sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

What's Next for Cancer Immunotherapy?

Ryan J. Sullivan, MD

Associate Director, Melanoma Program

Massachusetts General Hospital Cancer Center

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

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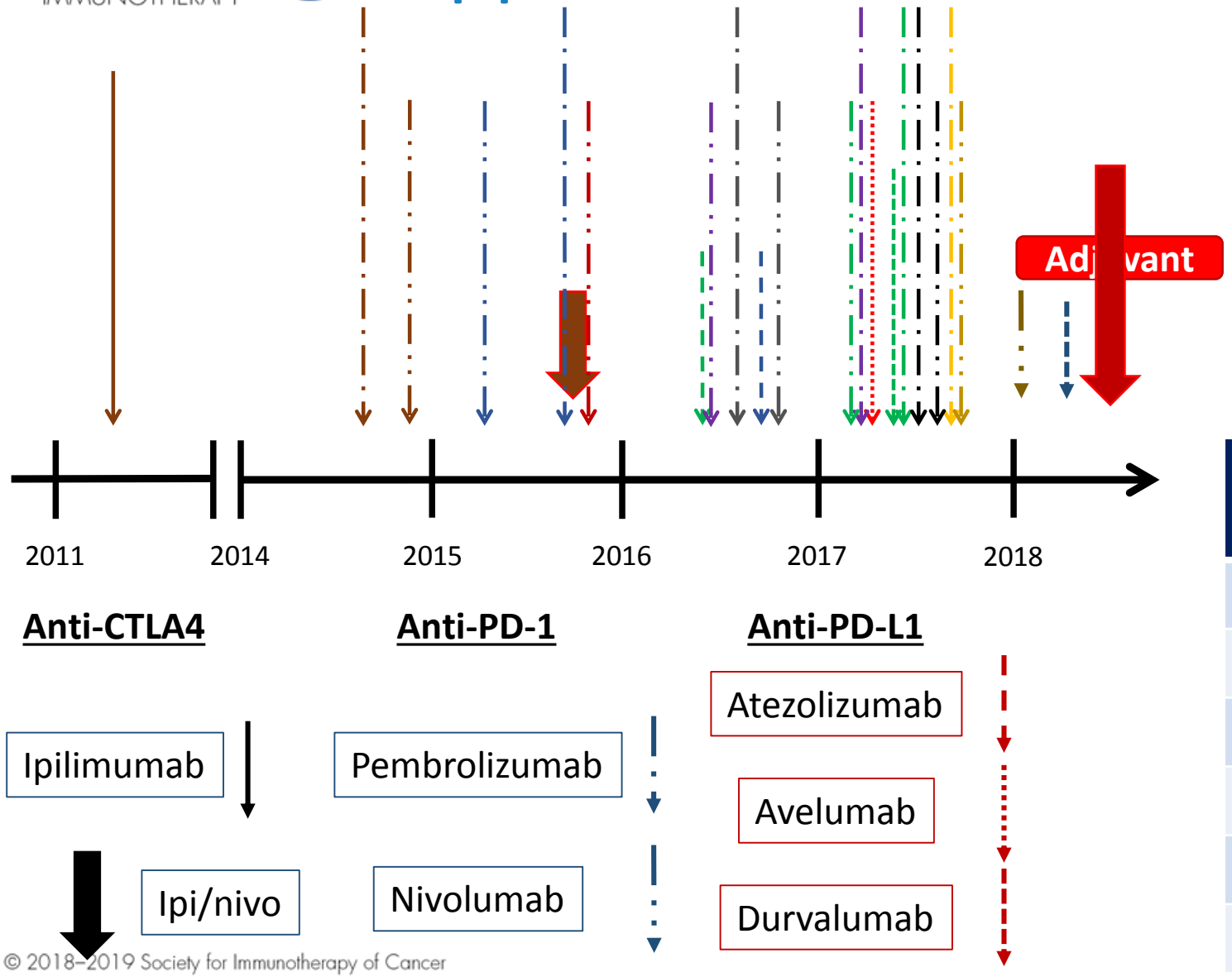
Disclosures

- Advisory Board/Consulting:
  - Novartis
  - Amgen
  - Merck
  - Array
  - Syndax
  - Replimmune

- Research Sponsorship:
  - Amgen
  - Merck

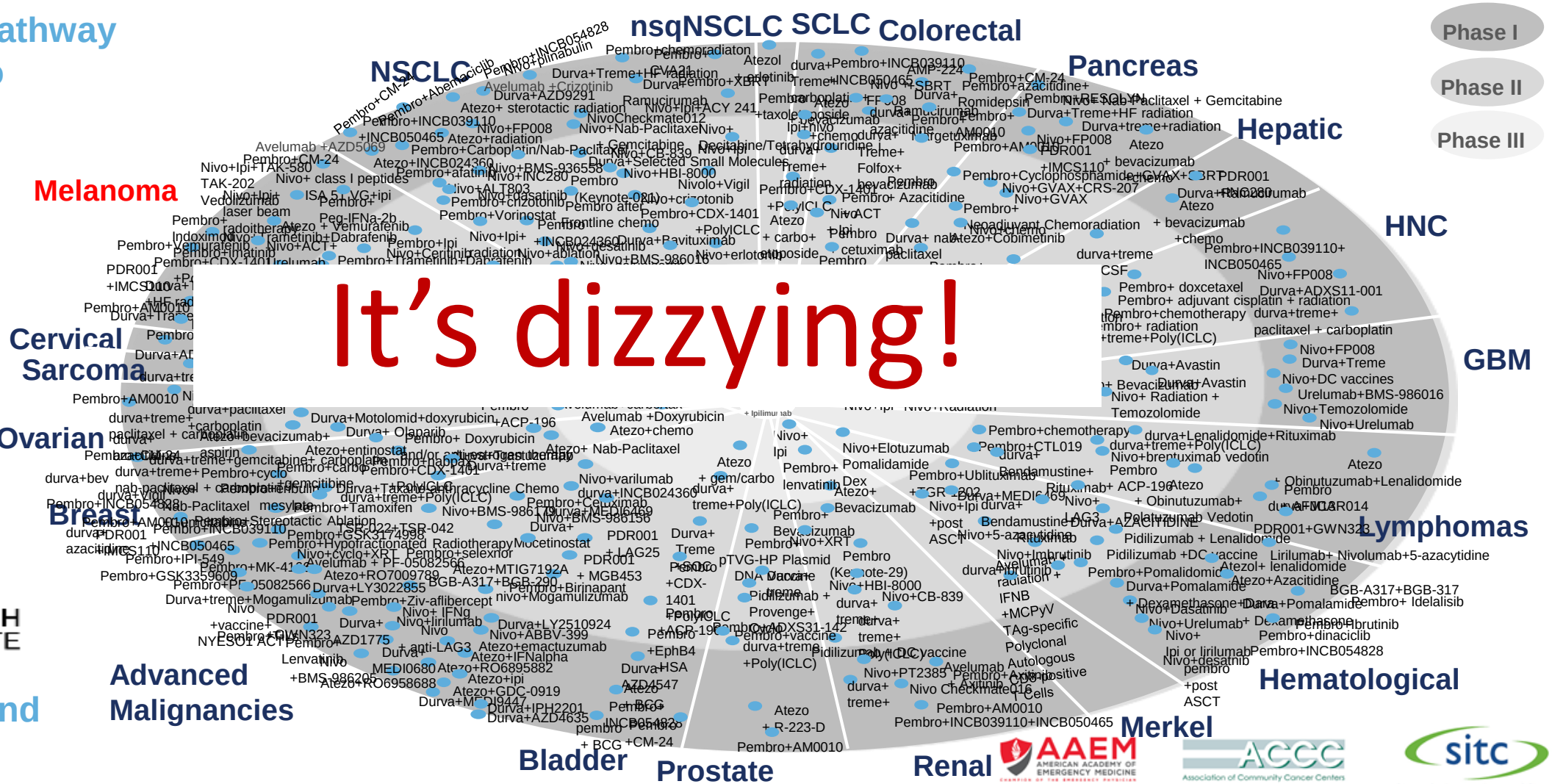
Immune Checkpoint Inhibitors and US FDA Approvals



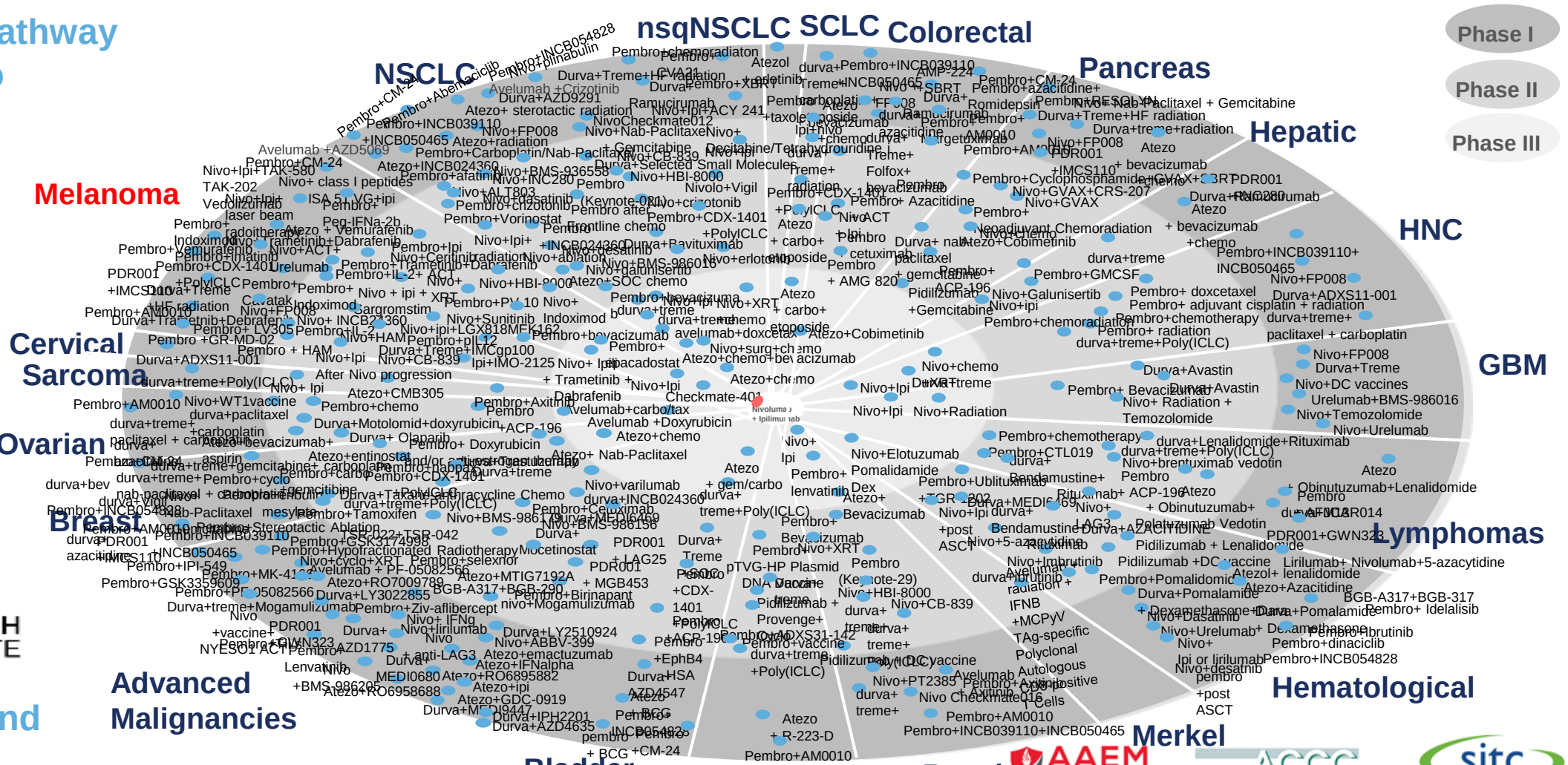
- Melanoma
- NSCLC
- Renal Cell Carcinoma
- Urothelial Bladder Cancer
- Hodgkin Lymphoma
- Head and Neck Squamous Cell Carcinoma
- Merkel Cell Carcinoma
- MSI Cancers
- Gastric Cancer
- Hepatocellular Carcinoma

Year	Drugs	Approvals	Disease indications
2011	1	1	1
2014	2	2	1
2015	3	4	3
2016	3	5	4
2017	4	9	6
2018	4	3	3

What about combination therapy?



What about combination therapy?



CRI Venture Fund Landscape

What are the unmet needs?

1. More effective therapies (combinations)

2. Better predictive biomarkers of benefit

3. Improve our understanding of mechanisms of therapeutic resistance

Anti-CTLA4
Anti-CD137/41BB (agonist)
Anti-Ox40 (agonist)
Anti-CD27 (agonist)
IL2
IL-12

Vaccines
IFN-g
GM-CSF
Anti-CD40
TLR agonists
Oncolytic virus

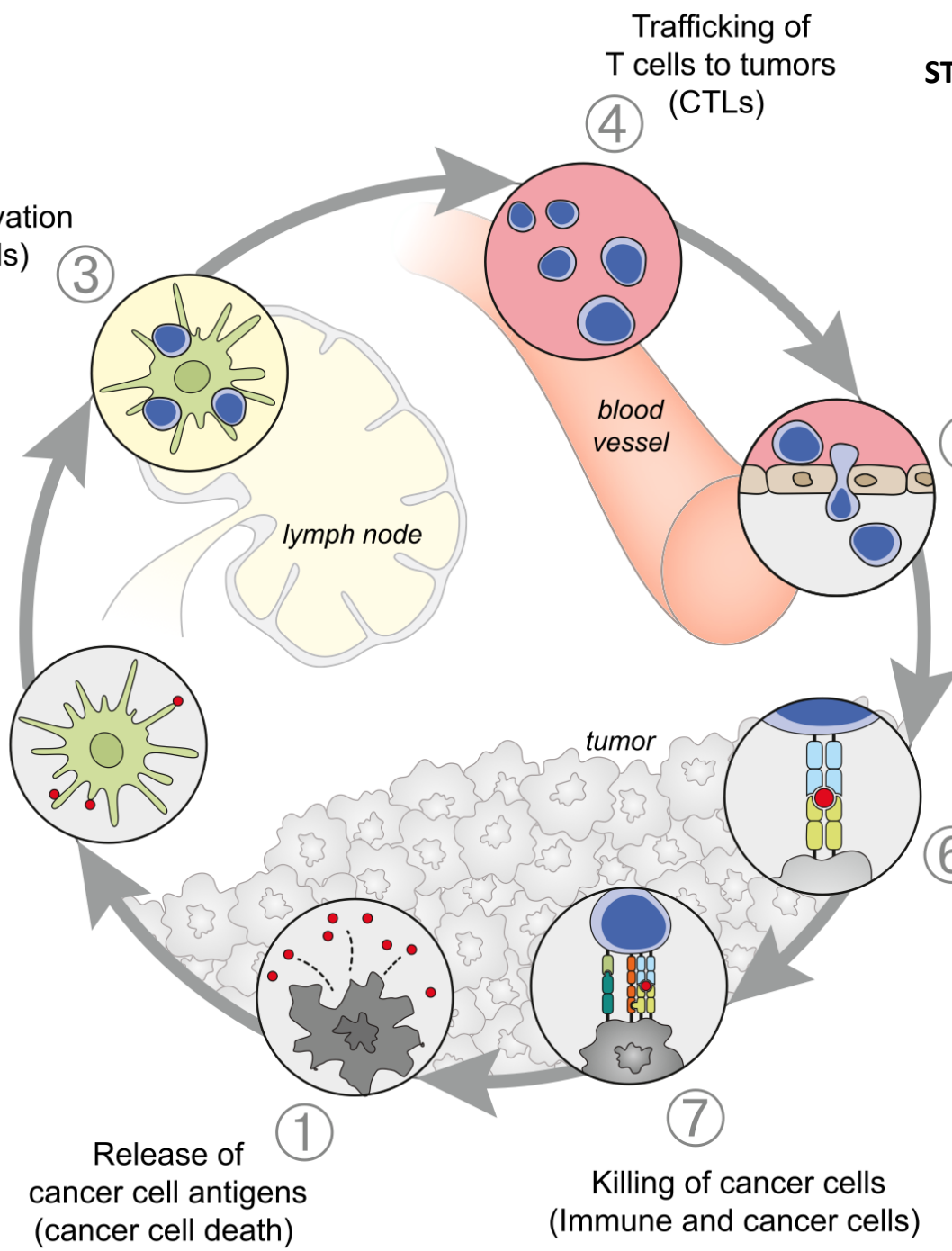
Chemotherapy
Radiation therapy
Targeted therapy
Oncolytic virus

STING agonist

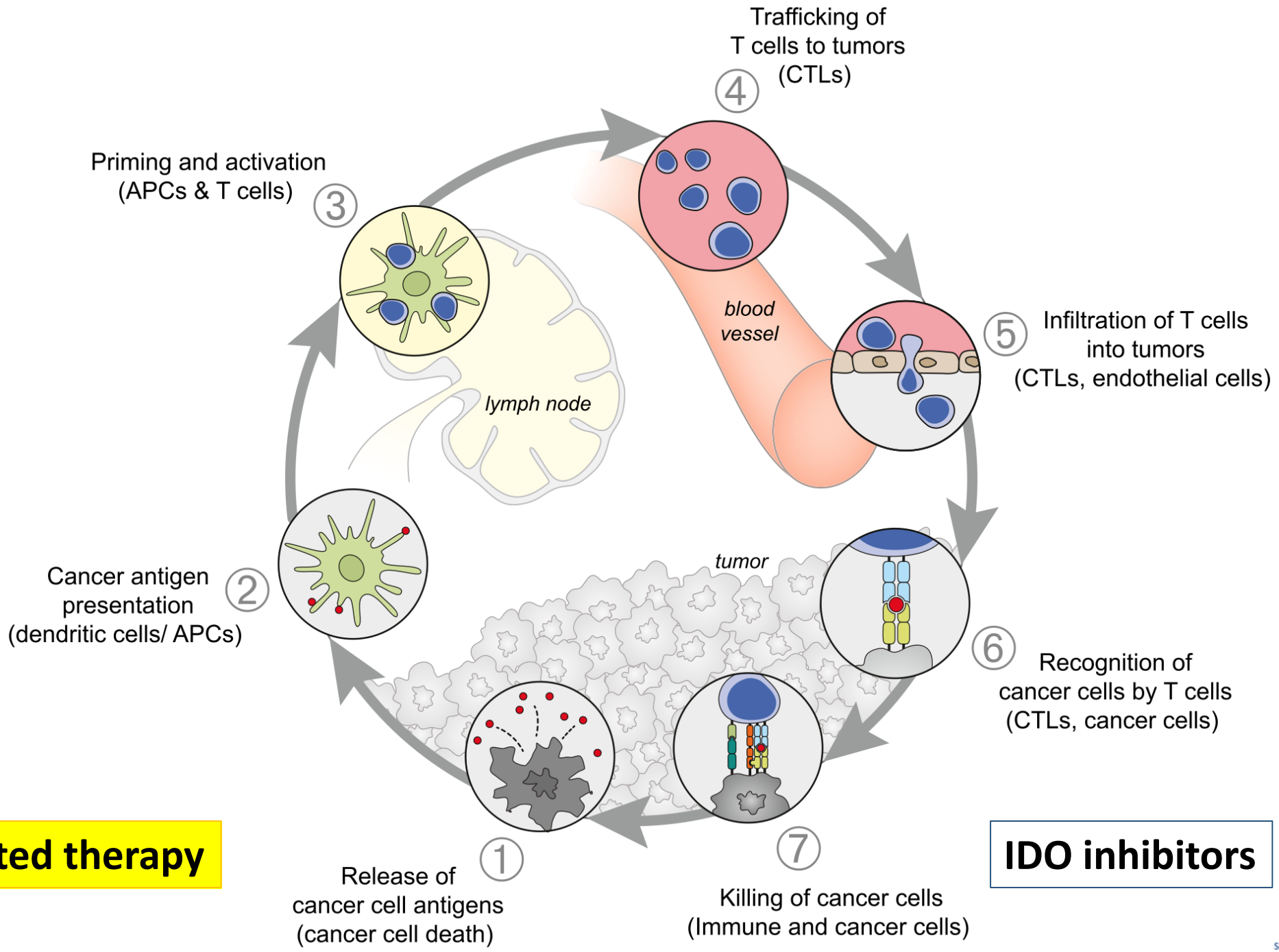
Anti-VEGF
Oncolytic virus
Anti- PI3K-gamma
Anti-TGF-beta

Adoptive Cell Therapy
TCR-Ts
CAR-Ts
BiTEs

Anti-PD-1/PD-L1
Anti-CTLA4 (effects on T-Reg)
IDO inhibitors



Modified from Chan and Melman, Immunity 2015



Targeted therapy

IDO inhibitors

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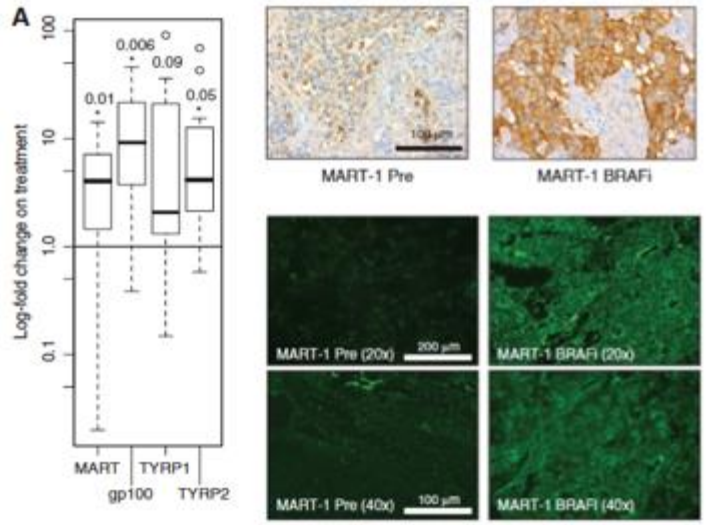
Modified from Chan and Melman, Immunity 2015

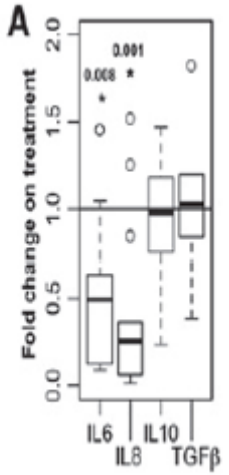
BRAFi effects on tumor microenvironment predict optimal combination is with anti-PD1/PD-L1 inhibition

Frederick et al. Clin Cancer Res 2013

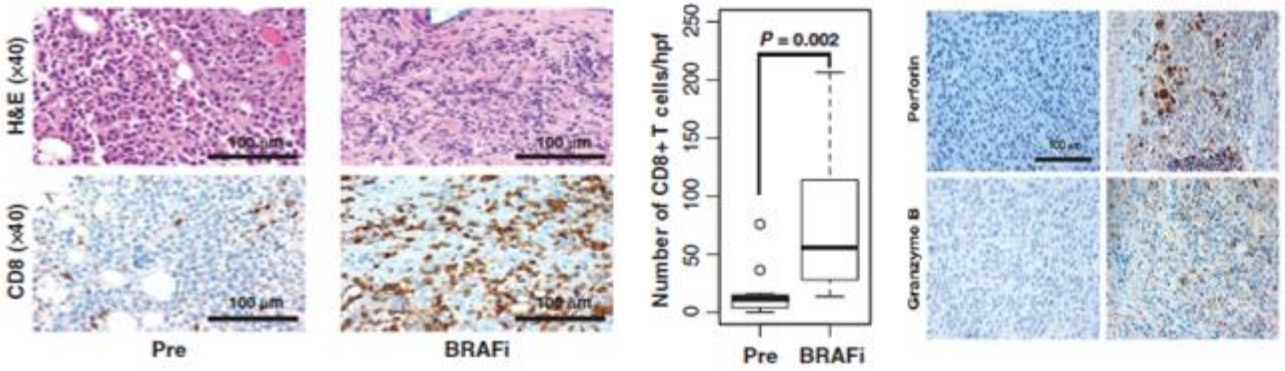
1. Increase antigen expression

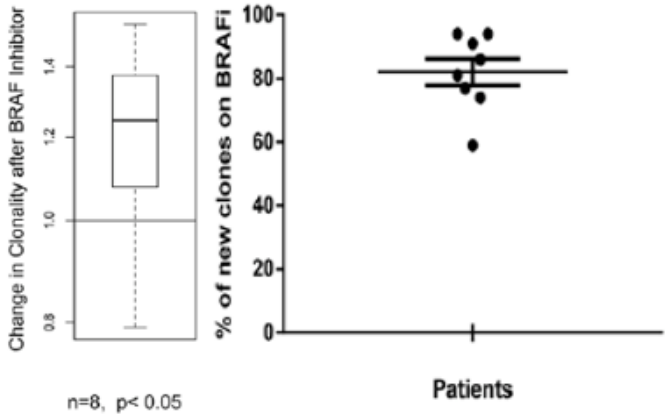


2. Decreased immunosuppresive cytokine production

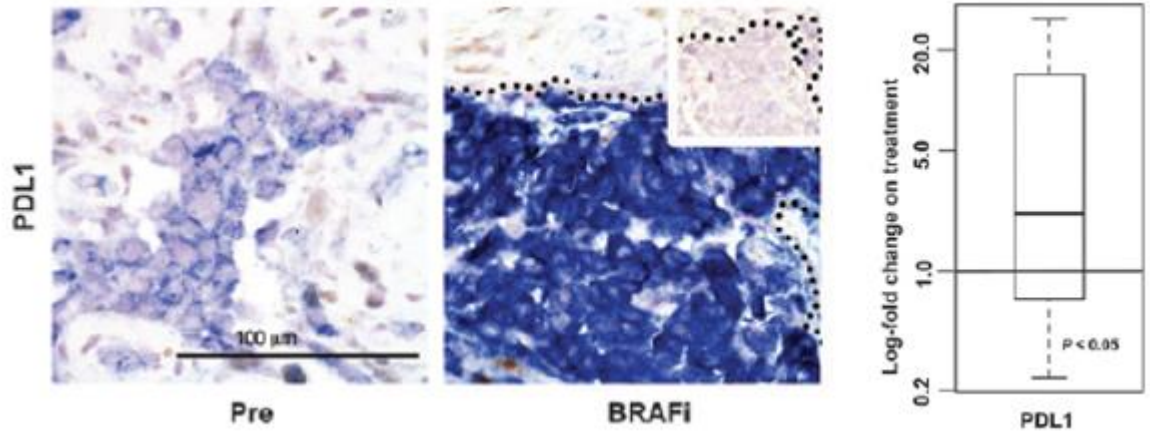


3. Increase CD8+ T-cell infiltration





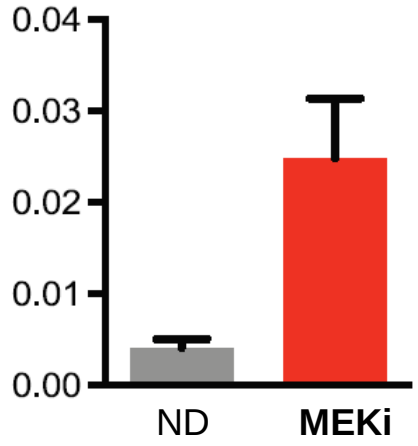
4. Increase T-cell clonality (Adaptive Biotechnologies)



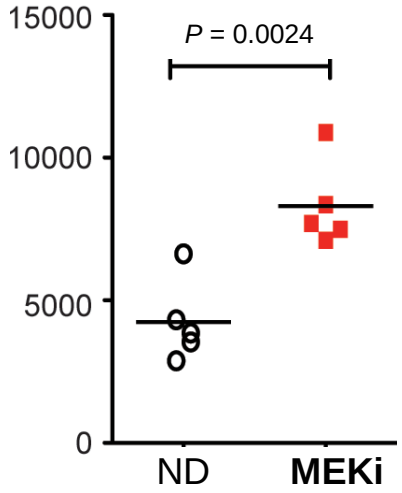
5. Increased PD-L1 expression

MEKi has similar effects in a colon cancer model…

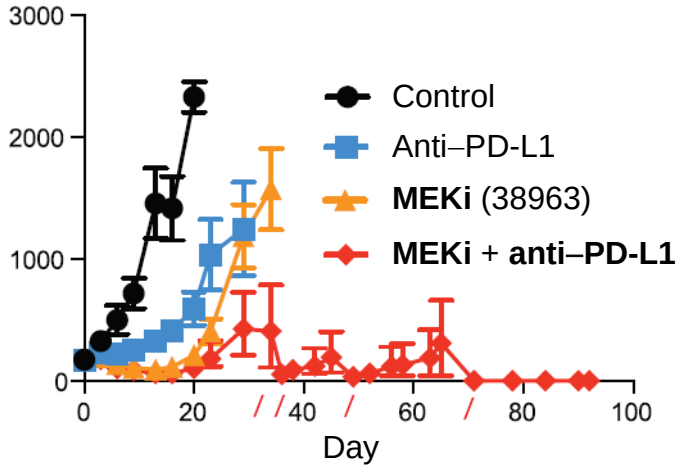
CD8+ T cell per Tumor Cell



Class I MHC



Tumor Volume (mm^3)



Intratumoral T cell accumulation

Tumor cell visibility

Efficacy
(CT26 syngeneic mouse model)

Ebert P et al. Immunity 2016.

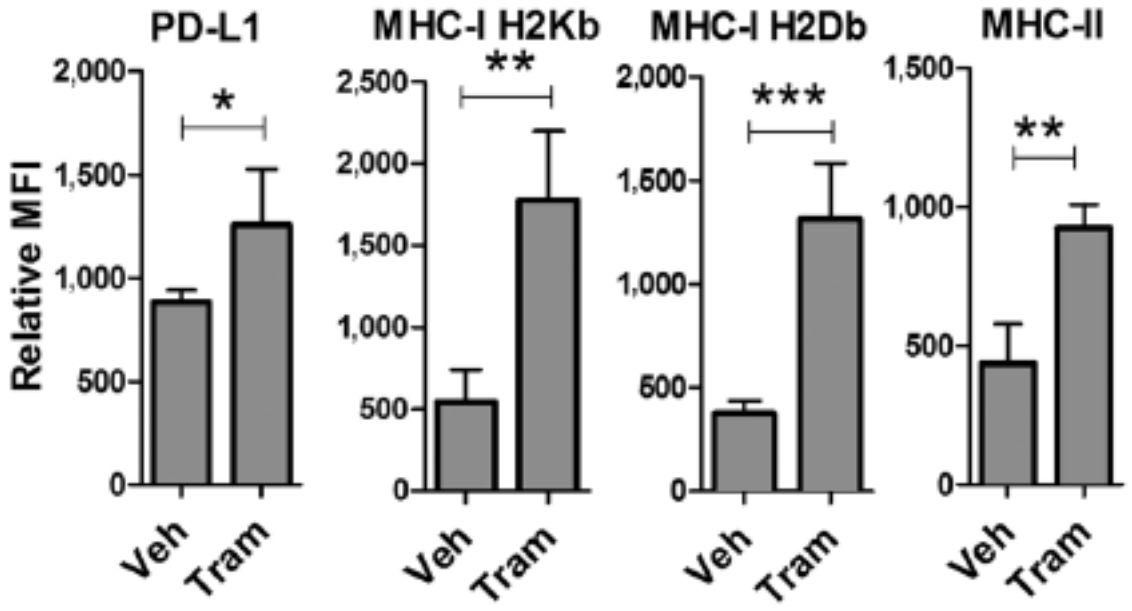
… and in Triple Negative Breast Cancer

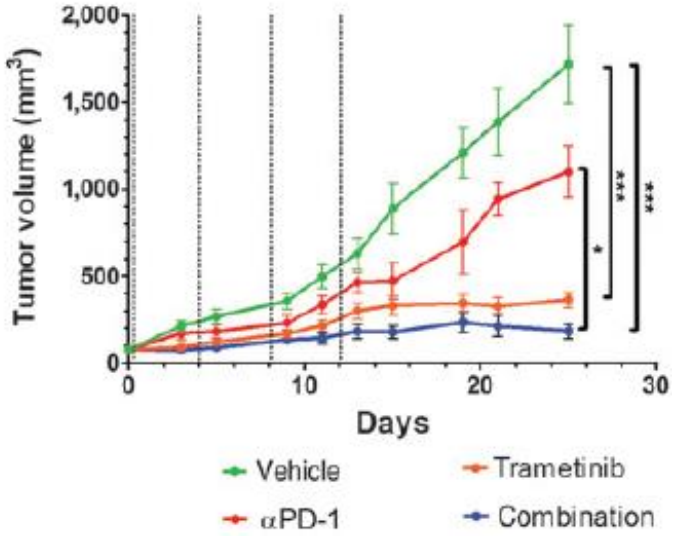
Biology of Human Tumors

Clinical Cancer Research

RAS/MAPK Activation Is Associated with Reduced Tumor-Infiltrating Lymphocytes in Triple-Negative Breast Cancer: Therapeutic Cooperation Between MEK and PD-1/PD-L1 Immune Checkpoint Inhibitors

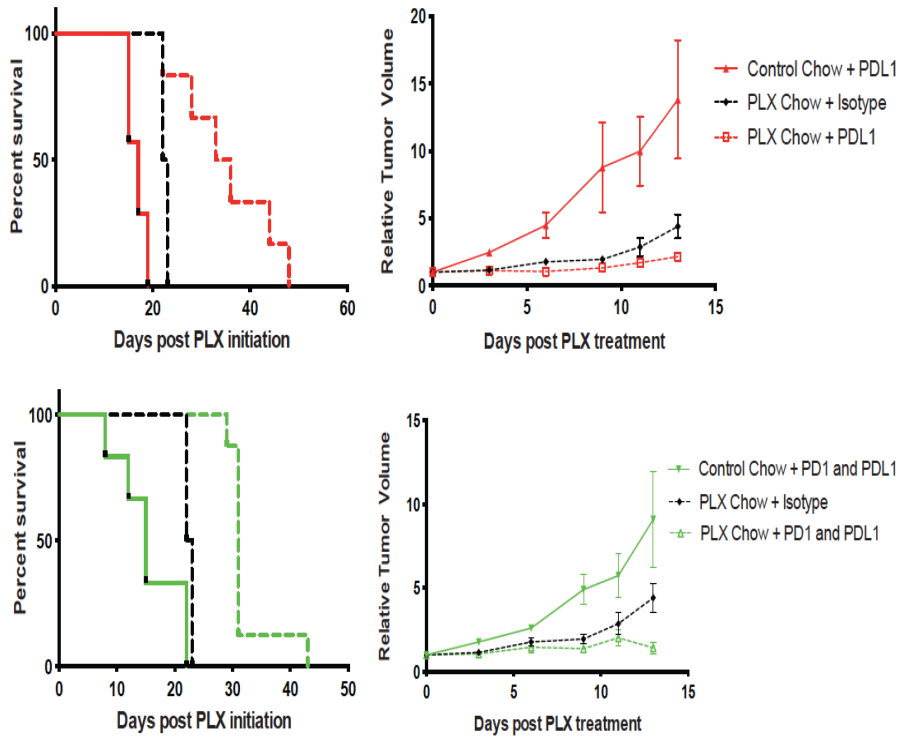
Sherene Loi[1,2], Sathana Dushyanthen[1], Paul A. Beavis[1], Roberto Salgado[3], Carsten Denkert[4], Peter Savas[1], Susan Combs[5], David L. Rimm[5], Jennifer M. Giltnane[6,7], Monica V. Estrada[7], Violeta Sánchez[7], Melinda E. Sanders[6,7], Rebecca S. Cook[7,8], Mark A. Pilkinton[9], Simon A. Mallal[6,9], Kai Wang[10], Vincent A. Miller[10], Phil J. Stephens[10], Roman Yelensky[10], Franco D. Doimi[11], Henry Gómez[11], Sergey V. Ryzhov[12], Phillip K. Darcy[1,2], Carlos L. Arteaga[7,8,9], and Justin M. Balko[7,9]





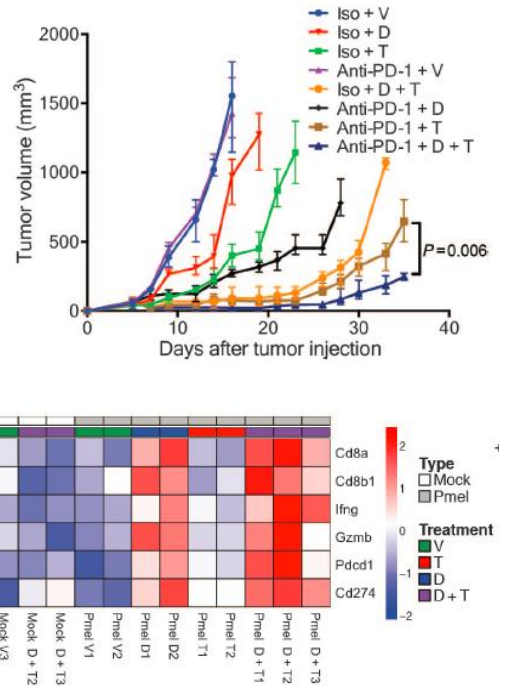
Loi et al. Clin Cancer Res 2016.

Preclinical data predicts synergy between MAPK targeting and PD1/PDL1 inhibition

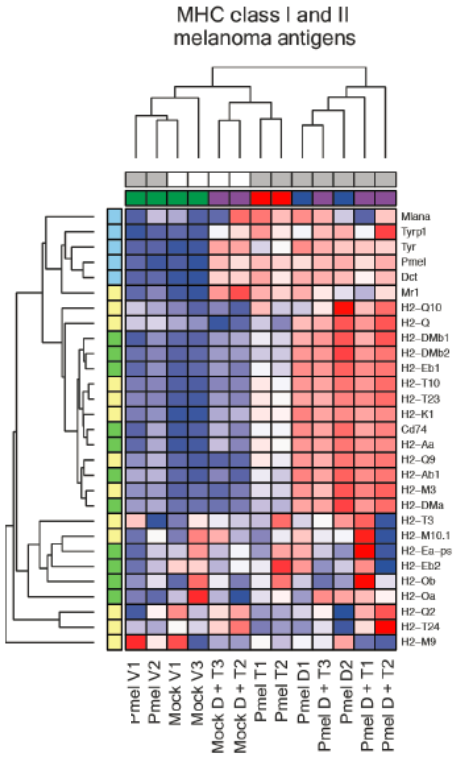


Cooper et al Cancer Immunol Res 2014

Antitumor activity of combined BRAFi+MEKi plus anti-PD-1[3]

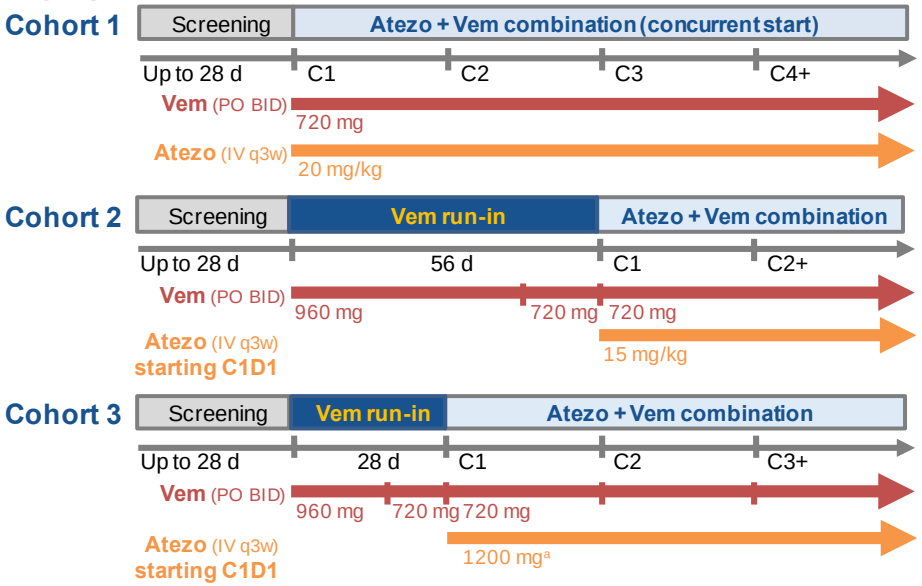


↑ MHC and melanoma antigen expression[3]

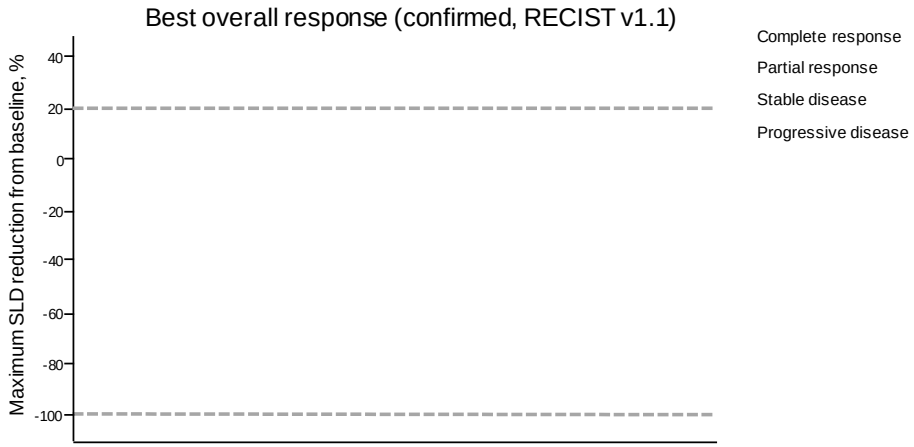


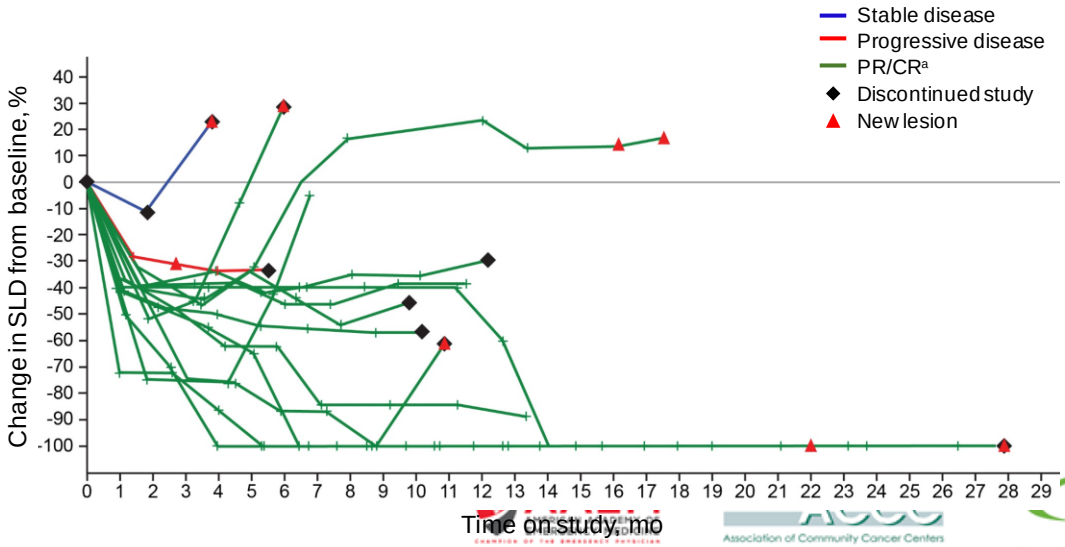
Hu-Lieskovan et al. Sci Transl Med 2015.

Vemurafenib plus atezolizumab



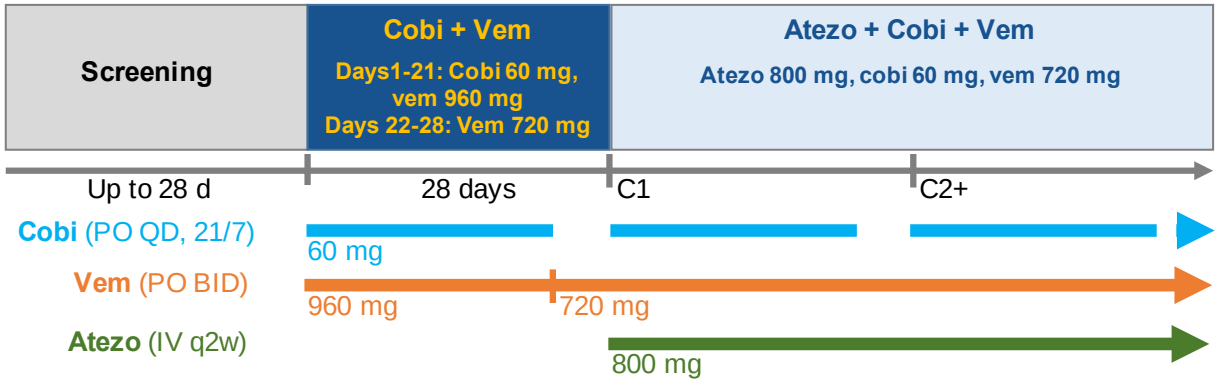
	All N = 17	Concurrent atezo + vem	Staggered atezo + vem	
		C1 n = 3	C2 n = 8	C3 n = 6
Median safety follow-up, mo	12.3	6.5	10.6	14.2
All treatment-emergent AEs	100%	100%	100%	100%
Grade 3 atezo-related AEs	41%	67%	38%	33%
Grade 3 vem-related AEs (during combination period)	59%	100%	50%	50%



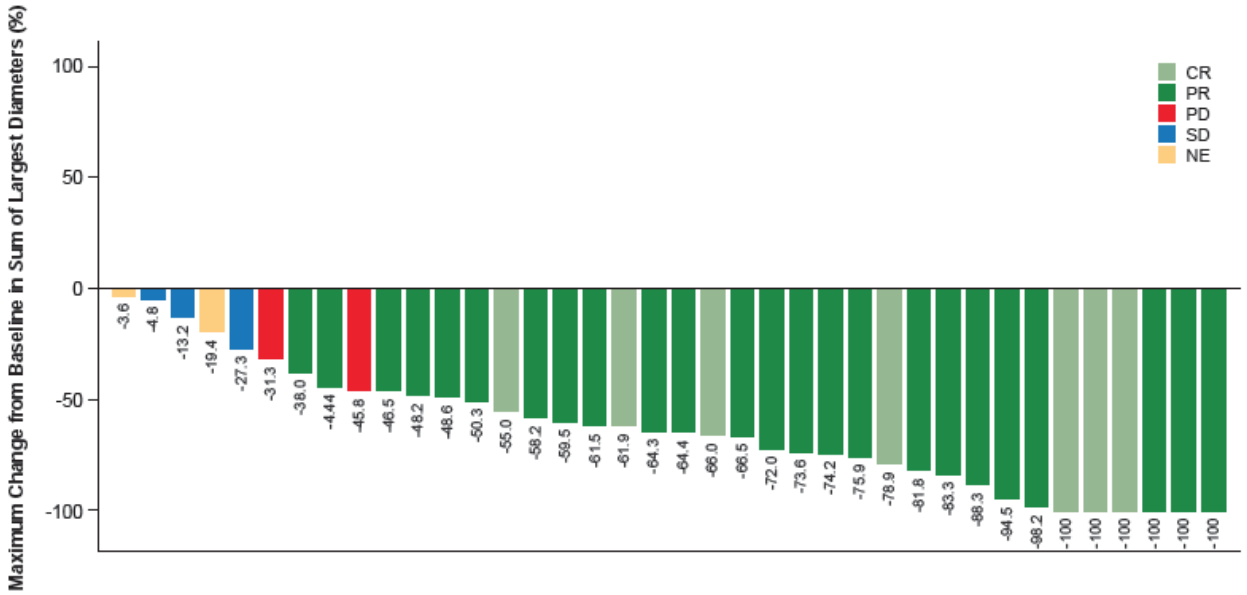


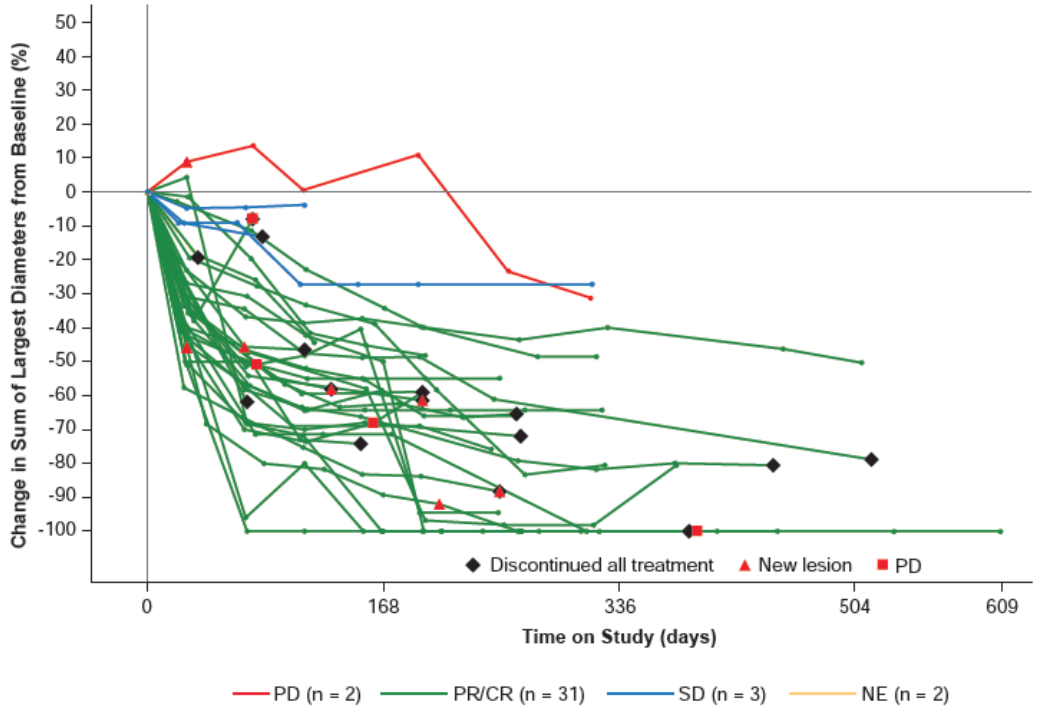
Hamid et al. SMR 2015

Vem/Cobi/Atezo



Best Objective Response (RECIST v1.1) N = 38	n (%)	95% CI
ORR[a]	31 (81.6%)	65.7, 92.3
CR	7 (18.4%)	7.7, 34.3
PR	24 (63.2%)	46.0, 78.2
SD	3 (7.9%)	1.7, 21.4
PD	2 (5.3%)	0.6, 17.8
NE[b]	2 (5.3%)	–





Sullivan et al. SMR 2016; updated ASCO 2017

Safety Summary

Safety during triple combination	N = 39; n (%)
Treatment-emergent AEs during combination period	
All grade atezo- and/or cobi- and/or vem-related AEs	37 (95%)
Grade 3-4 atezo- and/or cobi- and/or vem-related AEs	16 (41%)
Grade 3-4 atezo-related AEs	11 (28%)
Treatment-related SAEs	6 (15%)
All treatment discontinuations	6 (16%)

- The triple combination treatment was generally well tolerated; no unexpected AEs occurred
- No Grade 5 AEs occurred
- All AEs were manageable and reversible with dose interruption and/or reduction
- Treatment-related SAEs:
  - All six patients continued with treatment after study drug interuption

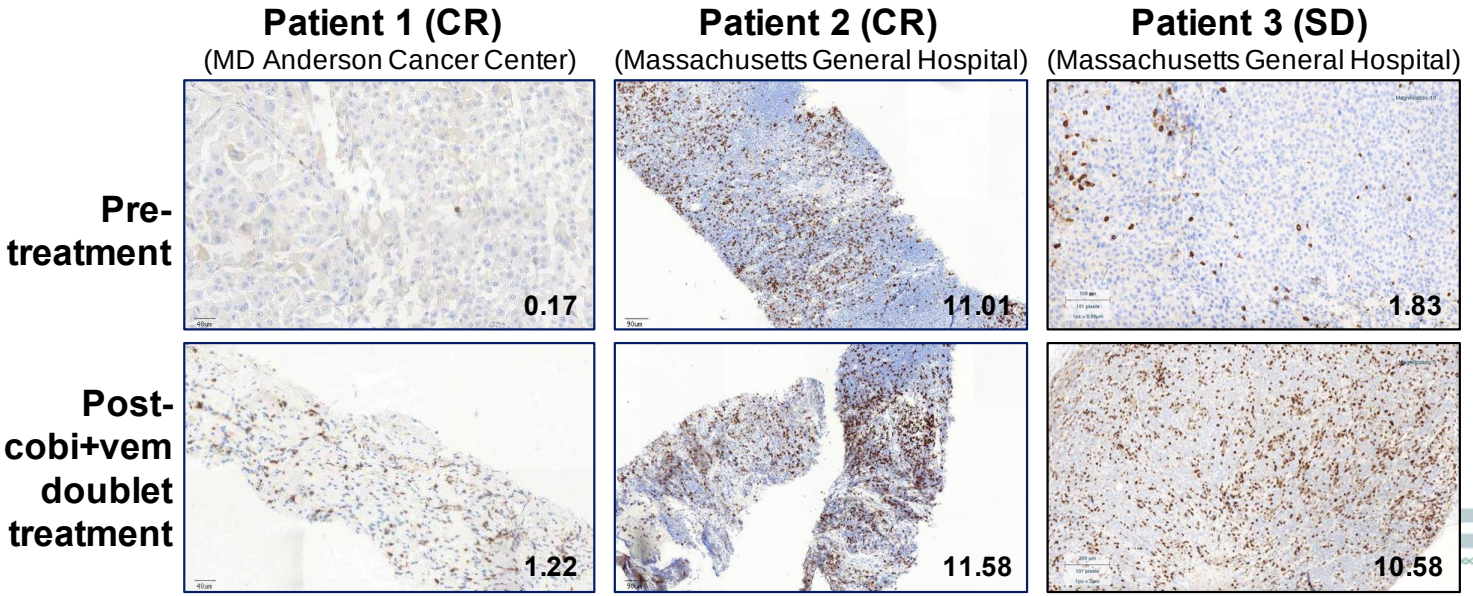
Grade 3-4 AEs^^	N = 39 n (%)
ALT increased	5 (12.8)
AST increased	4 (10.3)
Hypophosphatemia	3 (7.7)
Blood creatinine phosphokinase increased	2 (5.1)
Diarrhea	2 (5.1)
Blood bilirubin increased	2 (5.1)
Rash	2 (5.1)

^^1 each of the following: Nausea, vomiting, stomatitis, pyrexia, lubmar spinal stenosis, hyponatremia, anemia, bilateral UE rash, sepsis, hypertension, autoimmune hepatitis, diverticulitis

Sullivan et al. SMR 2016; updated ASCO 2017

Summary of Vem/Cobi/Atezo

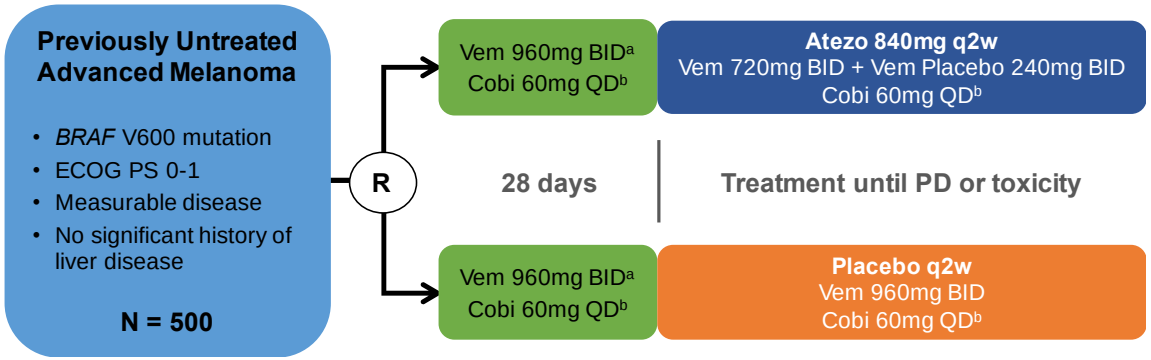
- Atezo + cobi + vem treatment is relatively safe
- The triple combination demonstrated promising antitumor activity
  - Unconfirmed response rate was 81.6%
- A dosing schedule that includes a cobi and vem lead-in was safe and efficacious, and merits further investigation
- Increased tumor CD8+ T-cell accumulation after cobi + vem treatment may result in enhanced immunotherapy responsiveness and supports the mechanistic rationale for this study



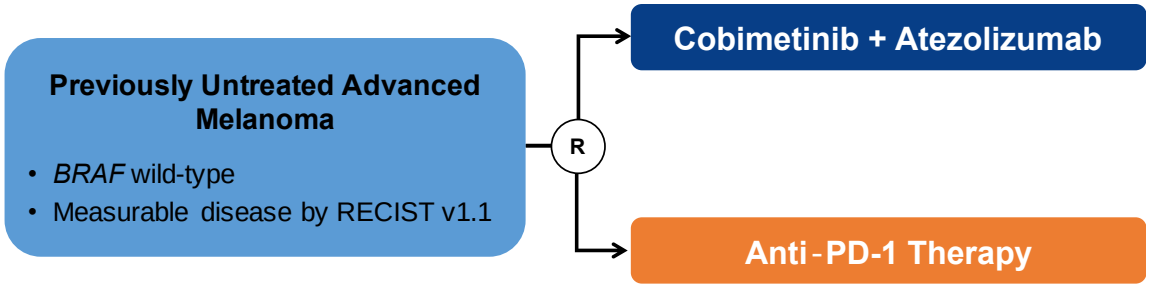
Sullivan et al. SMR 2016; updated ASCO 2017

Next Steps

Randomized trials

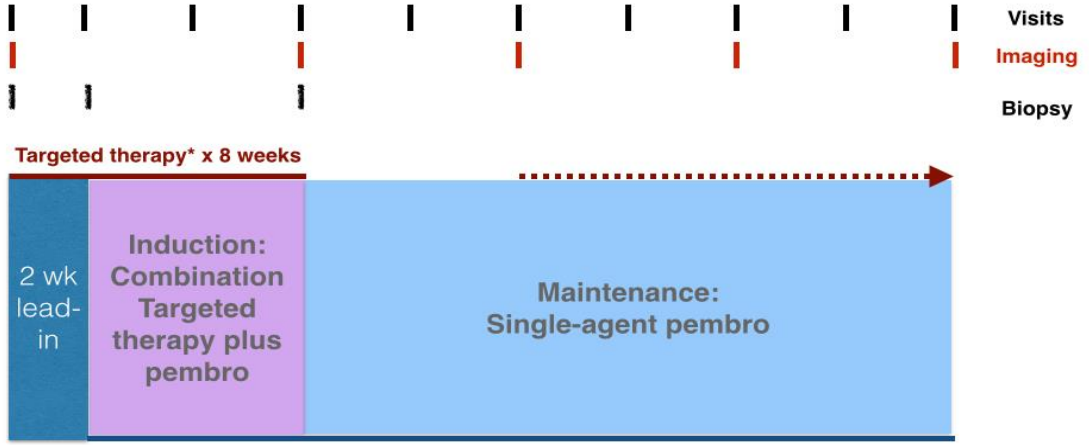


NCT02908672



CO39722; NCT pending

Novel design/endpoint trials

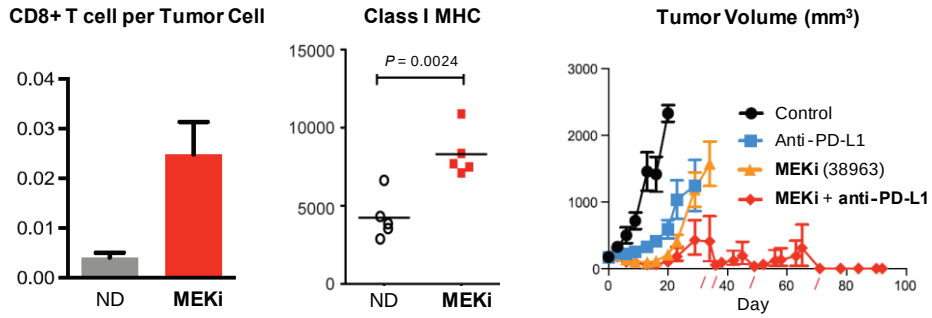


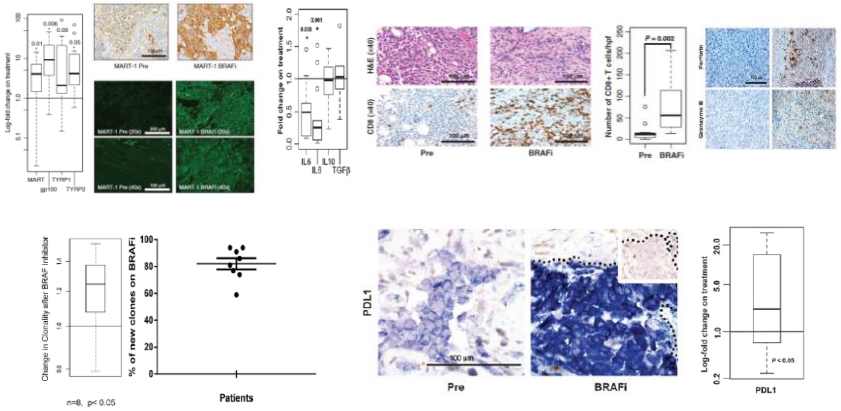
NCT03149029

Primary endpoint: CBR at 24 weeks
Secondary endpoints:
COUNTLESS!

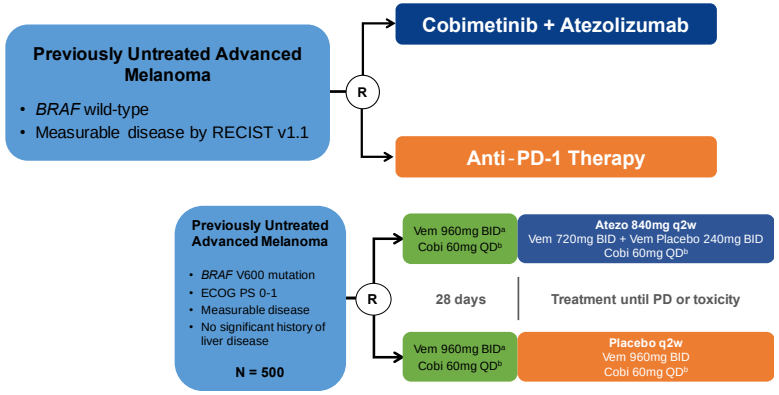
Summary – Targeted Therapy

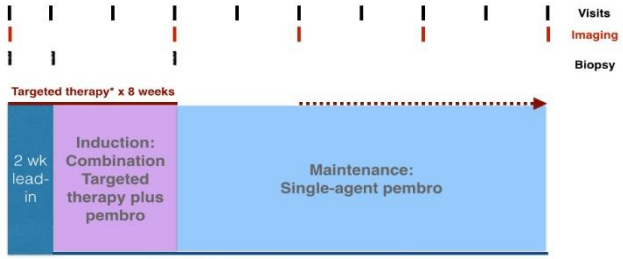
There is a strong rationale to combine MAPK inhibitors with anti-PD-1, anti-PD-L1 inhibitors in BRAF mutant *AND* BRAF wild-type melanoma

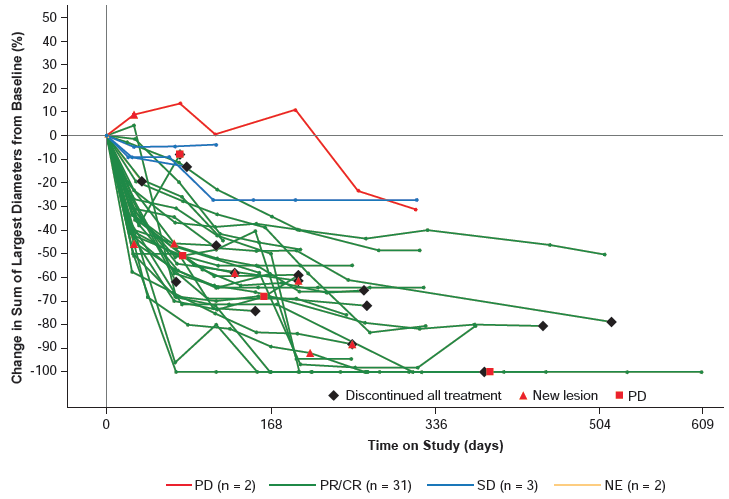




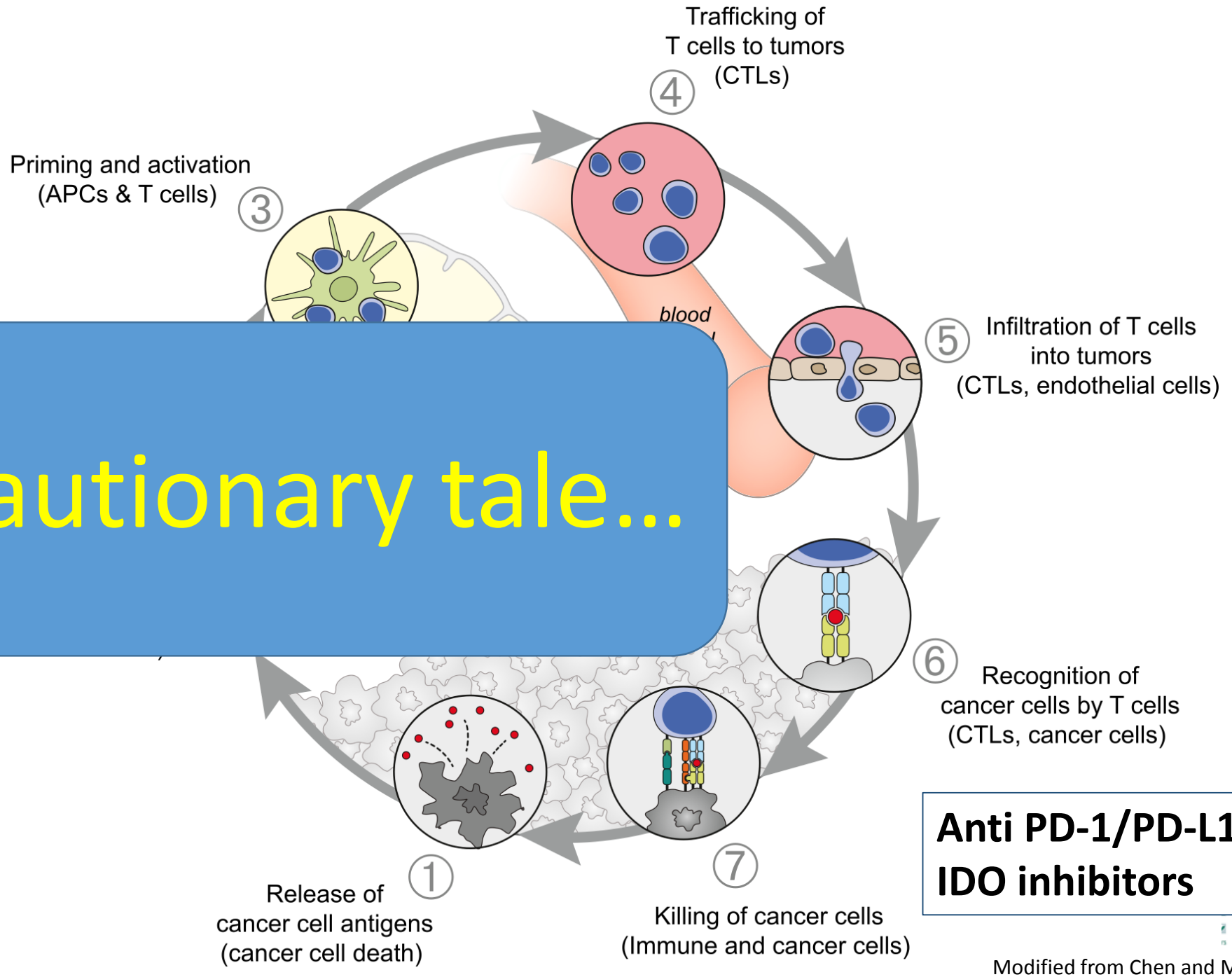
Regimens combining MAPK-targeted therapy plus anti-PD-1/anti-PD-L1 therapy show promising efficacy and safety







More trials are needed to justify use of these combinations as standard of care



A cautionary tale…

Anti PD-1/PD-L1
IDO inhibitors

Modified from Chen and Melman, Immunity 2015

Epacadostat Plus Pembrolizumab in Patients With Advanced Melanoma: Phase 1 and 2 Efficacy and Safety Results From ECHO-202/KEYNOTE-037

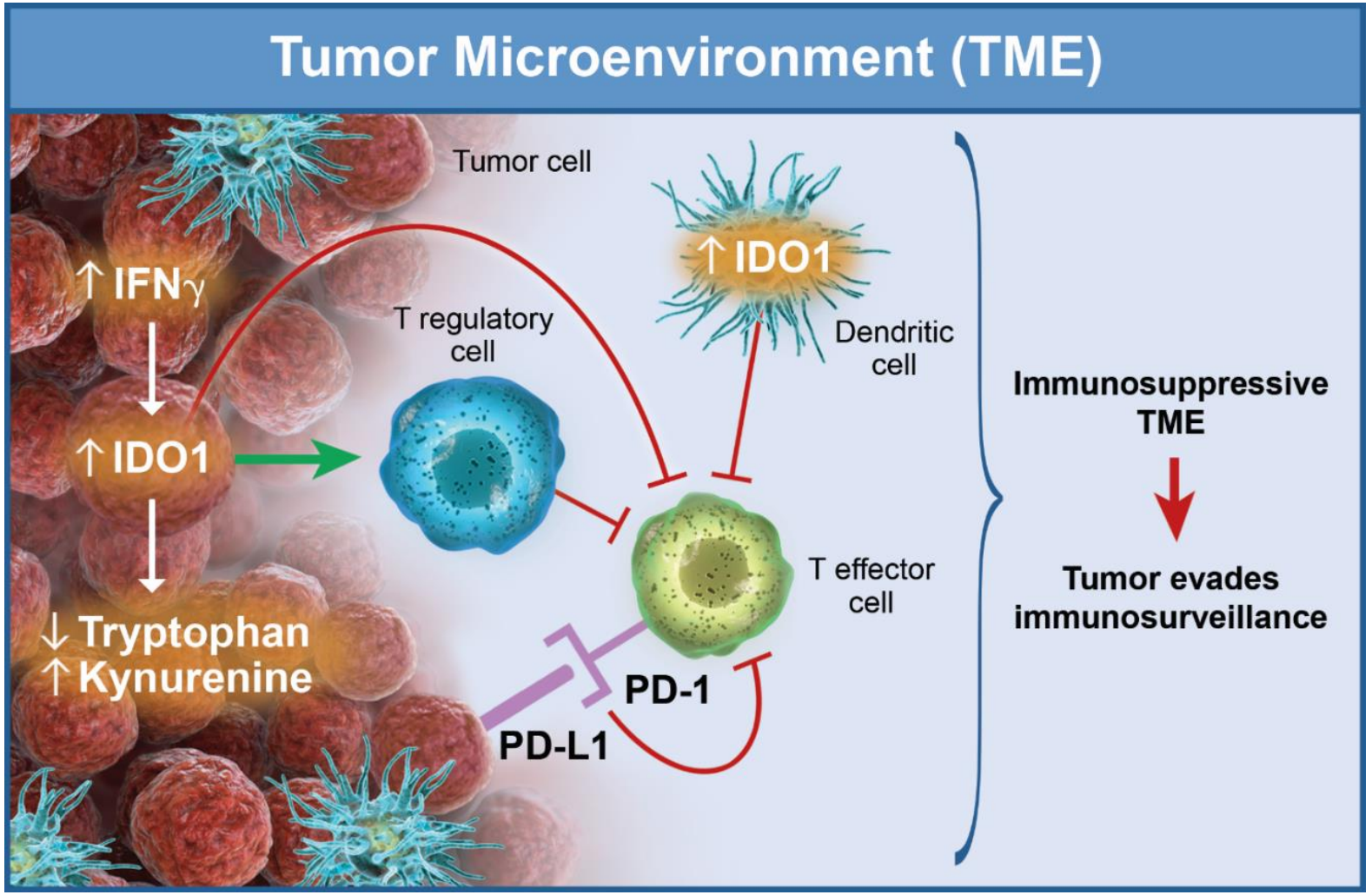
O. Hamid,[1] T. F. Gajewski,[2] A. E. Frankel,[3] T. M. Bauer,[4] A. J. Olszanski,[5] J. J. Luke,[2] A. S. Balmanoukian,[1] E. V. Schmidt,[6] B. Sharkey,[7] J. Maleski,[7] M. M. Jones,[7] T. C. Gangadhar[8]

[1]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [2]University of Chicago, Chicago, IL, USA; [3]University of Texas Southwestern Medical Center, Dallas, TX, USA*; [4]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [5]Fox Chase Cancer Center, Philadelphia, PA, USA; [6]Merck & Co., Inc., Kenilworth, NJ, USA; [7]Incyte Corporation, Wilmington, DE, USA; [8]Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA

Presentation #1214O
Session: Melanoma and Other Skin Tumours
Presented at the ESMO Annual Meeting 2017
Madrid, Spain
September 9, 2017

IDO1 mediates an immunosuppressive tumor microenvironment

- **IDO1**
  - IFNγ-induced intracellular enzyme
  - catalyzes the first and rate-limiting step of tryptophan degradation in the kynurenine pathway
  - depletion of tryptophan and production of kynurenine and other metabolites shift the local TME to an immunosuppressive state that helps tumor cells evade immunosurveillance



Best Objective Response by RECIST v1.1

Epacadostat Plus Pembrolizumab, P1/2 Advanced Melanoma

	All Patients (N=65)	Treatment-Naive for Advanced Disease, All E Doses (n=54)	Treatment-Naive for Advanced Disease, E 100 mg (n=39)
Per-protocol evaluable,* n (%)	**n=63**	**n=53**	**n=38**
ORR (CR+PR)	**35 (56)**	**29 (55)**	**22 (58)**
CR	9 (14)	7 (13)	3 (8)
PR	26 (41)	22 (42)	19 (50)
SD	10 (16)	9 (17)	6 (16)
DCR (CR+PR+SD)	**45 (71)**	**38 (72)**	**28 (74)**
PD or death	18 (29)	15 (28)	10 (26)
Not evaluable†	**n=2**	**n=1**	**n=1**

- For all patients, based on irRECIST (n=63*): ORR=59% (9 CR, 28 PR); DCR=75% (10 SD)

Epacadostat Plus Pembrolizumab Versus Pembrolizumab Alone in Patients With Unresectable or Metastatic Melanoma: Results of the Phase 3 ECHO-301/KEYNOTE-252 Study

Georgina V. Long,[1] Reinhard Dummer,[2] Omid Hamid,[3] Thomas Gajewski,[4] Christian Caglevic,[5] Stephane Dalle,[6] Ana Arance,[7] Matteo S. Carlino,[8] Jean-Jacques Grob,[9] Tae Min Kim,[10] Lev Demidov,[11] Caroline Robert,[12] James Larkin,[13] James R. Anderson,[14] Janet Maleski,[15] Mark Jones,[15] Scott J. Diede,[14] Tara C. Mitchell[16]

[1]Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, Australia; [2]University Hospital Zürich, Zurich, Switzerland; [3]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [4]University of Chicago Medical Center, Chicago, IL, USA; [5]Fundacion Arturo Lopez Perez, Santiago, Chile; [6]Hospices Civils De Lyon, Cancer Research Center of Lyon, Claude Bernard University Lyon, Pierre Benite, France; [7]Hospital Clínic de Barcelona, Barcelona, Spain; [8]Westmead and Blacktown Hospitals, Melanoma Institute Australia, The University of Sydney, Sydney, Australia; [9]Aix-Marseille University, Marseille, France; [10]Seoul National University Hospital, Seoul, South Korea; [11]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [12]Gustave Roussy Comprehensive Cancer Center, Villejuif, France; [13]The Royal Marsden NHS Foundation Trust, London, United Kingdom; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Incyte Corporation, Wilmington, DE, USA; [16]Abramson Cancer Center of the University of Philadelphia, Philadelphia, PA, USA.

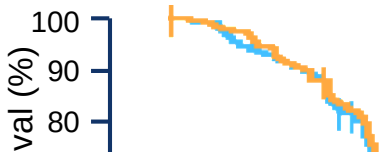
ASCO 2018: Presented by Georgina V. Long

Echo 301/KN252

Key

- Unresectable st
  advanced/metas
  - Patients with
    received prior
  - Prior anti-CTL
    setting permit
- ECOG performa

Progression-Free Survival (RECIST v1.1, BICR)



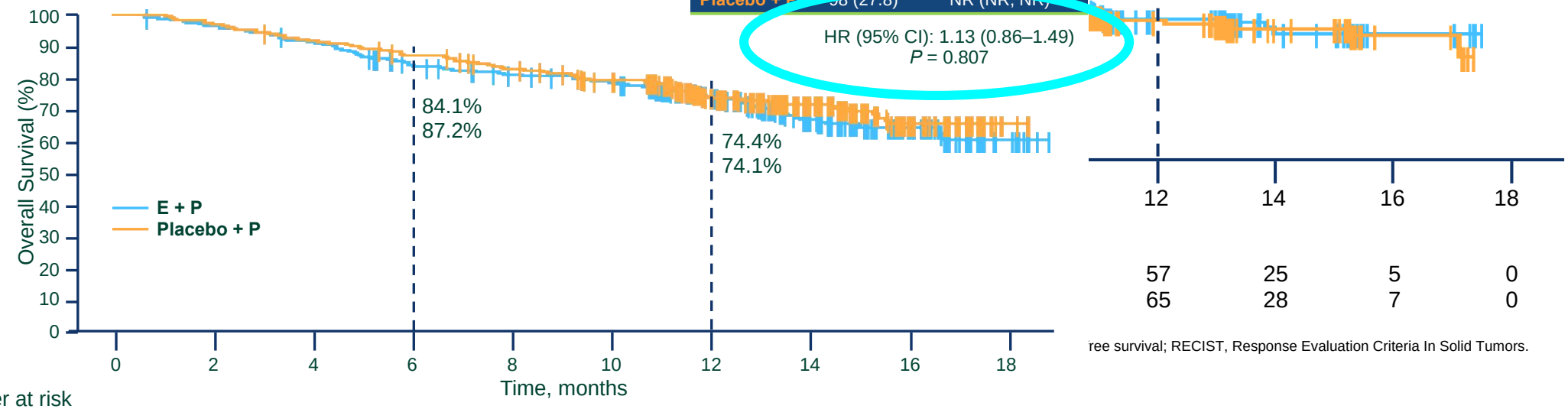
	Events, n (%)	Median PFS, months (95% CI)
E + P	218 (61.6)	4.7 (2.9-6.8)
Placebo + P	219 (62.2)	4.9 (2.9-6.8)

HR (95% CI): 1.00 (0.83-1.21)
P = 0.517

Overall Survival

	Events, n (%)	Median OS, months (95% CI)
E + P	106 (29.9)	NR (NR, NR)
Placebo + P	98 (27.8)	NR (NR, NR)

HR (95% CI): 1.13 (0.86–1.49)
P = 0.807



Number at risk

E + P	354	340	322	290	274	263	183	96	42	5
Placebo + P	352	342	323	304	285	263	186	115	43	2

12 14 16 18
57 25 5 0
65 28 7 0

ree survival; RECIST, Response Evaluation Criteria In Solid Tumors.

CI, confidence interval; E, epacadostat; HR, hazard ratio; NR, not reached; OS, overall survival; P, pembrolizumab.

Lessons to be learned from epacadostat fiasco

1. We need to be more careful
2. Amazing efficacy in a single-arm, open-labeled combination cohort may not be predictive of efficacy
3. Propose at least one of the following criteria need to be met:

- Single agent efficacy of both agents
- Efficacy in small, randomized cohorts
- Efficacy more prominent in a biomarker defined populations

DRUG DEVELOPMENT 101

What are the unmet needs?

1. More effective therapies (combinations)

2. Better predictive biomarkers of benefit

3. Improve our understanding of mechanisms of therapeutic resistance

A topic for an other day

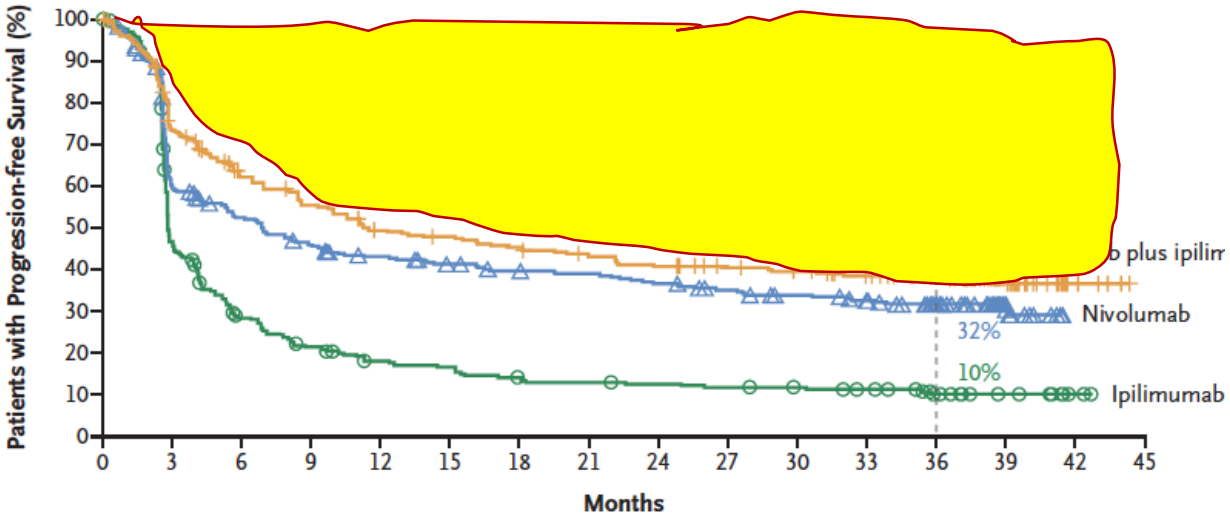
What are the unmet needs?

1. More effective therapies (combinations)

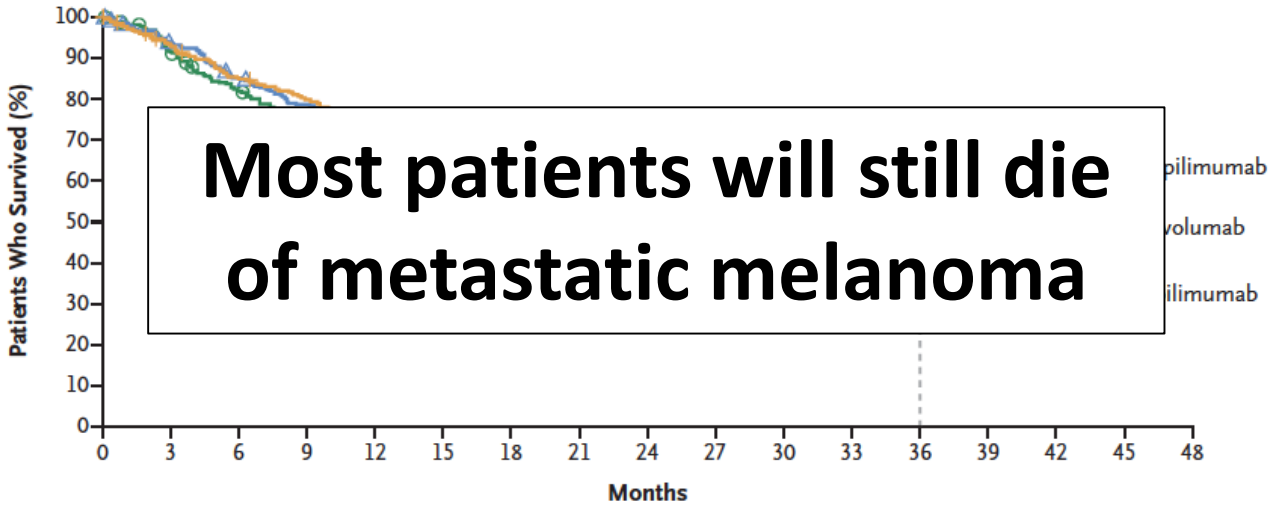
2. Better predictive biomarkers of benefit

3. Improve our understanding of mechanisms of therapeutic resistance

Most patients develop resistance



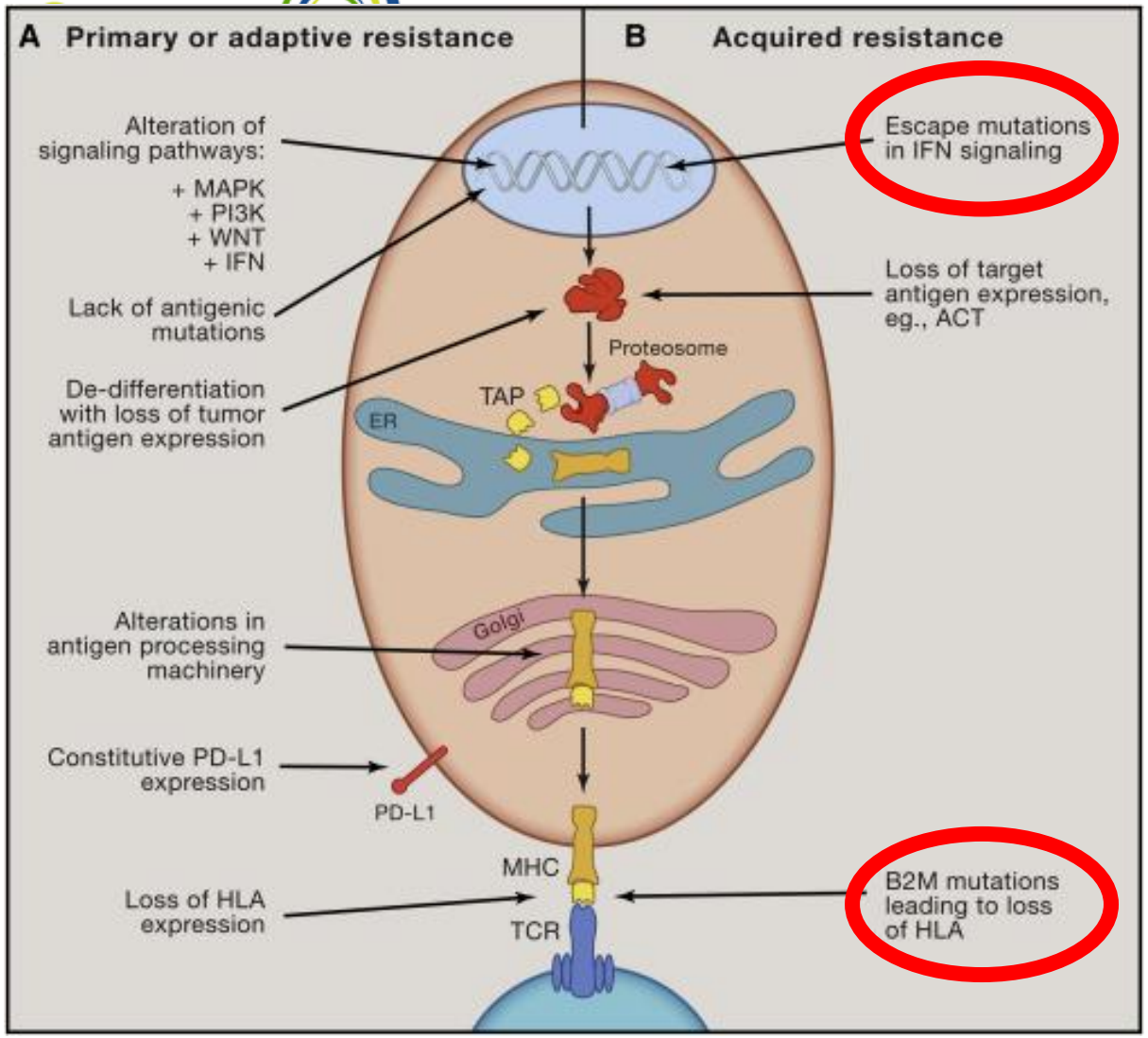
Tail on the curve



Most patients will still die of metastatic melanoma

Median survival > 3 years!

Wolchok et al. NEJM 2017



Sharma et al. Cell 2017

RESEARCH ARTICLE

Primary Resistance to PD-1 Blockade Mediated by *JAK1/2* Mutations

Daniel Sanghoon Shin[1], Jesse M. Zaretsky[1], Helena Escuin-Ordinas[1], Angel Garcia-Diaz[1], Siwen Hu-Lieskovan[1], Anusha Kalbasi[1], Catherine S. Grasso[1], Willy Hugo[1], Salemiz Sandoval[1], Davis Y. Torrejon[1], Nicolaos Palaskas[1], Gabriel Abril-Rodriguez[1], Giulia Parisi[1], Ariel Azhdam[1], Bartosz Chmielowski[1,2], Grace Cherry[1], Elizabeth Seja[1], Beata Berent-Maoz[1], I. Peter Shintaku[1], Dung T. Le[3], Drew M. Pardoll[3], Luis A. Diaz, Jr[3], Paul C. Tumeh[1], Thomas G. Graeber[1,2], Roger S. Lo[1,2], Begoña Comin-Anduix[1,2], and Antoni Ribas[1,2]

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 1, 2016 VOL. 375 NO. 9

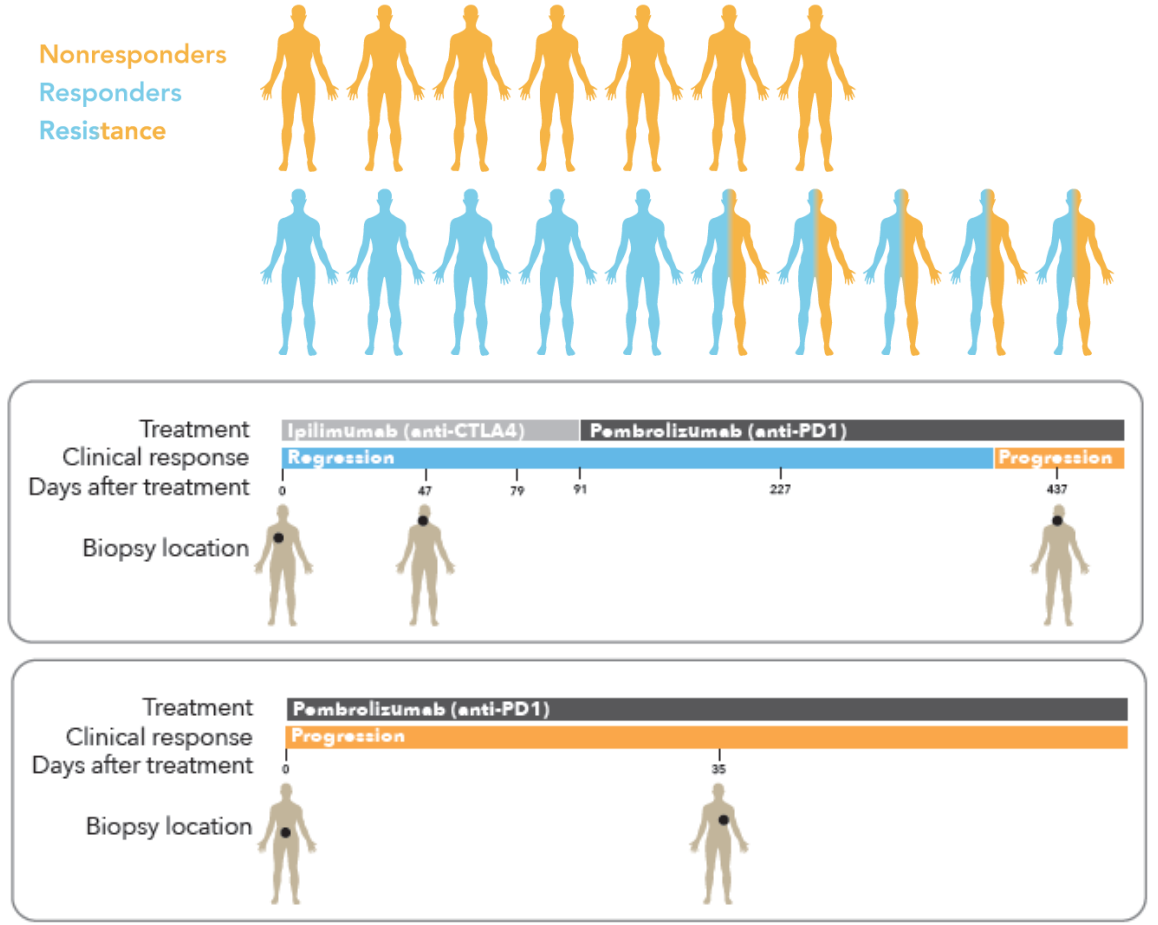
Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma

Jesse M. Zaretsky, B.S., Angel Garcia-Diaz, Ph.D., Daniel S. Shin, M.D., Helena Escuin-Ordinas, Ph.D., Willy Hugo, Ph.D., Siwen Hu-Lieskovan, M.D., Ph.D., Davis Y. Torrejon, M.D., Gabriel Abril-Rodriguez, M.Sc., Salemiz Sandoval, Ph.D., Lucas Barthly, M.Sc., Justin Saco, B.S., Blanca Homet Moreno, M.D., Riccardo Mezzadra, M.Sc., Bartosz Chmielowski, M.D., Ph.D., Kathleen Ruchalski, M.D., I. Peter Shintaku, Ph.D., Phillip J. Sanchez, Ph.D., Cristina Puig-Saus, Ph.D., Grace Cherry, R.N., N.P., Elizabeth Seja, B.A., Xiangju Kong, M.Sc., Jia Pang, B.S., Beata Berent-Maoz, Ph.D., Begoña Comin-Anduix, Ph.D., Thomas G. Graeber, Ph.D., Paul C. Tumeh, M.D., Ton N.M. Schumacher, Ph.D., Roger S. Lo, M.D., Ph.D., and Antoni Ribas, M.D., Ph.D.

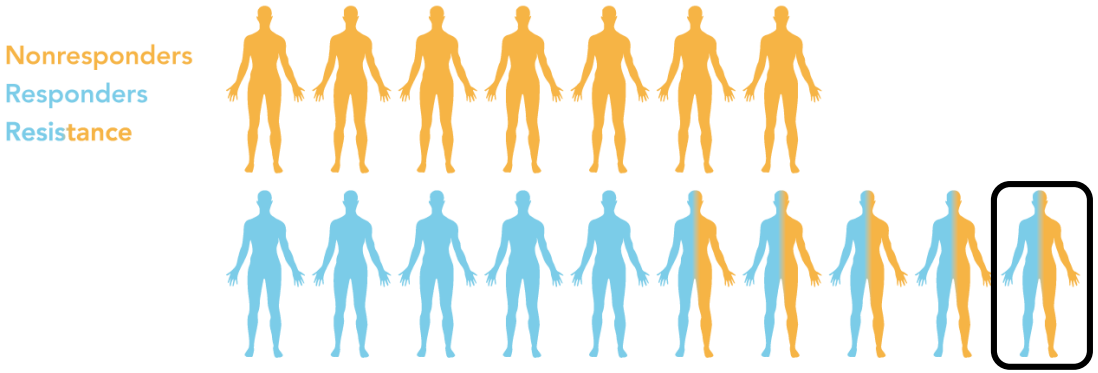
AAEM American Academy of Emergency Medicine
ACCC Association of Community Cancer Centers
sitc Society for Immunotherapy of Cancer

MGH Cancer Center Longitudinal Series

Analysis of longitudinal biopsies collected from 17 metastatic melanoma patients treated with checkpoint inhibitor therapy was performed to evaluate for potential mechanisms of resistance



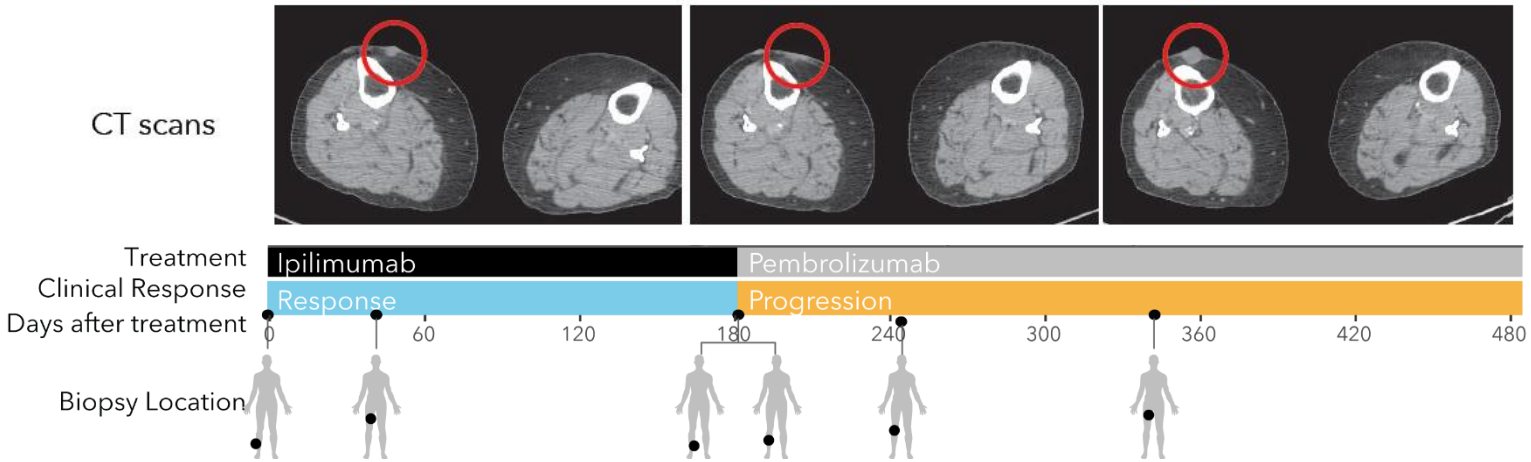
Sade-Feldman, et al. Nat Commun. 2017



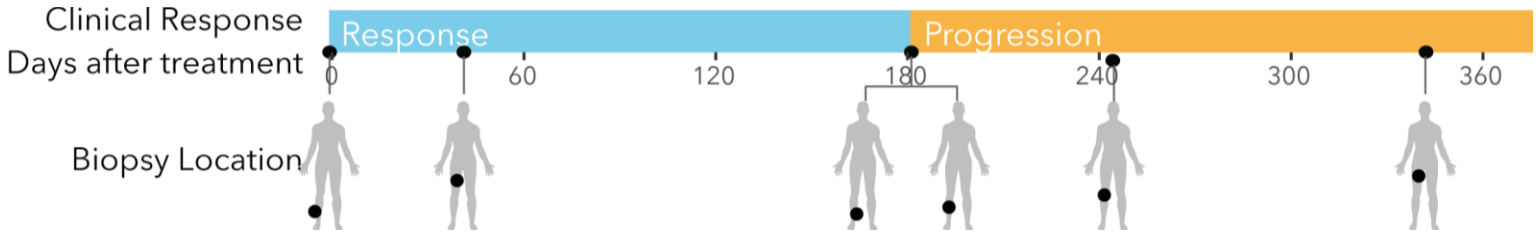
Focused on a patient that developed resistance to CPB:

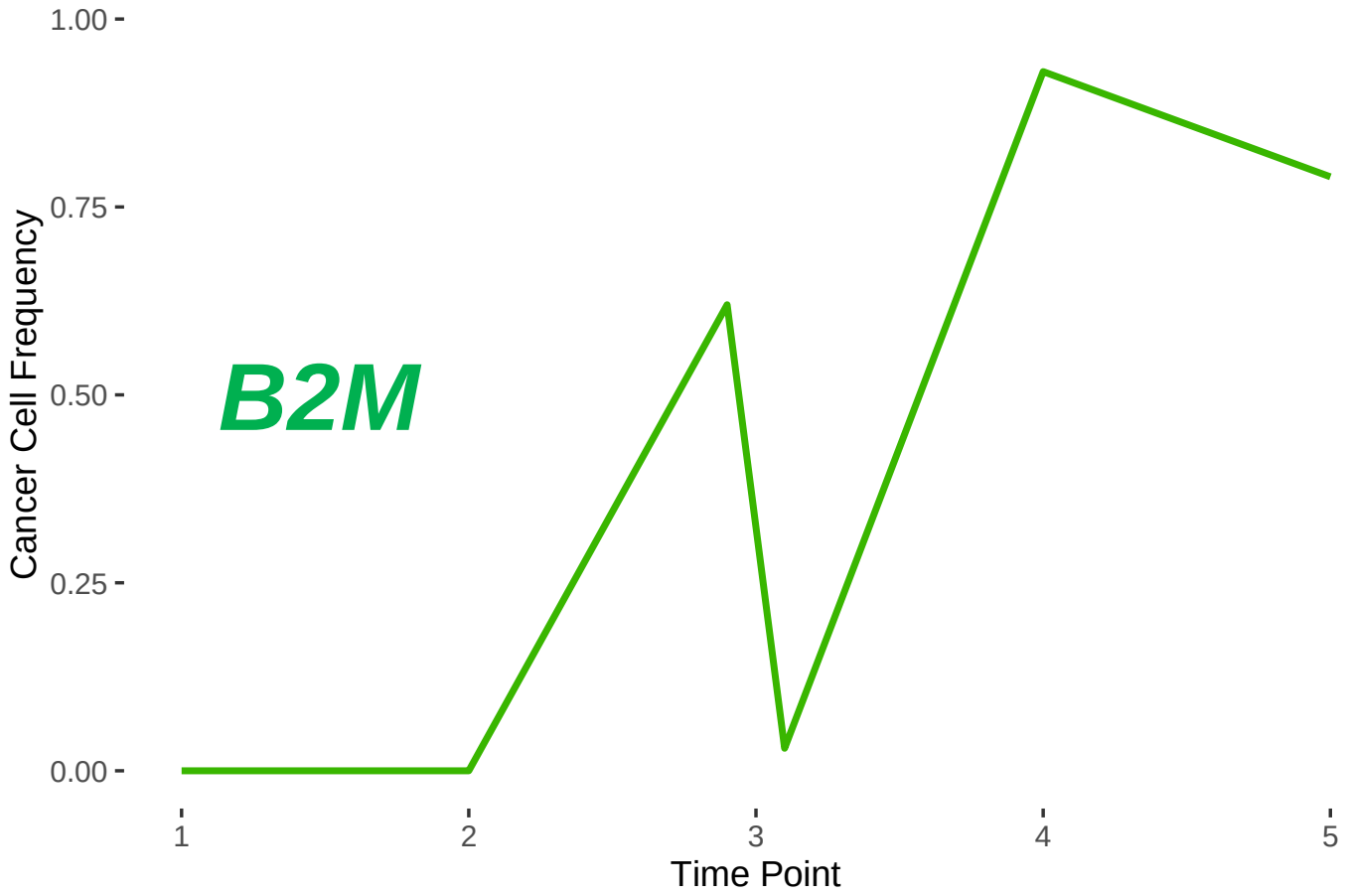
Responded for 6 months, then relapsed

Has 6 high quality biopsies at baseline, disease regression, and disease progression



Sade-Feldman, et al. Nat Commun. 2017

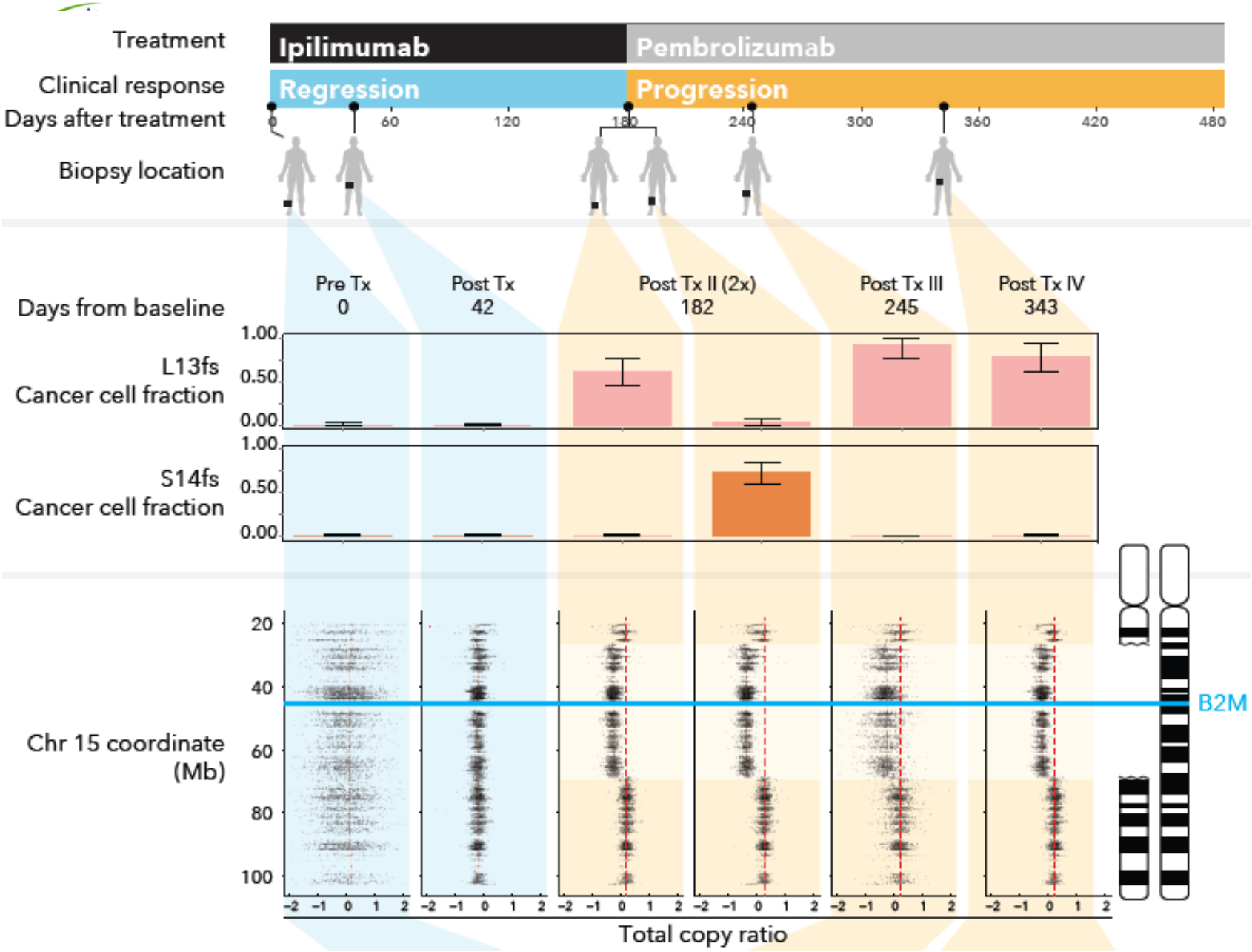




The following criteria were used to ID potential drivers:

1. **Genes with multiple non-silent mutations and LOH that are dominant only during PD**
2. **Only 1 of 5761 mutations satisfied these criteria**

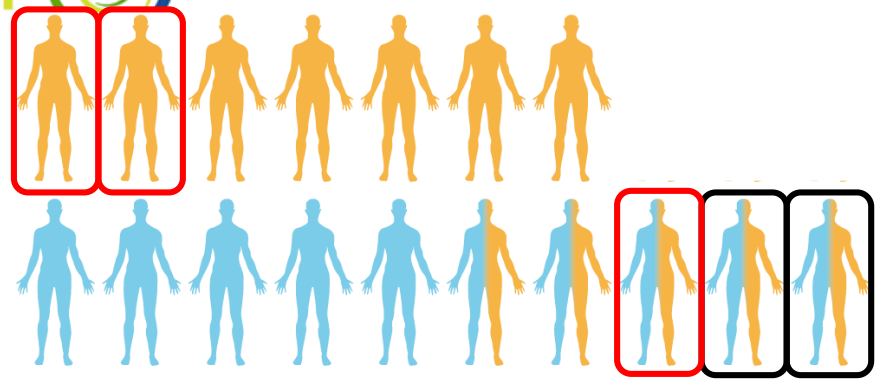
Sade-Feldman, et al. Nat Commun. 2017

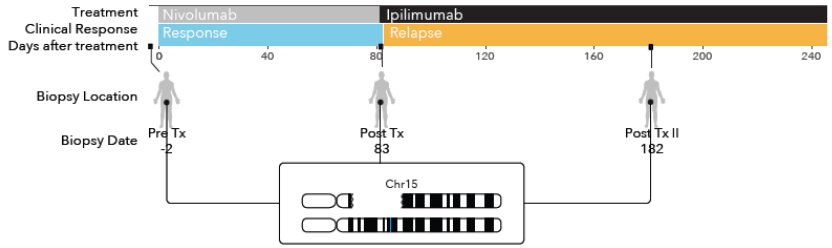


Two distinct mutations in B2M occurred in parallel at progression

Sade-Feldman, et al. Nat Commun. 2017

Can we detect additional B2M alterations in our cohort?





Patient	Phenotype	Samples	*B2M* alterations
Patient 1	Resistance	On treatment (relapse)	LOH, p.Leu13fs and p.Ser14fs mutations
Patient 2*	Resistance	On treatment (relapse)	p.Ser14fs (50-90% of cancer cells) and p.Gly63fs (70-90% of cancer cells) mutations
Patient 3	**Resistance**	**Baseline/on treatment**	**LOH**
Patient 4	**Non responder**	**Baseline/on treatment**	**LOH**
Patient 5	**Non responder**	**Baseline/on treatment**	**LOH**

29.4% of patients within our cohort have abnormalities in *B2M*

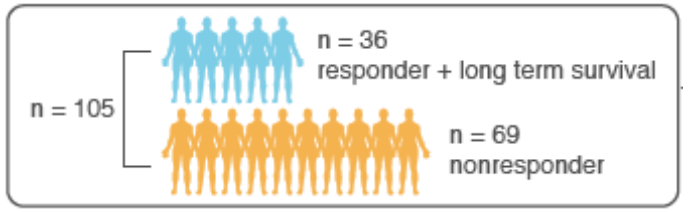
Sade-Feldman, et al. Nat Commun. 2017

sitc Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

REPORT

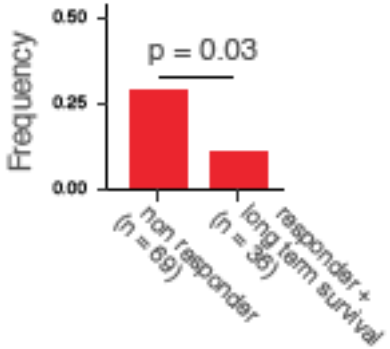
Genomic correlates of response to CTLA-4 blockade in metastatic melanoma

Eliezer M. Van Allen[1,2,3,*], Diana Miao[1,2,*], Bastian Schilling[4,5,*], Sachet A. Shukla[1,2], Christian Blank[6], Lisa Zimmer[4,5], Antje Sucker[4,5], Uwe Hillen[4,5], Marnix H. Geukes Foppen[6], Simone M. Goldinger[7], Jochen Utikal[5,8,9], Jessica C. Hassel[10], Benjamin Weide[11], Katharina C. Kaehler[12], Carmen Loquai[13], Peter Mohr[14], Ralf Gutzmer[15], Reinhard Dummer[7], Stacey Gabriel[2], Catherine J. Wu[1,2], Dirk Schadendorf[4,5,†], Levi A. Garraway[1,2,3,†]



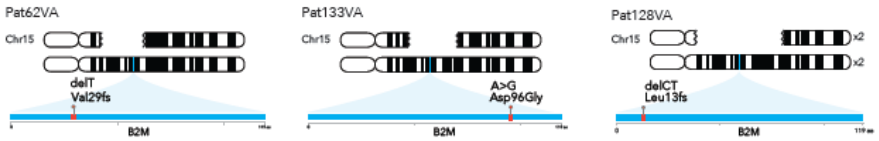
B2M LOH found in: **20/69** non-responders
4/36 responders

Odds ratio 3.2
p = 0.03



Complete loss of *B2M* in: **6/69** non-responders

0/36 responders



28.9% of NR patients have abnormalities in *B2M*

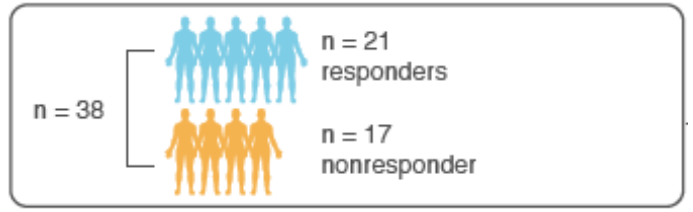
Sade-Feldman, et al.
Nat Commun. 2017

Cell

Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma

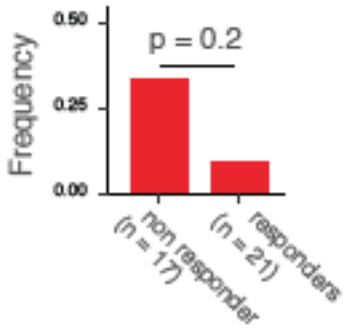
Willy Hugo,[1,6,9] Jesse M. Zaretsky,[2,6,9] Lu Sun,[1,6] Chunying Song,[1,6] Blanca Homet Moreno,[3] Siwen Hu-Lieskovan,[3] Beata Berent-Maoz,[3] Jia Pang,[3] Bartosz Chmielowski,[3] Grace Cherry,[3] Elizabeth Seja,[3] Shirley Lomeli,[1,6] Xiangju Kong,[1,6] Mark C. Kelley,[7] Jeffrey A. Sosman,[8] Douglas B. Johnson,[8] Antoni Ribas,[2,3,4,5,6] and Roger S. Lo[1,2,5,6,*]

[1]Division of Dermatology, Department of Medicine
[2]Department of Molecular and Medical Pharmacology
[3]Division of Hematology & Oncology, Department of Medicine
[4]Division of Surgical Oncology, Department of Surgery
[5]Jonsson Comprehensive Cancer Center
[6]David Geffen School of Medicine
University of California, Los Angeles, CA 90095-1662, USA
[7]Department of Surgery, Vanderbilt-Ingram Cancer Center, Nashville, TN 37232, USA
[8]Department of Medicine, Vanderbilt-Ingram Cancer Center, Nashville, TN 37232, USA
[9]Co-first authors
*Correspondence: rlo@mednet.ucla.edu
http://dx.doi.org/10.1016/j.cell.2016.02.065



B2M LOH found in: **5/17** non-responders
2/21 responders

Odds ratio 3.6
p = 0.2



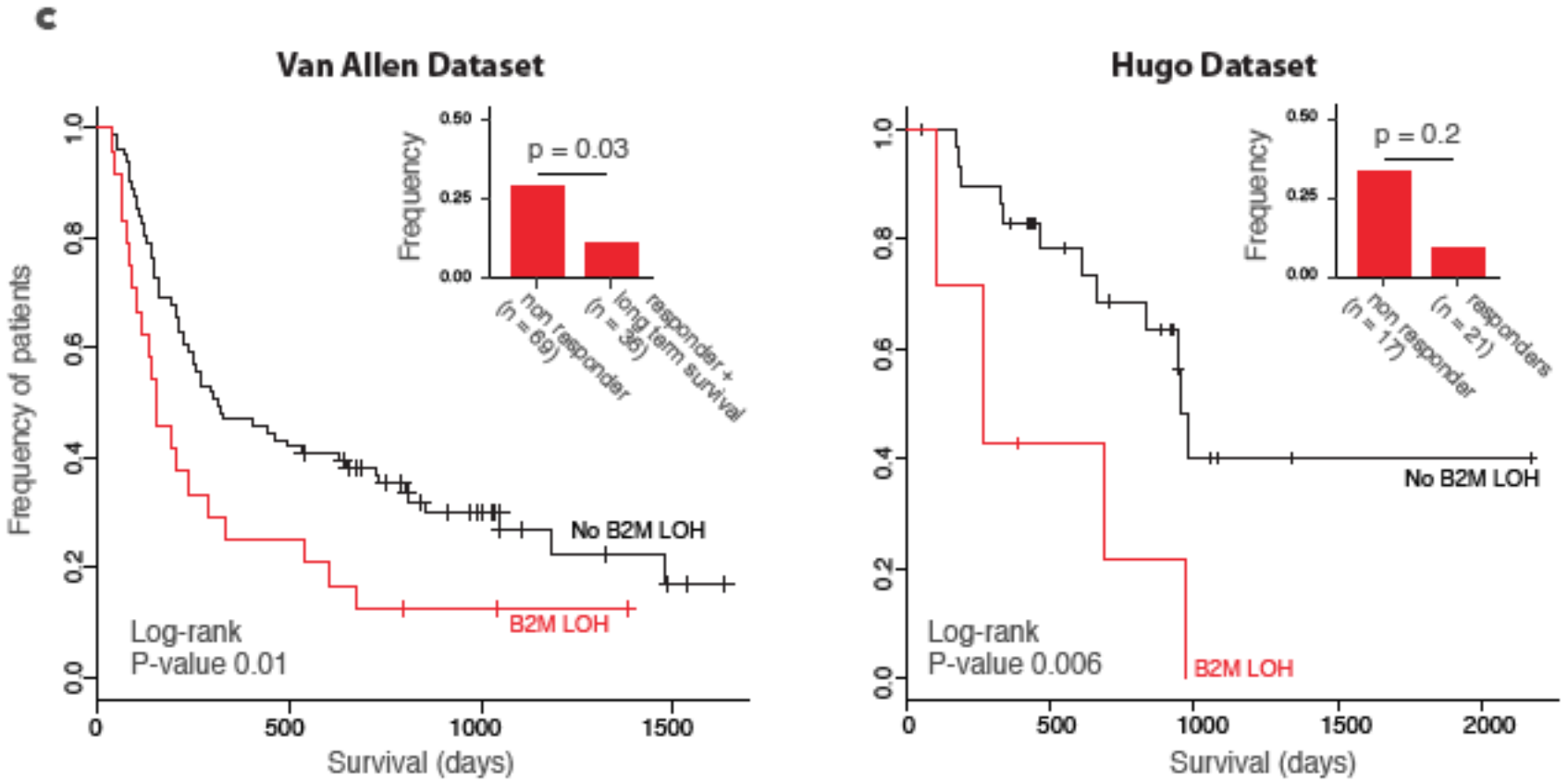
No B2M nucleotide mutations found

29.4% of NR patients have abnormalities in *B2M*

Cohort	% of B2M aberrations in NR	% of B2M aberrations in R
MGH- 17 patients (49 samples)	**29.4**	0
Van Allen- 105 patients	**28.9**	11.1 (only LOH)
Hugo- 38 patients	**29.4**	9.5 (only LOH)

Sade-Feldman, et al. Nat Commun. 2017

B2M LOH is significantly associated with lower overall survival

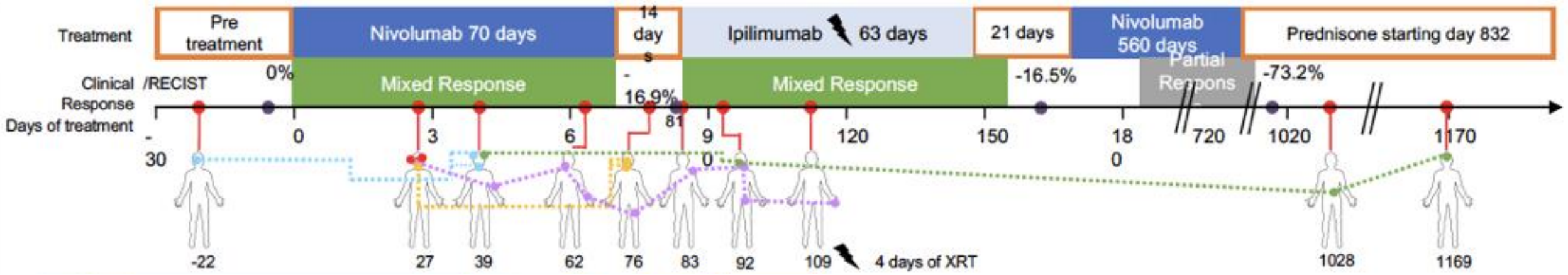


Sade-Feldman, et al. Nat Commun. 2017

Summary

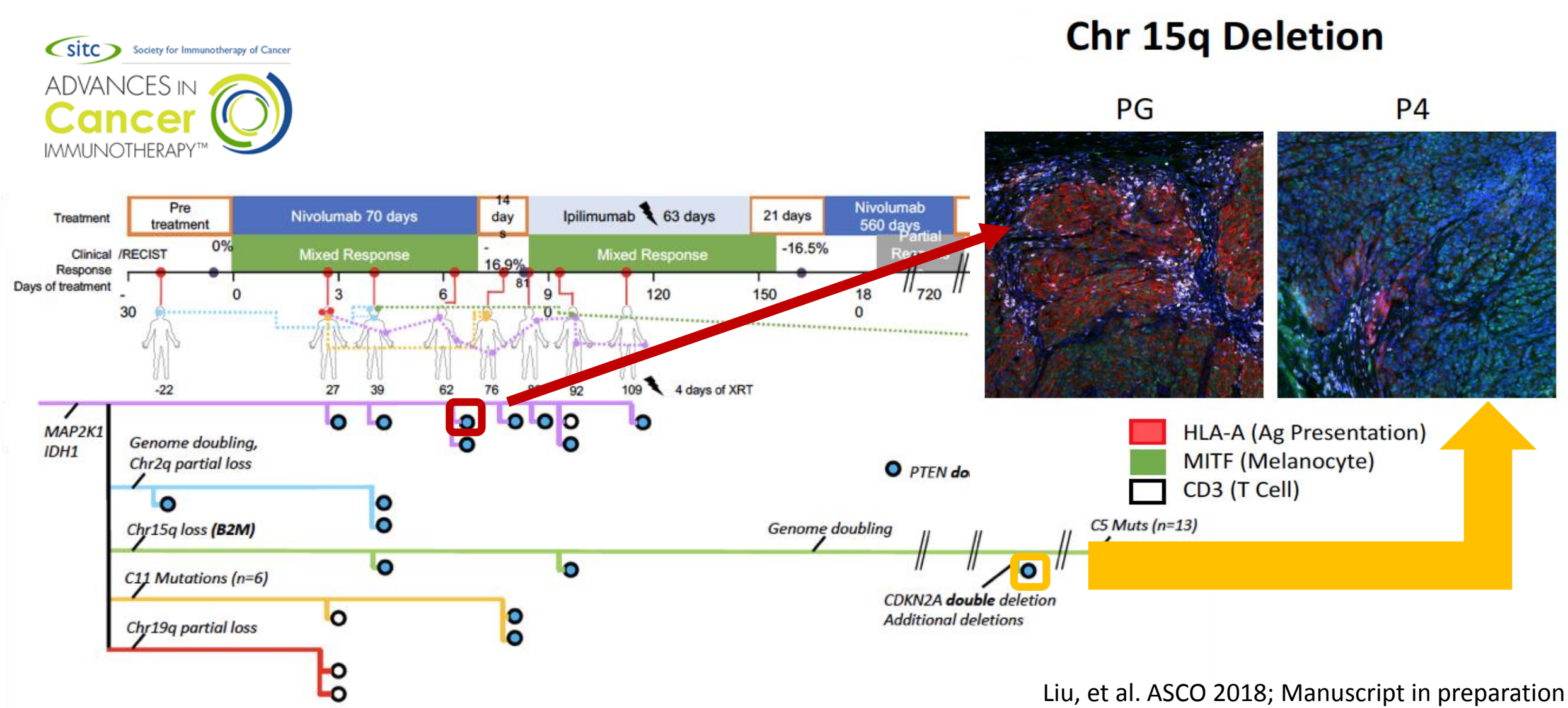
- B2M aberrations, including loss of function mutations and deletions, are associated with acquired resistance to immune checkpoint inhibitors
- B2M LOH in pretreatment samples is associated with poorer response rates, PFS, and OS with ipilimumab and anti-PD1 agents

The case of a remarkable responder



21 biopsies taken over three years, including two from late recurrences in small bowel (d. 1028) and brain (d. 1169); WES, IHC, IF, RNA sequencing performed on all samples

Liu, et al. ASCO 2018; Manuscript in preparation



Liu, et al. ASCO 2018; Manuscript in preparation

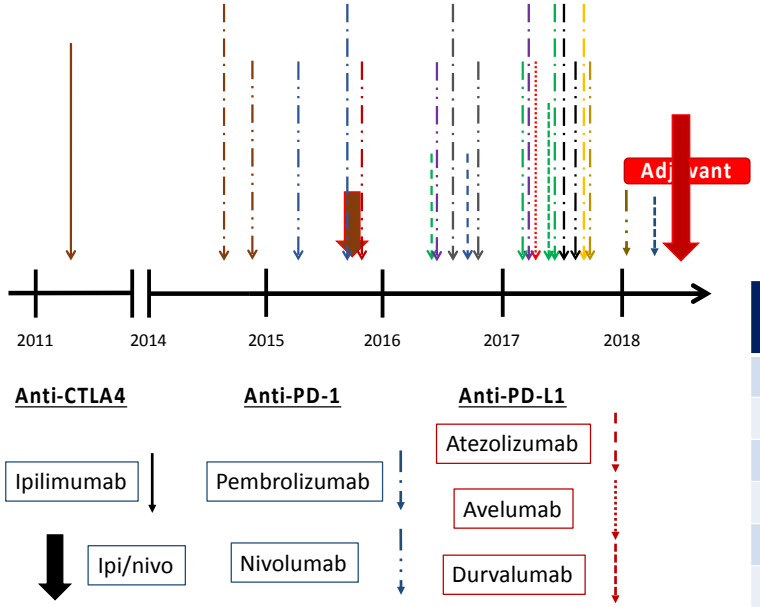
The most persistent clone is the only one with 15q deletion, associated with *B2M* loss and HLA loss

Summary (cont.)

- B2M aberrations, including loss of function mutations and deletions, are associated with acquired resistance to immune checkpoint inhibitors
- B2M LOH in pretreatment samples is associated with poorer response rates, PFS, and OS with ipilimumab and anti-PD1 agents
- In an analysis of longitudinal samples categorizing clonal evolution over 3+ years, the most persistent clones in a patient otherwise with long-term disease control from ICI contained 15q deletion (*B2M* loss) leading to HLA loss

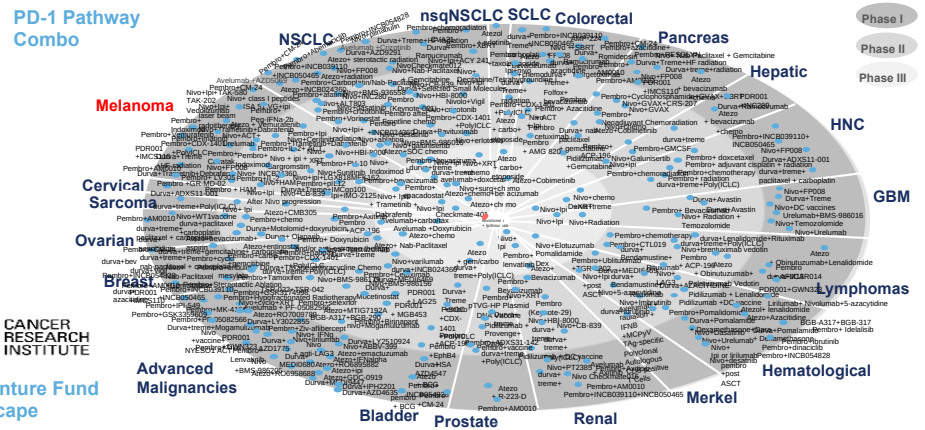
Concluding Thoughts

We are definitively in the immune checkpoint inhibitor era…



Melanoma
NSCLC
Renal Cell Carcinoma
Urothelial Bladder Cancer
Hodgkin Lymphoma
Head and Neck Squamous Cell Carcinoma
Merkel Cell Carcinoma
MSI Cancers
Gastric Cancer
Hepatocellular Carcinoma

Year	Drugs	Approvals	Disease indications
2011	1	1	1
2014	2	2	1
2015	3	4	3
2016	3	5	4
2017	4	9	6
2018	4	3	3



…yet unmet needs exist

1. More effective therapies (combinations)
2. Better predictive biomarkers of benefit
3. Improve our understanding of mechanisms of therapeutic resistance

The future will be all about identifying the right patient for the right combination