Abstract #7030

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

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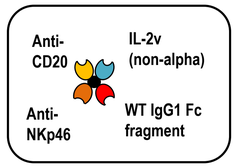
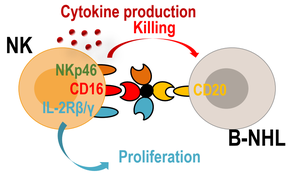
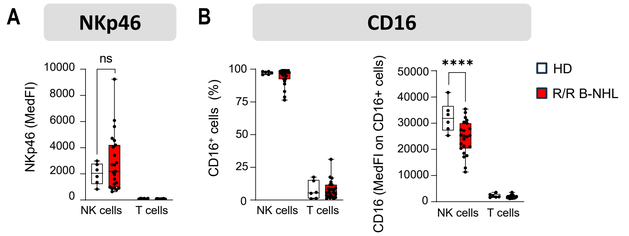


The therapeutic landscape for relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL) is evolving toward targeted T-cell based immunotherapies, including CD19-targeted CAR-T and CD3xCD20 T-cell engaging (TCE) bispecific antibodies. Yet, there remains an unmet medical need for patients who are 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 Myeloïd 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-2Rα), limiting Treg activation and potential IL-2-related side effects.

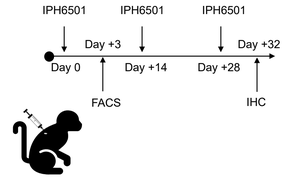


NKp46 is maintained on peripheral NK cells of R/R B-NHL patients whereas CD16 is down modulated

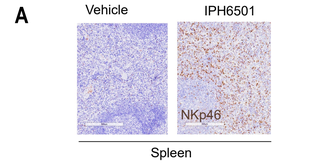


B-NHL patients were resistant or relapsing to at least one line of treatment including rituximab. (A) NKp46 expression (MedFi), (B) % of CD16+ cells and CD16 expression (MedFI) on cells from PBMC

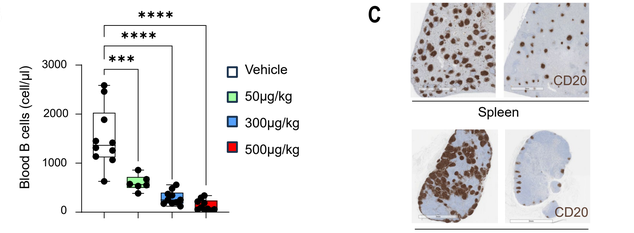
In NHP, IPH6501 stimulates NK cell expansion and CD20+ B cell depletion in blood and lymphoid organs



NK cell expansion

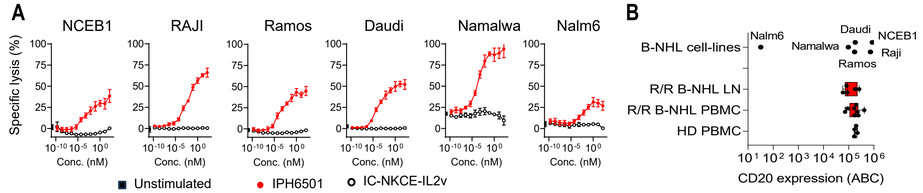


CD20+ cell depletion at safe doses



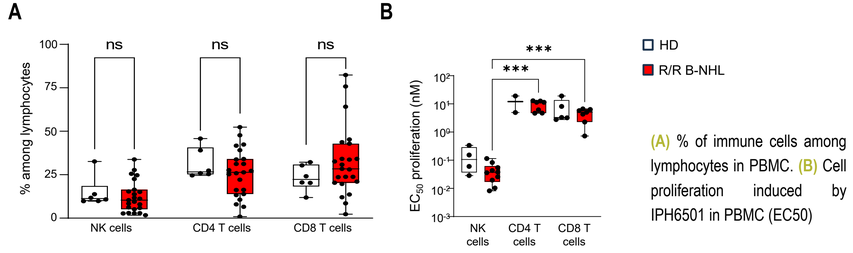
(A) Representative IHC monitoring NK cell expansion in spleen induced by 500µg/kg of IPH6501.
(B) CD20+ B cell depletion in blood induced by the indicated doses of IPH6501 and
(C) Representative IHC monitoring CD20+ cell depletion in spleen and lymph nodes induced by 500µg/kg IPH6501

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



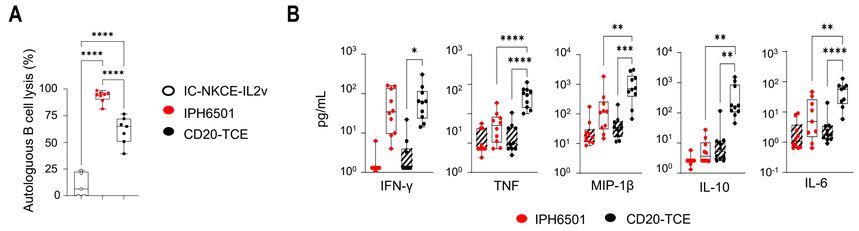
(A) IPH6501 stimulates cytotoxic activity of NK cells purified from healthy donors against various B-NHL tumor cell lines, even those expressing very low level of CD20. (B) CD20 expression on B-NHL cell lines and primary B cells from PBMC of HD or R/R B-NHL patients, and B cells from R/R B-NHL tumoral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

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



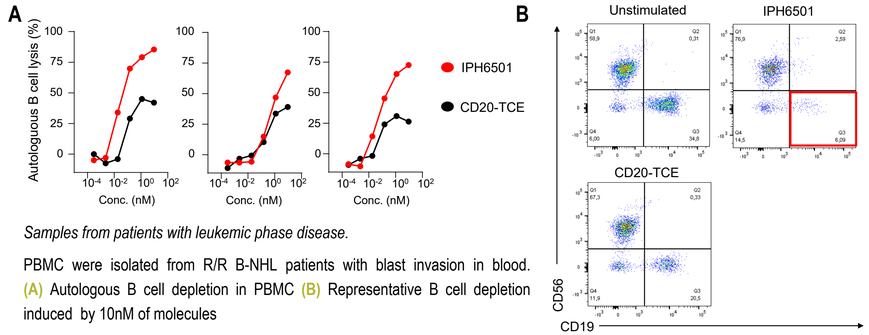
(A) % of immune cells among lymphocytes in PBMC. (B) Cell proliferation induced by IPH6501 in PBMC (EC50)

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.

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



Samples from patients with leukemic phase disease.

PBMC were isolated from R/R B-NHL patients with blast invasion in blood. (A) Autologous B cell depletion in PBMC (B) Representative B cell depletion induced by 10nM 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

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IPH6501 is emerging as a promising innovative candidate within the treatment landscape for R/R B-NHL and is currently being investigated in a global, first-in-human phase 1/2 study (NCT06088654) presented in TiP poster #TPS7095.

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