

# OncoResponse

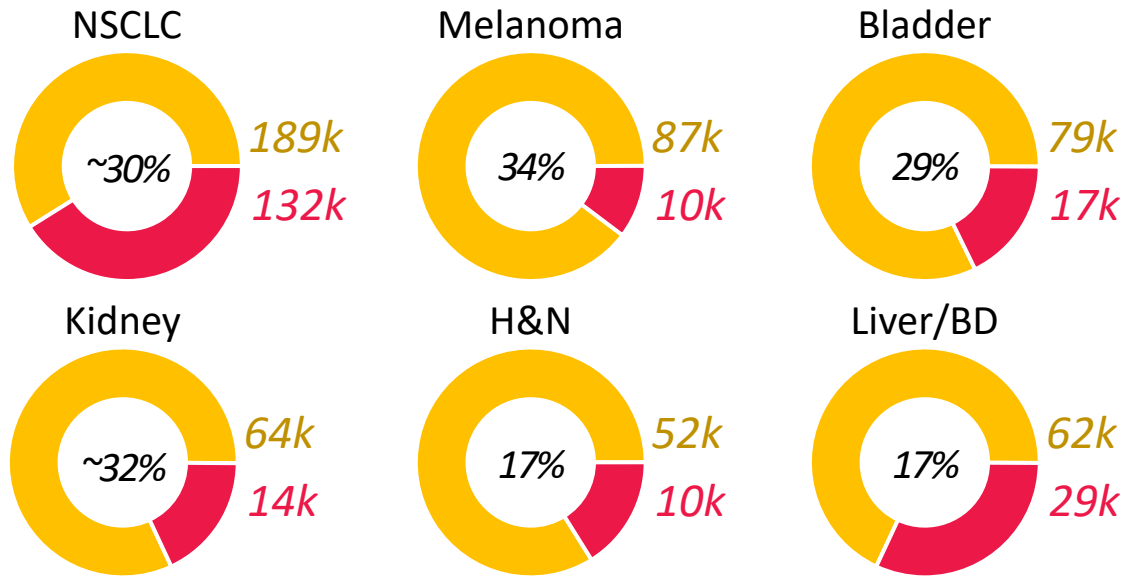
Interrogating for Cures™

**Reprogramming human macrophages to relieve  
immunosuppression in the tumor microenvironment**

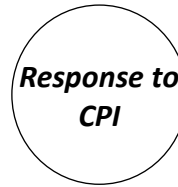
**Kamal D. Puri**  
**Festival of Biologics**  
**March 20-22, 2023**

# The Immuno-Oncology opportunity

## CPI-Responsive Cancer Types

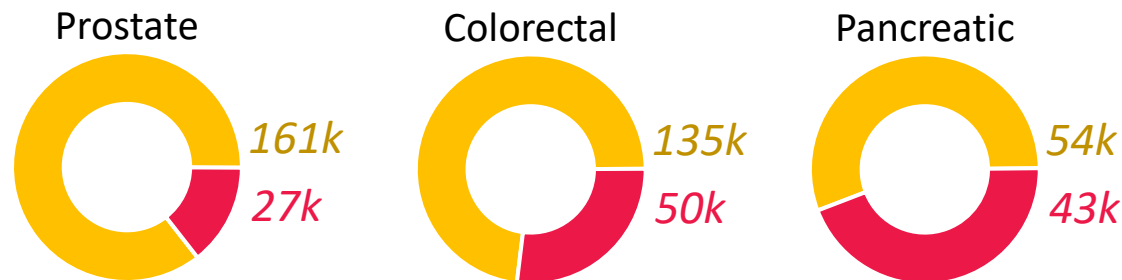


■ Annual New US Cases  
■ Annual US Deaths



- Response to checkpoint inhibitors (CPI) continue to be low in part due to the suppressive Tumor Microenvironment (TME)
- Large unmet need to overcome immune suppression in the TME to increase response and survival
- B cell enrichment in the tumors correlates with response to CPI in melanoma, sarcoma, lung, head and neck, and kidney cancer<sup>1-6</sup>
- CPI can directly modulate B cell responses and induce antibodies, including to clinically relevant immunomodulatory targets<sup>7-10</sup>

## CPI-Non-Responsive Cancer Types

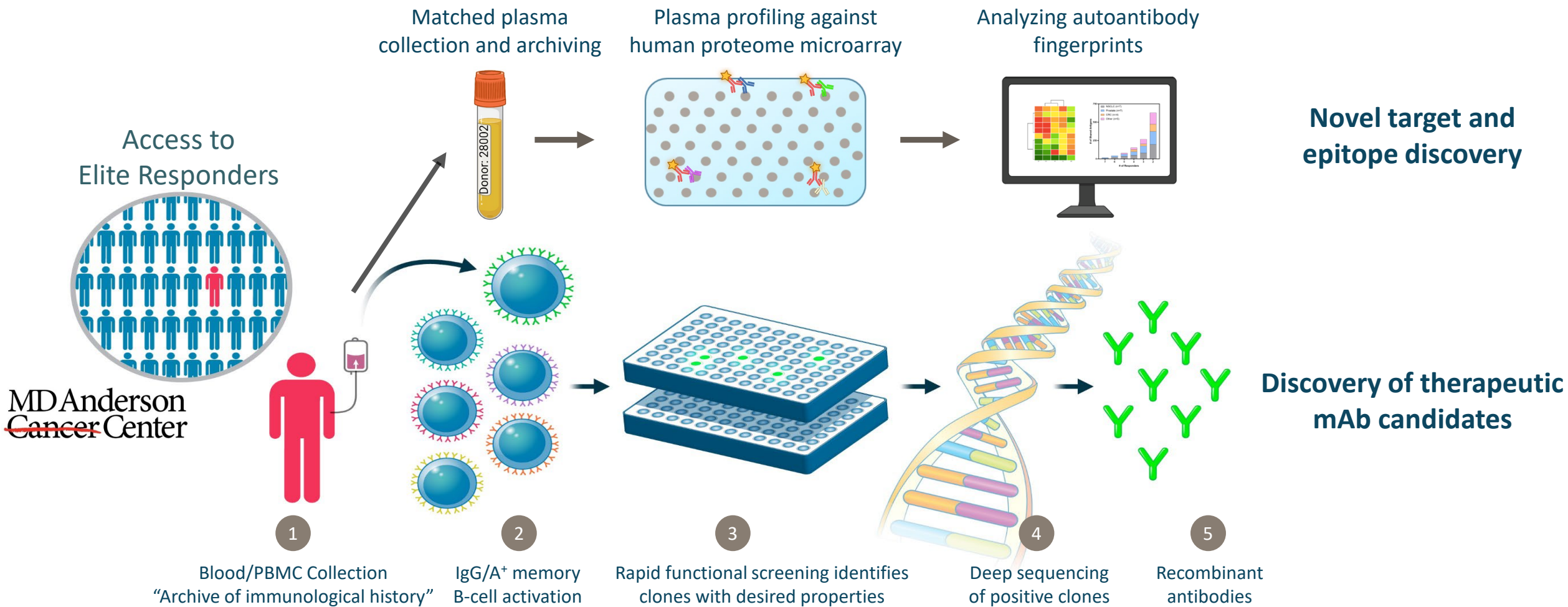


Cancer patients who have successfully responded to CPI, Elite Responders, may harbor antibodies that contribute to the clinical response

<sup>1</sup>Helmink, et al. Nature. 2020, <sup>2</sup>Petitprez, et al. Nature. 2020, <sup>3</sup>Cabrita, et al. Nature. 2020, <sup>4</sup>Kim, et al. Clin. Cancer Res. 2020, <sup>5</sup>Ruffin, et al. Nat Commun. 2021, <sup>6</sup>Patil, et al. Cancer Cell. 2022, <sup>7</sup>Jinushi, et al. PNAS. 2006, <sup>8</sup>Schoenfeld, et al. Cancer Res. 2010, <sup>9</sup>Kwek, et al. J Immunol. 2012, <sup>10</sup>Kouo, et al. Cancer Immunol Res. 2015



# The OncoResponse platform interrogates the antibody and B-cell repertoire of Elite Responders for clues to attack cancer



# OncoResponse pipeline summary

ANTIBODY	Mechanism	Discovery	IND-Enabling	Phase 1	Phase 2
OR2805 (anti-CD163)	Reprograms TAMs/MDSCs	▶			
OR502 (anti-LILRB2)	Reverses immunosuppression & reprograms TAMs	▶			
TME 2.0	Interrogate B-cell repertoire for mAb candidates	▶			

- Lead drug OR2805 advancing through clinical studies across multiple tumor types
- Several antibodies in development that modulate immune cell activity
- Platform for ongoing discovery of rare human antibodies from Elite Responders

Abbreviations: TAM, tumor-associated macrophage; MDSC, myeloid-derived suppressor cell; mAb, monoclonal antibody

OncoResponse

**OR2805**

**Anti-CD163 human-derived mAb**

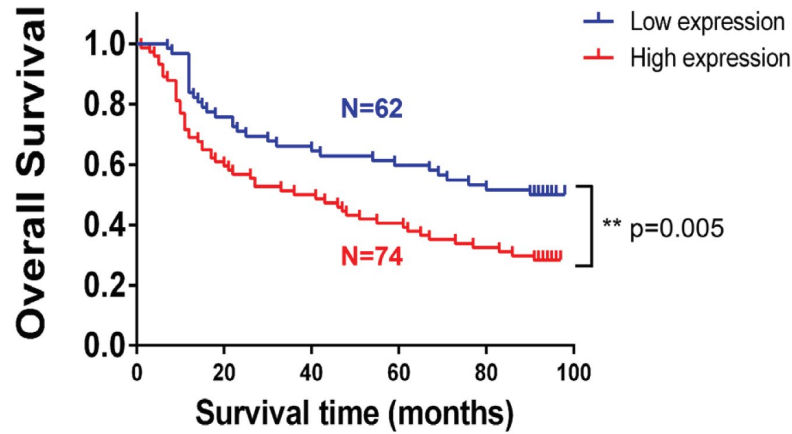
*Targeting M2 macrophages to reverse immunosuppression of the tumor microenvironment*



# CD163 is a negative prognostic marker in cancer

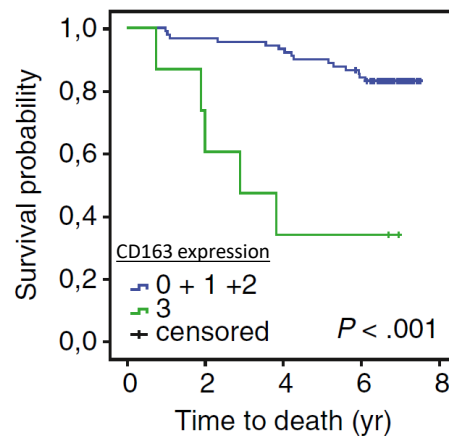
## Gastric Cancer<sup>12</sup>

Overall survival



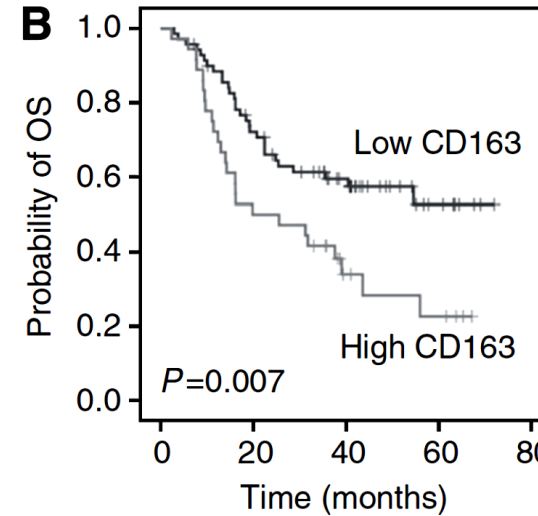
## Breast Cancer<sup>13</sup>

Survival probability

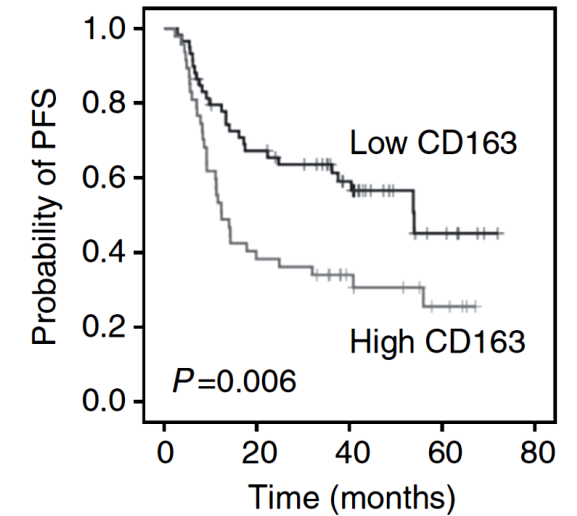


## Head and Neck Cancer<sup>14</sup>

Overall survival

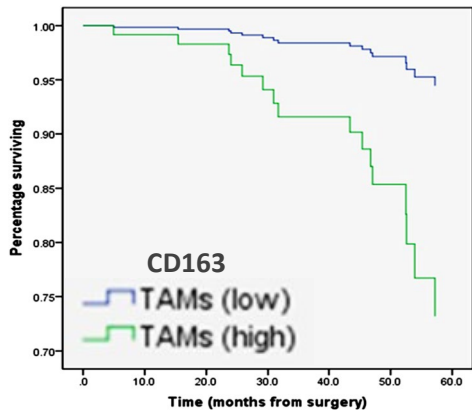


Progression-free survival

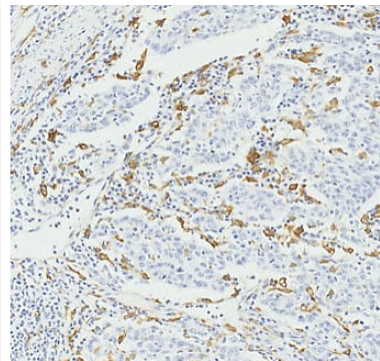


## Colorectal Cancer<sup>16</sup>

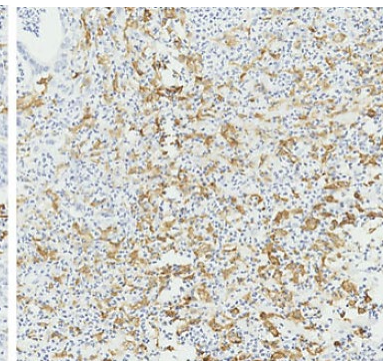
Overall Survival



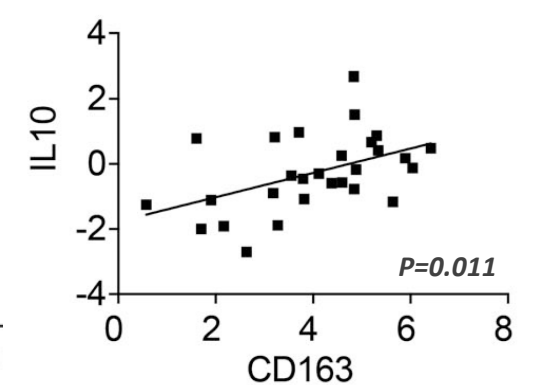
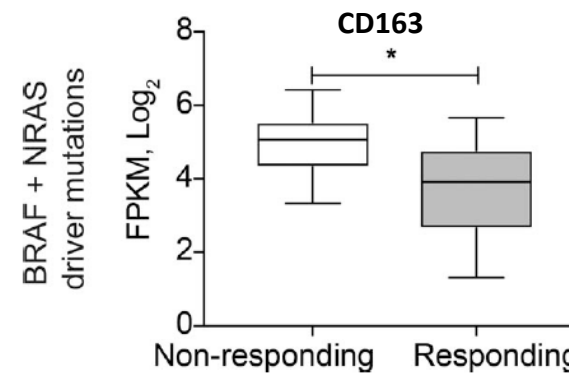
Low TAM Infiltration



High TAM Infiltration

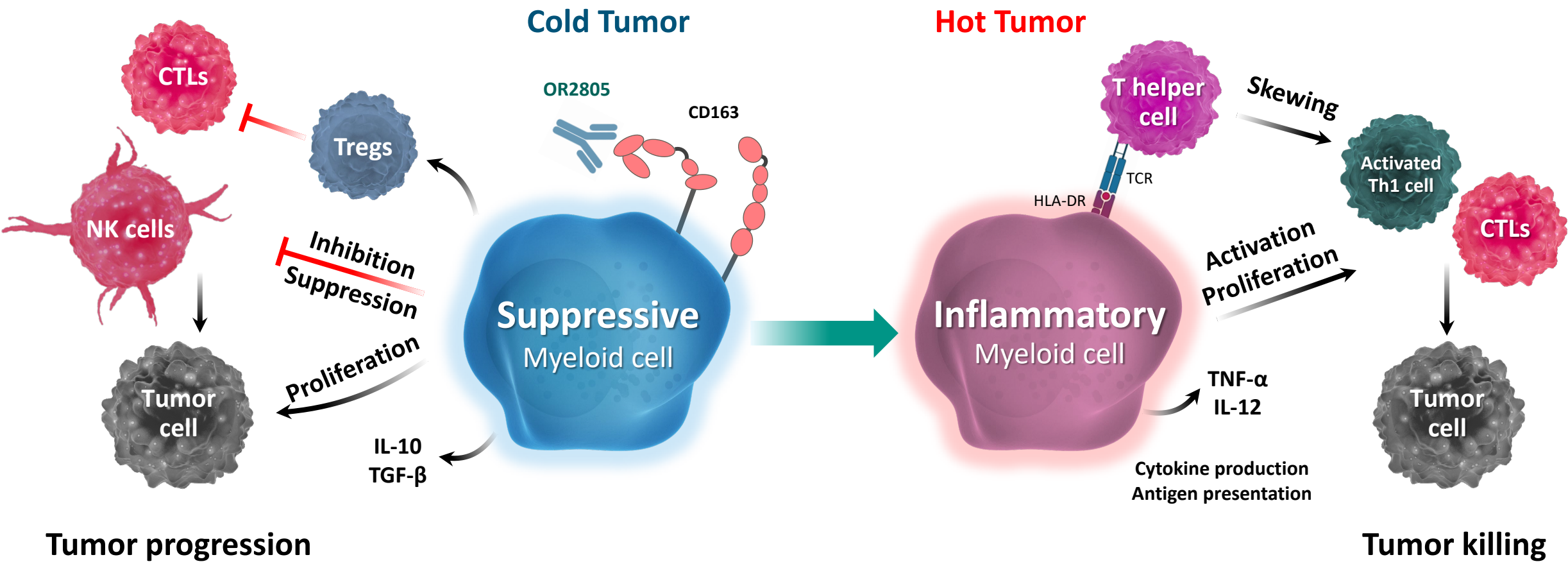


## Melanoma patients on anti-PD-1 therapy<sup>15,38</sup>



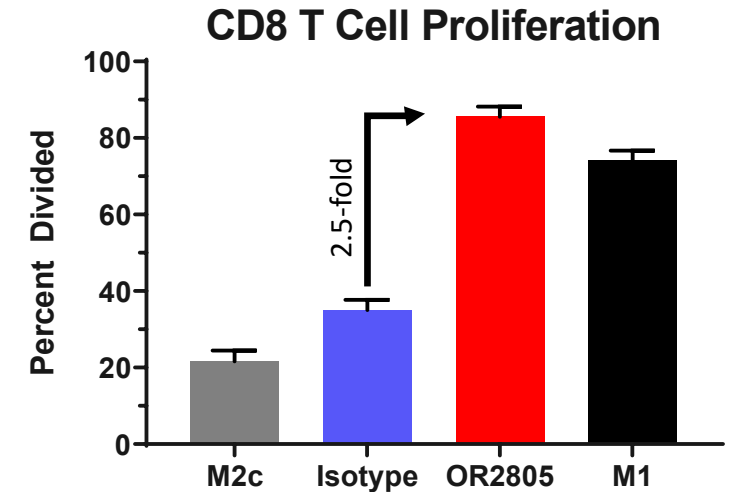
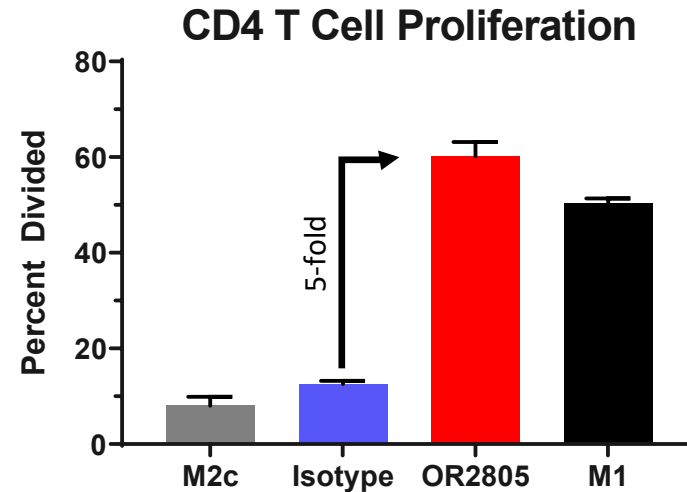
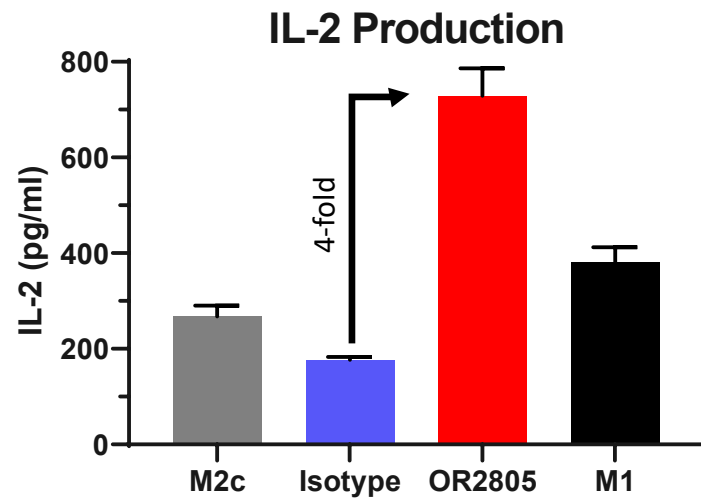
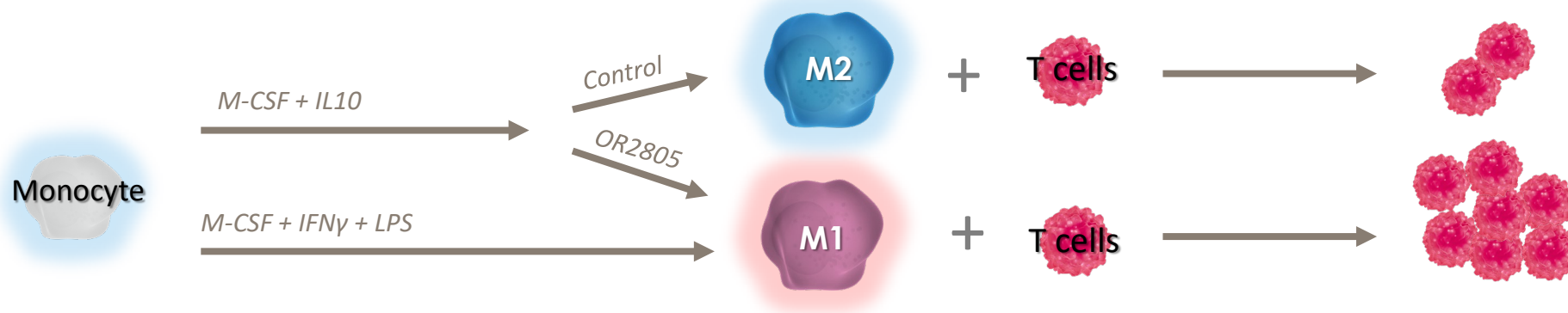
<sup>12</sup>Oncotarget 2017;8:87244, <sup>13</sup>BMC Cancer 2012;12:306, <sup>14</sup>Br J Cancer 2014;111:1509, <sup>15</sup>J Exp Med. 2019;216:2394, <sup>16</sup>World J Surg Oncol. 2021;19:186, <sup>38</sup>Cell 2016;165:35.

# OR2805 relieves myeloid cell mediated immune suppression in the TME



OR2805 targets CD163 and reprograms the immune suppressive functions of tumor-associated macrophages (TAMs)

# OR2805-treated M2c macrophages promote T-cell activation & proliferation



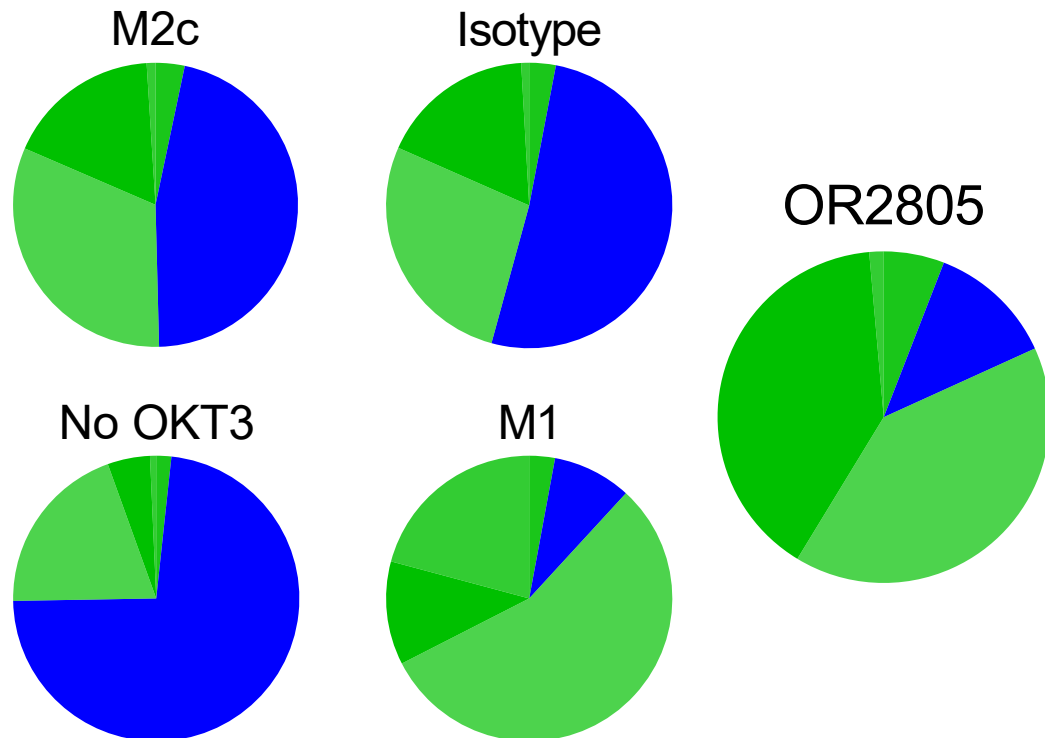
Representative data of 12+ donors

OR2805-treatment reduces the ability of M2c to suppress T-cell activation leading to greater T-cell stimulation (IL-2, IL-1 $\beta$ , IFN $\gamma$ , TNF $\alpha$ , CCL4 & perforin production) and both CD4<sup>+</sup> and CD8<sup>+</sup> T-cell proliferation




# OR2805-treated M2c macrophages skew T cells to activated Th1 phenotype

## Distribution of CD4<sup>+</sup> T cells phenotypes



- CXCR3 expression promotes CD8<sup>+</sup> infiltration
- IFN $\gamma$  enhances CXCR3-mediated T-cell recruitment
- CXCR3-expressing CD8<sup>+</sup> T cells show enhanced anti-tumor cytotoxicity


### Resting T cells


 CXCR3<sup>-</sup> CD69<sup>-</sup> CD25<sup>-</sup>


### Activated CXCR3<sup>-</sup> T cells


 CXCR3<sup>-</sup> CD69<sup>+</sup> CD25<sup>+</sup>

### Activated CXCR3<sup>+</sup> T cells

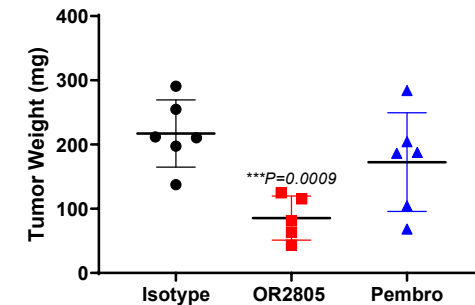
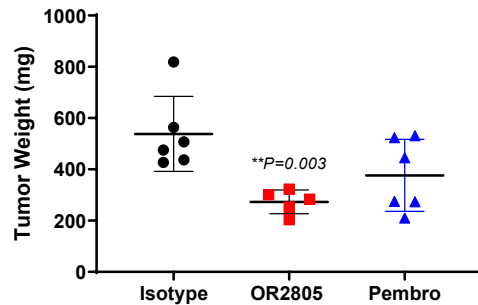
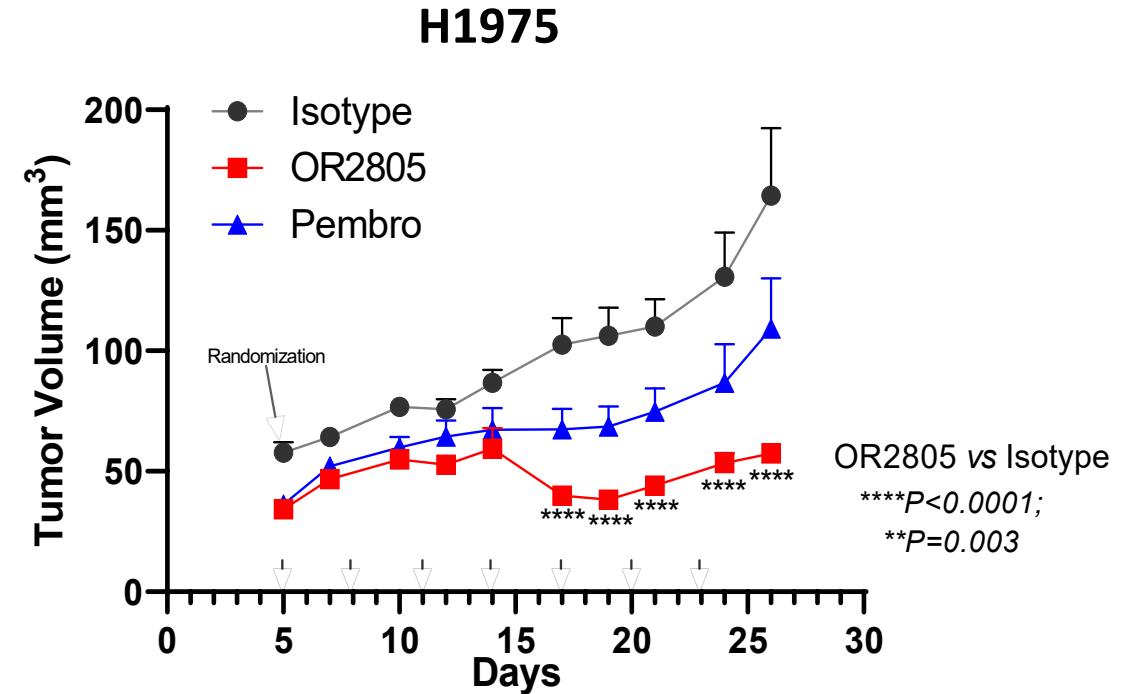
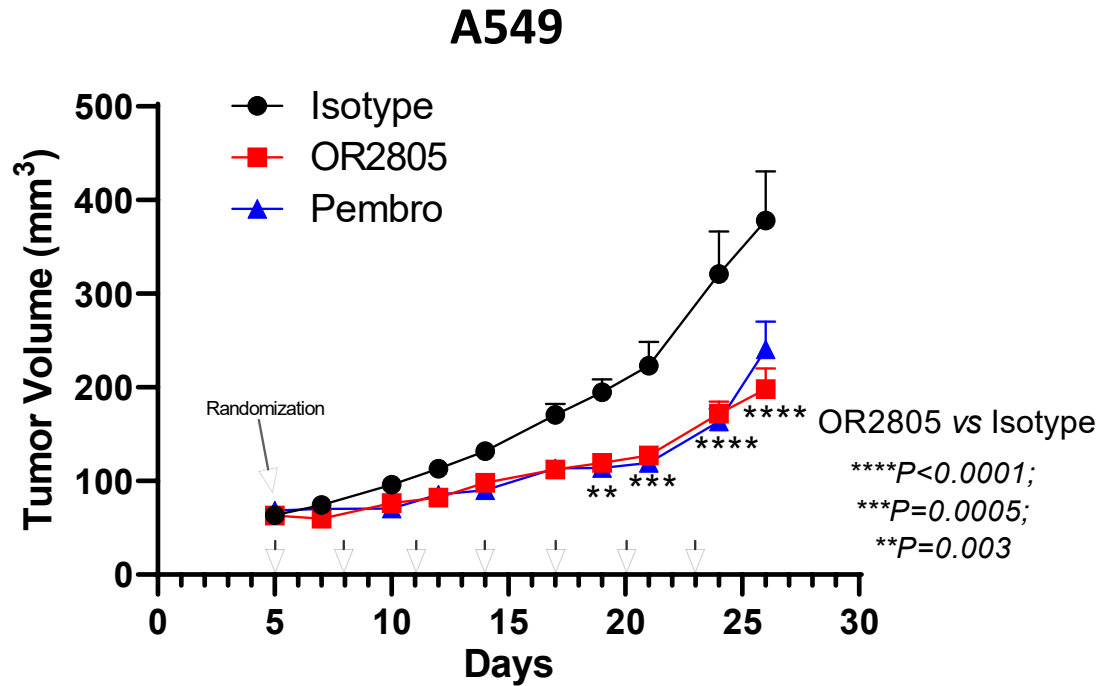
 CXCR3<sup>+</sup> CD69<sup>+</sup> CD25<sup>+</sup>

 CXCR3<sup>+</sup> CD69<sup>+</sup> CD25<sup>-</sup>

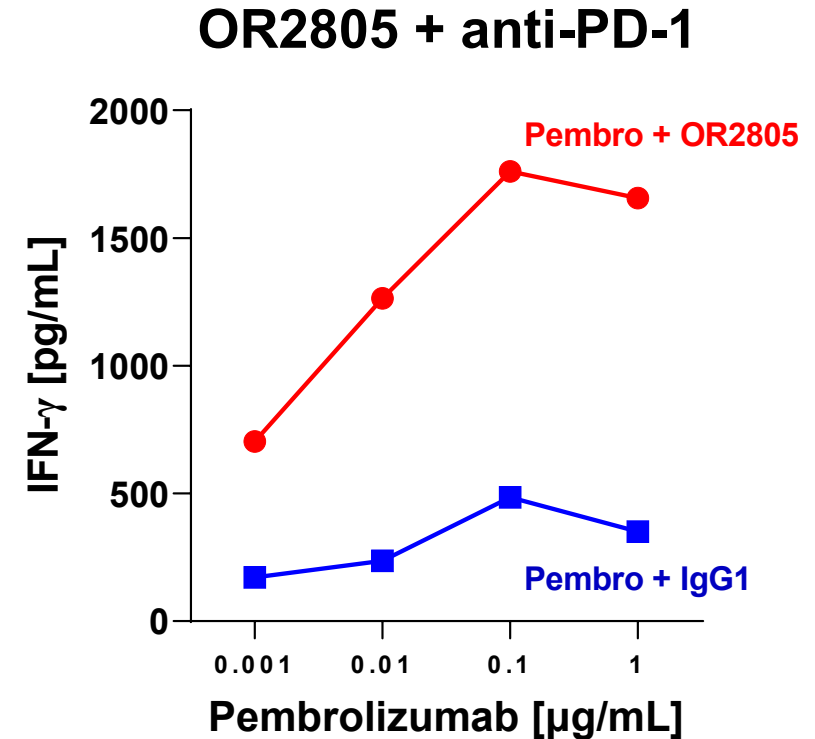
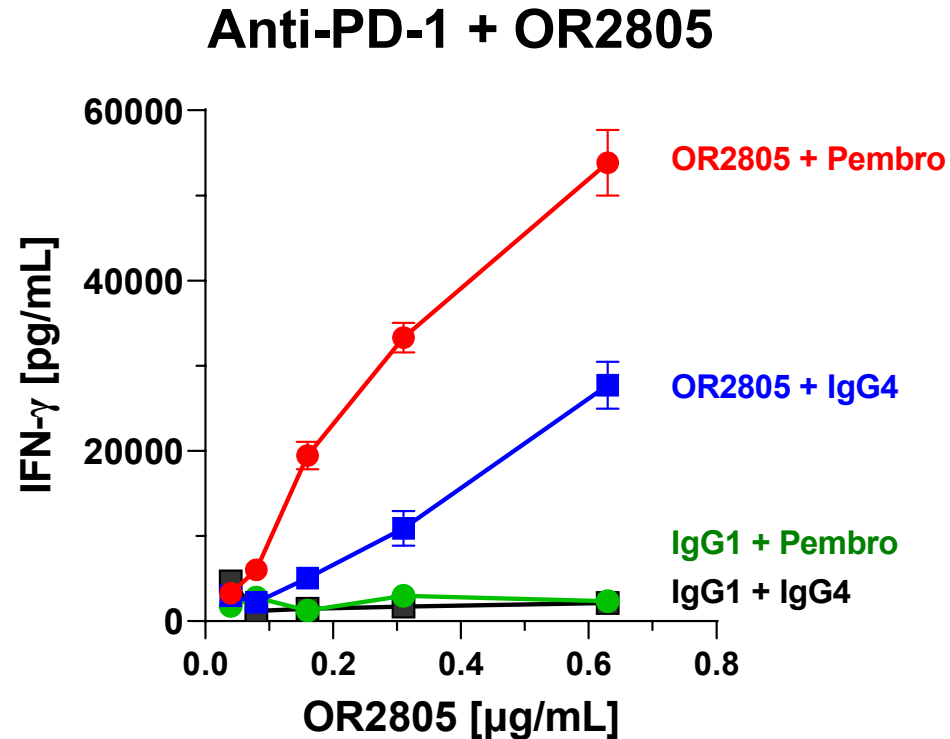
 CXCR3<sup>+</sup> CD69<sup>-</sup> CD25<sup>+</sup>

 OR2805-treated macrophages promote T-cell activation leading to greater expression of T-cell activation markers (CD69, ICOS, OX40)

# OR2805 induces anti-tumor activity in humanized NSG-SGM3 mice



# Combination with OR2805 enhances activity of anti-PD-1 in M2c/Exhausted T cell coculture assays



IFN-γ production is enhanced by combination of OR2805 with anti-PD-1 antibody in M2c/Exhausted T cell coculture assays



# Summary: OR2805 relieves immunosuppression caused by myeloid cells in the tumor microenvironment

- Binds with high specificity to M2 TAMs
- Minimizes M2 suppressive effect on T-cell activation and proliferation and skews T cells towards anti-tumor Th1 phenotype
- Shows enhanced expression of activation markers and cancer-killing ability in cocultured T cells
- Demonstrates robust anti-tumor activity in lung cancer xenograft models
- Combination with OR2805 amplifies anti-PD-1 activity in coculture assays
- A phase 1-2 study of OR2805 alone or in combination in subjects with advanced solid tumors is ongoing (NCT05094804)



**OR2805 has therapeutic potential as a single agent or in combination with checkpoint inhibitors**

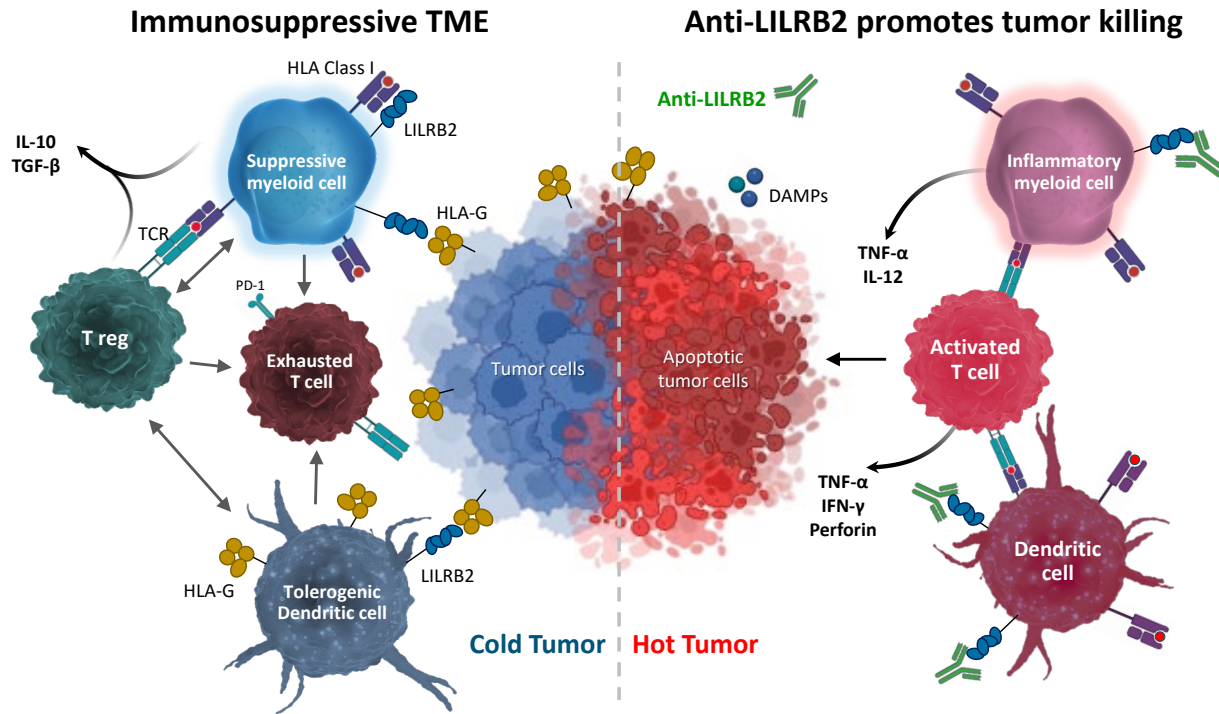
OncoResponse

**OR502**

**Anti-Leukocyte Immunoglobulin Like Receptor B2 (LILRB2)**

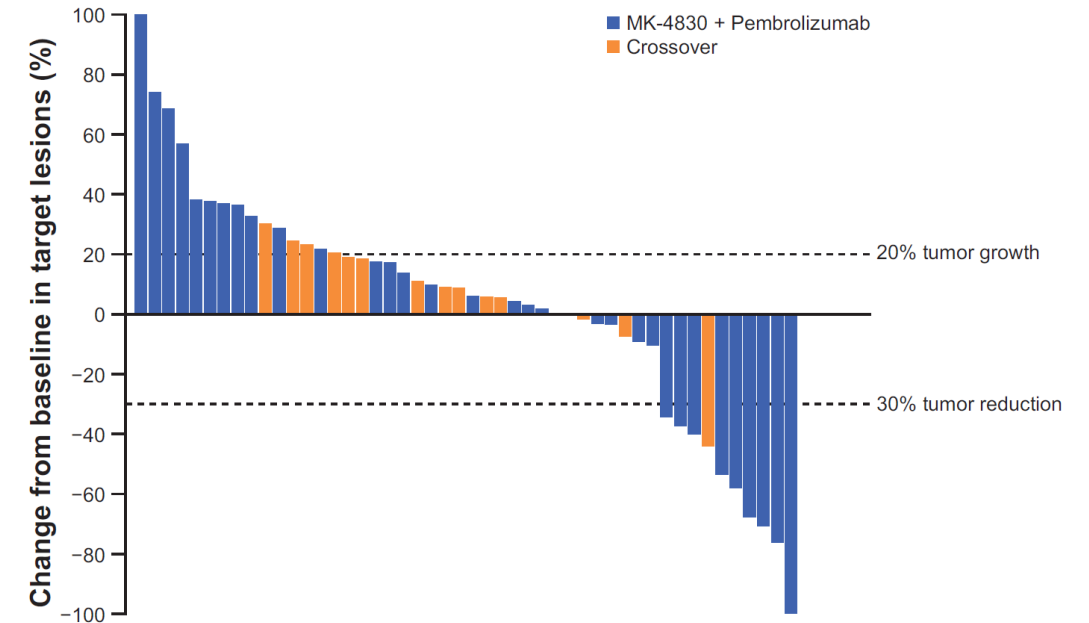
*Targeting LILRB2–HLA-G binding to reverse immunosuppression in cancer*

# LILRB2 promotes immunosuppression and blockade drives clinical anti-tumor activity



- Inhibitory receptor on myeloid cells that contributes to CPI resistance
- Blockade reverses anti-PD-(L)1 resistance
- Expression correlates with poor survival in multiple cancers
- LILRB2 has multiple immune inhibitory activities

## MK-4830 Phase 1 Data



- MK-4830 is a clinically validated anti-LILRB2 antibody
- Monotherapy demonstrated one PR in ovarian cancer
- Combination with pembrolizumab demonstrated a 24% ORR
- 5 of 11 subjects with prior anti-PD-1 treatment responded to the combination

J Clin Invest. 2018;128:5647, Biochim Biophys Acta. 2018;1869:278, Clin. Cancer Res. 2021;28:57-70, J Immunol. 1998;160:3096-3100, Eur. J. Immunol. 1998;28:3423-34., Nat Immunol., 2002;3:237-43, PNAS 2003;100:8856-61



# OncoResponse OR502: Superior characteristics versus MK-4830

Criteria	OR502	MK-4830
Binding $K_D$ to LILRB2	1.2 nM	3.5 nM
Blocks LILRB2 binding to HLA-G	Yes	Yes
Blocks LILRB2 binding to angiopoietin-like protein ligands 2 & 5	Yes	Yes
LILRB2 binding epitope	Distinct from other Abs	
Blocks LILRB2 binding to HLA Class I	<b>Yes</b>	No
Co-engagement of FcR	<b>Yes</b>	No
LPS-induced IFN $\gamma$ secretion by human PBMC	<b>Strong</b>	Modest
T cell activation and proliferation (M2/T cell coculture)	<b>Yes</b>	No
IFN $\gamma$ production (M2/Exhausted T cell coculture)	<b>Yes</b>	No
SK-MEL-5 xenograft in humanized NSG-SGM3 mice	<b>79% TGI 33% Regression</b>	26% TGI 11% Regression

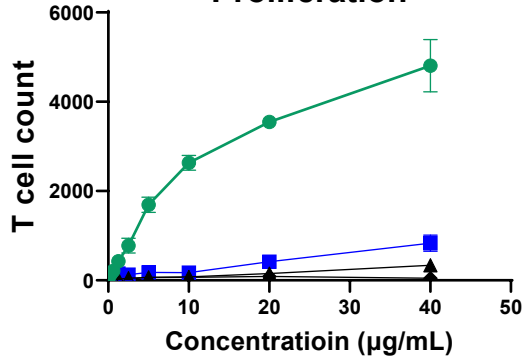
# OR502 is safe and restores anti-cancer T cell responses better than MK-4830

*Amplifies anti-PD-1 activity in M2/T cell coculture assays*

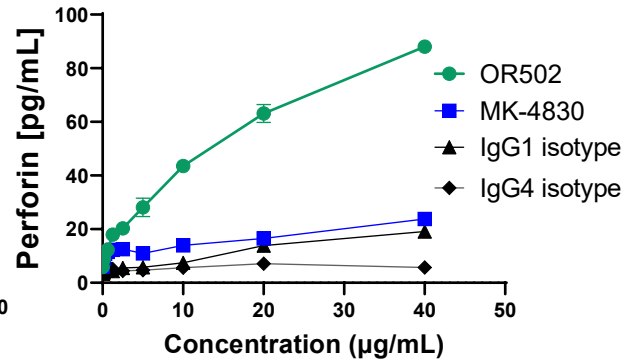
## M2c/T cell coculture

(Rescues T cell proliferation and activation)

### Proliferation

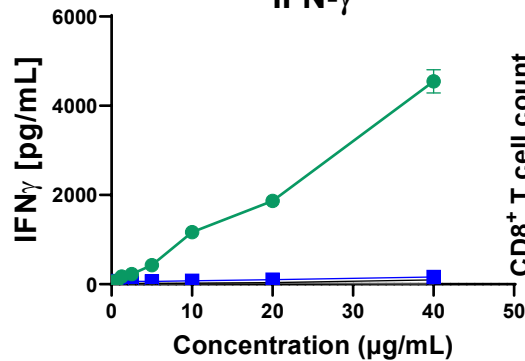


### Perforin

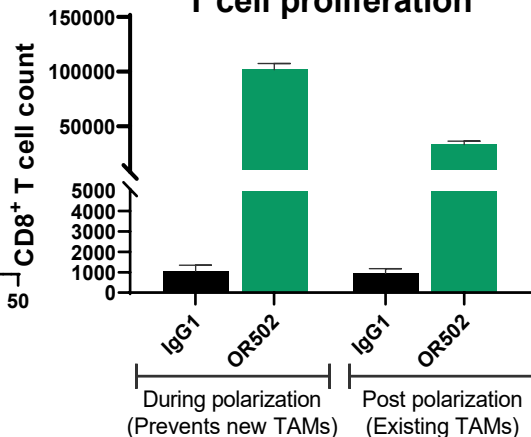


(Reduces and prevents immunosuppressive phenotype of existing and new TAMs)

### IFN-γ



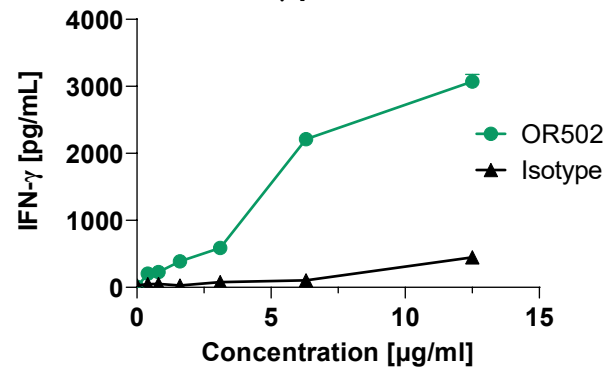
### T cell proliferation



## M2c/Exhausted T cell coculture

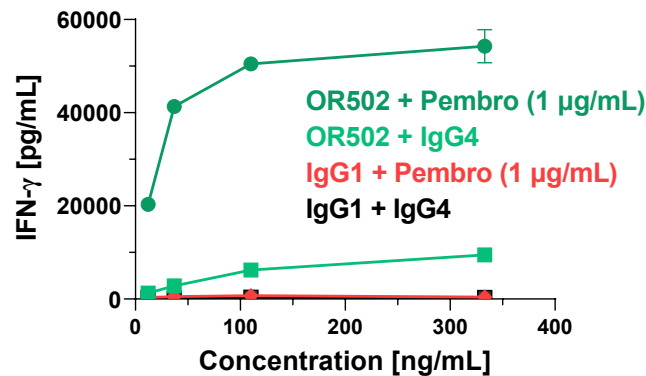
(Rescues IFN-γ production)

### IFN-γ production



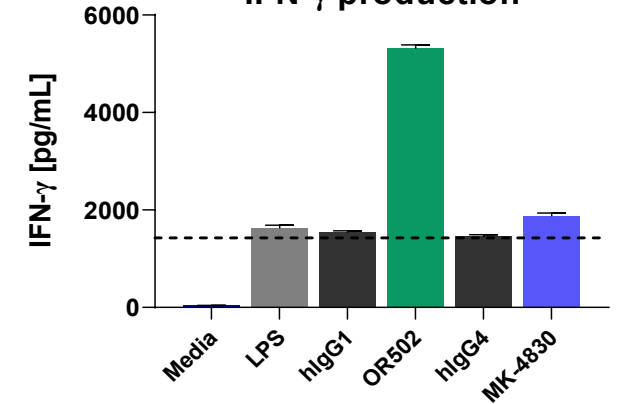
(Amplifies anti-PD-1 activity)

### IFN-γ production



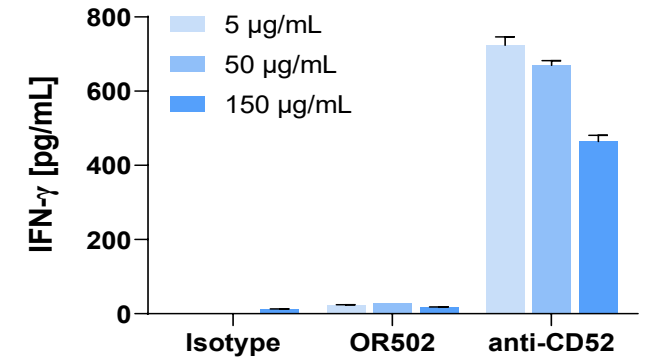
## Boosts LPS-induced IFN-γ secretion

### IFN-γ production

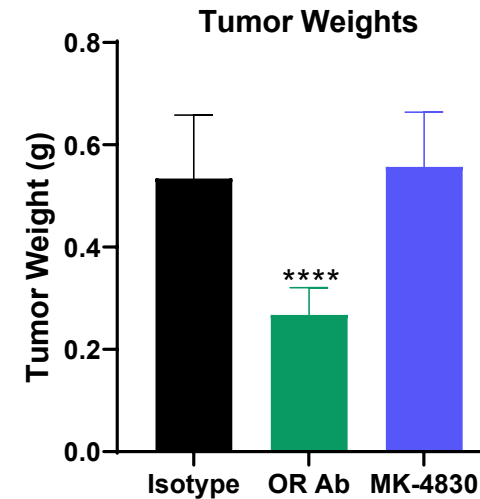
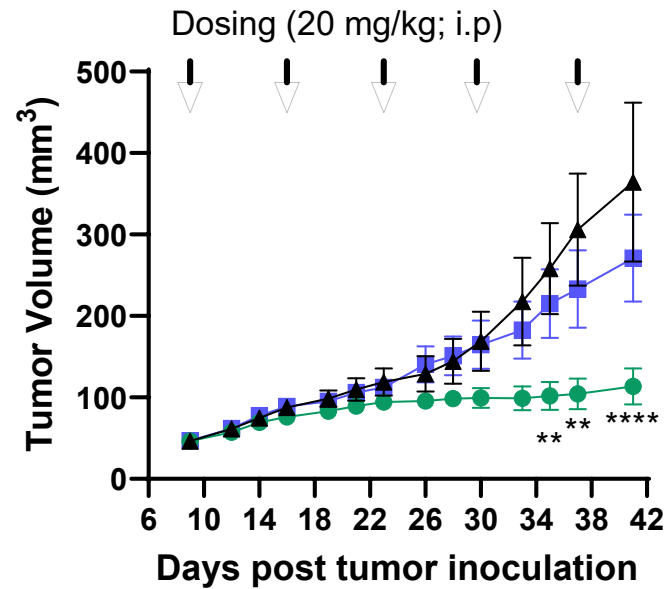


## Whole blood cytokine release

(Minimal or no risk of cytokine release syndrome)



# OncoResponse anti-LILRB2 antibody significantly inhibits growth of SK-MEL-5 melanoma in NSG-SGM3 mice



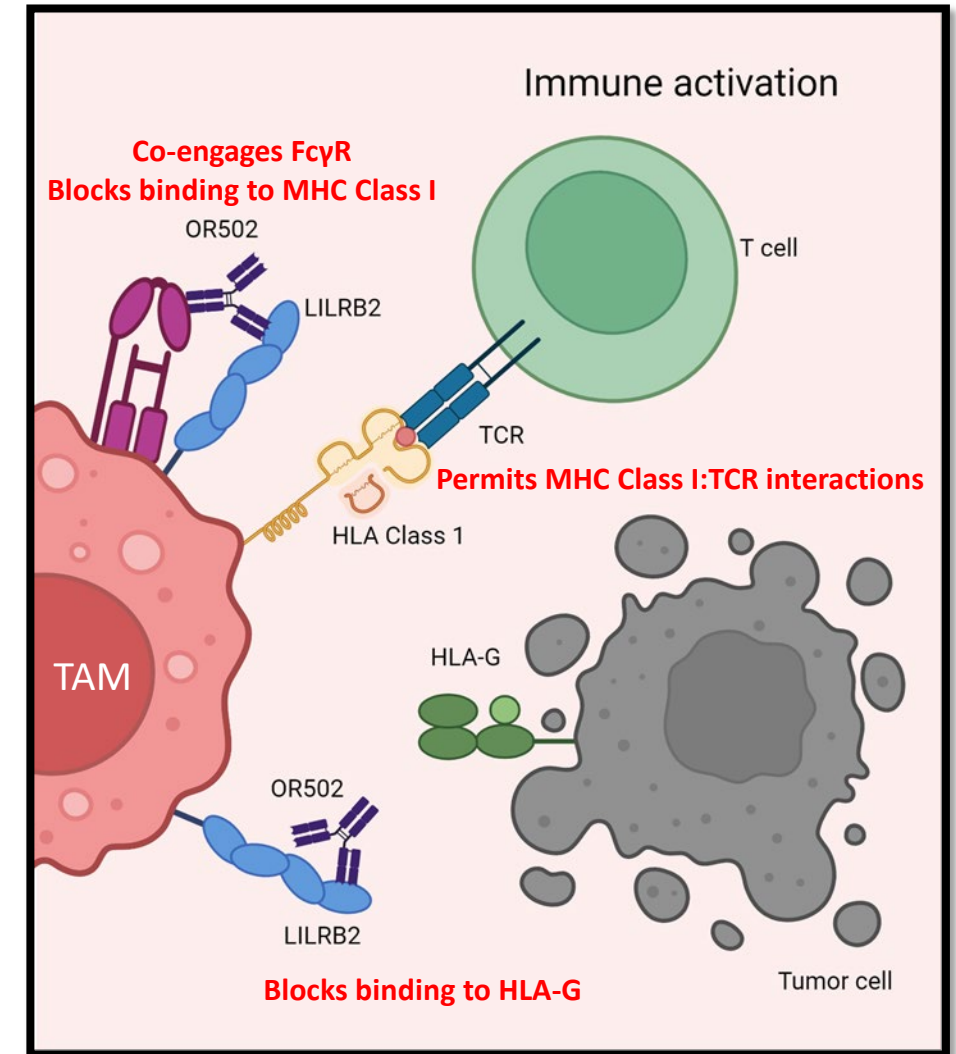
- Dosing: 20 mg/kg i.p.
  - Dosing Days: 9, 16, 23, 30, 37
- All groups N=9

Group	Tumor Growth Inhibition (%)						Regression (%)
	d28	d30	d33	d35	d37	d41	d41
Anti-LILRB2 (OncoResponse)	47	57	69	74	78	79	33
MK-4830 (Merck)	-5	3	16	17	24	26	11



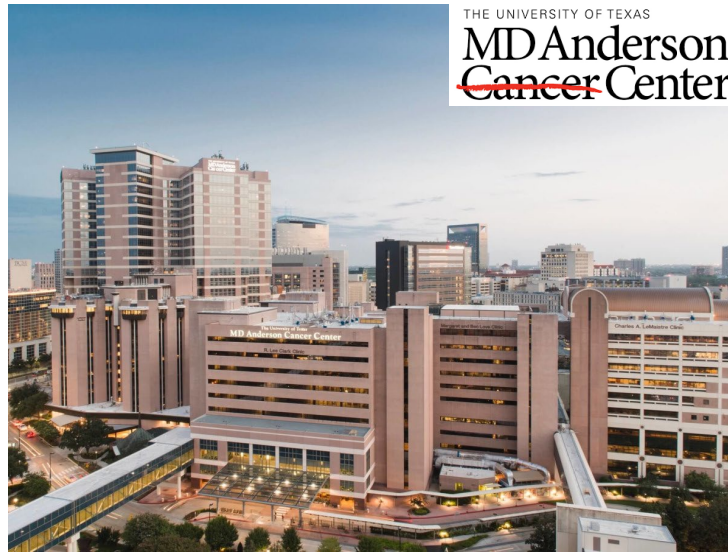
# OR502 is a superior anti-LILRB2 antibody that reverses immunosuppression caused by myeloid cells in the TME

- Superior preclinical characteristics versus MK-4830
- Reverses and prevents immunosuppressive phenotype of existing and new TAMs
- Amplifies anti-PD-1 activity in M2/T cell coculture assays
- Superior anti-tumor activity (TGI 79%) in SK-MEL-5 tumor model compared to MK-4830 (TGI 26%)
- Specific for LILRB2 and binds to a distinct epitope
- Blocks HLA-G, MHC Class 1 and angiopoietin-like protein ligands binding of LILRB2
- Co-engagement of FcγR provides an additional signal for myeloid reprogramming
- No safety liabilities are identified



# Acknowledgements

OncoResponse



THE UNIVERSITY OF TEXAS  
MD Anderson  
Cancer Center

## Scientific Advisors

Anil Singhal

David G. DeNardo

David Hong

James Welsh

Michael Curran

Mike Gallatin

Miriam Merad

Bob Lechleider

Kate Harrop

Ramya Chandrasekaran

Clifford Stocks

Kevin Green

Ray Fox

Darbie Whitman

Lauren Loh

Stephen Willingham

Doug Spicer

Meghan Zuck

Tatyana Pisarenko

Francisco Zapata

Meilyn Sylvestre

Tiffany Feist

Gajendra Naika

Myriam Bouchlaka

Tom Graddis

Huyen Dinh

Peter Probst

Xin Wu

Jacob Heit

Phil Hammond

Patients who provided precious tissue  
samples for this study

OncoResponse





**CLIMB**  
TO FIGHT CANCER®  
2023

Climb a...  
Save a...

GOODWIN affinity

elevatebio

Agilent Technologies  
Axiom Healthcare Str  
Canaan • Chapl  
Ge Li & Ning Ze  
Latham & Watkins L  
Timmerm



# OncoResponse

Interrogating for Cures™

## Thank You.

For more information, please visit  
[www.OncoResponse.com](http://www.OncoResponse.com)