IPH4102 (an anti-KIR3DL2 antibody) in refractory cutaneous T cell lymphoma

SCAN ME

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Abstract

The aim of this phase 1 trial was to evaluate the tolerance and efficacy of IPH4102, a monoclonal antibody targeting KIR3DL2, expressed on cutaneous T cell lymphoma. IPH4102 selectively depletes tumor cells through antibody-dependent cell-cytotoxicity and -phagocytosis.

Thirty-five (35) Sézary Syndrome (SS) patients having failed ≥2 prior systemic therapies (txt) were included. IPH4102 was administered IV 4 times QW, then10 times Q2W then Q4W. KIR3DL2$^+$ cells were monitored in skin and blood by immunohistochemistry (IHC) and flow cytometry. Molecular Residual Disease (MRD) was measured by deep sequencing of the clonal TCR.

No dose limiting toxicity was identified and the maximum tolerated dose was not reached. 42.9% patients experienced confirmed global response. Median duration of response and progression free survival were 13.8 and 11.7 months. IPH4102 induced drastic elimination of KIR3DL2$^+$ aberrant cells in skin and blood. Decrease of KIR3DL2-expressing tumor cells in IHC after 4 weeks of treatment predicted clinical response 9 weeks later. MRD results confirmed the significant disappearance of the tumor clones in skin and blood.

In conclusion, this study shows a favorable safety profile and clinical activity of IPH4102 in relapsed/refractory SS. Based on these results, the FDA granted IPH4102 Fast Track designation for the treatment of relapsed/refractory SS. A phase 2 study is currently enrolling, to confirm the clinical activity in SS and to evaluate the potential of IPH4102 in other T-cell malignancies.

IPH4102-101 Study Design

Dose-escalation

- 10 dose levels (up to 10mg/kg) accelerated 3+3 design
- All CTCL subtypes
- ≥ 2 prior systemic therapies
- KIR3DL2 ≥5% in skin and/or blood

Cohort expansion

- Recommended Phase 2 dose (RP2D) (750mg)
- SS and tMF only
- ≥ 2 prior systemic therapies
- Any KIR3DL2 expression level

4 admin. weekly — W5 — **10 admin. Q2W** — W26 — **N admin. Q4W**

- **Dosing regimen**, until progression or unacceptable toxicity
- Intra-patient dose-escalation allowed after week 5 (W5) in the dose-escalation part

Study objectives & Baseline Disease Characteristics

- **Primary objective:** determination of Maximal Tolerated Dose (MTD) and RP2D, safety
- **Secondary objectives**:
  - ✓ Overall Response Rate (ORR)(*Olsen 2011*), duration of response (DOR) and Progression-Free Survival (PFS)
  - ✓ PK and immunogenicity
  - ✓ Quality of Life (QOL): SkinDex29 & pruritus (Visual Analogue Scale)
- **Exploratory objectives**:
  - ✓ Early changes (W5) in KIR3DL2$^+$ cells, and in MRD, in skin and blood

Focus on patients with Sézary Syndrome	**Total N = 35**
Median age [years] (range)	70 (37 – 90)
Evidence of LCT*, n (%)	7 (20%)
KIR3DL2 expression, n (%) - *Skin* - *Blood* - *Skin and/or blood*	 *27 (77%)* *33 (94%)* *33 (94%)*
Med. time from diagnosis [months] (range)	23 (6 – 268)
Med. N. of prior systemic therapy (range) - *Treated with IPH4102 as ≥ 5 systemic txt*	2 (1 – 9)^ *12 (35%)*
Prior txt with HDAC inhibitors, n (%)	13 (37%)
Prior txt with mogamulizumab, n (%)	7 (20%)

* LCT: large cell transformation based on central testing on frozen tissue.
^ One patient had a protocol violation, treated with only one prior line of systemic therapy.

Results

IPH4102 Safety *(data cut-off: Oct. 15, 2018)*

Dose escalation: **no DLT / MTD not reached**

RP2D = 10 mg/kg - 750 mg flat dose for cohort expansion

Common AEs	All AEs		Related AEs*	
	All grades	Grade 3-4	All grades	Grade 3-4
Peripheral edema	10 (29%)	0	0	0
Asthenia	9 (26%)	0	5 (14%)	0
Fatigue	8 (23%)	0	3 (9%)	0
Cough	7 (20%)	0	0	0
Pyrexia	7 (20%)	0	3 (9%)	0
Arthralgia	6 (17%)	0	2 (6%)	0
Lymphopenia	5 (14%)	2 (6%)	5 (14%)	2 (6%)
Diarrhea	5 (14%)	0	1 (3%)	0

Only 3 patients (9%) stopped treatment for an AE.

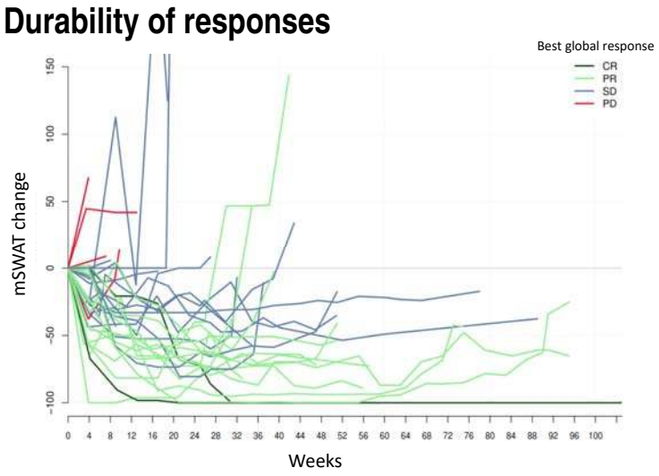
Four patients developed 5 possibly related grade ≥ 3 AEs: grade 5 hepatitis (n=1)**, grade 4 sepsis (n=1), grade 3 lymphopenia (n=3), grade 3 hypotension (n=1).

* According to investigator assessment

** 6 weeks after stopping IPH4102, evidence of HHV-6B infection

IPH4102 Clinical Efficacy *(data cut-off: Oct. 15, 2018)*

Durability of responses

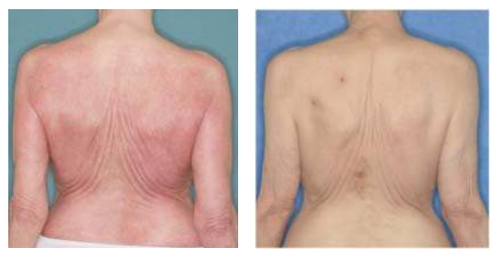


Subgroup Analysis, Response Rate

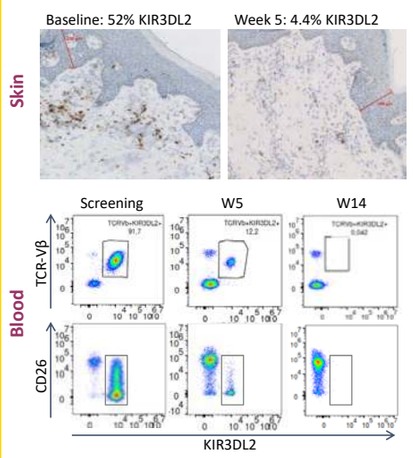
	All SS N=35	SS without LCT n=28	prior txt with mogamulizumab n=7
Best global response*	42.9% (28.0 – 59.1)	53.6% (35.8 – 70.5)	42.9% (15.8 – 75.0)
- CR	2 (5.7%)	2 (7.1%)	0
- PR	13 (37.2%)	13 (46.5%)	3 (42.9%)
- SD	16 (45.7%)	11 (39.3%)	3 (42.9%)
- PD	4 (11.4%)	2 (7.1%)	1 (14.2%)
Duration of Response**	13.8 (7.2 – NR)	13.8 (7.2 – NR)	13.8 (7.2 – NR)
Progression Free Survival**	11.7 (8.1 – NR)	12.8 (8.2 – NR)	16.8 (8.1 – NR)

* Mean (95% CI) ** Median [months] (95% CI) NR: Not Reached
LCT: Large Cell Transformation tested centrally on frozen tissue

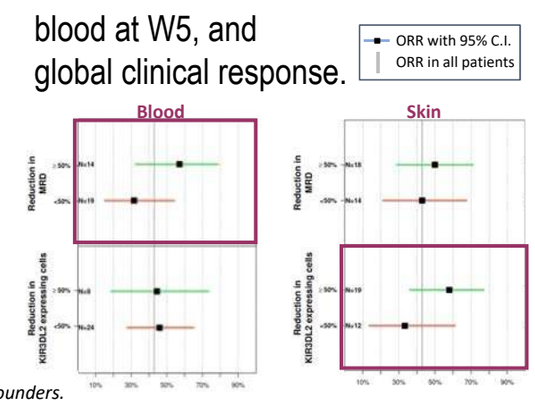
Representative example:
77-year-old woman, received 6 prior lines of systemic txt incl. bexarotene, IFN-α, HDAC-inhibitor and mogamulizumab.
In global PR since week 10, lasting 1 year and 8 months (Starting dose : 0.05 mg/kg).
Baseline mSWAT: 80.5/1/0 (left picture)
At Week 64, mSWAT: 5.2/0/0 (right picture)



Exploratory Biomarkers



Association between reduction in KIR3DL2$^+$ cells or MRD in skin and blood at W5, and global clinical response.



Exploratory analyses unadjusted for possible confounders.

Quality of Life

SkinDex29

Best response in skin, and overall

Conclusions

IPH4102 is safe and well tolerated in heavily pretreated relapsed/refractory SS. IPH4102 shows impressive clinical activity, demonstrated by high and durable response rate and long PFS. IPH4102 substantially improved QOL even in patients with stable disease. Exploratory biomarker analyses show relevant pharmacodynamics effects of IPH4102 in skin and in blood.

Based on these results, the FDA granted IPH4102 Fast Track designation for the treatment of relapsed/refractory SS. IPH4102 is now being evaluated further in an international multi-cohort phase 2 study, TELLOMAK (NCT03902184), in patients with various relapsed/refractory T-Cell Lymphomas.