Defining and Understanding Resistance to Checkpoint Inhibitor Therapy

Ryan Sullivan, MD

Associate Professor, Harvard Medical School

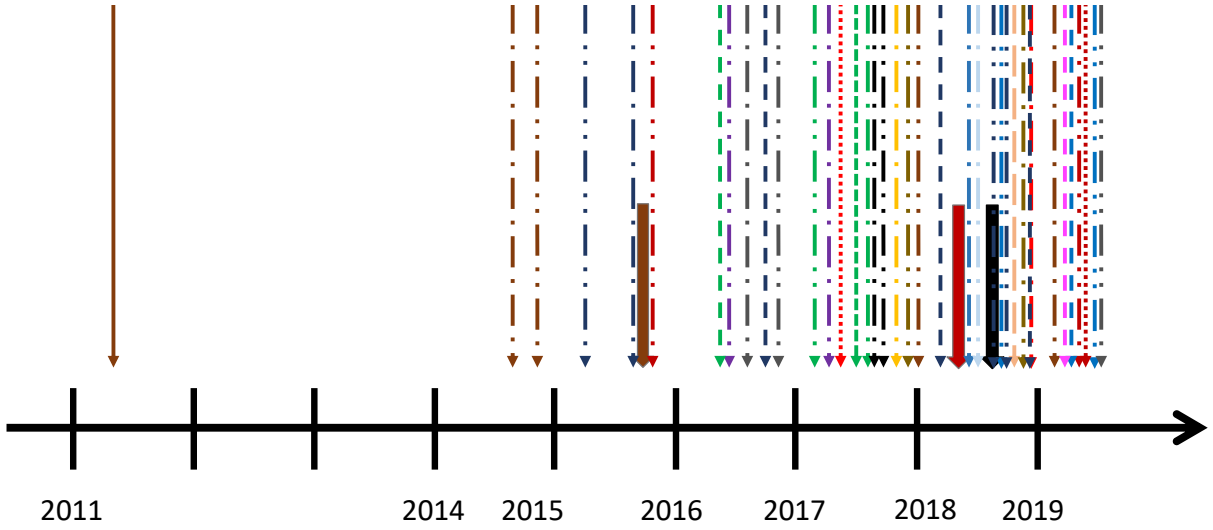
Associate Director Melanoma Program, Mass General Cancer Center

Relevant Disclosures

- Consulting Fees: Bristol Myers Squibb, Merck, Marengo, Novartis, Pfizer, Replimune
- Contracted Research: Merck
- Royalties: Up-to-date
- Support for clinical trials to my institution: Alkermes, Asana, BiomedValley Discoveries, BMS, Compugen, Constellation, Cytositebio, GSK, InxMed, Iovance, Lilly, Mapkure, Merck, Moderna, Novartis, Pfizer, Roche-Genentech, Sincha Therapeutics, Strategia Therapeutics Inc

I am a melanoma specialist so much of my content is biases to melanoma study data

Immune checkpoint inhibitors and US FDA approvals



Anti-CTLA4

- Ipilimumab
- Tremelimumab#

Anti-PD-1

- Pembrolizumab
- Nivolumab
- Cemiplimab
- Dostarlimab
- Retifanlimab

Anti-PD-L1

- Atezolizumab
- Avelumab
- Durvalumab

Anti-LAG-3

- Relatlimab*

Combos

- Ipi/nivo
- Nivo/rela*
- Treme#/Durva

Melanoma
NSCLC
Renal Cell Carcinoma
Urothelial Bladder Cancer
Hodgkin Lymphoma
HNSCC
Merkel Cell Carcinoma
Esophageal
Endometrial
Gastric Cancer
MSI Cancers
Cervical SCC
Small cell lung cancer
cuSCC
Triple neg breast cancer
Primary mediastinal BCL
Hepatocellular Carcinoma
TMB high
MSI high Colorectal cancer
Basal Cell Carcinoma

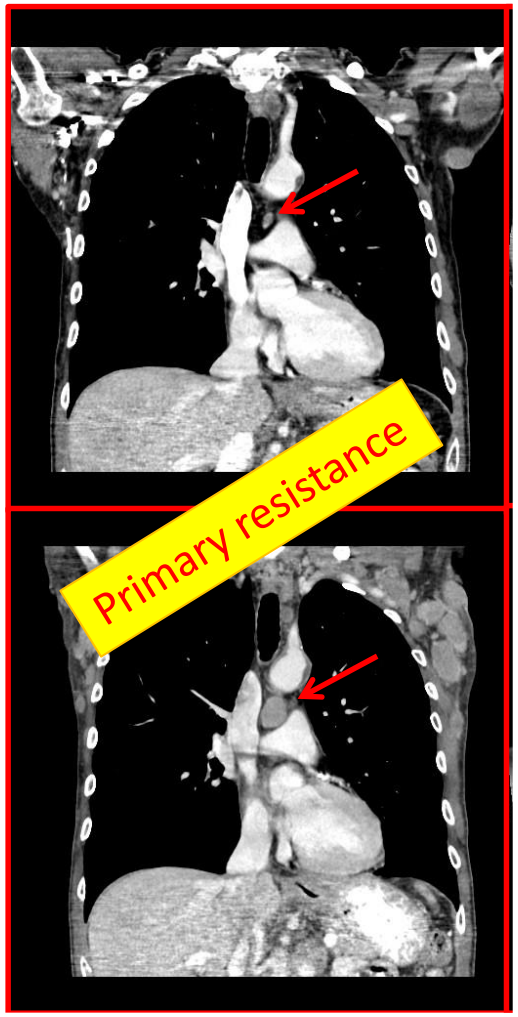
Year	Drugs	Approvals	Diseases	Combos	Adj/Neo
2011	1	1	1	0	0
2014	2	2	1	0	0
2015	3	4	3	1	1
2016	3	5	4	0	0
2017	4	10	7	0	1
2018	5	12	10	5	1
2019	4	7	5	6	1
2020	6	8	8	3	0
2021	5	17	9	8	5
2022	7	9	5	8	1
2023	4	5	3	2	1

What is the unmet need?

Most patients are not receiving benefit

How do we define resistance?

Non-responder



Secondary resistance

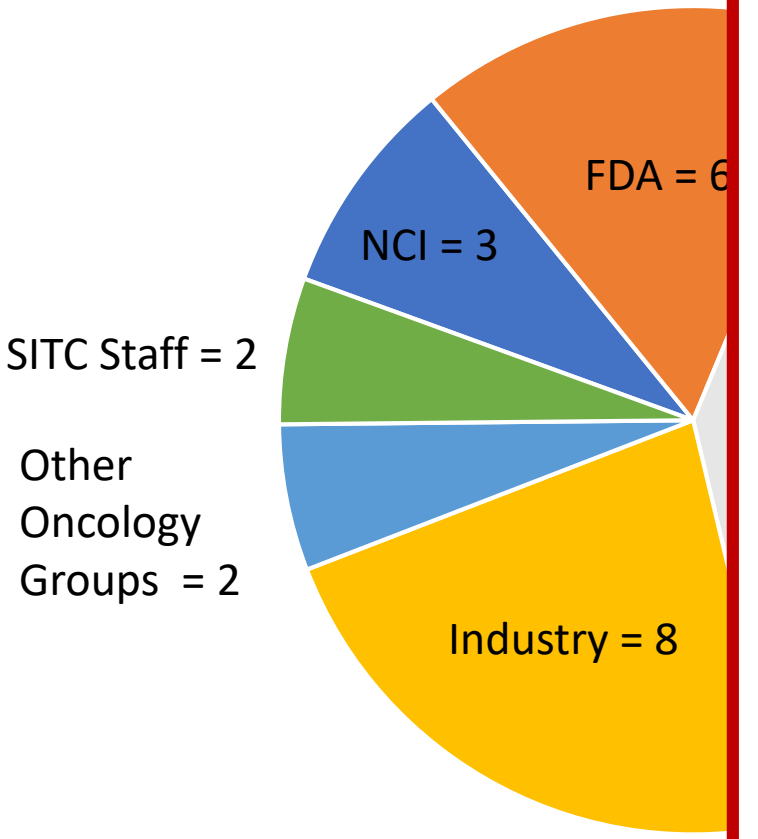
SITC PD-1 Resistance Taskforce (April 1, 2019; Atlanta GA)

- Who: Immunologists, Clinical Trialists, Industry Members, NCI, FDA
- Aim:
  - Come to consensus about defining resistance to single-agent anti-PD-(L)1 therapy
  - “False-resistance” rate of <5%
  - Could be adopted rapidly into clinical trials evaluating agents/combos in this space
- Chose
  - Three scenarios:
    - Primary resistance
    - Secondary resistance
    - Resistance after treatment discontinuation

SITC PD-1 Resista

019; Atlanta GA)

Workshop A



Total Workshop A

Open access Position article and guidelines

Defining tumor resistance to PD-1 pathway blockade: recommendations from the first meeting of the SITC Immunotherapy Resistance Taskforce

Harriet M. Kluger,[1] Hussein A. Tawbi,[2] Maria L. Ascierto,[3] Michaela Bowden,[4] Margaret K. Callahan,[5] Edward Cha,[6] Helen X. Chen,[7] Charles G. Drake,[8] David M. Feltquate,[4] Robert L. Ferris,[9] James L. Gulley,[7] Shilpa Gupta,[10] Rachel W. Humphrey,[11] Theresa M. LaVallee,[12] Dung T. Le,[13] Vanessa M. Hubbard-Lucey,[14] Vassiliki A. Papadimitrakopoulou,[2] Michael A. Postow,[6] Eric H. Rubin,[15] Elad Sharon,[7] Janis M. Taube,[16] Suzanne L. Topalian,[17] Roberta Zappasodi,[6] Mario Sznol,[1] Ryan J. Sullivan[17]

ABSTRACT

As the field of cancer immunotherapy continues to advance at a fast pace, treatment approaches and drug development are evolving rapidly to maximize patient benefit. New agents are commonly evaluated for activity in patients who had previously received a programmed death receptor 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitor as standard of care or in an investigational study. However, because of the kinetics and patterns of response to PD-1/PD-L1 blockade, and the lack of consistency in the clinical definitions of resistance to therapy, the design of clinical trials of new agents and interpretation of results remains an important challenge. To address this unmet need, the Society for Immunotherapy of Cancer convened a multistakeholder taskforce—consisting of experts in cancer immunotherapy from academia, industry, and government—to generate consensus clinical definitions for resistance to PD-(L)1 inhibitors in three distinct scenarios: primary resistance, secondary resistance, and progression after treatment discontinuation. The taskforce generated consensus on several key issues such as the timeframes that delineate each type of resistance, the necessity for confirmatory scans, and identified caveats for each specific resistance classification. The goal of this effort is to provide guidance for clinical trial design and to support analyses of emerging molecular and cellular data surrounding mechanisms of resistance.

INTRODUCTION

Cancer immunotherapy utilizes the immune system to mount an antitumor effect—most commonly through activation of tumor antigen-specific T cells—and includes multiple modalities including cell therapies, vaccines, and monoclonal antibodies that target immune checkpoints.[1 2] Specifically, immune checkpoint inhibitors (ICIs) have rapidly altered the treatment paradigm for cancer patients, across multiple settings and indications, primarily by providing durable clinical benefit—defined as tumor response or prolonged stable disease (SD), as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, lasting 6 months or greater[3]—to an increased number of patients compared with chemotherapy and radiation. Nevertheless, a majority of patients have disease that exhibits either no clinical response or response followed by progression to inhibitors of the programmed death receptor 1 (PD-1) or its major ligand programmed death-ligand 1 (PD-L1).[4] As such, the development of effective immunotherapies following PD-(L)1 inhibition for "ICI-resistant" populations across treatment settings and scenarios represents a significant challenge and a pressing priority for the field of oncology.

Resistance to PD-(L)1 inhibitors is clinically complex and can present at various time points during treatment, including immediately after treatment initiation (primary resistance), weeks or months after evidence of initial clinical benefit (secondary resistance), or after treatment has been halted for a variety of reasons. Due to this complexity and the rapid advancement of immunotherapy into the clinic, uniform definitions of PD-(L)1 inhibitor resistance have not yet been developed. While there have been initial efforts to characterize primary resistance and delayed progression following treatment with PD-(L)1 inhibitors in patients with unresectable or metastatic melanoma,[5] limited data are available that would allow for generation

J Immunother Cancer: first published as 10.1136/jitc-2019-000436 on 1 April 2020. Downloaded from http://jitc.bmj.com/ on April 1, 2020 at Partners HealthCare System. Protected by copyright.

Leadership

me

Hussein Tawbi, MD, PhD
MD Anderson Cancer Center

presentatives

uibb
utics

logy Groups

Institute
or Cancer Immunotherapy

May 2021 Combination Immunotherapy Resistance Workshop

- **Draft Resistance Definitions Generated**
  - Definitions Drafted for Various Combinations
    - IO/IO
    - IO/Chemo
    - IO/Small Molecule (targeted therapy/cytokines)

- **Manuscript Development for Combination Resistance Definitions**
  - Manuscript Initiation Q2 2021
  - Manuscript Submission to JITC Q2 2022
  - Acceptance of all three manuscripts to JITC late 2022/early 2023

Resistance phenotype	Drug exposure requirement	Best response
Primary Resistance	8–12 weeks* (2 cycles)	PD SD < 6 months
Secondary Resistance	>6 months	CR, PR, SD ≥ 6 months
Neoadjuvant	6+ weeks	<50% tumor death in resection sample
Adjuvant	6+ weeks	Recurrence on or <12 week after last dose

Defining Resistance to IO combination therapy offers different challenges

Atkins et al. accepted at JITC

Summary of Resistance Efforts

- Published definitions for single-agent anti-PD-1/PD-L1 and combination therapies – IO/IO, IO/Chemo, IO/targeted therapy
  - Atkins et al. JITC 2023, , Rizvi et al. JITC 2023
- SITC efforts continue – next frontier is to validate the definitions
- Data is emerging about mechanisms of resistance (MOR), but no wide-scale approach has been applied to link MORs to primary or secondary resistance
- Efforts are ongoing to apply definitions of resistance and MORs into clinical trial efforts

Building on Resistance Definitions

Future Questions and Aspects Concerning Immunotherapy Resistance

1) **Collecting and analyzing data concerning patients with primary/secondary resistant tumors**
2) **Linking definitions to mechanisms of resistance**
3) **Targeting resistance populations with novel therapies**

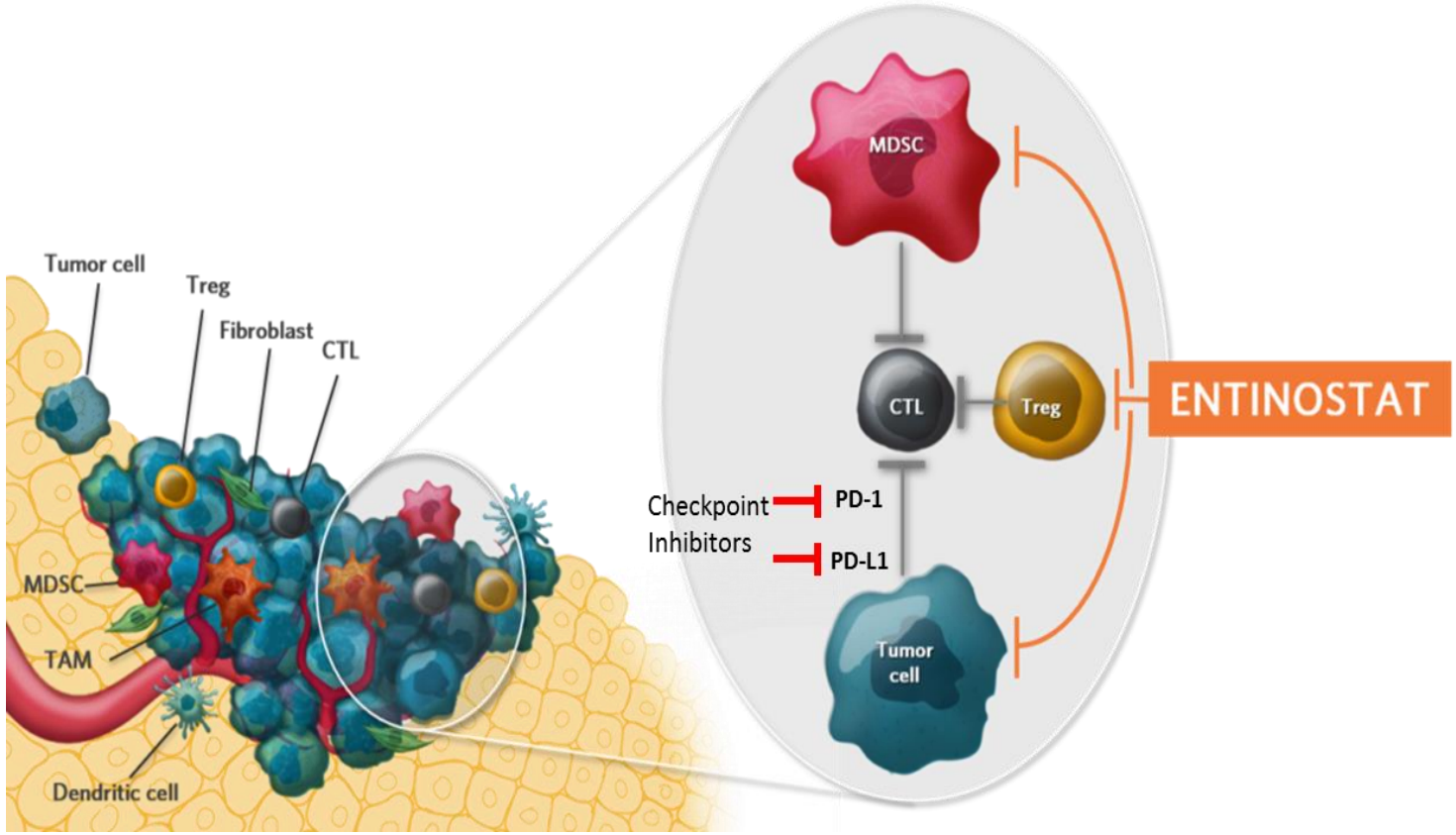
Building on Resistance Definitions

Future Questions and Aspects Concerning Immunotherapy Resistance

1) Collecting and analyzing data concerning patients with primary/secondary resistant tumors
2) Linking definitions to mechanisms of resistance
3) **Targeting resistance populations with novel therapies**

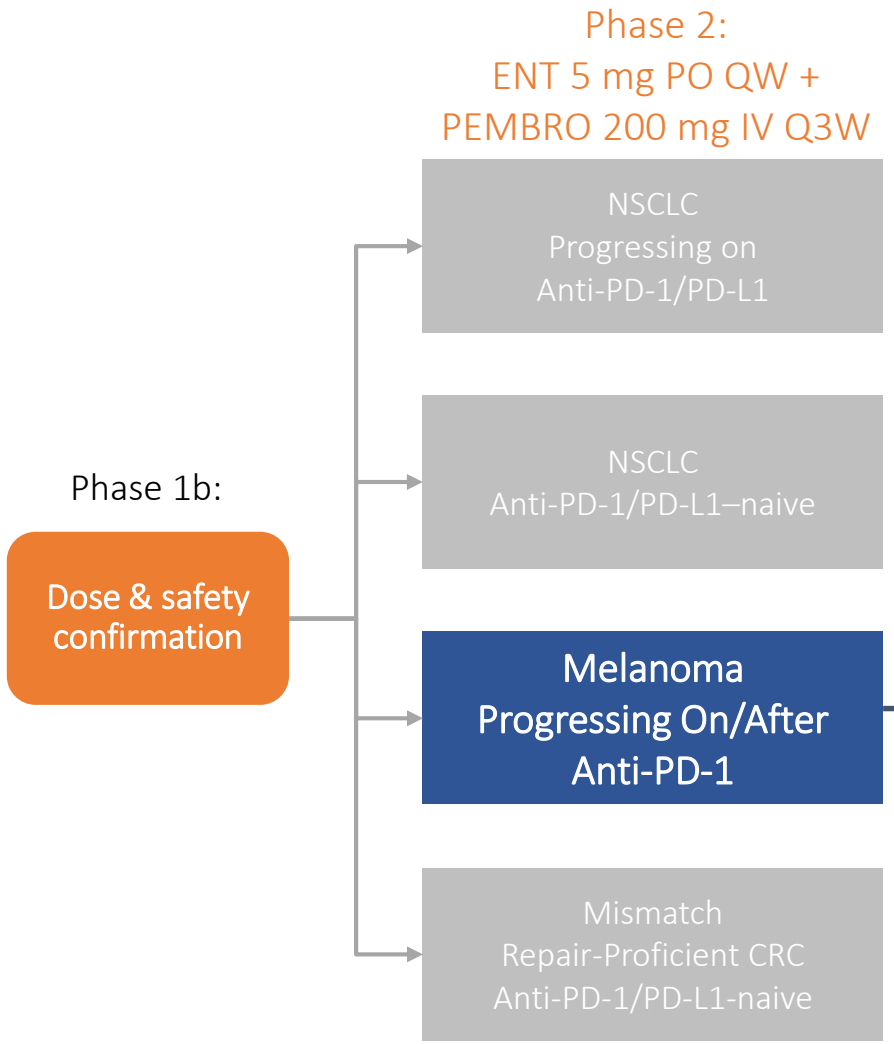
Proposed MOA of HDAC inhibition as IO

- Entinostat (ENT) is an oral class I-selective histone deacetylase inhibitor
- ENT reduces MDSC and Treg number & function
- ENT induces pro-inflammatory cascade in TME
- ENT enhances antigen presentation
- Additional beneficial effects on Teff & NK cells
- Synergy with anti-PD1 inhibition in preclinical models



Ramalingam et al. AACR 2019

ENCORE-601: Open-Label Study Evaluating ENT + PEMBRO in Patients With Recurrent or Metastatic Melanoma and Prior Progression On or After Anti-PD-1 Therapy



- Inclusion Criteria:
  - Recurrent or metastatic melanoma, measurable by RECIST 1.1
  - Prior progression on or after anti-PD-(L)1 treatment
  - Prior BRAF treatment if indicated
  - ECOG Performance Status < 2
  - Willingness to participate in baseline and on-treatment biopsy and blood samples

Primary Endpoint

- ORR (irRECIST)

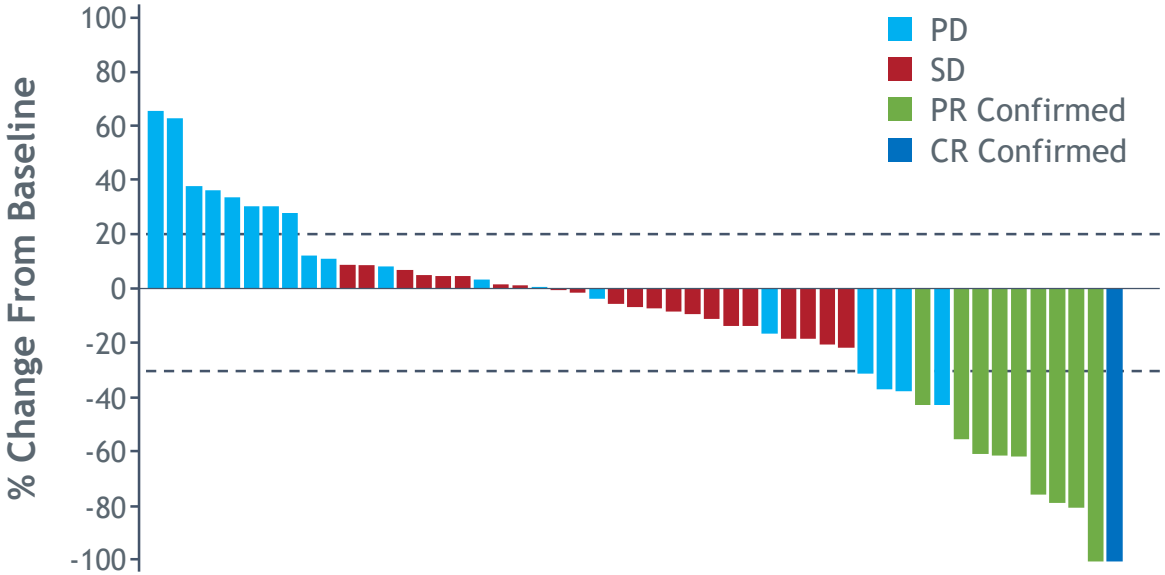
Secondary Endpoints

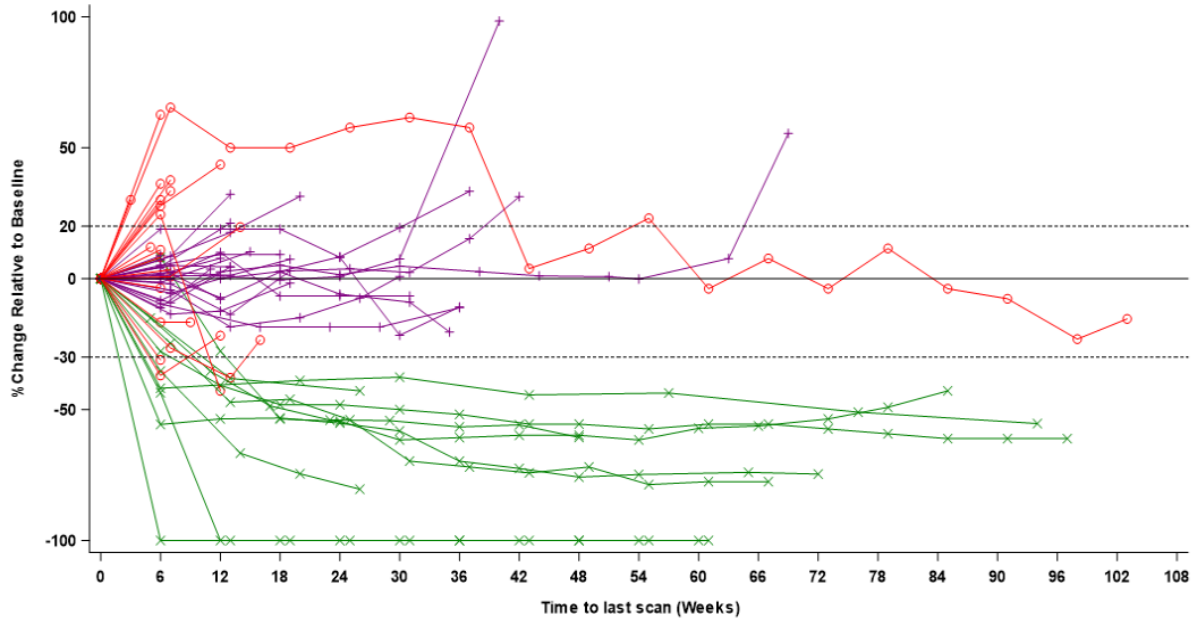
- CBR, PFS, OS, safety & tolerability

53 patients enrolled, last patient enrolled April 2018

Sullivan et al. AACR 2019

ENT plus pembro is associated with durable responses in patients who previously progressed on anti-PD-1 therapy



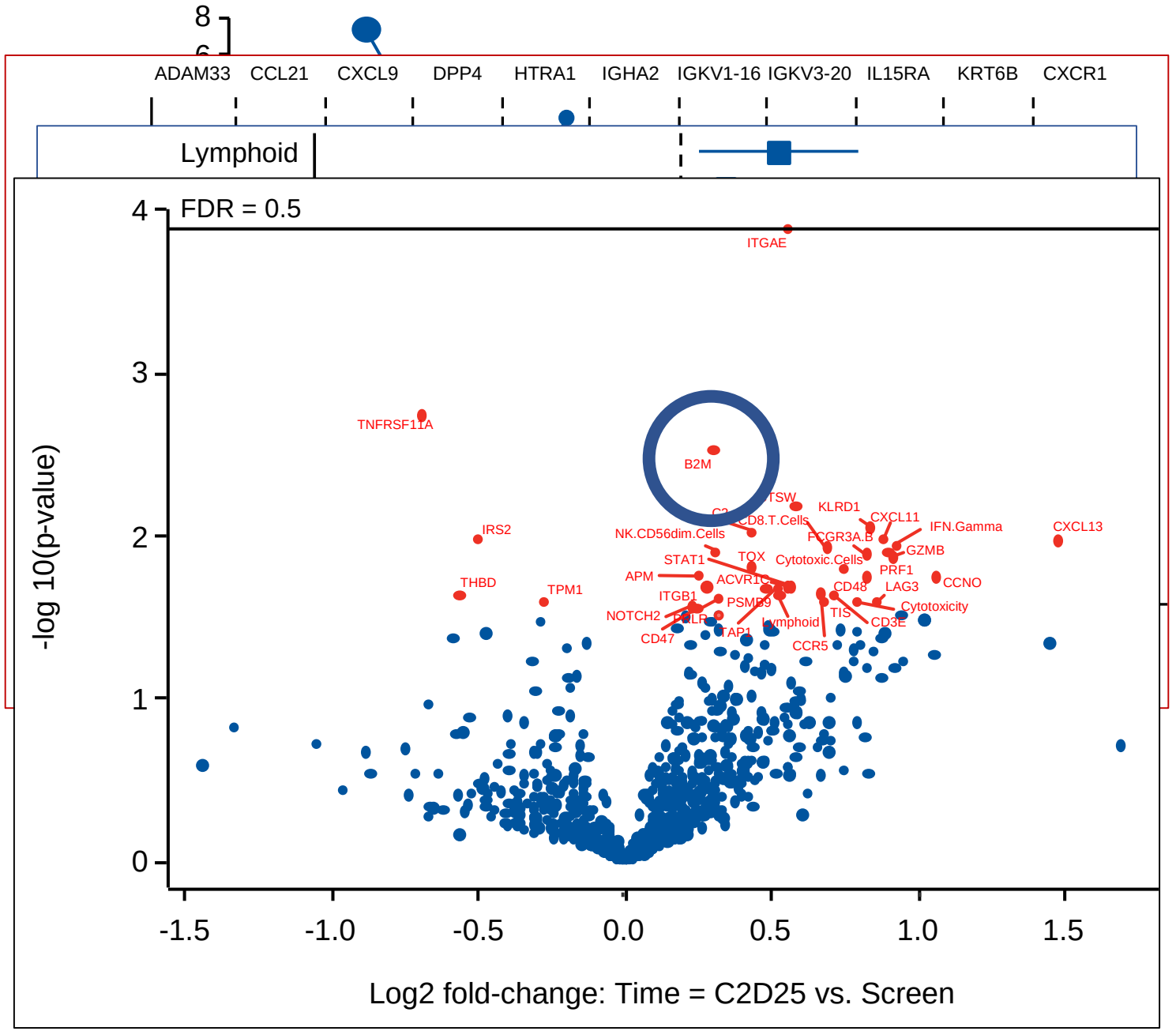


- 10 confirmed responses of 53 treated [19% ORR (95% CI: 9%-32%)]
  - 1 CR, 9 PRs
- Median duration of response: 13 months (range 3-20)
  - 4 responders ongoing
- An additional 9 patients have had SD for >6 months
  - 36% CBR (95% CI: 23%-50%)

Sullivan et al. AACR 2019

Pharmacodynamic effects of pembro plus ENT in melanoma….

1. Consistent reduction in circulating MDSCs
2. Genes whose expression in pre-/on- tumors are most altered are immune-related (RNA seq)
3. Marked change in immune-related gene sets pre/on (Nanostring)
4. Some interesting genes come in terms of those most changed with treatment (Nanostring)

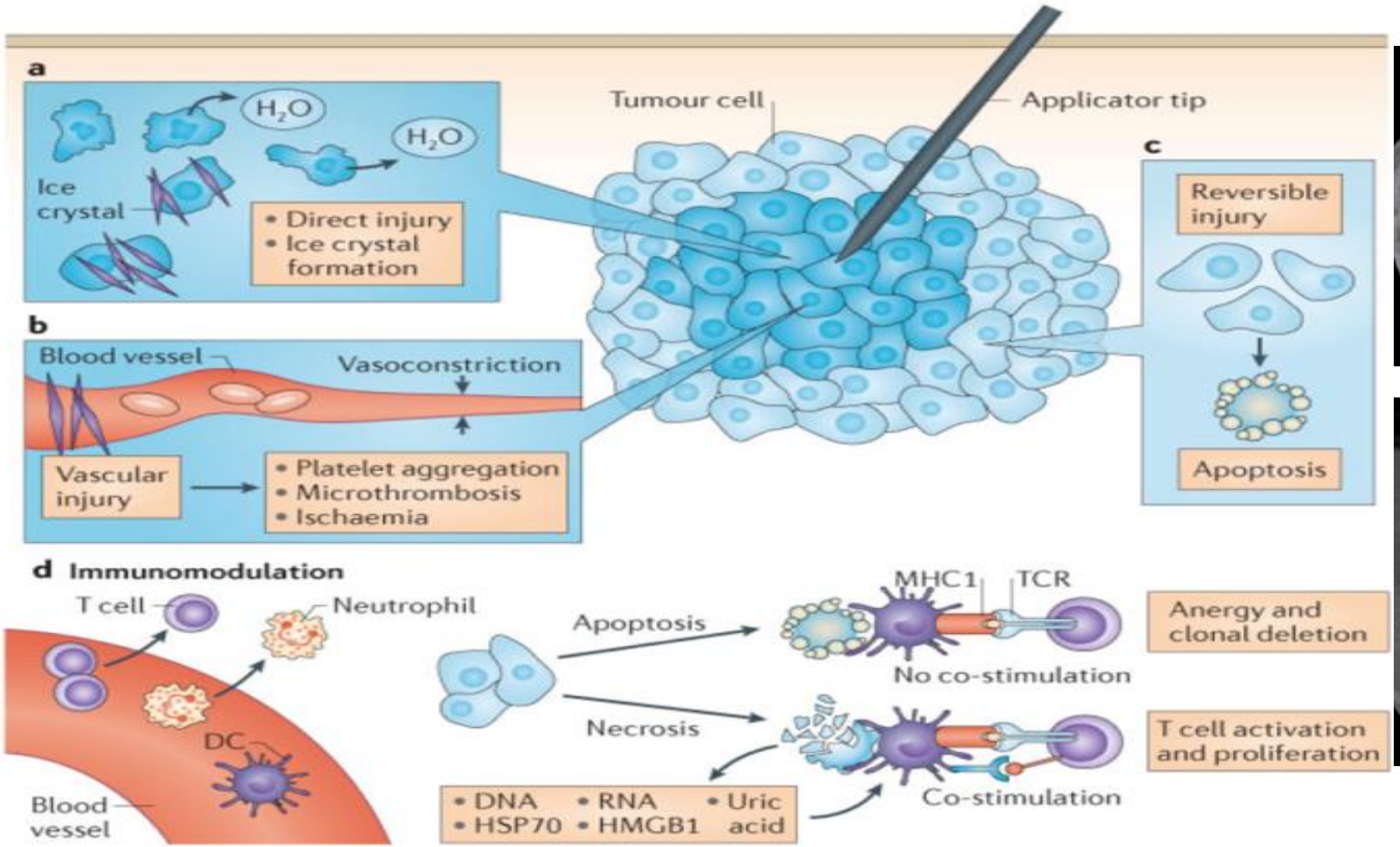


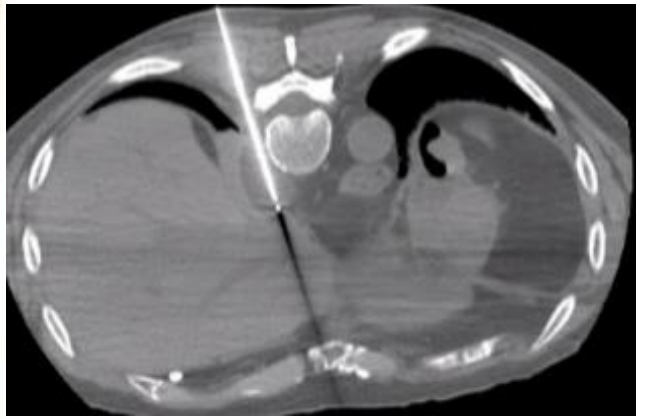
Building on Resistance Definitions

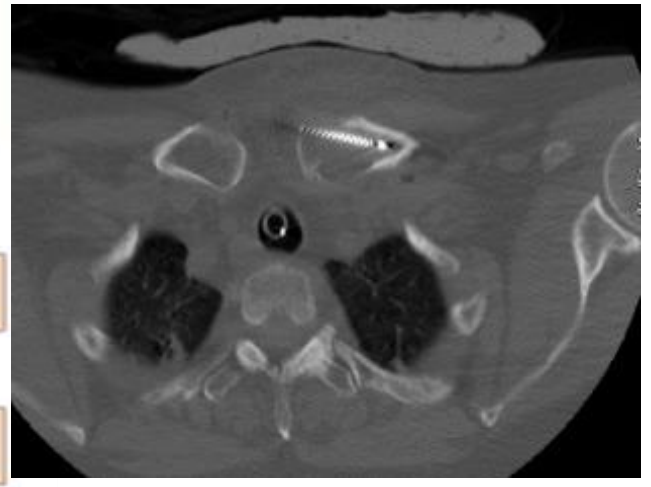
Future Questions and Aspects Concerning Immunotherapy Resistance

1) Collecting and analyzing data concerning patients with primary/secondary resistant tumors
2) Linking definitions to mechanisms of resistance
3) **Targeting resistance populations with novel therapies (2)**

Cryoablation can augment the immune response







Nature Reviews Cancer **14,** 199–208 (2014)

TITLE: A phase II study of core needle biopsy and cryoablation of an enlarging tumor in patients with advanced lung cancer or melanoma receiving post-progression immune checkpoint inhibitor therapy

ClinicalTrials.gov Identifier: NCT03290677

DF/HCC Protocol 17-264

Patients with lung cancer or melanoma progressing on ICI with:

1) Enlarging tumor amenable to cryo
2) Additional disease per RECIST
3) Eligible for 2 cycles of post-cryo ICI

→

***CT-guided percutaneous needle biopsy** to confirm diagnosis, followed by **CT-guided percutaneous cryoablation**.*

Monitor for radiologic response on post-progression immune checkpoint inhibitor therapy.

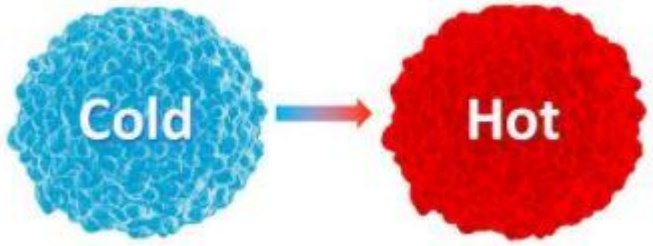
Monitor for progression-free and overall survival.

***N=10**, expansion to N=20 based on a 2-stage design.*

Objectives:

- To determine the safety and feasibility of cryo in pts receiving post-progression ICI
- To determine the ORR/DCR of cryo/ICI in ICI refractory cases

MASSACHUSETTS GENERAL HOSPITAL
IMAGING



*Meghan Mooradian, MD
*Florian Fintelmann, MD

Melanoma Cohort

20 patients screened

- 2 screen fails
- Lesions regressed prior to cryo (n=1)
  - No evaluable disease post-cryo per TIMC (n=1)

*Meghan Mooradian, MD
*Florian Fintelmann, MD

18 patients treated on protocol

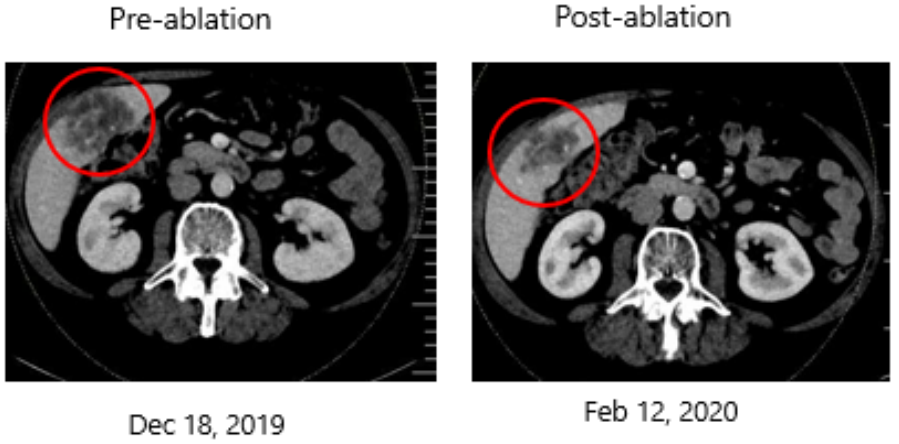
- One patient enrolled in hospice prior to receiving subsequent ICI and/or scans

17 patients evaluable

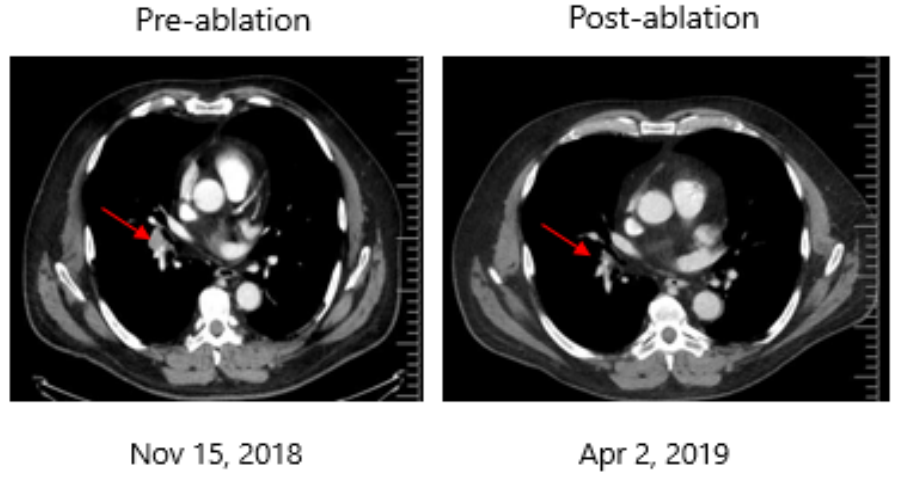
- **Best response**:
- PR, n=4
- SD, n=3
- PD, n=10

ORR: 24%
DCR: 41%

67% had primary ICI resistance



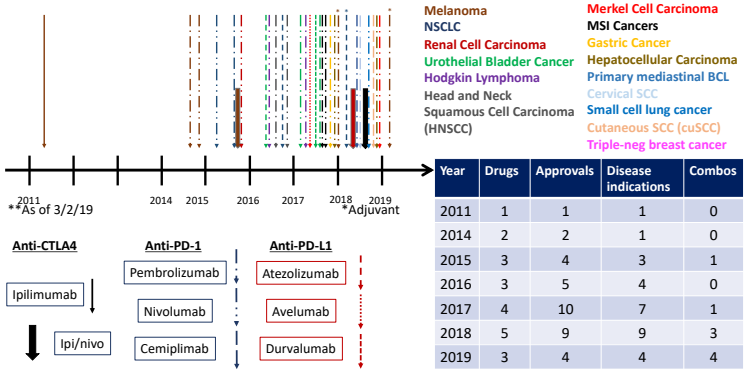
Cryoablation of a liver lesion
-> Tumor burden ↓ 10%
= Stable disease



Cryoablation of a lung lesion
-> Tumor burden ↓ 45%
= Partial response

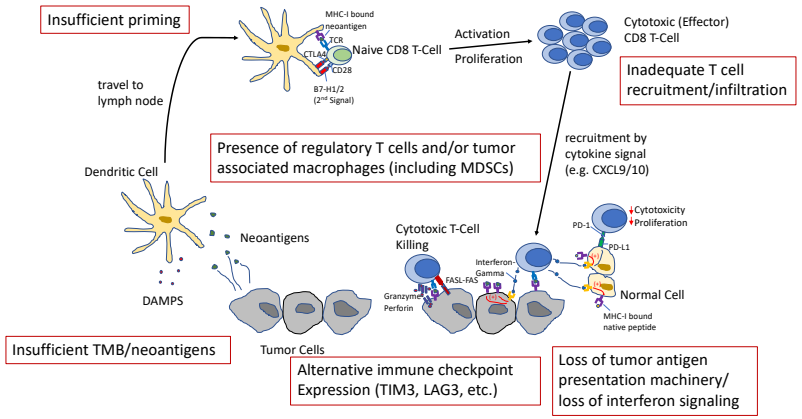
Concluding thoughts (1)

Immune checkpoint inhibitors and US FDA approvals



Year	Drugs	Approvals	Disease indications	Combos
2011	1	1	1	0
2014	2	2	1	0
2015	3	4	3	1
2016	3	5	4	0
2017	4	10	7	1
2018	5	9	9	3
2019	3	4	4	4

Immune checkpoint inhibitor therapy is changing the way we treat cancer

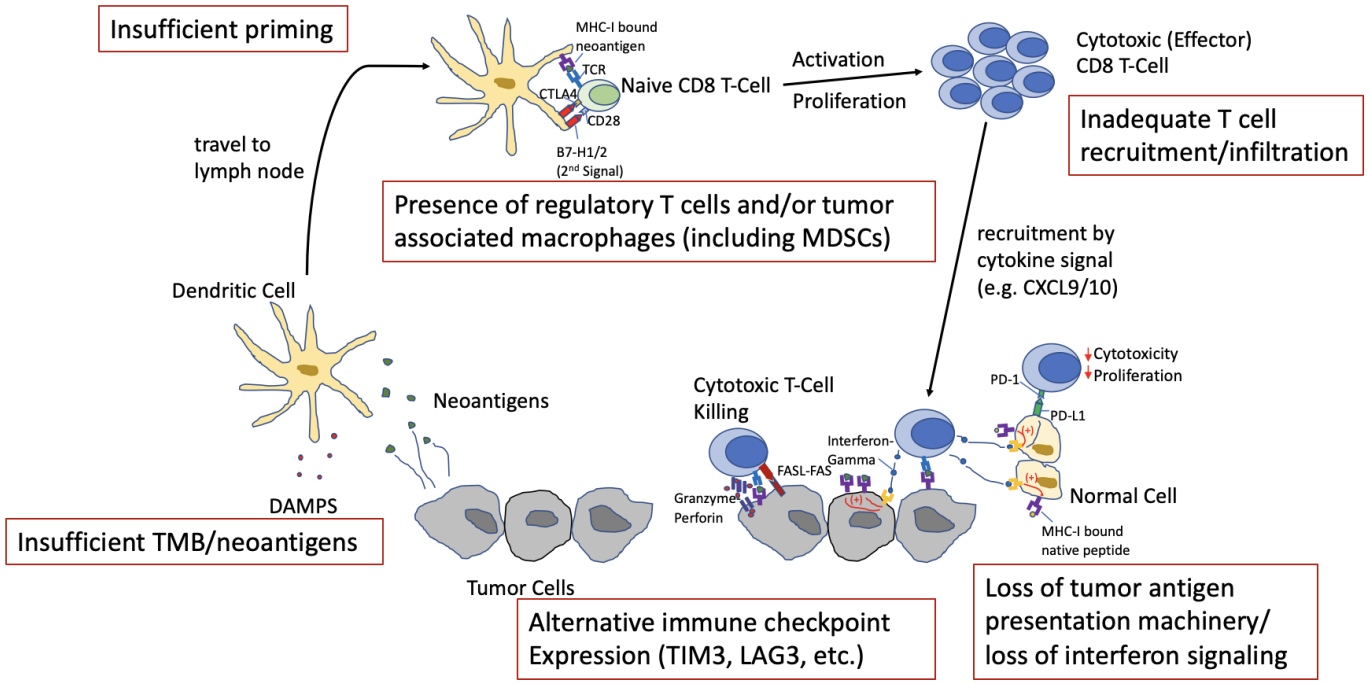


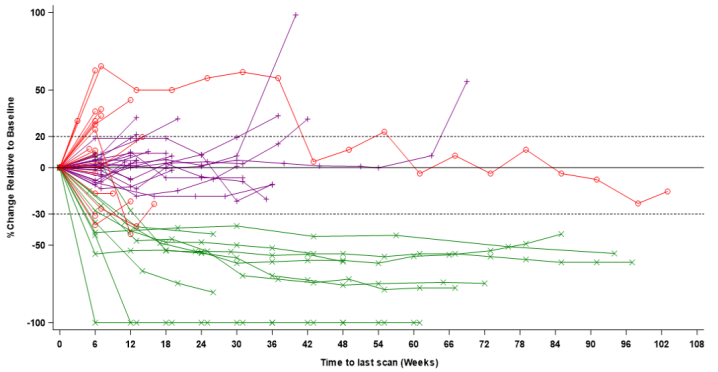
Defining resistance is a critical step in developing the next breakthroughs for the ICI-resistant population

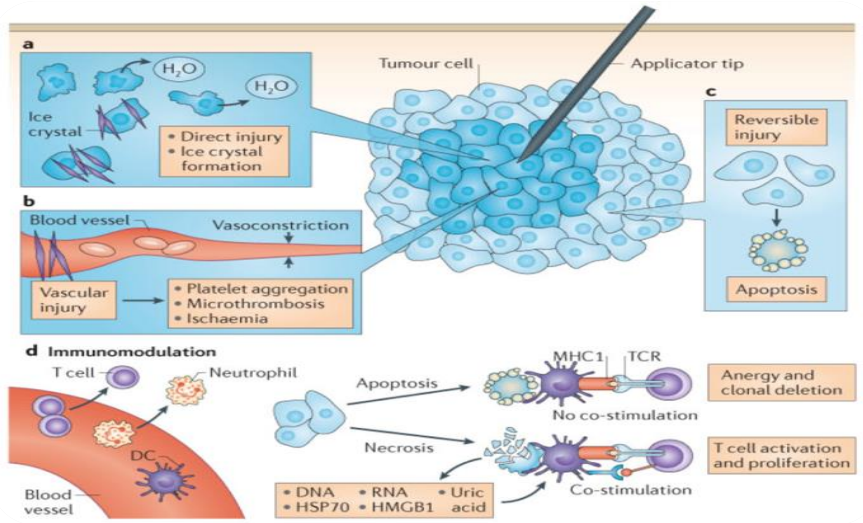
Resistance Phenotype	Drug Exposure Requirement	Best response	Confirmatory Scan for PD Requirement	Confirmatory Scan Time Frame
Primary Resistance	≥ 6 Weeks	PD; SD for < 6 months	Yes	At least 4 weeks after initial disease progression
Secondary Resistance	≥ 6 Months	CR, PR, SD for > 6 months	Yes	At least 4 weeks after disease progression

Concluding thoughts (2)

An better understanding of resistance…







…is leading to promising data in and strategies for the resistant population.

Acknowledgements

Center for Melanoma
Keith Flaherty
Don Lawrence
Justine Cohen
Meghan Mooradian
Aleigha Lawless
Russ Jenkins
David Miller
Howard Kaufman
Juliane Czapla

Melanoma Translational Research Laboratory
Genevieve Boland
William Michaud
Dennie T. Frederick
Tatyana Sharova

MGH Radiology
Florian Fintelmann

SITC PD-1 Resistance Committee
Harriet Kluger
Hussein Tawbi
David Feltquate
Theresa LeVallee
Jeff Sosman
Naiyer Rizvi

SITC Staff
Peter Intile
Christian Miller
Mary Dean

ENCORE-601
Patients and their family members
Syndax (Michael Myers, Peter Ordentlich, Yvette Ng), Merck
Co-Investigators and staff
Nanostring – Amy Sullivan, Sarah Church
The Wistar Institute – Fang Wang, Dmitry Gabrilovitch
Rancho BioSciences – Dan Rozelle

Nir Hacohen
Moshe Sade-Feldman

Anita Giobbie-Hurder

U54 CA224086
P01 CA163222-06
1R01 CA193970