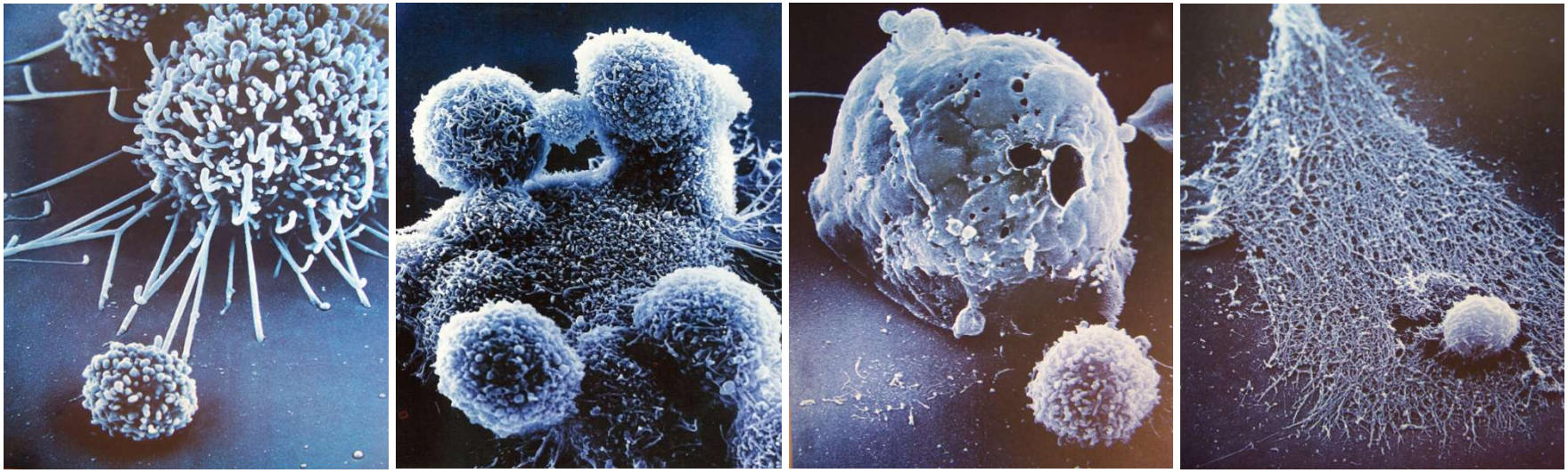
Advances in Immunotherapy



Arta M. Monjazeb, M.D., Ph.D.
Associate Professor of Radiation Oncology
Laboratory of Cancer Immunology
CCSG Staff Investigator for Immunotherapy
UC Davis Comprehensive Cancer Center

UCDAVIS
COMPREHENSIVE
CANCER CENTER

ARTA MONJAZEB, MD, PHD

SYSTEMIC IMMUNOTHERAPY COMBINATIONS

RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

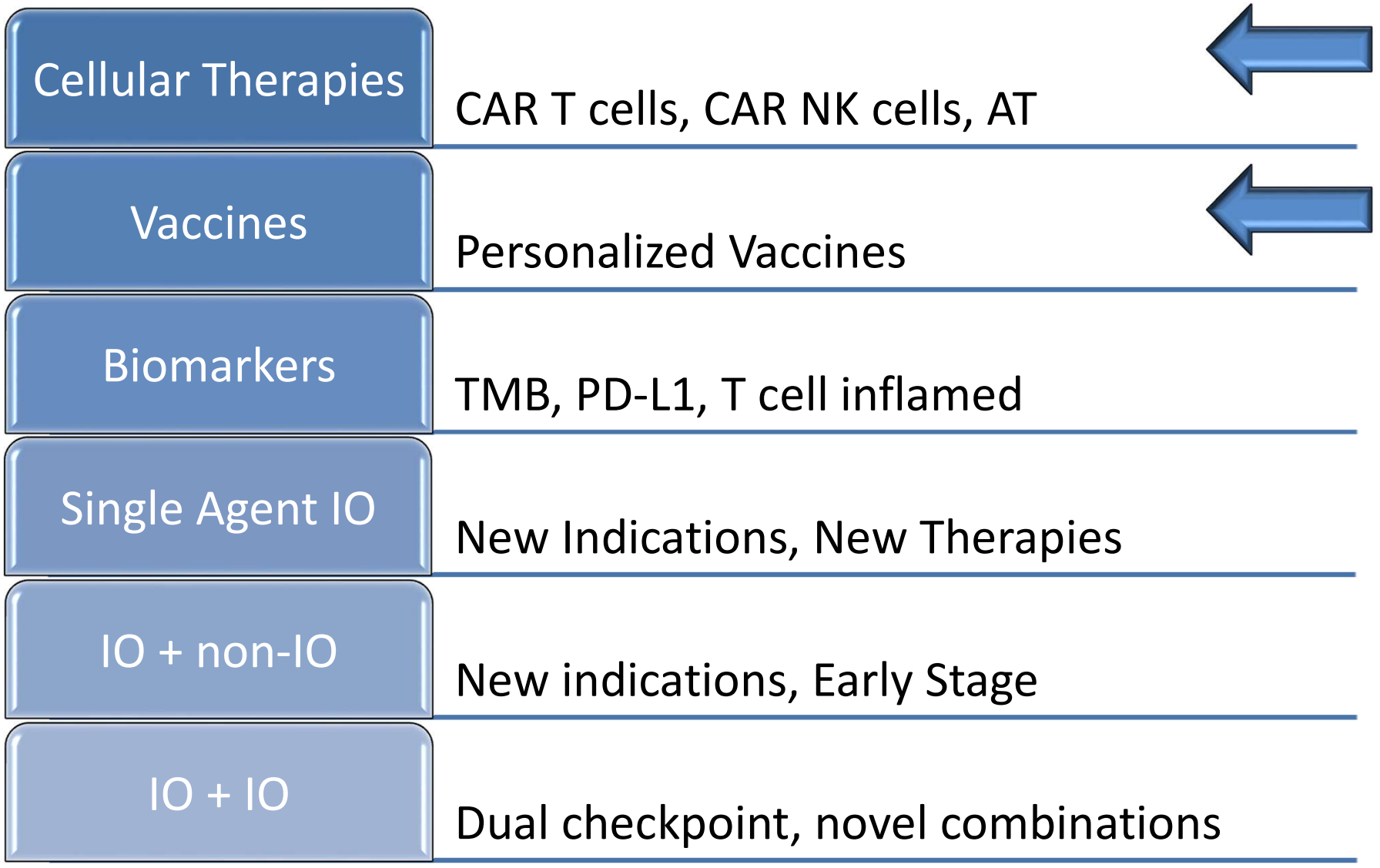
GRANT/RESEARCH SUPPORT: MERCK, TRANSGENE, BMS, INCYTE, DYNAVAX, GENENTECH
CONSULTANT: ASTRA-ZENECA, DYNAVAX, INCYTE

THE SPEAKER WILL DIRECTLY DISCLOSURE THE USE OF PRODUCTS FOR WHICH ARE NOT LABELED (E.G., OFF LABEL USE) OR IF THE PRODUCT IS STILL INVESTIGATIONAL.

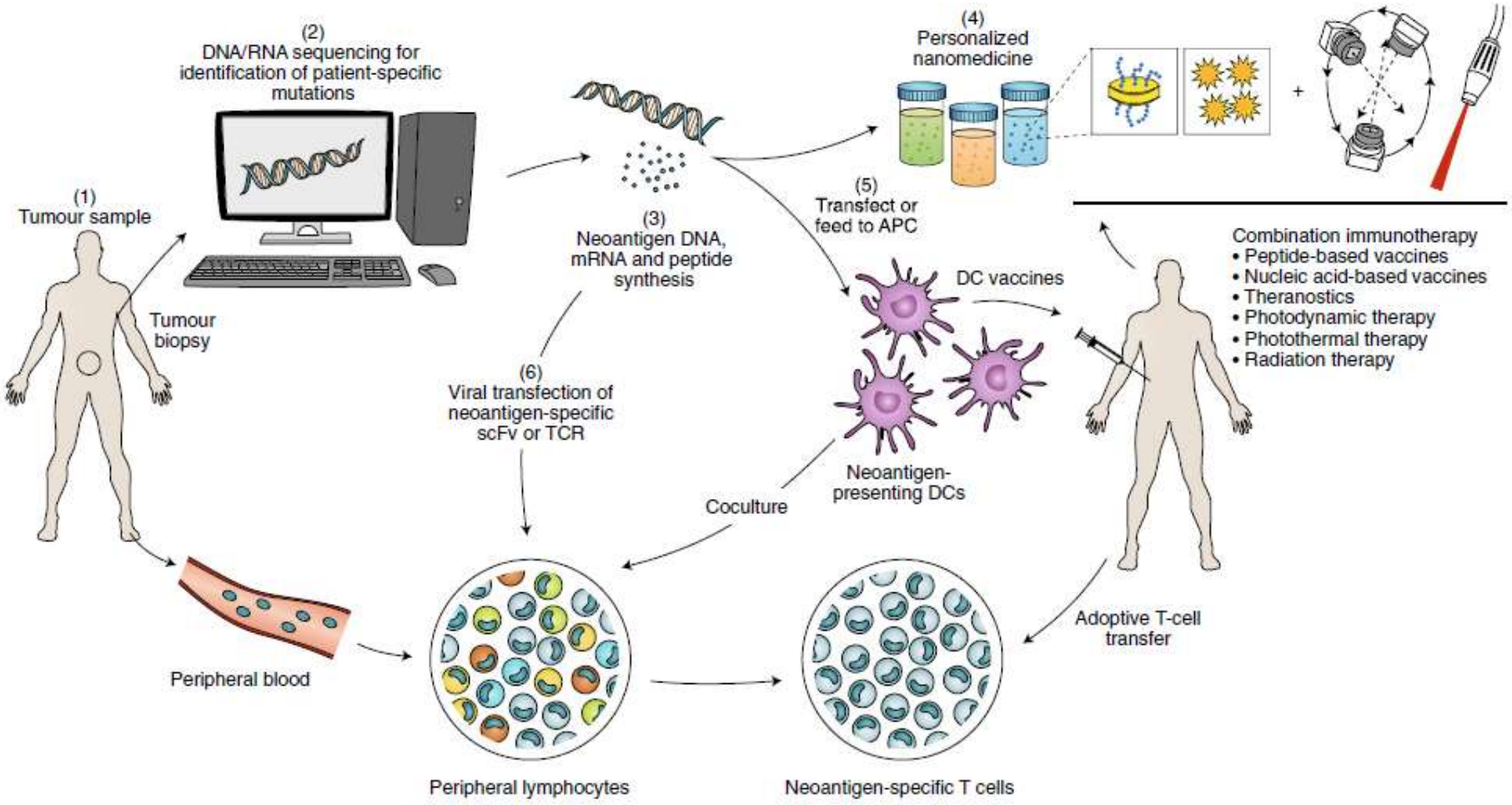
Advances in Immunotherapy

Cellular Therapies	CAR T cells, CAR NK cells, AT
Vaccines	Personalized Vaccines
Biomarkers	TMB, PD-L1, T cell inflamed
Single Agent IO	New Indications, New Therapies
IO + non-IO	New indications, Early Stage
IO + IO	Dual checkpoint, novel combinations

Advances in Immunotherapy



Personalized Immunotherapy



Kruger et al. Journal of Experimental & Clinical Cancer Research (2019) 38:268
https://doi.org/10.1186/s13046-019-1266-0

Journal of Experimental & Clinical Cancer Research

REVIEW Open Access

Advances in cancer immunotherapy 2019 – latest trends

Stephan Kruger[1,3*†], Matthias Ilmer[2,6†], Sebastian Kobold[3], Bruno L. Cadilha[3], Stefan Endres[3], Steffen Ormanns[4], Gesa Schuebbe[1], Bernhard W. Renz[2,6], Jan G. D'Haese[2], Hans Schloesser[5], Volker Heinemann[1,6], Marion Subklewe[1,6,8], Stefan Boeck[1,6], Jens Werner[2] and Michael von Bergwelt-Baildon[1,6,7,8]

nature biomedical engineering

PERSPECTIVE

https://doi.org/10.1038/s41551-019-0436-x

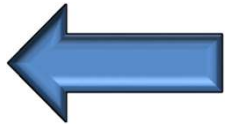
Engineering patient-specific cancer immunotherapies

Lindsay Scheetz[1,2,7], Kyung Soo Park[2,3,7], Qiao Li[4], Pedro R. Lowenstein[5,6], Maria G. Castro[5,6], Anna Schwendeman[1,2] and James J. Moon[1,2,3*]

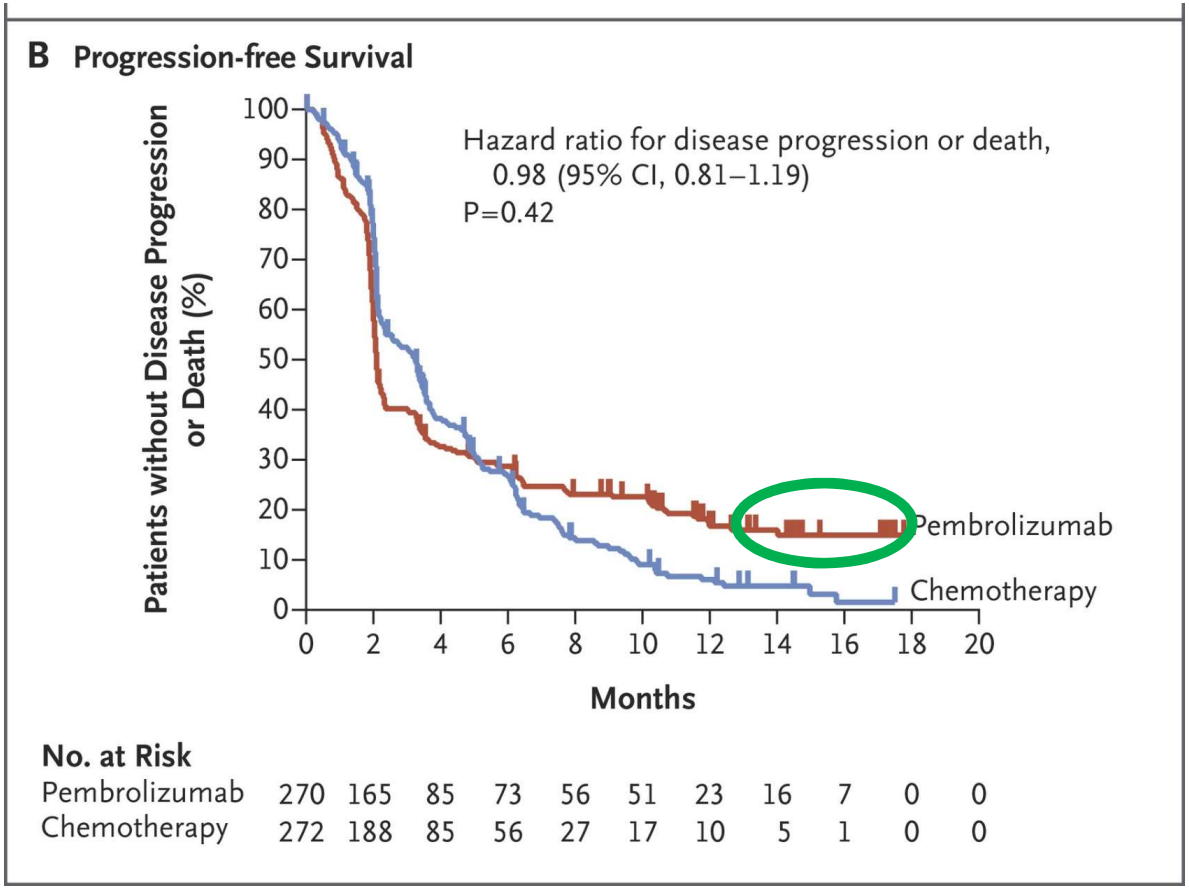
UCDAVIS

Advances in Immunotherapy

Cellular Therapies	CAR T cells, CAR NK cells, AT
Vaccines	Personalized Vaccines
Biomarkers	TMB, PD-L1, T cell inflamed
Single Agent IO	New Indications, New Therapies
IO + non-IO	New indications, Early Stage
IO + IO	Dual checkpoint, novel combinations



ONLY A MINORITY OF PATIENTS RESPOND TO TREATMENT



WE CAN CURE CANCERS PREVIOUSLY THOUGHT TO BE INCURABLE

Bellmunt et al– NEJM- 2017

Biomarkers

Adv Ther
https://doi.org/10.1007/s12325-019-01051-z

REVIEW

Existing and Emerging Biomarkers for Immune Checkpoint Immunotherapy in Solid Tumors

Sanjeevani Arora · Rodion Velichinskii · Randy W. Lesh · Usman Ali · Michal Kubiak · Pranshu Bansal · Hossein Borghaei · Martin J. Edelman · Yanis Boumber

Biomarkers – liquid biopsy

Marker	Drug	Malignancy	End-point results	References
T-cell markers and sPD-L1	Ipilimumab	Melanoma	High CD4(+)CD25(+)FoxP3(+)-Treg better survival $P < 0.001$	Martens et al. [147]
	Ipilimumab	Melanoma	Increased baseline T-cell receptor diversity associated with improved response, no survival difference $P = 0.01$	Postow et al. [156]
	Nivolumab	NSCLC	Increased SOX-2 reactive T-cells in periphery better response $P = 0.04$	Dhodapkar et al. [157]
	PD-1 and PD-L1 Antibodies	NSCLC	Increased PD-1, Ki-67 + CD8 T-cells 4 weeks into treatment correlated with clinical benefit. $P < 0.0001$	Kamphorst et al. [158]
	PD-1 and PD-L1 Antibodies	NSCLC	Baseline elevated PD-L1 as a poor prognostic marker $P = 0.002$	Boffa et al. [159]
	PD-1 and PD-L1 Antibodies	OSCC	Elevated PD-L1 mRNA expression in peripheral blood could contribute to increased metastatic behavior (higher grade cancer, node positive status) $P < 0.05$	Weber et al. [160]
	Ipilimumab Pembrolizumab	Melanoma	High pretreatment levels of sPD-L1 were associated with increased likelihood of progressive disease $P = 0.0015$	Zhou et al. [50]
B cell-antibody markers	Ipilimumab	Melanoma	NYESO antibody seropositive have better ORR $P = 0.02$	Yuan et al. [161]
	Ipilimumab	Melanoma	Soluble CTLA4 antibody associated with improved response $P = 0.02$	Leung et al. [162]
Soluble CD25	Ipilimumab	Melanoma	Elevated baseline CD25 associated with shorter OS $P = 0.056$	Hannani et al. [144]

Biomarkers – liquid biopsy

Marker	Drug	Malignancy	End-point results	References
LDH	Ipilimumab Pembrolizumab Nivolumab	Melanoma	Elevated baseline LDH = lower ORR $P = 0.0292$ Elevated baseline LDH = decreased response rate of 22.3, 95% CI (17.1–28.1) compared to 42.0, 95% CI (36.6–47.5)	Diem et al. [153] Ribas et al. [8]
Neutrophil-lymphocyte ratio (NLR)	Nivolumab	NSCLC	Baseline NLR > 3 shorter PFS predictive marker at 2 and 4 weeks $P = 0.484$ 2 weeks $P = 0.00528$ 4 weeks $P = 0.00515$	Nakaya et al. [154]
	Ipilimumab	Melanoma	Baseline NLR > 5 worse PFS and OS PFS $P = 0.0006$ OS $P < 0.0001$	Ferrucci et al. [155]
Absolute eosinophil count	Pembrolizumab	Melanoma	High count–low response rate $P < 0.001$	Weide et al. [126]
	Ipilimumab	Melanoma	High count–low response rate $P < 0.0001$	Ferrucci et al. [127]
Monocyte count and myeloid derived suppressor cells (MDSCs)	Ipilimumab	Melanoma	Low baseline levels show a favorable response $P < 0.001$	Martens et al. [147]

Marker	Drug	Malignancy	End-point results	References
bTMB	Atezolizumab	NSCLC	bTMB correlated with TMB, bTMB correlated with PFS, bTMB did not associate with high PD-L1 expression bTMB $P = 0.035$ PD-L1 $P = 0.160$	Gandara et al. [41]

UCDAVIS

Immune Health

nature medicine

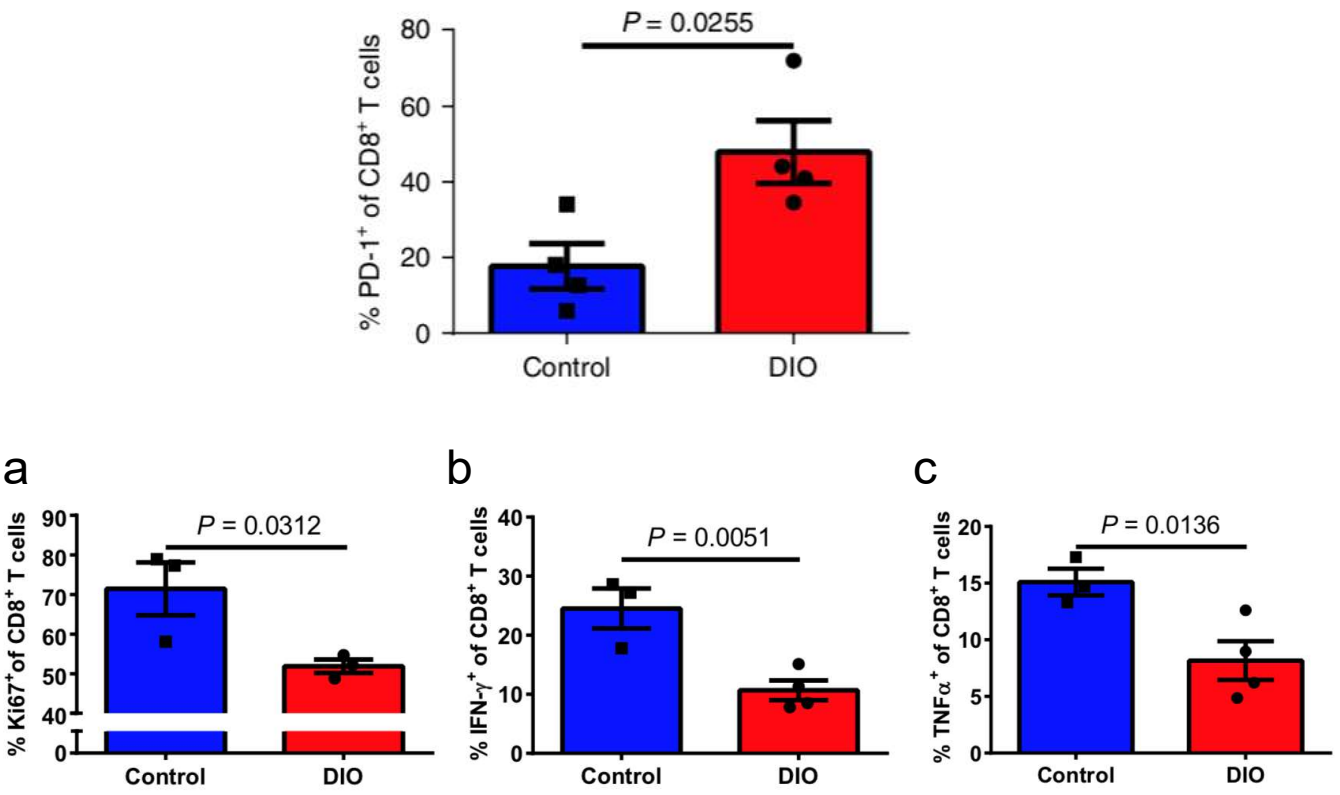
ARTICLES

https://doi.org/10.1038/s41591-018-0221-5

Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade

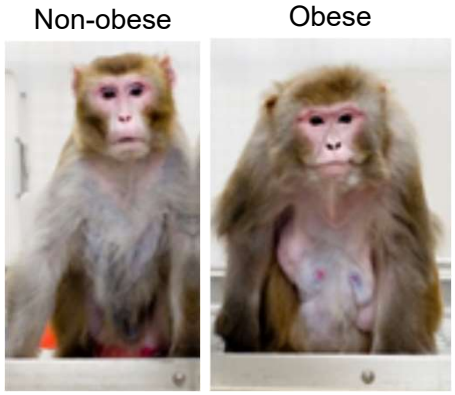
Ziming Wang[1,20], Ethan G. Aguilar[1,20], Jesus I. Luna[1], Cordelia Dunai[1], Lam T. Khuat[1], Catherine T. Le[1], Annie Mirsoian[1], Christine M. Minnar[1], Kevin M. Stoffel[1], Ian R. Sturgill[1], Steven K. Grossenbacher[1], Sita S. Withers[2], Robert B. Rebhun[2], Dennis J. Hartigan-O'Connor[3,4,5], Gema Méndez-Lagares[4,5], Alice F. Tarantal[5,6,7], R. Rivkah Isseroff[1,8], Thomas S. Griffith[9], Kurt A. Schalper[10], Alexander Merleev[1,11], Asim Saha[12], Emanual Maverakis[1,11], Karen Kelly[13], Raid Aljumaily[14], Sami Ibrahimi[14], Sarbajit Mukherjee[14], Michael Machiorlatti[15], Sara K. Vesely[15], Dan L. Longo[16], Bruce R. Blazar[17], Robert J. Canter[18], William J. Murphy[1,13,21*] and Arta M. Monjazeb[19,21]

T Cells in Mouse Model

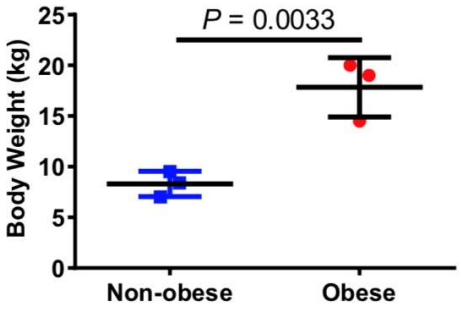


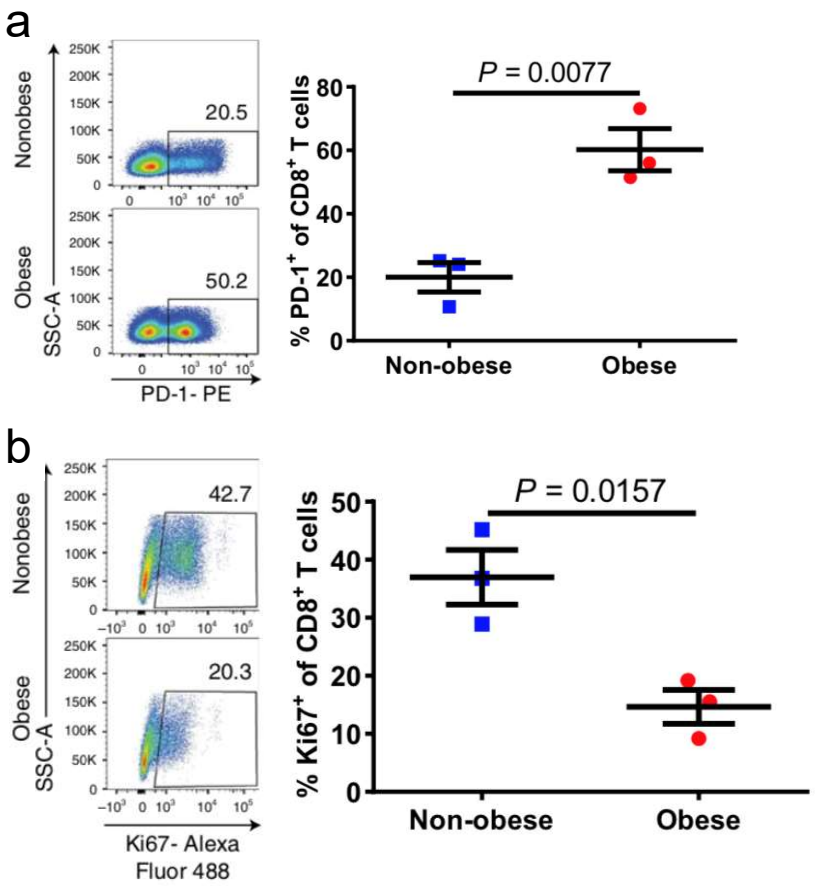
Wang Z. et al. Nature Med. 2019.

T Cells in Non-human Primate



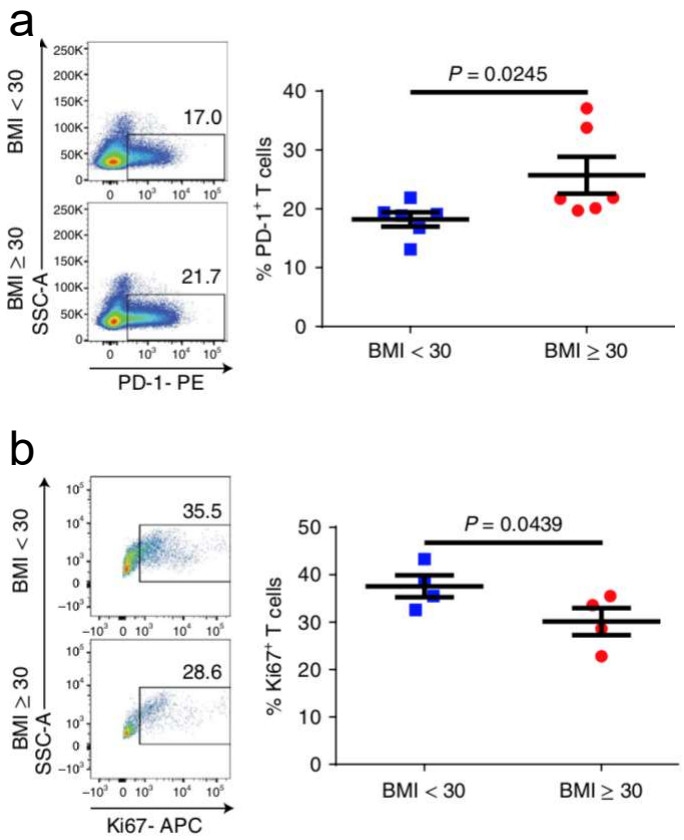
Peripheral blood





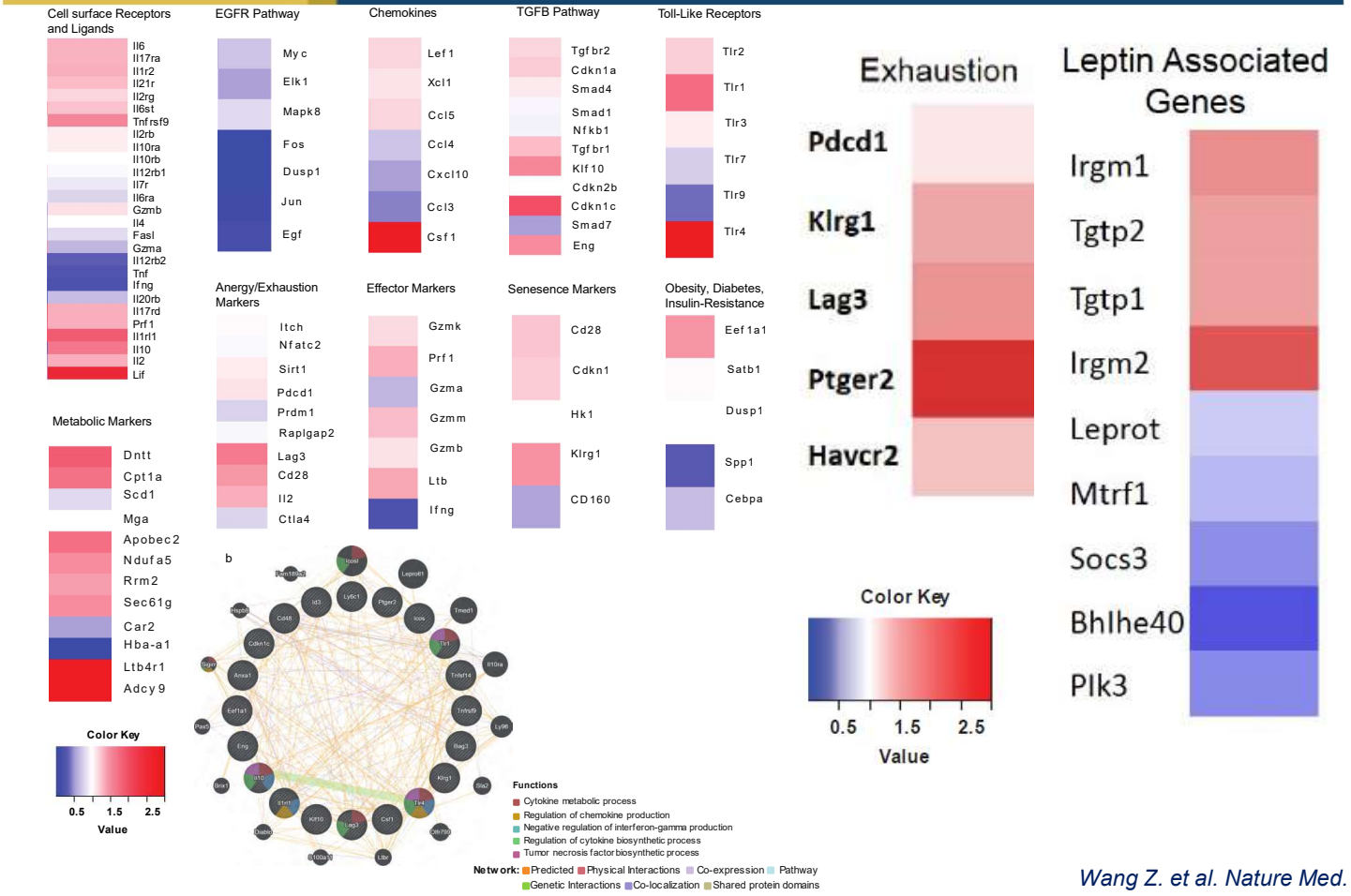
Wang Z. et al. Nature Med. 2019.

T Cells in Human



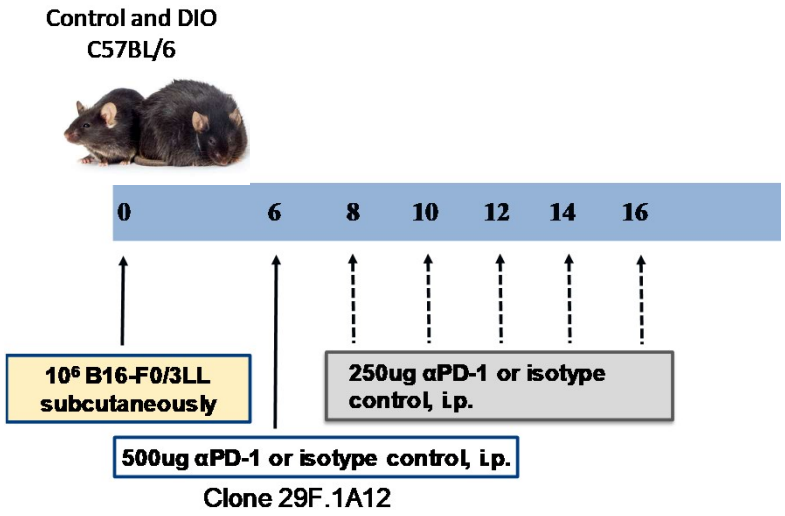
Wang Z. et al. Nature Med. 2019.

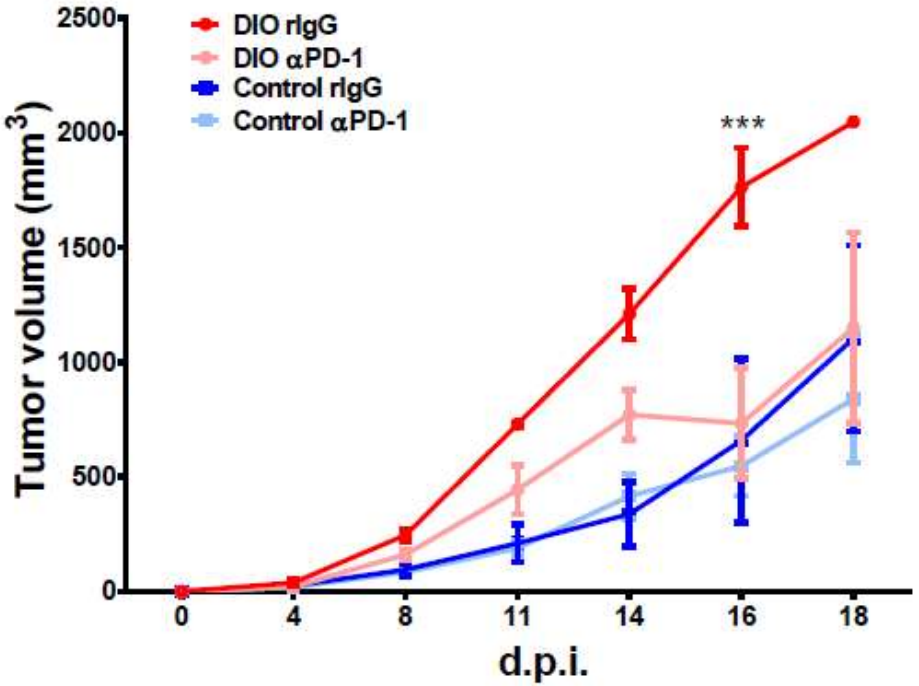
Global Gene Signature Differences in CD8+ T cells of Tumor-bearing DIO Mice



Wang Z. et al. Nature Med. 2019.

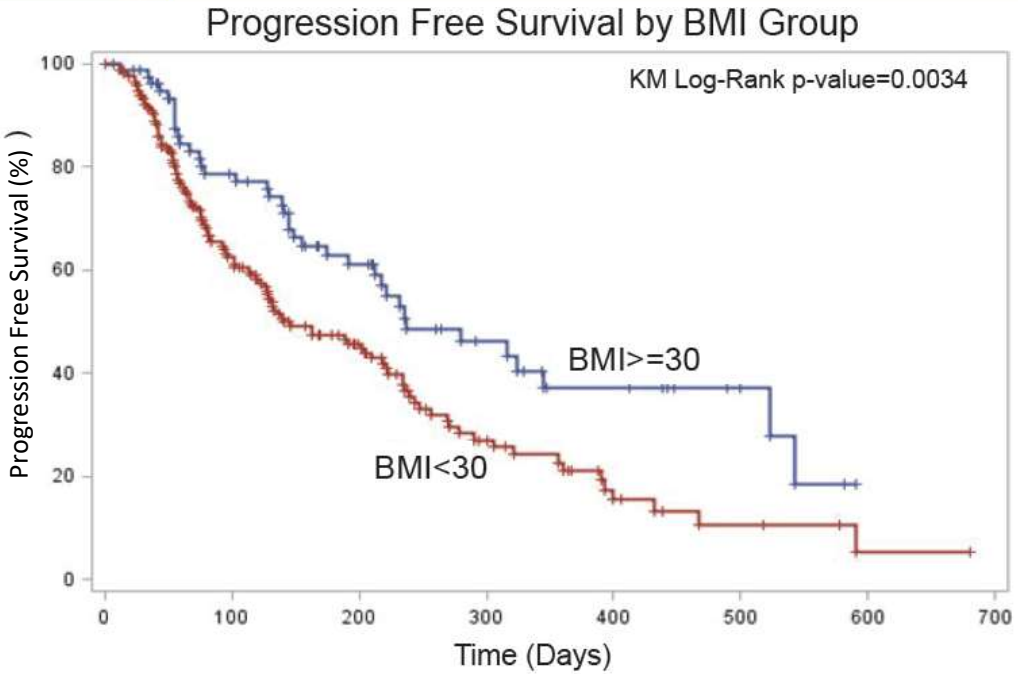
Increased Efficacy of PD-1 Blockade in DIO Mice

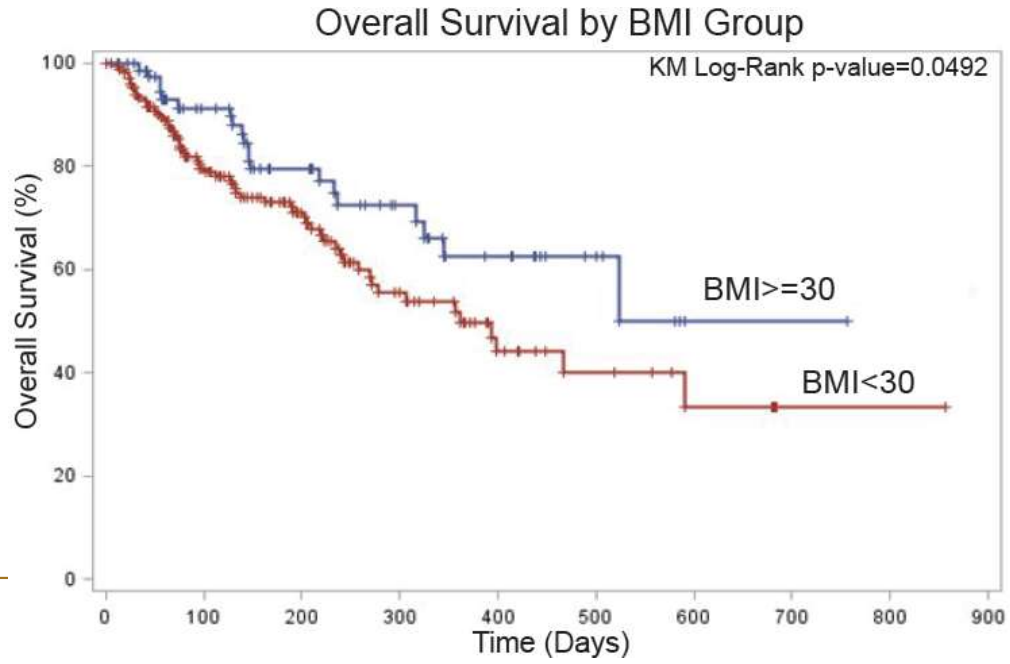




Wang Z. et al. Nature Med. 2019.

Obesity Impacts the Efficacy of PD-1/PD-L1 Checkpoint Blockade in Cancer Patients



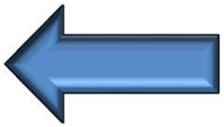


UCDAVIS

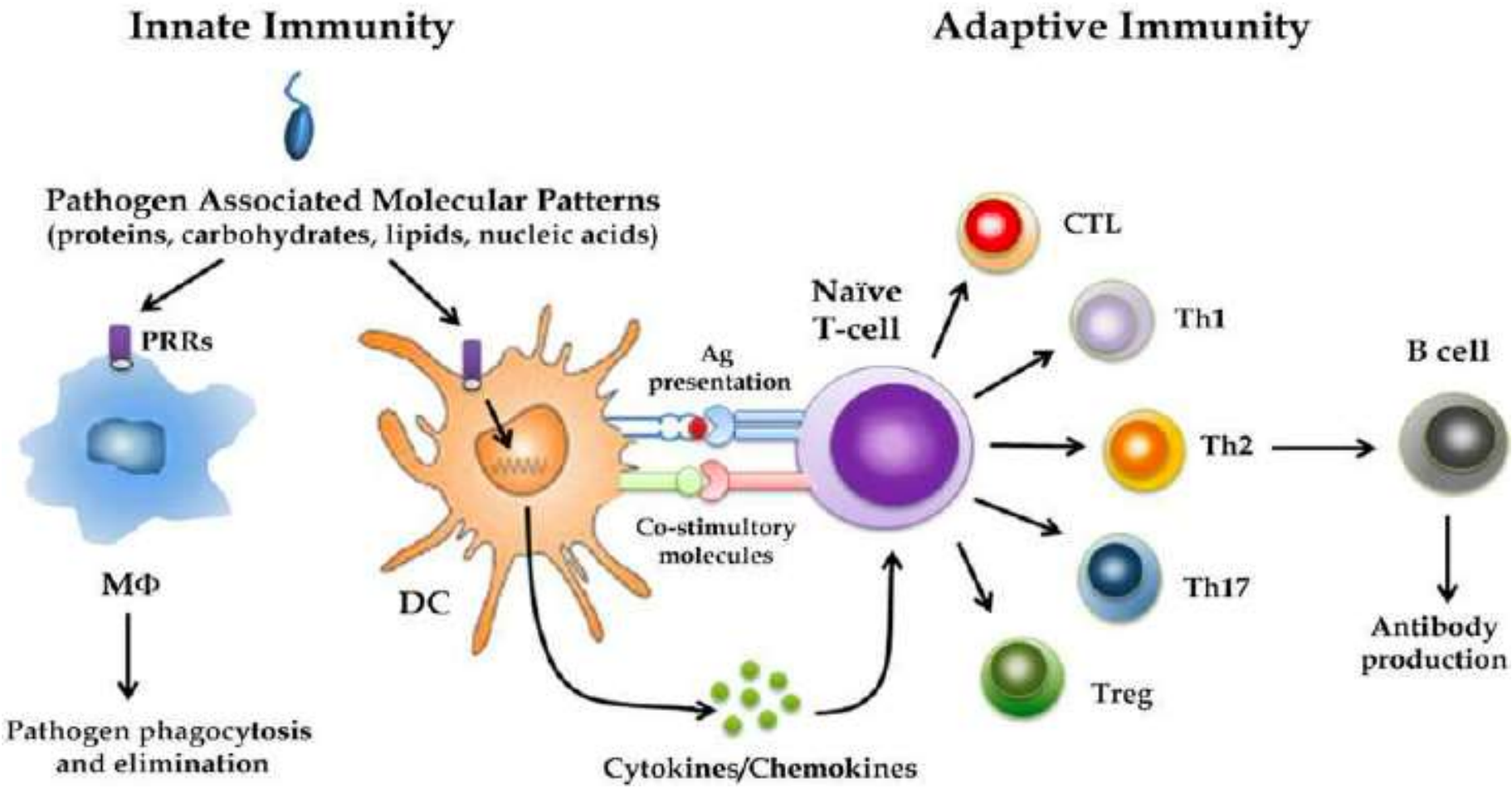
Wang Z. et al. Nature Med. 2019.

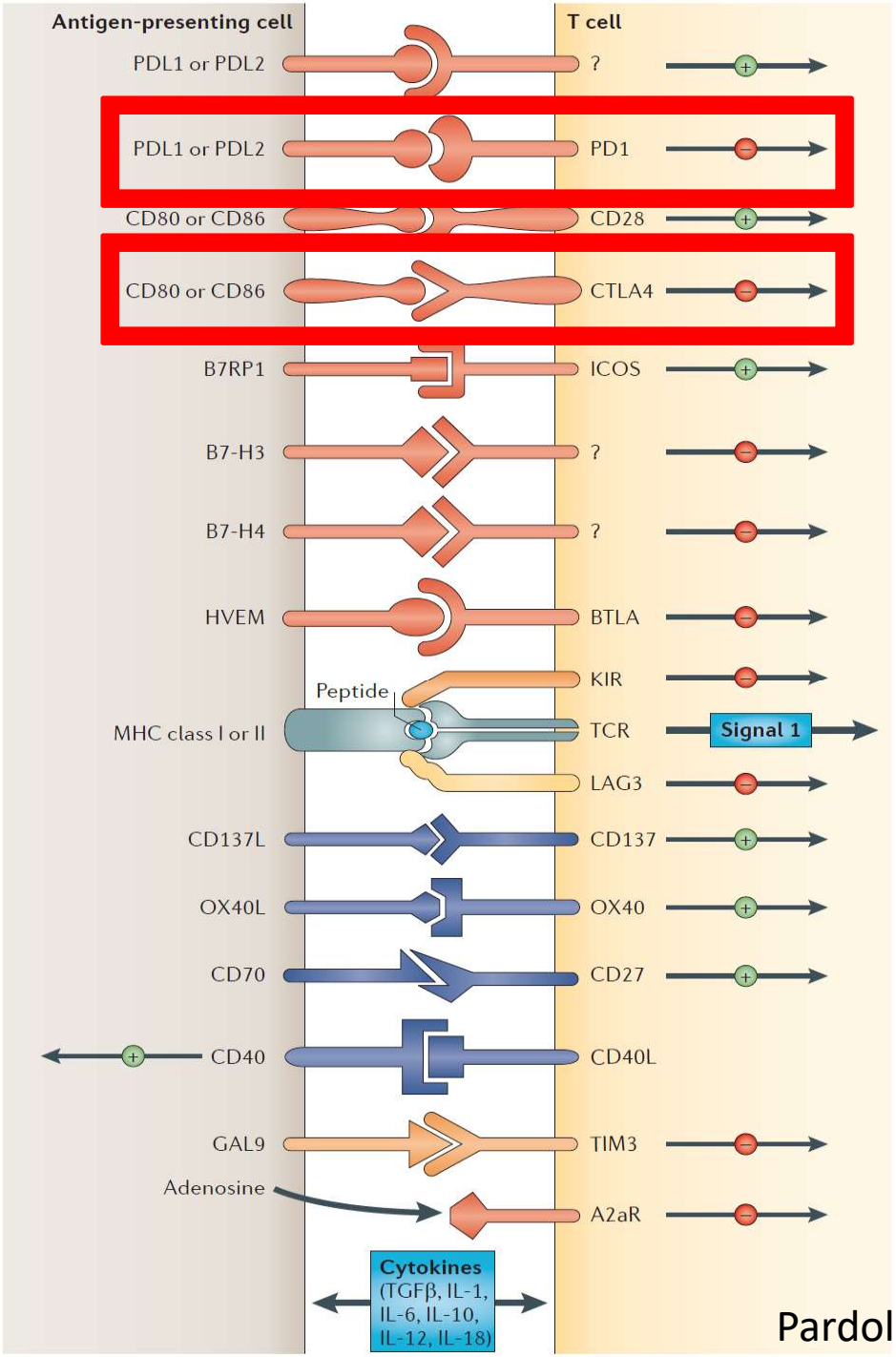
Advances in Immunotherapy

Cellular Therapies	CAR T cells, CAR NK cells, AT
Vaccines	Personalized Vaccines
Biomarkers	TMB, PD-L1, T cell inflamed
Single Agent IO	New Indications, New Therapies
IO + non-IO	New indications, Early Stage
IO + IO	Dual checkpoint, novel combinations

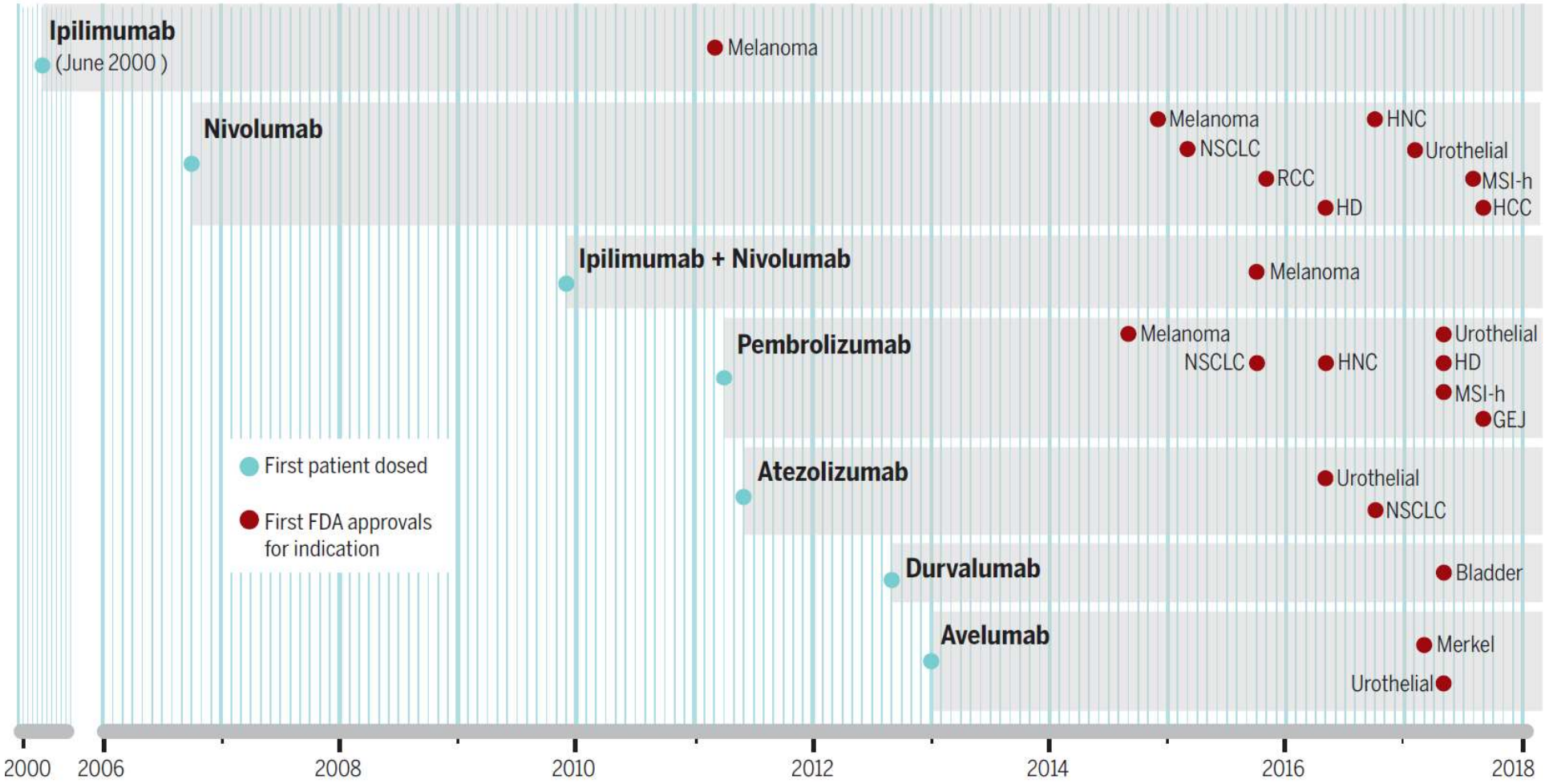


How the Immune System recognizes non self





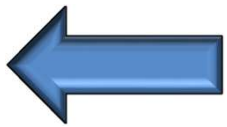
Pardoll– Nature Reviews- 2012

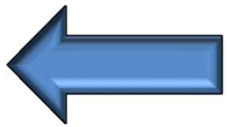


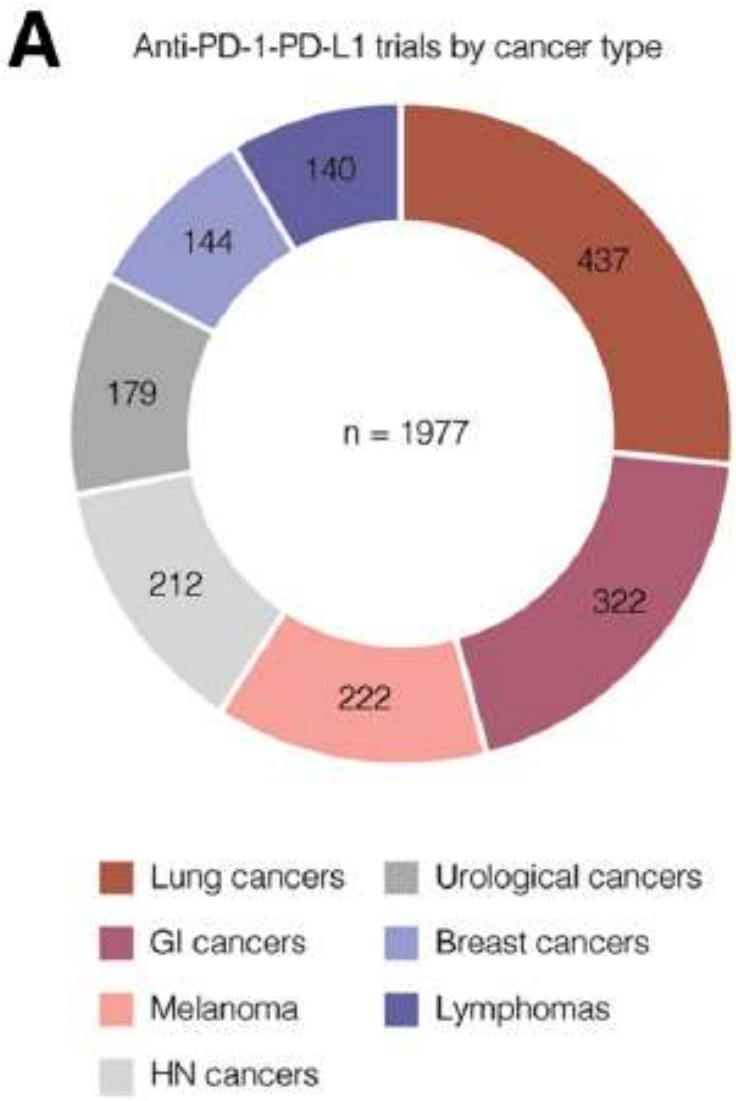
Ribas– Science- 2018

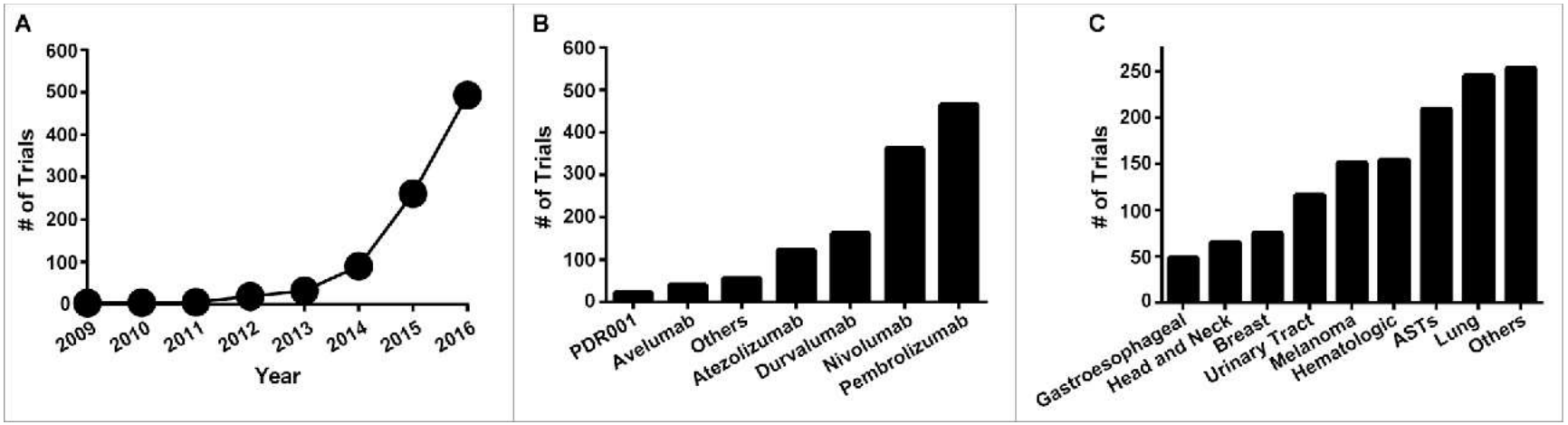
Advances in Immunotherapy

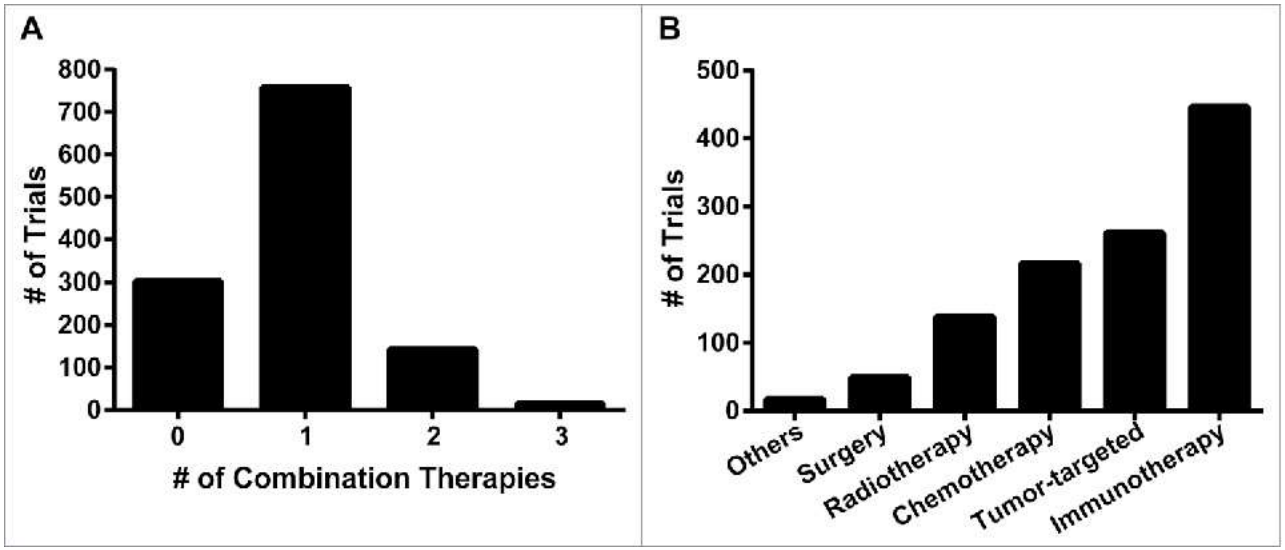
Cellular Therapies	CAR T cells, CAR NK cells, AT
Vaccines	Personalized Vaccines
Biomarkers	TMB, PD-L1, T cell inflamed
Single Agent IO	New Indications, New Therapies
IO + non-IO	New indications, Early Stage
IO + IO	Dual checkpoint, novel combinations






A
Anti-PD-1-PD-L1 trials by cancer type
140
144
437
179
n = 1977
212
322
222
Lung cancers
Urological cancers
GI cancers
Breast cancers
Melanoma
Lymphomas
HN cancers





Bryce Johnson et al- Oncoimmunology 2018

There have been 1700+ IO combination trials testing 240 targets

(CRI Landscape analysis 2018)

What had worked

- **Nivolumab + Ipilimumab** (Melanoma; SCLC)
- **Anti-PD-1/L1 + Chemotherapy** (NSCLC, SCLC, TNBC)
- **Anti-PD-1 + VEGF TKI** (pembrolizumab and axitinib) (RCC)

** Additive or synergistic? Who needs the combination?*

What had "failed" (in phase III trials)

- **Pembrolizumab + lenalidomide (**MM**)**
- **Pembrolizumab + Epacadostat (**IDOi**) (**melanoma**)**
- **Atezolizumab + cobimetinib (**MEKi**)** (MSS CRC; Melanoma)

Many early, signal-seeking trials can be negative or uninterpretable

Slide courtesy of Dr. Helen Chen, NCI, CTEP

The Successes

- PACIFIC
  - Stage III NSCLC – ChemoRT +/- Durva
  - Improved OS and PFS
- IMpassion130
  - mTNBC – nab-paclitaxel +/- atezo
  - Improved OS and PFS, most pronounced in PD-L1+ subgroup
- Keynote 48
  - 1st line R/M HNSCC – Pembro vs Pembro + chemo vs. chemo / cetuximab
  - Pembro/chemo improved outcomes in all patients
  - Pembro improved outcomes in PD-L1+ patients

Table 2 Recent phase 2/3 NSCLC, urothelial cancer, melanoma studies utilizing PD-L1 as a biomarker

Study, year	Treatment Arms	Total pts	OS, months or % OS (or PFS)	PD-L1 predicts outcome?
CKI alone 2nd line for NSCLC stage IV				
CheckMate 017, 2015	Nivolumab vs. docetaxel	272	9.2 vs. 6.0	No
CheckMate 057, 2015	Nivolumab vs. docetaxel	582	12.2 vs. 9.4	Yes
Keynote 010, 2016	Pembrolizumab vs. docetaxel	1033	10.4 vs. 8.5	Yes
OAK, 2017	Atezolizumab vs. docetaxel	850	13.8 vs. 9.6	Yes
CKI alone 1st line for NSCLC stage IV				
Keynote 024, 2016	Pembrolizumab vs. PltD	305	30.2 vs. 14.2	Yes
CheckMate 026, 2017	Nivolumab vs. PltD	541	13.2 vs. 14.4	No
CKI with chemotherapy and/or bevacizumab for stage IV NSCLC in 1st line				
Keynote 189, 2018	Pembrolizumab + PltD vs. PltD	616	69% vs. 49% at 12 months	Yes
Keynote 407, 2018	Pembrolizumab + PltD vs. PltD	559	15.9 vs. 11.3	No
IMpower 131, 2018	Atezolizumab + PltD vs. PltD	1021	12-months PFS 25% vs. 12%	No
IMpower 150, 2018	Atezolizumab + bevacizumab + PltD vs. bevacizumab + PltD	692	Median OS, 19 vs. 15 months	No
CKI after initial chemoradiation for NSCLC stage III				
PACIFIC, 2017	chemoXRT, followed by durvalumab × 1 year vs. observation	709	66% vs. 55% at 24 months	Maybe
CKI after chemotherapy for metastatic urothelial carcinoma				
Phase 2 study, 2016	Atezolizumab after Plt	315	11.4 months in IC2/3; 8.8 months in IC1/2/3; 7.9 in all patients	Yes
CKI alone for previously treated advanced melanoma				
Keynote-001, 2016	Pembrolizumab	655	Hazard ratio 0.76 in PD-L1 + melanoma	Yes

NSCLC non-small cell lung carcinoma, *CKI* checkpoint inhibitor, *Pts* patients, *PltD* platinum doublet chemotherapy

Selected Cancer Immunotherapy Targets/Strategies

- Inhibitory Signals
  - CTLA-4, PD-1/PD-L1, LAG-3, TIM-3, VISTA, BTLA
- Stimulatory Signals
  - ICOS, CD40, OX40, 41BB
- Cytokines
  - IL-2, IL-12, IL-15, TGF-beta blockade
- CARS
- Adoptive Cell Transfer
- Vaccines
  - PANVAC, Provenge, Muc-1 etc.
- Oncolytic Virus
- TLR agonists
- Inhibitory Enzymes
  - IDO, Arginase

Why the failures

- **Wrong or <u>incomplete</u> hypothesis ..** mechanisms and molecular context of synergy?
  - **Wrong drug?** … no or incomplete target inhibition
    - **Wrong dose/schedule?** …. too low, too high, bell-shaped?
      - **Wrong patients? … u**nknown patient selection bias
        - » **Wrong trial design? … p**hase 1-2-3 go no go decisions

The case of IDO-1 inhibitor Epacadostat

- **Scientific issues**
  - IDO-1 K/O had incomplete effect. Tumor regrew after initial suppression
  - Pathways are redundant. IDO1, TDO and IDO2 all involved in tryptophan to KU metabolism
- **Drug and dose issues**
  - Serum PD effect (Kynurenine reduction) 50% (plateau at 100-400 mg BID)
  - Tumor PD effects observed across doses, but degree of inhibition variable
  - ? Effect on compensatory pathways
- **Trial design** - Promising single arm results not validated in randomized trials
- **No patient selection** – while IDO is presumably a immune evasion mechanism in "Inflamed tumors"

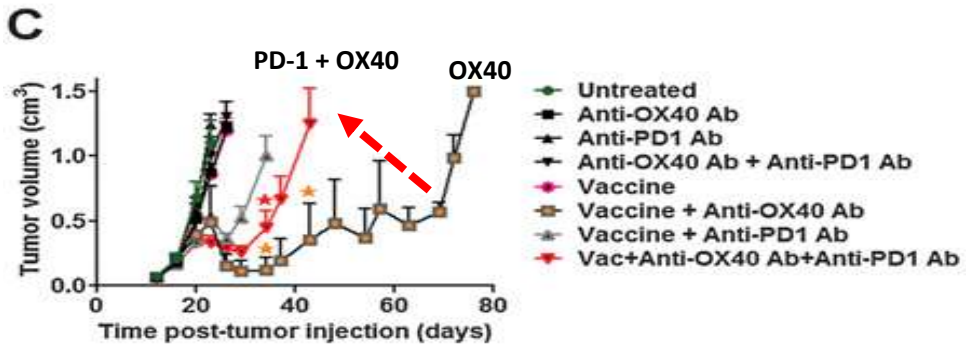
Dose and schedule matters

Full or low dose or bell-shaped dose effects?

Continuous or intermittent

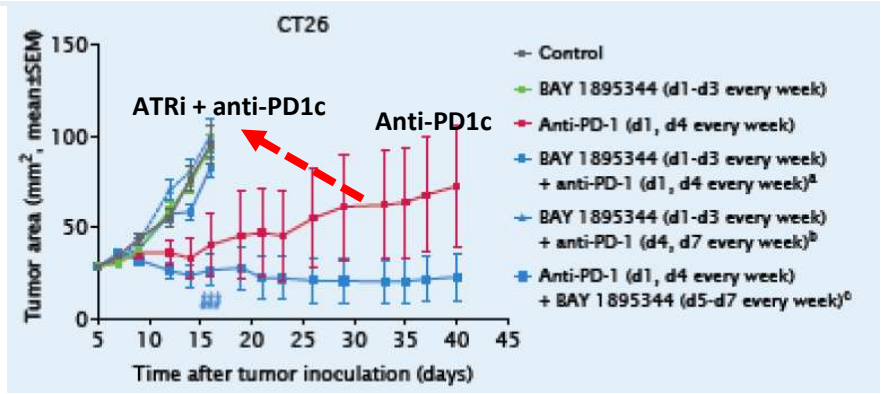
Concurrent or sequential, in what sequence

Concurrent anti-PD1 reduced activity of OX40 **(**Anti-PD1 enhanced T-effector activation, followed by significant apoptosis)



Shrimali … Khleif et al, Ca Imm Res September 2017
(Similar findings by *Messenheimer.. Fox, CCR Aug 2017*)

Concurrent ATR inhibitor + anti-PD-1 was antagonistic (delaying ART I was "synergistic")



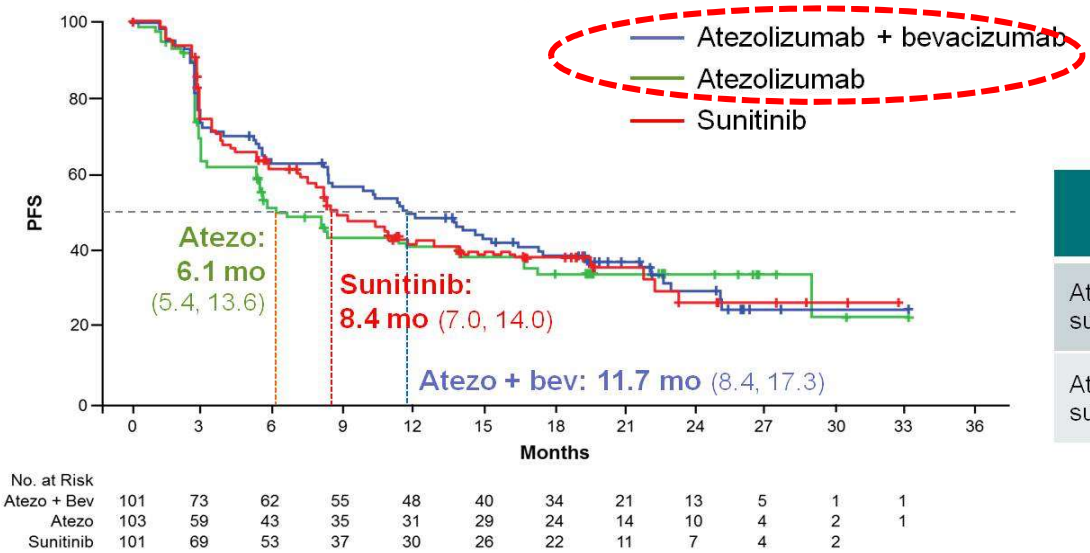
Wengner et al, AACR 2019 (Abs 272)

Slide courtesy of Dr. Helen Chen, NCI, CTEP

A given combination may only work in a small subset of patients

IMmotion150: A Phase II Trial In Untreated Metastatic Renal Cell Carcinoma Patients of Atezolizumab And Bevacizumab Vs And Following Atezolizumab Or Sunitinib

Michael Atkins,[1] David McDermott,[2] Thomas Powles,[3] Robert Motzer,[4] Brian Rini,[5] Lawrence Fong,[6] Richard W. Joseph,[7] Sumanta Pal,[8] Mario Sznol,[9] John Hainsworth,[10] Walter M. Stadler,[11] Thomas Hutson,[12] Alain Ravaud,[13] Sergio Bracarda,[14] Cristina Suarez,[15] Toni Choueiri,[16] Jiaheng Qiu,[17] Mahrukh A. Huseni,[17] Christina Schiff,[17] Bernard Escudier[18]



	Stratified HR (95% CI)	*P* Value[a]
Atezo + bev vs sunitinib	1.00 (0.69, 1.45)	0.982
Atezo vs sunitinib	1.19 (0.82, 1.71)	0.358

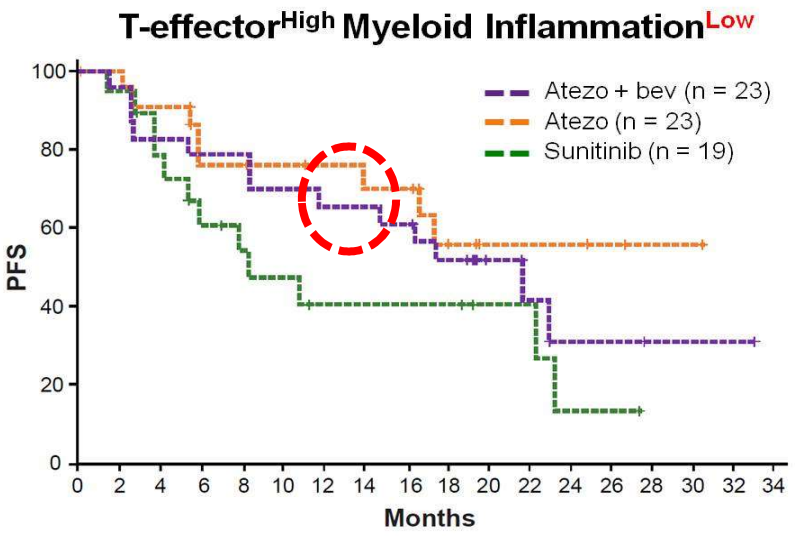
Atezo, atezolizumab; bev, bevacizumab.
PFS measured by independent review facility.
[a] *P* values are for descriptive purposes only and not adjusted for multiple comparisons.
Clinical cutoff, Oct 17, 2016. Median duration of follow-up, 20.7 mo. McDermott, ASCO GU 2017.

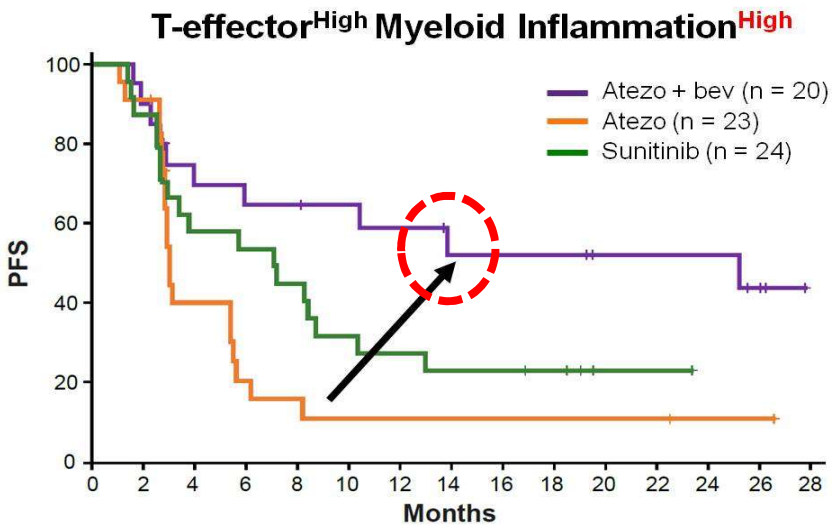
UCDAVIS

Slide courtesy of Dr. Helen Chen, NCI, CTEP

In the subgroup of high myeloid signature, bevacizumab significantly enhance the Atezo activity

Addition of Bevacizumab to Atezolizumab in 1L Was Associated With Improved Benefit in T-Effector^{High} Myeloid Inflammation^{High} Subgroup





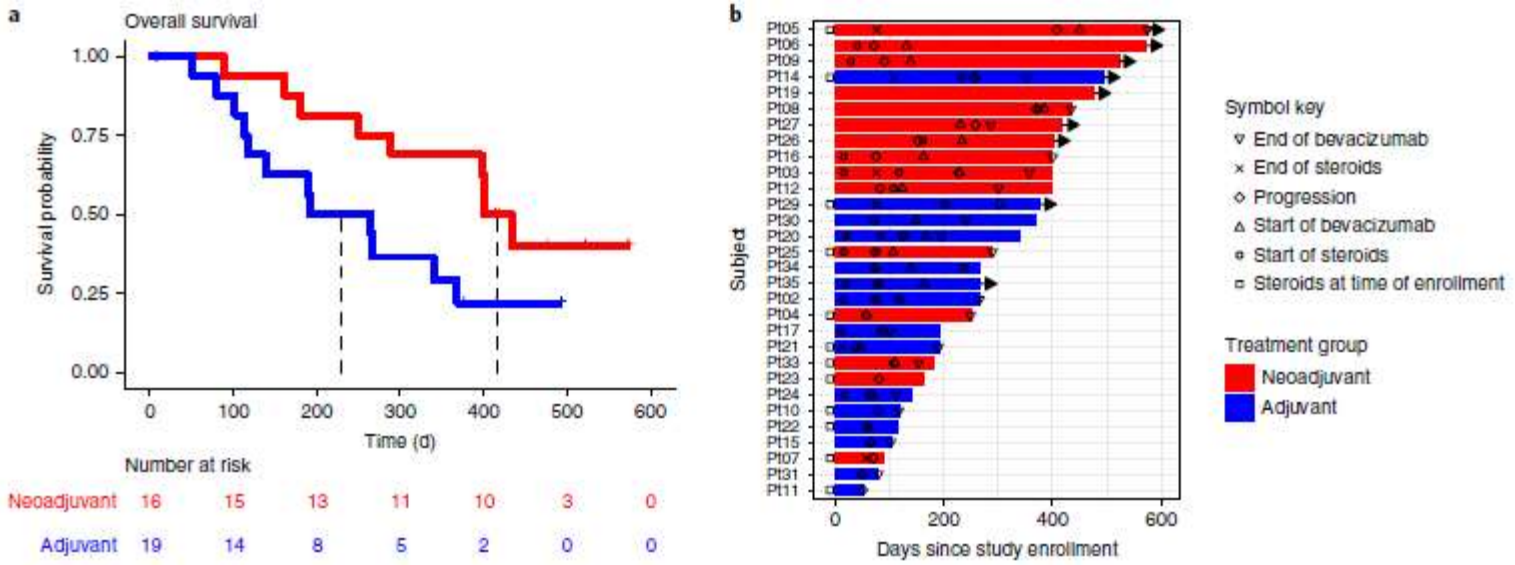
PFS measured by independent review facility.
T-effector gene signature: *CD8A*, *EOMES*, *PRF1*, *IFNG*, *CD274*.
High, ≥ median expression; low, < median expression. McDermott, AACR 2017.

Slide courtesy of Dr. Helen Chen, NCI, CTEP

nature medicine
FOCUS | ARTICLES
https://doi.org/10.1038/s41591-018-0337-7

Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma

Timothy F. Cloughesy[1,2,3,18*], Aaron Y. Mochizuki[4,18], Joey R. Orpilla[5], Willy Hugo[6], Alexander H. Lee[2,3], Tom B. Davidson[3,4], Anthony C. Wang[5], Benjamin M. Ellingson[3,7], Julie A. Rytlewski[8], Catherine M. Sanders[8], Eric S. Kawaguchi[9], Lin Du[9], Gang Li[3,9], William H. Yong[10], Sarah C. Gaffey[11], Adam L. Cohen[12], Ingo K. Mellinghoff[13], Eudocia Q. Lee[11], David A. Reardon[11], Barbara J. O'Brien[14], Nicholas A. Butowski[15], Phioanh L. Nghiemphu[1], Jennifer L. Clarke[15], Isabel C. Arrillaga-Romany[16], Howard Colman[17], Thomas J. Kaley[13], John F. de Groot[14], Linda M. Liau[3,5], Patrick Y. Wen[11,19] and Robert M. Prins[2,3,5,17,19*]



Abstract CT004: A Phase Ib study of CD40 agonistic monoclonal antibody APX005M together with gemcitabine (Gem) and nab-paclitaxel (NP) with or without nivolumab (Nivo) in untreated metastatic ductal pancreatic adenocarcinoma (PDAC) patients

Mark H. O'Hara, Eileen M. O'Reilly, Mick Rosemarie, Gauri Varadhachary, Zev A. Wainberg, Andrew Ko, George A. Fisher, Osama Rahma, Jaclyn P. Lyman, Christopher R. Cabanski, Erica L. Carpenter, Travis Hollmann, Pier Federico Gherardini, Lacey Kitch, Cheryl Selinsky, Theresa LaVallee, Ovid C. Trifan, Ute Dugan, Vanessa M. Hubbard-Lucey, and Robert H. Vonderheide

58% PR and 33% SD

Systemic clinical tumor regressions and potentiation of PD1 blockade with in situ vaccination

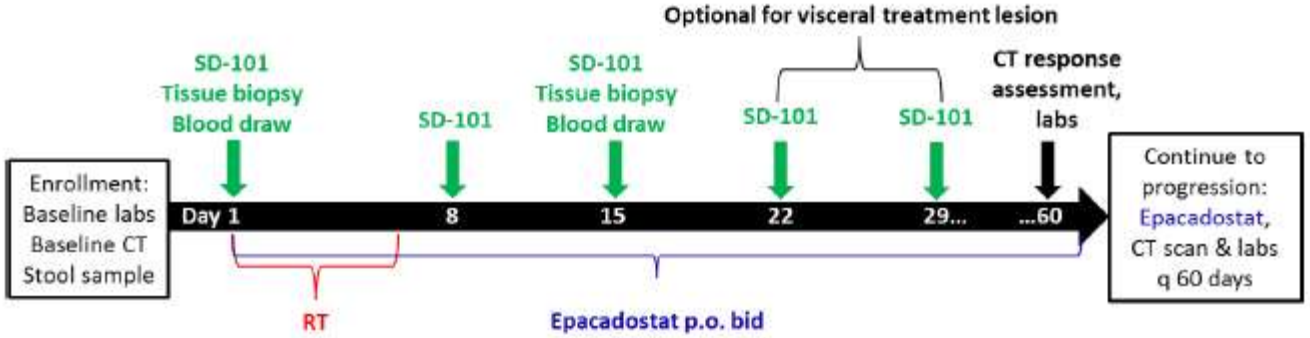
Linda Hammerich, Thomas U. Marron, Ranjan Upadhyay, Judit Svensson-Arvelund, Maxime Dhainaut, Shafinaz Hussein, Yougen Zhan, Dana Ostrowski, Michael Yellin, Henry Marsh, Andres M. Salazar, Adeeb H. Rahman, Brian D. Brown, Miriam Merad & Joshua D. Brody

Nature Medicine **volume 25**, pages814–824 (2019)

SCHEMA

General Enrollment Criteria

- Advanced refractory solid tumors or lymphoma
- Age ≥18
- 14 day treatment washout period
- At least one candidate treatment lesion (subcutaneous, nodal, or visceral)
  - Accessible for RT
  - Accessible and safe for repeat intralesional injections
- At least one candidate target lesion, outside of the RT field evaluable for response per irRECIST
- Adequate hematologic and end organ function
- No active autoimmune disease
- Patients with previous checkpoint blockade therapy are eligible



Concurrent RT (Days 1-5)

- Cohort 1 (solid tumors): (8 Gy x 3) or (4 Gy x 5)
- Cohort 2 (lymphoma): (8 Gy x 3) or (4 Gy x 5) or (2 Gy x 2)

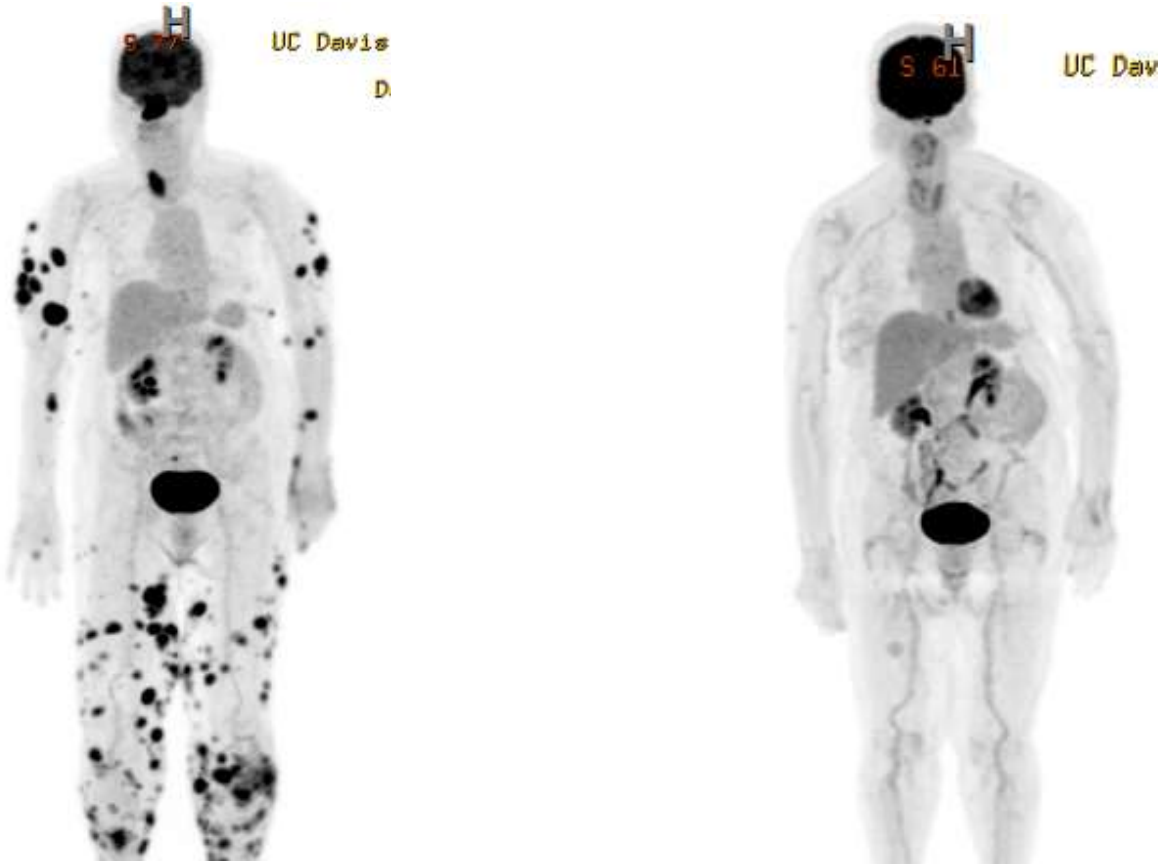
+

Intralesional SD-101 (Day 1, 8, 15, 22, 29)
4 mg injection into RT treatment lesion

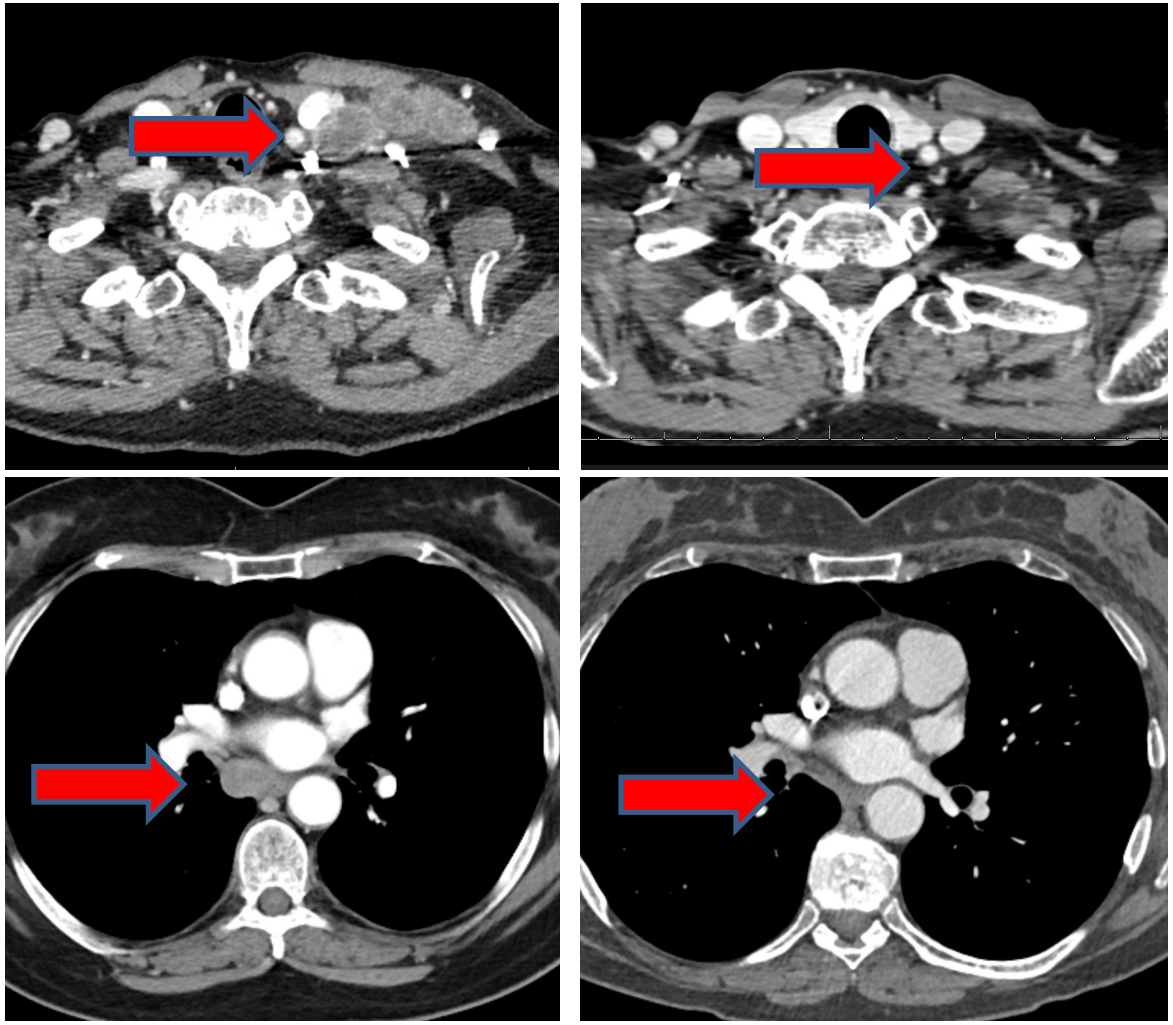
+

Epacadostat
100-300 mg PO bid

Response Pt 15



Response Pt 4



Acknowledgements

- UC Davis Comprehensive Cancer Center
- Michael S Kent, DVM
- Rob Rebhun, DVM, PhD
- William Culp, DVM
- Robert Canter, MD
- Peter Dickinson, BVSc, PhD
- Elizabeth E. Sparger, PhD
- Jenna Burton, DVM, MS
- Karen [illegible], MD
- Megan [illegible], MD
- Emanual Maverakis, MD, PhD
- UC Davis Laboratory of Cancer Immunology
- Robert Canter, MD
- William J. Murphy, PhD