MAYO CLINIC

FAVORABLE MODULATION OF CHIMERIC ANTIGEN RECEPTOR T CELLS SAFETY AND EFFICACY BY THE NON-COVALENT BTK INHIBITOR VECABRUTINIB

ABSTRACT 151073

Mohamad M. Adada, MD, PhD, Reona Sakemura, MD, PhD, Michelle J. Cox, MS, Claudia Manriquez-Roman, MS, Elizabeth L. Siegler, PhD, Erin E. Tapper, Carli M. Stewart, Kendall J. Schick, Ismail Can, Ekene J. Ogbodo, PhD, Evandro D. Bezerra, MD, Lionel A. Kankeu Fonkoua, MD, Mehrdad Hefazi, MD, Michael W. Ruff, MD, Pietro Taverna, PhD, Judith A. Fox, PhD, Gloria Olivier, PhD, Susan L. Slager, PhD, Wei Ding, MD, PhD, Sameer A. Parikh, MD, Neil E. Kay, MD and Saad S.Kenderian, MB, ChB.

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DISCLOSURES

- **Sakemura:** *Humanigen:* Patents & Royalties.
- **Cox:** *Humanigen:* Patents & Royalties.
- **Fox:** *Sunesis Pharmaceuticals:* Current Employment.
- **Ding:** *Merck:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Octapharma:* Membership on an entity's Board of Directors or advisory committees; *DTRM:* Research Funding.
- **Parikh:** *Pharmacyclics, MorphoSys, Janssen, AstraZeneca, TG Therapeutics, Bristol Myers Squibb, Merck, AbbVie, and Ascentage Pharma:* Research Funding; *Pharmacyclics, AstraZeneca, Genentech, Gilead, GlaxoSmithKline, Verastem Oncology, and AbbVie:* Membership on an entity's Board of Directors or advisory committees.
- **Kay:** *MEI Pharma:* Research Funding; *Sunesis:* Research Funding; *Rigel:* Membership on an entity's Board of Directors or advisory committees; *AstraZeneca:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Membership on an entity's Board of Directors or advisory committees; *CytomX Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *TG Therapeutics:* Research Funding; *Juno Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Bristol Meyer Squib:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Celgene:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Behring:* Membership on an entity's Board of Directors or advisory committees; *Genentech:* Research Funding; *Morpho-sys:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Targeted Oncology:* Membership on an entity's Board of Directors or advisory committees; *Tolero Pharmaceuticals:* Research Funding; *Dava Oncology:* Membership on an entity's Board of Directors or advisory committees; *Acerta Pharma:* Research Funding; *Agios Pharm:* Membership on an entity's Board of Directors or advisory committees; *Pharmacyclics:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Oncotracker:* Membership on an entity's Board of Directors or advisory committees.
- **Kenderian:** *Humanigen, Inc.:* Consultancy, Honoraria, Research Funding.

INTRODUCTION

BACKGROUND

- CD19-targeted chimeric antigen receptor T cell (CART19) therapy has been remarkably successful in treating a subset of patients with hematological malignancies.
- Limitations:
  - Toxicities
  - Short durable responses
  - Patients develop resistance due to intrinsic CART cell dysfunction

INTRODUCTION
BACKGROUND

- Combination of various strategies are in development to overcome these limitations.
- Irreversible BTK inhibition with Ibrutinib that is combined with CART19 has shown promising results in preclinical and clinical studies.
  - Limitations:
    - Data that it inhibits CART cell proliferation[1]
    - Lack specificity[2]
    - More side effects[2]

[1]*Ruella M, et.al. The Addition of the BTK Inhibitor Ibrutinib to Anti-CD19 Chimeric Antigen Receptor T Cells (CART19) Improves Responses against Mantle Cell Lymphoma. Clin Cancer Res. 2016 Jun 1;22(11):2684-96. doi: 10.1158/1078-0432.CCR-15-1527. Epub 2016 Jan 27. PMID: 26819453.*

[2]Zain R, Vihinen M. Structure-Function Relationships of Covalent and Non-Covalent BTK Inhibitors. *Front Immunol*. 2021;12:694853. Published 2021 Jul 19. doi:10.3389/fimmu.2021.694853

INTRODUCTION

BACKGROUND - **VECABRUTINIB**

- Potent, reversible, selective, non-covalent inhibitor of BTK.
- Unlike other covalent BTK inhibitors, it does not interact with the cysteine 481 residue, which is a well-established resistance mechanism.
- Has better bioavailability and longer half life
- Very well tolerated
- Has shown limited efficacy in the treatment of patients with B-cell malignancies (NCT03037645) .
- In the murine Eμ-TCL1 model, combination of vecabrutinib with venetoclax augmented their antitumor activity relative to their use as single agents and significantly improved survival (Jebaraj et al., Blood, 2021).

INTRODUCTION

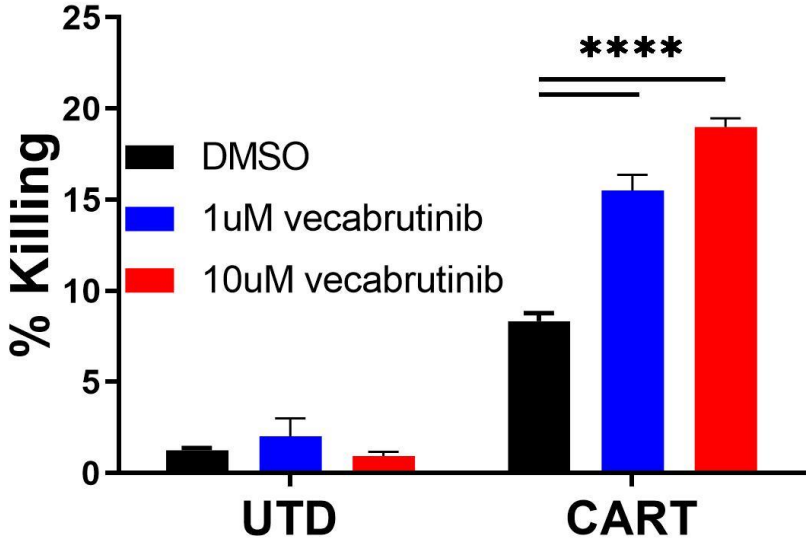
AIM AND RELEVANCE

- Other reversible BTK inhibitors proven to be good immunomodulators and potentially helpful in the treatment of autoimmune diseases *
- Aim:
  - Test Vecabrutinib as a potential CART19 immunomodulator
- There is a critical need in the field of adoptive cellular immunotherapy to improve the CART cell product through:
  - Increasing CART efficacy
  - Decrease associated toxicities

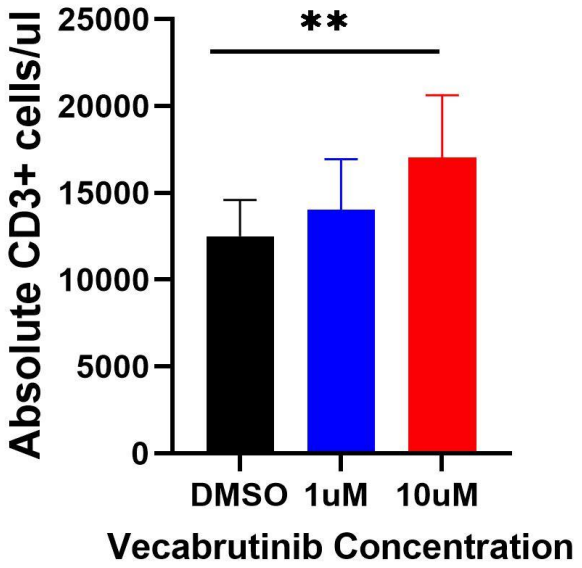
* Zhang D, Gong H, Meng F. Recent Advances in BTK Inhibitors for the Treatment of Inflammatory and Autoimmune Diseases. *Molecules*. 2021;26(16):4907. Published 2021 Aug 13. doi:10.3390/molecules26164907

VECABRUTINIB EFFECTS ON CART19 CELL FUNCTIONS IN-VITRO

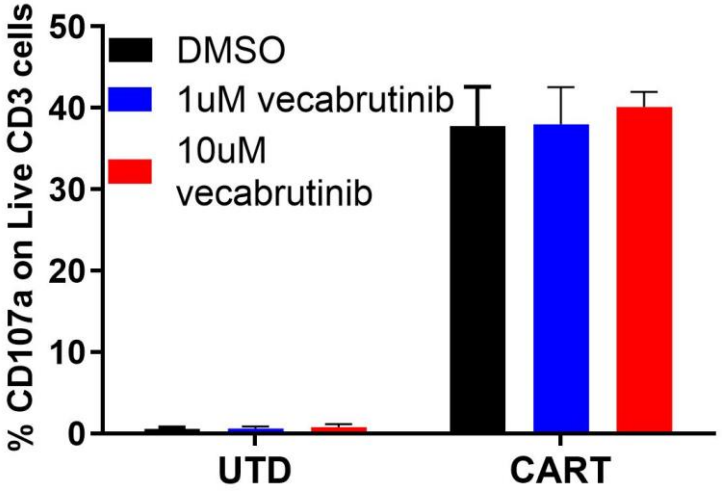
VECABRUTINIB DOES NOT IMPAIR CART CELLS EFFECTOR FUNCTIONS



CART19:JeKo-1 cells (1:1 ratio)



CART19 : Irradiated JeKo-1 cells (1:1 ratio)

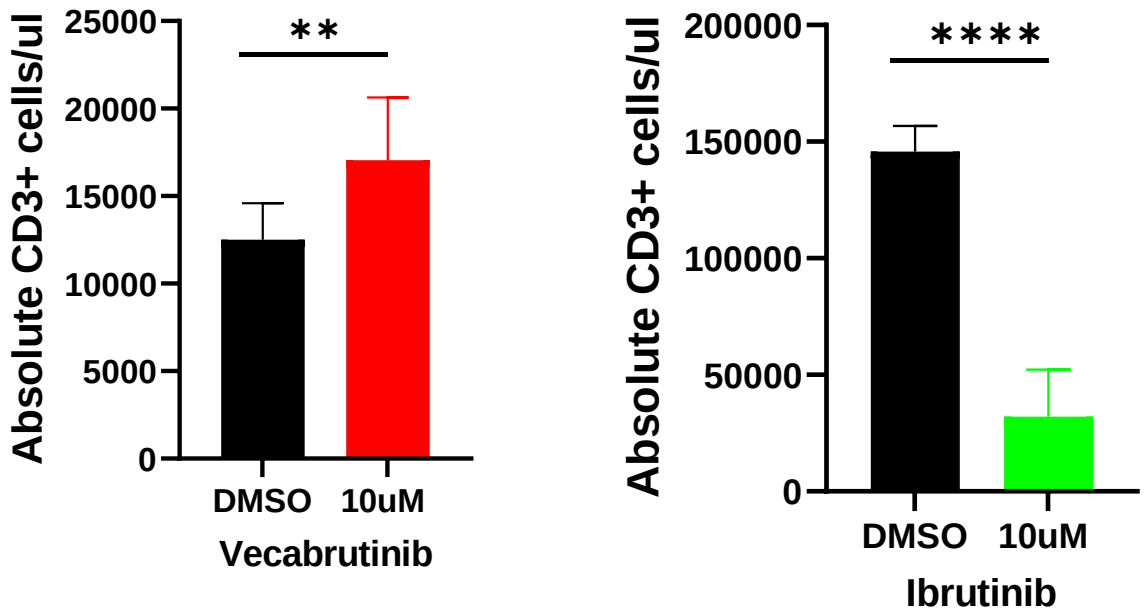


CART19:JeKo-1 cells (1:1 ratio)

****p<0.0001, **p<0.01, two-way ANOVA

VECABRUTINIB EFFECTS ON CART19 CELL FUNCTIONS IN-VITRO

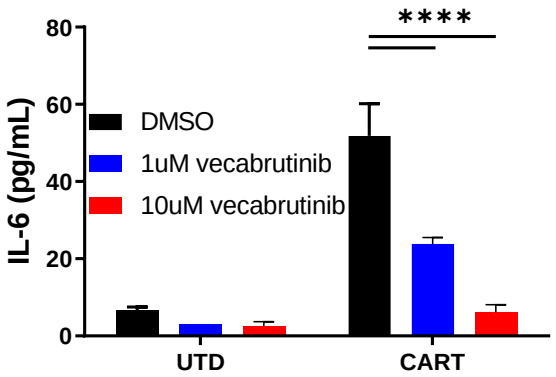
UNLIKE IBRUTINIB, VECABRUTINIB INDUCES CART PROLIFERATION AT HIGH DOSAGE

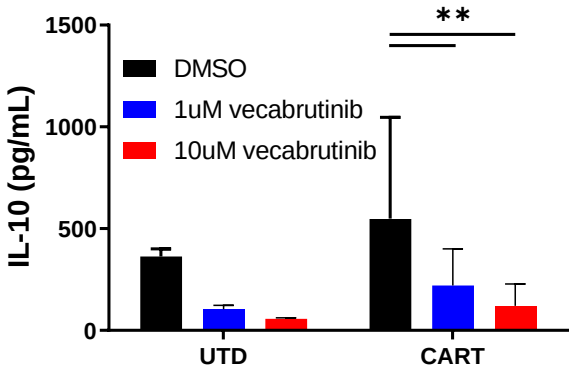


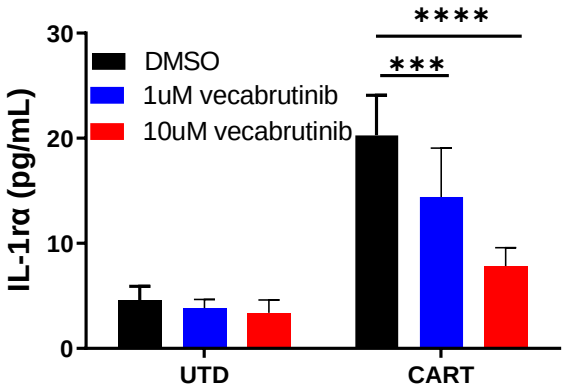
CART19 : Irradiated JeKo-1 cells (1:1 ratio)

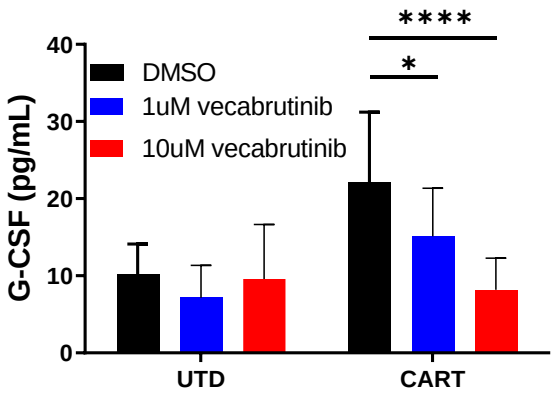
VECABRUTINIB EFFECTS ON CART19 CELL FUNCTIONS IN-VITRO

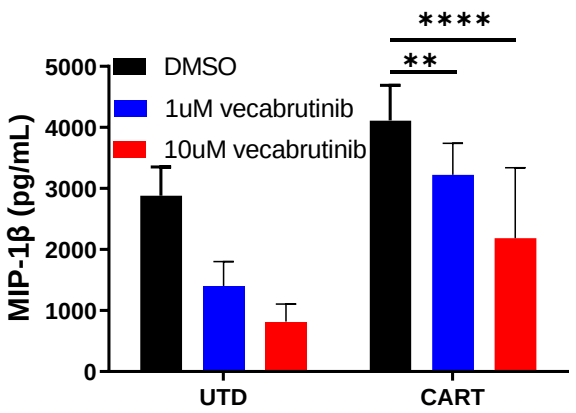
VECABRUTINIB REDUCES THE SECRETION OF PRO-INFLAMMATORY CYTOKINES

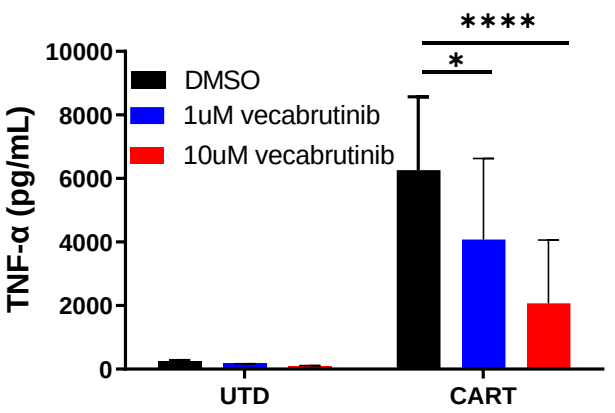






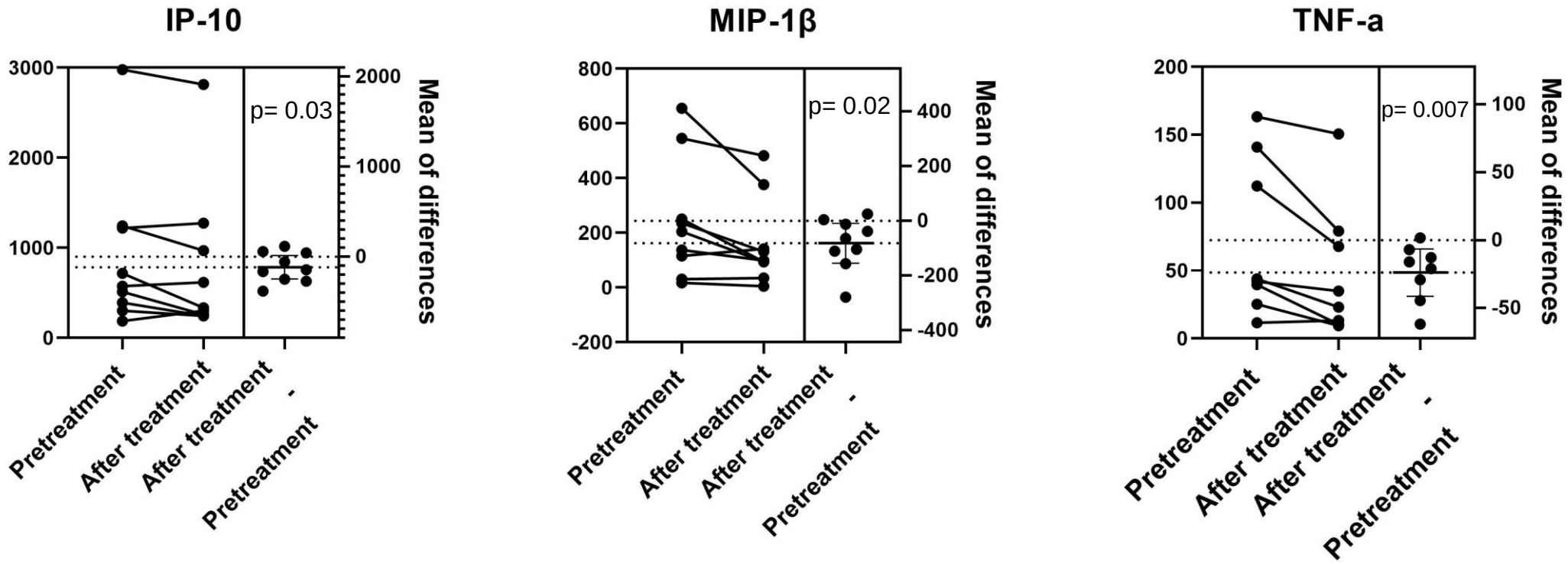






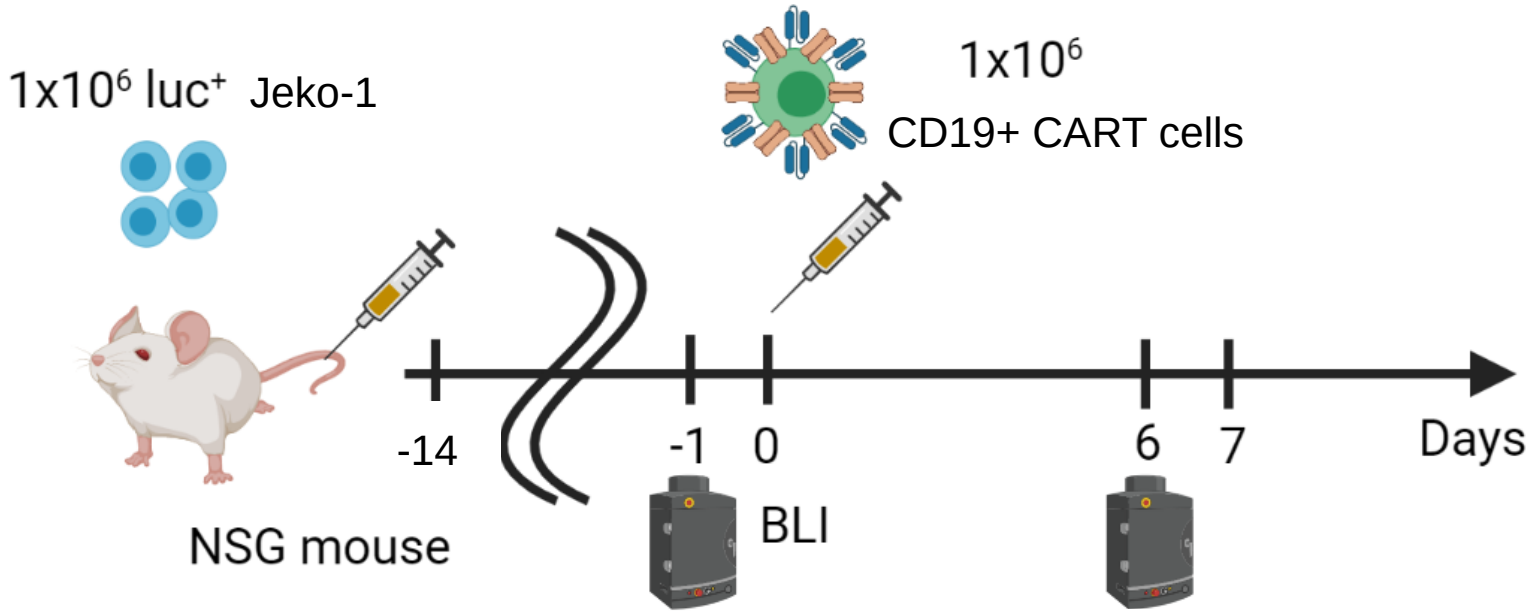
****p<0.0001, ***p<0.001 **p<0.01, two-way ANOVA

VECABRUTINIB SIGNIFICANTLY REDUCED THE LEVELS OF MULTIPLE PRO-INFLAMMATORY CYTOKINES LINKED TO CAR T CELL TOXICITY AMONG PATIENTS THAT MAINTAINED STABLE DISEASE (NCT03037645)



VECABRUTINIB EFFECTS ON CART19 CELL FUNCTIONS IN-VIVO

IN-VIVO MOUSE MODEL

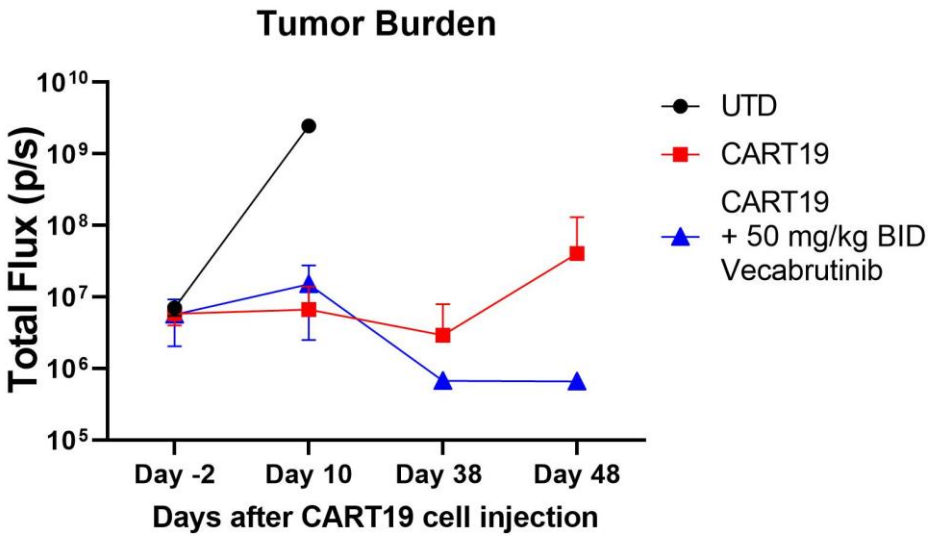


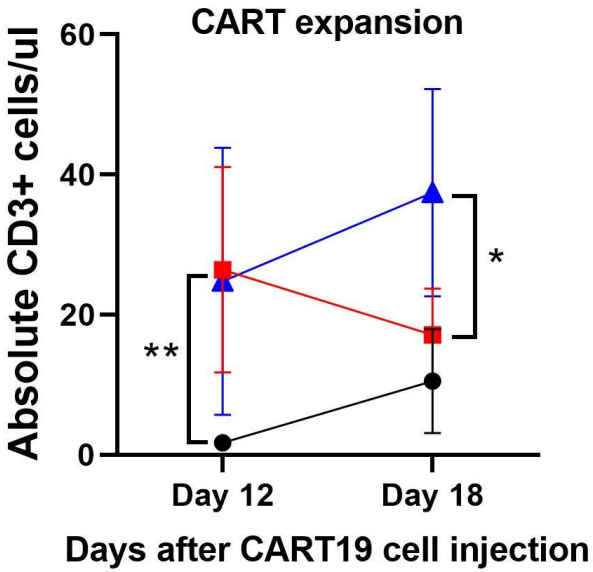
- Imaging
- Randomization
- Gavage with Vecabrutinib twice daily for 1 month

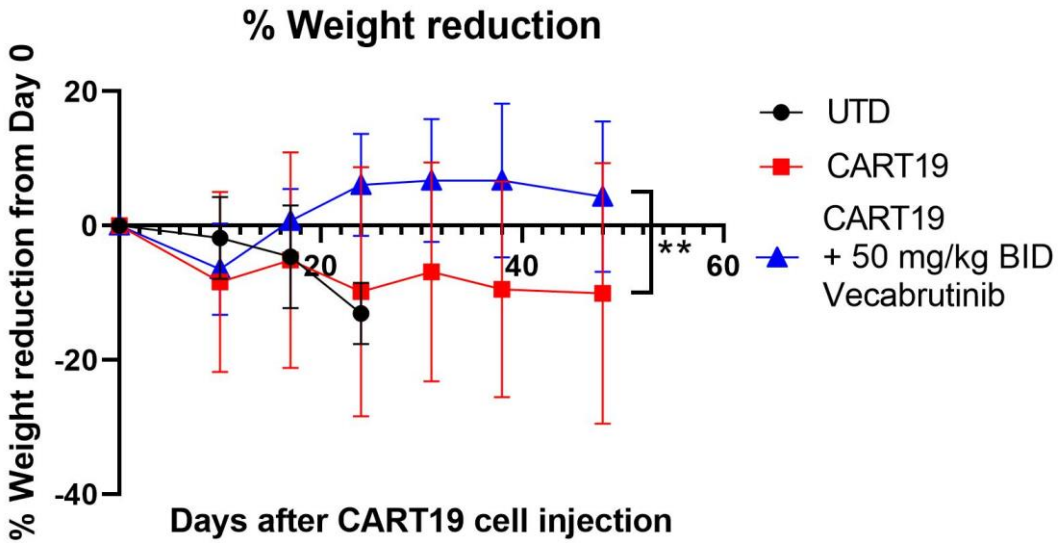
- Weekly imaging
- Weekly bleeding and flow cytometry
- Weekly weighing

VECABRUTINIB EFFECTS ON CART19 CELL FUNCTIONS IN-VIVO

VECABRUTINIB IMPROVED CART19 EXPANSION AND TUMOR CONTROL



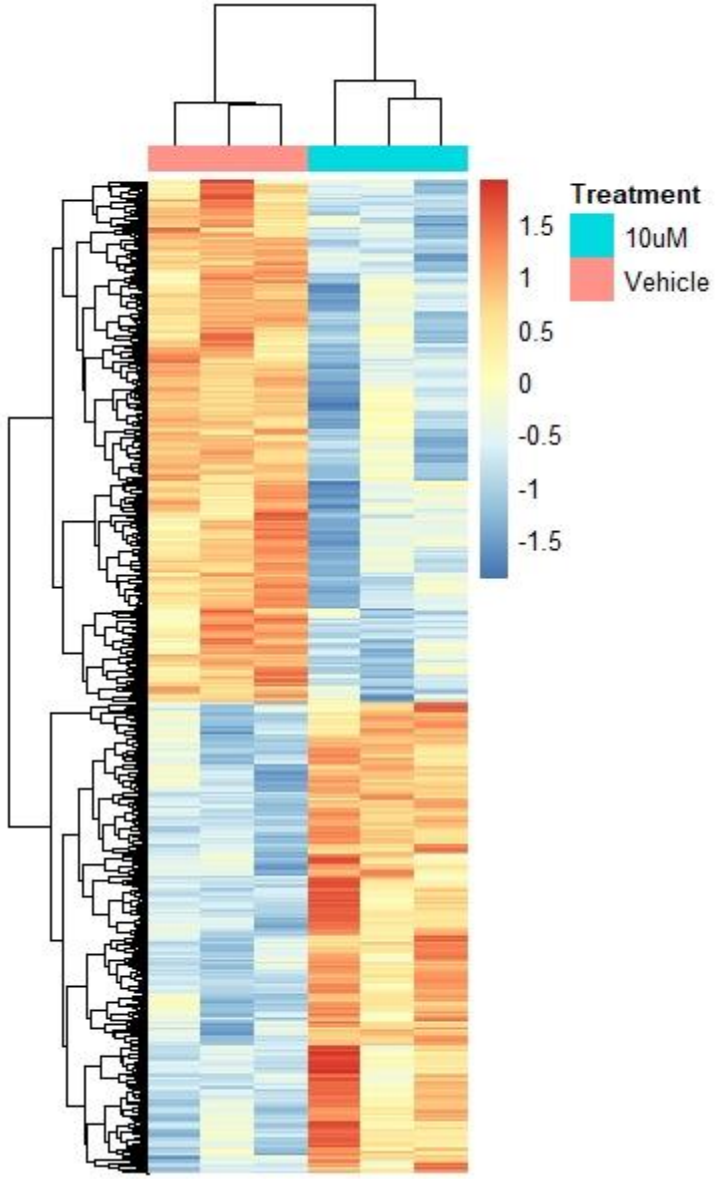




*p<0.05, **p<0.01, one-way ANOVA

UNDERSTANDING THE MECHANISM OF VECABRUTINIB-INDUCED CART19 MODULATION

VECABRUTINIB INDUCED SIGNIFICANT TRANSCRIPTOMIC CHANGES SUGGESTING ALTERATIONS IN SIGNALING PATHWAYS



SUMMARY

KEY TAKE-AWAY POINTS

- There is strong evidence that reversible BTK inhibition may improve CART cell-mediated efficacy and decreases associated toxicity:
- In-vitro, vecabrutinib:
  - Markedly increases CART19 cell-mediated cytotoxicity,
  - Enhances CART19 cells proliferation (unlike Ibrutinib)
  - Decreases the levels of multiple pro-inflammatory cytokines that are known players in CRS
- *In-vivo,* vecabrutinib:
  - Enhances CART19 expansion
  - Leads to sustained anti-tumor activity
- Vecabrutinib induces transcriptomic changes which upregulate the PI3K/AKT pathway; this could explain its effects on CART proliferation.

SUMMARY

FUTURE DIRECTIONS

- Understand in more depth the mechanism by which reversible BTK inhibition with vecabrutinib modulate CART cell function
- Evaluate clinical development options to assess the combination of vecabrutinib and CART19 cell therapy

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https://www.mayo.edu/research/labs/t-cell-engineering/overview

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QUESTIONS & ANSWERS

Adada.Mohamad@mayo.edu