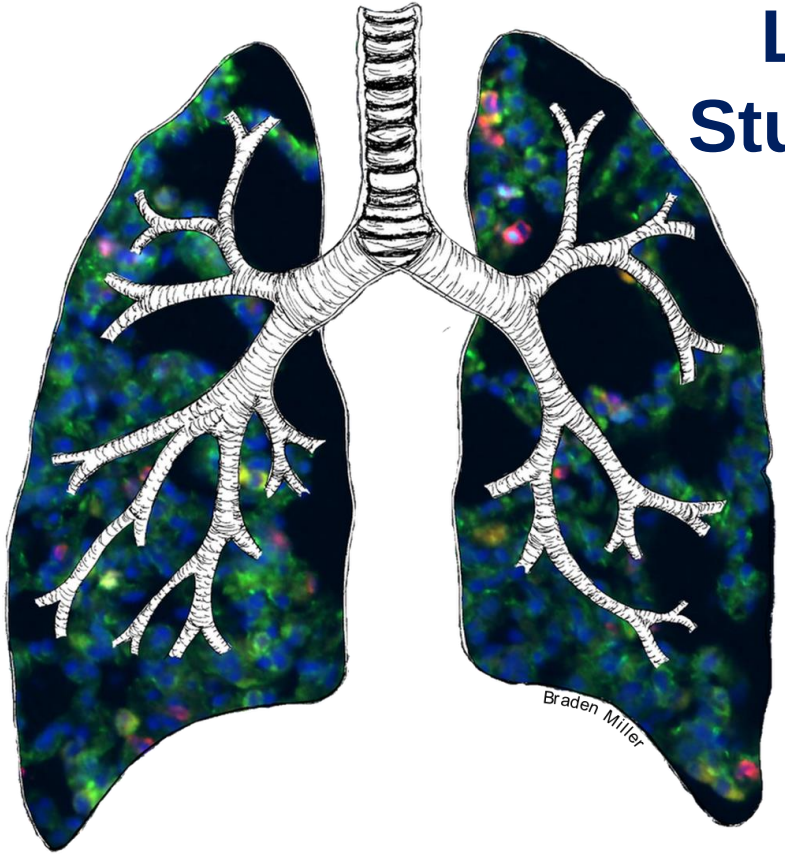


Leveraging Mouse Models to Study Sensitivity and Resistance to Cancer Therapies

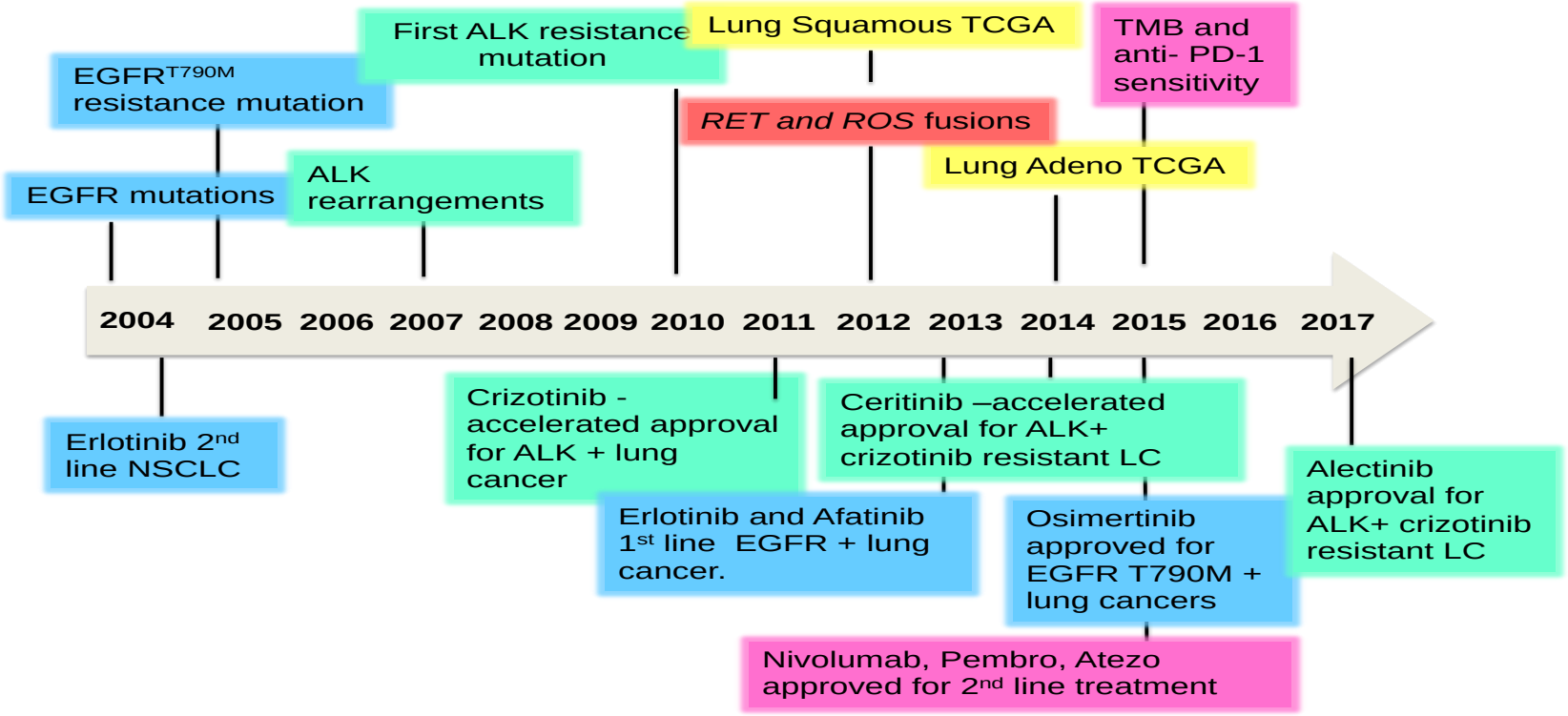
SITC Cancer Immune Responsiveness Workshop
May 14th 2018

Katerina Politi, PhD
Associate Professor
Departments of Pathology and Internal Medicine
Yale School of Medicine

Disclosures

- 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, Gilead and Symphogen.

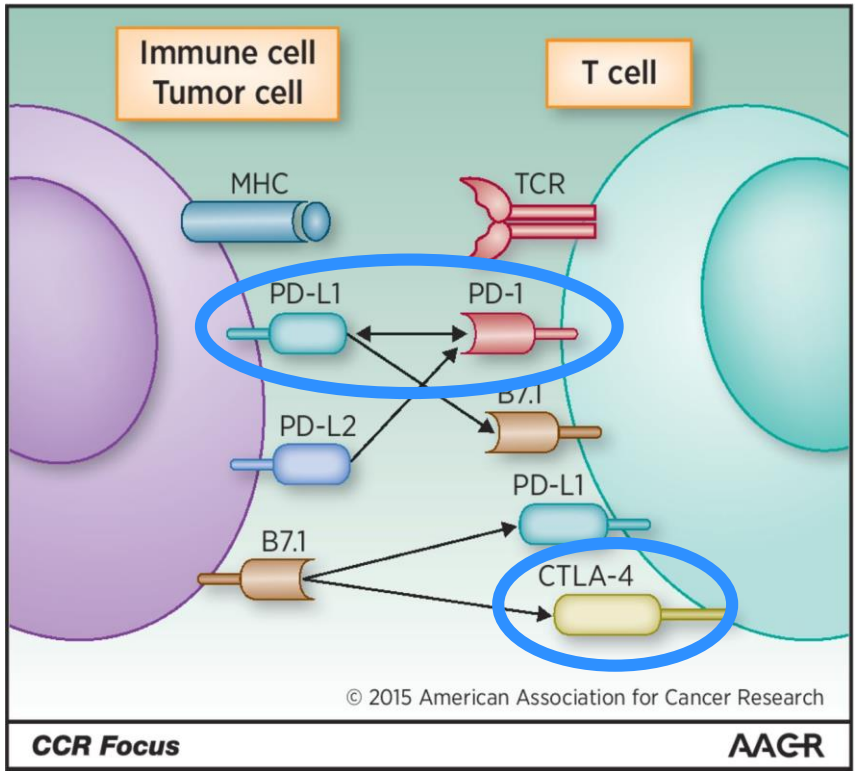
Timeline of Recent Advances in Lung Cancer



Targeted therapies and immunotherapies have transformed the lung cancer treatment landscape

Adapted from K. Politi and R. Herbst, CCR (2015) and R S Herbst *et al. Nature* **553,** 446–454 (2018)

Immune Checkpoints as Therapeutic Targets



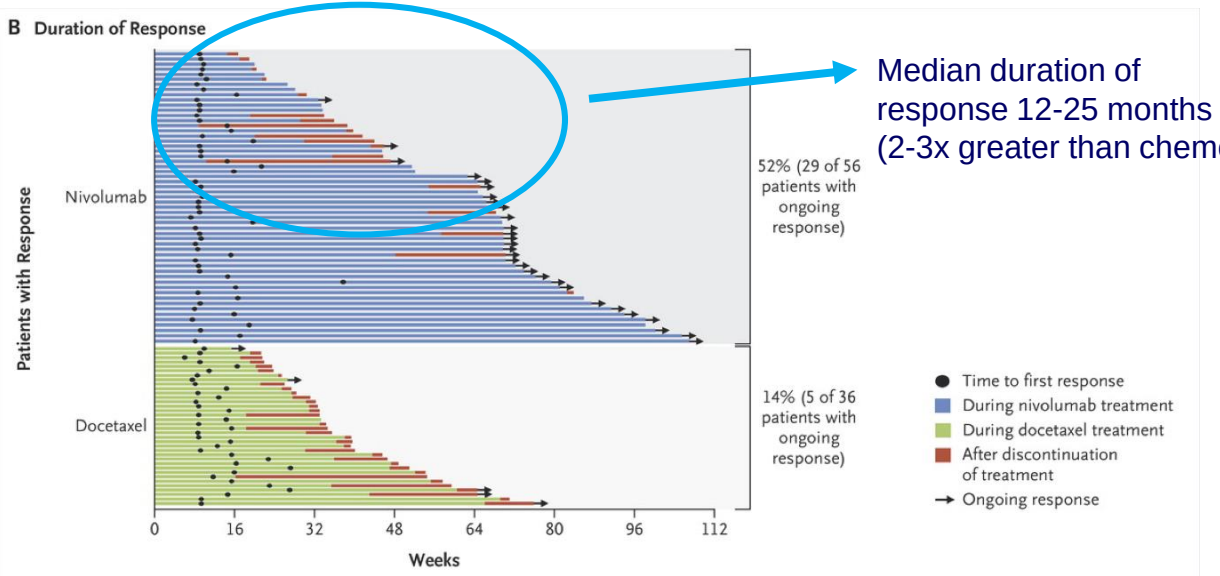
Nivolumab (anti-PD1)
2nd line approval 2015

Pembrolizumab (anti-PD1)
2nd line approval 2015
1st-line approval 2016
PD-L1 positive tumors

Atezolizumab (anti-PDL1)
2nd line approval 2015

Jean-Charles Soria et al. CCR 2015;21:2256-2262

Immune Checkpoint Inhibitors are Frequently Not Curative in Lung Cancer

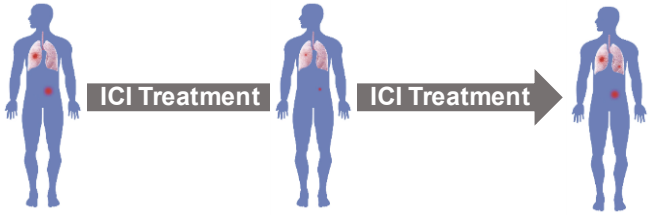


Median duration of response 12-25 months (2-3x greater than chemo)

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

Borghaei et al., NEJM 2015

Cohort of Patients with Resistance to Immune Checkpoint Inhibitors



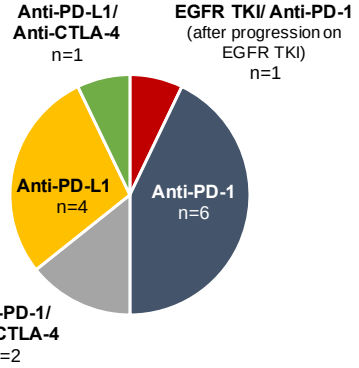
Pre-Treatment
(+/- Intervening Therapy)
- Tumor Tissue
- Germline DNA

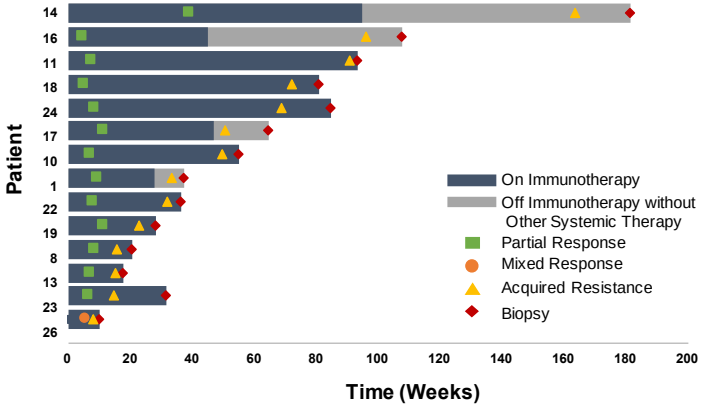
Response

Resistance
- Tumor Tissue
- PDX

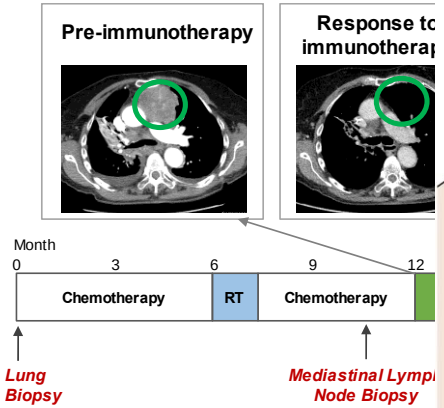
Analysis
- Exome Sequencing
- RNA Sequencing
- Quantitative Immunofluorescence

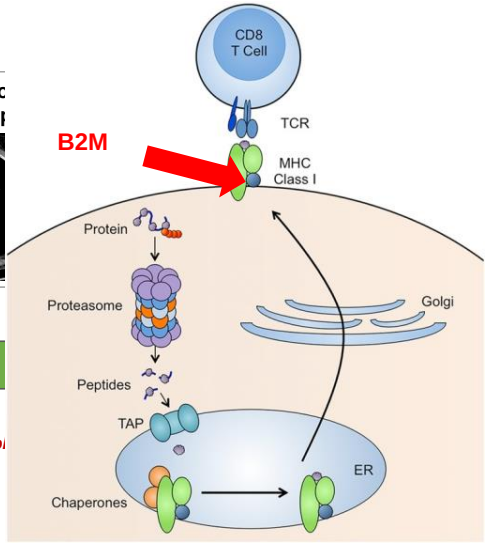
Identification of Resistance Specific Alterations



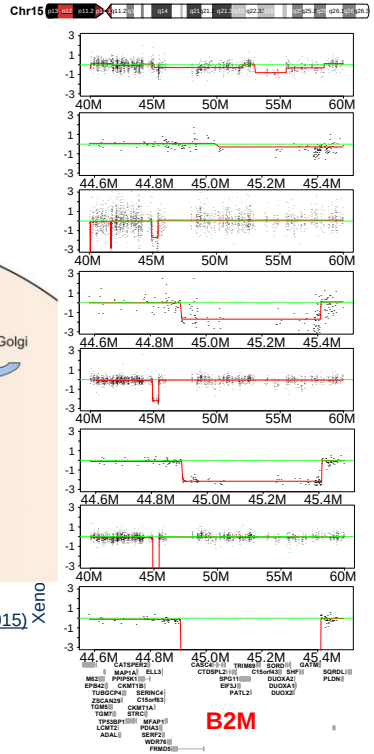


Acquired Resistance to Anti-PD-L1 plus Anti-CTLA4





McCarthy MK, Weinberg JB Front Microbiol (2015)



Xeno

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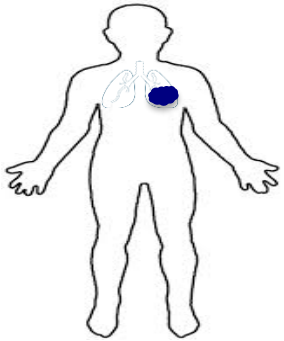
Gettinger, Choi, Hastings, Truini, Datar et al., Cancer Disc. 2017

What is Next?



Candidate Resistance Drivers

Functionally test mechanisms of acquired resistance in vivo

Establish strategies to overcome resistance

- **Immunocompetent system**
- **Sensitive to the immunotherapy under investigation**

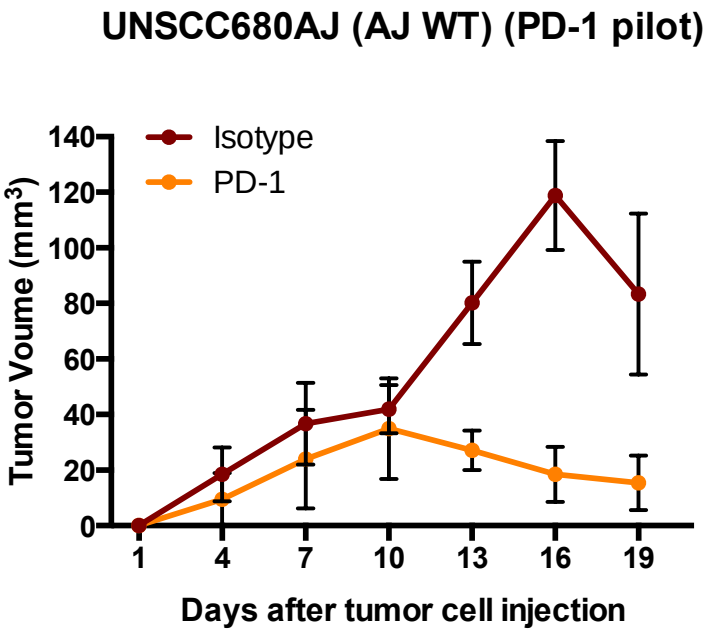
A Transplantable Lung Cancer Model with Sensitivity to PD-1 Blockade

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

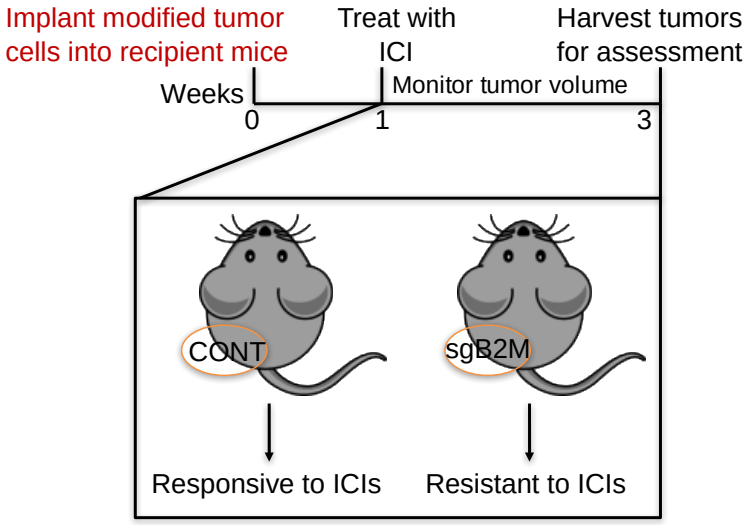
Arantza Azpilikueta, BSc,[a] Jackeline Agorreta, PhD,[b,c] Sara Labiano, BSc,[a] José Luis Pérez-Gracia, MD, PhD,[d] Alfonso R. Sánchez-Paulete, BSc,[a] M. Angela Aznar, PhD,[a] Daniel Ajona, PhD,[b,e] Ignacio Gil-Bazo, MD, PhD,[d] Marta Larrayoz, PhD,[a,c] Alvaro Teijeira, PhD,[a] María E. Rodriguez-Ruiz,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

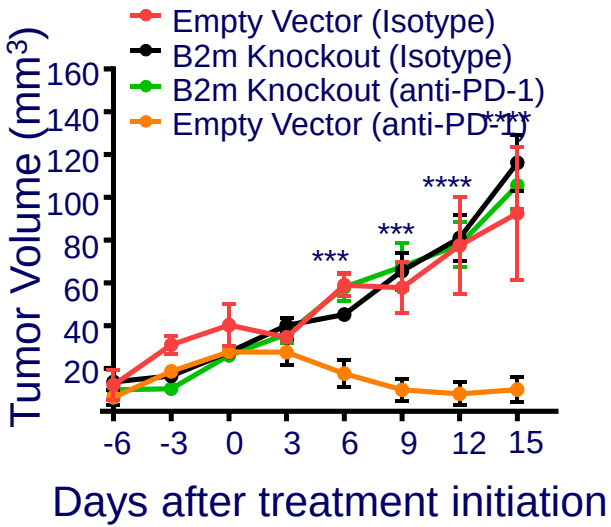
[a]Department of Immunology, Center for Applied Medical Research, Universidad de Navarra
[b]Program in Solid Tumors and Biomarkers, Center for Applied Medical Research, Universidad de Navarra
[c]Department of Histology and Pathology, Universidad de Navarra
[d]Department of Oncology and Clinical Trial Unit, Clínica Universidad de Navarra
[e]Department of Biochemistry and Genetics, Universidad de Navarra

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



B2M Loss Confers Resistance to anti-PD1 *In Vivo*





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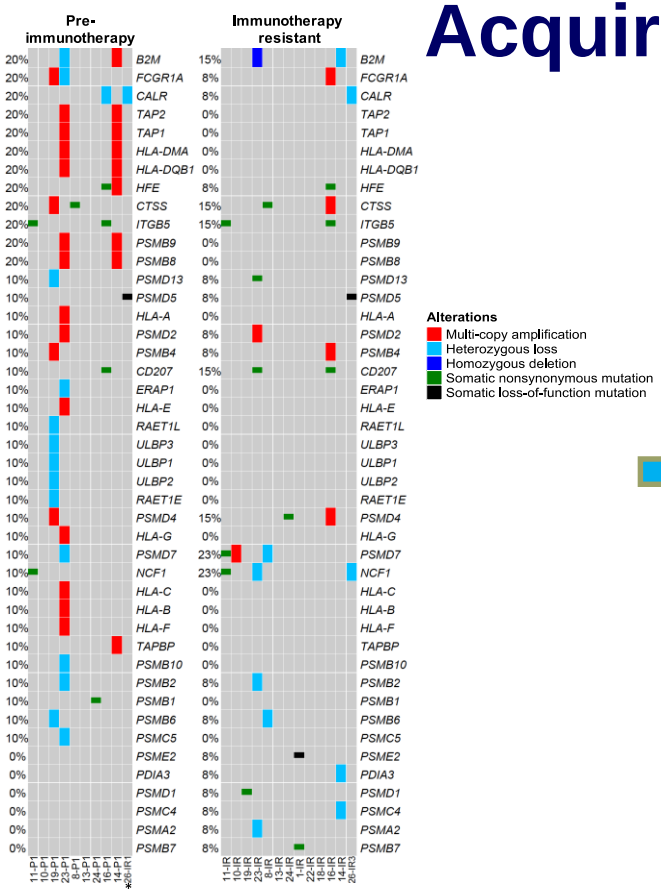
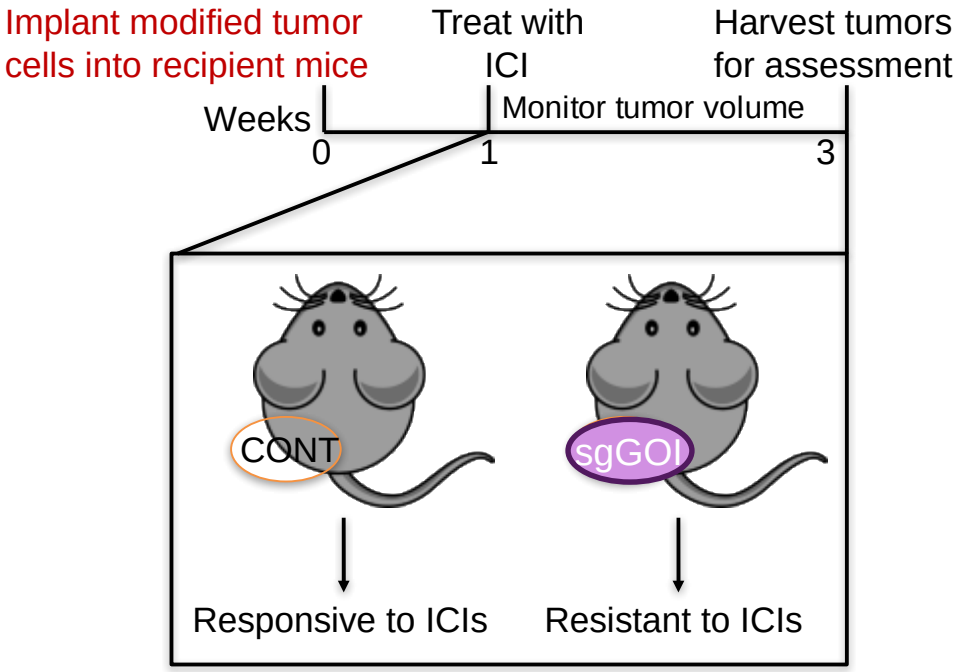
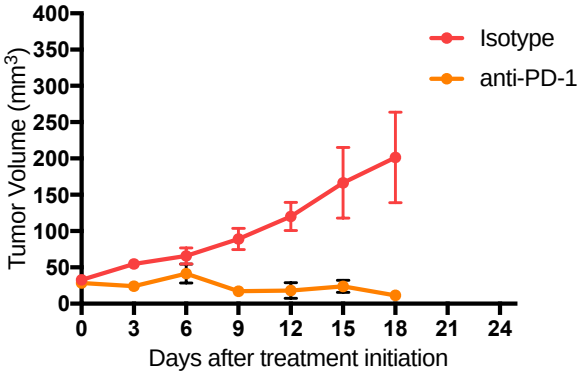
Testing other Candidate Resistance Drivers of Acquired Resistance to ICIs



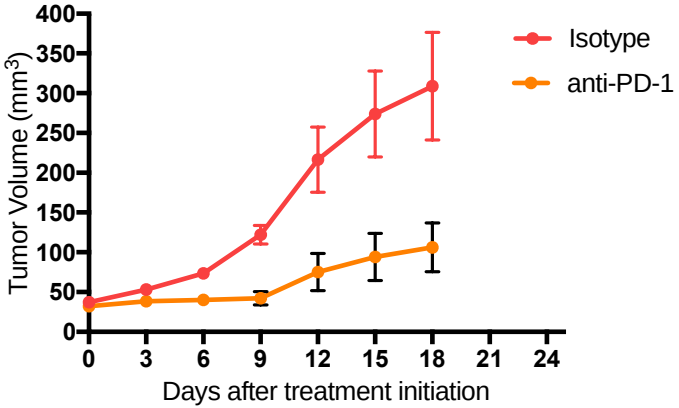


Modeling and Overcoming Resistance to ICIs

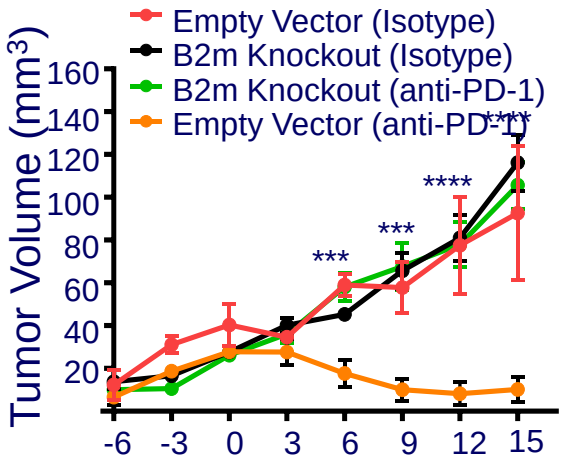
Empty Vector



Pten loss



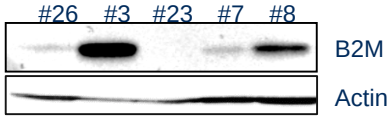
- VEGF blockade

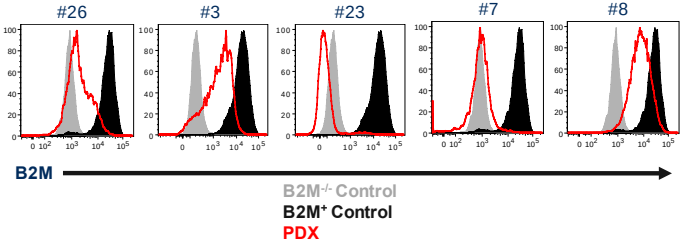


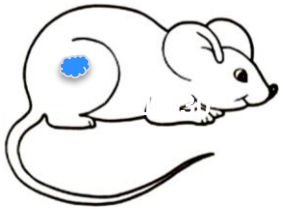
Days after treatment initiation

- NK cells
- Myeloid cells
- CAR T cells
- T-cell/tumor cell antibodies

B2M Loss at Resistance to ICIs in PDXs

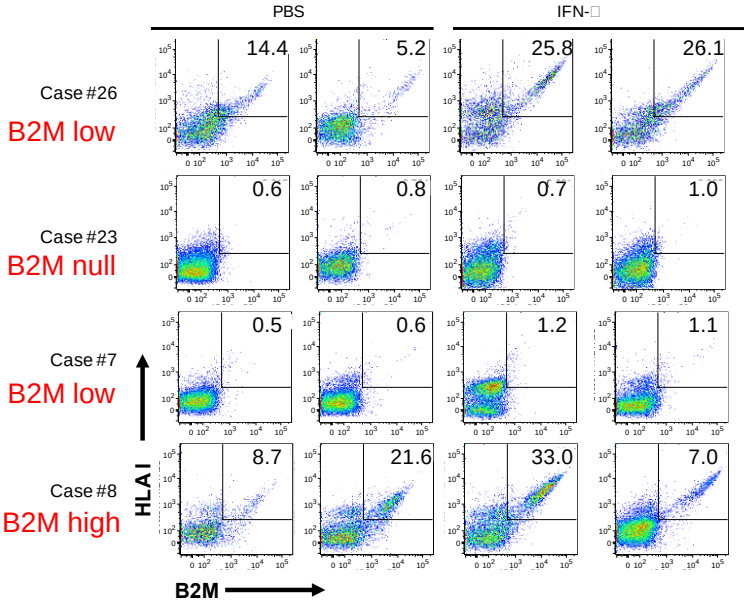






PBS

IFNγ



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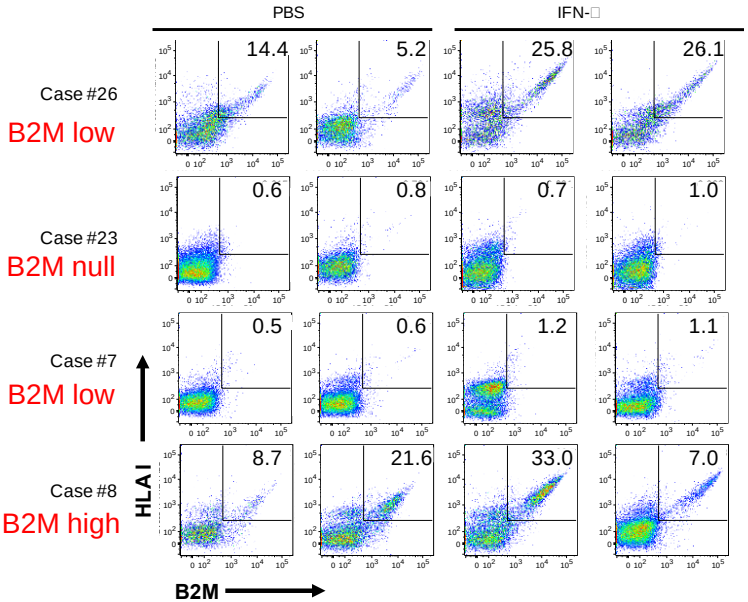
Multiple Genetic and Non-genetic Processes can Lead to Defects in MHC I Antigen Presentation



Immune inhibitory signaling?

Epigenetic silencing of MHC I genes?
Other mechanisms?

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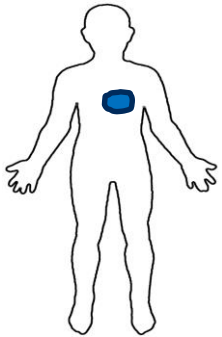
Summary

Transplantable models can be used to model resistance to ICIs *in vivo* and to study approaches to overcome resistance.

PDXs of tumors resistant to immune checkpoint inhibitors are valuable tools to understand the permissiveness of the tumor to respond to immune stimulation and confirm genomic alterations.

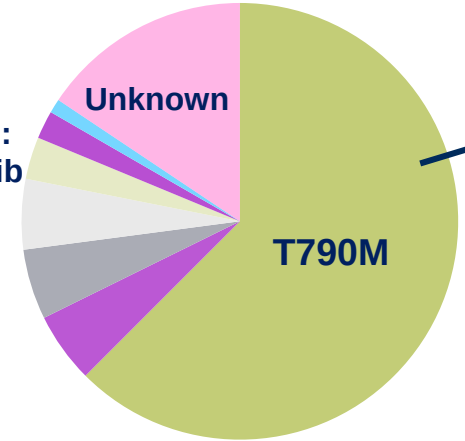
Treatment Paradigms for EGFR Mutant Lung Cancer



TKI-Naïve EGFR mutant tumor

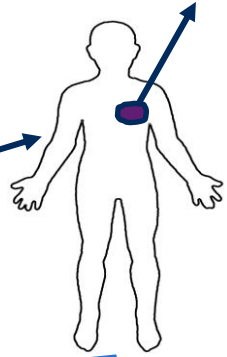
1st or 2nd Gen. EGFR TKI: Erlotinib, gefitinib, afatinib

PFS ~ 12 months
Response Rate ~ 70%



T790M
HER2
SCLC
MET
EMT
BRAF
PIK3CA

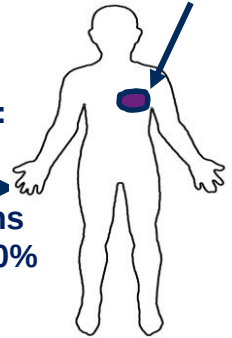
T790M+



3rd Gen. EGFR mutant-specific TKI: osimertinib

PFS ~ 9 - 13 months
Response Rate ~ 70%

C797S+



PFS ~ 19 months
Response Rate ~ 80%

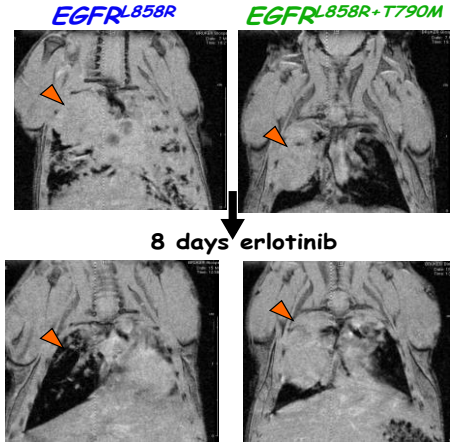
Adapted from Politi et al., Cancer Cell 2015
Soria et al., NEJM 2017

Mouse Models of EGFR Mutant Lung Cancer

DOX

Mutant *EGFR* expressed in Type II lung epithelial cells when mice are given doxycycline

- Immuno-competent mouse model
- Tetracycline inducible
- Reversible

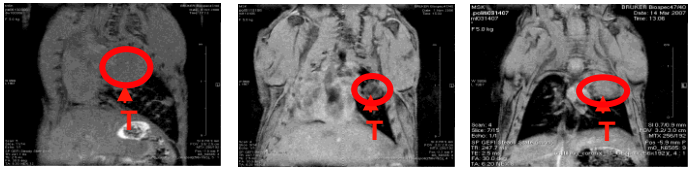


Weeks

0-Pretreatment **3-ON Erlotinib** **22-ON Erlotinib**

Tumor volume

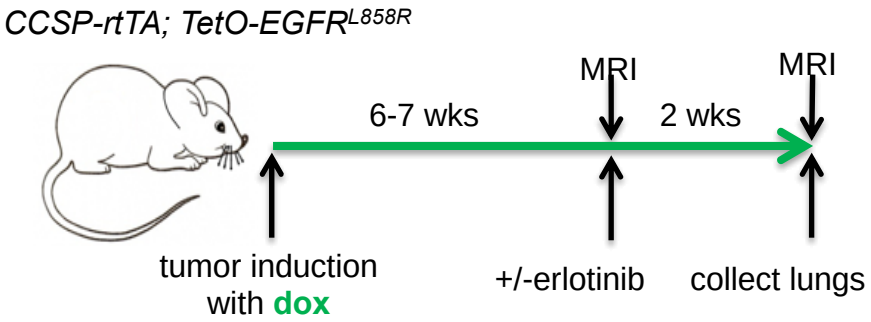
0.17 cm^3 **0.02 cm^3** **0.12 cm^3**

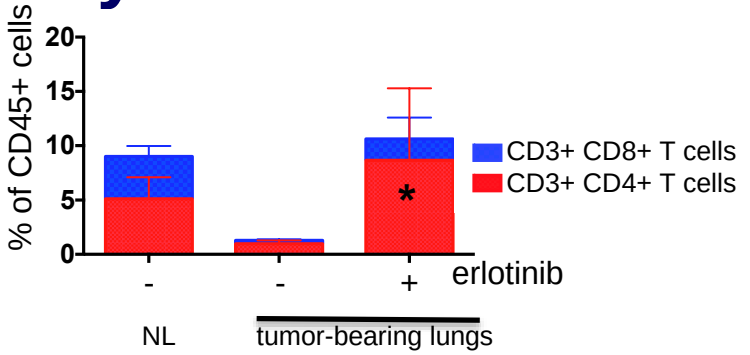


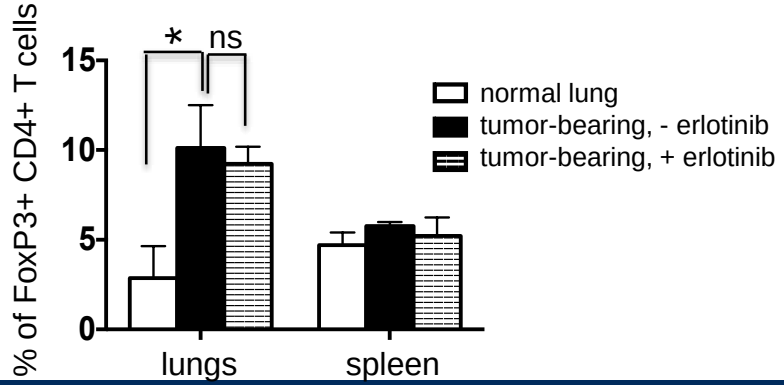
Politi et al., 2006
Regales et al., 2007
Politi et al., 2010

Takezawa et al., 2012
De Bruin et al., 2014
Pirazzoli et al., 2014

The Immunosuppressive Microenvironment in Murine $EGFR^{L858R}$ –induced Lung Adenocarcinomas is Partially Reversed by Erlotinib.

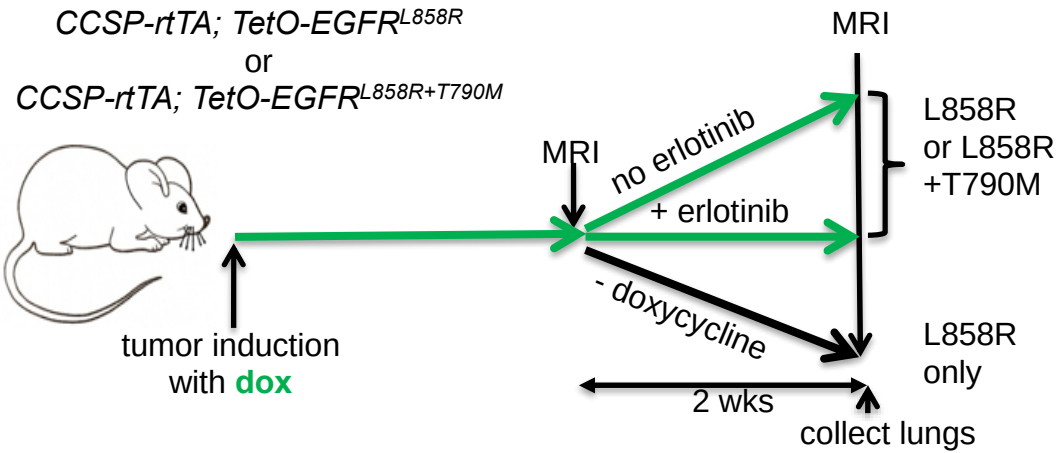


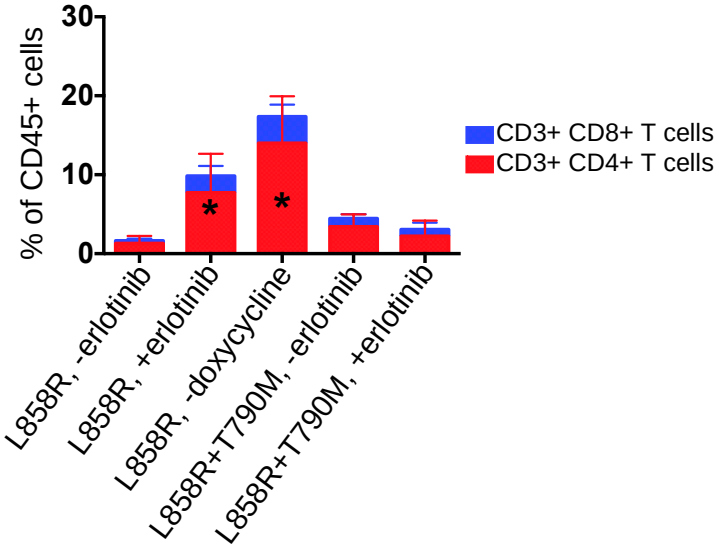




Ayeni et al., bioRxiv 254847; doi: https://doi.org/10.1101/254847

Changes in T cells in the Immune Microenvironment are Due to Tumor Regression





Ayeni et al., bioRxiv 254847; doi: https://doi.org/10.1101/254847

Summary

Genetically engineered mouse models can be valuable tools to study:

- What the characteristics of the immune microenvironment are in specific tumor models.
- How therapies like EGFR TKIs modulate the immune microenvironment.
- What role immune cells play in tumorigenesis and response to therapy.
- What is the therapeutic efficacy of drug combinations that include immunotherapies.

There are limitations to these models. For example, the tumor mutational burden is often different between the mouse tumors and human tumor.

The Politi Lab

medicine.yale.edu/labs/politi

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