
sitc
1985
35th ANNIVERSARY
2020
Reimagined
SITC 2020
NOVEMBER 9–14
sitc
Society for Immunotherapy of Cancer

Preclinical development of a novel colon-targeted therapeutic for the treatment of Immune Checkpoint Inhibitor-colitis

Nazli Dizman, MD[1,2]; Milton Greenberg, PhD[3]; Andrew C. Newman, PhD[3]; Jonathan Skupsky, MD, PhD[4]; JoAnn Hsu, BSc[1], Zeynep Zengin, MD[1]; Nick Salgia, BSc[1]; Luis Meza, MD[1]; Sabrina Salgia, BSc[1]; Sumanta K. Pal, MD[1]

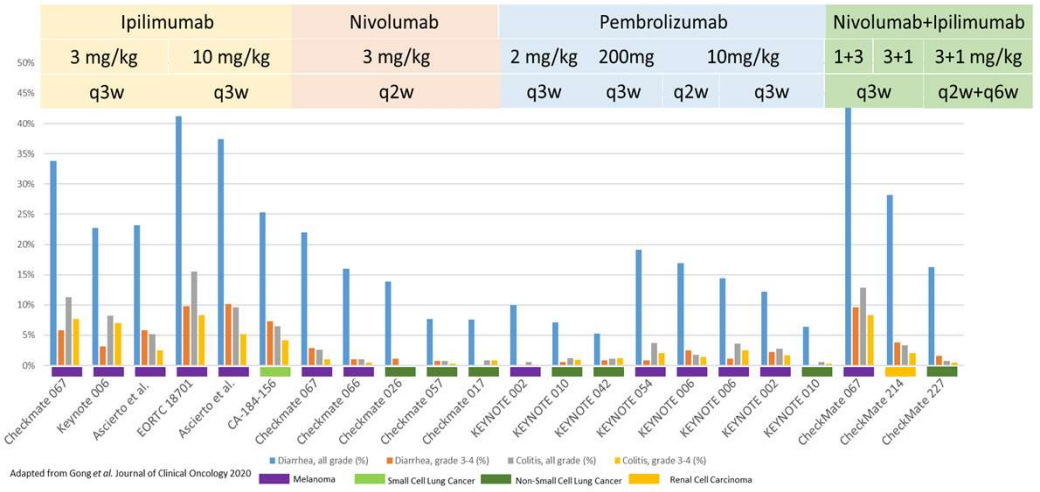
[1]City of Hope Comprehensive Cancer Center, Duarte, CA
[2]Yale University, Yale New Haven Hospital, New Haven, CA
[3]Vivreon Gastrosciences, Inc., San Diego, CA
[4]VA Long Beach Healthcare System, Long Beach, CA

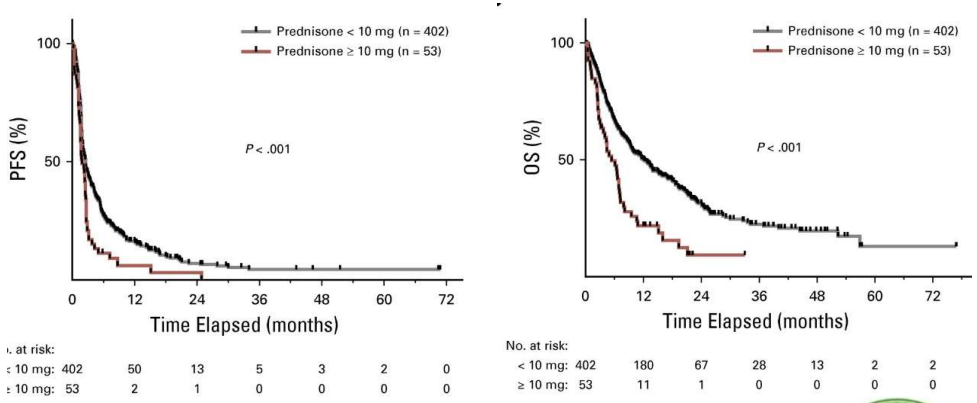
Disclosures

- None.

Background

- Immune checkpoint inhibitors (ICPIs) have led to durable responses in multiple cancer types
- ICPI colitis has emerged as a frequent toxicity leading to ICPI discontinuation
- Steroids represent the mainstay of therapy for ICPI colitis but the impact on clinical efficacy of ICPIs is debatable
- Novel therapies that do not interfere with ICPI therapy are needed for ICPI colitis

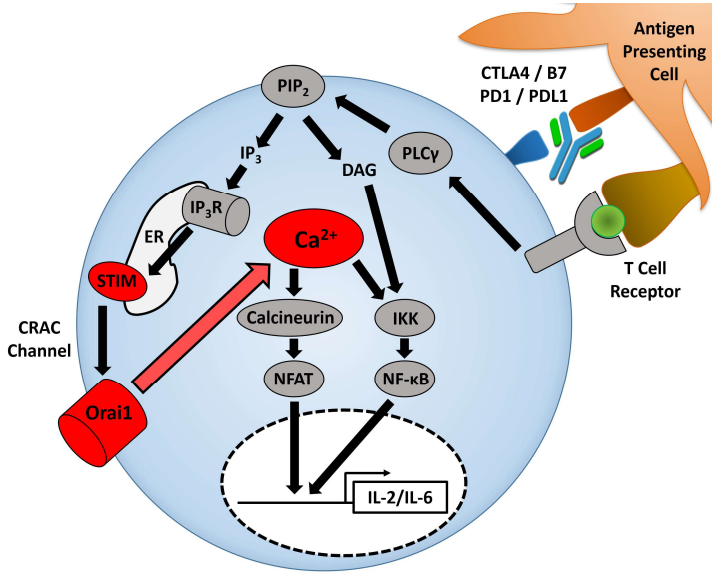


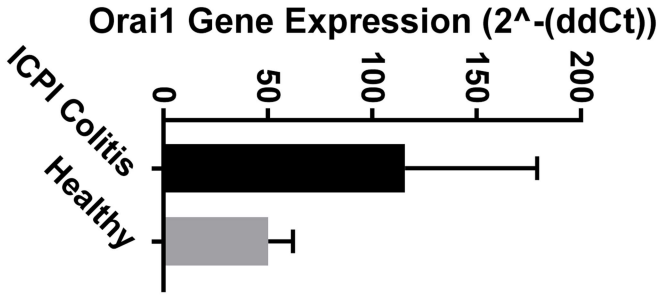


Arbour *et al.* Journal of Clinical Oncology

Background

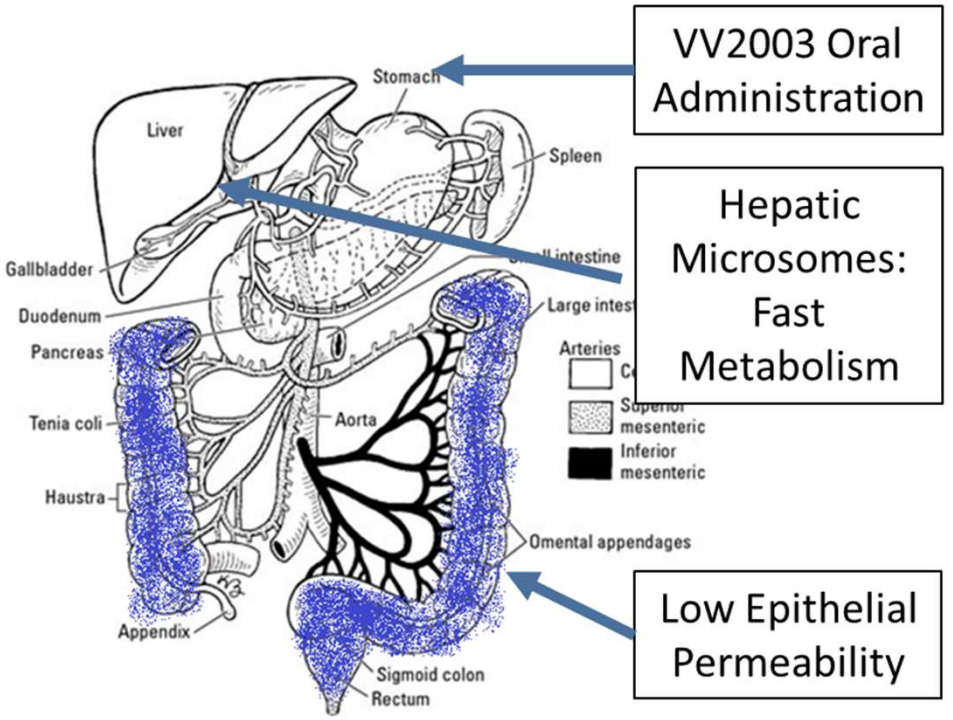
- The Ca^{2+} release-activated Ca^{2+} (CRAC) channel is activated by antigen presentation to T-cells
- CRAC drives production of inflammatory mediators such as NF-κB and NFAT
- Intestinal tissue from ICPI colitis patients has higher levels of *Orai1* gene expression (a constituent of CRAC channel) versus healthy patients
- We hypothesize that inhibition of the CRAC channel could ameliorate ICPI colitis





VV2003

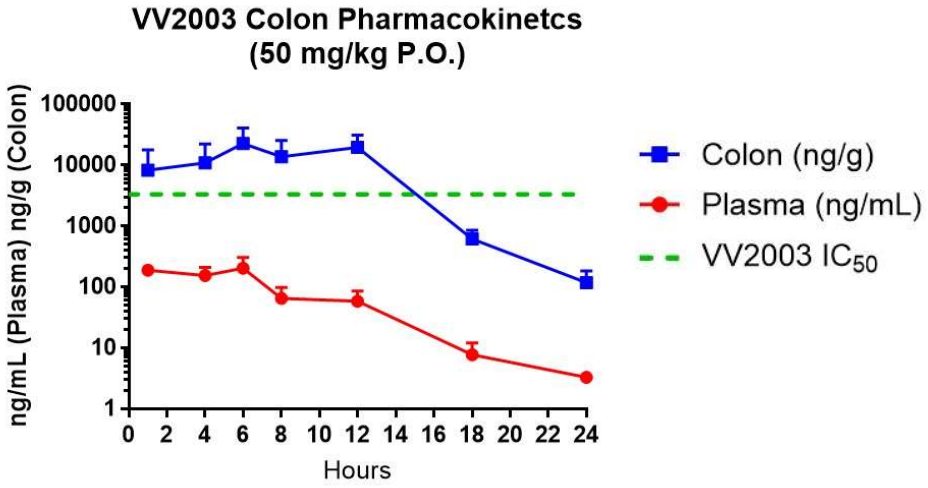
- First-in-class potent and selective CRAC channel inhibitor
- Low epithelial permeability likely confers gut retention and minimal systemic absorption
- Agent is rapidly metabolized by hepatic microsomes
- We hypothesize that VV2003 could ameliorate ICPI colitis while ICPI therapy is maintained

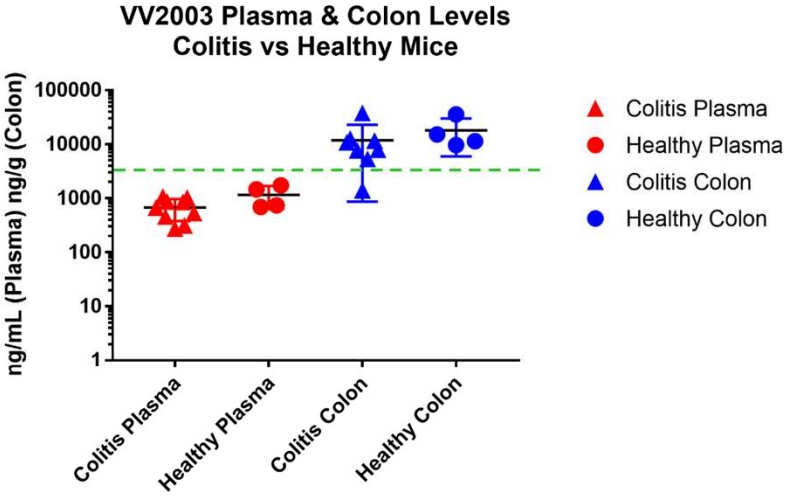


Objectives

- To characterize the preclinical pharmacokinetics of VV2003, a first-in-class CRAC inhibitor
- To characterize the activity of VV2003 in murine models of immune-related colitis
- To determine if VV2003 modulates the activity of ICPIs
- To characterize the activity of VV2003 in *ex vivo* tissues of patients with ICPI colitis

Pharmacokinetics

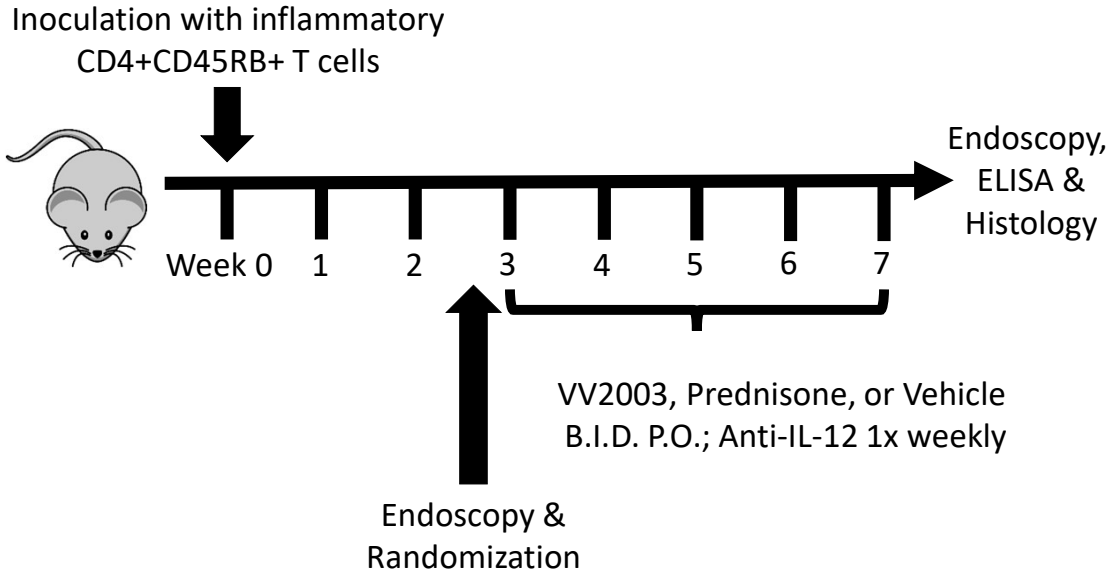


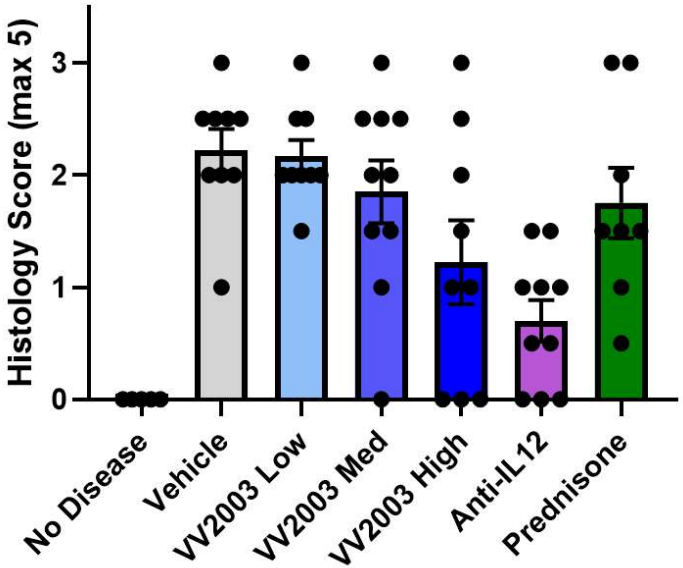


- Single oral dose in mice of VV2003
- Colon tissue and plasma were collected at indicated time points
- VV2003 is found at levels above the IC_{50} in colon homogenate after oral dosing

- Other agents may penetrate healthy tissue but not damaged tissue
- VV2003 is found at high levels in colon tissue regardless of disease status

Activity of VV2003 in murine models of ICPI-colitis



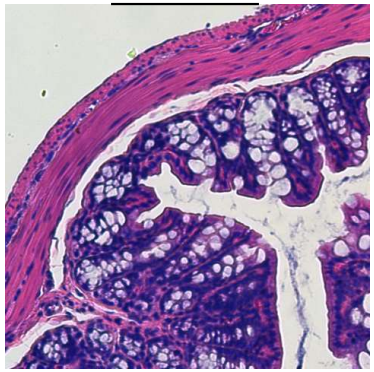


- Adoptive T-cell colitis model is a systemic inflammatory model that presents as colitis, mirroring clinical disease state
- High doses of VV2003 resulted in significant improvement in colitis score

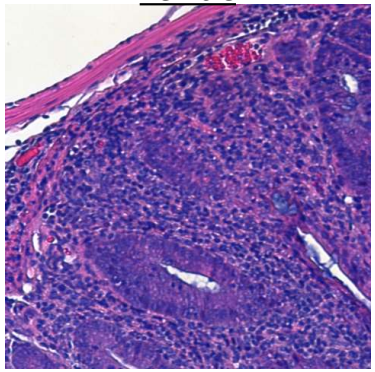
Activity of VV2003 in murine models of ICPI-colitis

- No Disease
- Normal crypt architecture and goblet cells
- No infiltrating lymphocytes or neutrophils
- No mucosal hyperplasia

No Disease



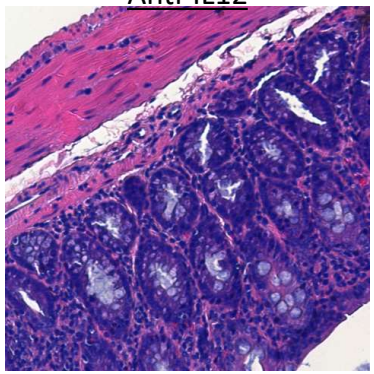
Vehicle



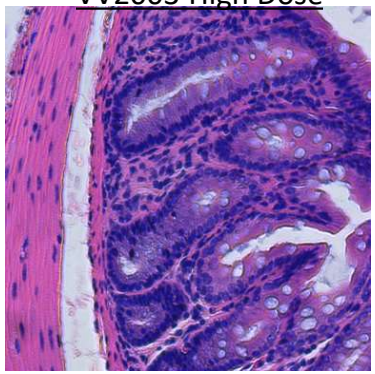
- Moderate disease
- Abnormal crypt architecture with goblet cell loss
- Moderate infiltrating lymphocytes and neutrophils
- Moderate mucosal hyperplasia with focal hemorrhage

- Mild disease
- Preserved crypt architecture with minimal goblet cell drop-out
- Mild infiltrating lymphocytes and neutrophils
- Mild mucosal hyperplasia

Anti-IL12

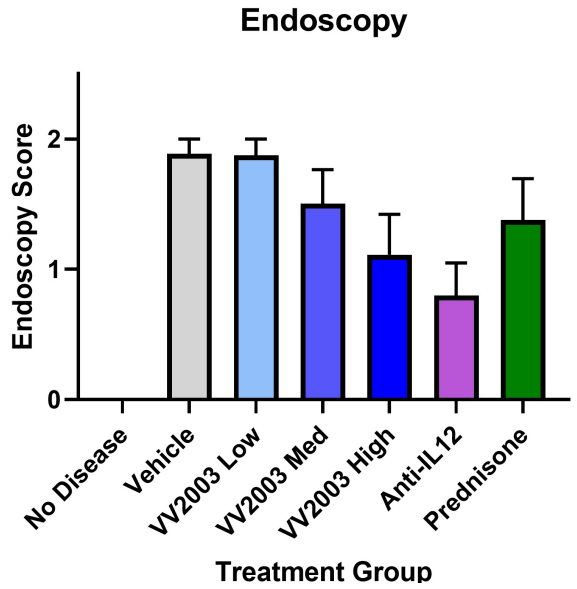


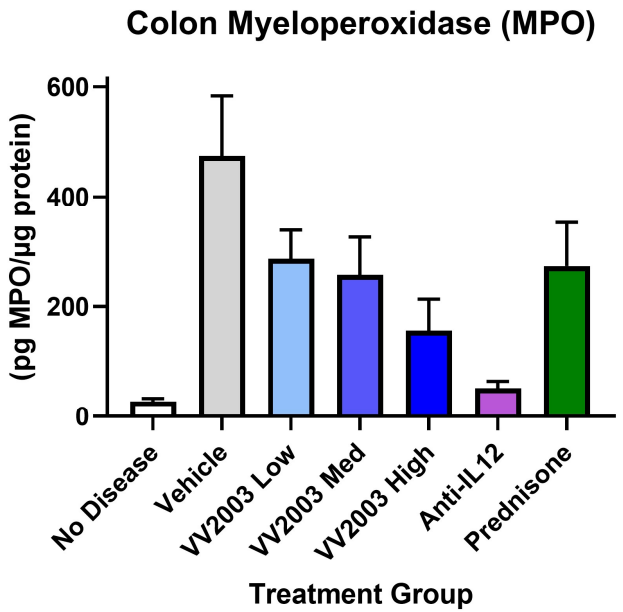
VV2003 High Dose



- Mild disease
- Preserved crypt architecture with some goblet drop-out
- Mild infiltrating lymphocytes and neutrophils
- Mild mucosal hyperplasia

Activity of VV2003 in murine models of ICPI-colitis





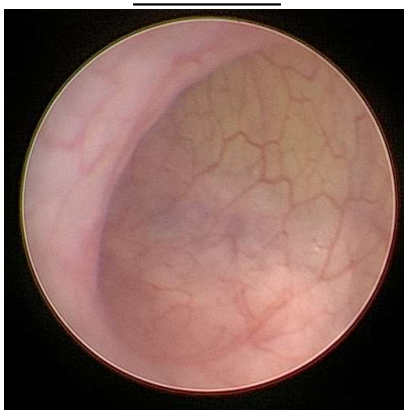
Comparison of VV2003 groups and vehicle
One-way ANOVA, Brown-Forsythe test: p = 0.046
Comparison of VV2003 High group to vehicle
One-Tailed Mann-Whitney U test: p = 0.035

Comparison of VV2003 groups and vehicle
One-way ANOVA: p = 0.041
Comparison of VV2003 High group to vehicle
Unpaired t test: p = 0.020

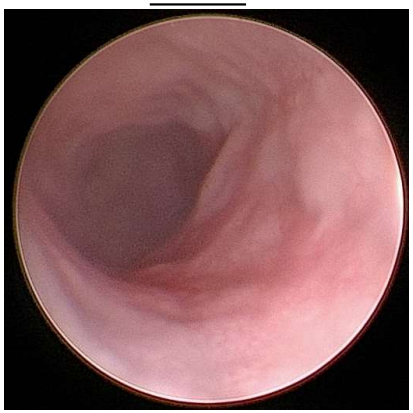
Activity of VV2003 in murine models of ICPI-colitis

- No Disease
- Shiny mucosa
- Clear vascular pattern
- No erythema, friability or erosions

No Disease



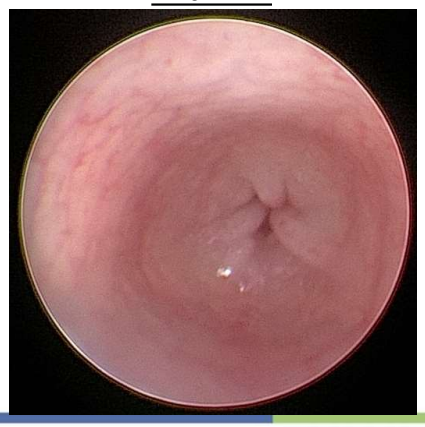
Vehicle



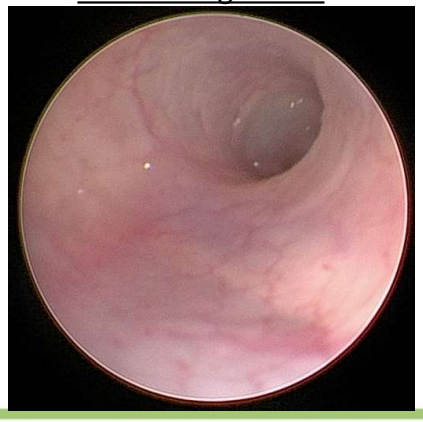
- Moderate disease
- Dull mucosa
- Absent vascular pattern
- Marked erythema
- Moderate friability and erosions

- Mild Disease
- Shiny mucosa
- Decreased vascular pattern
- Mild erythema
- No friability or erosions

Anti-IL12

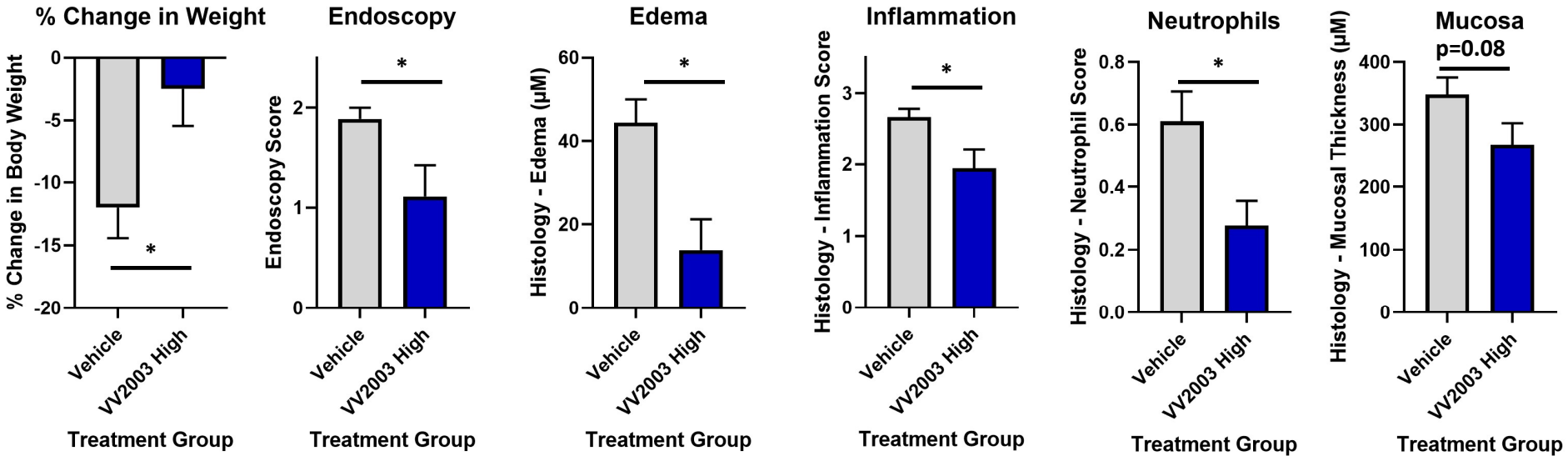


VV2003 High Dose



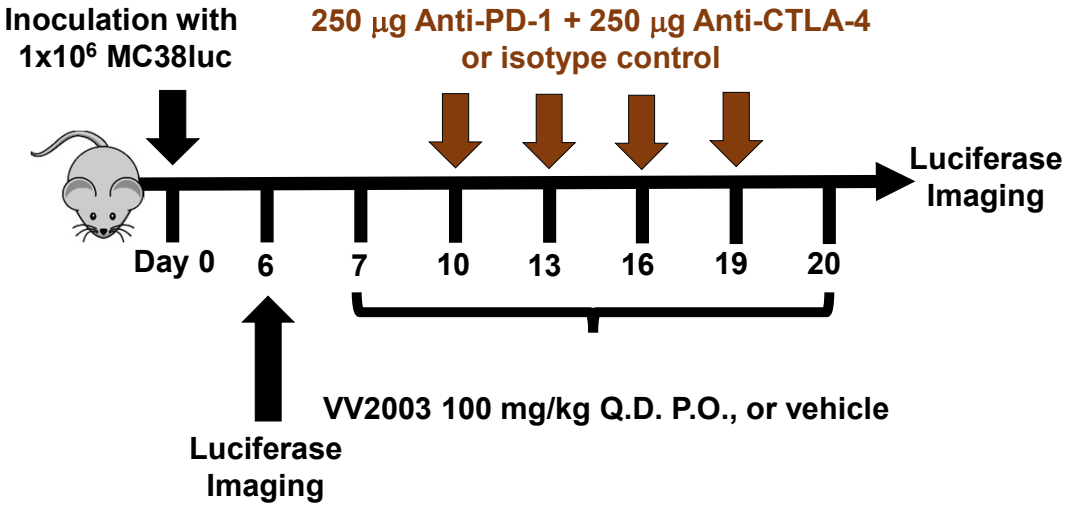
- Mild disease
- Shiny mucosa
- Decreased vascular pattern
- Mild erythema
- No friability or erosions

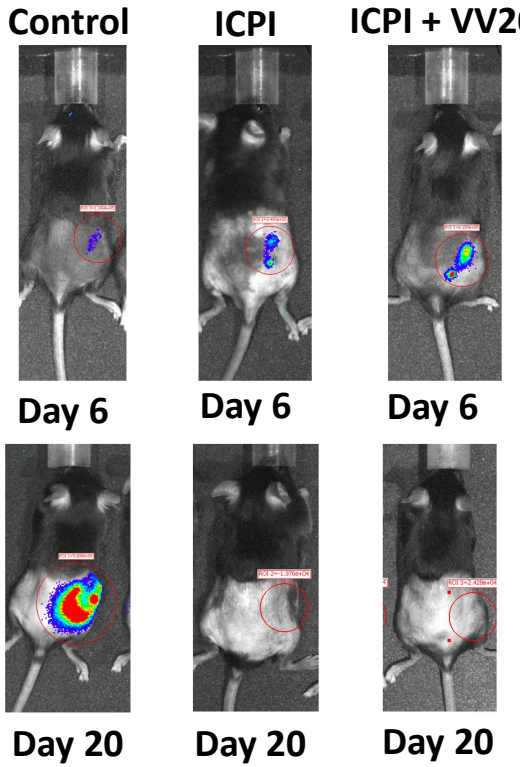
Activity of VV2003 in murine models of ICPI-colitis

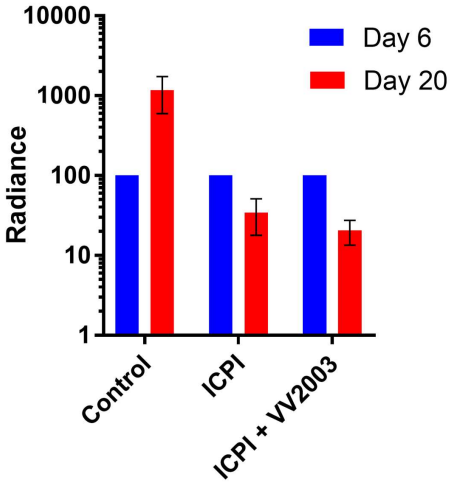


*: $p<0.05$

VV2003 does not interfere with ICPI activity





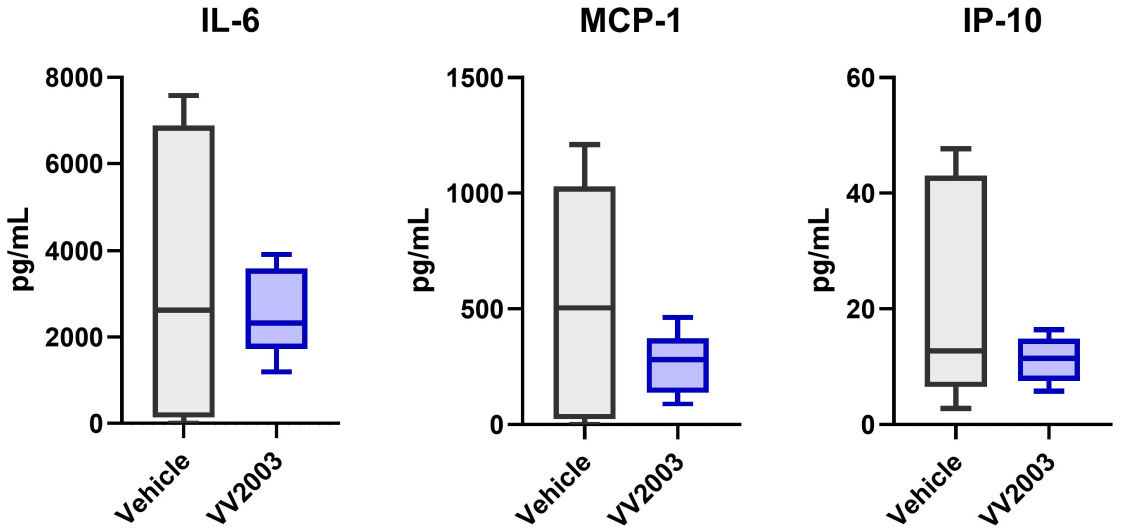


Activity of VV2003 in *ex vivo* tissue from patients with ICPI colitis

- Ongoing single-institution prospective study
- Eligibility
  - Clinician suspicion for ICPI-colitis
  - No prior receipt of corticosteroids
- Intervention/Methods
  - Colonoscopy with multiple biopsies of affected areas
  - Biopsy specimens immediately placed in culture media
  - Specimens treated with VV2003

Activity of VV2003 in *ex vivo* tissue from patients with ICPI colitis

- First study to directly interrogate tissue from ICPI colitis patients
- Study has enrolled 2 patients with confirmed ICPI colitis
- MCP-1, a chemokine that recruits monocytes and T cells to sites of active inflammation, appears to be decreased with VV2003
- Study is actively recruiting across multiple histologies



Conclusions

- VV2003, a first-in-class CRAC channel inhibitor, maintains effective concentrations in the gut with limited systemic absorption in murine models
- In novel murine models of ICPI-colitis, VV2003 mitigates damage to colonic tissue as evidenced by:
  - Improvement in histologic score and endoscopic findings
  - Improvement in other surrogates such as body weight, colonic edema and neutrophil count
- An ongoing study is characterizing the effect of VV2003 *ex vivo*
- A planned phase Ia/b study will clinically test and characterize activity of VV2003 in patients affected by ICPI colitis

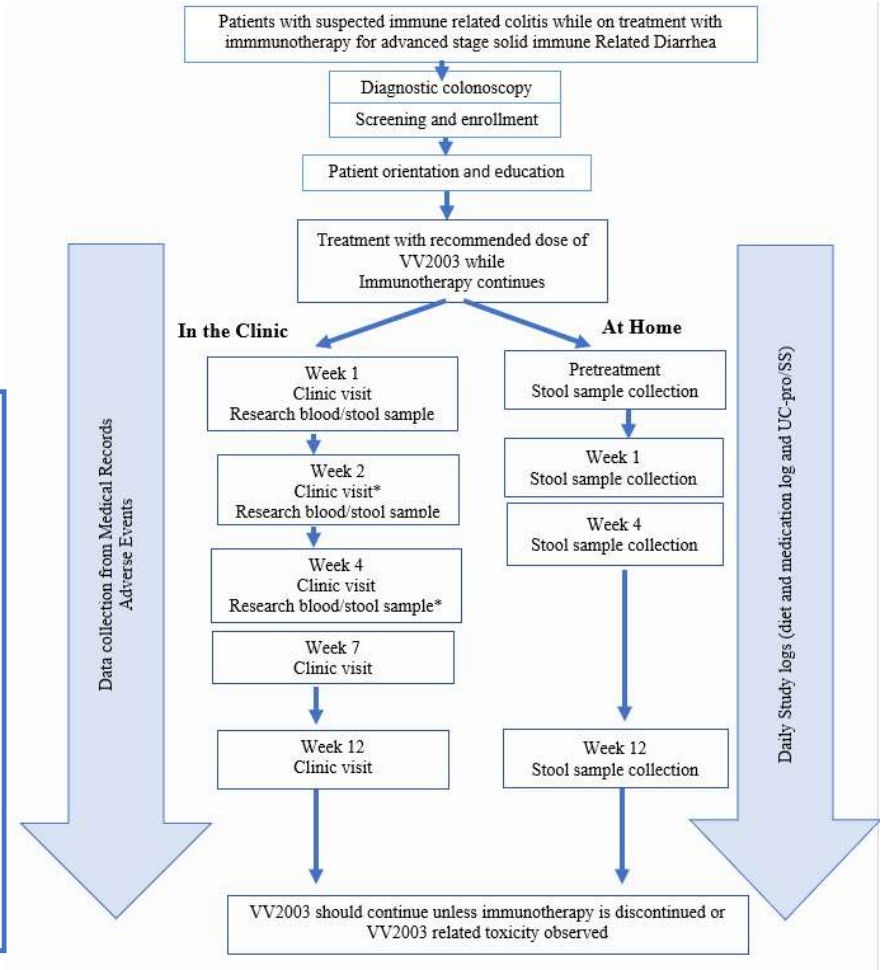
A Phase 1a/b Dose Escalation/Expansion Study to Evaluate Safety and Tolerability oral VV2003 in Healthy Volunteers and Immune Checkpoint Inhibitor Induced Colitis Patients

<u>Primary Objectives</u>

- To determine the safety and tolerability of VV2003 in healthy volunteers and in ICPI colitis patients

<u>Secondary Objectives</u>

- To investigate the clinical pharmacokinetics and pharmacodynamics of VV2003
- To assess the treatment discontinuation rate of immunotherapy due to immune related colitis in patients receiving VV2003 compared with historical cohorts



Acknowledgements

- Patients and families
- **City of Hope/Beckman Research Institute**

Sumanta K. Pal, MD (@montypal)

JoAnn Hsu, BSc (@hsuperjo88)

Zeynep Zengin, MD (@ZeynepZengin)

Nick Salgia, BSc (@NickSalgia)

Luis Meza, MD (@LuisMezaco)

Sabrina Salgia, BSc

- **Vivreon Gastrosciences, Inc.**

Milton Greenberg, PhD (@VivreonB)

Andrew C. Newman, PhD

- **VA Long Beach**

Jonathan Skupsky, MD, PhD


@montypal

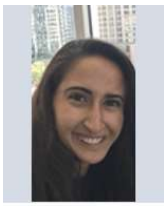

@NazliDizman

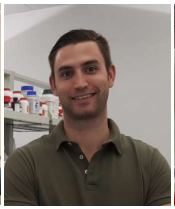

@Hsuperjo88


@ZeynepZengin


@NickSalgia


@LuisMezaco






@VivreonB

For questions, please contact:

Nazli Dizman, MD at n.dizman@outlook.com or @NazliDizman