SITC 2019

Gaylord National Hotel
& Convention Center

Nov. 6-10

NATIONAL HARBOR, MARYLAND

sitc

Society for Immunotherapy of Cancer

SITC Sparkathon 2018

SITCure: *When is it safe to stop immunotherapy?*

A Randomized Trial of Early Cessation of Immunotherapy in Patients with Melanoma after 6 Months or More of Stable Disease on Nivolumab Maintenance

&

ECOG *EA6192* *(collaboration with Dr. Geoffrey Gibney)*

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Disclosures – Thomas Marron

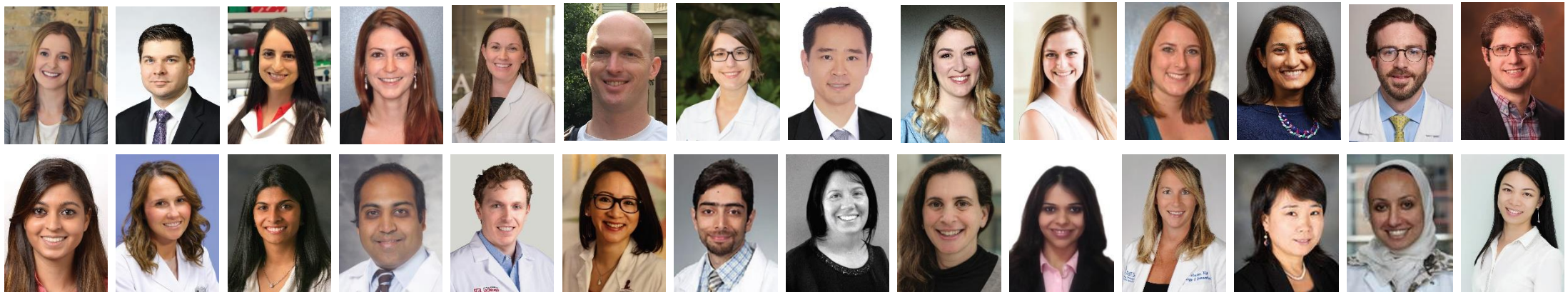
Advisory Boards
Regeneron, Boehringer Ingelheim, Atara, Genentech, AstraZeneca

Industry Sponsored Trials
Corvus, Bristol-Meyers Squibb, EMD Serono, Merck, AstraZeneca (Medimmune), Regeneron, Nektar, Astellas, Pfizer, Curis, Celldex, Exelixis, Oncovir, Astellas, Mersana

Research Funding (Grants)
Cancer Research Institute, Regeneron, Bristol-Myers Squibb, Merck, Boehringer Ingelheim

SITC Sparkathon Class 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.



2018 SITC Sparkathon Hurdles

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

Biomarker and biospecimen issues

- Lack of resources and commitment for tissue collection and storage
- Bioinformatic tools 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 and workforce *issues*

- Insufficient funding for basic tumor immunobiology
- Very high cost of treatment
- Insufficient training of scientists to enter the field
- Educate non-oncology healthcare providers on immunotherapy

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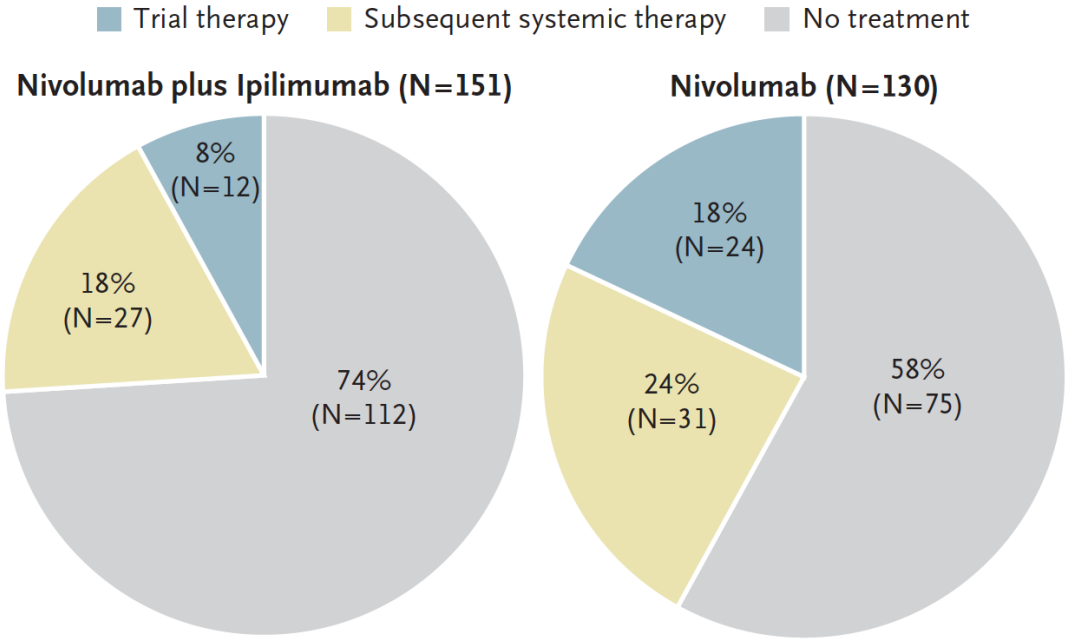
5-Year survival suggests many patients are attaining durable responses

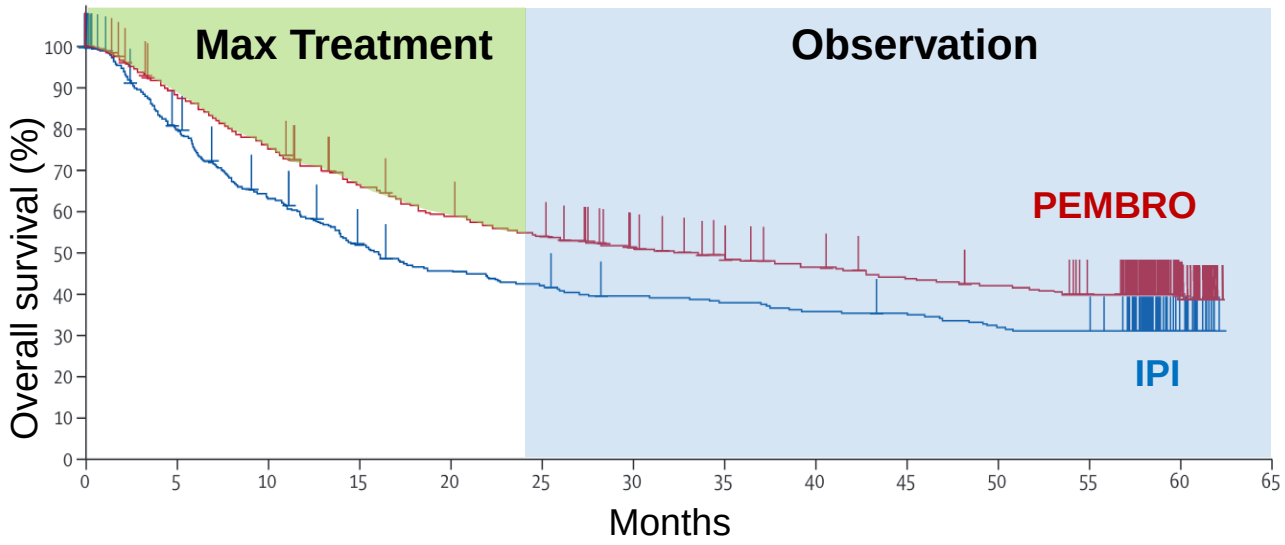
CheckMate 067: indefinite therapy

Larkin et al, NEJM, 2019



KEYNOTE-006: Up to 2 years of therapy

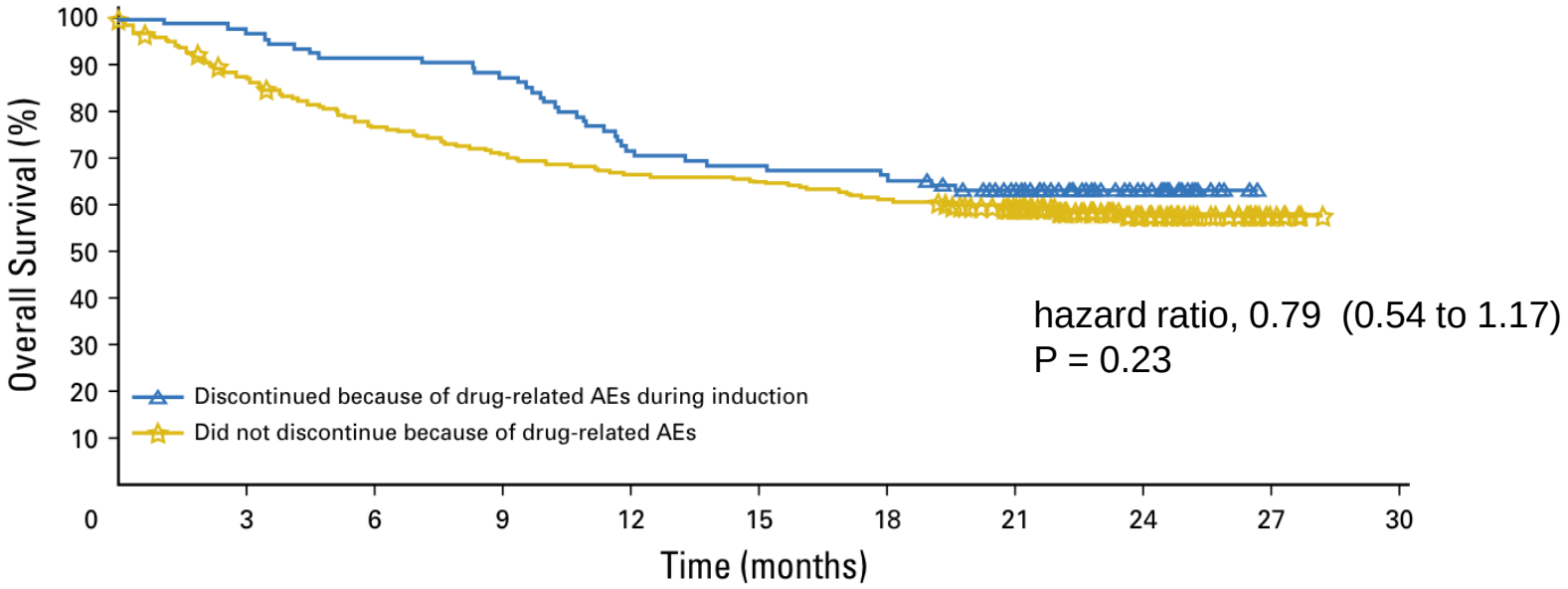
Adapted from ***Robert et al, Lancet Oncology, 2019***



Discontinuation does not correlate with progression

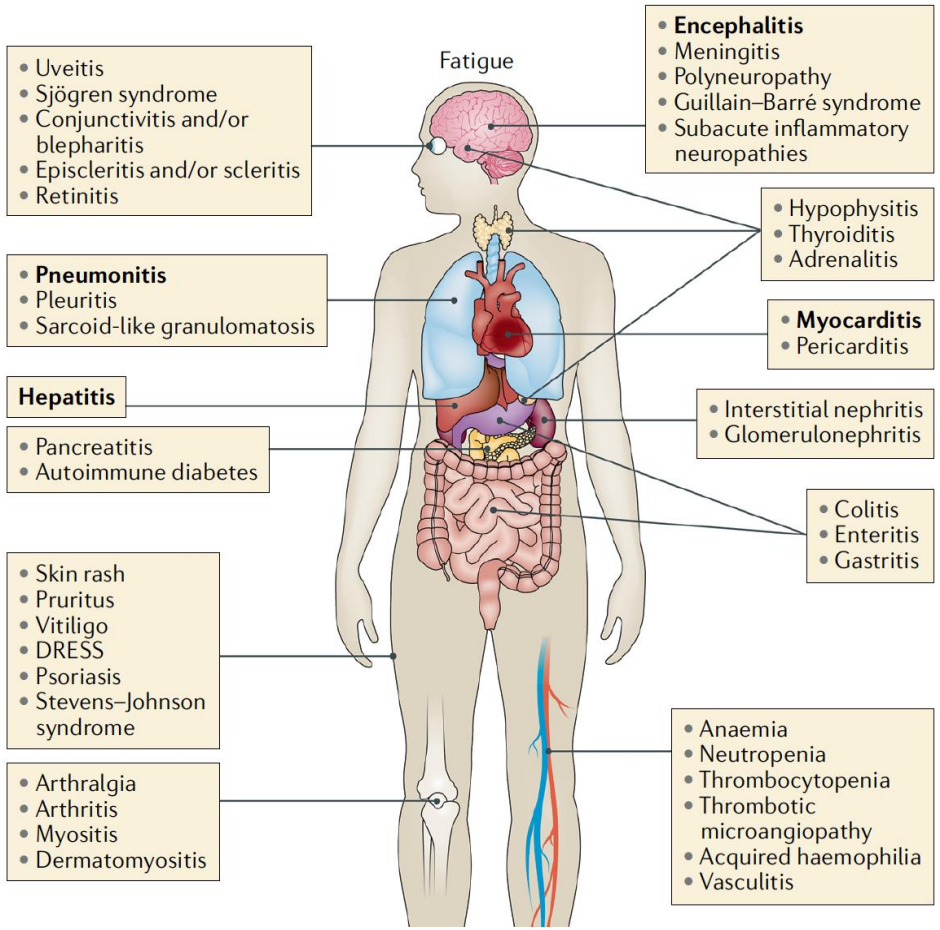
OS data from Ph2/3 nivo/ipi trials.
Patients with AEs **discontinued** during induction vs **continued** therapy

Schadendorf et al, JCO, 2017



hazard ratio, 0.79 (0.54 to 1.17)
P = 0.23

Long-Term and delayed *physical* toxicities associated with immunotherapy



Martins *et al*, *Nature Reviews*, 2018

- irAEs are variable in presentation and time-course
- 10% of patients may develop irAE >1y of tx
  (*Shah et al, JCO, 2018)*
- Many reports of toxicity even following discontinuation
- Delayed irAEs are likely underreported
  (*Couey et al, JITC, 2019)*

Personal financial burden associated with immunotherapy

$100,000+ annual cost of immunotherapy

- Many additional costs related to infusions, clinic visits, imaging, AE management ± hospitalizations
- Co-pays deplete savings → financial-based medical decisions

Societal financial burden associated with immunotherapy

$3 billion
- Cost of melanoma healthcare treatment in 2018

$173 billion
- Cost of cancer care in the United States by 2020

Shortening the duration of IO tx → cost reduction → improve accessibility of IO agents

Yu PP et al, JITC, 2019
Verma et al, JITC, 2019

SITCure Proposal 2018:

- There is **no** evidence supporting perpetual IO treatment
- There is **lots** of evidence supporting long-term physical toxicity
- There is **lots** of evidence supporting long-term personal financial toxicity
- There is **lots** of evidence supporting long-term societal financial toxicity

How soon can we stop therapy??

A randomized trial of early cessation of immunotherapy in patients with melanoma after 6 months or more of stable disease on nivolumab maintenance

Proposed 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

2y observation

1y further anti-PD-1

SD?

1y observation

Deposit data into SITCure database

Proposed trial Inclusion/Exclusion Criteria

Inclusion Criteria

- > 18 years old
- Unresectable Stage III or Stage IV melanoma (AJCC)
- **Received SOC NIVO/IPI → NIVO maintenance**
- SD, PR, or CR for least 6mo of (e.g. achieved a CR and then no further changes for 6mo)
- Received at least 9 months of NIVO 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
- 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, uncontrolled HIV

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Proposed trial statistical design

Thanks to Anita Giobbie-Hurder (DFCI)

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%**
- Non-inferiority margin of 10%: one-year recurrence rate in the discontinuation arm <27%

- 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. continuation) of 1.69
- Accrual to be uniform over approximately 5.5 years, final analysis at 6.5 years
- Three interim analyses at 30%, 40% and 50% accrual

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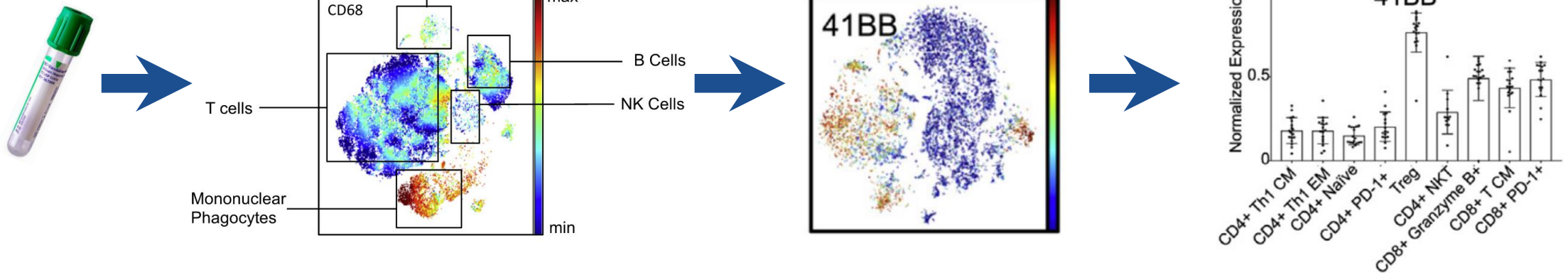
Exploratory Objectives – Peripheral Blood Immune Profiling

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



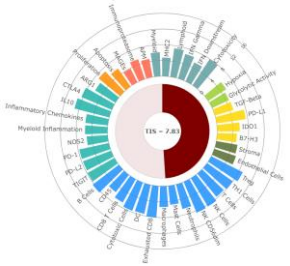
Immune and tumor activation status (gene expression profile with NanoString platform)

Pre-treatment FFPE (if available)

Pre-discontinuation and post-discontinuation PBMCs

Nanostring

Gene expression

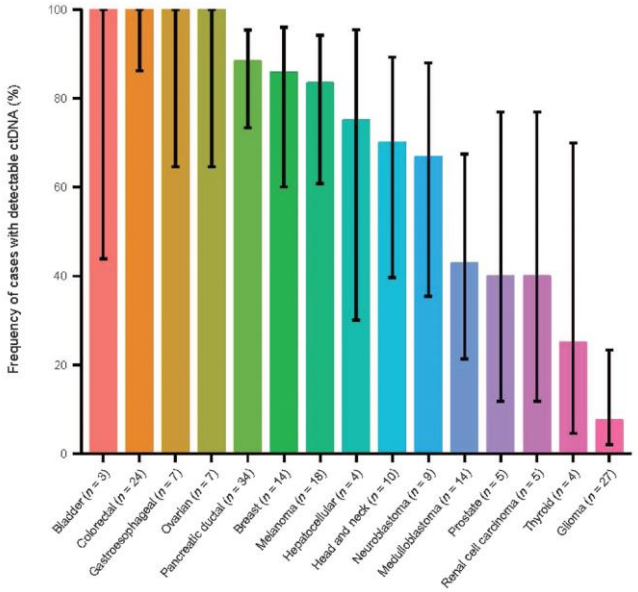


IO360 gene signature
- Tumor inflammation signature (*Ayers et al. JCI 2017*)
- Immune cell abundance

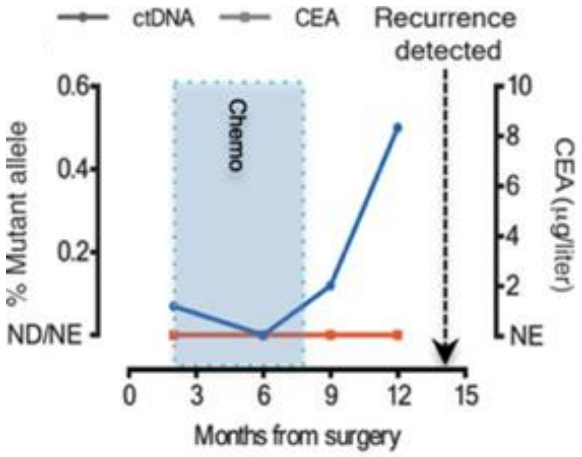
Adapted from Lavin *et al. Cell,* 2017

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

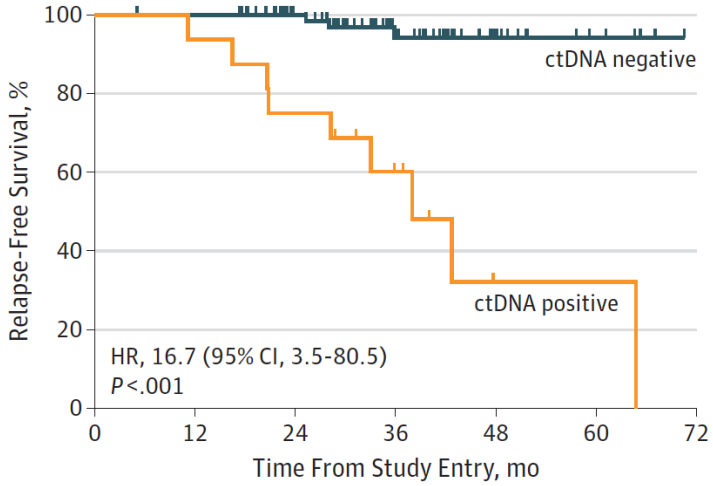
Most MM patients should have ctDNA



ctDNA may precede radiographic recurrence



ctDNA may be the best predictor



- Does ctDNA baseline detection associate with later recurrence?
- Does on-treatment detection of ctDNA predate clinical and radiographic recurrence?
- Does absence of ctDNA associate with prolonged response?

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

Current Status: Milestones Reached

Months 0-3

- Merged 3 Sparkathon teams into one SITCure team: Bi-monthly team calls to develop full protocol

Months 3-6

- Subgroups wrote full trial protocol (introduction, design, biospecimens plan, statistical analysis plan)
- Developed three hypotheses focusing on ctDNA, CyTOF, and NanoString to measure tumor, immune, and immune programming gene expression

Months 6-9

- Developed relationships with potential funding sources: BCBS, Kaiser Permanente, PICI
- Geoffrey Gibney's trial approved by ECOG

Months 9-12

- NanoString collaboration for analysis of biospecimens
- Identify co-investigator sites

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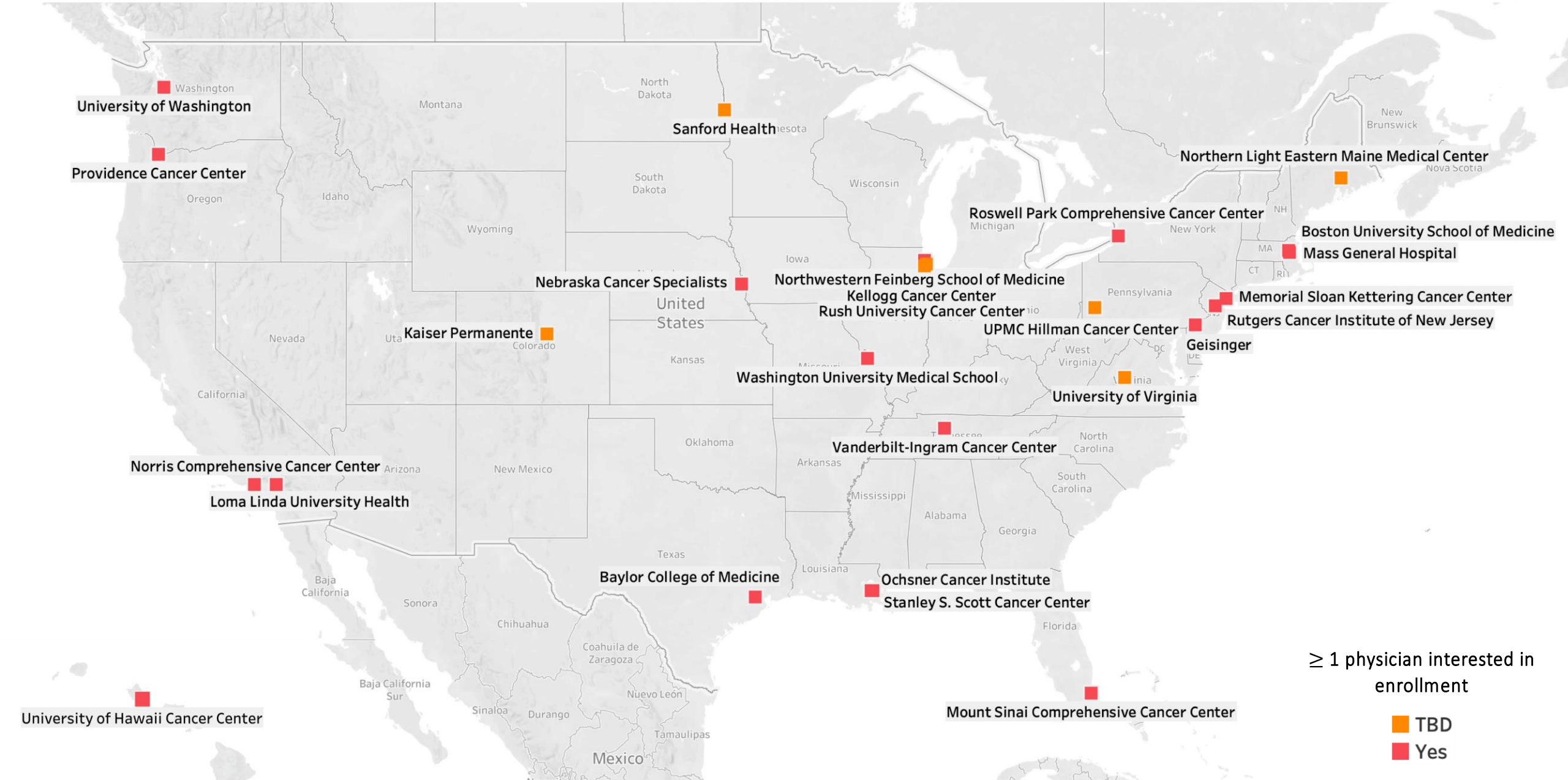
Provider interest in the trial to date



≥ 1 physician interested in enrollment

TBD

Yes

Plan for funding and accrual

De-escalation trials are important, though funding is often lacking

Goal: to accrue funding from interested parties

- Private insurers (e.g. BCBS)
- HMOs (e.g. Kaiser)
- Scientific foundations (e.g. PICI, CRI)
- Patient advocacy groups

We are still looking for **sites** and **funding**, please contact us!

education@sitcancer.org

thomas.marron@mountsinai.org

In the meantime we will collaborate with an ECOG-ACRIN effort

EA6192: A Phase II Study of Biomarker Driven Early Discontinuation of Anti-PD-1 Therapy in Patients with Advanced Melanoma

Geoffrey T. Gibney, MD
Co-leader, Melanoma Disease Group
Medical Director, Adult Outpatient Infusion Services
Lombardi Comprehensive Cancer Center
Medstar Georgetown University Hospital

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

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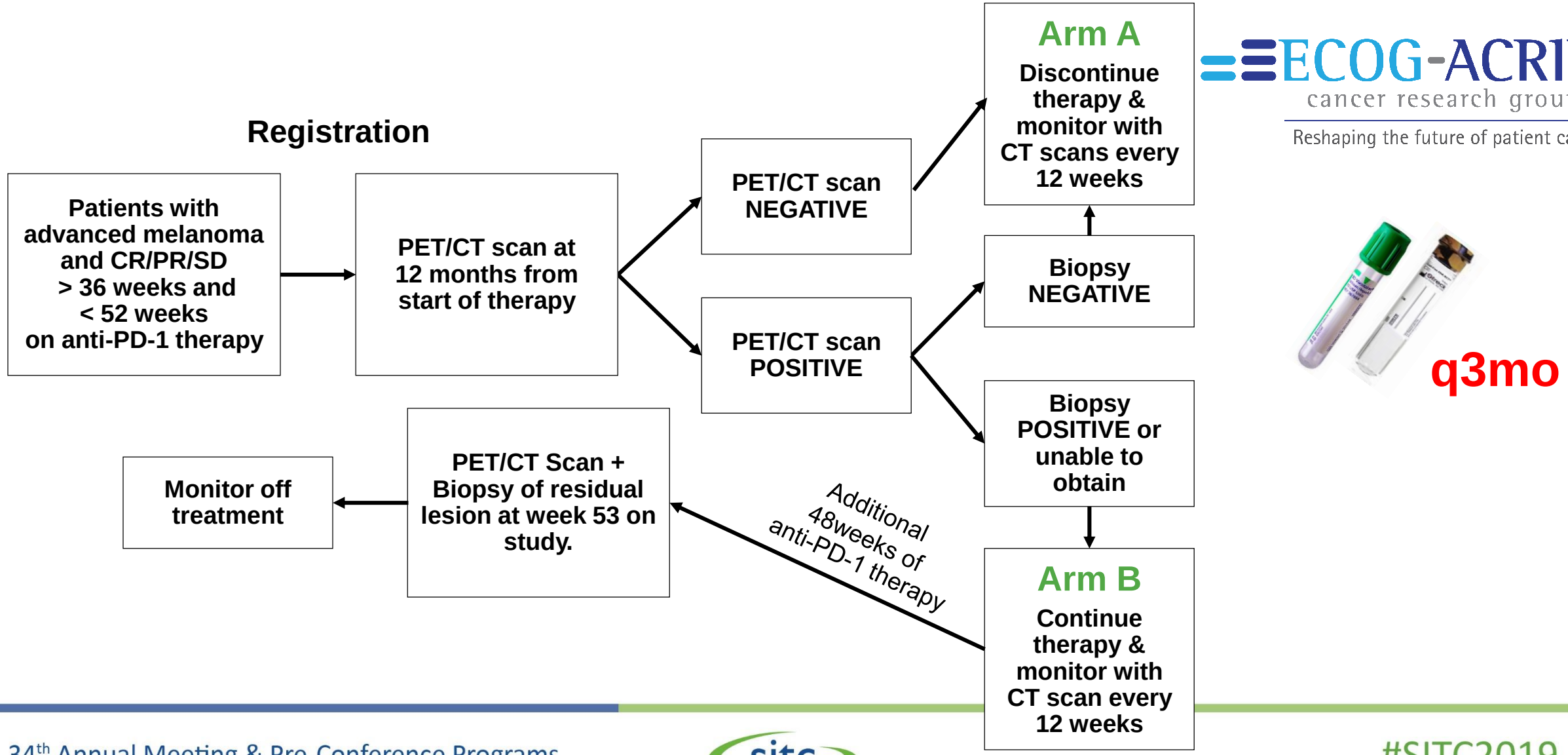

Adapted From Geoff Gibney's Slides

Plan for biomarker analysis for EA 6192 mirrors our cessation trial

ECOG-ACRIN cancer research group
Reshaping the future of patient care

ctDNA

- Is liquid biopsy more sensitive than biopsy of FDG avid stable lesions?
- Can the presence of ctDNA at baseline or during observation predict recurrence?

PBMC CyTOF

- Is there an immune phenotype at baseline or post-D/C that correlates with recurrence?

NanoString

- Is there a transcriptomic signature associated with recurrence?

Thank You

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

ECOG *EA6192* Team
- Geoffrey Gibney
- Michael Atkins
- Terence Wong
- Sandra Lee
- John Kirkwood

Sparkathon Anonymous Donor
Celgene
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