

## Introduction

- Previously, we demonstrated that radiation therapy (RT) combined with Bempegaldesleukin (BEMPEG;NKTR-214), a first-in-class CD122-preferential IL-2 pathway agonist, enhanced the anti-tumor efficacy of radiation therapy (RT) through a T cell-dependent mechanism, although systemic responses were modest.
- Therefore, we explored alternative approaches to improve systemic tumor-specific immunity.
- Because toll-like receptor (TLR) signaling can induce antigen-presenting cell differentiation and reduce intratumoral immune suppression, we evaluated whether intratumoral NKTR-262, a polymer-modified TLR 7/8 agonist, combined with systemic BEMPEG treatment resulted in improved tumor-specific immunity and survival compared to BEMPEG combined with RT.
- Finally, comparison of BEMPEG combined with either RT or NKTR-262 will reveal mechanisms driving systemic anti-tumor responses.

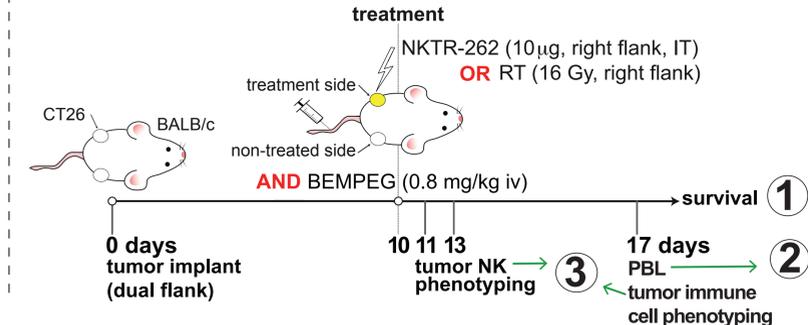
## Hypothesis

We hypothesized that BEMPEG/NKTR-262 therapy would be superior to BEMPEG/RT because TLR7/8 agonists enhance priming and antigen presentation, resulting in potent proinflammatory, anti-tumor immunity.

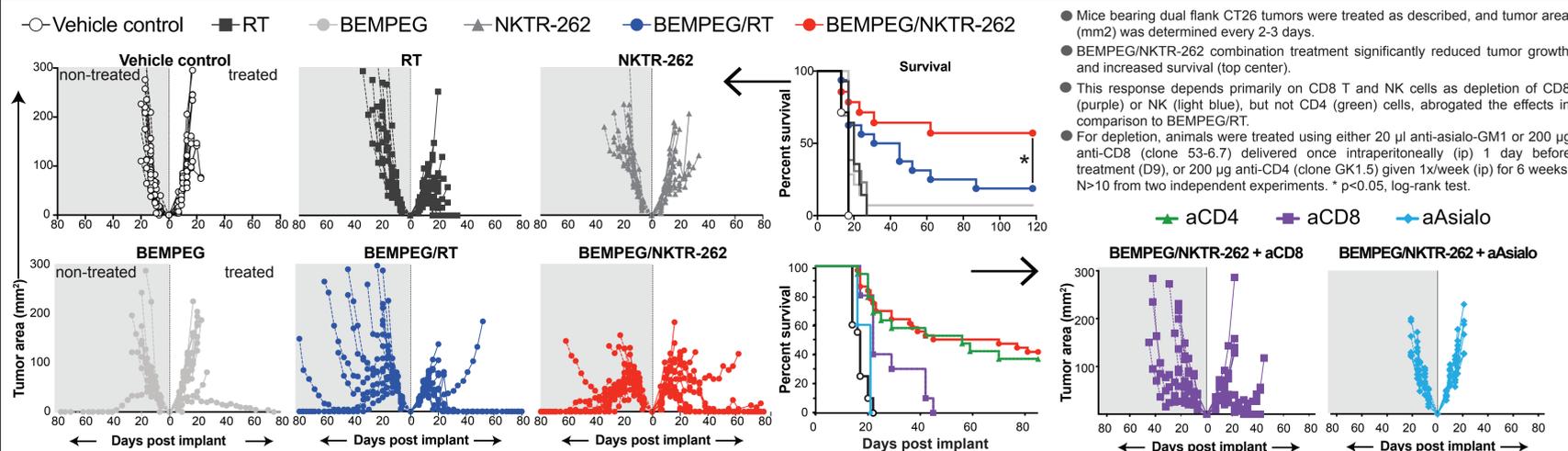
## Treatment groups

- Vehicle control
- RT
- BEMPEG
- NKTR-262
- BEMPEG/RT
- BEMPEG/NKTR-262

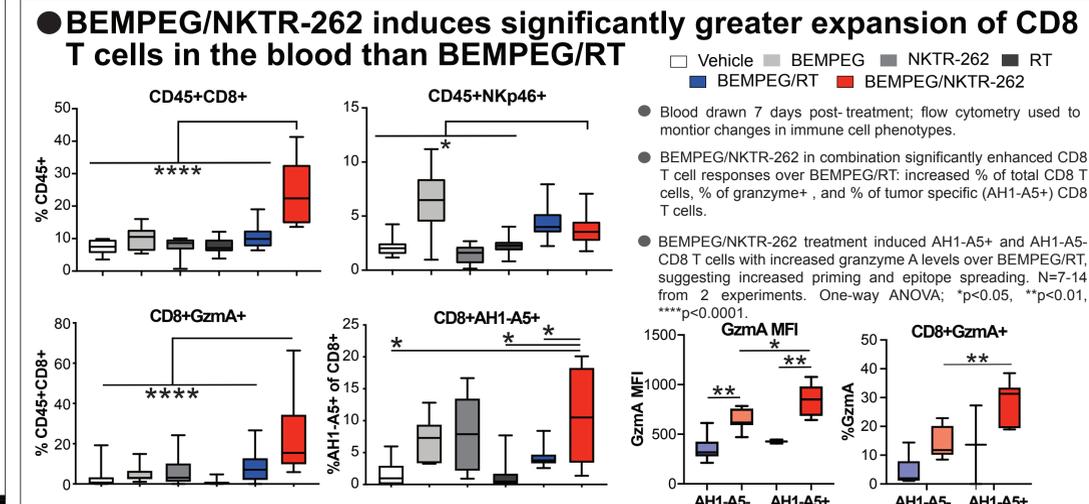
## Methods



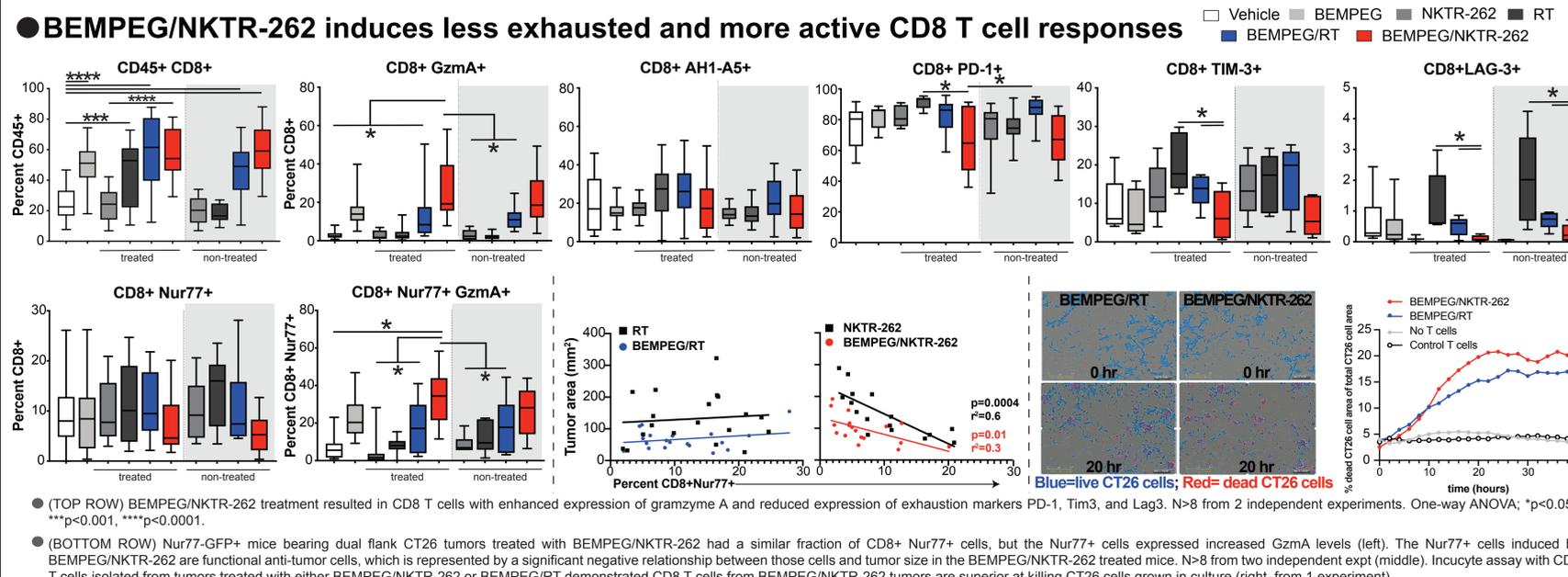
## 1 BEMPEG/NKTR-262 treatment improves survival over BEMPEG/RT and depends on CD8 T and NK cells



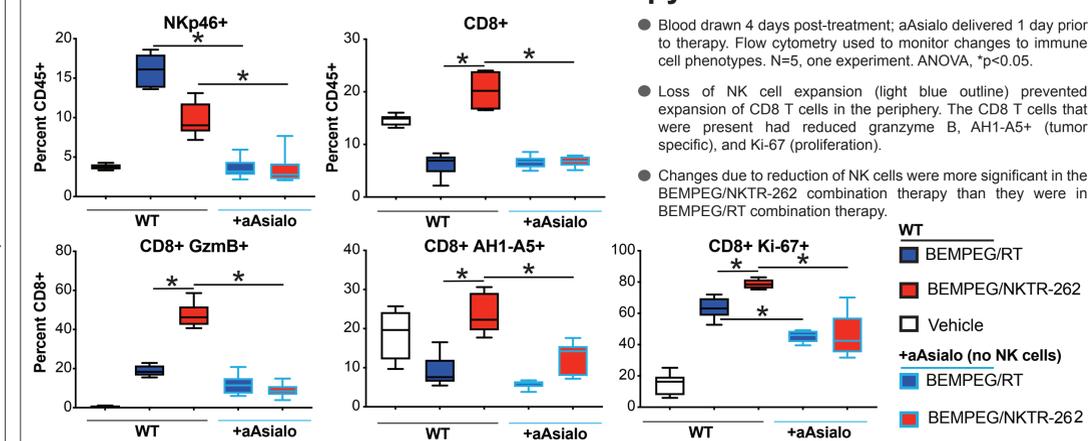
## 2 Peripheral blood immune cell phenotyping



## 3 Tumor infiltrating immune cell phenotyping



## 4 NK cells are required for CD8 T cell expansion after BEMPEG/NKTR-262 combination therapy



## Conclusions

- BEMPEG/NKTR-262 treatment produces a higher fraction of activated tumor antigen-specific cytotoxic CD8 T cells systemically, correlating with superior anti-tumor efficacy relative to BEMPEG combined with RT.
- Efficacy of BEMPEG/NKTR-262 combination therapy depends on CD8 T cells and NK cells.
- BEMPEG/NKTR-262 combination therapy induces intratumoral CD8 T cells that have increased activity as demonstrated by increased granzyme expression and increased tumor killing, and reduced conversion to an exhausted phenotype (PD-1+, TIM-3+, LAG-3+).
- Loss of NK cells reduces CD8 T cell percentages and function in the peripheral blood and in the tumor, suggesting a connection between early NK cell function and anti-tumor adaptive immune responses.

## Acknowledgements

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