IPH4102 IN REFRACTORY CUTANEOUS T CELL LYMPHOMA (CTCL): RESULTS OF THE FIRST-IN-HUMAN MULTICENTER PHASE 1 STUDY

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IPH4102-101

CONFLICTS OF INTEREST

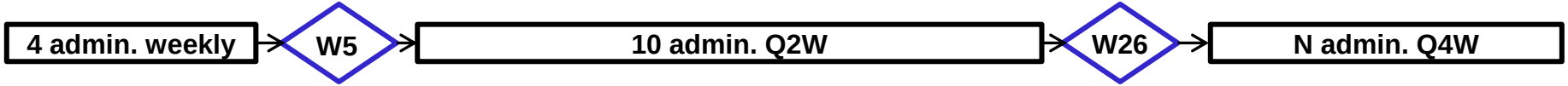
Research Support/P.I.	– Galderma, Innate Pharma, Kyowa, Takeda
Employee	–
Consultant	–
Major Stockholder	–
Speakers Bureau	–
Honoraria	–
Scientific Advisory Board	– Actelion, Innate Pharma, Kyowa, Takeda

IPH4102-101 STUDY DESIGN

All CTCL subtypes → **Sézary Syndrome and transformed MF**

- **Dose-escalation**
  - 10 dose levels – accelerated 3+3 design
  - ≥ 2 prior systemic therapies
  - ≥ 5% KIR3DL2pos aberrant cells in skin or blood
  - if Mycosis Fungoides/Sézary Syndrome (MF/SS) stage ≥ IB
- **Cohort expansion**
  - Recommended Phase 2 dose (RP2D)
  - ≥ 2 prior systemic therapies
  - Irrespective of KIR3DL2 expression

- **Dosing regimen**, until progression or unacceptable toxicity



- Intra-patient dose-escalation allowed after Week 5 (W5) in the dose-escalation portion

IPH4102-101 STUDY OBJECTIVES

- **Primary objective**: determination of Maximal Tolerated Dose (MTD) and RP2D, overall safety
- **Secondary objectives**:
  - Clinical activity: Overall Response Rate (ORR, Olsen JCO 2011 criteria), Progression-Free Survival (PFS)
  - PK and immunogenicity
- **Exploratory objectives**:
  - Changes in KIR3DL2pos cells in involved compartments (skin and blood)
  - Molecular Residual Disease (MRD) in involved compartments
  - NK cell function pre-dose
- **Quality of Life**
  - Pruritus (Visual Analogue Scale)
  - SkinDex29

BASELINE DISEASE CHARACTERISTICS

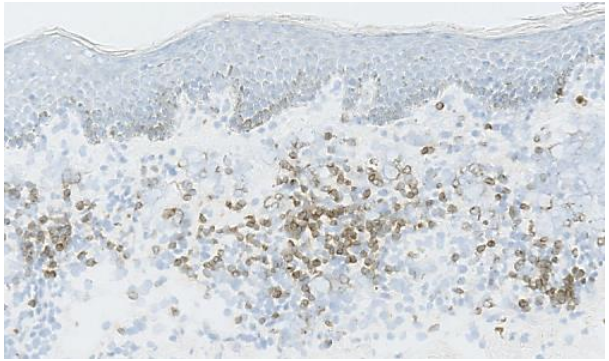
	Dose-escalation n = 25	Cohort Expansion n = 19	TOTAL N = 44
Age (years), **median** (min; max)	**71** (42; 90)	**64** (37; 87)	**69** (37; 90)
MF/SS CTCL type, n (%)			
Mycosis fungoides (MF)	4 (16%)	4 (21%)	8 (18%)
With evidence of large-cell transformation, n (%)	*4 (16%)*	*4 (21%)*	*8 (18%)*
Sézary Syndrome (SS)	20 (80%)	15 (79%)	35 (80%)
With evidence of large-cell transformation, n (%)	*3 (12%)*	*4 (21%)*	*7 (16%)*
Non MF/SS CTCL type, n (%)	1 (4%)	0	1 (2%)
$CD4^+$ T-cell lymphoma, NOS			
Clinical stage at study entry (MF/SS), n (%)			
IB	1 (4%)	1 (5.3%)	2 (4.5%)
IIB	3 (12%)	3 (15.8%)	6 (13.6%)
IIIA	-	1 (5.3%)	1 (2.3%)
IVA1	20 (80%)	11 (57.9%)	31 (70.5%)
IVA2	-	2 (10.6%)	2 (4.5%)
IVB	-	1 (5.3%)	1 (2.3%)
No. of regimen systemic received, **median** (min; max)	**3** (2; 10)	**2** (1; 13)	**3** (1; 13)

BASELINE KIR3DL2 EXPRESSION IN SKIN AND BLOOD

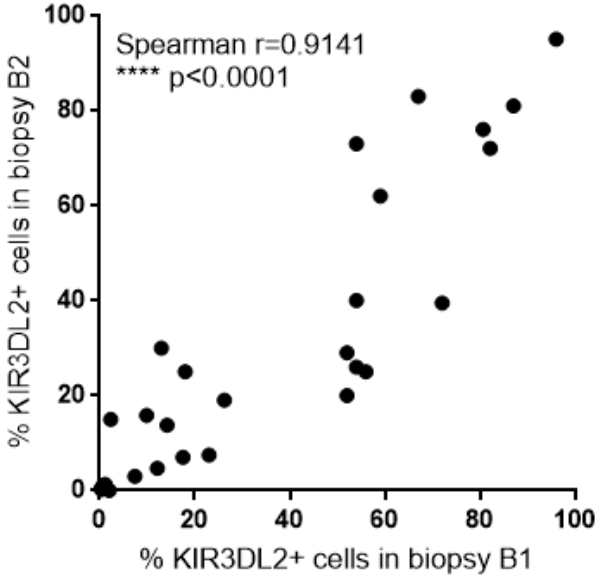
Baseline KIR3DL2 positivity	Dose-escalation (n = 25)		Cohort Expansion (n = 19)	
	SS	Non-SS	SS	tMF
Skin	17/20	5/5	11/14*	0/4
Blood	20/20	NA	13/15	NA
Skin or Blood	20/20	5/5	13/14*	0/4

*One patient not evaluable in skin at baseline
NA: Not Applicable

Representative baseline KIR3DL2 expression in SS (38% KIR3DL2pos cells)



High correlation of KIR3DL2 expression in both baseline skin biopsies (n=29 pts)



AEs REPORTED IN ≥ 10% PATIENTS (N=44)

Adverse event	All grades, N (%)	Grade 3-4, N (%)
Peripheral edema	12 (27%)	0 (0%)
Asthenia	9 (20%)	0 (0%)
Fatigue	9 (20%)	0 (0%)
Cough	7 (16%)	0 (0%)
Pyrexia	7 (16%)	0 (0%)
Diarrhea	7 (16%)	0 (0%)
Arthralgia	7 (16%)	0 (0%)
Fall	6 (14%)	0 (0%)
Headache	6 (14%)	0 (0%)
Lymphopenia	6 (14%)	2 (5%)
Constipation	5 (11%)	0 (0%)
Dyspnea	5 (11%)	0 (0%)
Chills	5 (11%)	0 (0%)
Anemia	5 (11%)	1 (2%)
Hypertension	5 (11%)	2 (5%)

Five patients developed 6 possibly related grade ≥ 3 AEs

- grade 5 hepatitis (n=1)
- grade 4 sepsis (n=1)
- grade 3 AST elevation (n=1)
- grade 3 lymphopenia (n=2)
- grade 3 hypotension (n=1).

Only 3 patients (7%) stopped treatment for an AE.
Neither skin rash nor other immune-mediated reactions related to IPH4102 were reported.

ABNORMALITIES IN LIVER FUNCTION TESTS IRRESPECTIVE OF BEING REPORTED AS AEs (N=44)

Event	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)
AST increased	6 (14)	0 (0)	1 (2)*	1 (2)^
ALT increased	10 (23)	0 (0)	0 (0)	1 (2)^
ALP increased	9 (20)	1 (2)	0 (0)	0 (0)
Blood bilirubin increased	3 (7)	1 (2)	0 (0)	1 (2)^
Hypoalbuminemia	18 (41)	5 (11)	1 (2)*	0 (0)

^Patient had grade 5 hepatitis 6 weeks after the last administration. He received IPH4102 for one year, achieved a PR, then treatment was discontinued for PD. He had normal liver function throughout the treatment course. Liver biopsy and serology performed one week before death showed evidence of HHV-6B infection.

*Patient developed grade 3 AST and grade 1 ALT elevation after the 4th administration. He had grade 2 hypoalbuminemia at baseline. The event improved to grade 1 one week later despite the 5th administration. AST elevation completely resolved on Day 55. The AST/ALT ratio was not consistent with acute drug induced liver injury.

CLINICAL EFFICACY RESULTS (CUT-OFF JUNE, 28 2018)

Update

	Escalation (n=25)	Escalation SS only (n=20)	Expansion SS (n=15)	Total (N=44)[$]	Total without LCT (n=29)
Best global response	**11 (44%)**	**10 (50%)**	**5 (33.3%)**	**16 (36.4%)**	**15 (51.7%)**
- CR	1 (4%)	1 (5%)	1 (6.7%)	2 (4.5%)	2 (6.9%)
- PR	10 (40%)	9 (45%)	4 (26.7%)	14 (31.8%)	13 (44.8%)
- SD	12 (48%)	8 (40%)	8 (53.3%)	24 (54.5%)	12 (41.4%)
- PD	2 (8%)	2 (10%)	2 (13.3%)	4 (9%)	2 (6.9%)
Follow up*	18.2 (2–31+)	19.3 (2–31+)	8.1 (2–11+)	12.7 (2–31+)	14.9 (1.9–31+)
Time to Response*	4.9 (0.9–26.8)	4.9 (0.9–26.8)	5.8 (0.8–9)	NR (0.8–26.8)	4.8 (0.9–25.8)
Duration of Response*	9.9 (2.1–26.4+)	11.9 (2.1–26.4+)	NR (1.4–9+)	13.8 (1.4–26.4+)	13.8 (2.1–26.4+)
Progression Free Survival*	8.1 (0.9–31.3+)	11.3 (0.9–31.3+)	NR (0.8–11.1+)	8.2 (0.8–31.3+)	12.9 (0.8–31.2+)

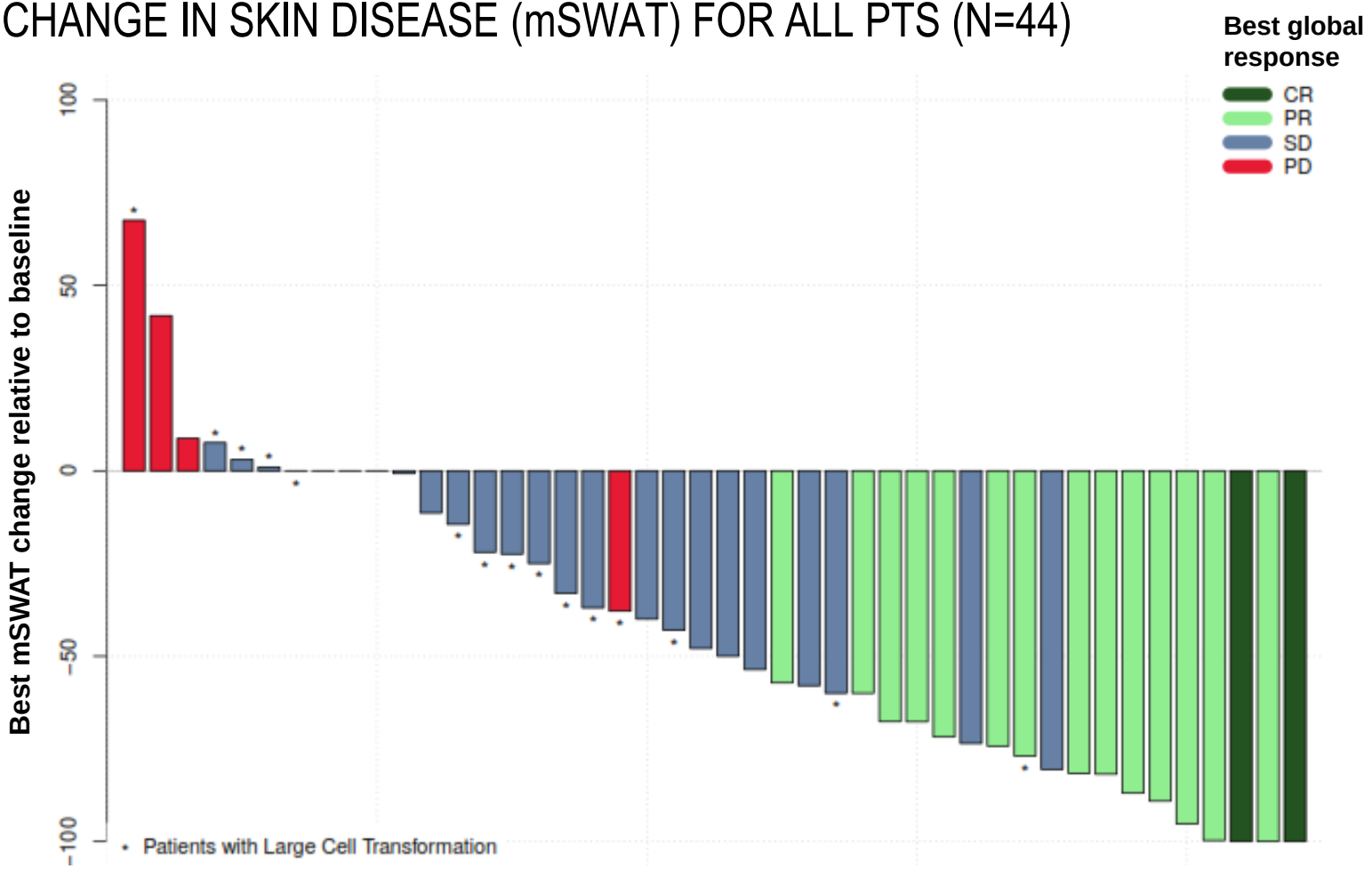
**** All in months, median (range)***

NA: Not Applicable; NR: Not Reached
LCT: Large-Cell Transformation

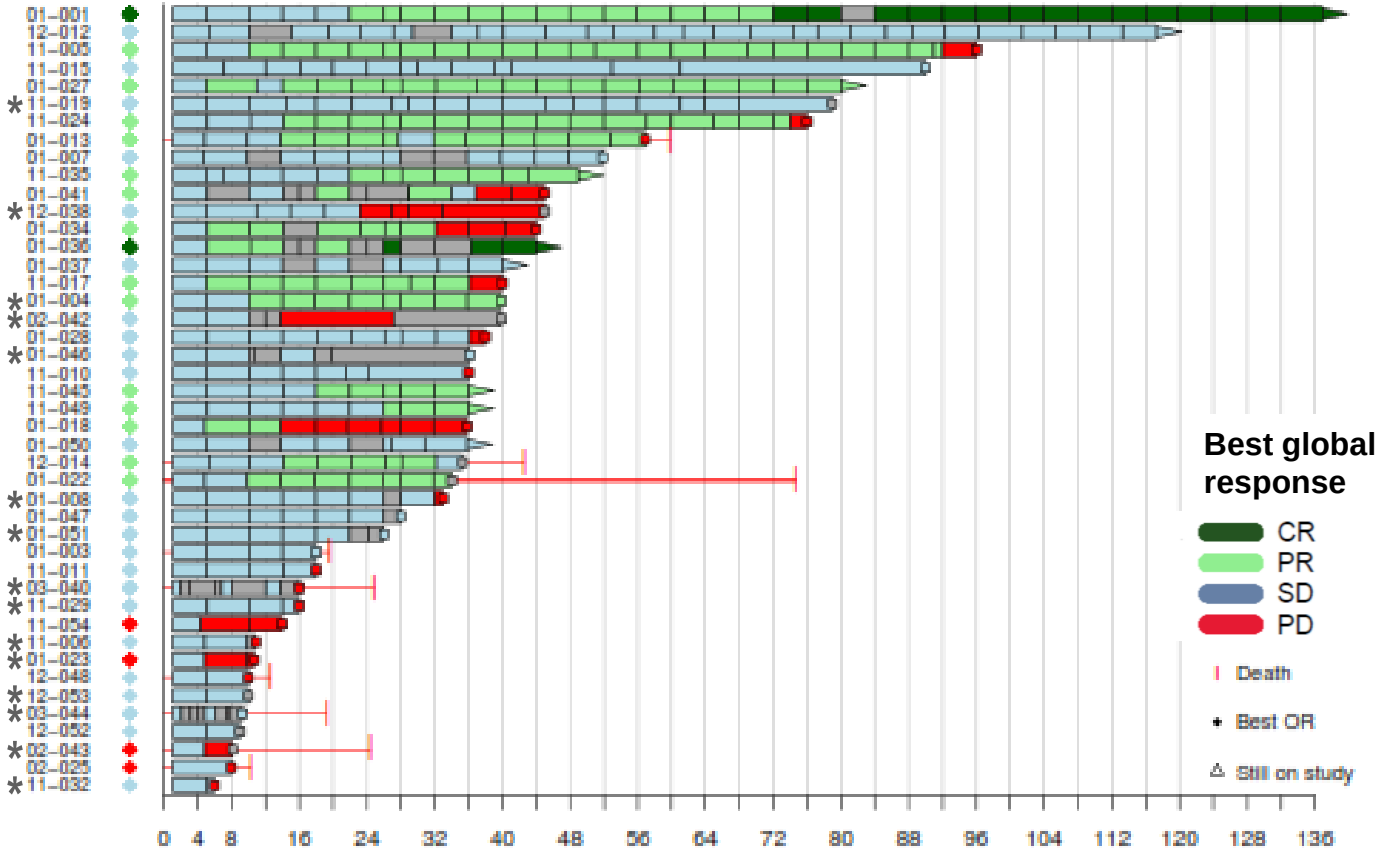
Nine patients are still on treatment at cut-off date.

[$]Four tMF (MF with LCT) were enrolled in the expansion. All have best response of SD.

CHANGE IN SKIN DISEASE (mSWAT) FOR ALL PTS (N=44)

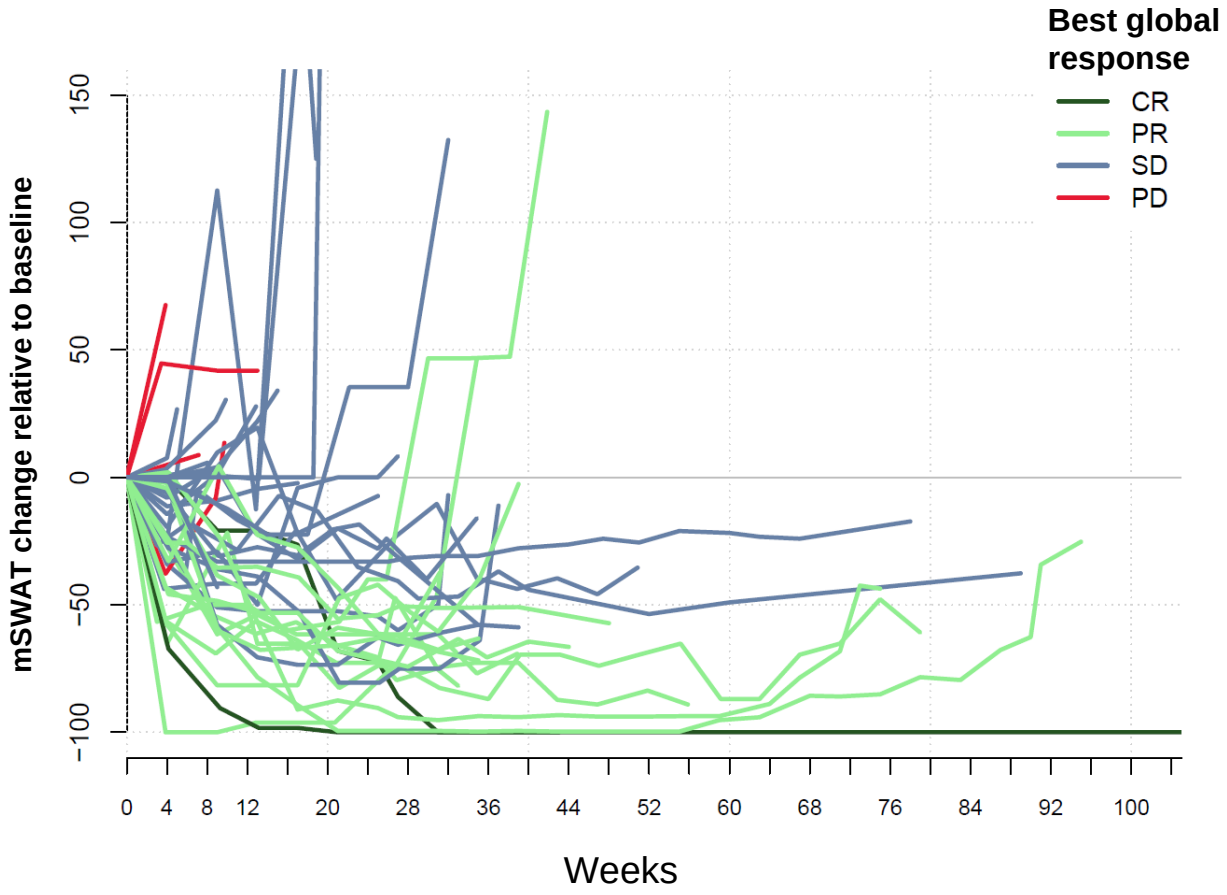


SWIMMER'S PLOT FOR ALL PATIENTS (N=44)

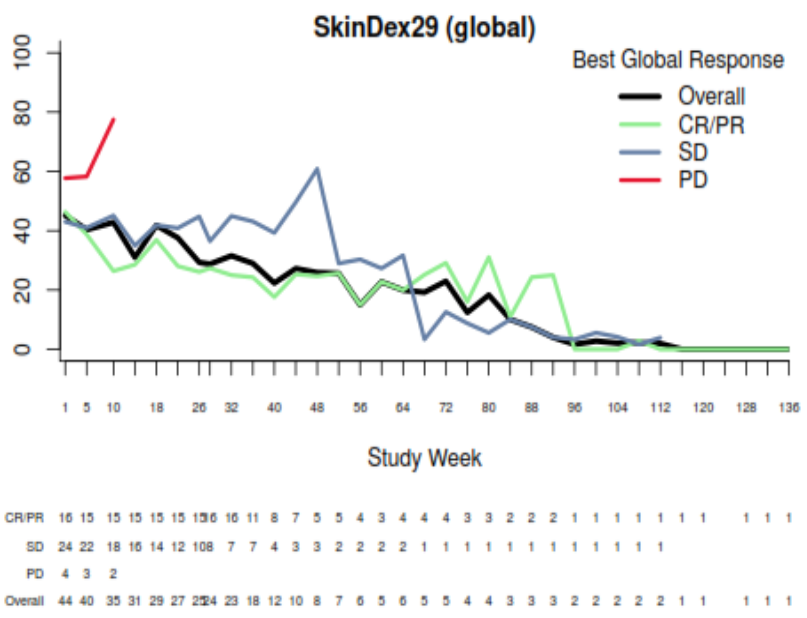


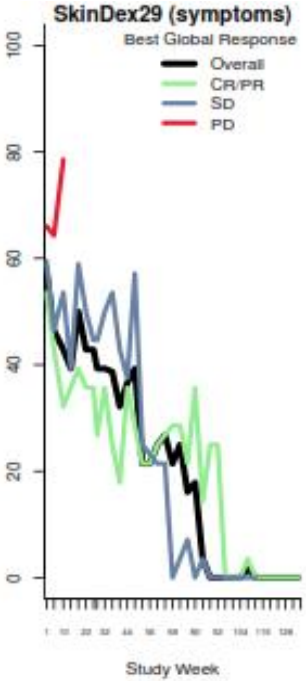
* Patients with LCT

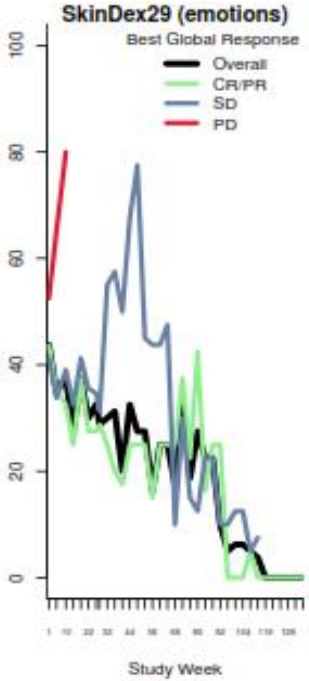
CHANGE IN mSWAT OVER TIME FOR ALL PTS (N=44)

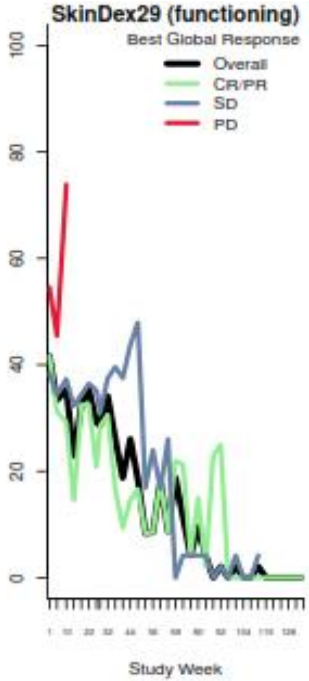


QUALITY OF LIFE BY SKINDEX29 IN ALL PATIENTS (N = 44)









IPH4102 improves Skindex29 global, symptoms, emotional and functional scores over time, including in patients in global SD

KIR3DL2 REDUCTION IN SKIN PREDICTS GLOBAL CLINICAL RESPONSE

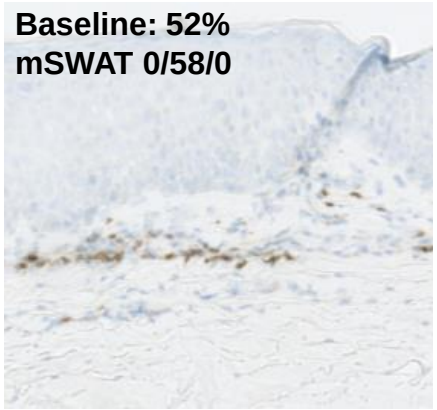
Decrease in %KIR3DL2 cells in skin at W5	Global Response	
	CR/PR	SD/PD
≥ 25%	9	6
< 25%	2	11

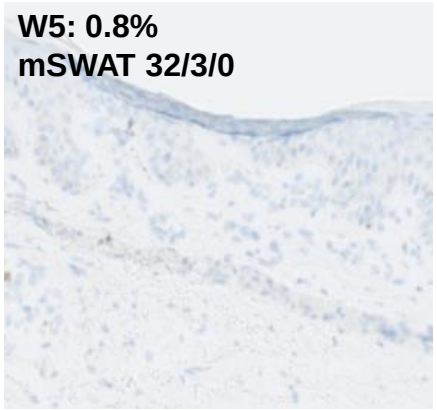
Sensitivity: 82%
Specificity: 65%

Decrease in %KIR3DL2 cells in skin at W14	Global Response	
	CR/PR	SD/PD
≥ 50%	10	5
< 50%	2	9

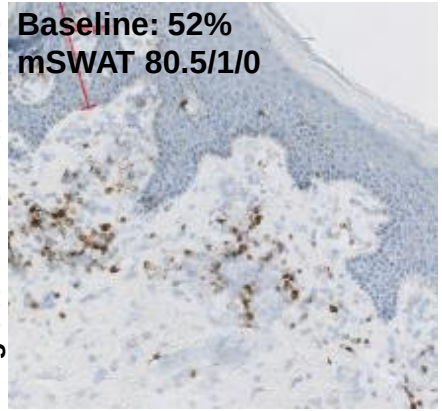
Sensitivity: 83%
Specificity: 64%

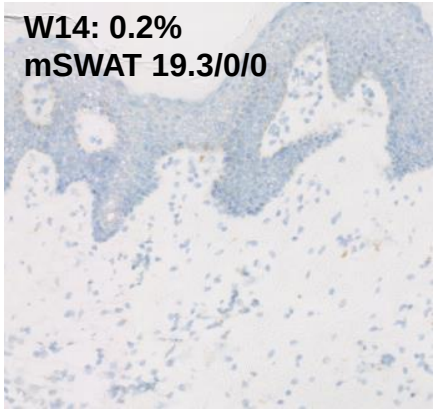
SS patient 01-036
In global CR since Week 36





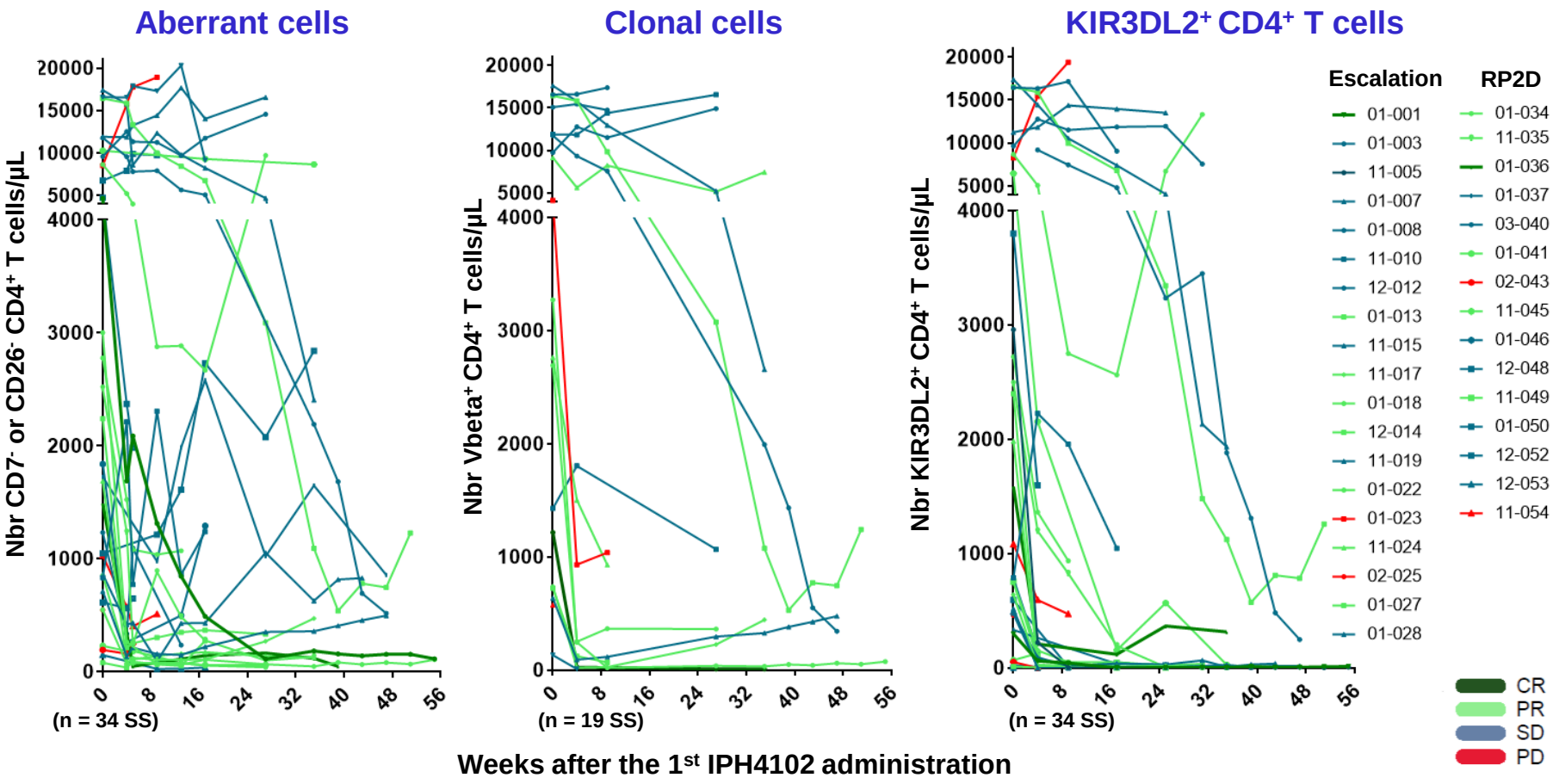
SS patient 11-005
In global PR for > 80 weeks





Cut-off were determined with the ROC curves at each time point

DEPLETION OF SEZARY/ATYPICAL CELLS BY IPH4102 IN BLOOD



CONCLUSIONS

- IPH4102 is safe and well tolerated in heavily pretreated relapsed/refractory CTCL.
- IPH4102 shows clinical activity, demonstrated by high response rate and long progression free survival, and these results point to a higher potential in patients without LCT
  - > SS patients treated in the dose-escalation portion have an updated median PFS of 11.3 months
  - > In the totality of the study, for patients without LCT, ORR is 51.7% and median PFS is 12.9 months
- IPH4102 has positive impact on QOL, which is substantially improved in patients achieving global response but also stable disease.
- IPH4102 induces depletion of Sézary/KIR3DL2-positive cells in blood and in skin
- Relationship between KIR3DL2 expression and efficacy will be assessed in a larger patient population. KIR3DL2 will be explored in future clinical trials as potential predictive biomarker of clinical activity.
- A Phase II in relapsed/refractory SS, MF and PTCL is planned.

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All our patients and their families…