Preclinical Characterization of IPH6501: A Novel IL2v-Armed Tetraspecific NK Cell Engager Targeting CD20 in Relapsed or Refractory B cell Non-Hodgkin Lymphoma Subtypes and post CAR-T Therapy

Abstract 1083

SCAN ME

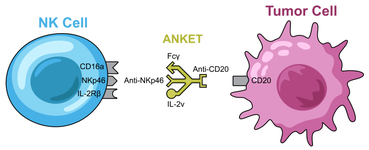
Florent Carrette[1], Olivier Demaria[1], Pascale André[1], Jean-Baptiste Vallier[1], Mélanie Le Van[1], Justine Galluso[1], William Baron[1], Manon Clemeceau[1], Sylvia Trichard[1], Rachel Courtois[1], Mathilde Girard-Madoux[1], Camille Bigenwald[2], Caroline Denis[1], Marie Vétizou[1], Romain Remark[1], Marie-Laure Thibult[1], Cécile Bonnafous[1], Ariane Morel[1], Yannis Morel[1], Sonia Quaratino[1], Carine Paturel[1], Eric Vivier[1,3]

1, Innate Pharma, Marseille, France; 2, Gustave Roussy Cancer Campus, Villejuif, France ; 3, Aix-Marseille University, CNRS, INSERM, CIML, Marseille, France.

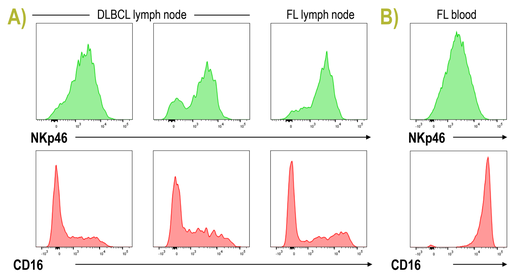
Background

The therapeutic landscape for relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL) is evolving from chemotherapy and CD20-targeting antibodies towards 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 new 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*) for B-NHL therapy. IPH6501 stimulates NK cells by engaging the activating receptors CD16 and NKp46, and together with a non-alpha IL-2 (IL-2v) moiety selectively induces their proliferation. The IL-2v does not bind to CD25 (IL-2Rα), limiting Treg activation and potential IL-2-related side effects. Finally, IPH6501 targets CD20, effectively inducing NK cell-mediated cytotoxicity of B-NHL tumor cells.

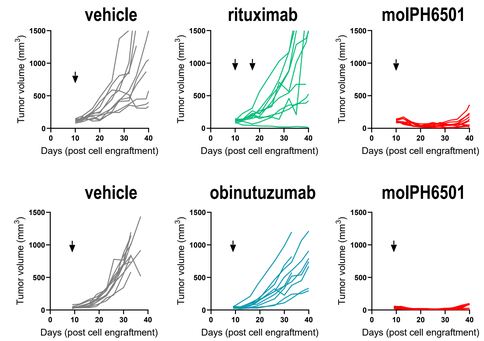


1. NKp46 expression is maintained on lymph node NK cells, a key advantage over CD20 antibodies



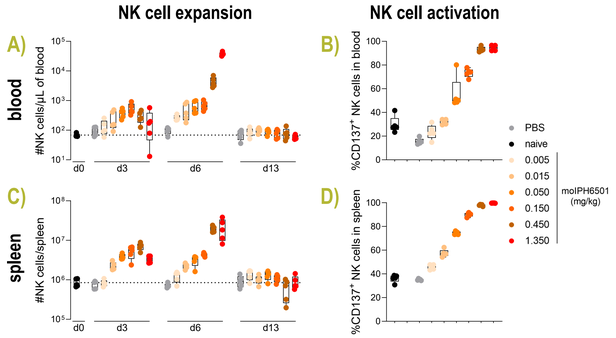
Lymph nodes from R/R B-NHL patients were collected, and NK cells were analyzed for NKp46 and CD16 expression by flow cytometry (A). A representative example of NKp46 and CD16 expression on NK cells from a R/R FL patient is shown (B).

2. IPH6501 shows strong antitumor efficacy in a tumor model resistant to rituximab and obinutuzumab



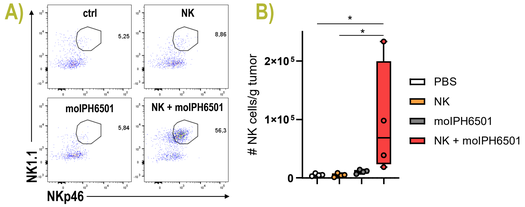
CB17-SCID mice were injected s.c with $5x10^6$ Raji tumor cells (endogenous CD20 expression). Animals were treated i.v. 9 or 10 days later with 20mg/kg of rituximab (A) 75mg/kg of obinutuzumab (B), or with 1mg/kg (A) or 3mg/kg (B) of a mouse surrogate of IPH6501 (molPH6501).

3. molPH6501 promotes dose-dependent NK cell expansion and activation in blood and lymphoid organs



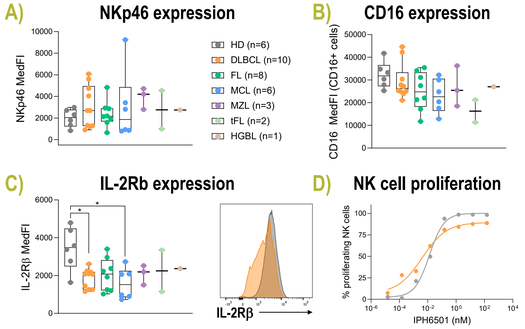
C57BL/6J mice were injected i.v. with $1x10^6$ B16-F10 huCD20 tumor cells. Animals were treated i.v. one day later with a single injection of increasing doses of molPH6501 or PBS. NK cells counts were analyzed in blood (A) and spleen (C) at indicated timepoints, and expression of the early activation marker CD137 was analyzed at d3 in blood (B) and spleen (D).

4. molPH6501 promotes NK cell recruitment from the periphery to the tumor microenvironment



NK cell-deficient mice were subcutaneously engrafted with B16F10-huCD20. Animals were treated on day 8 with 1.25 mg/kg of molPH6501. $8x10^6$ NK cells from WT animals were infused 30 minutes later. A representative NK cell detection in tumors 5 days post NK cell infusion is shown in (A). Quantification is shown in (B).

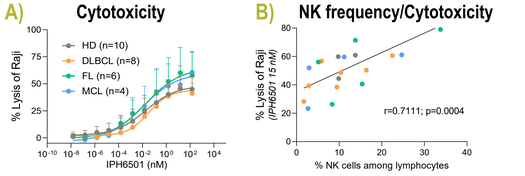
5. IPH6501 targets (NKp46, CD16 and IL-2Rβ) are expressed on patient blood NK cells across R/R B-NHL subtypes



PBMCs from R/R B-NHL patients were collected. NK cells were analyzed for NKp46 (A) and CD16 (B) expression (MedFI: median fluorescence intensity). IL-2Rβ expression and a representative example are shown in (C). IPH6501-mediated proliferation of NK cells from the representative example in (C) is shown in (D).

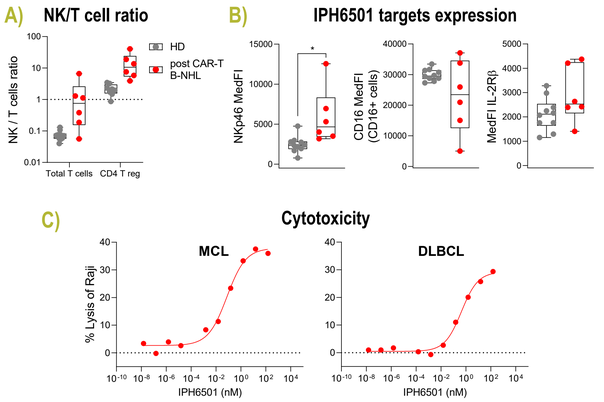
HD: healthy donor, DLBCL: diffuse large B-cell lymphoma, (t)FL: (transformed) follicular lymphoma, MCL: mantle cell lymphoma, MZL: marginal zone lymphoma, HGBL: high grade B-cell lymphoma.

6. IPH6501-induced tumor cell killing in various R/R B-NHL subtypes correlates with NK cell frequency among PBMCs



PBMC were isolated from indicated subtypes of R/R B-NHL patients and incubated with ^{51}Cr-loaded Raji tumor cells at a 50:1 ratio.
IPH6501-mediated Raji lysis was determined in a 4h ^{51}Cr release assay (A).
The correlation between target cells lysis and % NK cells among lymphocytes was determined (B).

7. IPH6501 potential in post CAR-T patients is supported by NK/T cell ratios, targets expression and tumor killing



PBMC were isolated from B-NHL patients post CAR-T treatment or healthy donors (HD). The NK/T cell ratio was determined against indicated T cell populations (A). NKp46, CD16 and IL-2Rβ expression on NK cells (B) were determined by flow cytometry.
PBMC were isolated from indicated subtypes of post-CAR-T patients and incubated with ^{51}Cr-loaded Raji tumor cells at a 50:1 ratio. IPH6501-mediated Raji lysis was determined in a 4h ^{51}Cr release assay (C).

Conclusions

- **IPH6501 advantage over antibody-based CD20-targeting therapies**: NK cells from B-NHL patients lymph nodes express low levels of CD16 while NKp46 is maintained
- **IPH6501 expand and mobilize peripheral NK cells for tumor killing**: IPH6501 mouse surrogate potently induces NK cells activation, proliferation and recruitment from the periphery to the tumor microenvironment in mouse models
- **IPH6501 has applications across subtypes of B-NHL, and potential in post CAR-T setting:**
  - IPH6501 targets (NKp46, CD16, IL-2Rβ) are expressed on blood NK cells,
  - IPH6501 shows potent in vitro antitumor activity on patient PBMCs,
  - Post-lymphodepletion NK recovery *(Piperoglou et al., 2021, J. Leuk. Biol)* supports IPH6501 potential in post CAR-T patients.

IPH6501 is emerging as a promising, innovative candidate treatment for B-NHL and is currently being investigated in a first-in-human study (NCT06088654).

We thank the biological resource center of the CHU of Montpellier and its scientific manager Dr Jerôme Moreaux, and the Cevi Collection Project from the CALYM Carnot Institute for providing patient samples.

innate pharma