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2017
November 8-12
NATIONAL HARBOR
MARYLAND
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Society for Immunotherapy of Cancer

November 8-12 • NATIONAL HARBOR, MD

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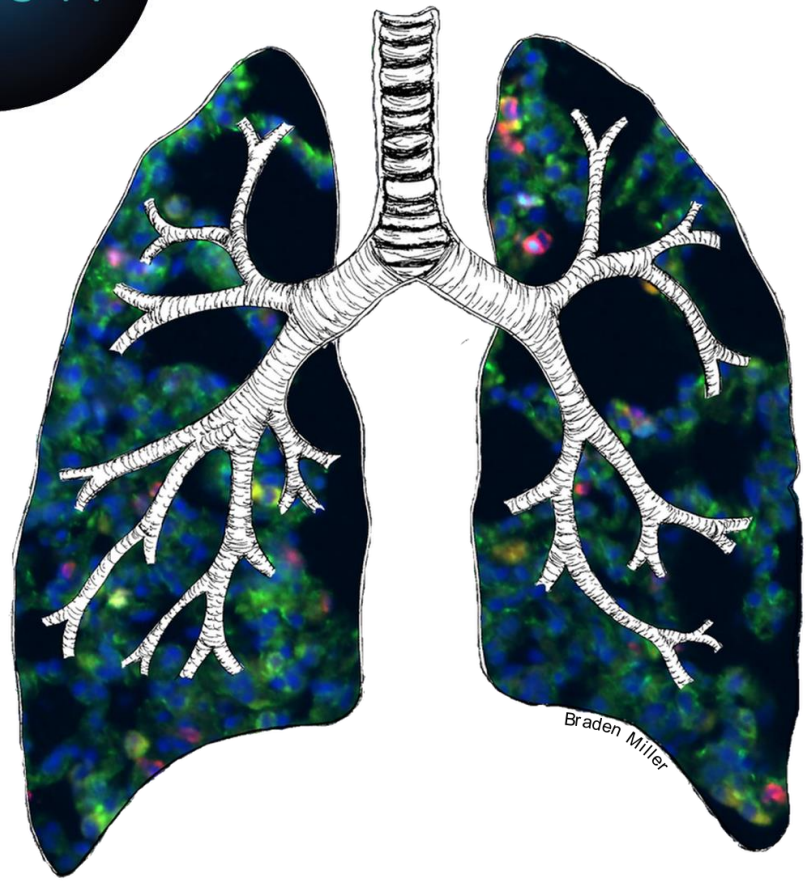

Acquired Resistance in Immune Checkpoint Inhibitors in Lung Cancer

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Presenter Disclosure Information

Katerina Politi

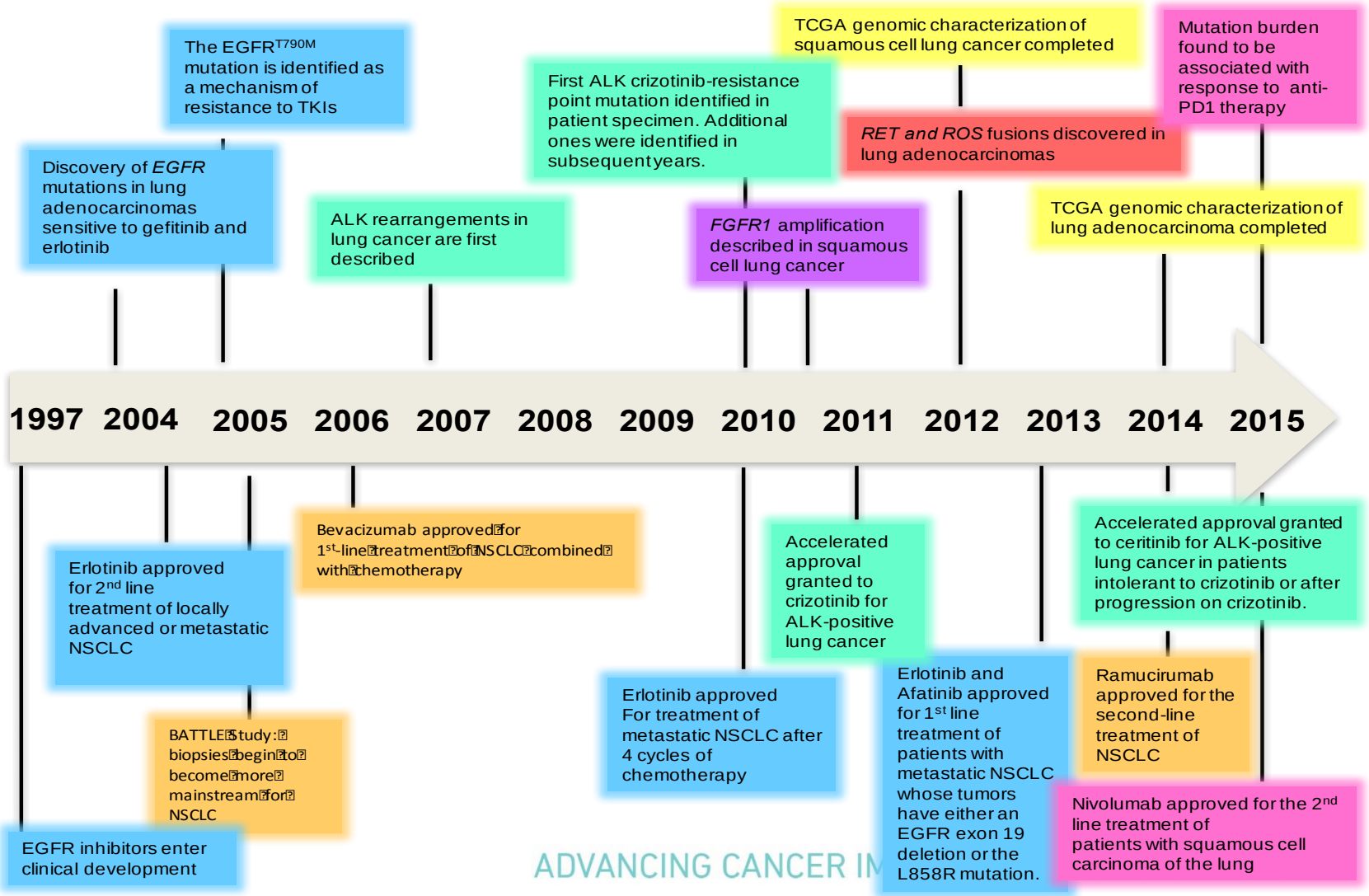
- Co-Inventor on a Patent Licensed to Molecular MD for EGFR T790M mutation testing (through MSKCC).

- Consultant fees: Takeda, NCCN, Novartis, Merck, AstraZeneca, Tocagen

- There will be discussion about the use of products for non-FDA approved indications in this presentation

- I receive/d research support from AstraZeneca, Kolltan, Roche and Gilead.

Timeline of Recent Advances in Lung Cancer



Molecular discoveries

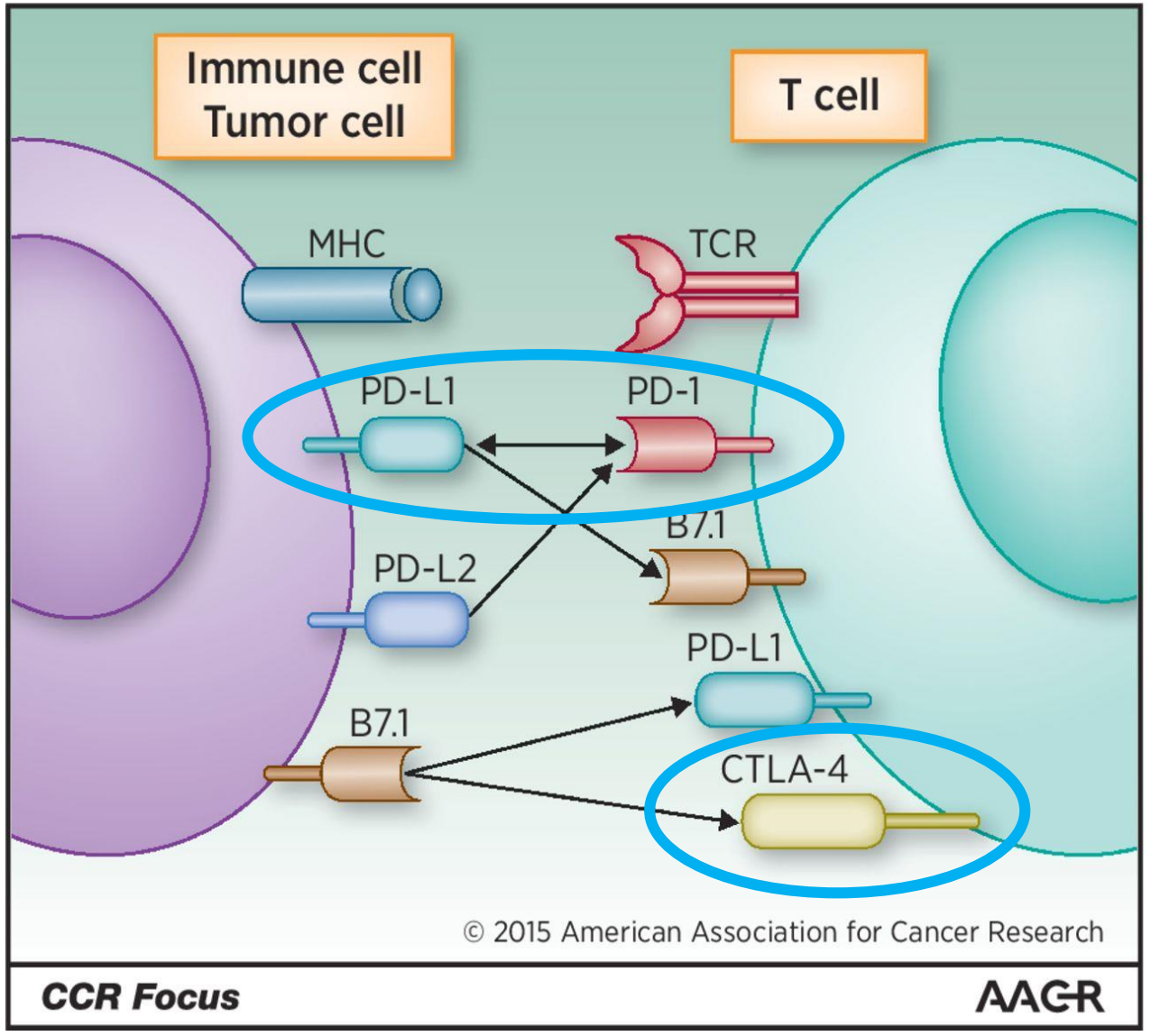
Pembrolizumab
2nd line approval 2015
1st-line approval 2016
PD-L1 positive tumors

Atezolizumab
2nd line approval 2015

Drug development

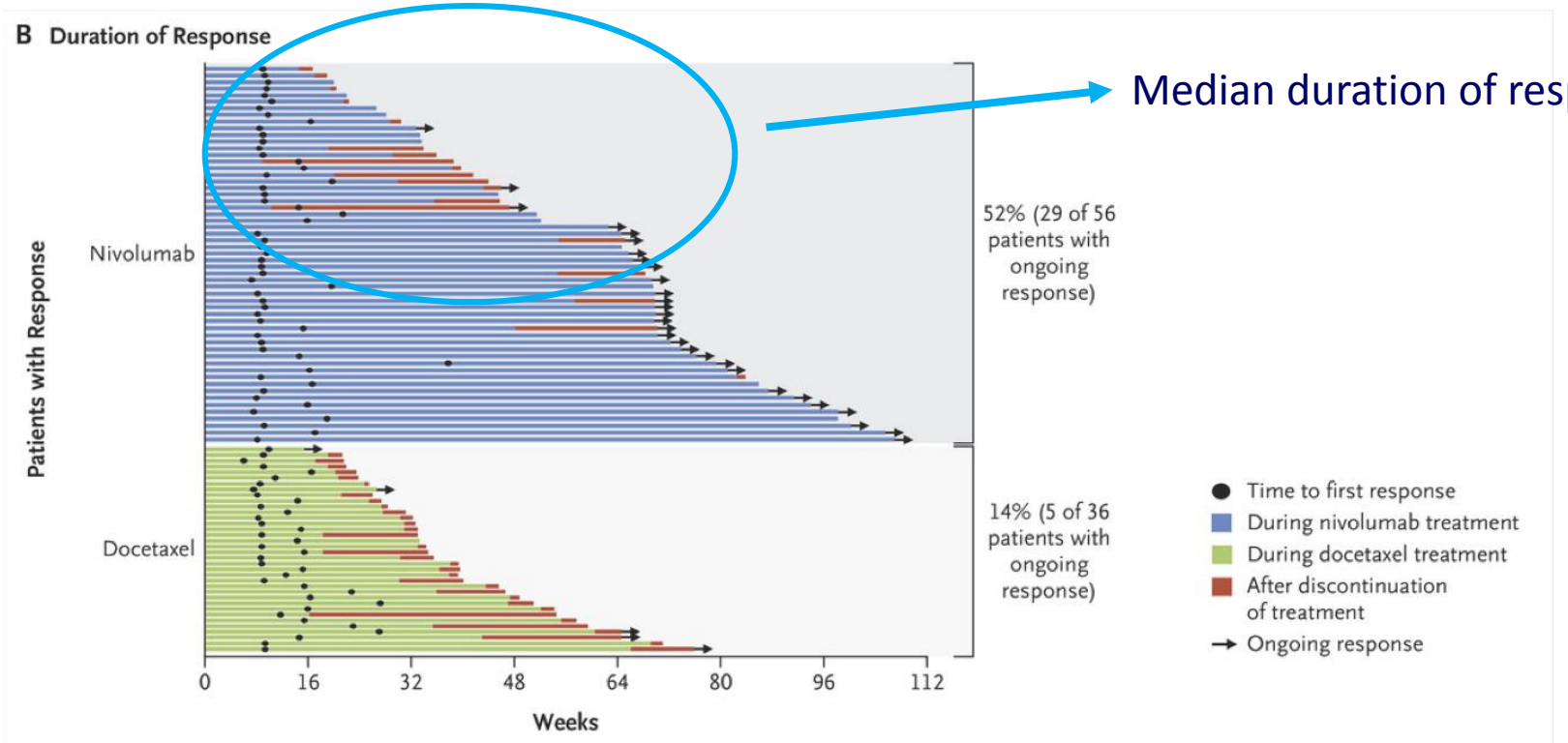
Politi and Herbst, CCR 2015

Immune Checkpoints as Therapeutic Targets



Jean-Charles Soria et al.
Clin Cancer Res 2015;21:2256-2262

Immune Checkpoint Inhibitors are Frequently Not Curative in Lung Cancer



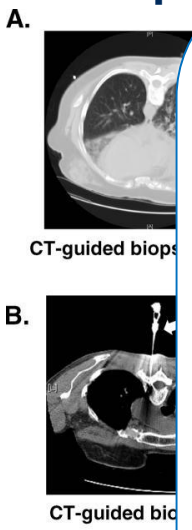
Median duration of response 12-25 months

What are the cellular and molecular mechanisms of acquired resistance to immune checkpoint inhibitors in lung cancer?

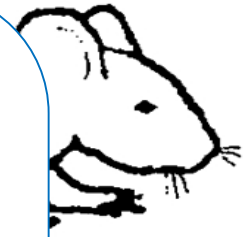
Reck et al., NEJM 2016
Borghaei et al., NEJM 2015

Approaches to Study Sensitivity and Resistance to Lung Cancer Therapies

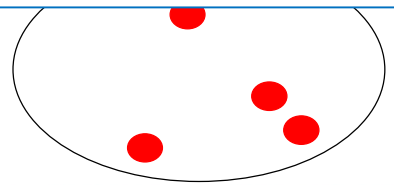
Patient Specimens



Genetically engineered mouse models
Xenografts/Patient-derived xenografts

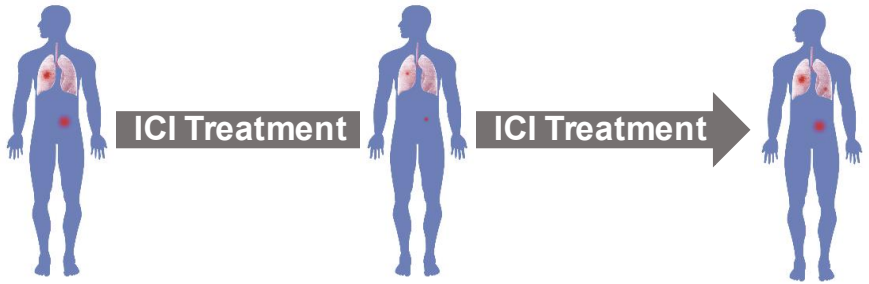


- Relationship between genotype and sensitivity
- Discovery of resistance mechanisms
- Identification of new therapeutic strategies to overcome and or prevent drug resistance.



Cell lines

Cohort of Patients with Resistance to Immune Checkpoint Inhibitors



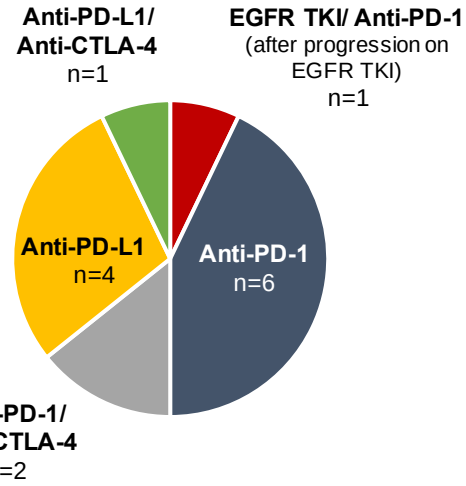
Pre-Treatment
(+/- Intervening Therapy)
- Tumor Tissue
- Germline DNA

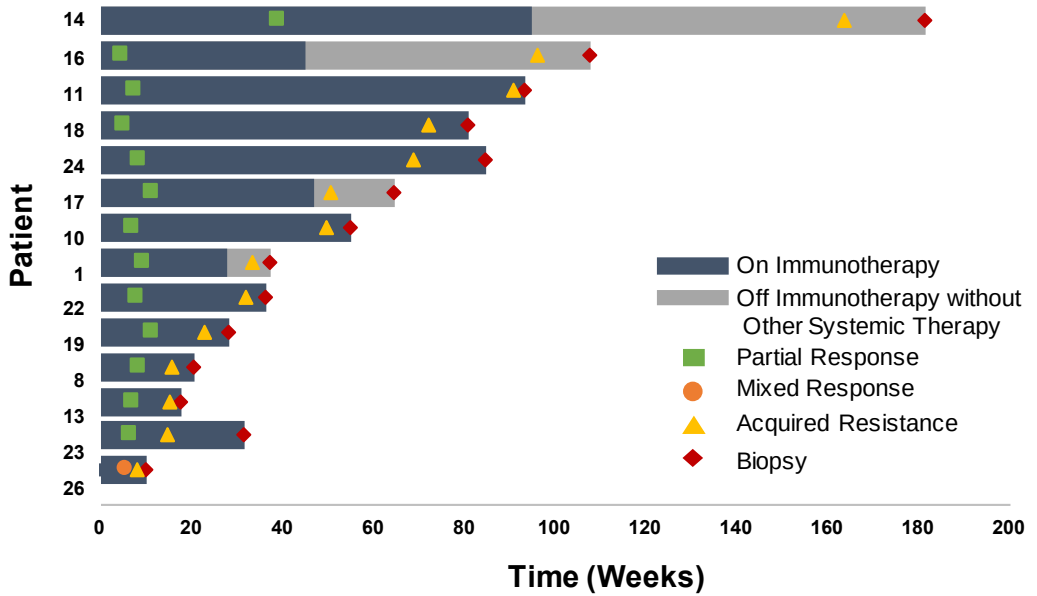
Response

Resistance
- Tumor Tissue
- PDX

Analysis
- Exome Sequencing
- RNA Sequencing
- Quantitative Immunofluorescence

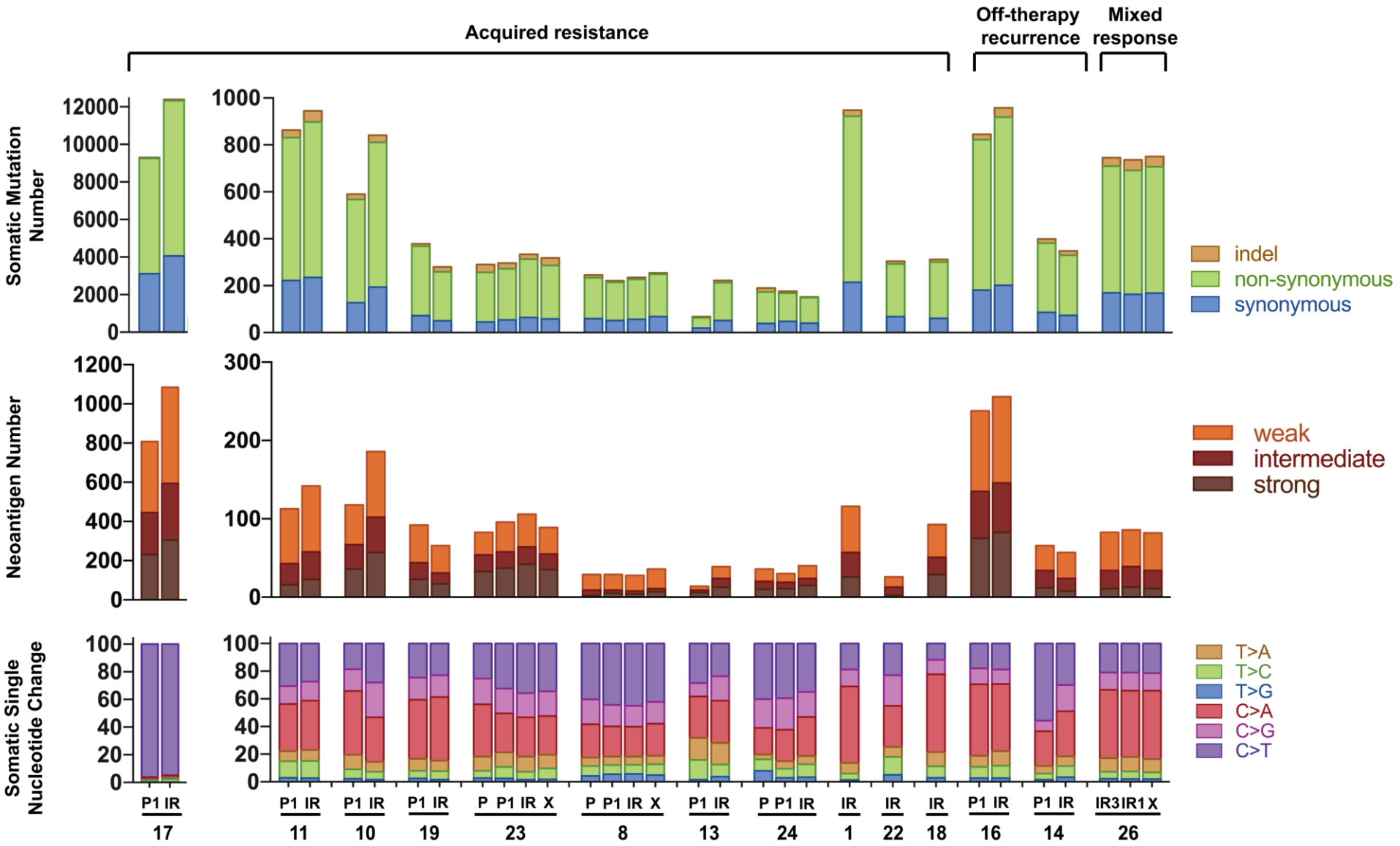
Identification of Resistance Specific Alterations



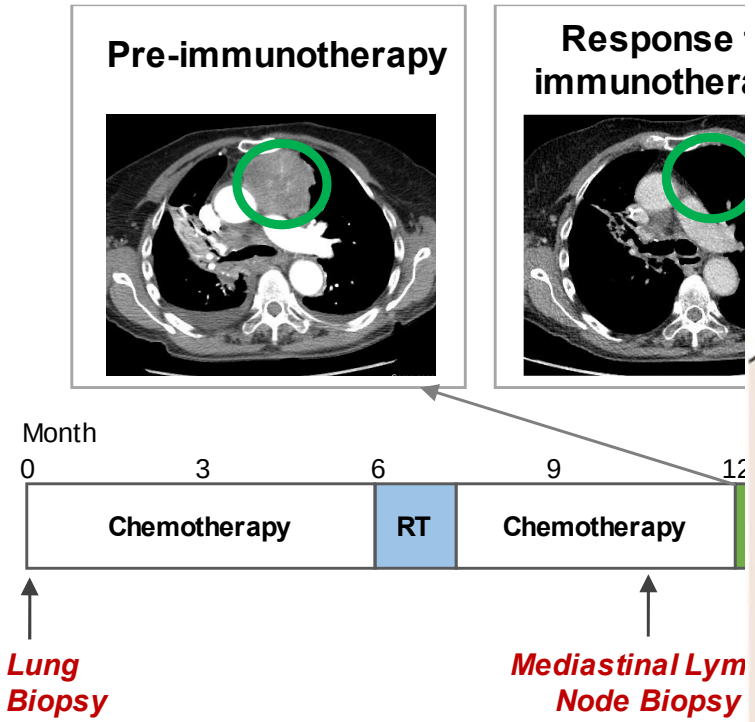


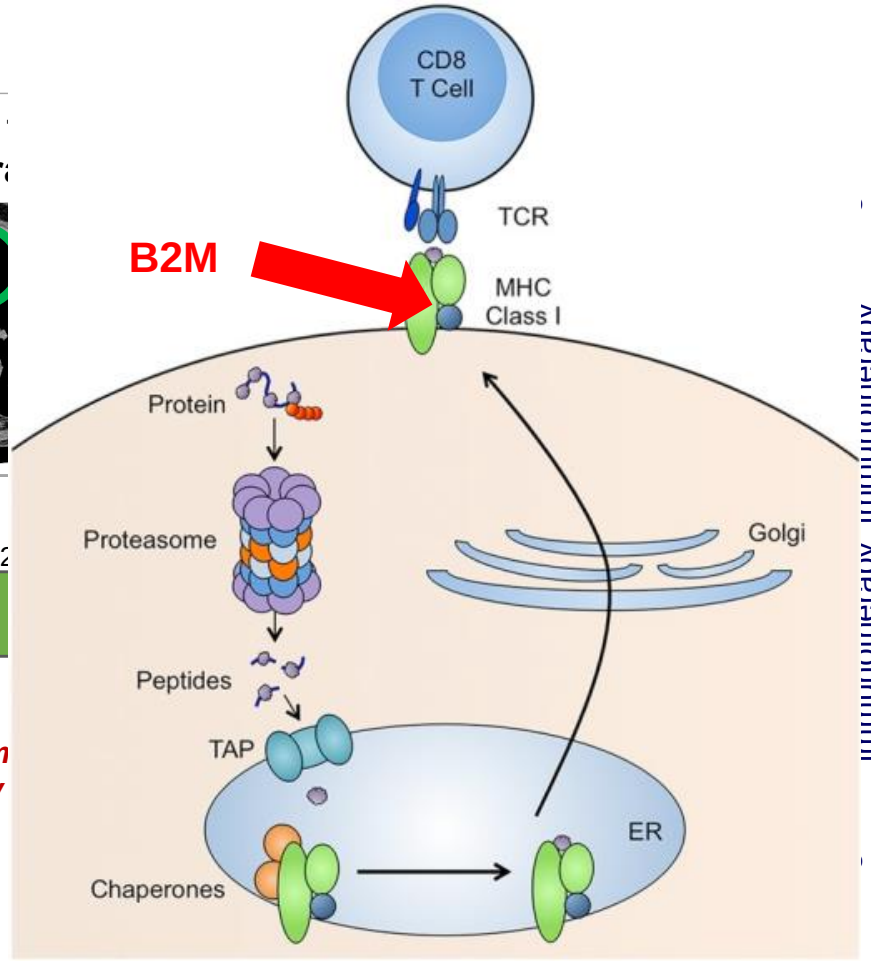
Gettinger, Choi, Hastings, Truini, Datar et al., Cancer Disc. 2017

The Genomic Landscape Resistant Tumors

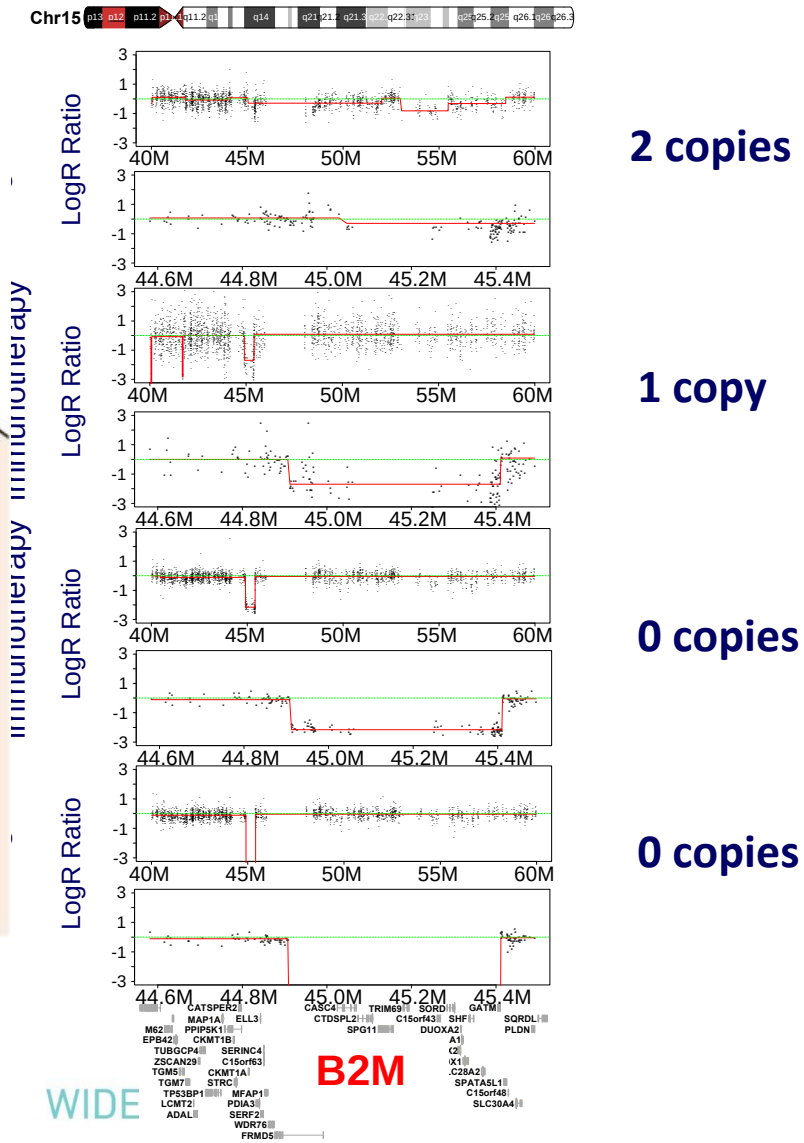


Acquired Resistance to Anti-PD-L1 plus Anti-CTLA4





McCarthy MK, Weinberg JB Front Microbiol (2015)



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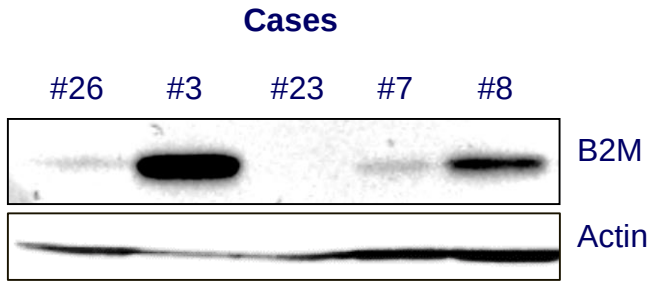
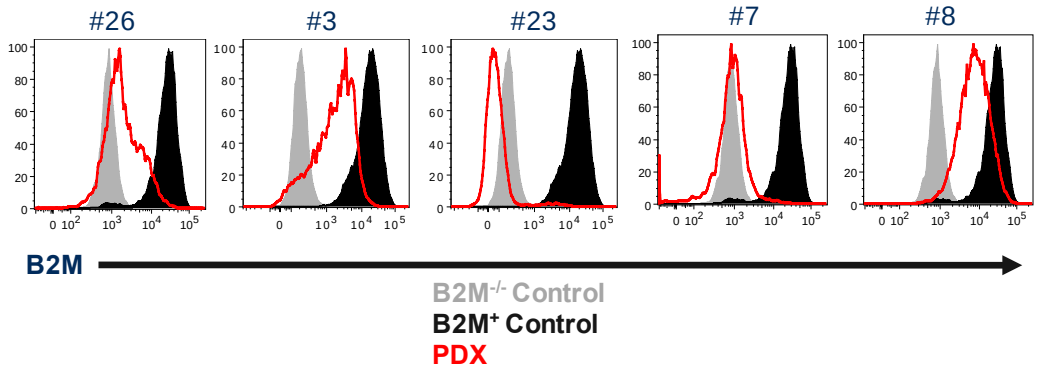
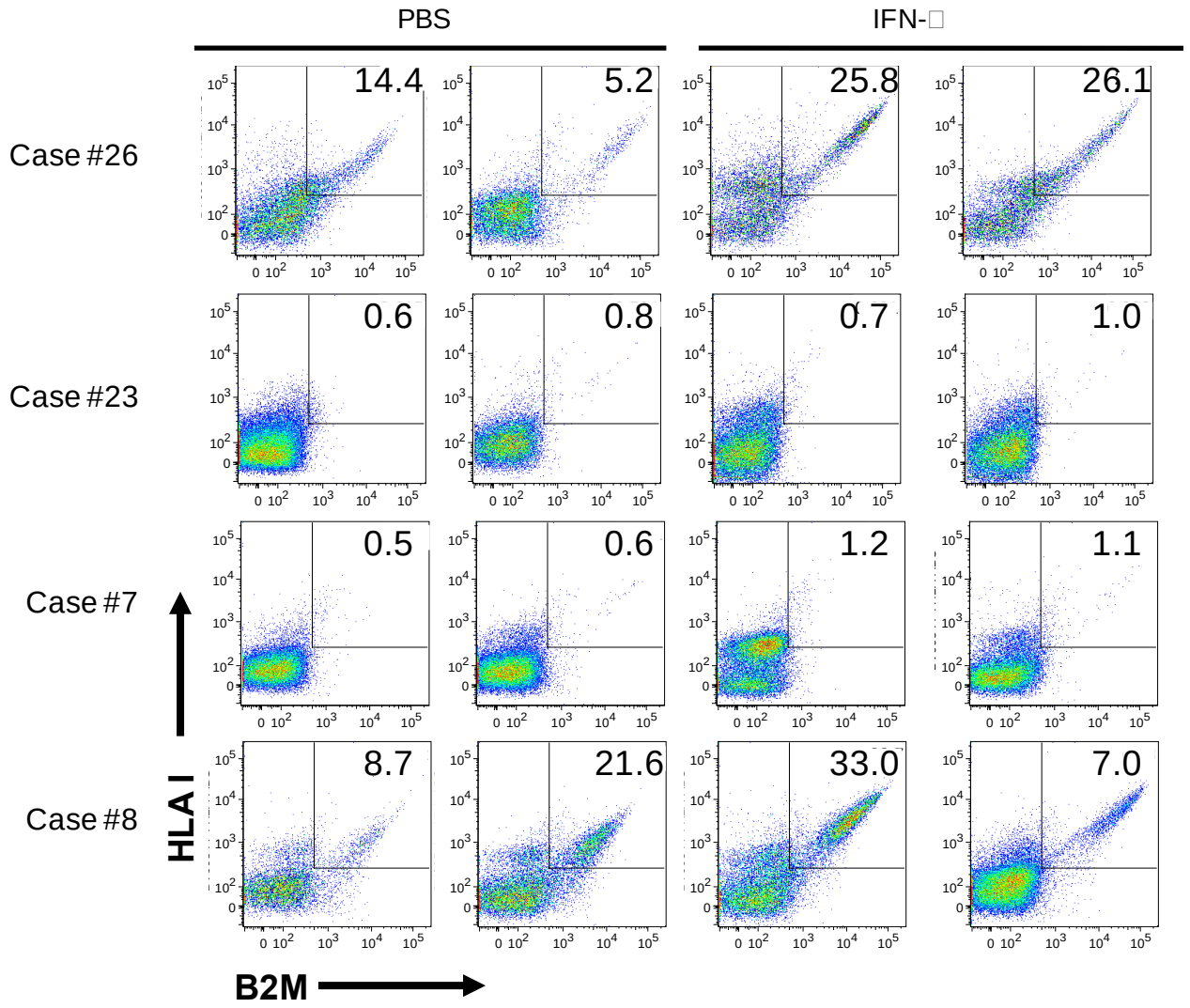
Beta 2 microglobulin Loss at Acquired Resistance to ICIs







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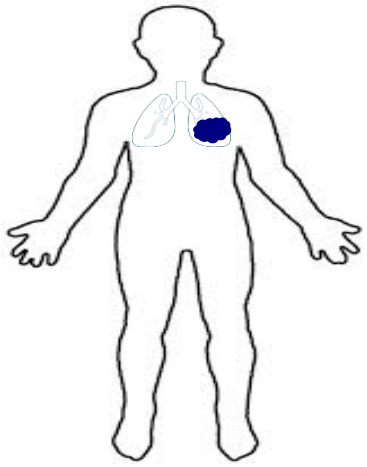
What is Next?



Candidate Resistance Drivers

→

Functionally test mechanisms of acquired resistance in vivo

→

Establish strategies to overcome resistance

A Transplantable Lung Cancer Model with Sensitivity to PD-1 Blockade

Successful Immunotherapy against a Transplantable Mouse Squamous Lung Carcinoma with Anti-PD-1 and Anti-CD137 Monoclonal Antibodies

Arantza Azpilikueta, BSc,[a] Jackeline Agorreta, PhD,[b,c] Sara Labiano, BSc,[a] José Luis Pérez-Gracia, MD, PhD,[d] Alfonso R. Sánchez-Paulete, BSc,[a] M. Angela Aznar, PhD,[a] Daniel Ajona, PhD,[b,e] Ignacio Gil-Bazo, MD, PhD,[d] Marta Larrayoz, PhD,[a,c] Alvaro Teijeira, PhD,[a] María E. Rodriguez-Ruiz, MD, PhD,[b] Ruben Pio, PharmD, PhD,[b,e] Luis M. Montuenga, PhD,[b,c] Ignacio Melero, MD, PhD[a,d,*]

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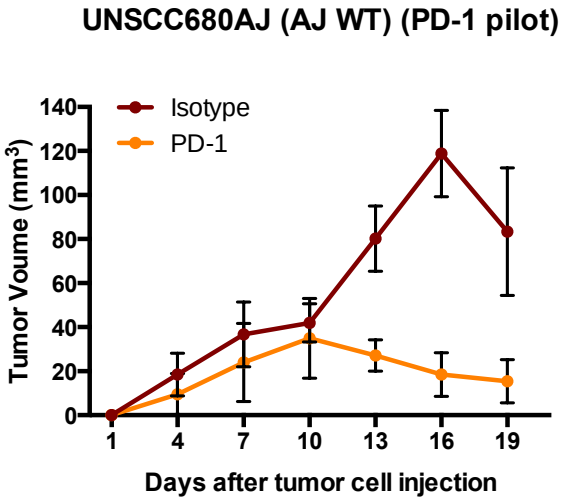
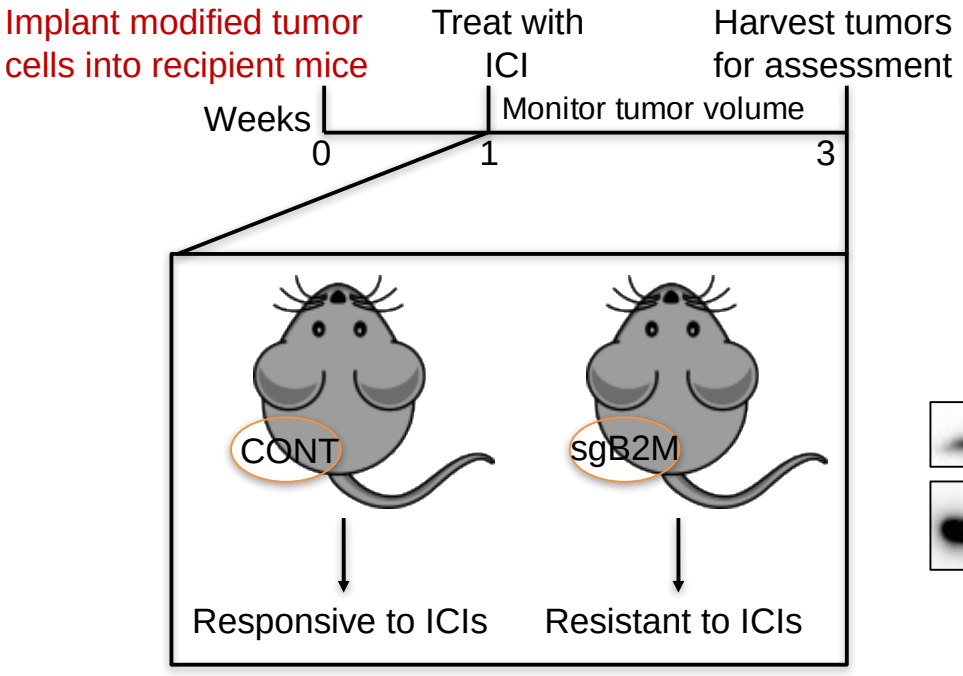
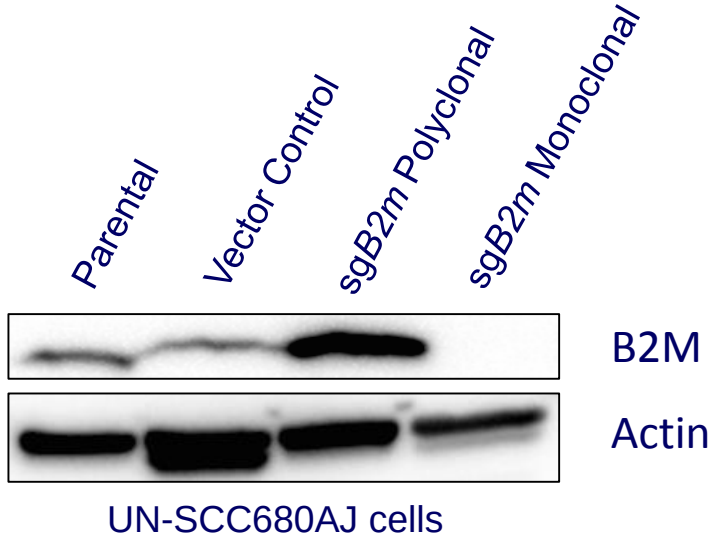
[c]Department of Histology and Pathology, Universidad de Navarra
[d]Department of Oncology and Clinical Trial Unit, Clinica Universidad de Navarra
[e]Department of Biochemistry and Genetics, Universidad de Navarra

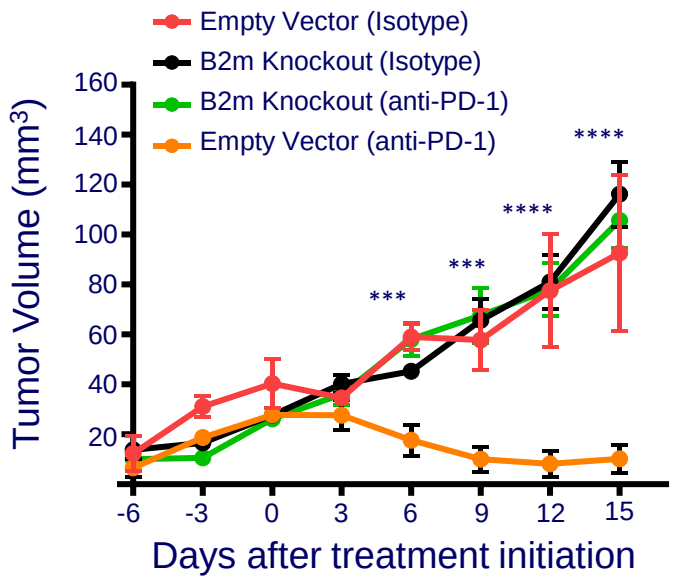


- UN-SCC680AJ line derived from NCTU carcinogen treatment
- Kras mutation
- ~200 non-synonymous mutations

Establish whether candidate resistance drivers modulate sensitivity to PD-1 axis blockade

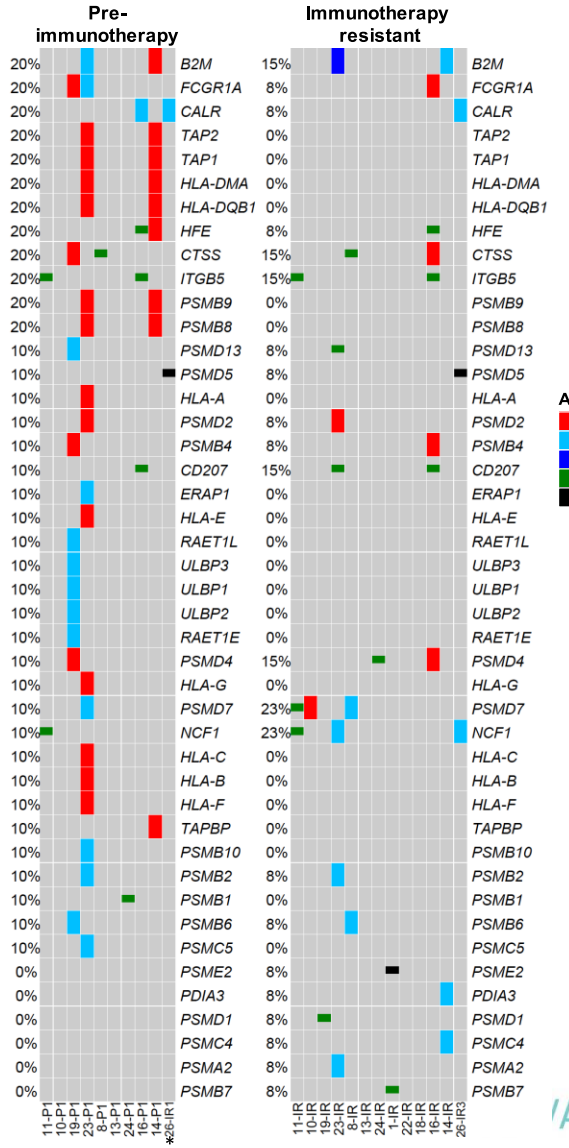


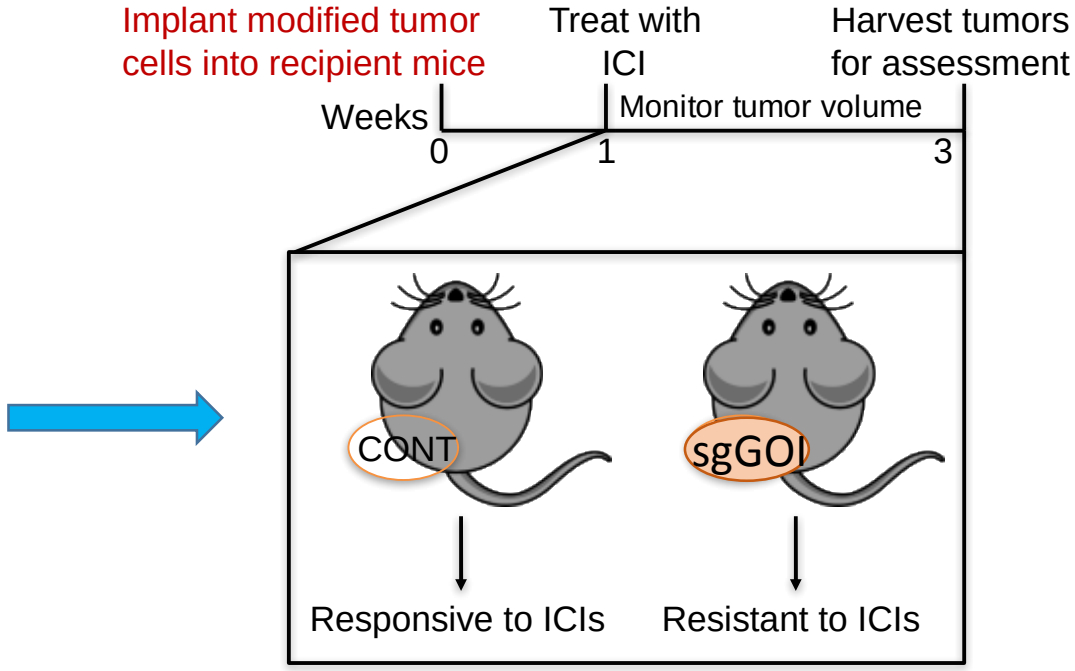




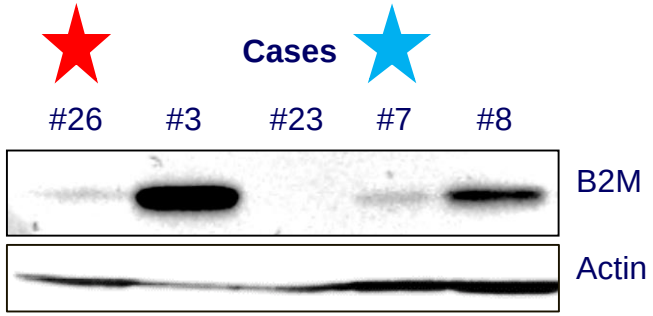
Katherine Hastings, Anna Truini

Testing Candidate Resistance Drivers at Acquired Resistance to ICIs

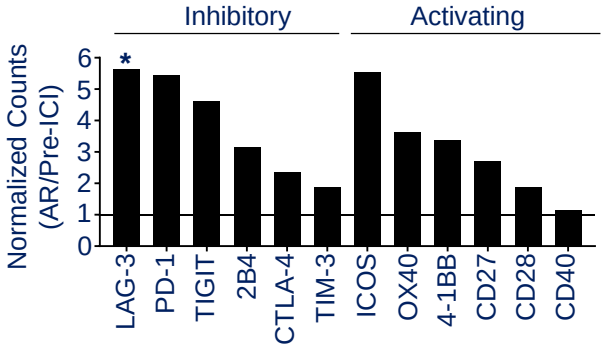


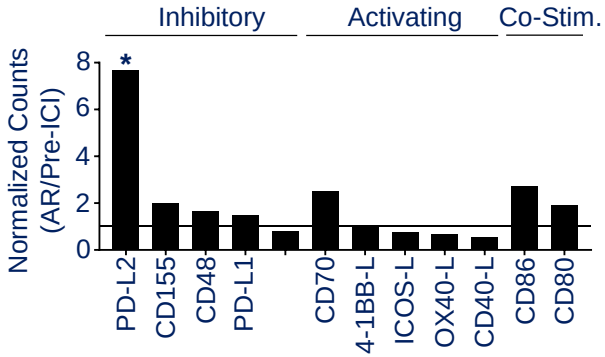


Multiple Genetic and Non-genetic Processes can Lead to Defects in MHC I Antigen Presentation



Immune inhibitory signaling?

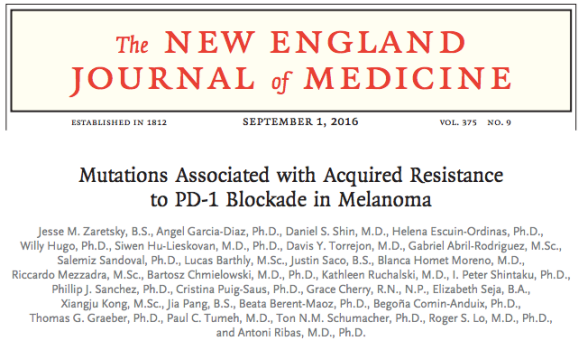




Epigenetic silencing of MHC I genes?
Other mechanisms?

Conclusions and Future Directions

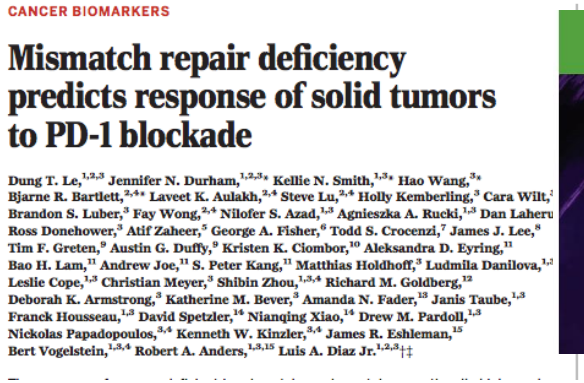
Impaired MHC I antigen presentation either through defects in the pathway or changes in neoantigens are mechanisms of resistance to immune checkpoint inhibitors.


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., Wily 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.


CANCER BIOMARKERS

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le,[1,2,3] Jennifer N. Durham,[1,2,3]* Kellie N. Smith,[1,3]* Hao Wang,[3]* Bjarne R. Bartlett,[2,4]* Laveet K. Aulakh,[2,4] Steve Lu,[2,4] Holly Kemberling,[3] Cara Wilt,[1] Brandon S. Luber,[3] Fay Wong,[2,4] Nilofer S. Azad,[1,3] Agnieszka A. Rucki,[1,3] Dan Laheru Ross Donehower,[3] Atif Zaheer,[5] George A. Fisher,[6] Todd S. Crocenzi,[7] James J. Lee,[8] Tim F. Greten,[9] Austin G. Duffy,[9] Kristen K. Ciombor,[10] Aleksandra D. Eyring,[11] Bao H. Lam,[11] Andrew Joe,[11] S. Peter Kang,[11] Matthias Holdhoff,[3] Ludmila Danilova,[1,3] Leslie Cope,[1,3] Christian Meyer,[3] Shibin Zhou,[1,3,4] Richard M. Goldberg,[12] Deborah K. Armstrong,[3] Katherine M. Bever,[3] Amanda N. Fader,[13] Janis Taube,[1,3] Franck Housseau,[1,3] David Spetzler,[14] Nianqing Xiao,[14] Drew M. Pardoll,[1,3] Nickolas Papadopoulos,[3,4] Kenneth W. Kinzler,[3,4] James R. Eshleman,[15] Bert Vogelstein,[1,3,4] Robert A. Anders,[1,3,15] Luis A. Diaz Jr.[1,2,3]†‡


BRIEF REPORT

T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer

Eric Tran, Ph.D., Paul F. Robbins, Ph.D., Yong-Chen Lu, Ph.D., Todd D. Prickett, Ph.D., Jared J. Gartner, M.Sc., Li Jia, M.Sc., Anna Pasetto, Ph.D., Zhili Zheng, Ph.D., Satyajit Ray, Ph.D., Eric M. Groh, M.D., Isaac R. Kriley, M.D., and Steven A. Rosenberg, M.D., Ph.D.

Impaired MHC I antigen presentation:

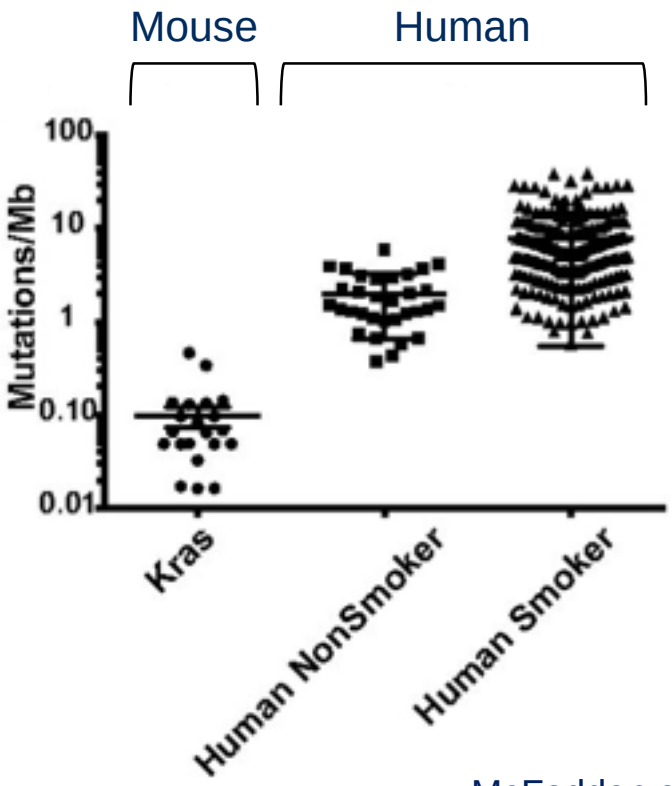
- **Why?** –spectrum of mechanisms that give rise to it and contribute to resistance.
- **What** is the frequency in resistant tumors?
- **How** can we overcome these defects?

Ideal Preclinical Models to Study Sensitivity and Resistance to Immune Checkpoint Inhibitors

- Immunocompetent
- Genomic features of human disease

Type of Model	Functional Immune System	Genetic complexity
GEM models	✓	X
PDXs	X	✓
Immune PDXs	✓ / X	✓

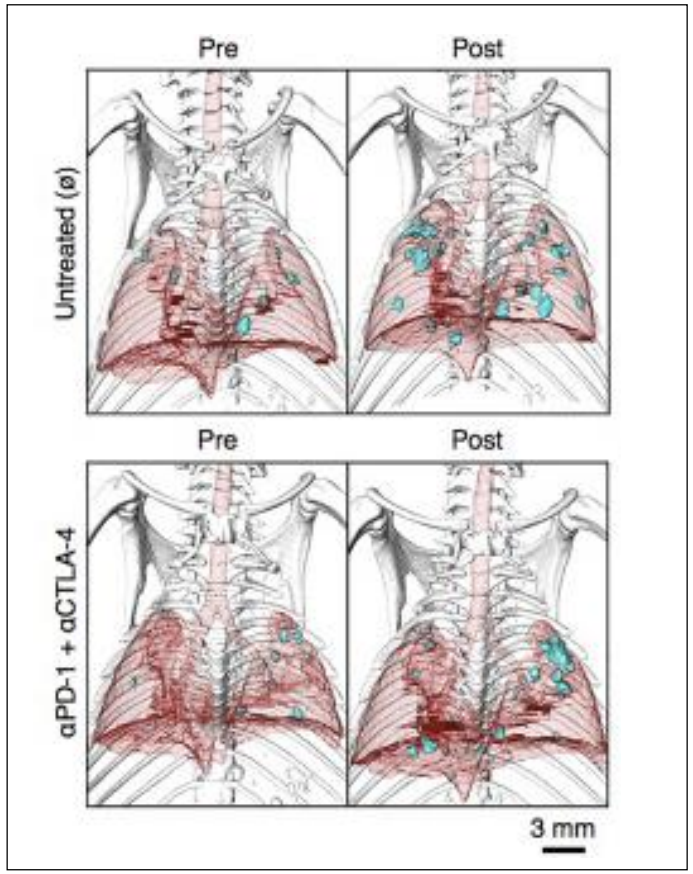
Mouse model vs. Human tumor mutation load



McFadden et al, PNAS 2016

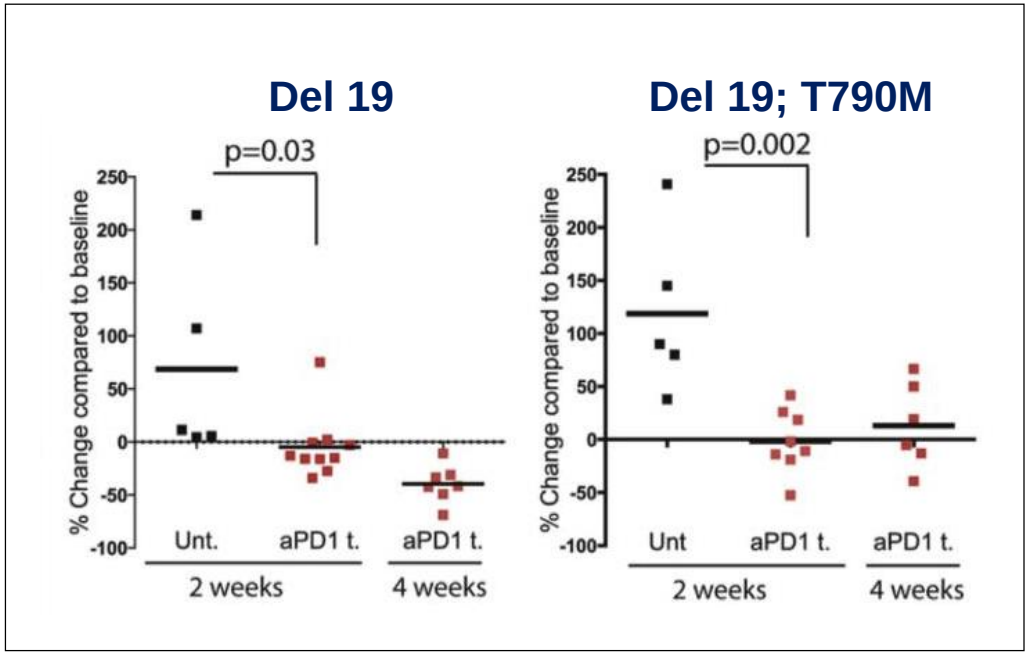
Low efficacy of immunomodulatory agents in GEM models of lung adenocarcinoma

Kras, p53



Pfirschke et al., Immunity, 2016, 343–354

EGFR



Akbay et al., Cancer Discovery. 2013 1355-63

Initiatives to model sensitivity and resistance to immunotherapy in lung cancer

Generating murine lung tumors models that better **model sensitivity and resistance to immune checkpoint inhibitors**

Transgenic/ Knockout mice

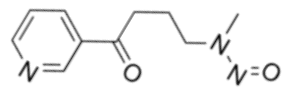
CRISPR *(DNA repair genes)*

Introduce defects in DNA repair

Carcinogen treatment

DNA adducts

Creating more genetically diverse tumors through carcinogen administration

NNK 

(4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone):

Naturally occurring tobacco product

Pros: single injection; tumors harvested @ 20-40 weeks :*Kras*^{G12} mutation induction

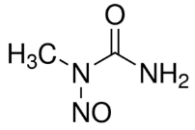
Cons: uncharacterized WES

MNU (*N*-Nitroso-*N*-methylurea)

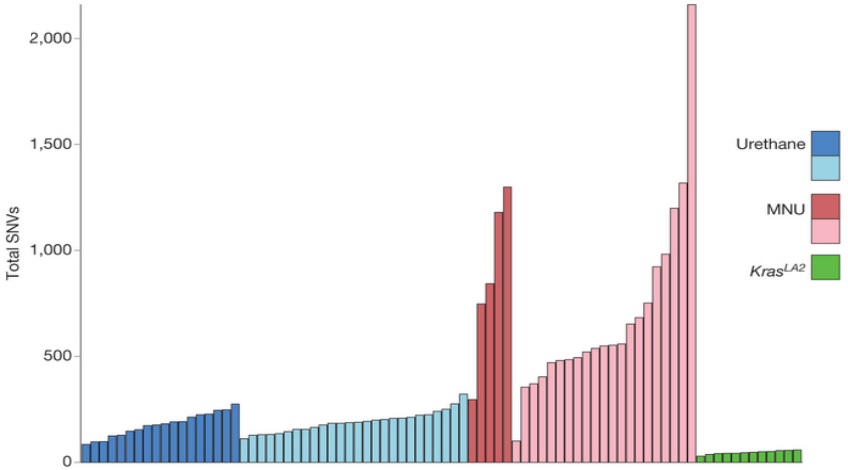
~400-800 mutations

Pros: single injection; *Kras*^{G12} mutation induction; tumors harvested at 20 weeks

Cons: weight loss

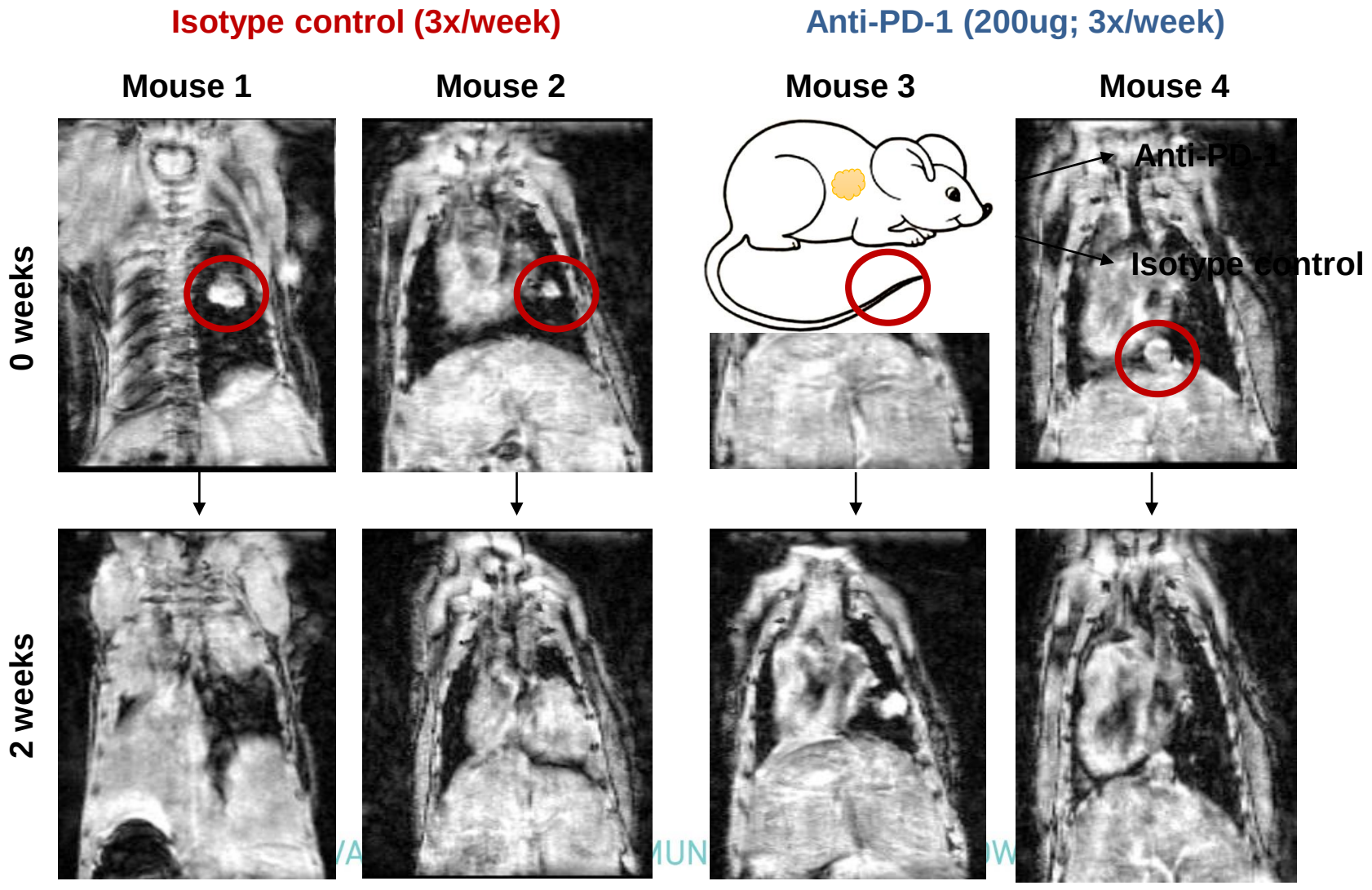


Elevated mutation load in carcinogen-induced lung adenocarcinomas



Westcott et al., Nature (2015)

Characterizing the sensitivity of carcinogen-induced lung tumor models to immune checkpoint inhibition



Katherine Hastings

The Politi Lab

medicine.yale.edu/labs/politi

ADVANCING CANCER IMMUNOTHERAPY WORLDWIDE

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Univ de Navarra

Ignacio Melero
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MGH

Soldano Ferrone