15th International Conference on Malignant Lymphoma
Palazzo dei Congressi, Lugano, Switzerland, June 18-22, 2019

KIR3DL2 is expressed in peripheral T-cell lymphomas and may be a therapeutic target

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INTRODUCTION

KIR3DL2, a killer immunoglobulin-like receptor normally expressed by a subset of natural killer (NK) cells is aberrantly expressed in cutaneous T-cell lymphomas (CTCL), particularly in Sézary Syndrome (SS)[1]. IPH4102, a monoclonal antibody directed against KIR3DL2, demonstrated *in-vitro* antitumor activity and has shown beneficial clinical activity in a phase 1 dose-escalation plus expansion cohort study in relapsed advanced CTCL patients (NCT02593045)[2].

OBJECTIVES

Based on these new findings, we made the hypothesis that KIR3DL2 could :

- **be expressed on peripheral T-cell lymphomas (PTCLs),**
- **serve as a new therapeutic target in these diseases with a dismal prognosis.**

METHODS

Patients and samples

We retrospectively studied **116 PTCLs** for KIR3DL2 expression using immunohistochemistry (IHC, n=73), or flow-cytometry (n=43). Frozen PTCL tissue samples and cells from peripheral blood and lymph node/tumor tissue were obtained from annotated collections (Tenomic and CeVI for PTCL tissues and cells, respectively, and PHRC KIRs for the SS controls).

KIR3DL2 protein expression studies

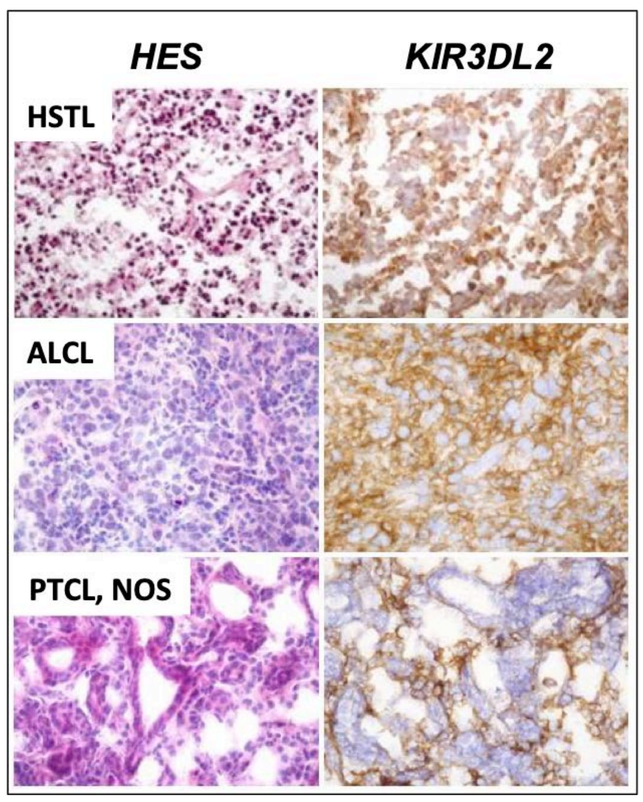
By IHC, KIR3DL2 expression was assessed independently by 2 pathologists using the specific anti-KIR3DL2 12B11 moAb (Innate Pharma).

***Ex-vivo* antibody dependent cell cytotoxicity (ADCC)**

ADCC assays were carried out on cell lines and primary PTCL cells, as well as on controls (CD4+ sorted T-cells from SS patients). Target cells were incubated overnight with healthy donor heterologous PBMCs at various effector/target ratios with either the IPH4102 anti-KIR3DL2 moAb (Innate Pharma) or an IgG1 isotype control both at a 1µg/mL concentration. The Fixable Viability Dye eFluor™ 780 (Life Technologies) was used to assess cell death on a LSR Fortessa X20 (BD Biosciences).

RESULTS

KIR3DL2 IS EXPRESSED IN MULTIPLE PTCL SUBTYPES

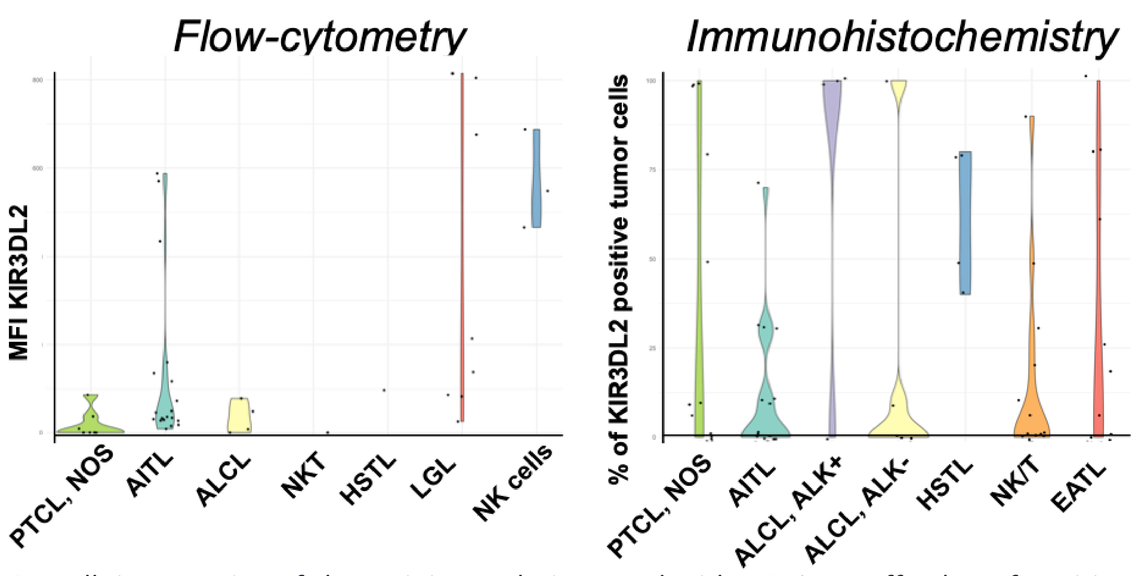


By IHC, within all PTCL categories, > 5% of lymphoid cells were KIR3DL2-positive in **37/73 cases (51 %)**. High expression (> 50% KIR3DL2-positive lymphoid cells) was found in 21/87 (24 %) patients.

In details, 8/14 PTCL not otherwise specified (PTCL,NOS 57%); 7/17 angioimmunoblastic TCL (AITL 41%), 4/4 hepatosplenic TCL (HSTL 100%); 5/10 anaplastic large cell lymphomas (ALCL 50%); 6/15 NK/T-cell lymphomas (40%) and 7/13 enteropathy-associated TCL (EATL 54%) expressed KIR3DL2.

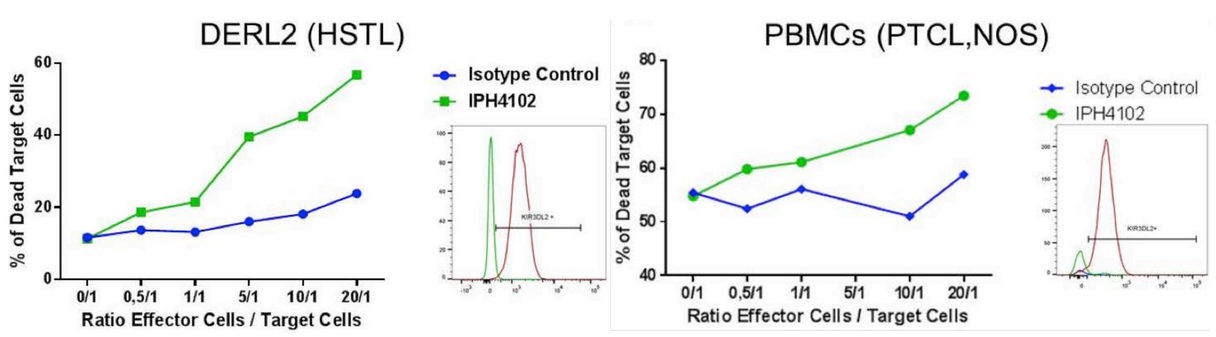
In addition, **by flow cytometry**, KIR3DL2 was expressed on tumor cells compared to isotype control in **19/43 PTCL (44%)**, including 1/9 PTCL,NOS (11%); 6/16 AITL (38%), 1/3 HSTL (33%); 2/4 ALCL (50%); 1 NK/T; 1/2 EATL (50%) and 7/8 large cell leukemia (LGL (88%).

KIR3DL2 expression on tumor cells



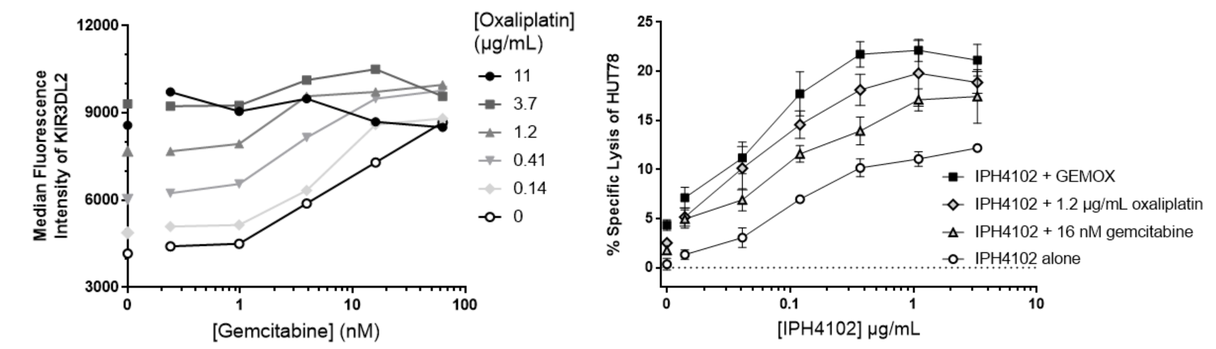
Overall, irrespective of the staining technique and with a 5% cut-off value of positive cells by IHC, **KIR3DL2 protein expression using the specific anti-KIR3DL2 moAb was evidenced in 55/116 (47%) samples.**

IPH4102 EFFICIENTLY ELIMINATES KIR3DL2+ PRIMARY TUMOR CELLS BY ADCC *ex-vivo*



Efficient *ex vivo* ADCC assays using IPH4102 were obtained on KIR3DL2+ HSTL cell lines DERL2 and DERL7**. Antitumor activity of IPH4102 against primary tumor cells** was observed and increased with the E/T ratio, in 3 KIR3DL2 positive patient samples tested, including one PTCL,NOS; one AITL and one HSTL patient.

COMBINATION OF IPH4102 WITH GEMOX HAS SYNERGISTIC ANTI-TUMOR ACTIVITY *in-vitro*



In-vitro, incubation of T-cell lines with GemOx (Gemcitabine and Oxaliplatin) can enhance baseline KIR3DL2 expression. In addition**, IPH4102 ADCC against KIR3DL2-positive tumor T-cell lines is increased by GemOx.**

CONCLUSIONS AND PERSPECTIVES

1. **KIR3DL2 is expressed in multiple PTCL subtypes including the most frequent like PTCL-NOS, AITL and ALCL, but also the rarer EATL, T-LGL and NK/T-cell lymphomas.**
2. **IPH4102 and GemOx combination improves anti-tumor activity against KIR3DL2-positive T-cell lines *in-vitro*.**
3. **The benefit of targeting KIR3DL2 by IPH4102 in combination with GemOx will be further investigated in relapsed PTCL patients in the Tellomak Phase 2 study.**

REFERENCES

1. Battistella M, et al. KIR3DL2 expression in cutaneous T-cell lymphomas: expanding the spectrum for KIR3DL2 targeting. Blood. 2017;130(26):2900–2902.
2. Bagot M, et al. Phase I Study of IPH4102, Anti-KIR3DL2 Mab, in Relapsed/Refractory Cutaneous T-Cell Lymphomas (CTCL): Dose-escalation Safety, Biomarker and Clinical Activity Results. Hematol. Oncol. 2017;35:48–49.