# CRB-601: A Highly Potent and Selective Blocking Antibody Targeting the $\alpha_v\beta_8$ Integrin

New York Academy of Sciences
Frontiers in Cancer Immunotherapy
May 11, 2022

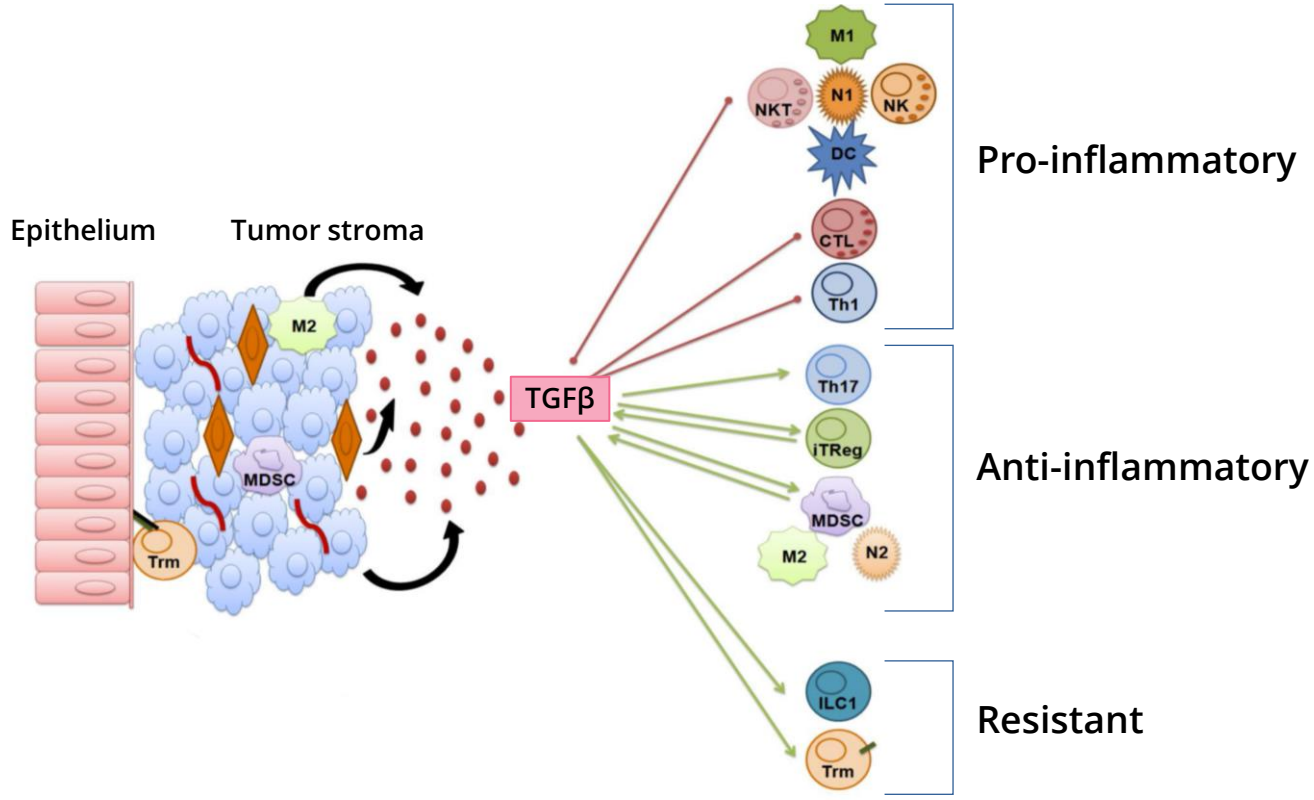
# Forward-Looking Statements

This presentation contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934 and Private Securities Litigation Reform Act, as amended, including those relating to the Company's restructuring, trial results, product development, clinical and regulatory timelines, market opportunity, competitive position, possible or assumed future results of operations, business strategies, potential growth opportunities and other statements that are predictive in nature. These forward-looking statements are based on current expectations, estimates, forecasts and projections about the industry and markets in which we operate and management's current beliefs and assumptions. These statements may be identified by the use of forward-looking expressions, including, but not limited to, "expect," "anticipate," "intend," "plan," "believe," "estimate," "potential," "predict," "project," "should," "would" and similar expressions and the negatives of those terms. These statements relate to future events or our financial performance and involve known and unknown risks, uncertainties, and other factors, including the potential impact of the recent COVID-19 pandemic and the potential impact of sustained social distancing efforts, on our operations, clinical development plans and timelines, which may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Such factors include those set forth in the Company's filings with the Securities and Exchange Commission. Prospective investors are cautioned not to place undue reliance on such forward-looking statements, which speak only as of the date of this press release. The Company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

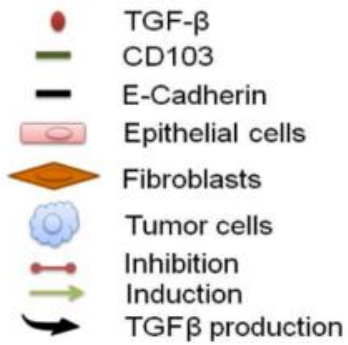
# Disclosures

- Authors are employees and shareholders of Corbus Pharmaceuticals
- CRB-601 is an investigational, pre-clinical stage candidate that has not entered clinical testing and is not approved by the FDA for any indication

# TGFβ plays a central role in immunoregulation and cancer




- TGFβ has been associated with immune cell exclusion in cancer
- Targeting TGFβ has been challenging
  - Local tumor versus systemic signaling may be key



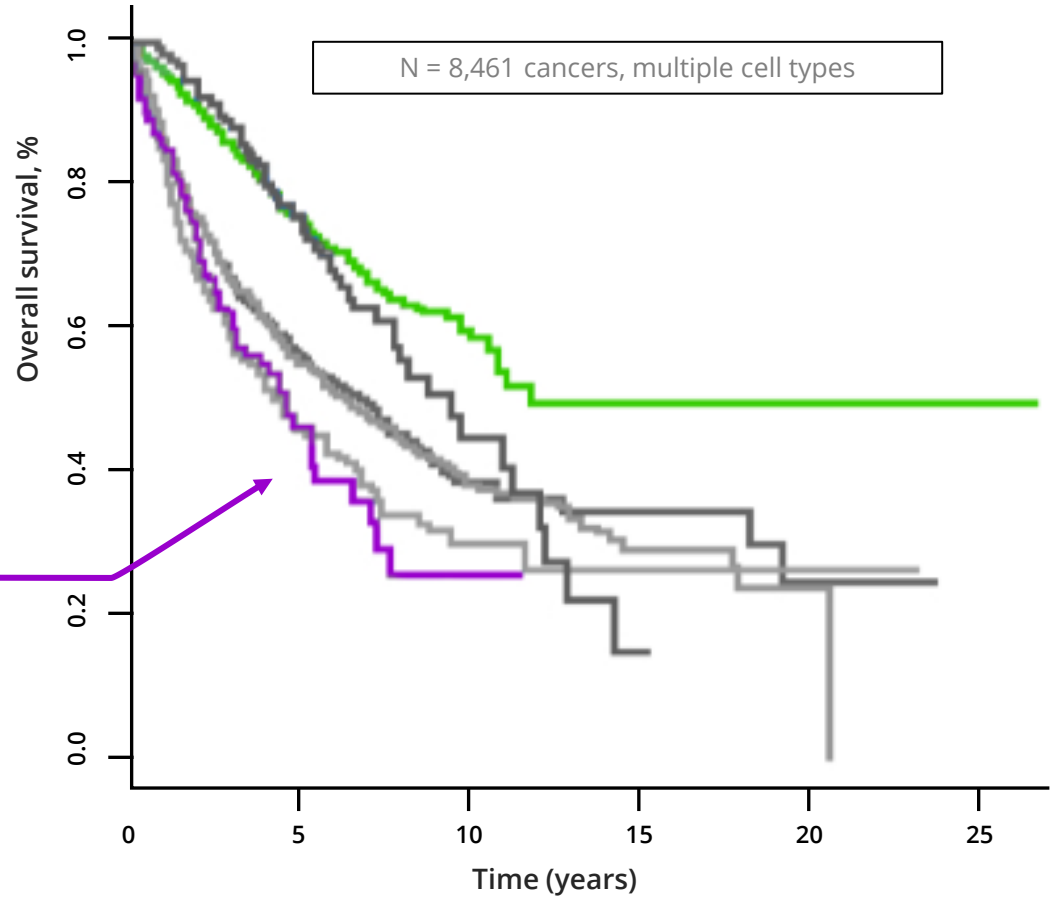

**Source:** Dahmani A, Delisle JS. TGF-β in T Cell Biology: Implications for Cancer Immunotherapy. *Cancers (Basel)*. 2018;10(6):194. Published 2018 Jun 11. doi:10.3390/cancers10060194

# TGFβ predicts poor clinical outcomes in a subset of cancer patients

## Immunogenomic subtypes in cancer

- C1 WOUND HEALING
- C2 INF-γ DOMINANT
- C3 INFLAMMATORY
- C4 LYMPHOCYTE DEPLETED
- C5 IMMUNOLOGICALLY QUIET
- C6 TGFβ DOMINANT

TGFβ predominance gene signature

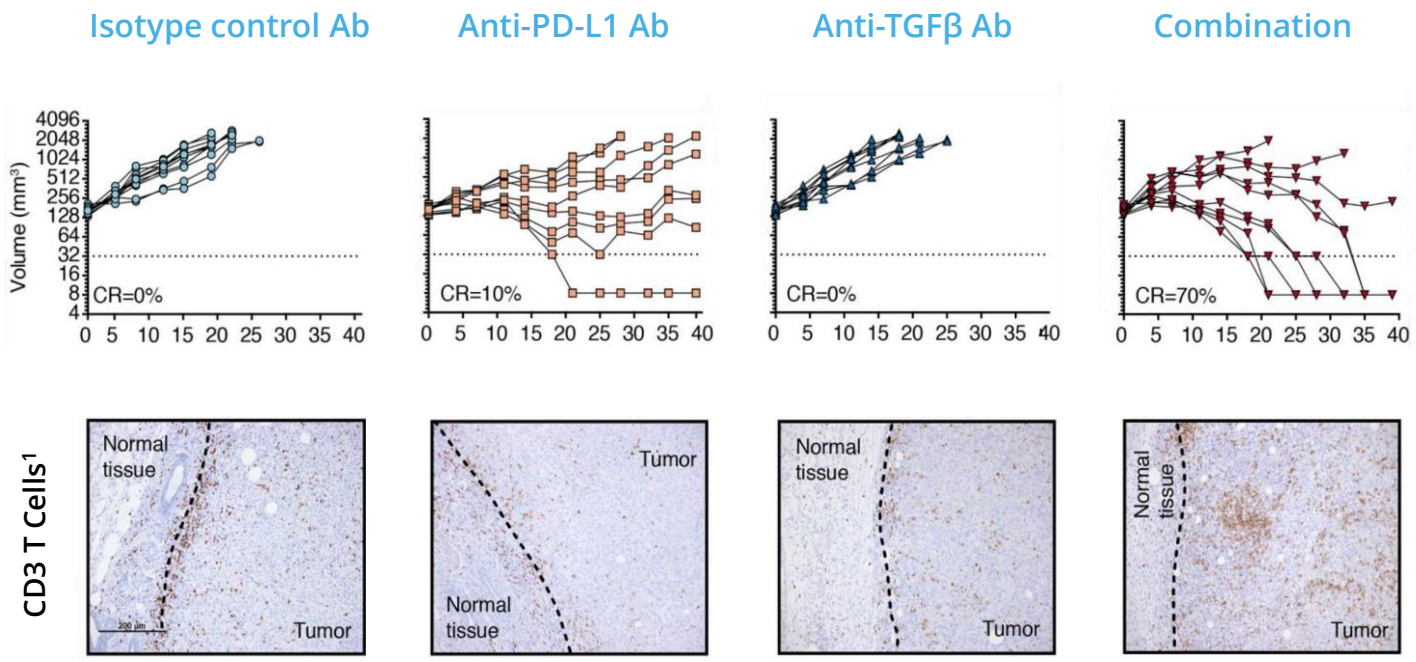



**Gene expression, immune cell quantification & network mapping**

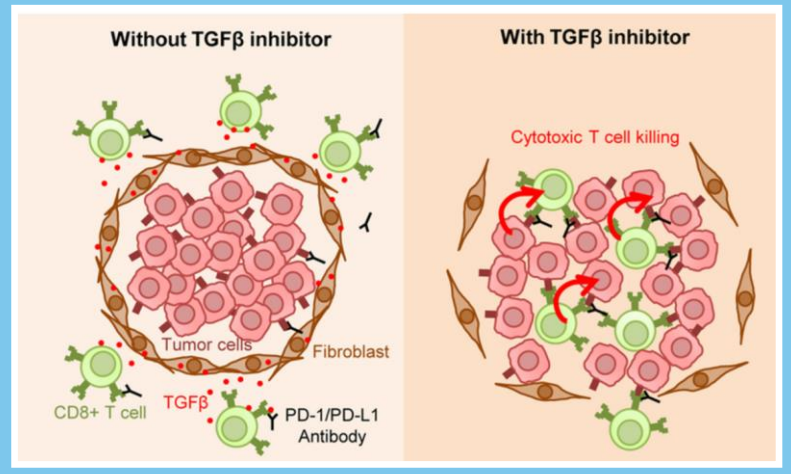
- 33 different cancer types / 8,000+ tumors

**Source:** Thorsson, et al. The Immune Landscape of Cancer, Immunity. 2018; 48:817

# Successfully blocking TGFβ overcomes immune exclusion




## Stromal TGFβ signaling is a determinant of immuno-exclusion[2]




- An increase in CD3 immune cell infiltration is associated with the anti-PD/L-1 and anti-TGFβ antibody combination
- Effective therapeutic targeting of TGFβ could be achieved via CRB-601 targeting the αvβ8 integrin

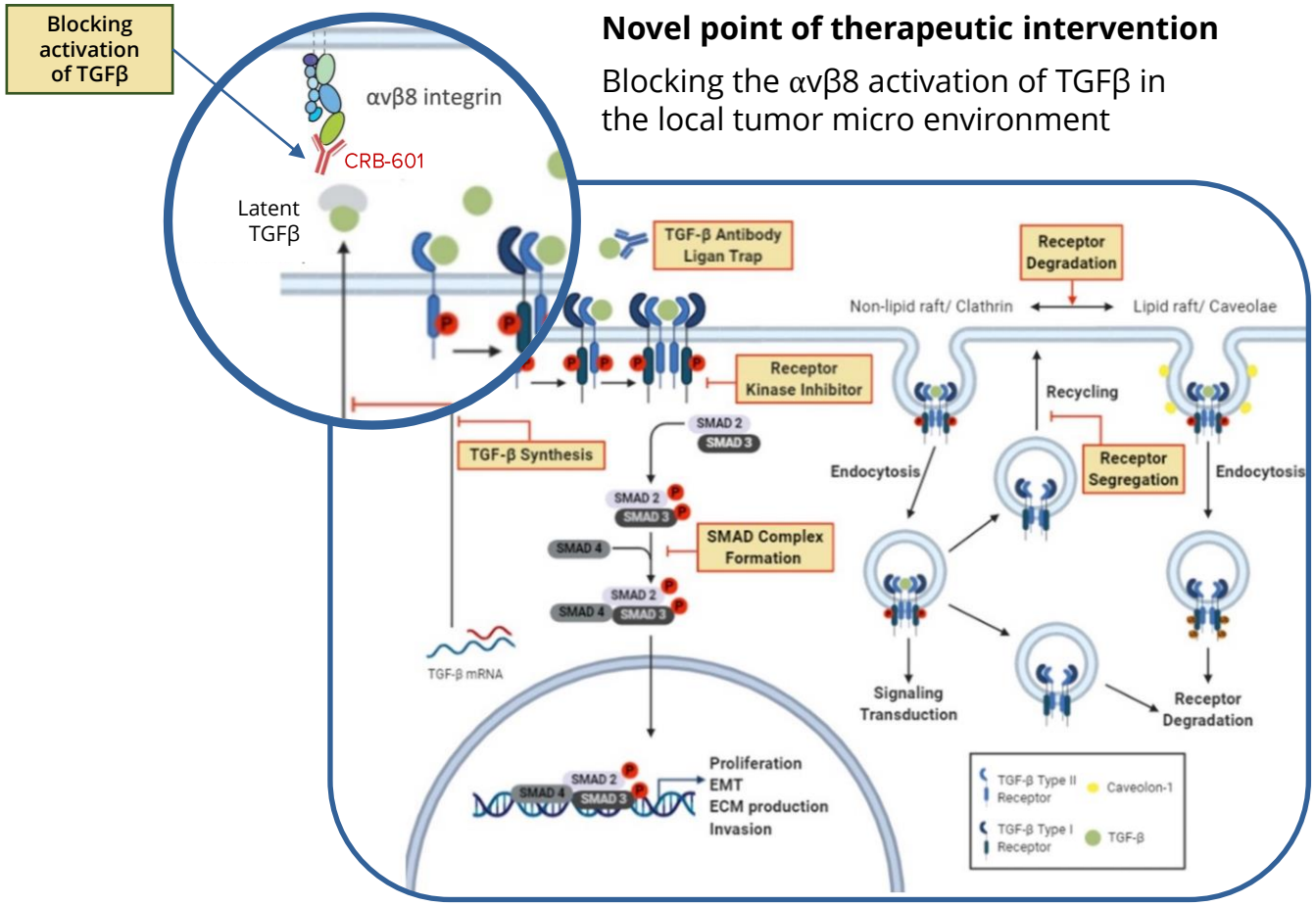
**Sources: 1.** Mariathsasan, et al., Nature. 2018; 554:547. **2.** Ganesh & Massagué., Immunity 2018: 626-628.

# Targeting the integrin αvβ8 represents a novel approach to regulating TGFβ

## Recent experience with TGFβ[1]

| TGFβ pathway | Investigational Compound | Modality |
|---|---|---|
| Anti sense TGFβ2 | Trabedersen | Anti sense oligo |
| αvβ3/5 Integrin inhibitor | Cilengitide | αvβ3/5 mAb |
| TGFβRI blockade | LY3022859 | mAb |
| TGFβ ligand Trap | Fresolimumab | mAb |
| TGFβ ligand Trap + PD-1 | Bintrafusp alfa | Bifunctional fusion protein |
| TGFβR1 Kinase inhibitor | Galunisertib | small molecule |

## TGFβ Pathway and Point of Therapeutic Intervention[2]

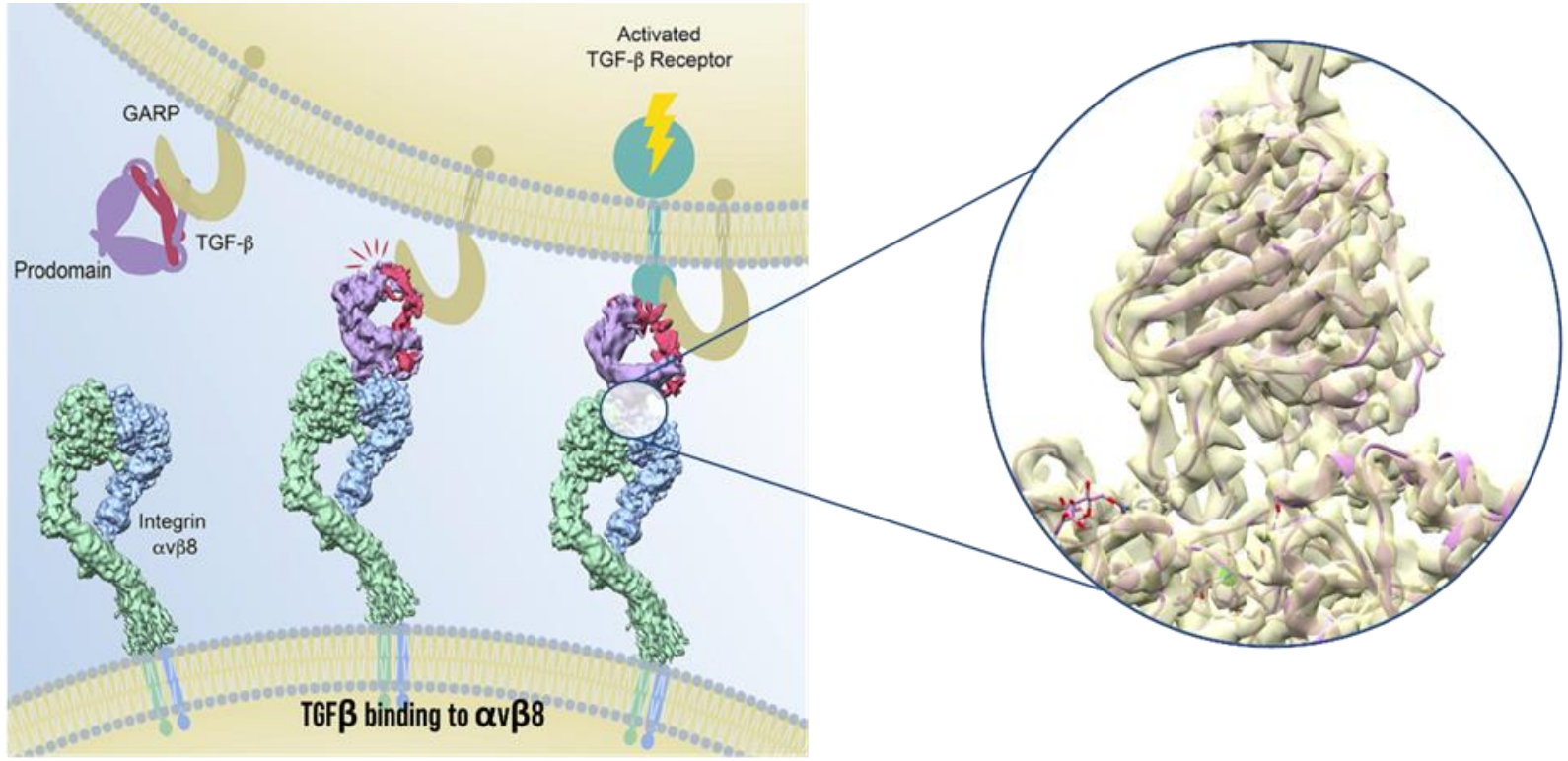



**Novel point of therapeutic intervention**

Blocking the αvβ8 activation of TGFβ in the local tumor micro environment

**Sources: 1.** Reviewed in Teixeria., 2020. **2.** Huang et al., 2021. Recent progress in TGFβ inhibitors for cancer therapy.

# CRB-601 binds at the Interface between TGFβ and αvβ8




Campbell, et al. *Cryo-EM Reveals Integrin-Mediated TGF-6 Activation without Release from Latent TGF-6*. Cell. 2020; 180:491-493.

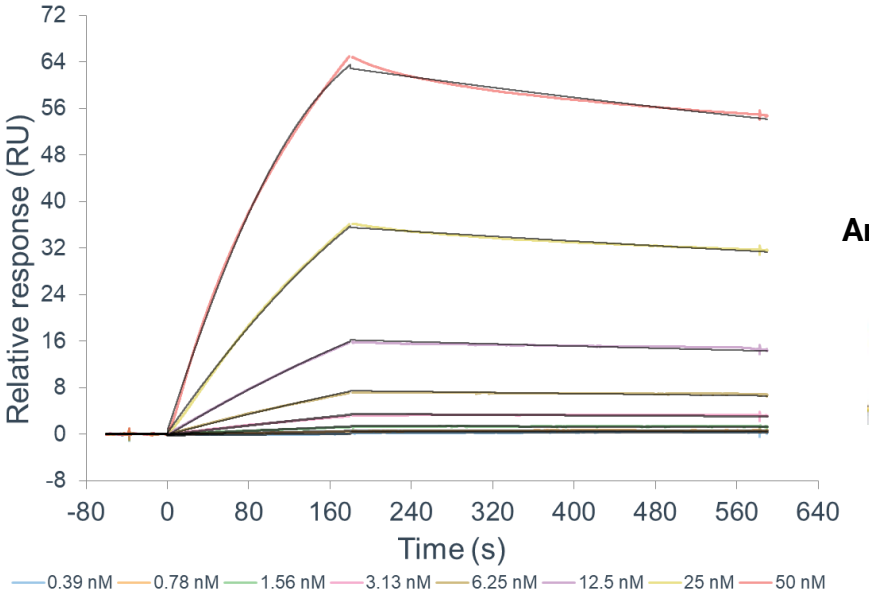
| | New Approaches to Targeting TGFβ[2] | |
|---|---|---|
| | Phase (Disclosed Indication) | Target |
| CORBUS PHARMACEUTICALS | IND H1-2023 Solid Tumors | αvβ8 |
| Pfizer | Phase 1 Solid Tumors | αvβ8 |
| Scholar Rock | Phase 1 Solid Tumors | GARP |
| PLIANT | Preclinical | αvβ8 |
| MORPHIC THERAPEUTIC | Preclinical | αvβ8 |

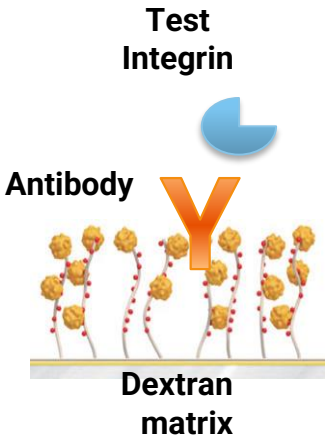
Monoclonal Antibody

Small Molecule

# CRB-601 binds to integrin αvβ8 with high affinity and selectivity

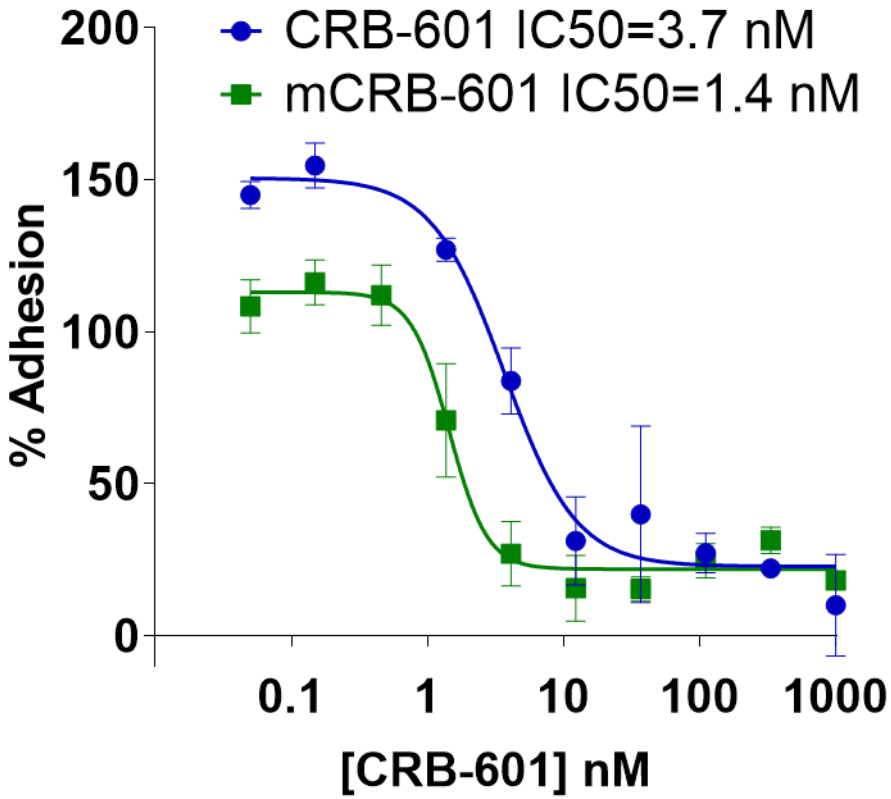
## Integrin Binding and Selectivity (Surface Plasmon Resonance)



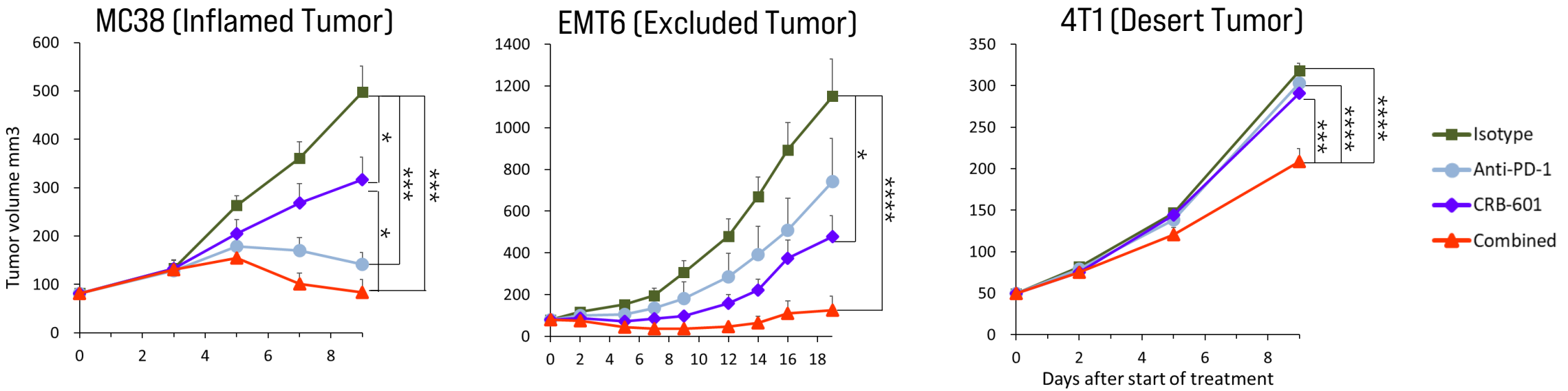

| | Kd, nM | | | | | |
|---|---|---|---|---|---|---|
| **Antibody** | $\alpha_v\beta_1$ | $\alpha_v\beta_3$ | $\alpha_v\beta_5$ | $\alpha_v\beta_6$ | $\alpha_v\beta_8$ | $m\alpha_v\beta_8$ |
| CRB-601 | >200 | >200 | >200 | >200 | 1.4 | 1.4 |

## L-TGFβ Binding Inhibition




mCRB-601 : murine isotype switched variant of CRB-601

# CRB-601 enhances anti-PD-1 therapy in checkpoint inhibition sensitive and resistant murine tumor models




Checkpoint blockade sensitivity

Sensitive

Resistant

| % TGI | MC38 | EMT6 | 4T1 |
|---|---|---|---|
| Anti-PD-1 | 86 | 38 | 6 |
| CRB-601 | 44 | 63 | 10 |
| Combo | 100 | 96 | 41 |

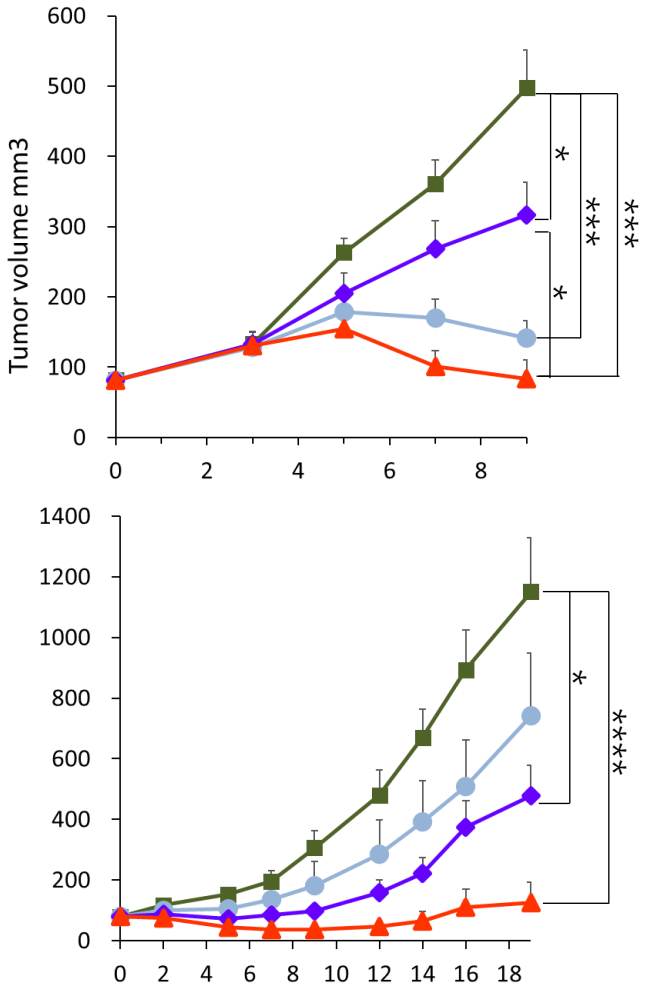
CRB-601: 10 mg/kg BIW
Anti-PD-1: 10 mg/kg BIW
10 animals / group
Animals randomized at 50-80 $mm^3$
Comparisons across arms
*$p$<0.05, ***$p$<0.001, ****$p$<0.0001

# CRB-601 enhances anti-PD-1 therapy in early and late intervention

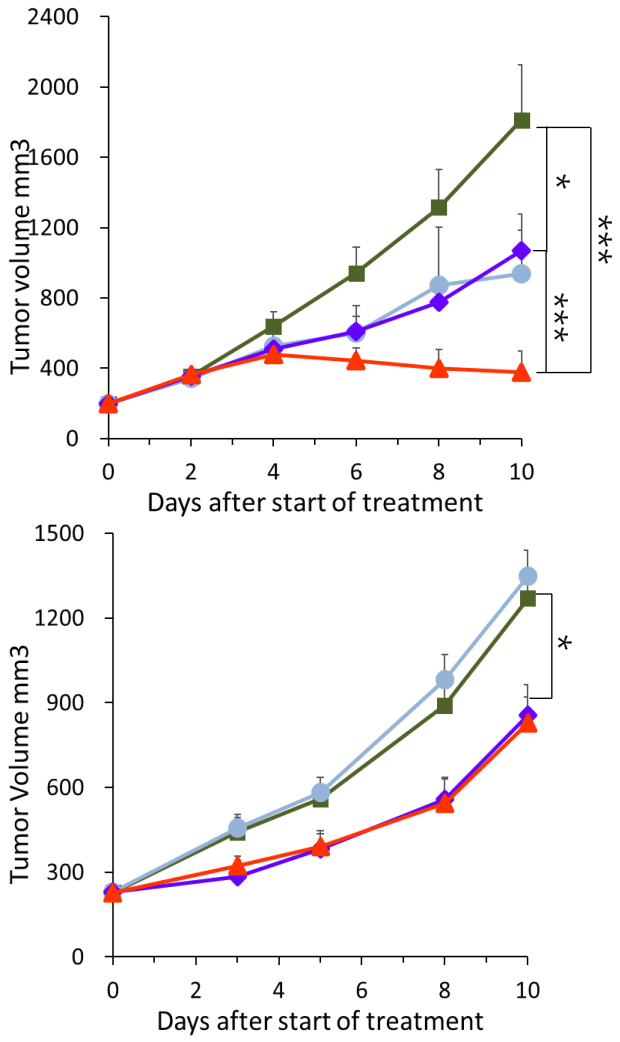
MC38
(Inflamed Tumor)

EMT6
(Excluded Tumor)

Early Intervention
Tumor volume = 50-80 mm$^3$




Late Intervention
Tumor volume = 200 mm$^3$




Isotype
Anti-PD-1
CRB-601
Combined

| | MC38 Early | MC38 Late | EMT6 Early | EMT6 Late |
|---|---|---|---|---|
| Anti-PD-1 | 86 | 54 | 38 | -8 |
| CRB-601 | 44 | 46 | 63 | 37 |
| Combo | 100 | 89 | 96 | 65 |

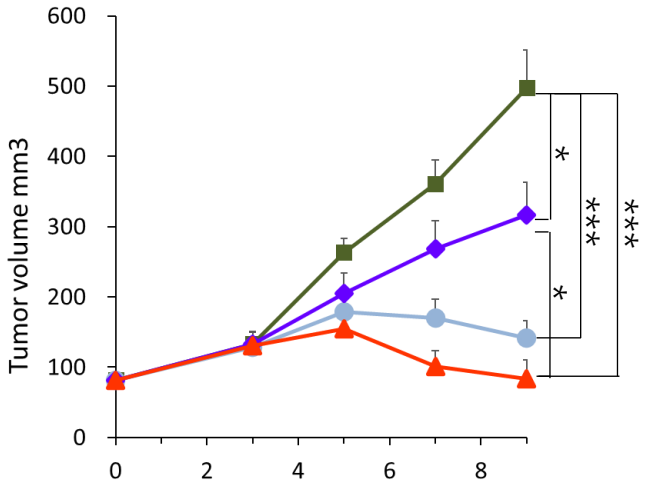
CRB-601: 10 mg/kg BIW
Anti-PD-1: 10 mg/kg BIW
8 (EMT6-late) or 10 animals/group
Comparisons across arms
*$p$<0.05, ***$p$<0.001, ****$p$<0.0001

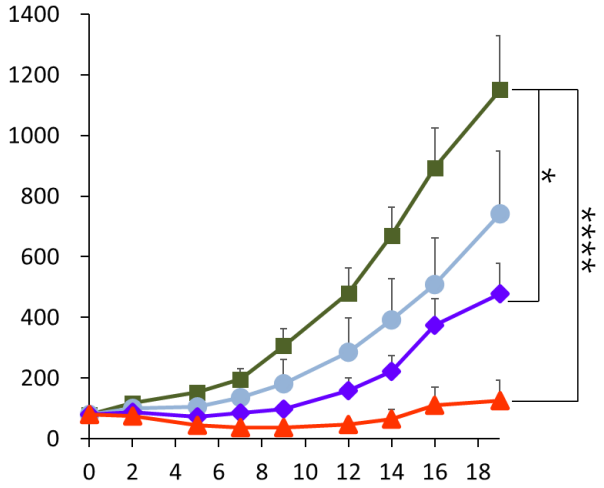
# CRB-601 enhances anti-PD-1 therapy in early and late intervention

MC38
(Inflamed Tumor)

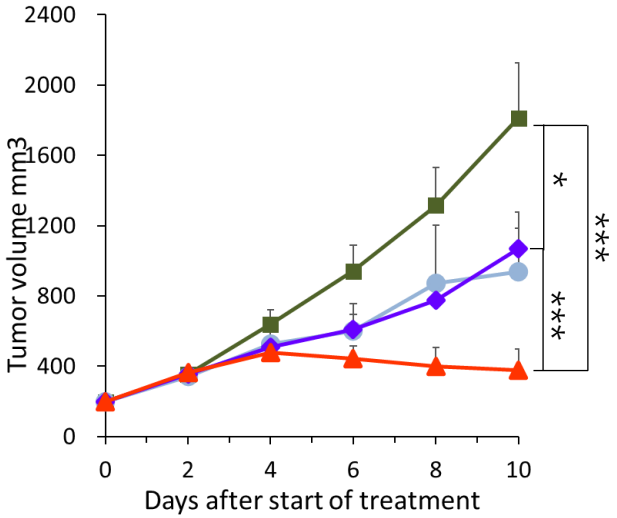
EMT6
(Excluded Tumor)

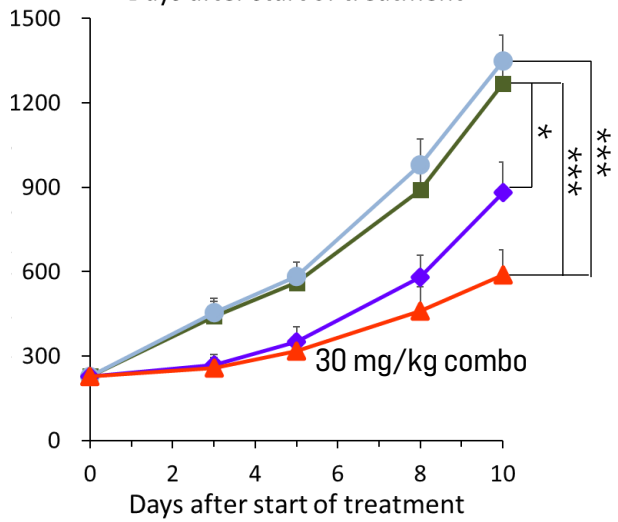
Early Intervention
Tumor volume = 50-80 $mm^3$

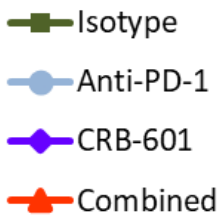



Late Intervention
Tumor volume = 200 $mm^3$



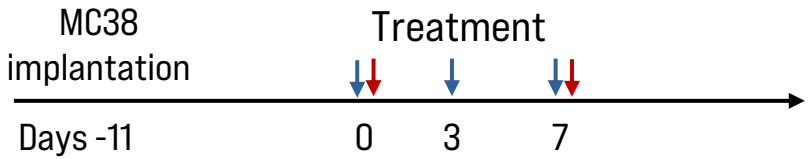




| | MC38 Early | MC38 Late | EMT6 Early | EMT6 Late |
|---|---|---|---|---|
| **Anti-PD-1** | 86 | 54 | 38 | -8 |
| **CRB-601** | 44 | 46 | 63 | 37 |
| **Combo** | 100 | 89 | 96 | 65 |

CRB-601: 10 mg/kg BIW
Anti-PD-1: 10 mg/kg BIW
8 (EMT6-late) or 10 animals/group
Comparisons across arms
*$p$<0.05, ***$p$<0.001, ****$p$<0.0001

# CRB-601 enhances the impact of anti-PD-1 therapy on the number of animals cured of their tumor burden

Immune inflamed tumor

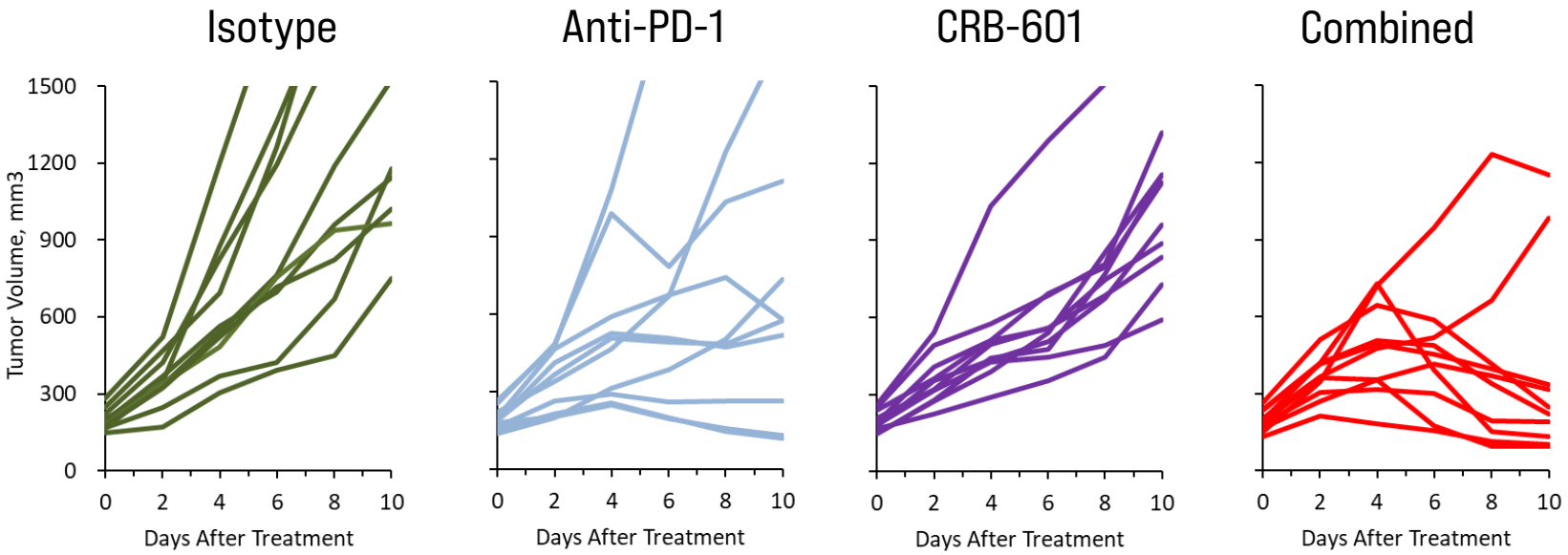


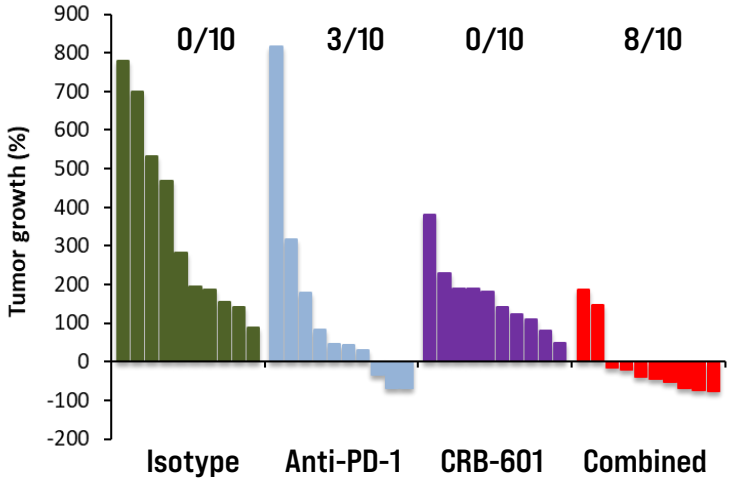

CRB-601, 10 mg/kg, IP

Anti-PD-1 (RMP1-14), 10 mg/kg, IP

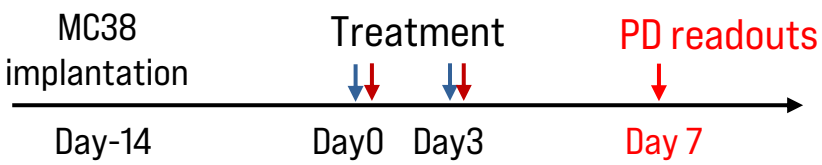
n=10/group

Tumor volume = 200 $mm^3$ (when treatment initiate)



# Tumor regression following treatment with CRB-601 and anti-PD-1 in MC38 tumors is associated with T cell infiltration and activation in tumors

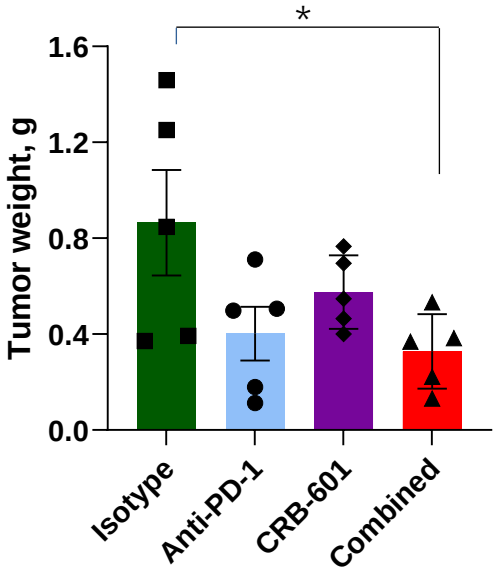



↓ CRB-601, 10 mg/kg, IP

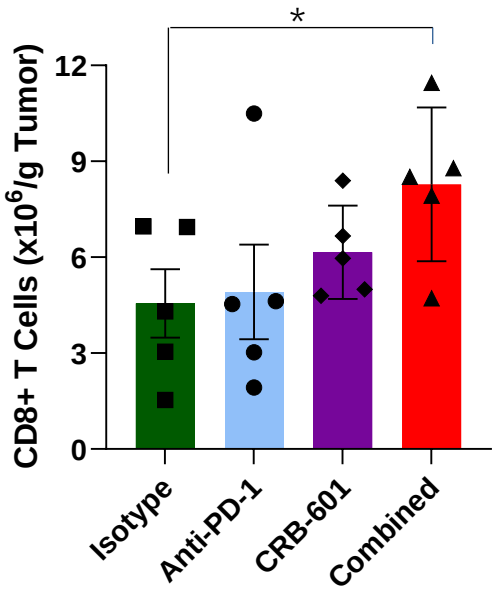
↓ Anti-PD-1 (RMP1-14), 10 mg/kg, IP

Tumor volume = 250 $mm^3$ (when treatment initiated)

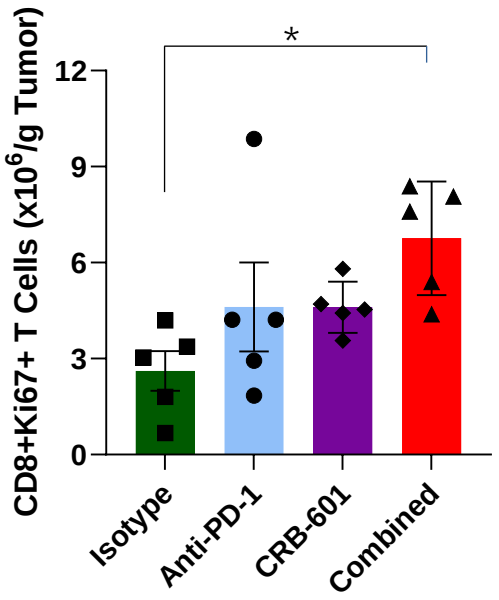
A Tumor weight (g)



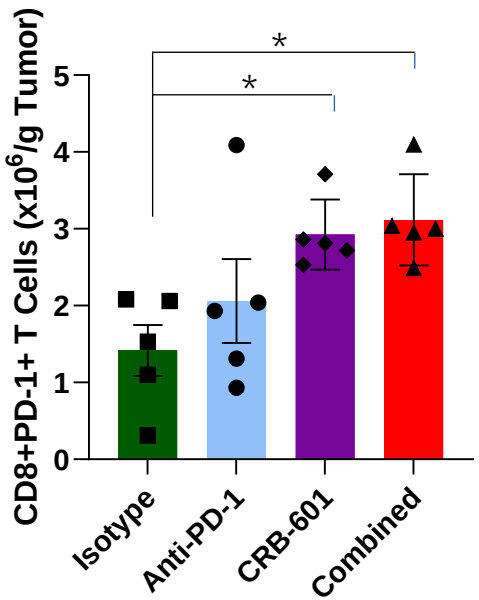

B CD8⁺ tumor-infiltrating lymphocytes (TILs)




C Proliferation of CD8⁺ TILs

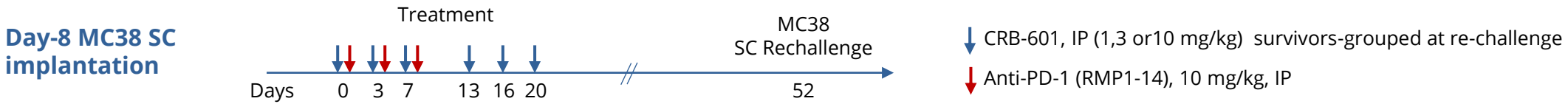



D PD-1 expression in CD8⁺ TILs

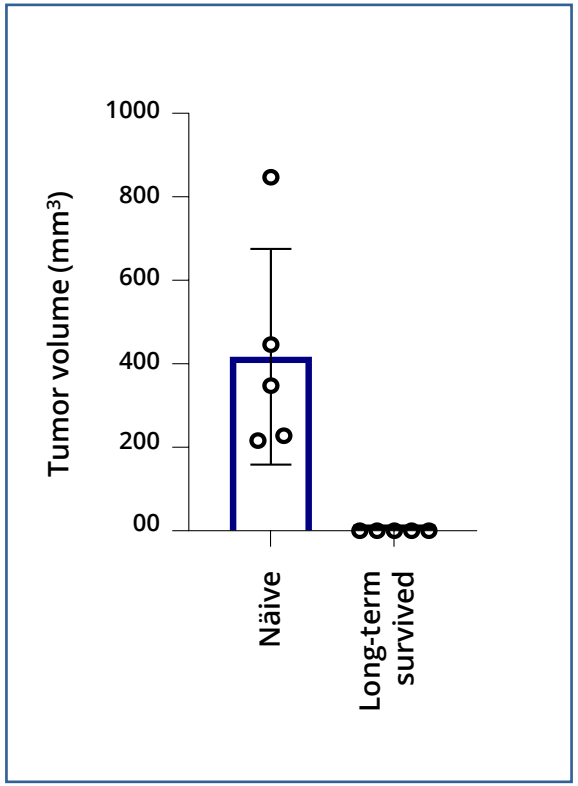


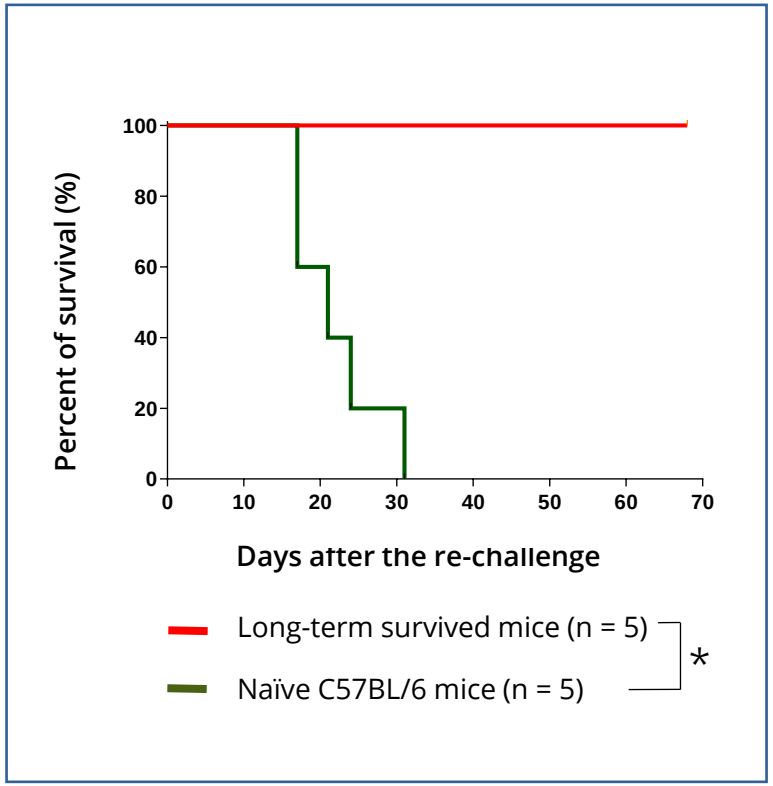

*$p$<0.05

# CRB-601 + anti-PD1 is associated with tumor-specific immune memory




- Surviving MC38 tumor bearing mice treated with CRB-601 + anti-PD1 were re-challenged with MC38 tumors at day 52 post treatment initiation
- Survival and regrowth compared to treatment näive mice was monitored for 70 days

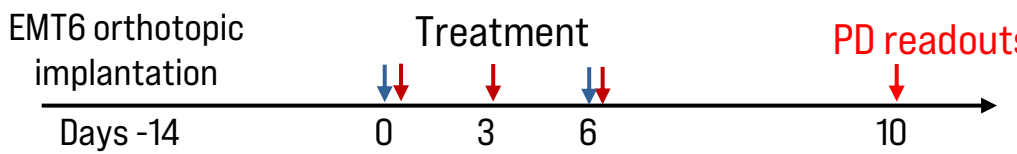



*p < 0.05, log-rank test

**Source:** Company data on file.

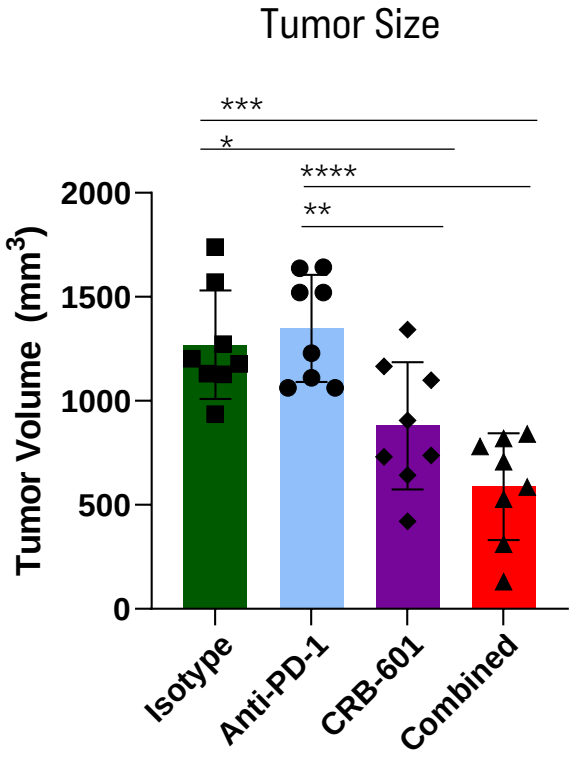
# Blockade of αvβ8 in combination with anti-PD-1 increased TIL populations in immune excluded EMT6 tumors

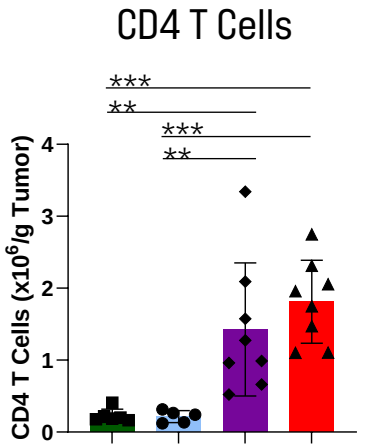


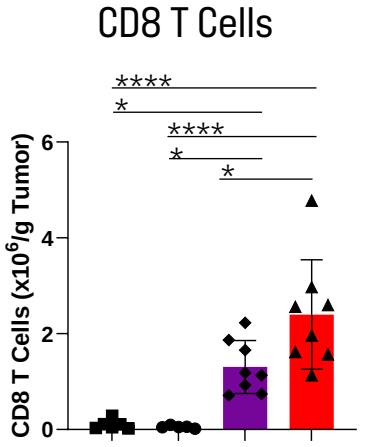

↓ CRB-601, 30 mg/kg, IP

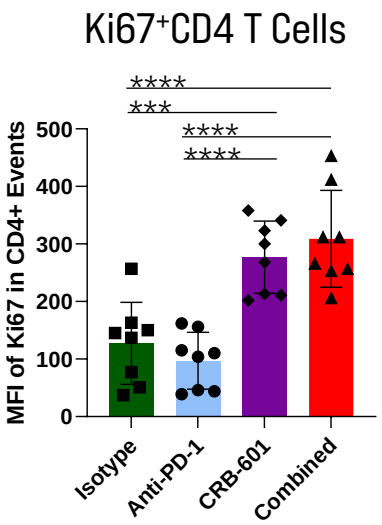
↓ Anti-PD-1, 10 mg/kg, IP

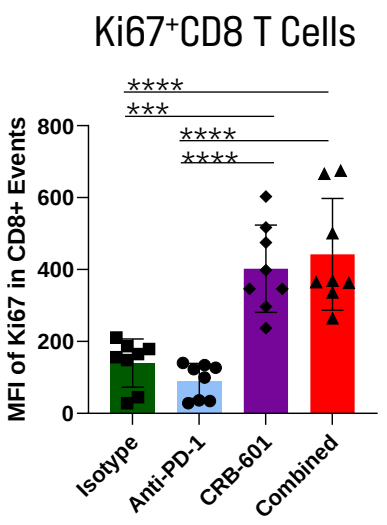
Tumor volume = 200 $mm^3$ (when treatment initiated)



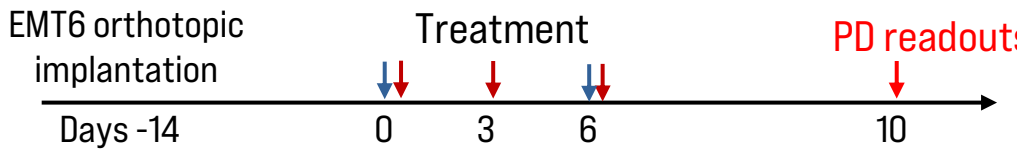






*$p$<0.05; **$p$<0.01; ***$p$<0.001; ****$p$<0.0001

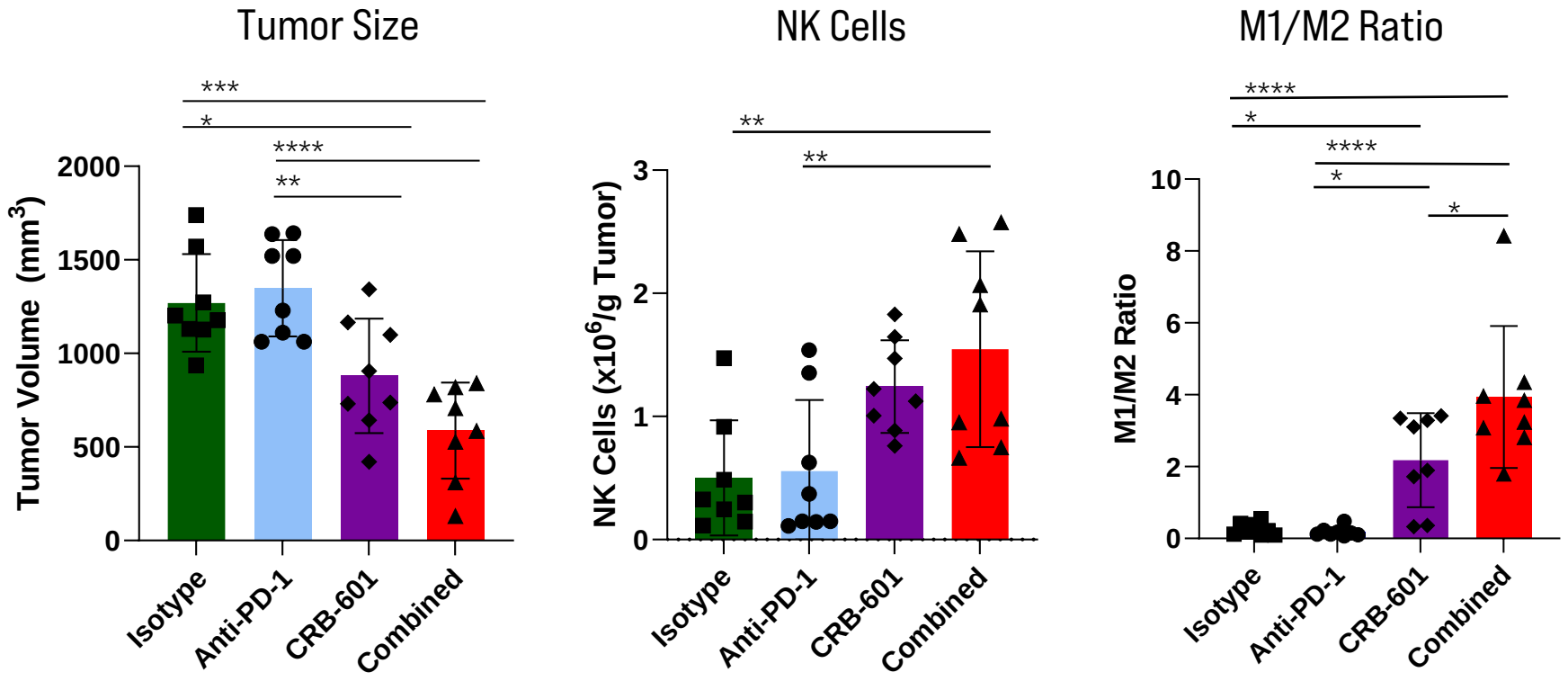
# Blockade of αvβ8 in combination with anti-PD-1 also increased NK and M1 macrophages in immune excluded EMT6 tumors




↓ CRB-601, 30 mg/kg, IP

↓ Anti-PD-1 (RMP1-14), 10 mg/kg, IP

Tumor volume = 200 $mm^3$ (when treatment initiated)






*$p$<0.05; **$p$<0.01; ***$p$<0.001; ****$p$<0.0001

# Summary and Conclusions

- CRB-601 exhibits high affinity (low nM Kd) to human and murine $\alpha_v\beta_8$ and high selectivity with no appreciable binding to other RGD-binding integrins
- CRB-601 significantly inhibits tumor growth as a single agent and enhances the efficacy of anti-PD-1 immunotherapy in checkpoint inhibitor-sensitive & resistant tumor models.
- CRB-601 alone or in combination with anti-PD-1 mAb led to a significant increase in tumor-infiltrating T cells, NK cells and M1 polarized macrophages within EMT6 tumors.
- CRB-601 holds promise as a potential combination partner for cancer immunotherapies.
- We are on track for an IND in H1 2023

# Collaborators

Corbus Pharmaceuticals:

- Daqing Wang
- Maneesh Singh
- Eric Haines
- Suzie Ferreira
- Rachael Brake

University of California, San Francisco

- Dr. Steven Nishimura

ZM Scientific

- Richard Morse
- Eugene Zhukovsky