Targeting PD-L1 expressing solid tumors with CR-002, a novel topoisomerase 1 inhibitor (TOP1i) ADC engineered for increased payload delivery

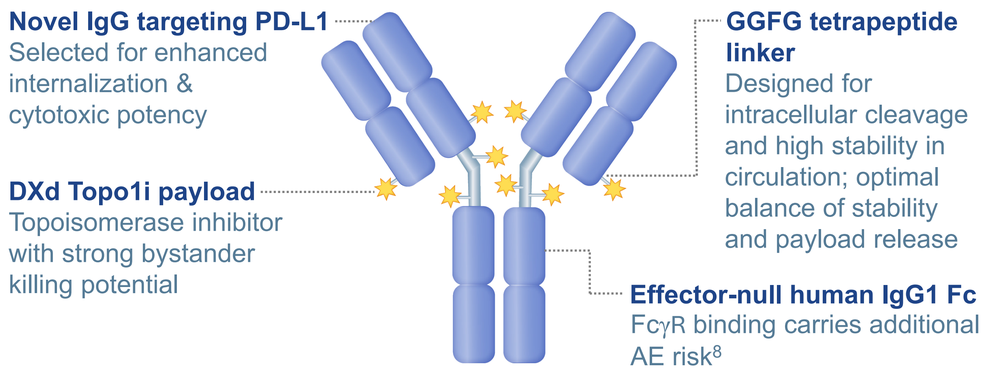
Kyle M. Fitzgerald[1], Jacquelynn Lucas[1], John Wickwire[1], Jennifer Kong[1], Justin C. Bader[1], Byron H. Kwan[2], Bernard A. Liu[2], Melissa L. Conerly[2], Alex Mitkas[2], Russell Sanderson[2], Ghassan Fayad[2], Joana Ministro[2], Hussam Shaheen[2], Jan Pinkas[1]

[1]Crescent Biopharma, Waltham, MA, USA; [2]Paragon Therapeutics, Waltham, MA, USA

Background

- CR-002 is a novel, fully human anti-PD-L1 antibody conjugated to the topoisomerase 1 inhibitor (TOP1i) payload DXd (**Figure 1**).
- CR-002 incorporates a PD-L1 antibody selected for high internalization to facilitate payload release in target cells and a linker designed for intracellular cleavage and high stability in circulation:
  - PD-L1 is expressed on tumor cells and reduces T-cell activation and cytotoxic function[1], promotes immunosuppressive Treg function and survival[2], and drives tumor cell proliferation and tissue invasion.[3]
  - PD-L1 expression is elevated in numerous solid tumors compared to normal tissues, making it an attractive ADC target.[4,5,6]
  - ADCs targeting PD-L1 have shown potent cytotoxicity *in vitro* and antitumor activity *in vivo.*[7]
- In this poster, we report preclinical studies characterizing the internalization and *in vitro* cytotoxic potency, the *in vivo* antitumor activity in PD-L1 expressing tumor models, and non-human primate tolerability and pharmacokinetic (PK) studies.

Figure 1. CR-002 – a topoisomerase 1 inhibitor ADC targeting PD-L1



Materials and methods

- A panel of antibodies targeting human PD-L1 were generated, with surface plasmon resonance (SPR) affinities ranging from ~100 pM to 10 nM.
- Internalization was measured using Karpas-299, a PD-L1 expressing non-Hodgkin's lymphoma (NHL) cell line and visualized using a Fab fragment with a pH-sensitive dye.
- These anti-PD-L1 antibodies, along with controls made in-house, were conjugated to the deruxtecan linker-payload to form ADCs with an average drug to antibody ratio (DAR) of 8.
- *In vitro* cytotoxicity was measured using Karpas-299 treated with our PD-L1 DXd ADCs.
- The *in vivo* antitumor activity of CR-002 was assessed in subcutaneous tumor growth inhibition (TGI) studies in models confirmed to express huPD-L1.
  - Cell line-derived xenograft (CDX) models Karpas-299 and luciferase expressing MDA-MB-231 (triple-negative breast cancer [TNBC]) were implanted into female CB-17 SCID or NOG mice, respectively.
  - MC38 mouse colorectal carcinoma cells were stably transfected to express human PD-L1 and implanted into B-hPD-1/hPD-L1/hVEGFA C57BL/6 mice.
- A tolerability study with PK evaluation of CR-002 was conducted in mixed gender, treatment naïve, cynomolgus monkeys (N=3 per treatment group, N=2 for vehicle control) at two dose levels (40 or 78 mg/kg) with dosing on day 1 of a 21-day cycle, for a total of two doses. Regular blood draws were taken for bioanalysis of Total Ab (TAb), Total ADC (TADC), and free payload. A necropsy was performed for all cynomolgus monkeys following the PK portion of the study. Standard clinical pathology and microscopic evaluation was performed.

Results

- There is an inverse correlation between cytotoxicity of anti-PD-L1 DXd ADCs and affinity of the unconjugated antibodies. CR-002 was selected among the anti-PD-L1 clones with optimal cytotoxicity (**Figure 2**).
- CR-002 was able to efficiently internalize into PD-L1 expressing target cells (**Figure 3**).

Figure 2. Cytotoxicity vs. affinity for anti-PD-L1 ADCs and antibodies

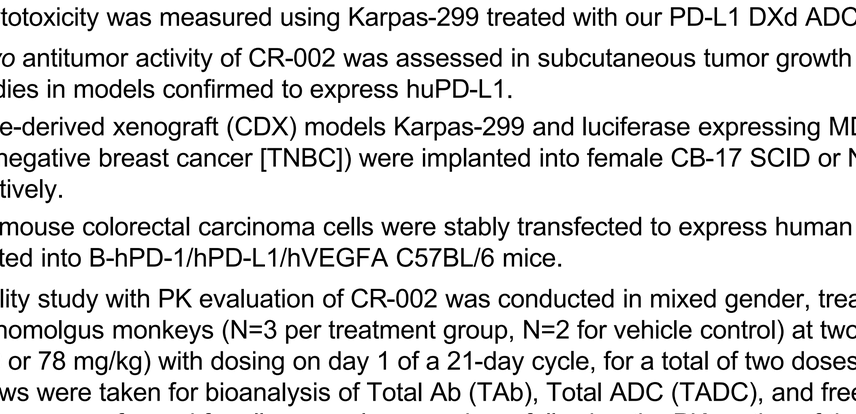
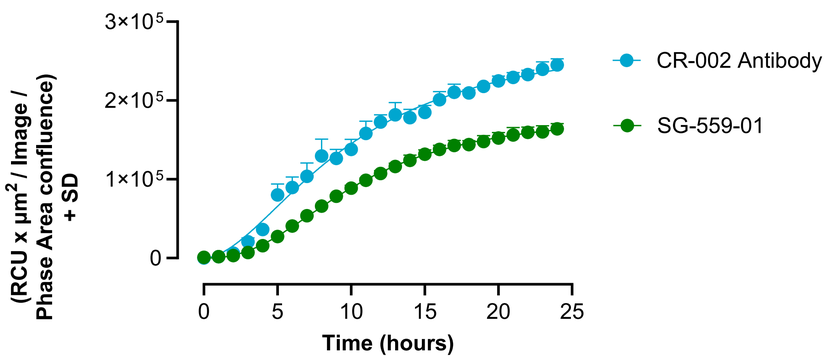


Figure 3. Internalization in Karpas-299



Results (continued)

- CR-002 demonstrated dose-dependent antitumor activity against a panel of CDX models in immunodeficient mice, as well as in a syngeneic mouse model engineered to express human PD-L1 (**Figures 4–6**).

Figure 4. Single dose TGI of anti-PD-L1 DXd ADCs in Karpas-299 (NHL) CDX model at 1 mg/kg

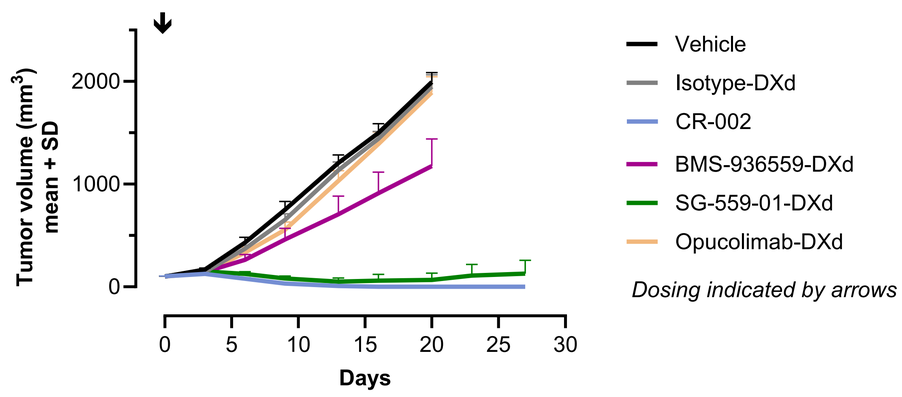


Figure 5. Repeat dose TGI of CR-002 in MDA-MB-231-luc (TNBC) CDX model

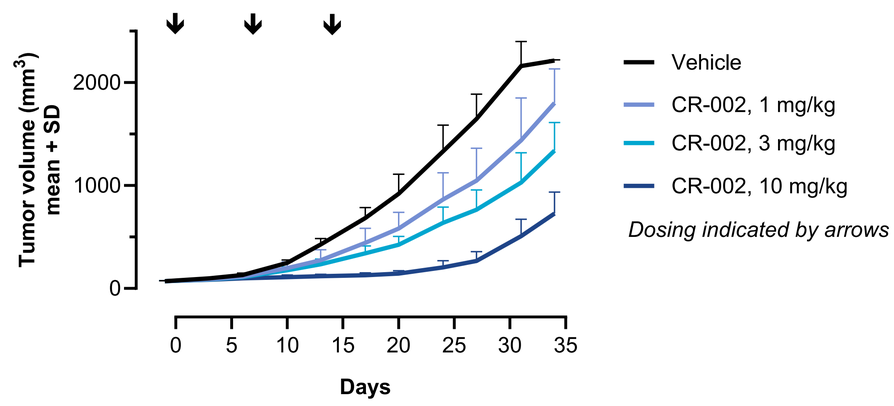
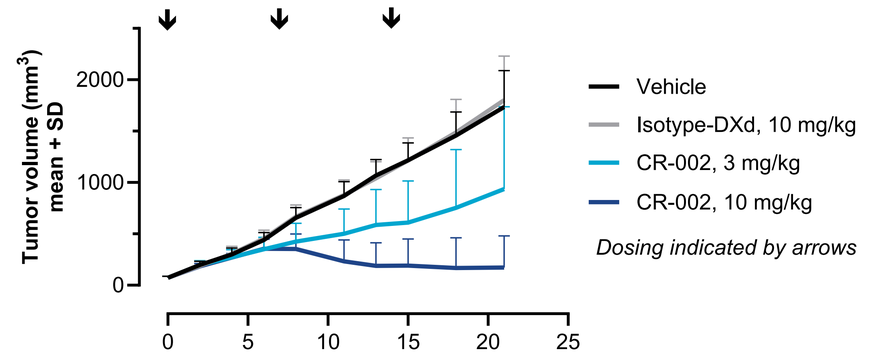
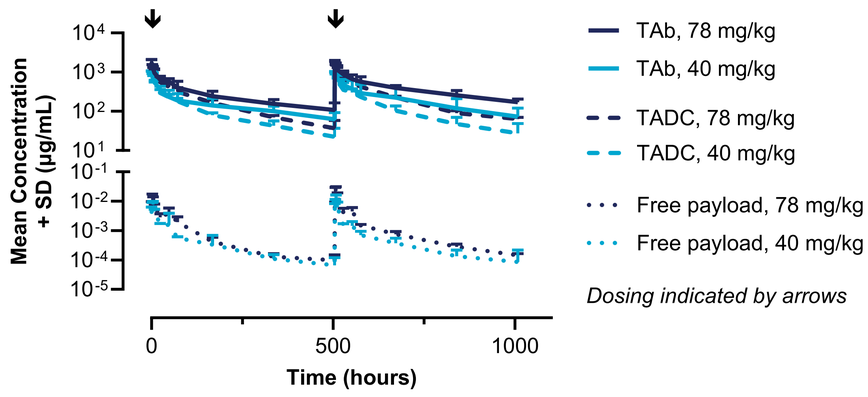


Figure 6. Repeat dose TGI of CR-002 in MC38-huPD-L1 in huPD-1/huPD-L1/huVEGF C57/BL6 mouse syngeneic model



- In a repeat-dose cynomolgus monkey study, CR-002 exhibited PK profiles consistent with other DXd ADCs[9] (**Figure 7**).
- Cynomolgus monkeys tolerated CR-002 up to the highest dose tested of 78 mg/kg with minor clinical pathology effects observed consisting of mildly to moderately higher levels of clinical chemistry parameters (ALT, AST and CK) and mildly prolonged PT and APTT. Microscopic observations included minimal findings in lymph tissues, thymus, kidney, and liver.

Figure 7. CR-002 PK profile in cynomolgus monkeys



Conclusions

- CR-002 is an anti-PD-L1 DXd ADC engineered to enhance payload delivery to PD-L1-expressing cancer cells.
- CR-002 demonstrated antitumor activity across three preclinical tumor models, including dose-dependent activity in the MDA-MB-231-luc and MC38-hPD-L1 models.
- In cynomolgus monkeys, CR-002 showed measurable systemic exposure and was generally tolerated at the doses evaluated.
- These data support the continued development of CR-002 for advanced solid tumors.
- A Phase 1/2 APOLLO global clinical trial to evaluate CR-002 in multiple solid tumor types (NCT07909031) is underway.

References and Disclosures

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