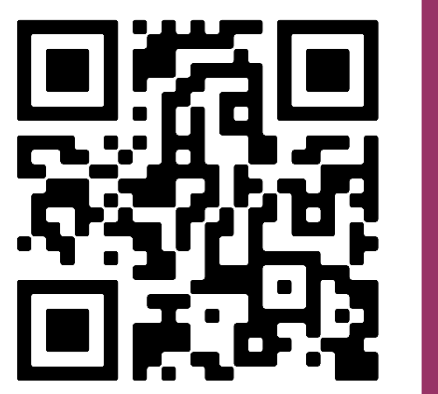


Anti-lymphoma activity of lacutamab (IPH4102), first-in-class anti-KIR3DL2 antibody, is augmented by PTCL chemotherapies

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Abstract

Introduction KIR3DL2, a killer immunoglobulin-like receptor expressed on subsets of T and natural killer (NK) lymphocytes, is widely expressed in most subtypes of T-cell lymphomas (TCL). Lacutamab (formerly IPH4102), first-in-class monoclonal antibody (mAb) directed against KIR3DL2, has demonstrated clinical activity in phase 1 in relapsed advanced cutaneous TCL (CTCL) in monotherapy (M. Bagot *et al.*, Lancet Oncology 2019) and was granted Fast Track designation by the FDA for the treatment of relapsed/refractory (r/r) Sézary Syndrome. Peripheral TCL (PTCL) is a group of diverse clinically aggressive diseases. Combination chemotherapies used for the treatment of PTCL include doxorubicin and cyclophosphamide frontline, and gemcitabine plus oxaliplatin (GemOx) after relapse. The relevance of combining lacutamab with these drugs was assessed *in vitro* and *in vivo*.

Methods *In vitro*, PTCL standard chemotherapies were added, either alone or combined, to lacutamab in an allogenic NK-mediated Antibody-Dependent Cell Cytotoxicity (ADCC) assay against KIR3DL2-positive tumor cell lines. The impact of these chemotherapies on KIR3DL2 surface expression on tumor cells was monitored by flow cytometry.

In addition, lacutamab combination with each of these chemotherapies was assessed in SCID mice engrafted intravenously with KIR3DL2-positive lymphoma cells.

Results KIR3DL2 is expressed in most sub-types of PTCL, as assessed by multiple techniques. Incubation of T-cell lines with gemcitabine, oxaliplatin, GemOx or doxorubicin enhance baseline KIR3DL2 expression on tumor cell lines, whereas incubation with cyclophosphamide does not. *In vitro*, lacutamab-mediated ADCC against KIR3DL2-positive tumor T-cell lines is increased by GemOx in a dose-dependent fashion. In mouse xenograft models, doxorubicin, gemcitabine and cyclophosphamide significantly increased anti-tumor efficacy of lacutamab, while oxaliplatin did not (but oxaliplatin did not show any stand-alone anti-tumor activity in this model either).

KIR3DL2 is expressed in multiple subtypes of PTCL, including leukemic-type ATL where it correlates with poorer survival

KIR3DL2 was assessed by IHC on PTCL biopsies and by flow cytometry (FC) on blood samples from Adult T-Cell Leukemia/Lymphoma (ATL). ATL cells were identified by the low expression of CD3 & CD4, activation markers (CD25 and/or HLA-DR) and CD7. By subtype (Figure 1): 57% PTCL, NOS; 41% AITL; 100% HSTL; 50% ALCL; 40% ENKT & 54% EATL expressed KIR3DL2 (M. Cheminant *et al.*, 15-ICML 2019 #157).

Figure 1: KIR3DL2 expression in PTCL

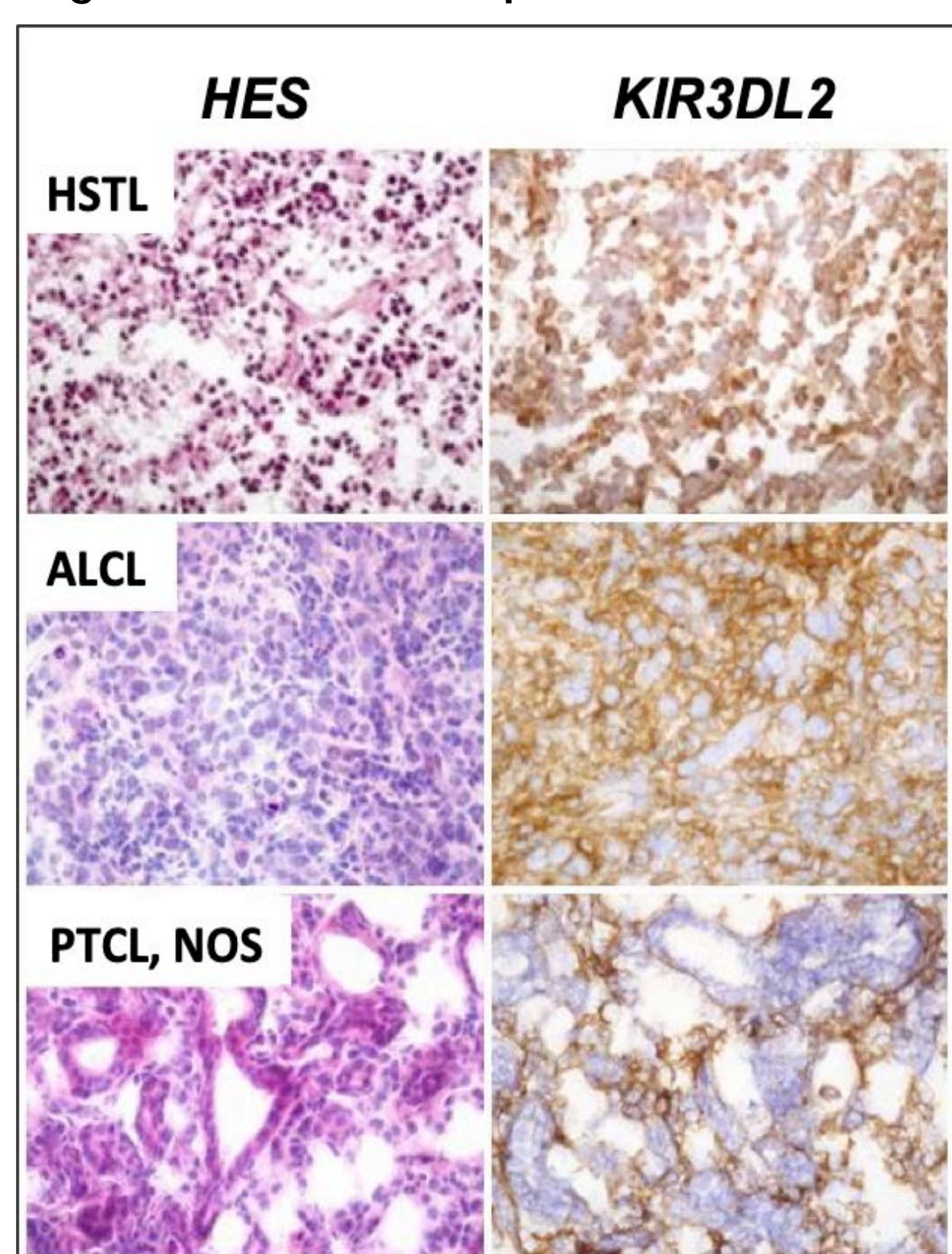
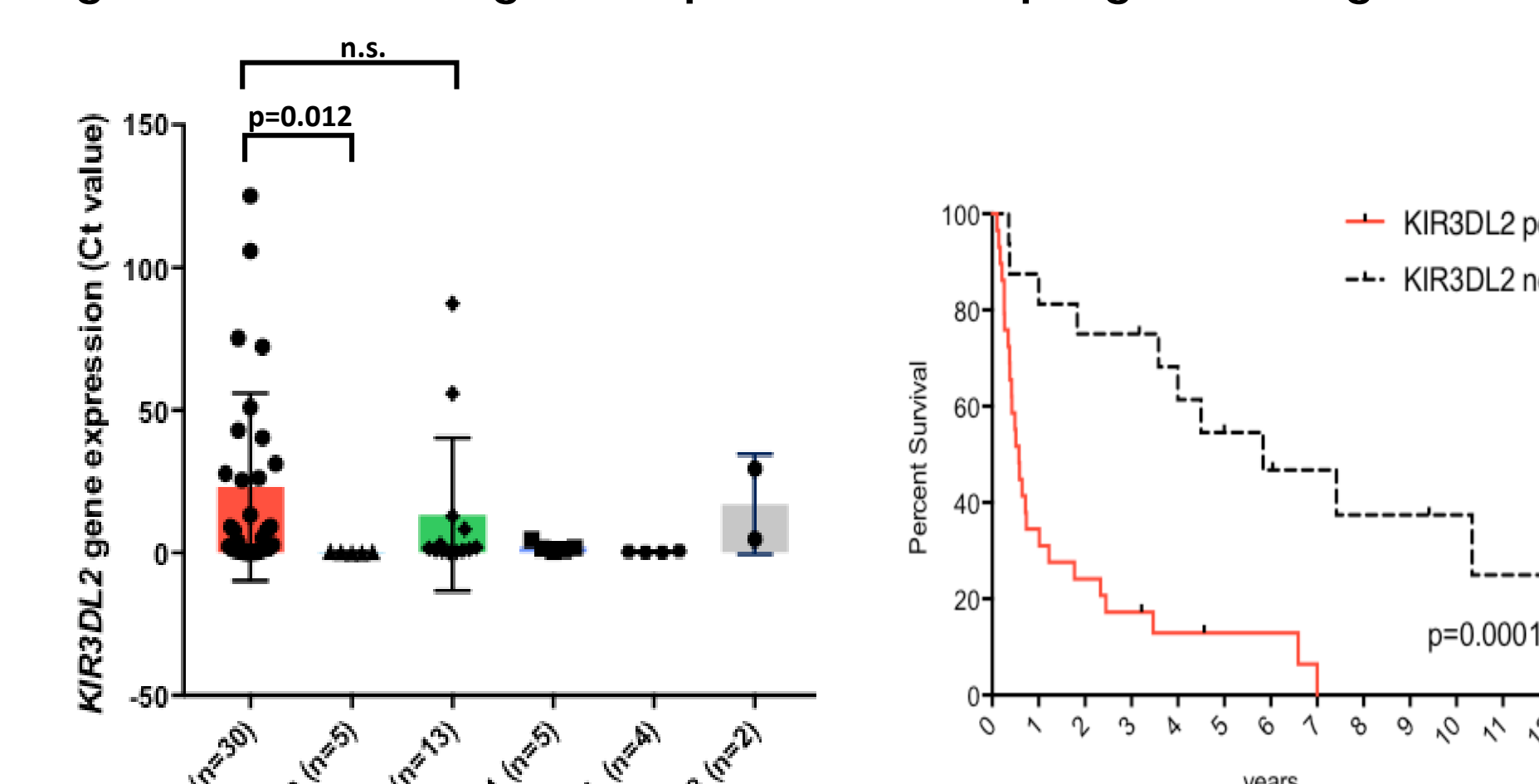


Figure 2: KIR3DL2 gene expression and prognostic significance in ATL



In most acute ATL patients, in IHC, abnormal lymphocytes harbor KIR3DL2 positivity (n=28/30, 93%) whereas lymphoma and chronic/smoldering cases are often negative for KIR3DL2 (n=2/8 and n=2/12 respectively, p=0.001) (M. Cheminant *et al.*, 15-ICML 2019 #218); mRNA analyses confirm these results (Figure 2).

PTCL, NOS: Peripheral T-Cell Lymphoma, Not Otherwise Specified; HSTL: Hepatosplenic T-cell Lymphoma; ALCL: Anaplastic Large-Cell Lymphoma; AITL: Angio-Immunoblastic T-Cell Lymphoma; EATL: Enteropathy-Associated T-Cell Lymphoma; ENKT: Extranodal NK/T-Cell Lymphoma; HES: Hematoxyline-Eosine-Safran.

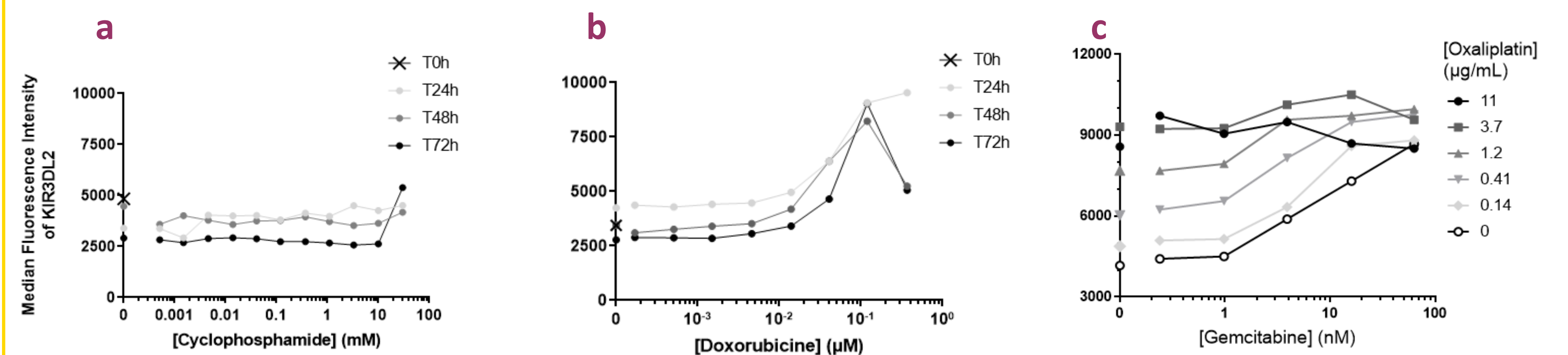
Conclusions

KIR3DL2 is expressed in multiple TCL subtypes, including primary CTCL and PTCL.

While lacutamab is developed in monotherapy for the treatment of r/r CTCL, the clinical aggressiveness of PTCL justifies therapeutic combinations: preclinical studies have established that some chemotherapies enhance KIR3DL2 surface expression on T-cell lymphomas. In addition, lacutamab anti-tumor activity can be improved *in vitro* and *in vivo* with various chemotherapeutic agents and in particular with GemOx combination.

Together with the Phase 1 clinical results of lacutamab in monotherapy, these findings support the design of lacutamab phase 2 study (NCT03902184): TELLOMAK is an international open-label multi-cohort phase 2 that aims to confirm lacutamab efficacy in r/r Sézary Syndrome, as well as to assess lacutamab clinical activity in monotherapy in r/r advanced Mycosis fungoides and in combination with GemOx in relapsed PTCL.

Doxorubicin, oxaliplatin, gemcitabine but not cyclophosphamide enhance KIR3DL2 expression on T-cell lymphoma cells *in vitro*

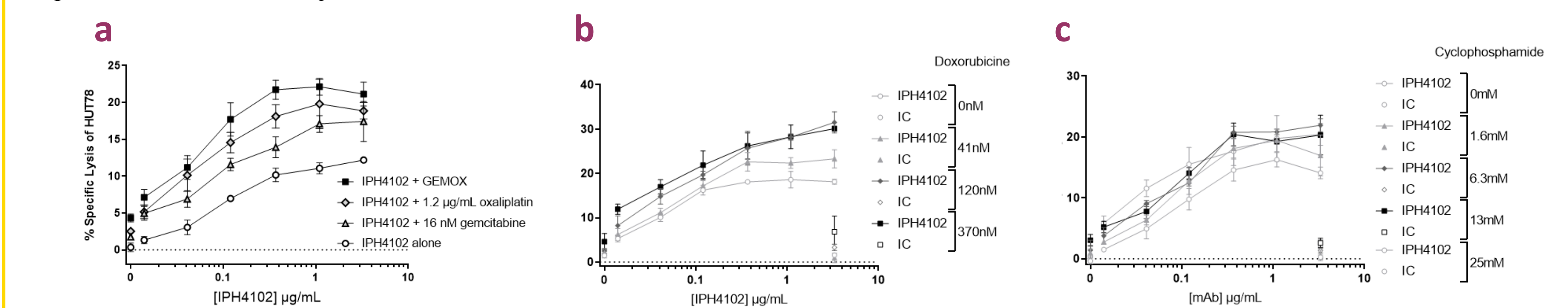


KIR3DL2⁺ T-cell lymphoma cell lines were incubated *in vitro*, for up to 72h, with increasing concentrations of cyclophosphamide (a), doxorubicin (b) or oxaliplatin and gemcitabine, alone or in combination (c). KIR3DL2 expression was monitored by flow cytometry.

Anti-lymphoma activity of lacutamab is increased by standard PTCL chemotherapies both *in vitro* and *in vivo*

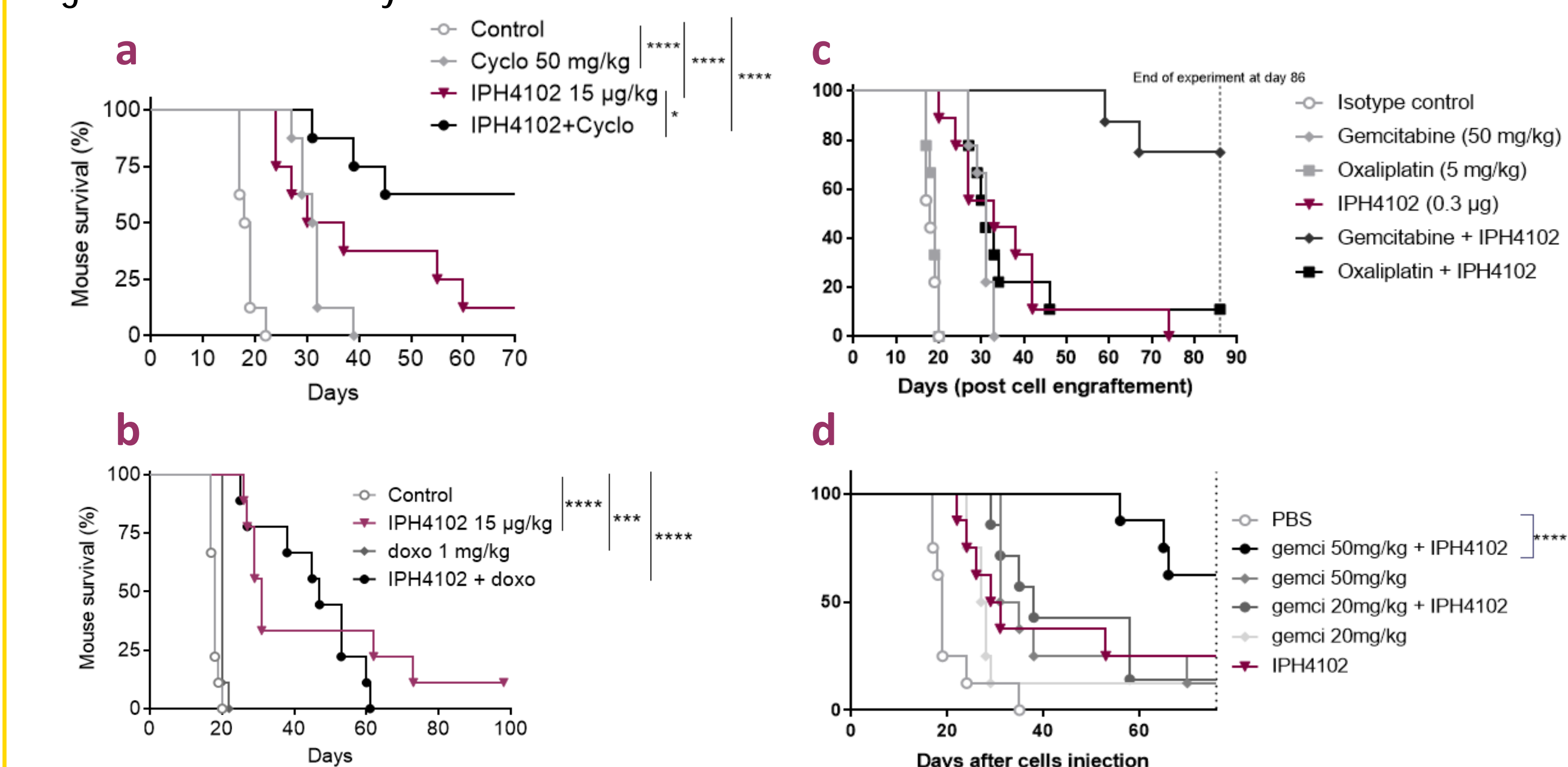
KIR3DL2⁺ tumor cells were pre-treated with gemcitabine plus oxaliplatin (GemOx) (3-a), doxorubicin (3-b) or cyclophosphamide (3-c) and their sensitivity to allogenic NK-mediated ADCC was further evaluated in the presence of lacutamab. When applicable, isotype control (IC) was used at the highest concentration only (3 µg/mL).

Figure 3: *In vitro* efficacy on HUT78 cells



SCID mice engrafted IV with 5.10⁶ RAJI-KIR3DL2 tumor cells (n = 8 per group) were treated at day 1 with suboptimal dose of lacutamab (0.3 µg/mouse, 15 µg/kg) combined with either cyclophosphamide (50 mg/kg) (4-a), doxorubicin (1 mg/kg) (4-b), gemcitabine (50 mg/kg) or oxaliplatin (5 mg/kg) (4-c), or increasing doses of gemcitabine (20 or 50 mg/kg) (4-d).

Figure 4: *In vivo* efficacy



Since oxaliplatin increased the toxicity of gemcitabine in this preclinical model, the triple combination of lacutamab and GemOx could not be tested.