What's next for cancer immunotherapy?

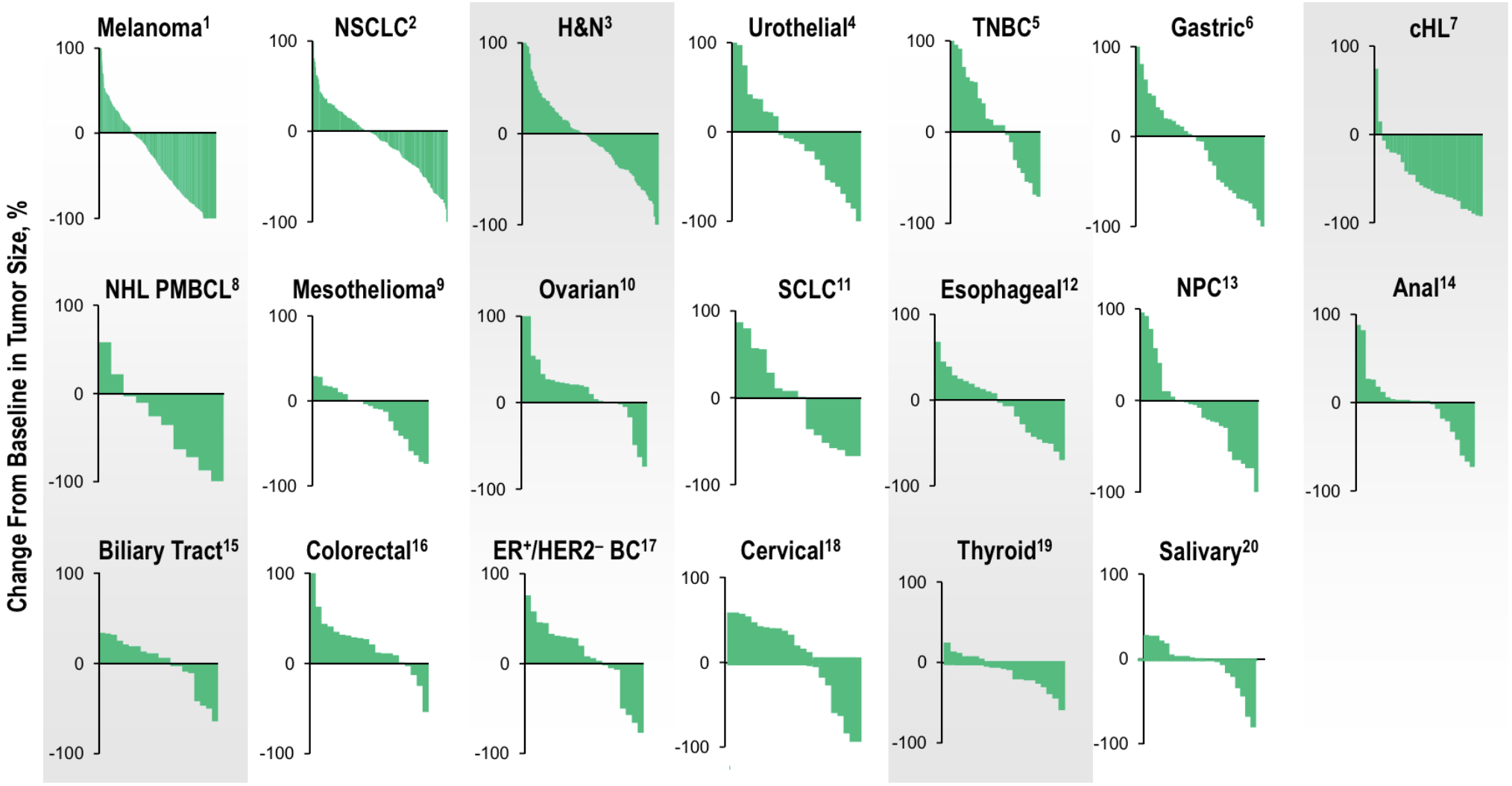
Adil Daud MBBS

Professor of Medicine and Dermatology

Disclosures

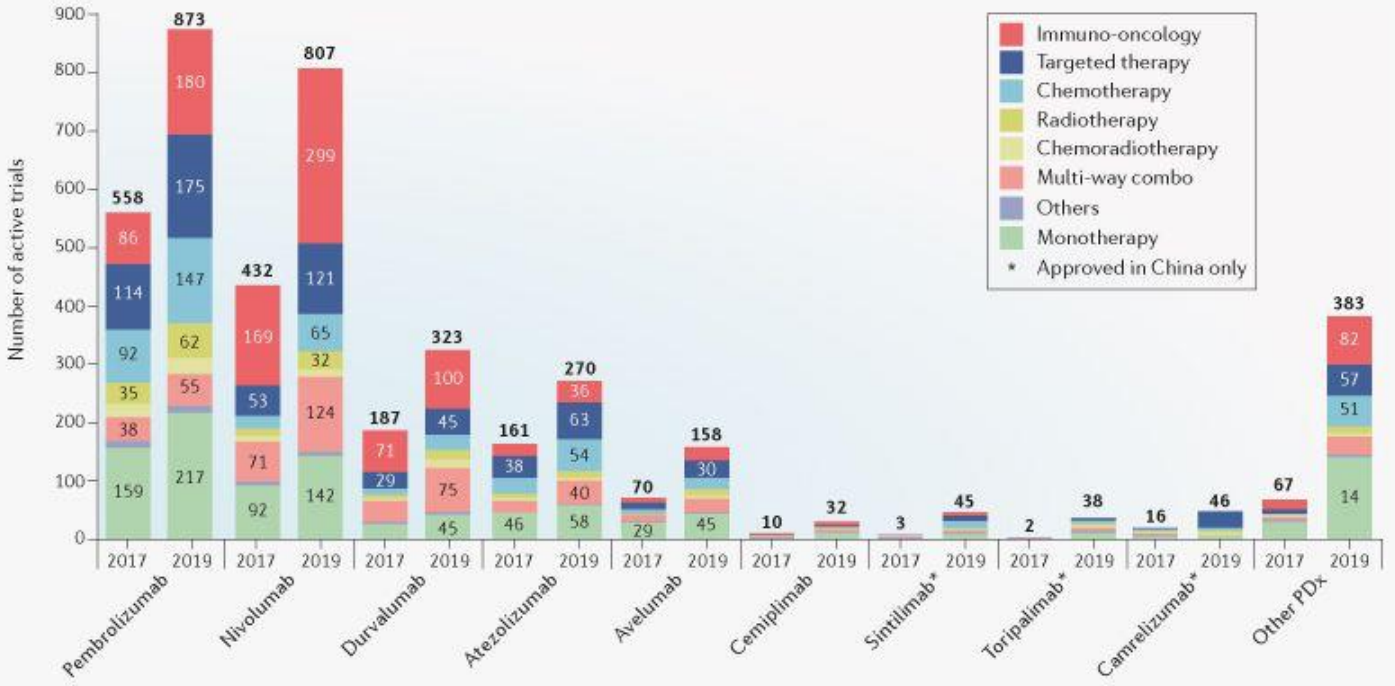
- No relevant financial relationships to disclose
- I will be discussing non-FDA approved indications during my presentation.

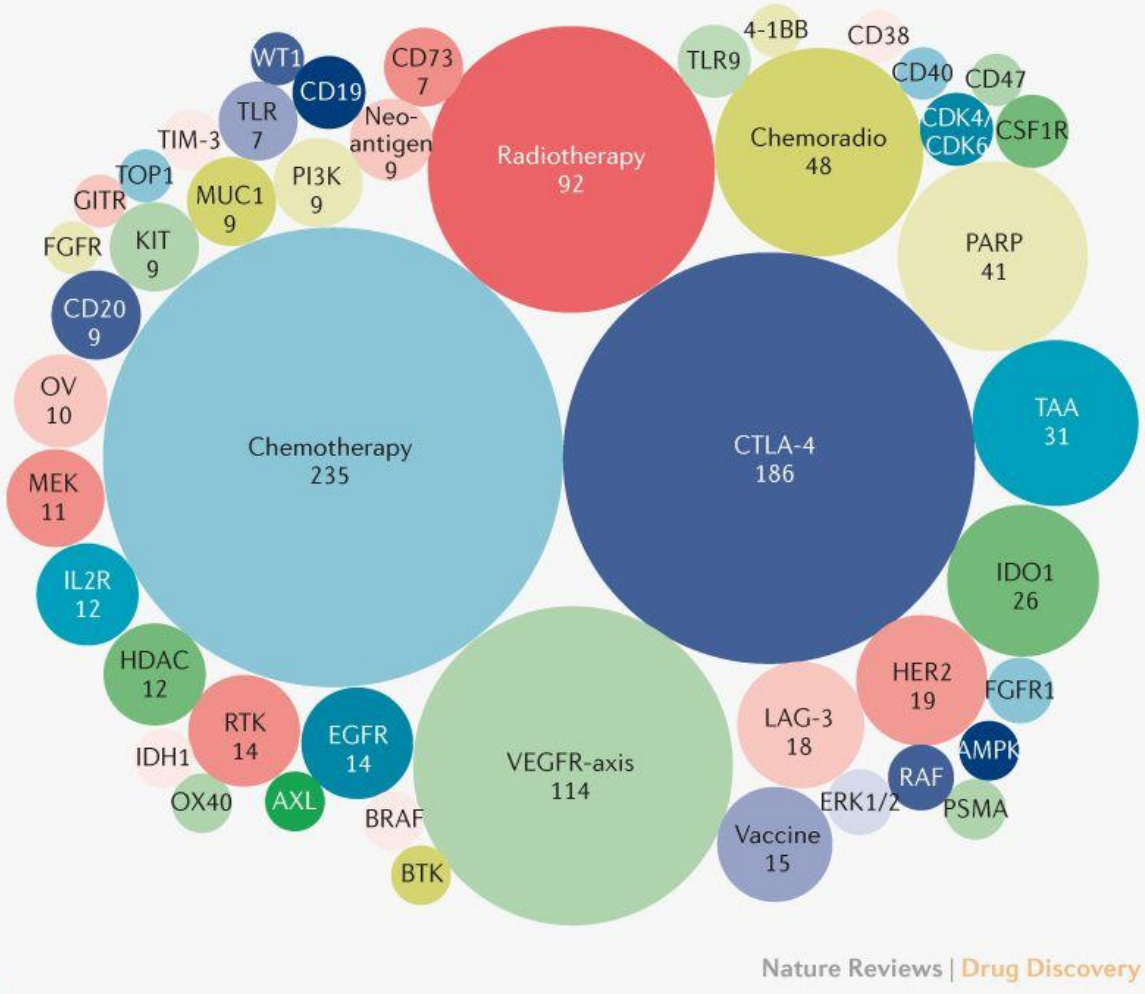
Activity of Pembrolizumab in Cancer



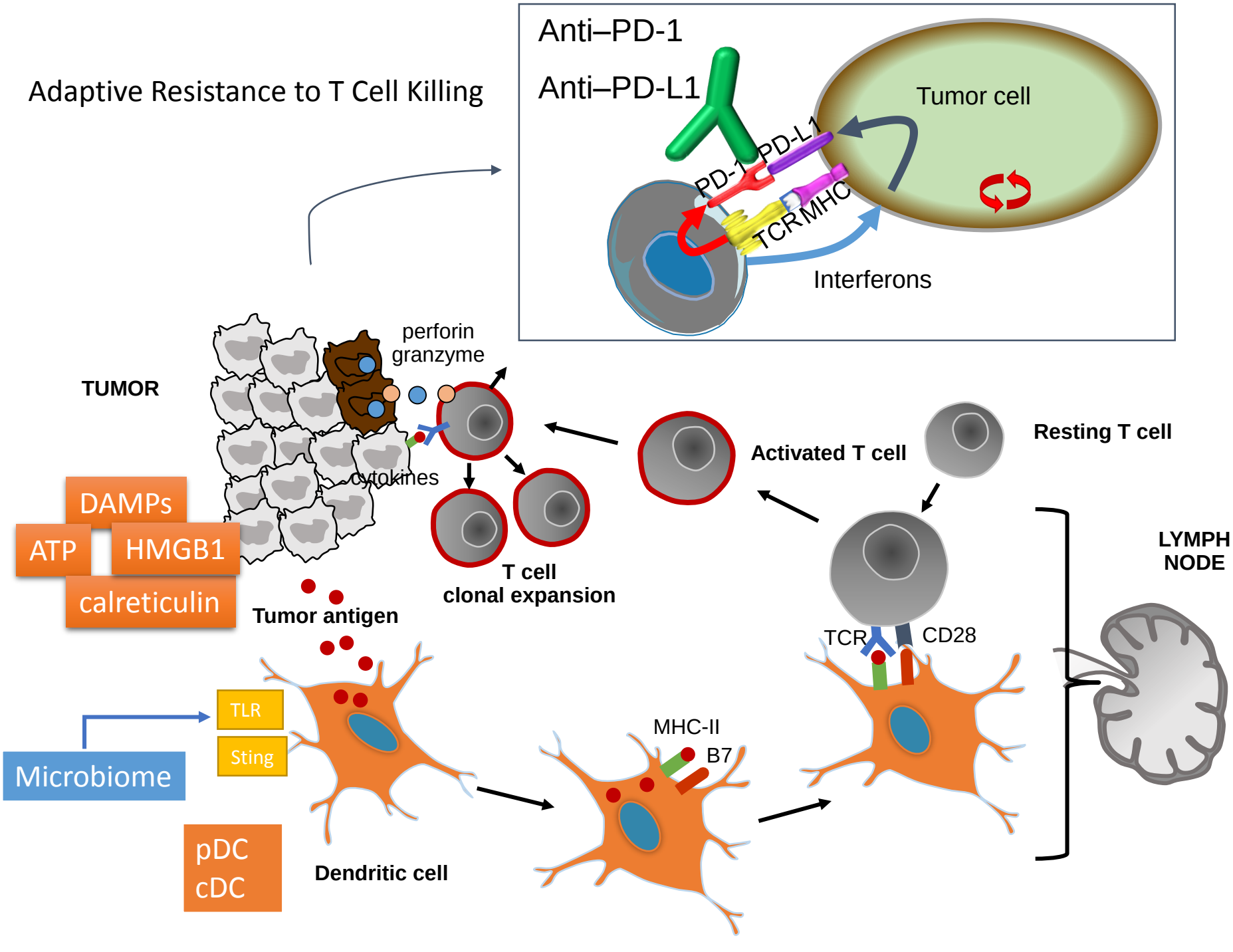
1. Daud A et al. ASCO 2015; 2. Garon EB et al. ESMO 2014; 3. Seiwert T et al. ASCO 2015; 4. Plimack E et al. ASCO 2015; 5. Nanda R et al. SABCS 2014; 6. Bang YJ et al. ASCO 2015 ; 7. Moskowitz C et al. ASH 2014; 8. Zinzani PL et al. ASH 2015; 9. Alley EA et al. AACR 2015; 10. Varga A et al. ASCO 2015; 11. Ott PA et al. 2015 ASCO; 12. Doi T et al. ASCO 2015; 13. Hsu C et al. ECC 2015; 14. Ott PA et al. ECC 2015; 15. Bang Y-J et al. ECC 2015; 16. O'Neil B et al. ECC 2015; 17. Rugo HS et al. SABCS 2015;

Immunotherapy is under ACTIVE INVESTIGATION !!!!@#$

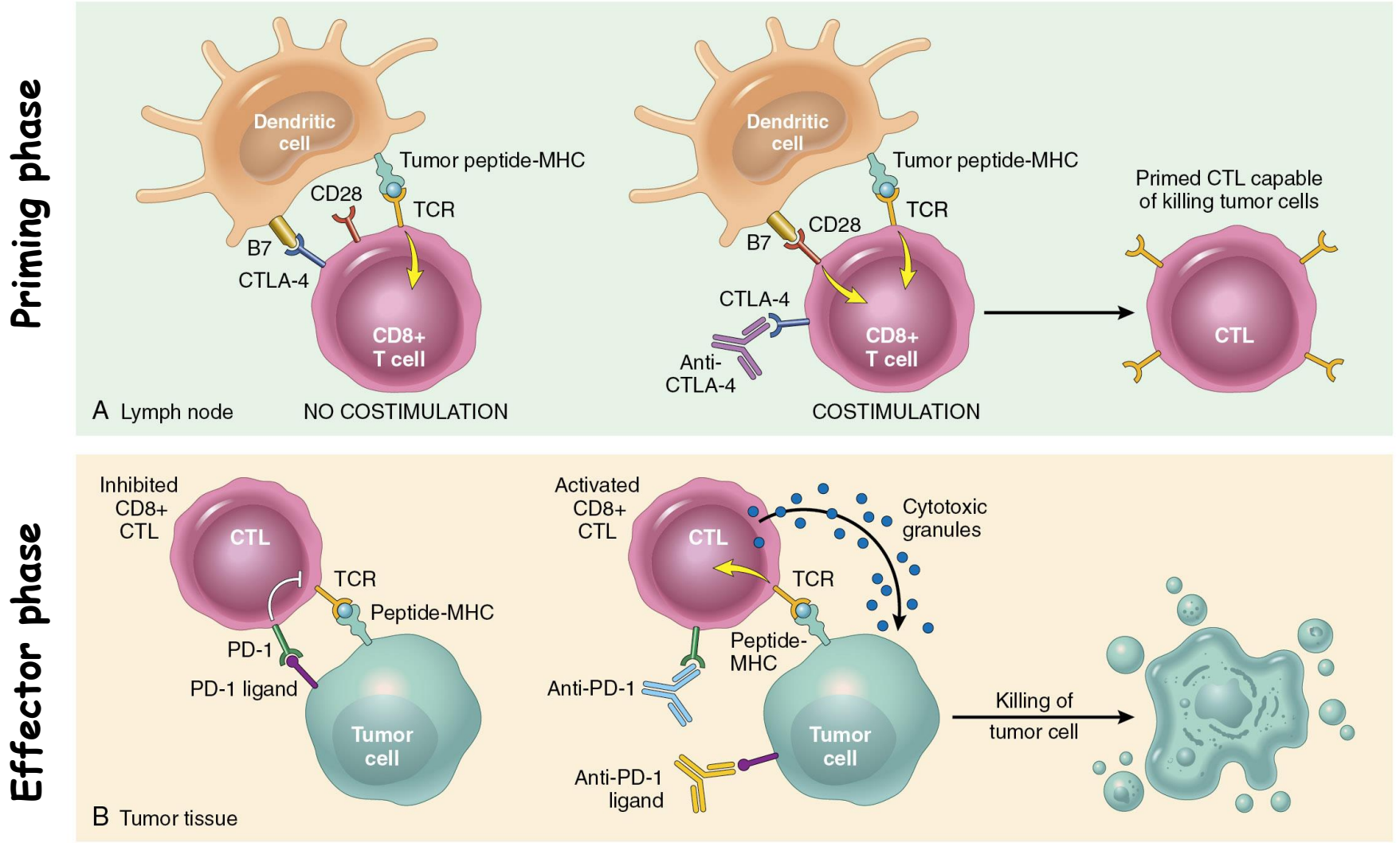




Adaptive Resistance to T Cell Killing

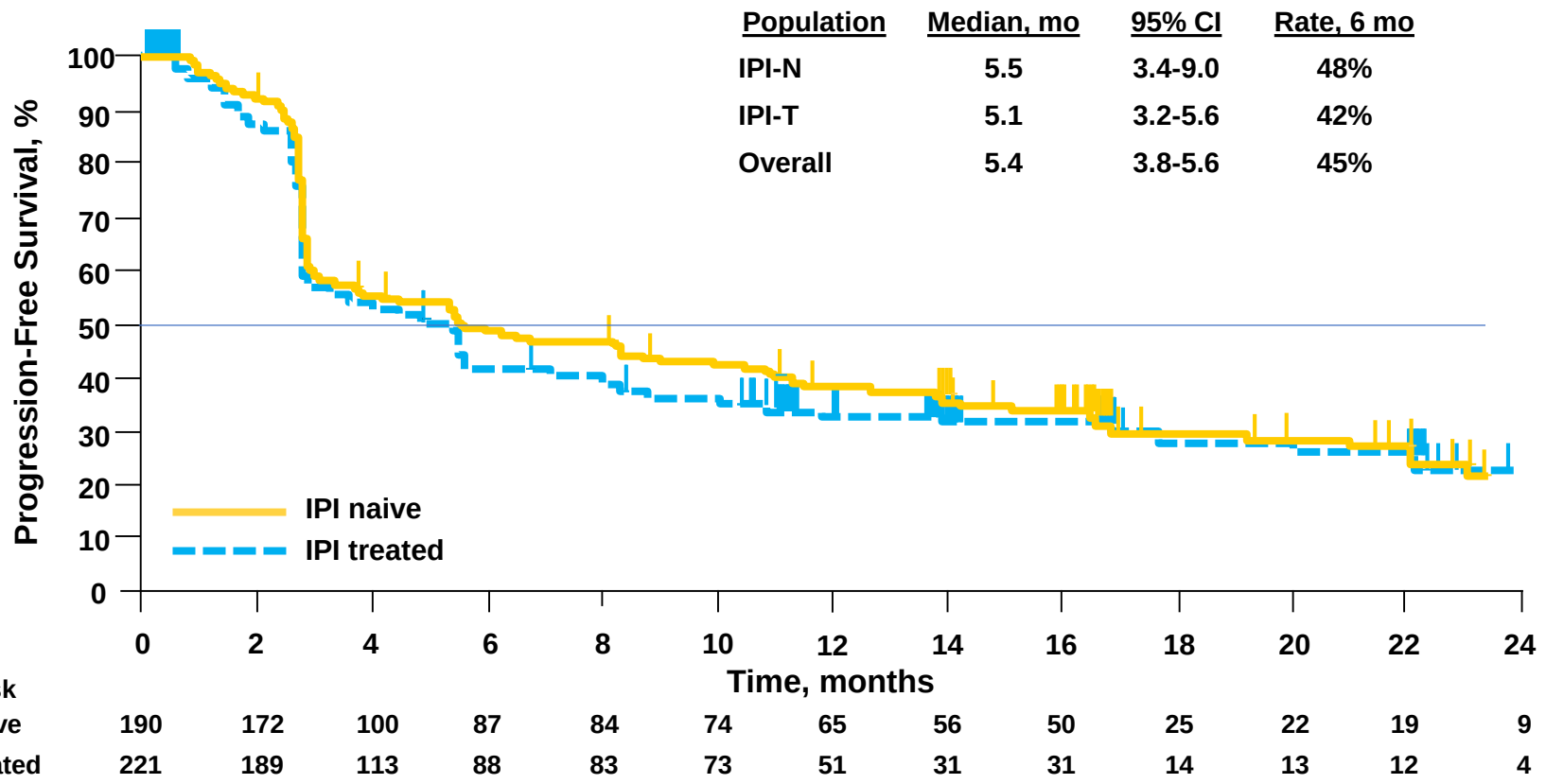


Checkpoint blockade for cancer immunotherapy



Courtesy of Abul K Abbas, MD

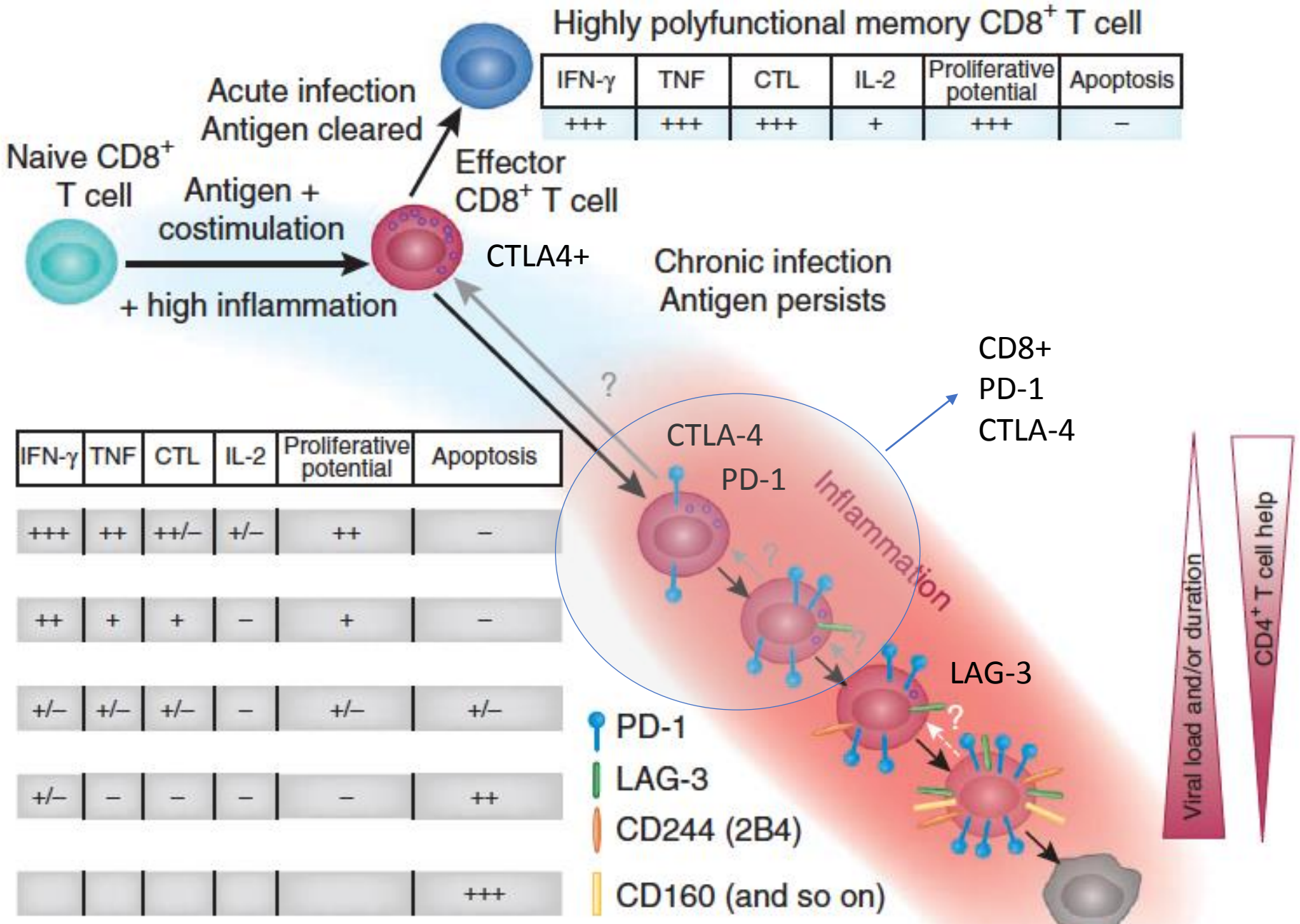
Keynote 001: Kaplan-Meier Estimate of PFS



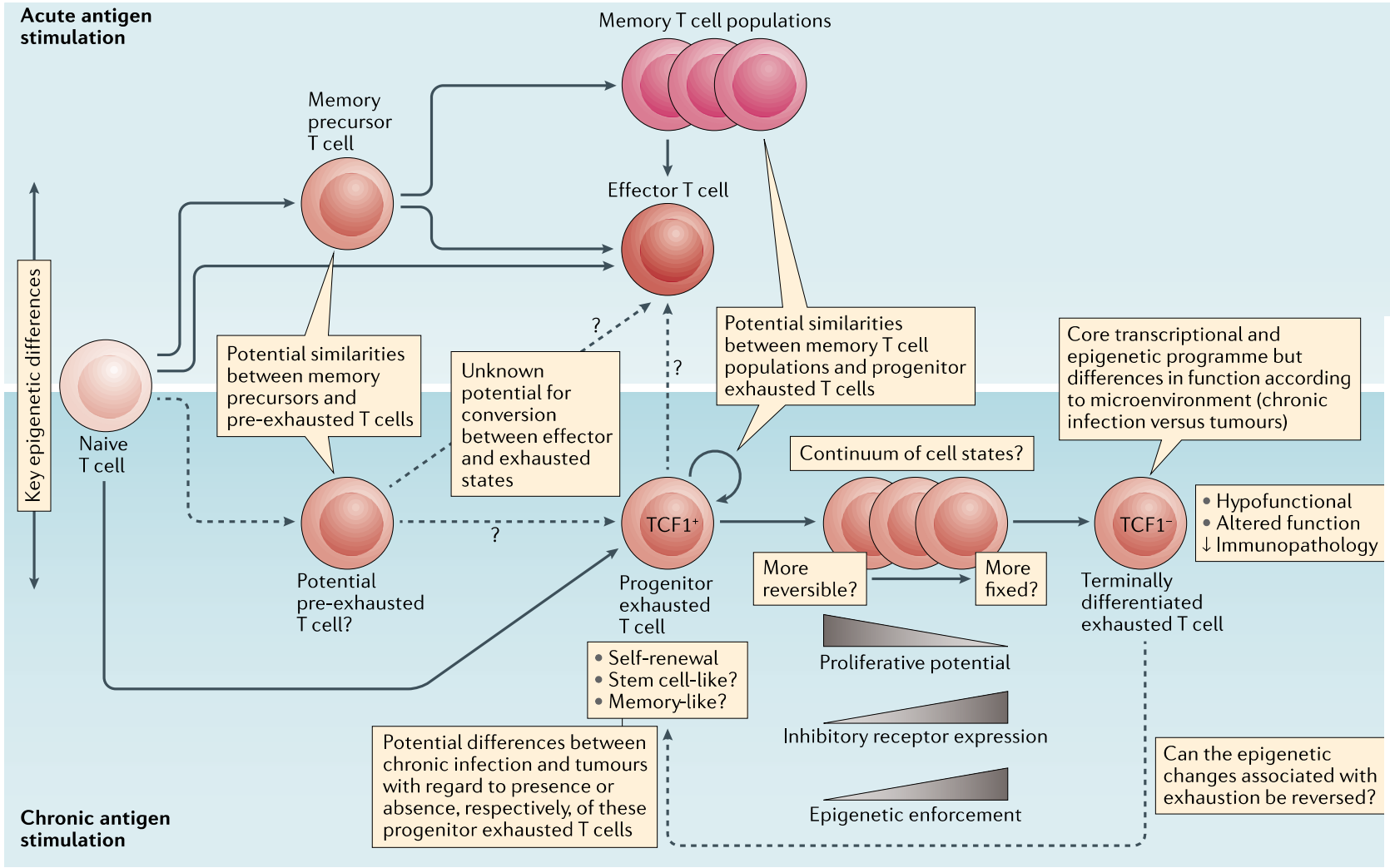
Population	Median, mo	95% CI	Rate, 6 mo
IPI-N	5.5	3.4-9.0	48%
IPI-T	5.1	3.2-5.6	42%
Overall	5.4	3.8-5.6	45%

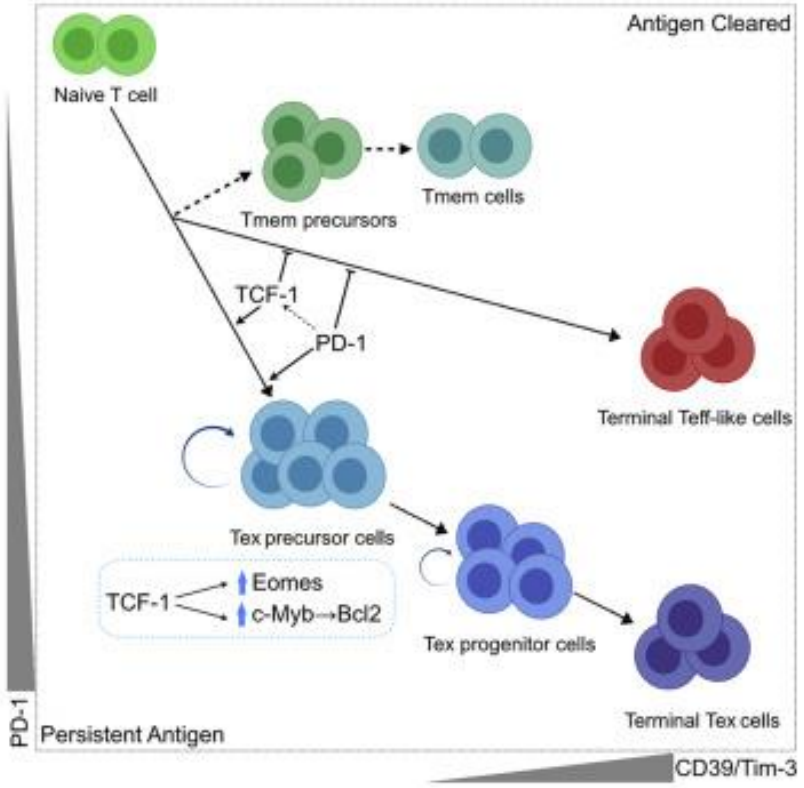
n at risk													
IPI naive	190	172	100	87	84	74	65	56	50	25	22	19	9
IPI treated	221	189	113	88	83	73	51	31	31	14	13	12	4

Analysis cut-off date: April 18, 2014.

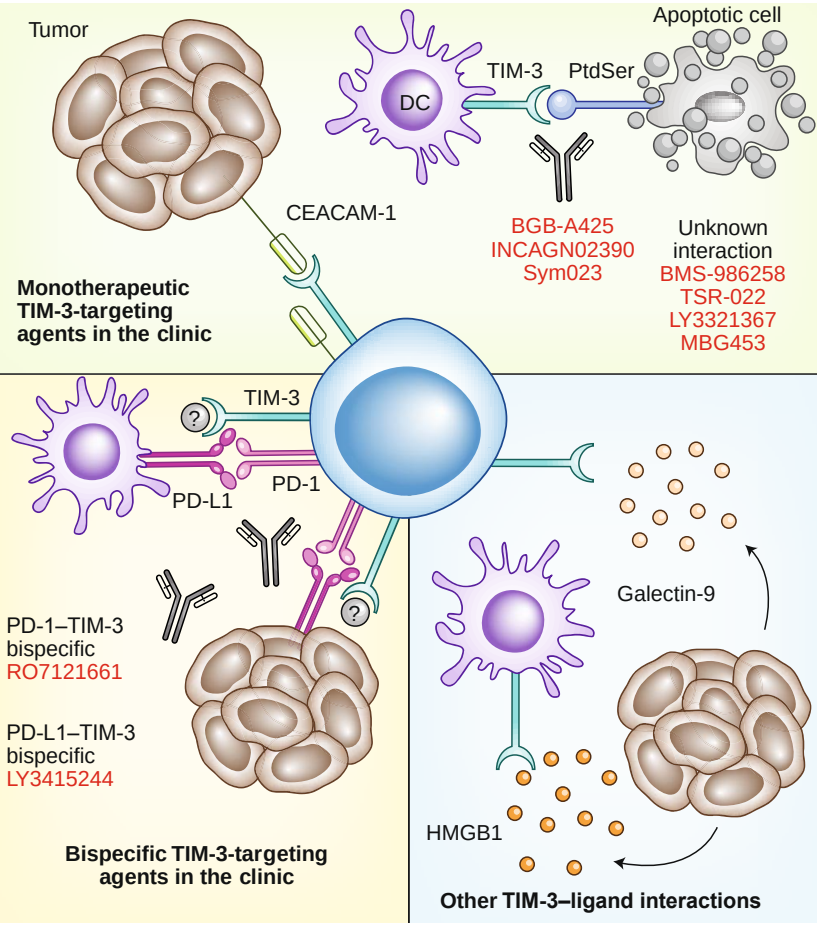


Modified from E John Wherry, Nature Immunology 12: 492-499, 2011

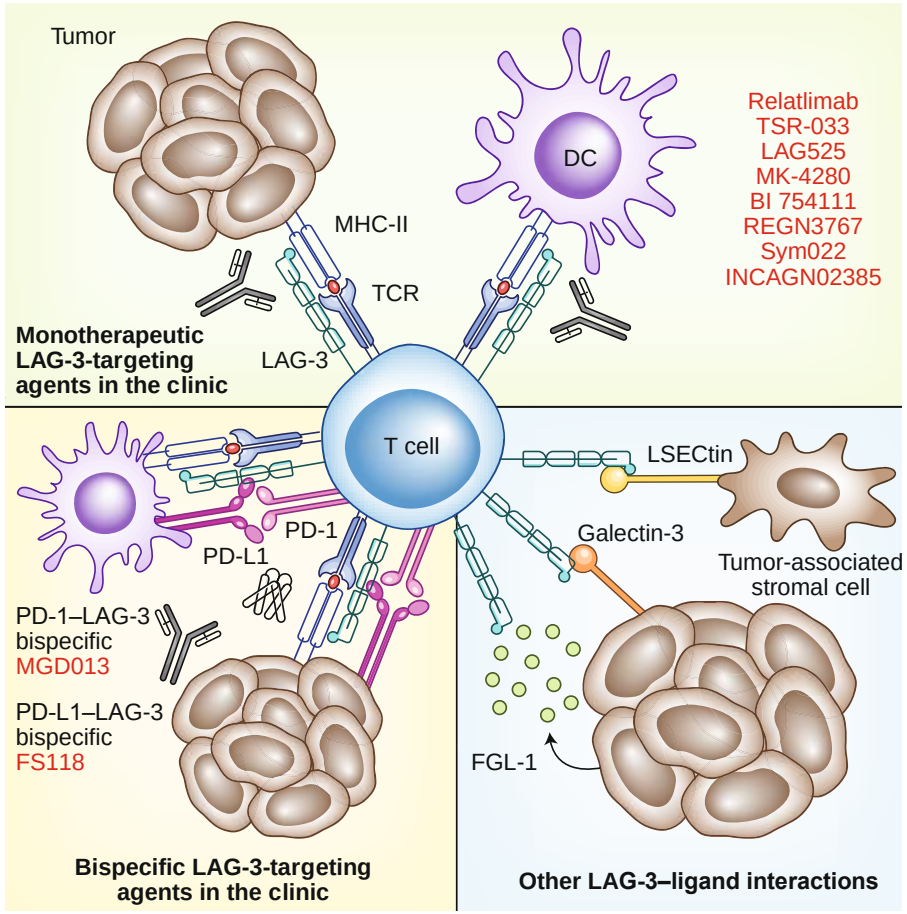




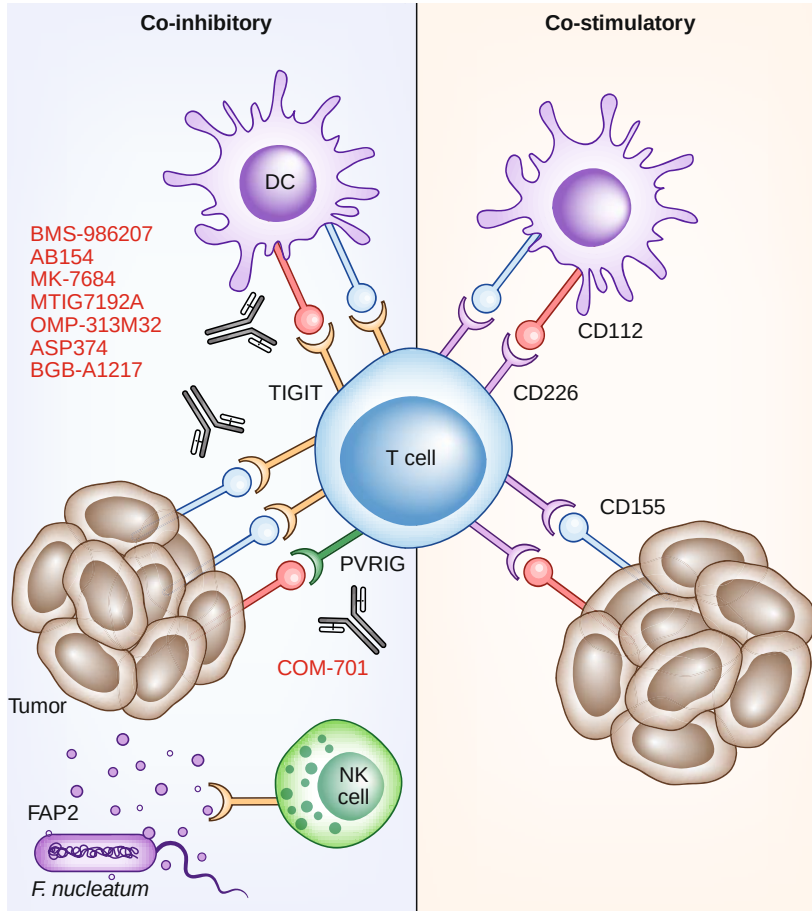
Nature Reviews Cancer, Blank et al, 2019



TIM-3



LAG-3



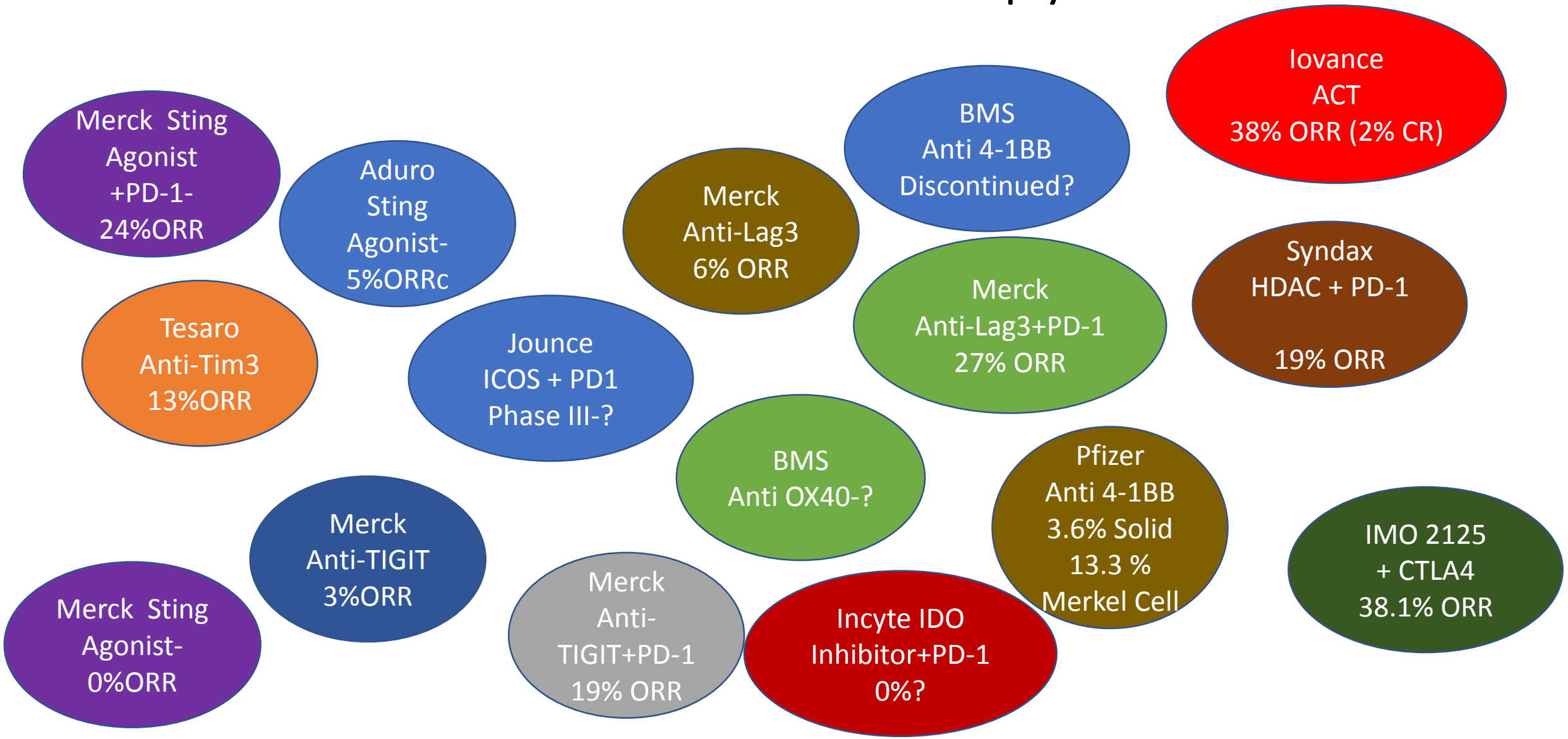
TIGIT

nature immunology
REVIEW ARTICLE
https://doi.org/10.1038/s41590-019-0512-0

Inhibitory receptors and ligands beyond PD-1, PD-L1 and CTLA-4: breakthroughs or backups

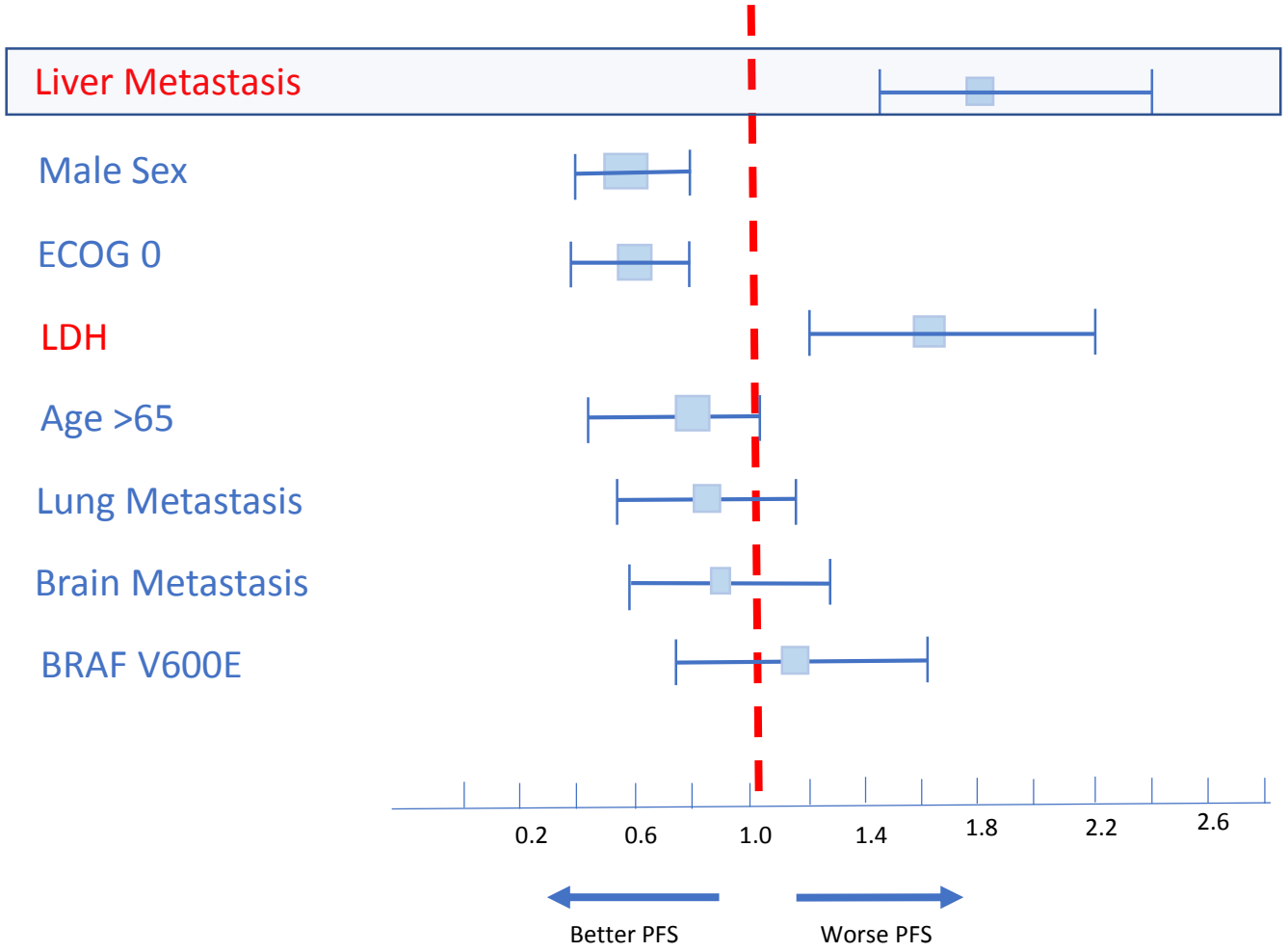
Lawrence P. Andrews[1], Hiroshi Yano[1,2] and Dario A. A. Vignali[1,3*]

What's Next for Immunotherapy??

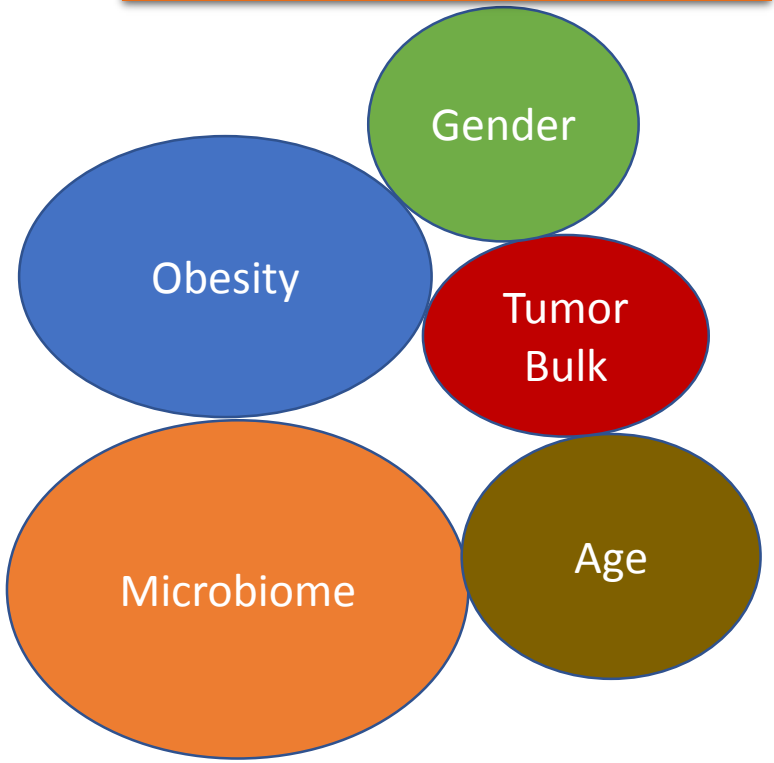


Liver Metastasis and Treatment Outcome with Anti-PD-1 in Patients with Melanoma and NSCLC

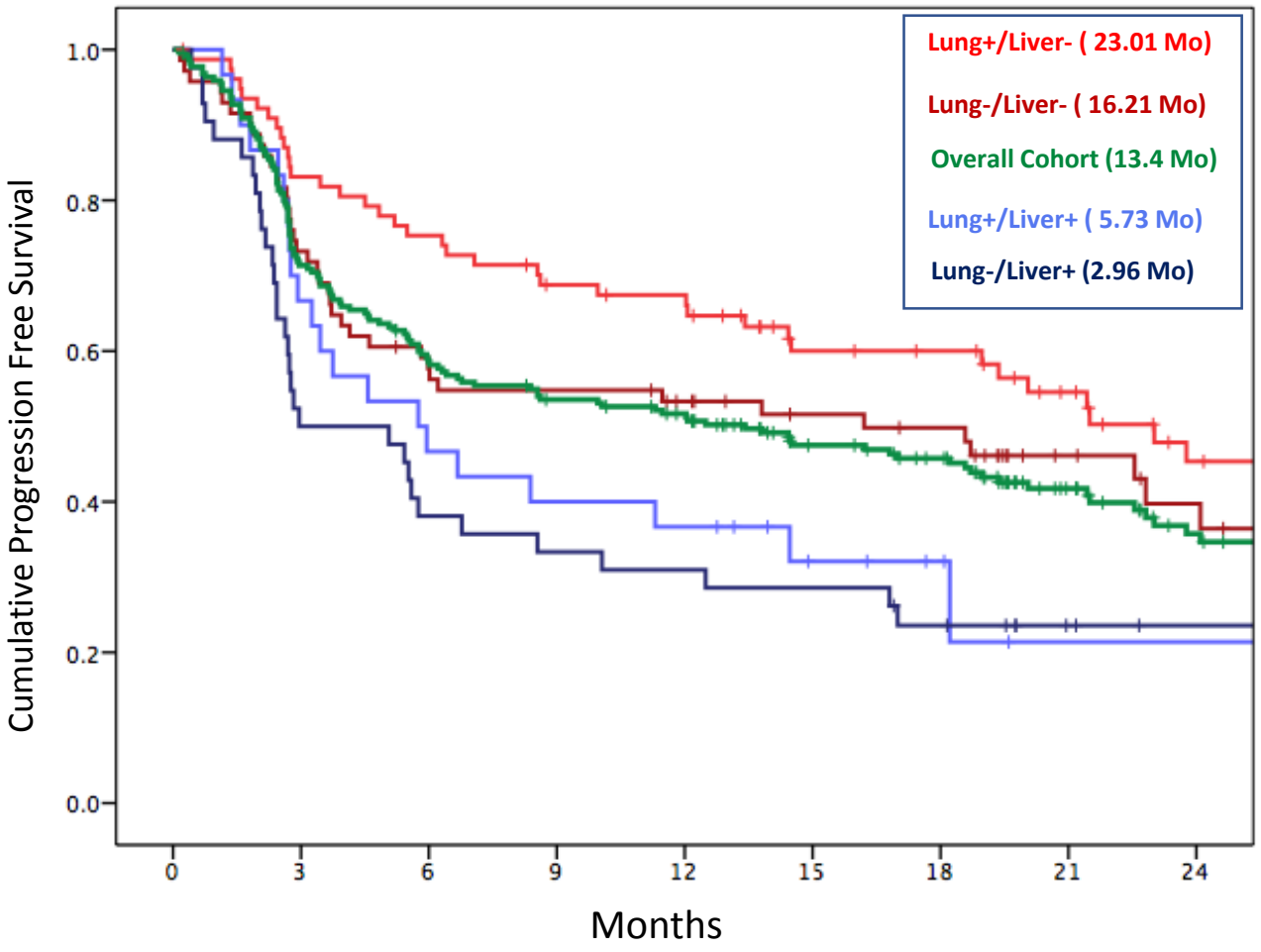
Paul C. Tumeh[1], Matthew D. Hellmann[2], Omid Hamid[3], Katy K. Tsai[4], Kimberly L. Loo[4], Matthew A. Gubens[4], Michael Rosenblum[4], Christina L. Harview[1], Janis M. Taube[5], Nathan Handley[4], Neharika Khurana[4], Adi Nosrati[4], Matthew F. Krummel[4], Andrew Tucker[1], Eduardo V. Sosa[4], Phillip J. Sanchez[1], Nooriel Banayan[1], Juan C. Osorio[2], Dan L. Nguyen-Kim[5], Jeremy Chang[1], I. Peter Shintaku[1], Peter D. Boasberg[3], Emma J. Taylor[1], Pamela N. Munster[4], Alain P. Algazi[4], Bartosz Chmielowski[1], Reinhard Dummer[5], Tristan R. Grogan[1], David Elashoff[1], Jimmy Hwang[4], Simone M. Goldinger[6], Edward B. Garon[1], Robert H. Pierce[7], and Adil Daud[4]

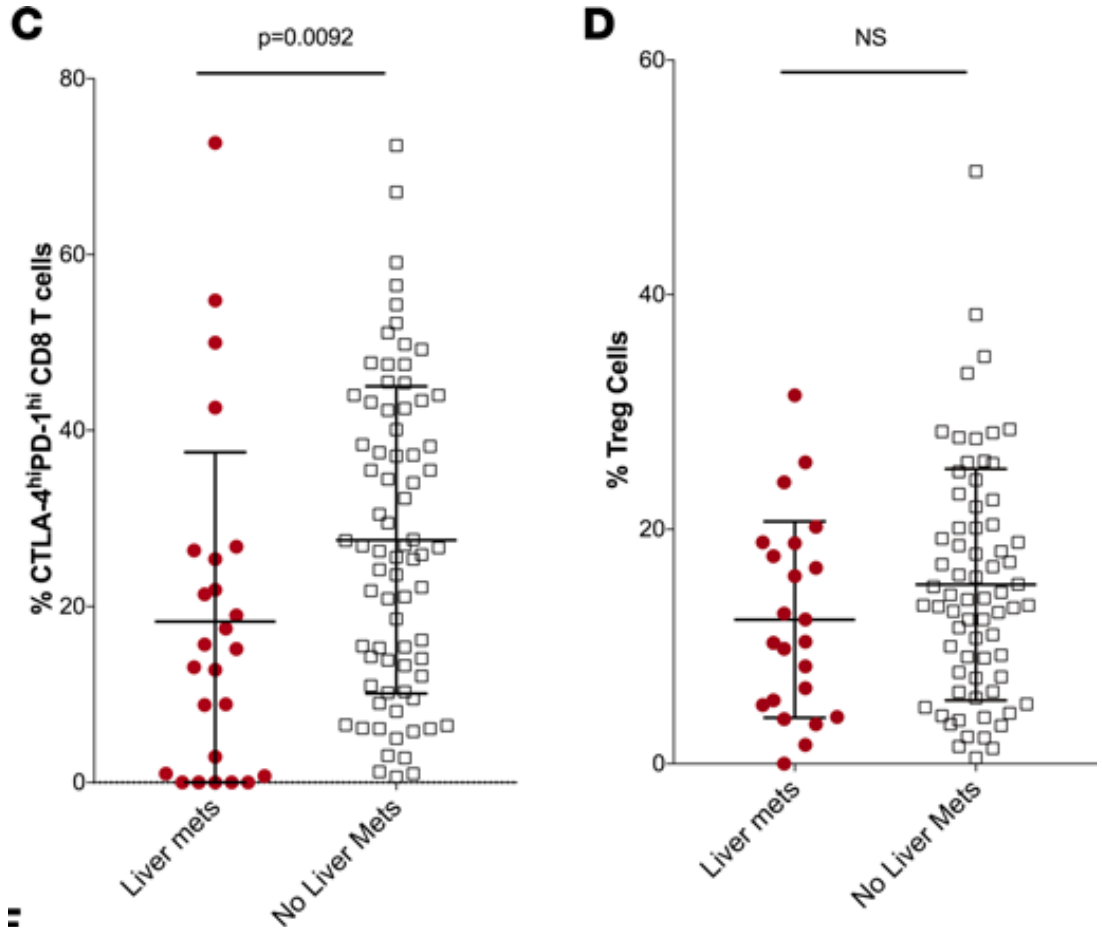


Tumor Extrinsic Factors known to affect PD-1



Cancer Immunology Research

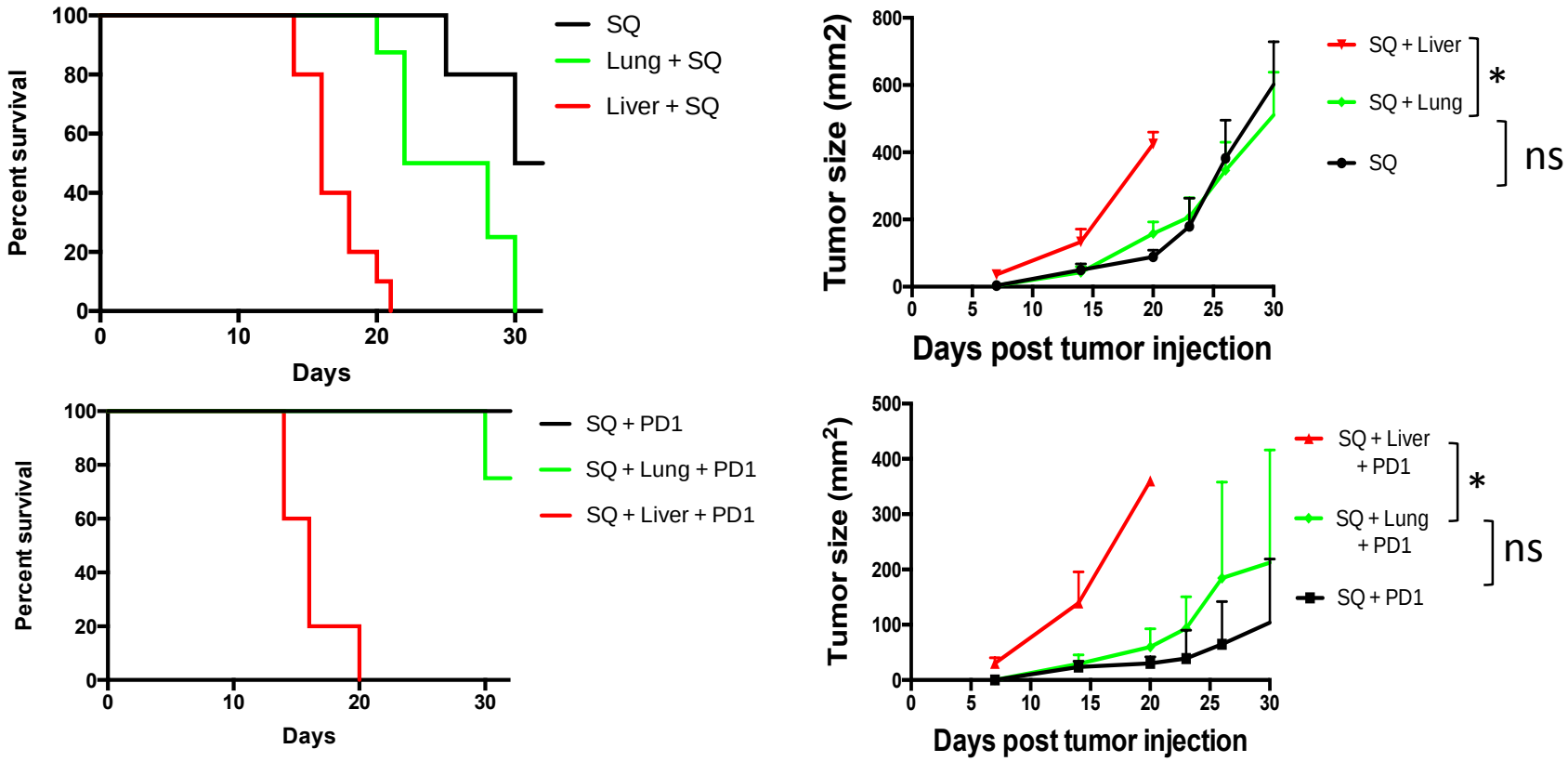




Partially exhausted tumor-infiltrating lymphocytes predict response to combination immunotherapy

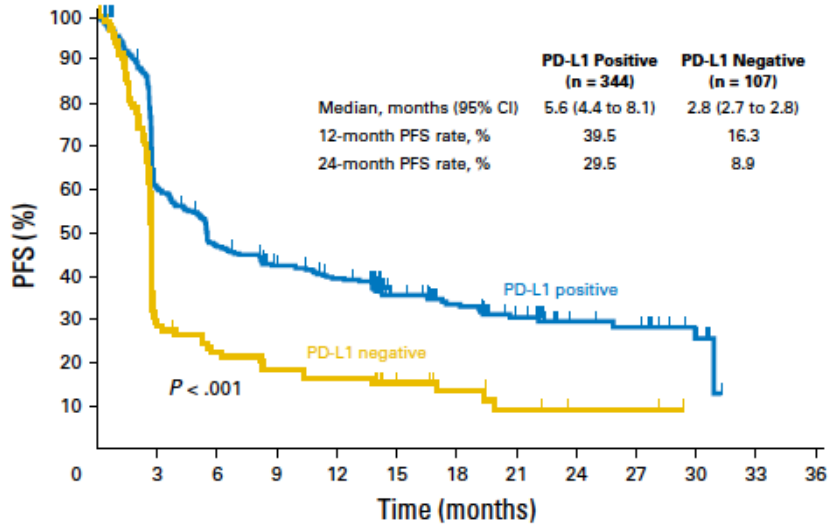
Kimberly Loo,[1] Katy K. Tsai,[1] Kelly Mahuron,[2] Jacqueline Liu,[1] Mariela L. Pauli,[3] Priscila M. Sandoval,[3] Adi Nosrati,[1] James Lee,[1] Lawrence Chen,[1] Jimmy Hwang,[5] Lauren S. Levine,[1] Matthew F. Krummel,[4] Alain P. Algazi,[1] Michael D Alvarado,[2] Michael D. Rosenblum,[3] and Adil I. Daud[1,3]

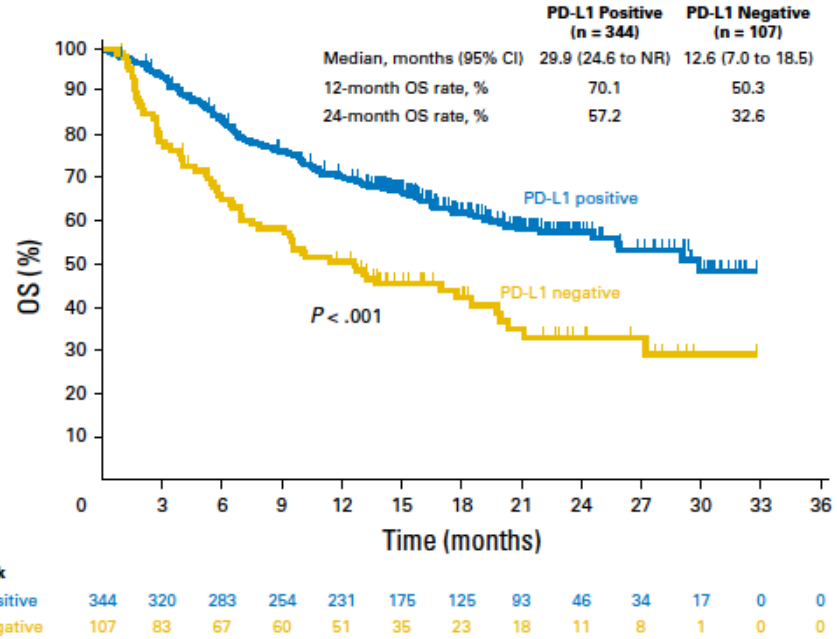
Experimental liver metastasis suppresses immunity against distant subcutaneous tumor.

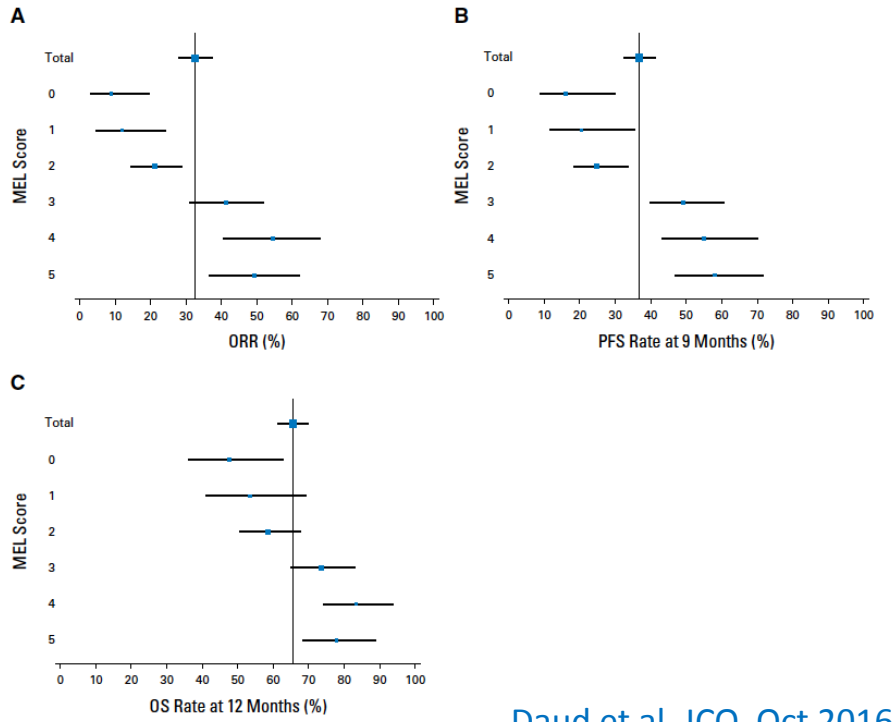


(A) C57BL/6 mice were each injected subcutaneously (SQ) with 5.0 x 10^5 MC38 tumor cells with or without experimental liver (via intrahepatic injection) or lung metastasis (via tail vein injection) established as described in *methods*. Kaplan Meier curves of percent mice survival are shown (mice with BCS < 2 or with tumor size > 2cm were sacrificed). **(B)** Kaplan Meier curves of mice with experimental liver metastasis, lung metastasis, or only subcutaneous tumor. **(C)** Seven days later, mice were intraperitoneally injected with 4 doses of anti-PD-1 mAb (100ug per dose, clone RMP 1-14), every other day. **(D)** Tumor growth curve of mice with experimental liver and lung metastasis treated with anti-PD-1 mAb.

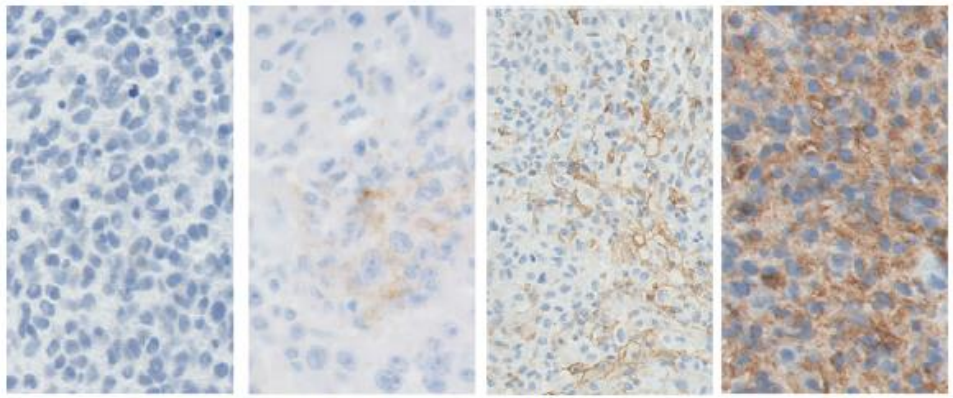
James Lee MD PhD and Jeff Bluestone PhD







Daud et al, JCO, Oct 2016

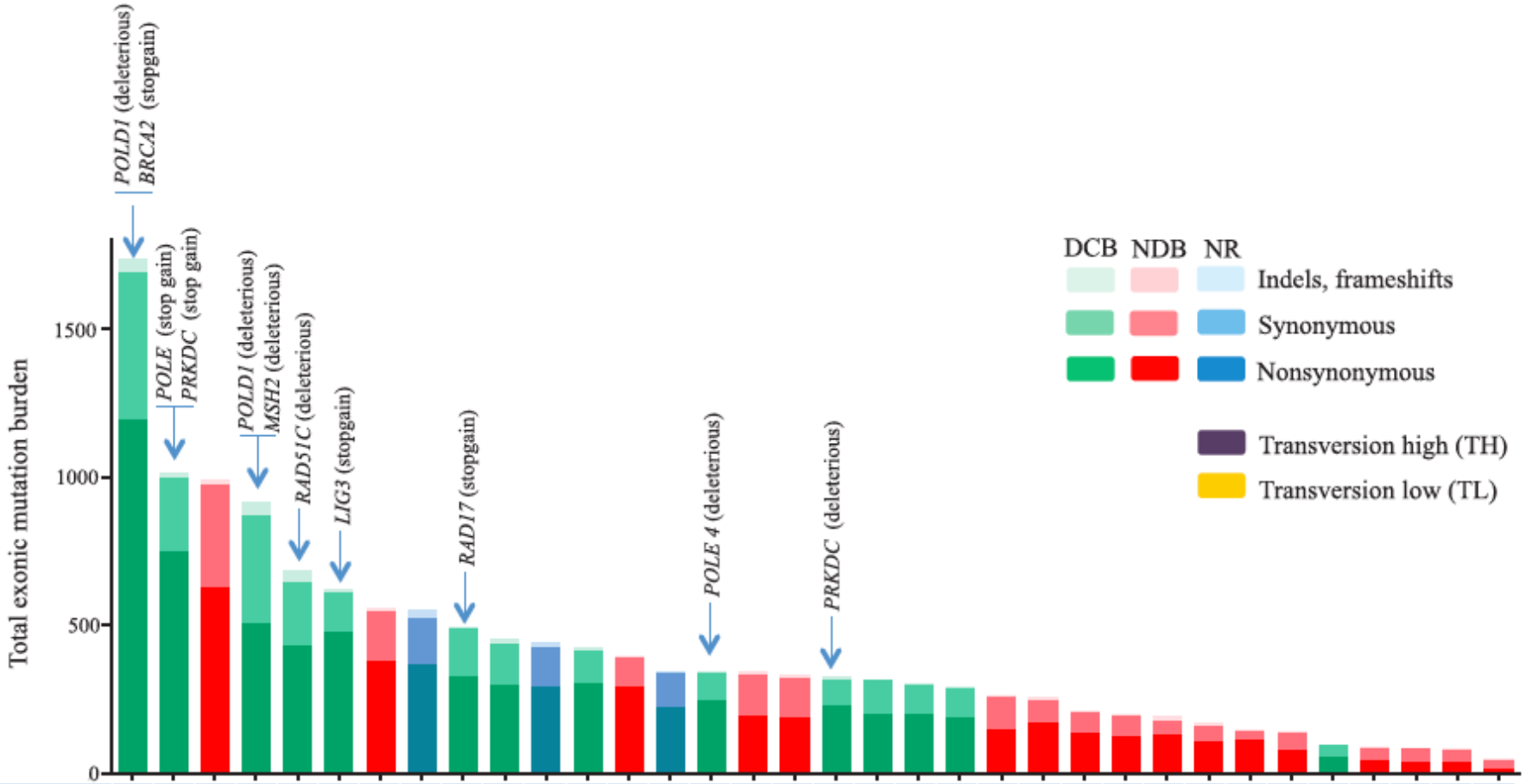


PD-L1 Negative
0% staining
MEL score, 0

PD-L1 Positive
1%-9% staining
MEL score, 2

PD-L1 Positive
10%-32% staining
MEL score, 3

PD-L1 Positive
66%-100% staining
MEL score, 5

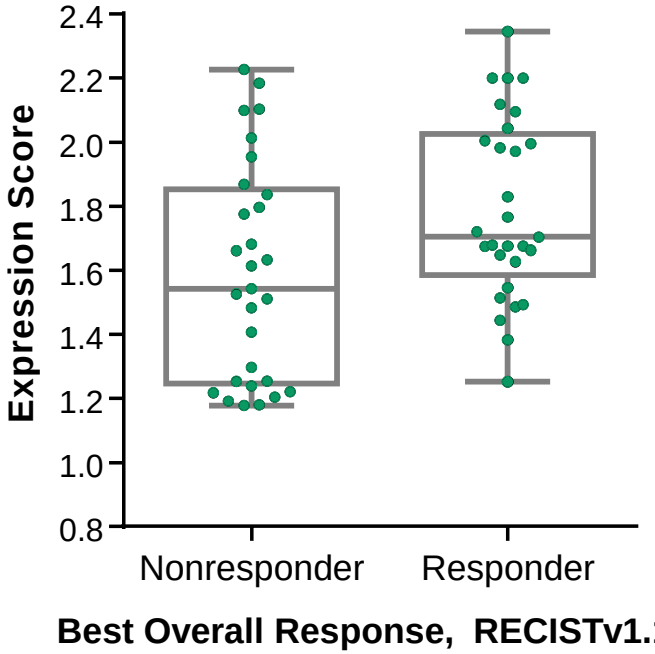


Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
Cohort	V	D	D	V	V	D	V	V	D	D	V	D	D	V	V	V	D	D	V	V	D	D	D	V	V	V	D	V	V	V	D	V	D	D
Objective Response	PR	PR	PD	SD	PR	PR	PD	SD	PR	PR	PR	SD	PD	PR	SD	PD	PD	PR	PR	PR	SD	SD	PD	PD	PD	PD	PD	SD	SD	PR	SD	PD	PD	SD
PFS (months)	8	14	2	8	14	16	2	4	15	13	4	8	2	4	8	3	3	10	27	10	8	7	2	2	1	2	2	4	6	8	4	2	2	6
Ongoing response	++	++			++	++		++		++	++			++	++			++	++	++														
Smoking signature	TH	TH	TH	TL	TH	TH	TL	TH	TH	TH	TH	TH	TH	TH	TH	TL	TL	TH	TL	TL	TH	TL	TH	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL

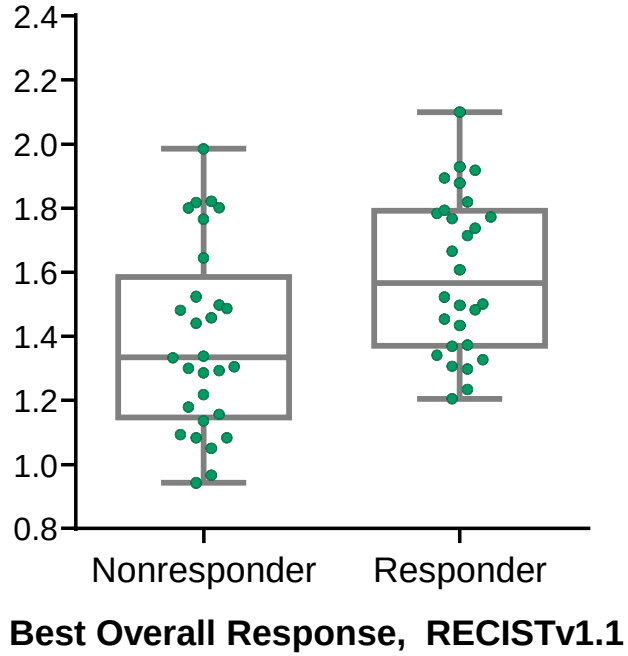
Rizvi et al, Science 2015

IFNγ and Expanded Immune Signatures Correlate With Response to Pembrolizumab in Melanoma

Preliminary IFNγ (10 gene)



Preliminary Expanded Immune (28 gene)



Correlation With Response in the Validation Set[a]

Signature	BOR by RECIST N = 51	PFS by RECIST N = 62	OS N = 62
Preliminary IFNγ	*P* = 0.047	*P* = 0.016	*P* = 0.090
Preliminary expanded immune	*P* = 0.027	*P* = 0.015	*P* = 0.105

[a]Development of the expanded immune signature was performed in an unsupervised manner by individuals blinded to response data.
Nominal one-sided *P* value from logistic regression (for best overall response per RECIST v1.1) or Cox regression (for PFS and OS).

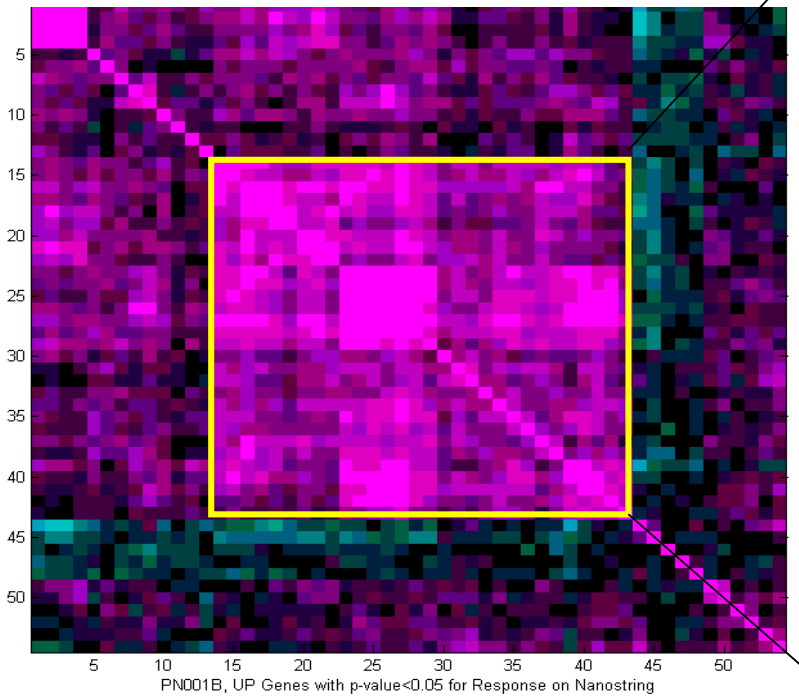
IFNγ Signature validated with clinical outcome

Melanoma Discovery Set

19 Patients

Melanoma Validation Set

62 Patients Independent Data Set



Correlation Matrix of Top Significant Genes in the Discovery Set Evaluated in the Validation Set

IFNγ Signature

IL2Rg
CXCR6
CD3d
CD2
ITGAL
TAGAP
CIITA
HLA-DRA
PTPRC
CXCL9
CCL5
NKG7
GZMA
PRF1
CCR5
CD3e
GZMK
IFNγ
HLA-E
GZMB
PDCD1
SLAMF6
CXCL13
CXCL10
IDO1
LAG3
STAT1
CXCL11

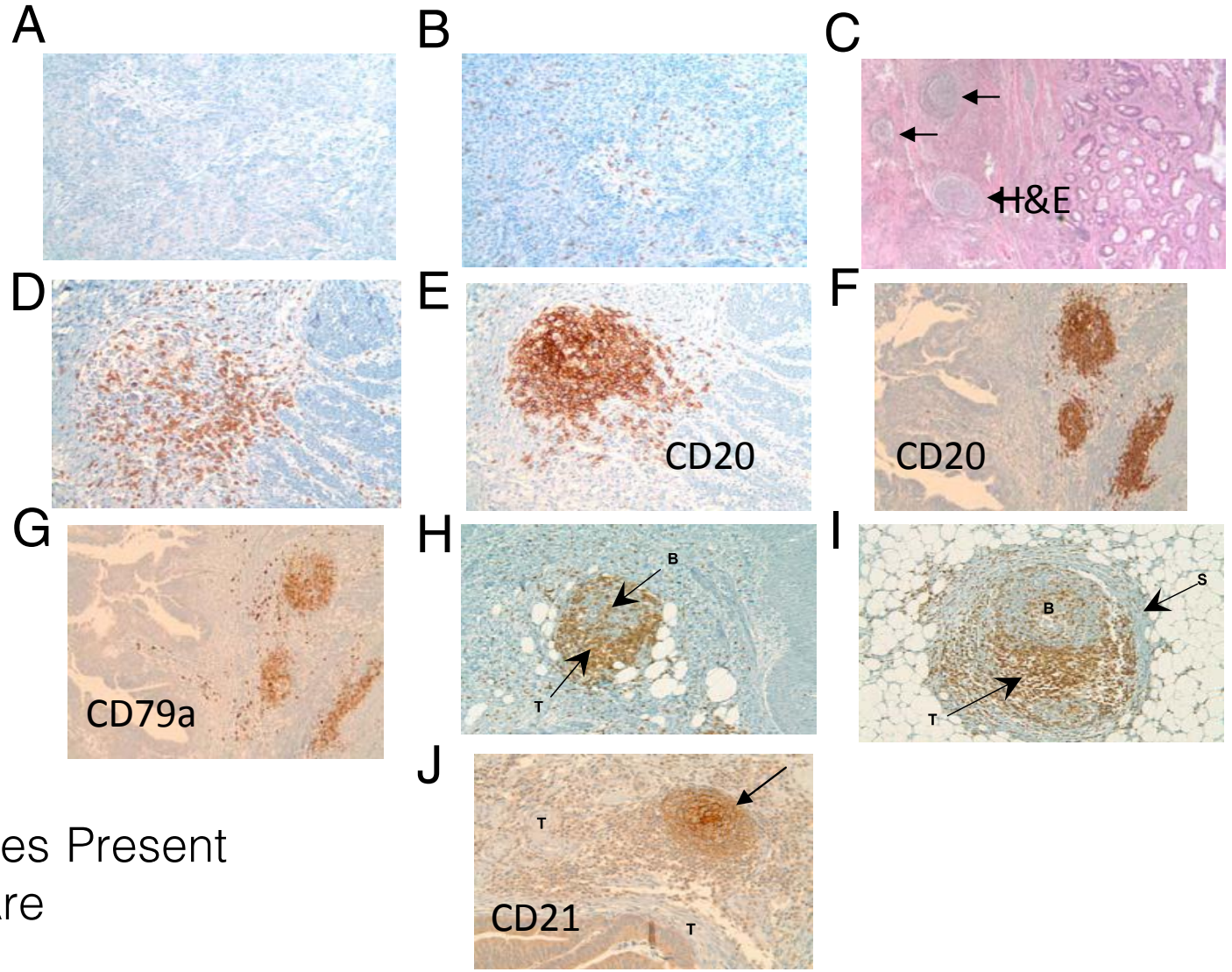
CCL2
CCL3
CCL4
CCL5
CCL8
CCL18
CCL19
CXCL9
CXCL10
CXCL11
CXCL13

IFNγ Signature or Tertiary Lymphoid Structure Signature?

CCL2
CCL3
CCL4
CCL5
CCL8
CCL18
CCL19
CXCL9
CXCL10
CXCL11
CXCL13

Domenico Coppola,* Michael Nebozhyn,† Farah Khalil,* Hongyue Dai,† Timothy Yeatman,‡ Andrey Loboda,† and James J. Mulé§

From the Anatomic Pathology Division, the Gastrointestinal Oncology Program,‡ and the Cutaneous Oncology Program,§ Moffitt Cancer Center, Tampa, Florida; and Oncology Molecular Profiling,† Merck Research Laboratories, West Point, Pennsylvania*



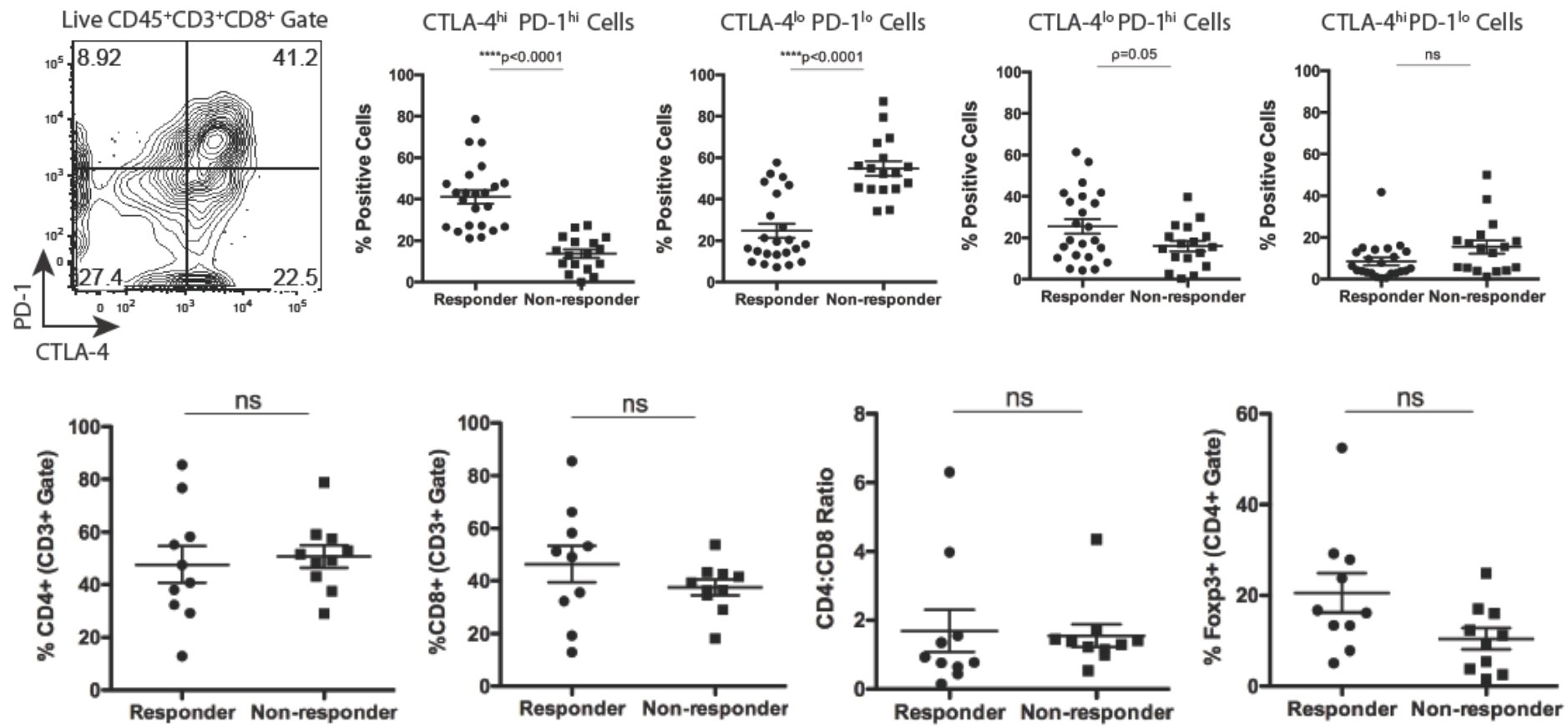
Unique Ectopic Lymph Node-Like Structures Present in Human Primary Colorectal Carcinoma Are Identified by Immune Gene Array Profiling

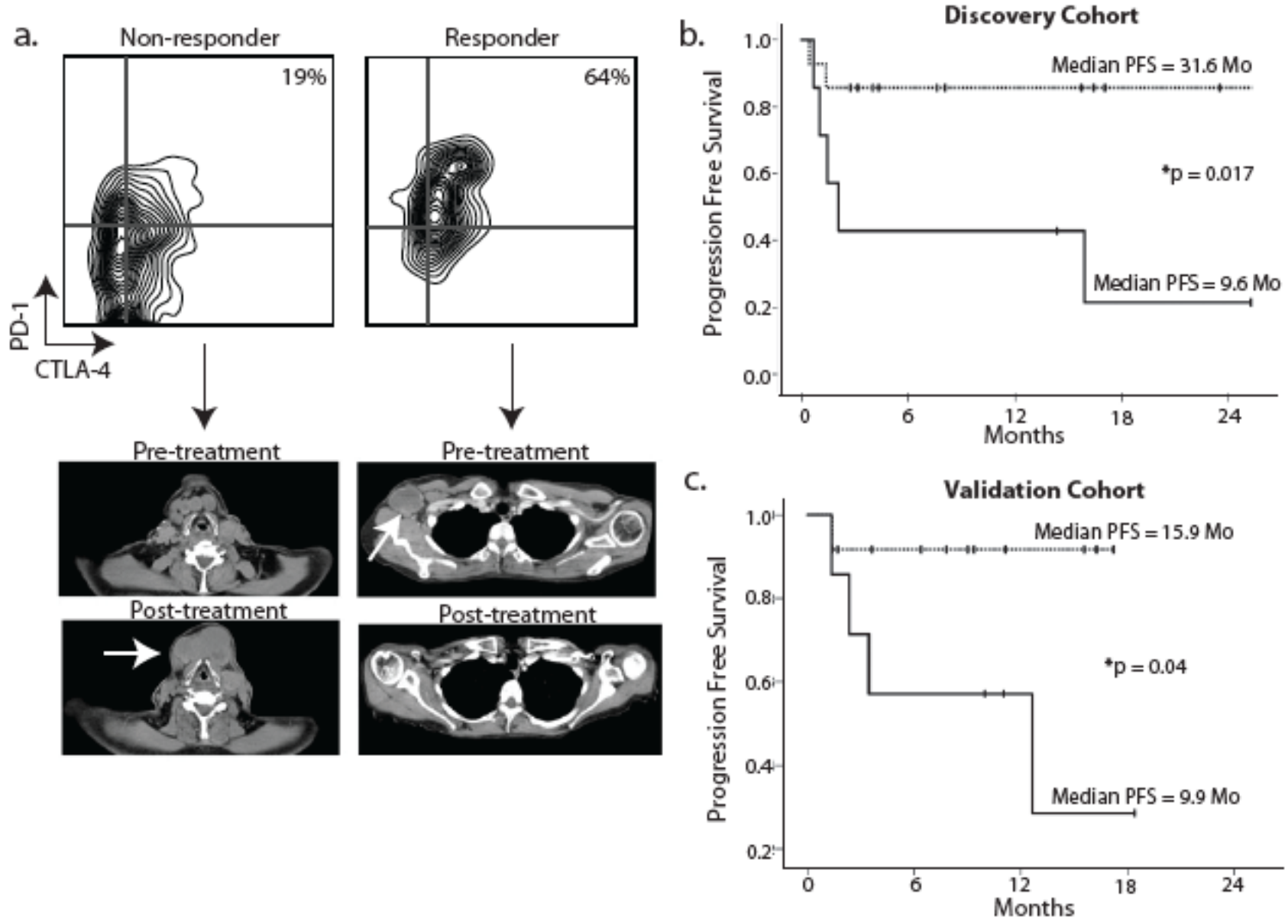
The Journal of Clinical Investigation CLINICAL MEDICINE

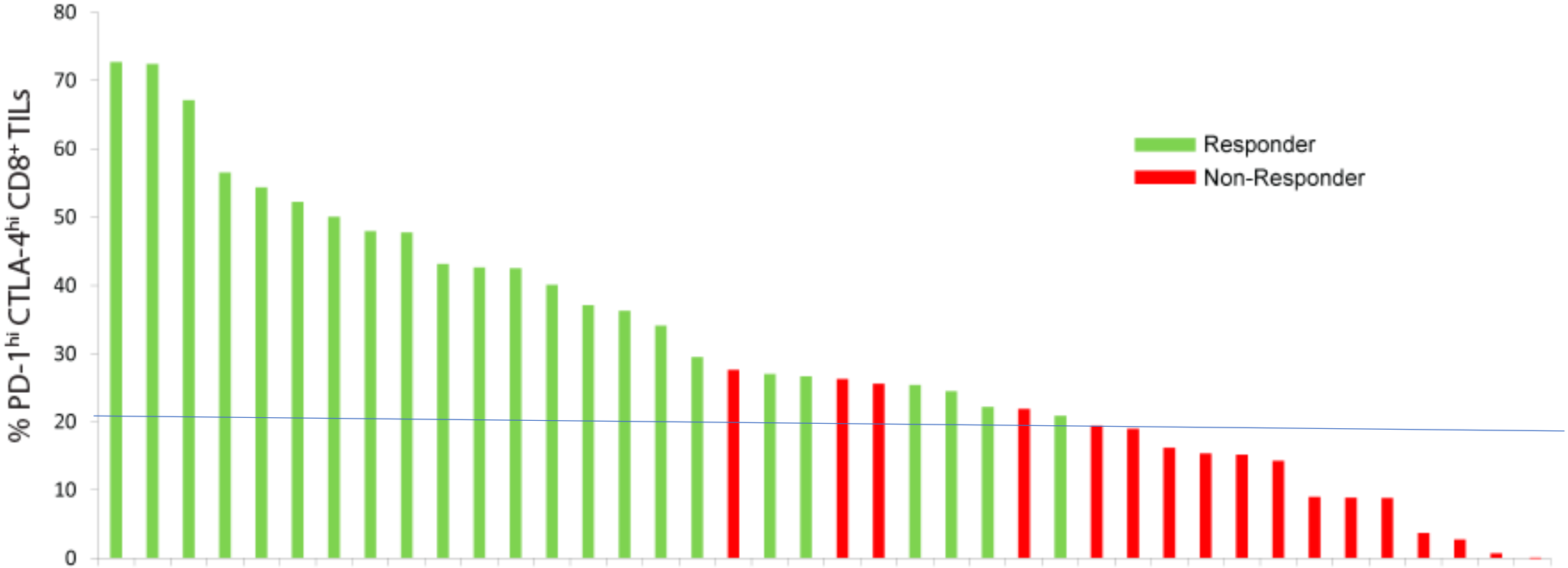
Tumor immune profiling predicts response to anti–PD-1 therapy in human melanoma

Adil I. Daud,[1] Kimberly Loo,[1] Mariela L. Pauli,[2] Robert Sanchez-Rodriguez,[2] Priscila Munoz Sandoval,[2] Keyon Taravati,[2] Katy Tsai,[1] Adi Nosrati,[1] Lorenzo Nardo,[3] Michael D. Alvarado,[1] Alain P. Algazi,[1] Miguel H. Pampaloni,[4] Iryna V. Lobach,[1] Jimmy Hwang,[1] Robert H. Pierce,[5] Iris K. Gratz,[6] Matthew F. Krummel,[4] and Michael D. Rosenblum[2]

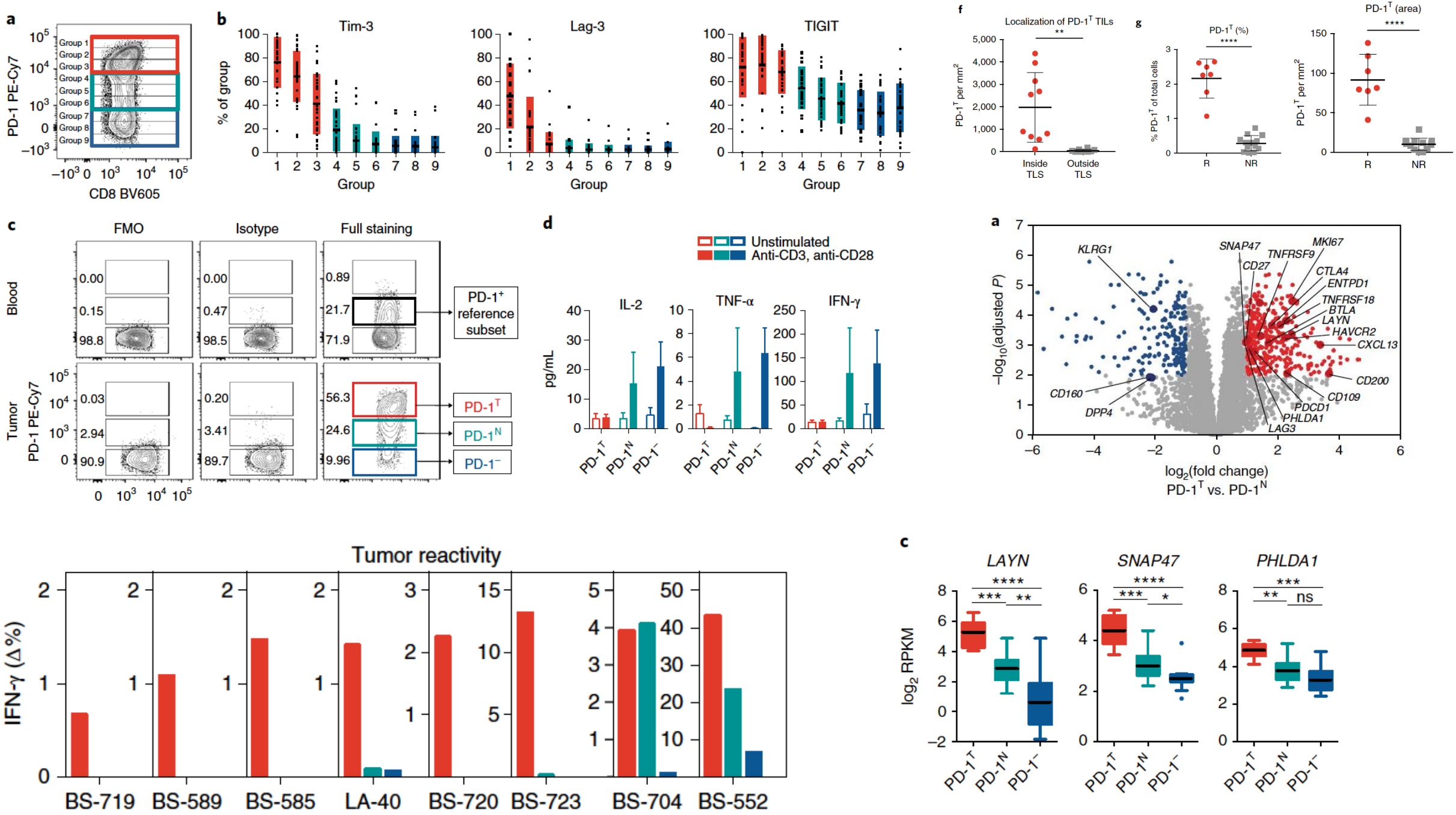
[1]Helen Diller Comprehensive Cancer Center, [2]Department of Dermatology, [3]Department of Radiology, and [4]Department of Pathology, UCSF, San Francisco, California, USA. [5]Oncosec Inc., San Diego, California, USA. [6]Department of Molecular Biology, University of Salzburg, Salzburg, Austria.




a.
Non-responder
Responder
19%
64%
PD-1
CTLA-4
Pre-treatment
Pre-treatment
Post-treatment
Post-treatment
b.
Discovery Cohort
Median PFS = 31.6 Mo
*p = 0.017
Median PFS = 9.6 Mo
Progression Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
6
12
18
24
Months
c.
Validation Cohort
Median PFS = 15.9 Mo
*p = 0.04
Median PFS = 9.9 Mo
Progression Free Survival
1.0
0.8
0.6
0.4
0.2
0
6
12
18
24
Months



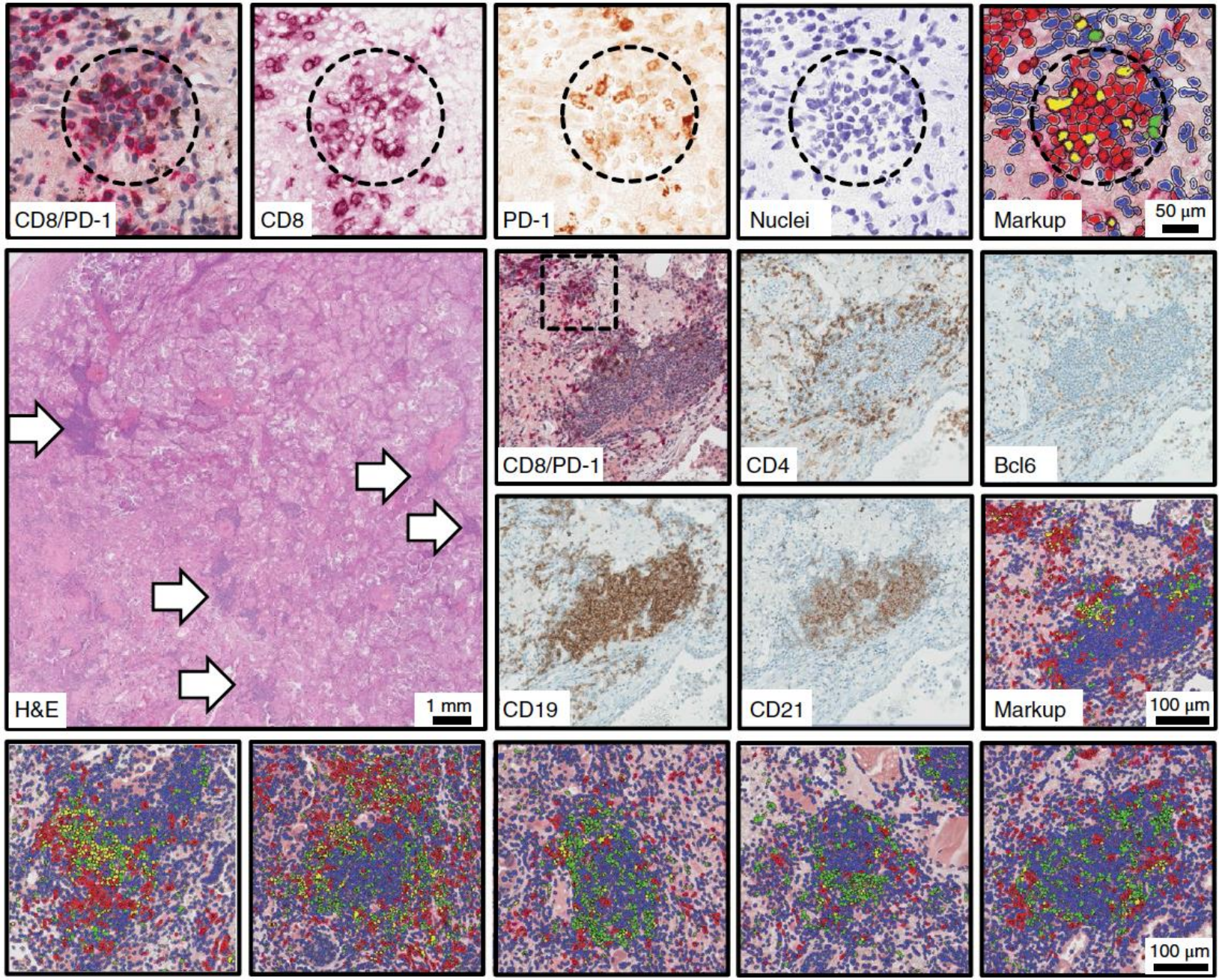
Subject	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Progression																					+	+				+		+	+	+		+			+	+				+
Death																					+	+				+			+		+	+			+	+				+
Liver Mets	+						+											+				+				+			+	+		+			+	+			+	
Elevated LDH	+						+		+	+		+				+		+			+					+						+		+	+	+			+	+
Prior Therapy		I	I		I				I	I/T		I			I/T	I/T	T	I/T	I	I	T		I	I		I	I/T	I	I/T	I		I/T	I	I/T		I	I/T		I	T

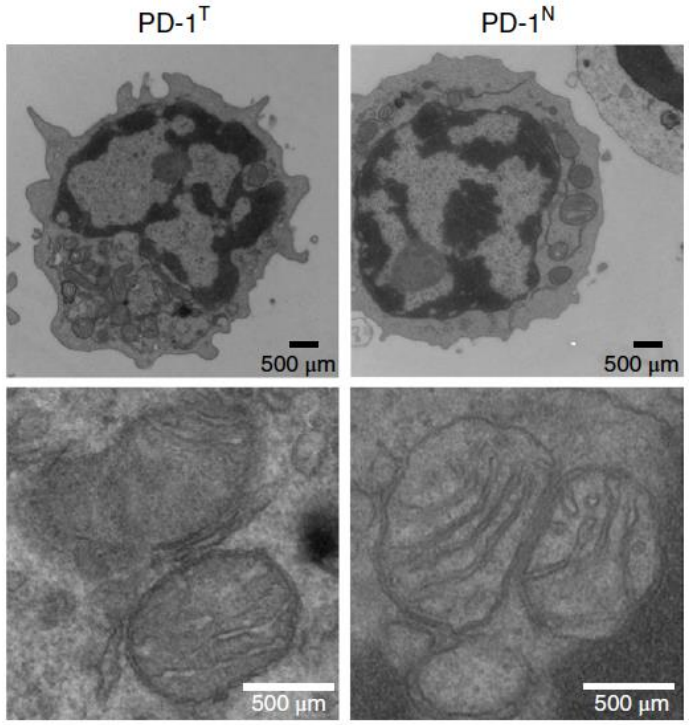

a
PD-1 PE-Cy7
CD8 BV605
Group 1
Group 2
Group 3
Group 4
Group 5
Group 6
Group 7
Group 8
Group 9
b
Tim-3
Lag-3
TIGIT
% of group
Group
f
Localization of PD-1T TILs
PD-1T per mm2
Inside TLS
Outside TLS
g
PD-1T (%)
% PD-1T of total cells
PD-1T (area)
PD-1T per mm2
R
NR
c
FMO
Isotype
Full staining
Blood
Tumor
PD-1+ reference subset
PD-1T
PD-1N
PD-1−
d
Unstimulated
Anti-CD3, anti-CD28
IL-2
TNF-α
IFN-γ
pg/mL
a
−log10(adjusted P)
log2(fold change)
PD-1T vs. PD-1N
KLRG1
SNAP47
MKI67
TNFRSF9
CD27
CTLA4
ENTPD1
TNFRSF18
BTLA
LAYN
HAVCR2
CXCL13
CD200
CD109
PDCD1
PHLDA1
LAG3
CD160
DPP4
Tumor reactivity
IFN-γ (Δ%)
BS-719
BS-589
BS-585
LA-40
BS-720
BS-723
BS-704
BS-552
c
LAYN
SNAP47
PHLDA1
log2 RPKM
ns

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-018-0057-z

A transcriptionally and functionally distinct PD-1^{+} CD8^{+} T cell pool with predictive potential in non-small-cell lung cancer treated with PD-1 blockade

Daniela S. Thommen[1,2*], Viktor H. Koelzer[3,4,13], Petra Herzig[1,13], Andreas Roller[5,13], Marcel Trefny[1], Sarah Dimeloe[6], Anna Kiialainen[5], Jonathan Hanhart[3], Catherine Schill[7], Christoph Hess[6], Spasenija Savic Prince[8], Mark Wiese[9], Didier Lardinois[9], Ping-Chih Ho[10], Christian Klein[11], Vaios Karanikas[11], Kirsten D. Mertz[3], Ton N. Schumacher[2,14] and Alfred Zippelius[1,12,14*]

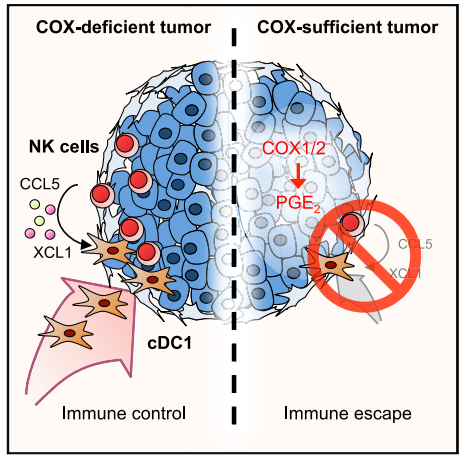




Cell

NK Cells Stimulate Recruitment of cDC1 into the Tumor Microenvironment Promoting Cancer Immune Control

Graphical Abstract



Authors

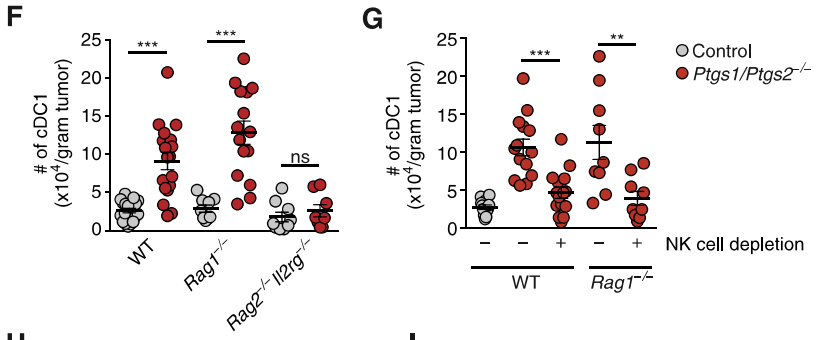
Jan P. Böttcher, Eduardo Bonavita, Probir Chakravarty, ..., Erik Sahai, Santiago Zelenay, Caetano Reis e Sousa

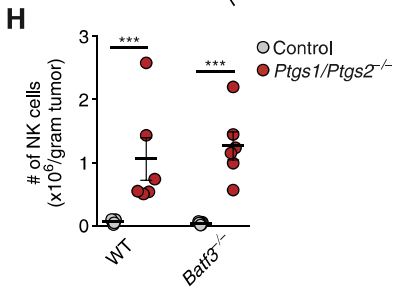
Correspondence

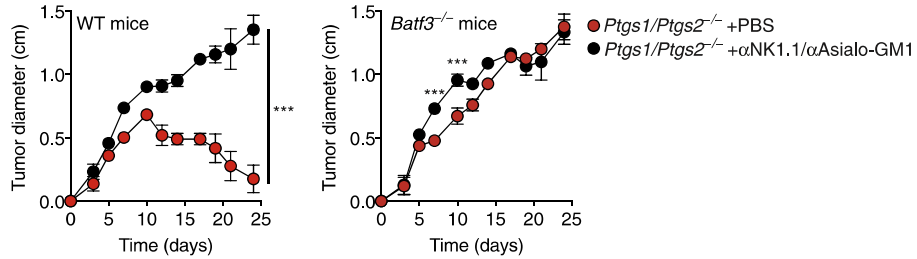
j.boettcher@tum.de (J.P.B.), caetano@crick.ac.uk (C.R.e.S.)

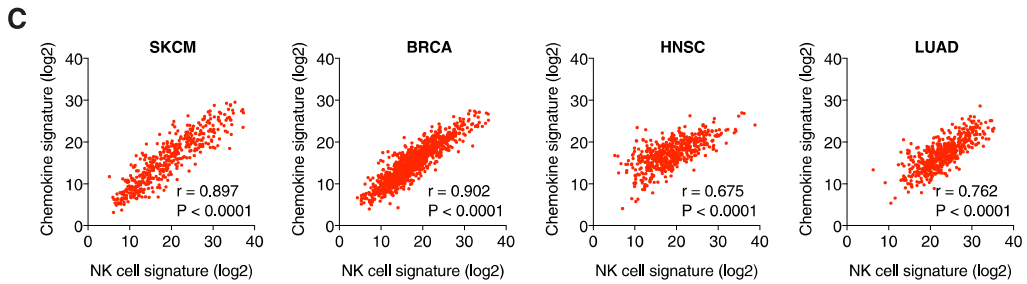
In Brief

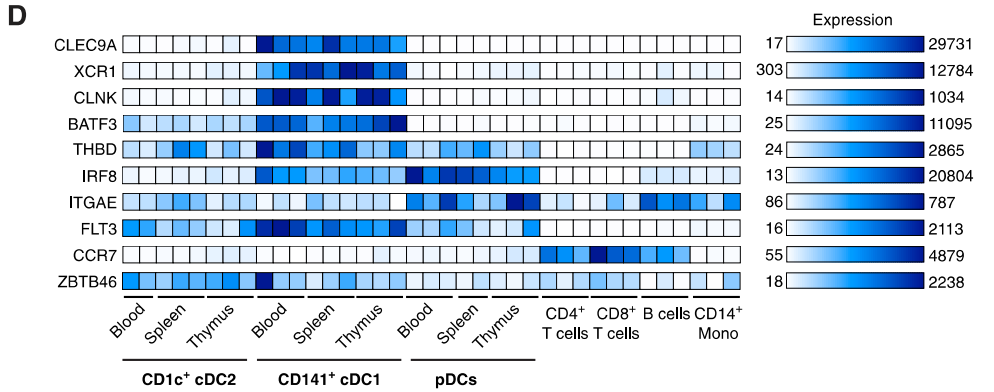
Natural killer cells recruit dendritic cells to the tumor microenvironment, and disruption of this process results in cancer immune evasion.

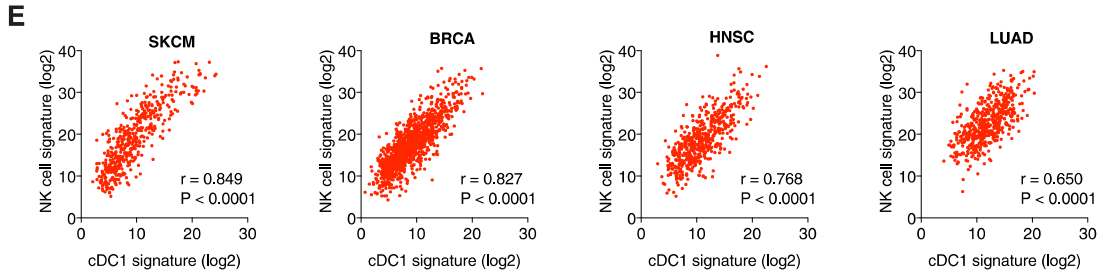


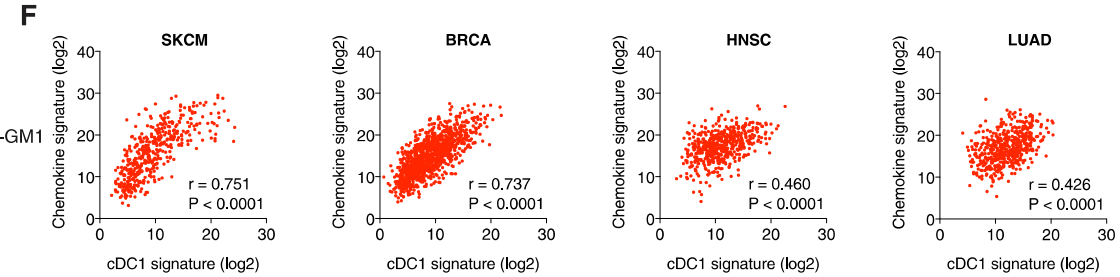


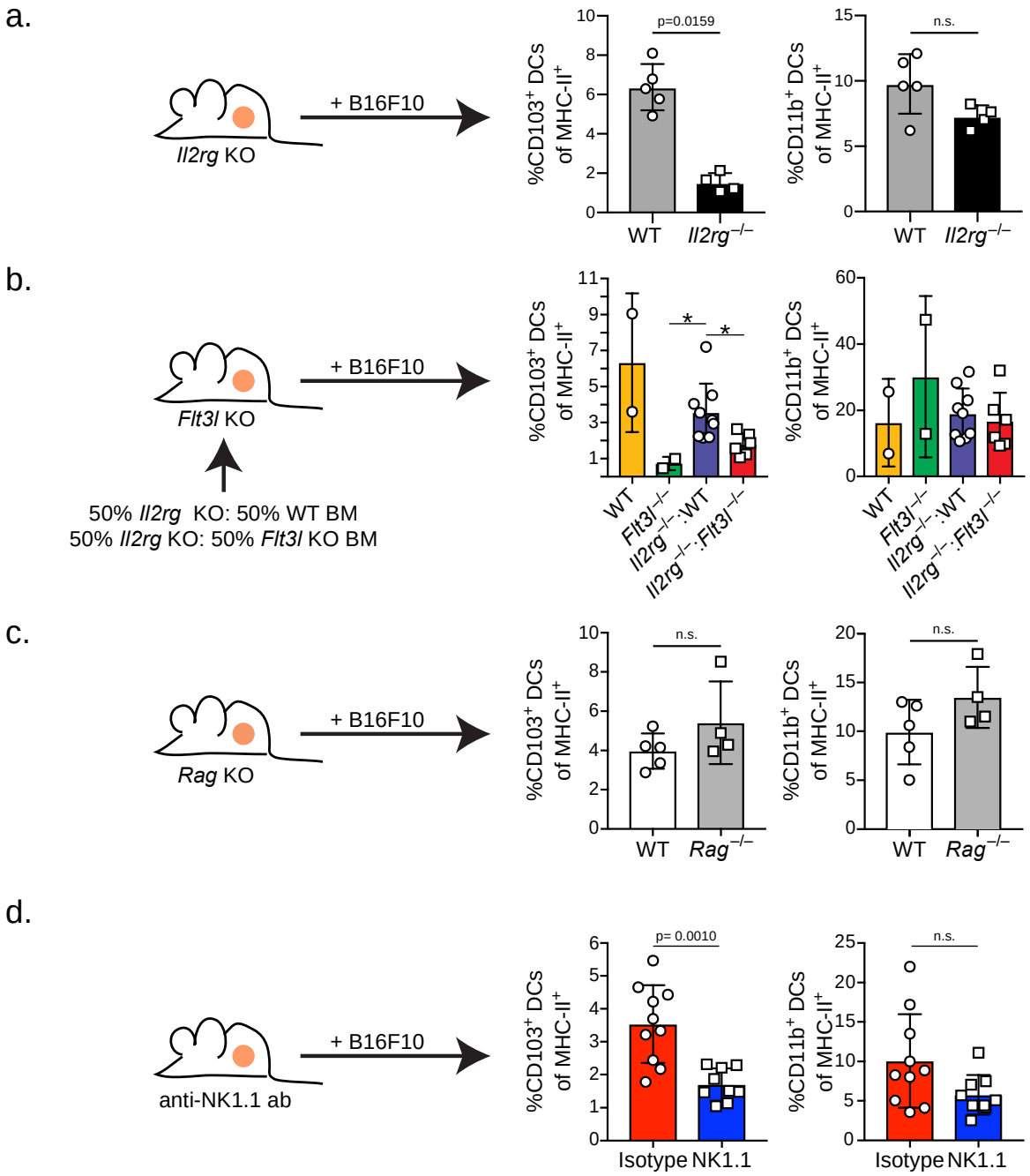


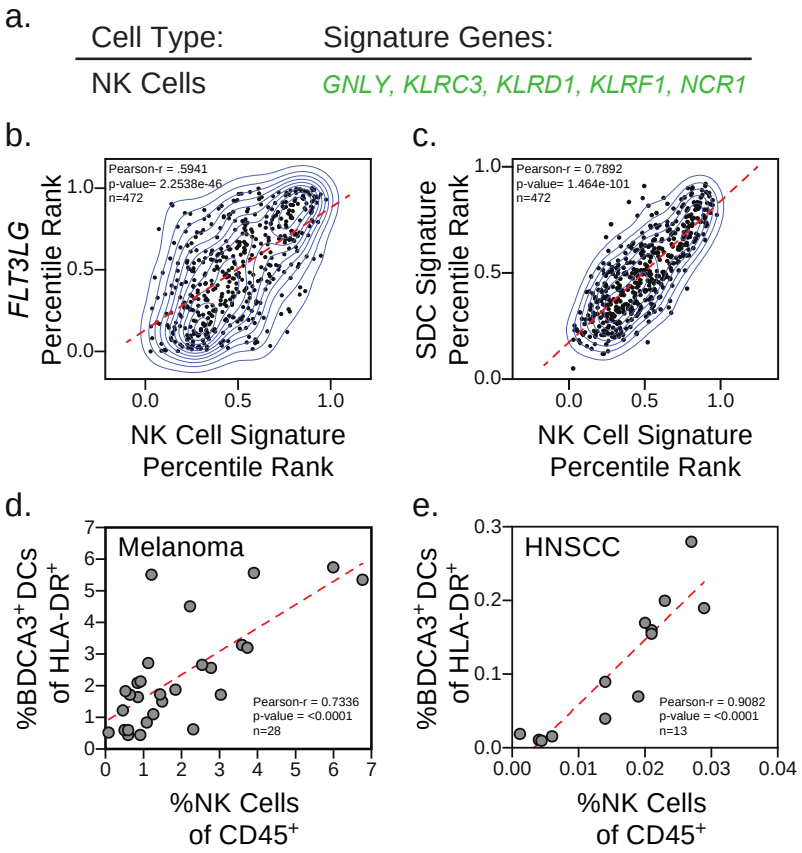












A natural killer–dendritic cell axis defines checkpoint therapy–responsive tumor microenvironments

Kevin C. Barry[1,2], Joy Hsu[1,2], Miranda L. Broz[1,2], Francisco J. Cueto[1,3,4], Mikhail Binnewies[1], Alexis J. Combes[1,2], Amanda E. Nelson[1,2], Kimberly Loo[2,5,6], Raj Kumar[1,2], Michael D. Rosenblum[6], Michael D. Alvarado[6], Denise M. Wolf[7], Dusan Bogunovic[8], Nina Bhardwaj[9], Adil I. Daud[6], Patrick K. Ha[10], William R. Ryan[10], Joshua L. Pollack[11], Bushra Samad[1,2], Saurabh Asthana[2], Vincent Chan[1,2] and Matthew F. Krummel[1,2*]

ARTICLE

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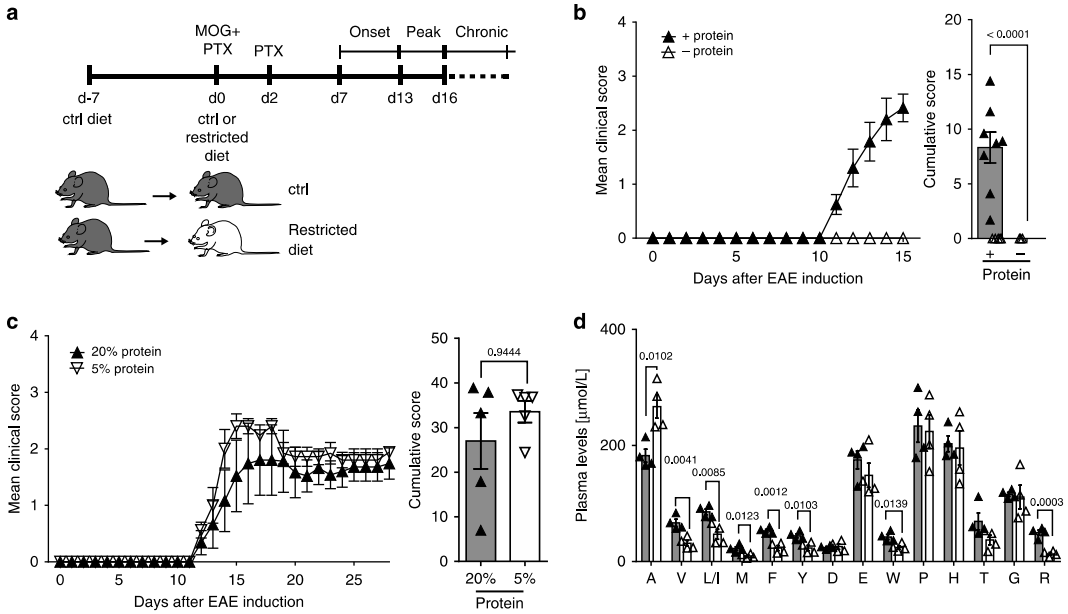
Dietary tryptophan links encephalogenicity of autoreactive T cells with gut microbial ecology

Jana K. Sonner[1,2,13,19], Melanie Keil[1,19], Maren Falk-Paulsen[3,19], Neha Mishra[3], Ateequr Rehman[3], Magdalena Kramer[1,2], Katrin Deumelandt[1,2,14], Julian Röwe[1], Khwab Sanghvi[1,2], Lara Wolf[1,2], Anna von Landenberg[1,2], Hendrik Wolff[4,21], Richa Bharti[3], Iris Oezen[1], Tobias V. Lanz[1,15], Florian Wanke[5,16], Yilang Tang[5,17], Ines Brandao[6], Soumya R. Mohapatra[7], Lisa Epping[8], Alexandra Grill[6], Ralph Röth[9], Beate Niesler[9], Sven G. Meuth[8], Christiane A. Opitz[7,10], Jürgen G. Okun[11], Christoph Reinhardt[6], Florian C. Kurschus[5,18], Wolfgang Wick[12], Helge B. Bode[4], Philip Rosenstiel[3,20] & Michael Platten[1,2,20*]



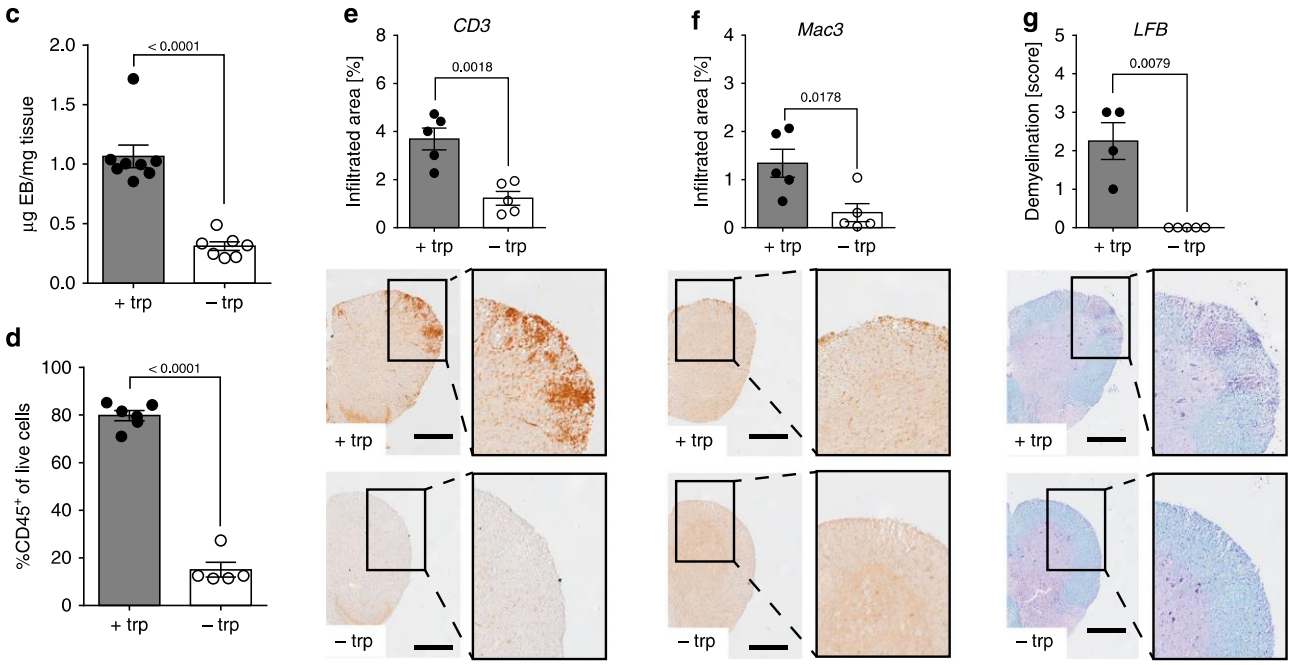
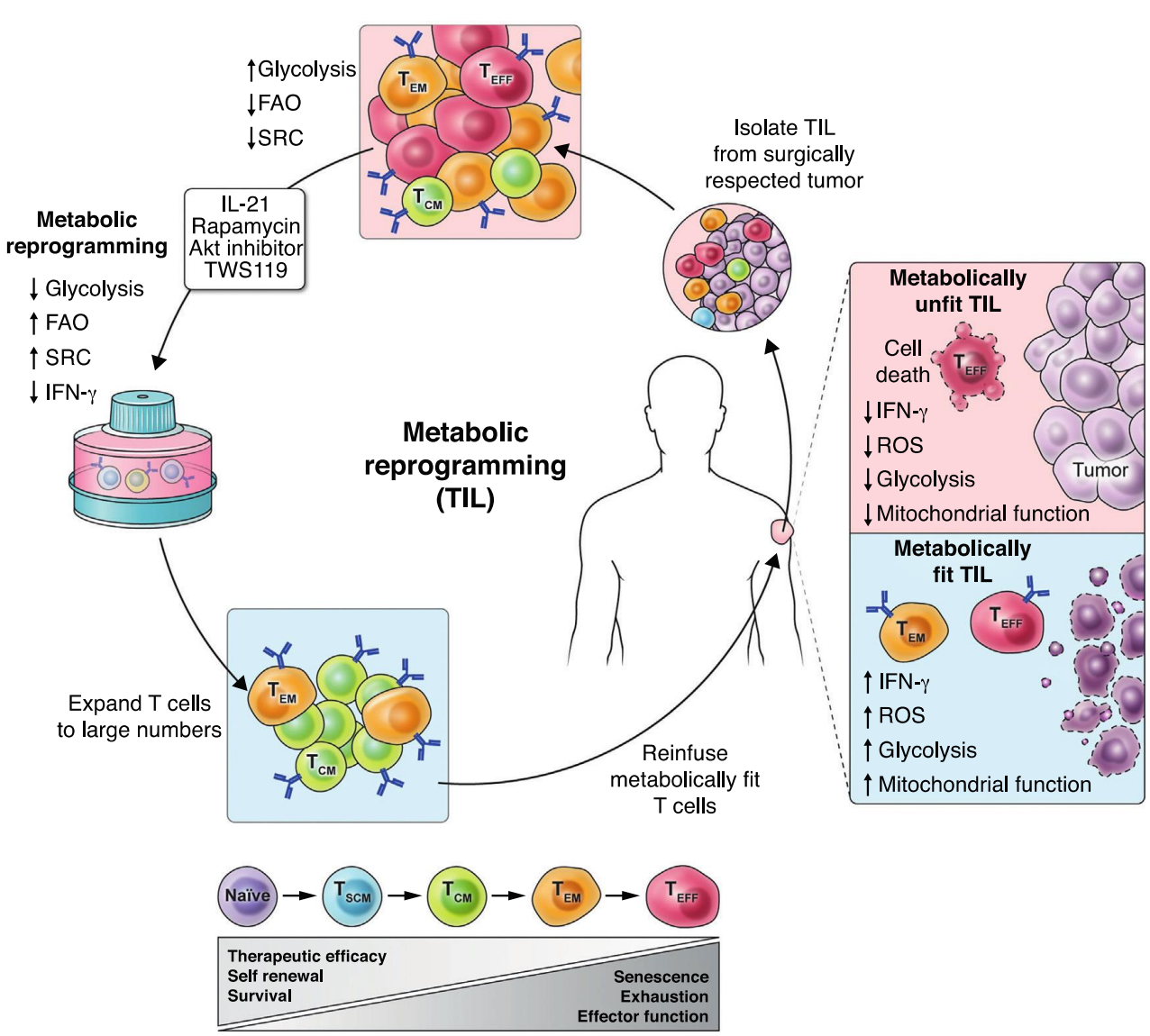
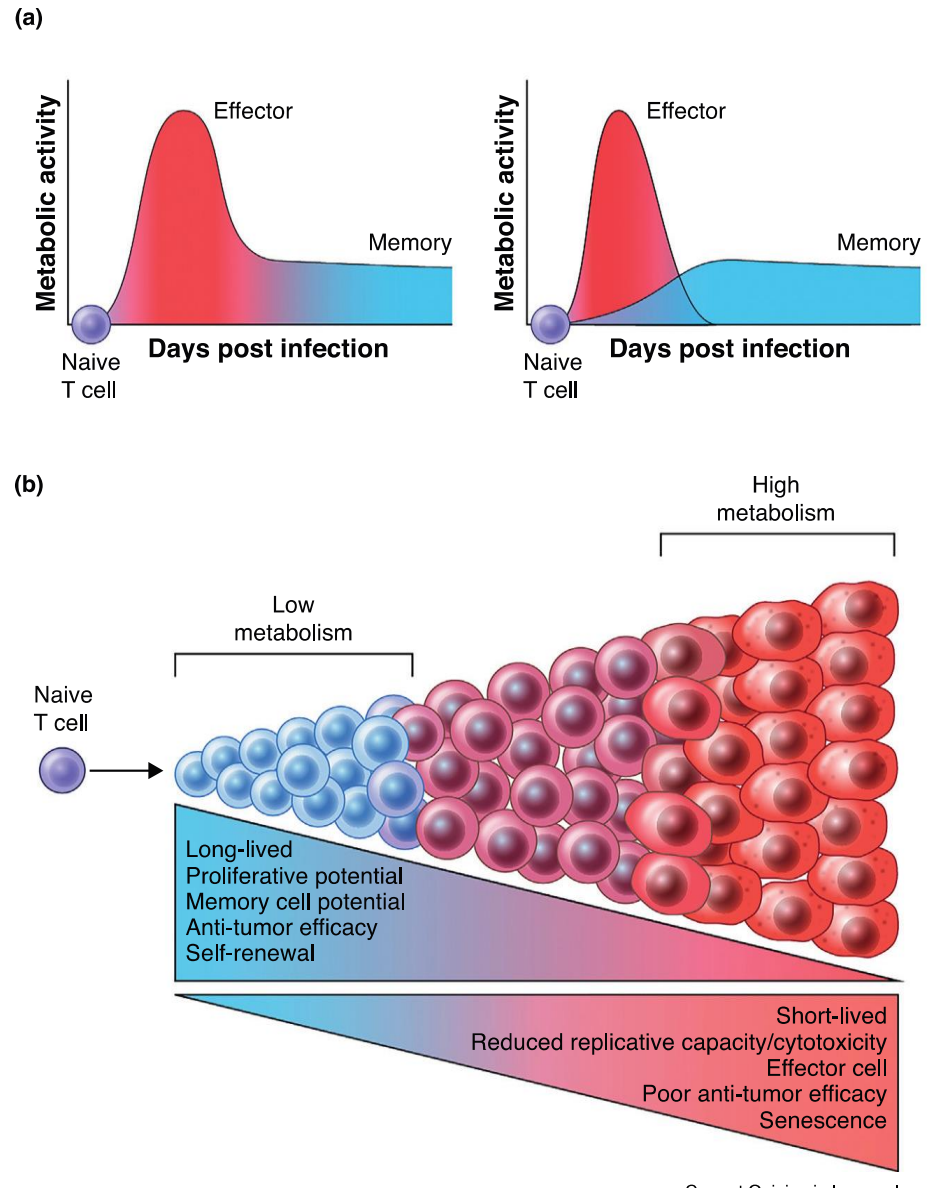


Fig. 2 DTR inhibits EAE. **a** Mean clinical EAE scores and cumulative scores (+trp: $n = 10$; −trp, $n = 10$). **b** Plasma amino acid concentrations 16 days post-immunization ($n = 6$). **c** Blood–brain barrier (BBB) disruption in spinal cord as assessed by Evan's Blue (EB) on d15 post-immunization (+trp: $n = 8$; −trp: $n = 7$). **d** Flow cytometric analysis of leukocyte infiltration into the spinal cord on d18 post-immunization (+trp: $n = 5$; −trp: $n = 6$). Displayed as $CD45^+$ cells of live single cells. **e–g** Spinal cord sections of EAE mice were stained for **e** T cells ($n = 5$ vs. $n = 5$), **f** macrophages ($n = 5$ vs. $n = 5$), and **g** demyelination ($n = 4$ vs. $n = 5$). Scale bars: 250 µm. Statistics: Mann–Whitney *U*-test for **a**, **g** unpaired two-tailed Student's *t*-test for **b–f**. Each dot represents one individual mouse. Data are presented as mean ± SEM. Source data are provided as a Source Data file

Metabolic reprograming of anti-tumor immunity

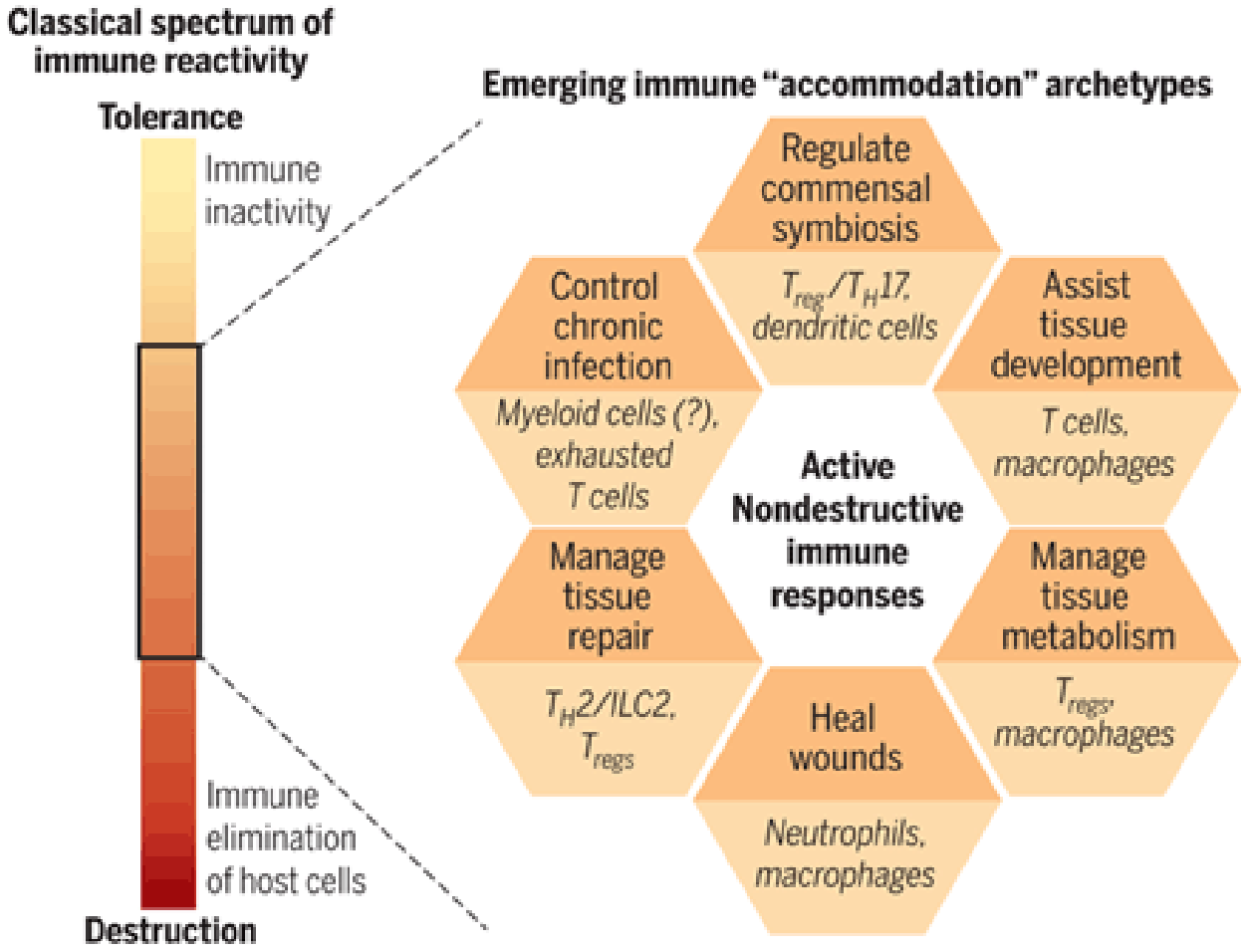
Madhusudhanan Sukumar[1,2], Rigel J Kishton[1,2] and Nicholas P Restifo[1,2]





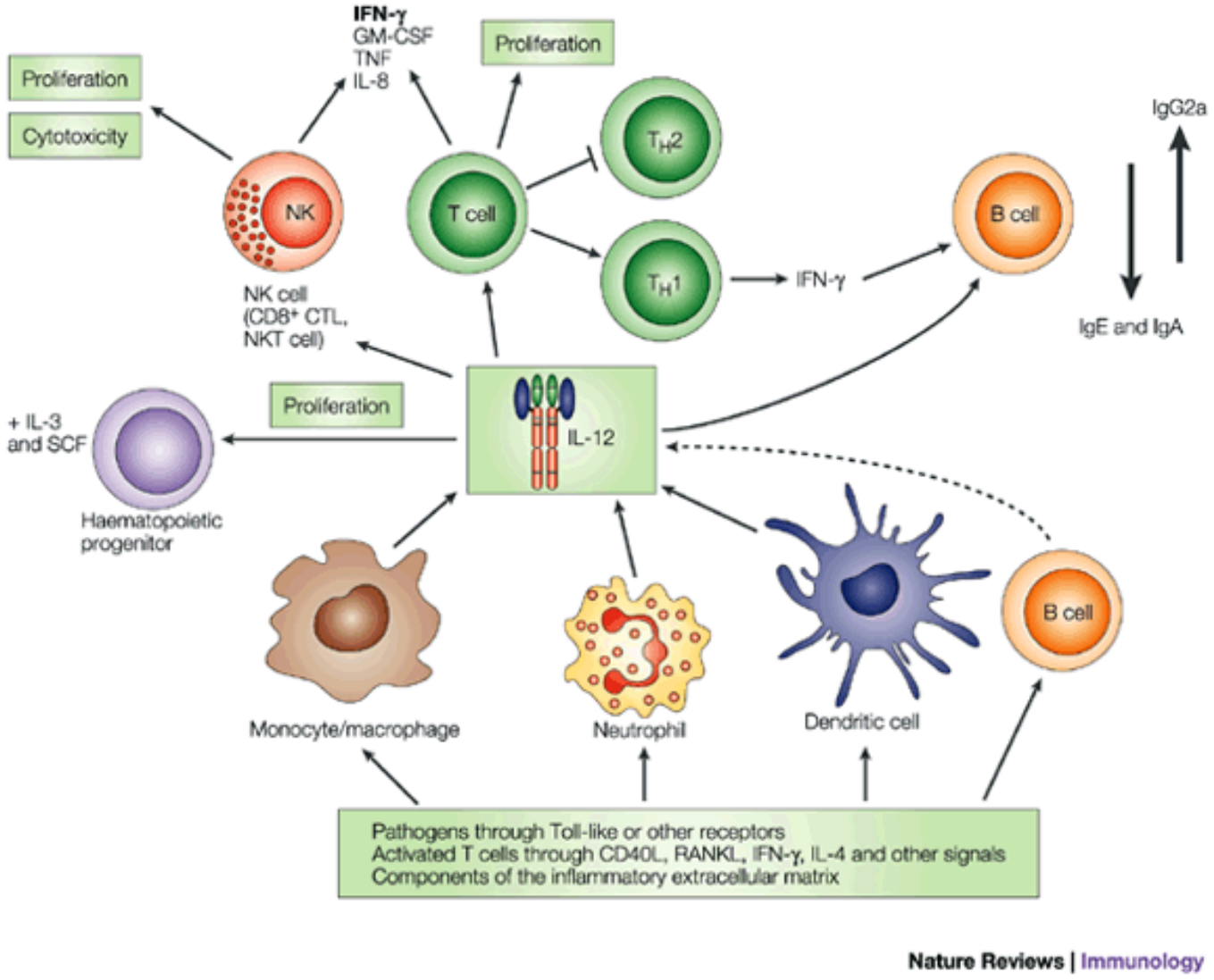
Accommodation archetypes

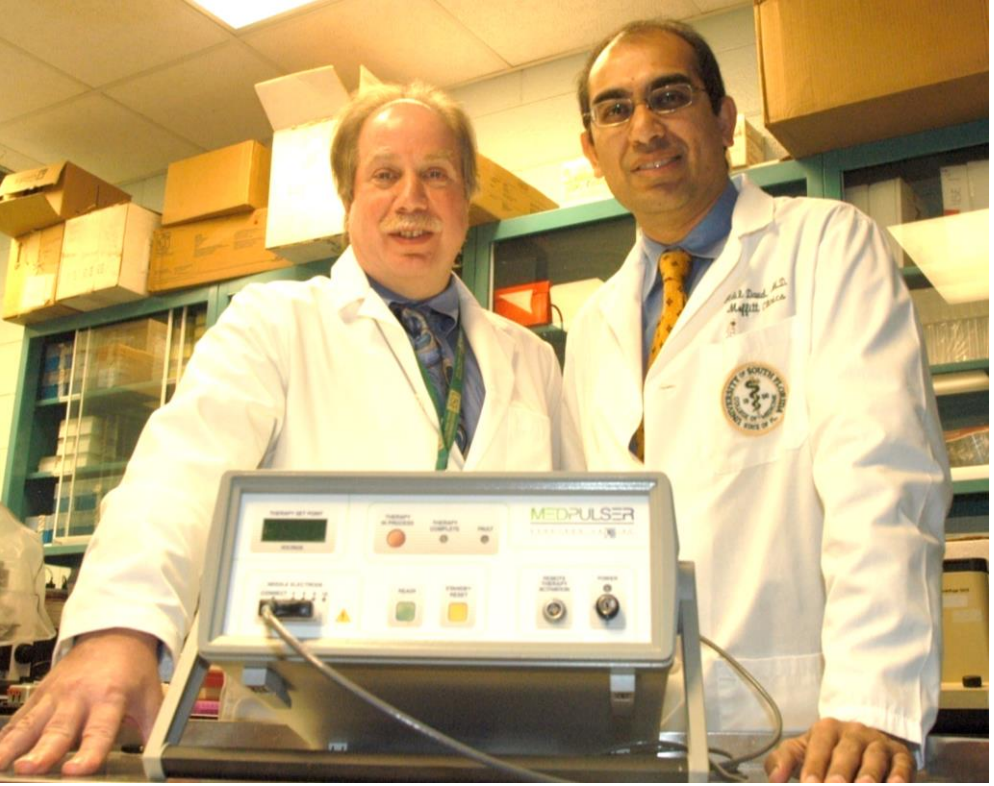
Traditional perspectives often reduce immune responses to tolerance and destruction. Emerging data show that the immune system has a larger palette of modular archetypes that accommodate healthy tissue. These archetypes can contribute to disease when dysregulated and/or dysfunctional.



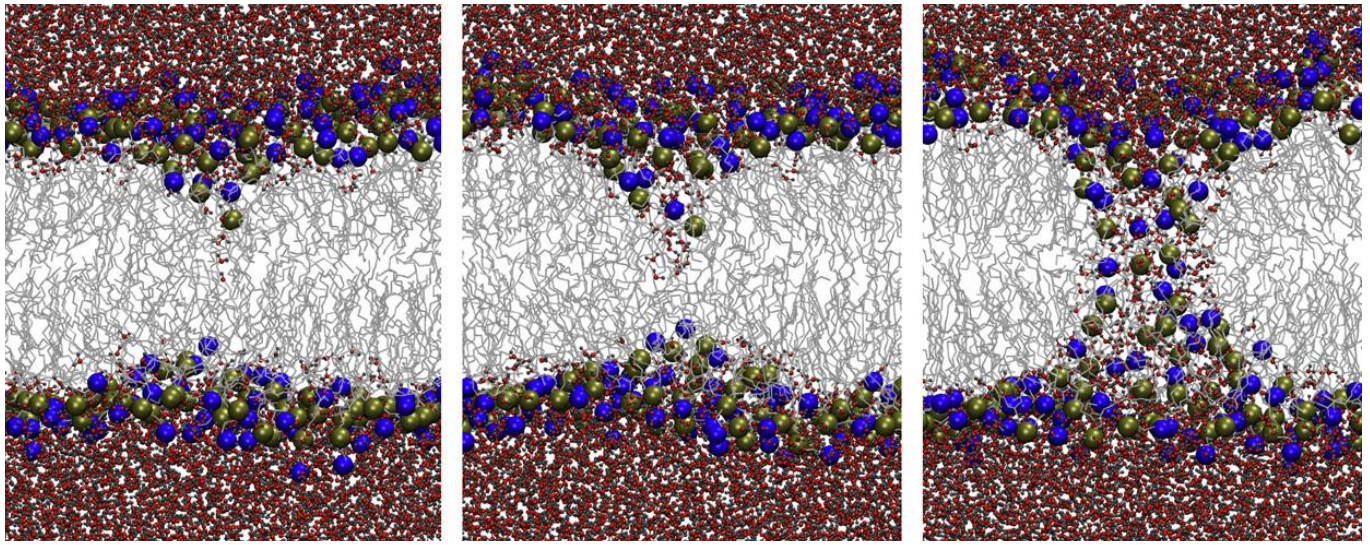
Model Proposed by Max Krummel PhD, UCSF

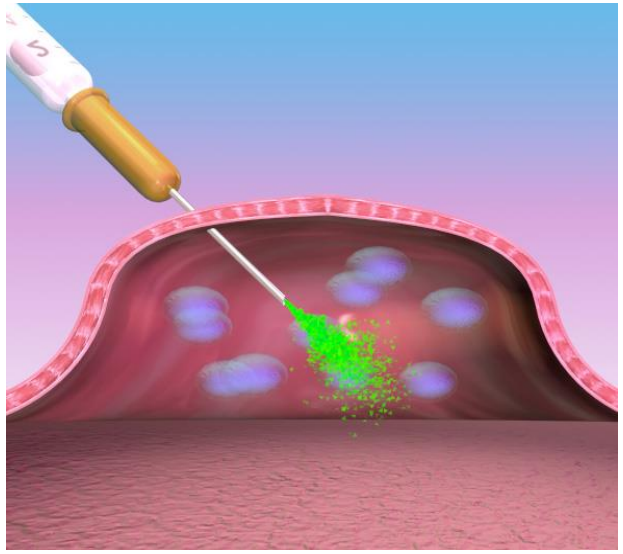
IL-12 is a key mediator of communication between DC/macrophages and effector-T cells and NK Cells



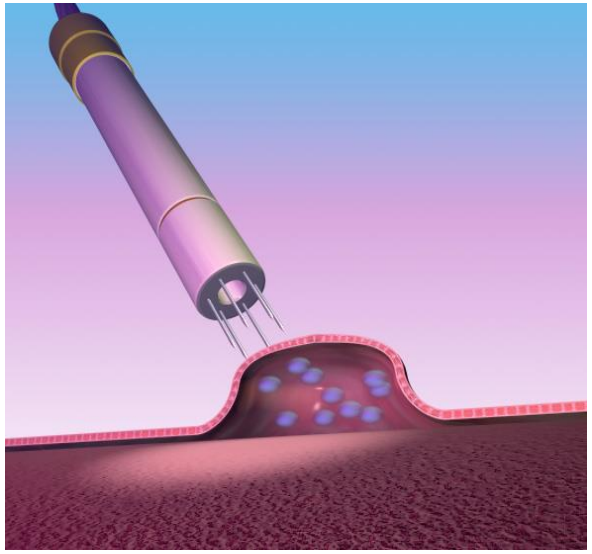


In-vivo Electroporation

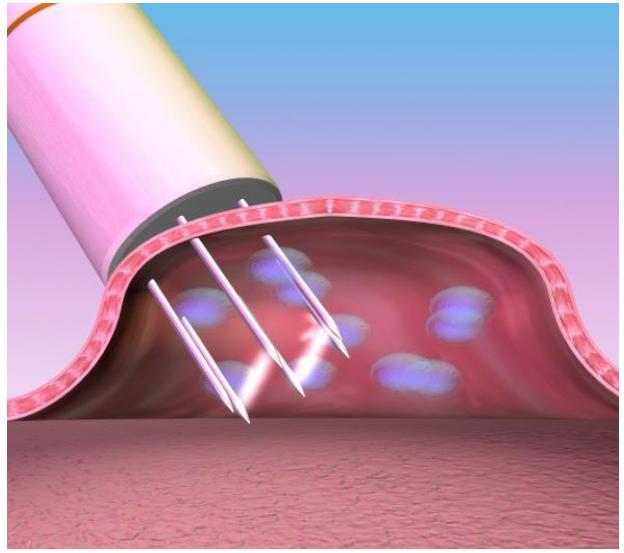




Injection of plasmid



Electrode Insertion



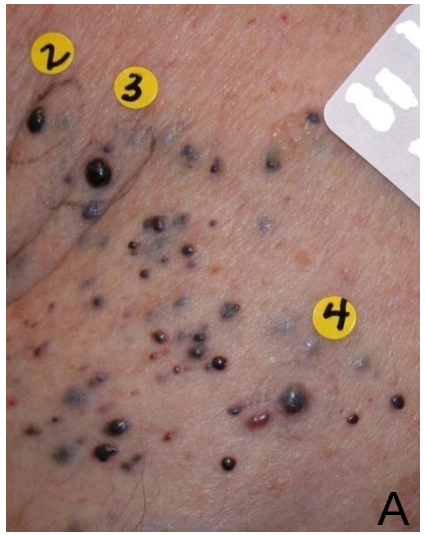
Electroporation

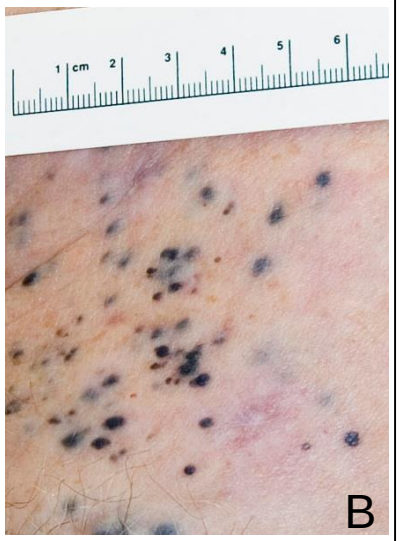
Pre-Tx

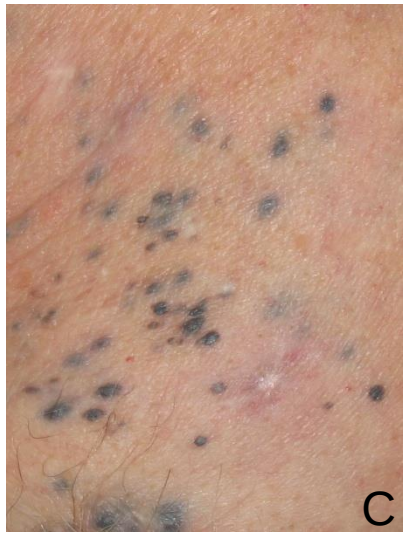
D 256

D 637

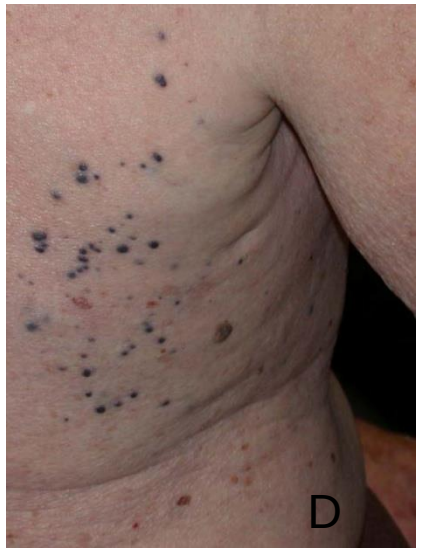
Patient 9
Cohort 3

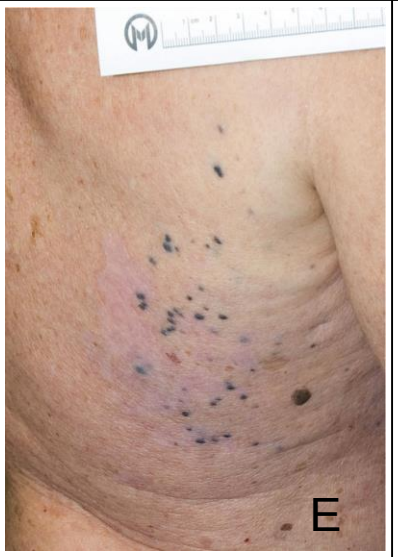


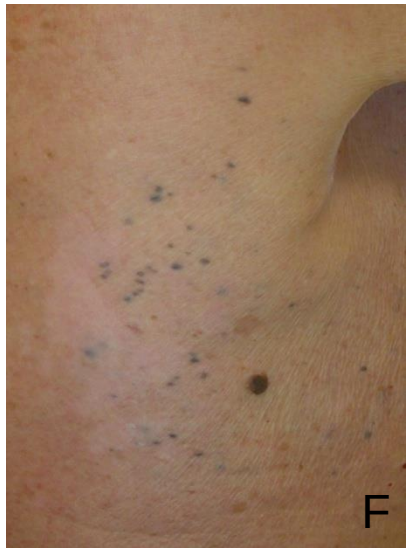




Chest

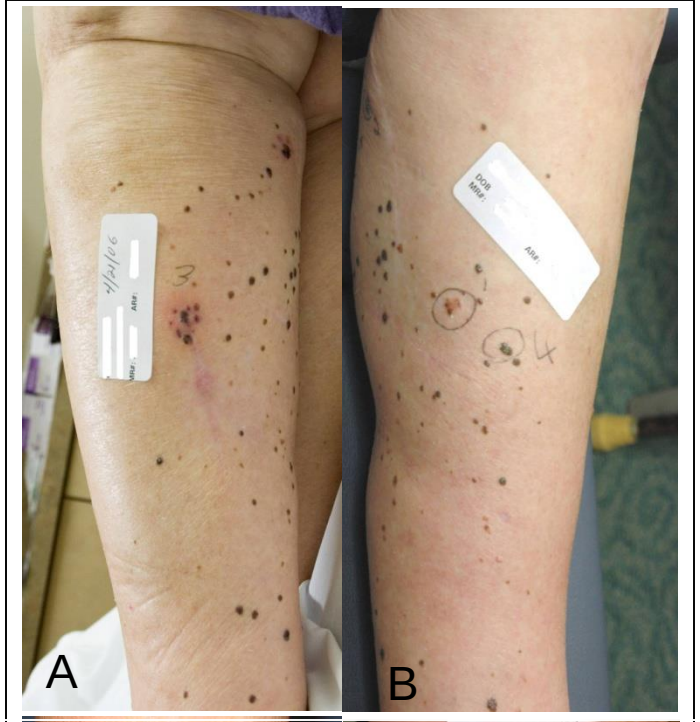




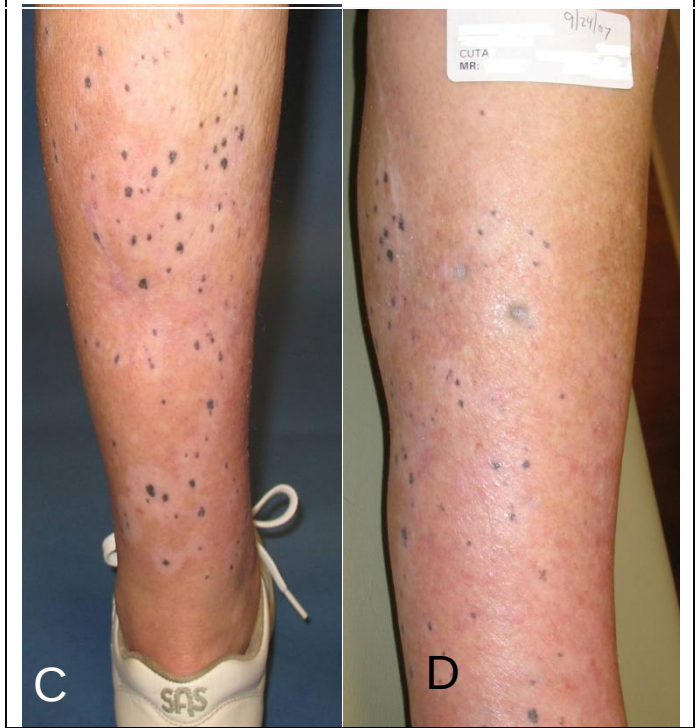


Back

Daud et al, Phase I trial of pIL-12 electroporation, J Clin Oncol



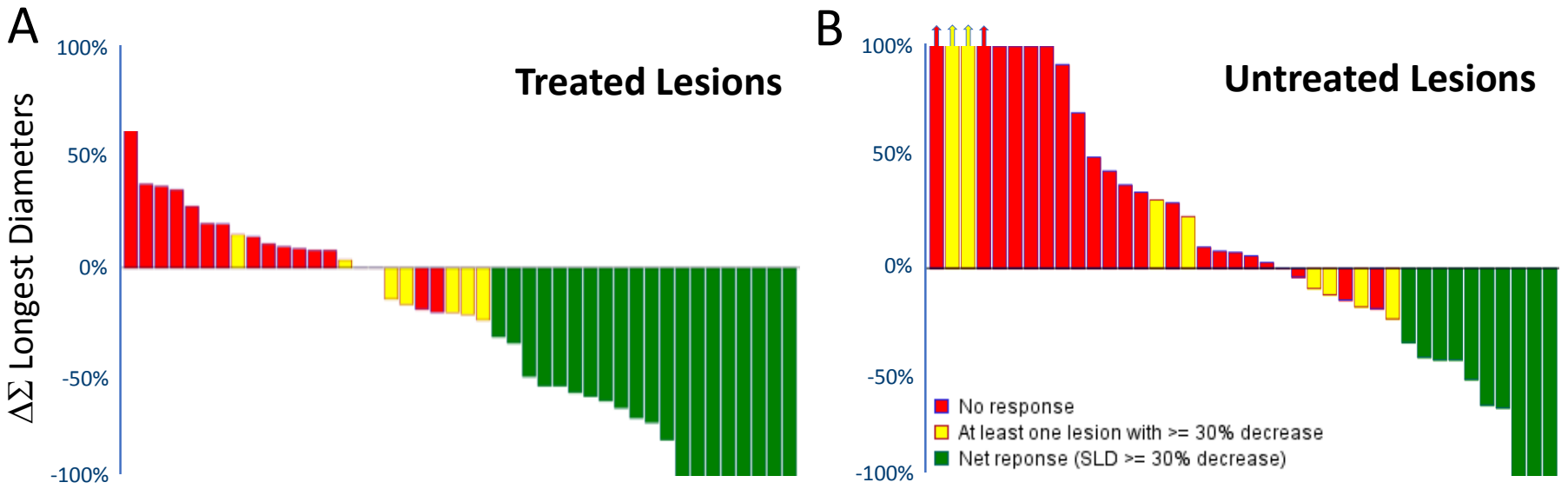
Day 5



Patient 14, Cohort 5
Post Limb Perfusion

Day 513

Phase II trial of Monotherapy i.t. Tavo



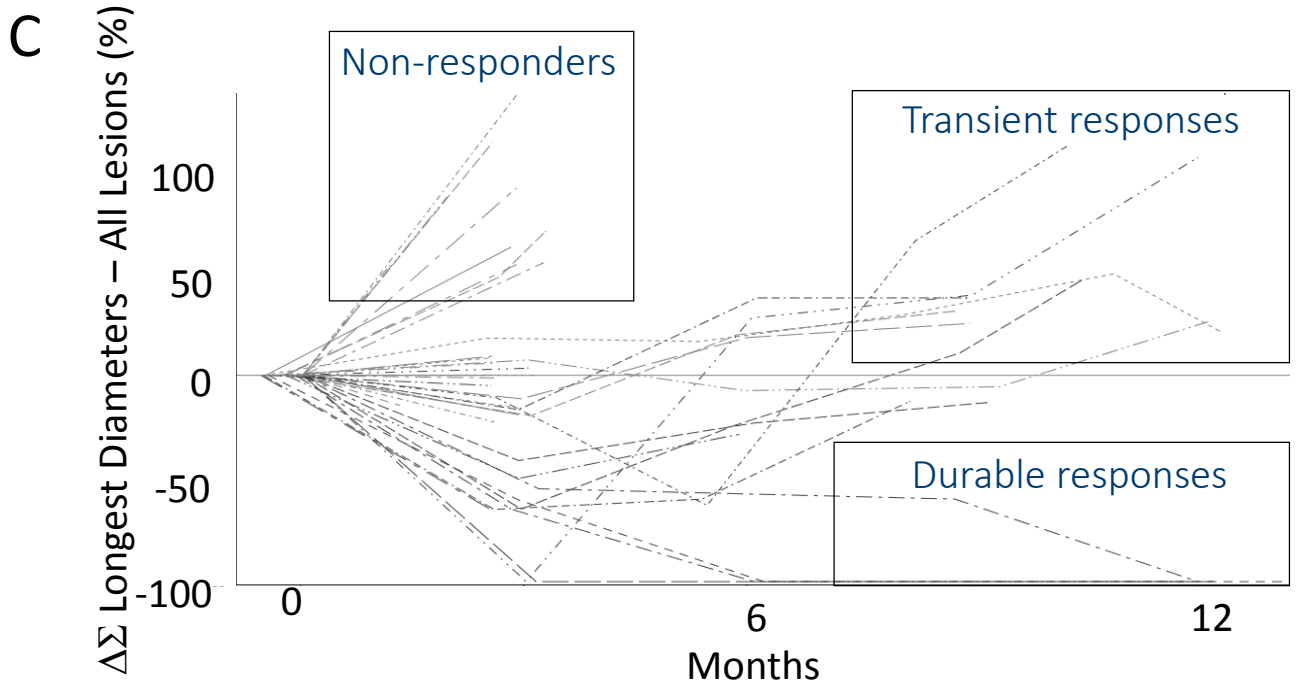
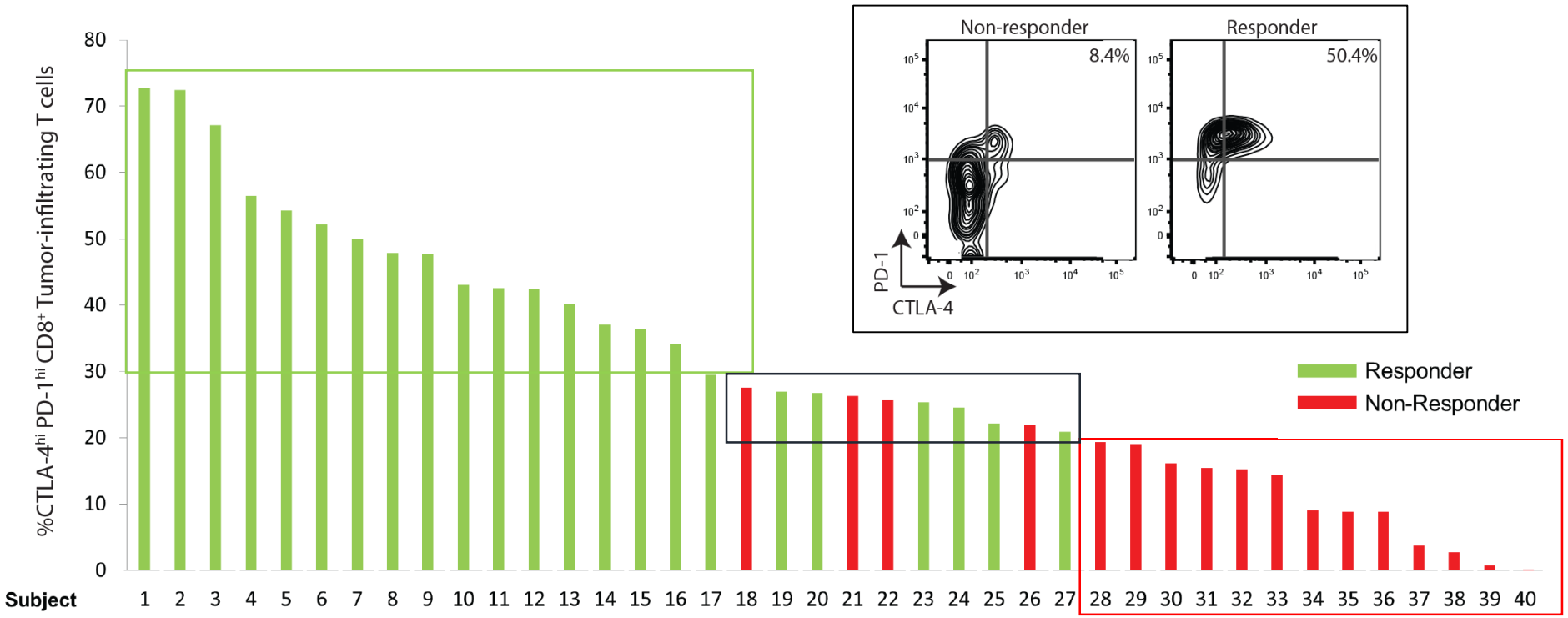
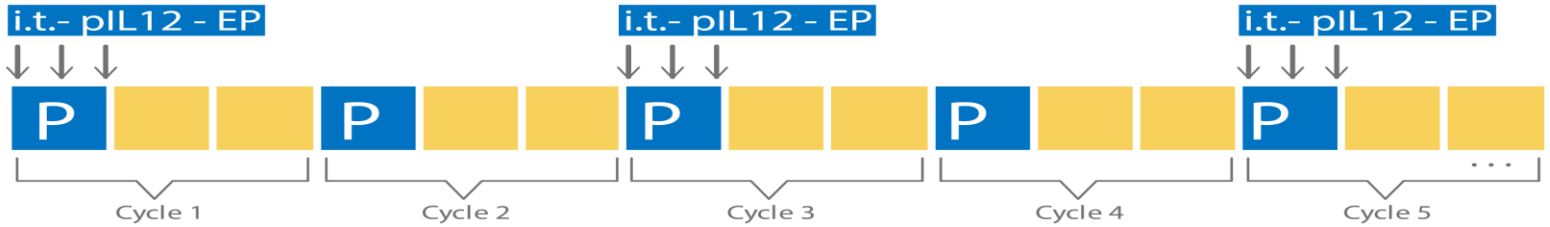


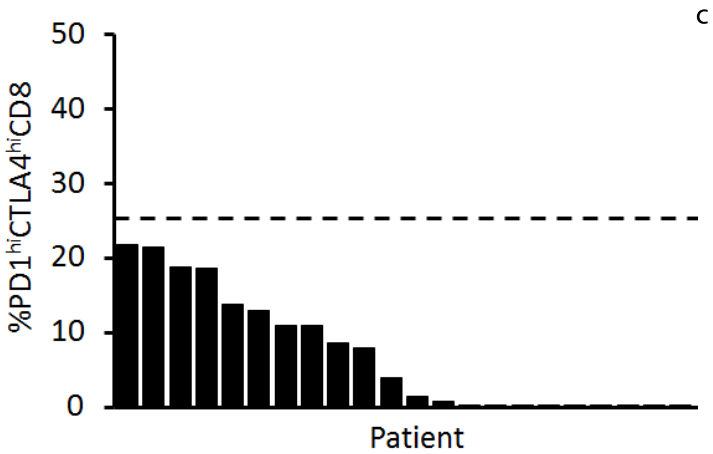
Figure 2. Best overall response in A. Sum of treated lesions and in B. Sum of untreated lesions. C. Overall change in tumor burden over time (N = 48).



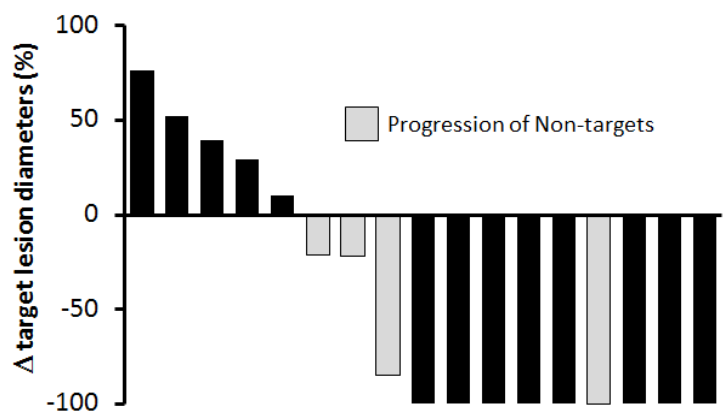
- 100% of patients with >30% of TILs exhibiting CTLA4^{hi}PD-1^{hi} biomarker phenotype went on to respond to anti-PD-1 (PR or CR)
- 100% of patients with <20% of TILs exhibiting CTLA4^{hi}PD-1^{hi} biomarker phenotype failed to respond to anti-PD-1 (SD or PD)
- 60% of patients with 20-30% of TILs exhibiting CTLA4^{hi}PD-1^{hi} biomarker phenotype responded to anti-PD-1 (PR or CR)

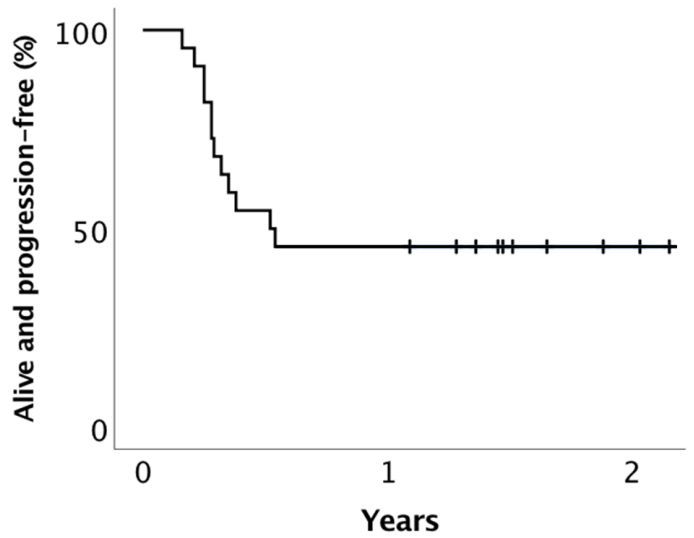
Daud (2016) JCI 126 (9): 3447


i.t.- pIL12 - EP
i.t.- pIL12 - EP
i.t.- pIL12 - EP
P
P
P
P
P
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5

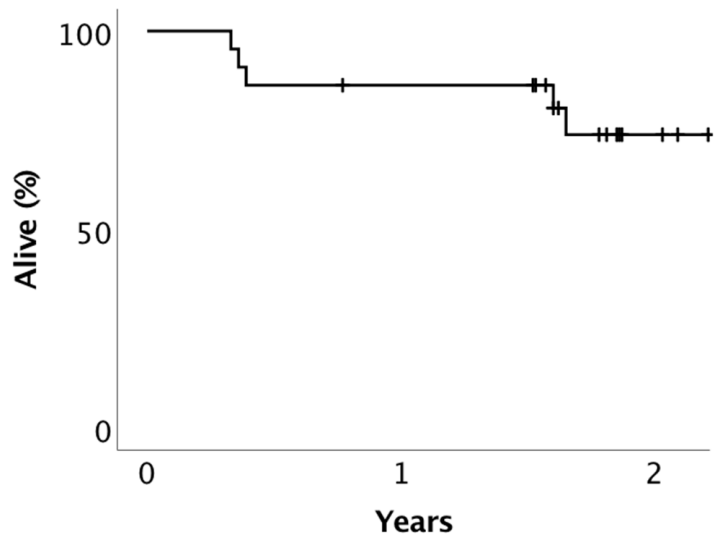

%PD1hiCTLA4hiCD8
50
40
30
20
10
0
Patient

c

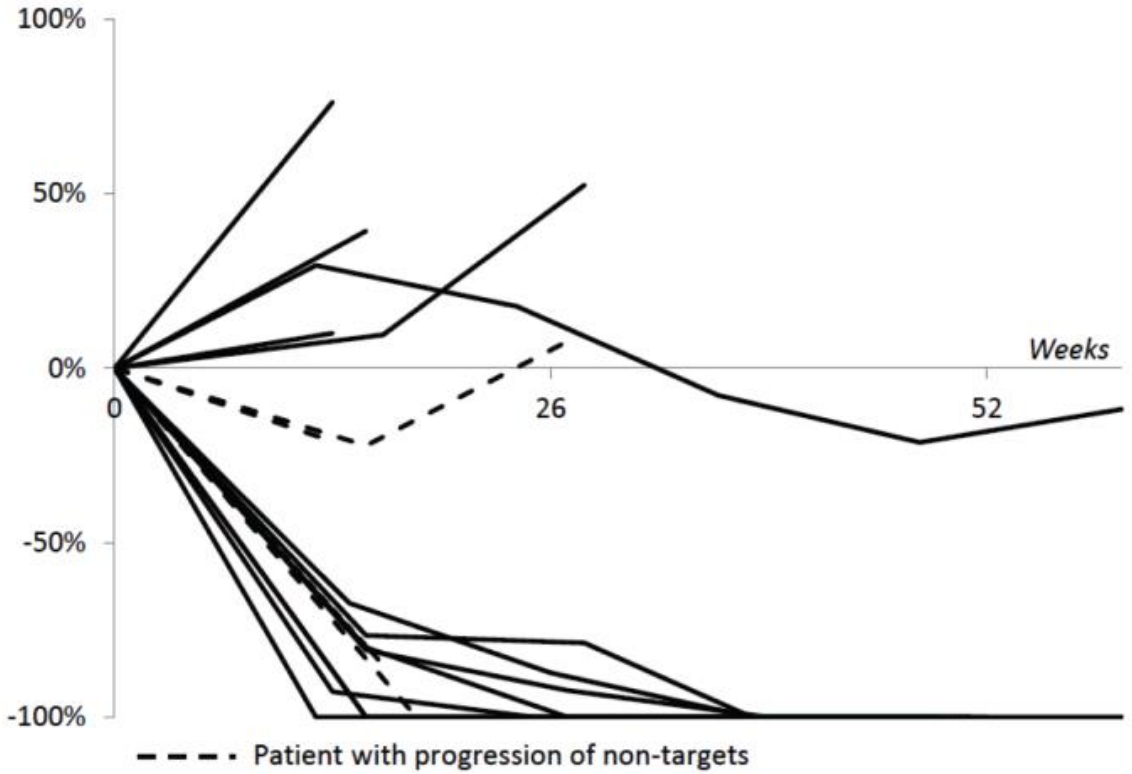

Δ target lesion diameters (%)
100
50
0
-50
-100
Progression of Non-targets


Alive and progression-free (%)
100
50
0
0
1
2
Years

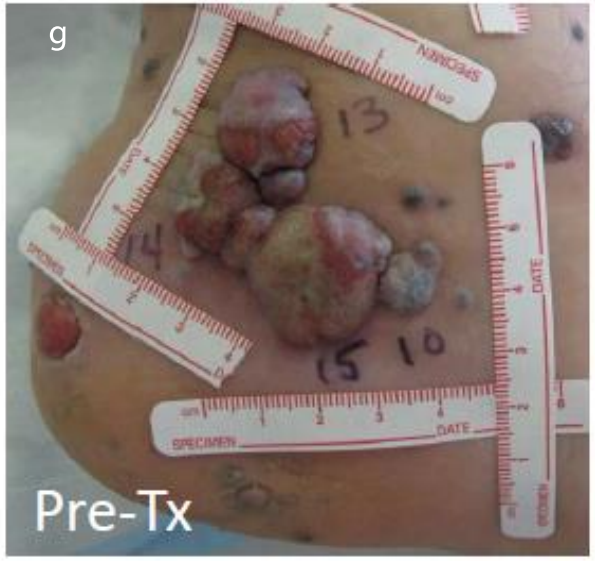
f

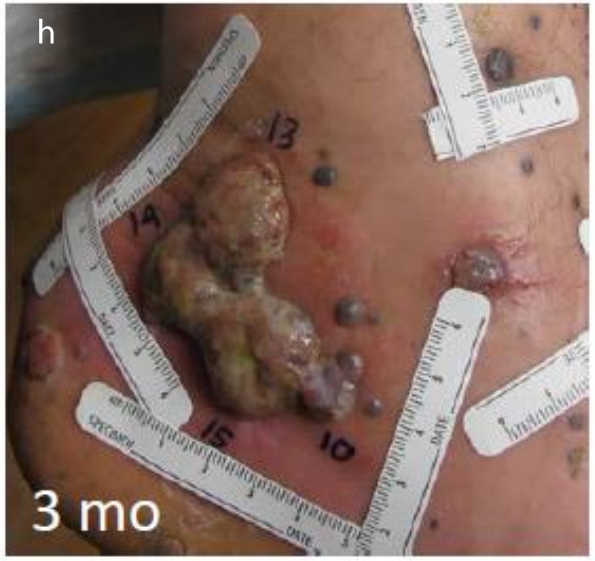

Alive (%)
100
50
0
0
1
2
Years

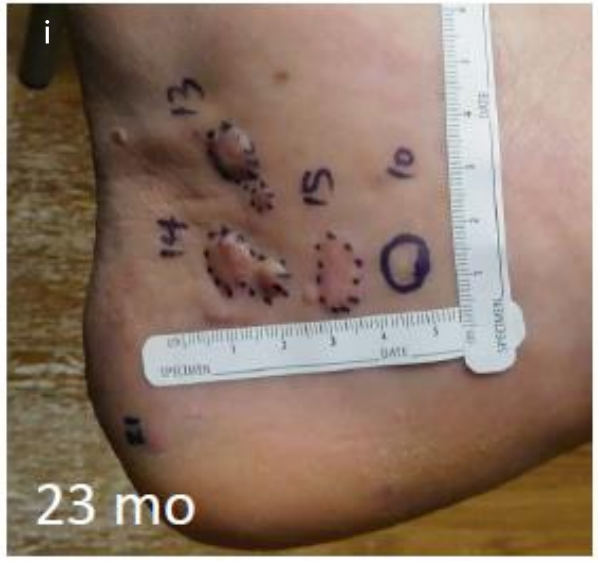

Pre-Tx peCTL%
by RECIST
by Clinical Assessmnet
22 PD PD
11 CR CR
NA PD PR
0 PD PD
8 CR CR
1 PD PD
4 CR CR
9 PD PD
<1 SD SD
2 PD PD
<1 CR CR
22 CR CR
19 PD PD
<1 SD SD
11 CR CR
14 CR CR
13 PD PD
19 CR CR
0 § CR
NA PD PD
NA PR PR
NA PD PD

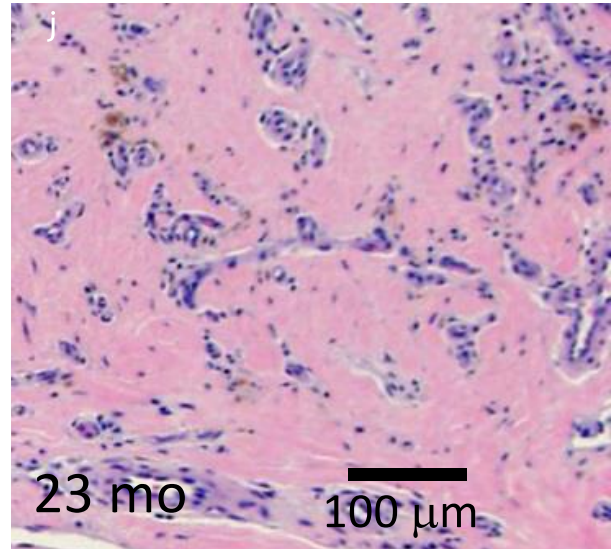


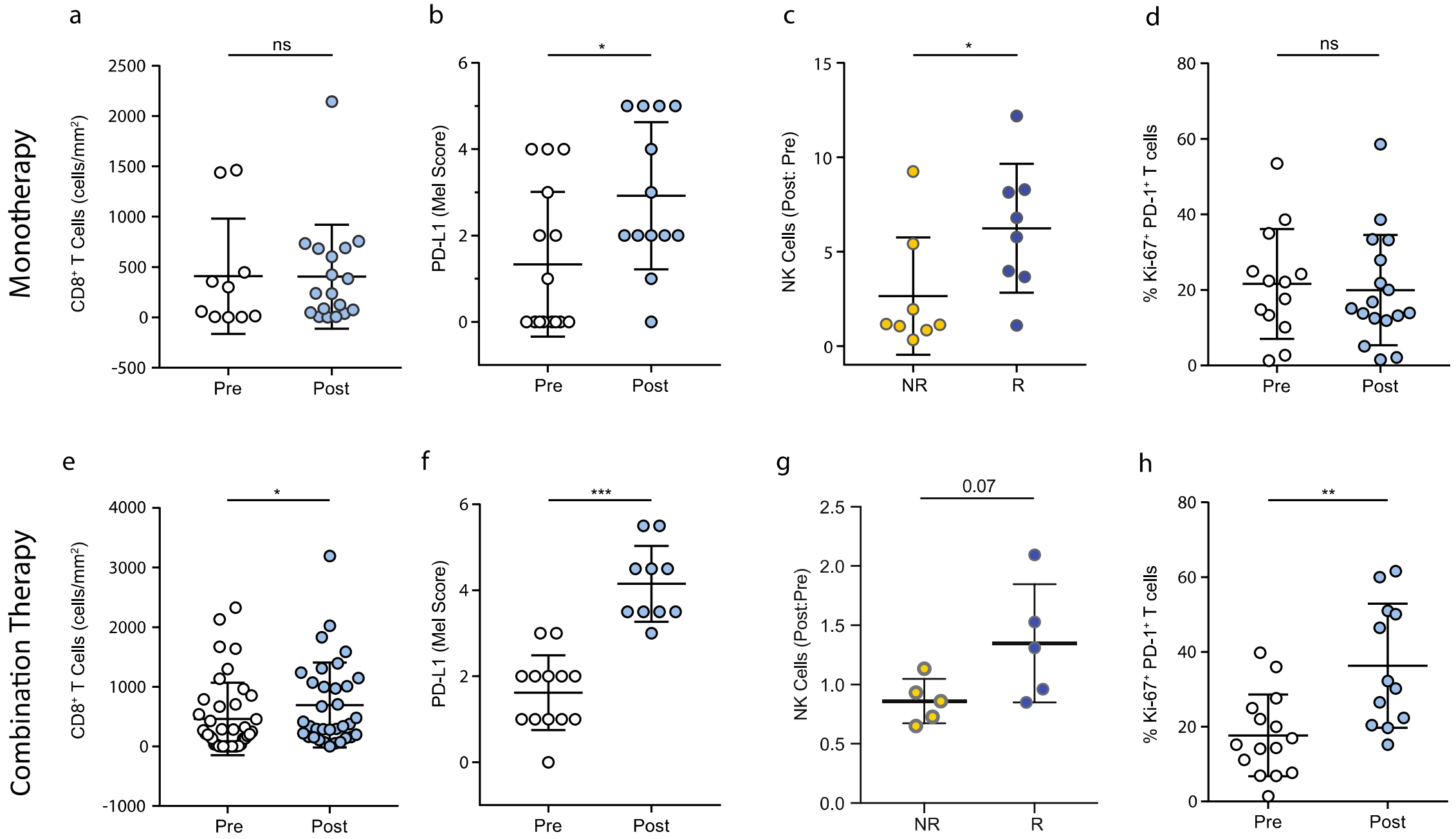
PD by RECIST
s/p ipilimumab
Nivolumab and Pembrolizumab
Extensive disease in the left LE





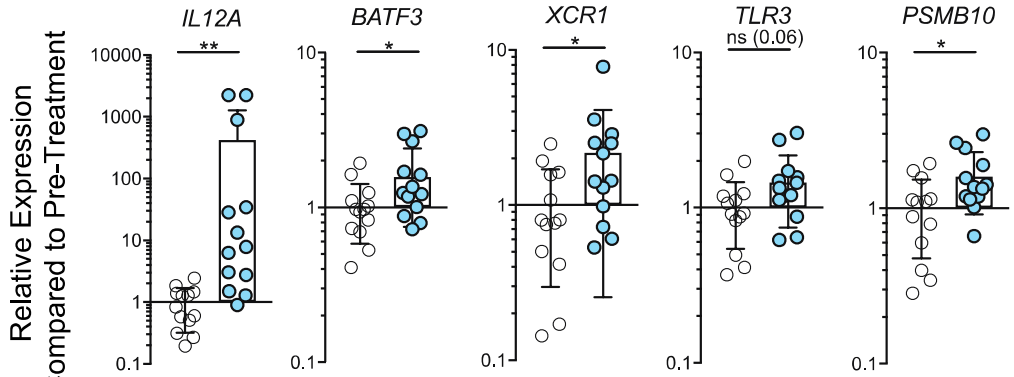


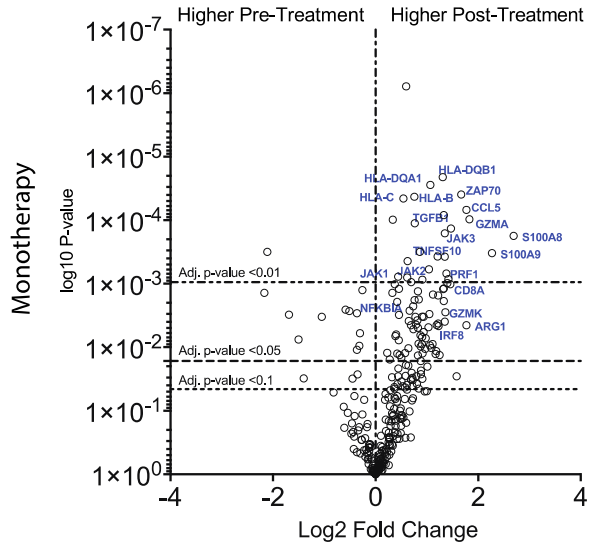


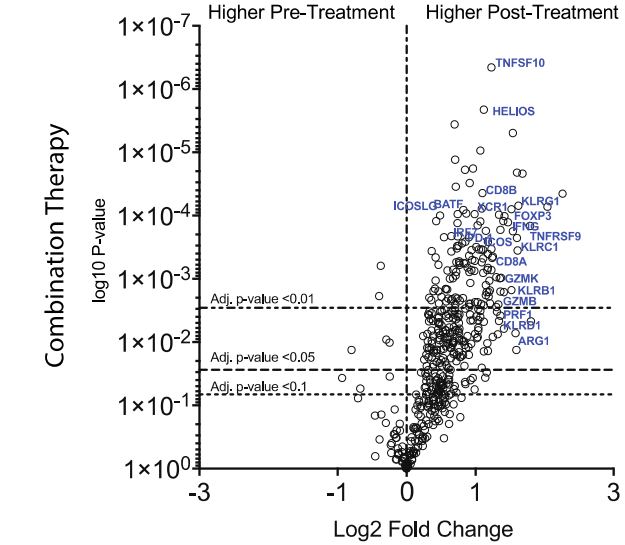

Monotherapy
Combination Therapy
a
b
c
d
e
f
g
h
ns
*
*
ns
*
***
0.07
**
CD8⁺ T Cells (cells/mm²)
PD-L1 (Mel Score)
NK Cells (Post: Pre)
% Ki-67⁺ PD-1⁺ T cells
NK Cells (Post:Pre)
Pre
Post
NR
R
2500
2000
1500
1000
500
0
-500
6
4
2
0
15
10
5
80
60
40
20
4000
3000
-1000
2.5
2.0
1.5
1.0
0.5
0.0

Innate Immunity

Antigen Presentation

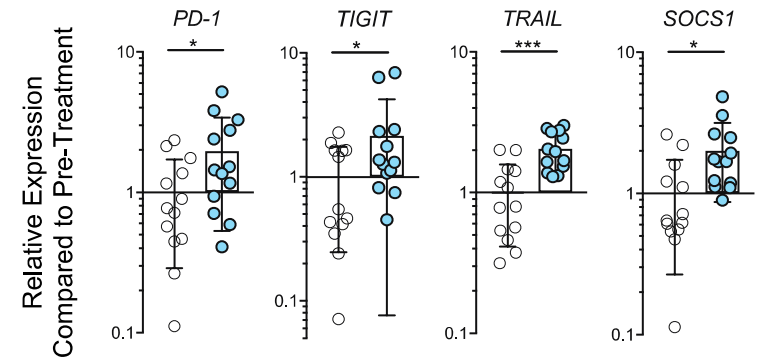




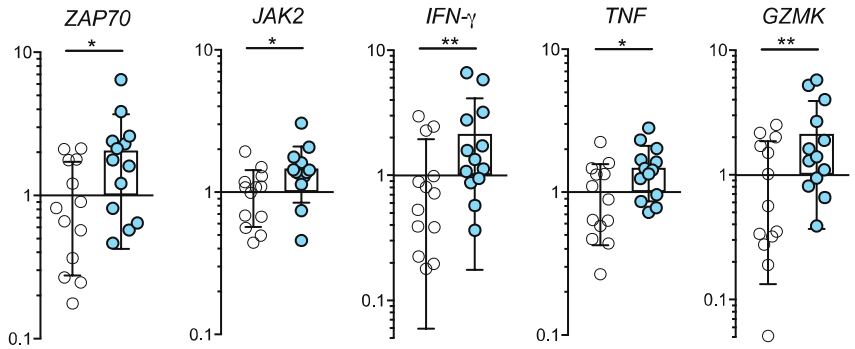


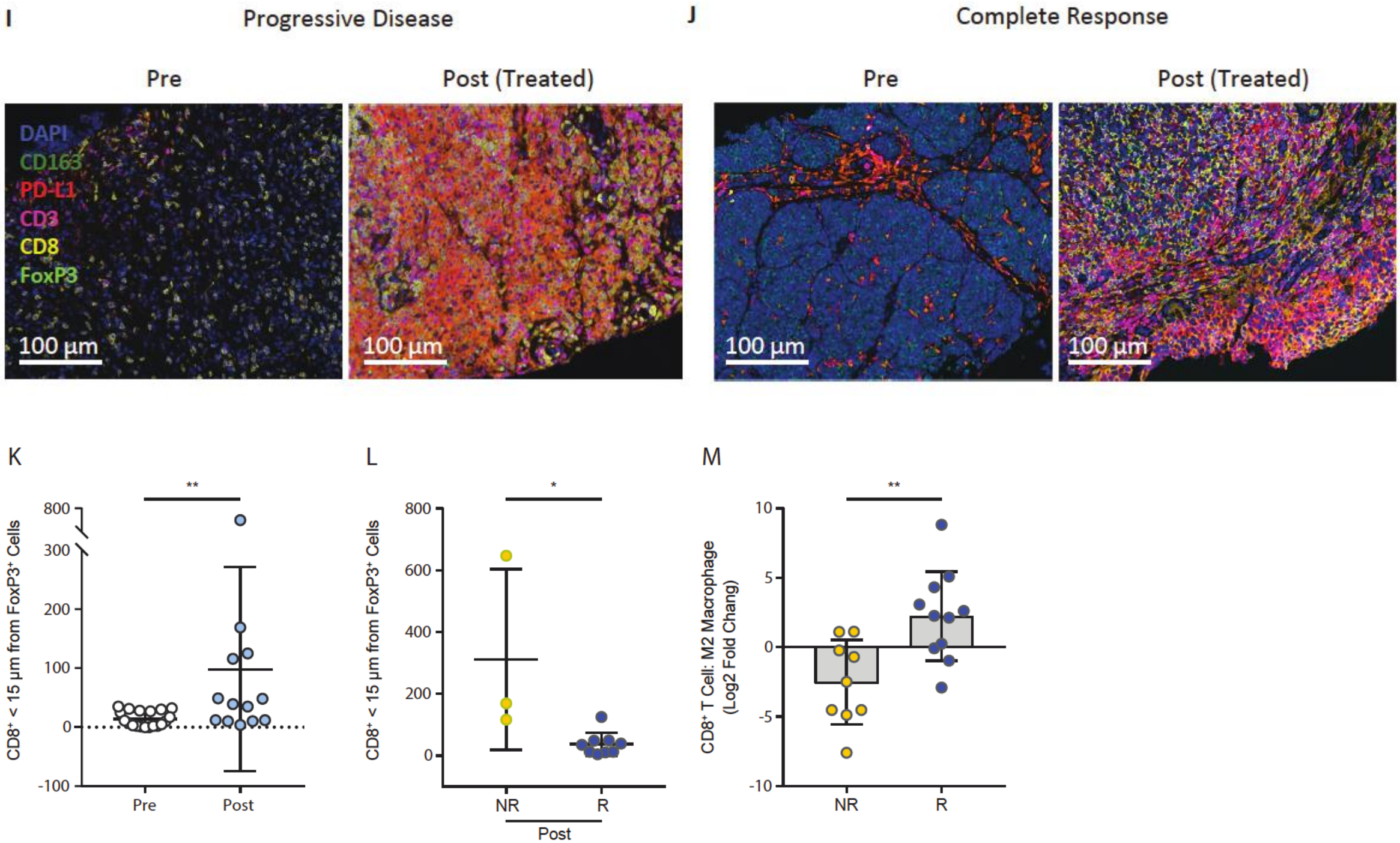
Adaptive Immunity

Adaptive Resistance



Activation




I
Progressive Disease
Pre
Post (Treated)
DAPI
CD163
PD-L1
CD3
CD8
FoxP3
100 µm
100 µm
J
Complete Response
Pre
Post (Treated)
100 µm
100 µm
K
**
CD8+ < 15 µm from FoxP3+ Cells
800
300
200
100
0
-100
Pre
Post
L
*
CD8+ < 15 µm from FoxP3+ Cells
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CD8+ T Cell: M2 Macrophage (Log2 Fold Chang)
10
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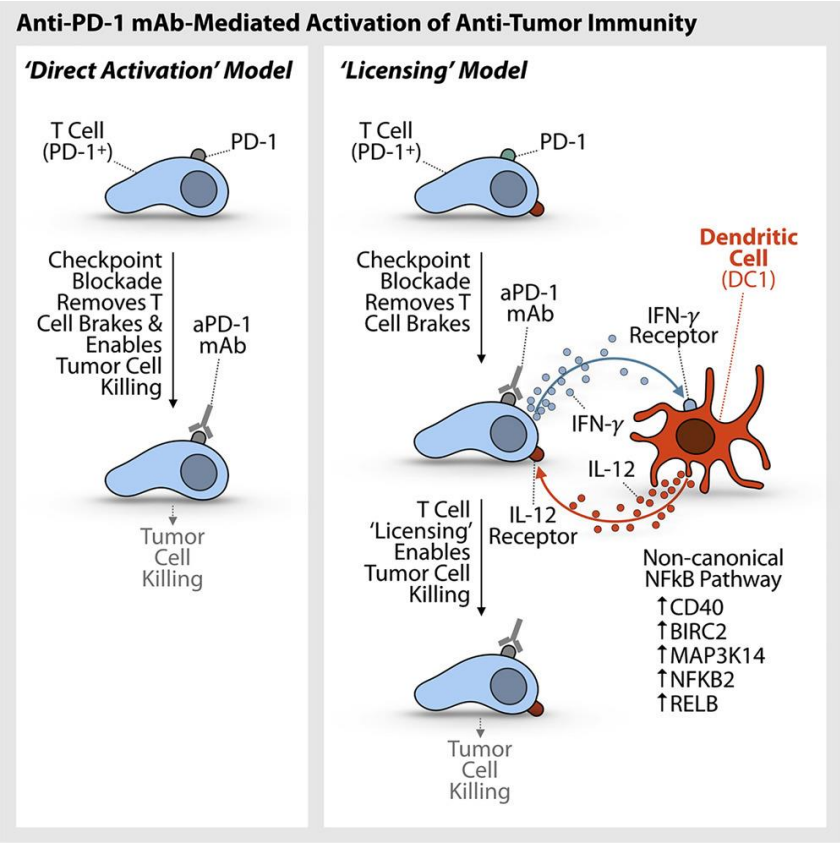
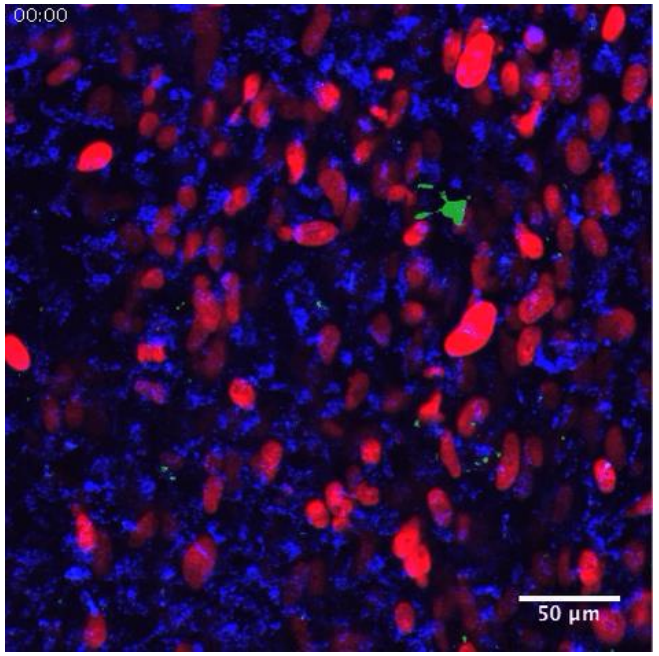
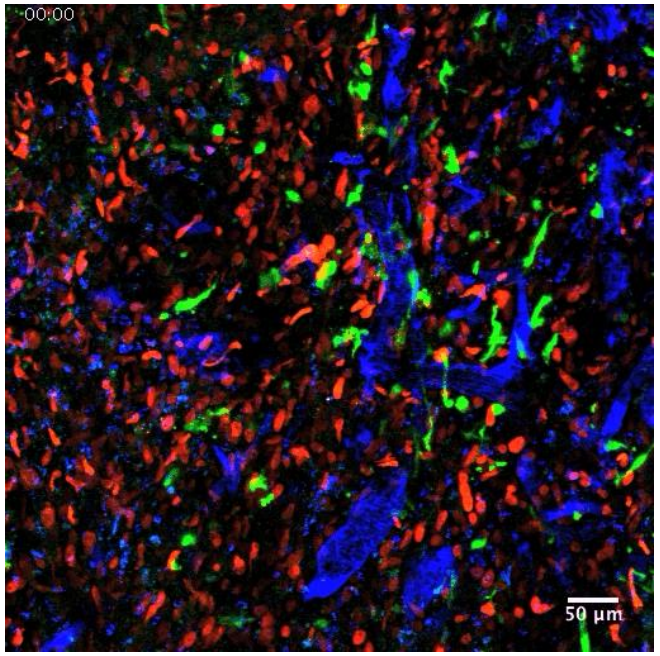
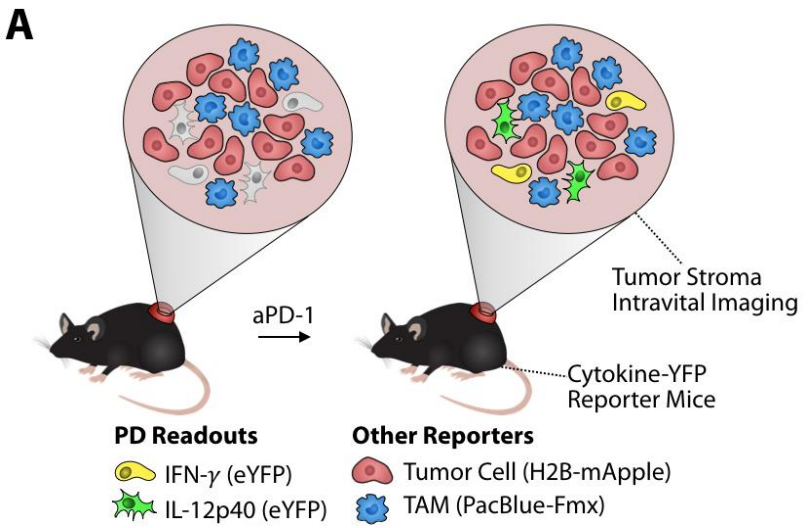




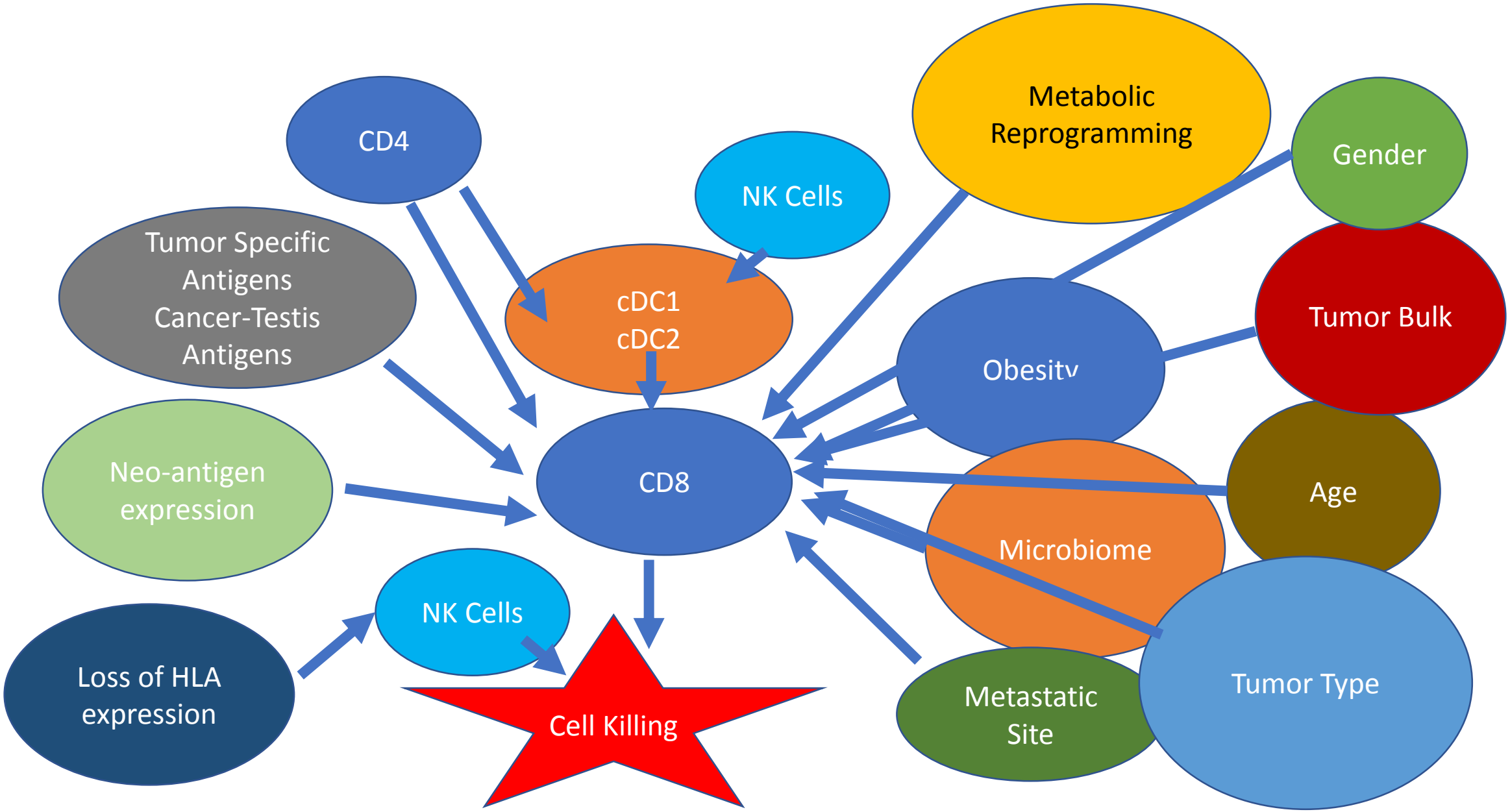




Successful anti-PD-1 cancer immunotherapy requires IL-12

Christopher S. Garris[1,2*], Sean P. Arlauckas[1,3*], Rainer H. Kohler[1], Marcel P. Trefny[4,5], Seth Garren[1], Cécile Piot[1], Camilla Engblom[1], Christina Pfirschke[1], Gordon J. Freeman[6], Sarah E. Warren[7], SuFey Ong[7], Erica Browning[8],, Christopher G. Twitty[8], Robert H. Pierce[8] Mai H. Le[8], Alain P. Algazi[9], Adil I. Daud[9], Sara I. Pai[10], Alfred Zippelius[4], Ralph Weissleder[1,3,11], Mikael J. Pittet[1,3#]

Emerging Picture of Immunotherapy



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