



AACR ANNUAL MEETING 2022

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Ernset N. Morial Convention Center
New Orleans, Louisiana

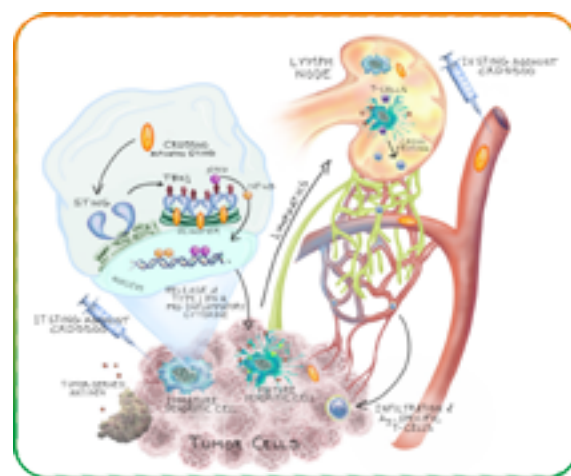
Intravenous administration of the small molecule STING agonist CRD5500 elicits potent anti-tumor immune responses in cold tumors

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Curadev Pharma, Noida, India; Curadev Pharma, Discovery Park, Sandwich, United Kingdom.



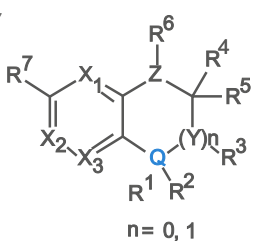
ABSTRACT

- Stimulator of Interferon Genes – (STING) is an innate immune mediator that activates Type I interferon and pro-inflammatory responses to drive **anti-viral and anti-tumor immunity**
- STING is activated as part of an early warning mechanism in many cell types by cyclic dinucleotides that are formed when the enzyme cGAS detects cytosolic DNA
- CRD5500 is a potent, first-in-class classical small molecule STING agonist with a distinctive binding site that is outside the CDN pocket. It displays strong anti-tumor effects against multiple tumor types in human STING knock-in mice when administered systemically by the IV route or directly by IT route.

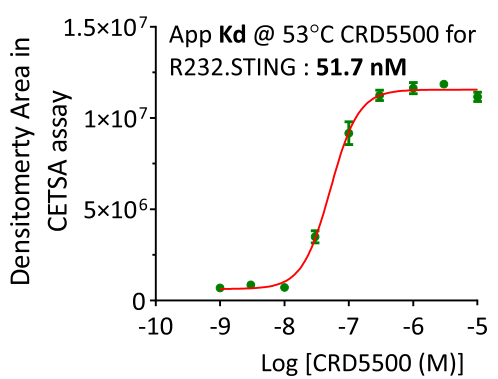


ATTRIBUTES

CHEMISTRY



BINDING



STING ACTIVATION ACROSS VARIANTS IN REPORTER GENE ASSAY

STING Variants	HEK293T cells					THP-1 Dual cells		HEK293T cells
	IRF axis					IRF axis	NF-kB axis	IRF axis
	R232	H232	HAQ	AQ	Q	HAQ	HAQ	Monkey
EC ₅₀ (nM)	9.2 (+2.6)	18.1 (+3.4)	12.1 (+5.5)	35.9 (+7.9)	62.2 (+12.7)	65.1 (+32.2)	76.5 (+64.5)	43.6 (+10.7)

CYTOKINE STIMULATION IN PBMCs

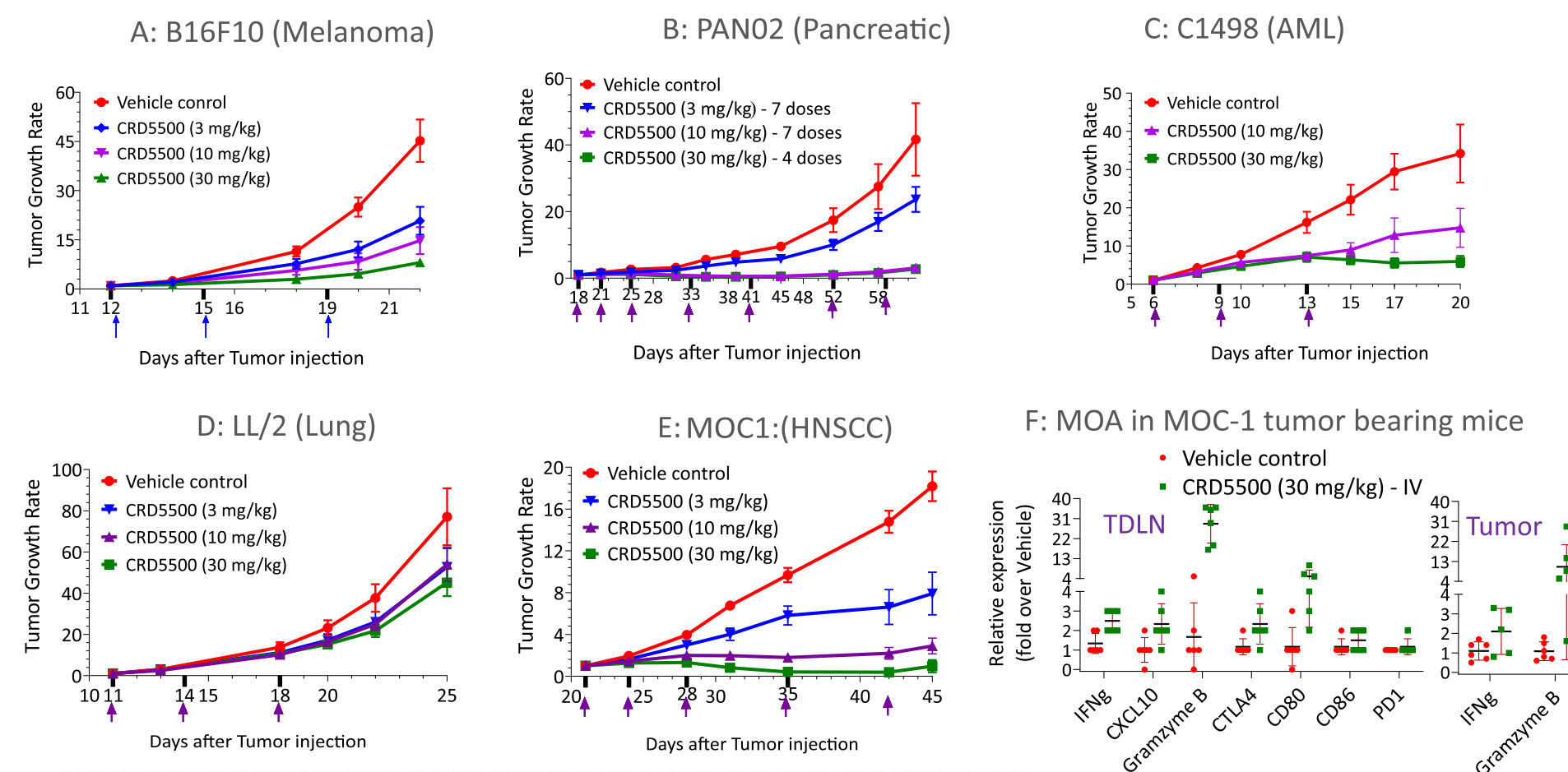
Cytokines	PBMC (EC ₅₀ ± SD) in μM		
	Human EC ₅₀ (n°)	Monkey EC ₅₀ (n°)	
IFNβ	0.22 ± 0.1 (4)	1.87 ± 0.93 (4)	
IFNα	1.48 ± 1.09 (7)	2.15 ± 0.88 (4)	
IL6	0.13 ± 0.06 (4)	1.94 ± 1.45 (4)	
CXCL10	0.04 ± 0.02 (6)	0.15 ± 0.04 (3)	

n° = number of human donors or animals

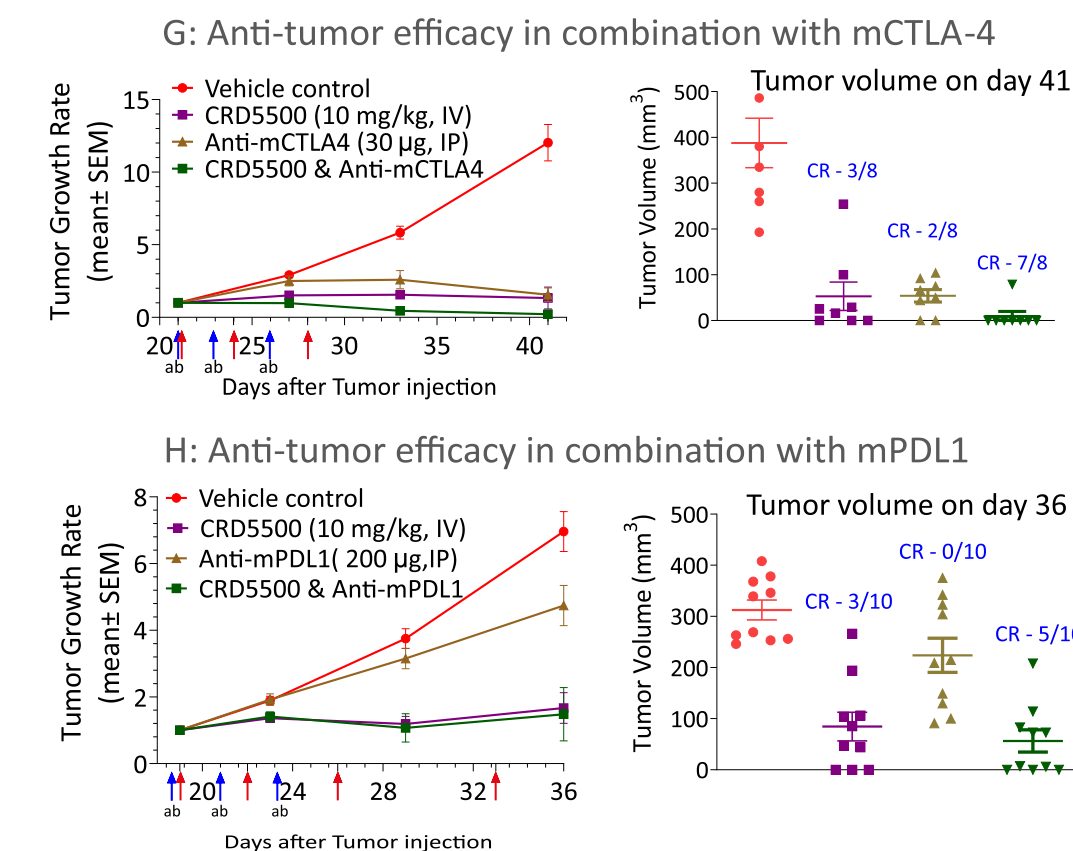
CRD5500:

- Induces thermal stabilization of cellular STING with a Kd of 52 nM
- Potently activates all the major human STING variants
- Potently stimulates pro-inflammatory cytokine release from human and monkey PBMCs
- Exhibits good drug like properties

MONOTHERAPY BY IV ROUTE



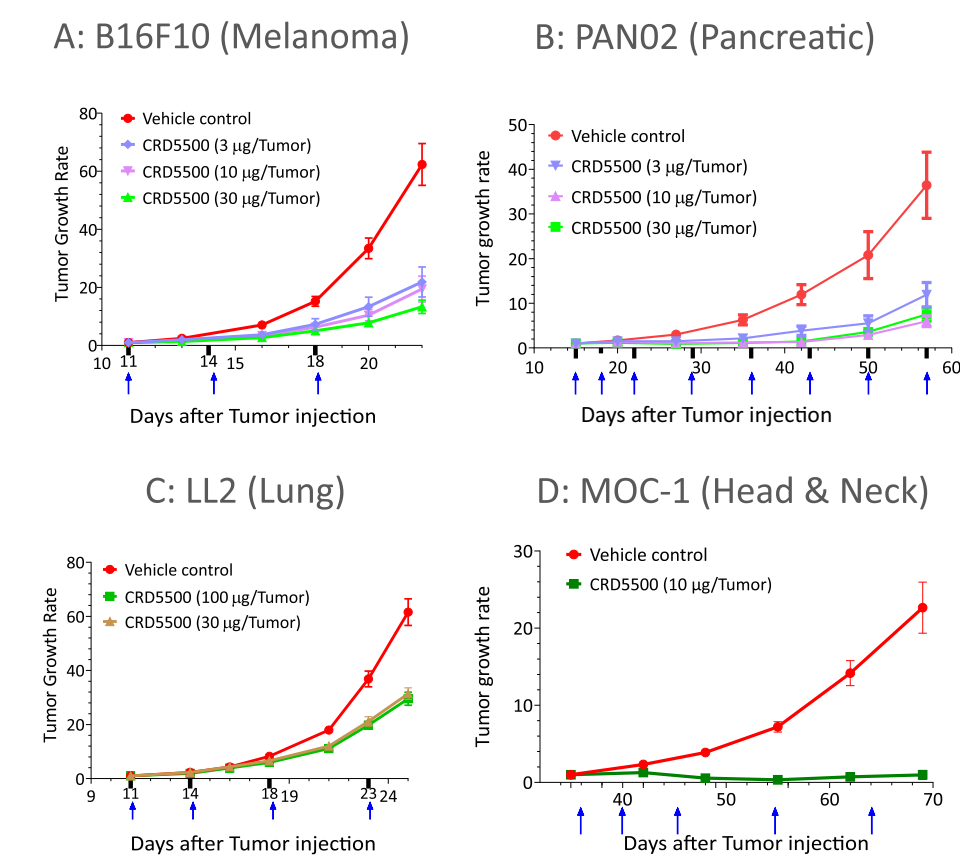
COMBINATIONS WITH CPI in MOC-1



IV dosed CRD5500 :

- A-E:** Displays robust dose dependent anti-tumor effects against multiple subcutaneously implanted tumor types as monotherapy
- Regimen followed: Bi-weekly for the 1st week followed by once a week till the end of the study
- F:** Induces change in tumor and TDLN immune contexture with a marked increase in the activated cytotoxic CD8 T-cell marker Granzyme B
- G-H:** Combines with anti-CTLA-4 and anti-PD-L1 to completely eradicate established MOC-1 tumors in several mice

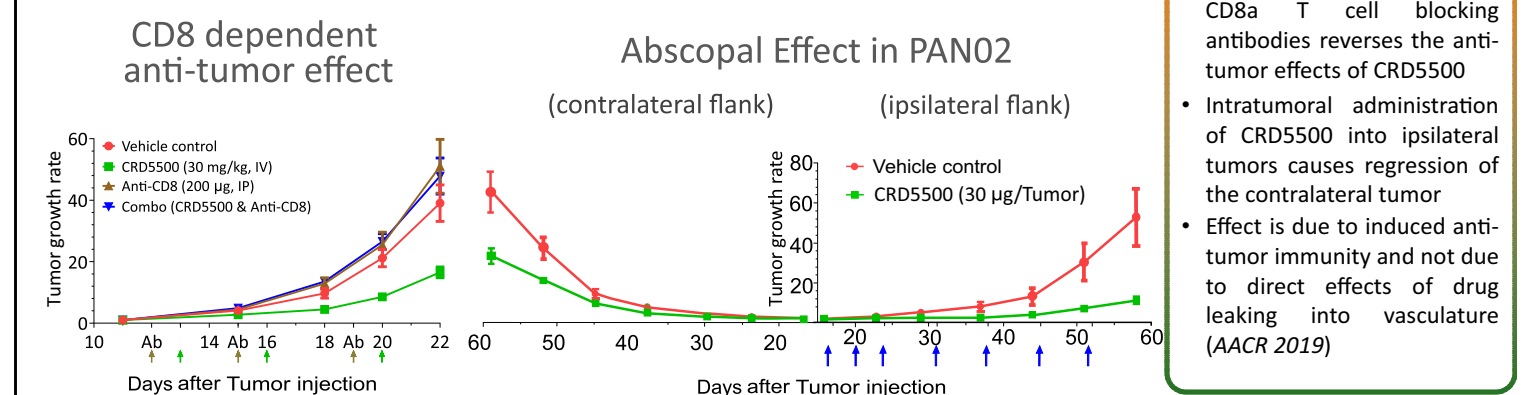
MONOTHERAPY BY IT ROUTE



IT dosed CRD5500:

- A-D:** Displays robust dose dependent anti-tumor effects in multiple tumors as monotherapy with complete eradication of MOC-1 tumors in several mice
- Regimen followed: Bi-weekly for the 1st week followed by once a week till the end of the study

MECHANISM OF ACTION



- The administration of anti-CD8a T cell blocking antibodies reverses the anti-tumor effects of CRD5500
- Intratumoral administration of CRD5500 into ipsilateral tumors causes regression of the contralateral tumor
- Effect is due to induced anti-tumor immunity and not due to direct effects of drug leaking into vasculature (AACR 2019)

CONCLUSIONS

- Agonists of STING, an innate immune mediator that activates pro-inflammatory Type I interferon responses are being pursued as a novel anti-tumor modality in the clinic
- CRD5500 – clinical candidate: (Supporting in-vitro and ex-vivo functional data had been presented at AACR'2019, Annual Meeting)
 - Potent, first-in-class classical small molecule STING agonist with a distinct binding site outside the cGAMP binding region
 - Demonstrates robust anti-tumor effects in multiple syngeneic murine tumors in human STING-knock in mice when administered either IV or IT as monotherapy or in combination with CPI
 - Displayed excellent systemic tolerability in 28-day repeat dose GLP studies in non-human primates
 - Scheduled for FIH trials in Q3 2022