S258 – 10/06/2023

IPH6501 IS A FIRST-IN-CLASS TETRASPECIFIC ANTIBODY-BASED NATURAL KILLER CELL ENGAGER THERAPEUTIC DEVELOPED FOR THE TREATMENT OF B-NHL

Olivier Demaria, PhD
Innate Pharma, Marseille, France

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Gene therapy and immunotherapy - Biology & translational research

DISCLOSURES

Innate Pharma (employee)

Need for new therapeutic approaches in Non-Hodgkin Lymphoma (NHL)

NHL estimation in United States in 2023	
New cases	80,550
% of all new cancer cases	4.1%
Deaths	20,180
% of all cancer deaths	3.3%

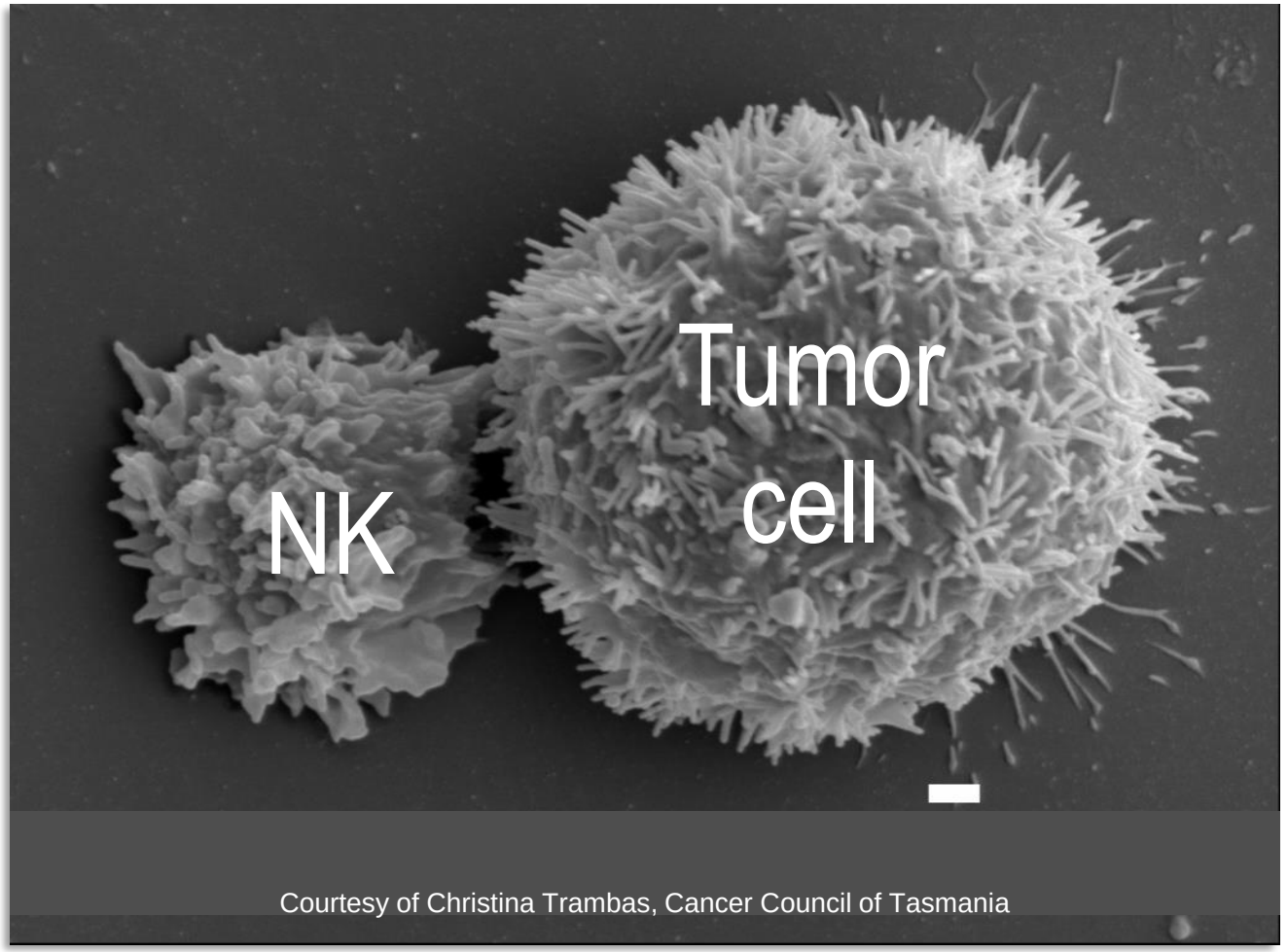
- *NHL is the most common hematological malignancy in adults*
- *Within NHL, 85% are B-cell and 15% T-cell*
- *CD20 is expressed on >90% of B-cell NHL*
- *High medical need in particular for R/R patients with aggressive B-NHL (5 years OS ≈ 60%)*

https://seer.cancer.gov/statfacts/html/nhl.html
Howlader, Noone et al. 2020
Cancer.net

Why targeting NK cells?

NK Cells

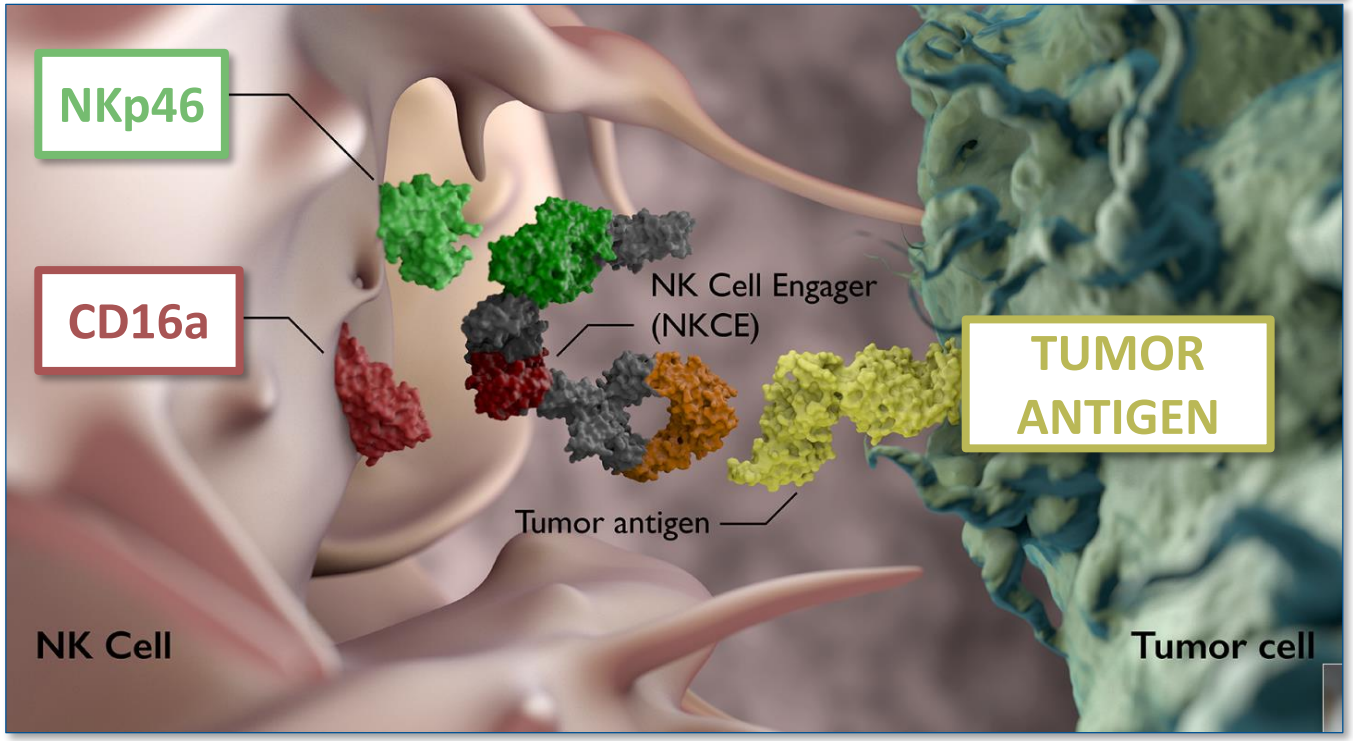
- Kill a vast array of tumor cells, including MHC-I negative
- No antigen-specific priming required
- Secrete cytokines and chemokines that initiate and shape T cell responses
- Anti-metastatic activity
- NK cell infusions:
  - Excellent safety profile
  - Clinical efficacy demonstrated in hematological malignancies



Courtesy of Christina Trambas, Cancer Council of Tasmania

ANKET® (Antibody-based NK cell Engager Therapeutics)

- ANKET® are antibody-based multispecific molecules
- Co-engagement of NKp46 and CD16a triggers strong NK cell activation
  - NKp46 expression is maintained on tumor infiltrating NK cells in contrast to CD16a, NKp30 and NKG2D
- Cytotoxic functions are triggered only when ANKET® bridges NK to tumor cells



SAR443579: first ANKET® in clinical evaluation and targeting CD123 in R/R hematological malignancies – granted FDA Fast Track designation in May 2023[1]

[1]*NCT05086315; J Clin Oncol 41, 2023 (suppl 16; abstr 7005)*

IPH6501 is a first in class tetraspecific ANKET® targeting CD20 and developed for the treatment of B-cell malignancies

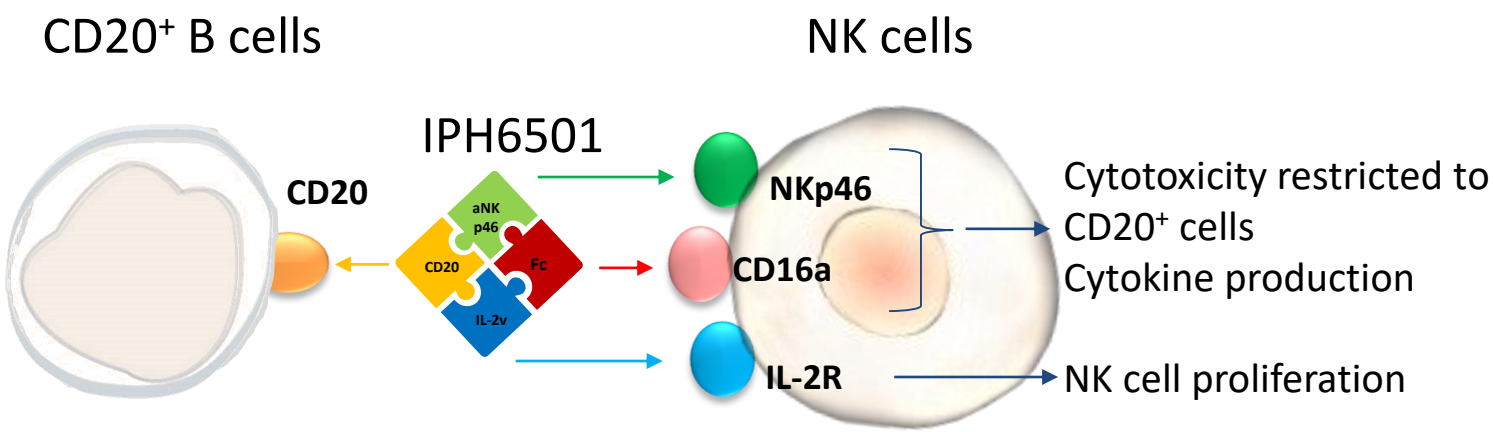
ANKET™ TECHNOLOGY

Trispecific ANKET®[1]

Tetraspecific ANKET® [2]

**IL-2v: IL-2 variant deprived of CD25 (IL-2Rα) binding to limit Treg activation and CD25 associated toxiciy*

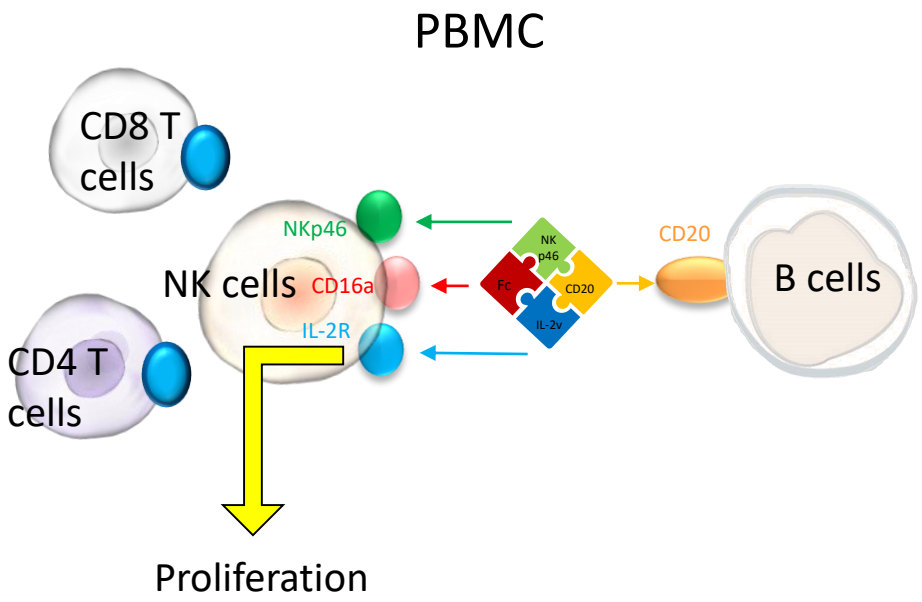
IPH6501: tetraspecific ANKET®

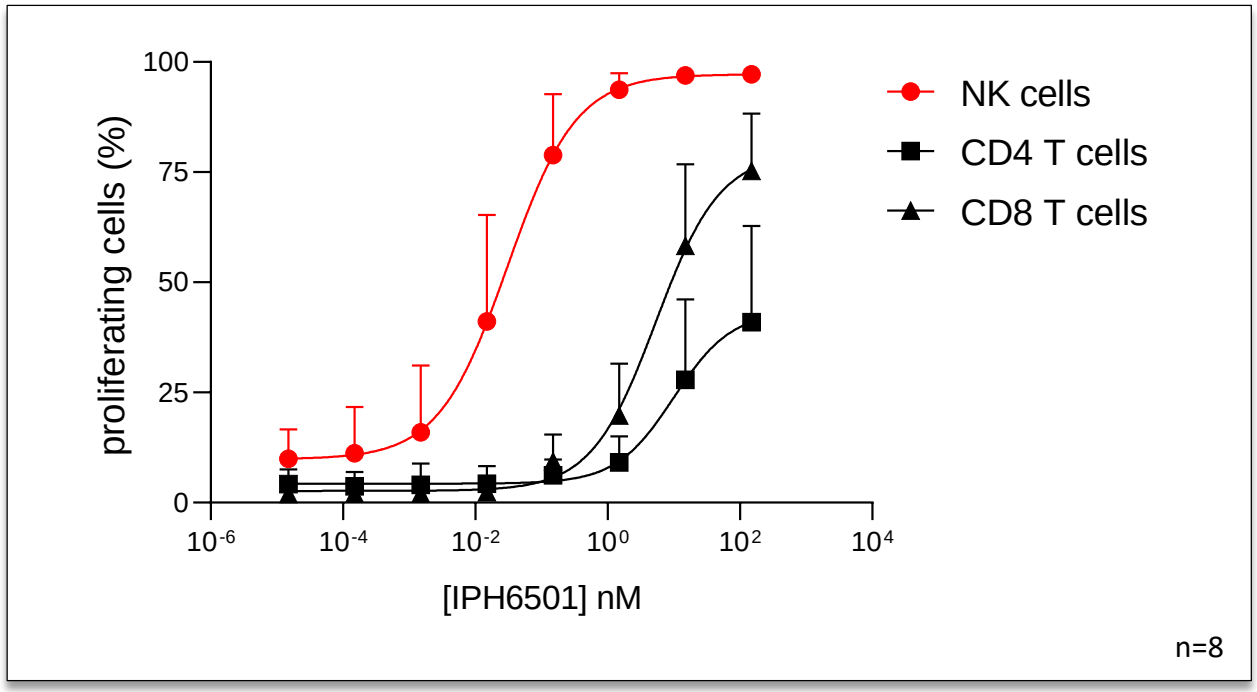


IPH6501 is designed to amplify and to redirect NK cell effector functions against CD20+ cancer cells

[1] *Gauthier L et al., Cell, 2019; Colomar-Carando N et al., Cancer Immunol Res, 2022; Gauthier L et al., Nature Biotech, 2023;*
[2] *Demaria O et al., Cell Rep Med, 2022*

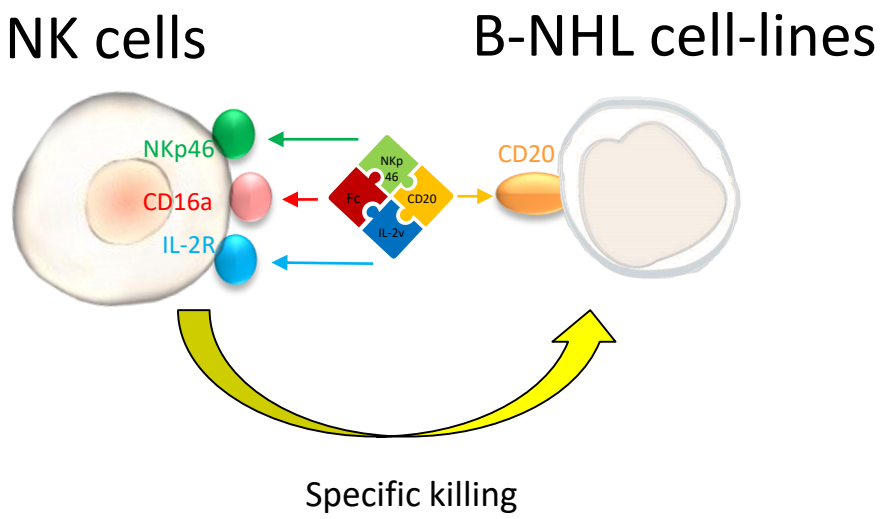
IPH6501 induced preferential NK cell proliferation over T cells among human PBMC

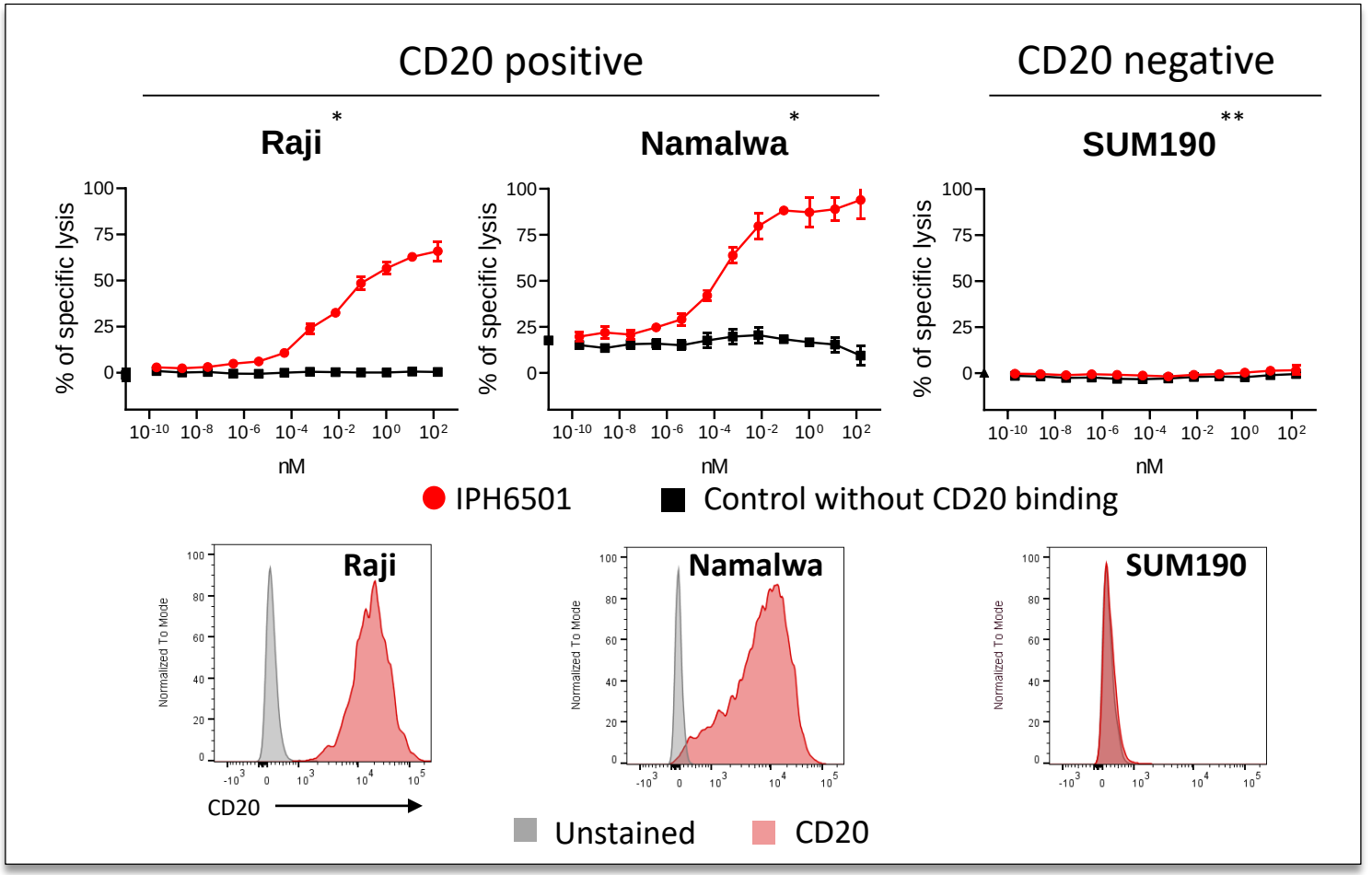




- IPH6501 induced NK cell proliferation with a lower EC_{50} and higher efficiency than T cells
- Low STAT5 phosphorylation on Treg induced by IPH6501 as compared to recombinant IL-2

IPH6501 induced NK cell specific killing of malignant B-cell lines expressing the CD20 antigen

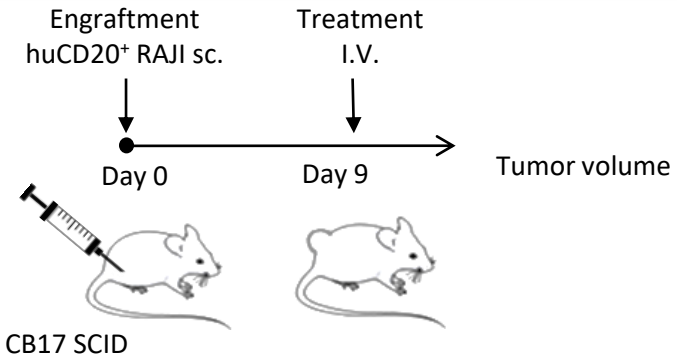


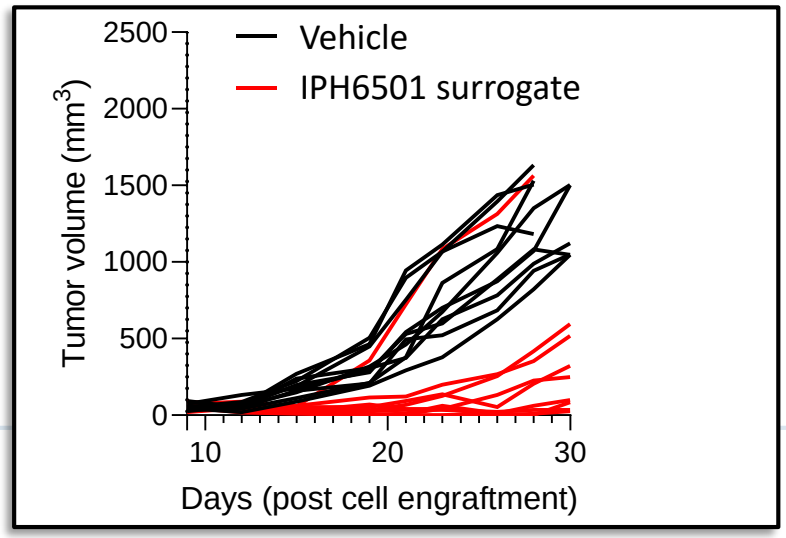


*Burkitt lymphoma cell lines **Breast cancer cell line

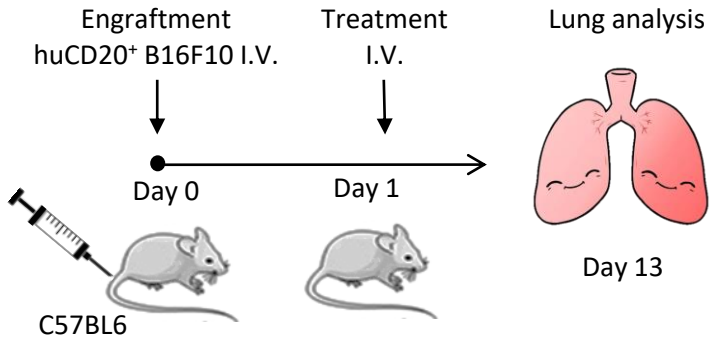
IPH6501 surrogate induced potent anti-tumor efficacy in human CD20+ tumor models in mice

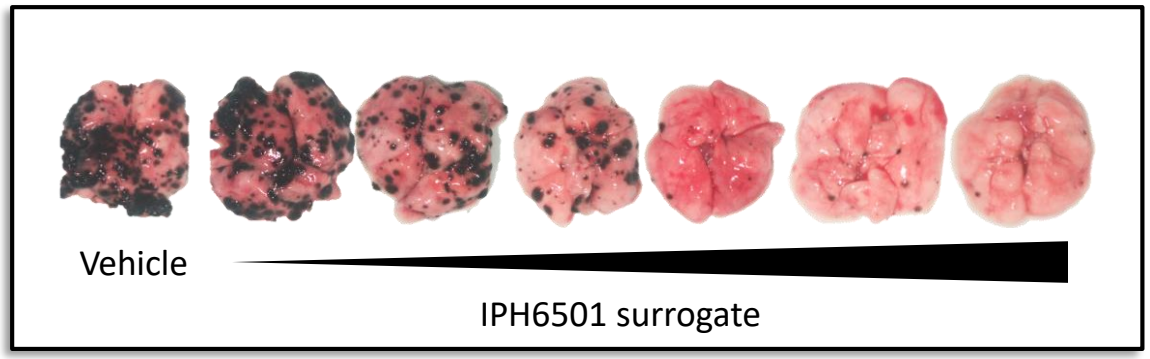
Subcutaneous B-NHL xenograft model
Raji





Disseminated syngeneic model
B16F10-huCD20





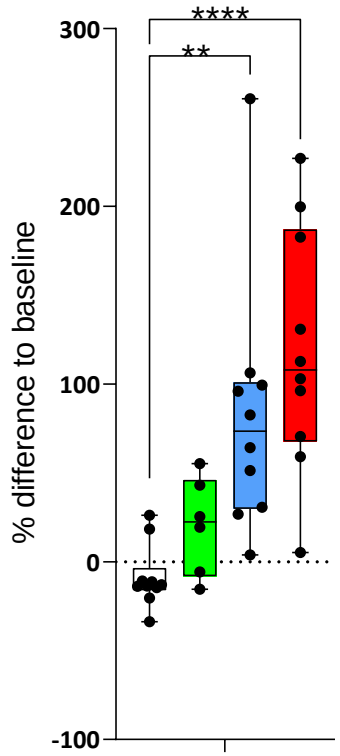
IPH6501 increased NK cell compartment in non-human primates

IPH6501

Vehicle
DL1
DL2
DL3

Blood immunophenotyping
Lymphoid organ IHC analysis

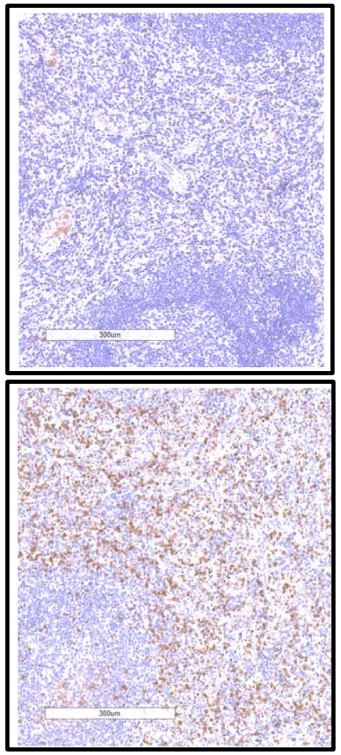
Blood NK cells



Spleen NK cells

Vehicle

IPH6501

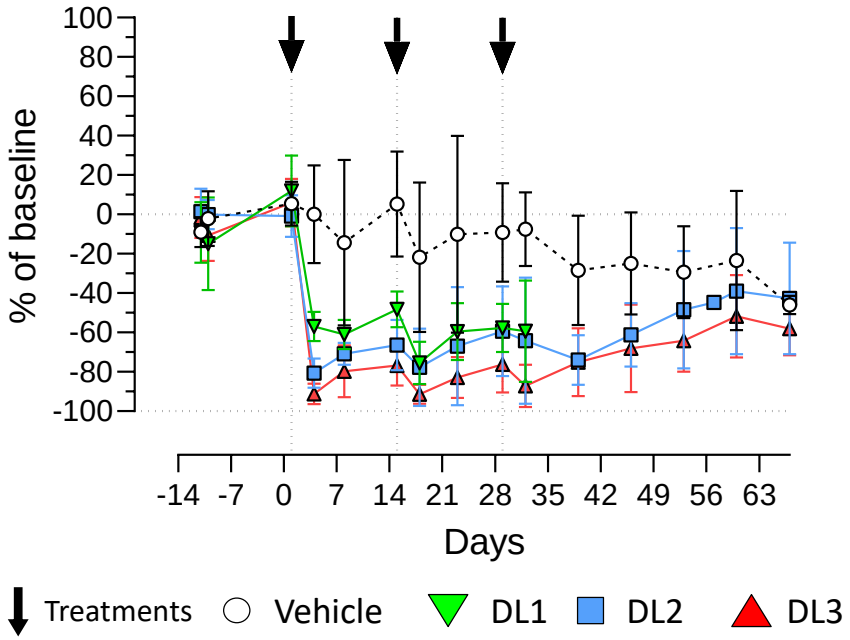


NKp46 staining

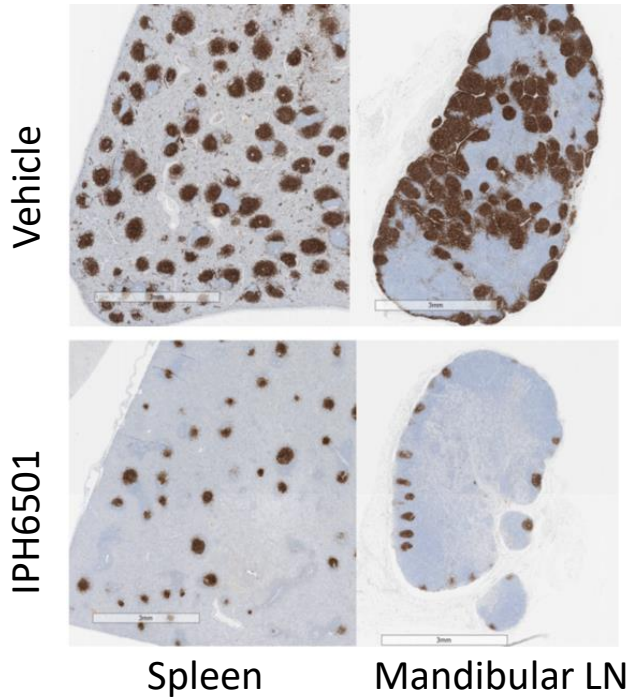
- IPH6501 increased NK cell counts in blood and lymphoid organs

IPH6501 depleted CD20⁺ B cells in non-human primates

CD20⁺ B cells in blood



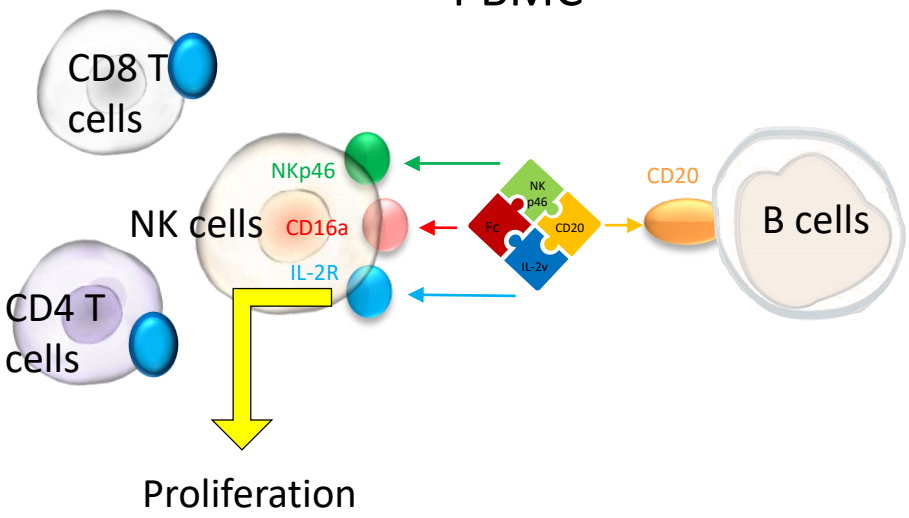
CD20 staining in lymphoid organs

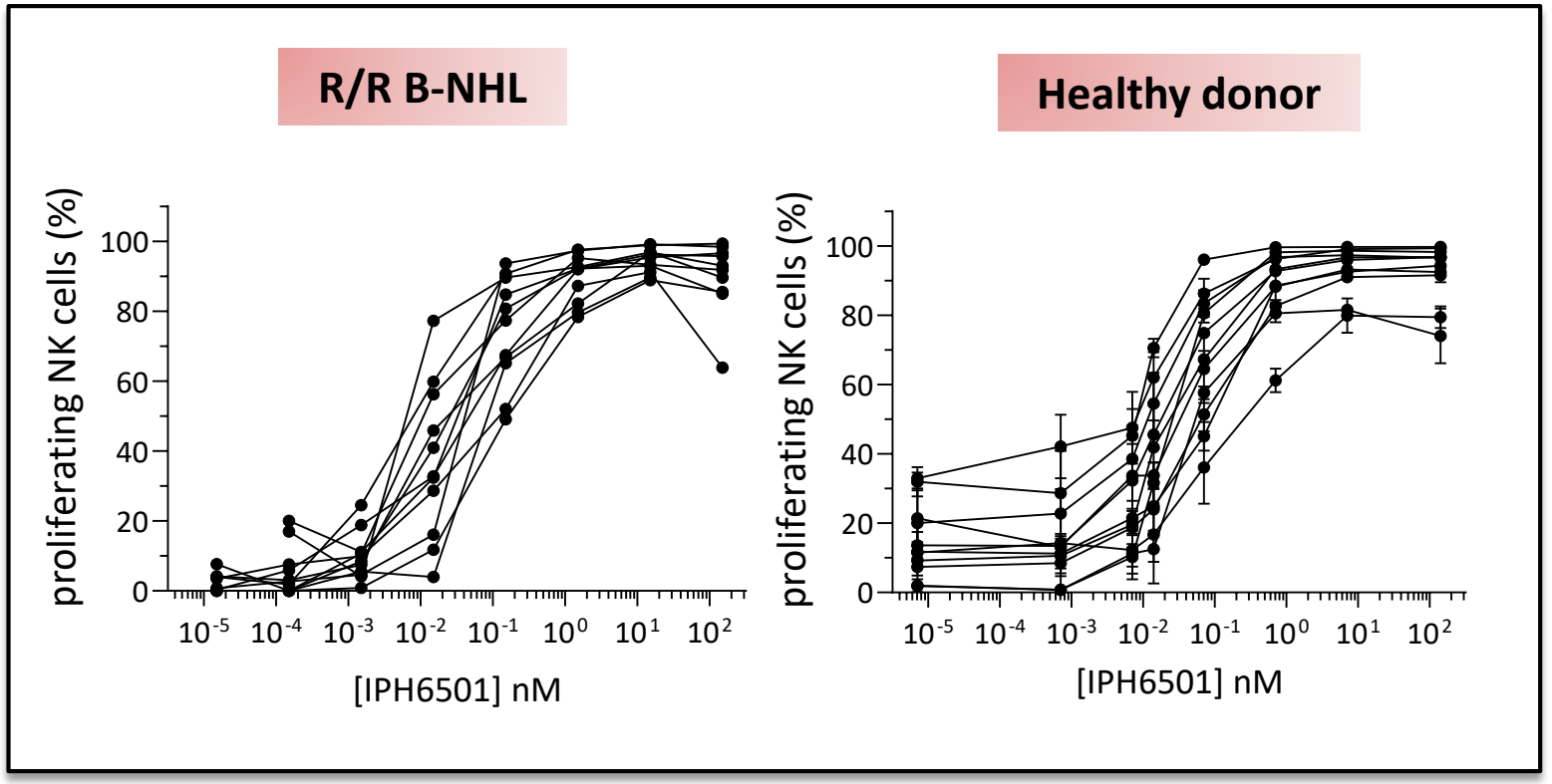


- IPH6501 induced CD20⁺ cell depletion in blood and lymphoid organs with low systemic cytokine release

IPH6501 stimulated NK cell proliferation from R/R B-NHL patients

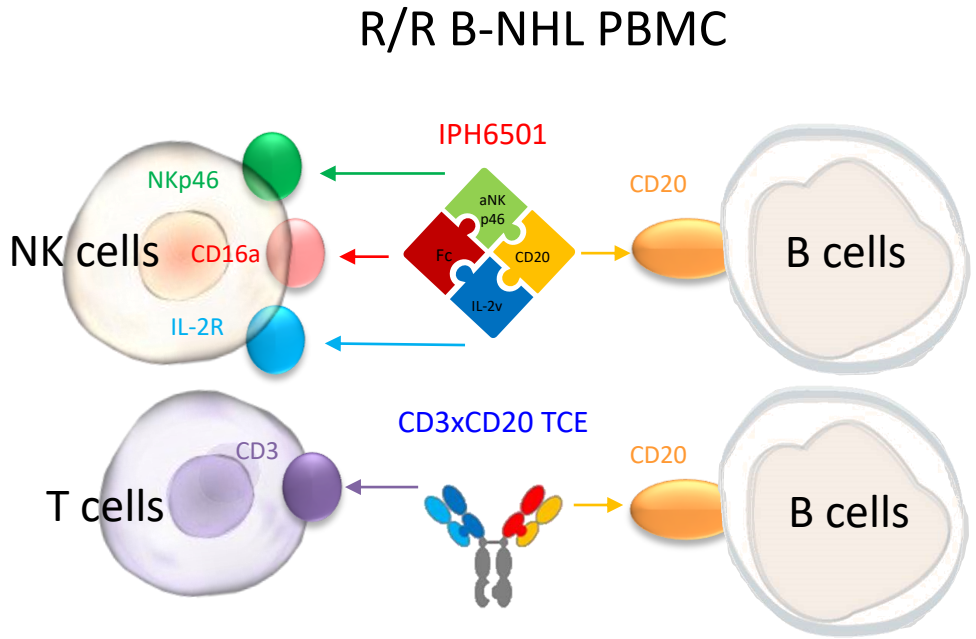
R/R B-NHL vs healthy donor PBMC

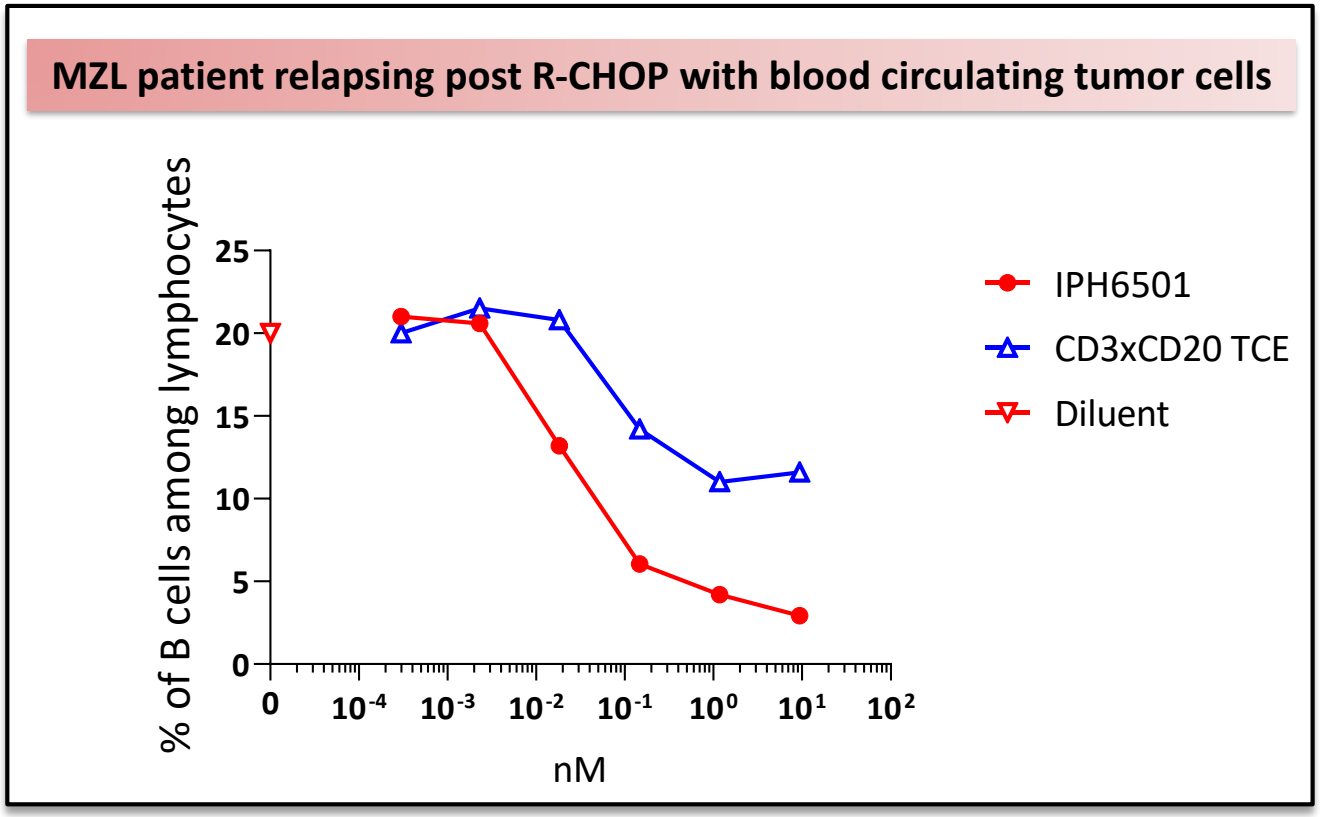




- IPH6501 stimulated NK cell proliferation in PBMC from R/R B-NHL patients with the same potency and efficacy as in healthy donor samples

IPH6501 induced autologous B cell depletion in PBMC from R/R B-NHL patients





- IPH6501 induced the elimination of CD20+ cells in samples from R/R B-NHL patients in leukemic phase
- In this pre-clinical setting, IPH6501 is more efficient than a T cell engager targeting CD20

IPH6501 is a first in class tetraspecific ANKET® targeting CD20 and developed for R/R B-NHL

- In preclinical *in vitro and in vivo* settings, IPH6501 induced effective NK cell proliferation and killing of CD20-positive cells
- NK cell therapies (including trispecific ANKET®, CAR-NK and allogeneic NK cell infusion) are well tolerated approaches in early clinical trials
- IPH6501 represents an innovative strategy to boost NK cell proliferation and antitumor functions, and is a promising alternative to T cell therapies
- IPH6501 is expected to enter Phase 1 clinical trial in 2023

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