NON CLINICAL EFFICACY & SAFETY PROFILE OF IPH4102, ANTI-KIR3DL2 MAB IN CTCL

TCL MEETING,
BOLOGNA
APRIL 2015

KIR3DL2 & IPH4102 IN CTCL

INTRODUCTION

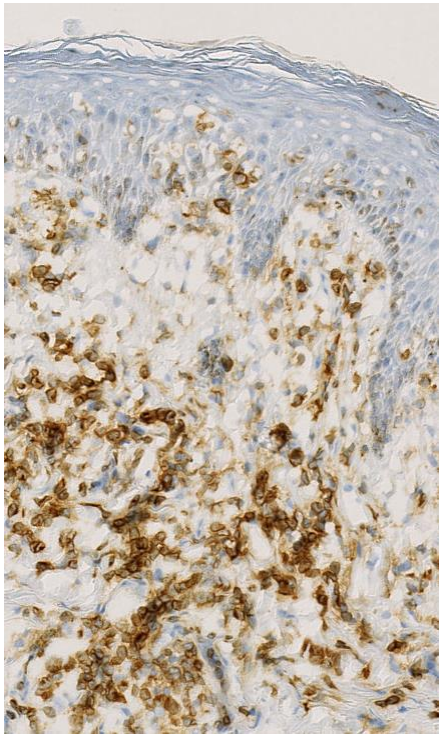
KIR3DL2, UNIQUE THERAPEUTIC TARGET IN CTCL

- Inhibitory receptor of the Killer Immunoglobulin-like family
- In healthy individuals, KIR3DL2 is expressed on ~25% NK cells and < 15% T cells
- KIR3DL2 is not found on the FDA panel of 42 human tissues (IHC study)
- KIR3DL2 is expressed on 50-90 % of CTCL cells irrespectively of disease stage and subtype (IHC study, N = 89 patients)
- Skin-resident $CD4^+$ T cells express KIR3DL2 and may be the normal counterparts of CTCL (Sako *et al*, 2014 CytomA)

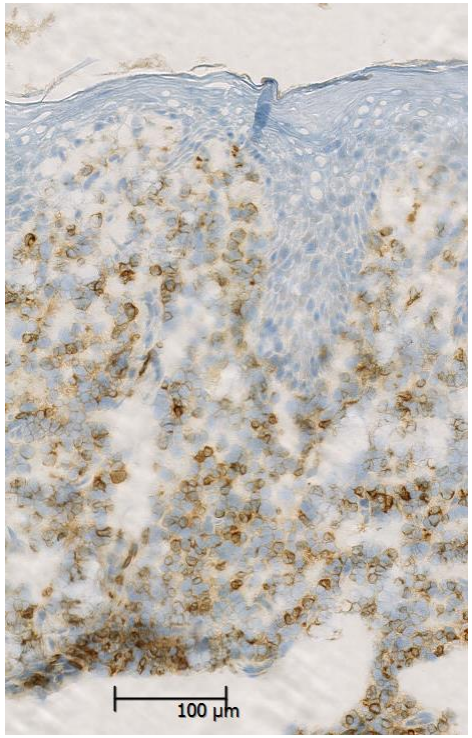
KIR3DL2 EXPRESSION ON ADVANCED CTCL CUTANEOUS LESIONS AND LEUKEMIC FORMS

KIR3DL2 IHC staining on skin biopsies

Grade IIIb Sézary Syndrome
86.5% KIR3DL2⁺ tumor cells

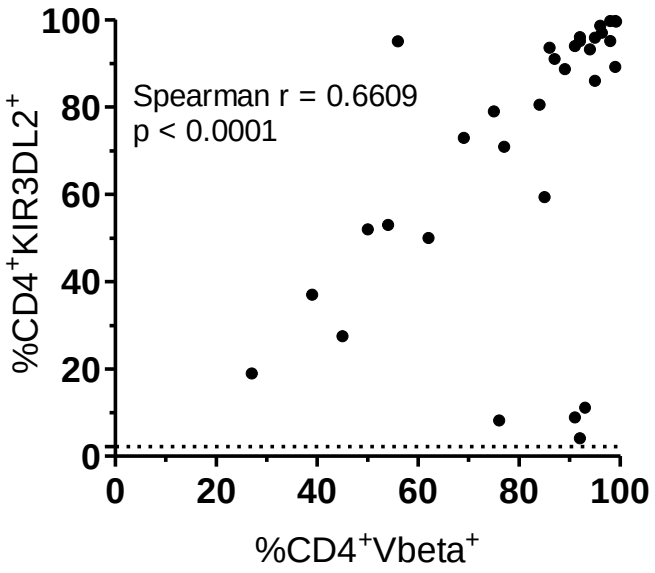


Grade IIb transformed MF
83% KIR3DL2⁺ tumor cells



Correlation of KIR3DL2 & TCR-Vβ expression in flow cytometry

(n = 32 Sézary pts)



Marie-Cardine *et al.*, Cancer Res. 2014

IPH4102 THERAPEUTIC CANDIDATE DEFINITION

IPH4102:

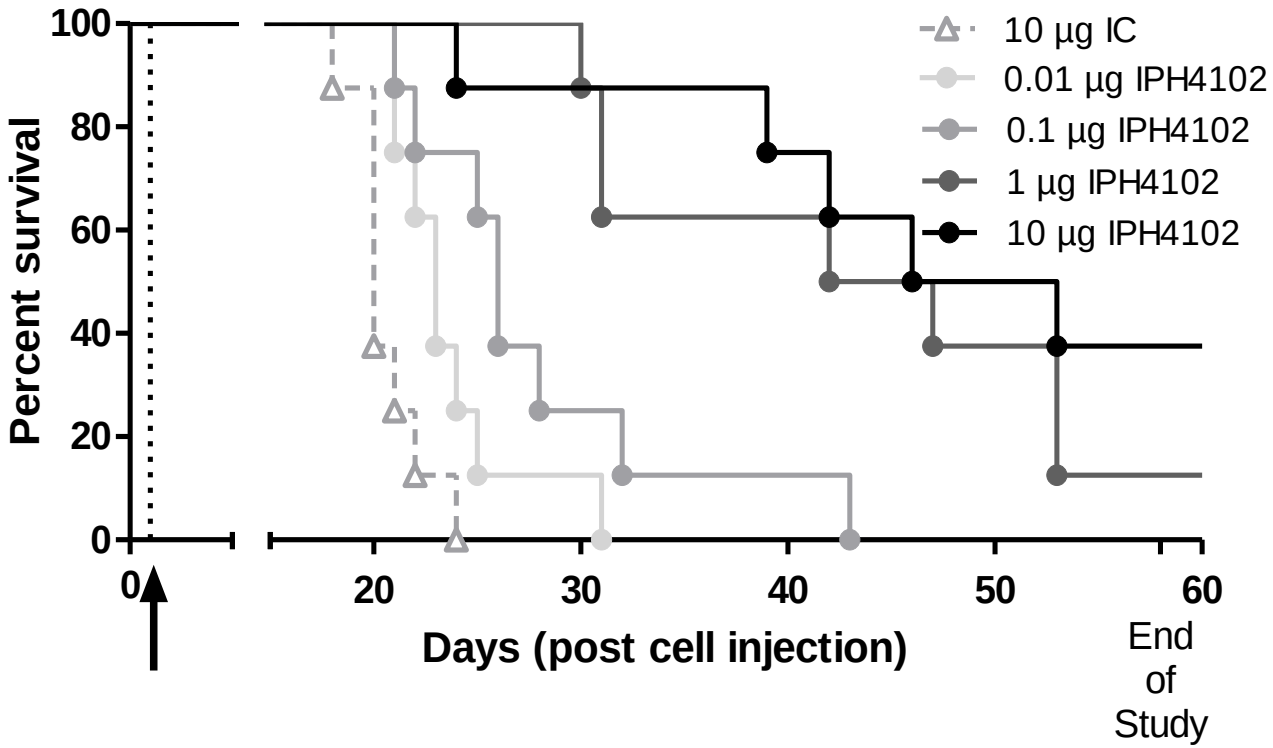
- Selectively binds human KIR3DL2 with high affinity
  - > No cross-reaction to other human KIRs
- Is a humanized IgG1 designed to deplete KIR3DL2-positive tumor cells
- Demonstrates compelling efficacy in non clinical studies (large set of *in vitro*, *in vivo* and *ex vivo* models*)*
  - > *Main MOA include ADCC and ADCP*
  - > *Reduces tumor growth and improves survival in mouse xenograft models of KIR3DL2^{+} tumors*
  - > *Induces killing of primary CTCL tumors in the presence of patient autologous NK cells*
- Distinct anti-KIR3DL2 mAbs developed for biomarker purposes (IHC and flow cytometry)

IPH4102 IN CTCL

NON CLINICAL EFFICACY SUMMARY

IPH4102 EFFICACY IN MOUSE IV MODELS

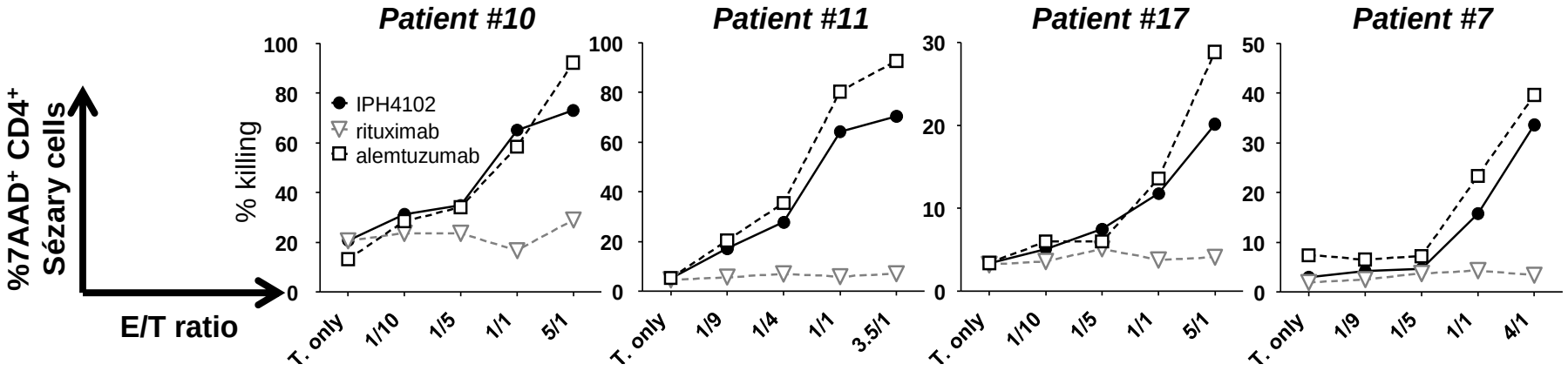
IPH4102 improves survival
& efficacy is dose-dependent



Mice: SCID (n = 8)
RAJI-KIR3DL2: 5 M IV at D0
IPH4102: single IV admin. at D1
Read-out: survival

IPH4102 EFFICACY *EX VIVO:* AUTOLOGOUS ADCC

EFFICACY RESULTS



IPH4102 as potent as alemtuzumab in *ex vivo* autologous ADCC assays

mAb: 10 µg/mL
Incubation time: 4 – 6 hours
Read-out: 7AAD incorporation
KIR3DL2 sites per cell: 1,000 to 4,000
%KIR3DL2+ cells among CD4+ > 85%
Total n = 15 patients

Marie-Cardine A. *et al*, Cancer Res. 2014

IPH4102 IN CTCL

RESULTS OF IND-ENABLING NON CLINICAL SAFETY STUDIES

IPH4102, 1ST-IN-CLASS ANTI-KIR3DL2 ANTIBODY

Prior to launching the Phase I clinical of IPH4102 in CTCL patients, regulatory non clinical safety studies were performed, which comprised 3 parts:

- Non-GLP and **GLP toxicology** studies in the non human primate (NHP)
- **Safety Pharmacology** to assess the risk of unintended and uncontrolled immune activation
- First Human dose calculation based on a MABEL strategy

NON CLINICAL SAFETY ASSESSMENT IN THE POST "TGNero" ERA

- TGN1412: superagonist anti-CD28 mAb intended to be developed in cancer and inflammatory diseases
- Classical non clinical safety evaluation failed at predicting the actual immunological risk and at calculating a safe starting dose
- TGN1412 Phase I trial turned into a catastrophe after infusion of the 1st dose… with massive cytokine storm and lymphocyte proliferation that almost killed the patients
- Revised regulatory guidelines state:
  - To qualify animal species for toxicology studies based on expression pattern and *function of the target*
  - To perform specific *in vitro* assays to assess potential immuno-toxicological risk (in solid phase and/or cross-linking of mAbs targeting immune receptors)
  - To calculate the first dose in Human based on a Minimal Anticipated Biological Effect Level (MABEL) in a relevant system, rather than based on a NoAEL in animals

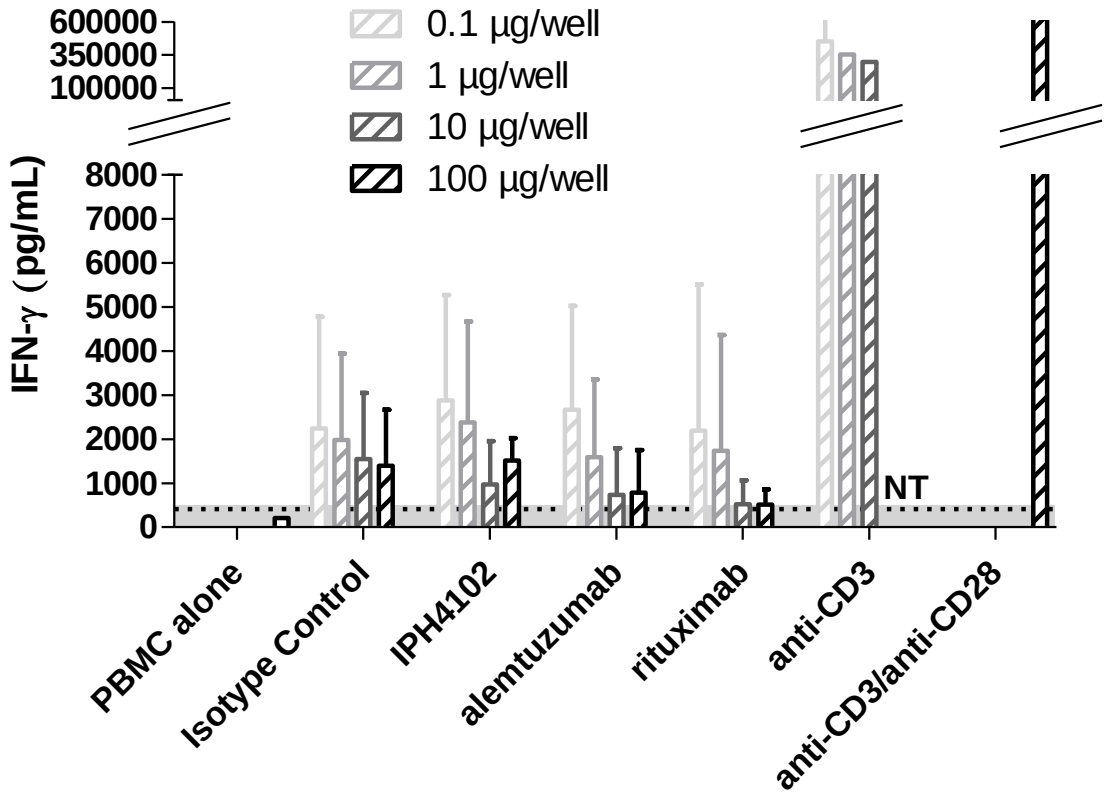
1- 28-DAY GLP TOXICOLOGY STUDY IN THE NHP

- **Design**:
  - > Cynomolgus monkey validated as phenotypically and functionally relevant species to evaluate IPH4102 toxicology
  - > Dose levels 0, 5, 50 and 100 mg/kg, 4 times weekly
  - > Full clinical, blood biochemistry, hematology, CNS and cardiologic evaluation
  - > At sacrifice (1 week after last dose): full anatomo-pathology
  - > Toxicokinetics (TK), Anti-Drug Antibodies (ADA), immunomonitoring of blood cells by flow cytometry + follow-up of KIR3DL2^{+} cells in quantitative RT-PCR
- **Results**:
  - > No clinically meaningful, safety-related finding, including in anatomo-pathology
  - > No ADA, exposure to IPH4102 as planned (dose-related PK)
  - > In qRT-PCR, dose-related decrease in KIR3DL2-gene expressing cells identified
  - > No Observed Adverse Effect Level (NOAEL) = 100 mg/kg 4 times weekly

2- IMMUNO-TOXICOLOGICAL RISK ASSESSMENT

- **Objective**
  - Assess a potential risk of unintended and uncontrolled immune activation, ie induction of lymphocyte proliferation and of massive release of cytokines when cross-linked, in the presence of human PBMC
- **Results**
  - No lymphocyte proliferation induced by IPH4102 in the chosen experimental conditions (whereas anti-CD3 and anti-CD3/anti-CD28 mAbs do) (PBMC from n = 5 donors)
  - Moderate cytokine/chemokine release (PBMC from n = 5 donors: MIP1β, TNFα, INFγ, MCP1, IL8 and IL6) (see next slide)

2- IMMUNO-TOXICOLOGICAL RISK ASSESSMENT RESULTS AND CONCLUSIONS



In the presence of PBMC, IPH4102 induces moderate cytokine release, that is:

- **much lower than true agonistic mAbs (anti-CD3/anti-CD28)**
- **similar to approved mAbs**
- **mainly driven by Fc binding rather than target binding**

These results are indicative of a low risk of uncontrolled/unintended immune activation by IPH4102

NON CLINICAL SAFETY KEY CONCLUSIONS

- The pattern of expression of KIR3DL2, which is limited to subsets of immune cells, is not indicative of a high “on target” safety risk

- IPH4102 is well tolerated in cynomolgus monkeys, up to 100 mg/kg IV weekly for 4 weeks

- IPH4102 does not present a significant risk of unintended and uncontrolled immune activation in the regulatory-compliant experimental conditions

How do we calculate the First Dose(s) in Human?

3- MABEL ASSAY SELECTION, SET-UP AND USE TO CALCULATE 1ST CLINICAL DOSES

- **Objective**
  - Determine a concentration of IPH4102 that results in a “Minimal Anticipated Biological Effect Level”
  - Through PK modeling, calculate the IPH4102 IV dose that will achieve this concentration
- **Design**
  - Uses fresh PBMC
    - From healthy donors, spiked with HUT78 Sézary cell line (n = 15)
    - From Sézary patients (n = 5)
  - *In vitro* assay that recapitulates all features of IPH4102 Modes-of-Action
    - Immune activation, Tumor cell death & Cytokine release
  - Wide range of IPH4102 concentrations (0.001 µg/mL to 10 µg/mL)
- **Outcome**
  - The EC_{10} of IPH4102 for tumor cell killing was selected as the MABEL

IPH4102 DEVELOPMENT STATUS

- IPH4102 was granted Orphan Drug designation in August 2014
- IPH4102 completed all IND-enabling studies in December 2014
- IPH4102 1st GMP batch produced and ready to use
- Regulatory documents are being finalized
- IPH4102-101 Phase I clinical trial regulatory submission in process

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