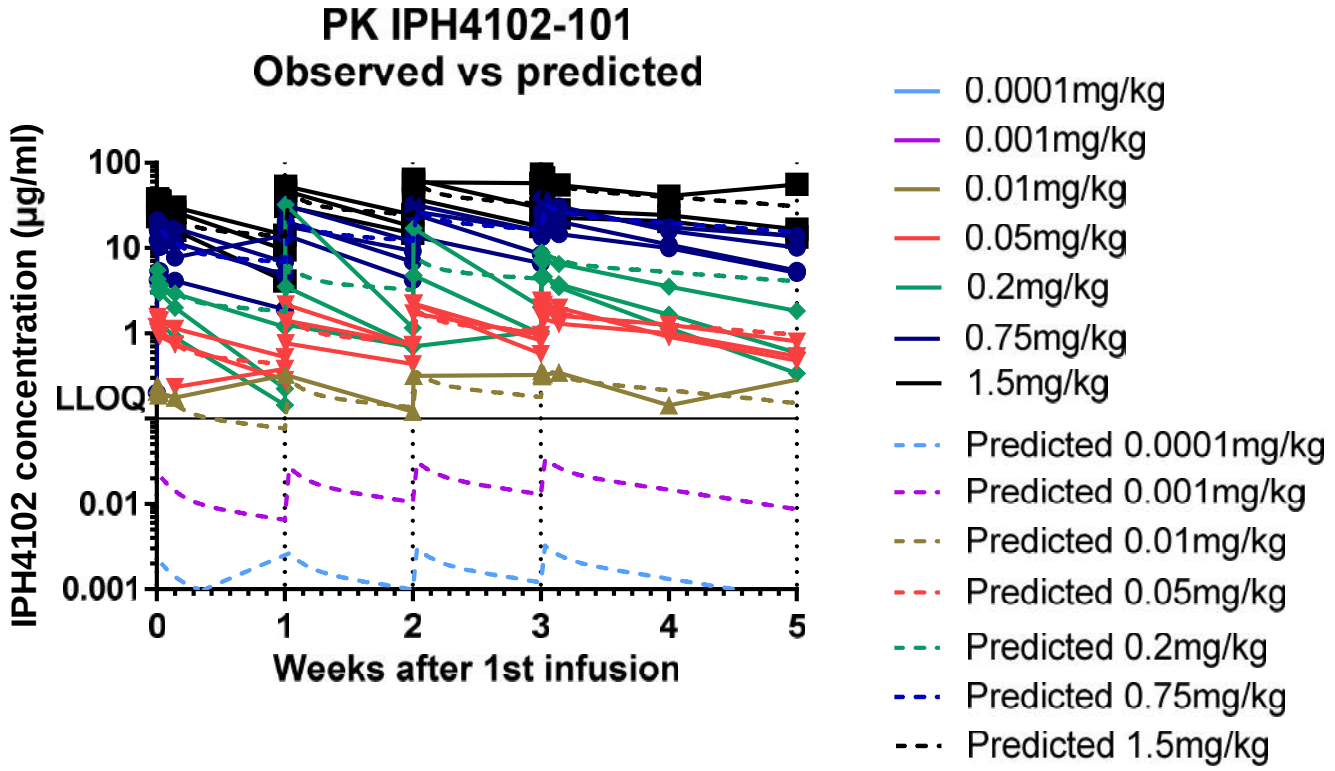


Flow cytometry analyses at pre-dose and W22



Preliminary IPH4102-101 PK/PD/IHC results are displayed on poster O-11.

PRELIMINARY CLINICAL PHARMACOKINETICS



So far, preliminary PK results fit the predictions
(>Lower Limit Of Quantification, up to dose-level 1.5 mg/kg).

CONCLUSION ON PRELIMINARY SAFETY AND CLINICAL ACTIVITY

- Sixteen patients were evaluable for safety and efficacy, including 13 SS, 2 MF and 1 $CD4^+$ TCL NOS
- IPH4102 is well tolerated with a good safety profile in an elderly and heavily pretreated patient population
- The majority of AE is typical for CTCL or reflects low grade infusion related reactions

- Preliminary best global ORR is 38% in the evaluable population and 38% in SS patients
- CR tend to appear in skin (n = 2) and in blood (n = 3) with higher doses and/or increased duration of exposure
- Preliminary PK findings are consistent with predictions
- Results of exploratory endpoints such as pharmacodynamics in skin and blood are in line with clinical activity results (see poster O-11)
- With a relatively short observation time (med. 126+ days), all responders are still ongoing
- Three additional dose-levels (3, 6 and 10 mg/kg) remain to be evaluated

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All our patients and their families…