Biomarker-Based Clinical Trials in Precision Oncology

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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

Outline

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

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

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

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 patient candidates more likely respond to the specific treatment

- Surrogate endpoints
  A measurement made before and after treatment to determine whether the treatment is working

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

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Use of Biomarkers in Late 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 patients that fail to respond to particular treatment
- Assess the mechanisms related with drug safety

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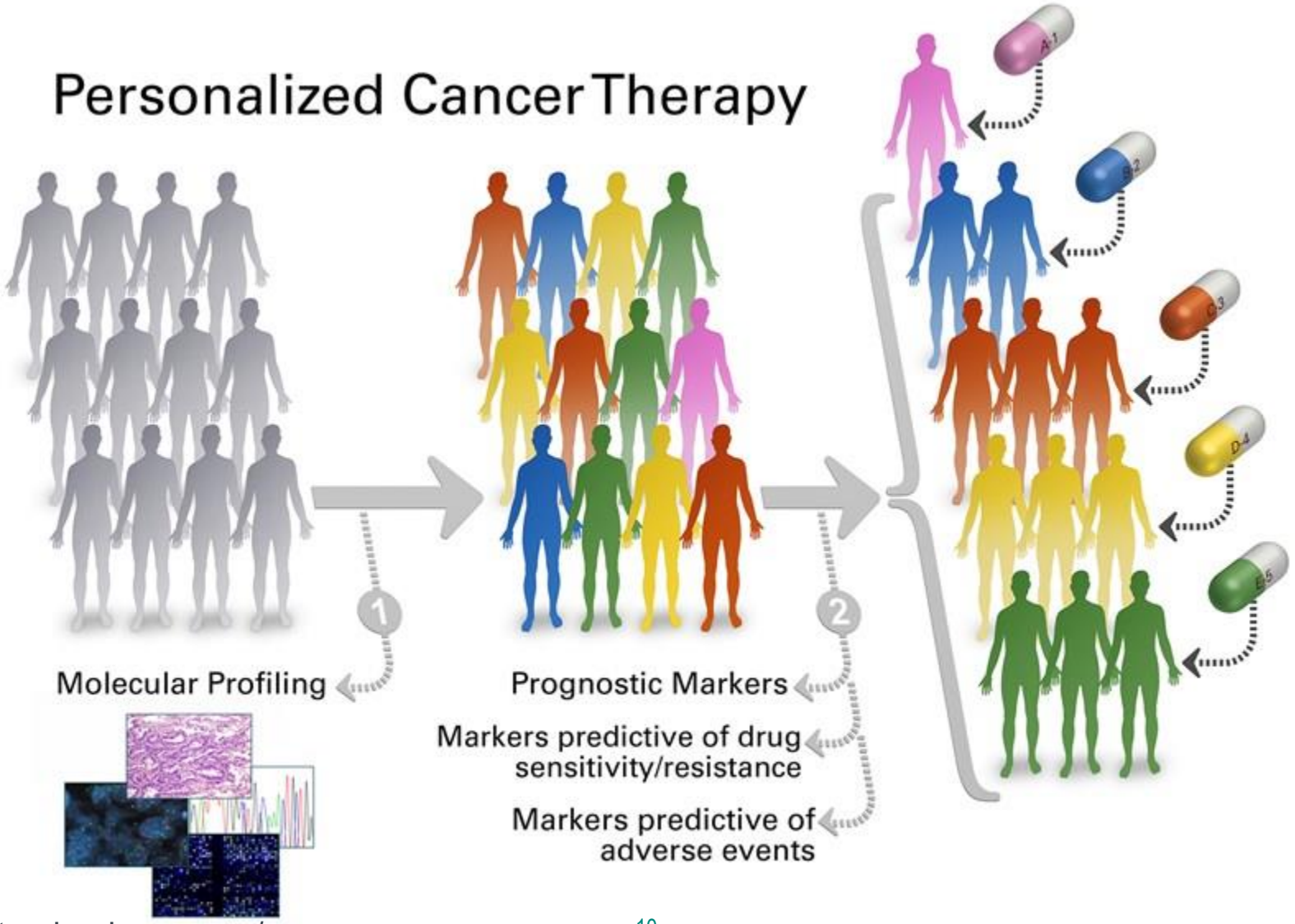
Use of Surrogate Endpoints in Late Drug Development

- 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

Biomarkers in Precision Oncology



Source: https://pct.mdanderson.org/

Biomarker in Forward and Reverse translation

Man Catching Rainbow In Funnel, Bruno Budrovic

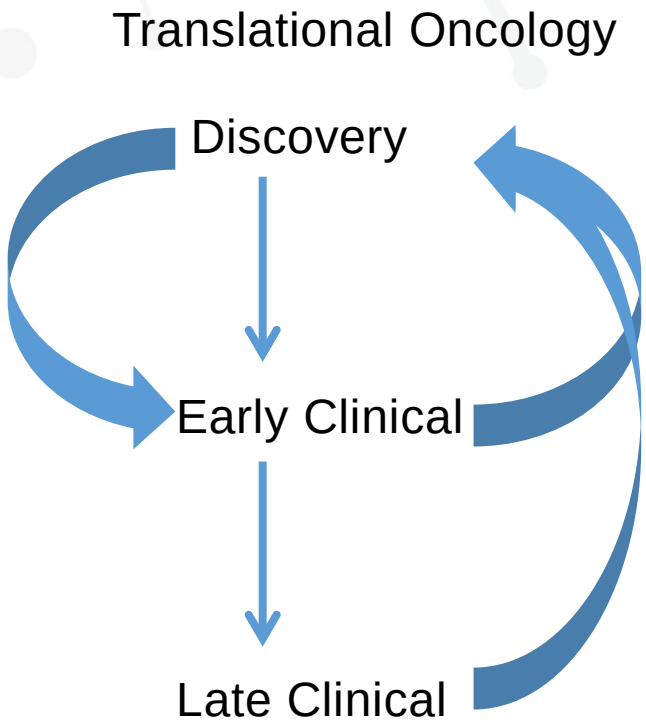
Purpose of Translational Oncology?

- 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



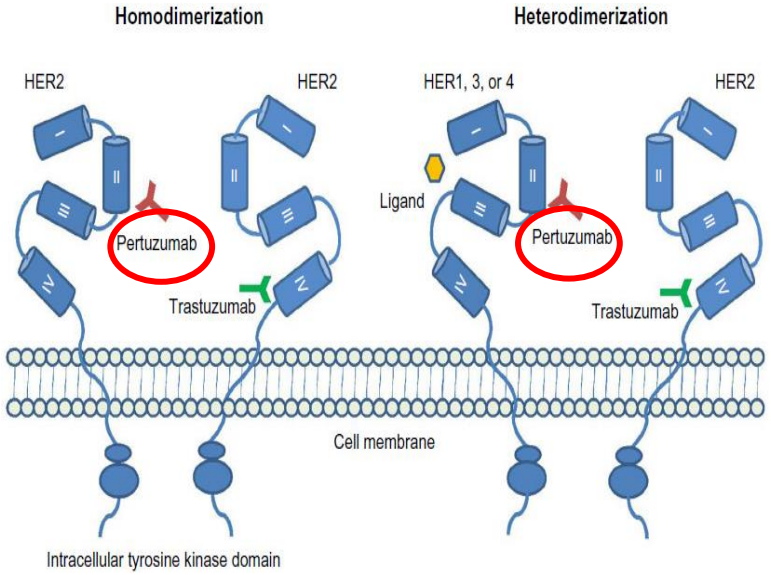
Slide courtesy of Alex Snyder

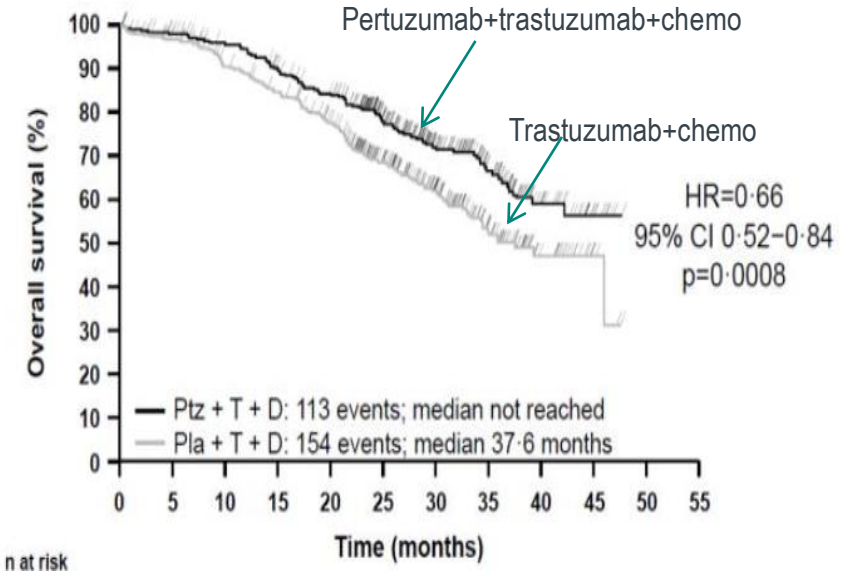
Forward Translation: Understand the Target→ Design the Drug
HER2 Amplification in Breast Cancer

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 NSCLC

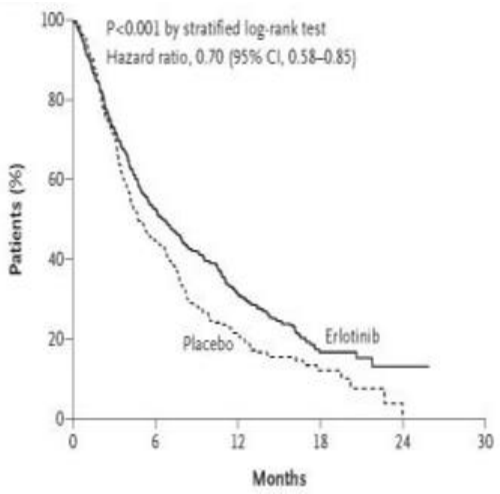
EGFR targeting in NSCLC was based on hypothesis of *EGFR* amplification as driver alteration

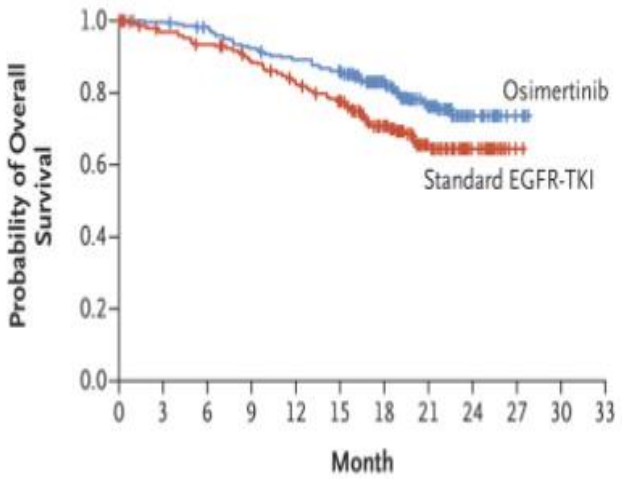
Initial Phase III study of erlotinib vs. placebo showed overall response rate of 8.9%, duration of response 7.9mo

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 demonstrated overall response rate 80%, duration of 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

Slide courtesy of Alex Snyder

New Agents Challenge Historical Dichotomy of Biomarkers

Targeted therapy

Biomarker assesses presence/absence of specific mutation or fusion <u>required for response</u>

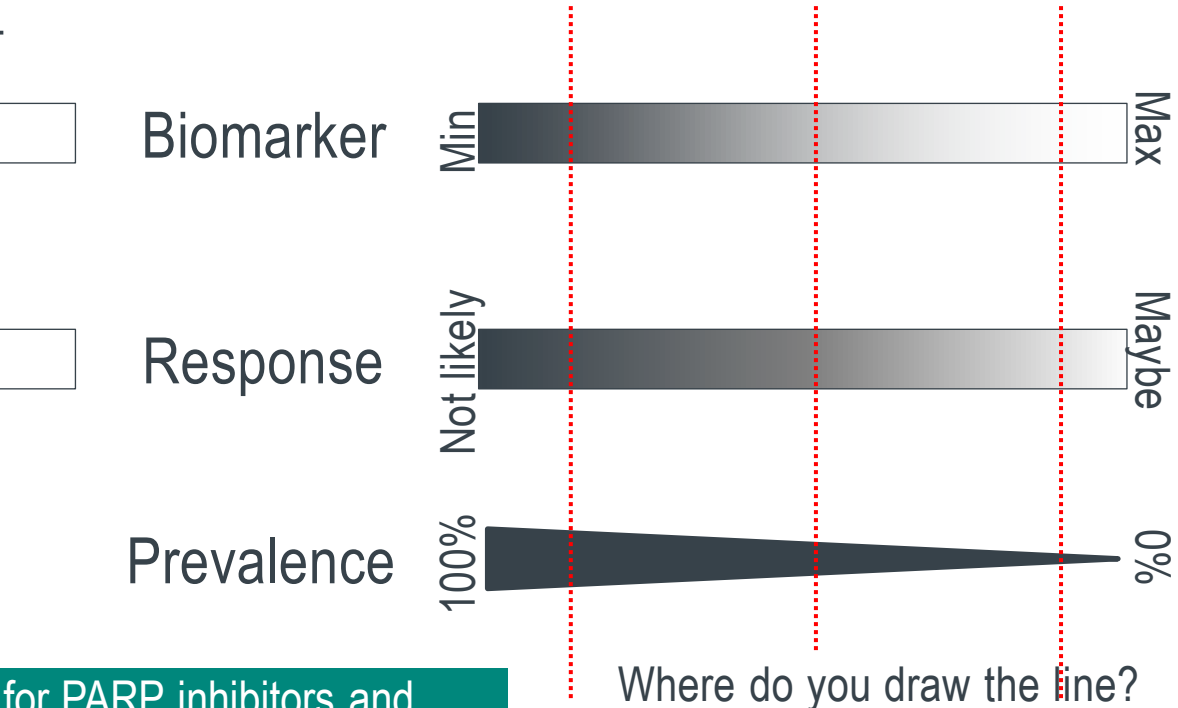
Absent	Present

NO	Maybe

Fixed for indication
Examples: *EGFR, KRAS* mutations

Immunotherapy

Biomarker assesses tumor/immune biology <u>related to response</u>



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

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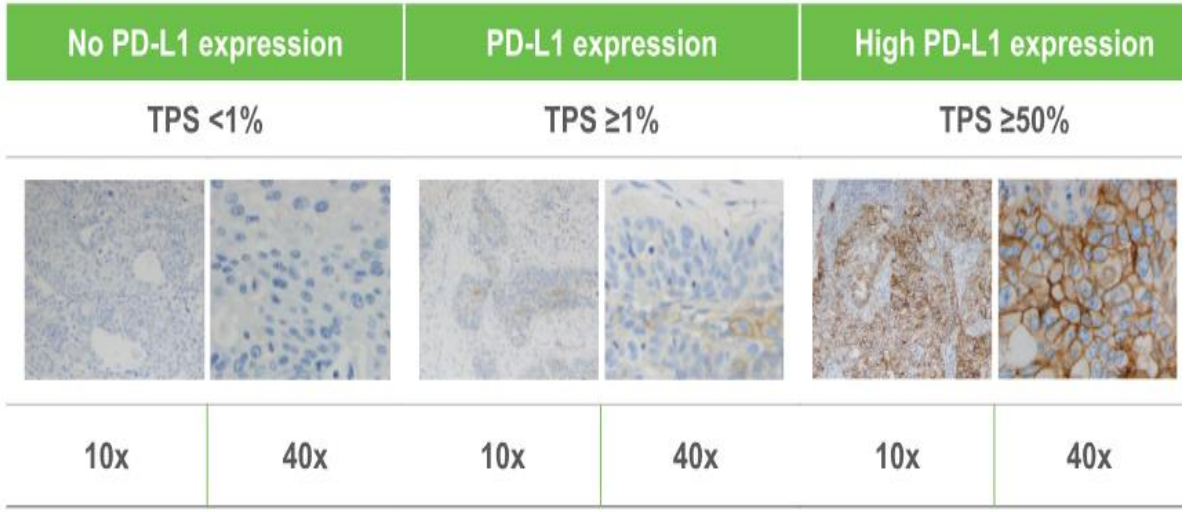
Forward Translation: Understand the Target →Design the Drug PD-(L)1

- 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 2013

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

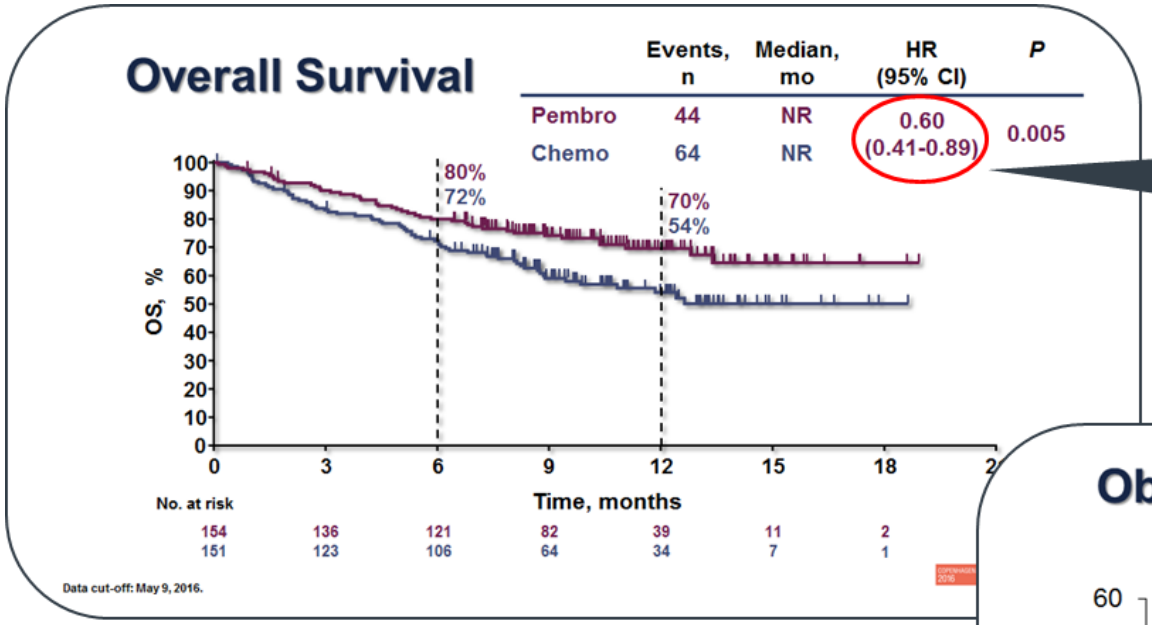
TPS=tumor proportion score



	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

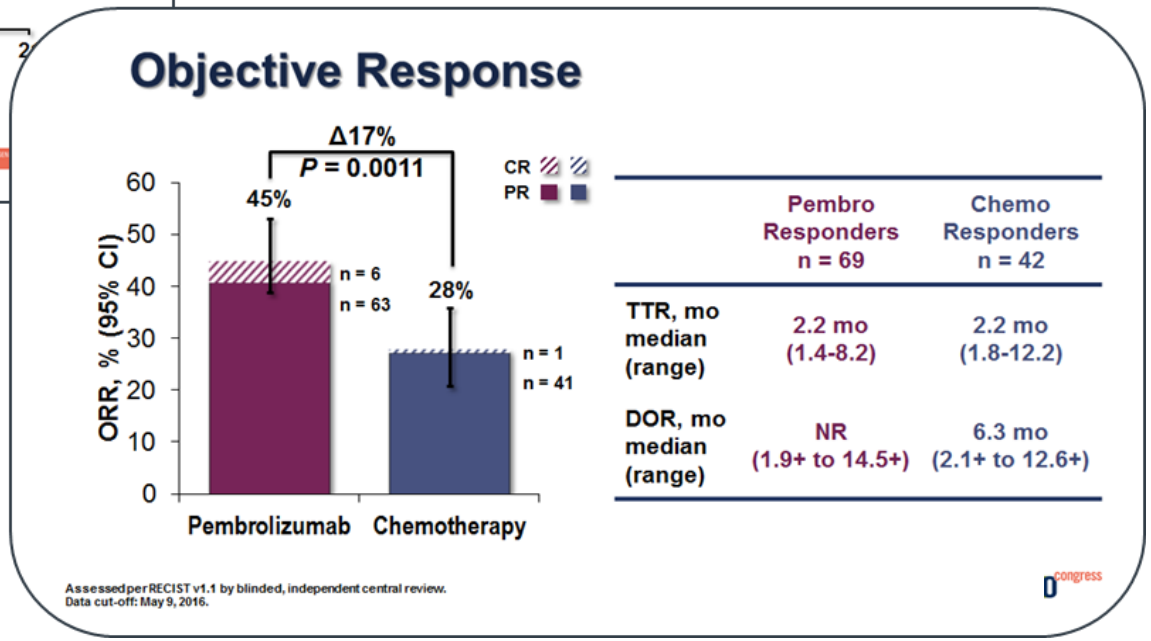
KEYNOTE-024
First-Line Pembrolizumab vs Chemotherapy



US Approval, October 2016

40% risk reduction of death

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



	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+)

Reck M et al, *NEJM* 2016; Oct 9. ESMO 2016.

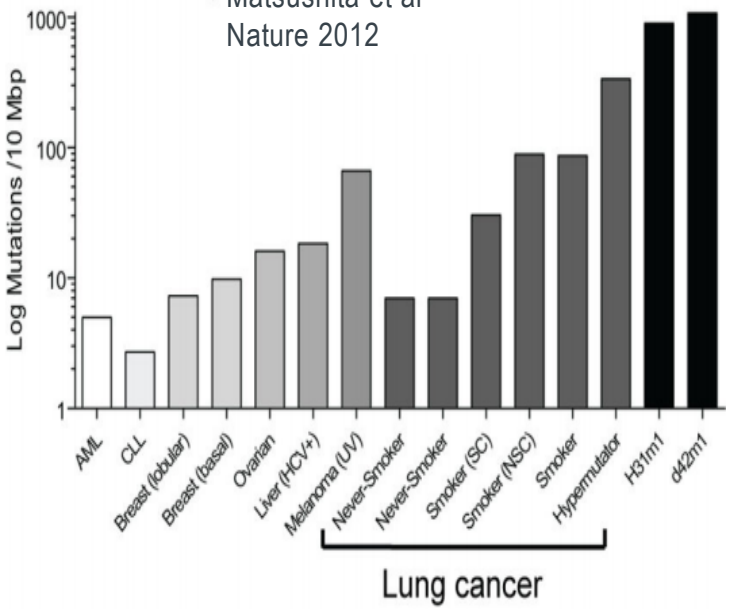
Forward Translation: Understand the Target
→Choose the Drug Mismatch Repair Deficiency and Pembrolizumab

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

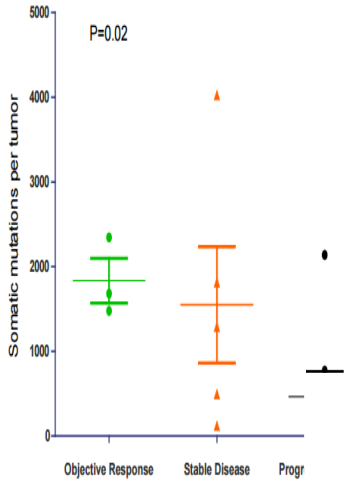
Schreiber lab used next generation sequencing in mouse model of carcinogen-induced sarcoma to support prior findings: many mutations → greater immunogenicity

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

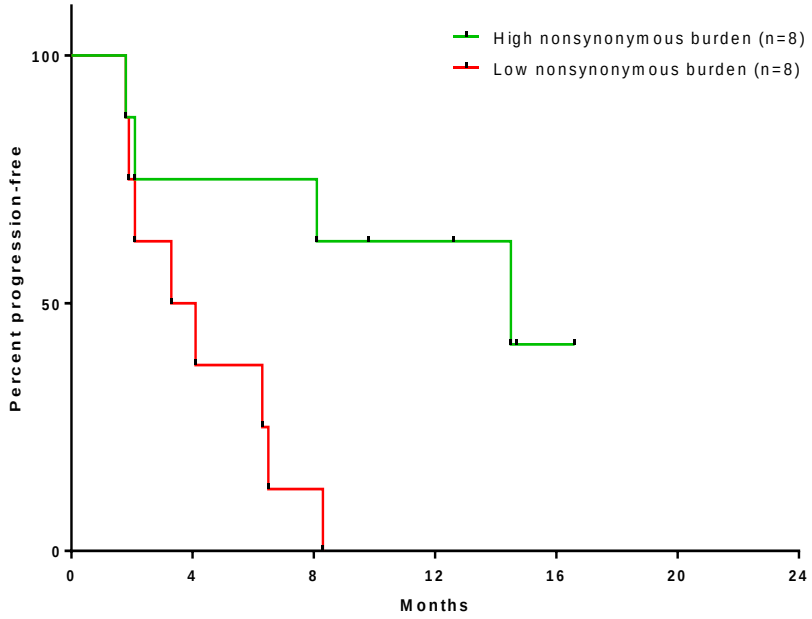
Matsushita et al
Nature 2012



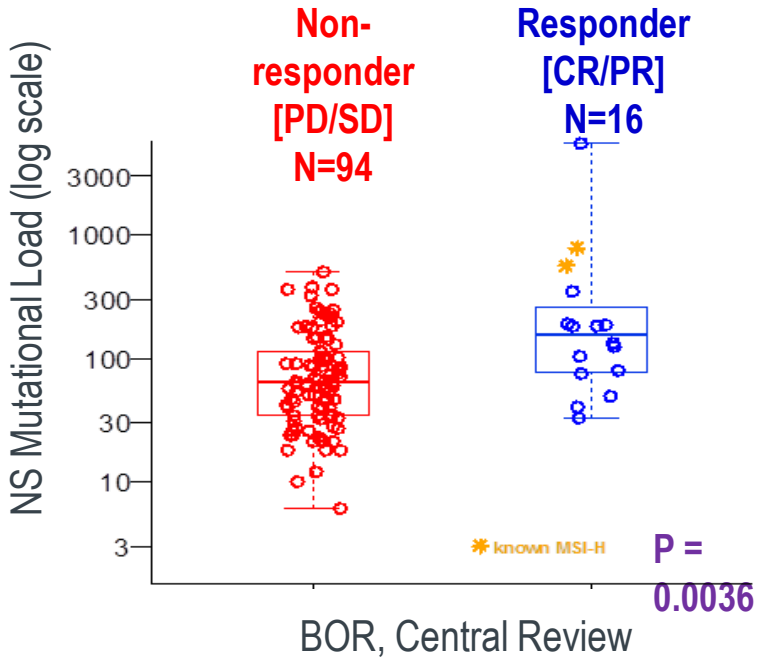
Le et al NEJM 2015
MSI-H CRC/anti-PD-1



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



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



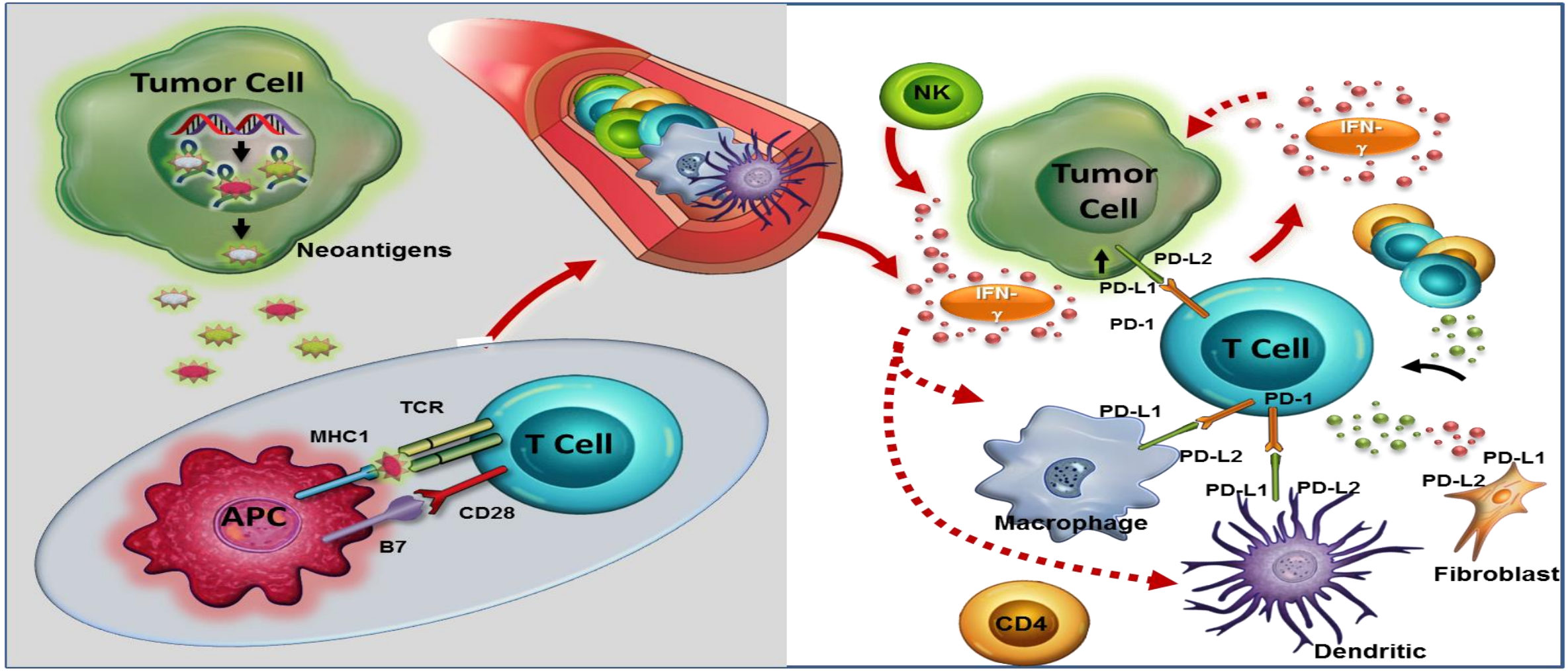
Subgroup of patients from KEYNOTE N012 and KEYNOTE 028 (n=119, representing 20 tumor types)

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.

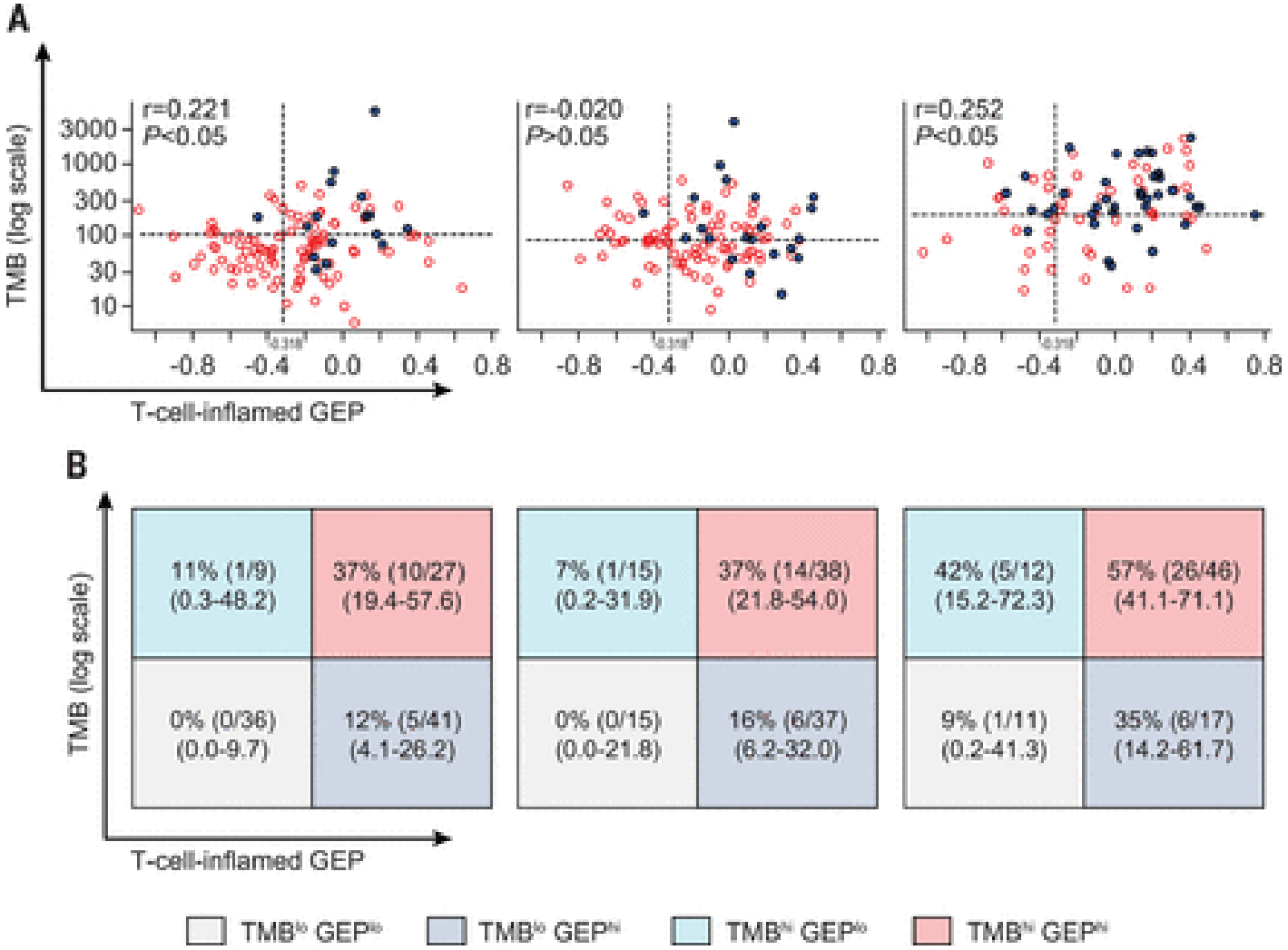
Dual Biomarker Strategy for Translational Oncology

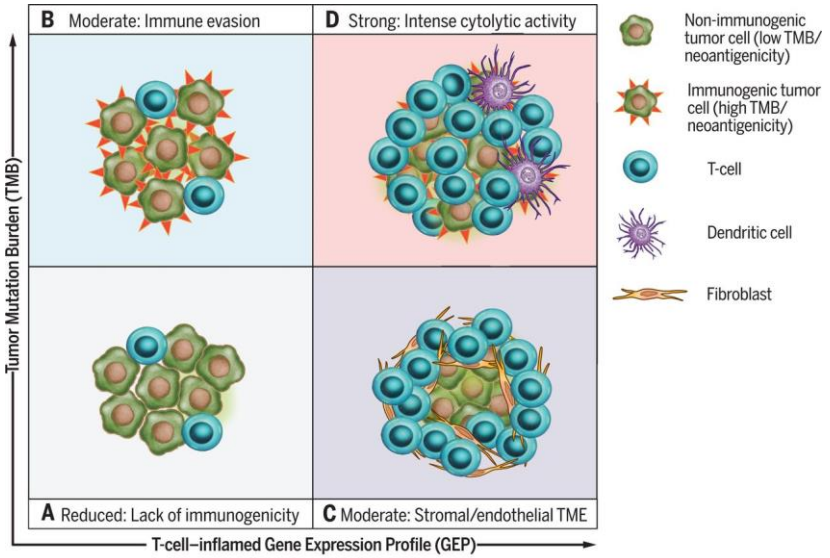
TMB measures tumor antigenicity

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



Joint Relationship of TMB or T Cell–inflamed GEP with anti–PD-1 Response across Multiple Patient Cohorts.





Higher response is in reduced population (lower prevalence)

Razvan Cristescu et al. Science 2018;362:eaar3593

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)

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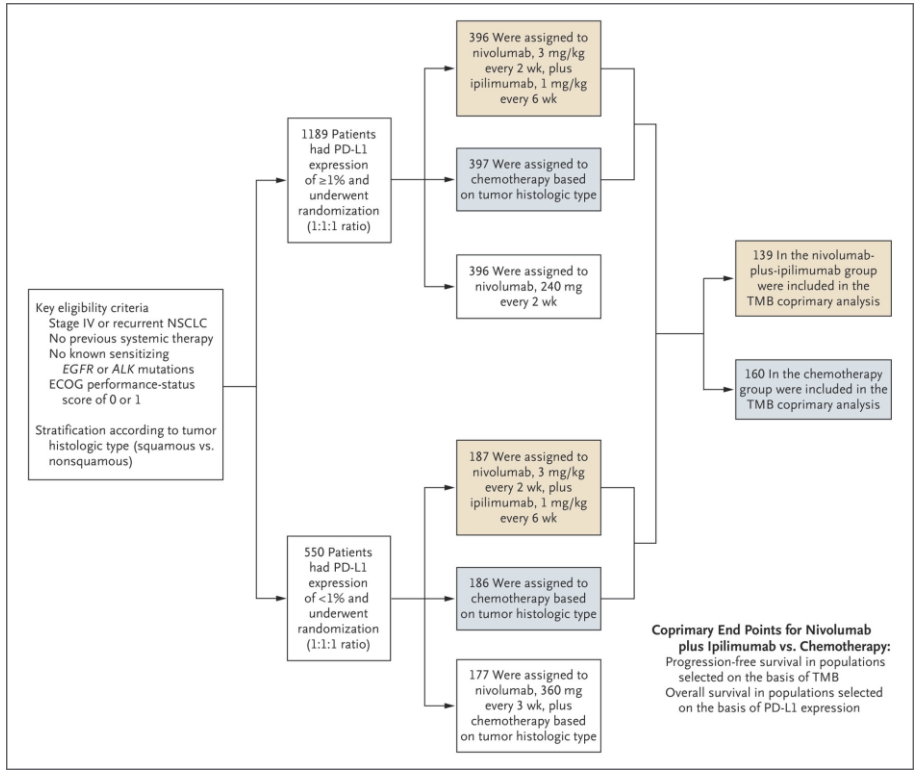
An Example (CheckMate 227): PD-L1 as Enrollment Biomarker

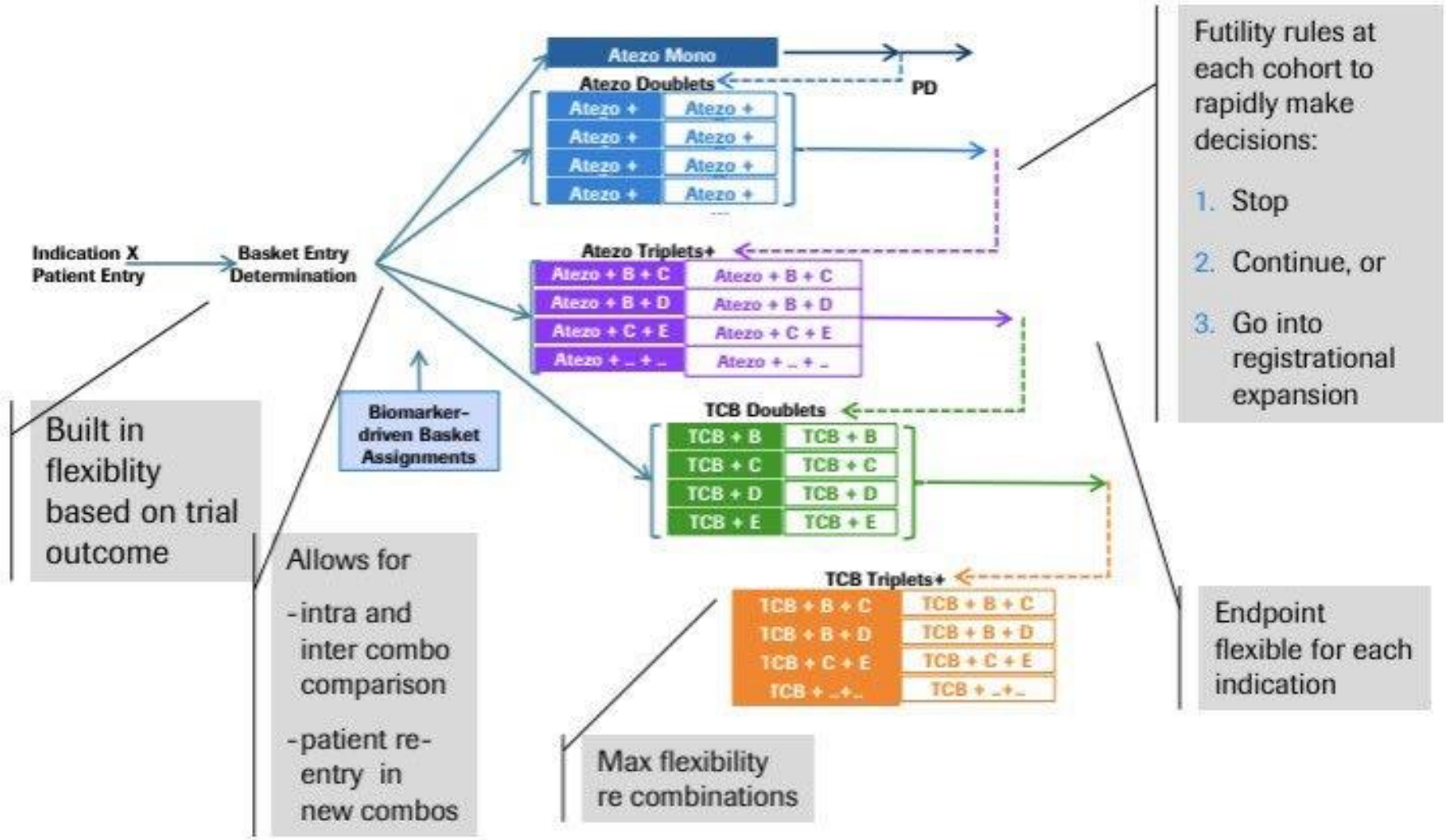
- Eligible: Stage IV or recurrent NSCLC not previously treated with chemotherapy.
- PD-L1 expression ≥ 1% were randomly assigned, in a 1:1:1 ratio, to receive nivolumab plus ipilimumab, nivolumab monotherapy, or chemotherapy;
- PD-L1 expression level of < 1% were randomly assigned, in a 1:1:1 ratio, to receive nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy.
- Tumor mutational burden (TMB) was determined by the FoundationOne CDx assay.
- Co-primary 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
N Engl J Med 2019: 381:2020-2031

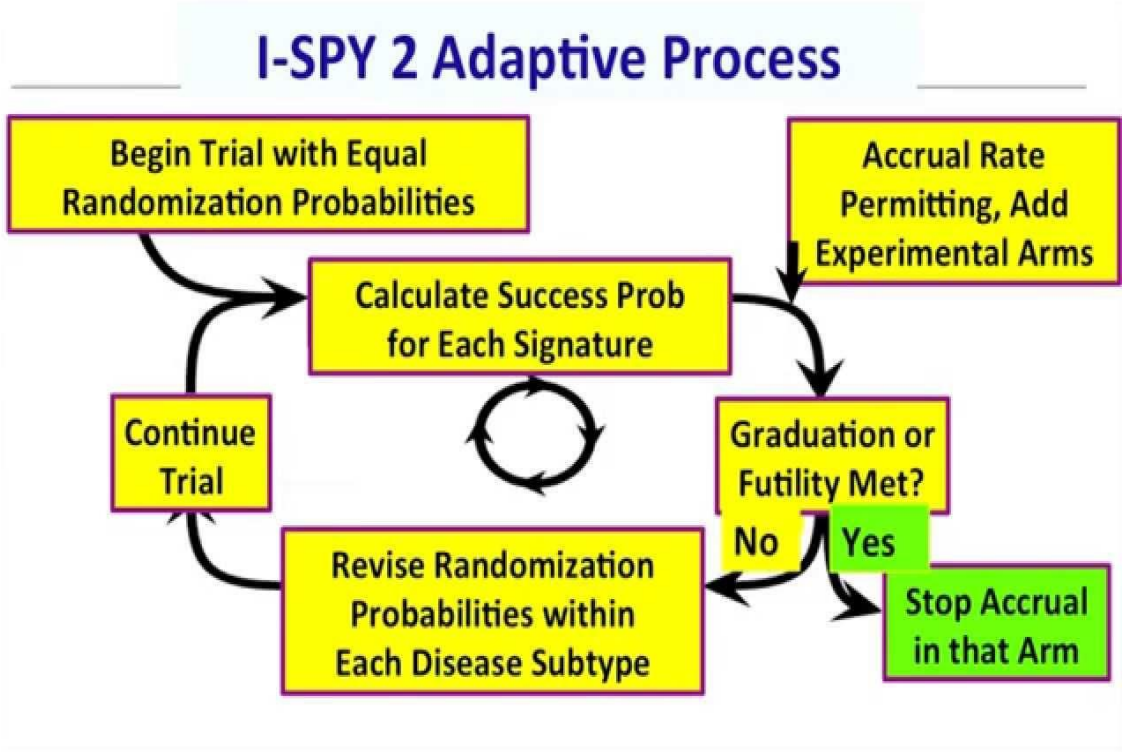
MORPHEUS: Applied trial concept – quick assessment of assets & speedy development

This or previous?



http://www.nmrc.gov.sg/docs/default-source/events-library/clinical-research-industry---ms-goh-siew-wei.pdf

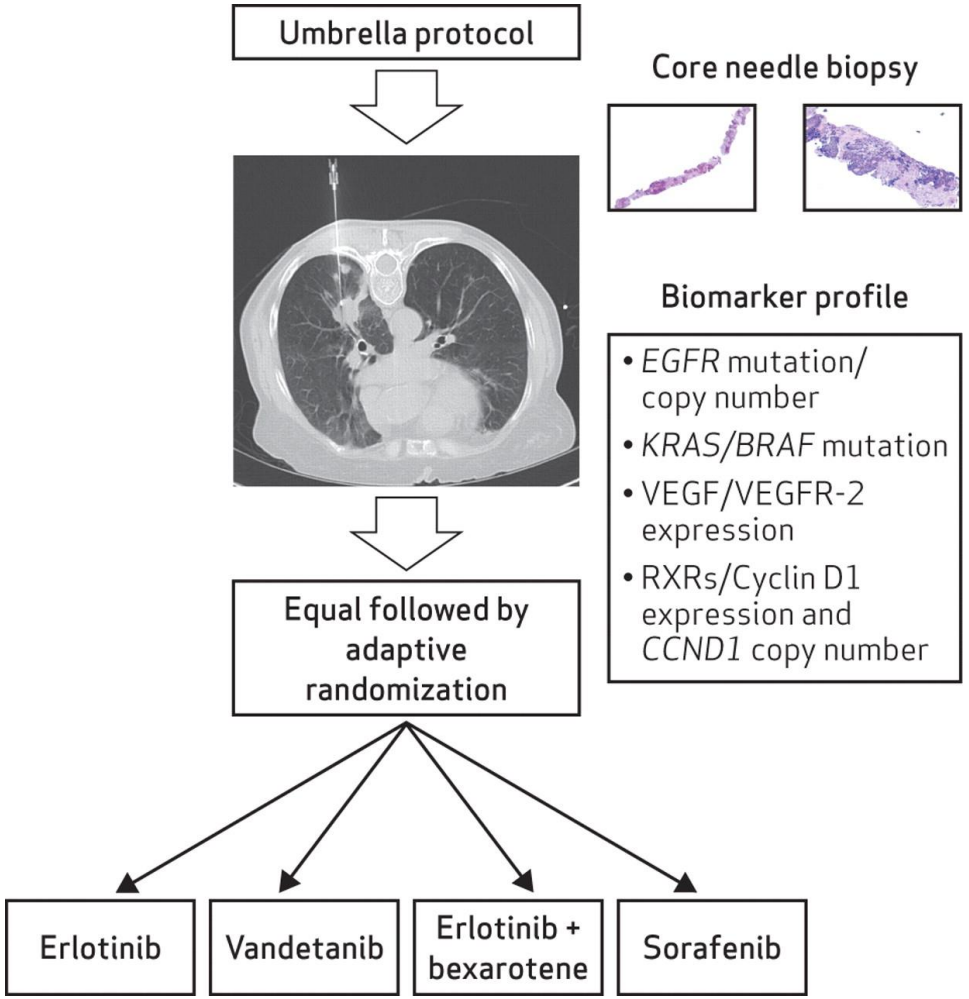
Adaptive Design and Biomarkers Used in I-SPY 2



Stratification Biomarkers	Qualifying Biomarkers	Exploratory Biomarkers
Used for Stratification, Response to Therapy (may require IDE)	Used to Validate Response to Therapy, done in CLIA Lab	Reflects Next Generation Technology (keeping pace)
ER, PR, HER2 (Community) MammaPrint (Agilent array) TargetPrint (Agilent array) MRI Volume (Sentinelle)	RPMA Pathway Markers Drug Sensitivity Predictor RCB Predictor (Affy Array)	DNA Methylation Exon Sequencing RNA Sequencing miRNA Circulating Tumor Cells Pharmacogenomics MRI SER Segmentation ....

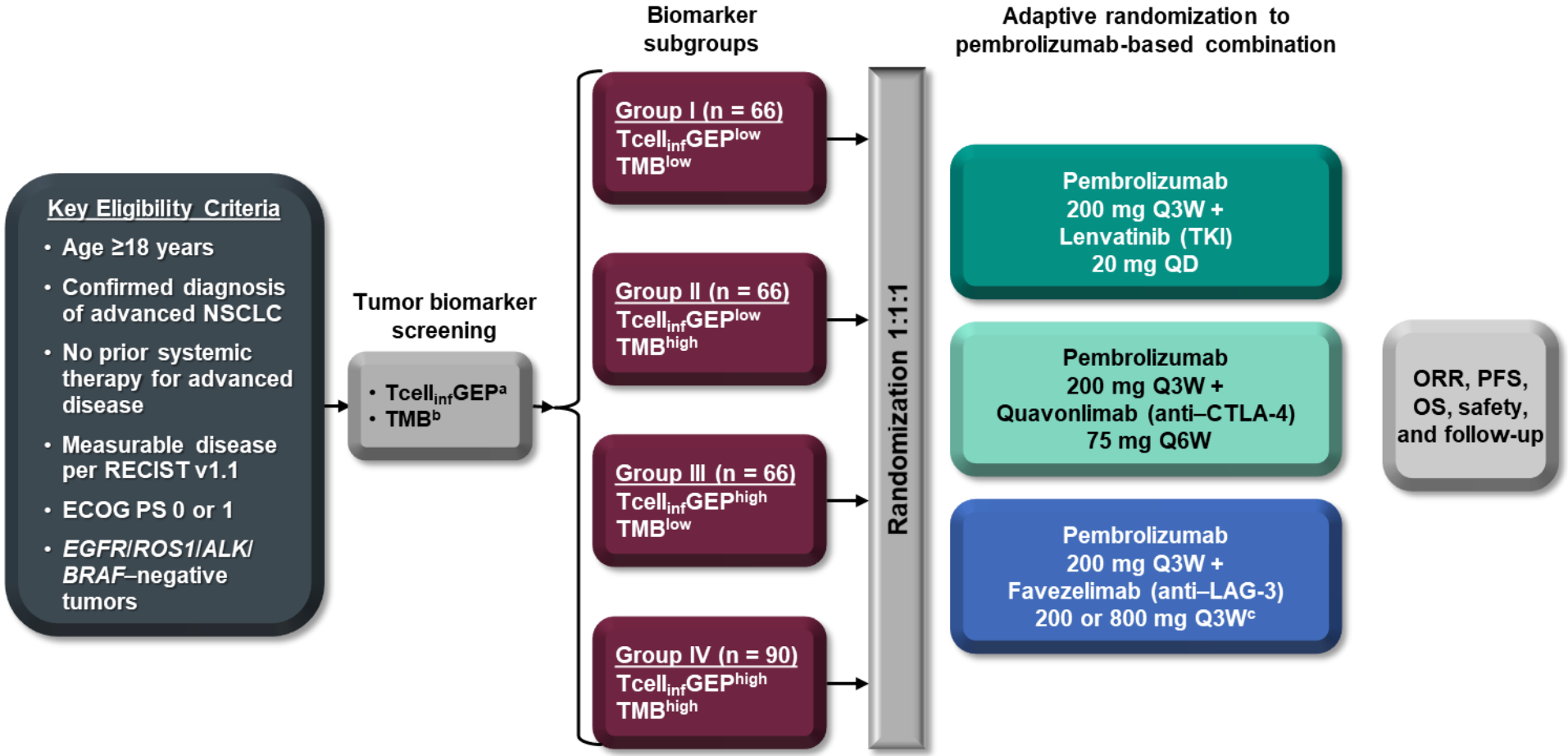
Source: I-SPY 2 and Other Platform Trials (Dr. Don Berry) and Dr. Sarah Davis's presentation

Adaptive Design and Multiple Biomarker: BATTLE Trial



Kim ES et al Cancer Discovery, 2011

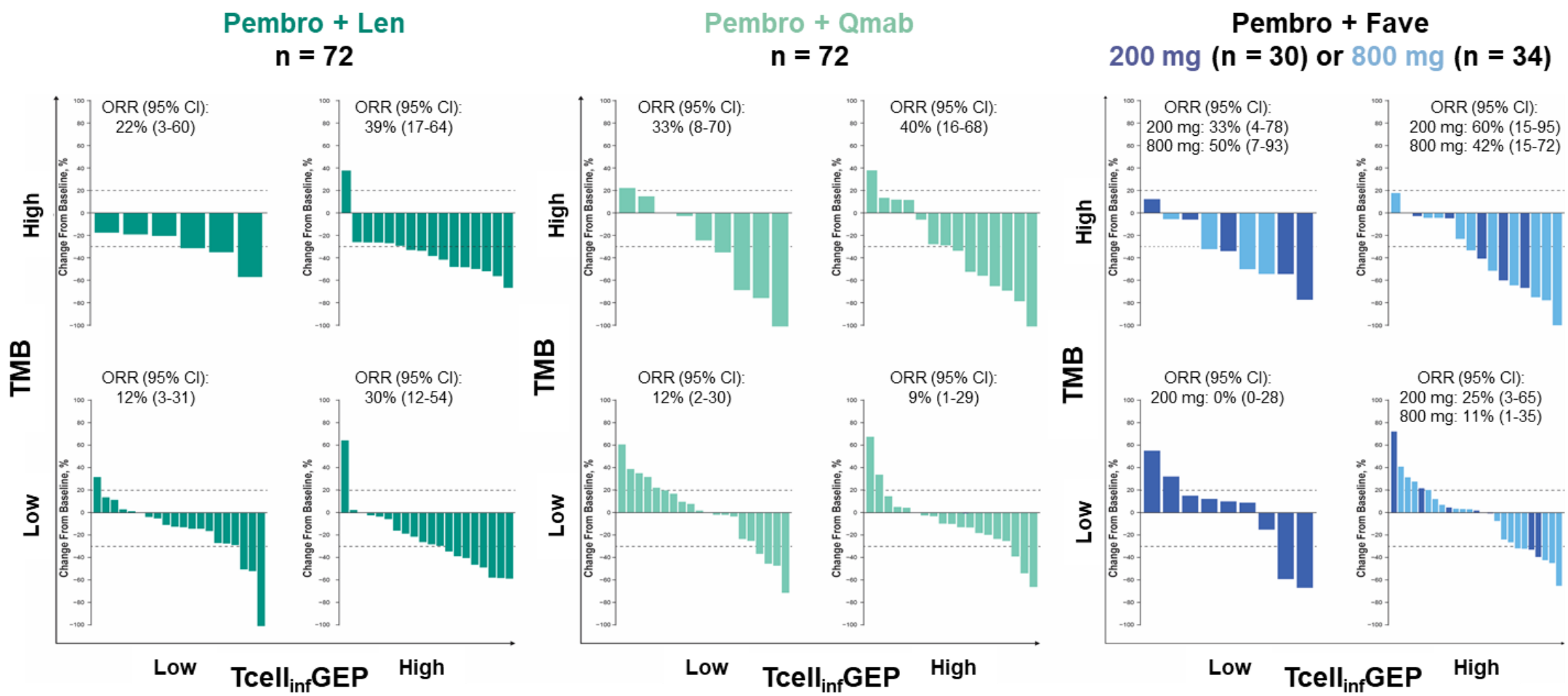
An Example (KeyImPaCT/KN495): TMB/GEP Dual Biomarker Precision Oncology Clinical Trial



[a]The cutoff of −0.16 used to define high and low.
[b]The cutoff of 175 mut/exome (equivalent to 10 mut/Mb on FoundationOne®CDx) was used to define high and low.
[c]The initial prespecified dose was 200 mg but was changed to 800 mg based on emerging data.

Gutierrez M et al, SITC 2020
ClinicalTrials.gov Identifier: NCT03516981

Best Percentage Change From Baseline in Target Lesion Size



Data cutoff date: January 11, 2021.

Gutierrez M et al, SITC 2020
ClinicalTrials.gov Identifier: NCT03516981

Thank YOU!

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