

Biomarker-Based Clinical Trials in Precision Oncology

Jianda Yuan MD. PhD.
Translational Oncology
Early Oncology Department
Merck & Co., Inc.
2021 SITC Winter School
February 22-24, 2021

Disclosure

- ❖ Full time Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA Employee; stock ownership Merck & Co., Inc., Kenilworth, NJ, USA



Society for Immunotherapy of Cancer

Outline

- ❖ Biomarker definition, classification, roles in early/late drug development and precision oncology
- ❖ Biomarkers in forward and reverse translation
- ❖ Balance between discovery science and biomarker CDx
- ❖ Dural biomarker strategy for translational oncology
- ❖ Immunotherapy biomarker clinical trials



Society for Immunotherapy of Cancer

Biomarker Definition

- ❖ “A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”

BIOMARKERS DEFINITIONS WORKING GROUP: BIOMARKERS AND SURROGATE ENDPOINTS: PREFERRED DEFINITIONS AND CONCEPTUAL FRAMEWORK. CLIN PHARMACOL THER 2001;69:89-95.

- ❖ FDA Pharmacogenomics Guidance further defines possible, probable and known valid biomarker categories depending on available scientific information on the marker



Society for Immunotherapy of Cancer

Why Are Biomarkers Important?

- ❖ Diagnosis is the foundation of therapy
- ❖ Biomarkers are quantitative measures that allow us to diagnose and assess the disease process and monitor response to treatment
- ❖ Biomarkers are also crucial to efficient medical product development
- ❖ As a consequence of scientific, economic and regulatory factors, biomarker development has lagged significantly behind therapeutic development



Society for Immunotherapy of Cancer

Biomarker Classification/Application

- ❖ Prognostic biomarkers
A measurement made before treatment to indicate long-term outcome for patients untreated or receiving standard treatment
- ❖ Predictive biomarkers
A measurement made before treatment to select good patient candidates for the specific treatment
- ❖ Surrogate endpoints
A measurement made before and after treatment to determine whether the treatment is working



Society for Immunotherapy of Cancer

Use of Biomarkers in Early Drug Development and Decision Making

- ❖ Evaluate activity in animal models to understand drug mechanisms
- ❖ Bridge animal and human pharmacology via proof-of-mechanism or other observations
- ❖ Evaluate safety in animal models, e.g., toxicogenomics
- ❖ Assess dose-response and select the right dose based upon PK/PD analyses
- ❖ Evaluate human safety early in development



Use of Biomarkers in Later Drug Development and Decision Making

- ❖ Evaluate optimal regimen for desired pharmacologic effect
- ❖ Identify the right patient who likely respond to the particular treatment
- ❖ Investigate the resistance mechanisms in patient fail to particular treatment
- ❖ Assess the mechanisms related with drug safety



Society for Immunotherapy of Cancer

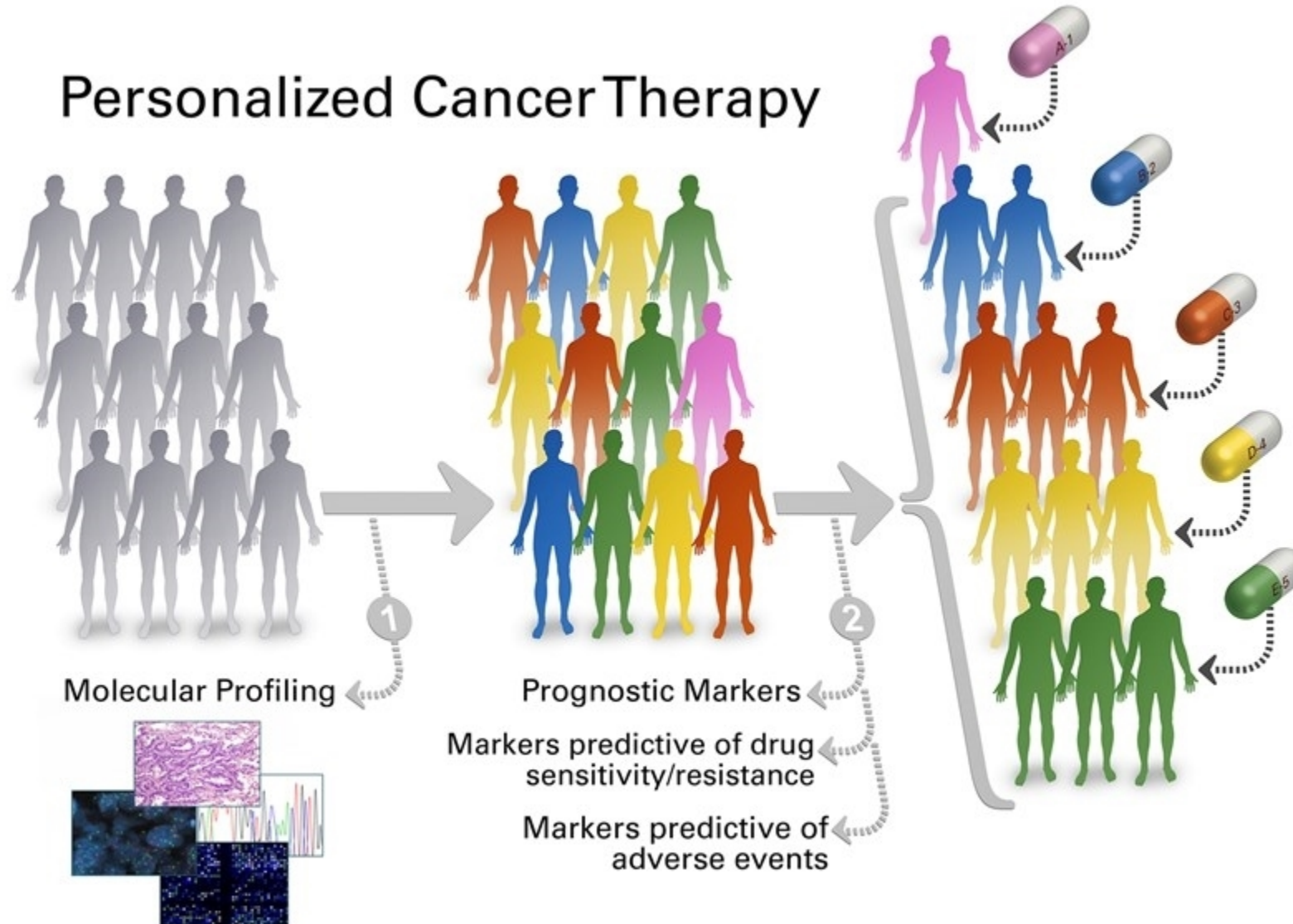
Use of Surrogate Endpoints in Late Drug Development

- ❖ Efficacy: Use to assess whether drug has clinically significant efficacy
- ❖ Surrogate endpoints may be used to support “accelerated approval” of a drug if the surrogate is deemed reasonably likely to predict a clinical endpoint of interest
- ❖ A few surrogate endpoints (e.g., blood pressure, tumor size by RECIST) are acceptable for full approval



Society for Immunotherapy of Cancer

Biomarkers in Precision Oncology



Biomarker in Forward and Reverse translation



Man Catching Rainbow In Funnel, Bruno Budrovic

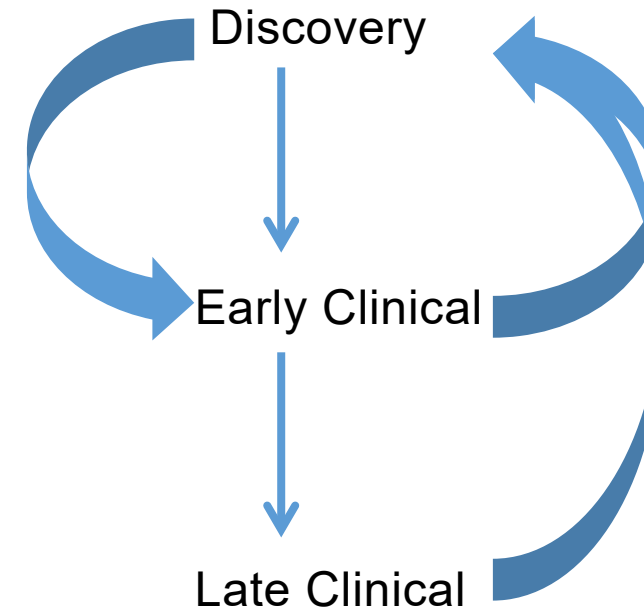
Purpose of Translational Oncology?

- Use scientific findings from our own analyses and translational collaborations to efficiently and effectively inform drug development

Whom are we serving?

- Discovery, Early and Late Development
- Difference between target therapy and immunotherapy

Translational Oncology

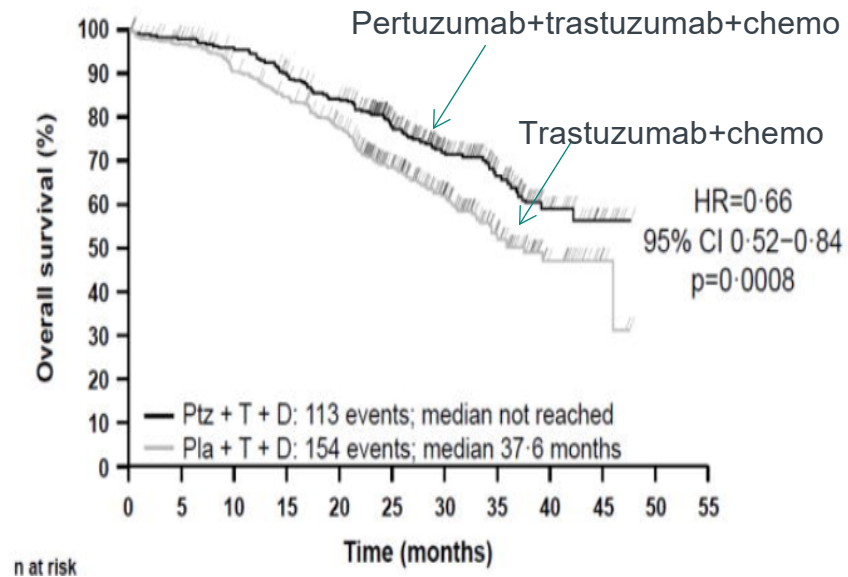
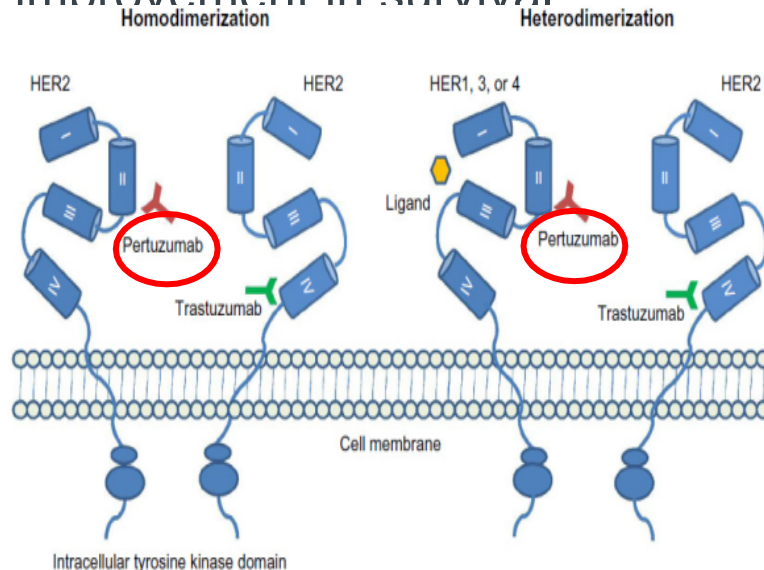


Forward Translation: Understand the Target → Design the Drug

HER2 amplification identified as a driver genetic alteration in breast cancer in the 1980s

Targeting by a monoclonal antibody, trastuzumab, based on that discovery

Pertuzumab subsequently developed to co-target HER family with further improvement in survival



Slide courtesy of Alex Snyder

Ulrich et al Nature 1984, Yamamoto T et al Nature 1987;
Slamon D et al Science 1989; Swain S et al Lancet
Oncol 2013; Lamond and Younis Int J Womens Health
2014

Reverse Translation: Make a Better Drug

EGFR mutations and EGFR inhibitors in

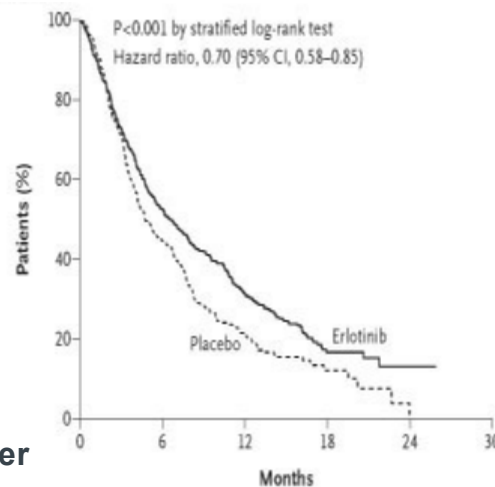
EGFR targeting in NSCLC was based on hypothesis of *EGFR* amplification as driver alteration

Initial Phase III study of erlotinib vs. placebo showed overall response rate of **8.9%**, duration of response **7.9mo**

Concurrent academic papers revealed the mechanism of sensitivity to 1st generation EGFR inhibitors: specific, sensitizing mutations

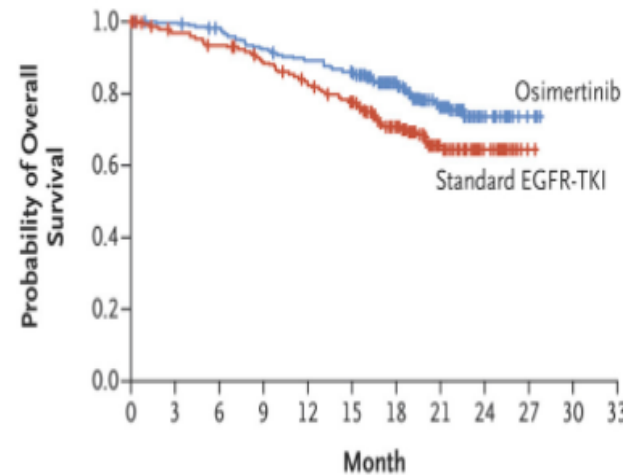
Identification of dominant resistance mechanism, *EGFR T790M* led to design of new EGFR inhibitors

Osimertinib de



Slide courtesy of Alex Snyder

Or



response **17.2mo**

Shepherd FA et al
NEJM 2005; Lynch
TJ NEJM 2004;
Paez JG et al
Science 2004; Pao
et al PNAS 2004;
Pao et al JCO
2005; Soria JC et al
NEJM 2018

New Agents Challenge Historical Dichotomy of Biomarkers

Targeted therapy

Biomarker assesses presence/absence of specific mutation or fusion

required for response



Fixed for indication

Examples: *EGFR*, *KRAS* mutations

Immunotherapy

Biomarker assesses tumor/immune biology related to response



Where do you draw the line?

Biomarkers for PARP inhibitors and immunotherapy exemplify this challenge.

Slide courtesy of Jeff Evelhoch

Continuous Biomarkers

❖ Homologous recombination deficiency

→ correlates with response to poly(ADP-ribose) polymerase (PARP) inhibitors

❖ PD-L1

❖ Tumor mutational burden

} correlate with response to PD-(L)1 inhibitors



Society for Immunotherapy of Cancer

Forward Translation: Understand the Target → Design the Drug PD-(L)1

- ❖ Mechanisms of PD-1 and PD-L1 discovered in preclinical models in the 1990s
- ❖ Nivolumab and pembrolizumab (targeting PD-1) presented first data in 2012
- ❖ Avelumab, durvalumab, atezolizumab (targeting PD-L1) and cemiplimab (PD-1) also have approved indications
- ❖ Selection by PD-L1 staining is required in some cancers
- ❖ Label revision to pembrolizumab and atezolizumab:
 - July 2018: FDA announcement that PD-L1-low urothelial cancers should not be treated with these agents
 - This change underscores the importance of the biology being targeted

Agata Y et al. Int Immunol. 1996; Ishida Y et al. EMBO J. 1992; Nishimura H et al. Immunity. 1999; Freeman GJ et al. J Exp Med. 2000; Brahmer J et al. NEJM 2012; Hamid O et al. NEJM 2018

PD-L1 Staining for Tumor or Tumor + Immune Cells Determines Therapeutic Options in Some

TPS=tumor
proportion
score

No PD-L1 expression		PD-L1 expression		High PD-L1 expression	
TPS <1%		TPS ≥1%		TPS ≥50%	
10x	40x	10x	40x	10x	40x

	No PD-L1 Expression (TPS <1%)	PD-L1 Expression (TPS 1% to 49%)	High PD-L1 Expression (TPS ≥50%)
First-line KEYTRUDA + cisplatin or carboplatin and pemetrexed (nonsquamous; no EGFR or ALK genomic tumor aberrations)	✓	✓	✓
First-line KEYTRUDA (nonsquamous or squamous; no EGFR or ALK genomic tumor aberrations)			✓
Second-line or greater KEYTRUDA (nonsquamous or squamous; prior treatment required for patients with EGFR or ALK genomic tumor aberrations)		✓	✓

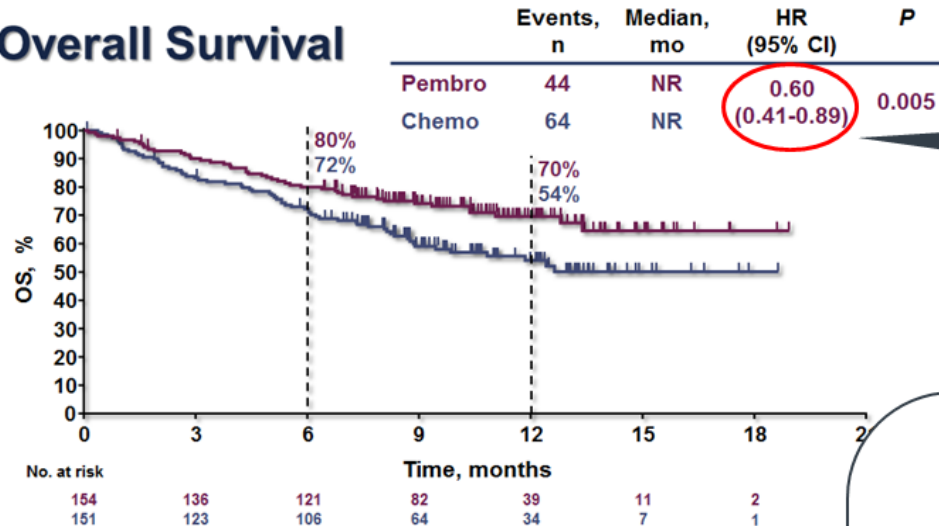
<https://www.keytruda.com/hcp/nsclc/pd-l1-expression-testing/#pathologists>

KEYNOTE-024

First-Line Pembrolizumab vs

US Approval, October 2016

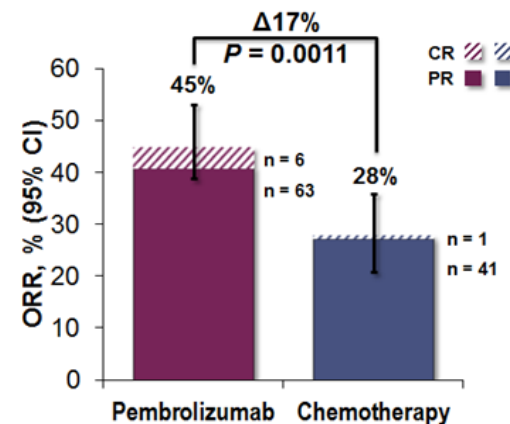
Overall Survival



40% risk reduction of death

50% crossover in ITT population
54% crossover excluding ongoing pts

Objective Response



	Pembro Responders n = 69	Chemo Responders n = 42
TTR, mo median (range)	2.2 mo (1.4-8.2)	2.2 mo (1.8-12.2)
DOR, mo median (range)	NR (1.9+ to 14.5+)	6.3 mo (2.1+ to 12.6+)

Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

2016 ESMO congress

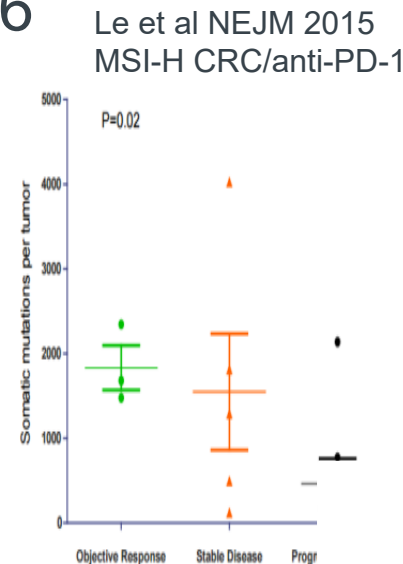
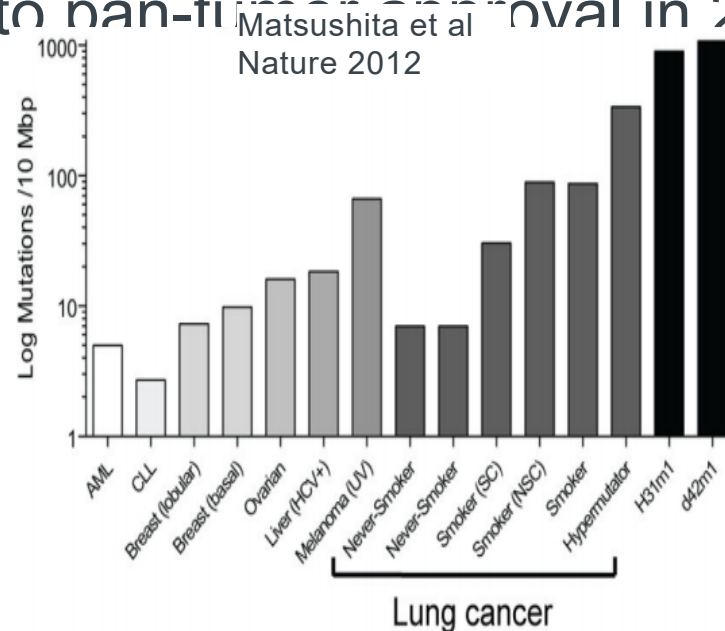
Forward Translation: Understand the Target

→ Choose the Drug Mismatch Repair Deficiency and

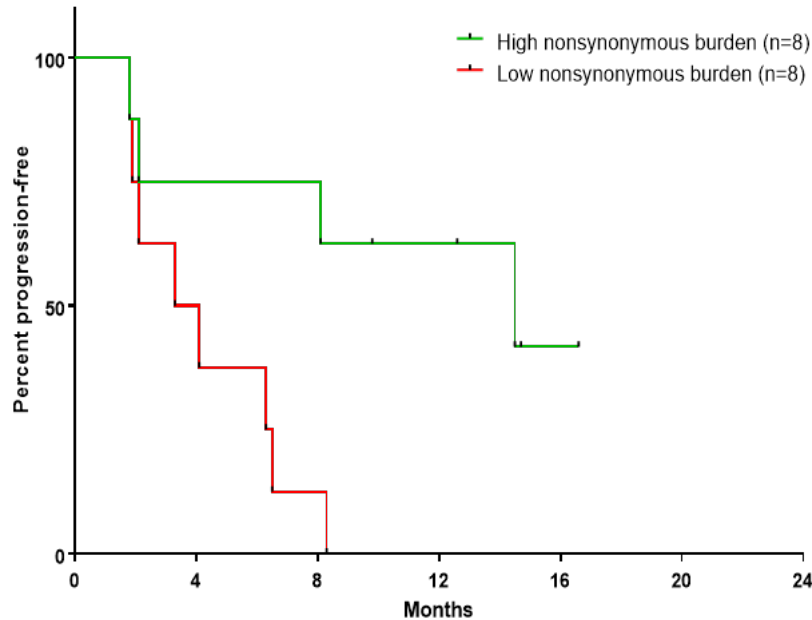
Concept of highly mutated, carcinogen-induced tumors being more immunogenic dates back to 1950s

Schreiber lab used next generation sequencing in mouse model of carcinogen-induced sarcoma to support prior findings: many mutations → greater immunogenicity

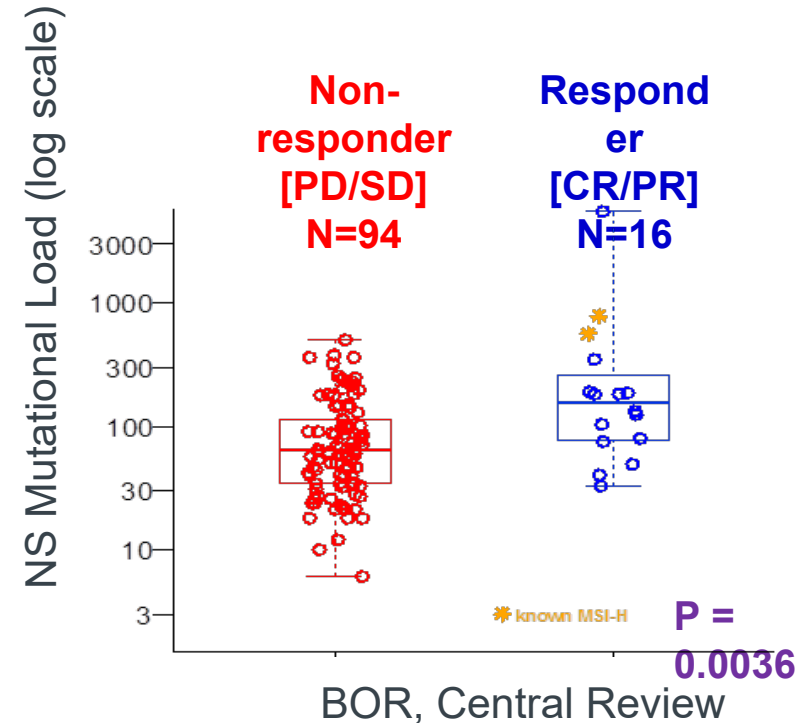
Investigator-initiated study of pembro in MSI-H cancers demonstrated efficacy that later led to pan-tumor approval in 2016



Forward Translation: Understand the Target → Choose the Drug Tumor Mutational Burden



Rizvi NA et al. Science 2015;348:124-128



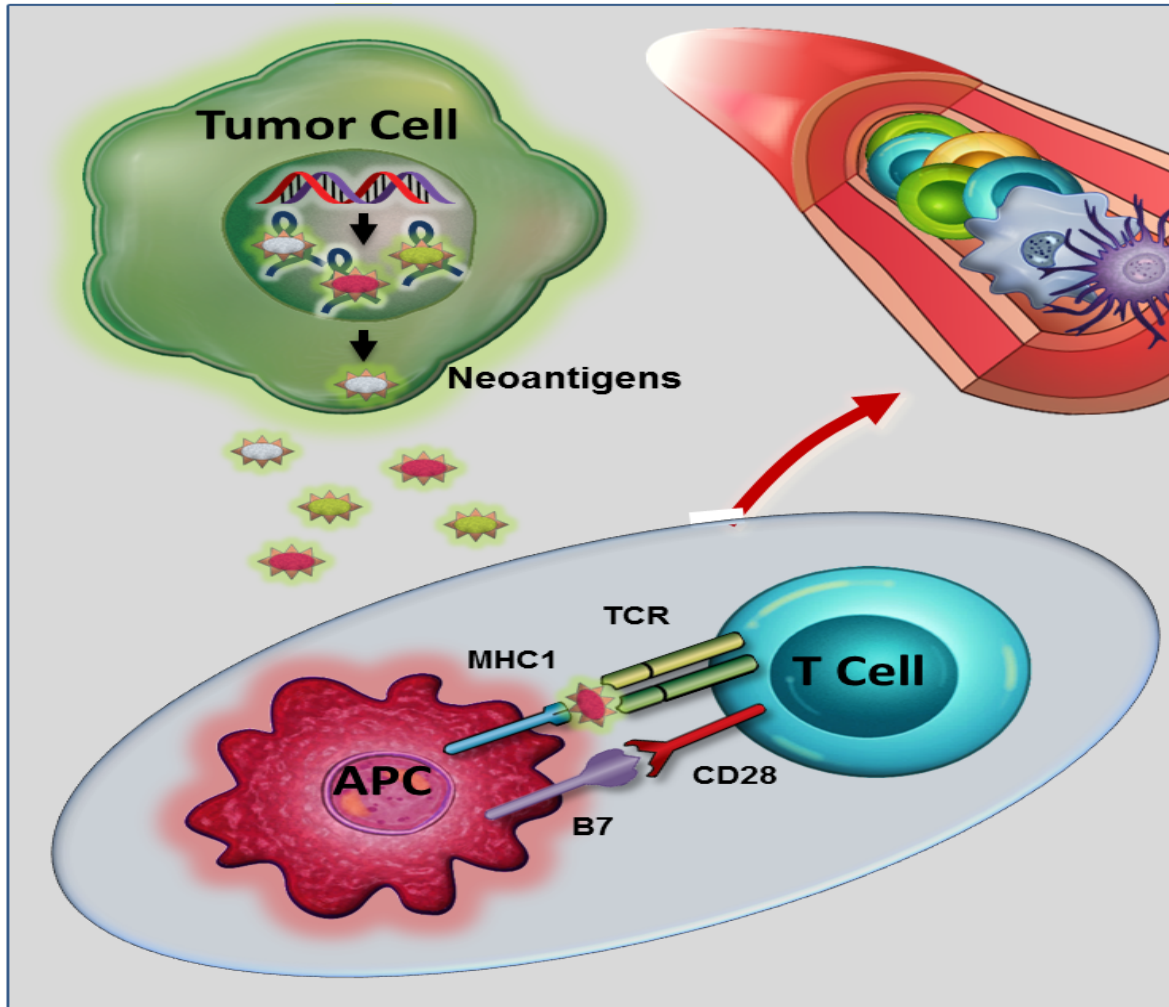
Subgroup of patients from KEYNOTE N012 and KEYNOTE 028 (n=119, representing 20 tumor types)



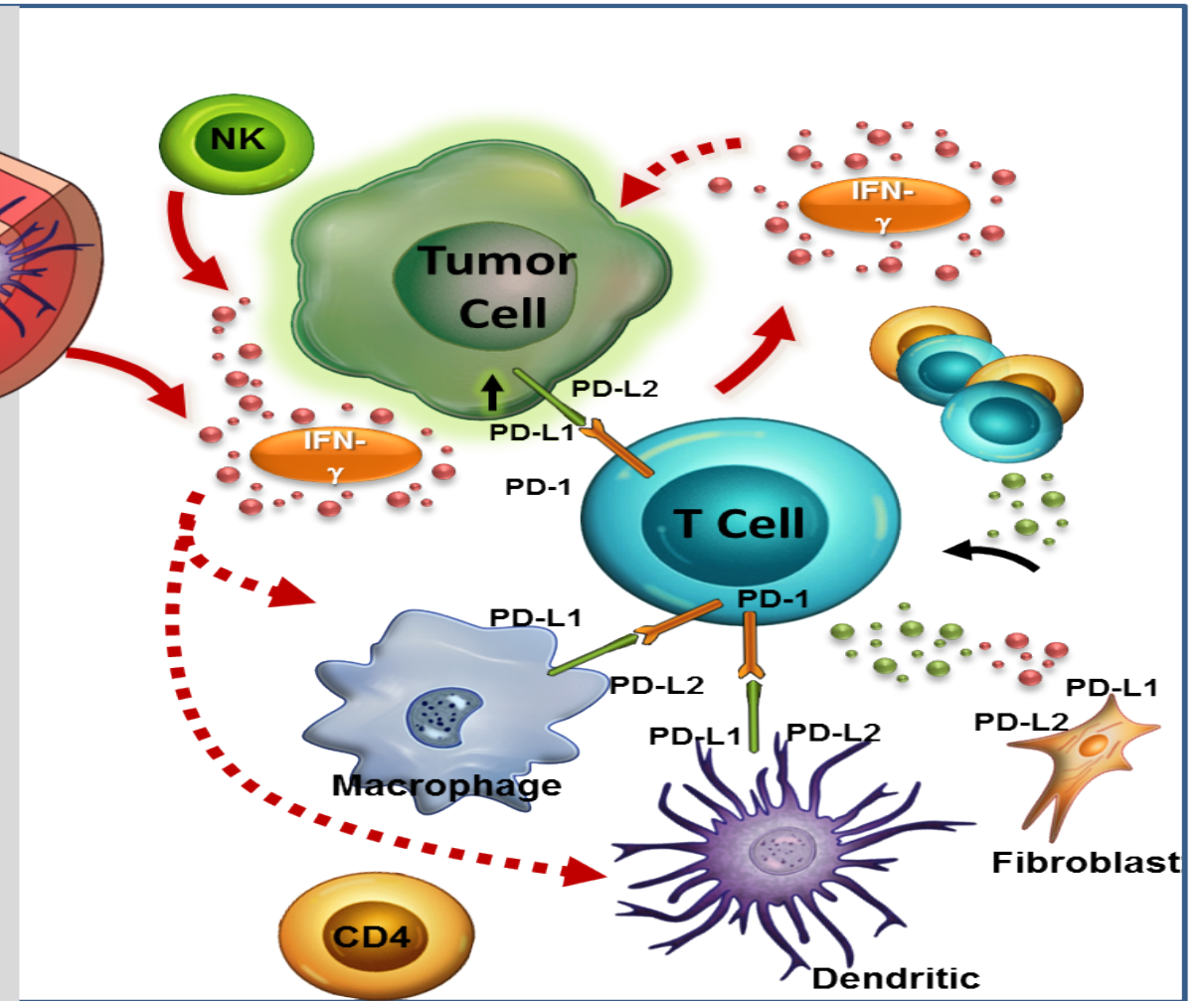
On June 16, 2020, the US Food and Drug Administration approved pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors with tissue tumor mutational burden–high (TMB-H; ≥ 10 mutations/megabase), as determined by an FDA-approved test, who have progressed following prior treatment and have no satisfactory alternative treatment options.

Dual Biomarker Strategy for Translational Oncology

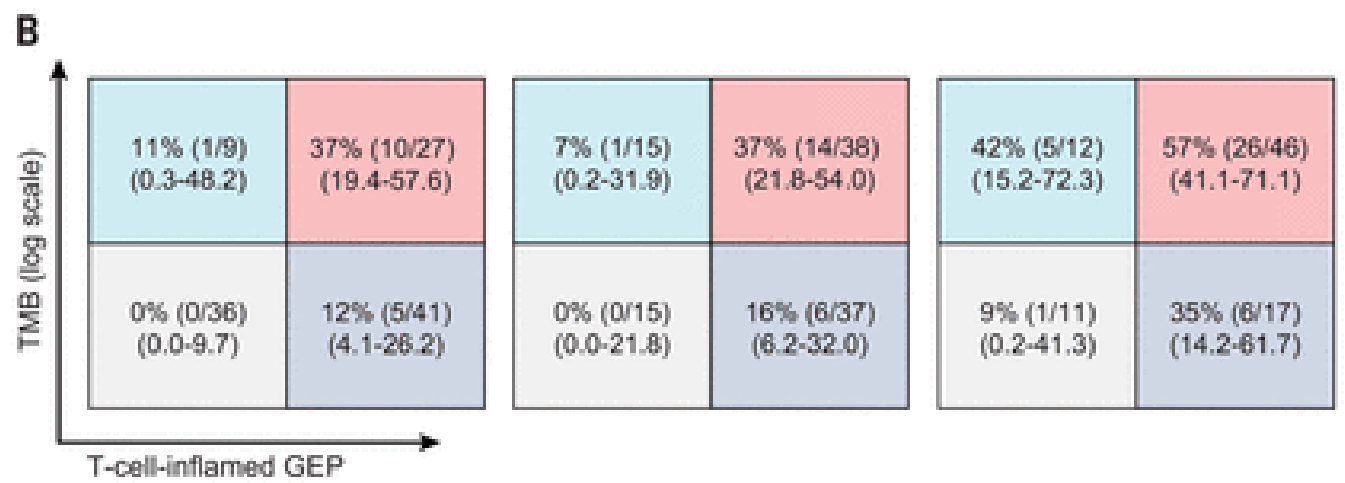
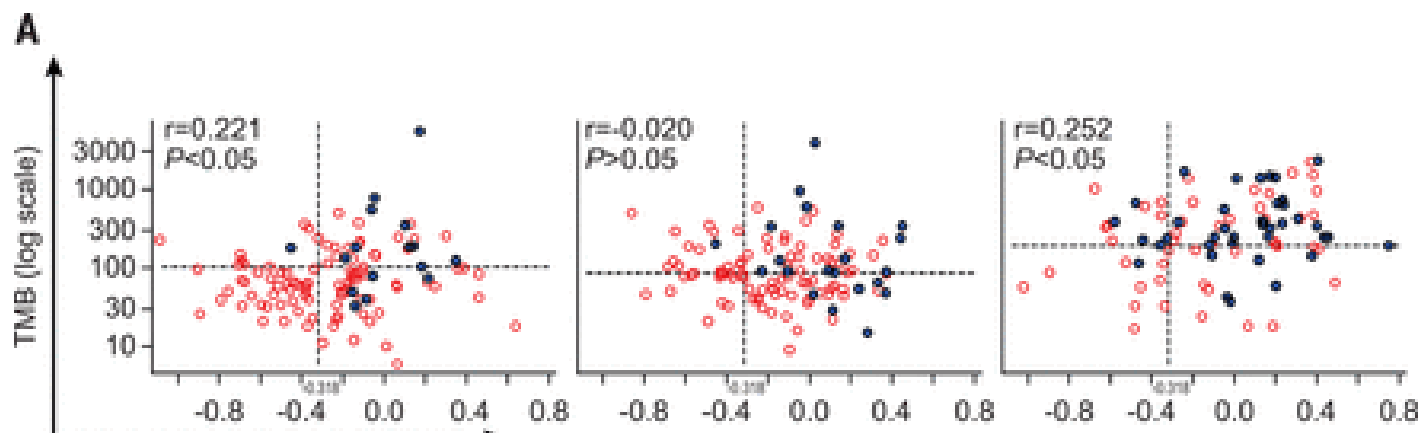
TMB measures tumor antigenicity



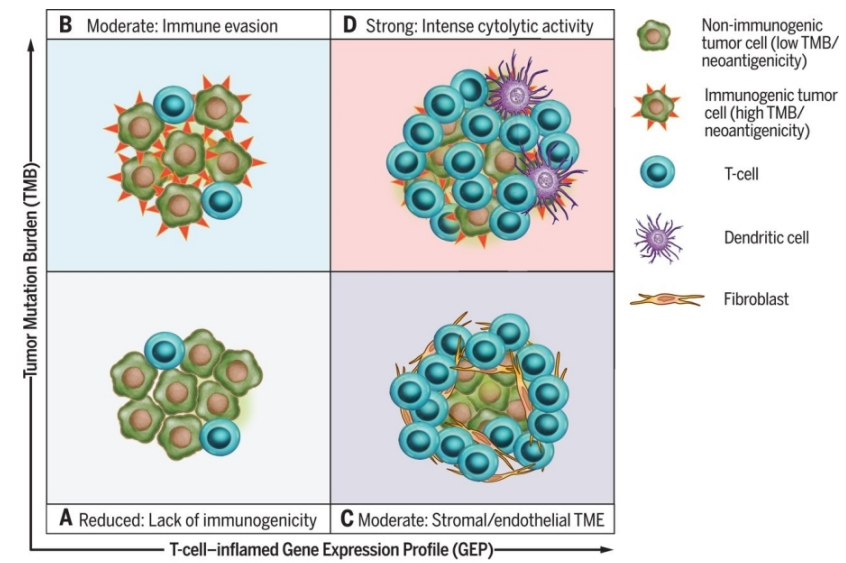
PD-L1/GEP measure activated T-cells in TME



Joint Relationship of TMB or T Cell–inflamed GEP with



TMB^{Lo} GEP^{Lo}
 TMB^{Lo} GEP^{Hi}
 TMB^{Hi} GEP^{Lo}
 TMB^{Hi} GEP^{Hi}



Higher response is in reduced population (lower prevalence)

Immunotherapy Biomarker Clinical Trials

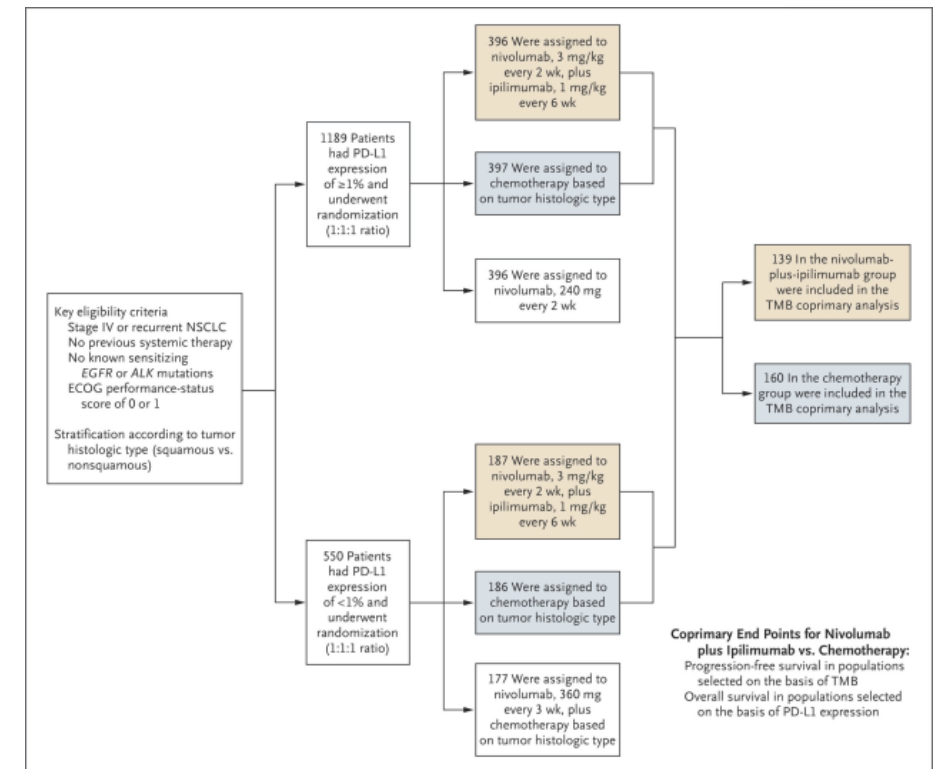
- ❖ Single biomarker design clinical trial (CheckMate 227)
- ❖ Multiple biomarker design clinical trial (Morpheus)
- ❖ Multiple biomarker and adaptive trials (I-SPY2, BATTLE)
- ❖ Dual biomarker and adaptive trial (KN495/KeyImPaCT)



Society for Immunotherapy of Cancer

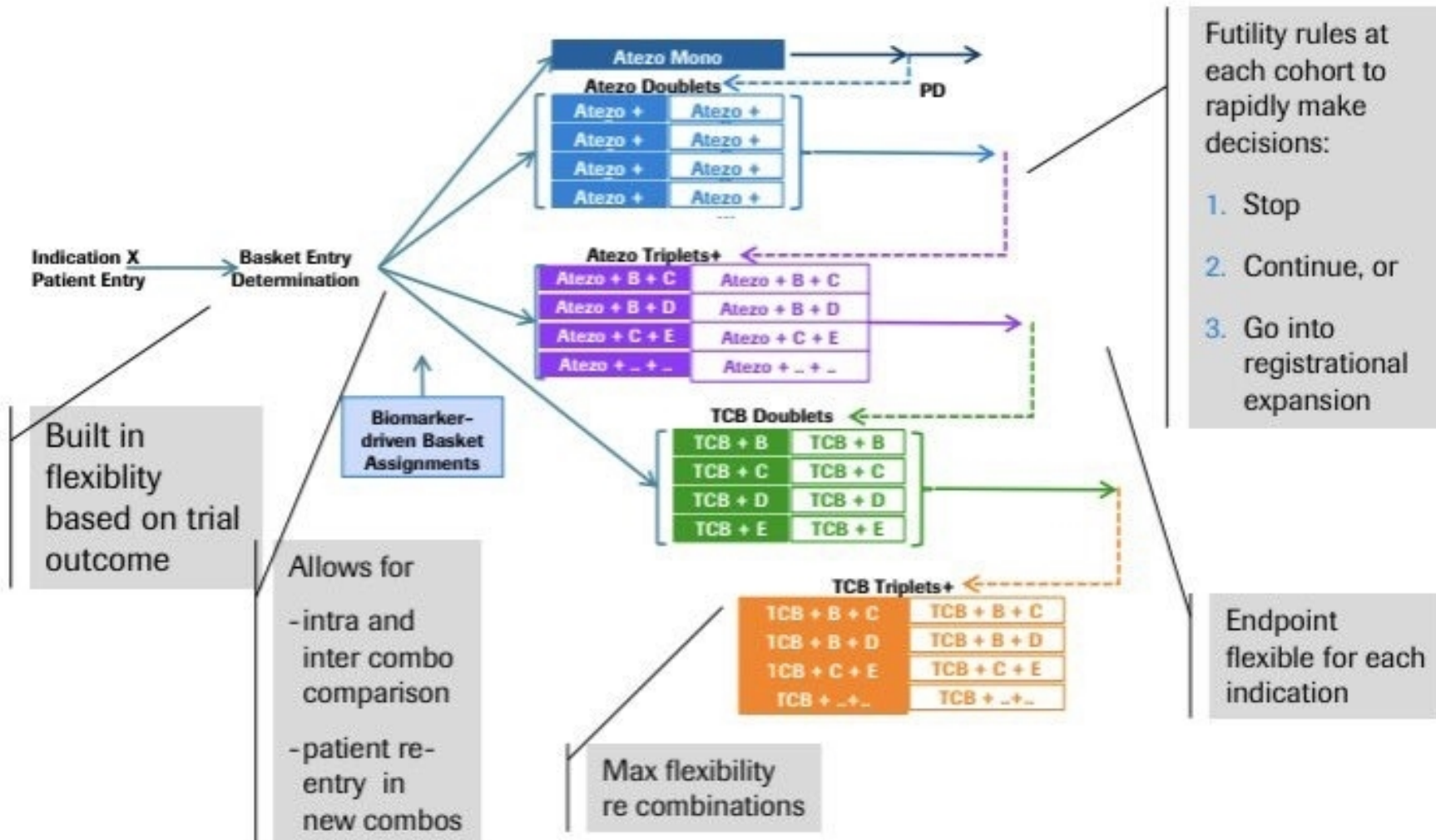
An Example (CheckMate 227): PD-L1 as Enrollment Biomarker

- Eligible: Stage IV or recurrent NSCLC not previously treated with chemotherapy.
- PD-L1 expression $\geq 1\%$ were randomly assigned, in a 1:1:1 ratio, to receive nivolumab plus ipilimumab, nivolumab monotherapy, or chemotherapy;
- PD-L1 expression level of $< 1\%$ were randomly assigned, in a 1:1:1 ratio, to receive nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy.
- Tumor mutational burden (TMB) was determined by the FoundationOne CDx assay.
- Coprimary EPs = PFS and OS
- The trial continues for the coprimary end point of overall survival among patients selected on the basis of PD-L1 expression level.



N Engl J Med 2018; 378:2093-2104

MORPHEUS: Applied trial concept – quick assessment of assets & speedy development This or previous?

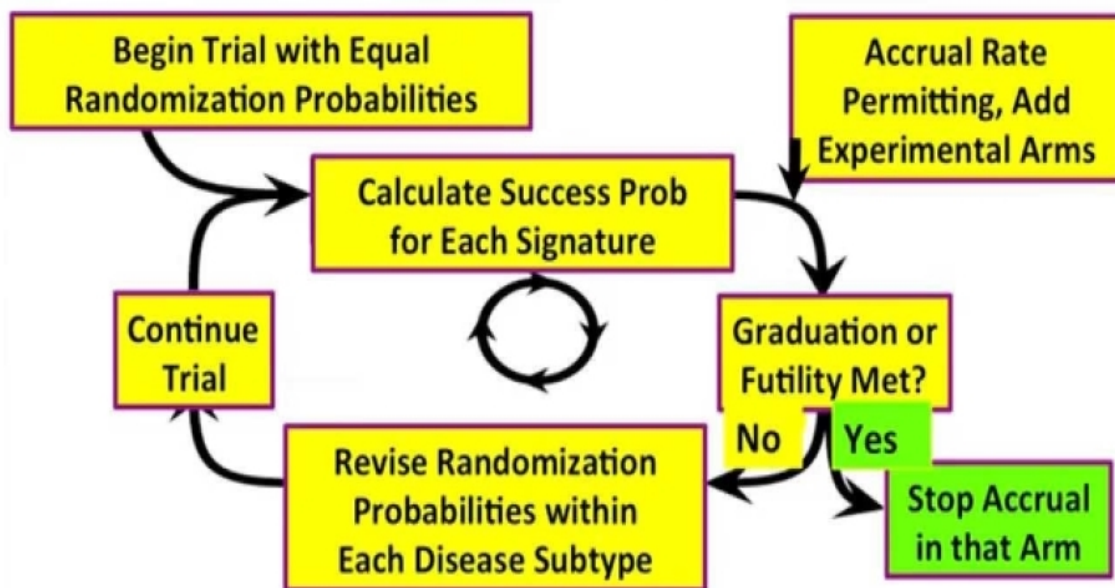


Adaptive Trials

- ❖ Adaptiveness in phase I and II trials can help optimize the dose/schedule, regimen, patient population in order to develop the right pivotal trial
- ❖ Most drugs fail because
 - They are toxic
 - They are ineffective
 - They are not tested in the right dose/schedule/regimen for the right population of patients
- ❖ Rushing to do the pivotal trial without sufficient data has high risk.
- ❖ Adaptiveness in phase III must be carefully structured to not interfere with the reliability and convincingness of the pivotal trial

Adaptive Design and Biomarkers Used in I-SPY 2

I-SPY 2 Adaptive Process



Stratification Biomarkers

Used for Stratification, Response to Therapy (may require IDE)

- ▶ ER, PR, HER2 (Community)
- ▶ MammaPrint (Agilent array)
- ▶ TargetPrint (Agilent array)
- ▶ MRI Volume (Sentinelle)

Qualifying Biomarkers

Used to Validate Response to Therapy, done in CLIA Lab

- ▶ RPMA Pathway Markers
- ▶ Drug Sensitivity Predictor
- ▶ RCB Predictor (Affy Array)
- ▶

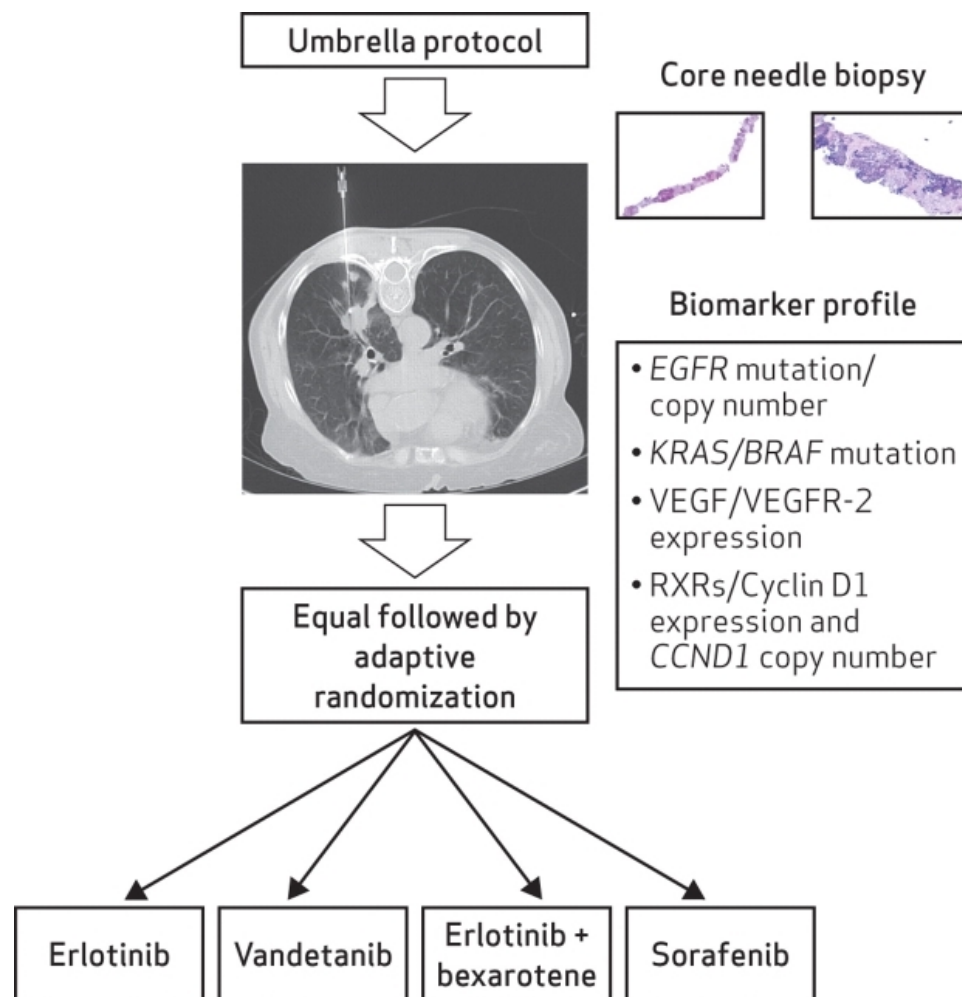
Exploratory Biomarkers

Reflects Next Generation Technology (keeping pace)

- ▶ DNA Methylation
- ▶ Exon Sequencing
- ▶ RNA Sequencing
- ▶ miRNA
- ▶ Circulating Tumor Cells
- ▶ Pharmacogenomics
- ▶ MRI SER Segmentation
- ▶

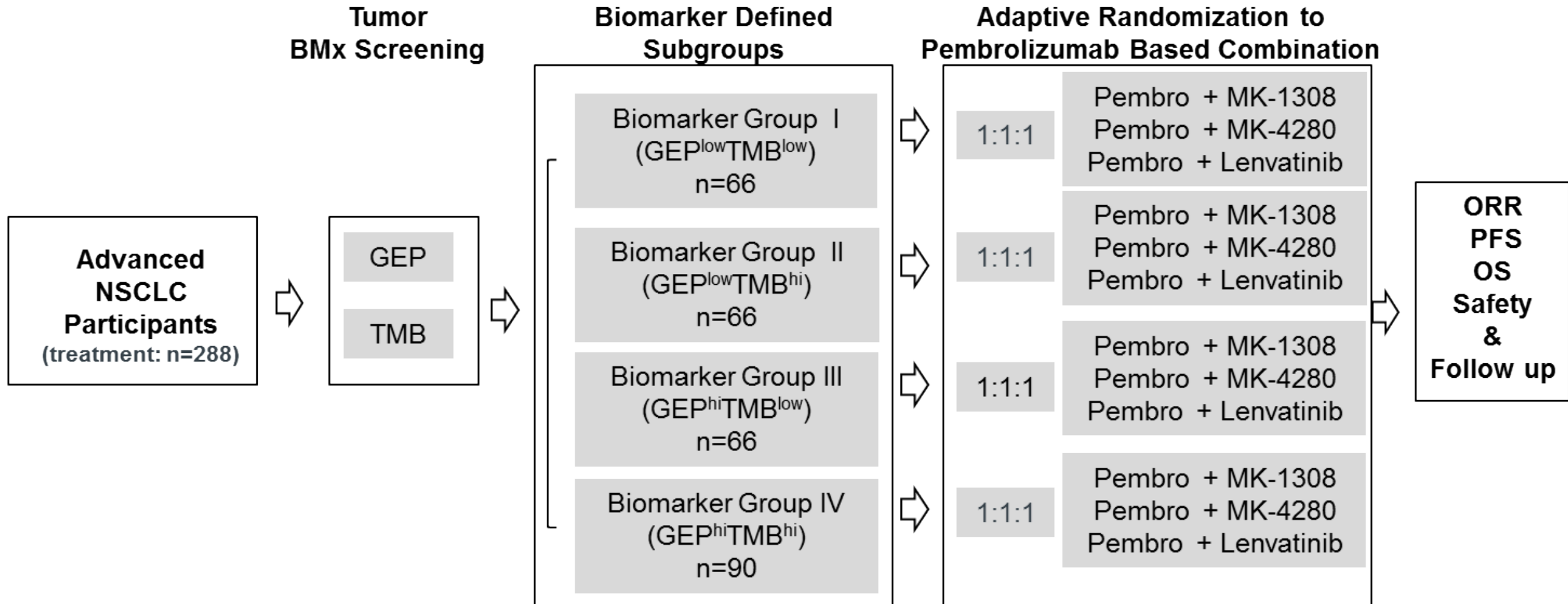
Source: I-SPY 2 and Other Platform Trials (Dr. Don Berry) and Dr. Sarah Davis's presentation

Adaptive Design and Multiple Biomarker: BATTLE Trial



Kim ES et al Cancer Discovery, 2011

An Example (KeyImPaCT/KN495): TMB/GEP Dual Biomarker Precision Oncology Clinical Trial



Gutierrez M et al, AACR, ASCO, ESMO 2019
ClinicalTrials.gov Identifier: NCT03516981

Thank YOU!



Society for Immunotherapy of Cancer