Preclinical development of CR-001, a novel tetravalent PD-1 x VEGF bispecific antibody with cooperative pharmacology and potent anti-tumor activity

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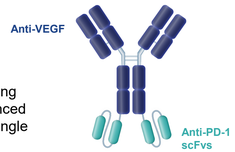
Background

- Immune checkpoint inhibitors, like PD-1 or PD-L1 inhibitors, have changed the standard of care in multiple tumors, but durable responses have only been observed in a subset of patients.
- Overexpression of VEGF is frequently found in various tumors and plays critical roles in tumor angiogenesis and suppression of anti-tumor immune response. Bispecific antibodies targeting PD-(L)1 and VEGF have shown promising efficacy with a favorable safety profile in clinical trials. Specifically, ivonescimab, a PD-1 x VEGF bispecific antibody with cooperative pharmacology, demonstrated superiority to pembrolizumab in a randomized Phase 3 trial.[1,2]

Figure 1. CR-001 is a highly potent PD-1 x VEGF bsAb



- CR-001 is a tetravalent bispecific antibody targeting PD-1 and VEGF. It consists of a bivalent, Fc-silenced anti-VEGF-A IgG1 antibody, with two anti-PD-1 single chain variable fragments fused to its C-terminus.
- In this poster we report preclinical studies characterizing the cooperative pharmacology of CR-001 in vitro, anti-tumor activity in vivo, and a single-dose pharmacokinetic study in cynomolgus monkeys.

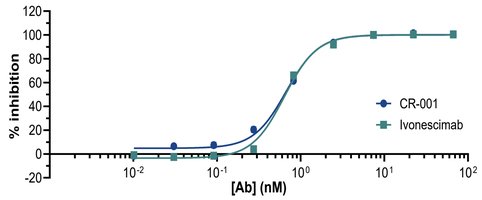
Results – Target binding and signaling blockade

Table 1. CR-001 binds to PD-1 and VEGF with high affinity

Target	EC_{50} (nM) via ELISA		KD (nM) via SPR	
	CR-001	Ivonescimab[1]	CR-001	Ivonescimab[1]
PD-1	0.2	0.3	32	40
VEGF	0.1	0.1	2	3

- The binding kinetics of CR-001 and ivonescimab to PD-1 and VEGF were measured by surface plasmon resonance (SPR) and the binding activities to plate-coated PD-1 and VEGF were assessed by ELISA.

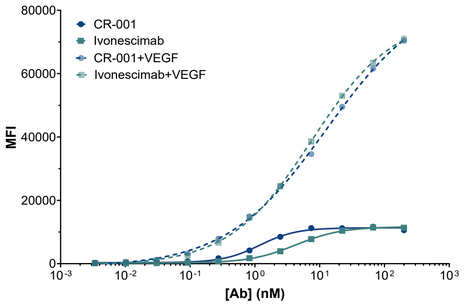
Figure 2. CR-001 blocks VEGF/VEGFR2 signaling



- Inhibition of VEGF/VEGFR2 signaling by CR-001 and ivonescimab in a reporter assay of VEGFR2-expressing HEK293 luciferase reporter cells in presence of recombinant VEGF

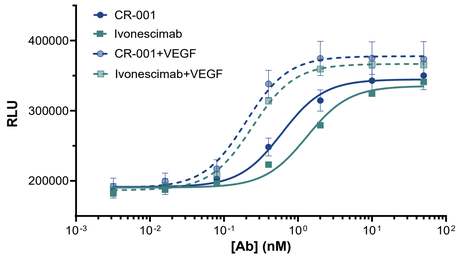
Results – Cooperative pharmacology

Figure 3. Increased PD-1 binding of CR-001 in presence of VEGF



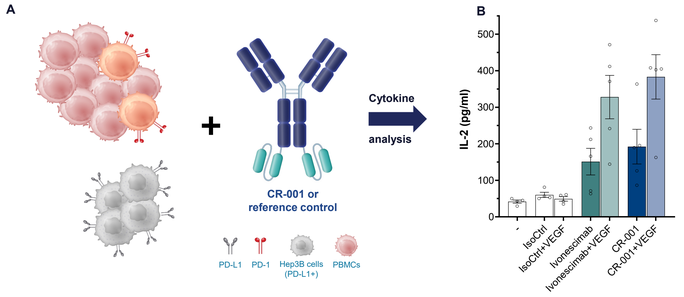
- The binding activity of CR-001 to PD-1 was evaluated in PD-1 positive Jurkat cells by flow cytometry in the presence and absence of VEGF.
- CR-001 or ivonescimab were mixed with VEGF at molar ratios of 1:2.

Figure 4. Increased potency of CR-001 to block PD1/PD-L1 signaling in presence of VEGF



- PD-1/PD-L1 blockade activity of CR-001 and ivonescimab in a reporter assay of PD-1-expressing Jurkat cells and PD-L1-expressing Hep3B-OS8 cells in the presence and absence of VEGF.
- Luciferase expression in the Jurkat cells is repressed by PD-1 signaling and PD-1/PD-L1 signaling blockade increases luciferase activity measured in RLU.
- CR-001 or ivonescimab were mixed with VEGF at molar ratios of 1:2.

Figure 5. Increased ability of CR-001 to promote T-cell activation in the presence of VEGF

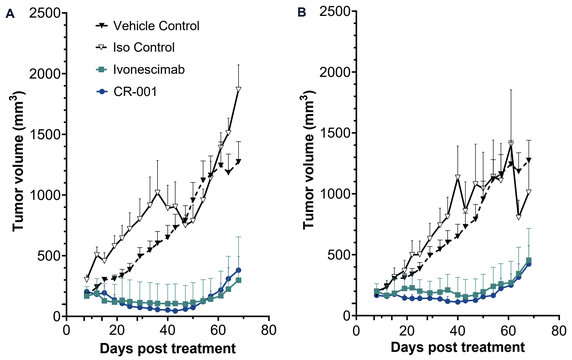


A. PBMC and PD-L1-expressing Hep3B-OS8 cell co-culture system was utilized to assess the ability of CR-001 to promote T cell activation.

B. IL-2 concentrations in the supernatants, as determined by ELISA after 3 nM of CR-001 or ivonescimab in the presence and absence of 6 nM VEGF.

Results – Anti-tumor activity

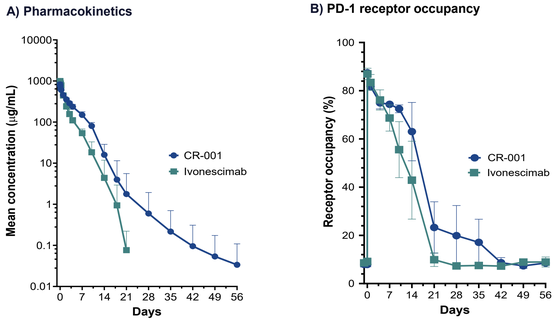
Figure 6. CR-001 exhibits potent anti-tumor activity in mice in two donors (A and B)



- SCID mice were co-injected with human PBMCs and HCC827 cells followed by weekly IV dosing of CR-001 and ivonescimab for 6 consecutive weeks at 14 mg/kg.

Results – PK and receptor occupancy (RO)

Figure 7. Pharmacokinetics and PD-1 receptor occupancy after a single dose of CR-001 at 30 mg/kg to cynomolgus monkeys



- Pharmacokinetics (A) and PD-1 receptor occupancy in CD3+/CD95+ T cells (B) after a single intravenous administration in 5 naïve male cynomolgus monkeys. Error bars represent standard deviation (SD) and standard error of the mean (SEM) in panel A and B, respectively.

Conclusions

- CR-001 demonstrated cooperative pharmacology with increased binding to PD-1 in the presence of VEGF, augmenting PD-1/PD-L1 signaling blockade and enhancing T cell activation in vitro, consistent with preclinical evaluation of ivonescimab.[1]
- In HCC827 xenograft model, CR-001 demonstrated potent anti-tumor activity.
- CR-001 was well-tolerated in the cynomolgus monkey after a single iv dose. CR-001 engagement of PD-1 receptor was observed with a peak receptor occupancy of >80%.
- These data support clinical development of CR-001, with initiation of a global trial in patients with solid tumors expected in Q1 2026.

References

1. Zhong T, et al. iScience 2024;28:111722.
2. Xiong A, et al. Lancet 2025;405:839–49.

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[1]Ivonescimab is a PD-1/VEGF bispecific antibody reference control which was generated using the International Nonproprietary Name (INN) Sequence for ivonescimab