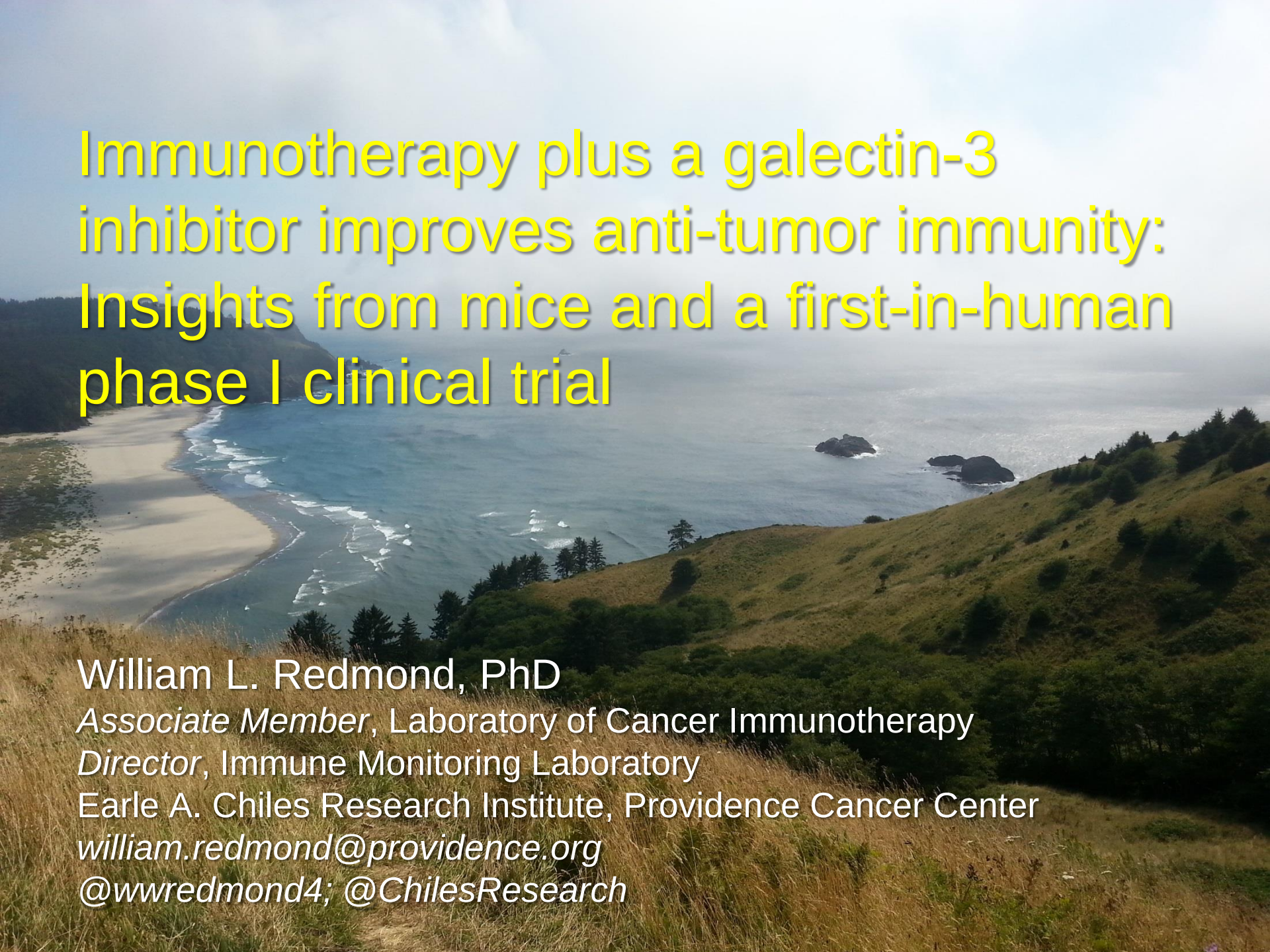
Immunotherapy plus a galectin-3 inhibitor improves anti-tumor immunity: Insights from mice and a first-in-human phase I clinical trial



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Disclosures

(Research grants, consulting, and/or royalties)

- Galectin Therapeutics, Merck, Nektar Therapeutics, Tesaro, IRX Therapeutics, CSRA Inc.

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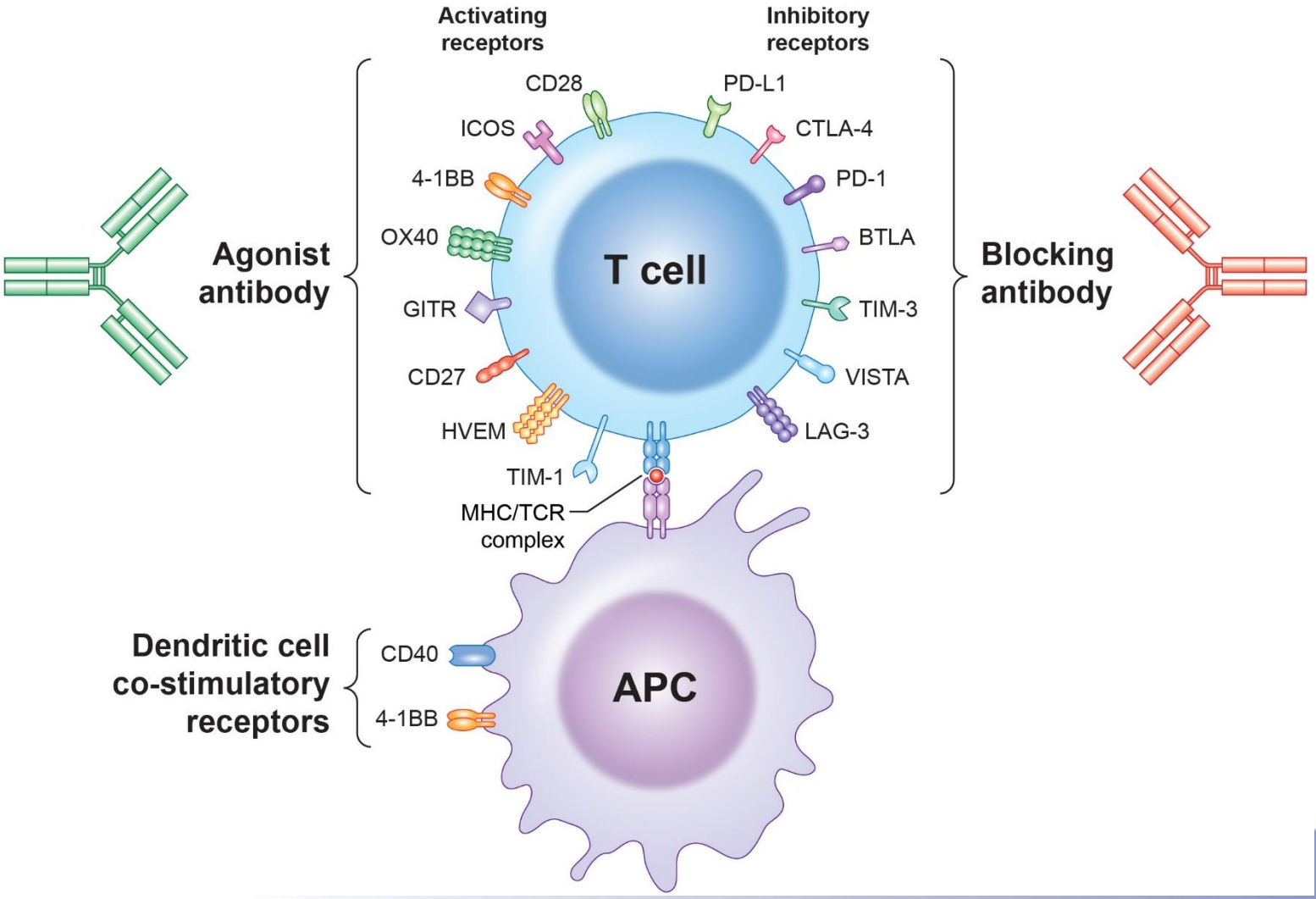
Immune-modulating antibodies



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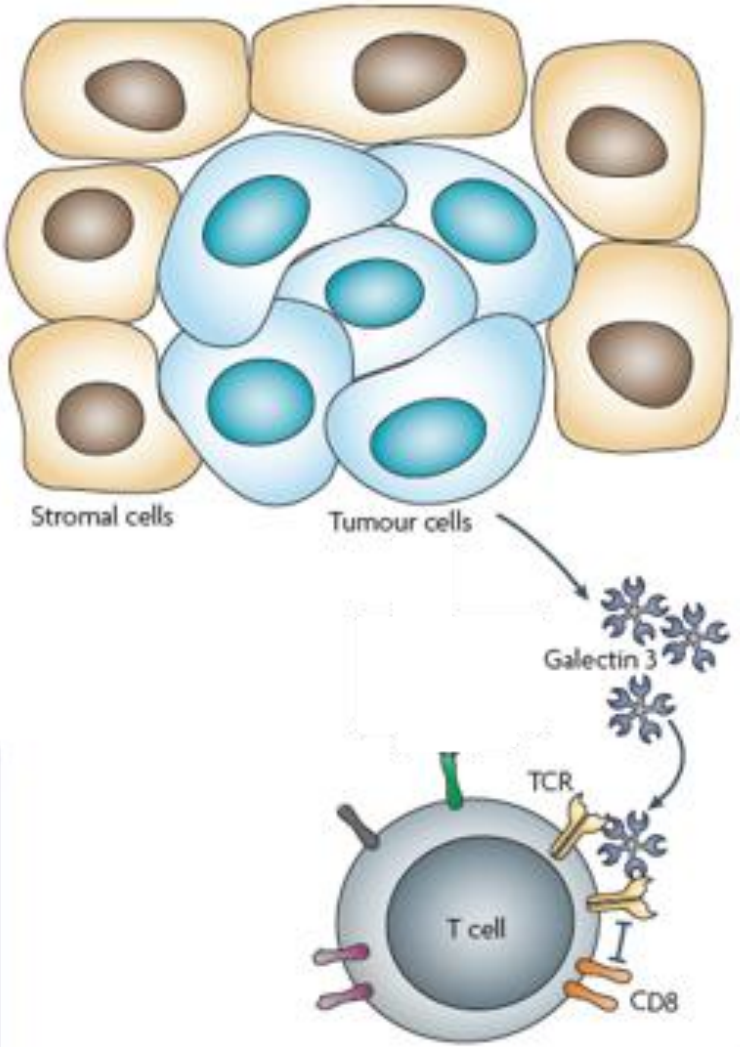
Galectin-3 and cancer

- Gal-3 is a lectin (carbohydrate binding protein) that is shed by tumor cells and suppresses “killer” T cell function
- Promotes angiogenesis and spread (metastasis) of cancer cells
- Highly expressed in a variety of tumors



Rabinovich G, *Nat Rev Immunol,* 2009

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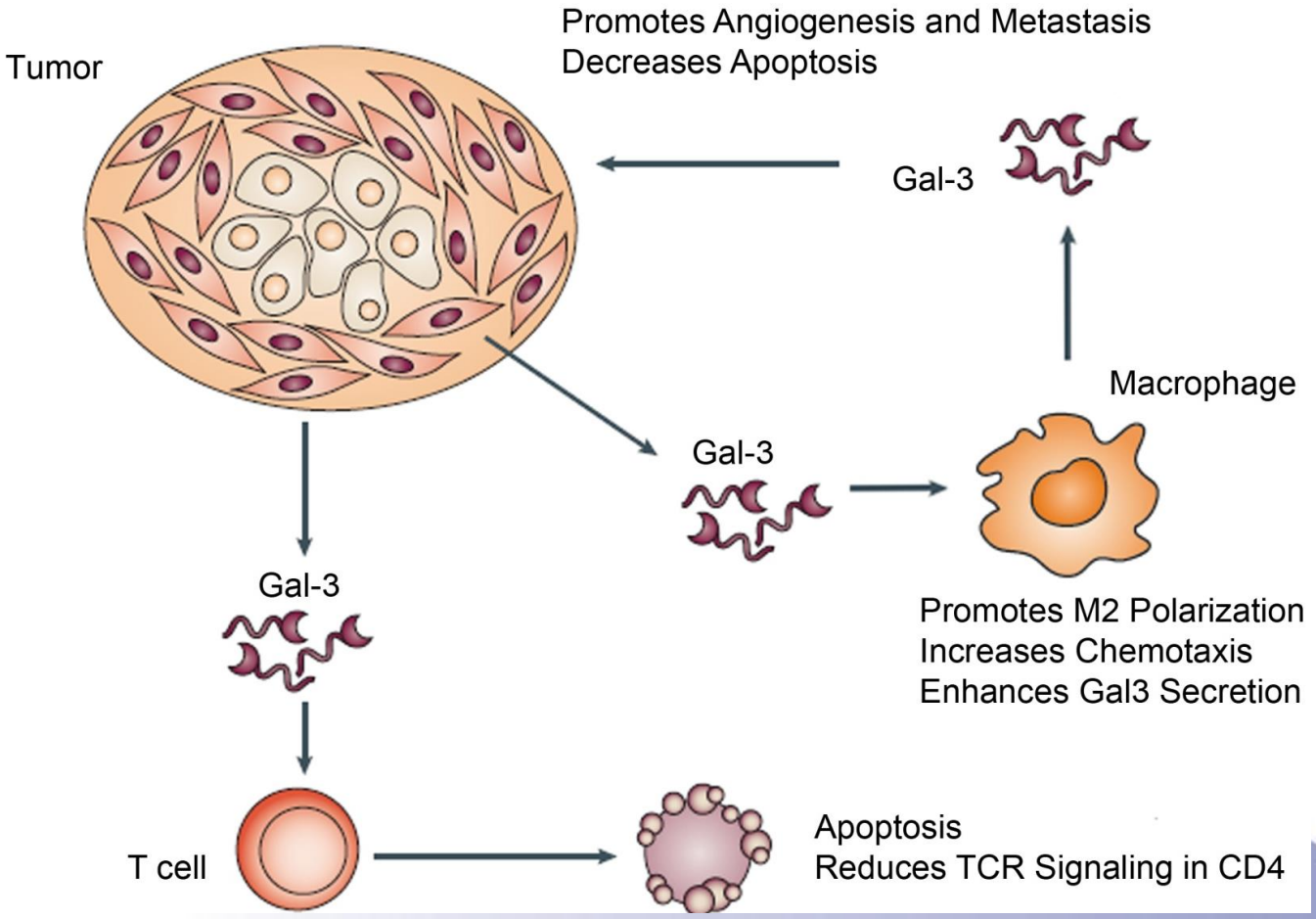
Immune suppression via galectin-3



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Galectin-3 inhibitor (GR-MD-02)

- Developed by our collaborator, Galectin Therapeutics, Inc. (http://galectintherapeutics.com)
- GR-MD-02 is considered a Non-biological Complex Drug (NBCD)
  - A glycopolymer (polysaccharide) derived from USP Apple Pectin
  - Drug binds to and inhibits galectin-3
- GR-MD-02 is being investigated in three galectin-3 dependent indications
  - Non-alcoholic steatohepatitis (NASH) with advanced fibrosis
    - Completed two Phase 1 and one Phase 2a trials
    - Phase 2b clinical trial in patients with NASH cirrhosis completely enrolled with top line data to be reported in December 2017
  - Severe skin disease, including moderate to severe plaque psoriasis and severe atopic dermatitis
  - Combination cancer immunotherapy

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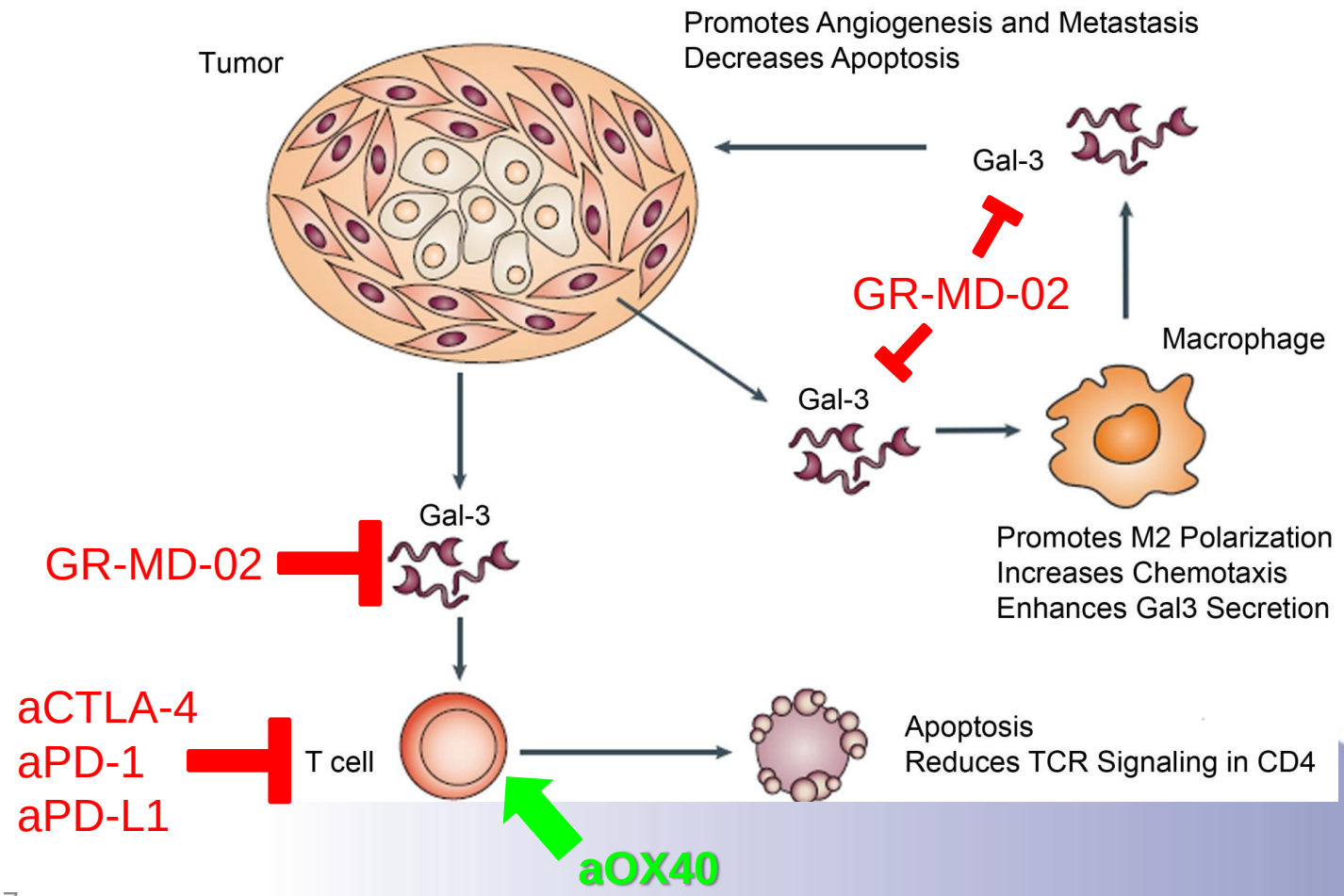
Does immunotherapy plus Gal-3 inhibition augment anti-tumor immunity?



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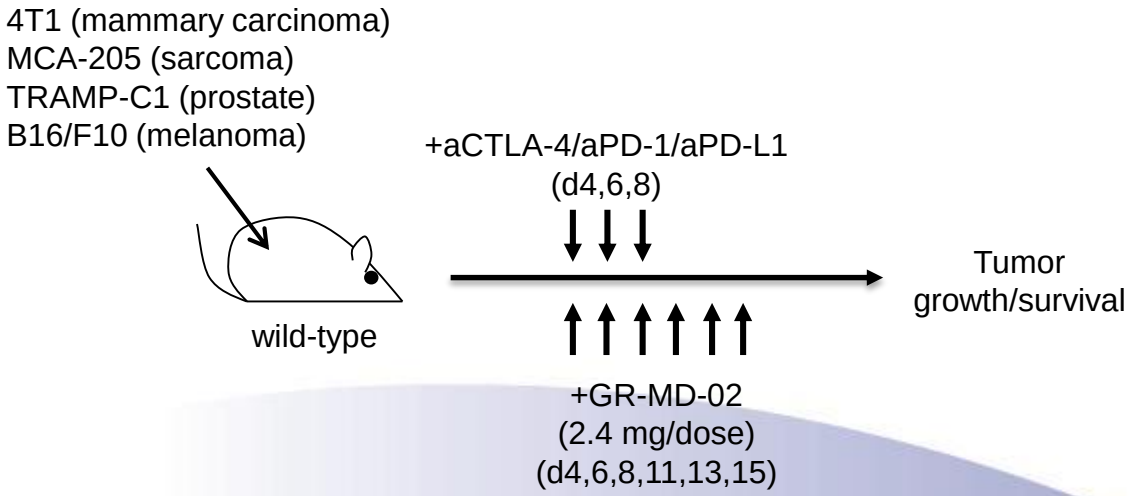
GR-MD-02 plus checkpoint blockade

Model



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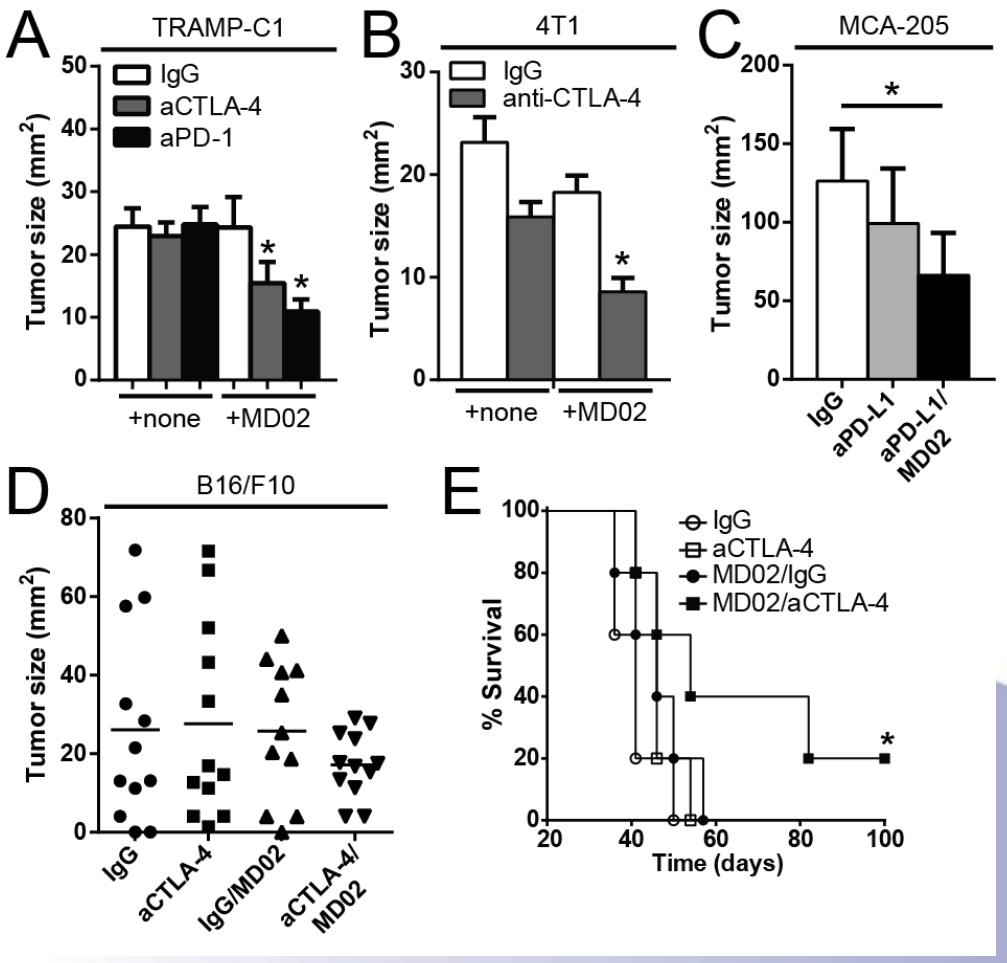
Reduced tumor burden and increased survival following GR-MD-02 plus checkpoint blockade



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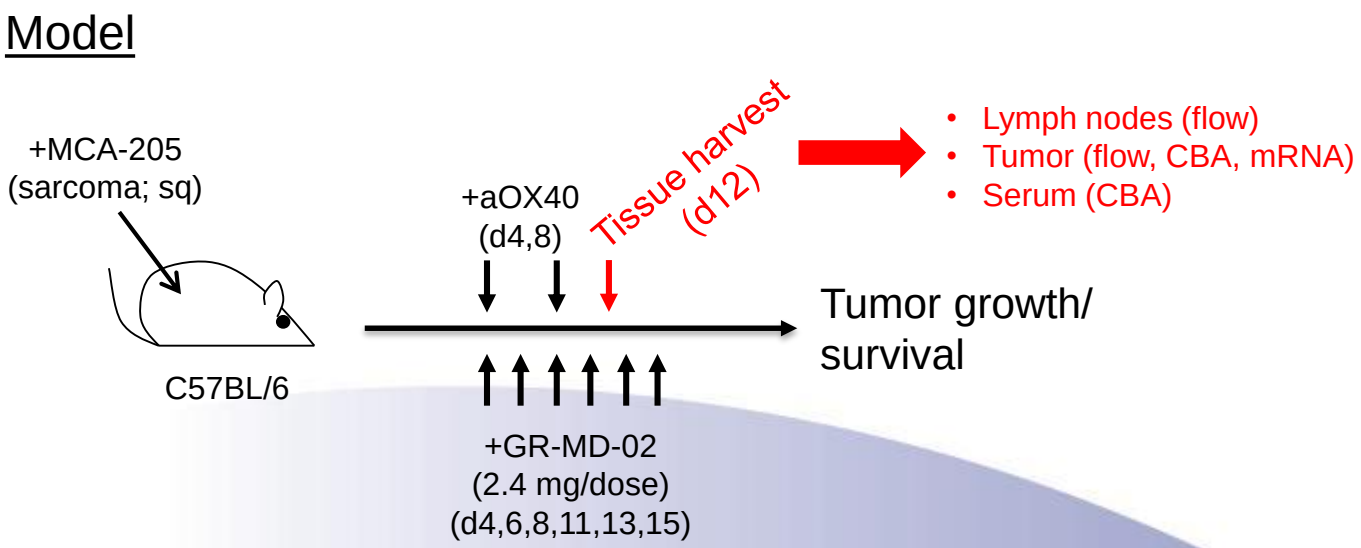
Combined GR-MD-02/aOX40 therapy to augment anti-tumor immunity



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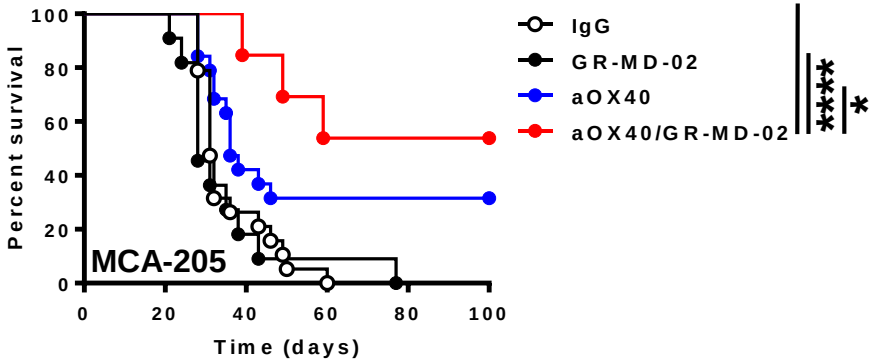
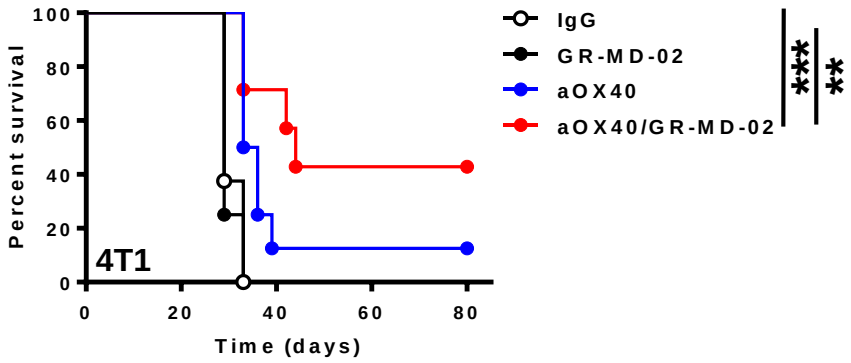
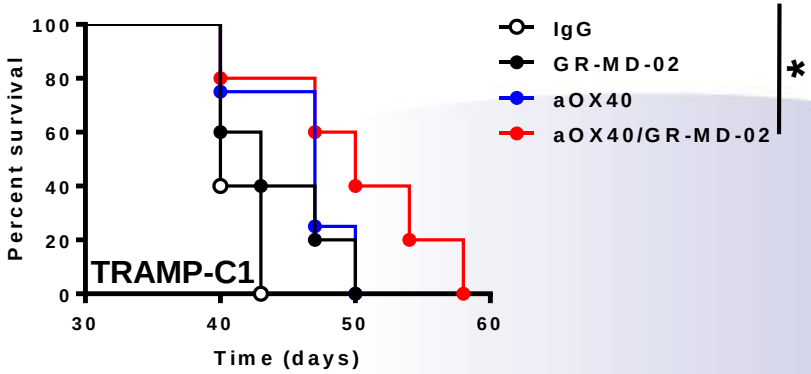
Combined GR-MD-02/aOX40 therapy improves survival







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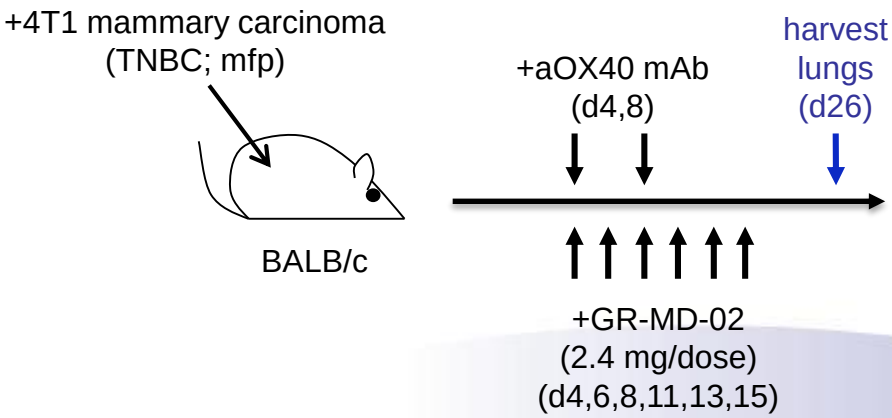
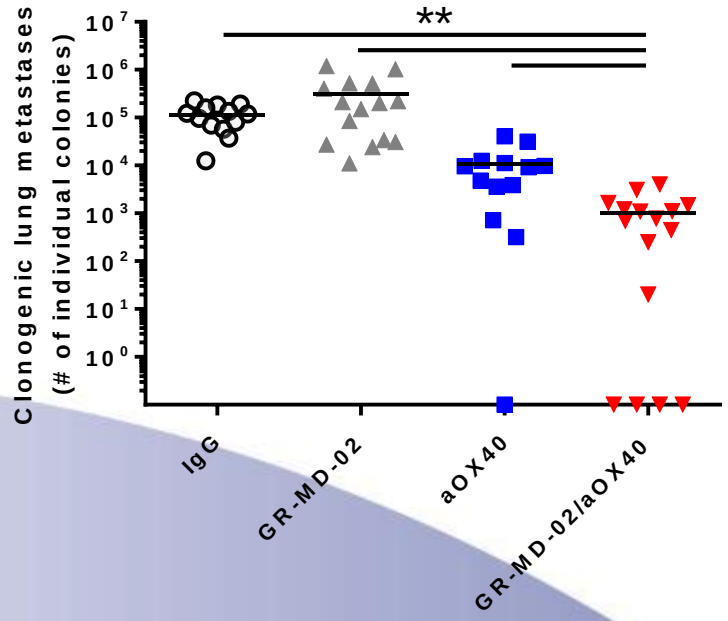
Combined GR-MD-02/aOX40 therapy reduces spontaneous lung metastases

Model





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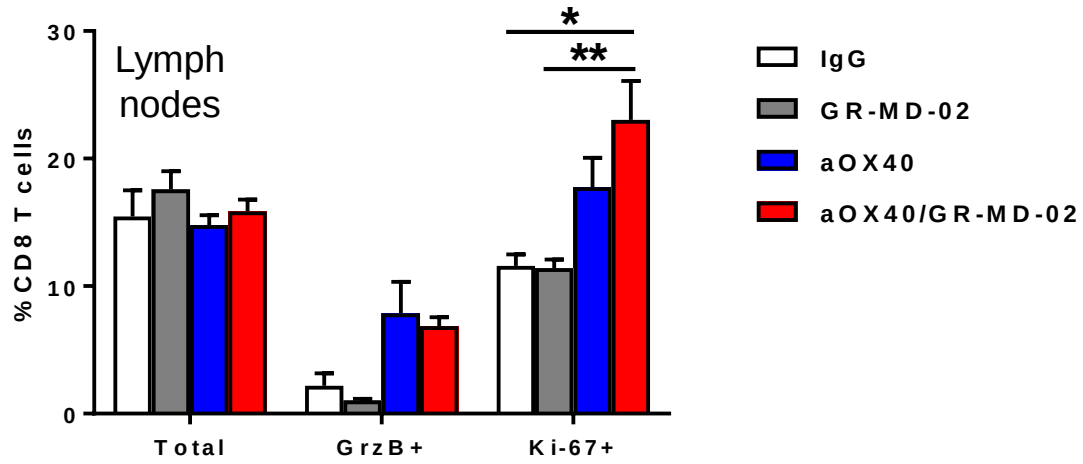
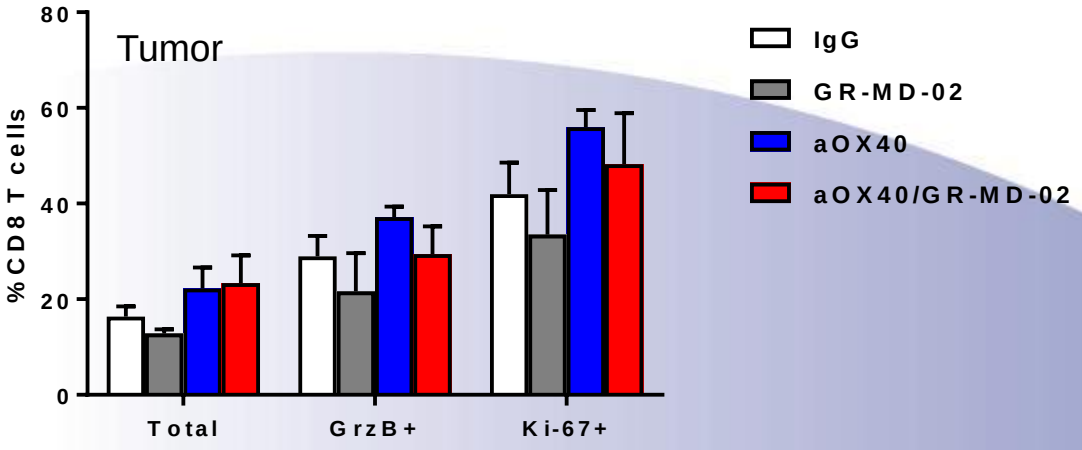
GR-MD-02/aOX40 increases CD8 T cell proliferation





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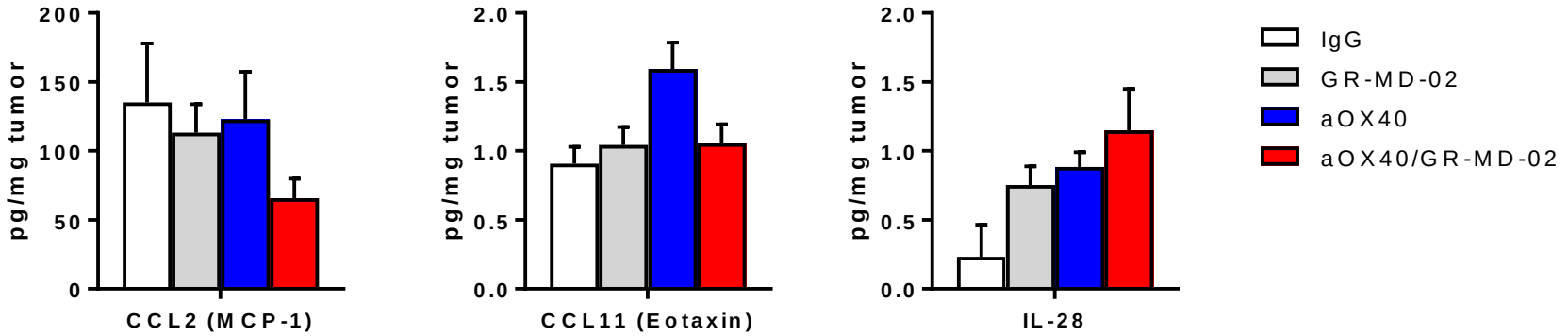
Effects of GR-MD-02/aOX40 on cytokine/chemokine profile

(tumor)



- CCL2: promotes monocyte recruitment to TME; suppresses T cell responses
- CCL11: Gal3 induces CCL11 and regulates eosinophil trafficking
- IL-28 (type III IFN): associated with improved anti-tumor immunity

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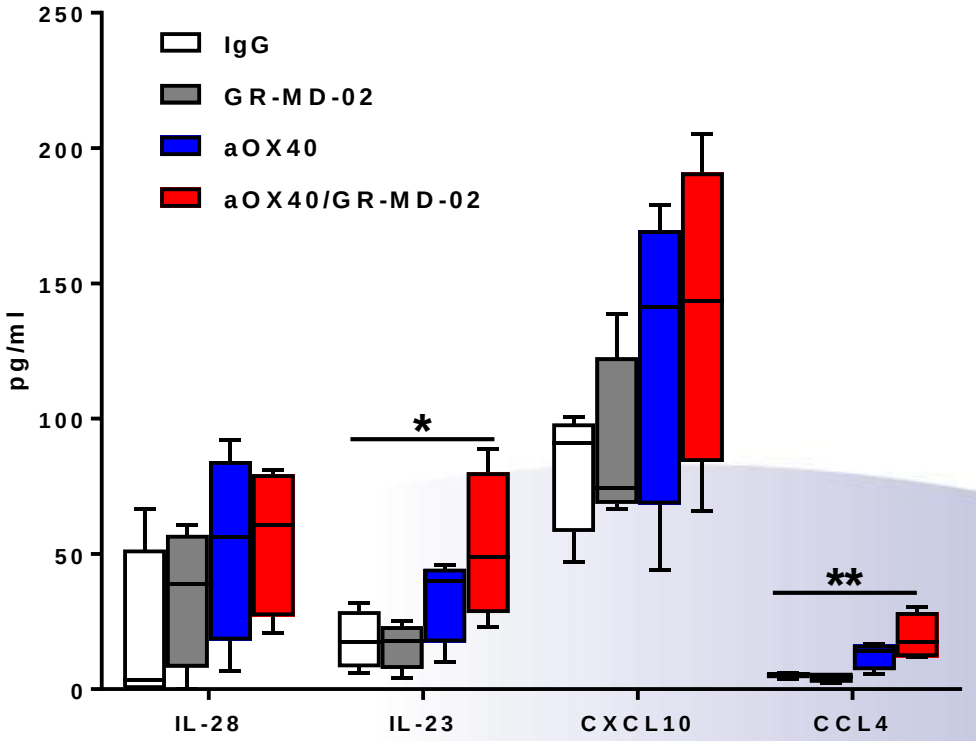
Effects of GR-MD-02/aOX40 on cytokine/chemokine profile

(serum)



- IL-23: promotes Th17 CD4 T cells
- CXCL10: Binds CXCR3 and affects CD8 T cell trafficking to the TME
- CCL4: Drives increased CD8 T cell recruitment and DC maturation

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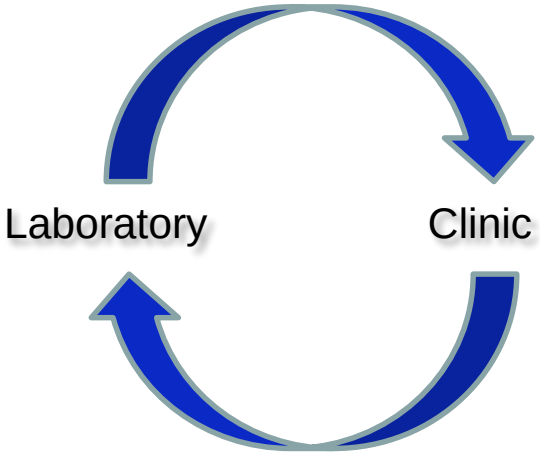
Translation to the clinic

Pre-clinical discoveries



Clinical trials

PI: Dr. Brendan Curti, MD

- Galectin Inhibitor (GR-MD-02) and Ipilimumab in Patients With Metastatic Melanoma (NCT02117362)
  - This trial was initiated in 2015, enrolled 7 subjects with GR-MD-02 doses of 1 and 2 mg/kg
  - There were no safety signals identified
  - In these initial cohorts, there were no notable changes in the peripheral immune signature
  - Due to changes in the standard of care for metastatic melanoma (i.e., approval of anti-PD-1), recruitment has been slowed significantly

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Galectin Inhibitor (GR-MD-02) and Pembrolizumab in Patients with Metastatic Melanoma, Non-Small Lung Cancer and Head and Neck Squamous Cell Carcinoma (NCT02575404)

1. Pembrolizumab is FDA-approved to treat:
   a. Melanoma after progression on ipilimumab: RR = 26%
   b. Oral head and neck squamous cell carcincoma (OHN) after progression on platinum-containing chemo: RR = 18%
   c. Non-small cell lung cancer where there is tumor-expression of PD-L1 and disease progression on platinum-containing chemo (or agents targeting EGFR or ALK when those mutations are present): RR = 45%

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Objectives

1. Primary
   a. Determine a safe dose of GR-MD-02 used in combination with pembrolizumab of 200 mg IV every 3 weeks
2. Secondary
   a. Measure the response rate to combined therapy with GR-MD-02 and pembrolizumab in patients with metastatic melanoma, OHN and NSCLC for whom pembrolizumab is considered standard of care
   b. Measure the response rate of combined therapy with GR-MD-02 and pembrolizumab in patients with metastatic melanoma, NSCLC or HNSCC with tumor progression after pembrolizumab monotherapy
   c. Assess the biological activity of GR-MD-02 and pembrolizumab
      i. Immune monitoring for changes in effector/memory T cells
      ii. Tumor-specific responses using autologous and/or HLA-matched tumor
   d. Examine the composition of the tumor immune infiltrate from tumor biopsies (when feasible)

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Main inclusion criteria

1. Patients with metastatic or unresectable melanoma, OHN and NSCLC for whom pembrolizumab would be considered standard of care
2. Patients who have radiographic progression using RECIST criteria currently on pembrolizumab or who have recently discontinued pembrolizumab treatment and meet all other eligibility criteria are also eligible
3. Patients must be ≥ 18 years of age
4. ECOG performance status of 0-2

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Main exclusion criteria

1. Patients who have previously received a galectin antagonist
2. Patients with active autoimmune disease except for autoimmune thyroiditis or vitiligo
3. Patients with history of autoimmune colitis
4. Patients with untreated brain metastases (pts w/ treated brain metastases who demonstrate control of brain metastases with follow-up imaging ≥4 wks post-Tx are eligible)
5. Need for chronic steroids (inhaled corticosteroids are acceptable)

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Treatment regimen

1. Pembrolizumab 200 mg (fixed dose) + GR-MD-02 IV every 3 weeks
   a. GR-MD-02 is given for 5 doses
   b. Pembrolizumab can continue until disease progression

Cohort	GR-MD-02 dose (mg/kg lean body mass)
1	2*
2	4
3	8**

* Dose level completed, beginning enrollment to cohort 2

** Consideration will be given to increasing dose further, dependent upon responses and adverse events

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Patient summary

(Cohort 1, 2 mg/kg GR-MD-02)

Study Number	Diagnosis	Patient Current status	Patient Notes
RWF_15-166	Melanoma	Enrolled	on treatment
RWF_15-166	Melanoma	Active FU	progression
RWF_15-166	Melanoma	Enrolled	mixed response
RWF_15-166	Melanoma	Enrolled	PR
RWF_15-166	Melanoma	Withdrawn	**Not enrolled**
RWF_15-166	OHN	Enrolled	progression
RWF_15-166	Melanoma	Enrolled	progression
RWF_15-166	OHN	Ineligible	**Not enrolled**

Note: Study design calls for 3 patients enrolled per cohort with 3 additional if there are adverse events. While there were no adverse events, 6 patients were enrolled because 3 had not completed protocol when others were identified

Adverse events

(GR-MD-02 + Pembrolizumab)

Toxicity	Attributed to Pembrolizumab	Attributed to GR-MD-02	Grade			
			1	**2**	**3**	**4**
Flu Symptoms	X		4			
Pruritis	X		3	1		
Rash	X		3			
Fatigue	X		2			
Lymphopenia	X		2			
Diarrhea	X		2			
Decreased WBC	X		1			
Decreased appetite	X		1			
Dysgeusia	X		1	1		
Vitiligo	X		1			
Infusion Reaction	X			1		
Anemia	X		1			
Nasal Congestion	X		1			
Tumor pain	X				1	
Watering eyes	X		1			
Dry eyes	X		1			
Dry Mouth	X		1			

Table summarizes maximum toxicity grade per patient attributed to study agent. Multiple instances of the same toxicity in an individual were counted only once

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Adverse events

(GR-MD-02 + Ipilimumab)

Toxicity	Attributed to Ipilimumab	Attributed to GR-MD-02	Grade			
			1	**2**	**3**	**4**
Diarrhea	X		3			
Pruritis	X		3			
Rash	X		2			
Fatigue	X		2			
Fever	X		1			
Infusion Reaction	X		1			
Decreased PMNs	X		1			
Decreased appetite	X		1			

Table summarizes maximum toxicity grade per patient attributed to study agent. Multiple instances of the same toxicity in an individual were counted only once

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Immune monitoring

1. Peripheral blood
   a. CD4, CD8, Treg, Th1/Th2/Th17, Tcm/Tem
   b. Ki-67, CD38/HLA-DR, perforin, granzyme
   c. Monocyte/DC panels (M1/M2 polarization)
   d. MDSC
2. Multispectral imaging (IHC)
3. Serum cytokine/chemokines (multiplex ELISA)

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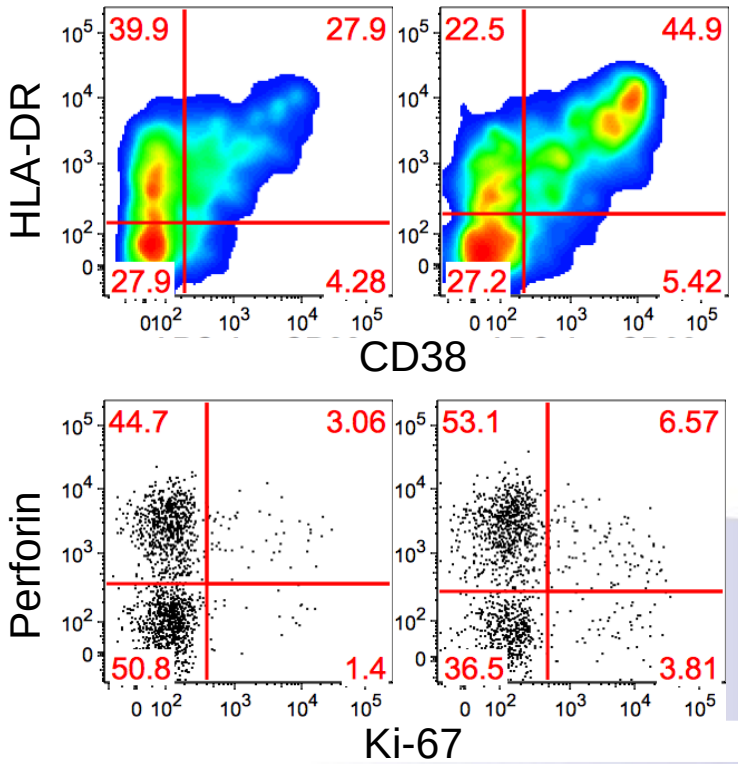
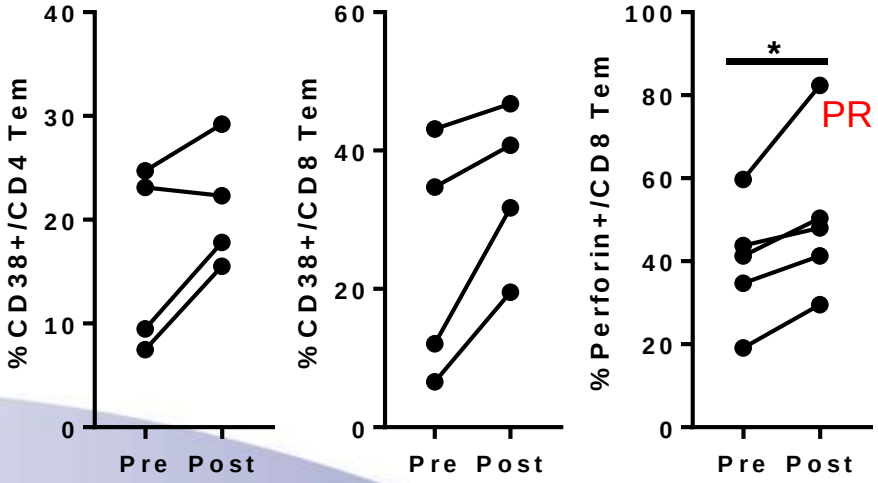
Immune monitoring

(PBL)





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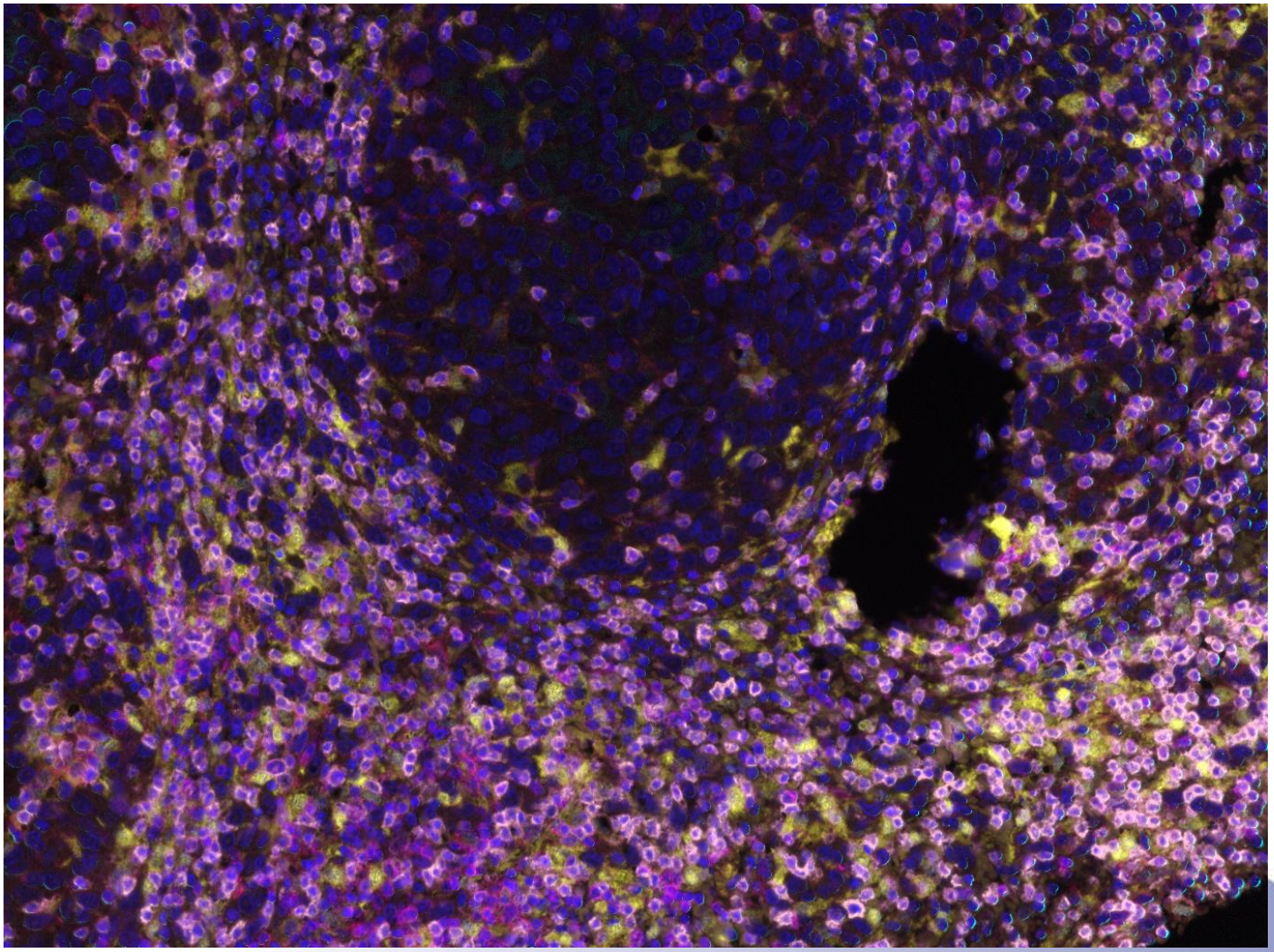
Multispectral imaging



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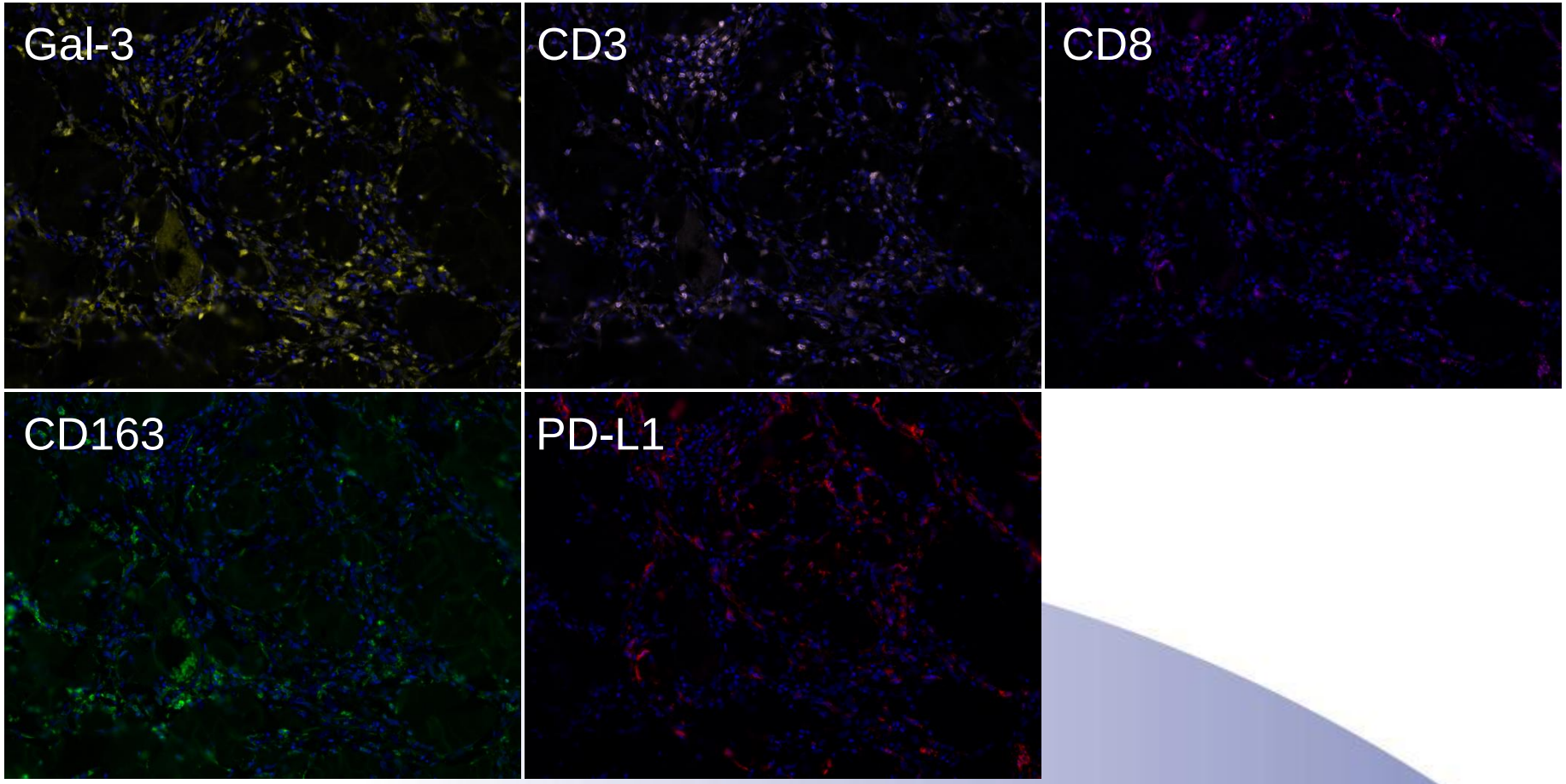
Multispectral imaging

(pre-treatment biopsy)



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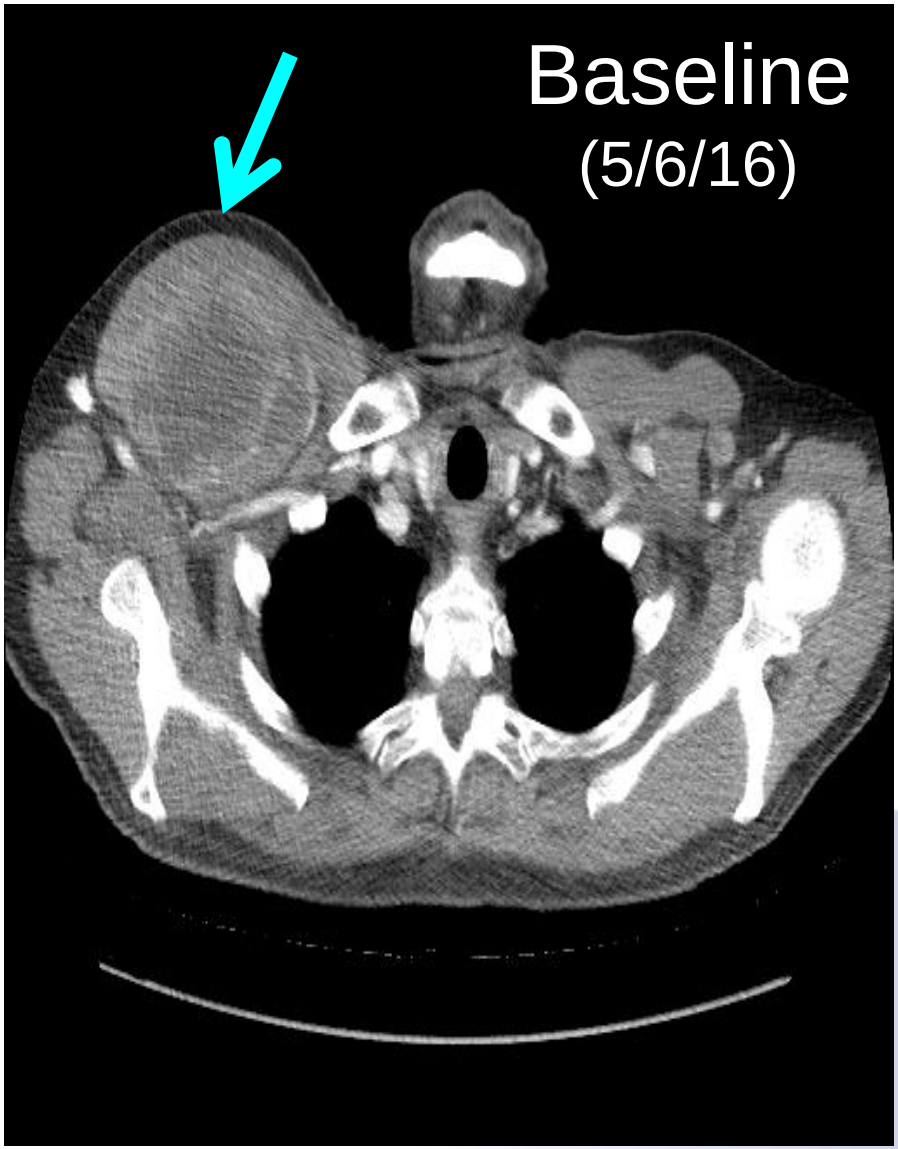
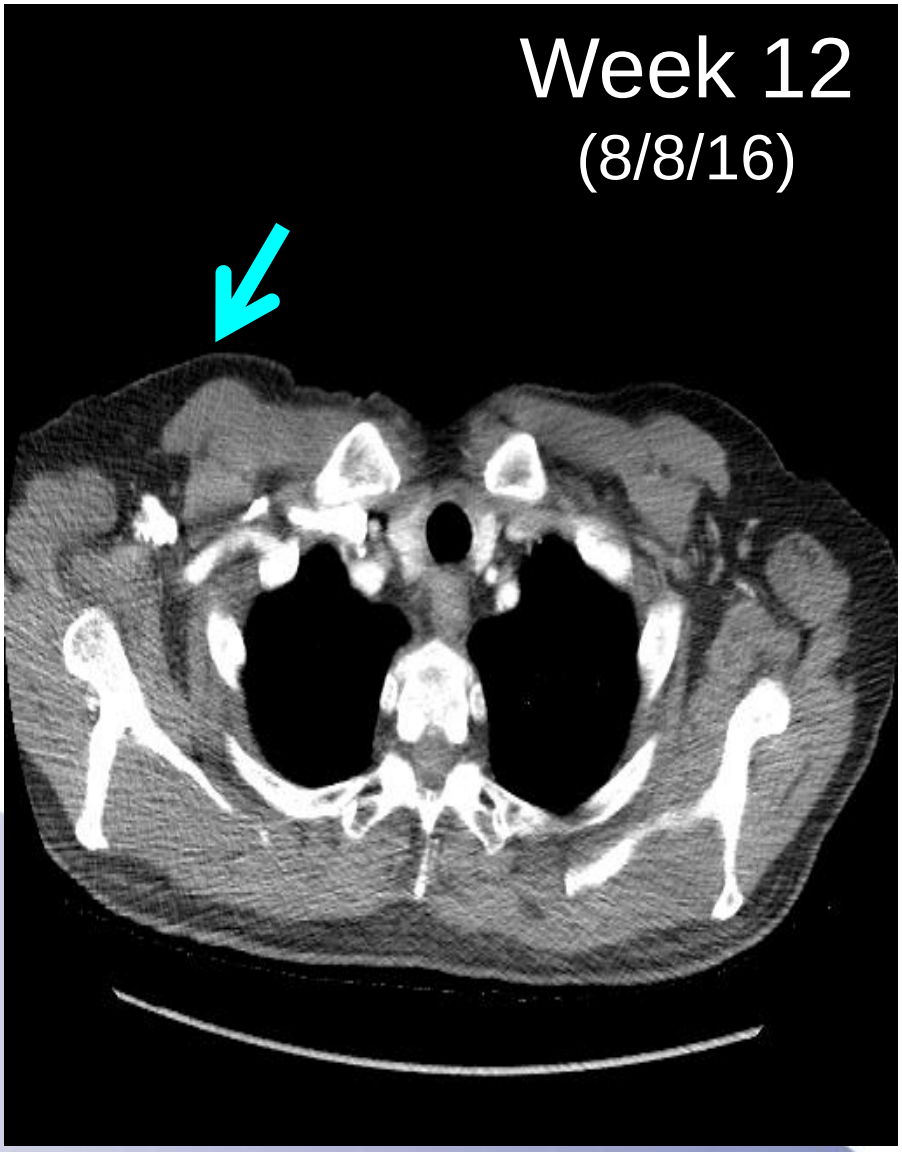
PR (on-going response)





PR (on-going response)

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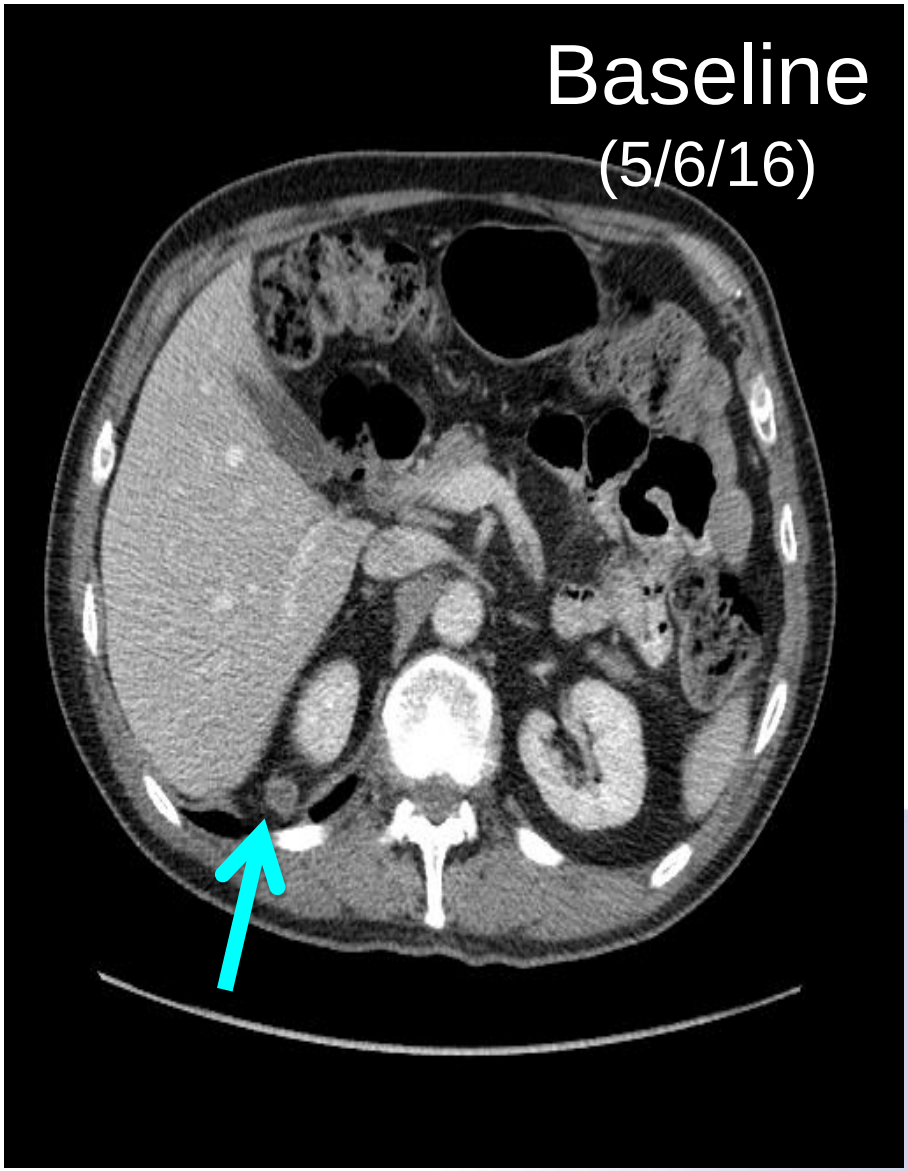

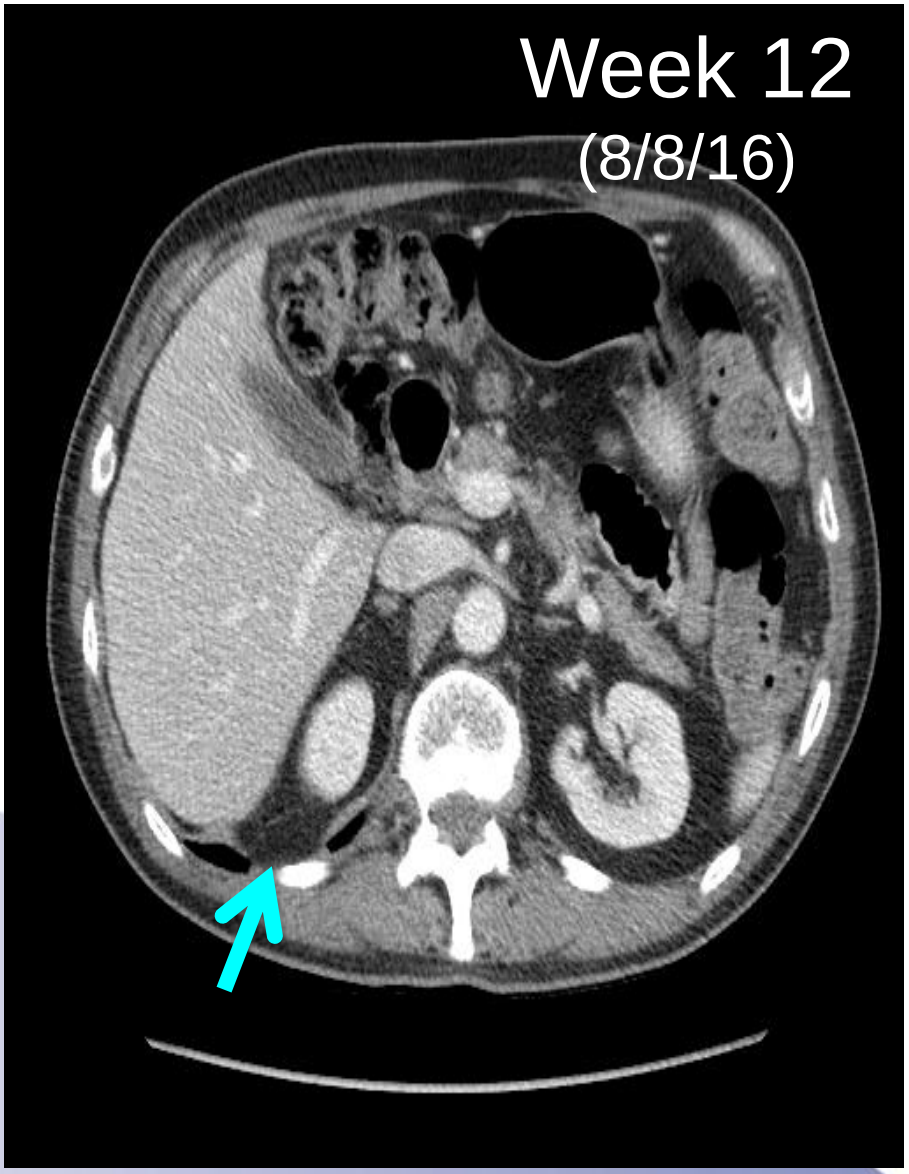

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Summary / future directions

1. GR-MD-02 plus immunotherapy augments anti-tumor immunity
   a. Reduced metastases, increased tumor regression, improved survival
   b. MOA?
      i. Cytokine/chemokine production
      ii. T cell function, M1/M2 polarization
      iii. Gene expression
2. First-in-human phase I clinical trials underway to test safety/efficacy of GR-MD-02 plus checkpoint blockade (melanoma, OHN, NSCLC)
   a. Immune monitoring and IHC analysis
   b. Progression to further development will be based on response rate as compared to historical response rates to pembrolizumab alone

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Program Timelines

Phase 1: Pembrolizumab + GR-MD-02

- Cohort 1 complete (2017; Q1)
- Cohorts 2-3 (2018; Q2)

Controlled Phase 2

- Ph2: GR-MD-02 + aPD-1 (start 2019; Q1)

Phase 1 with T cell agonist

- Ph1: GR-MD-02 + aOX40 (2018; Q4)

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Patients and their families!!!

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