What's Next for Cancer Immunotherapy?

Marcus Butler, MD

December 8, 2020

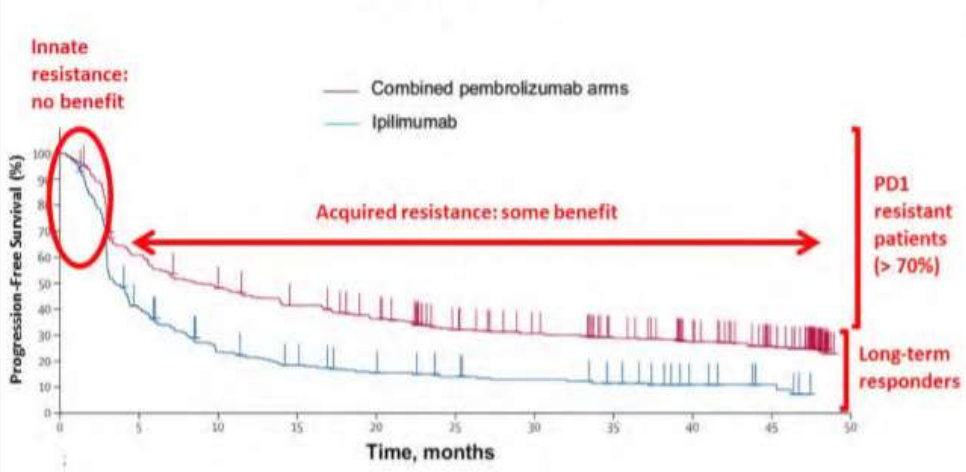
Disclosures

- Consulting Fees: Bristol-Myers Squibb, EMD Serono, GSK, Immunocore, Immunovaccine, Merck & Co., Novartis, Sanofi-Genzyme, Turnstone Biologics, Sun Pharma
- Contracted Research: Merck, Takara Bio

Even in Melanoma: Resistance develops

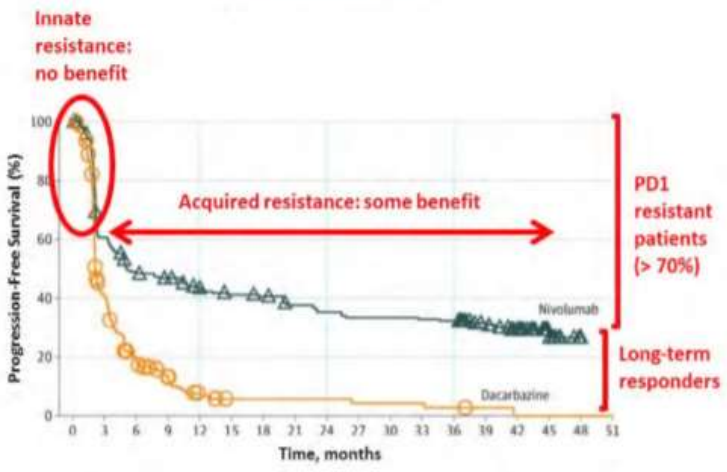
Background: 2/3 of advanced melanoma patients are resistant (innate or acquired) to PD1 monotherapy

KEYNOTE-006



Robert C, *et al*. The Lancet 2019

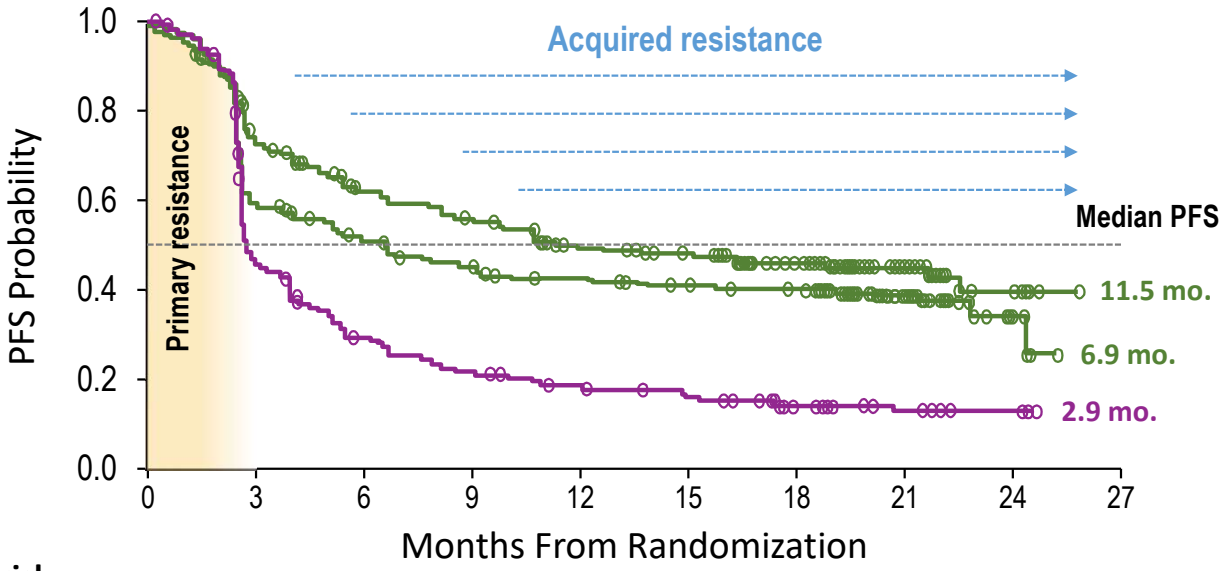
CheckMate-066



Robert C, *et al*. Lancet Oncol 2019

Even in Melanoma: Resistance develops

CheckMate-067– Melanoma with Combination Tx



Number at risk

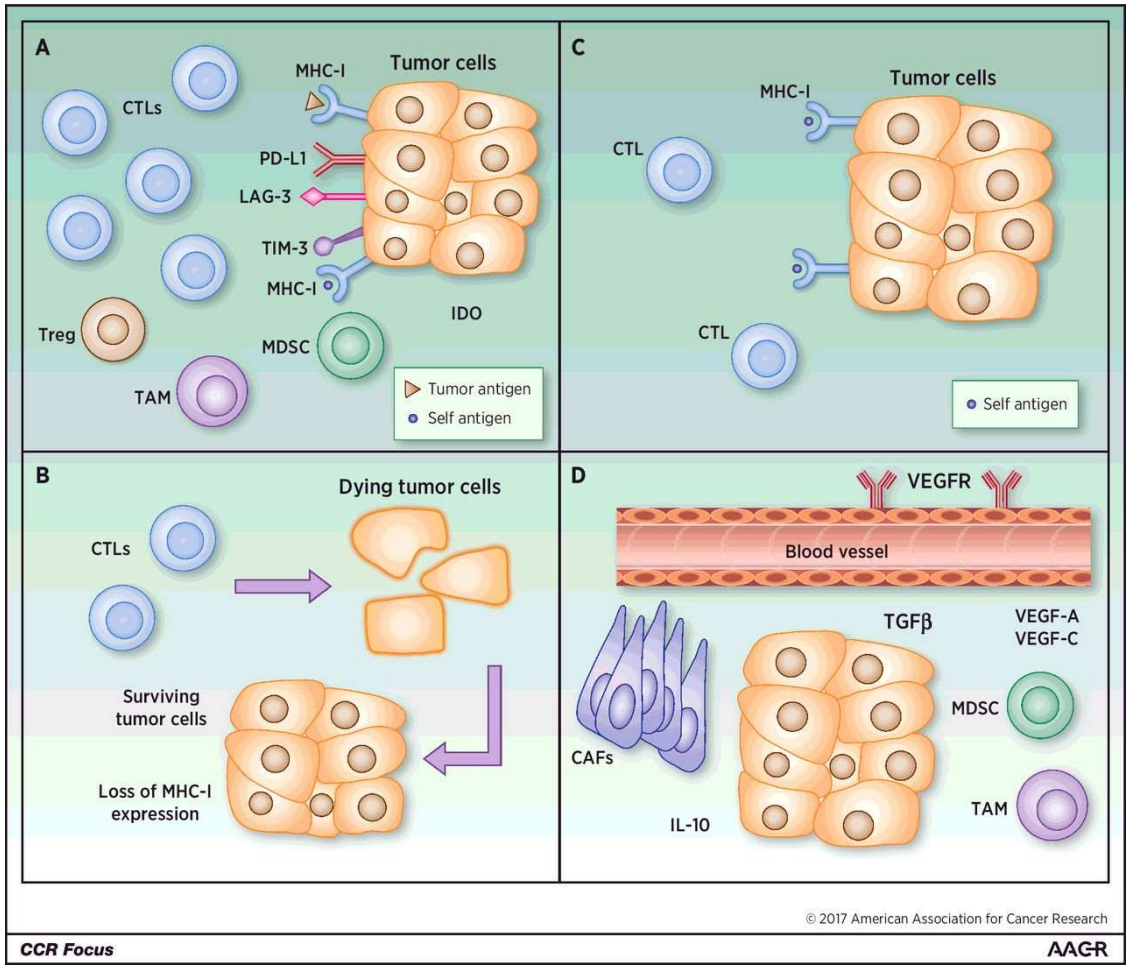
NIVO+IPI	314	219	174	156	133	126	103	48	8	0
NIVO	316	177	148	127	114	104	94	46	8	0
IPI	315	137	78	58	46	40	25	15	3	0

Wolchok JD, et al. *J Clin Oncol*. 2016;34 [abstract 9505].

Mechanisms of Immunotherapy Resistance

T cell immmunosuppression

Poor antigen presentation

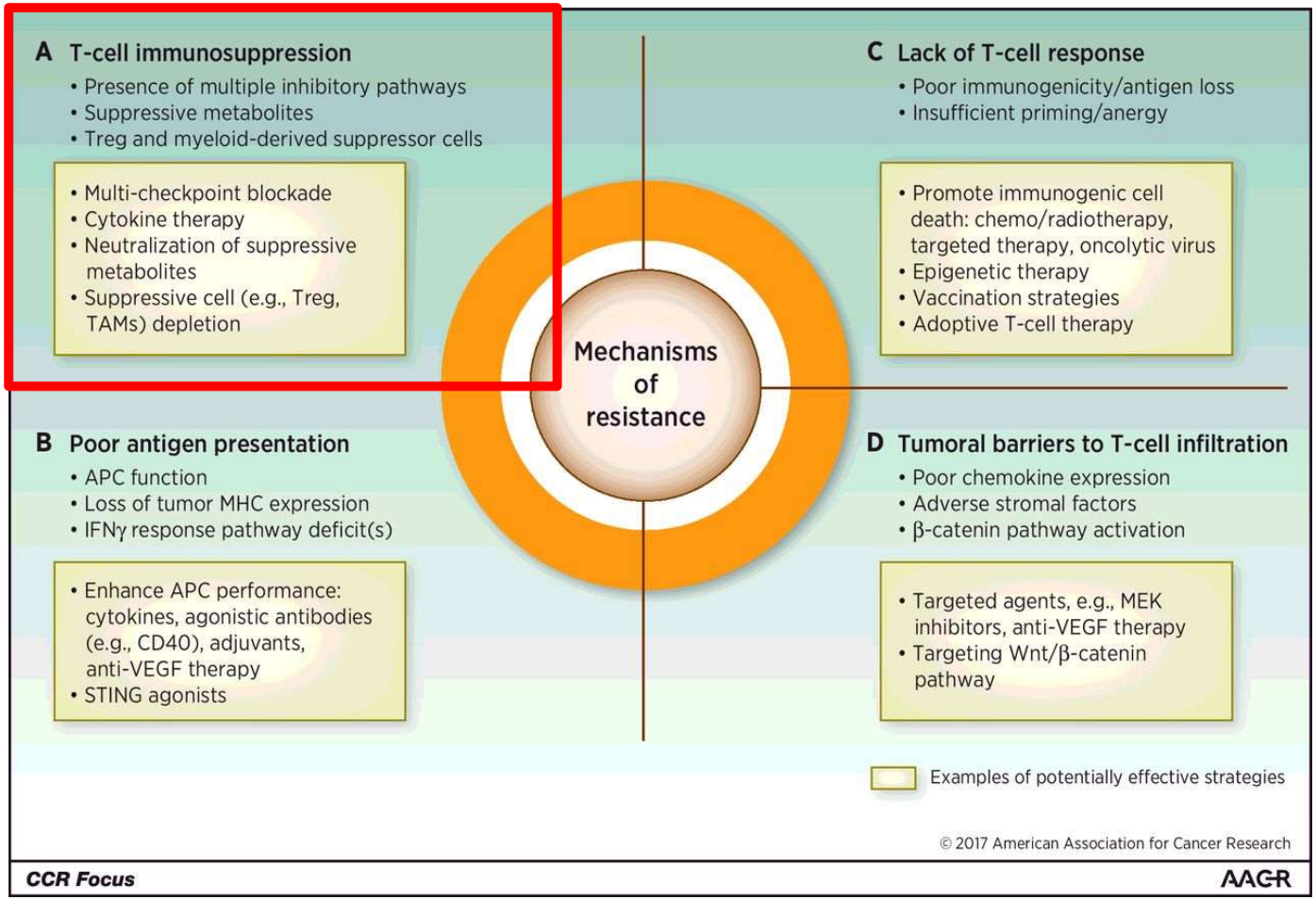


Lack of T cell response

Barriers of T cell infiltration

Tumor Immunotherapy Program

Therapeutic Strategies: Reverse anergy, ignorance



Daphne Day et al. Clin Cancer Res 2017;23:4980-4991

MADRID 2017 ESMO congress

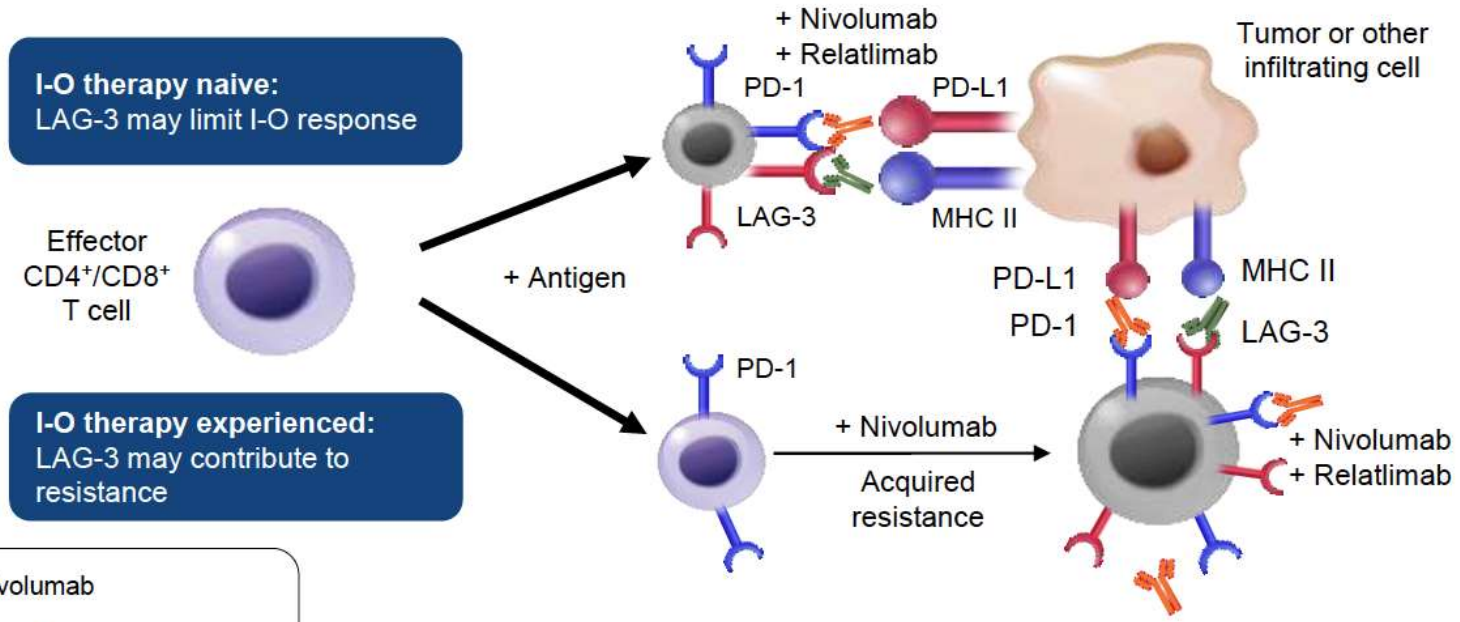
Efficacy of BMS-986016 (relatlimab), a Monoclonal Antibody That Targets Lymphocyte Activation Gene-3 (LAG-3), in Combination With Nivolumab in Patients With Melanoma Who Progressed During Prior Anti–PD-1/PD-L1 Therapy in All-Comer and Biomarker-Enriched Populations

Paolo Antonio Ascierto,[1] Petri Bono,[2] Shailender Bhatia,[3] Ignacio Melero,[4] Marta Nyakas,[5] Inge Marie Svane,[6] James Larkin,[7] Carlos A. Gomez-Roca,[8] Dirk Schadendorf,[9] Reinhard Dummer,[10] Aurélien Marabelle,[11] Christoph Hoeller,[12] Matthew Maurer,[13] Christopher Harbison,[13] Priyam Mitra,[13] Satyendra Suryawanshi,[13] Kent Thudium,[13] Eva Muñoz-Couselo[14]

[1]Istituto Nazionale Tumori Fondazione "G. Pascale," Napoli, Italy; [2]Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland; [3]University of Washington, Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, Seattle, WA; [4]Clinica Universidad de Navarra, Pamplona, Spain; [5]Oslo University Hospital, Oslo, Norway; [6]Copenhagen University Hospital, Herlev, Denmark; [7]Royal Marsden Hospital, NHS Foundation Trust, London, United Kingdom; [8]Institut Universitaire du Cancer, Oncopole, Toulouse, France; [9]Westdeutsches Tumorzentrum, University Hospital Essen & German Cancer Consortium, Essen, Germany; [10]UniversitätsSpital Zürich, Skin Cancer Center University Hospital, Zürich, Switzerland; [11]Gustave Roussy, Paris, France; [12]Medical University of Vienna, Vienna, Austria; [13]Bristol-Myers Squibb, Princeton, NJ; [14]Vall d´Hebron Institute of Oncology, Barcelona, Spain

Potential Role of LAG-3 in T-Cell Exhaustion and Anti–PD-1 Resistance

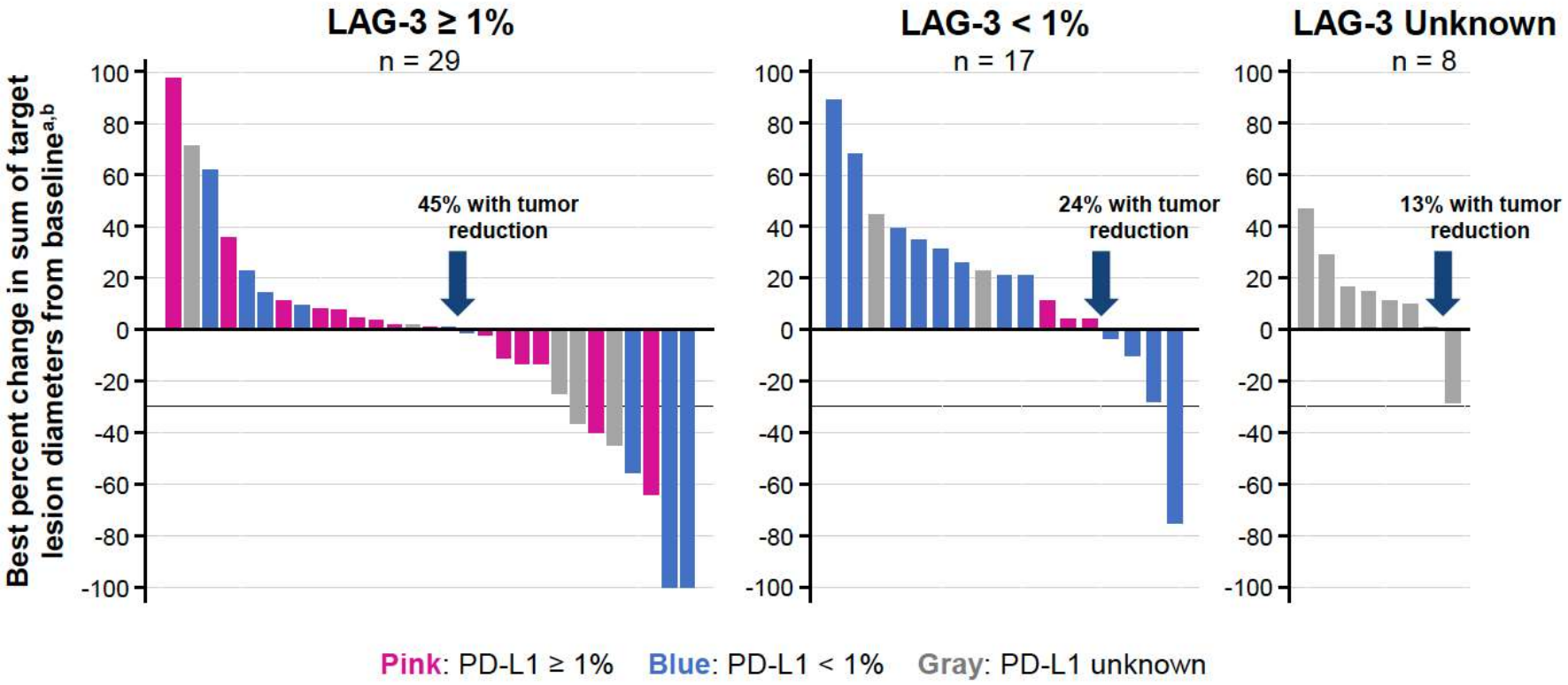
- **LAG-3 regulates a checkpoint pathway that limits the activity of T cells[1]**
- **LAG-3 and PD-1 receptors are overexpressed and/or co-expressed on tumor-infiltrating lymphocytes in melanoma[2,3]**



I-O, immuno-oncology; MHC II, major histocompatibility complex class II; PD-1, programmed death-1; PD-L1, programmed death ligand 1.

1. Grosso JF et al. *J Clin Invest*. 2007;117:3383–3392. 2. Goding SR et al. *J Immunol*. 2013;190:4899–4909. 3. Taube JM et al. *Clin Cancer Res*. 2015;21:3969–3976.

Best Change in Target Lesion Size by LAG-3 and PD-L1 Expression



[a]Six patients with clinical progression prior to their first scan and 1 with PD due to a new symptomatic brain metastasis prior to getting full scans were not included.
[b]One patient with best change from baseline > 30% had a best response of SD.

Significant antitumor activity for low-dose ipilimumab (IPI) with pembrolizumab (PEMBRO) immediately following progression on PD1 Ab in melanoma (MEL) in a phase II trial

Daniel J. Olson[1], Jason J. Luke[2], Andrew S. Poklepovic[3], Madhuri Bajaj[4], Emily Higgs[1], Timothy C. Carll[1], Brian Labadie[1], Thomas Krausz[1], Yuanyuan Zha[1], Theodore Karrison[1], Jose Lutzky[5], Sigrun Hallmeyer[6], Bruce Brockstein[7], Vernon K. Sondak[8], Zeynep Eroglu[8], Thomas F. Gajewski[1], Nikhil I. Khushalani[8]

1. The University of Chicago Comprehensive Cancer Center, Chicago, IL
2. The University of Pittsburgh, Hillman Cancer Center, Pittsburgh, PA
3. VCU Massey Cancer Center, Richmond, VA
4. Illinois Cancer Care, Peoria, IL
5. Mount Sinai Medical Center, Miami Beach, FL
6. Oncology Specialists, SC, Park Ridge, IL
7. NorthShore University Health System, Evanston, IL
8. H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

AT THE FOREFRONT UChicago Medicine

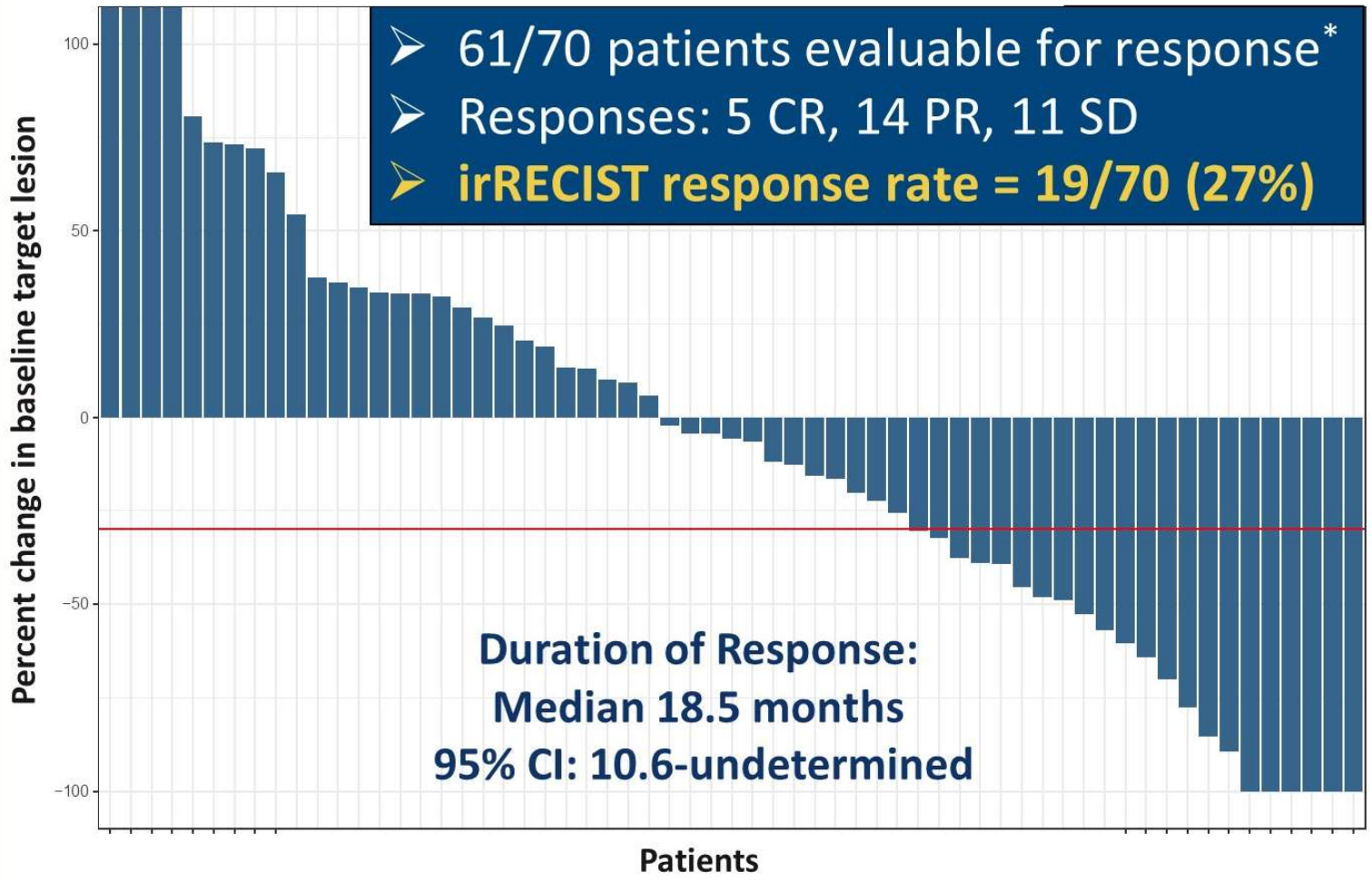
CONQUER CANCER® THE ASCO FOUNDATION MERIT AWARD RECIPIENT

Pembro + low-dose ipi after PD1 Ab failure: Patient demographics

Characteristic	Study patients receiving ≥ 1 dose (n=70)
Age (years)	
Median	64
Range	27 - 87
Sex	
M	47 (67%)
F	23 (33%)
BRAF Status	
Mutant (V600)	20 (29%)
Wild Type	50 (71%)
AJCC Stage	
IIIc (unresectable)	12 (17%)
IV	58 (83%)
M1a	15 (21%)
M1b	9 (13%)
M1c	27 (39%)
M1d	7 (10%)
Melanoma Subtypes	
Cutaneous	62 (89%)
Acral	7 (10%)
Mucosal	1 (1%)

Characteristic	Study patients receiving ≥ 1 dose (n=70)
Adjuvant PD1 Ab Progression	13 (19%)
Baseline LDH	
≤ ULN	50 (71%)
> ULN	15 (21%)
≥ 2x ULN	5 (7%)
History of Brain Metastases (treated)	
Yes	7 (10%)
No	53 (90%)
Liver Metastases	
Yes	17 (24%)
No	53 (76%)
Prior Lines Systemic Therapy (Mean = 1)	
PD1 Ab alone	60 (86%)
PD1 Ab combination (non-CTLA4 Ab)	10 (14%)
Prior BRAF directed therapy (pre-PD1 Ab)	5 (7%)

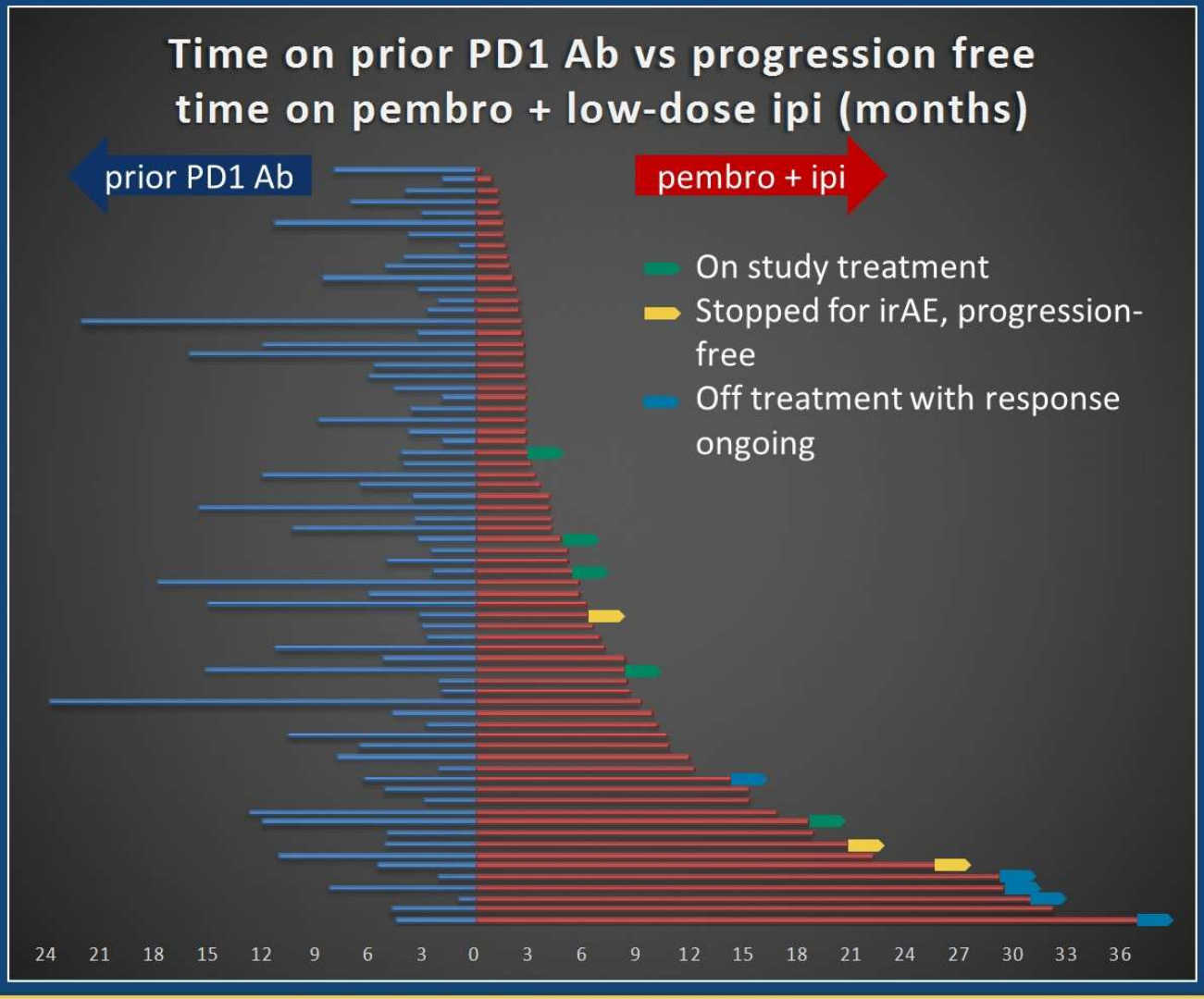
Best Overall Response



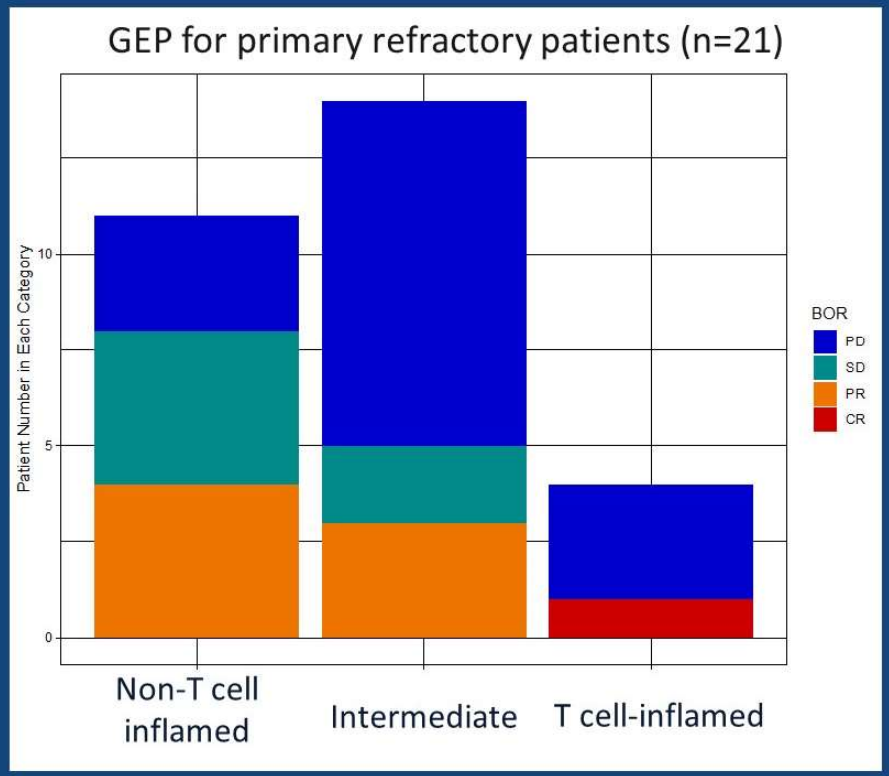
Pembro + low-dose ipi: study timeline

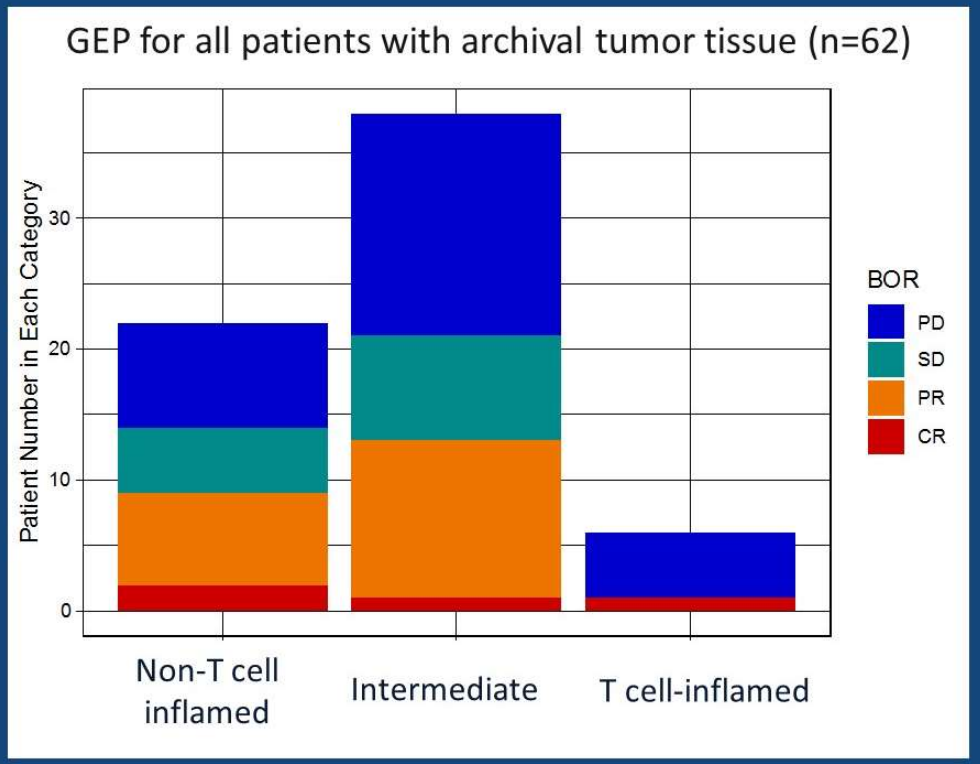
Median time on prior PD1 Ab = 4.8 months

Median PFS on Pembro + low-dose ipi = 5 months (95% CI: 2.8-8.3)



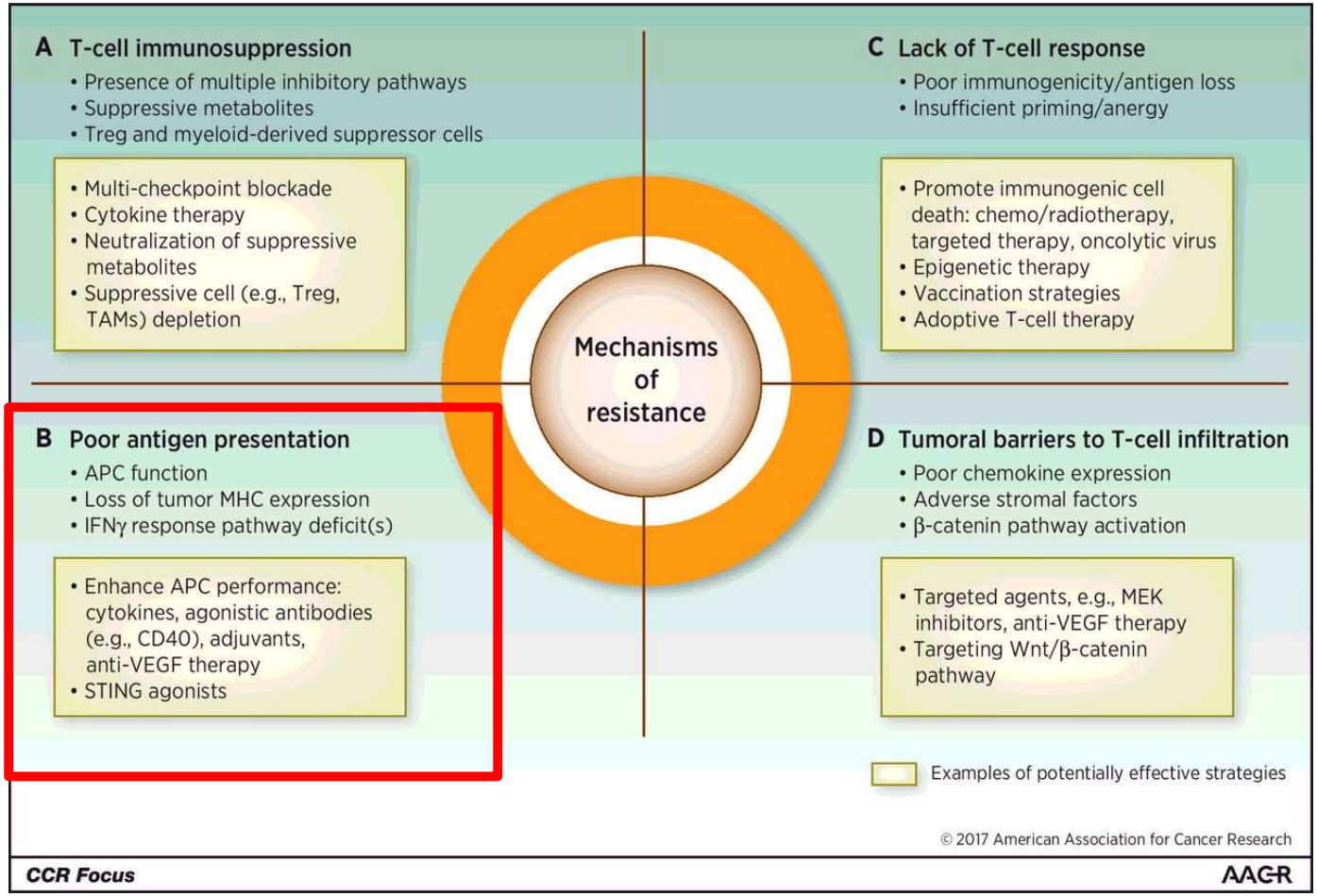
Pembro + low-dose ipi efficacy is observed in tumors with a non-T cell inflamed gene expression profile (GEP)





Spranger S, Luke JJ et al. PNAS 2016

Therapeutic Strategies: Reverse anergy, ignorance



Daphne Day et al. Clin Cancer Res 2017;23:4980-4991

VIRTUAL 2020 ESMO congress

Final Results from ILLUMINATE-204, a Phase 1/2 Trial of Intratumoral Tilsotolimod in Combination with Ipilimumab in PD-1 Inhibitor Refractory Advanced Melanoma

Cara L. Haymaker[1], Robert H.I. Andtbacka[2], Douglas B. Johnson[3], Montaser F. Shaheen[4], Shah Rahimian[5], Srinivas Chunduru[5], Nashat Gabrail[6], Gary Doolittle[7], Igor Puzanov[8], Joseph Markowitz[9], Chantale Bernatchez[10], Adi Diab[10]

[1]Department of Translational Molecular Pathology, University of Texas MD Anderson Cancer Center, Houston, TX. [2]Surgical Oncology Department of Surgery, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT. [3]Division of Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN. [4]University of Arizona, Department of Medicine and Cancer Center, Tucson, Arizona. [5]Idera Pharmaceuticals, Inc., Exton, PA. [6]Department of Oncology, Gabrail Cancer Center, Canton, OH. [7]Department of Oncology, University of Kansas Medical Center, Kansas, USA. [8]Roswell Park Comprehensive Cancer Center, Buffalo, NY. [9]Department of Cutaneous Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL. [10]Department of Melanoma Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX.

Adi Diab, MD

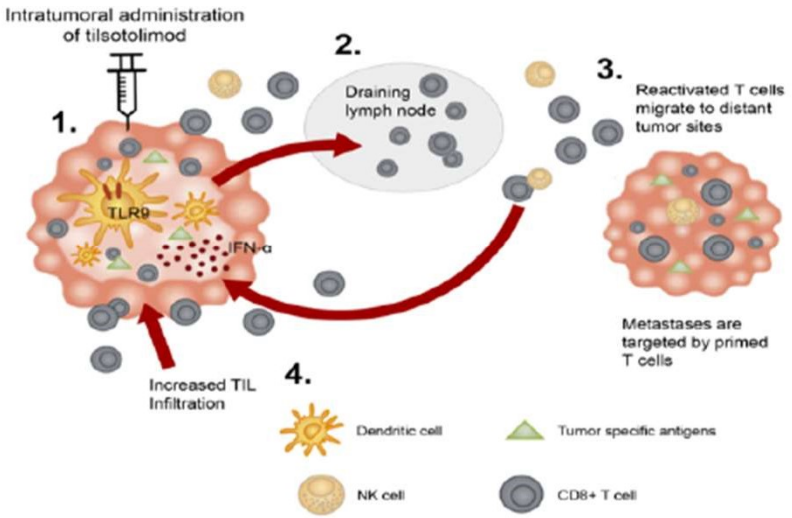
Background

Highly unmet need in post-PD-1 advanced melanoma

Patients with advanced melanoma that progressed on or after PD-1 inhibitor therapy have a poor prognosis

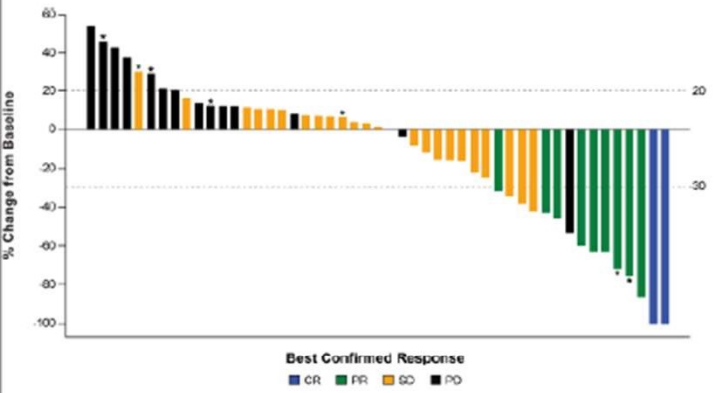
Resistance to checkpoint inhibitors may be overcome by combining them with other immune modulators

Tilsotolimod is an investigational TLR9 agonist that has been shown to activate innate and adaptive immune responses and rapidly upregulate type 1 IFN and dendritic cell activation following intratumoral injection



Clinical activity (8 mg intratumoral tilsotolimod with ipilimumab)

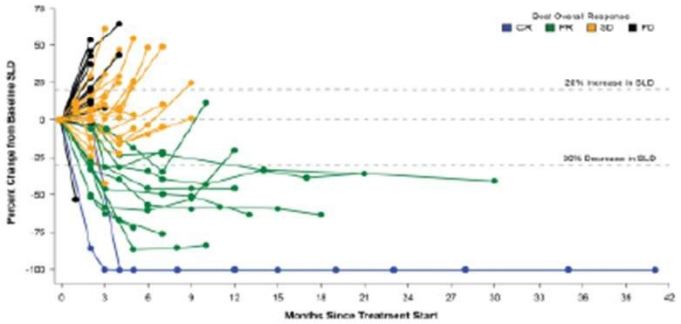
Maximum Percent Tumor Reduction

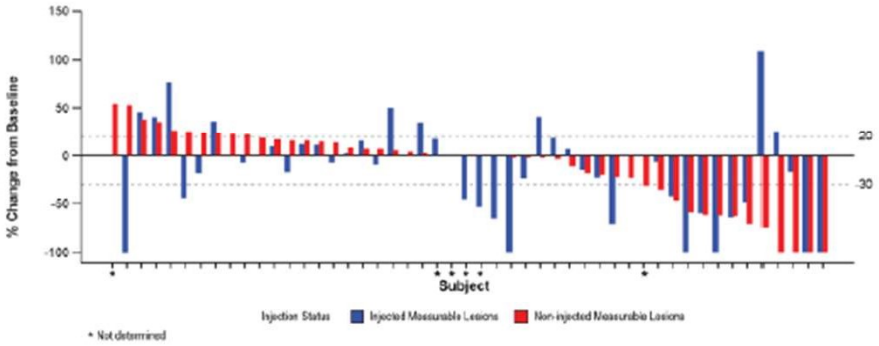


Response Assessment

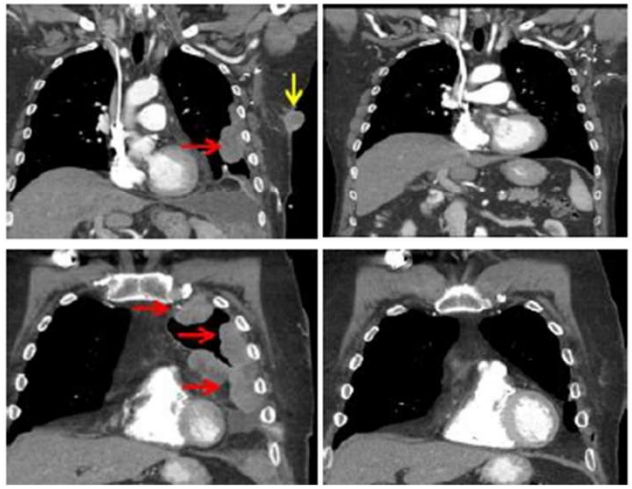
Best overall response, n (%)	
CR	2 (4.1)
PR	9 (18.4)
SD	24 (49.0)
PD	14 (28.6)
ORR (95% CI), %	22.4 (11.8-36.6)
DCR (95% CI), %	71.4 (56.7-83.4)
Median DOR (IQR), months	11.4 (4.2-NE)

Tumor Burden Change Over Time by Patient



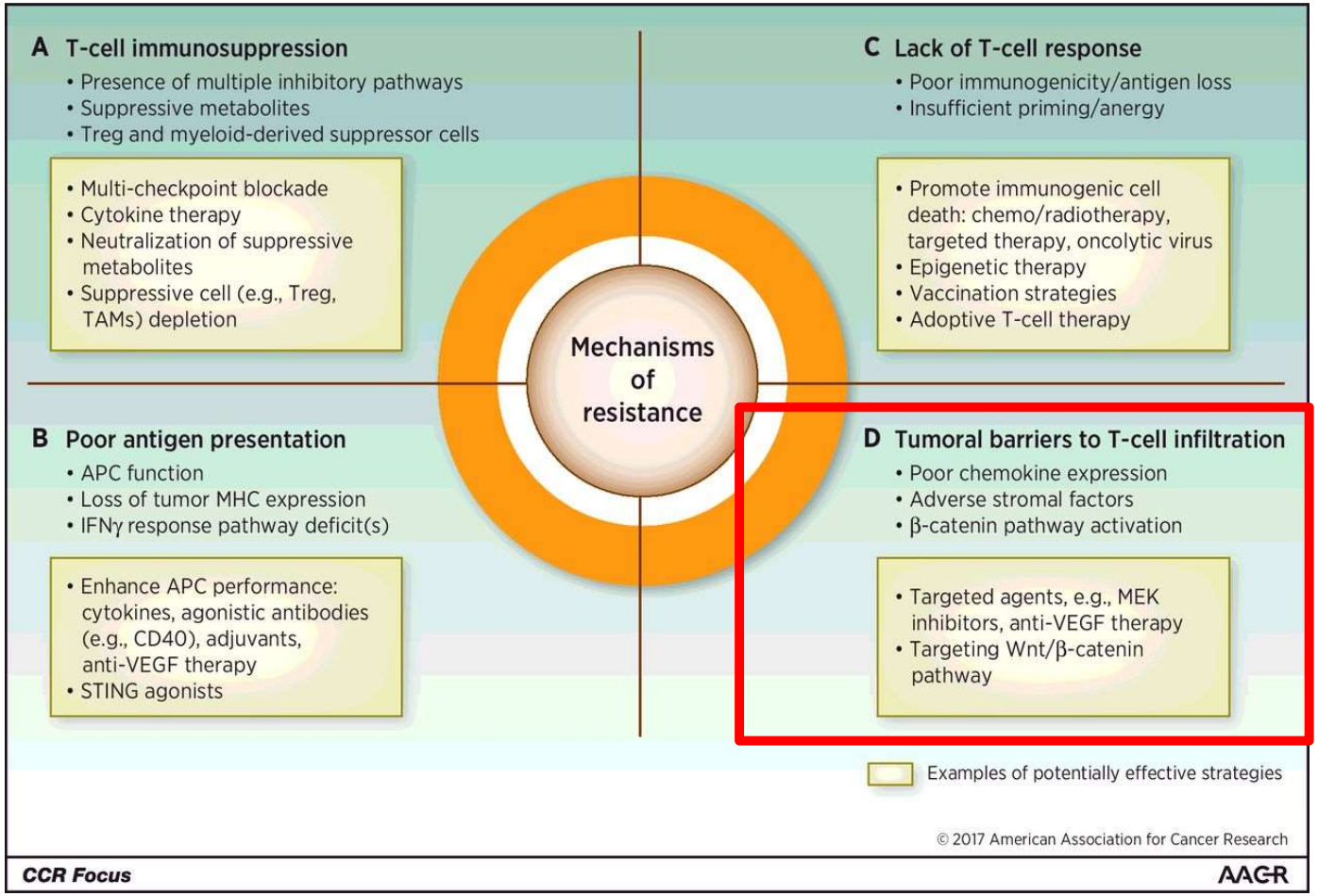


Pre-therapy (03/2016) **Post-therapy (08/2016)**



Injected Lesion
Distant Lesion

Therapeutic Strategies: Reverse anergy, ignorance



Daphne Day et al. Clin Cancer Res 2017;23:4980-4991

Lenvatinib Plus Pembrolizumab for Advanced Melanoma That Progressed on a PD-1 or PD-L1 Inhibitor: Initial Results of LEAP-004

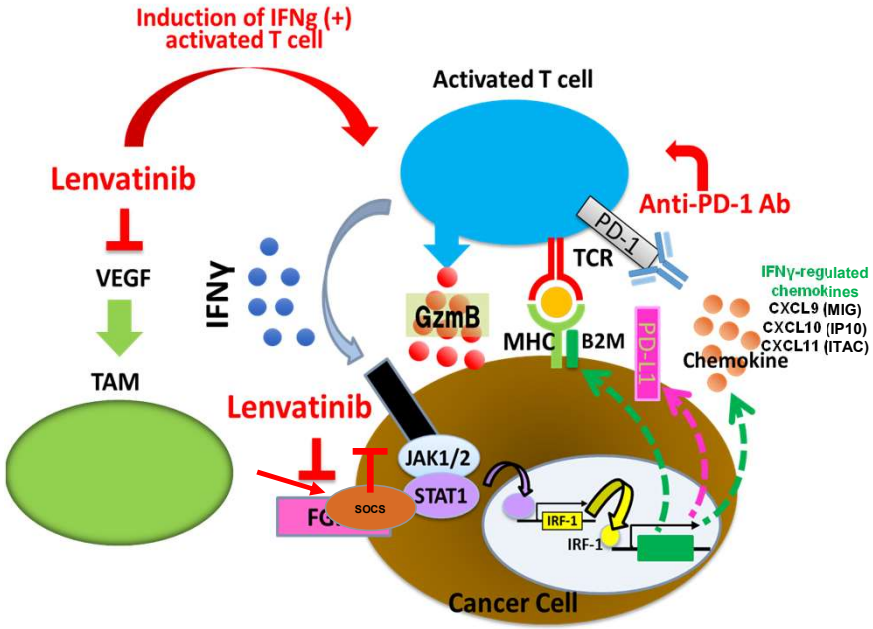
Ana Arance,[1] Steven J. O'Day,[2] Luis de la Cruz Merino,[3] Teresa M. Petrella,[4] Rahima Jamal,[5] Lars Ny,[6] Ana Carneiro,[7] Alfonso Berrocal,[8] Ivan Márquez-Rodas,[9] Anna Spreafico,[10] Victoria Atkinson,[11] Fernanda Costa Svedman,[12] Alan D. Smith,[13] Ke Chen,[14] Scott J. Diede,[14] Clemens Krepler,[14] Georgina V. Long[15]

[1]Hospital Clinic Barcelona, Barcelona, Spain; [2]John Wayne Cancer Institute, Santa Monica, CA, USA; [3]Hospital Universitario Virgen Macarena, Seville, Spain; [4]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [5]Centre hospitalier de l'Université de Montréal, Montréal, QC, Canada; [6]University of Gothenburg and Sahlgrenska University Hospital, Gothenburg, Sweden; [7]Skåne University Hospital and Lund University, Lund, Sweden; [8]Hospital General Universitario de Valencia, Valencia, Spain; [9]Hospital General Universitario Gregorio Marañón and CIBERONC, Madrid, Spain; [10]Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; [11]Princess Alexandra Hospital, University of Queensland, Brisbane, QLD, Australia; [12]Karolinska University Hospital, Stockholm, Sweden; [13]Eisai Ltd., Hatfield, United Kingdom; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Melanoma Institute Australia, University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

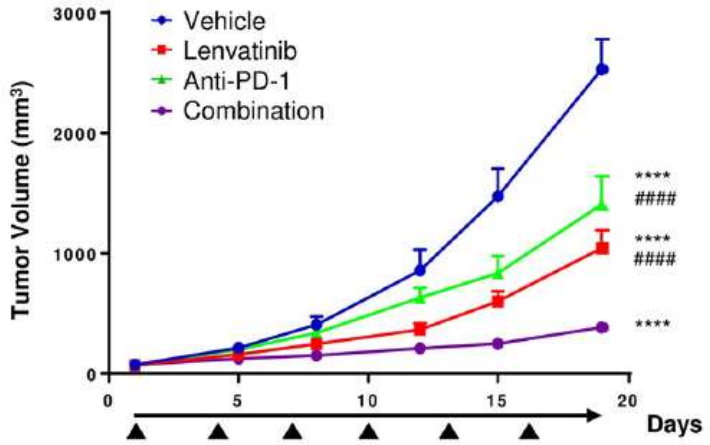
Presented at the European Society for Medical Oncology Virtual Congress 2020 (ESMO)
September 19 – 21, 2020

Rationale for Combining Lenvatinib and Pembrolizumab

Lenvatinib helps shift the tumor microenvironment to an immune stimulatory state by dual VEGFR and FGFR inhibition[1-3]



Combination of lenvatinib and anti–PD-1 has shown superior antitumor activity than either agent alone in a CT26 mouse model[1]



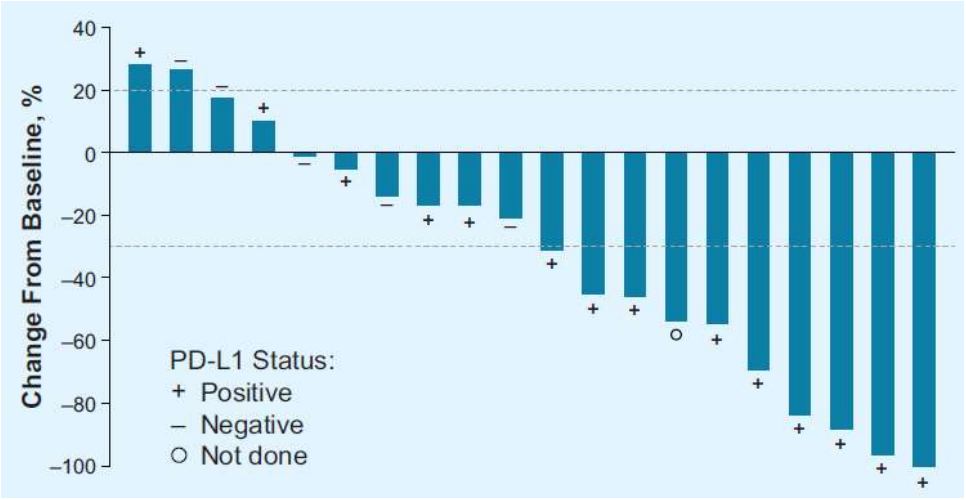
**** P<0.0001, Dunnett's test vs vehicle on day 19;
P<0.01, #### P<0.0001 vs combination.

- **1.** Kato Y et al. *PLoS One* 2019;14:e0212513; **2.** Kimura T et al. *Cancer Sci* 2018;109:3993-4002; **3.** Adachi Y et al. Poster 6637 presented at AACR 2020 Virtual Annual Meeting II. Figure in left panel provided by and used with permission of Eisai Inc., Woodcliff Lake, NJ, USA. Figure in right panel taken from Kato Y et al. *PLoS One* 2019;14:e0212513 and used in its native, unmodified form under the auspices of the Creative Commons Attribution-NonCommercial 4.0 license. See: http://creativecommons.org/licenses/by-nc/4.0.

Lenvatinib Plus Pembrolizumab Has Antitumor Activity in Melanoma

Arrance MK-7902 LEAP-004 2020

Phase 1b/2 Study of Patients with Metastatic Melanoma With ≤2 Prior Systemic Therapies



	N = 21
Median follow-up	16.0 months
ORR at 24 weeks[a]	47.6%
Median PFS	5.5 months
12-month PFS	34.7%

[a]Primary end point.

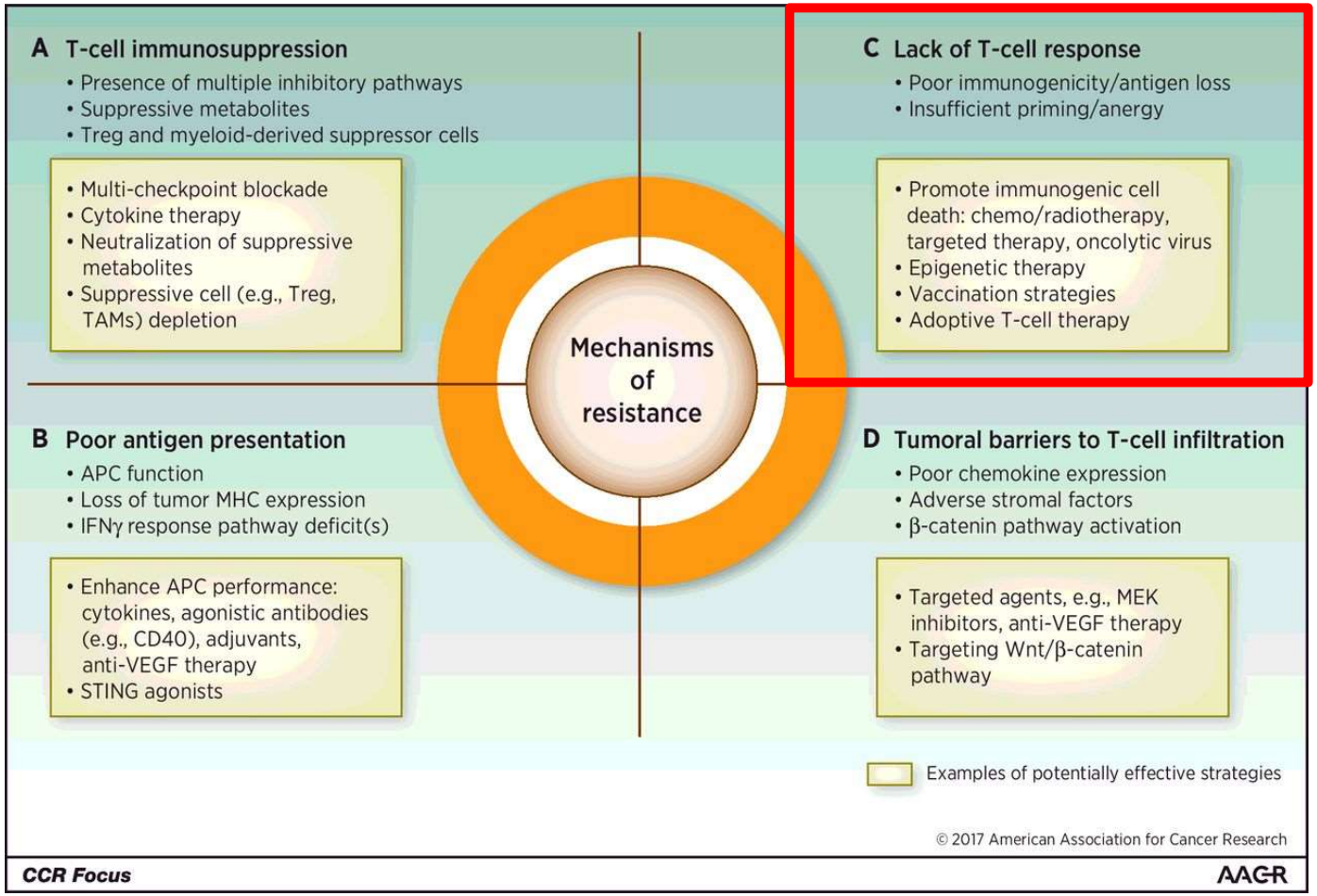
Taylor MH et al. Poster P391 presented at the Society for Immunotherapy of Cancer Annual Meeting; November 7–11, 2018; Washington, DC.

Phase II: Lavatinib + Pembrolizumab in Previously Treated melanoma
BICR-Confirmed Response by RECIST v1.1

	Total Population N = 103
ORR, % (95% CI)	**21.4% (13.9-30.5)**
DCR, % (95% CI)	65.0% (55.0-74.2)
Best overall response, n (%)	
CR	2 (1.9%)
PR	20 (19.4%)
SD	45 (43.7%)
PD	31 (30.1%)
Not assessed[a]	5 (4.9%)

[a]Patients who had no post-baseline imaging assessments.
Data cutoff date: June 10, 2020.

Therapeutic Strategies: Reverse anergy, ignorance

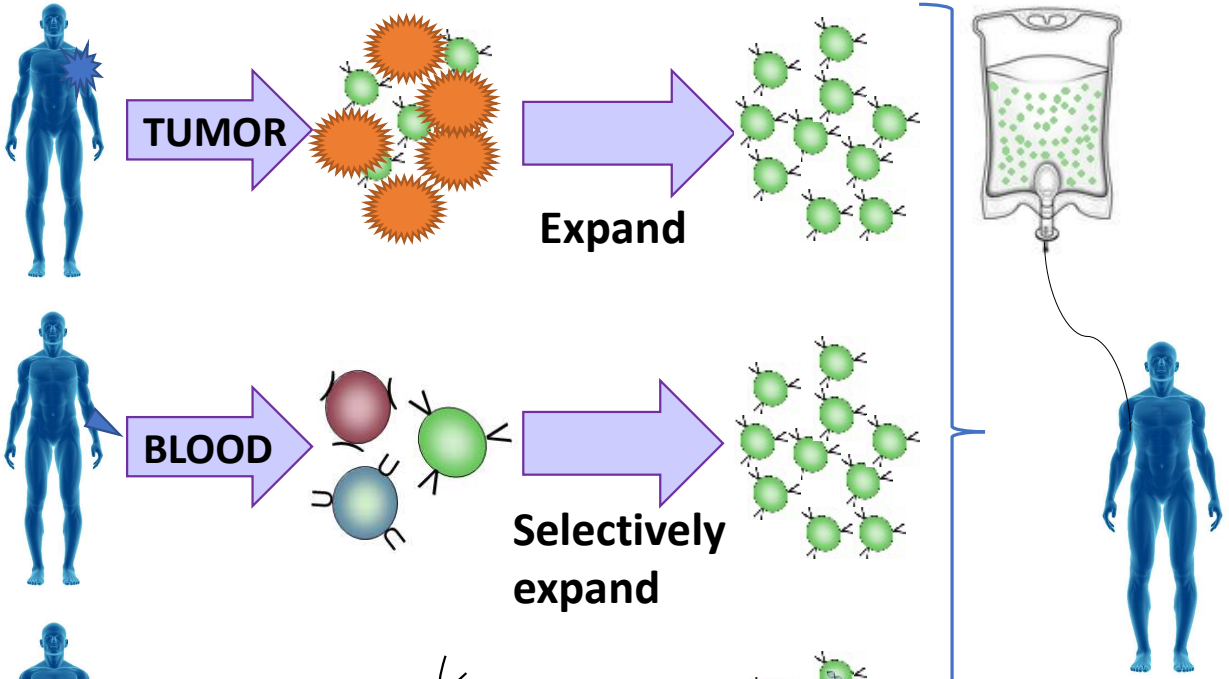


Daphne Day et al. Clin Cancer Res 2017;23:4980-4991

Approaches for adoptive T cell therapy

Cell therapies:

TILs
Tumor-Infiltrating Lymphocytes



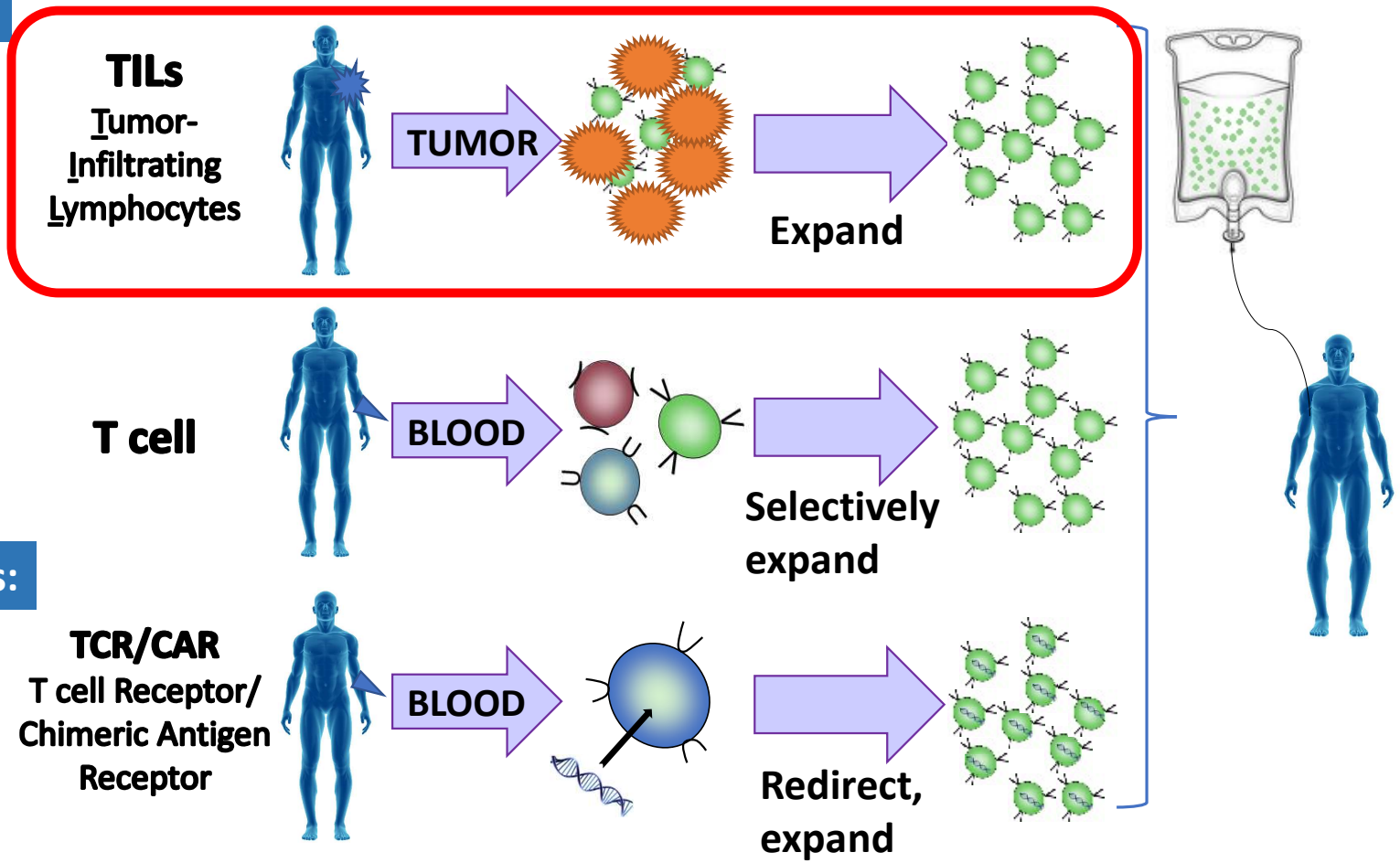
T cell

Gene therapies:

TCR/CAR
T cell Receptor/ Chimeric Antigen Receptor

Approaches for adoptive T cell therapy

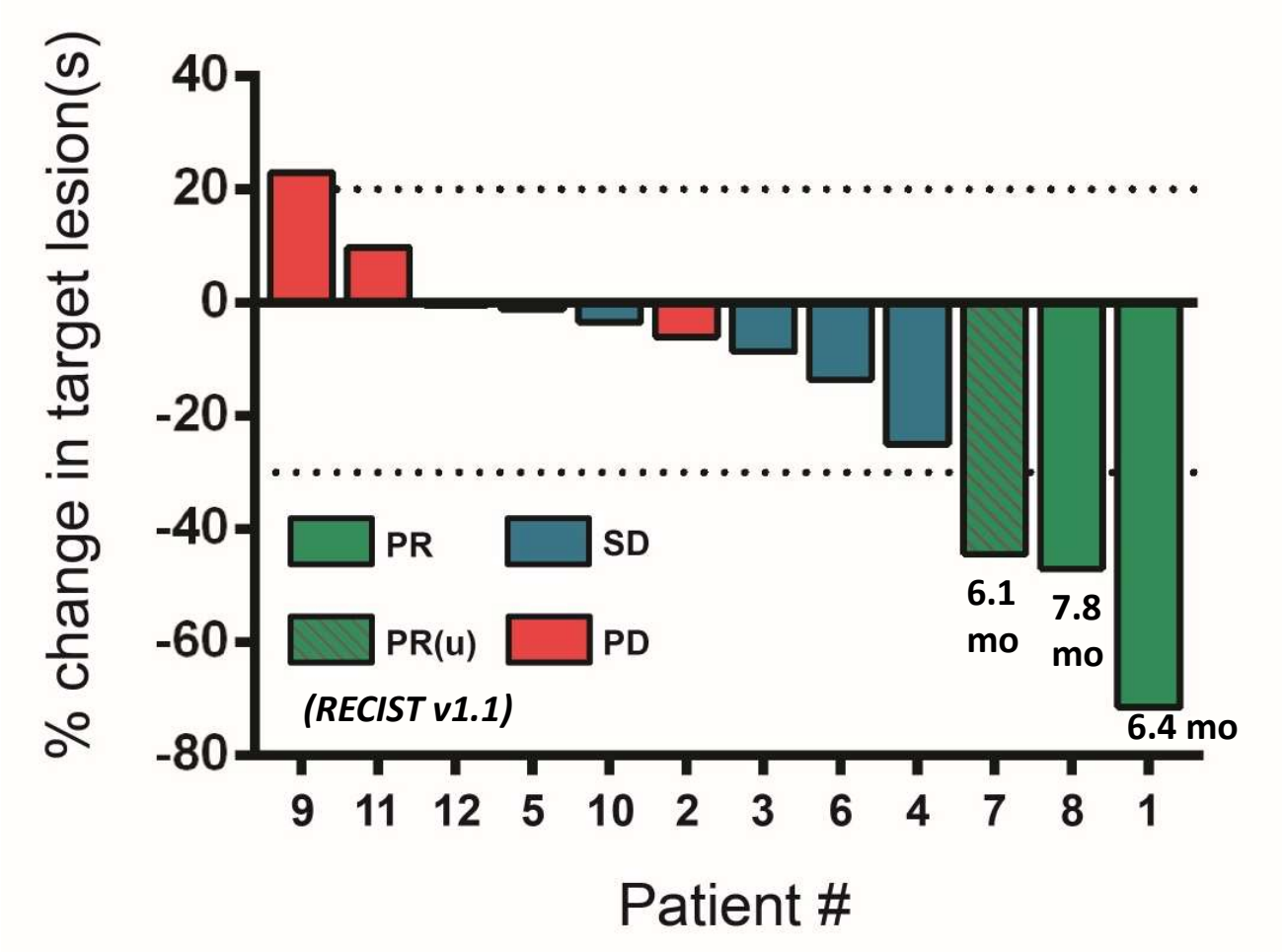
Cell therapies:



Melanoma TILs study: Patient characteristics

Patient	Sex	Age	Histology	BRAF status	M Stage[a]	Disease Sites	Previous Treatment
1	M	43	Cutaneous	WT	M1b	LN, SC, lung	None
2	M	64	Cutaneous	WT	M1c	LN, lung, liver, adrenal	Ipi/Nivo, Carbo-tax
3	F	35	Cutaneous	WT	M1c	Lung, Sp, PC, bowel	Carbo-tax, Ipi
4	M	48	Cutaneous	V600E	M1c	Brain, LN, lung, Sp, kidney, gallbladder, psoas	Dabrafenib +/- tremetinib, Ipi, Pembro
5	F	40	Mucosal	WT	M1c	SC, lung, liver, kidney, retroperitoneal	Carbo-tax, Ipi, DTIC
6	F	49	Mucosal	WT	M1c	LN, lung, pleura, uterus, bone	Ipi, Pembro, Carbo-tax
7	M	49	Cutaneous	WT	M1c	Brain, LN, SC, lung, pleura, chest wall, liver, Sp, small bowel	Ipi, Pembro
8	M	35	Cutaneous	WT	M1c	LN, SC, lung, Sp, kidney, bone, ureter, pancreas	DTIC, Ipi, Pembro, Carbo-tax
9	F	34	Cutaneous	WT	M1c	LN, SC, lung, PC, liver, kidney, breast	DTIC, Ipi, Pembro, IL-2 (injections)
10	M	61	Cutaneous	WT	M1c	Brain, LN, lung, kidney, pleura, peri-nephric	Ipi/Nivo, Pembro
11	M	42	Uveal	WT	M1c	LN, SC, lung, PC, liver, kidney, pleura	DTIC/Selumetinib, Ipi/Nivo, Pembro
12	M	61	Cutaneous	WT	M1c	Brain, LN, SC, lung, PC, liver, pericardial, adrenal	Nivo, anti-PD-1/anti-GITR, Carbo-tax

Clinical responses: Tumor Infiltrating Lymphocytes

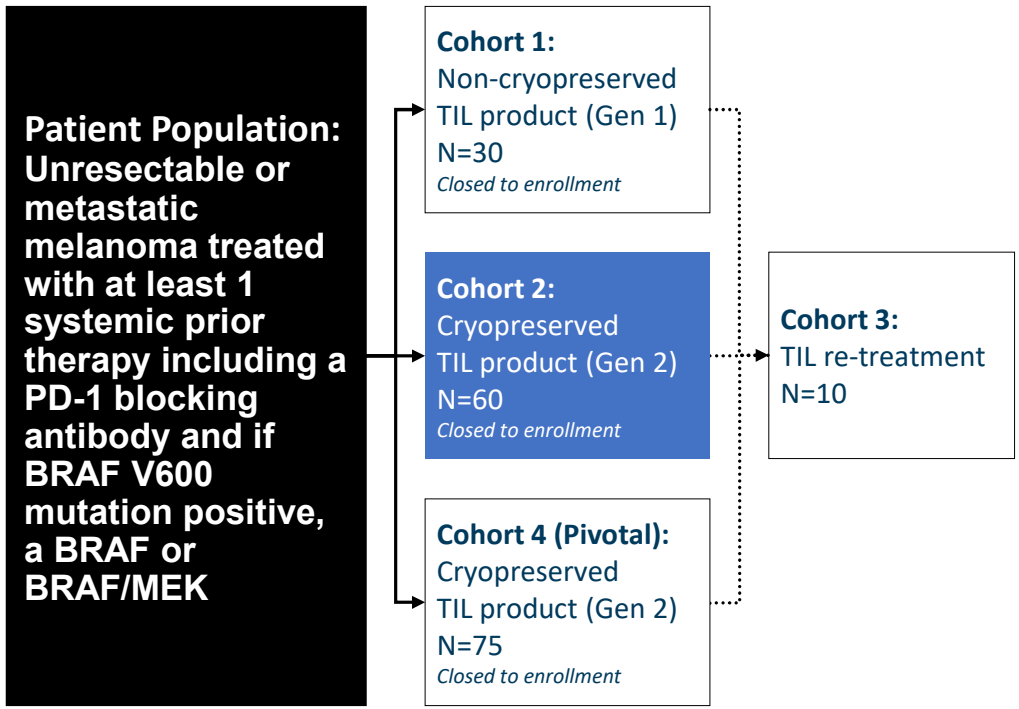


Long-term follow up of lifileucel (LN-144) cryopreserved autologous tumor infiltrating lymphocyte therapy in patients with advanced melanoma progressed on multiple prior therapies

Amod Sarnaik, MD
H. Lee Moffitt Cancer Center, Tampa, FL, USA

Iovance C-144-01 Study Design

Phase 2, multicenter study to assess the efficacy and safety of autologous Tumor Infiltrating Lymphocytes (lifileucel) for treatment of patients with metastatic melanoma (NCT02360579)



Cohort 2 Endpoints:

- Primary: Efficacy defined as investigator assessed Objective Response Rate (ORR) following RECIST 1.1
- Secondary: Safety and efficacy

Other Key Eligibility Criteria:

- One tumor lesion resectable for TIL generation (~1.5cm in diameter) and ≥ one tumor lesion as target for RECIST 1.1 assessment
- Age 18 years to 70 years at the time of consent
- ECOG Performance Status of 0-1

Methods:

- Data Extract: 23 April 2020 for Cohort 2
- Cohort 2 Safety & Efficacy sets: 66 patients who underwent resection for the purpose of TIL generation & received lifileucel infusion

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H. Lee Moffitt Cancer Center, Tampa, FL, USA

C-144-01 Cohort 2 Patient Characteristics

CHARACTERISTIC	Cohort 2, N=66, (%)
Gender, n (%)	
Female	27 (41)
Male	39 (59)
Age, years	
Median	55
Min, Max	20, 79
Prior therapies, n (%)	
Mean # prior therapies	3.3
Anti-CTLA-4	53 (80)
Anti-PD-1	66 (100)
BRAF/MEK	15 (23)
Progressive Disease for at least 1 prior therapy	
Anti CTLA-4	41 (77[1])
Anti-PD-1	65 (99)
Baseline ECOG score, n (%)	
0	37 (56)
1	29 (44)

CHARACTERISTIC	Cohort 2, N=66, (%)
BRAF Status, n (%)	
Mutated V600	17 (26)
Wild Type	45 (68)
Unknown	3 (5)
Other	1 (2)
Baseline LDH (U/L)	
Median	244
1-2 times ULN	19 (29)
> 2 times ULN	8 (12)
Target Lesions Sum of Diameter (mm)	
Mean (SD)	106 (71)
Min, Max	11, 343
Number of Target & Non-Target Lesions (at Baseline)	
>3	51 (77)
Mean (SD)	6 (2.7)
Patients with Baseline Liver and/or Brain Lesions	28 (42)

Cohort 2 patients have:

- 3.3 mean prior therapies, ranging from 1-9
- High tumor burden at baseline: 106 mm mean sum of diameters of the target lesions

[1] The denominator is the 53 patients who received prior anti CTLA 4.

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C-144-01 Cohort 2 Efficacy

RESPONSE	PATIENTS, N=66 n (%)
Objective Response Rate	**24 (36.4)**
Complete Response	2 (3.0)
Partial Response	22 (33.3)
Stable Disease	29 (43.9)
Progressive Disease	9 (13.6)
Non-Evaluable[1]	4 (6.1)
Disease Control Rate	53 (80.3)
Median Duration of Response	**Not Reached**
Min, Max (months)	2.2, 26.9+

(1) NE due to not reaching first assessment

- After a median study follow-up of 18.7 months, median DOR was still not reached (range 2.2, 26.9+)
- Response was seen regardless of location of tumor resected
- Mean number of TIL cells infused: 27.3 x 10^9

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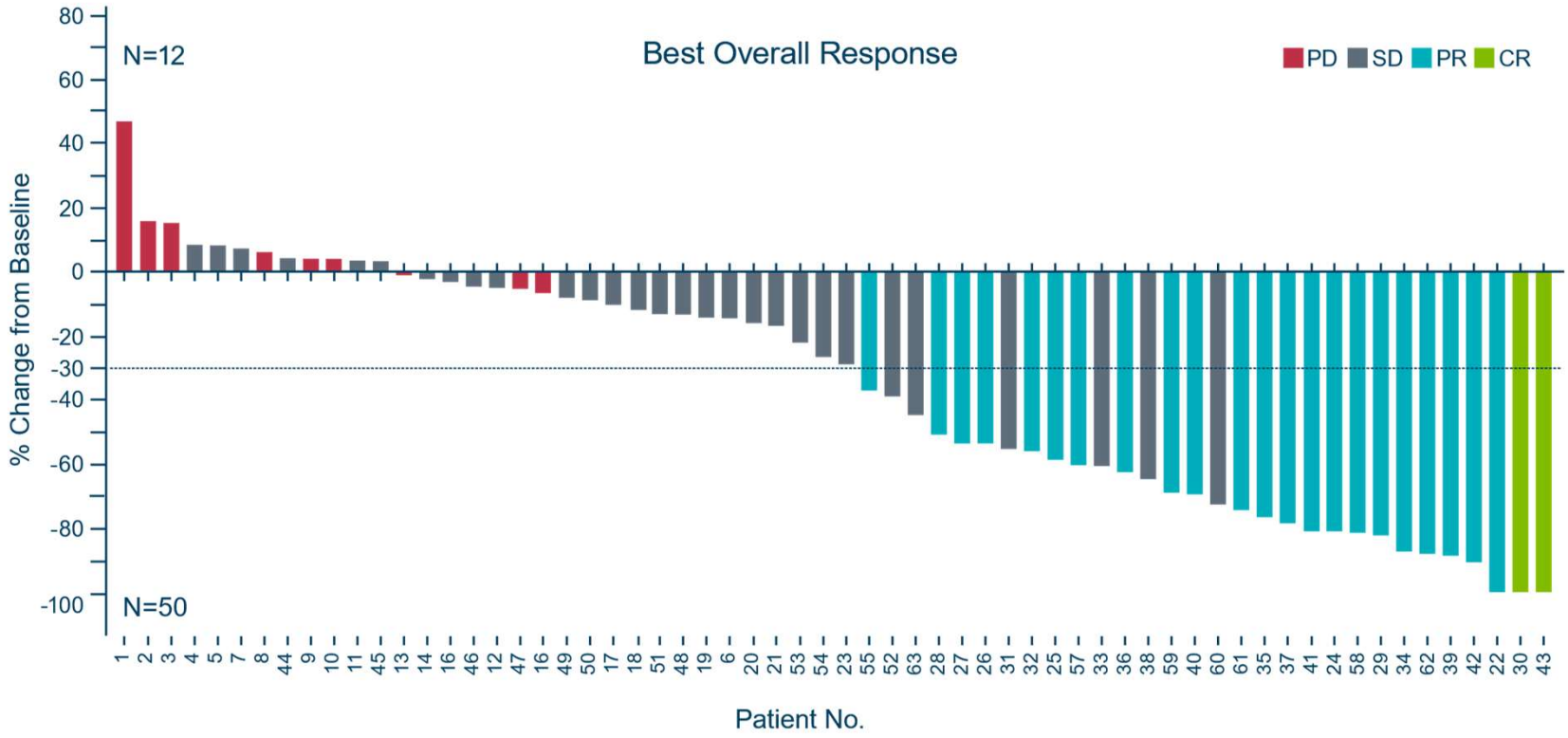
C-144-01 Cohort 2 Efficacy: Best Overall Response

- 81% (50/62) of patients had a reduction in tumor burden

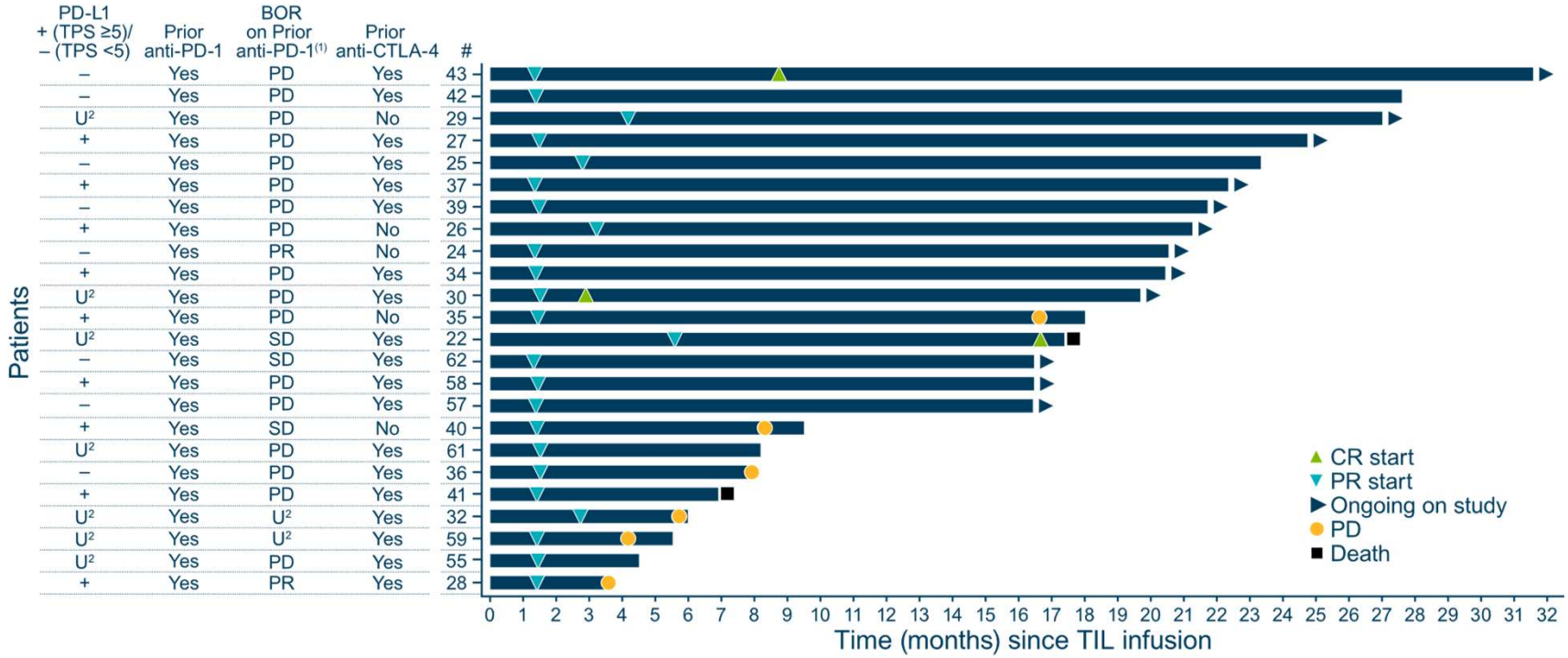


Three subjects had no post TIL disease assessment due to early death, and one due to start of new anti-cancer therapy

C-144-01 Cohort 2 Efficacy:

Time to Response for Evaluable Patients (PR or Better)

- 79% of responders had received prior ipilimumab
- Responses deepen over time



(1) BOR is best overall response on prior anti-PD-1 immunotherapy
(2) U: unknown
(3) Patient 22 BOR is PR

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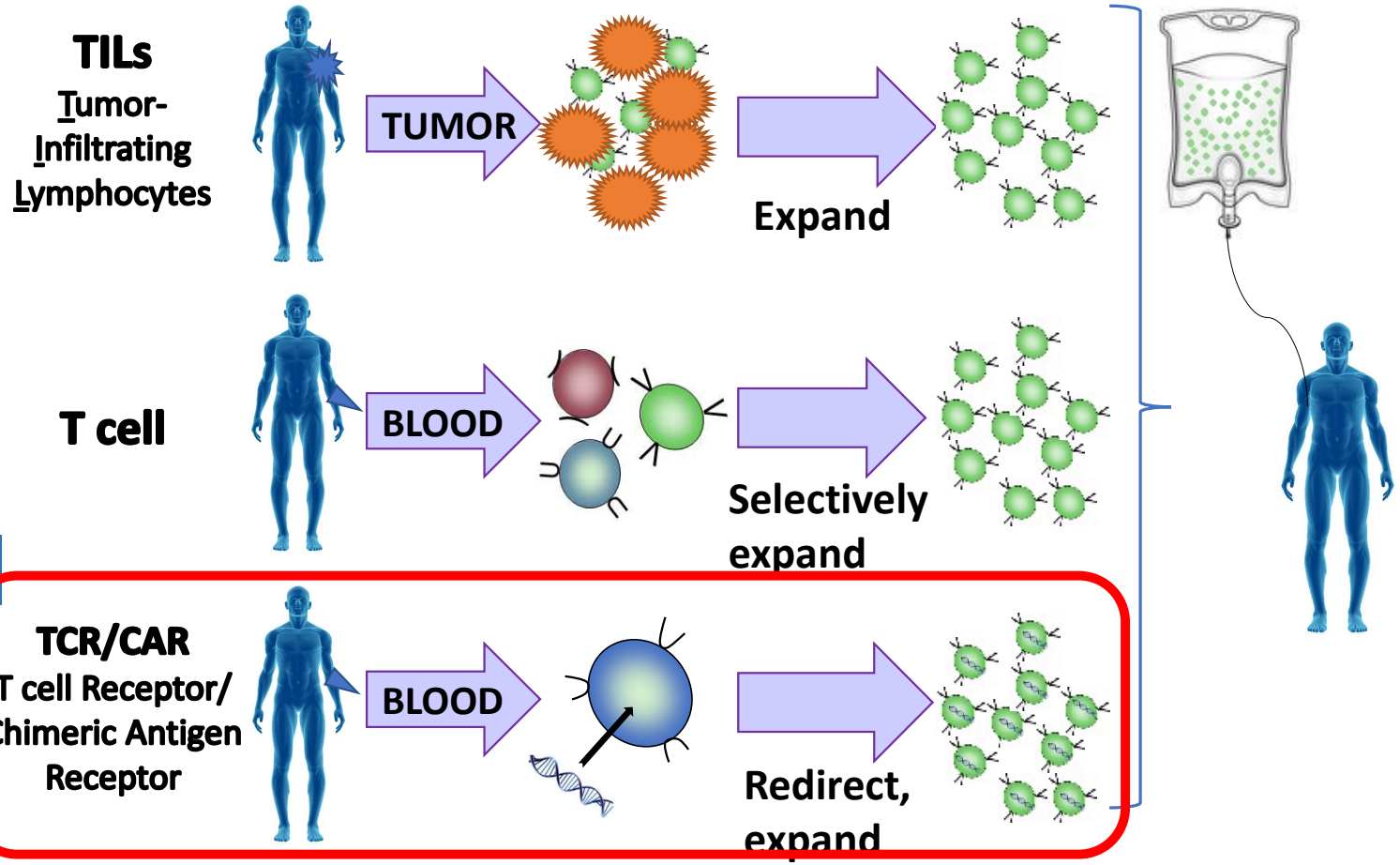
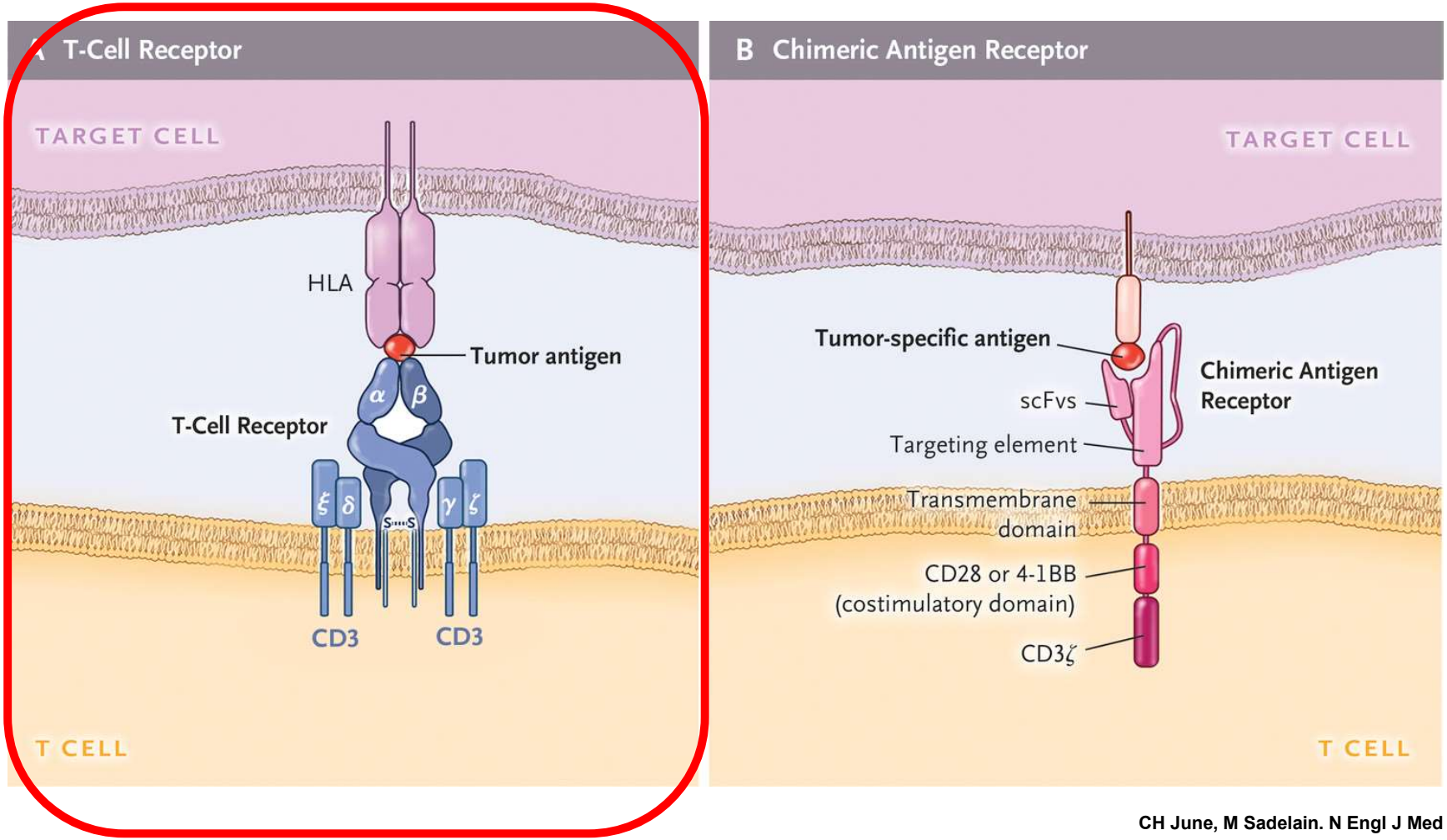
Approaches for adoptive T cell therapy

Cell therapies:

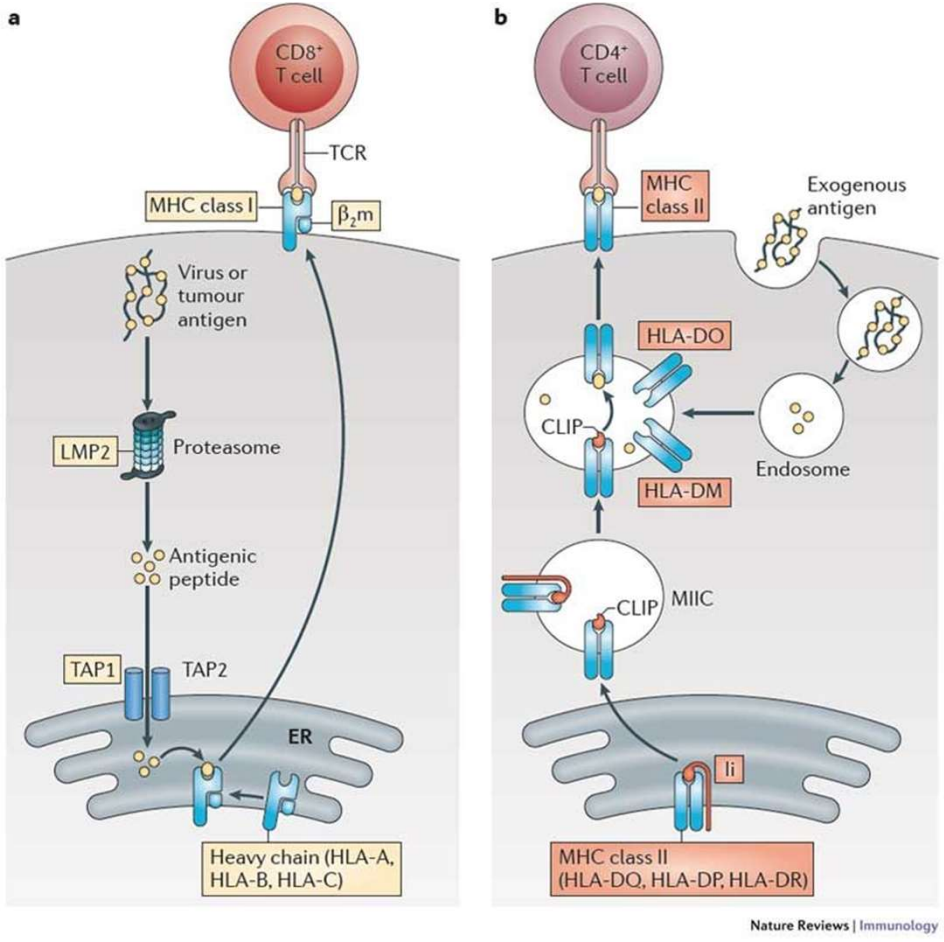


Gene-engineered T cells recognized cell surface

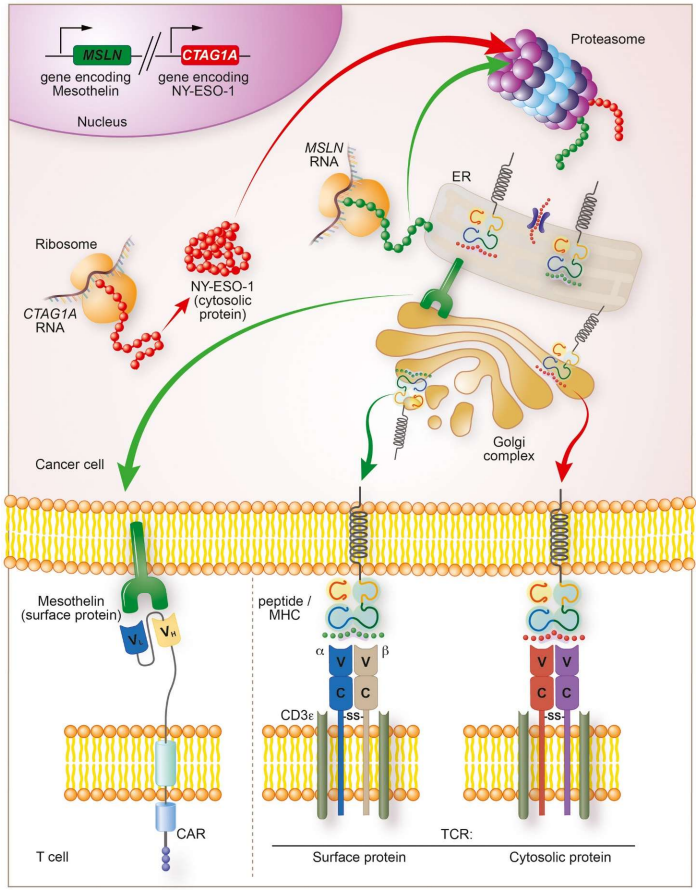


CH June, M Sadelain. N Engl J Med 2018;379:64-73.

Antigen processing and presentation

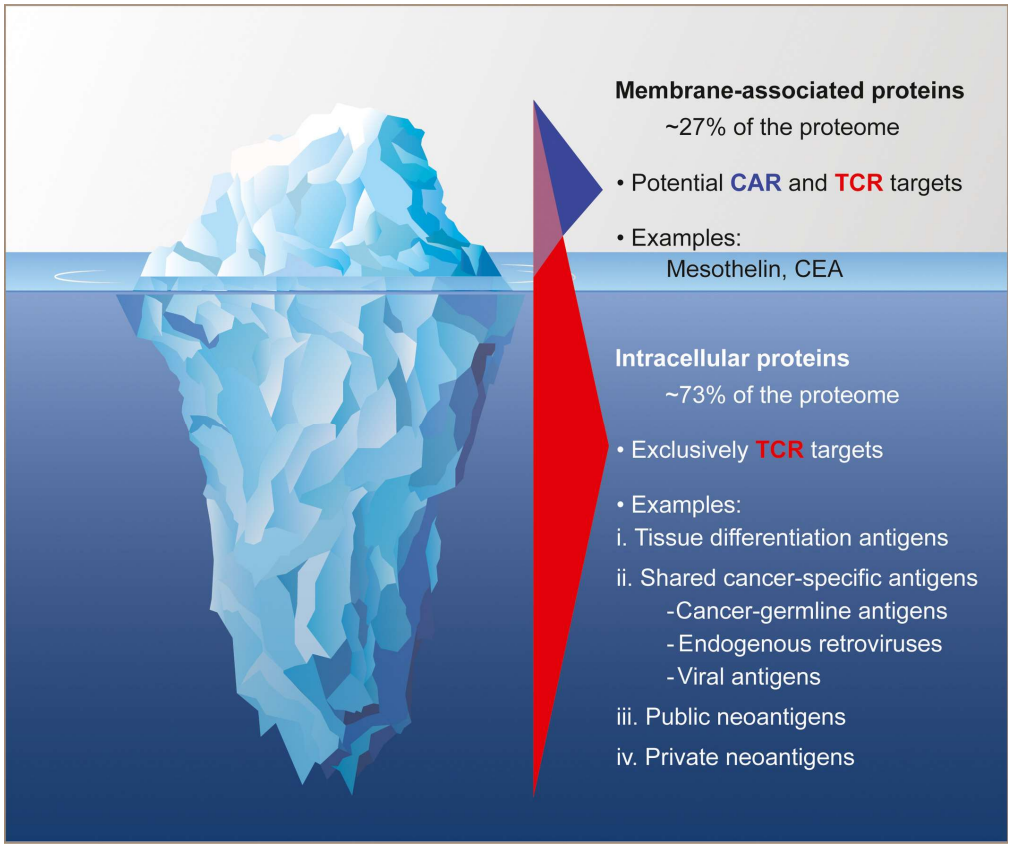


Kobajashi and van den Elsen; Nature Reviews Immunology volume 12, pages 813–820 (2012)

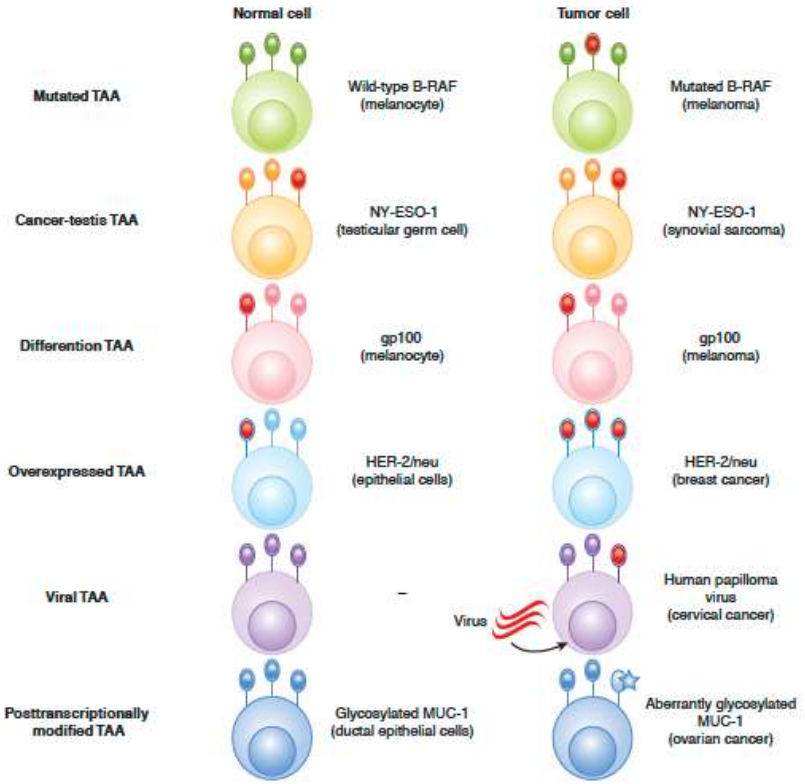


Chandran and Klebanoff; Immunological Reviews, Volume: 290, Issue: 1, Pages: 127-147.

Tumor Antigen Targets

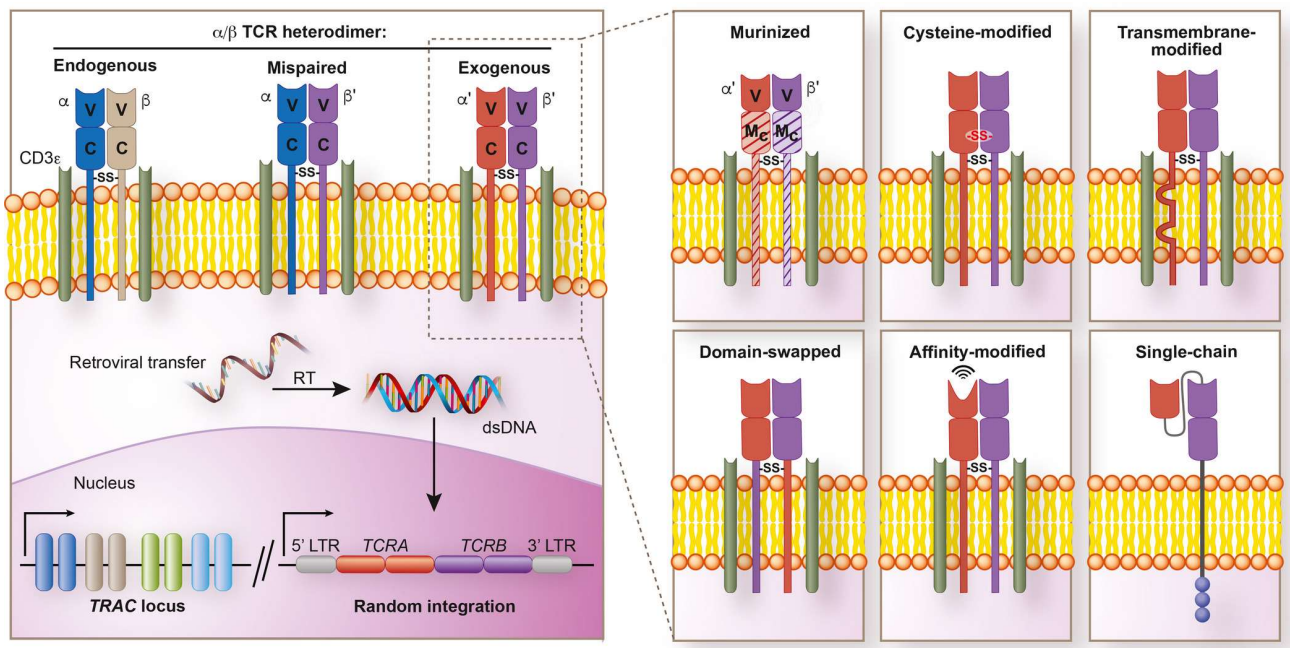


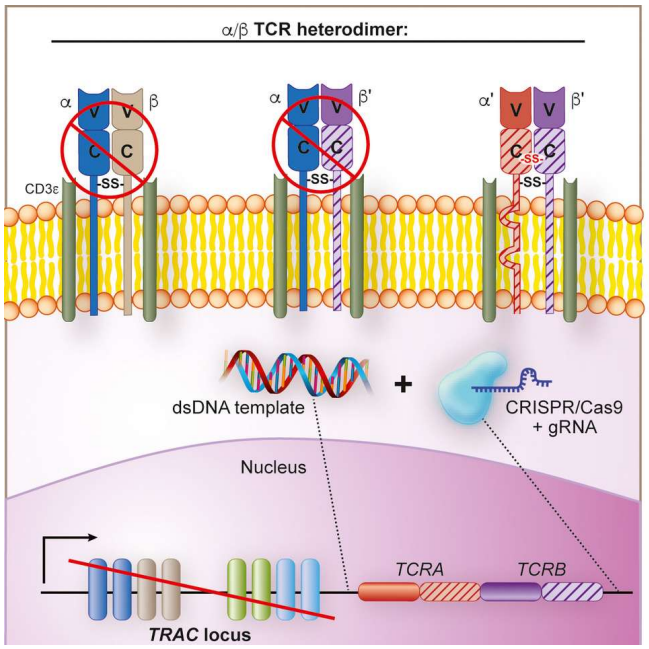
Chandran and Klebanoff; Immunological Reviews, Volume: 290, Issue: 1, Pages: 127-147.



Basic Science of Oncolog, in press.

Engineered TCR- problem of mispaired chains

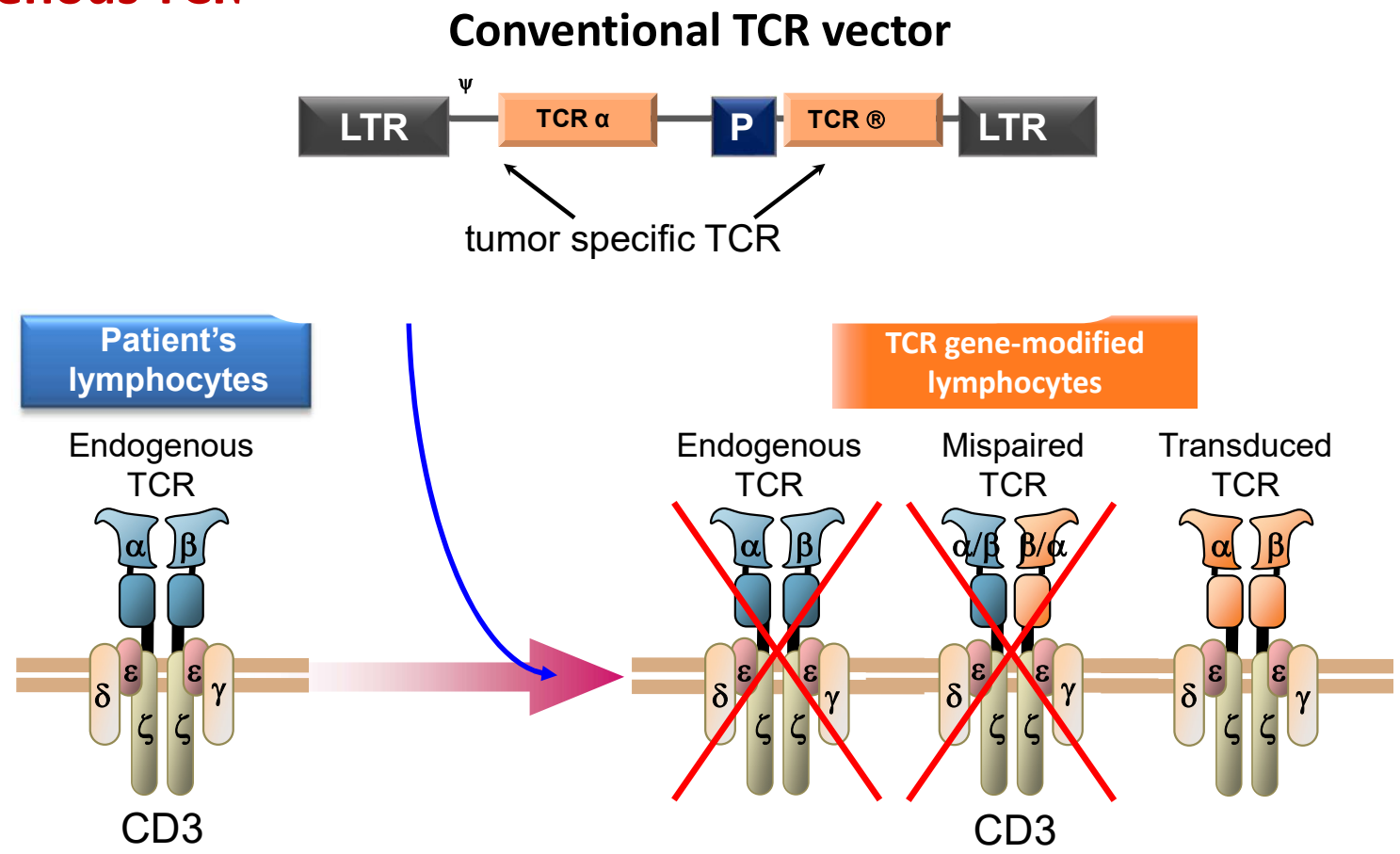




Chandran and Klebanoff; Immunological Reviews, Volume: 290, Issue: 1, Pages: 127-147.

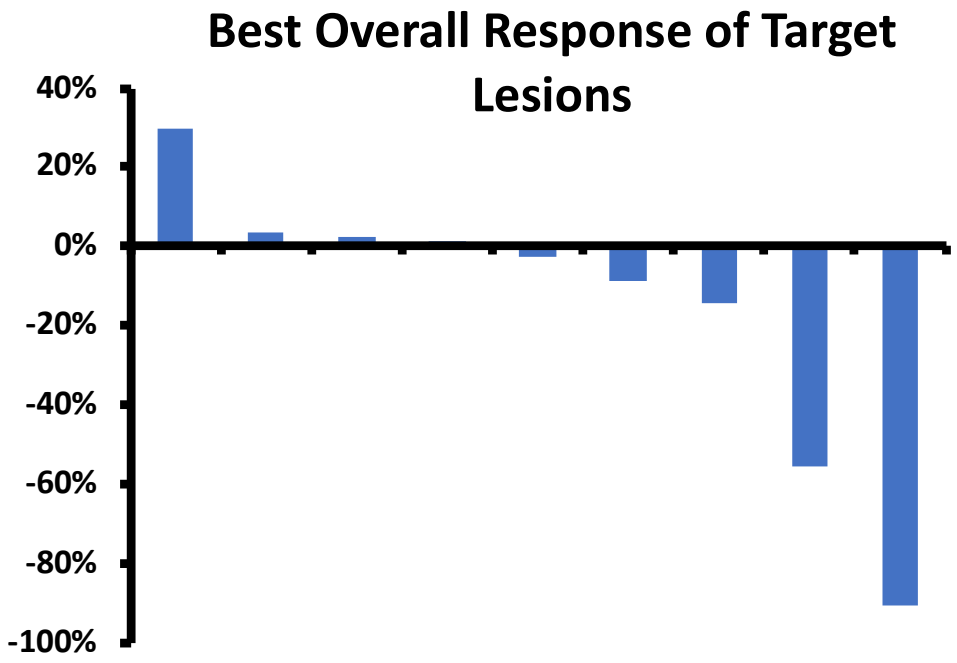
Retroviral vector (Takara Bio)

Conventional TCR vector-transduced TCR mispairs with endogenous TCR



First nine patients treated on TBI-1301 study

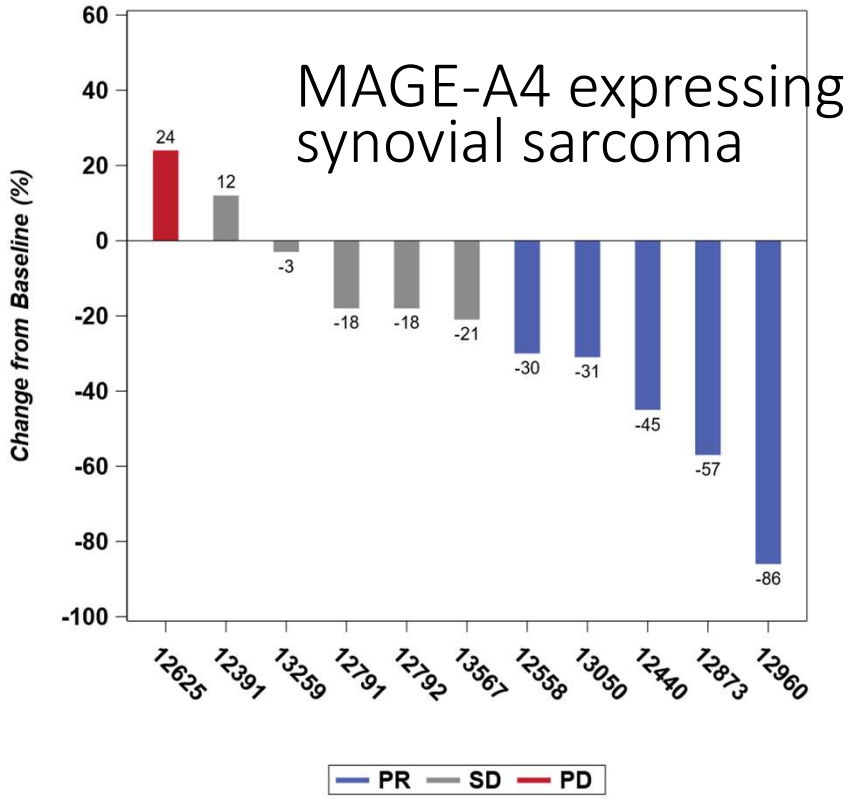
Pt	Age/Sex/Dx	Prior Tx	NYESO1 Expr	# Cells (x10^9)	CRS	Toci Tx	BOR	Time to Prog (mo)
060	40/F – Endometrial CA	carbo/tax, αPI3K, pembro, xrt	<5%	5.0	None	N	SD 3.6%	3.6
159	49/M – Synovial Sarc	doxo/ifos, xrt	>75%	2.14	Grade 2; fever, n/v, tumor pain	Y	SD -2.7%	5.5
208	38/M – Synovial Sarc	xrt, doxo/ifos	>75%	5.0	Grade 1; fever	N	PR -90.3%	6.2
003	30/F – Synovial Sarc	xrt, doxo/ifos, trem/durva	>75%	5.0	Grade 1; fever	N	PR -55.7%	10.5
109	60/F – Melanoma	encor/bini; pemb/C/T; niv/αLAG3	>75%	5.0	None	N	SD 2.2%	4.5
001	64/F – Melanoma	nivo; ipi; dab/tram, carbo/tax	<5%	5.0	None	N	PD 30%	1.7
298	28/F – Synovial Sarc	doxo/ifos, xrt; gem/tax; pazopanib	>75%	5.0	Grade 1; fever, tumor pain	N	SD -14.3%	7.3
222	50/M – Melanoma	encor/bini; ipi/nivo; pemb/αICOS; durv/IMCgp100	<5%	5.0	None	N	SD 1.3%	4.8
166	79/F – Ovarian Ca	carbo/tax; carbo/gem; doxil/αPDL1; wkly tax; phase 1; carbo	5-25%	5.0	Grade 2; fever, SVT	Y	SD -8.5%	2.9+



ASCO 2019: Butler et al.

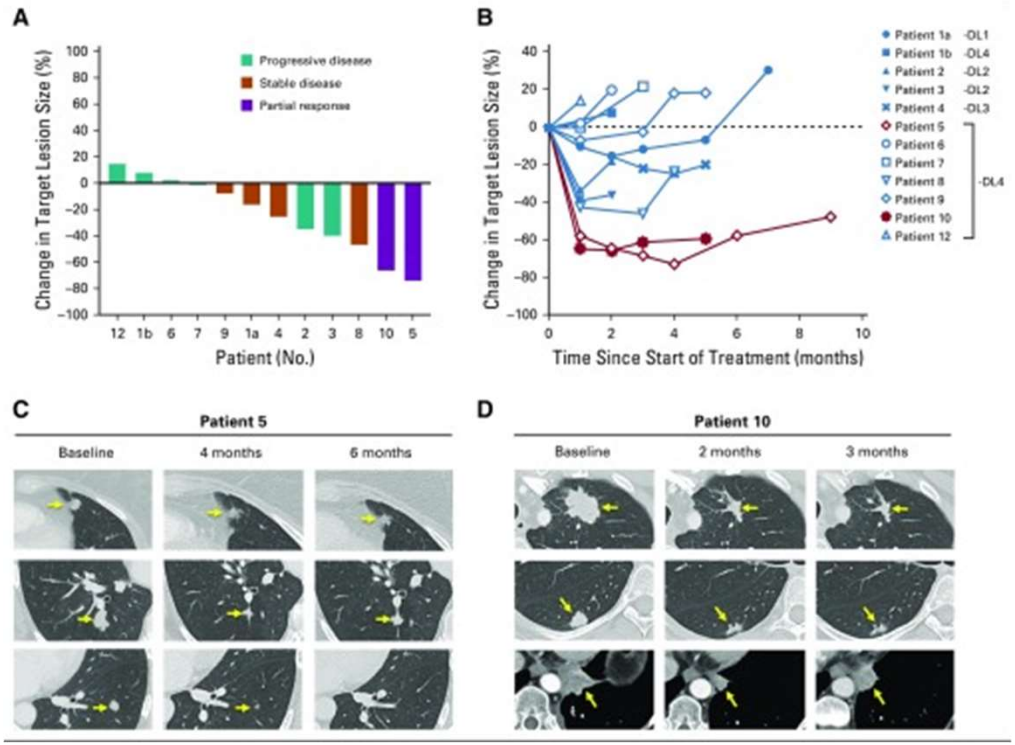
Beyond NY-ESO-1 TCR Therapy

ADP-A2M4 Spear T-cells



ESMO 2019

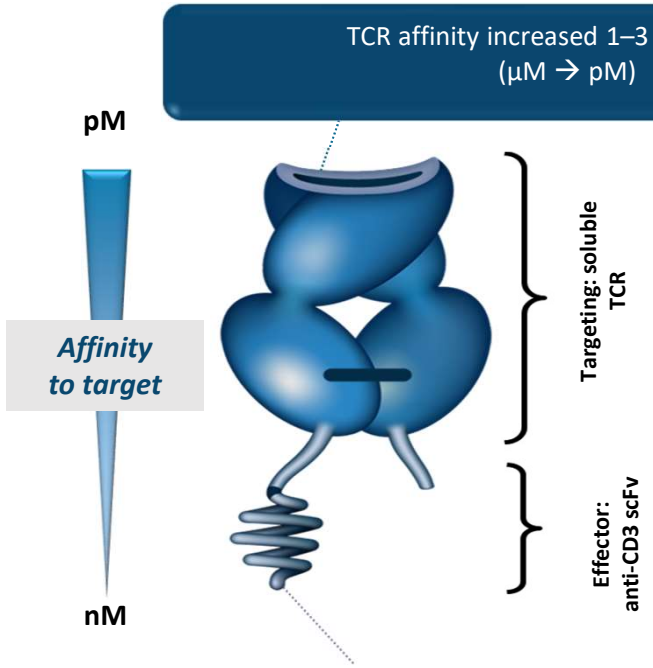
HPV16 E6 TCR



Doran et al, JCO October 2019.

Bispecifics T cell engagers: TCR-based, ImmTAC

ImmTAC: immune-mobilising monoclonal TCRs against cancer[1–3]



Recognise low level of cell surface epitopes
(as low as 5–10 epitopes per cell)

Redirect T-cell subsets
CD8+ and CD4+ T cells

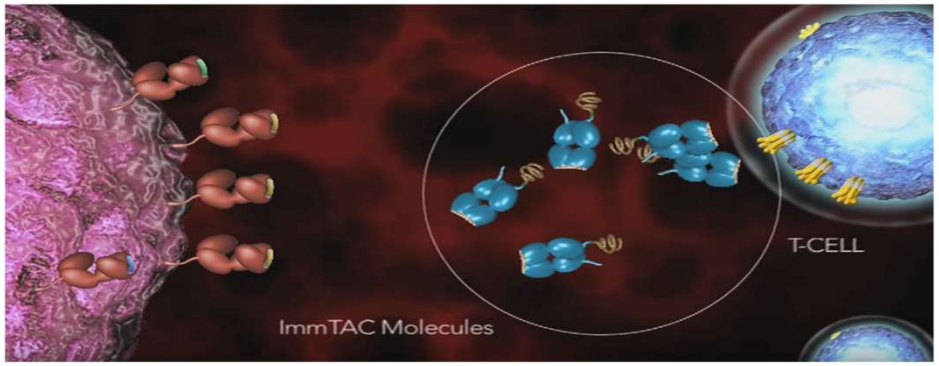
Anti-CD3 effector function; lower affinity allows killing of multiple target cells

CD: cluster of differentiation.

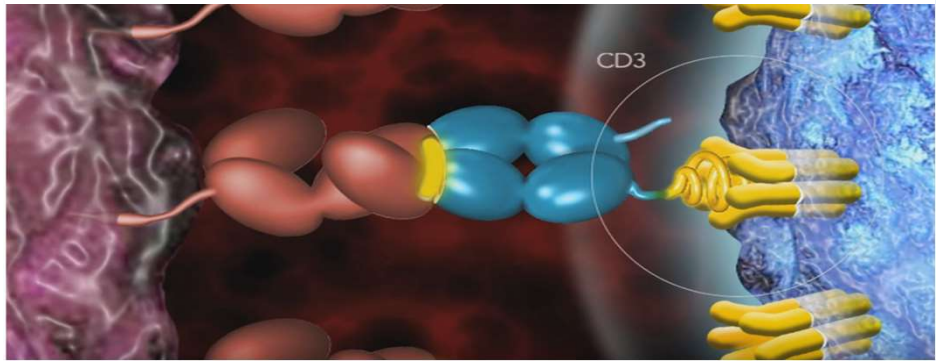
1. Boudousquie et al. 2017;
2. Oates et al. 2015;
3. Bossi et al. 2014.

Upcoming studies: NY-ESO-1 bispecific

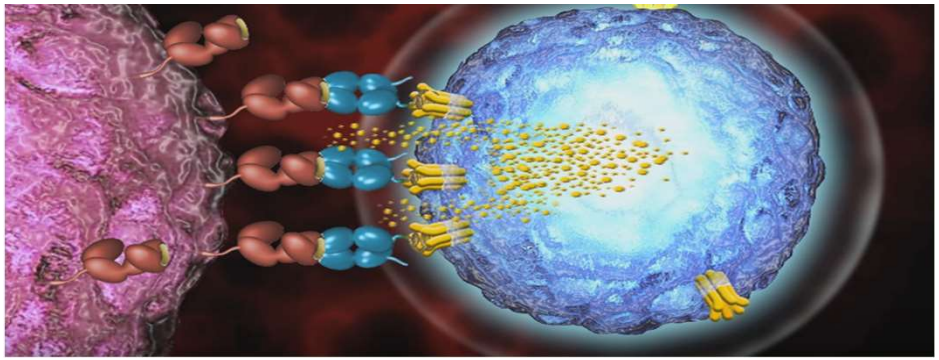
Step 1: ImmTAC molecules are infused[1–3]



Step 2: The TCR end recognises the **target HLA complex** on the cancer cell. The anti-CD3 engages the CD3 receptor on killer T cells[1–3]



Step 3: The T cell is activated and releases lytic granules, killing the cancer cell[1–3]

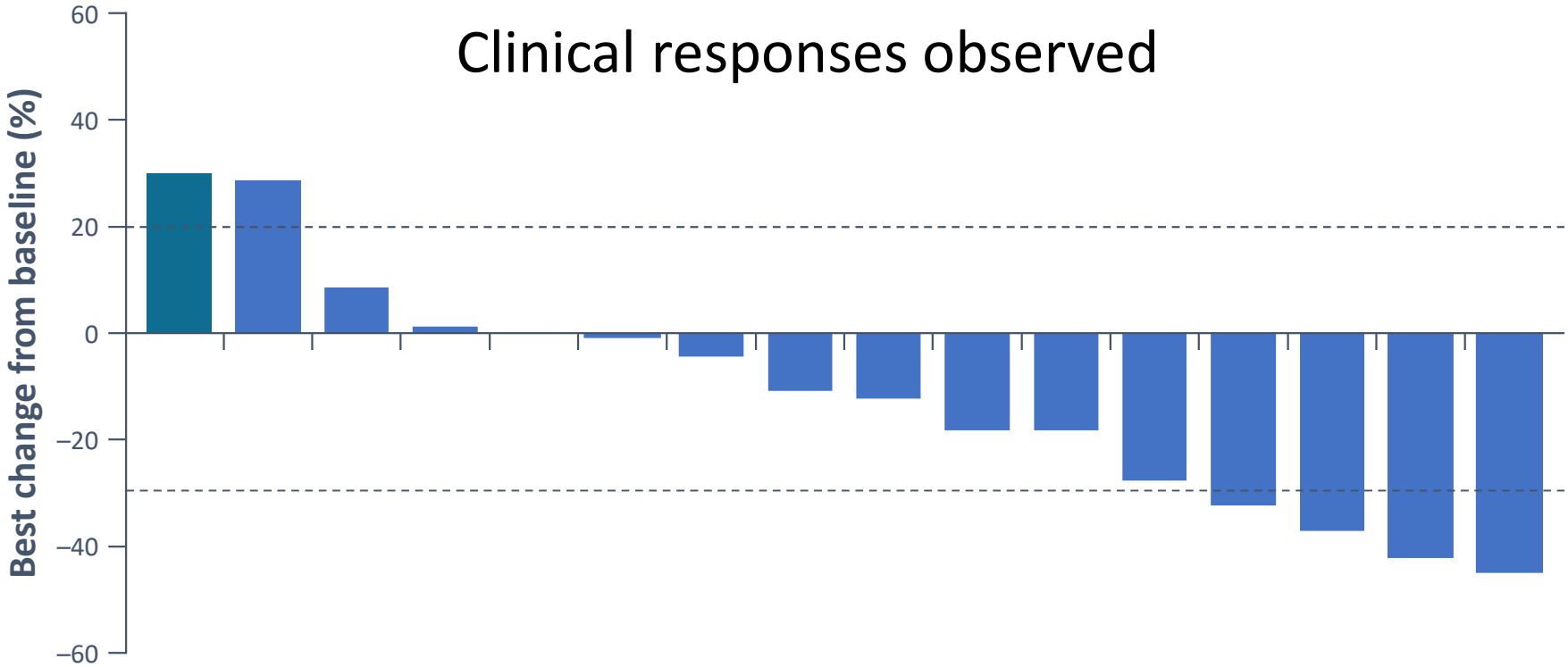


Immunocore

Tumor Immunotherapy Program

1. Boudousquie et al. 2017; 2. Oates et al. 2015; 3. Bossi et al. 2014.

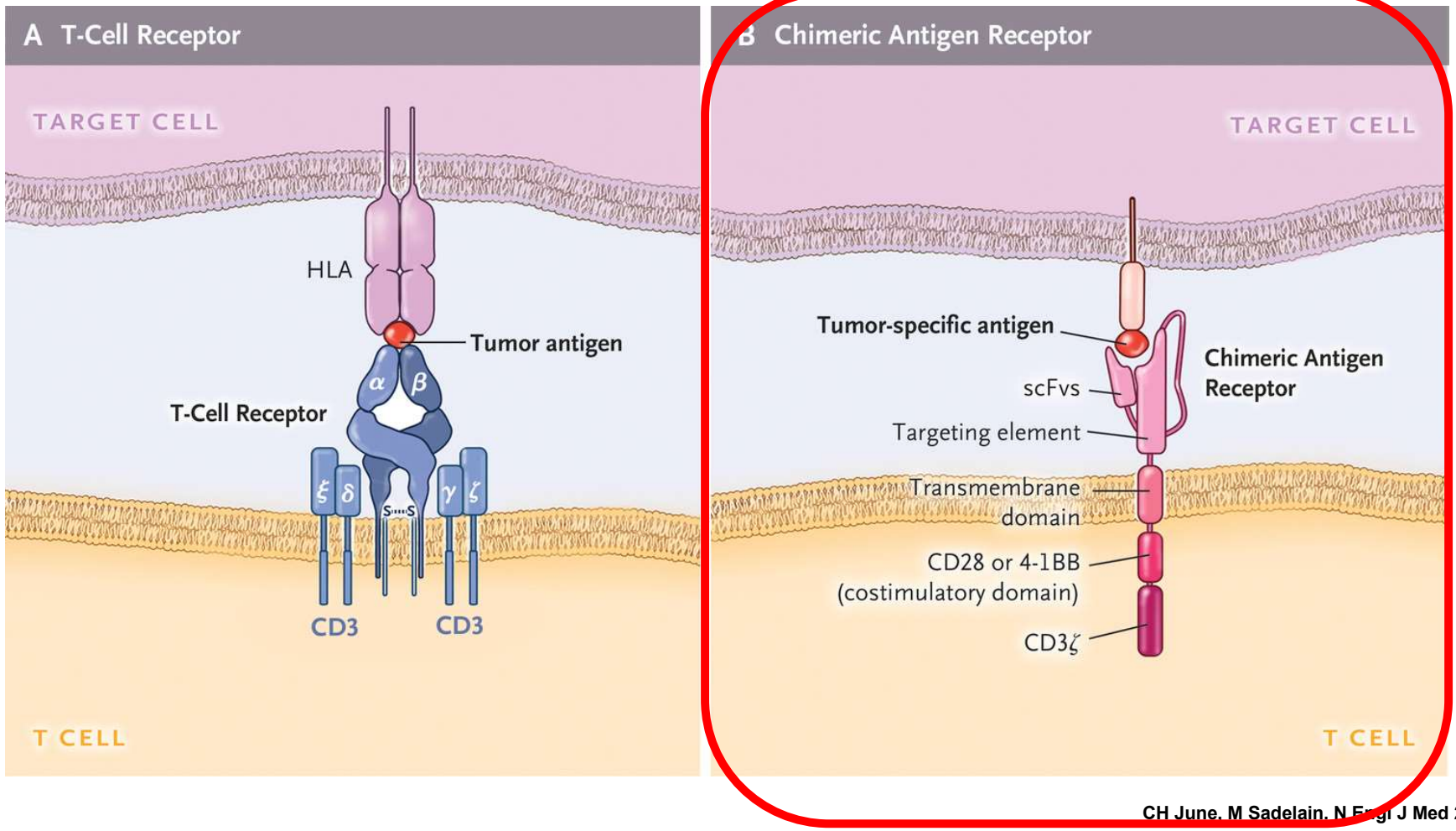
Phase I study of IMCgp100 in Uveal Melanoma



Immunocore

Sato T, et al. 2018.

Gene-engineered T cells recognized cell surface



CH June, M Sadelain. N Engl J Med 2018;379:64-73.

Survival of B-ALL Patients after CD19-Targeted CAR T Cells

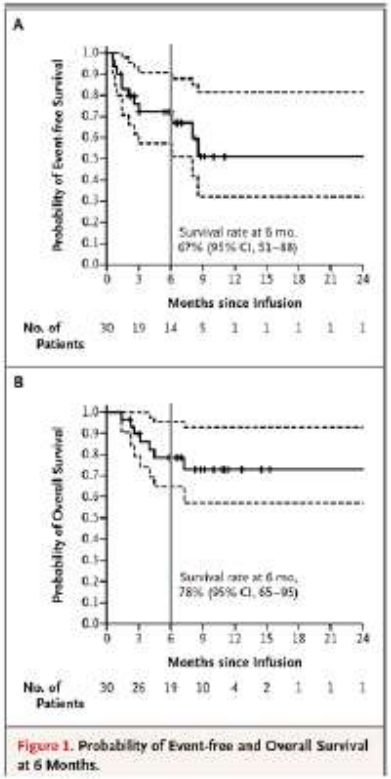
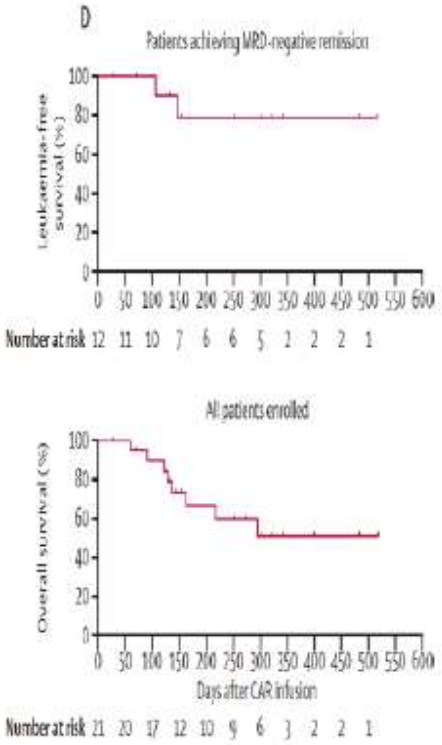
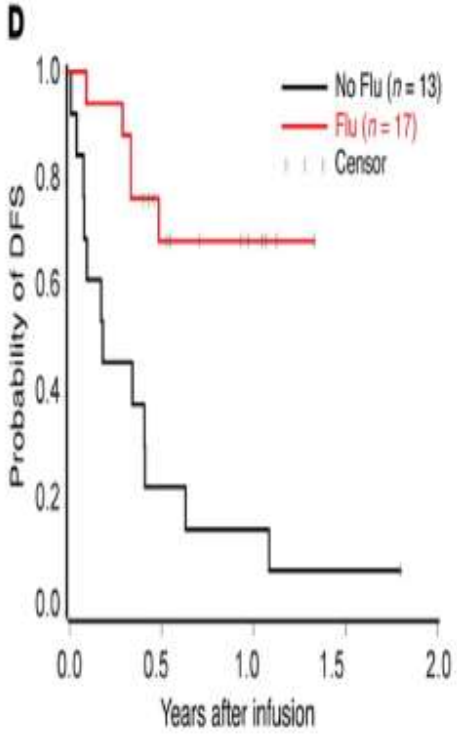


Figure 1. Probability of Event-free and Overall Survival at 6 Months.

Maude et al. *N Engl J Med*. 2014;371:1507-1517.

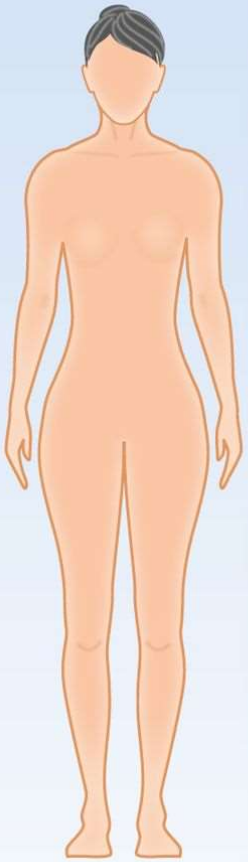


Lee et al. *Lancet* 2015;385:517-528.

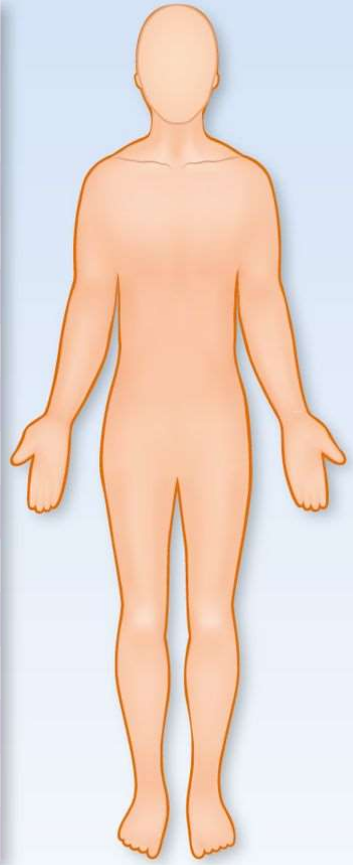


Turtle et al. *J Clin Invest*. 2016;126:2123-2138.

Solid tumor targets for CAR



Brain	EGFRvIII, HER2, IL13RA
Head and neck	ERBB family
Lung	CEA, HER2, MSLN
Pleura	FAP, MSLN
Breast	CEA, cMET, HER2, MSLN
Gastric	CEA, HER2
Liver	GPC3
Colon	CEA
Pancreas	CEA, MSLN
Renal	VEGFR2
Ovarian	FR, HER2, MSLN, MUC16
Prostate	PSMA
Skin	GD2, VEGFR2
Bone	GD2, HER2
Soft tissue	GD2, HER2
Neural	GD2, L1-CAM



Aurore Morello et al. Cancer Discov 2016;6:133-146

Mesothelin

Regional delivery of mesothelin-targeted CAR T cells for pleural cancers: safety and preliminary efficacy in combination with anti-PD-1 agent

2019 ASCO Annual Meeting, Chicago

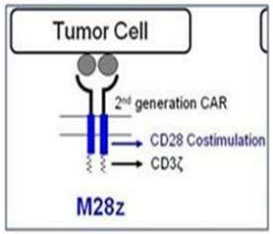
Memorial Sloan Kettering Cancer Center

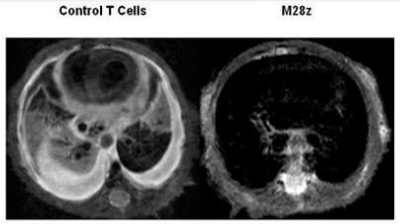
Prasad S. Adusumilli, Marjorie G Zauderer, Valerie W Rusch, Roisin E O'Cearbhaill, Amy Zhu, Daniel Ngai, Erin McGee, Navin Chintala, John Messinger, Waseem Cheema, Elizabeth F Halton, Claudia R Diamonte, John Pineda, Alain Vincent, Shanu Modi, Steve Solomon, David R Jones, Renier J Brentjens, Isabelle C Riviere, Michel W Sadelain

Presented By Prasad Adusumilli at 2019 ASCO Annual Meeting

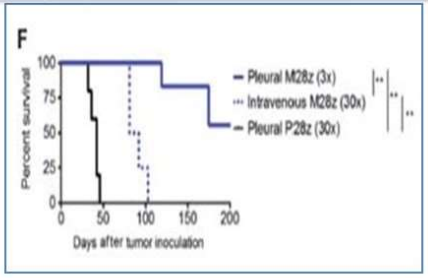
Intrapleural administration potentiates CAR T cell efficacy

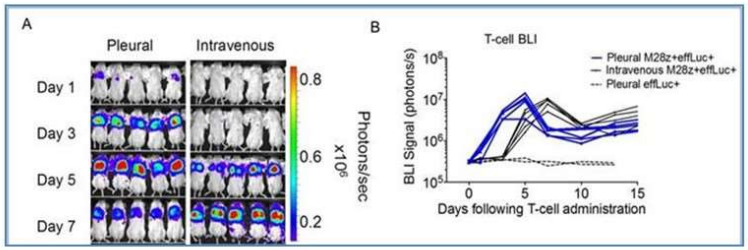
Second generation CD28 co-stimulated CAR

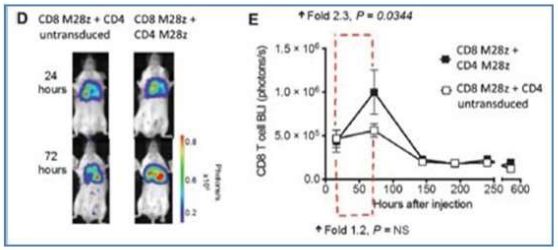




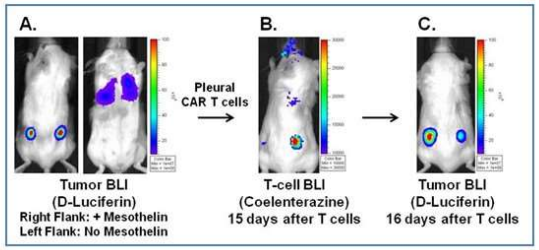
MRI Scan in Representative Mice Administered with Control or Mesothelin-Targeted M28z CAR T Cells







CD4 dependent additive efficacy



Regional administration promotes systemic immunosurveillance

Adusumilli PS, Sadelain M. *Sci Transl Med* 2014

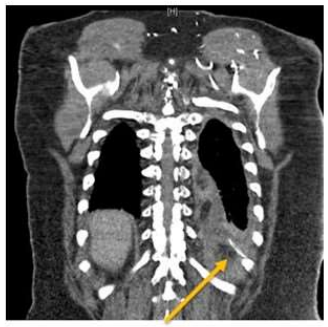
Single dose of CAR T cells administered intrapleurally

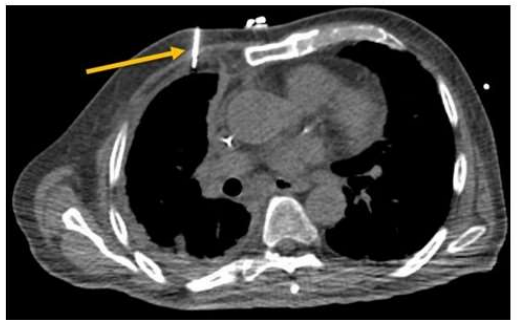
Cohort	PT #	Age/ Sex	Diagnosis	Histology	Stage	CAR T Line of Therapy	Route of Administration
1 3e5/kg (no cyclo)	1	59F	Lung Cancer	Adeno Ca	IV	4	Pleural catheter
	2	69M	Mesothelioma	Epithelioid	IV	6	Pleural catheter
	3	66F	Mesothelioma	Epithelioid	IV	5	Pleural catheter
2 3e5/kg	4	56M	Mesothelioma	Epithelioid	IV	6	Pleural catheter
	5	70F	Breast Cancer	Intraductal Ca	IV	9	IR
	6	72M	Mesothelioma	Biphasic	IIIA	2	IR
3 1e6/kg	7	70M	Mesothelioma	Epithelioid	IIIA	2	Pleural catheter
	8	73M	Mesothelioma	Epithelioid	IIIB	6	Pleural catheter
	9	66M	Mesothelioma	Epithelioid	IV	4	IR
4 3e6/kg	10	70M	Mesothelioma	Epithelioid	IIIB	2	Pleural catheter
	11	74M	Mesothelioma	Epithelioid	IIIB	2	Pleural catheter
	12*	66M	Mesothelioma	Epithelioid	IIIB	2 / 5	Pleural catheter
5 6e6/kg	13	76M	Mesothelioma	Epithelioid	IIIA	2	IR
	14	69M	Mesothelioma	Epithelioid	IIIA	2	IR
	15	71M	Mesothelioma	Epithelioid	IIIB	2	Pleural catheter
6 1e7/kg	16	77F	Mesothelioma	Epithelioid	IV	7	IR
	17	71M	Mesothelioma	Biphasic	IIIA	2	IR
	18	53M	Mesothelioma	Epithelioid	IIIB	3	IR
	19	64M	Mesothelioma	Epithelioid	IIIB	3	IR
	20	70M	Mesothelioma	Epithelioid	IIIA	3	Pleural catheter
	21	61F	Mesothelioma	Epithelioid	IIIB	2	IR
7 3e7/kg	22	73M	Mesothelioma	Epithelioid	IIIB	2	IR
	23	71F	Mesothelioma	Epithelioid	IV	2	IR
	24	70M	Mesothelioma	Epithelioid	IV	5	IR
8 6e7/kg	25	55M	Mesothelioma	Epithelioid	IV	14	IR
	26	61M	Mesothelioma	Epithelioid	IV	3	IR
	27	77M	Mesothelioma	Epithelioid	II	2	IR

37% had ≥3 lines of therapy

Cyclophosphamide preconditioning in cohorts 2-8

IR - intervention radiology





* Patient #12 re-infused at week 51

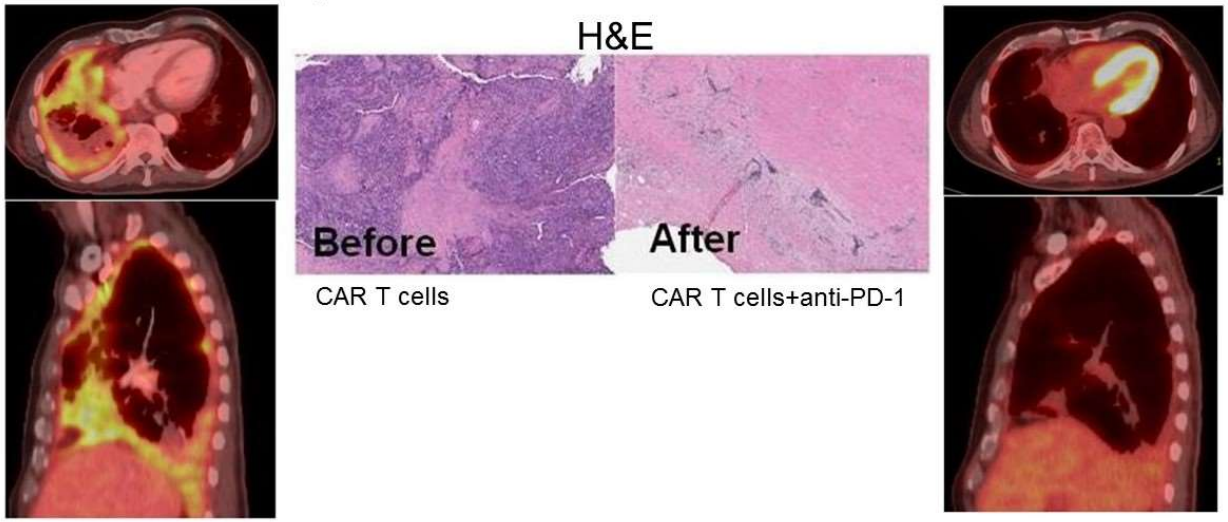
Presented By Prasad Adusumilli at 2019 ASCO Annual Meeting

Mesothelin-targeted CAR T-cell therapy

MSLN CAR T-cells + anti PD-1 agent
Complete response in patient #6 (16 months)

73 yr old h/o served in a battle ship diagnosed with **BIPHASIC** mesothelioma

- April 2017 – Unresectable disease following chemotherapy
- May 2017 – 3e5 CAR T cells/kg following Cyclophosphamide administered
- July 2017 – Pembrolizumab started (PD-L1 <1%, low mutational burden)
- Nov 2017 – Complete metabolic response, Serum SMRP normal
- Feb 2018 – CAR T cells detected at 32 weeks in blood and tissue
- No additional therapies for 16 months



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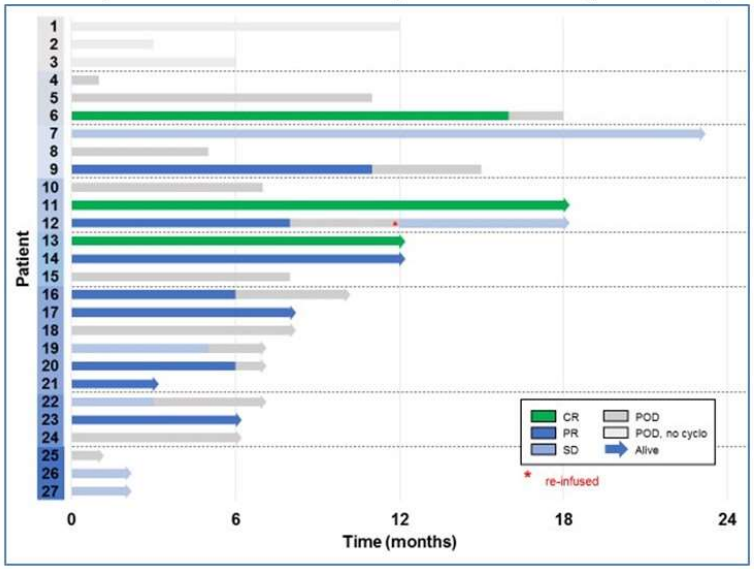
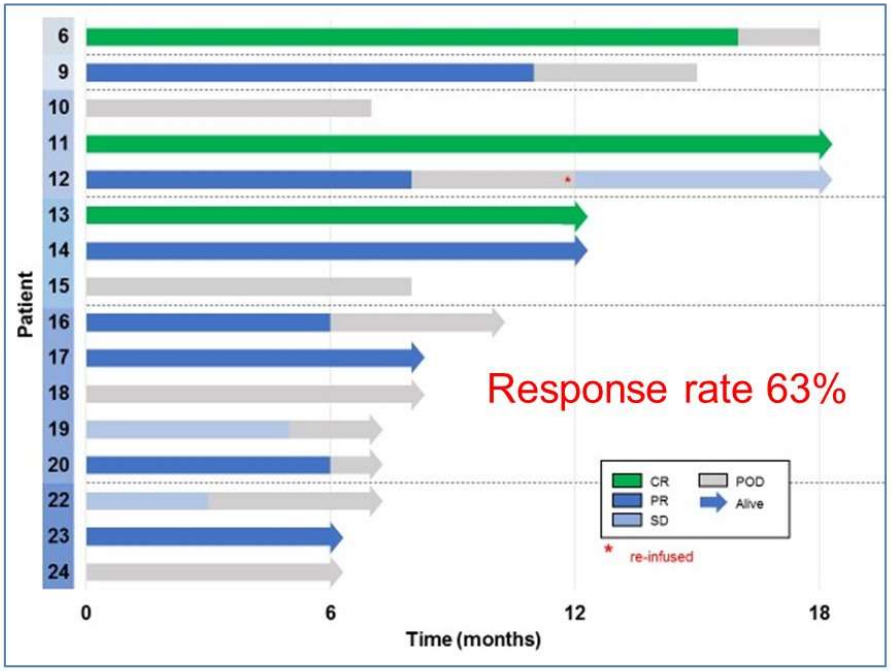
Clinical responses with and without addition of anti-PD-1 antibody

Responses of all patients (n=27)



CR – Complete response
PR – Partial response
SD – Stable disease
POD – Progression of disease

Responses of mesothelioma patients (n=16) that received Cyclophosphamide and CAR T-cells and at least 3 doses of anti-PD1 antibody with minimum 3 months follow-up



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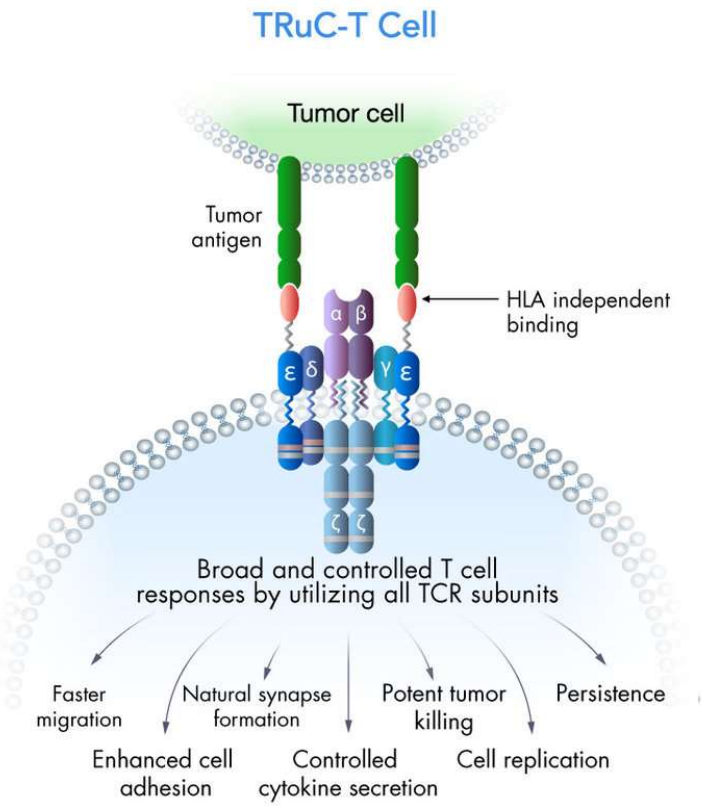
Upcoming study: TRuC-T targeting mesothelin

TRuC-T cell (TCR2 Therapeutics)

- Mesothelin expressing tumors
  - NSCLC
  - Ovarian Cancer
  - Mesothelioma
  - Cholangiocarcioma



TCR^2 Therapeutics

Summary:

- Immunotherapy resistance
  - Primary and secondary resistance a major problem
- New therapeutic approaches
  - Combination approaches
  - Targeting multiple suppressive factors
  - Engineering anti-tumor responses
- Next steps
  - Clinical studies needed to advance cancer care

Tumor Immunotherapy Program – Thanks to a great team

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Correlatives Studies Program

TIP Tumor Immunotherapy Program
BioCanRx Biotherapeutics for Cancer Treatment Biothérapies pour le traitement du cancer
TaKaRa
OICR Ontario Institute for Cancer Research
The Princess Margaret Cancer Foundation UHN