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

ABSTRACT 151073

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• **Sakemura**: *Humanigen*: Patents & Royalties.

• **Cox**: *Humanigen*: Patents & Royalties.

• **Fox**: *Sunesis Pharmaceuticals*: Current Employment.

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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\(^2\)


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

VECABRUTINIB EFFECTS ON CART19 CELL FUNCTIONS IN-VITRO

VECABRUTINIB DOES NOT IMPAIR CART CELLS EFFECOR FUNCTIONS

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

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

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

CART19:JeKo-1 cells (1:1 ratio)
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)
VECBRUTINIB EFFECTS ON CART19 CELL FUNCTIONS IN-VITRO

VECBRUTINIB 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)

- **IP-10**: Pretreatment vs. After treatment, $p=0.03$
- **MIP-1β**: Pretreatment vs. After treatment, $p=0.02$
- **TNF-a**: Pretreatment vs. After treatment, $p=0.007$
VECABRUTINIB EFFECTS ON CART19 CELL FUNCTIONS IN-VIVO
IN-VIVO MOUSE MODEL

1x10^6 luc+ Jeko-1

NSG mouse

1x10^6 CD19+ CART cells

-14

0

-1

6

7

BLI

Days

• 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

*T<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

Viracta
QUESTIONS & ANSWERS

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