FRIENDS OF CANCER RESEARCH

Annual Meeting

Panel 2

Immuno-Oncology Drug Development for Patients with Disease Progression After Initial anti-PD-(L)1 Therapy

#FriendsAM19

Password: FOCR2019

Panel 2 Participants

Moderator: Ryan Sullivan, Massachusetts General Hospital

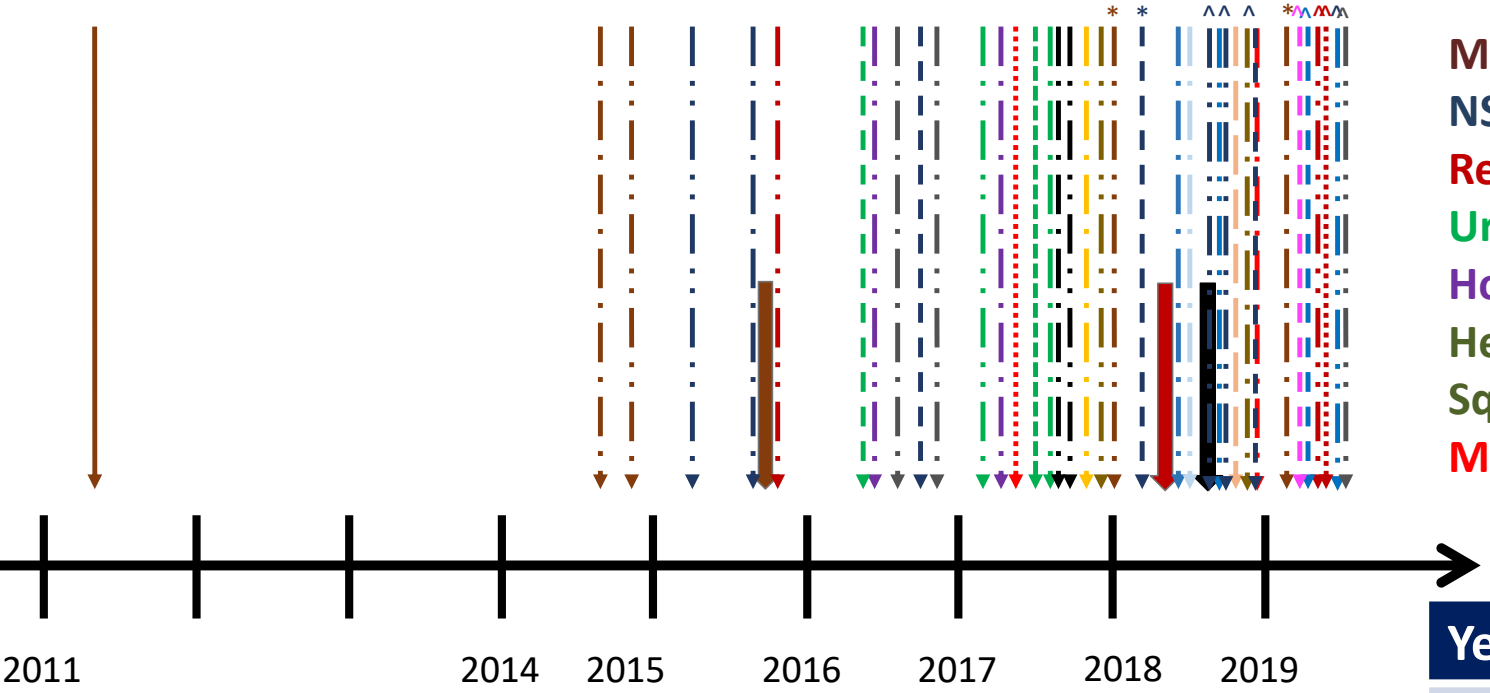
- Eric Rubin, Merck
- T.J. Sharpe, Patient Advocate
- Marc Theoret, FDA
- Maurizio Voi, Novartis

Immuno-Oncology drug development for patients with progression after initial anti-PD-1 therapy

Ryan J. Sullivan, MD*
Associate Director, Melanoma Program
Massachusetts General Hospital Cancer Center
Harvard Medical School

*on behalf of Bharani Dharan, Julie Brahmer, Illaria Conti, Eric Rubin, T.J. Sharpe, Marc Theoret, and Maurizio Voi

Immune checkpoint inhibitors and US FDA approvals



Melanoma
NSCLC
Renal Cell Carcinoma
Urothelial Bladder Cancer
Hodgkin Lymphoma
Head and Neck
Squamous Cell Carcinoma
Merkel Cell Carcinoma

MSI Cancers
Gastric Cancer
Hepatocellular Carcinoma
Primary mediastinal BCL
Cervical SCC
Small cell lung cancer
Cutaneous SCC (cuSCC)
Triple neg breast cancer

Anti-CTLA4

Ipilimumab

Ipi/nivo

Anti-PD-1

Pembrolizumab

Nivolumab

Cemiplimab

Anti-PD-L1

Atezolizumab

Avelumab

Durvalumab

Year	Drugs	Approvals	Diseases	Combos
2011	1	1	1	
2014	2	2	1	
2015	3	4	3	1
2016	3	5	4	
2017	4	10	7	
2018	5	12	10	5
2019	4	7	5	6

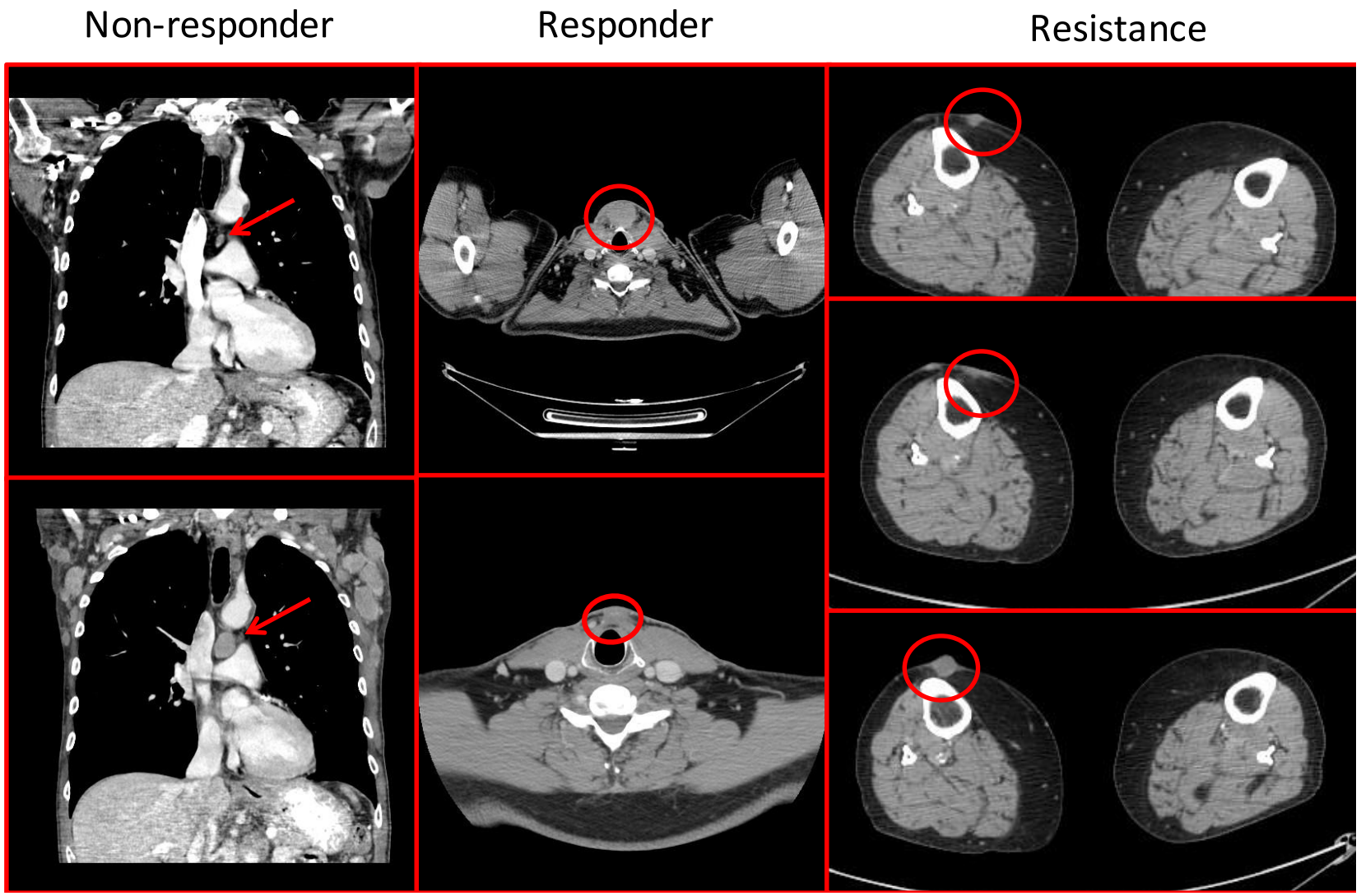
What is the unmet need?

Most patients are not receiving benefit

How do we address unmet need?

1. Definition of resistance
2. Improve our understanding of mechanisms of therapeutic resistance
3. Better predictive biomarkers of single-agent benefit
4. Develop more effective therapies (e.g. combinations)

Defining response and non-response radiographically



FOCR White Paper

- Convened a working group of 8 experts from Academia, Industry, Patient Advocacy, and U.S. FDA
- Polled six major pharmaceutical companies about their “definitions” of PD-(L)1 inhibitor Relapse/Refractory disease
- Outlined key principles and considerations in defining relapsed/refractory disease
- Provided a case study of the development of pembrolizumab and nivolumab in patients with advanced melanoma following ipilimumab
- Identified key outstanding questions

FOCR White Paper

- Convened a working group of 8 experts from Academia, Industry, Patient Advocacy, and U.S. FDA

- **Polled six major pharmaceutical companies about their "definitions" of PD-(L)1 inhibitor Relapse/Refractory disease**

  - **5/6 had a definition for relapsed/refractory, all 5 agreed that different settings deserved specific language**
  - **3/6 had a harmonized definition of relapsed/refractory disease for their IO protocols**

FOCR White Paper

- Convened a working group of 8 experts from Academia, Industry, Patient Advocacy, and U.S. FDA
- Polled six major pharmaceutical companies about their “definitions” of PD-(L)1 inhibitor Relapse/Refractory disease
- **Outlined key principles and considerations in defining relapsed/refractory disease**
- **Provided a case study of the development of pembrolizumab and nivolumab in patients with advanced melanoma following ipilimumab**
- **Identified key outstanding questions**

Key principles and considerations?

1) **Adequate exposure**
    a) # doses?
    b) Duration of therapy?
2) **Confirmation of disease progression**
    a) Which response evaluation criterion (e.g. RECIST vs irRC vs iRECIST)
    b) Repeat imaging necessary to rule out pseudoprogression?
    c) If so, what is the optimal interval (e.g. 2, 4, 6 weeks) on confirmatory scans?
3) **Does treatment setting requires individual definitions?**
    a) Primary resistance
    b) Secondary resistance
    c) Resistance after stopping therapy
        a) Does timing post-exposure matter?
        b) Does reason for discontinuation matter?

FOCR White Paper

- Convened a working group of 8 experts from Academia, Industry, Patient Advocacy, and U.S. FDA
- Polled six major pharmaceutical companies about their “definitions” of PD-(L)1 inhibitor Relapse/Refractory disease
- Outlined key principles and considerations in defining relapsed/refractory disease
- **Provided a case study of the development of pembrolizumab and nivolumab in patients with advanced melanoma following ipilimumab**
- **Identified key outstanding questions**

FOCR White Paper

- Convened a working group of 8 experts from Academia, Industry, Patient Advocacy, and U.S. FDA
- Polled six major pharmaceutical companies about their “definitions” of PD-(L)1 inhibitor Relapse/Refractory disease
- Outlined key principles and considerations in defining relapsed/refractory disease
- Provided a case study of the development of pembrolizumab and nivolumab in patients with advanced melanoma following ipilimumab
- **Identified key outstanding questions**

Key outstanding questions?

- What data is needed to better understand when re-challenge of same/similar anti-PD-(L)1 when used in combination with another agent?
- What preclinical models or clinical-translational data will be helpful to identify best, next line IO therapies in setting of R/R disease? What is the role of biomarkers in helping?
- What are optimal trial designs to study the R/R population?
  - Early futility studies?
  - Adaptive randomization?
  - Cross over?
- Are there better monitoring tools to be implemented in the adjuvant setting to identify which patients are “responders” versus “non-responders”?

Acknowledgements

- Friends of Cancer Research particularly Diana Merino

FRIENDS OF CANCER RESEARCH

Annual Meeting

Panel 2

Immuno-Oncology Drug Development for Patients with Disease Progression After Initial anti-PD-(L)1 Therapy

#FriendsAM19

Password: FOCR2019

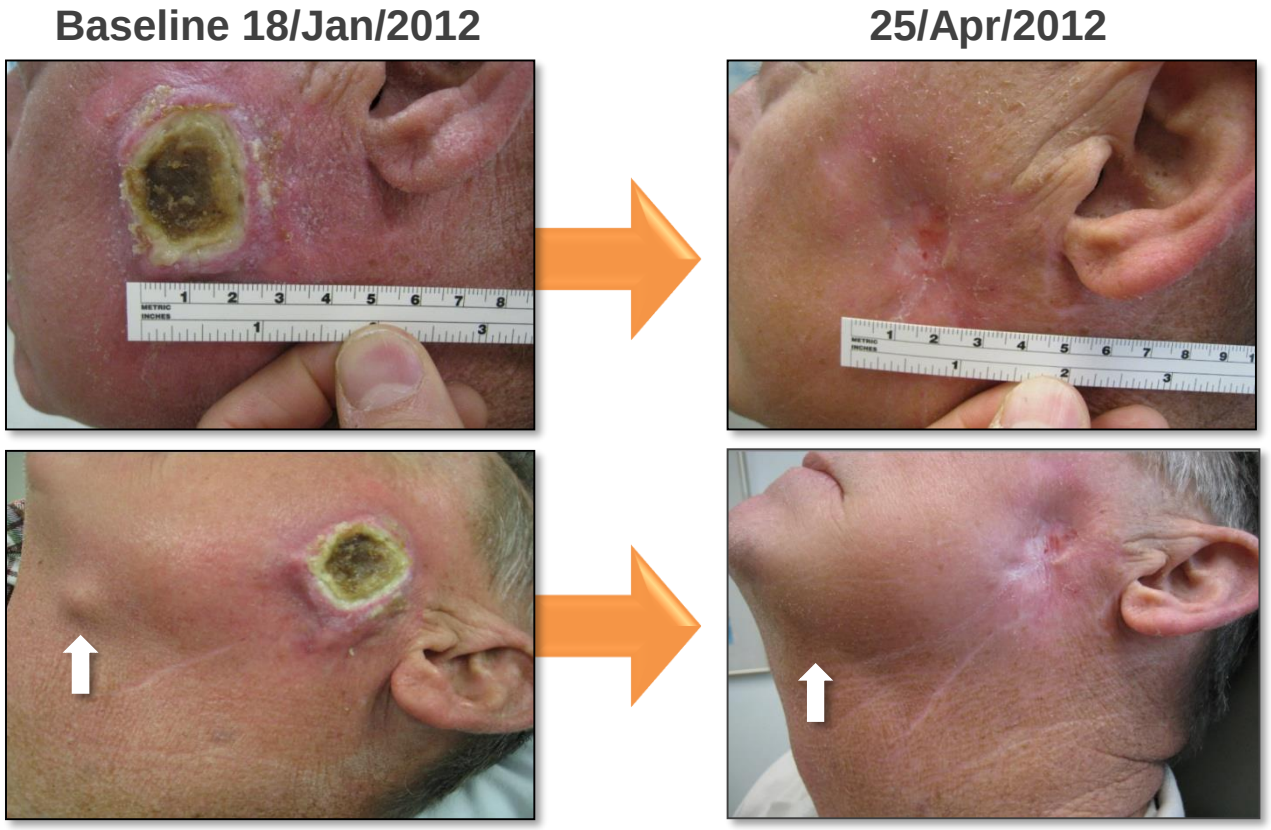
Clinical Trial Approach to a Patient Population Refractory to Immunotherapy
Keynote 001 Example

Eric H. Rubin

First in Human Study for Pembrolizumab Keynote-001

- Initiated in 2011 - 3+3 dose escalation with expansion cohort in melanoma, estimated sample size 32
- Striking responses observed in initial melanoma patients enrolled in dose escalation cohort
  - Led to increase in expansion cohort sample size to 60, including ipilimumab-naïve and ipi-treated patients
  - 97% power to exclude null hypothesis of 10% ORR and 30% disease-control rate (DCR) in ipi-naïve patients, with alternative hypothesis of 30% ORR or 55% DCR (Hochberg), one-sided p= 0.05
  - Included interim futility analysis after evaluation of 11 ipi-naïve patients

Clinical Activity in a Melanoma Patient



Courtesy of
A. Ribas, MD,
B. Chimielowski, MD
P. Tumeh, MD

54-yr-old male with desmoplastic melanoma, progressed on ipilimumab

Hamid et al NEJM, 2013

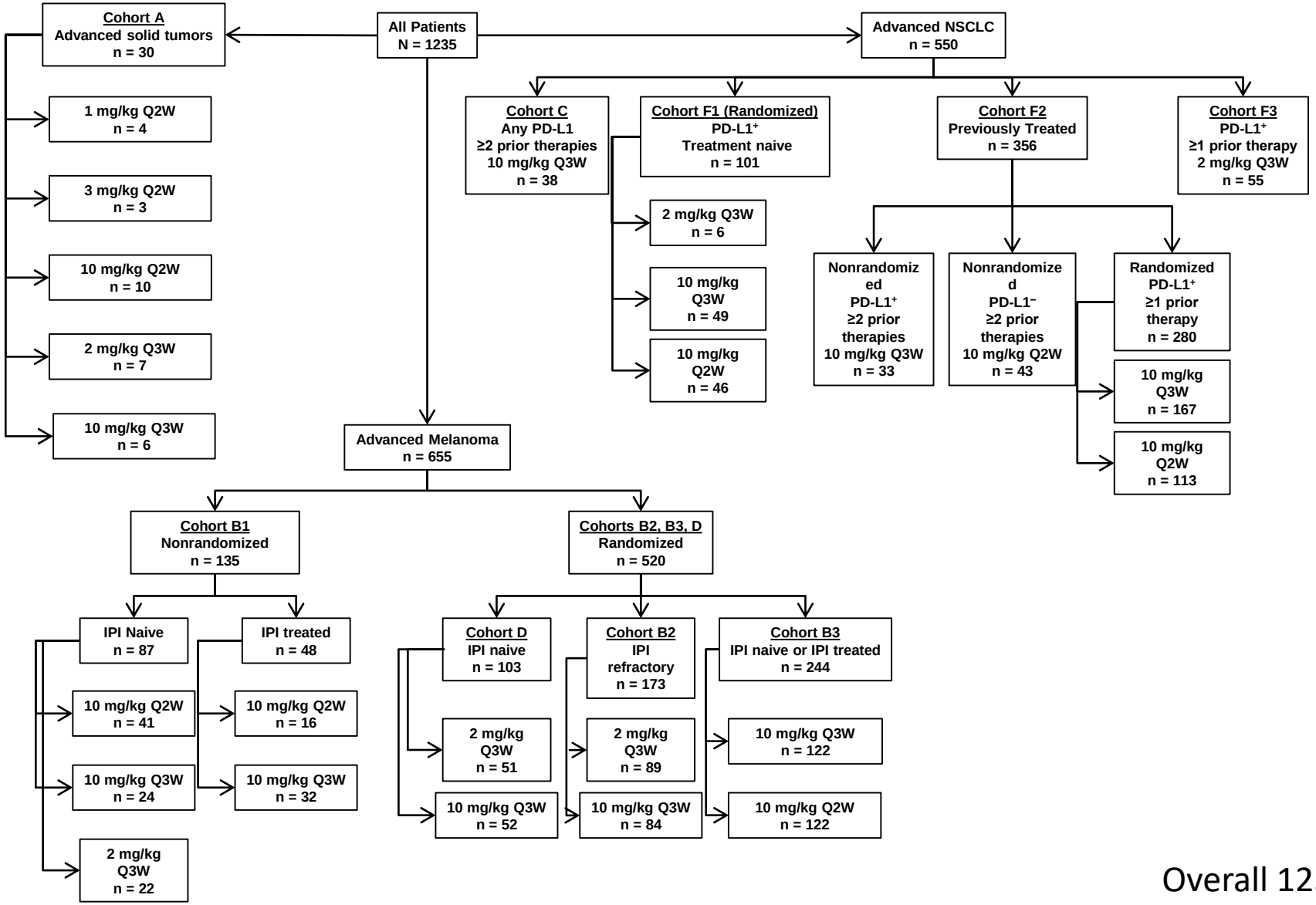
Approach to Ipi-Refractory Cohort B2

- Given preliminary evidence of activity in ipi-treated patients, added ipi-refractory cohort B2 to evaluate efficacy in a strictly defined population with high unmet need
  - Discussed cohort design with FDA to allow for potential accelerated approval
  - To address concern over pseudoprogression, required previous treatment with at least two doses of ipilimumab 3 mg/kg or higher administered every 3 weeks
  - Confirmed disease progression using immune-related response criteria within 24 weeks of the last dose of ipilimumab (confirmatory CT scan required)
- Randomized cohorts to confirm recommended dose of 2 mg/kg (vs 10 mg/kg) Q3W
- 80 ipilimumab-refractory patients at each dose
  - 85% power to detect a 15% difference in ORR between the two doses at 10% type 1 error (one-sided) when the ORR in the inferior group was 10%

Robert et al., Lancet 2014

Keynote-001 Treatment Cohorts

4 “phase 2 study-like” parts including 3 randomized dose comparison sub-studies



Overall 1235 patients treated

Keynote-001 Results

This adaptive “phase 1” study was the basis for 3 FDA approvals:

1. Accelerated approval for patients with ipi-refractory melanoma (first FDA approval of anti-PD-1 antibody)
2. Accelerated approval for patients with previously treated NSCLC with tumors that express PD-L1
3. Dako PD-L1 IHC 22C3 pharmDx test, the first FDA-approved test designed to detect PD-L1 expression in NSCLC

Benefits of Large Adaptive Ph1 Studies

- Can efficiently address multiple hypotheses with appropriate type 1 error control
  - Population, dose, and biomarker development
- Aligned with single-arm trial design as one of the accepted approaches to seeking accelerated approval
- Can be performed with sufficient rigor to support regulatory filings (e.g. central independent review of efficacy)
- Accelerates development and approval for drugs that are transformative in nature based on early and strong efficacy signals
  - Avoids multiple trials replicating the initial findings
  - Makes transformative therapies available to patients at earliest opportunity, particularly where effective therapies do not exist

Challenges of Large Adaptive Ph1 Studies

- Operational burden on sites and sponsor due to rapid accrual in multiple separate cohorts
- Multiple amendments generate protocol complexity and potential adherence issues
- Complexity of analysis and interpretation of data supporting multiple hypotheses tested simultaneously rather than sequentially
  - E.g. dose hypotheses evaluated in NSCLC simultaneously with melanoma, rather than waiting for melanoma data
  - Must ensure statistical rigor
- Multiple database locks during an ongoing study
  - Programming challenges to “isolate” one cohort for submission purposes

FRIENDS OF CANCER RESEARCH

Annual Meeting

Panel 2

Immuno-Oncology Drug Development for Patients with Disease Progression After Initial anti-PD-(L)1 Therapy

#FriendsAM19

Password: FOCR2019

Platform Studies: Evaluating novel PD(L)1 based combinations

Maurizio Voi, MD
Novartis Pharmaceutical Corporation

NOVARTIS

Background

- Patients who do not respond or progress or who do not derive long- term benefit from treatment with PD(L)1 inhibitors have limited treatment options

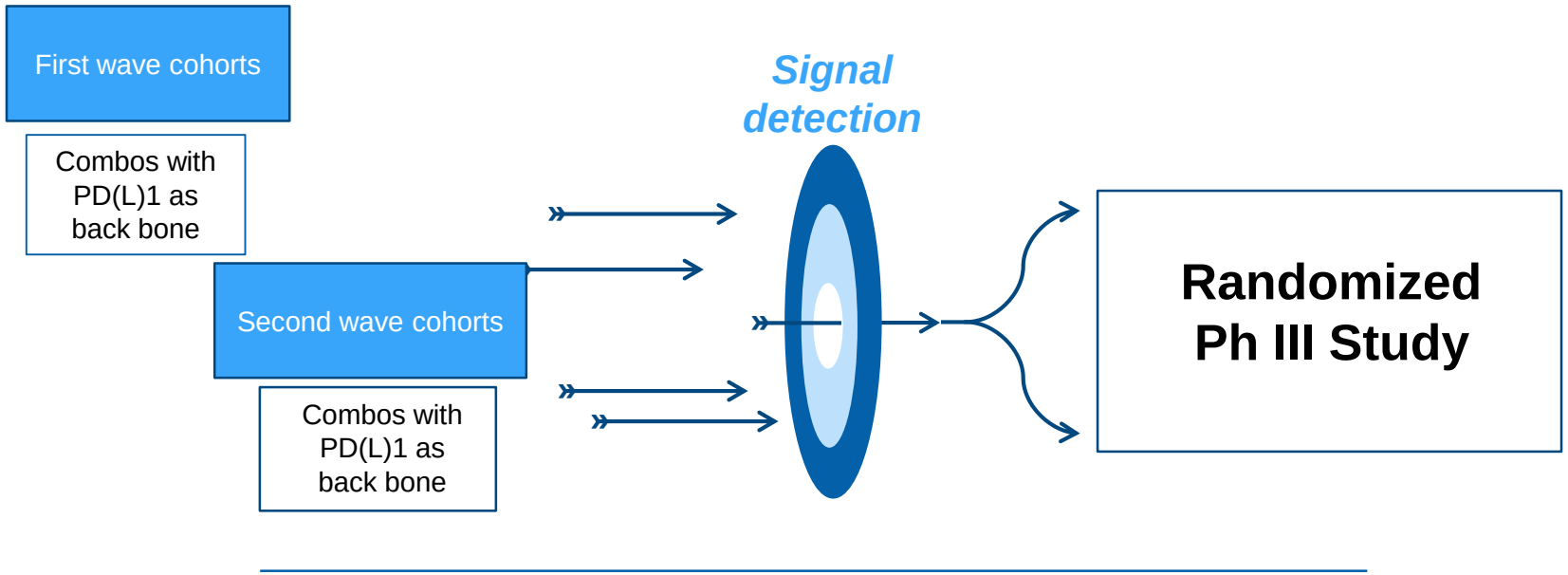
- A combination of intrinsic or extrinsic tumor-cell resistance mechanisms may play a role
  - Intrinsic mechanisms may include lack of antigen expression, alterations in signaling pathways, or insensitivity to tumor cell death
  - Extrinsic mechanisms may include expression of inhibitory immune checkpoints (e.g., PD-1 and LAG-3). Cytokines and metabolites are released into the tumor microenvironment

“Platform Trial: Pick the Winner Design ”

Enables Accelerated Development, Exploration and Development of multiple combinations and associated biomarkers within 1 single trial

“Pick the Winner Multi-cohort Phase II Design”

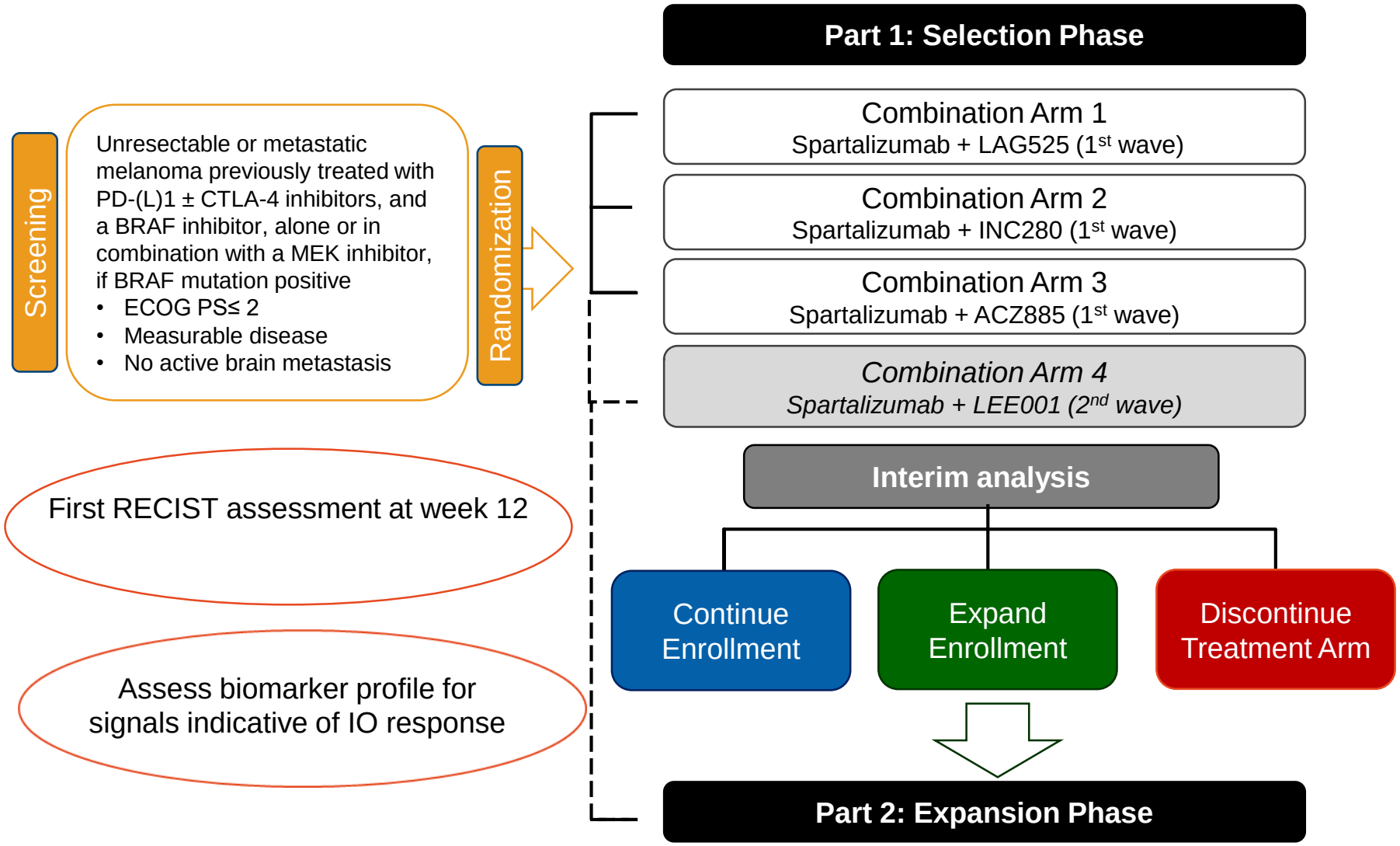
Rapid and Adaptable Enrollment based on Early Clinical Signals



Increased “Proof of Confidence” through Clinical and Mechanistic Rationale

Robust Understanding of PD-1 r/r disease; Systematic/standard platform for inter-cohort evaluation; Comprehensive assessment of molecular, immunologic, pathologic, and radiologic relationships

PLATforM: Study Schema



NCT03484923

PLATforM: Biomarker Assessments

Biomarker parameter - changes before/after treatment	Analysis	Mandatory biopsy samples
Number of tumor infiltrating T-cells (TILs)	CD8+ T-cell numbers within tumoral regions assessed by IHC	• Screening • Early on-treatment @ 3-4 weeks (C1D21-C2D1)
Activation level of TILs	T-cell activation marker (Granzyme B & Ki67) levels within tumoral regions assessed by multiplex immunofluorescence	
Modulations in immune gene expression signatures	Changes in expression profiles of gene signatures established to be relevant for response to IO therapy	

- Interim biomarker analyses focused on T cell quantification and characterization support secondary study endpoints
- The proportion of patients with a favorable biomarker profile for T-cells, defined as having increases in ≥ 2 of above T-cell parameters, is calculated for each treatment arm.
- Biomarker data assist decision-making for treatment arm continuation, expansion or futility.

The HUDSON Study

- Rational combination of immunotherapy with other agents based on the genetic profile of each individual patient
- A phase 2 non-randomized study that assesses novel biomarker-directed drug combinations which include durvalumab, as a backbone in patients with metastatic NSCLC who progressed on an anti-PD-(L)1 containing therapy, and a platinum doublet.
- An umbrella study with a modular design, allowing assessment of efficacy and safety in multiple arms.
- This flexible design also allows future treatment arms to be added as needed via protocol amendment
  - Five combination doublets open to date (AZD9150, AZD6738, Vistusertib, Olaparib, Oleclumab)

Panel 2 Participants

Moderator: Ryan Sullivan, Massachusetts General Hospital

- Eric Rubin, Merck
- T.J. Sharpe, Patient Advocate
- Marc Theoret, FDA
- Maurizio Voi, Novartis