November 8-12 • NATIONAL HARBOR, MD

SITC 2017

Session 202: Mechanisms of Acquired Resistance to Immunotherapies
9:55- 10:20 a.m

Acquired Resistance to PD-1 Blockade in Melanoma

Antoni Ribas, M.D., Ph.D.
Professor of Medicine, Surgery, Molecular and Medical Pharmacology
Director, Tumor Immunology Program, Jonsson Comprehensive Cancer Center (JCCC)
Director, Parker Institute for Cancer Immunotherapy (PICI) Center at UCLA
University of California Los Angeles (UCLA)
Chair, Melanoma Committee at SWOG

sitc
Society for Immunotherapy of Cancer

#SITC2017

Presenter Disclosure Information

Antoni Ribas

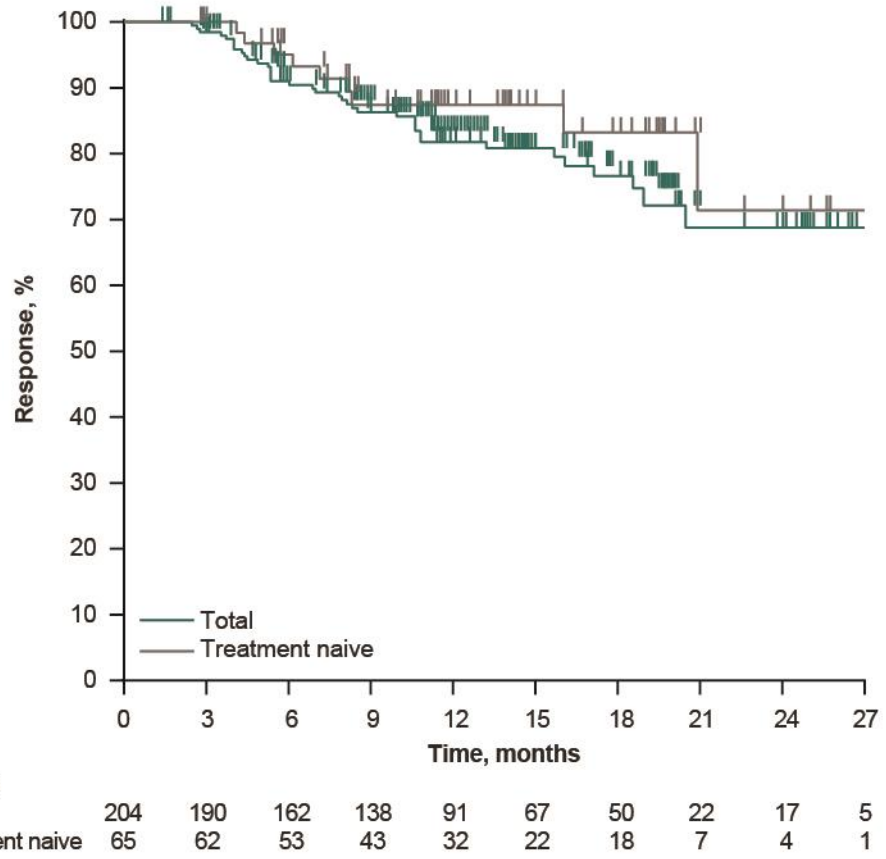
Consultant – Honoraria: Amgen, BMS, Celldex, Chugai, Genentech, Merck, Novartis

Scientific Advisory Board – Stock: Advaxis, Arcus, BioOncoTech, Compugen, CytomX, Five Prime, FLX-Bio, ImaginAb, Isoplexis, Kite Pharma, Lutris, Rgenix

Co-founder – Stock: Acteris, PACT, Tango

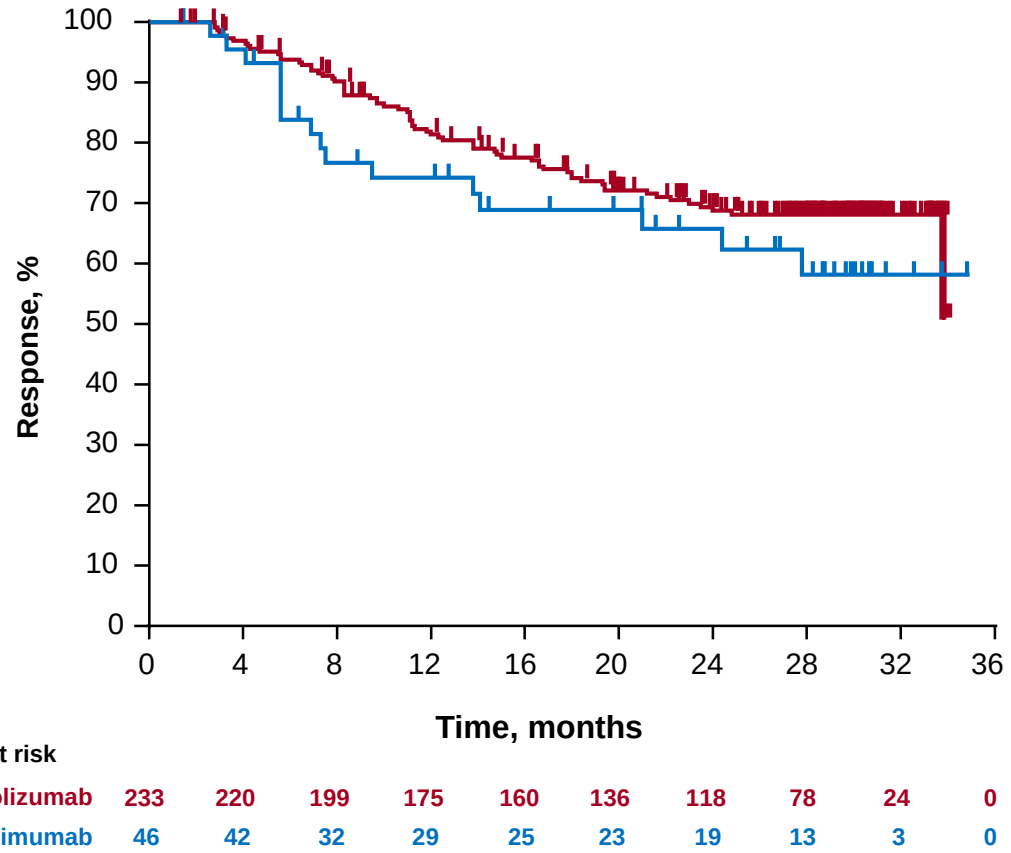
Frequency of Acquired Resistance to PD-1 Blockade in Patients with Advanced Melanoma

KM of duration of response in patients treated with pembrolizumab in the Keynote 001 trial



Ribas *et al*. JAMA 2016

KM of duration of response in patients treated with pembrolizumab or ipilimumab in the Keynote 006 trial



Robert *et al*. ASCO 2017

Primary Resistance

Acquired Resistance

Leading Edge
Review

Cell

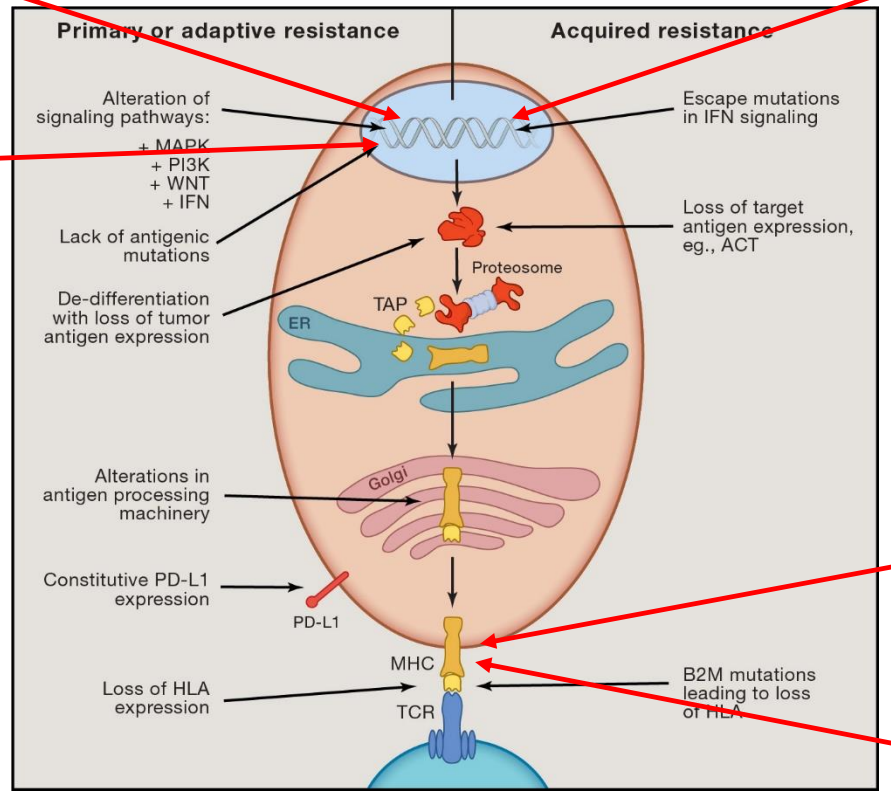
Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy

Padmanee Sharma,[1,*] Siwen Hu-Lieskovan,[2] Jennifer A. Wargo,[3] and Antoni Ribas[2,*]

JAK1/2 and other IFN-g pathway LoF mutations
Shin *et al*. Cancer Discovery 2016
Gao *et al*. Cell 2016
Sucker *et al*. Nature Communications 2017

JAK1/2 LoF mutations
Zaretsky *et al*. NEJM 2016
Sucker *et al*. Nature Communications 2017

T cell exclusion by WNT signaling
Spranger *et al*. Science 2015



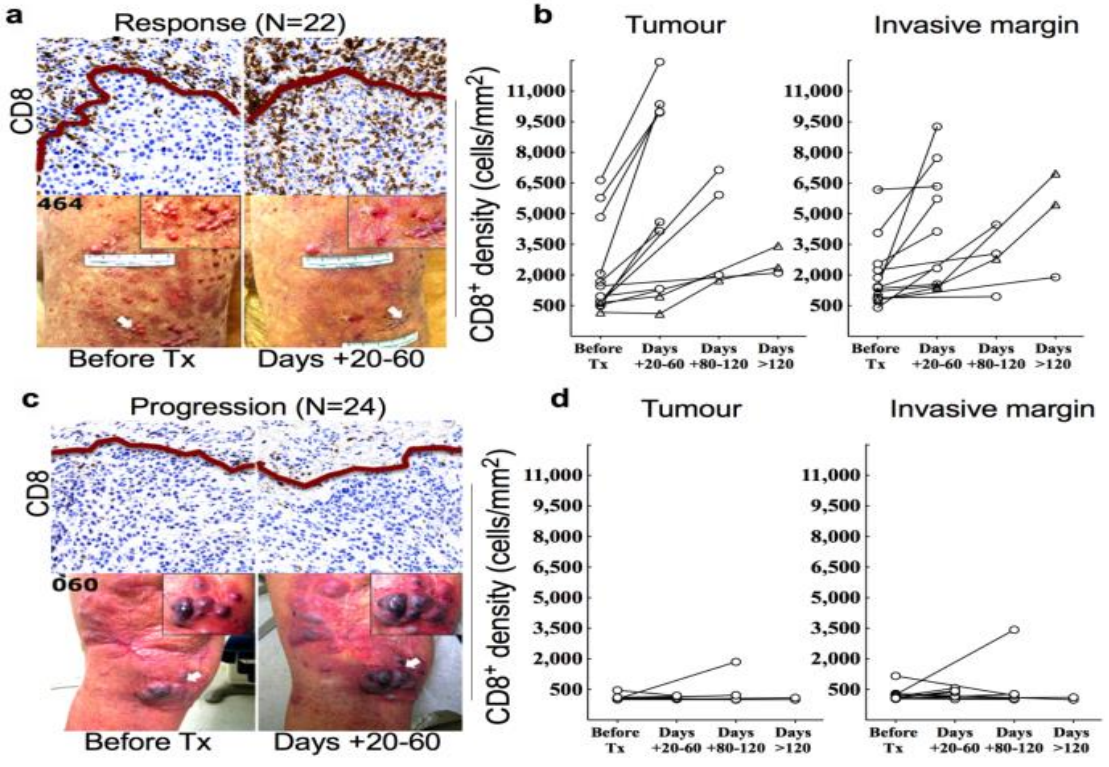
Loss of neoantigen expression
Anagnostou et al. Cancer Discovery 2017

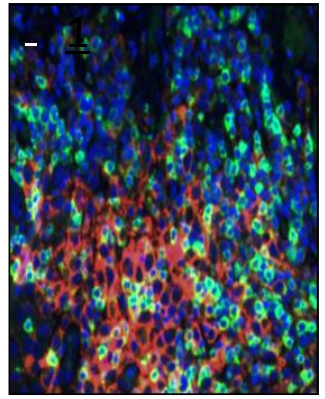
JAK1/2 LoF mutations
Zaretsky *et al*. NEJM 2016

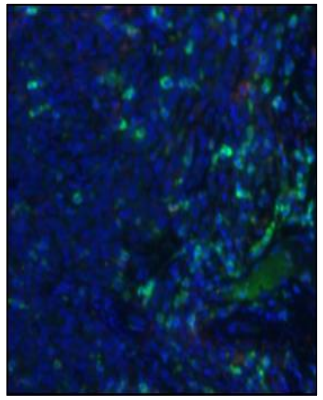
Cell. 2017 Feb 9; 168 (4): 707-723

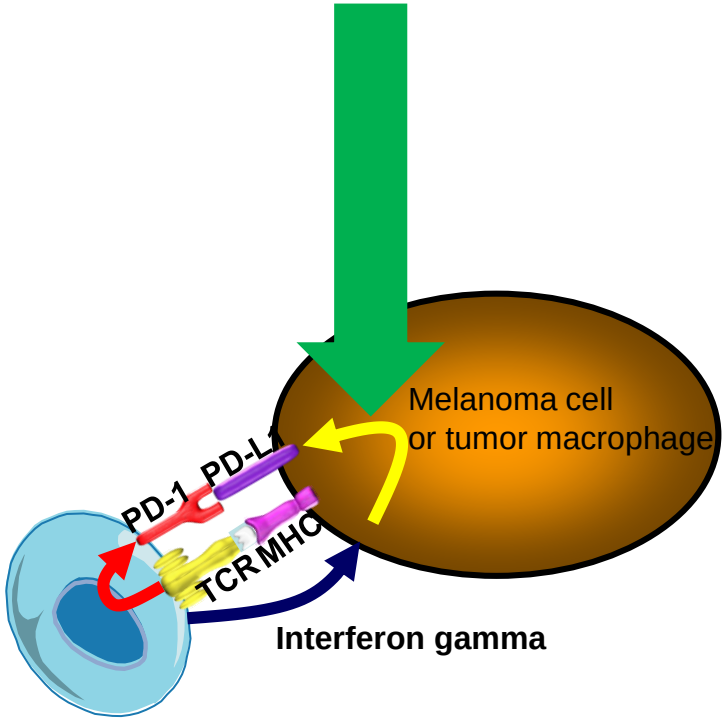
How does the cancer sense IFN-gamma and reactively expresses PD-L1?

PD1/PDL1









Tumeh *et al*., Nature 2014

Role of the IFN-g receptor pathway in resistance to checkpoint blockade therapy

CANCER DISCOVERY

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 Thi 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]

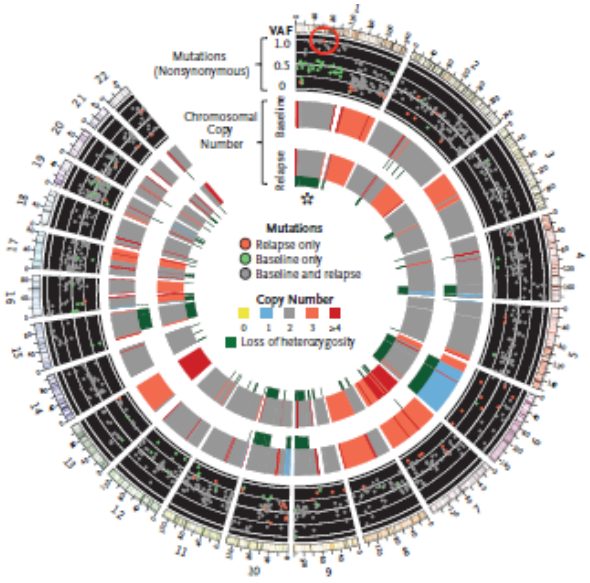
Journal for ImmunoTherapy of Cancer (JITC) 2015, 3: P311
Cancer Discovery 2017, *7*, 188-201

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

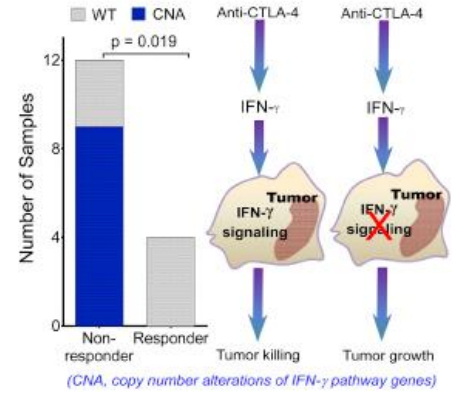
Jesse M. Zaretsky, B.S., Angel Garcia-Diaz, Ph.D., Daniel S. Shin, M.D., Helena Escuin-Ordinas, Ph.D., Willy Hugo, Ph.D., Siwen Hu-Lieskovan, M.D., Ph.D., Davis Y. Torrejon, M.D., Gabriel Abril-Rodriguez, M.Sc., Salemiz Sandoval, Ph.D., Lucas Barthly, M.Sc., Justin Saco, B.S., Blanca Homet Moreno, M.D., 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.



Cell

Loss of IFN-γ Pathway Genes in Tumor Cells as a Mechanism of Resistance to Anti-CTLA-4 Therapy

Jianjun Gao,[1,6] Lewis Zhichang Shi,[1,6] Hao Zhao,[4,6] Jianfeng Chen,[1] Liangwen Xiong,[1] Qiuming He,[1] Tenghui Chen,[4] Jason Roszik,[2] Chantale Bernatchez,[2] Scott E. Woodman,[2] Pei-Ling Chen,[3] Patrick Hwu,[2] James P. Allison,[4] Andrew Futreal,[5] Jennifer A. Wargo,[3,5] and Padmanee Sharma[1,4,7,*]



(CNA, copy number alterations of IFN-γ pathway genes)

nature COMMUNICATIONS

ARTICLE

Received 7 Sep 2016 | Accepted 29 Mar 2017 | Published 31 May 2017 DOI: 10.1038/ncomms15440 OPEN

Acquired IFNγ resistance impairs anti-tumor immunity and gives rise to T-cell-resistant melanoma lesions

Antje Sucker[1,2], Fang Zhao[1,2], Natalia Pieper[1,2], Christina Heeke[1,2], Raffaela Maltaner[1,2], Nadine Stadtler[1,2], Birgit Real[1,2], Nicola Bielefeld[1,2], Sebastian Howe[3], Benjamin Weide[4], Ralf Gutzmer[5], Jochen Utikal[6], Carmen Loquai[7], Helen Gogas[8], Ludger Klein-Hitpass[9], Michael Zeschnigk[10], Astrid M. Westendorf[11], Mirko Trilling[3], Susanne Horn[1,2], Bastian Schilling[1,2,12], Dirk Schadendorf[1,2], Klaus G. Griewank[1,2] & Annette Paschen[1,2]

ARTICLE

doi:10.1038/nature23270

In vivo CRISPR screening identifies *Ptpn2* as a cancer immunotherapy target

Robert T. Manguso[1,2,3], Hans W. Pope[1,3], Margaret D. Zimmer[1,3], Flavian D. Brown[1,2], Kathleen B. Yates[1,3], Brian C. Miller[1,3,4], Natalie B. Collins[1,3,5], Kevin Bi[1,3], Martin W. LaFleur[1,2], Vikram R. Juneja[6], Sarah A. Weiss[1], Jennifer Lo[7], David E. Fisher[7], Diana Miao[2,3], Eliezer Van Allen[2,3], David E. Root[3], Arlene H. Sharpe[5,8], John G. Doench[3] & W. Nicholas Haining[1,3,5]

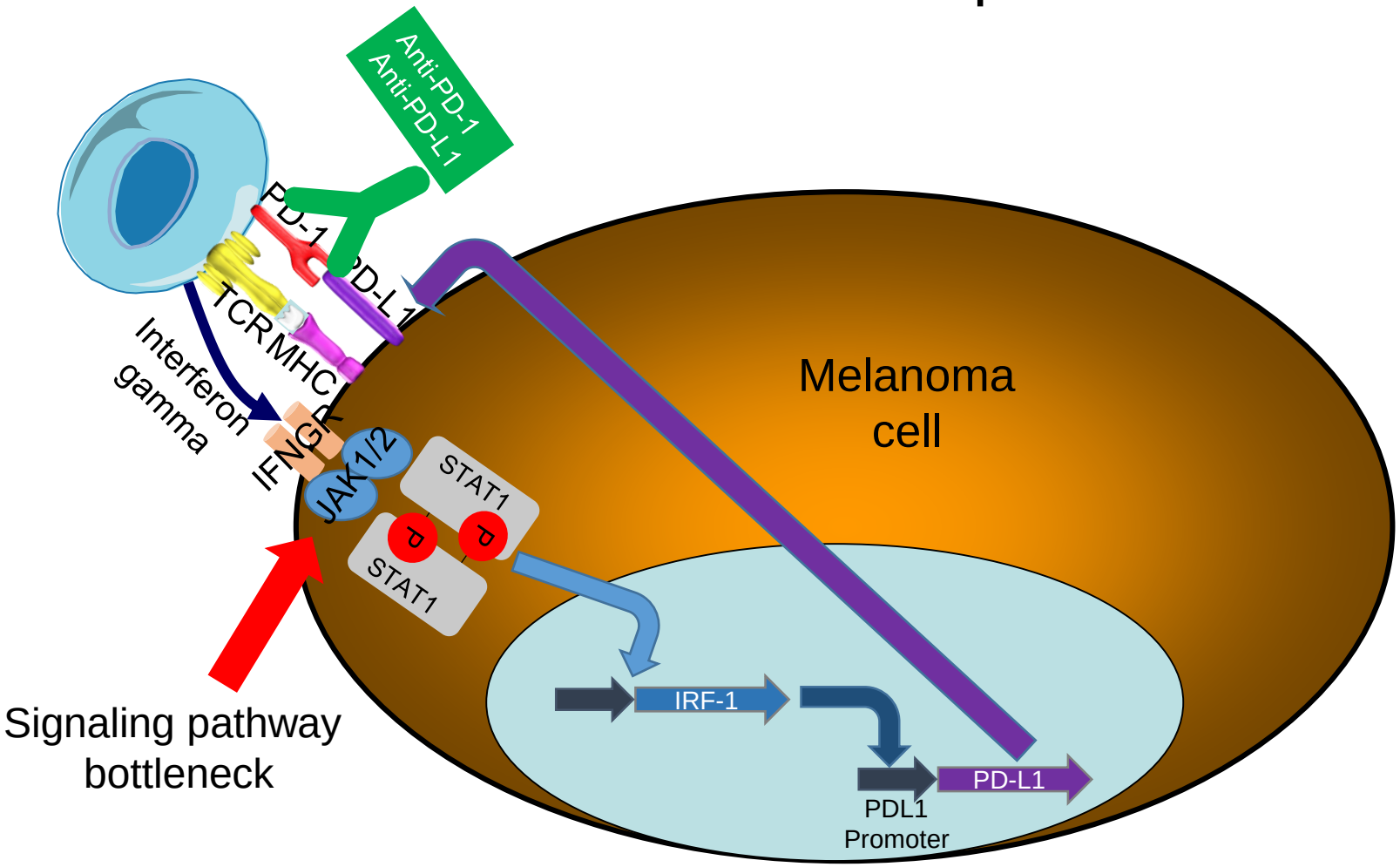
ARTICLE

doi:10.1038/nature23477

Identification of essential genes for cancer immunotherapy

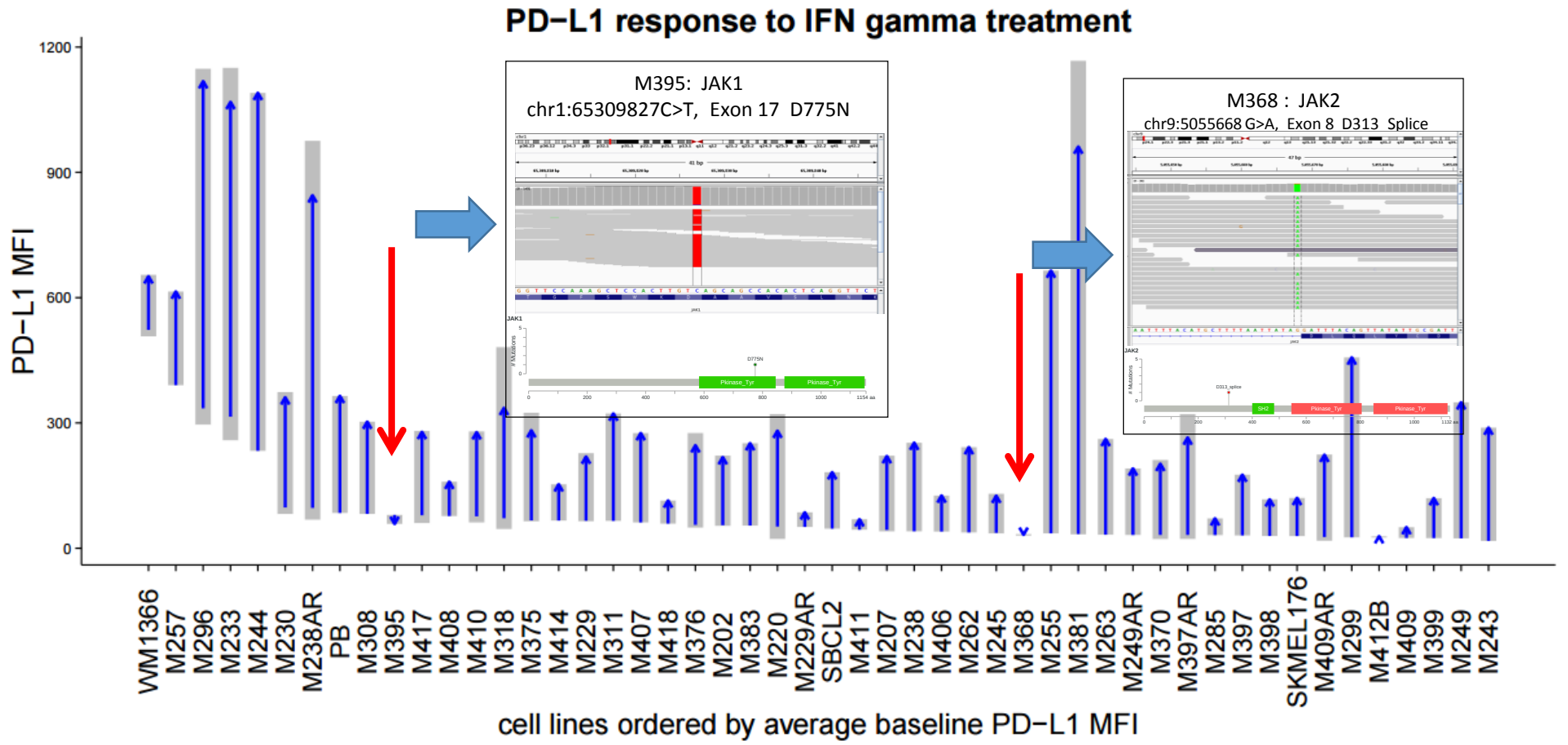
Shashank J. Patel[1,2*], Neville E. Sanjana[3,4*], Rigel J. Kishton[1], Arash Eidizadeh[1], Suman K. Vodnala[1], Maggie Cam[1], Jared J. Gartner[1], Li Jia[1], Seth M. Steinberg[1], Tori N. Yamamoto[1,5], Anand S. Merchant[1], Gautam U. Mehta[1], Anna Chichura[1], Ophir Shalem[6], Eric Tran[1], Robert Eil[1], Madhusudhanan Sukumar[1], Eva Perez Guijarro[1], Chi-Ping Day[1], Paul Robbins[1], Steve Feldman[1], Glenn Merlino[1], Feng Zhang[7,8] & Nicholas P. Restifo[1,9]

Interferon gamma receptor pathway regulating reactive PD-L1 expression



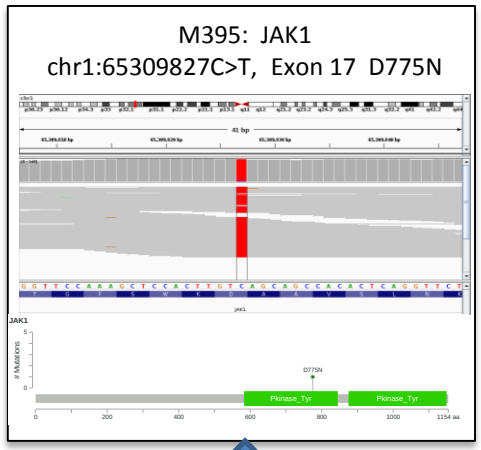
Adapted from Shin *et al*. Cancer Discovery 2017 and Garcia-Diaz *et al*. Cell Reports 2017

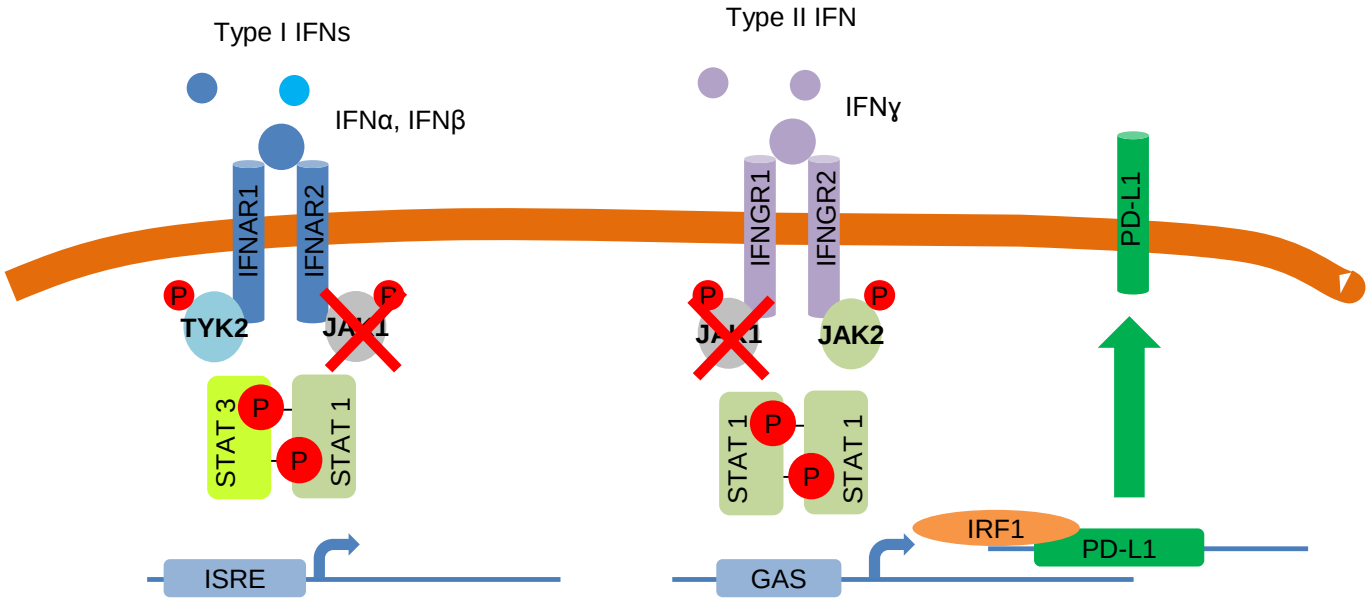
2 out of 48 melanoma cell lines had *JAK1/2* LOF mutations and did not respond to IFN-gamma by expressing PD-L1



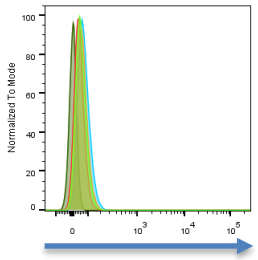
Shin et al. Cancer Discovery 2017, 7, 188-201

Loss of Function (LoF) *JAK1/2* Mutations Inhibiting IFN-gammaR signaling

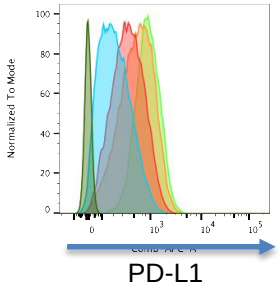


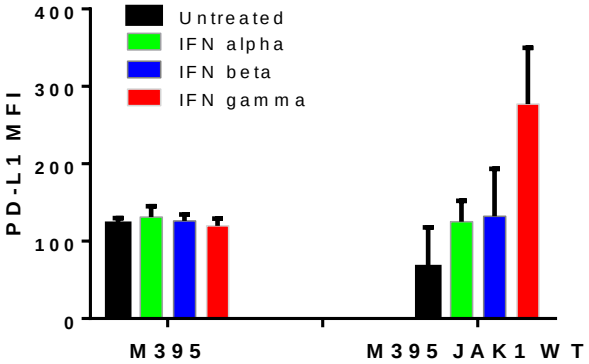


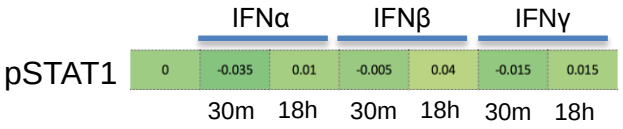
M395

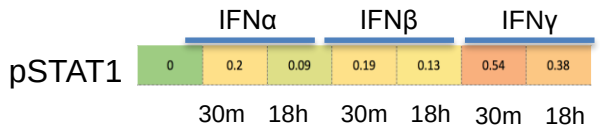


M233



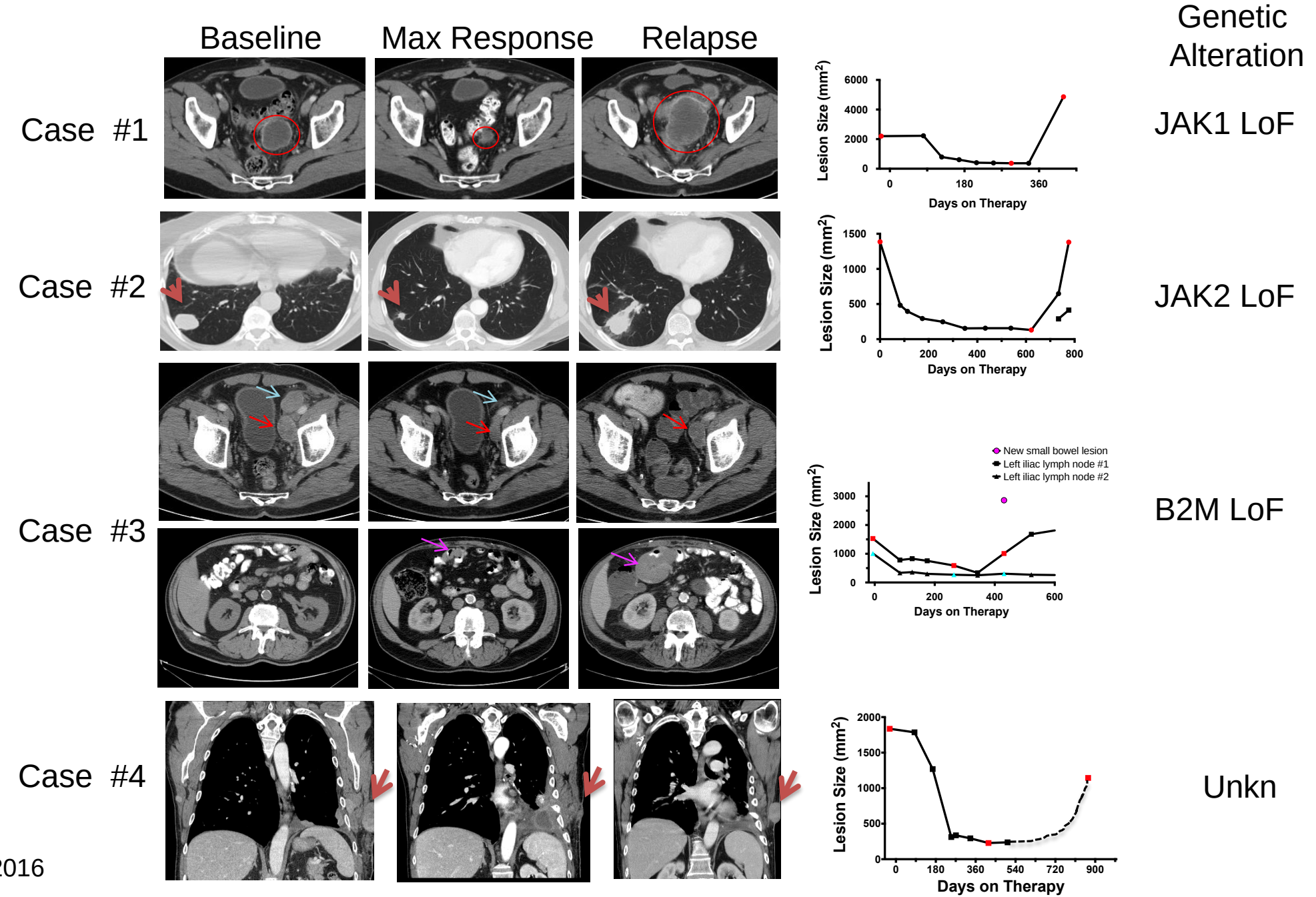






Shin *et al*. Cancer Discovery 2016

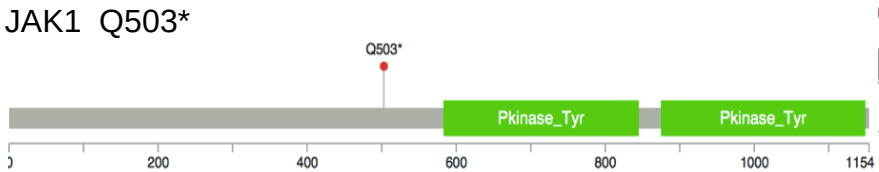
Analysis of Four Acquired Resistance Cases

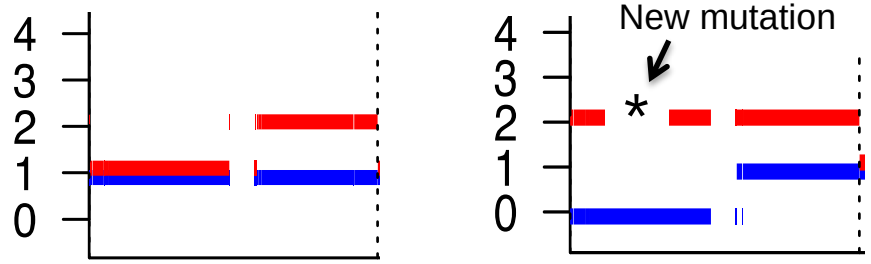


Zaretsky *et al.* NEJM 2016

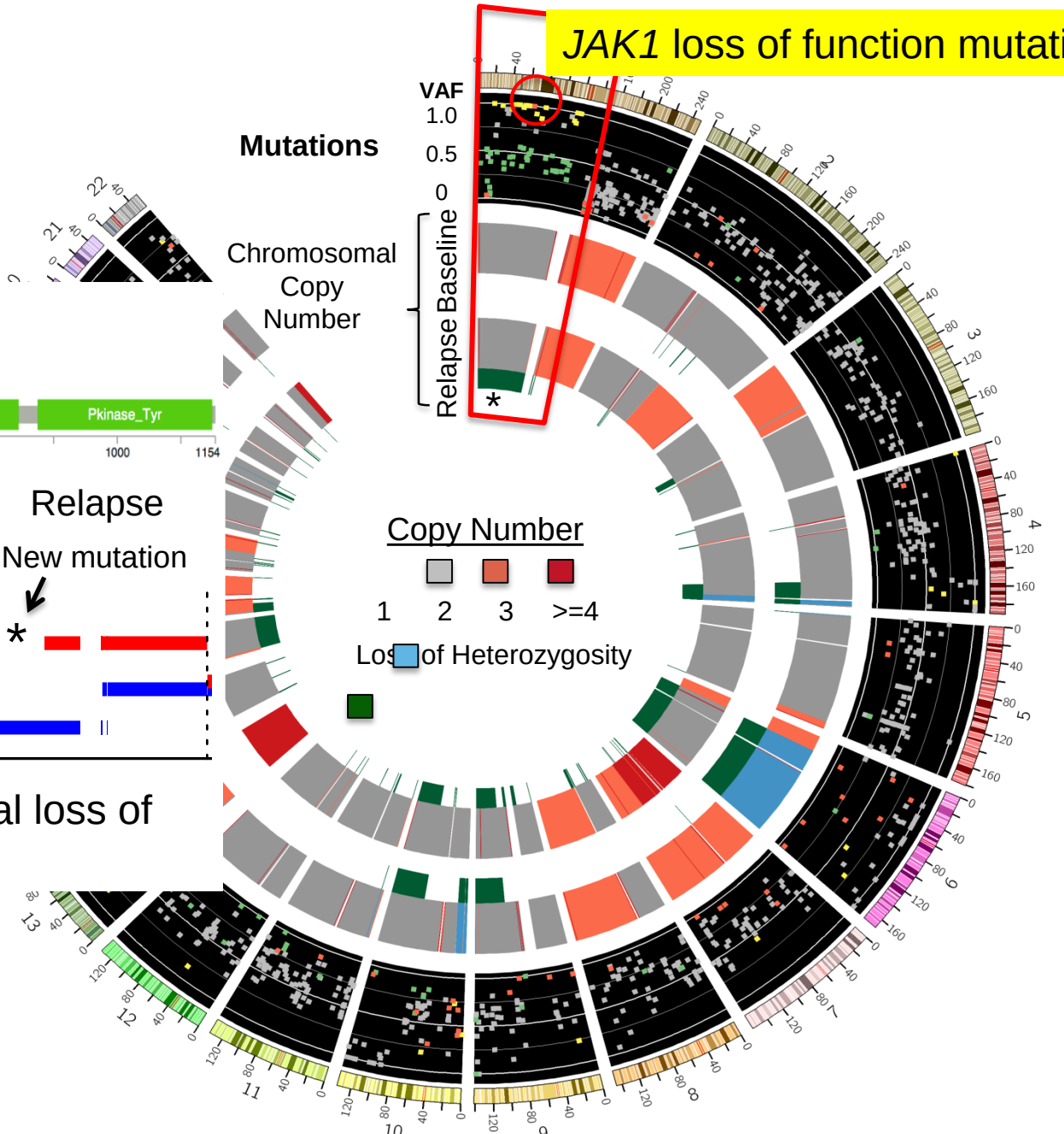
JAK1 disruption with cn-LOH as the only new and homozygous mutation in the relapsed metastasis

Case #1





Cn-LOH: copy number neutral loss of heterozygosity



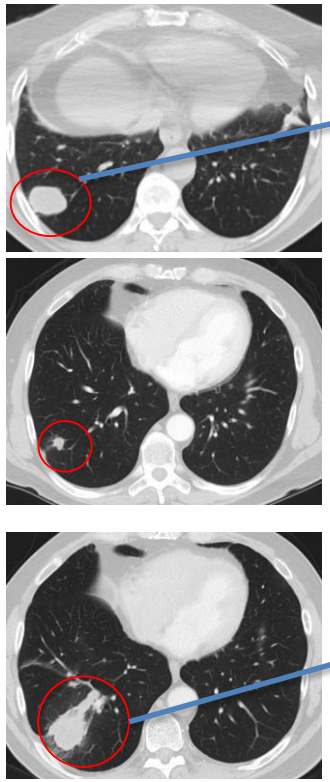
1073 Total baseline non-synonymous mutations

- 92.5% Shared btw baseline and relapse
- 87 Lost or subclonal (baseline-only)
- 53 New (relapse-only)

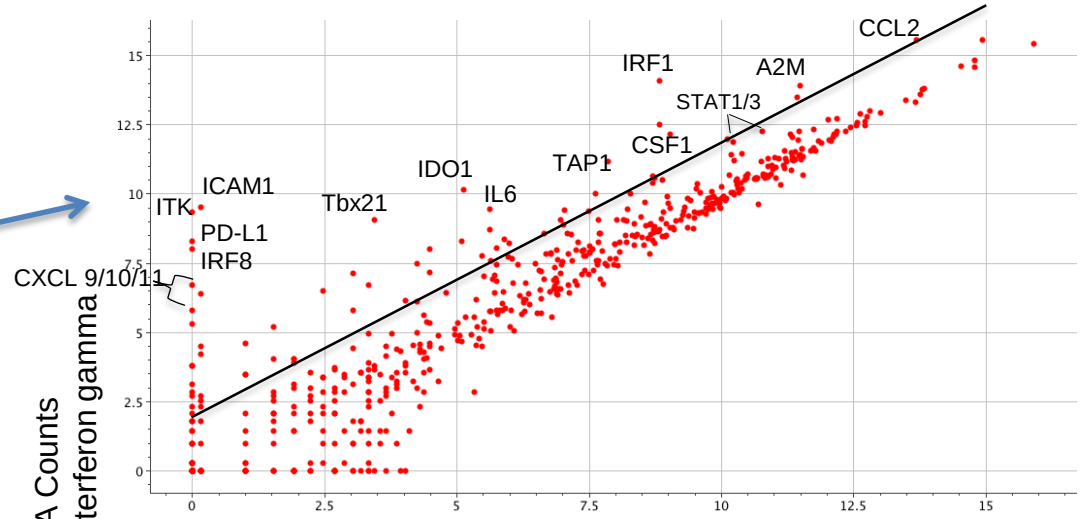
Jesse Zaretsky
UCLA MSTP

Loss of IFN-g transcriptional induction with *JAK2* LoF

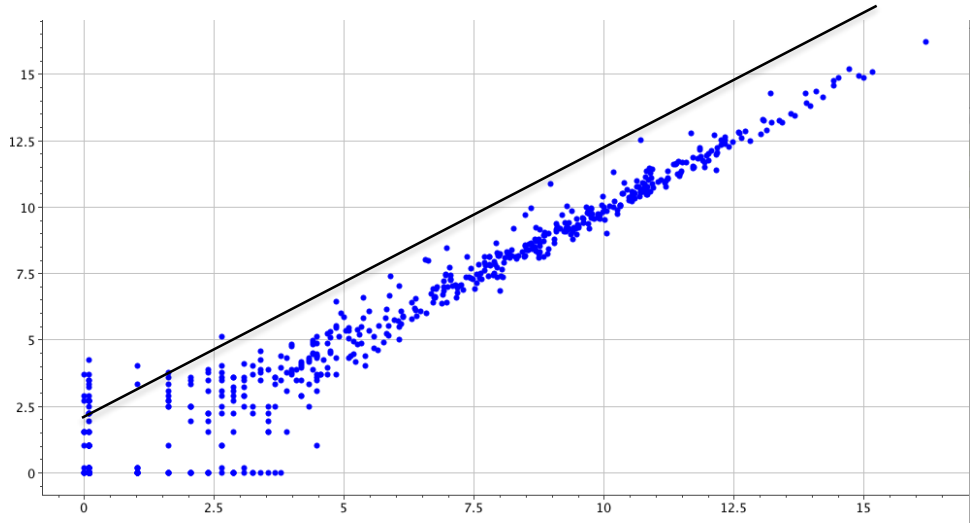
Case #2



Baseline cell line (M420)

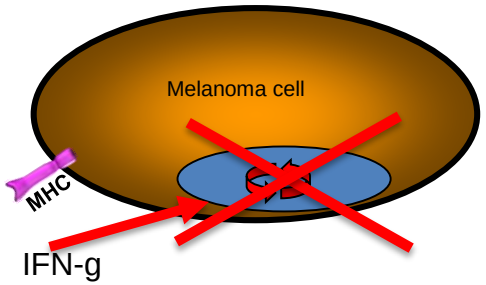


Acquired resistance cell line (M464)

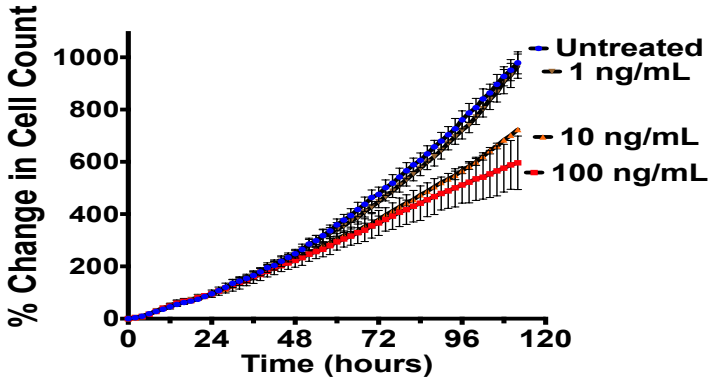


Angel Garcia-Diaz, PhD

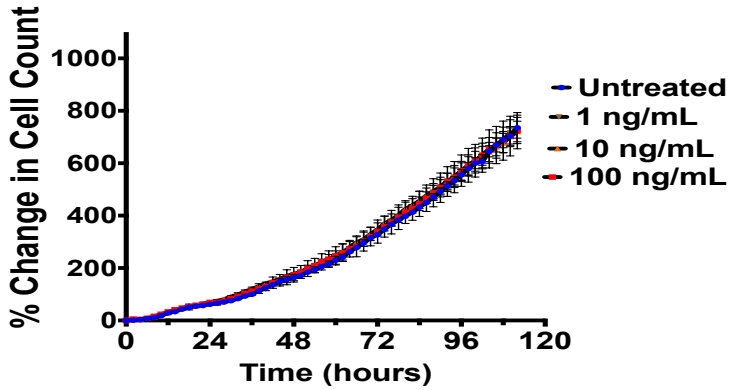
T cell recognition resistance to IFN-g-induced growth arrest with JAK2 KO



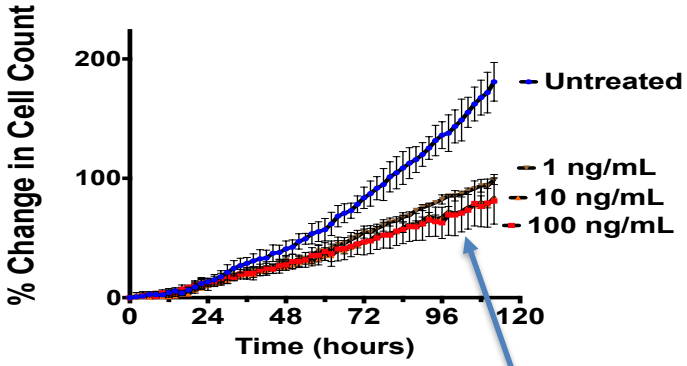
M407



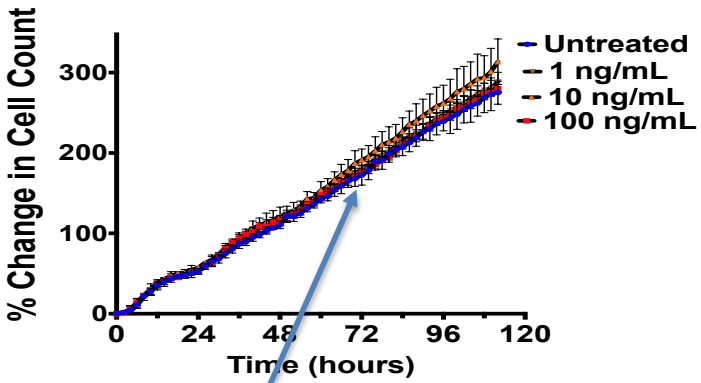
M407 JAK2 K.O



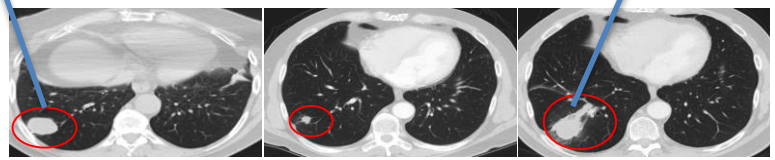
Baseline (M420)



Relapse (M464)

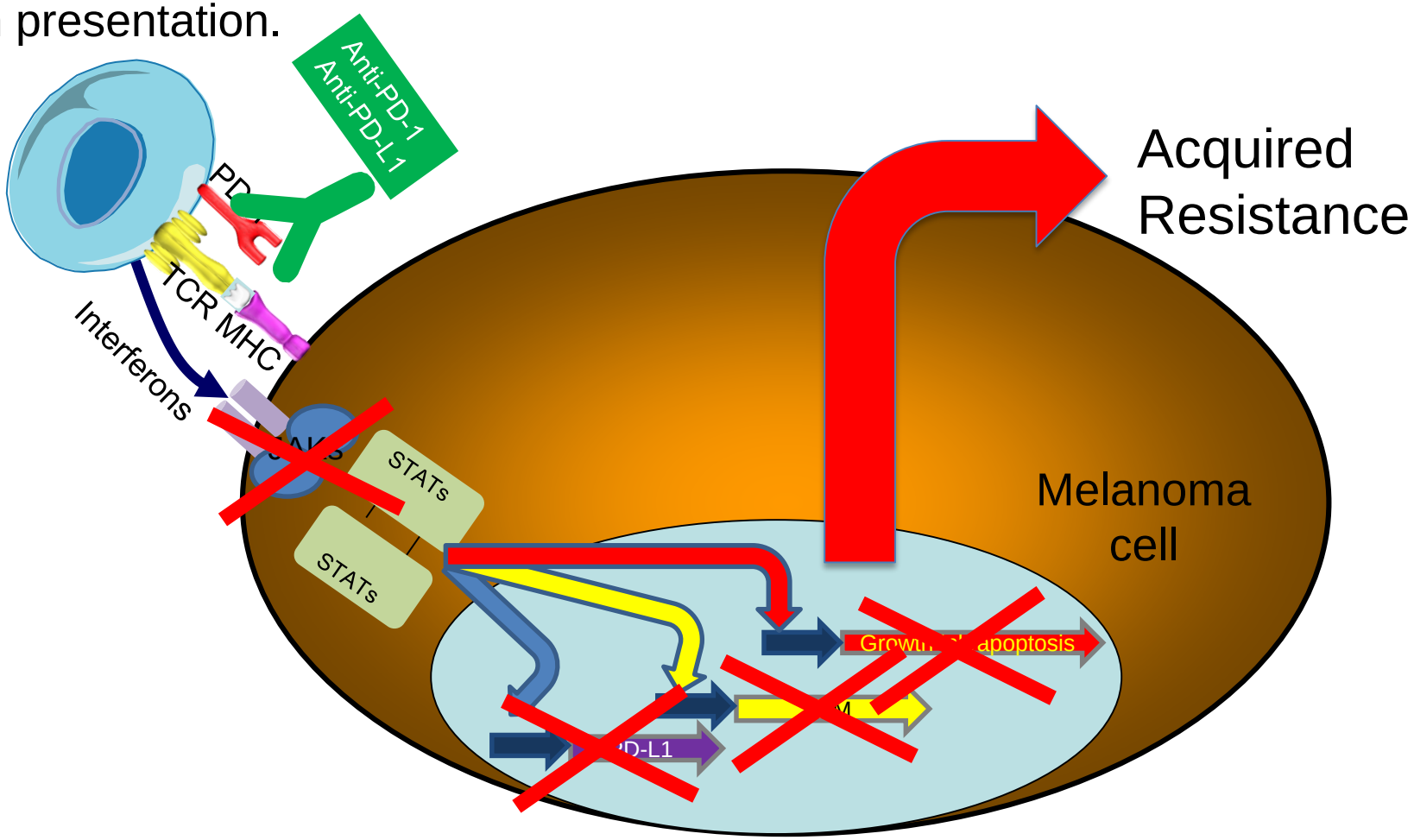


Case #2

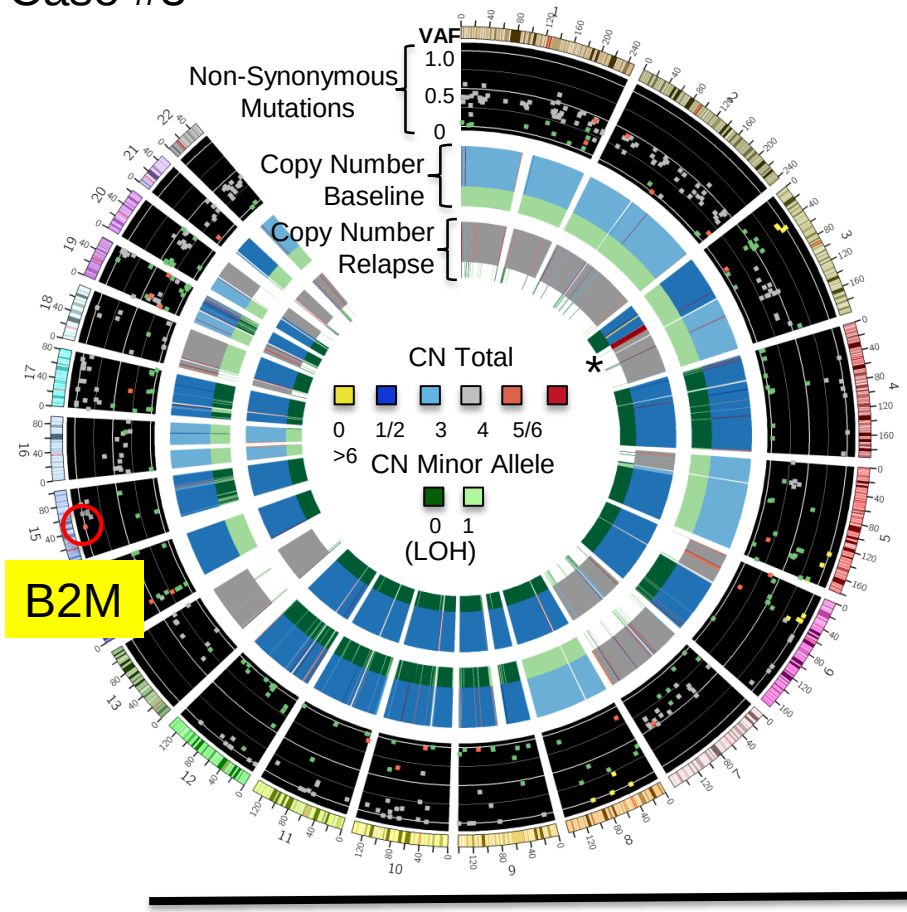


Interferon-gamma Sensitivity Model:

- Initially, benefits of PD-L1 suppression outweigh immune sensitizing effects.
- PD-L1 expression is of no benefit after PD-1/L1 blockade; selective pressure is *flipped*.
- The cancer has an incentive to lose INF-γ sensitivity, avoid apoptosis, enhanced antigen presentation.



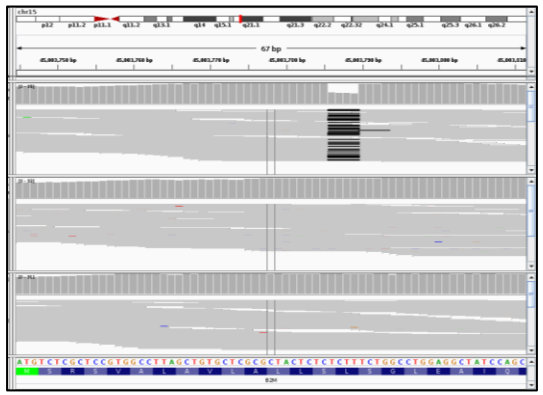
Case #3



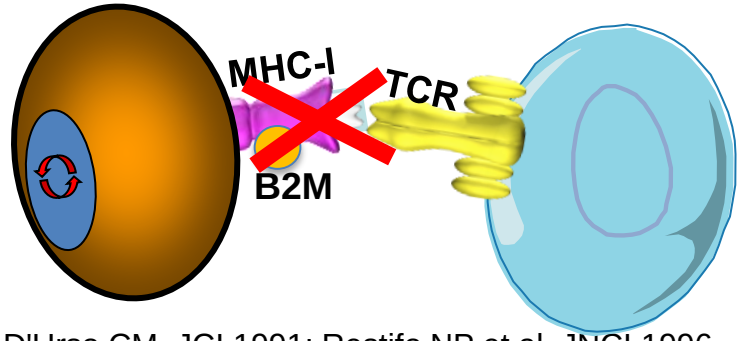
Relapse

Baseline (M437)

Normal



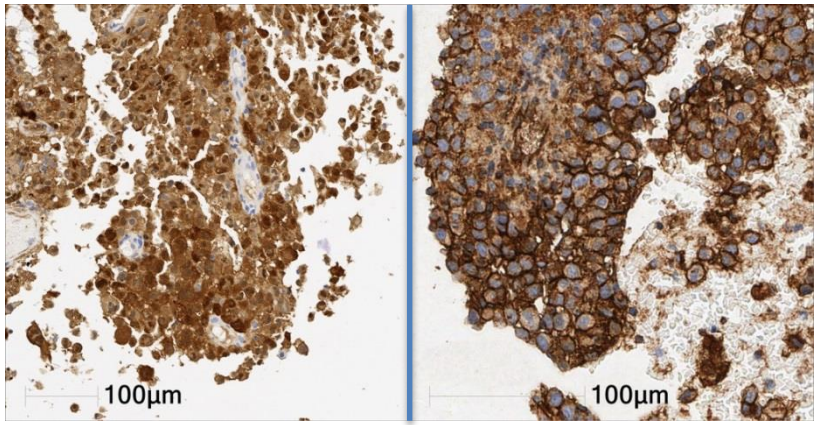
Zaretsky et al. NEJM 2016



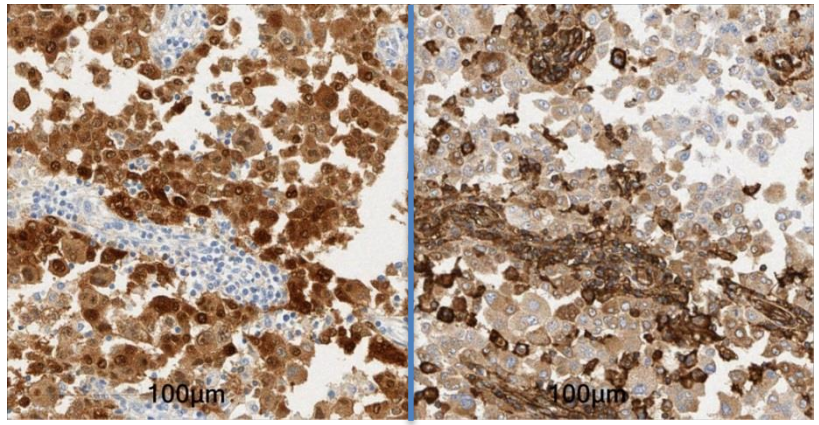
D'Urso CM, JCI 1991; Restifo NP et al. JNCI 1996

S100 MHC Class I

Baseline



Relapse



B2M cn-LOH in resistance to PD-1 blockade therapy

nature COMMUNICATIONS

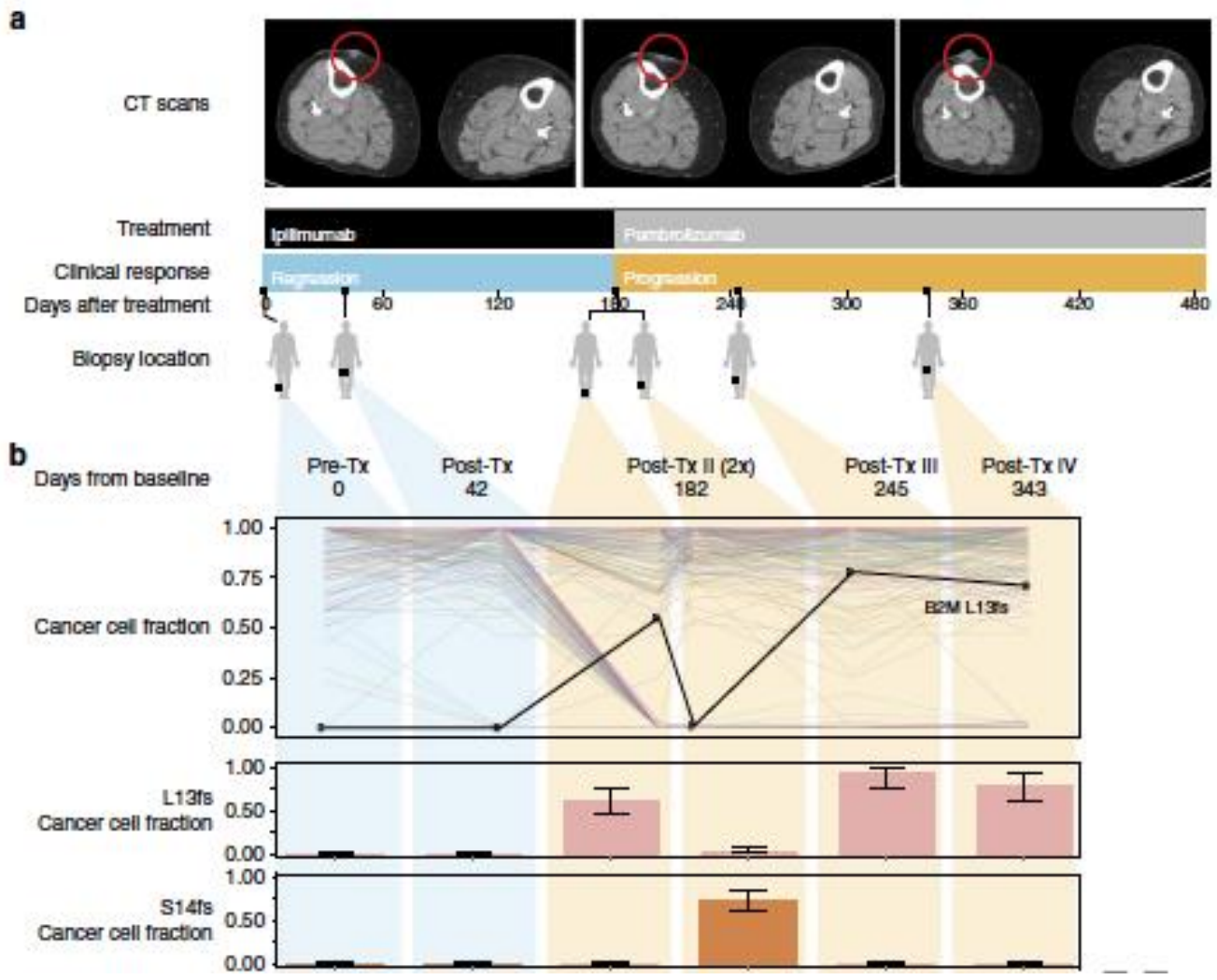
ARTICLE

DOI: 10.1038/s41467-017-01062-w OPEN

Resistance to checkpoint blockade therapy through inactivation of antigen presentation

Moshe Sade-Feldman[1,2], Yunxin J. Jiao[2,3], Jonathan H. Chen[2,4], Michael S. Rooney[2], Michal Barzily-Rokni[1], Jean-Pierre Eliane[4], Stacey L. Bjorgaard[1,2], Marc R. Hammond[1], Hans Vitzthum[1], Shauna M. Blackmon[1], Dennie T. Frederick[1], Mehlika Hazar-Rethinam[1], Brandon A. Nadres[1], Emily E. Van Seventer[1], Sachet A. Shukla[2,5], Keren Yizhak[2], John P. Ray[2], Daniel Rosebrock[2], Dimitri Livitz[2], Viktor Adalsteinsson[2], Gad Getz[2,4], Lyn M. Duncan[4], Bo Li[6], Ryan B. Corcoran[1], Donald P. Lawrence[1], Anat Stemmer-Rachamimov[4], Genevieve M. Boland[7], Dan A. Landau[2,8,9], Keith T. Flaherty[1], Ryan J. Sullivan[1] & Nir Hacohen[1,2]

NATURE COMMUNICATIONS | 8: 1136 | DOI: 10.1038/s41467-017-01062-w | www.nature.com/naturecommunications



B2M cn-LOH in resistance to PD-1 blockade therapy

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ARTICLE

DOI: 10.1038/s41467-017-01062-w OPEN

Resistance to checkpoint blockade therapy through inactivation of antigen presentation

Moshe Sade-Feldman[1,2], Yunxin J. Jiao[2,3], Jonathan H. Chen[2,4], Michael S. Rooney[2], Michal Barzily-Rokni[1], Jean-Pierre Eliane[4], Stacey L. Bjorgaard[1,2], Marc R. Hammond[1], Hans Vitzthum[1], Shauna M. Blackmon[1], Dennie T. Frederick[1], Mehlika Hazar-Rethinam[1], Brandon A. Nadres[1], Emily E. Van Seventer[1], Sachet A. Shukla[2,5], Keren Yizhak[2], John P. Ray[2], Daniel Rosebrock[2], Dimitri Livitz[2], Viktor Adalsteinsson[2], Gad Getz[2,4], Lyn M. Duncan[4], Bo Li[6], Ryan B. Corcoran[1], Donald P. Lawrence[1], Anat Stemmer-Rachamimov[4], Genevieve M. Boland[7], Dan A. Landau[2,8,9], Keith T. Flaherty[1], Ryan J. Sullivan[1] & Nir Hacohen[1,2]

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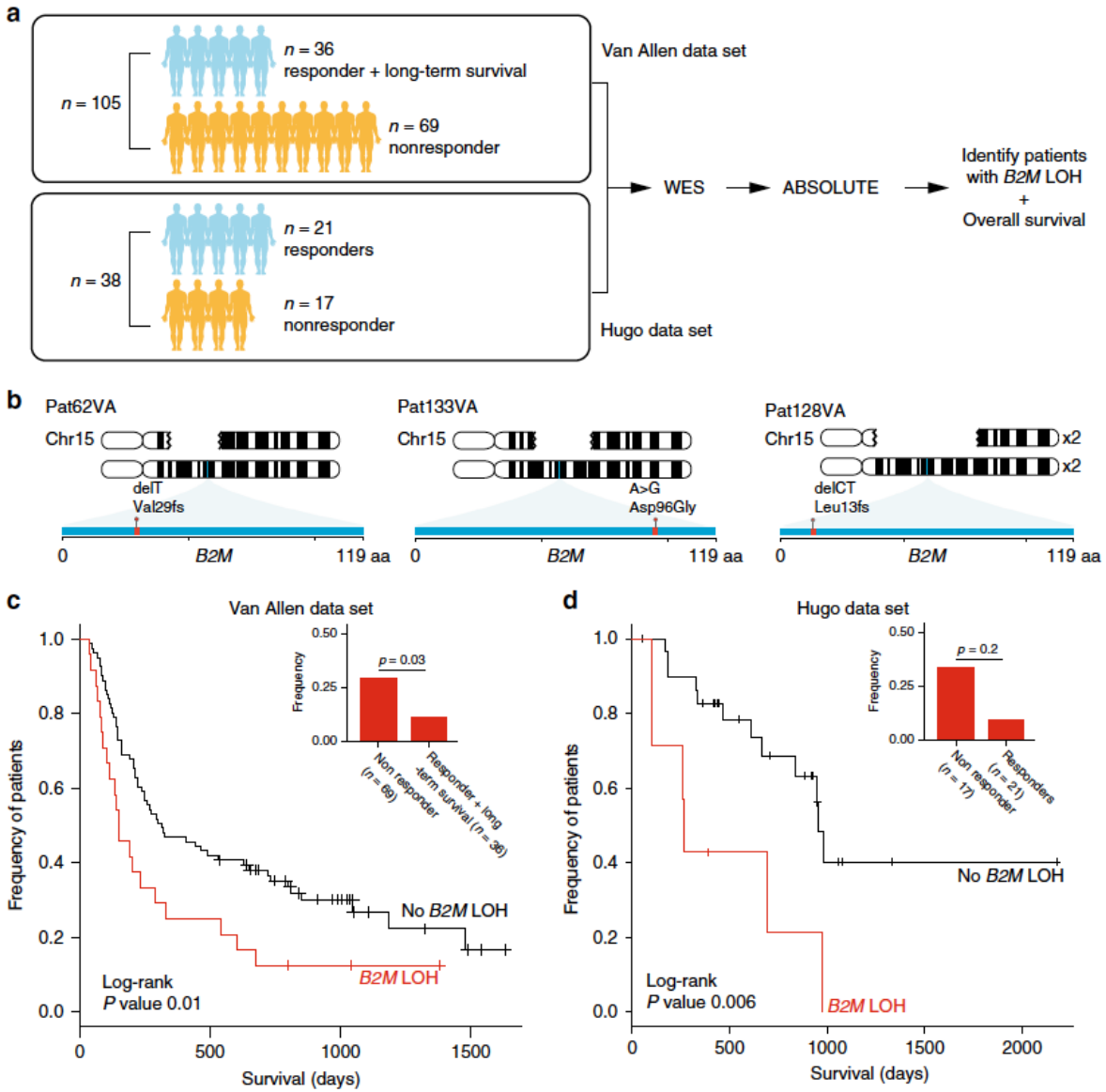
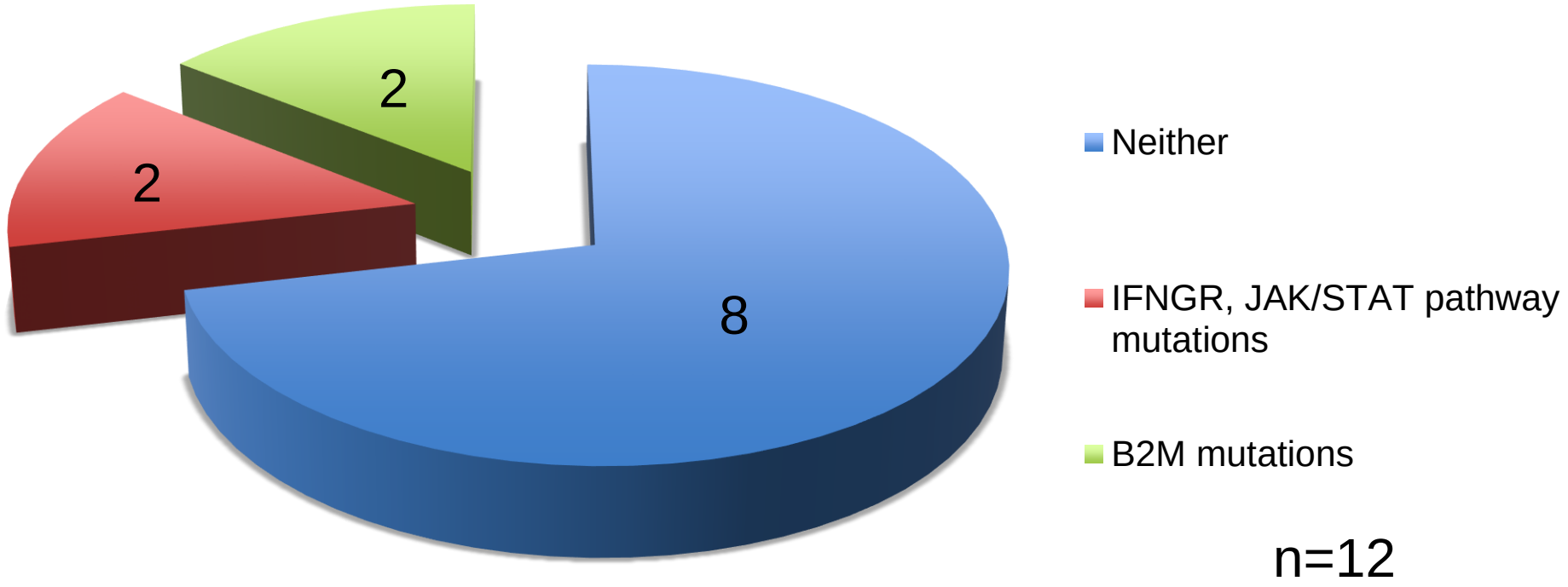


How prevalent are *JAK* and *B2M* loss-of-function mutations In patients with PD-1 blockade acquired resistance?



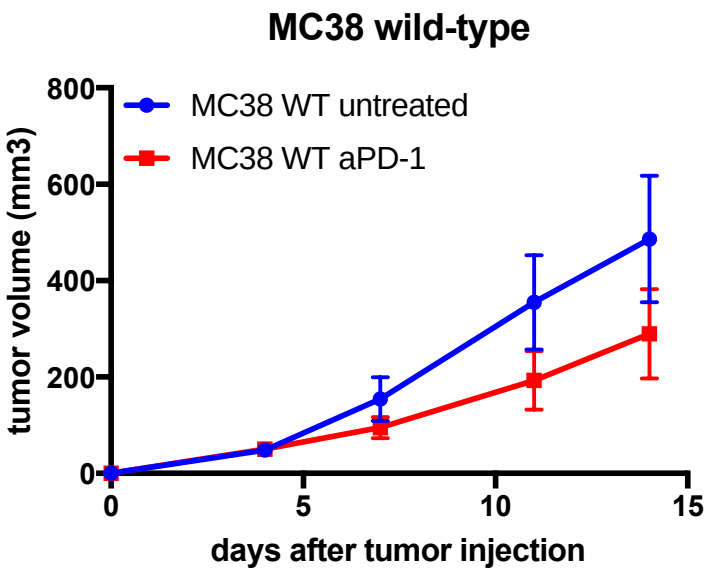
n=12

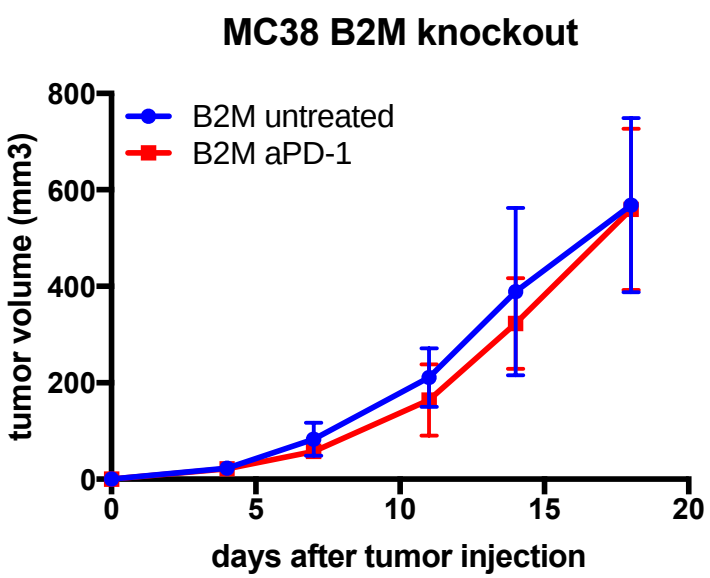
In 8 additional paired biopsies:

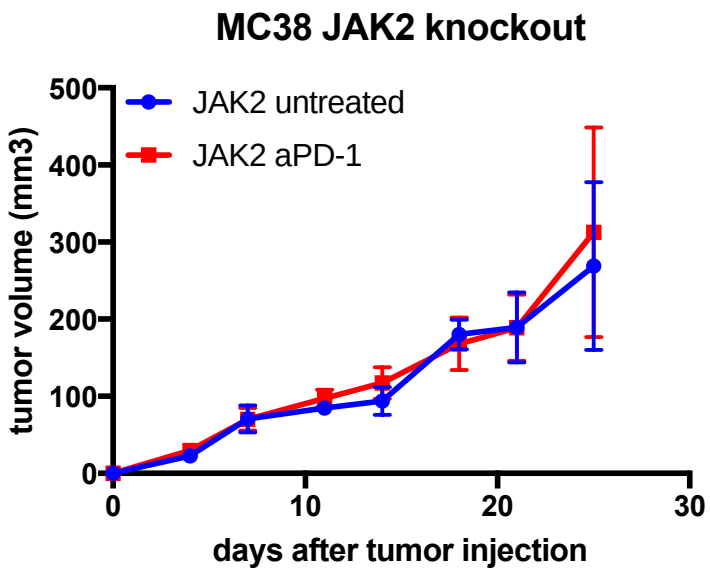
- One additional *B2M* LoF mutation
- No additional *JAK1/2, IFNGR, IRF1* or *STAT1/3/5* LoF mutations

Jesse Zaretsky, Antoni Ribas (unpublished)

Confirmation of *B2M* and *JAK* as genetic mechanisms of resistance to anti-PD-1 using CRISPR/Cas9 knock out sublines







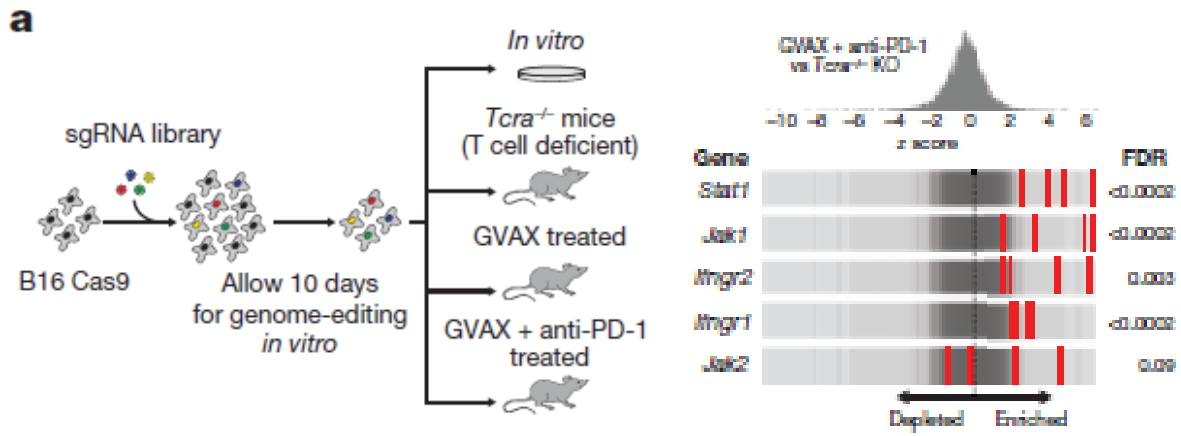
Davis Torrejon, Gabriel Abril Rodriguez, Siwen Hu-Lieskovan (unpublished)

doi:10.1038/nature23270

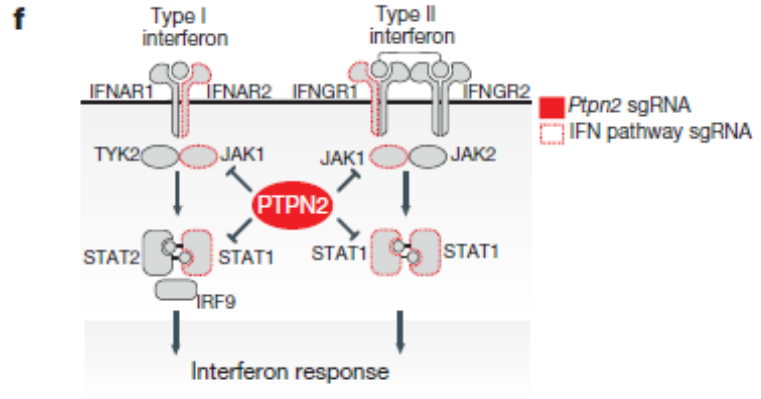
In vivo CRISPR screening identifies *Ptpn2* as a cancer immunotherapy target

Robert T. Manguso[1,2,3], Hans W. Pope[1,3], Margaret D. Zimmer[1,3], Flavian D. Brown[1,2], Kathleen B. Yates[1,3], Brian C. Miller[1,3,4], Natalie B. Collins[1,3,5], Kevin Bi[1,3], Martin W. LaFleur[1,2], Vikram R. Juneja[6], Sarah A. Weiss[1], Jennifer Lo[7], David E. Fisher[7], Diana Miao[2,3], Eliezer Van Allen[2,3], David E. Root[3], Arlene H. Sharpe[5,8], John G. Doench[3] & W. Nicholas Haining[1,3,5]

Defects in the IFNγ pathway induce resistance



Loss of *Ptpn2* increases IFNγ sensing by tumour cells

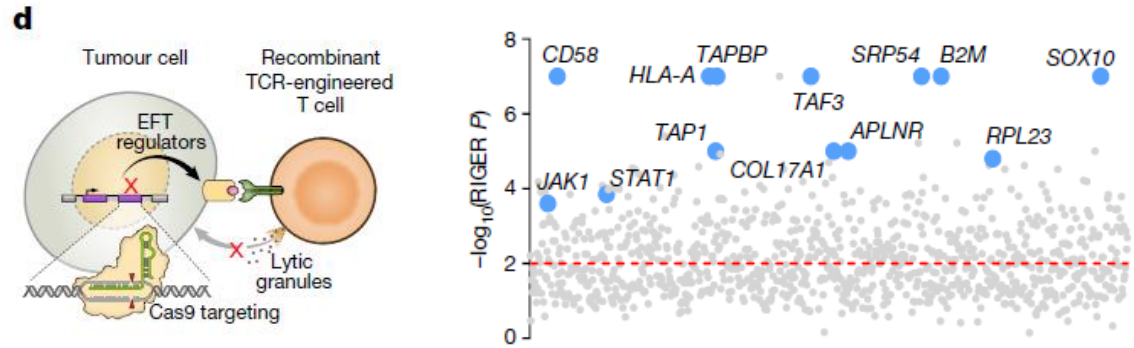


doi:10.1038/nature23477

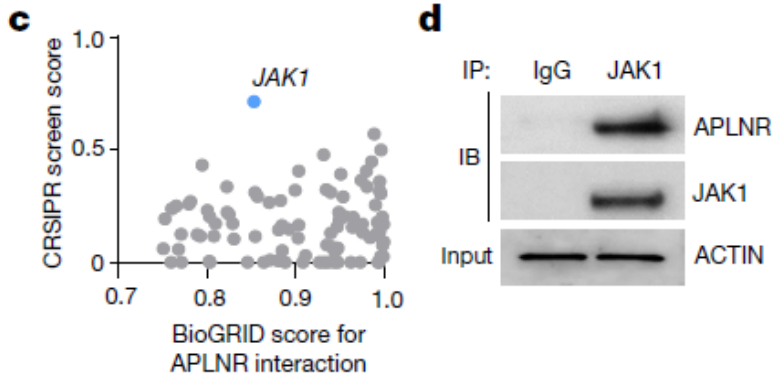
Identification of essential genes for cancer immunotherapy

Shashank J. Patel[1,2]*, Neville E. Sanjana[3,4]*, Rigel J. Kishton[1], Arash Eidizadeh[1], Suman K. Vodnala[1], Maggie Cam[1], Jared J. Gartner[1], Li Jia[1], Seth M. Steinberg[1], Tori N. Yamamoto[1,5], Anand S. Merchant[1], Gautam U. Mehta[1], Anna Chichura[1], Ophir Shalem[6], Eric Tran[1], Robert Eil[1], Madhusudhanan Sukumar[1], Eva Perez Guijarro[1], Chi-Ping Day[1], Paul Robbins[1], Steve Feldman[1], Glenn Merlino[1], Feng Zhang[7,8] & Nicholas P. Restifo[1,9]

Genome-wide CRISPR mutagenesis reveals essential genes for the effector function of T cells in a target cell.



Functional loss of APLNR reduces efficacy of cancer Immunotherapy, which IPs with JAK1



Conclusions

- Inhibiting adaptive immune resistance is the mechanistic basis of the antitumor activity of PD-1 blockade therapies
- Combination therapies aimed at increasing T cell infiltration in tumors may improve the antitumor activity of PD-1 blockade
- Loss of function mutations in IFN-gamma receptor signaling or antigen presenting machinery mediate some cases of primary resistance and acquired resistance to PD-1 blockade therapy

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P01 CA168585 (Ribas)
P01 CA132681 (Baltimore)
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R01 CA170689 (Heath-Ribas)

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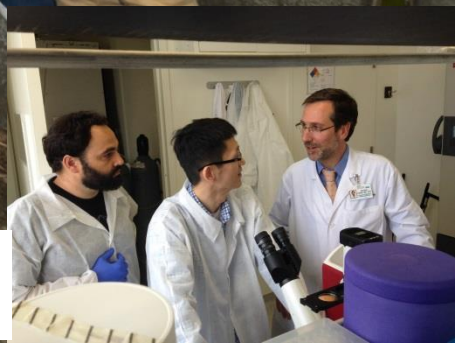
Siwen Hu-Lieskovan, MD, PhD



Angel Garcia Diaz, PhD
Daniel Shin, MD