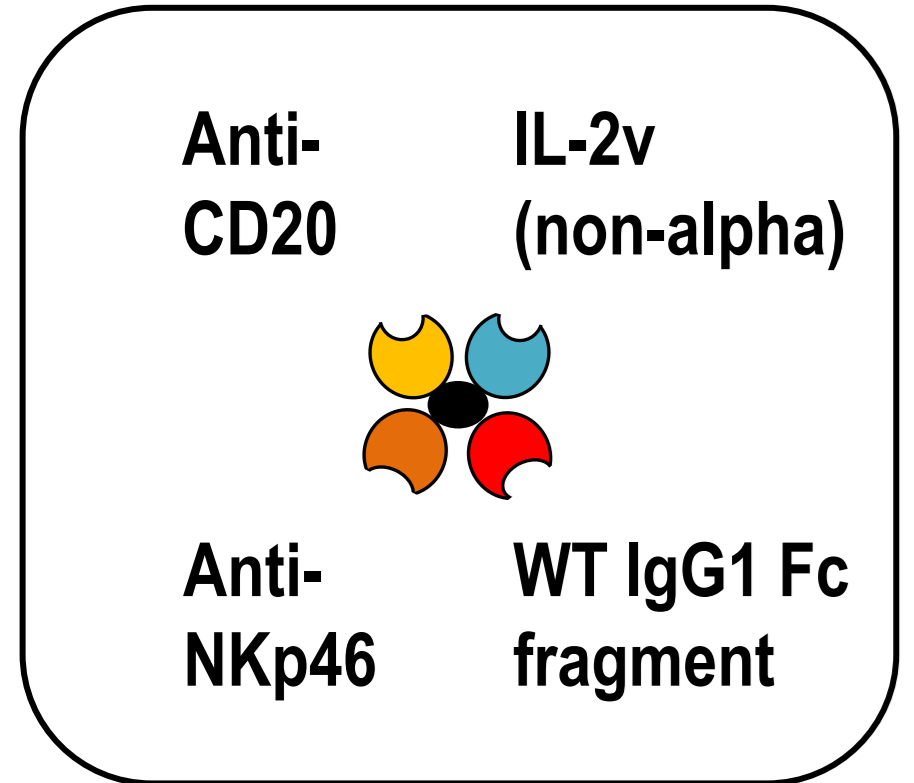


# Preclinical assessment of IPH6501, a first-in-class IL2v-armed tetraspecific NK cell engager directed against CD20 for R/R B-NHL



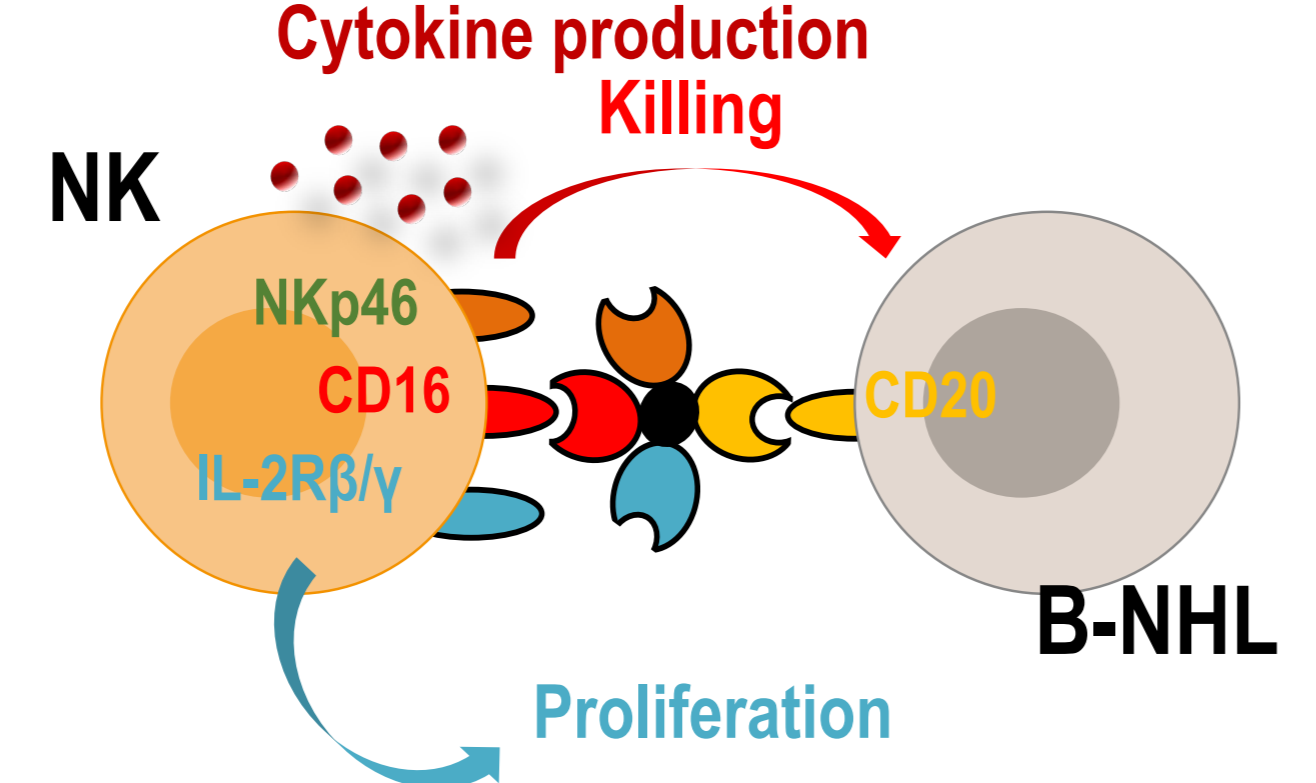
Olivier Demaria<sup>1</sup>, Marie Vetizou<sup>1</sup>, Romain Remark<sup>1</sup>, Laura Chiossone<sup>1</sup>, Constance Vagne<sup>1</sup>, Rachel Courtois<sup>1</sup>, Caroline Denis<sup>1</sup>, Aurélie Maguer<sup>1</sup>, François Le Floch<sup>1</sup>, Agnès Represa<sup>1</sup>, Audrey Blanchard Alvarez<sup>1</sup>, Laurent Gauthier<sup>1</sup>, Sonia Quaratino<sup>1</sup>, Carine Paturel<sup>1</sup>, Eric Vivier<sup>1,2</sup>

1/ Innate Pharma, Marseille, France; 2/ Aix Marseille University, CNRS, INSERM, CIML, Marseille, France.

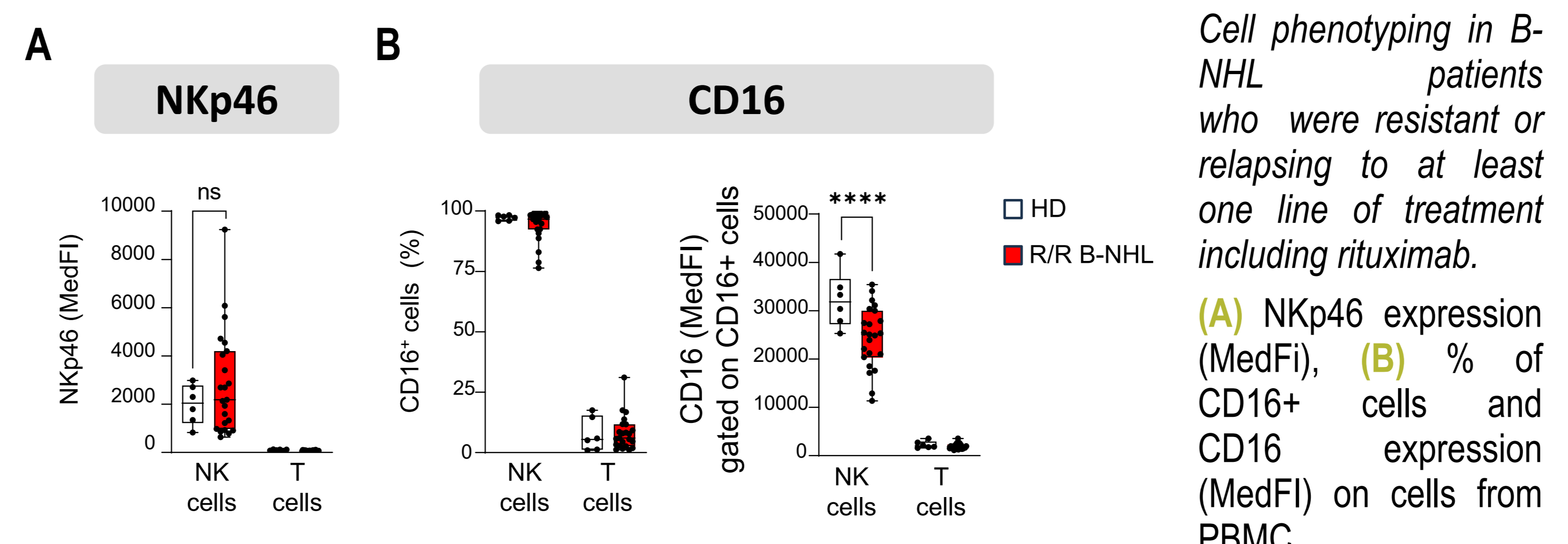


The therapeutic landscape for relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL) is evolving toward targeted T-cell based immunotherapies, including CD19-targeted CAR-T and CD3xCD20 T-cell engaging (TCE) bispecific antibodies. Yet, there remains an unmet medical need for patients who are refractory to, or ineligible for these treatments. Leveraging natural killer (NK) cells emerges as a promising strategy in hematological malignancies (Vivier *E et al.*, *Nature*, 2024), as shown in a Phase 1 study with IPH6101/SAR'579 in R/R Acute Myeloid Leukemia (Stein, ASCO 2023; Bajel, ASH 2023).

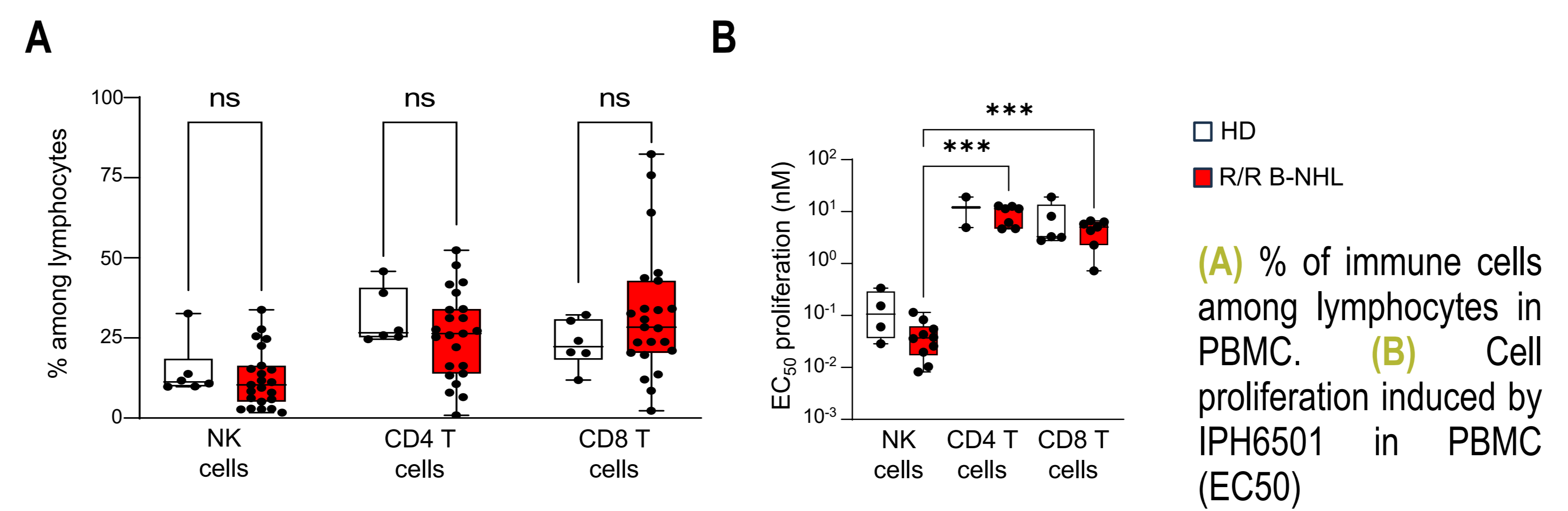
We developed IPH6501, a tetraspecific antibody-based NK cell engager (Demaria *et al.*, *Cell Reports Med*, 2022) that simultaneously targets on NK cells the CD16a and NKp46 receptors, the IL-2 receptor with an engineered IL-2 variant (IL2v) and on B-NHL cells the CD20 antigen. This approach boosts NK cell activation and proliferation, cytotoxicity against tumor cells, and cytokine production. The IL-2 variant is designed with mutations that prevent binding to CD25 (IL-2R $\alpha$ ), limiting Treg activation and potential IL-2-related side effects.



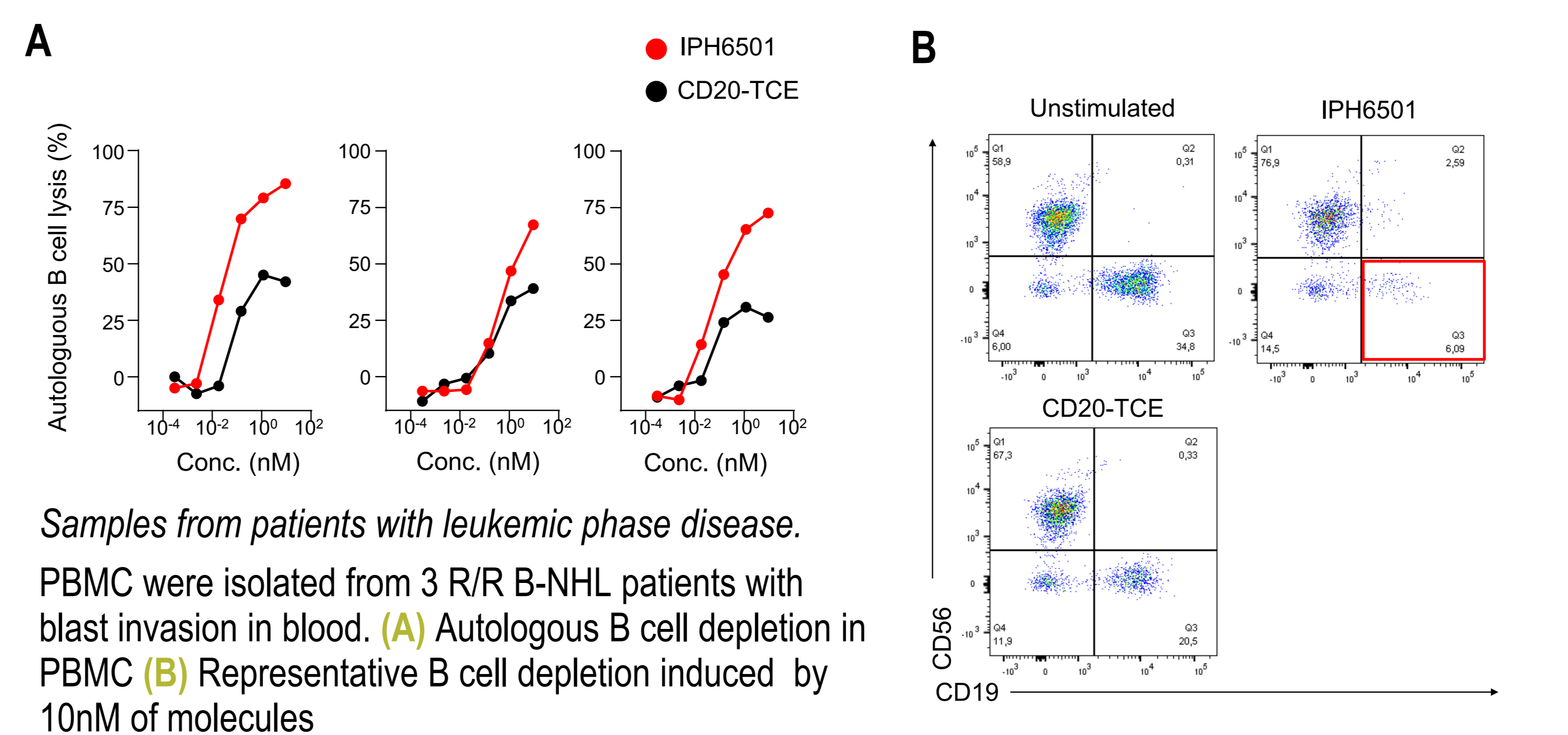
## NKp46 and CD16 activating receptors are expressed on peripheral NK cells of R/R B-NHL patients



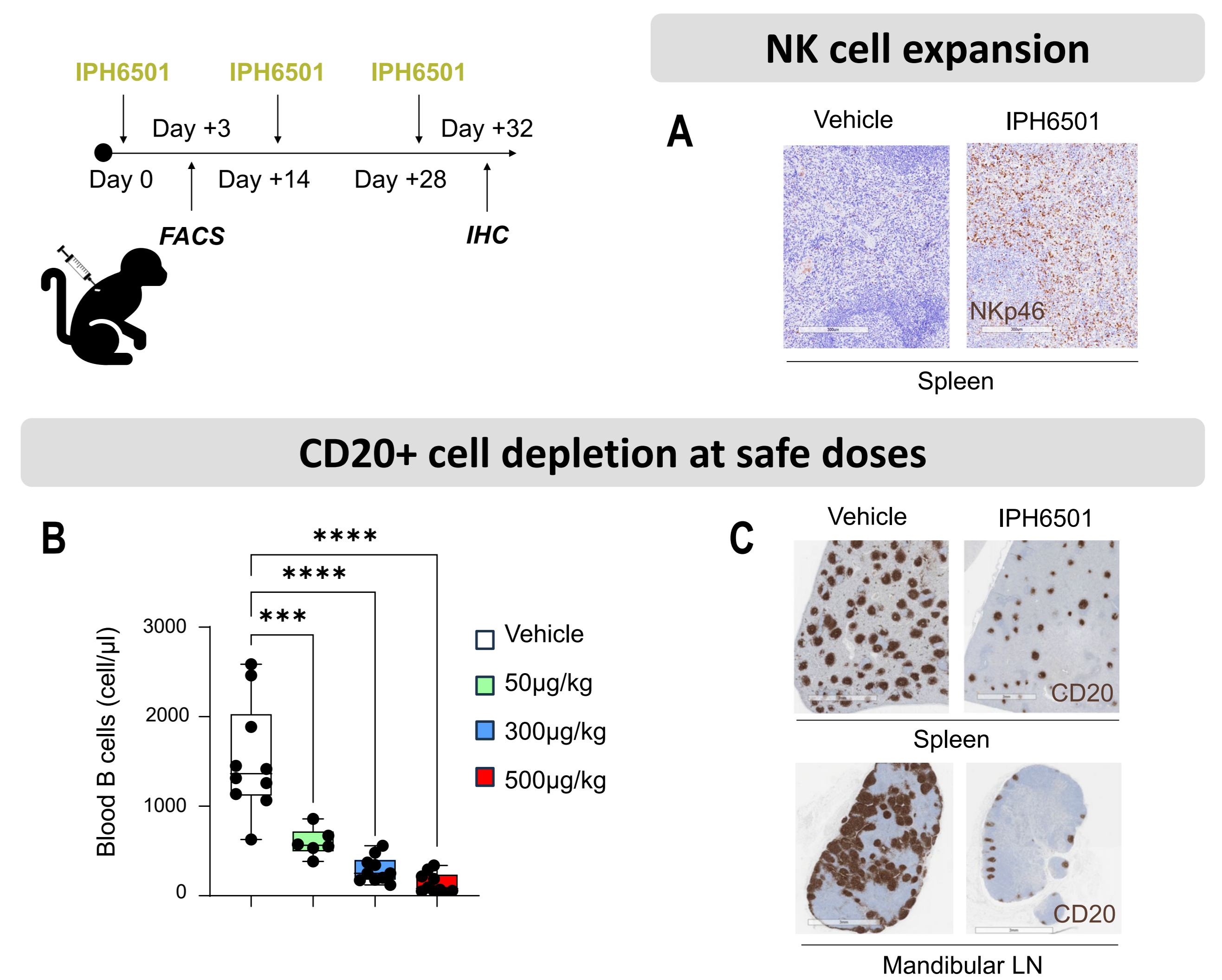
## As in HD samples, IPH6501 effectively and preferentially stimulates NK cell proliferation from PBMC of R/R NHL patients



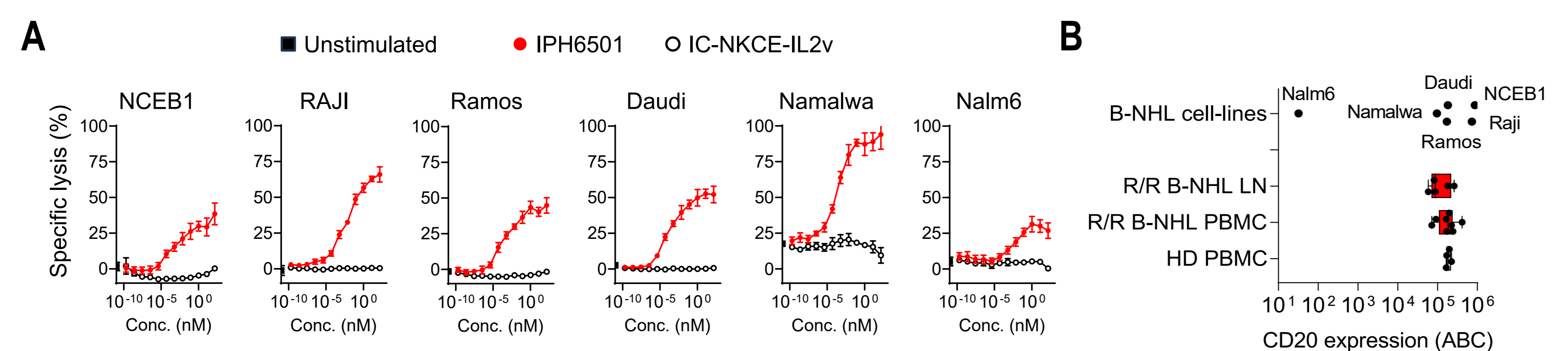
## In PBMC samples from R/R B-NHL patients, IPH6501 outperforms a CD20-TCE in eliminating autologous CD20+ cells



## In NHP, IPH6501 stimulates NK cell expansion and CD20+ B cell depletion in blood and lymphoid organs

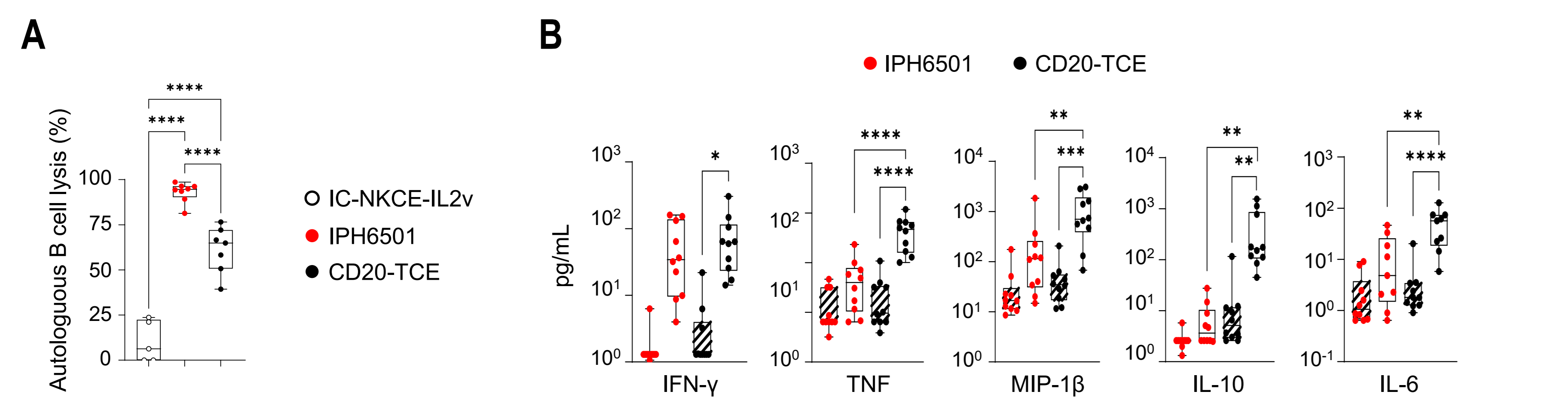


## IPH6501 induces NK cell cytotoxicity against CD20+ B-NHL cell lines expressing CD20 in a similar range than R/R B-NHL samples



(A) IPH6501 stimulates cytotoxic activity of NK cells purified from healthy donors against various B-NHL tumor cell lines, even those expressing very low level of CD20. (B) CD20 expression on B-NHL cell lines and primary B cells from PBMC of HD or R/R B-NHL patients, and B cells from R/R B-NHL tumoral lymph nodes.

## IPH6501 depletes autologous CD20+ B cells from HD with greater efficacy and lower induction of pro-inflammatory cytokines than a CD20-TCE



HD PBMC were incubated with IPH6501, a CD20 targeting TCE or the IC-NKCE-IL2v (IPH6501 w/o CD20 binding element). (A) Autologous B cell lysis induced by 10nM of molecules. (B) Cytokine secretion in culture supernatant induced by 9.4 nM (empty bar) or 0.14pM (dashed bar) of molecules.

## Preclinical data of IPH6501 compared to a CD20-TCE show:

- Higher efficacy in depleting autologous CD20+ B cells in PBMC from HD and from R/R B-NHL patients (leukemic phase disease)
- Reduced induction of pro-inflammatory cytokines compared to a CD20-TCE in PBMCs from HD.

In NHP, tolerable doses of IPH6501 stimulate NK cell expansion and deplete CD20+ B cell in blood and lymphoid organs.

IPH6501 is emerging as a promising, innovative candidate treatment for B-NHL and is currently being investigated in a first-in-human study (NCT06088654). The trial-in-progress of the Phase 1 study has been presented at EHA and ASCO in 2024 (EHA abstract PB3041 and in ASCO poster TPS7095).

We thank the biological resource center of the CHU of Montpellier and its scientific manager Dr Jérôme Moreaux, and the Cevi Collection Project from the CALYM Carnot Institute (funded by the French National Research council) for providing patient samples.

