sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

What's Next for Cancer Immunotherapy?

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Disclosures

- Research Grants: TEVA Pharmaceuticals
- Patents: Targeting the Cell Stress Response for Cancer Immunotherapy (Full under review)
- I will be discussing non-FDA approved indications during my presentation.

Outline: What's next for Cancer Immunotherapy?

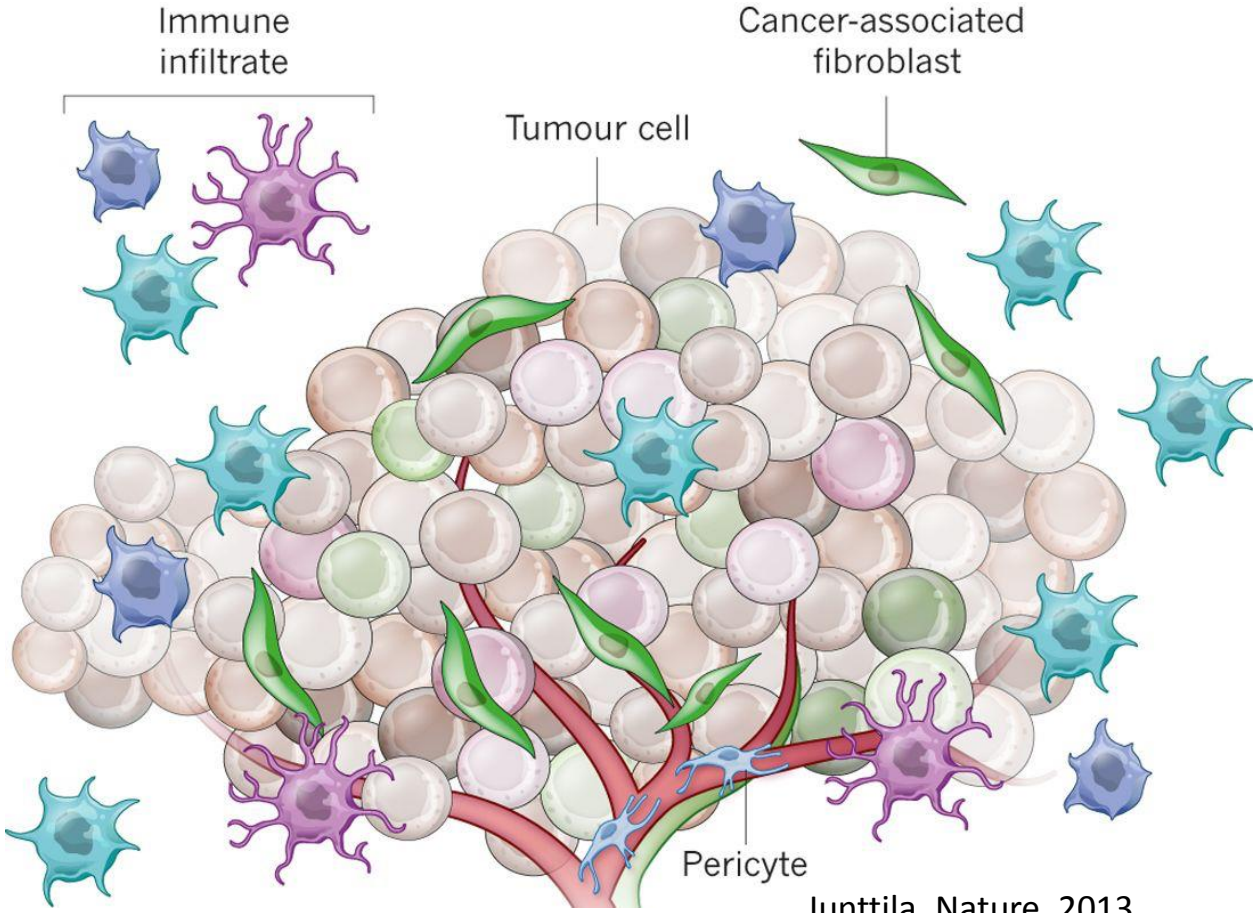
- Emerging concepts at the bench
  - *How can we enhance the power of immunotherapy?*
  - *Harnessing the cell response to stress and priming anti-tumor metabolism*

- Emerging concepts in the clinic
  - *When is it safe to stop immunotherapy?*
  - *Emergence of cessation clinical trials*

Klapper et al. Cancer 2008

Improving the Efficacy of Therapy:
Overcoming Barriers Immune Cells Face in Tumors

Immune Cells In The Tumor Microenvironment



Junttila, Nature, 2013

Hostile Conditions:

Nutrient Deprivation
- **Low Glucose**
- **Amino Acid Starvation**
- **Etc.**

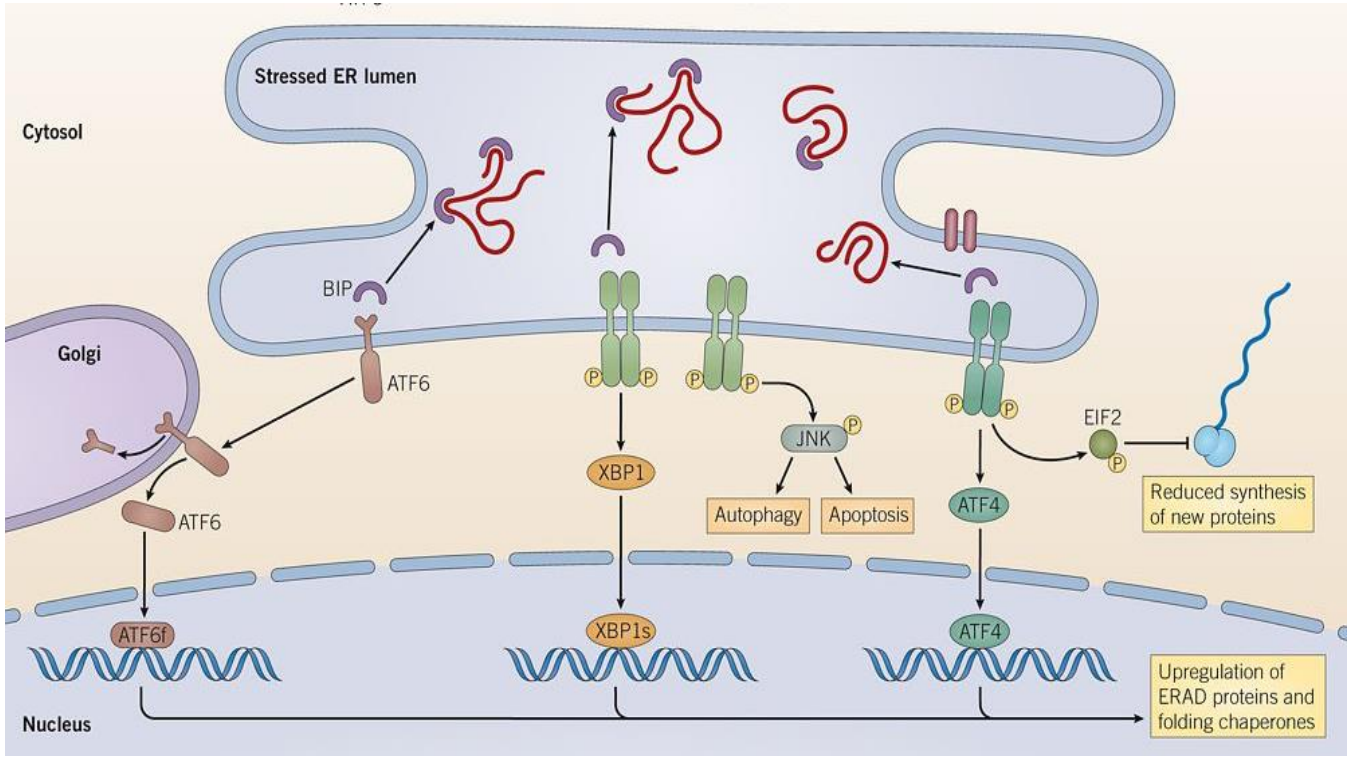
Pockets of Low O_2 (Hypoxia)

Acidity

Reactive Oxygen Species

Improving the Efficacy of Therapy:
Overcoming Barriers Immune Cells Face in Tumors

Immune Cells: Stressed Out in the Tumor Microenvironment



Cells Respond to Environmental/ Physical Stress through Signaling in the Endoplasmic Reticulum (ER)

The stress response is controlled by three stress sensors that mediate

- **Basic Cell Functions**
- **Cell Metabolism**
- **Cell Death**

Adapted: https://www.tocris.com/cell-biology/er-stress-upr

Improving the Efficacy of Therapy:
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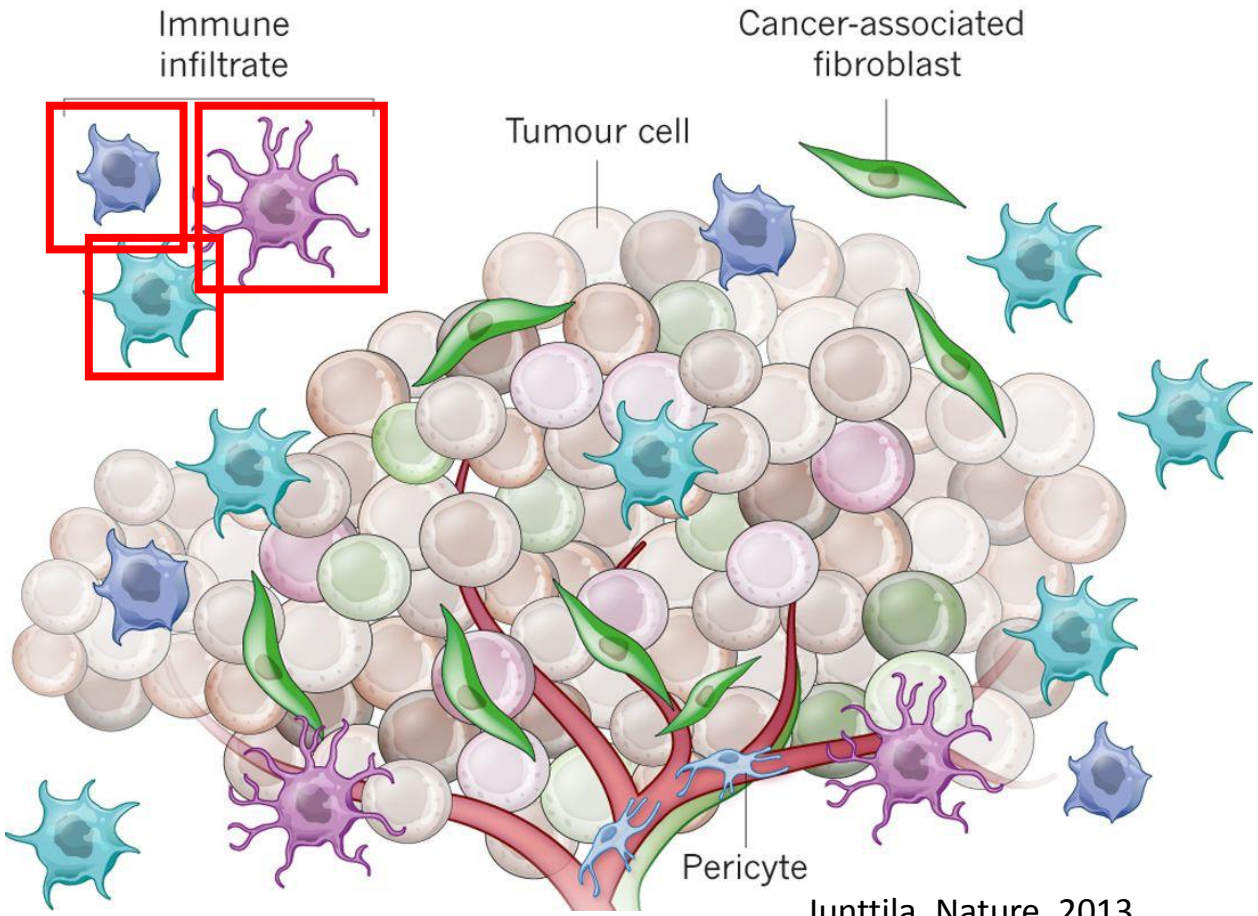
Immune Cells: Stressed Out in the Tumor Microenvironment



Junttila, Nature, 2013

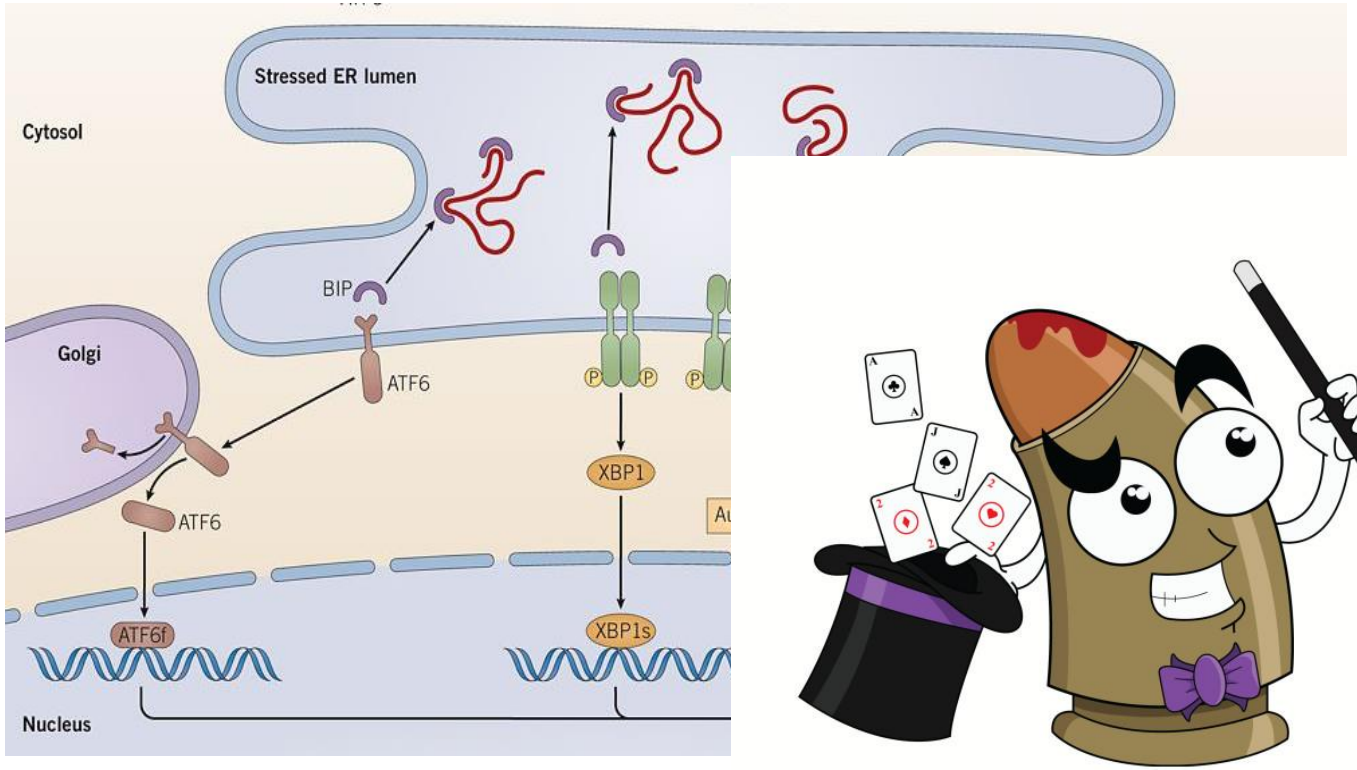
Dendritic Cells: Tumor Antigen Presentation to T Cells

T Cells: Metabolism (ATP for therapeutic response) is Repressed in Environment of Tumors

Myeloid Derived Suppressor Cells (MDSCs): Repress Anti-Tumor Immunity through Secretion of Suppressive Factors in Tumor

Improving the Efficacy of Therapy: *Overcoming Barriers Immune Cells Face in Tumors*

Targeting the Cell Response to Stress: *Is This is A Magic Bullet?*



Targeting the Cell Response to Stress:

- **Restrict Tumor Cell Growth**

(Tameire, Nature Cell Biology, 2019)

- **Restore Dendritic Cell Basic Function in Tumors**

(Cubillos-Ruiz, Cell, 2016)

- **Enhance Efficacy of T Cells**

(Hurst, Can Immunol Res, 2019)

- **Prohibit Myeloid Cell Suppression**

(Thevenot, Immunity, 2014)

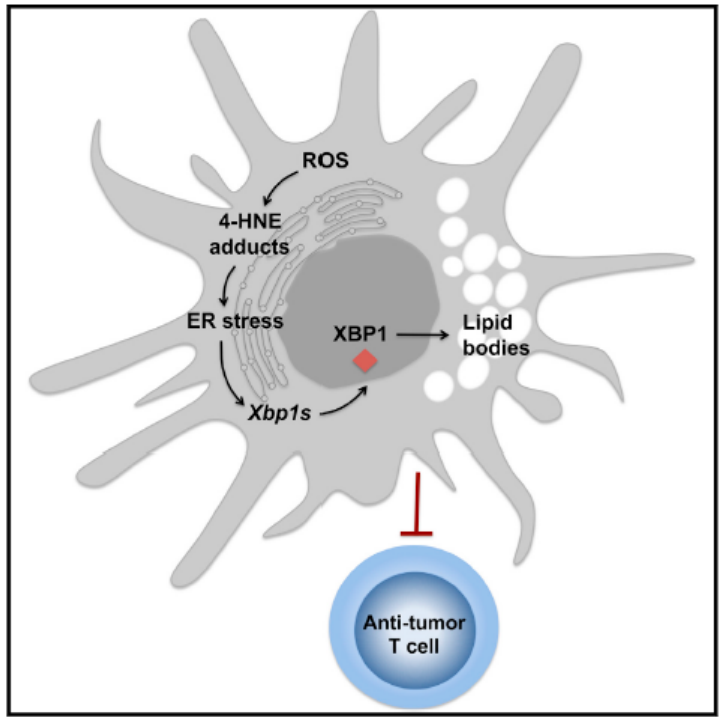
Improving the Efficacy of Therapy: *Overcoming Dendritic Cell Stress*

Article

Cell

ER Stress Sensor XBP1 Controls Anti-tumor Immunity by Disrupting Dendritic Cell Homeostasis

Graphical Abstract



Authors

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Correspondence

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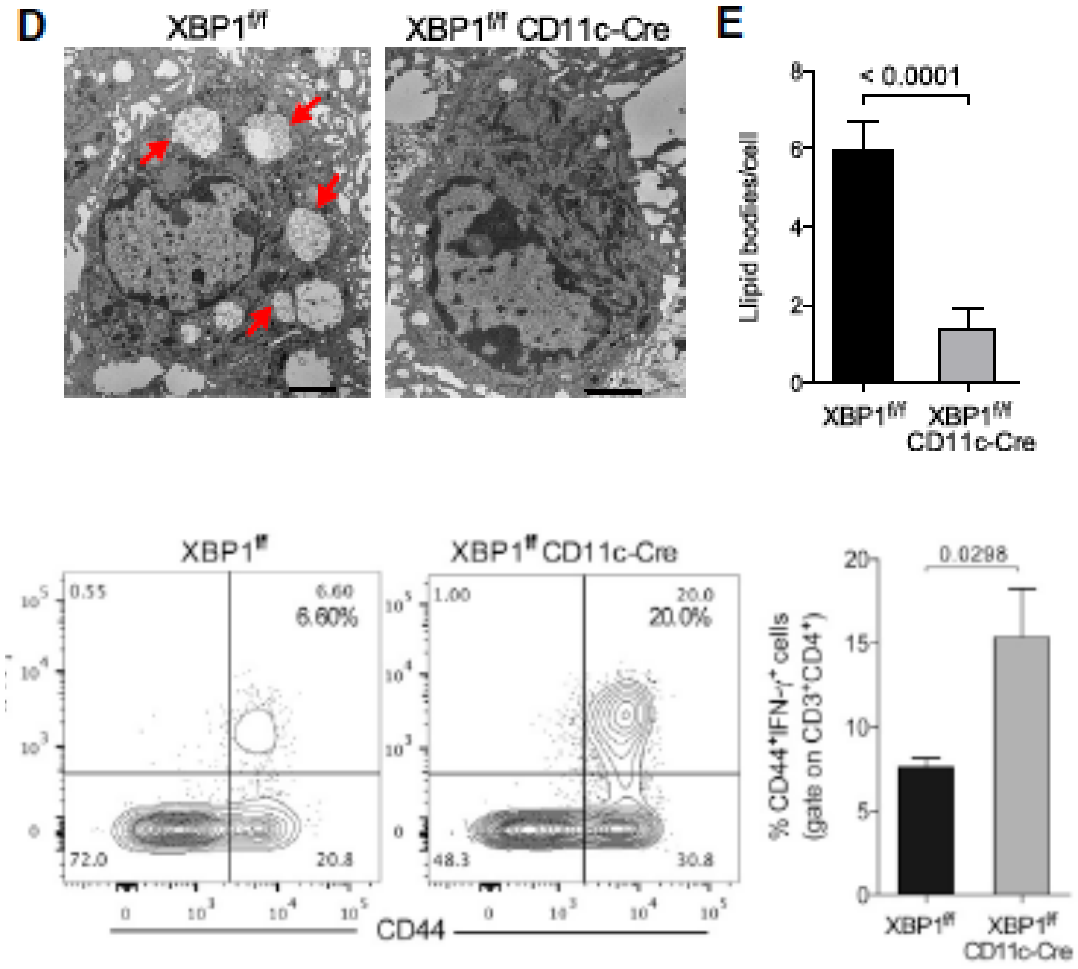
In Brief

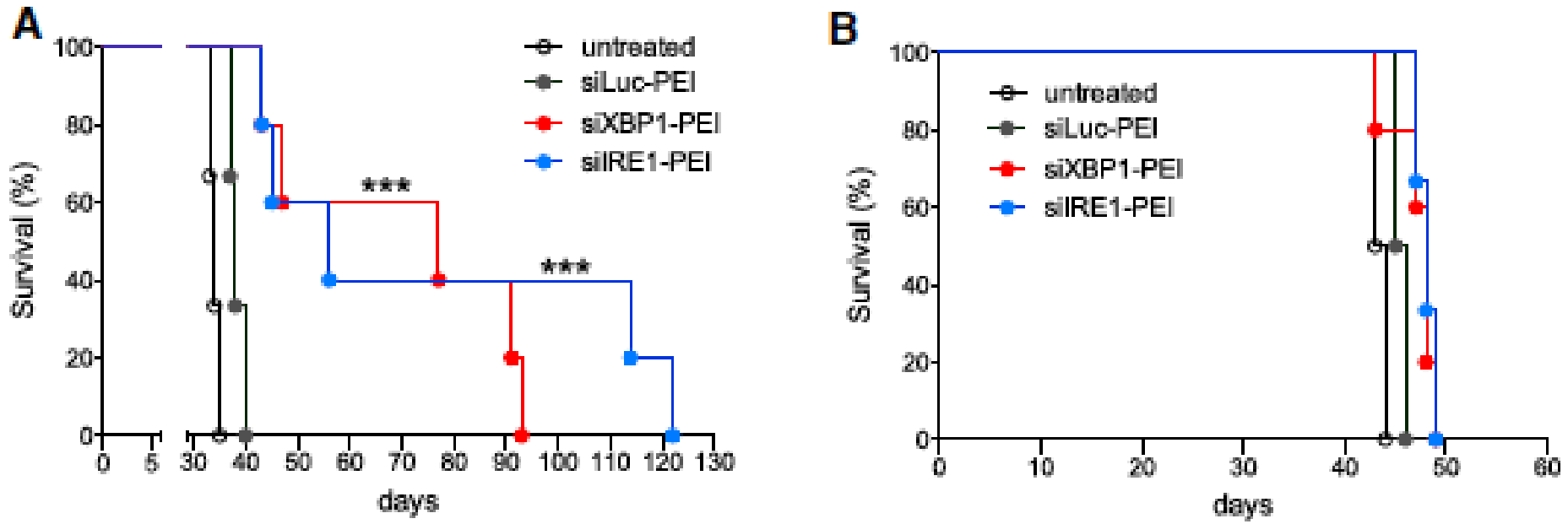
Aggressive tumors inhibit protective T cell responses by triggering ER stress-driven lipid metabolism in dendritic cells, thereby impairing antigen presentation and limiting the ability of the immune system to eliminate malignant cells. Relieving ER stress in immune cells may offer a new approach to cancer immunotherapy.

Highlights

Accession Numbers



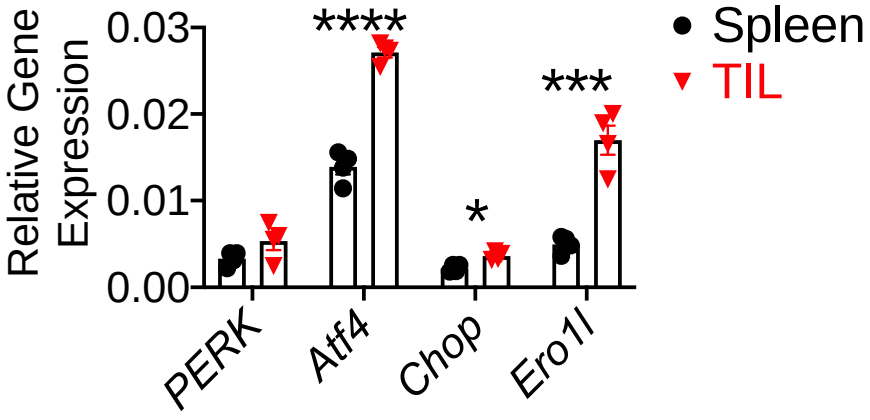
Improving the Efficacy of Therapy: *Overcoming Dendritic Cell Stress*



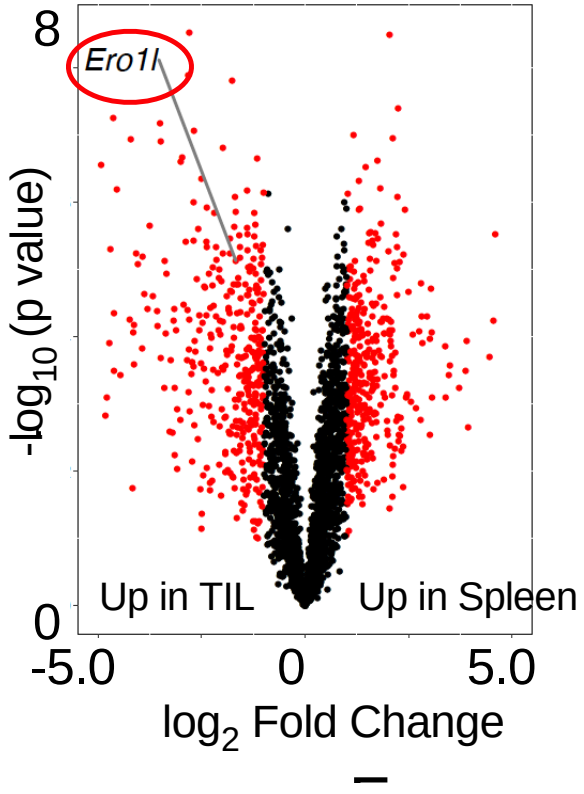
Cubillos-Ruiz, Cell 2016

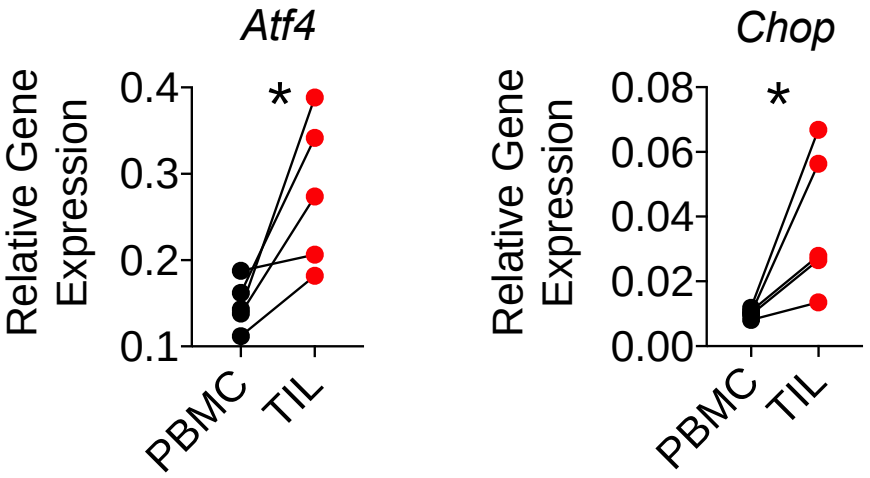
Alleviating the cell stress response repairs dysregulated dendritic cell antigen presentation and promotes T cell response in tumors

Improving the Efficacy of Therapy: *Overcoming T Cell Stress*



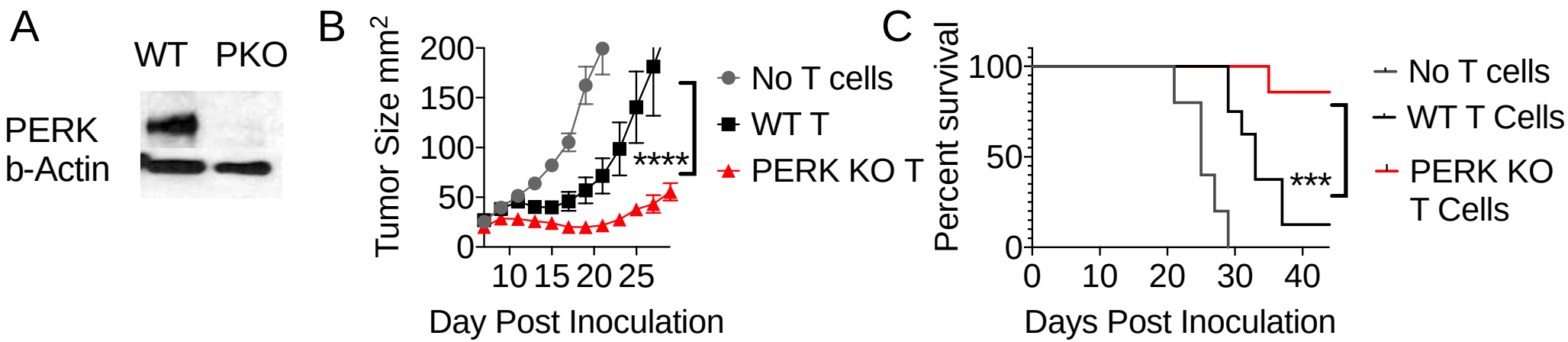
Hurst, Can Immunol Res, 2019





Unpublished Data, Thaxton Lab

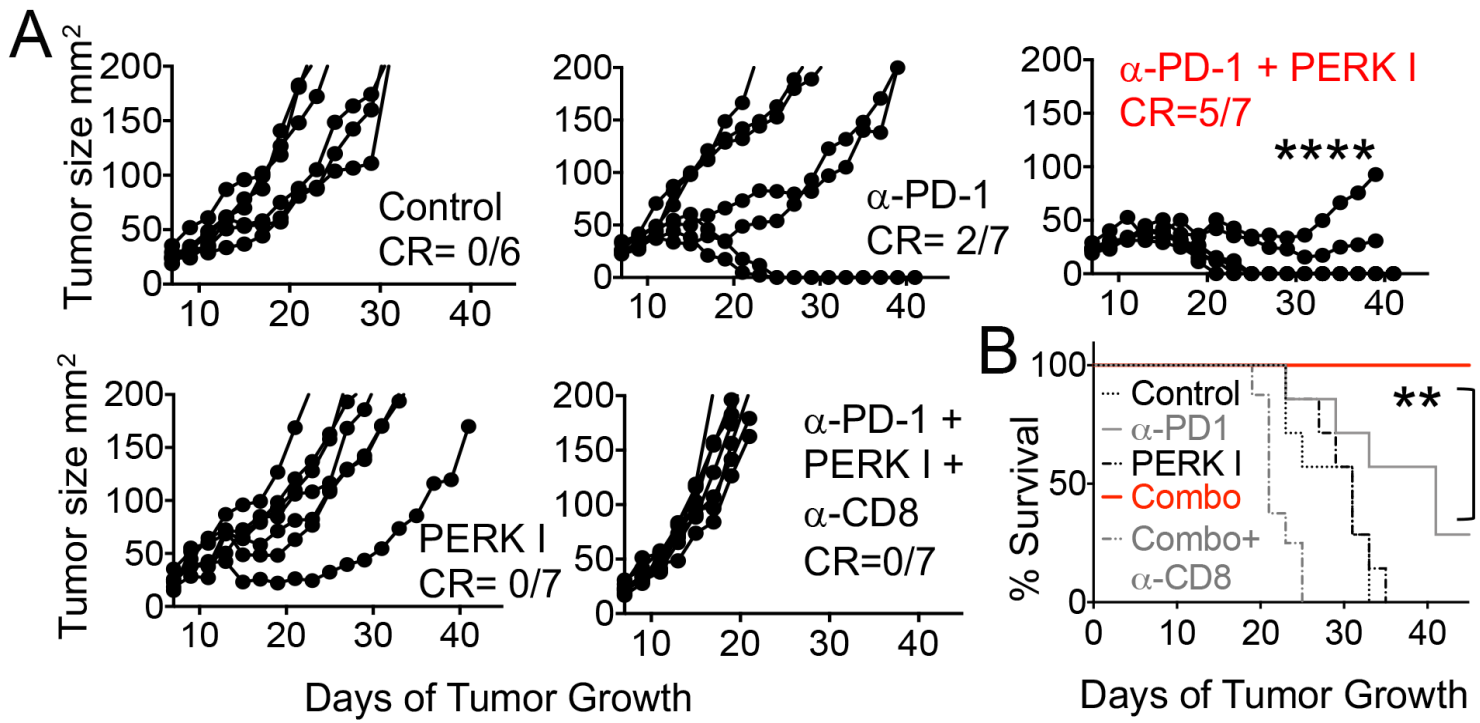
Improving the Efficacy of Therapy: *Overcoming T Cell Stress*



Hurst, Can Immunol Res, 2019

Alleviating the cell stress response promotes T cell tumor control

Improving the Efficacy of Therapy: *Overcoming T Cell Stress*



Hurst, Can Immunol Res, 2019

Alleviating the cell stress response promotes T cell tumor control

Improving the Efficacy of Therapy:
Overcoming Myeloid Suppression in Tumors

In multiple human tumor types, MDSC presence in peripheral blood predicts reduced survival

Immunity
Article

The Stress-Response Sensor Chop Regulates the Function and Accumulation of Myeloid-Derived Suppressor Cells in Tumors

Paul T. Thevenot,[1] Rosa A. Sierra,[1] Patrick L. Raber,[1,2] Amir A. Al-Khami,[1] Jimena Trillo-Tinoco,[1] Parisa Zarreii Augusto C. Ochoa,[1,3] Yan Cui,[1,2] Luis Del Valle,[1] and Paulo C. Rodriguez[1,2,*]
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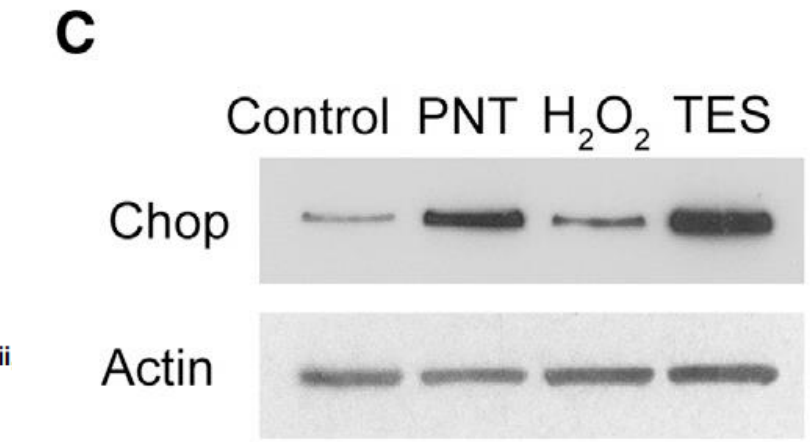
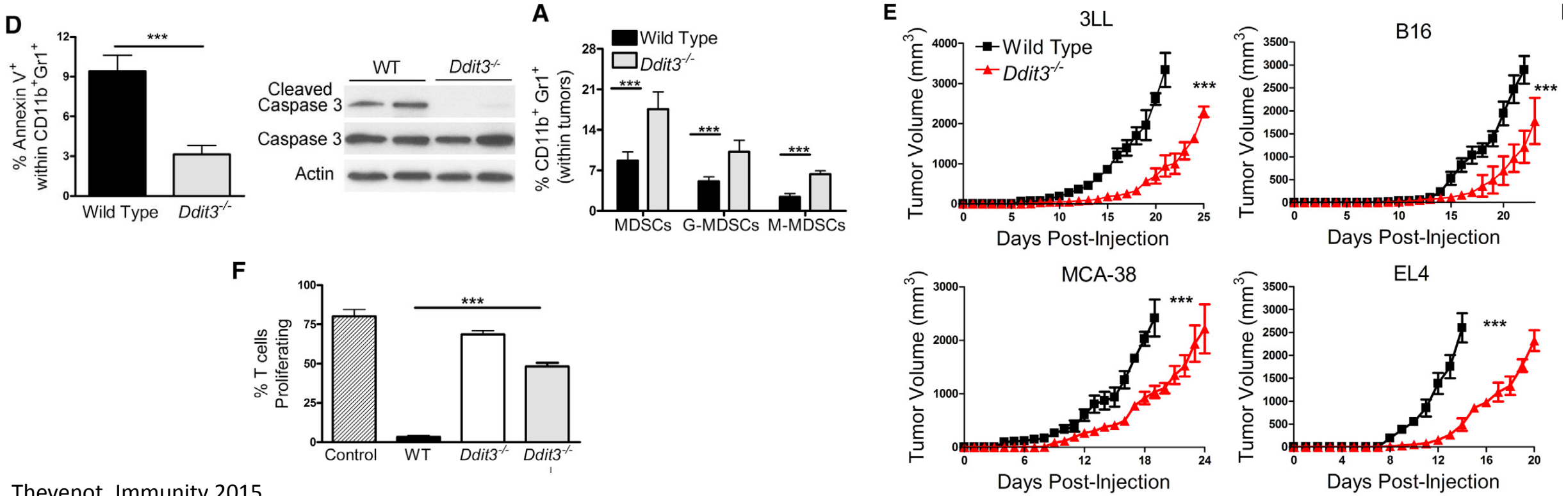
http://dx.doi.org/10.1016/j.immuni.2014.08.015



Improving the Efficacy of Therapy:
Overcoming Myeloid Suppression in Tumors



Thevenot, Immunity 2015

Inhibition of myeloid death by targeting the cell response to stress reduces myeloid cell suppressive capacity and increases tumor control

Improving the Efficacy of Therapy:
Targeting The Stress Response in Tumors

Summary

Targeting the Cell Response to Stress is a Unique Strategy to Globally:

Restore Dendritic Cell Antigen Presentation in Tumors

Enhance T Cell Mediated Tumor Control

Prohibit Intratumoral Immune Suppression by Myeloid Cells

Restrict Tumor Cell Growth

Powering Immunotherapy: What happens when the bench works? *Looking to the Future*

- Emerging concepts in the clinic
  - *When is it safe to stop immunotherapy?*
  - *Emergence of cessation clinical trials*

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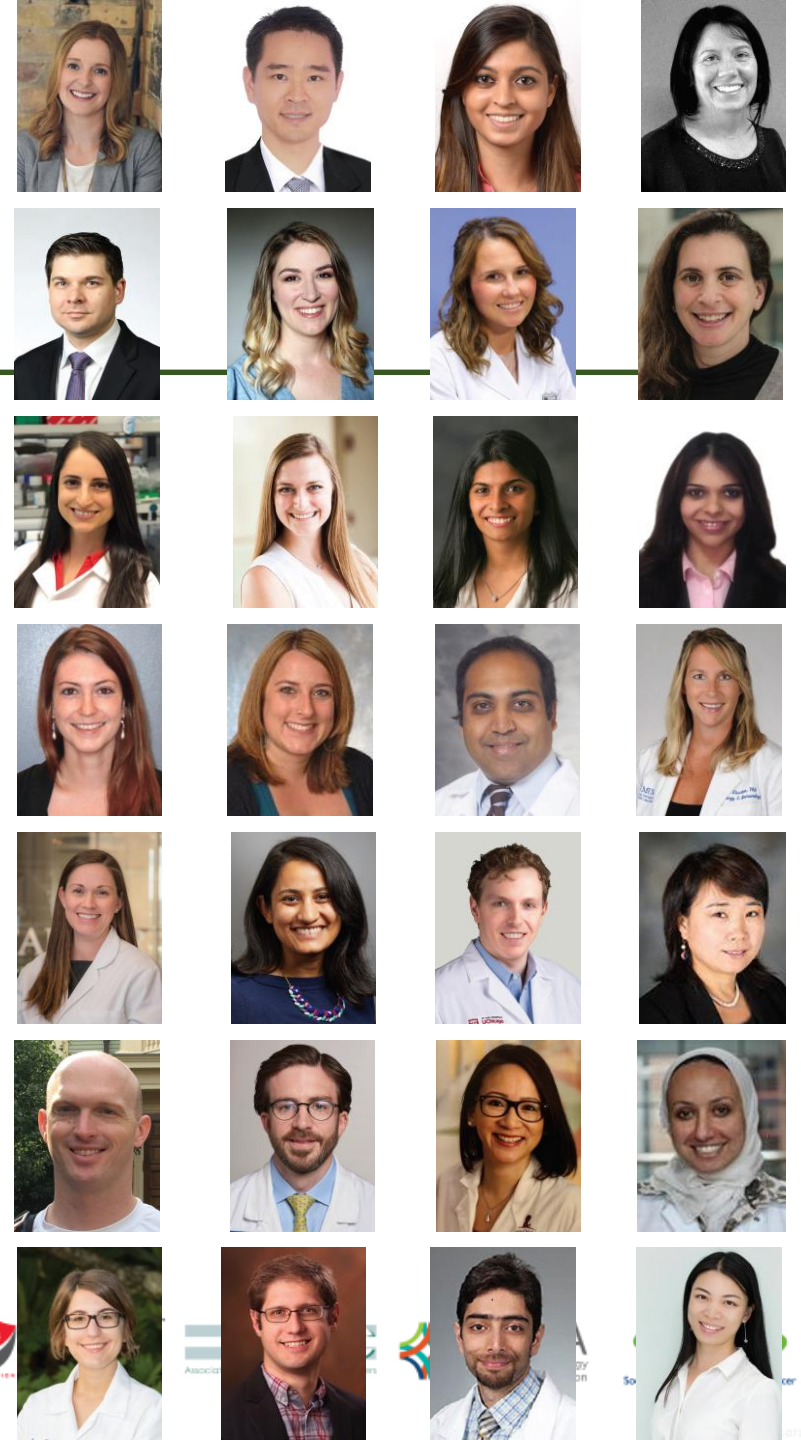
SITC Sparkathon 2018

The purpose of Sparkathon is to bring together investigators early in their career with various backgrounds, degrees, and professional experiences to collaboratively address hurdles the field of cancer immunotherapy faces today



SPARKATHON
Emerging Leaders Igniting Innovation

Future Hurdles Facing Cancer Immunotherapy: Identified by SITC Leadership

Mechanisms of anti-tumor activity and toxicity with tumor immunotherapy
Limitations of current animal models
Poor understanding of tumor antigen-specific T cell priming
Lack of suitable antigens for development of CAR T cell in solid tumors
Limited availability of T cell-independent immunotherapeutic approaches
Understanding the basic mechanism of immune-mediated toxicity
Ability to characterize tumor heterogeneity

Host and environmental interactions with tumor immunotherapy
Poor understanding of tumor host relationship across diseases
How non-tumor related factors affect antigen specific immune responses
Systemic immune suppression by tumor

Mechanisms of drug resistance with tumor immunotherapy
Complexity of primary and acquired immune resistance

Clinical trial design and endpoint issues
Need for more contemporary and relevant clinical trial designs

Biomarker and biospecimen issues
Lack of resources and commitment for tissue collection and storage
Bioinformatics tools, approaches and resources to interpret complex data

Clinical trial conduct issues
Too many clinical studies and combination regimens to test
Supporting research and regulatory advancement for cellular therapies

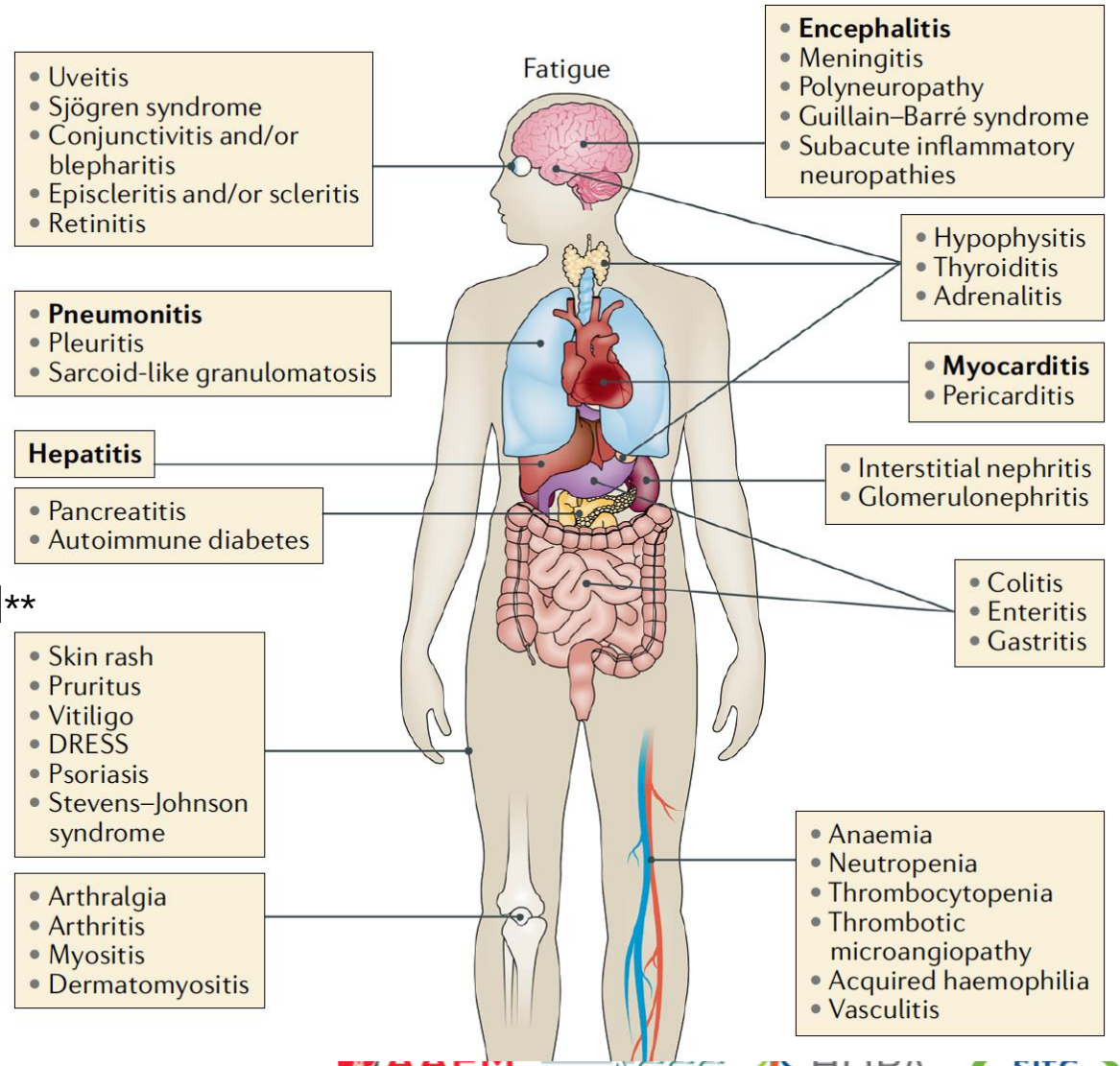
Funding Issues
Insufficient funding for basic tumor immunobiology
Very high cost of treatment

Workforce Issues
Insufficient training of scientists to enter the field
Educate non-oncology healthcare providers on immunotherapy

Understanding when it is safe to stop immunotherapy treatment
Lack of novel statistical endpoints and biomarkers

Long term and delayed *physical* toxicities associated with immunotherapy

- irAEs are variable in presentation and time-course
- Most toxicity occurs within the first 6 months
- 10% of patients may develop irAE >1y of tx*
- Delayed Immune-Related Events likely underreported**



*Shah et al, JCO 2018. **reviewed by Couey et al, JITC 2019

Martins *et al, Nature Reviews* 2018

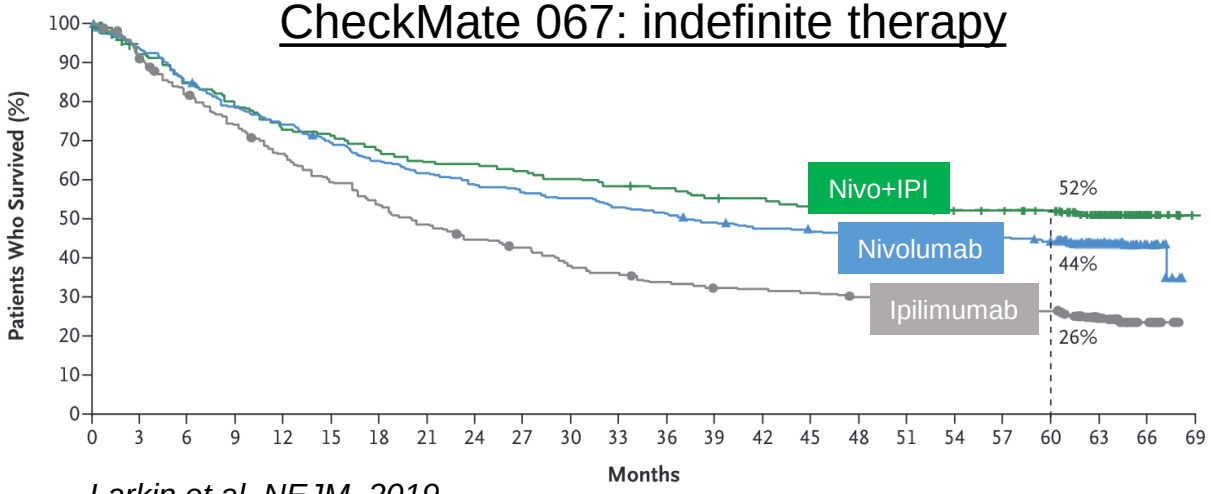
Financial toxicities associated with immunotherapy

- Annual per patient cost of Nivolumab or Pembrolizumab ranges from $180,000-200,000
- Personal costs can surpass $100,000, depleting savings, and forcing financial-based medical decisions
- Cost of melanoma healthcare treatment in 2018 was projected to reach $3 billion
- Cancer care in the United States s expected to reach $173 billion by 2020
- Consideration of cost-effectiveness in treatment decisions more relevant than ever

Yu PP et al, JITC 2019
Mariotto et al JNCI 2011
Kohn et al JCO 2017
Rogiers et al J Oncol 2019

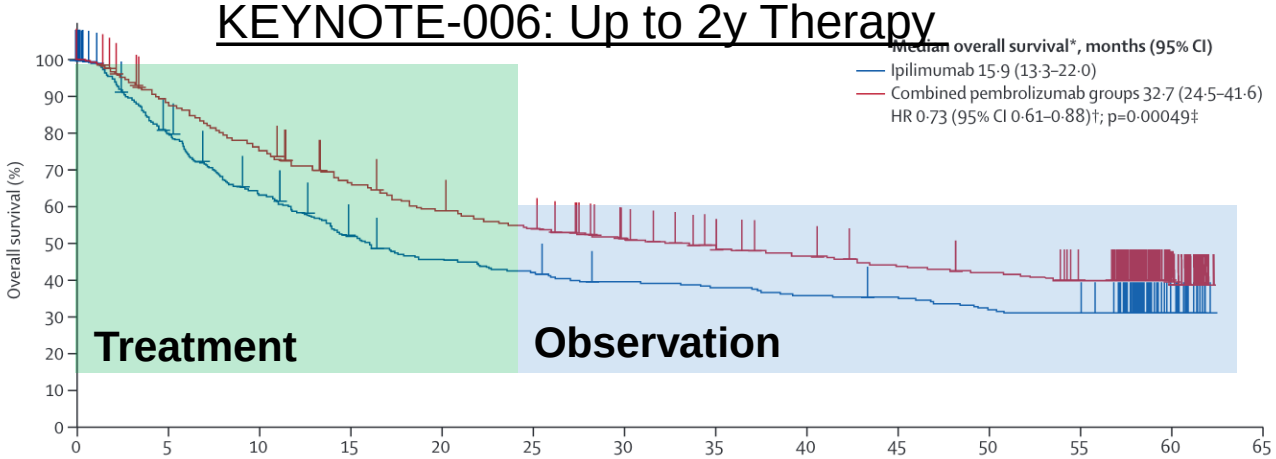
5 Year Survival suggests many patients are attaining durable response

CheckMate 067: indefinite therapy



Larkin et al, NEJM, 2019

KEYNOTE-006: Up to 2y Therapy



Robert et al, Lancet Oncology, 2019

Trial Schema

Metastatic Melanoma

- >6mo of SD from BOR
- >9mo of total anti-PD-1
- Non-inferiority

Samples

q3months

SOC imaging

- Radiomics

SOC labs

Blood

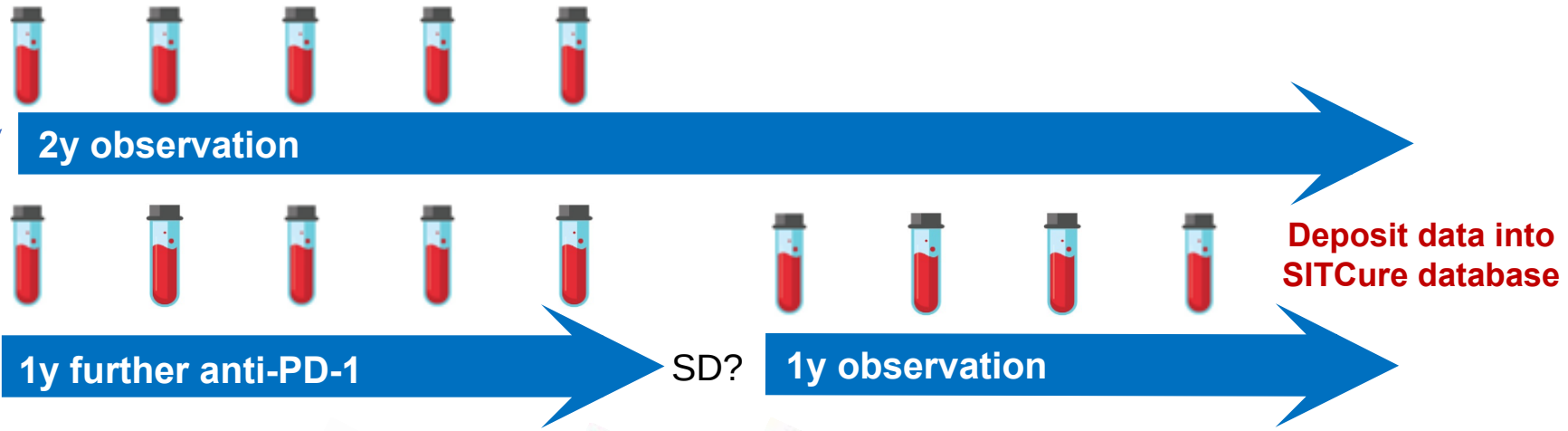
- PBMC
- Serum/Plasma
- CTC/ctDNA

Stool

Nivolumab/Ipilimumab
Combo → nivo maintenance

1:1

2 arm, Randomized, Non-Inferiority



SPARKATHON
Emerging Leaders Igniting Innovation

Proposed Trial Inclusion/Exclusion Criteria

Inclusion Criteria

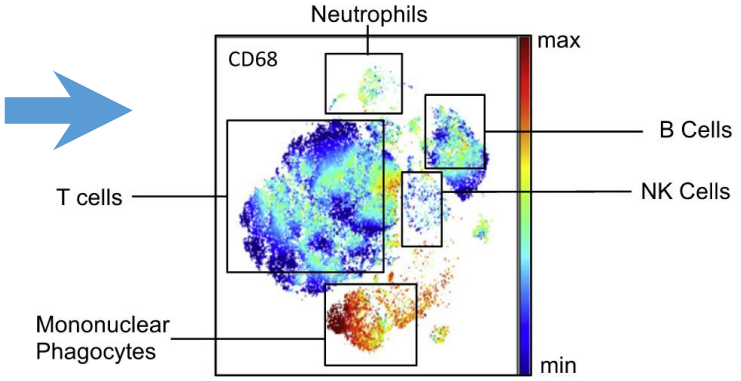
- > 18 years old
- Unresectable Stage III or Stage IV melanoma (AJCC)
- Have received SOC nivolumab/ipilimumab→nivolumab maintenance
- Stable response for least 6mo of SD, PR, or CR
  (e.g. achieved a CR and then no further changes for 6mo)
- Received at least 9 months of nivolumab therapy before randomization
- ECOG 0-1
- Willing to provide blood and stool specimens at time of enrollment and every 3 months

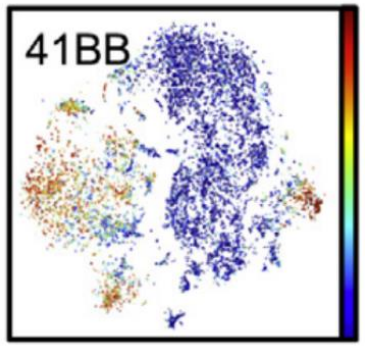
Exclusion Criteria

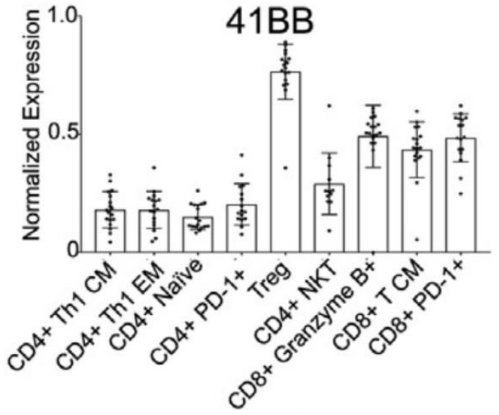
- Uveal and mucosal melanoma subjects are not eligible.
- Active autoimmune disease that has required systemic treatment in the past 1 year
- Patients with primary immunodeficiency
- Active (PCR-positive) hepatitis B or hepatitis C, and patients with uncontrolled HIV

Power of the Trial: *Exploratory Objectives – Peripheral Blood Immune Profiling*

PBMC resolution and phenotyping over time (myeloid and lymphoid CyTOF panels)







Immune and tumor activation status, determined by signature gene expression (NanoString)

Pre-treatment FFPE (when available)

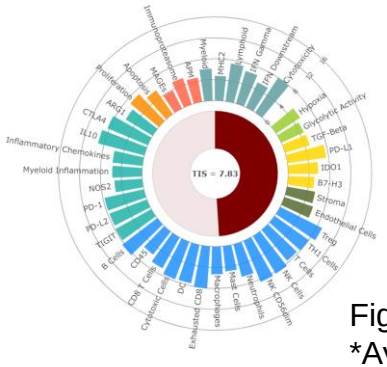
Pre-discontinuation and post-discontinuation PBMCs

RNA

NanoString platform

Gene expression data

400–680 genes on custom platform - Immune focused -



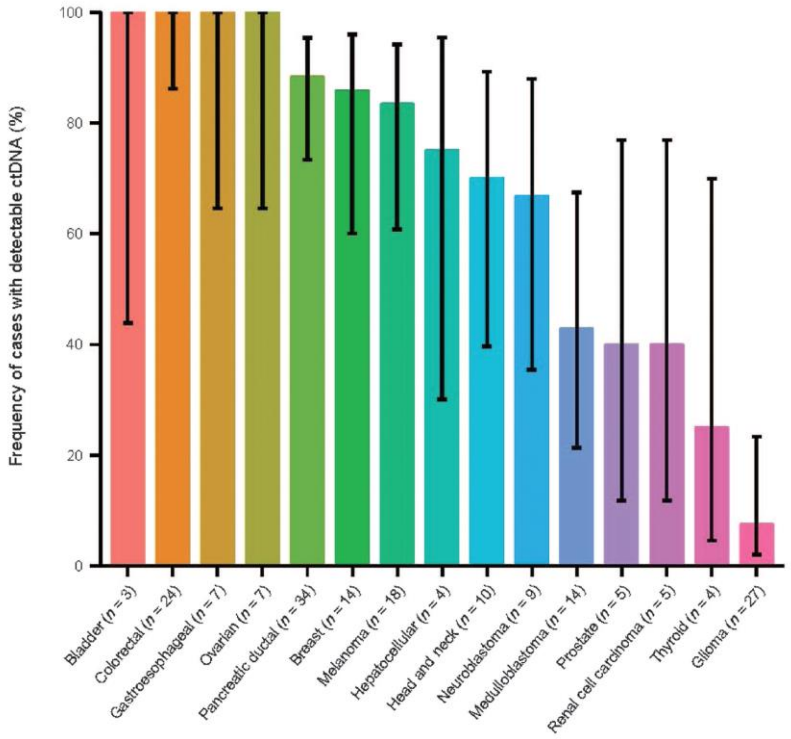
IO360 gene signature characterization

- Tumor inflammation signature*
- Immune cell abundance

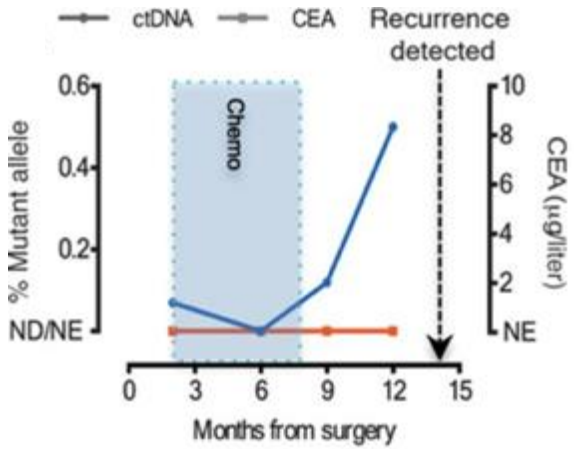
Figure adapted from Lavin *et al. Cell,* 2017
*Ayers et al. *JCI* 2017

Power of the Trial: Exploratory Objectives – Can ctDNA predict the who/when of recurrence?

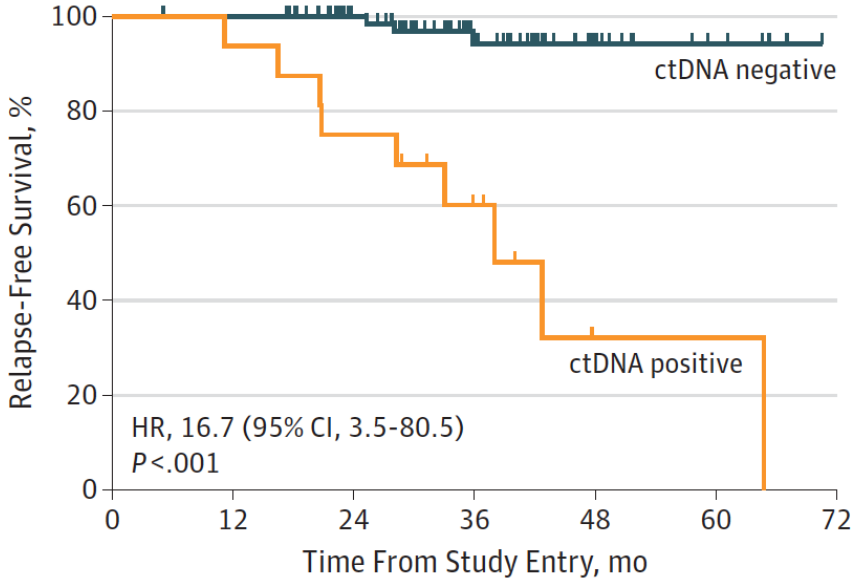
Most MM patients should have ctDNA



ctDNA may precede radiographic recurrence



ctDNA may be the best predictor



Bettegowda et al, Sci Trans Med 2014
Tie et al Sci Trans Med 2016
Garcia-Murillas, Jama Onc 2019

SITCure Team

SITCure Advisory Panel

- Lisa Butterfield
- Paolo Ascierto
- Daniel Chen
- James Gulley
- David Kaufman
- Kim Margolin

David Rosen

SITC Staff

- Anne Hahn
- Rebecca Borzon
- Sam Deges

Anita Giobbie-Hurder

Acknowledgements

ACI Charleston Organizers

Dr. David Neskey
Dr. Chrystal Paulos

SITC Staff

Allison Joost
Lianne Wiggins

Charleston ACI Presenters

Dr. Michelle Hudspeth
Dr. Antonio Giordano
Dr. Theodore Gourdin
Dr. John Wrangle
Hannah Knochelmann
Michelle Neskey

Proposed Trial Statistical Design

N=276
Non-inferiority, type-1 error 5%, 90% Power
One-sided alternative hypothesis of inferiority for the discontinuation arm

Based on PhIII Data:

- Estimated one-year recurrence rate in the continued therapy arm is 17%
- A one-year recurrence rate in the discontinuation arm <27% considered clinically non-inferior.
  → non-inferiority margin of 10%

- Expected recurrence-free rate 83% from time of randomization
- Drop to lower than 73% with discontinuation would be considered unacceptable
- Hazard ratio of (discontinuation vs. continued) of 1.69
- Accrual to be uniform over approximately 5.5 years, final analysis at 6.5 years
- Three planned interim analyses at 30%, 40% and 50% accrual