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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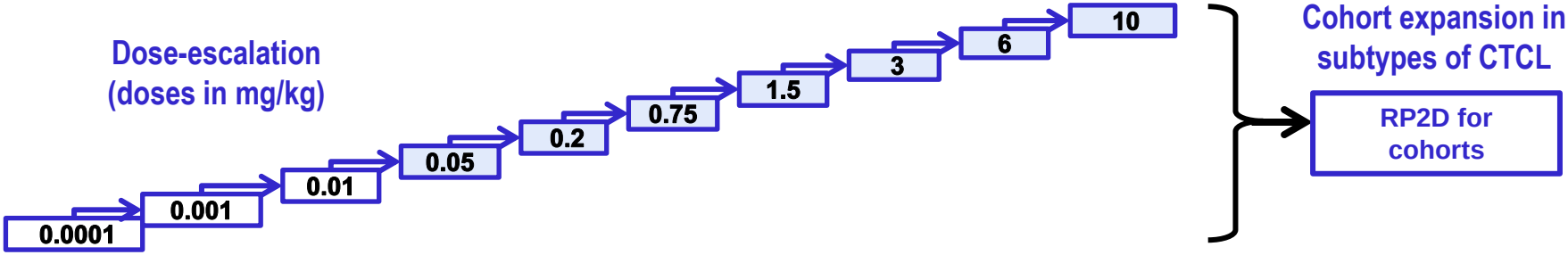
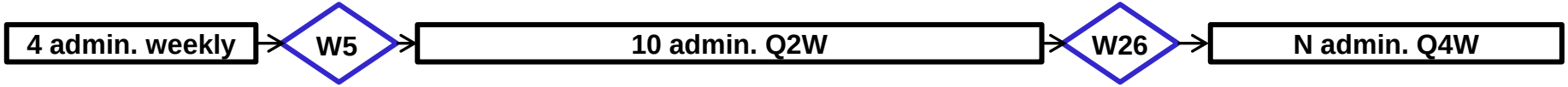
IPH4102-101

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

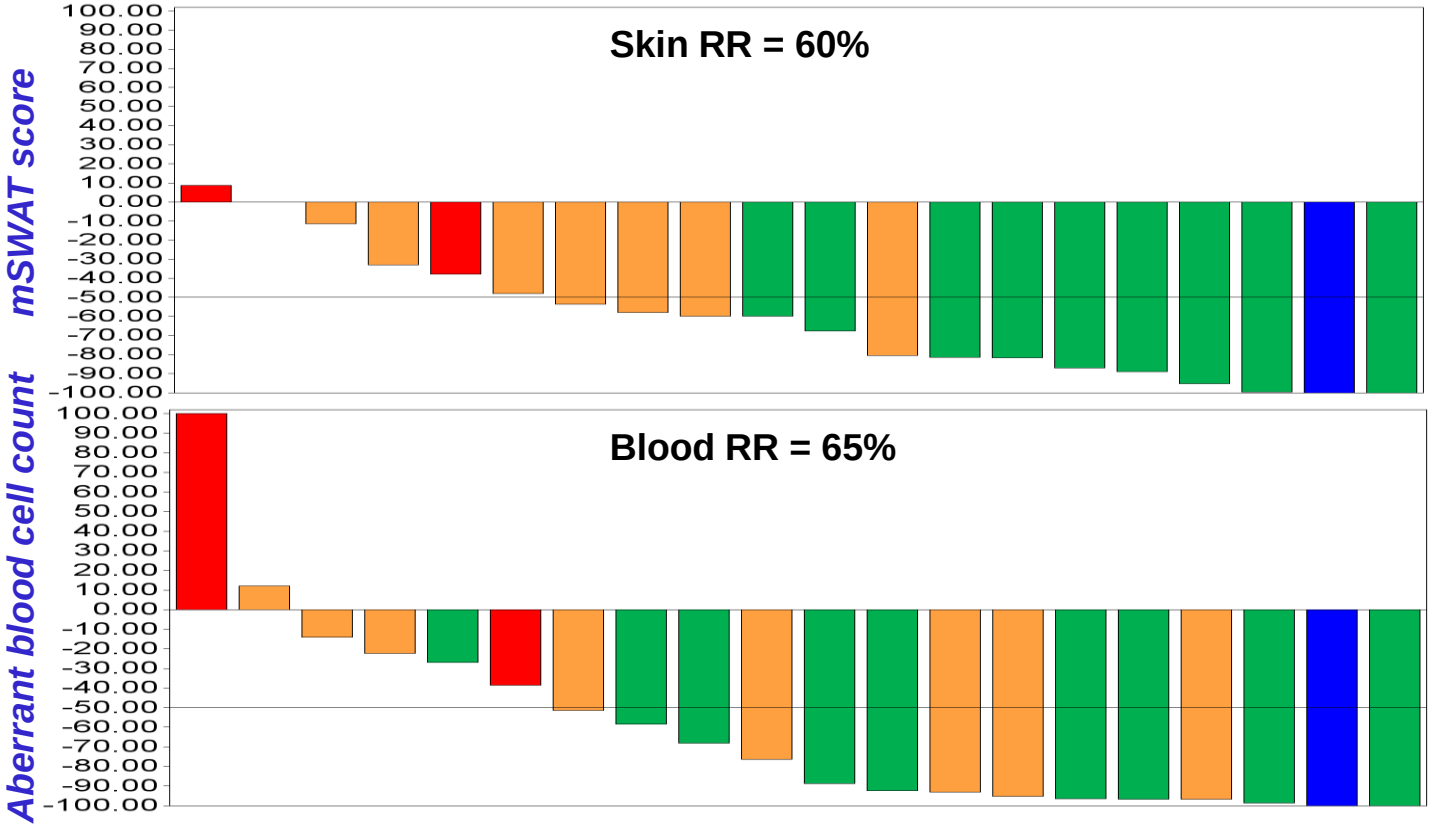
PRELIMINARY CLINICAL RESPONSE RESULTS

	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

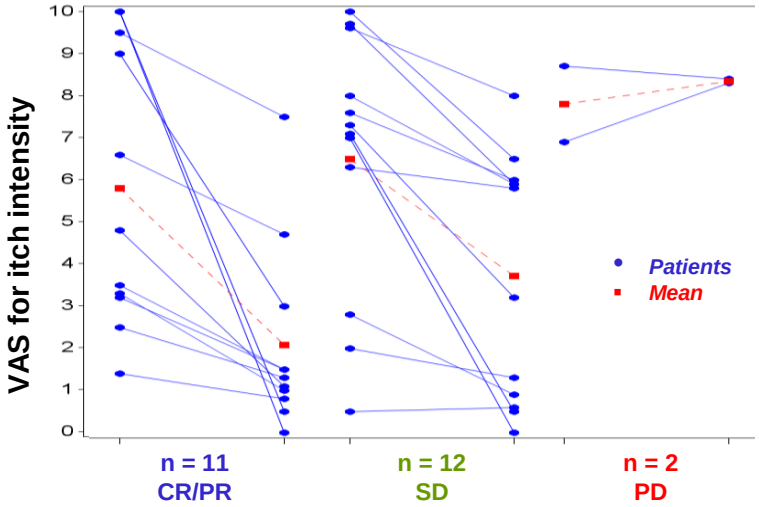


Best Global Response:

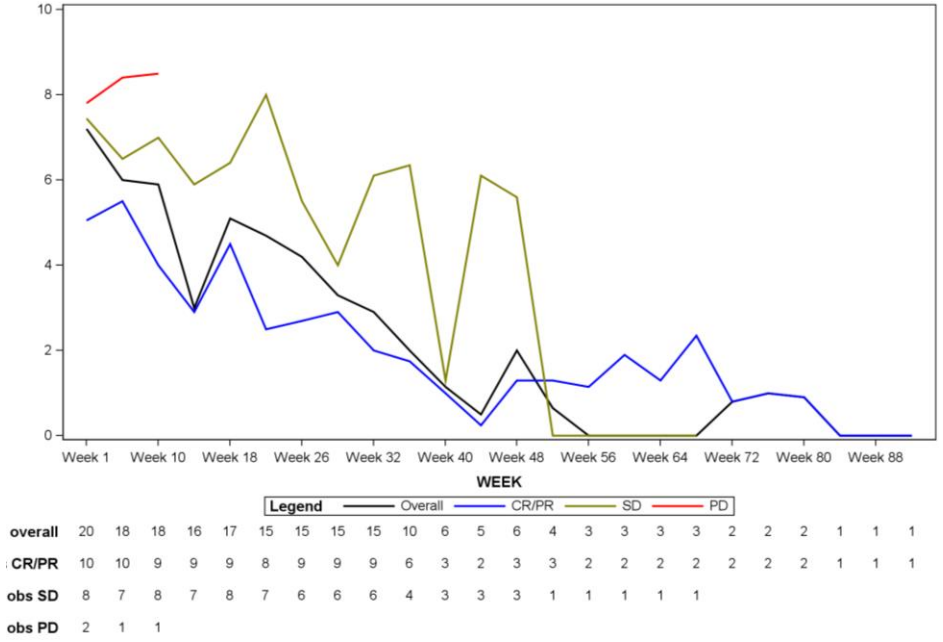
- CR
- PR
- SD
- PD

PRURITUS IMPROVEMENT BY VAS SCORE

Baseline vs Best change in VAS



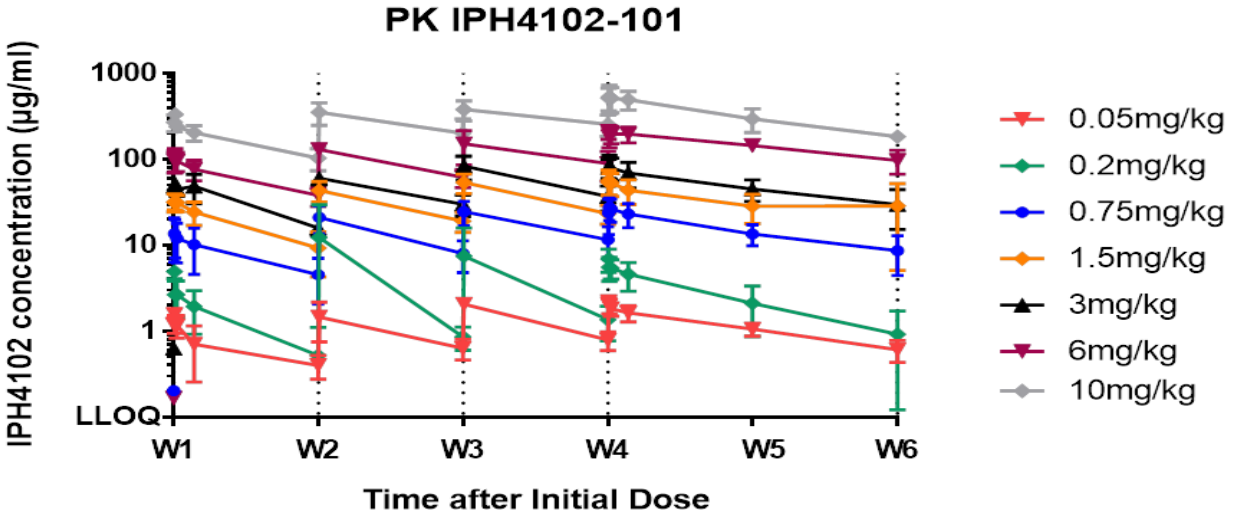
Median VAS change over time



overall	20	18	18	16	17	15	15	15	15	10	6	5	6	4	3	3	3	3	2	2	2	1	1	1
CR/PR	10	10	9	9	9	8	9	9	9	6	3	2	3	3	2	2	2	2	2	2	2	1	1	1
obs SD	8	7	8	7	8	7	6	6	6	4	3	3	3	1	1	1	1	1						
obs PD	2	1	1																					

VAS: Visual Analogue Scale

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)

IPH4102-101 HIGHLIGHTS
SAFETY, CLINICAL ACTIVITY AND PK

- 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 PK is dose-proportional from 0.75 to 10 mg/kg; 1 patient developed ADA
- Biomarker results were presented by M. Battistella *et al.*, Abstract O-27

- **Expansion cohorts started accruing in July 2017 at the flat dose of 750 mg**
- **As of today, 12 patients started treatment in the cohort expansion part**

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All our patients and their families…

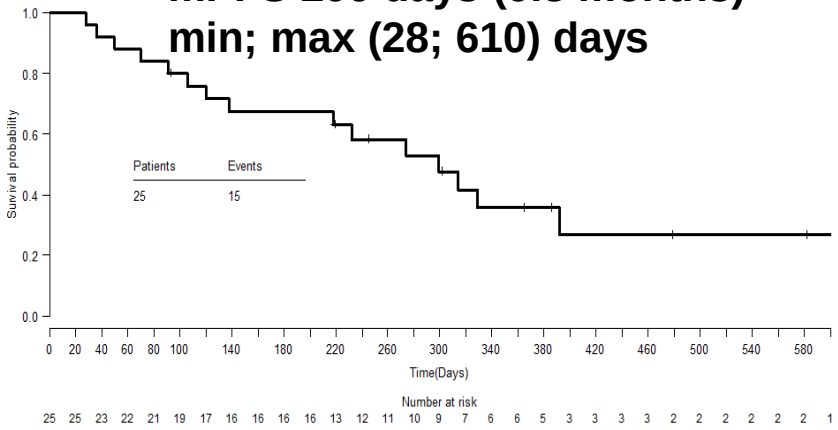
BACK-UP SLIDES

IPH4102-101

EFFICACY – PROGRESSION-FREE SURVIVAL

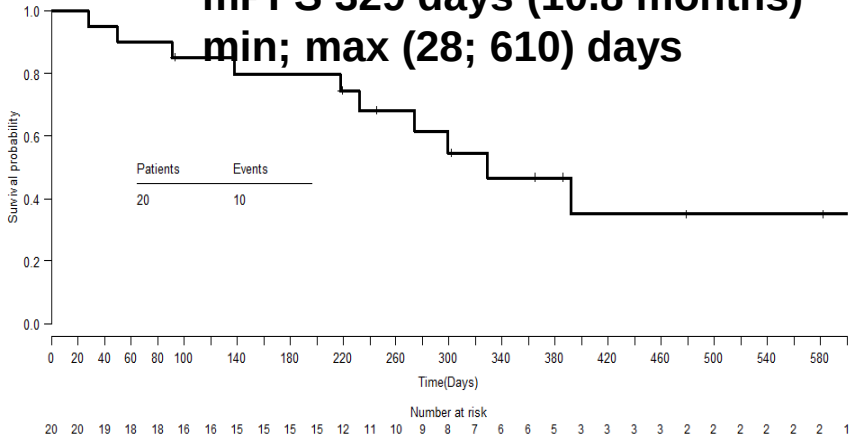
All Patients

mPFS 299 days (9.8 months)
min; max (28; 610) days



SS Patients

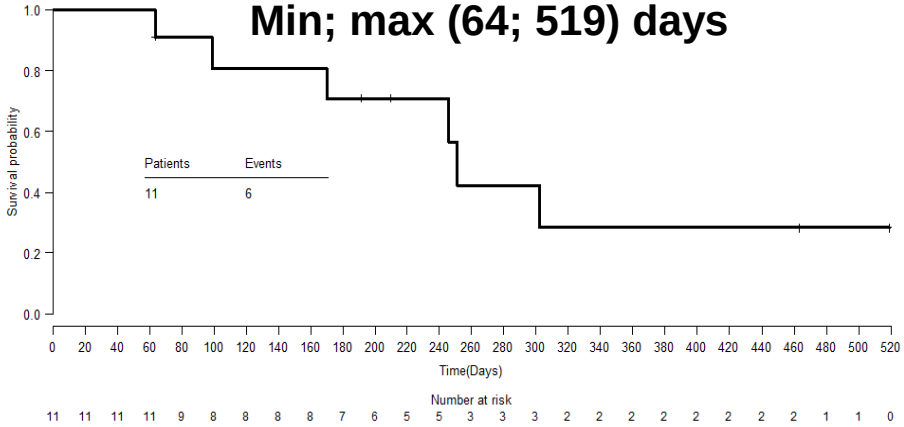
mPFS 329 days (10.8 months)
min; max (28; 610) days



EFFICACY – DURATION OF RESPONSE

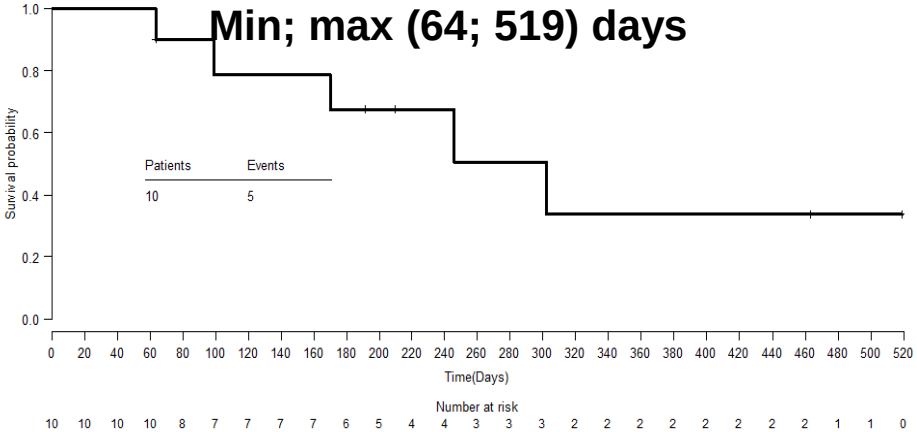
All Patients

mDOR: 251 days (8.2 months)
Min; max (64; 519) days



SS Patients

mDOR: 302 days (9.9 months)
Min; max (64; 519) days



PATIENT 01-013: SAE OF POSSIBLY RELATED HEPATITIS CASE

- SS diagnosed in March 2013; received multiple chemotherapies including CHOP, Gemcitabine, MTX
- IPH4102 administrations: March 2016 to May 2017 with escalating doses
- Best global response of PR; treatment discontinuation due to PD
- Grade 4 elevated transaminases observed 4 weeks after the last IPH4102 administration
- Workup of primary cytolytic hepatitis revealed no clear cause, in particular viral screen was negative except for HHV-6B (positive in the liver and blood)
- Patient died with hepatitis two weeks after
- Liver biopsy was suspicious of either viral infection or drug induced liver injury

- No significant change in liver enzymes was detected in any other patients of the study, across dose levels: ALT values over time