BIOMARKERS OF PHARMACOLOGICAL AND CLINICAL ACTIVITY OF IPH4102, FIRST-IN-CLASS HUMANIZED ANTI-KIR3DL2 MAB, IN A PHASE I STUDY IN PATIENTS WITH RELAPSED/REFRACTORY CTCL

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IPH4102-101

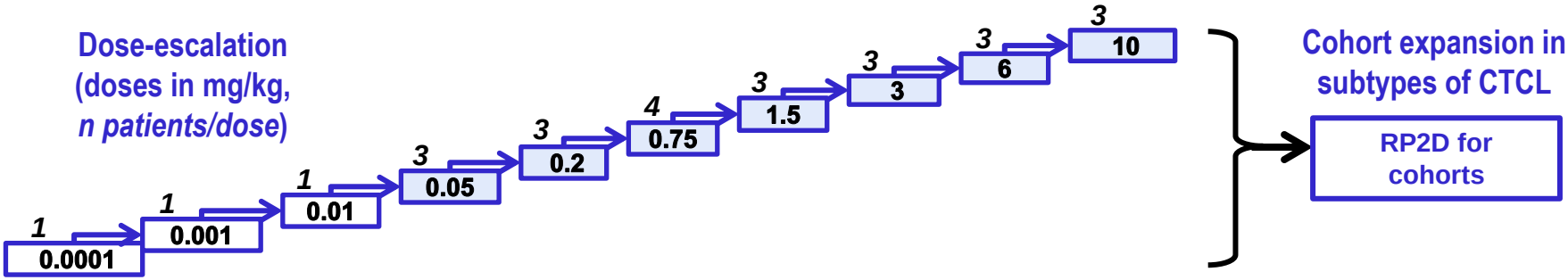
KIR3DL2 IS A THERAPEUTIC TARGET IN CTCL

- KIR3DL2 belongs to the Killer Ig-like Receptor family of receptors that modulate NK and T cell activity
- KIR3DL2 is expressed on ~30% of normal NK and <10% normal T cells
- KIR3DL2 is expressed on CTCL cells (skin lesions and blood aberrant cells)
  - > Irrespective of disease clinical stage
  - > With a higher prevalence in Sézary syndrome (SS), $CD30^+$ LPD and Mycosis fungoides with large-cell transformation
- KIR3DL2 may have prognostic significance in SS

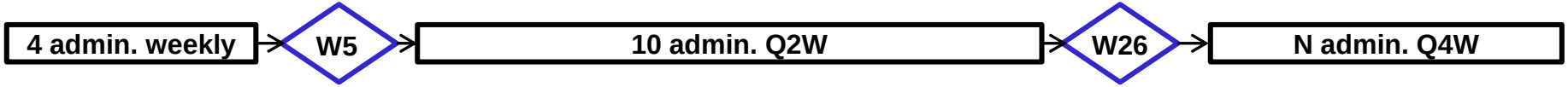
- IPH4102 is an anti-KIR3DL2 IgG1 antibody that was selected and designed to specifically target KIR3DL2 and deplete $KIR3DL2^+$ cancer cells

Marie-Cardine *et al*, 2014, Cancer Res. 74(21) - Battistella *et al*, 2016, Br J Dermatol. 175(2) - Hurabielle *et al*, 2017, Clin Cancer Res.

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

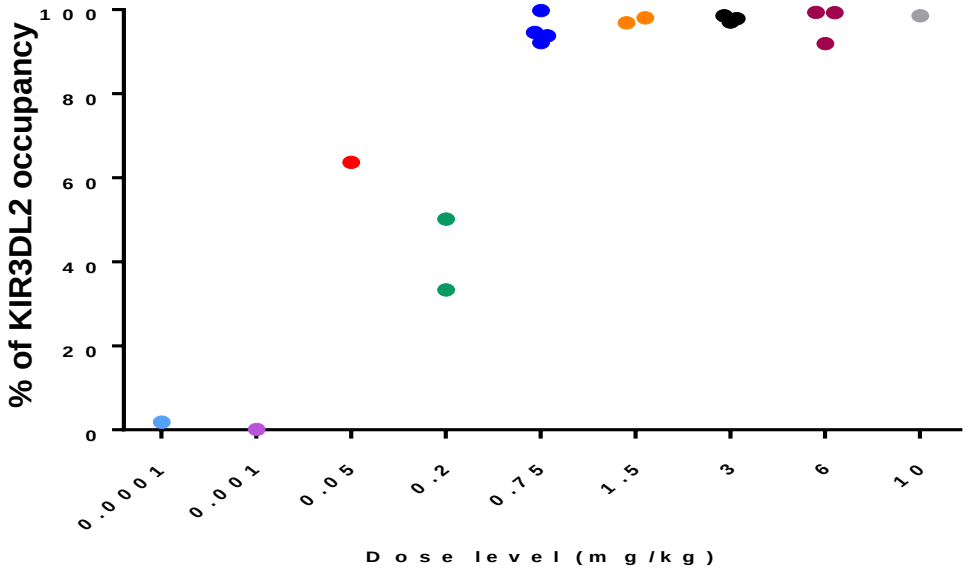


METHODS FOR BIOMARKER ANALYSIS

- Immuno-monitoring in blood by flow cytometry:
  - > Proportion of KIR3DL2 receptor occupancy by IPH4102
  - > Absolute counts of aberrant cells ($CD26^-$ and/or $CD7^-$ CD4 T cells), clonal CD4 T cells (defined by their Vβ chain), $KIR3DL2^+$ CD4 T cells
  - > $KIR3DL2^+$ “normal” lymphocytes (NK, CD8 T cells)
- *Ex vivo* function of NK cells at baseline in autologous ADCC assay (SS patients)
- Immuno-histochemistry (IHC) staining of KIR3DL2-expressing cells and other immune cell subsets (CD4, CD8,…) in skin biopsies

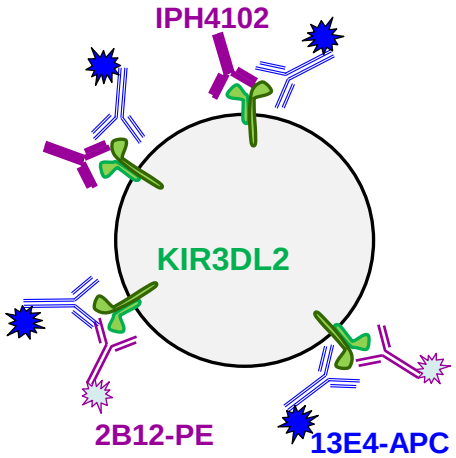
KIR3DL2 IS 100% OCCUPIED BY IPH4102 AT DOSES ≥ 0.75 MG/KG

KIR3DL2 occupancy on blood CD4⁺ T cells
1 week after the 1st administration of IPH4102



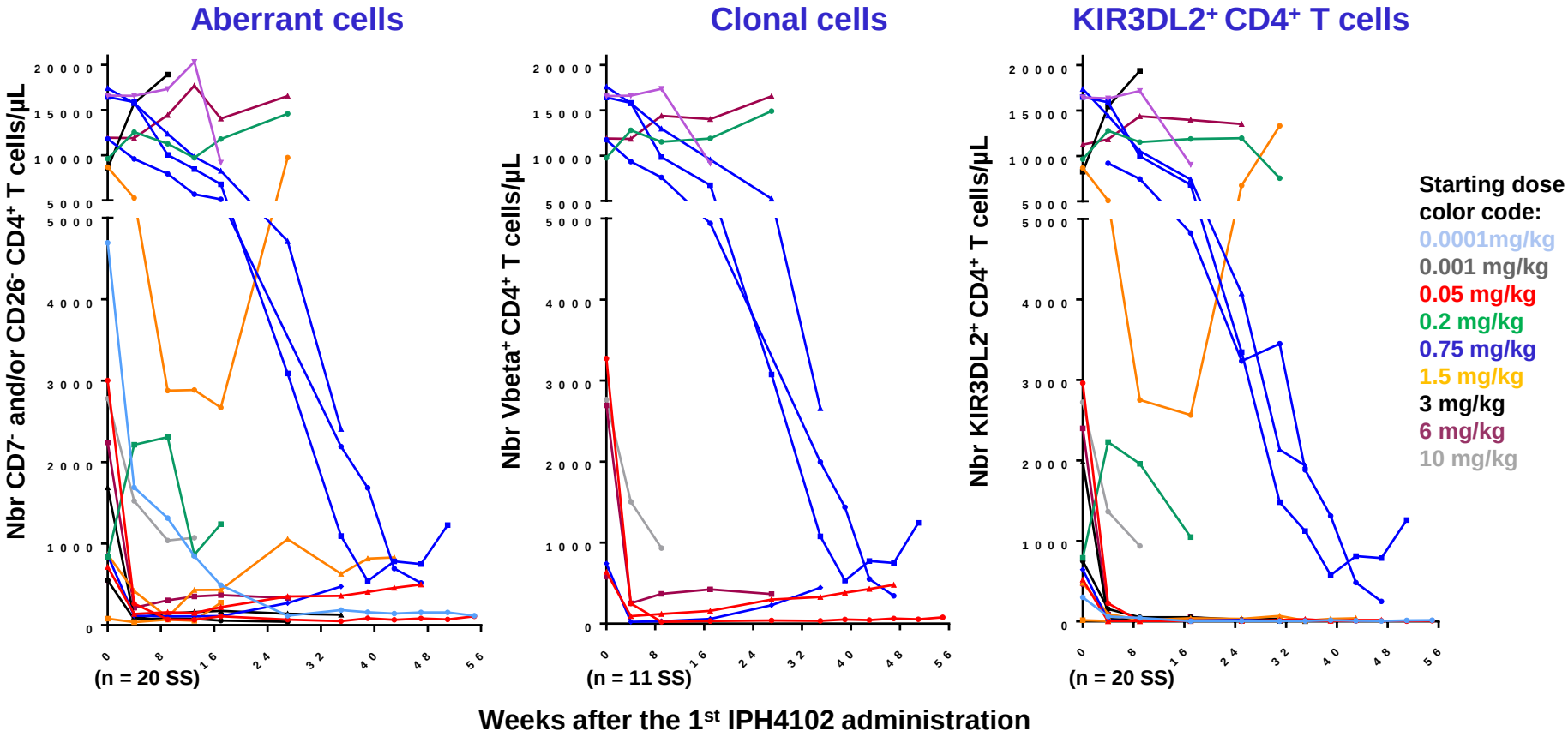
Available anti-KIR3DL2 clones:

- 2B12, same as IPH4102
- 13E4, binding to a different epitope than 2B12, to determine the “100% level”



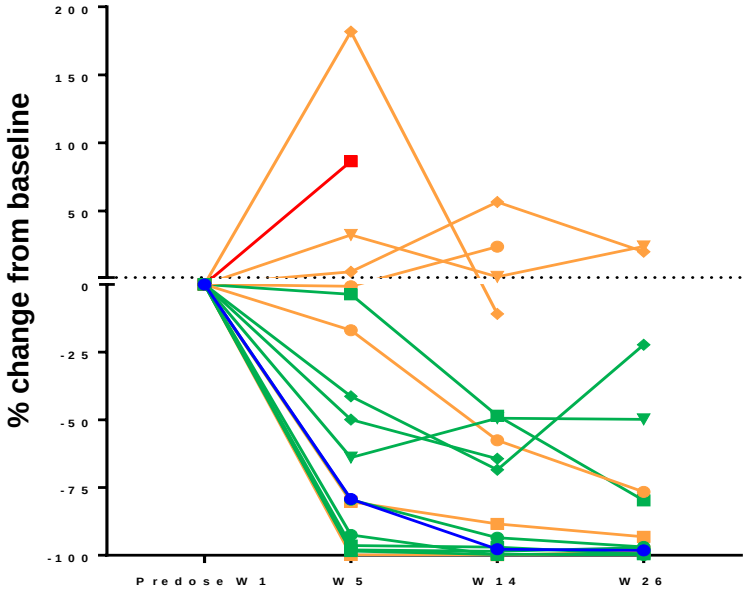
Only applicable to SS patients with > 5% of KIR3DL2 on CD4⁺ T cells

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

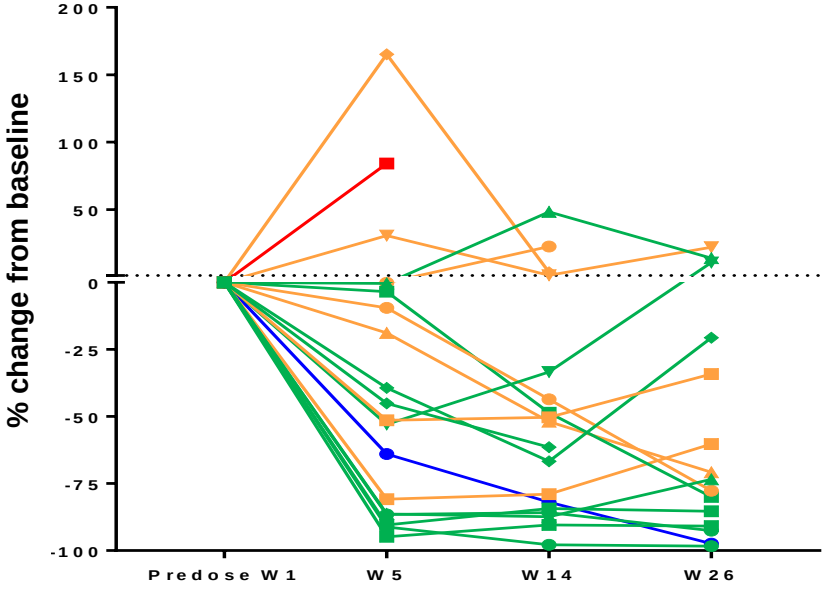


ABERRANT BLOOD CELLS CHANGES FROM BASELINE TEND TO BE RELATED TO GLOBAL CLINICAL RESPONSE

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



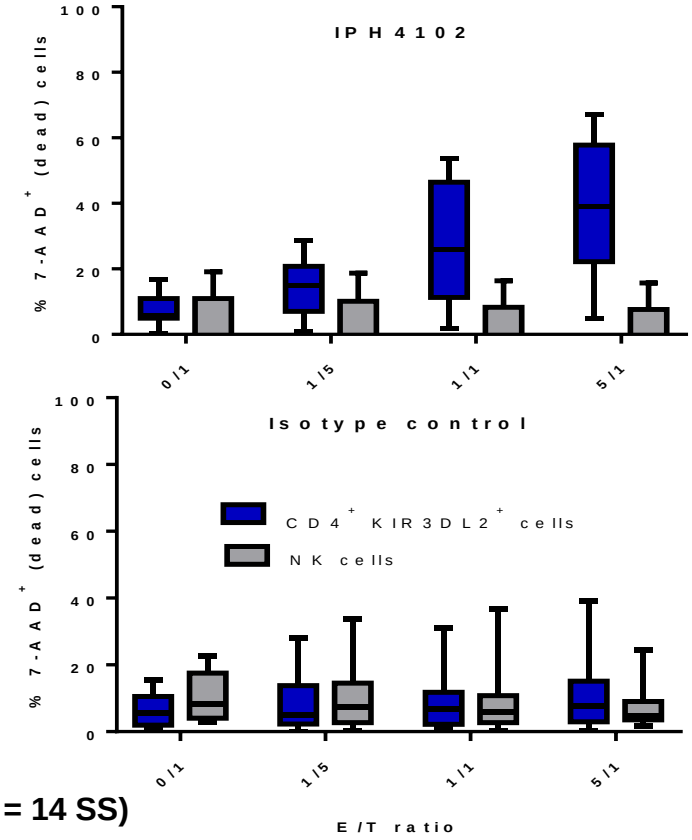
Aberrant CD7^{-} and/or CD26^{-} CD4^{+} T cells *versus* best Global Response



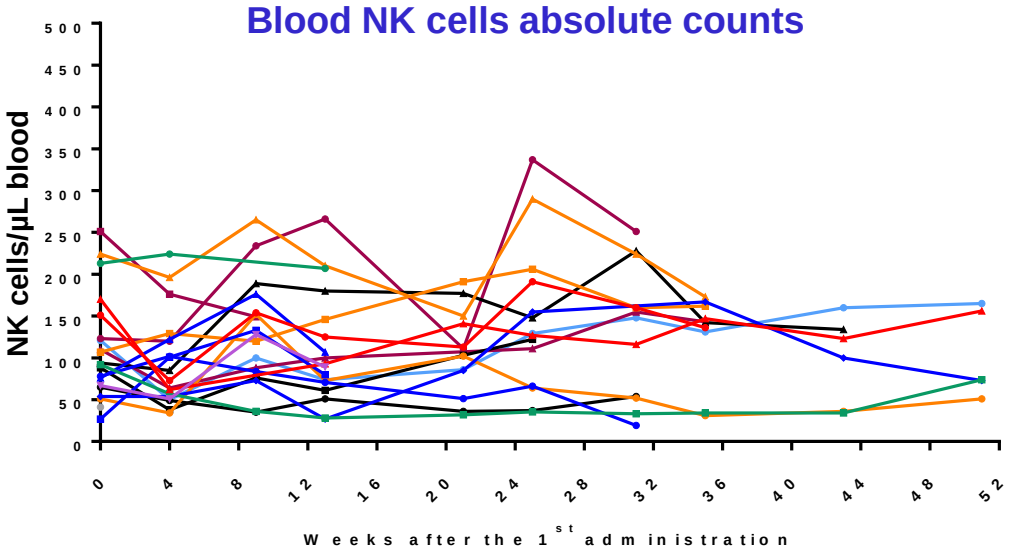
Best global response: CR PR SD PD

(n = 20 SS)

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



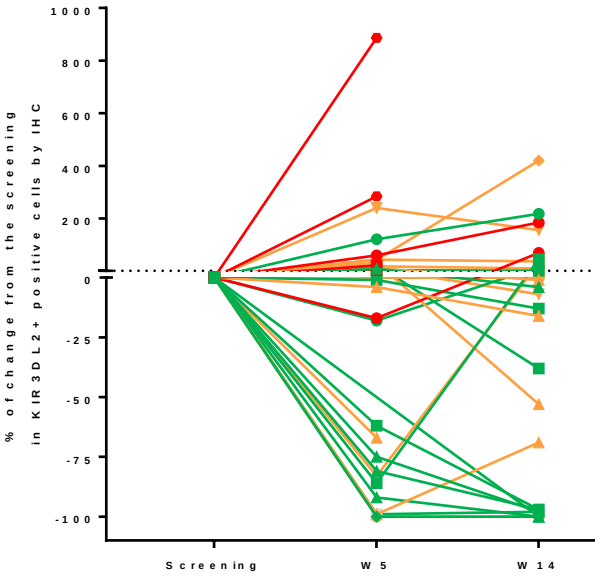
(n = 14 SS)



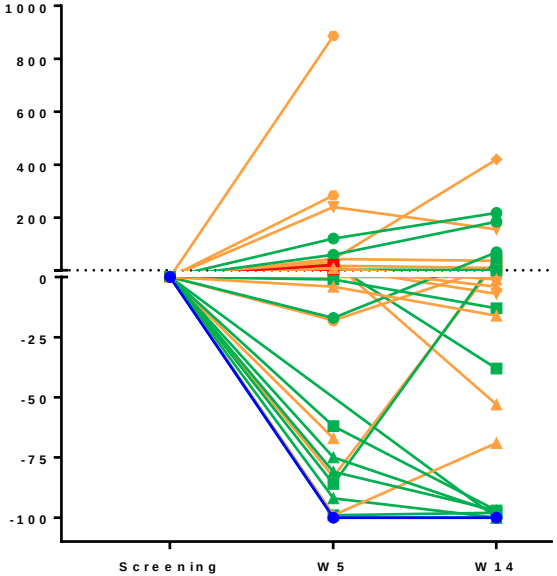
(n = 20 SS)

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

Relation to response in skin at W14

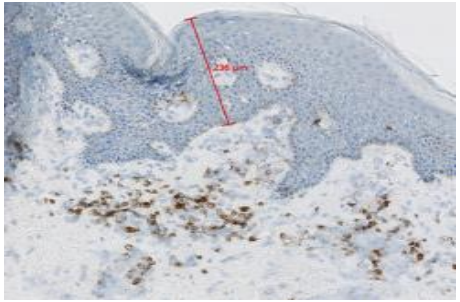


Relation to best Global Response

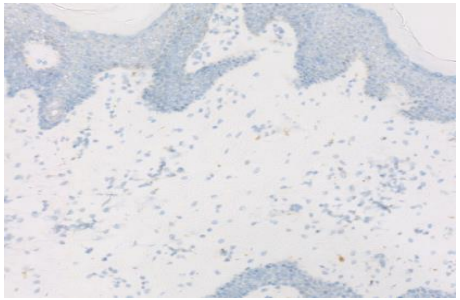


CR PR SD PD

SCR: 52% KIR3DL2⁺ cells



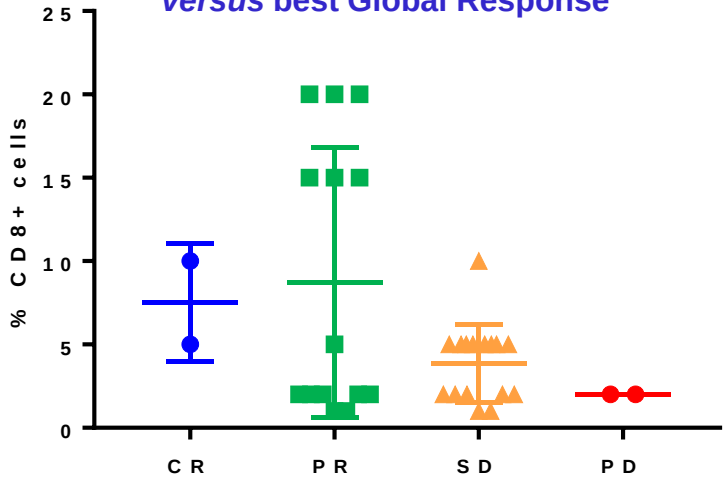
Week 14: 0.2%



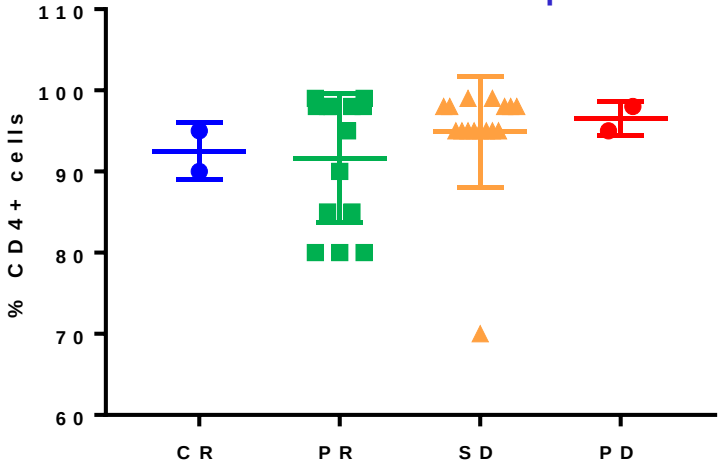
1 plot / biopsy, 1 or 2 biopsies / patient – n = 22 patients - percentage of KIR3DL2⁺ cells among mononuclear cells

HIGHER CD8⁺ CELLS AT SCREENING IN LESIONS TEND TO BE RELATED TO GLOBAL CLINICAL RESPONSE

%CD8⁺ cells in skin biopsies at Screening *versus* best Global Response



%CD4⁺ cells in skin biopsies at Screening *versus* best Global Response

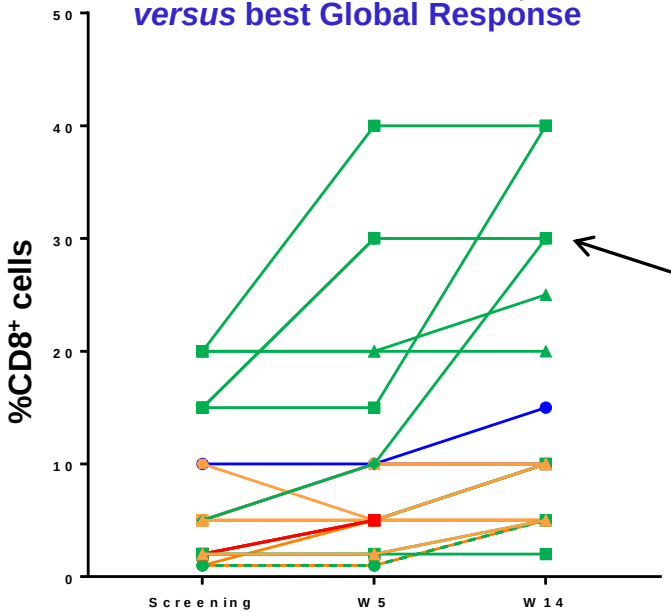


Best global response: CR PR SD PD

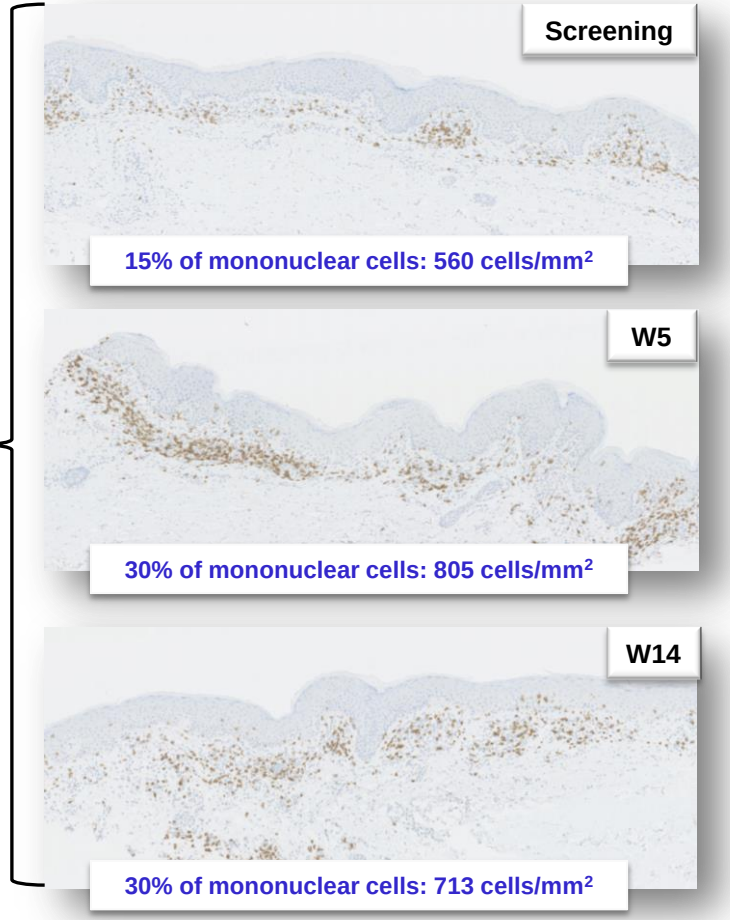
1 plot / biopsy, 1 or 2 biopsies / patient – n = 22 patients - percentage of CD4 or CD8⁺ cells among mononuclear cells

PATIENTS WITH CR/PR SHOW AN INCREASE OF %CD8⁺ IN THE SKIN

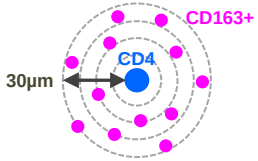
Variation of %CD8⁺ cells in skin biopsies during treatment *versus* best Global Response



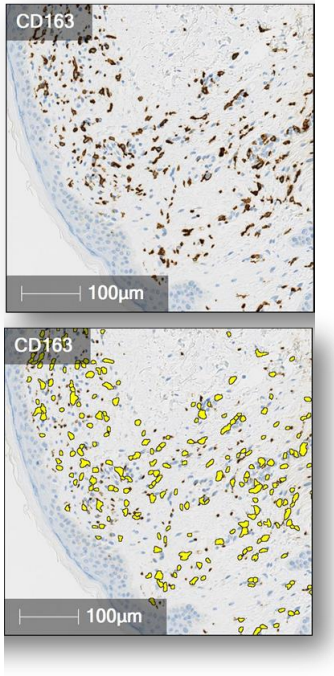
Best global response: CR PR SD PD

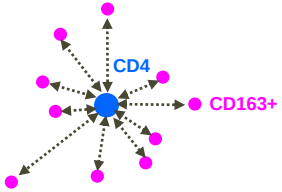


ANALYSIS OF CD163+ CELL CHANGES IN THE TUMOR MICROENVIRONMENT DURING IPH4102 TREATMENT

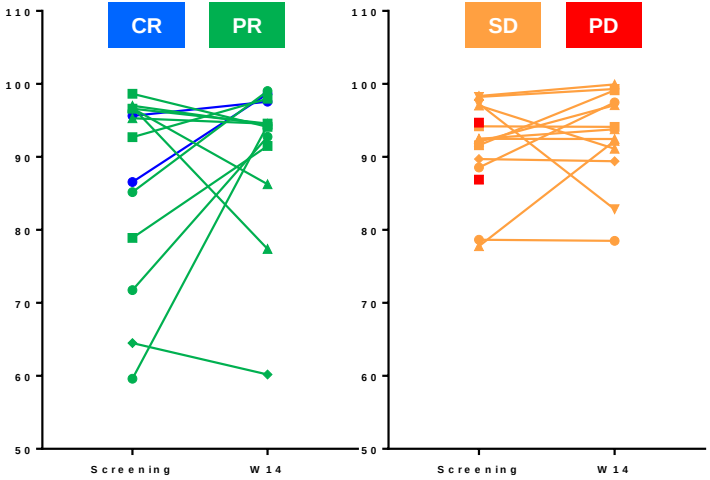


HALO software analysis

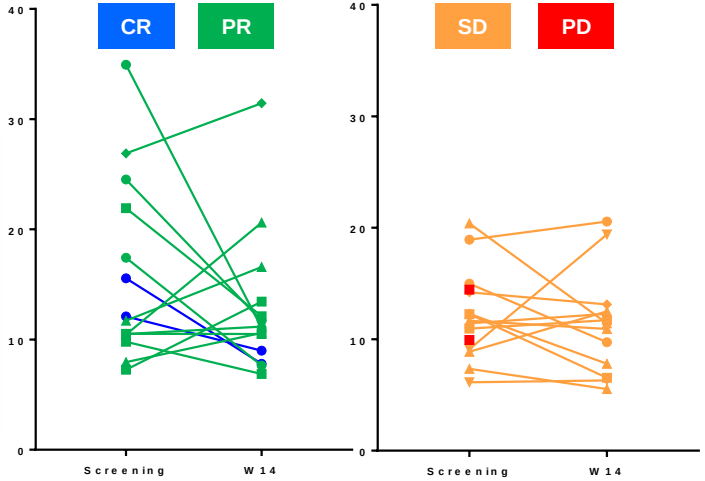




%CD163+ within 30 µm of CD4+ cells in skin biopsies *versus* best Global Response



CD163+ average distance (µm) to CD4+ cells in skin biopsies *versus* best Global Response



CONCLUSIONS AND PERSPECTIVES

- IPH4102 was evaluated in a dose-ranging first-in-man Phase 1 trial in relapsed advanced CTCL patients and was found safe and clinically active across all doses tested (see Bagot *et al* abstract O-53)
- KIR3DL2 full occupancy on blood CD4 T cells by IPH4102 is achieved at doses ≥ 0.75 mg/kg
- Sézary patient NK cells are functional pre-dose and are not decreased during treatment
- 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
- Some biomarkers in blood and skin tend to be associated with global clinical response
  - > Decrease in KIR3DL2^{+} cells in blood and skin during treatment
  - > Higher CD8^{+} cells in lesions at baseline and increase during treatment
- These results deserve to be confirmed in the cohort-expansion part of the study, where additional patients will be treated at the RP2D

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All our patients and their families…