# VCR-036 VINCOBODY:
# A novel, highly potent, pentavalent, toxicity-sparing PD-1/CTLA-4 VHH neutralizer with robust pre-clinical safety and efficacy

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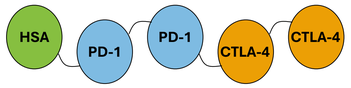
## BACKGROUND

- **Combination immunotherapy blockade** of PD-1 and CTLA-4 has shown improved clinical benefit across multiple tumor types but also confers significant increases in Grade 3/4 toxicity.
- **VINCOBODIES** are novel proprietary **VHH antibody (Ab) fragments** designed to deliver the efficacy of combination regimens while addressing the toxicity limitations of current monoclonal Abs.
- **VCR-036** is a novel pentavalent, **bispecific PD-1/CTLA4** VINCOBODY under development for the treatment of multiple cancers.




## METHODS

### SAFETY - MOUSE

- 4 treatment groups of double knock-in hPD-1/CTLA4 Balb/c mice (n=4 per group):
  1. **Vehicle**: phosphate-buffered saline
  2. **Ipilimumab + pembrolizumab**: 10 mg/kg ipi + 15 mg/kg pembro (1**X** mg) Q3D (6 total doses)
  3. **VCR-036**: 4**X** mg Q2D (10 total doses)
  4. **VCR-036**: 12**X** mg QD (16 total doses)
- Endpoints: survival, biomarkers, histopathology

### EFFICACY - MOUSE

- 15-day study in double knock-in hPD1/hCTLA4 C57B/6 mice using MC38 HuCells.
- Q3D dosing of 6 treatment groups (n=5 per group):
  1. **Vehicle**: phosphate-buffered saline
  2. **Nivolumab + ipilimumab**: 2 mg/kg nivo + 5 mg/kg ipi
  3. **VCR-036**: 4 dosing groups: 0.1, 0.5, 1.0, and 5.0 mg/kg
- Endpoints: tumor volume at 15 days and after tumor rechallenge at Day 20

### PHARMACOKINETICS – CYNOMOLGUS MONKEY

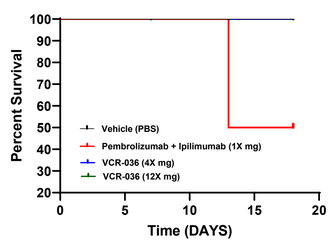
- 28-day study in 3 cynomolgus monkeys
- QW repeat subcutaneous (SQ) dosing of 1 mg/kg of VCR-036
- Endpoints: VCR-036 serum concentration over time; vital signs; tolerability

## RESULTS

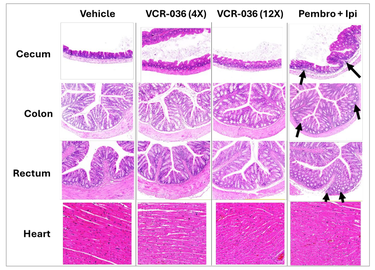
### SAFETY - MOUSE

- After treatment with VCR-036, 100% of mice survived, while treatment with pembro + ipi resulted in the death of 50% of mice (due to immune-related adverse events).
- Combination pembro + ipi treatment also resulted in more swelling, inflammation, and lymphocyte infiltration than treatment with VCR-036.

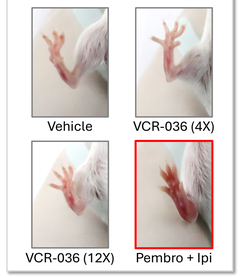
**100% of mice receiving VCR-036 survived vs. 50% of mice receiving pembro + ipi**



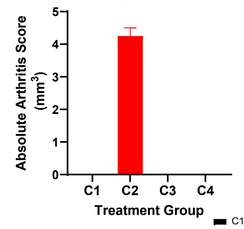

**Combination pembro + ipi results in more severe and diffuse lymphocytic infiltration**



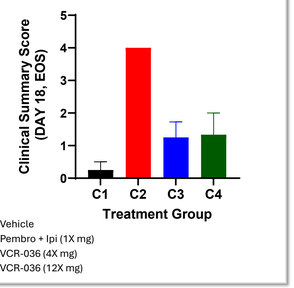

**Paw inflammation after treatment**




**Absolute Arthritis Score**



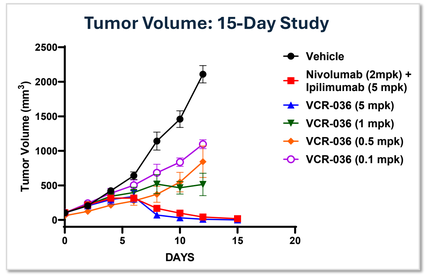

**Clinical Summary Score**
(combined arthritis + colitis scores)



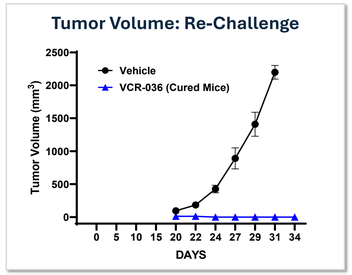

### EFFICACY - MOUSE

- 1000X higher binding affinity of VCR-036 compared to standard of care was previously demonstrated in vitro: for CTLA-4, the KD (M) of VCR-036 was 2.25E-14 vs 5.01E-10 for ipi.
- Full tumor regression was observed in both the 5 mg/kg VCR-036 and the ipi + nivo group.
- Cured VCR-036 mice remained in remission after tumor rechallenge with no further dosing.

**Tumor Volume: 15-Day Study**



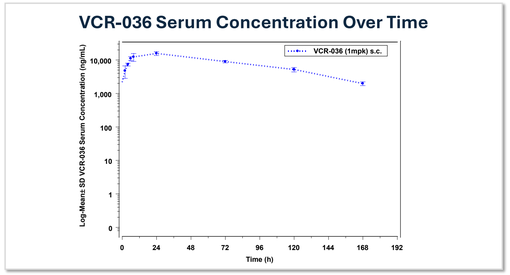

**Tumor Volume: Re-Challenge**




### PHARMACOKINETICS – CYNOMOLGUS MONKEY

- SQ injections resulted in no abnormal manifestations such as mental status or behavioral activity that affected the results.
- Cytokines of animals in each group showed no significant abnormalities during the study.

**VCR-036 Serum Concentration Over Time**




## DISCUSSION

- Early preclinical studies of VCR-036 demonstrated superior safety over the current standard of care.
- VCR-036 at the 5 mg/kg dose fully eradicated tumors by Day 15, with sustained efficacy after tumor rechallenge in cured mice (without further treatment).
- The range of doses evaluated in the efficacy mouse study informs dose schedule and optimization.
- The projected human equivalent dose based on the cynomolgus PK study is ~0.01 mg/kg (or ~1 mg flat dose) SQ every 6 weeks.
- Further evaluation of VCR-036 for the treatment of solid tumors is warranted.

## ACKNOWLEDGMENTS

Crown Biosciences performed the mouse studies.

JOINN Biologics performed the cynomolgus monkey study.