OncoResponse

Interrogating for Cures™

Taking Clues from Patients to Target Tumor-Associated Macrophages

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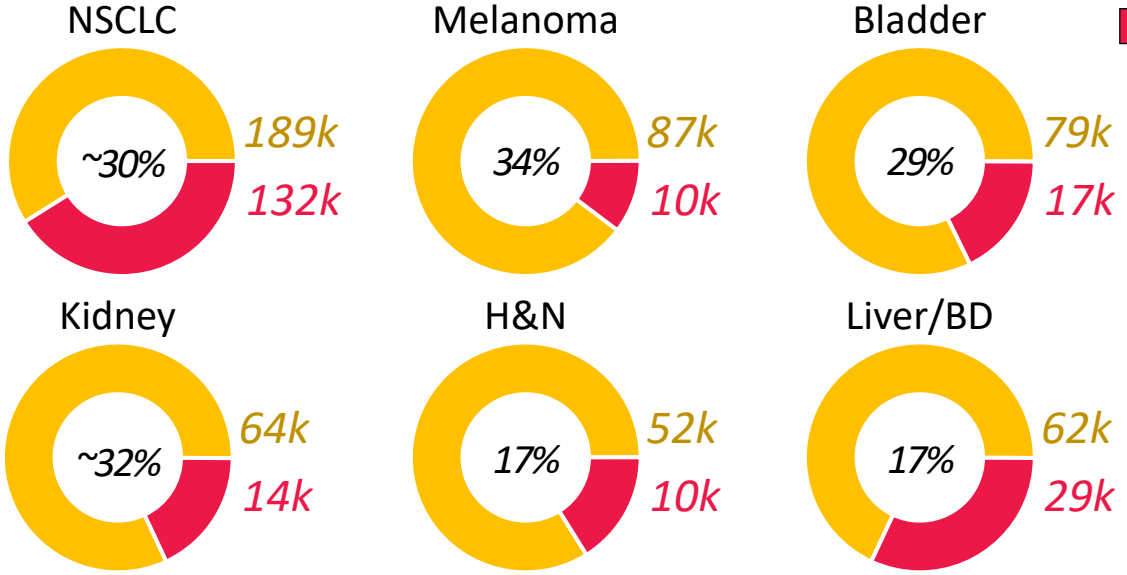
Emerging Technologies for IO Targeting and Discovery

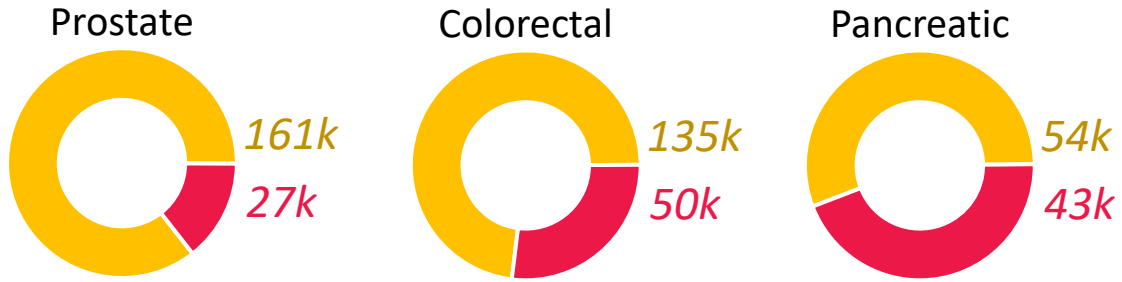
August 7-9, 2023

The Immuno-Oncology opportunity

CPI-Responsive Cancer Types



CPI-Non-Responsive Cancer Types

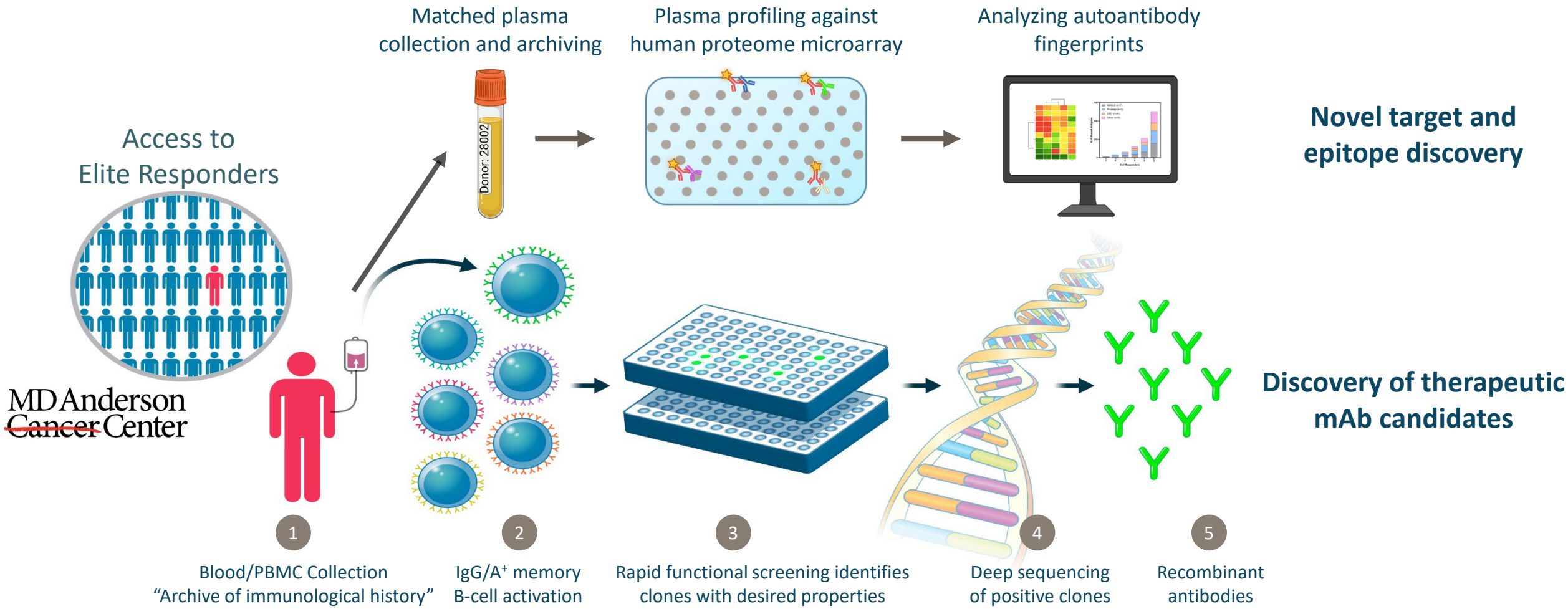


- Response to checkpoint inhibitors (CPI) continue to be low in part due to the suppressive Tumor Microenvironment (TME)
- Large unmet need to overcome immune suppression in the TME to increase response and survival
- B cell enrichment in the tumors correlates with response to CPI in melanoma, sarcoma,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

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

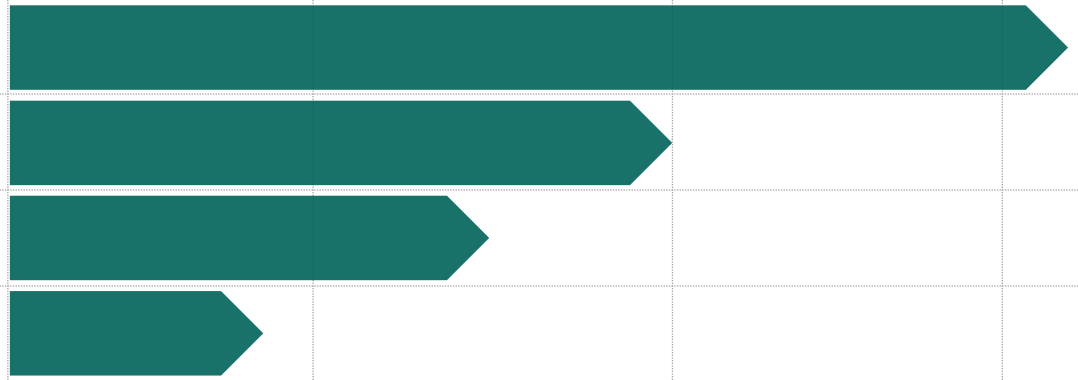
[1]Helmink, et al. Nature. 2020, [2]Petitprez, et al. Nature. 2020, [3]Cabrita, et al. Nature. 2020, [4]Kim, et al. Clin. Cancer Res. 2020, [5]Ruffin, et al. Nat Commun. 2021, [6]Patil, et al. Cancer Cell. 2022, [7]Jinushi, et al. PNAS. 2006, [8]Schoenfeld, et al. Cancer Res. 2010, [9]Kwek, et al. J Immunol. 2012, [10]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	Targets CD163 and reprograms TAMs/MDSCs				
OR502	Targets LILRB2 (ILT4) relieves immunosuppression				
OR641	Targets LILRB2/1 (ILT4/ILT2)				
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; LILRB, leukocyte immunoglobulin like receptor B

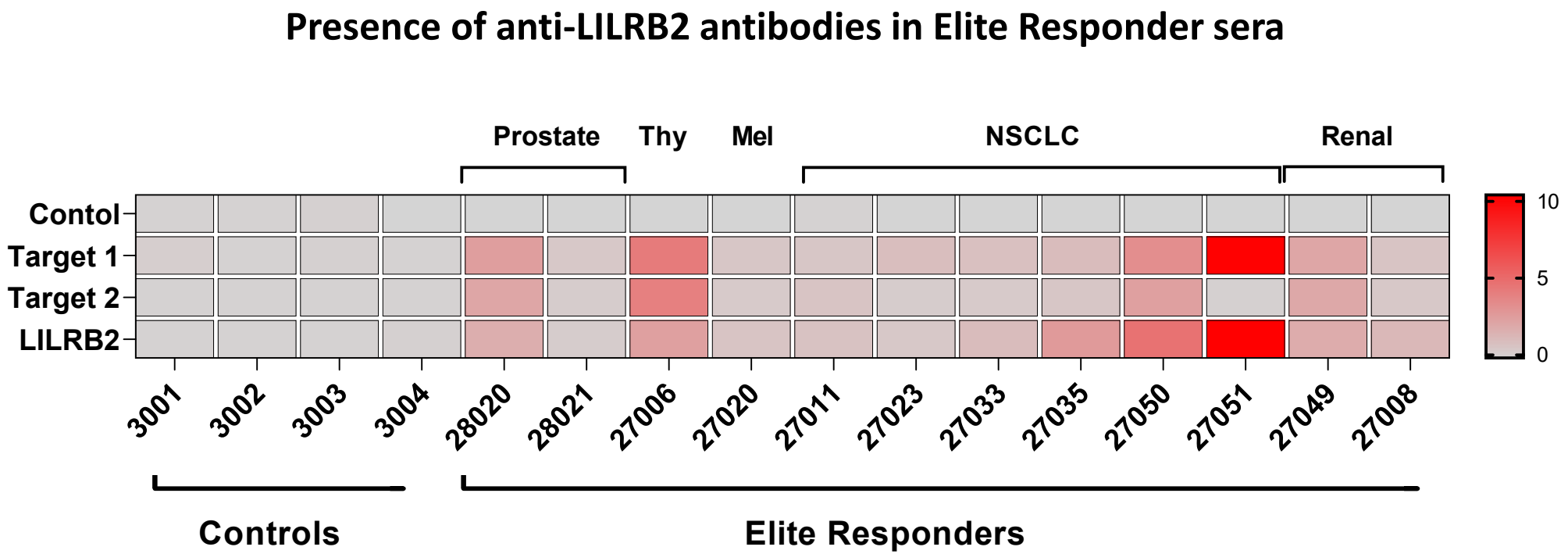
OncoResponse

OR502

Anti-Leukocyte Immunoglobulin Like Receptor B2 (LILRB2)

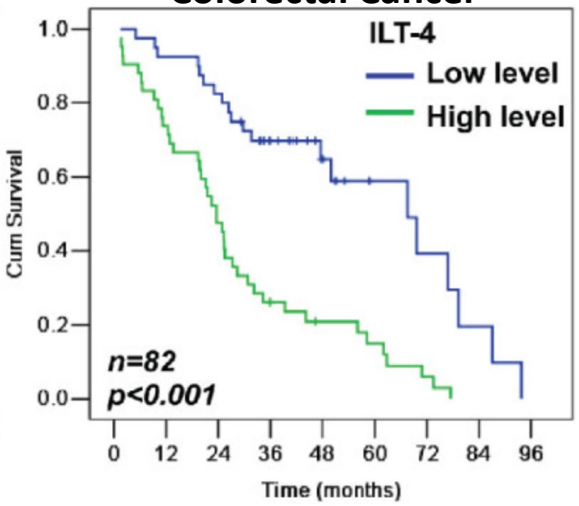
Targeting LILRB2 to reverse immunosuppression in cancer

Elite Responders of immunotherapy mount a strong antibody response to LILRB2

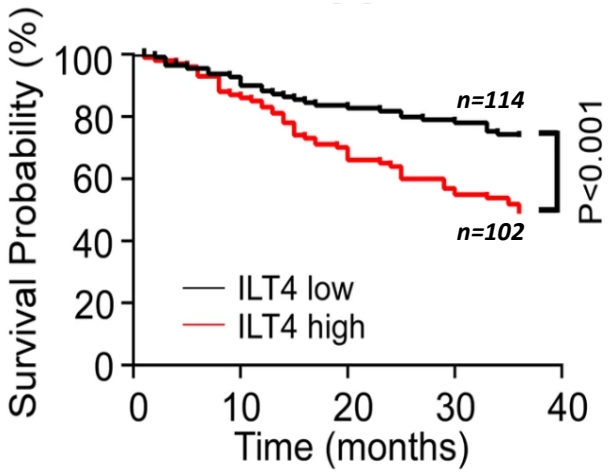


LILRB2 is a negative prognostic marker in cancer

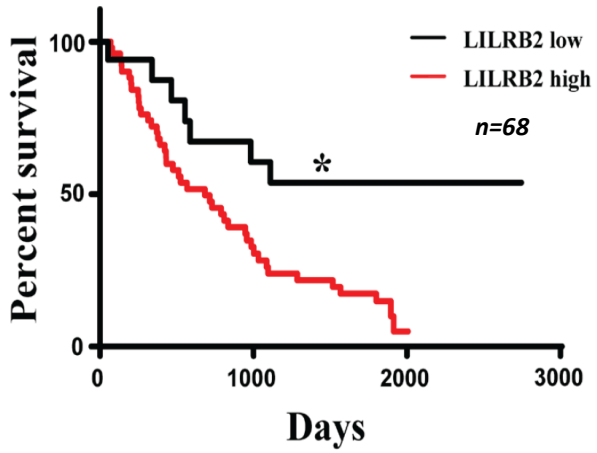
Colorectal Cancer[1]



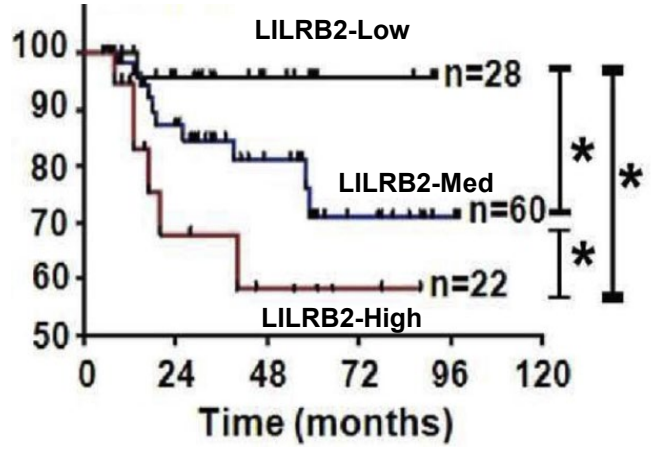
Lung Adenocarcinoma[2]



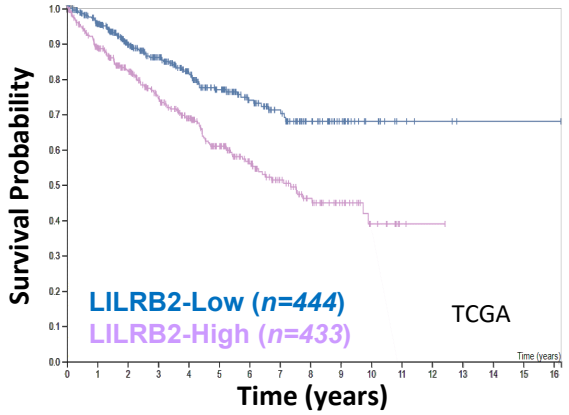
NSCLC[3]



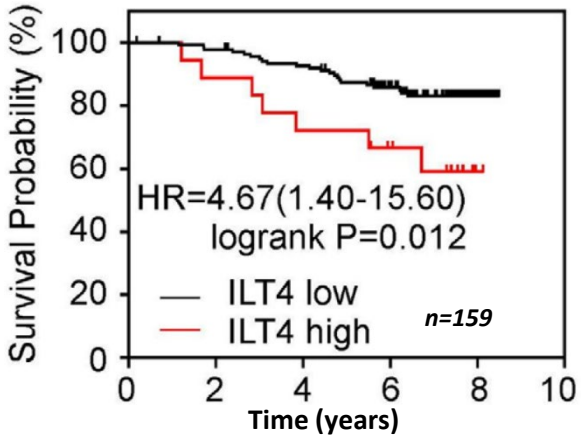
Endometrial Cancer[4]



Renal Cancer

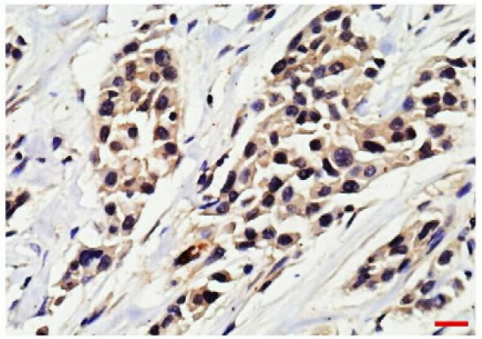


Breast Cancer[5]

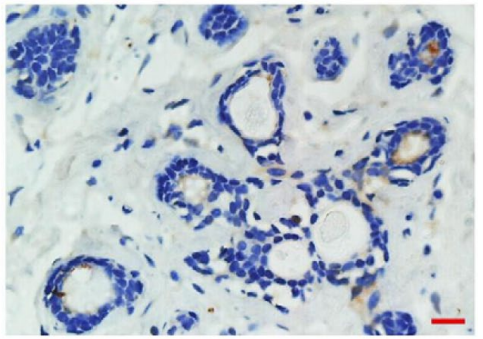


Breast Cancer[5]

Cancer tissue

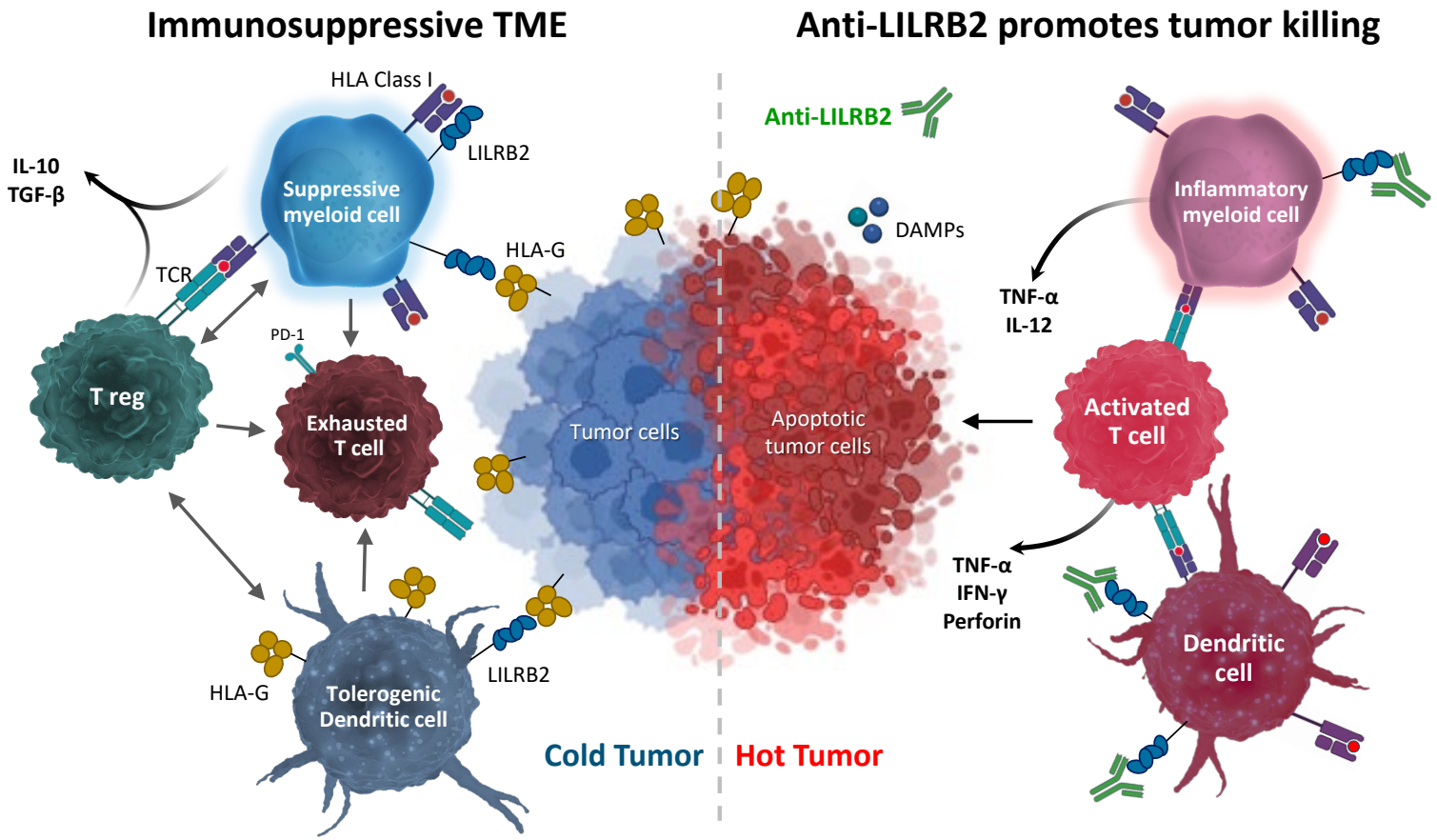


Adjacent normal tissue



[1]Front Immunol. 2021; 12:679090, [2]Biomarker Res. 2020; 8:11, [3]Oncotarget 2015; 6:21004, [4]BBRC 2018; 506:243, [5]J Immunother Cancer 2021; 9:e001536

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

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

LILRB2 clinical landscape

Name	Company	Results
MK-4830 (IgG4)	Merck (Agenus)	All in combo: NSCLC, SCLC, Ovarian, Melanoma, RCC, ESCC 11 active trials Mono: 50 pts. 1 PR (ovarian), 11 SD Combo: 34 pts. 1 CR, 7 PR, 9 SD. 24% ORR, 5 of 11 subjects with prior anti-PD-1 treatment responded to the combination
JTX-8064 (IgG4)	Jounce Acquired by Concentra Biosciences	OC, RCC, TNBC, SCCHN, NSCLC, CSCC, Sarcomas • MTD not reached, RP2D 700 mg q3w • Mono : 22 pts. 0 PR/CR, 7 SD • Combo: 9 pts. 1 PR (cholangio), 3 SD
IO-108 (IgG4)	Immune-Onc	No DLTs up to 1800 mg in monotherapy and in combo with pembro • Mono: 11 pts. 1 CR, 0 PR, 4 SD • Combo: 13 pts. 0 CR, 3 PR, 4 SD
BMS-986406 (IgG1 Fc null)	Bristol-Myers Squibb	Ph1 on March 31, 2022 Monotherapy and Combo with Nivo
CDX-585/BSI-585 Anti-LILRB2/PD-1 Tetravalent bispecific Ab	Celldex/Biosion	First patient dosed May 31, 2023

Clarivate Cortellis Drug Discovery Intelligence, July 2023

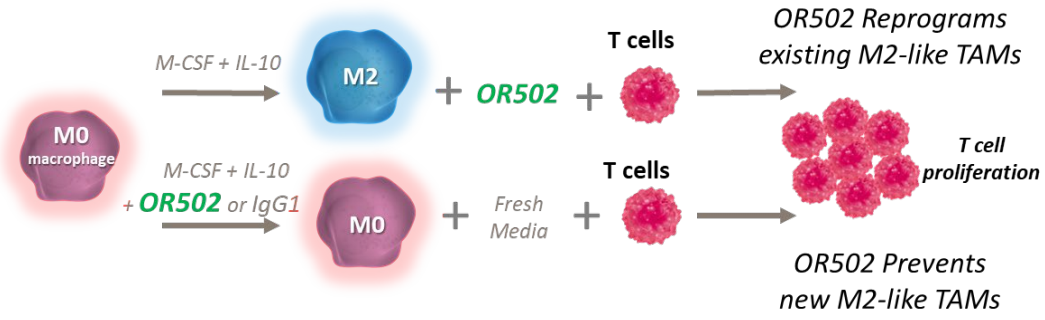
OncoResponse OR502: Superior characteristics versus MK-4830

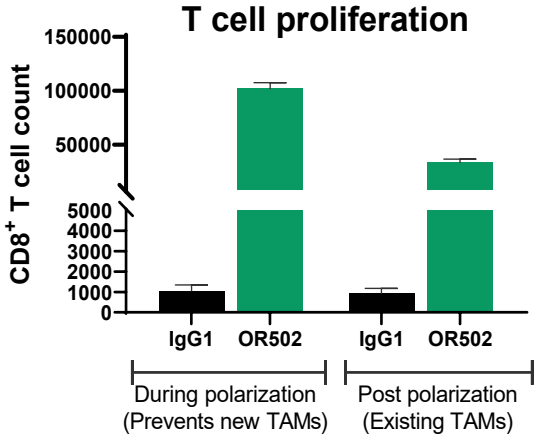
Criteria	OR502	MK-4830 (1E1)
Binding K_D to LILRB2	1.2 nM	3.5 nM
Blocks LILRB2 binding to ligands (HLA-G, angiopoietin-like protein ligands 2 & 5)	Yes	Yes
LILRB2 binding epitope	Distinct from other Abs	
Co-engagement of FcR	**Yes**	No
LPS-induced IFNγ production by human PBMC	**Strong**	Modest
T cell activation and proliferation (M2/T cell coculture)	**Yes**	No
IFNγ production (M2/Exhausted T cell coculture)	**Yes**	No
SK-MEL-5 xenograft in humanized NSG-SGM3 mice	**79% TGI** **33% Regression**	26% TGI 11% Regression

OR502 restores anti-cancer T cell responses better than MK-4830

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

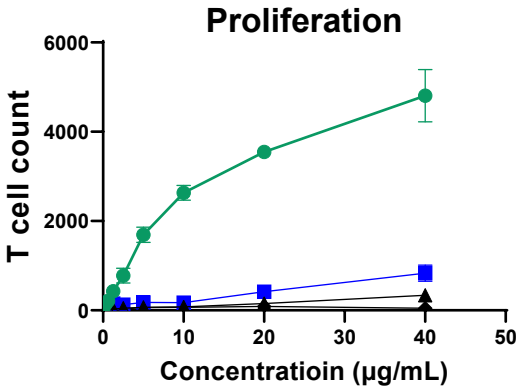
Reprograms immunosuppression of M2-like TAMs

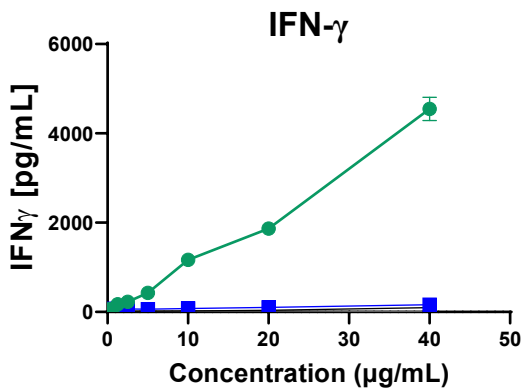


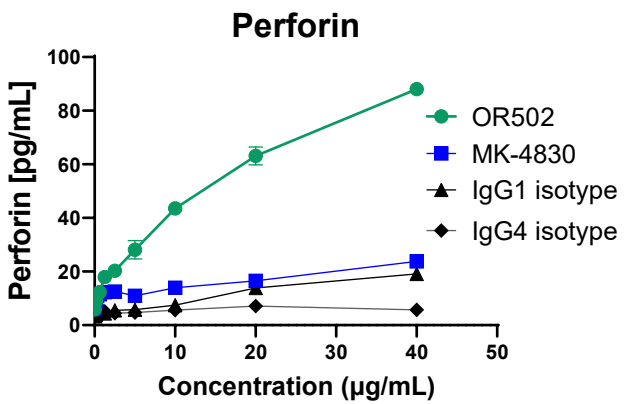


M2c/T cell coculture

(Rescues T cell proliferation and activation)

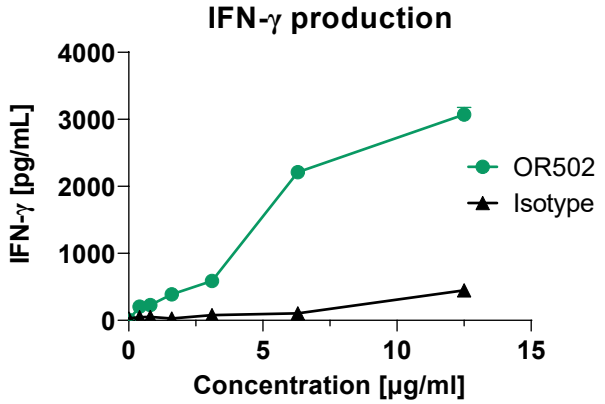




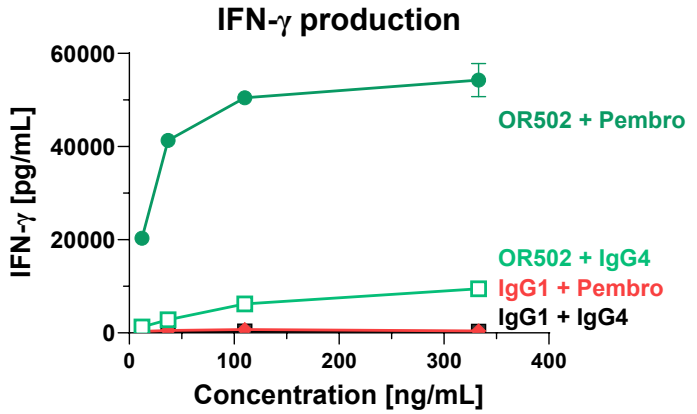


M2c/Exhausted T cell coculture

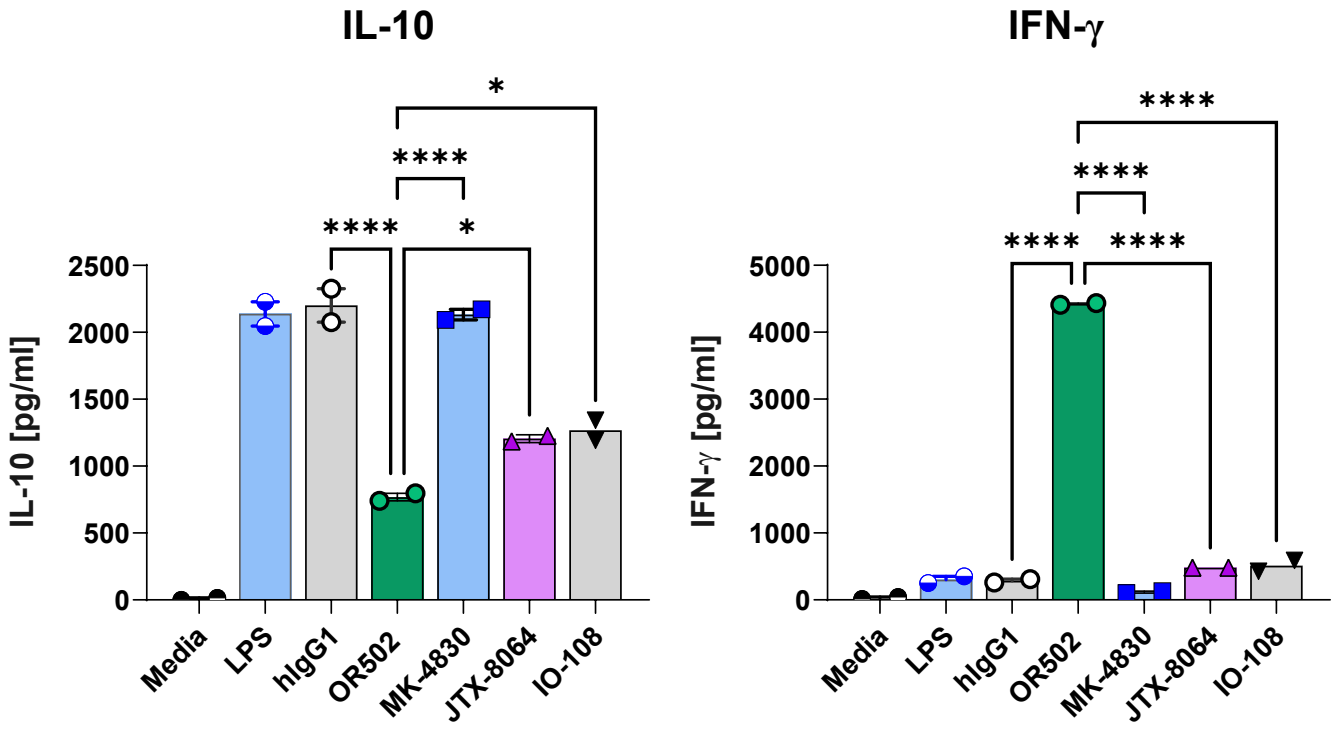
(Rescues IFN-γ production)



(Amplifies anti-PD-1 activity)



OR502 uniquely enhances Th1-like innate immune responses

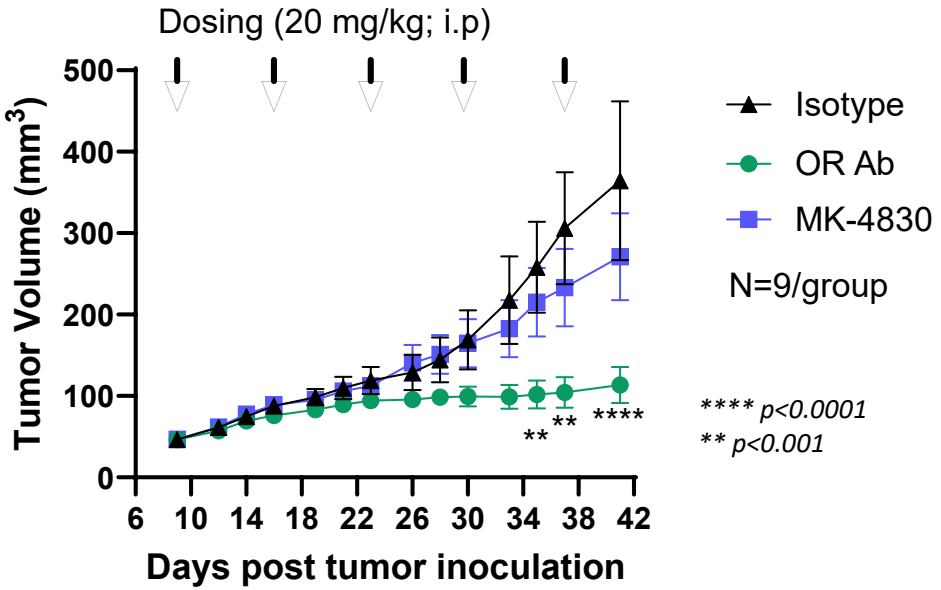


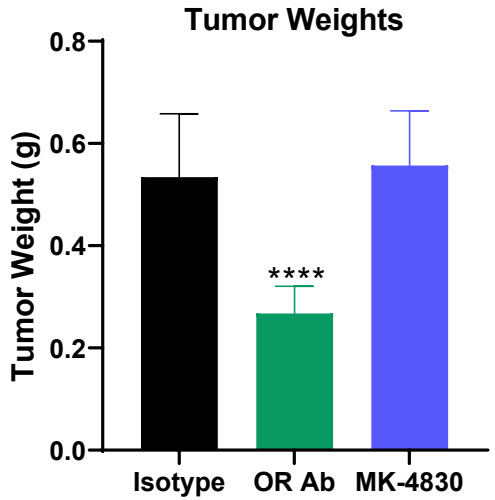
- OR502 reduced LPS-induced IL-10 secretion by PBMC superior to MK-4830
- OR502 increased LPS-mediated IFN-γ secretion by PBMC significantly better than MK-4830, JTX-8064 and IO-108
- Intratumor microbes are associated with immunosuppressive TME by inducing TLR mediated release of IL-10 that impacts the anti-tumor response and efficacy of CPI therapy[1,2]

MK-4830 (clone 1E1), JTX-8064 (clone J19), IO-108 (clone B2-19-16)

[1]Morad et al. Cell, 2021, [2]Pushalkar et al, Cancer Discovery 2018

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

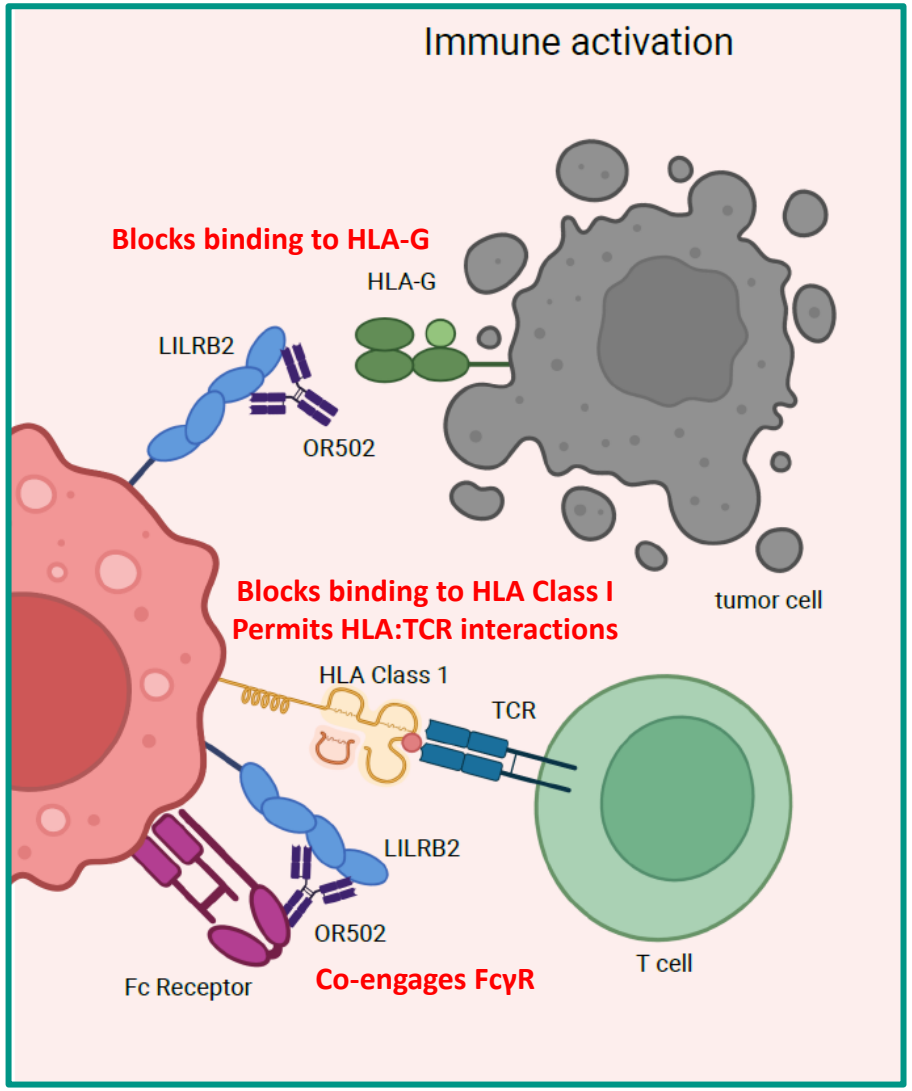




	Tumor Growth Inhibition (%)						Regression %
Group	***d28***	***d30***	***d33***	***d35***	***d37***	***d41***	***d41***
OR502 parental mAb	47	57	69	74	78	79	33
MK-4830 (Merck)	-5	3	16	17	24	26	11

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

- Reverses and prevents immunosuppressive phenotype of new and existing TAMs
- Amplifies anti-PD-1 activity in M2/T cell coculture assays
- Superior in vivo anti-tumor activity in SK-MEL-5 tumor model compared to benchmark
- 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
- IND filing in 2023



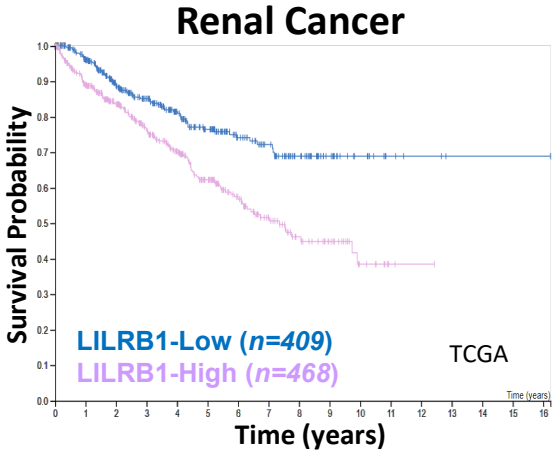
OncoResponse

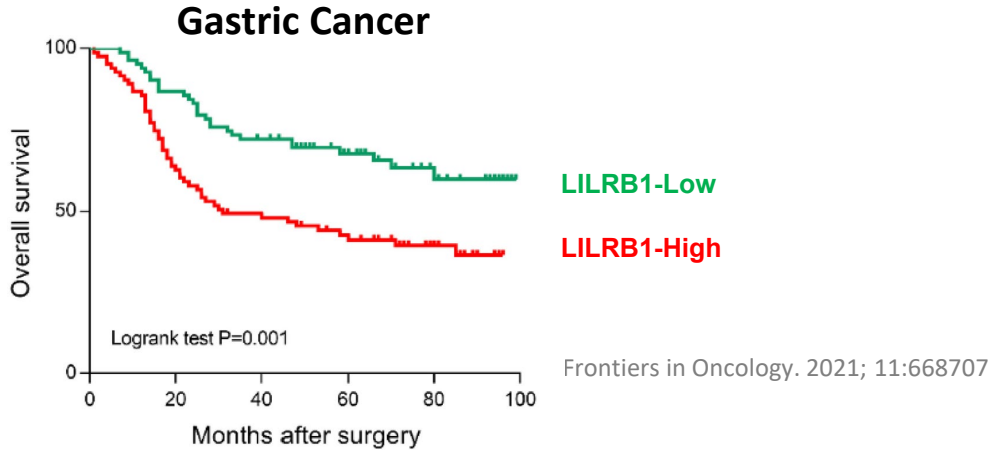
OR641

Dual Antagonist Antibody Targeting Both LILRB1 and LILRB2

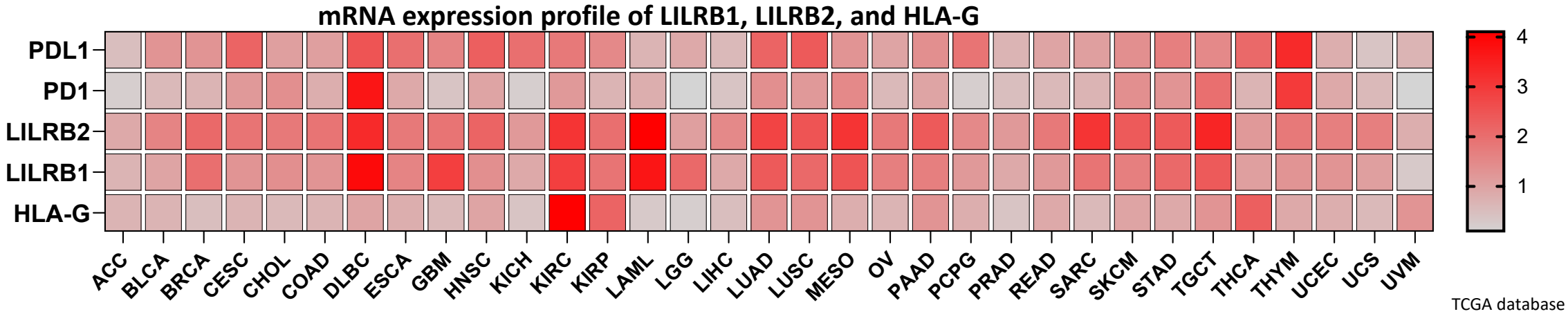
Combining myeloid and lymphoid checkpoint inhibition for broader target coverage and therapeutic applications

Overexpression of LILRB1 or LILRB2 is associated with poor patient outcomes in cancer



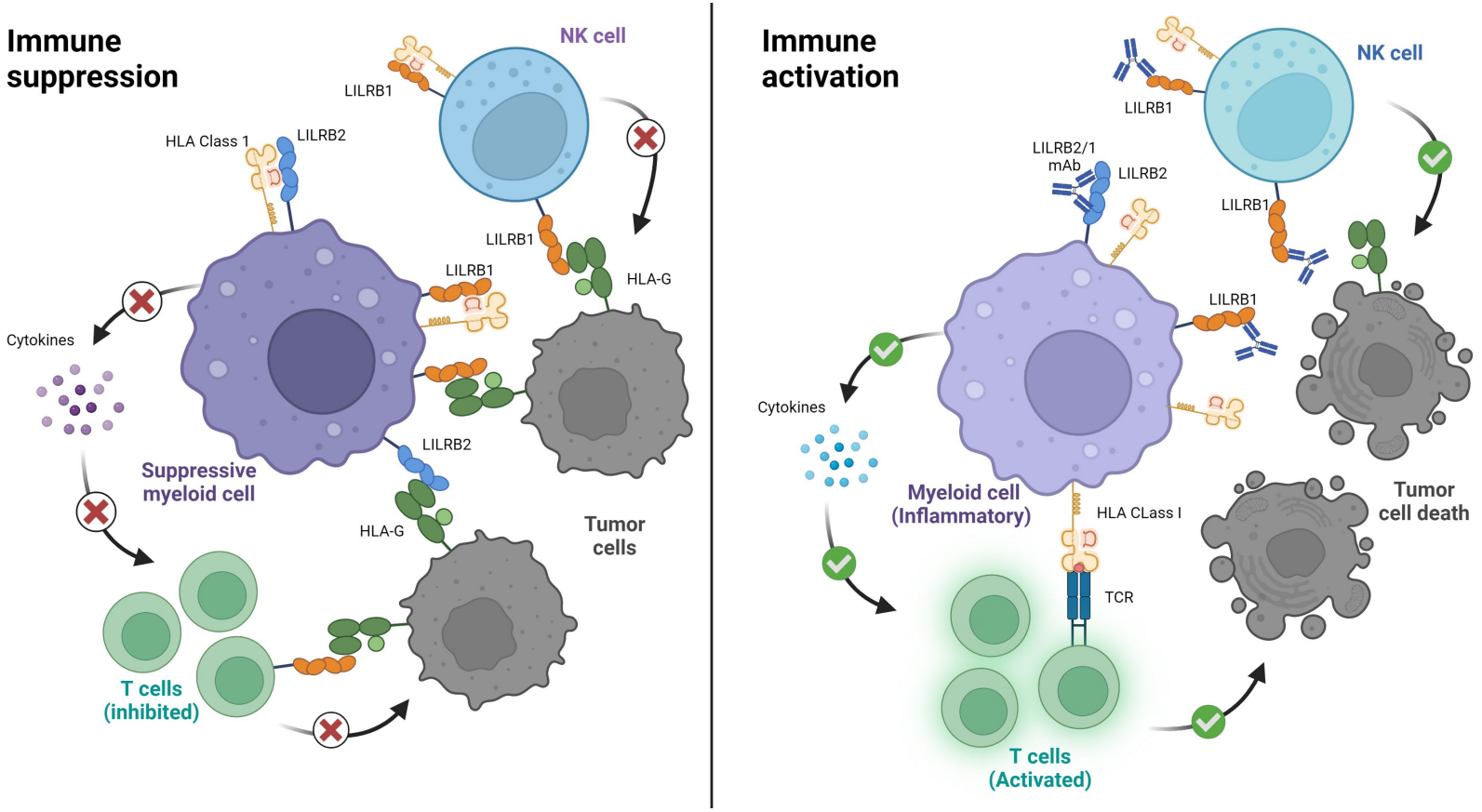


Frontiers in Oncology. 2021; 11:668707



- Many primary cancer types express high LILRB1 and LILRB2 suggesting dual antagonism may have broader application

LILRB1 and LILRB2 dual antagonism drives anti-tumor activity



- LILRB2 antagonism reverses myeloid cell immune suppression
- LILRB1 antagonism promotes tumor cell killing by NK and CD8 T cells
- Dual antagonism of LILRB1 and LILRB2 may act additively to reverse suppression of immune cells in the TME

Dual LILRB2/1 clinical landscape

Name	Company	Results
NGM707 (IgG1 Fc null) Dual LILRB1/2 Ab	NGM Bio	Ph1 data Mono: RCC, CRC, OC Combo: NSCLC, SCCHN • Escalation up to 1800 mg q3w completed; MTD not reached • Mono: 24 pts. 1 PR, 6-7 SD • Tumor shrinkage in 5 pts, max 70% • Prelim evidence of macrophage reprogramming (CD163)
IOS-1002 (HLA-B54-Fc) decoy to LILRB1/LILRB2/KIR3DL	ImmunOS Therapeutics	Apr 2023: Ph1 initiated Mono and combo with anti-PD-1
TTX-080 (IgG4) HLA-G antagonist	Tizona Therapeutics	Ph1 Mono & Combo Advanced Solid Refractory/Resistant Solid Tumors

Clarivate Cortellis Drug Discovery Intelligence, July 2023

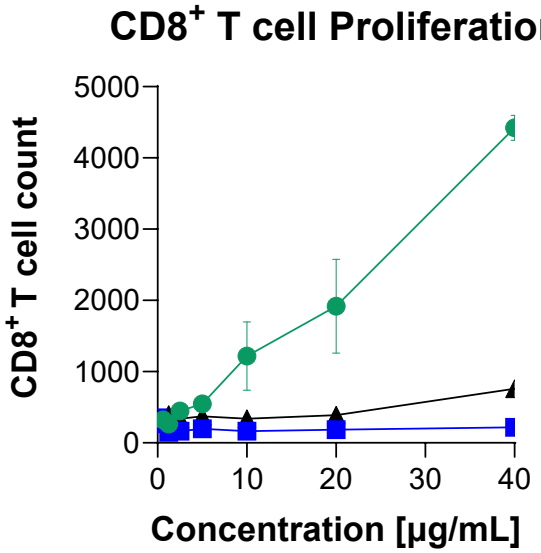
OncoResponse OR641: Superior characteristics versus NGM707

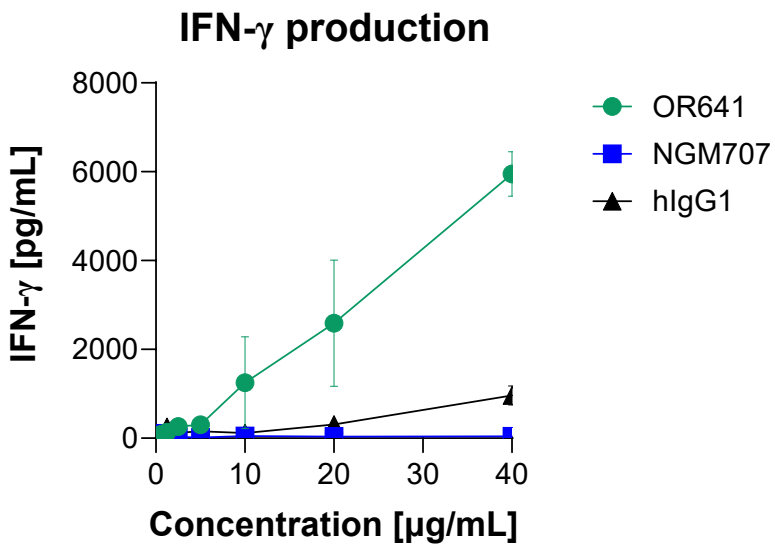
Criteria	OR641	NGM707 (73D1)
Binding K_D to LILRB1 and LILRB2	2.4 pM, <1 pM	9.3 pM, 2.2 pM
Blocks LILRB1 and LILRB2 binding to HLA Class I	Yes	Yes
LILRB1 binding epitope	Distinct	
LILRB2 binding epitope	Distinct	
Co-engagement of FcR	**Yes**	No
TLR2 and TLR4-induced IFNγ production by human PBMC	**Strong**	Minimal
T cell activation and proliferation (M2/T cell coculture)	**Yes**	No
IFNγ production (M2/Exhausted T cell coculture)	**Yes**	No
Enhances NK cell mediated cytotoxicity	**Yes**	No
Phagocytosis of HLA-G expressing cancer cells by M2 cells	**Yes**	No

OR641 restores T cell activation and proliferation better than NGM707 in M2/T cell coculture assay

M2c/T cell coculture

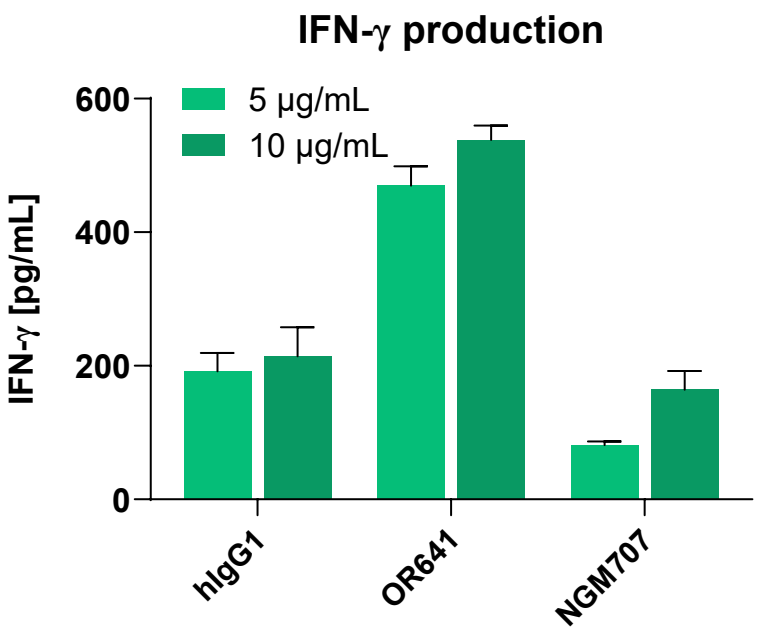
(Rescues T cell proliferation and activation)



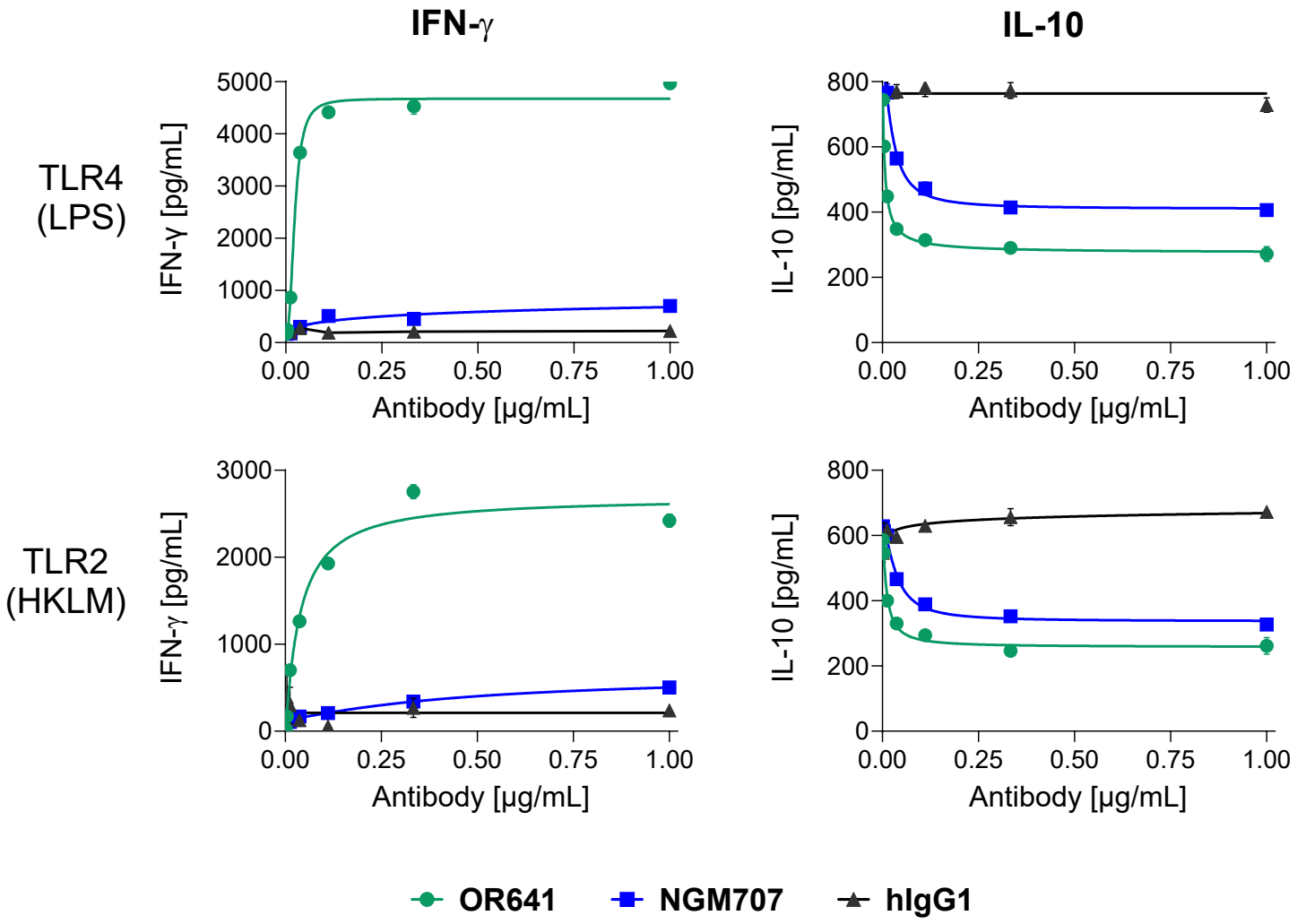


M2c/Exhausted T cell coculture

(Rescues IFN-γ production)



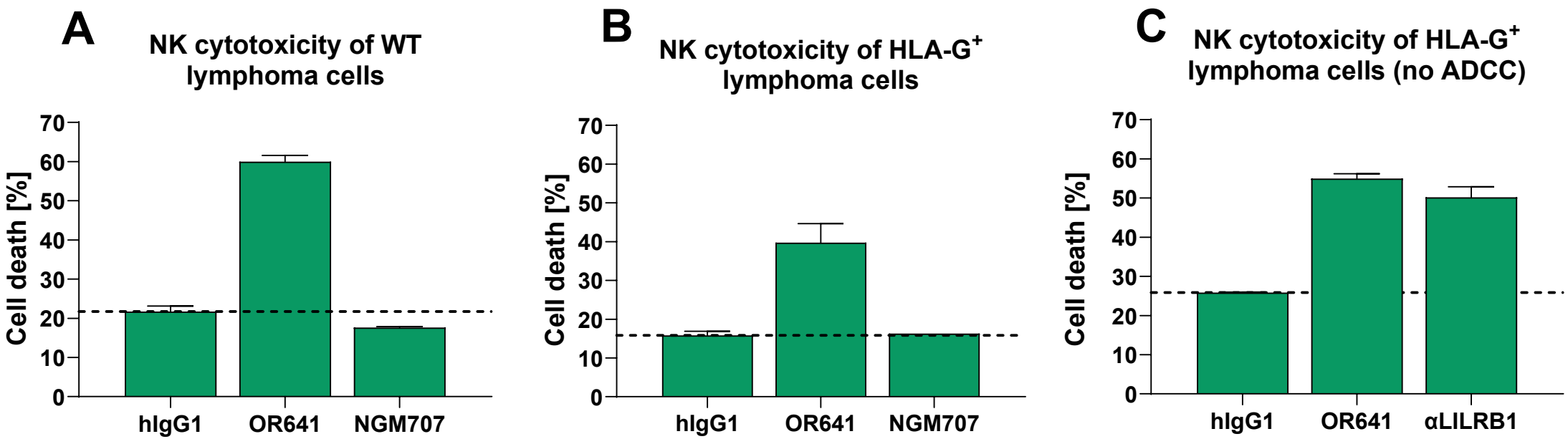
OR641 enhances TLR2- and TLR4-induced IFN-γ and reduces IL-10 production in human PBMCs



- Intratumoral microbes are associated with immunosuppressive TME and can impact anti-tumor response and efficacy of CPI therapy[1]
- OR641 enhances IFN-γ and reduces IL-10 production and may augment innate immune response for better sensitivity to CPI therapy

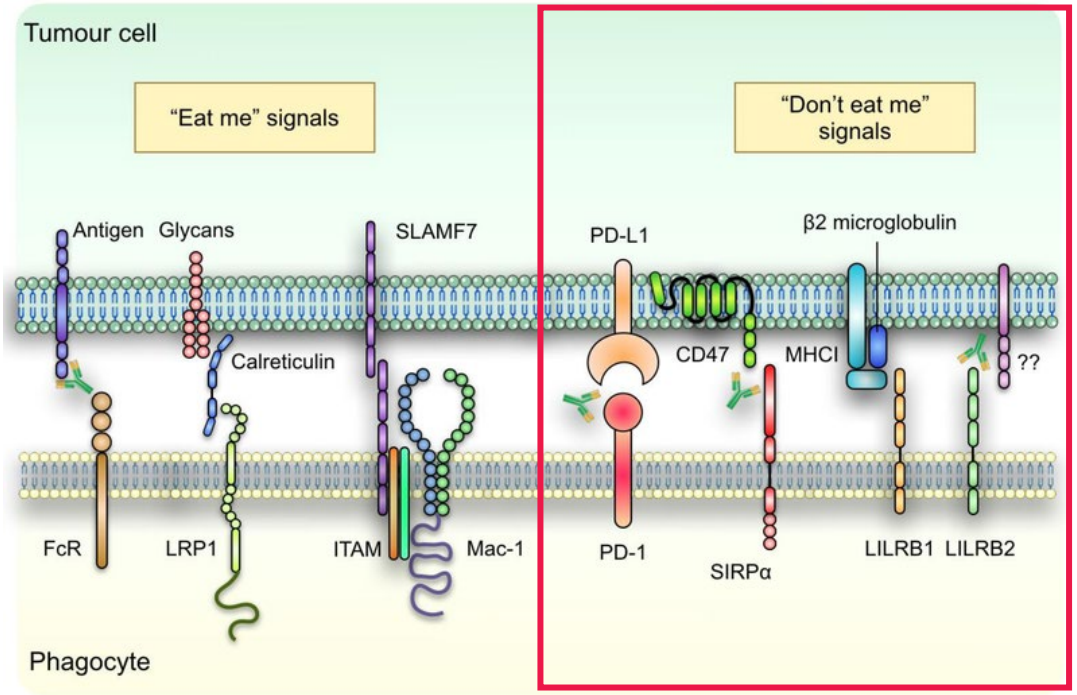
[1]*Morad et al. Cell, 2021*

OR641 enhances NK cell cytotoxicity better than NGM707

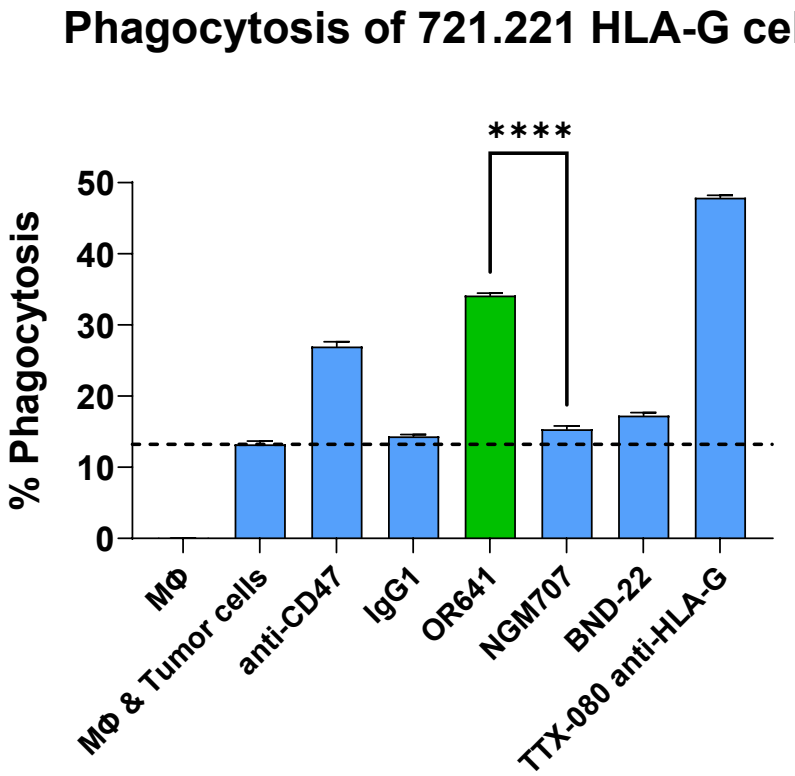


- Treatment with OR641 enhances NK cell mediated cytotoxicity of A) wild type, B) HLA-G$^+$, C) HLA-G$^+$ 721.221 B-cell lymphoma cells pretreated with OR641-IgG2

OR641 enhances phagocytosis of HLA-G$^+$ lymphoma cells by macrophages



Nat Rev Cancer. 2019; 19: 568–586



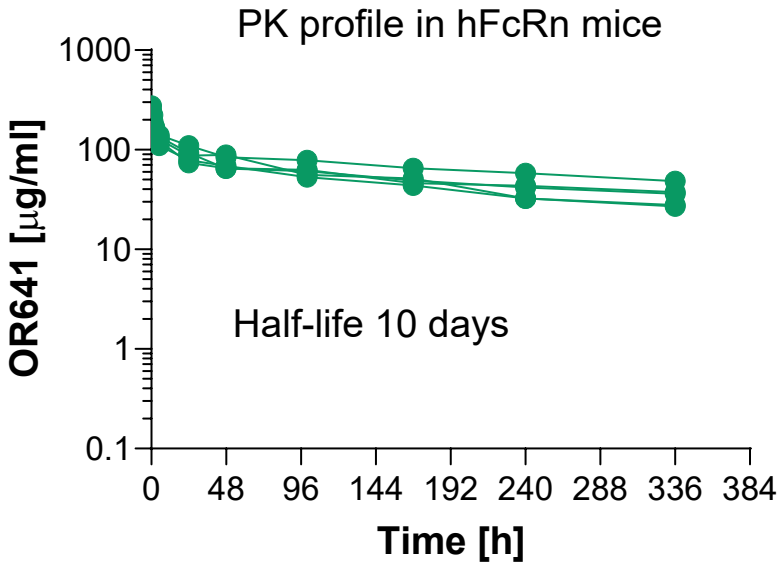
Representative data from n=4 donors

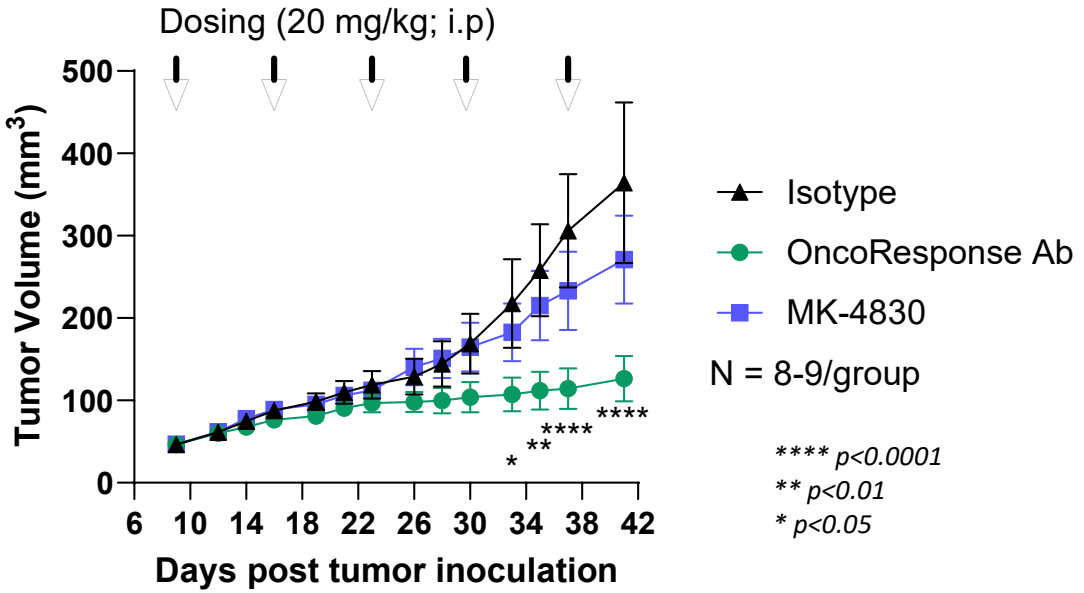
NGM707 (clone 73D1), BND-22 (clone 15G8), TTX-080 (clone 38426)

- OR641 enhanced phagocytosis of HLA-G$^+$ lymphoma cells significantly better than NGM707

PK profile of OR641 and in vivo anti-tumor activity of the parent antibody

OncoResponse dual anti-LILRB2/1 antibody significantly inhibits growth of SK-MEL-5 melanoma in NSG-SGM3 mice



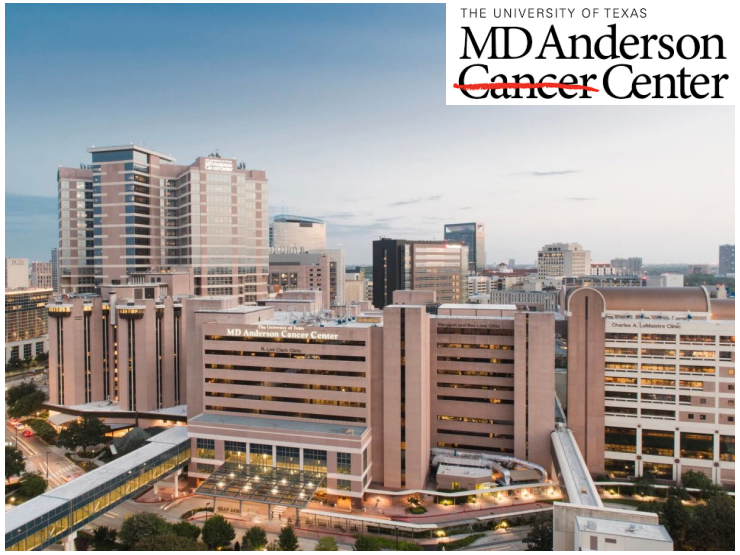


	Tumor Growth Inhibition (%)						Regression %
Group	***d28***	***d30***	***d33***	***d35***	***d37***	***d41***	***d41***
Anti-LILRB2/1 (OncoResponse)	45	53	64	69	74	75	38
MK-4830 (Merck)	-5	3	16	17	24	26	11

OR641 is a superior anti-LILRB2/1 antibody that reverse immunosuppression caused by myeloid and lymphoid cells

- Modulates the immunosuppressive phenotype of macrophages and restores T cell activation and proliferation in M2/T cell coculture assay
- Enhances NK cell mediated cytotoxicity
- Enhances IFN-γ and reduces IL-10 production in human PBMCs in response to TLR2 and TLR4 stimuli
- Parental antibody demonstrates robust anti-tumor activity in SK-MEL-5 tumor model
- Co-engagement of FcγR provides an additional signal for myeloid reprogramming
- Minimal risk for cytokine release syndrome
- Half-life of ~10 days in humanized FcRn mice
- IND submission in 2024

Acknowledgements



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