Biomarkers in Precision Oncology Clinical Trials

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2020 SITC Winter School
January 13–17, 2020
Houston, USA

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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

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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

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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 good patient candidates for 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 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

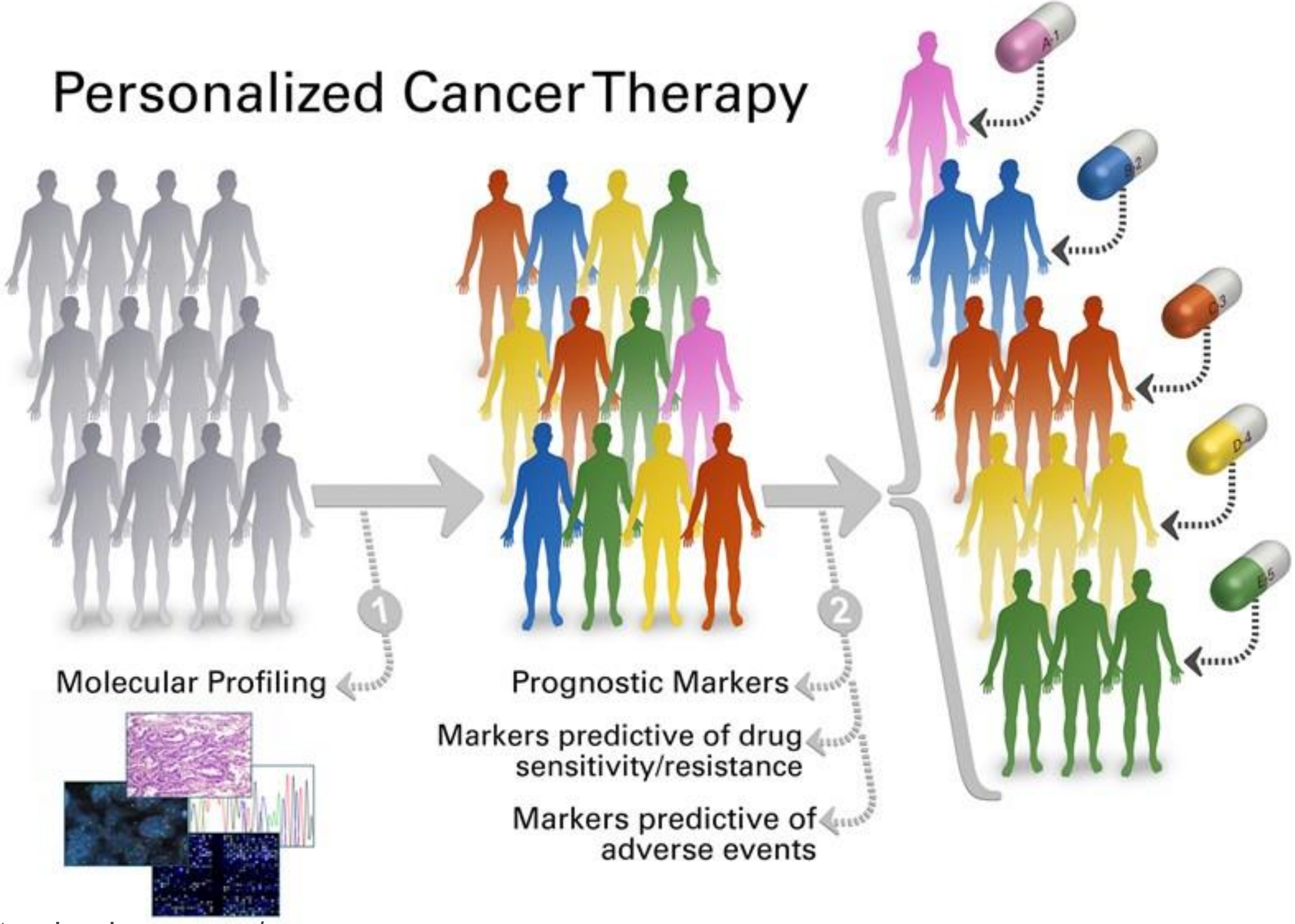
Use of Surrogate Endpoints in Late Drug Development

- 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



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

An Example: Dynamic Translational Oncology Biomarker Research Strategies

To elucidate target engagement, pharmaco-kinetic and pharmaco-dynamic changes	To understand the potential mechanisms of action	To find new correlates associated with clinical benefits and/or immune related adverse events	To identify new targets and patients potentially responding to therapy	To develop novel combination therapies upon understanding of mechanisms of action and resistance
↓	↓	↓	↓	↓
Right dose	MOA	Right patient	New target	Right combo

Biomarker in Forward and Reverse translation

Man Catching Rainbow In Funnel, Bruno Budrovic

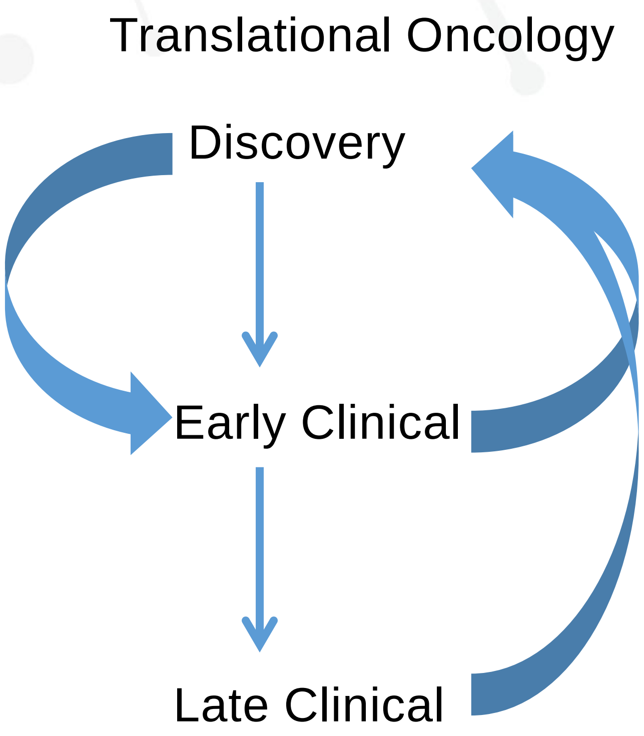
Purpose of Translational Oncology?

- 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



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Slide courtesy of Alex Snyder

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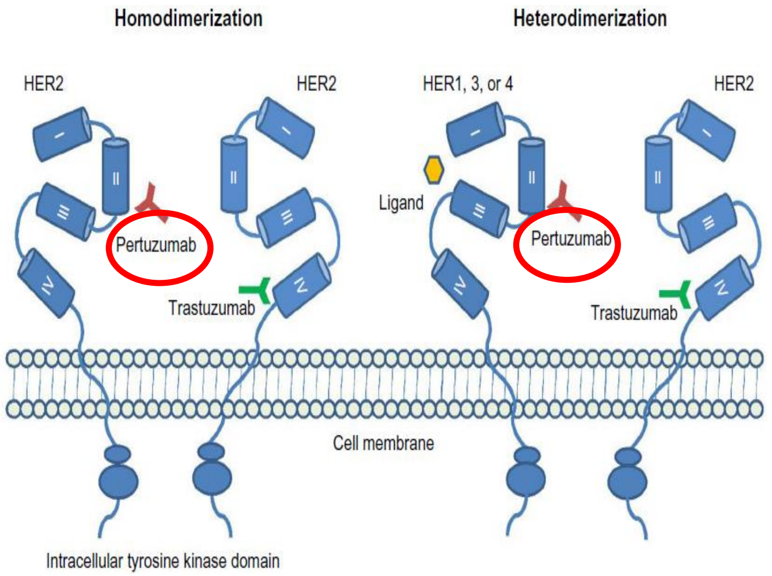
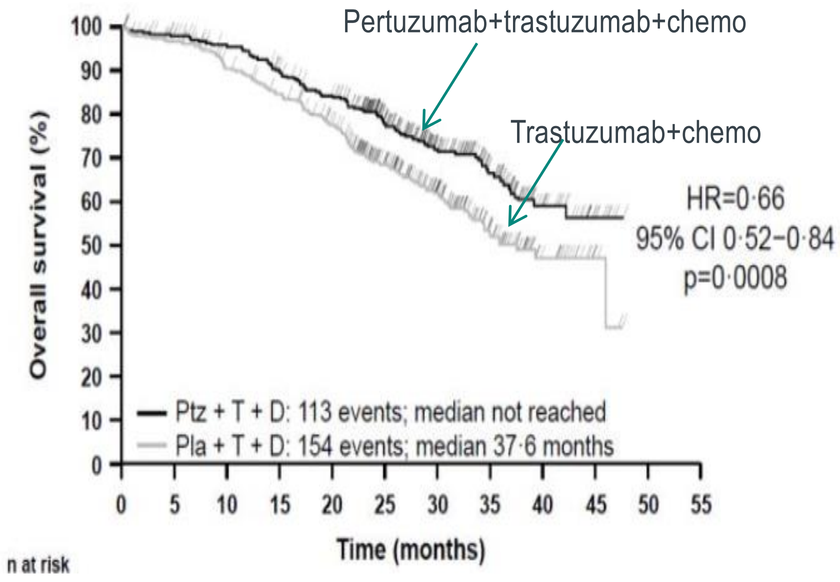
Forward Translation: Understand the Target→Design the Drug
HER2 Amplification in Breast Cancer

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



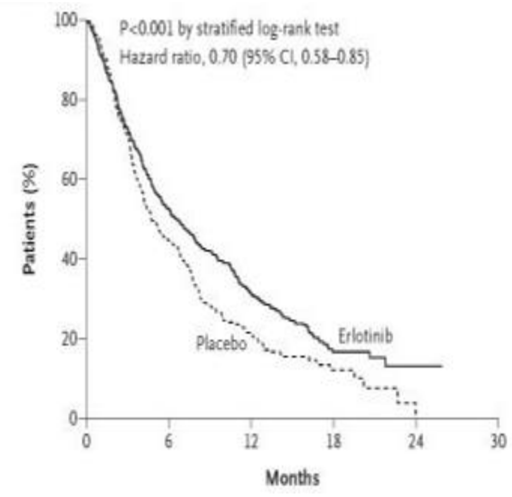


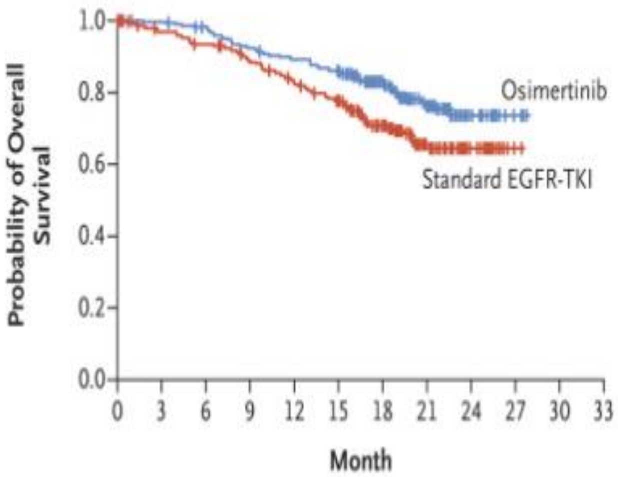
Slide courtesy of Alex Snyder

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

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New Agents Challenge Historical Dichotomy of Biomarkers

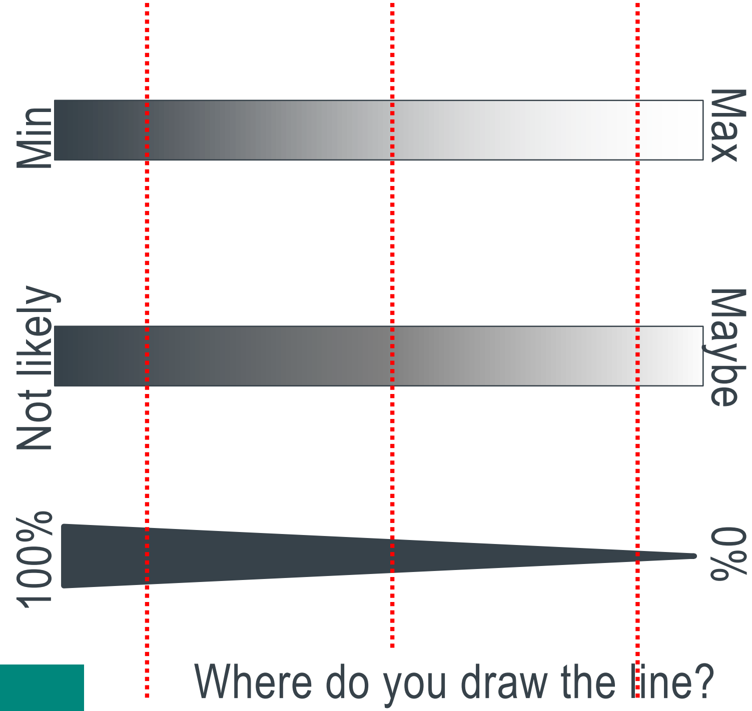
Targeted therapy

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

Immunotherapy

Biomarker assesses tumor/immune biology related to response

Targeted therapy			Immunotherapy
Absent	Present	Biomarker	Min → Max
NO	Maybe	Response	Not likely → Maybe
Fixed for indication Examples: *EGFR, KRAS* mutations		Prevalence	100% → 0%



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

A Paradigm Shift in Cancer Immunotherapy

Checkpoint blockade

To “turn on” the immune response to fight cancer (i.e. vaccine)

To “release the brakes” on the immune system to unleash a pre-existing immune response against cancer. (i.e.CTLA-4, PD-1/PD-L1)

Brake

Personalized

Slide courtesy of Jedd Wolchok

Unique Features of Personalized Cancer Immunotherapy

- ❖ Unleashing the immune system to fight cancer [1,2]
- ❖ A durable and long-lasting response in cancer patients[3,4]
- ❖ Clinical activity across a broad spectrum of tumor types[5]
- ❖ New tumor response pattern, immune related adverse events, immune related response criteria[6,7,8]
- ❖ Improving cancer survival with combination immunotherapy[9]
- ❖ Biomarkers associated with clinical outcome and precision oncology[10]

1. Mellman I, et al Nature 2011,
2. Pardoll DM, et al Nature Reviews Cancer 2012,
3. Ott PA, et al Clinical Cancer Res 2013,
4. Sharma P, et al Nature Reviews Cancer 2011
5. Zou WP, et al Science Transl Med, 2016
6. Wolchok JD, et al Clinical Cancer Research, 2009
7. Gyorki DE, et al Clinical Transl Immunology, 2013
8. Hofmann L, et al Eur J Cancer, 2016
9. Wolchok JD, et al NEJM 2013
10. Yuan J, et al J Immunother Cancer, 2016

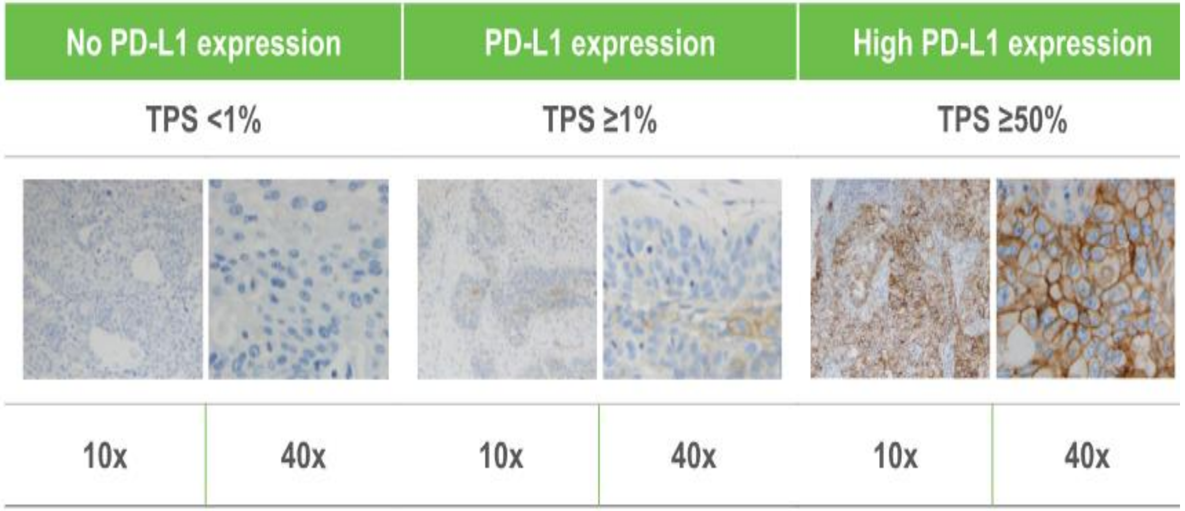
Forward Translation: Understand the Target→Design the Drug
PD-(L)1

- ❖ 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)		✓	✓

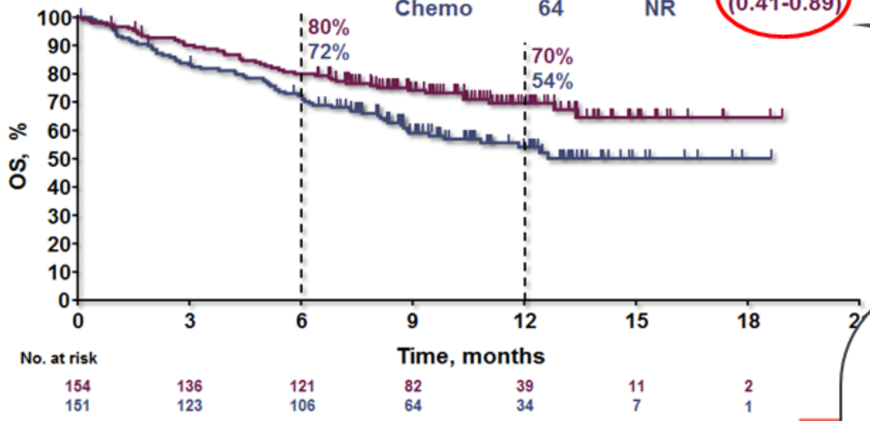
https://www.keytruda.com/hcp/nsclc/pd-l1-expression-testing/#pathologists

KEYNOTE-024
First-Line Pembrolizumab vs Chemotherapy

US Approval, October 2016

Overall Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	44	NR	0.60 (0.41-0.89)	0.005
Chemo	64	NR		

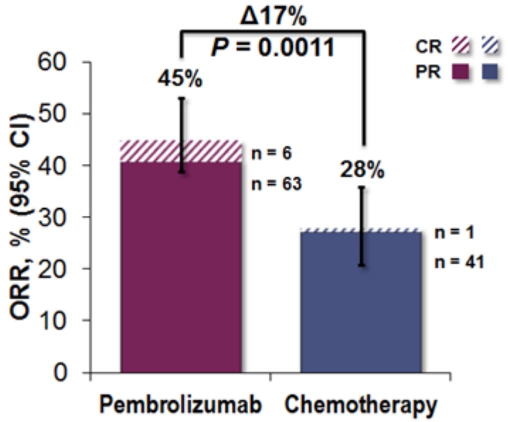


Data cut-off: May 9, 2016.

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.

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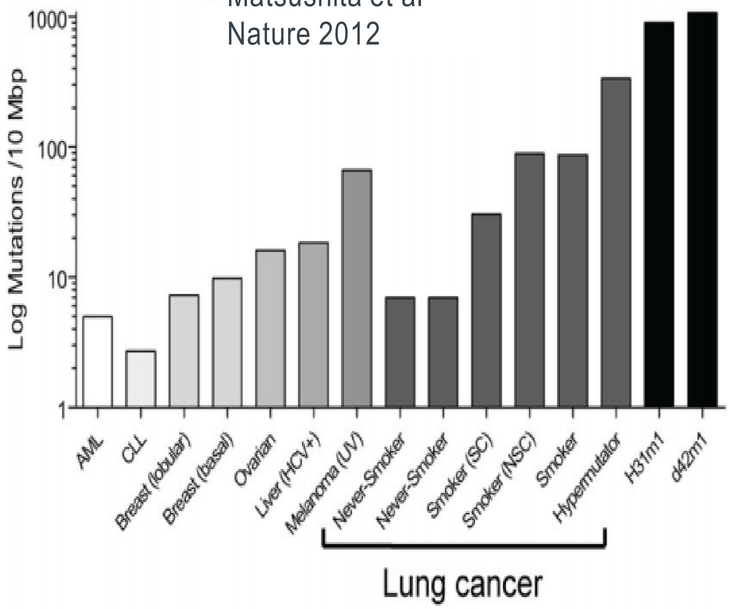
Reck M et al, *NEJM* 2016; Oct 9. ESMO 2016.

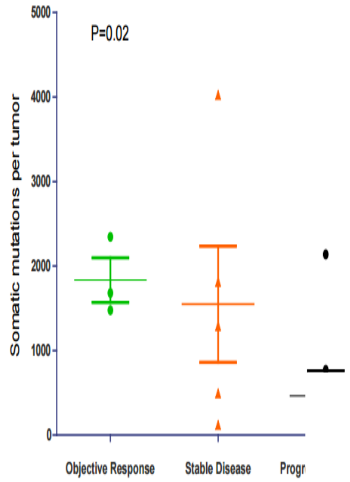
Forward Translation: Understand the Target→Choose the Drug
Mismatch Repair Deficiency and Pembrolizumab

- 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

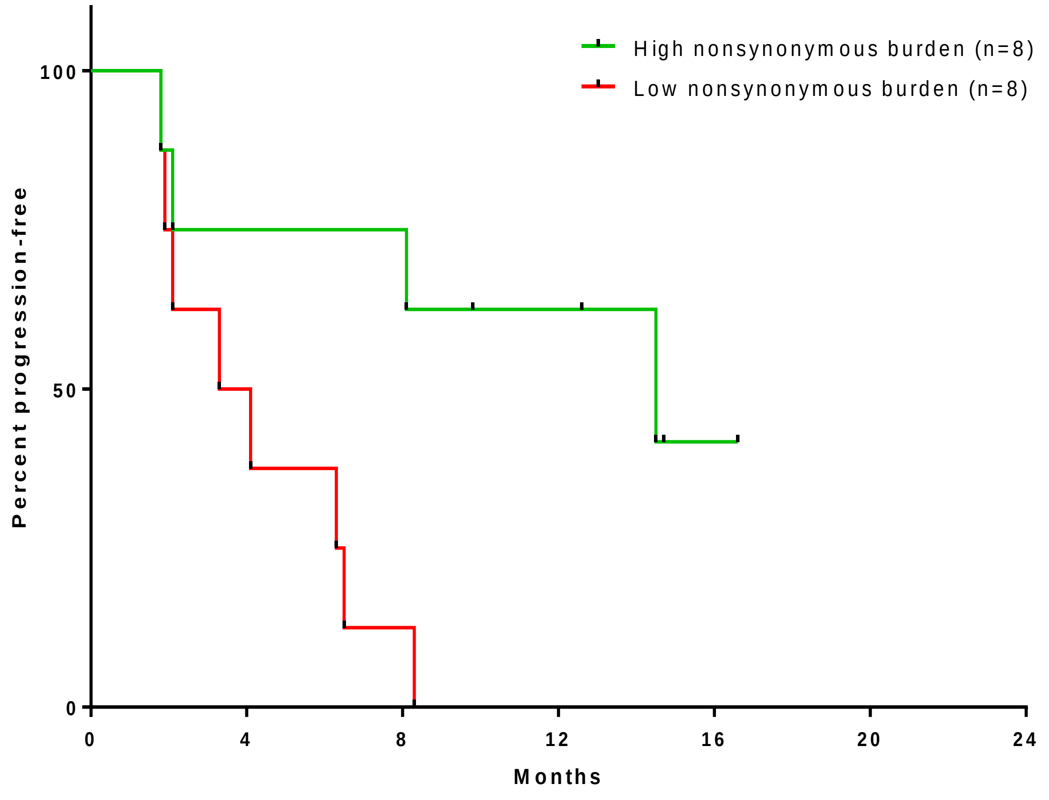
Matsushita et al
Nature 2012



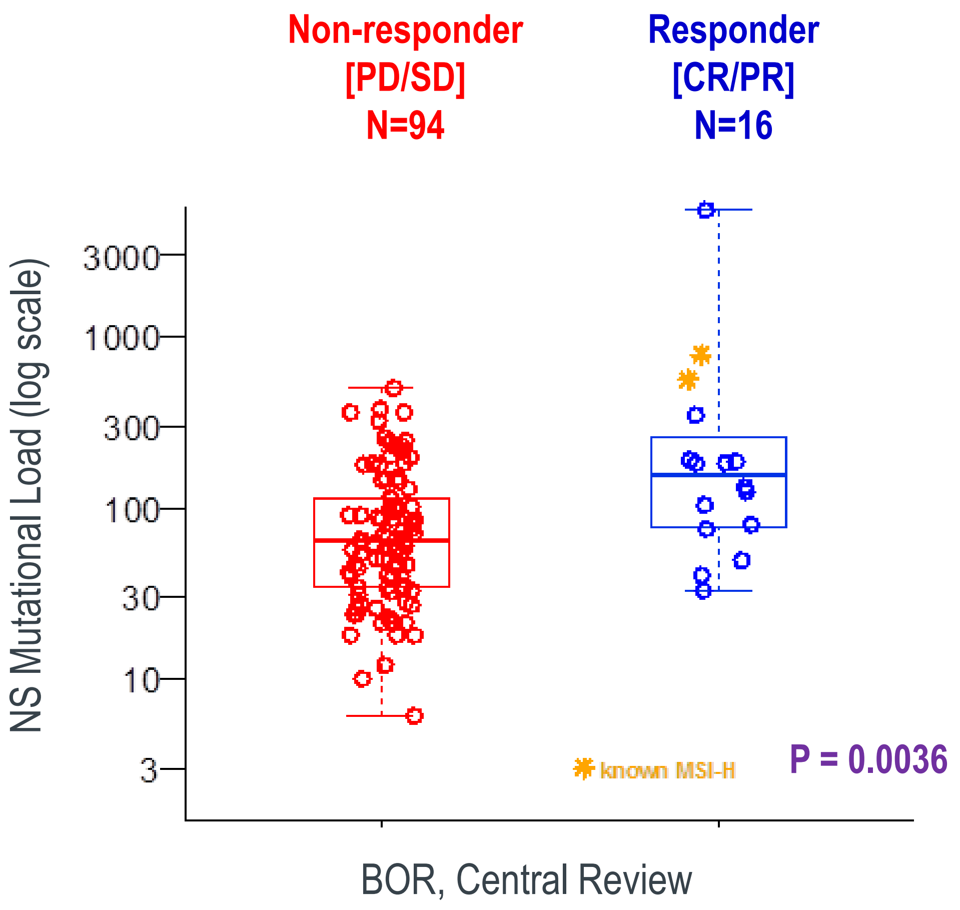
Le et al NEJM 2015
MSI-H CRC/anti-PD-1



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)

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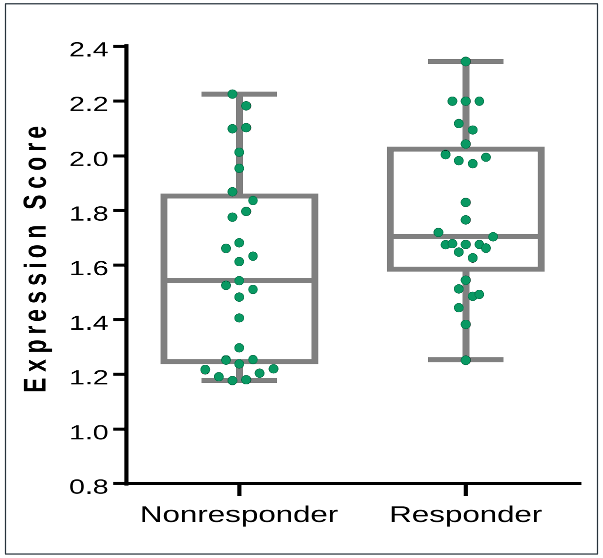
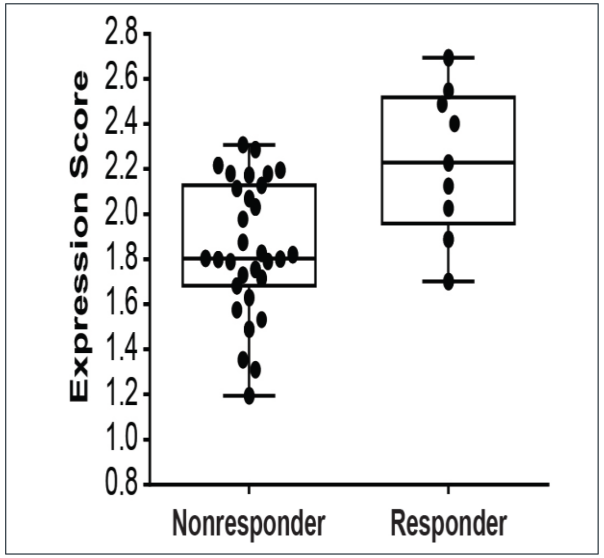
Forward Translation: Understand the Target→Choose the Drug
T-Cell Inflamed Gene Expression Profile (GEP)

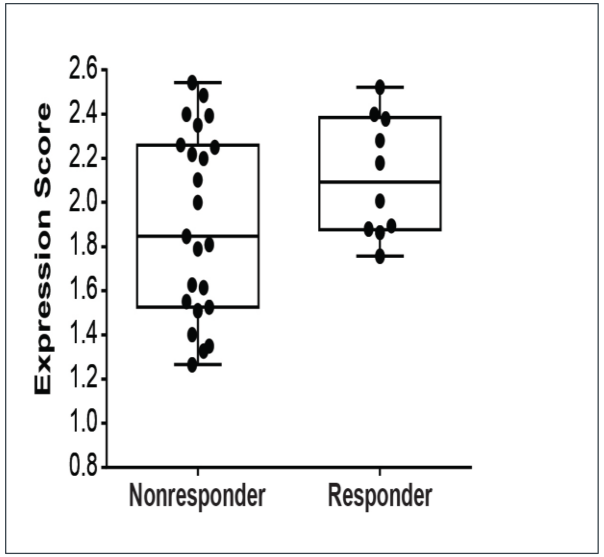
Signatures Defined and Validated in Melanoma → Signatures Validated and Refined in SCCHN and Gastric CA → Final GEP Generated Using Penalized Regression Model in 9 Solid Tumors



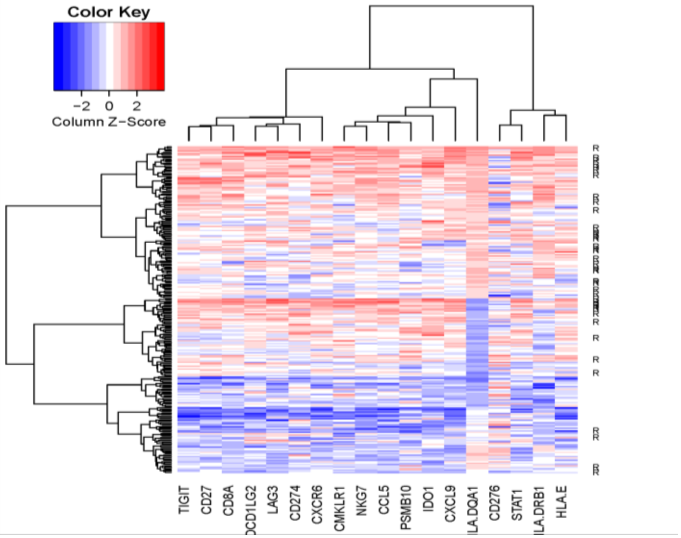
(N=19 training, N=62 validation)



SCCHN (N=43)

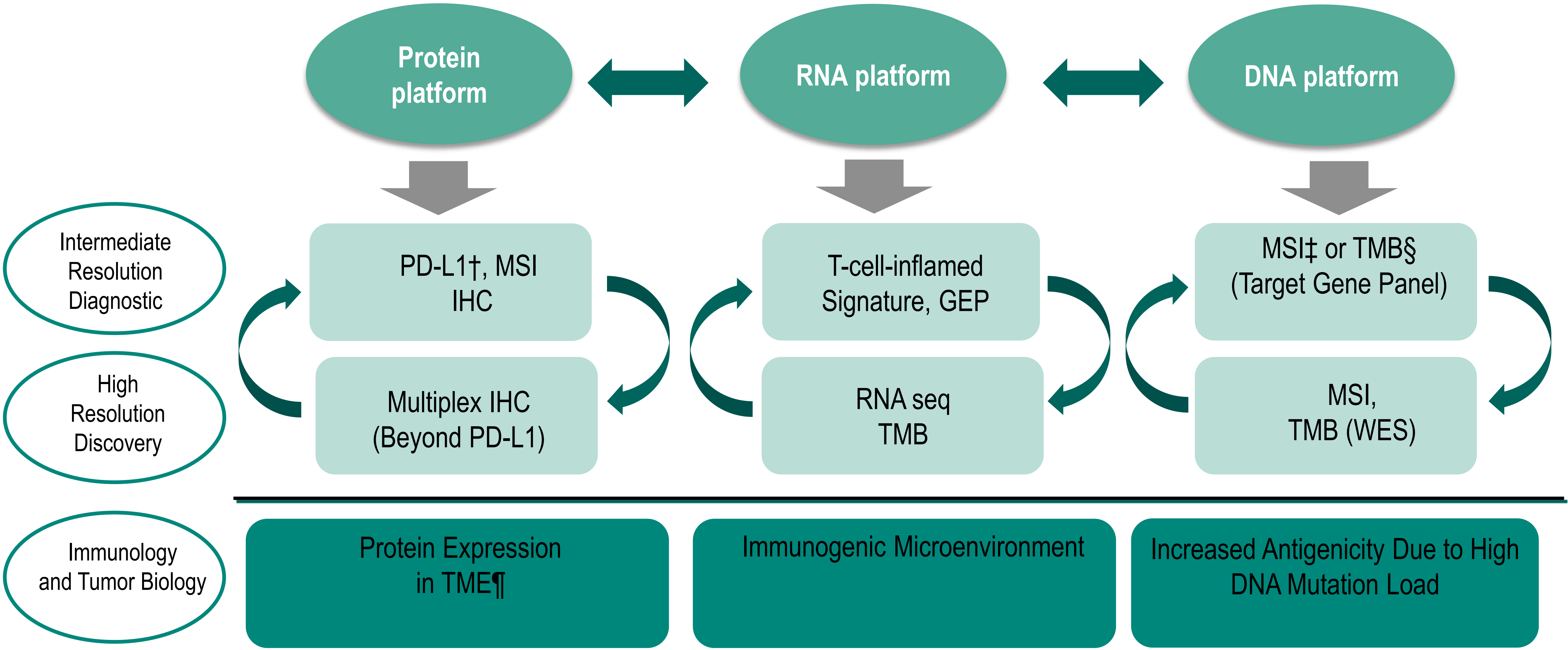


Gastric CA (N=33)



N=220 (gastric, TNBC, SCCHN, urothelial, anal, biliary, colorectal, esophageal and ovarian cancers)

Balance between Discovery Science and Biomarker CDx

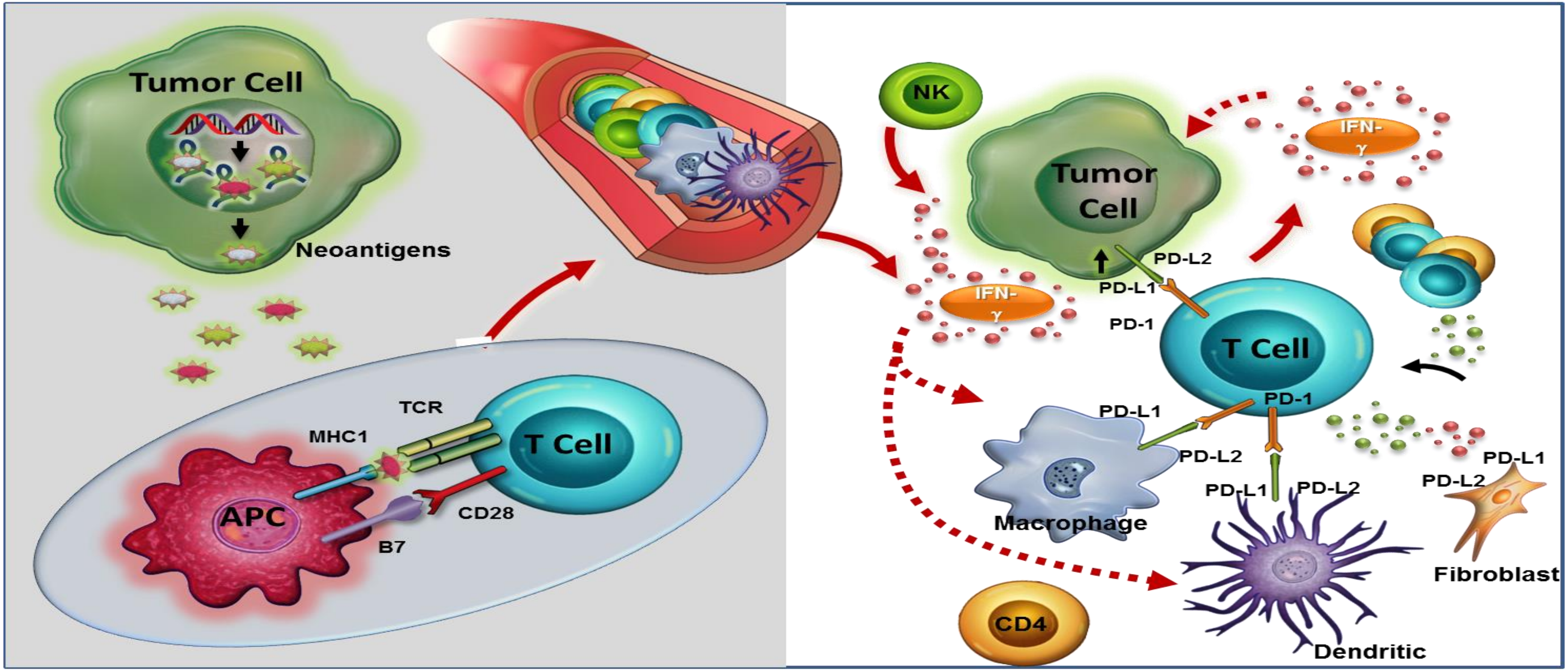


†Approved PD-L1 expression companion diagnostic assay; ‡ Approved tumor-agnostic predictive biomarker; §Approved TMB diagnostic panel (Foundation Medicine, F1CDx Panel, 315 genes);¶Tumor and immune cells

Dual Biomarker Strategy for Translational Oncology

TMB measures tumor antigenicity

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



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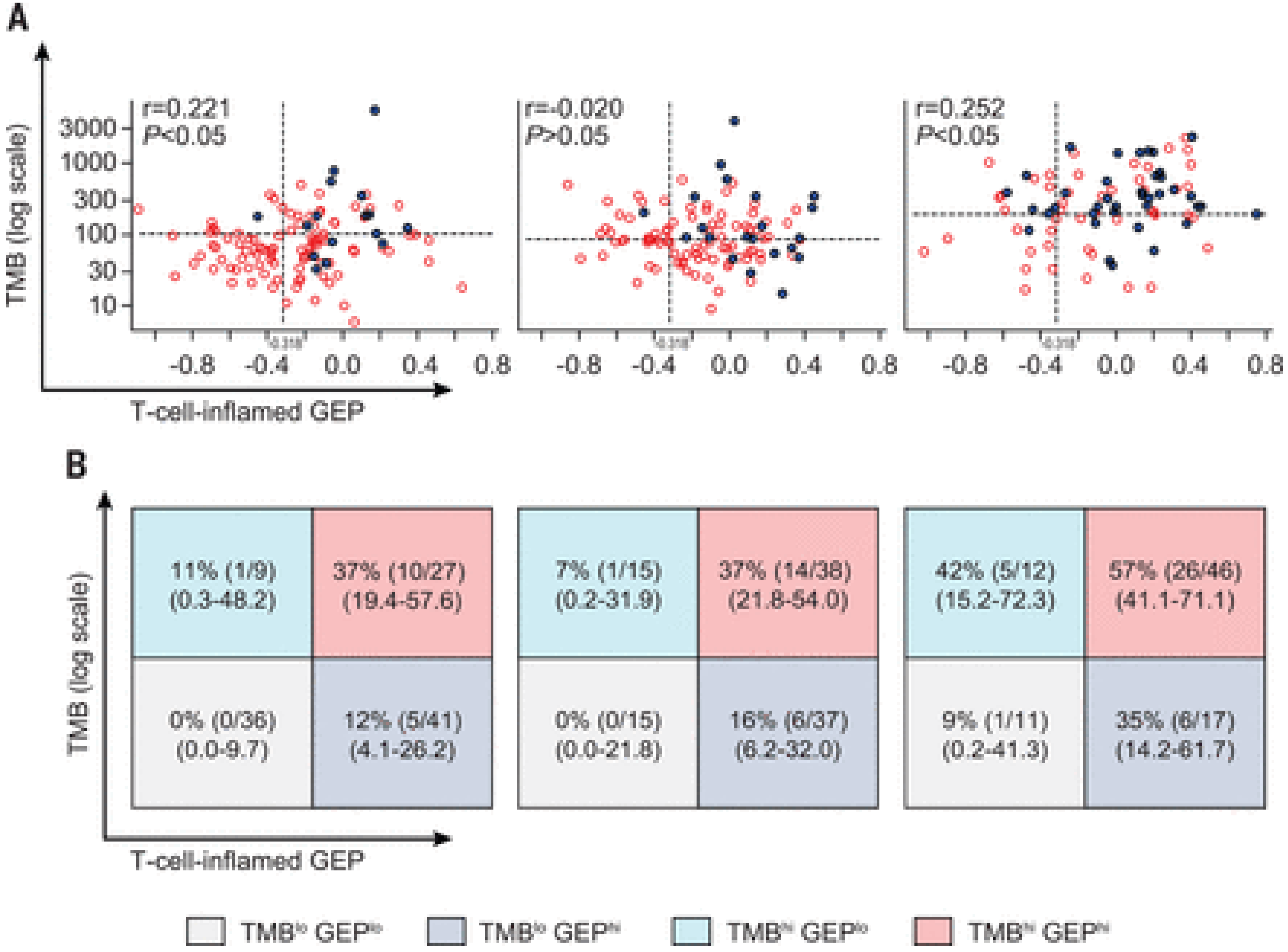
Joint Relationship of TMB or T Cell–inflamed GEP with anti–PD-1 Response across Multiple Patient Cohorts.



Higher response is in reduced population (lower prevalence)

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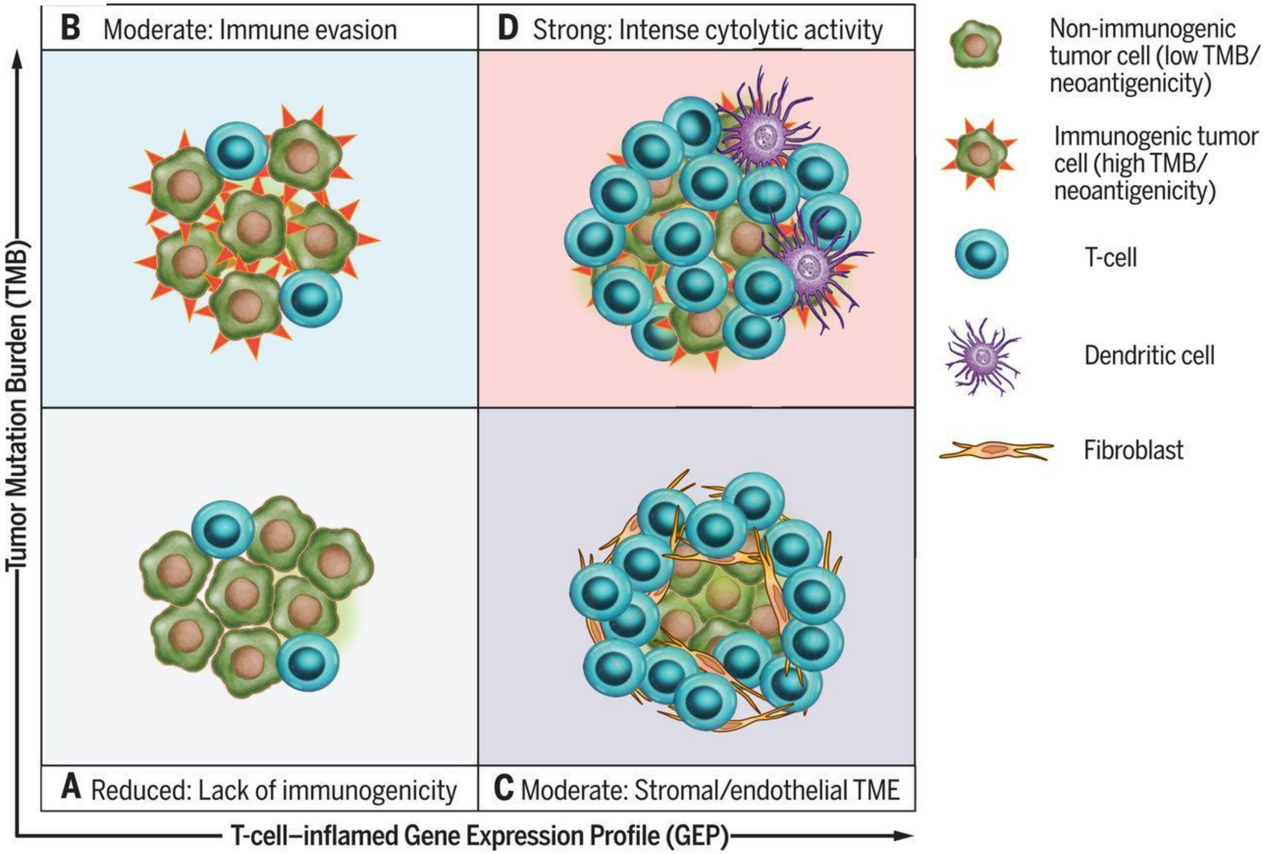
Razvan Cristescu et al. Science 2018;362:eaar3593

Precision Oncology Study KN495
TMB and GEP Stratify Targetable Biology

- TMB and GEP are independent predictors of pembrolizumab monotherapy
- Four groups defined by GEP and TMB have different biological properties that suggest unique, targetable resistance mechanisms
  - Evaluated ~40 modules of pathway gene signatures, each consisting of ~100-200 genes
  - 4 pathway gene signatures had distinct patterns in relation to GEP and TMB status
  - These upregulated pathways represent potential resistance mechanisms and thus avenues for combinations
  - Different combinations may benefit different patients according to the GEP/PDL1 and TMB scaffold.



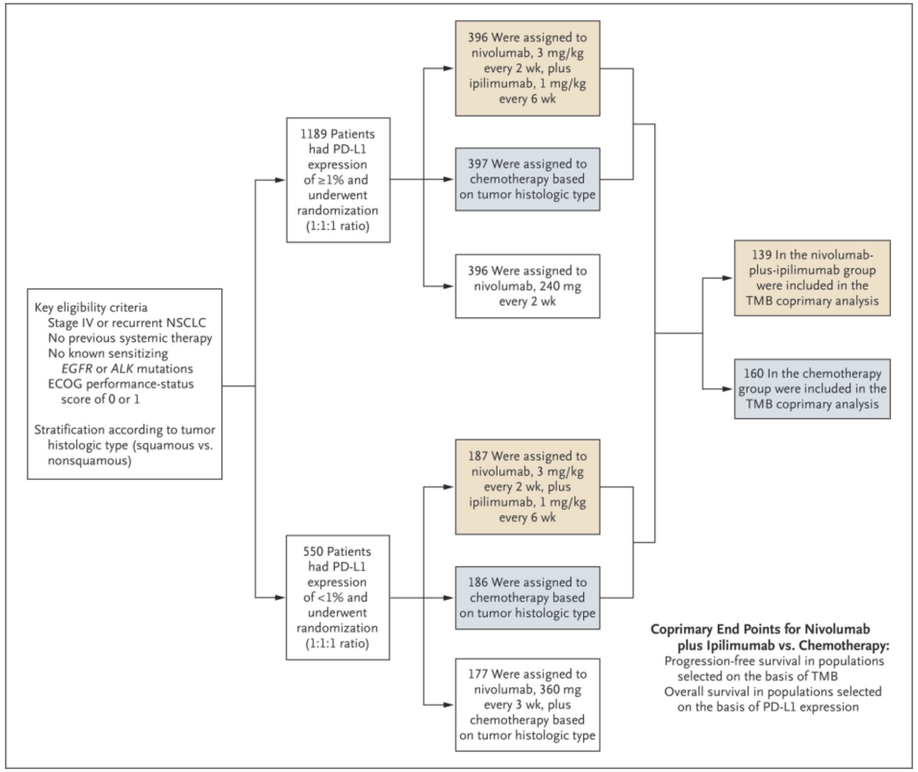
Razvan Cristescu et al. Science 2018;362:eaar3593

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)

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

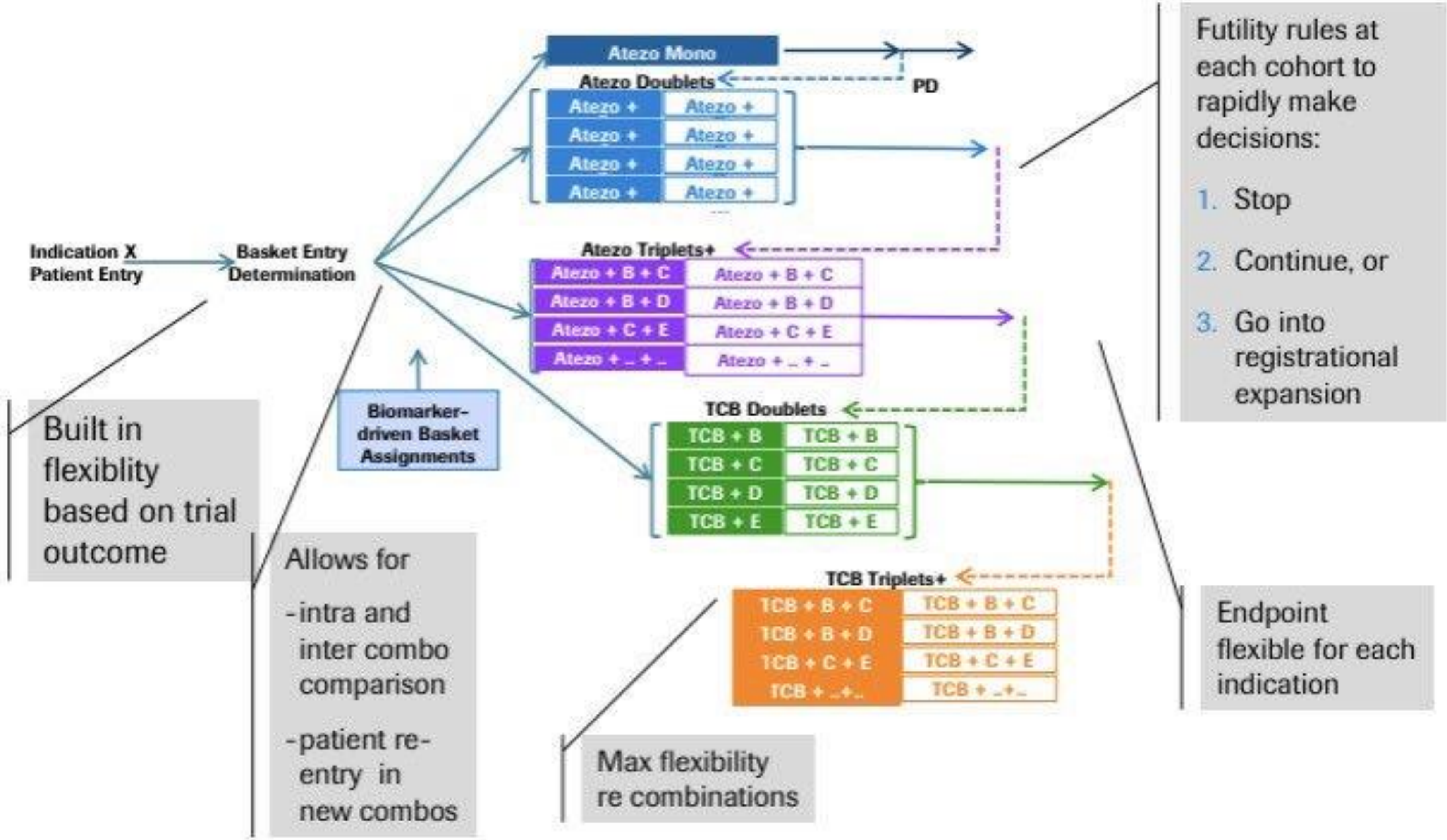
- Eligible: Stage IV or recurrent NSCLC not previously treated with chemotherapy.
- PD-L1 expression ≥ 1% were randomly assigned, in a 1:1:1 ratio, to receive nivolumab plus ipilimumab, nivolumab monotherapy, or chemotherapy;
- PD-L1 expression level of < 1% were randomly assigned, in a 1:1:1 ratio,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



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

Adaptive Trials

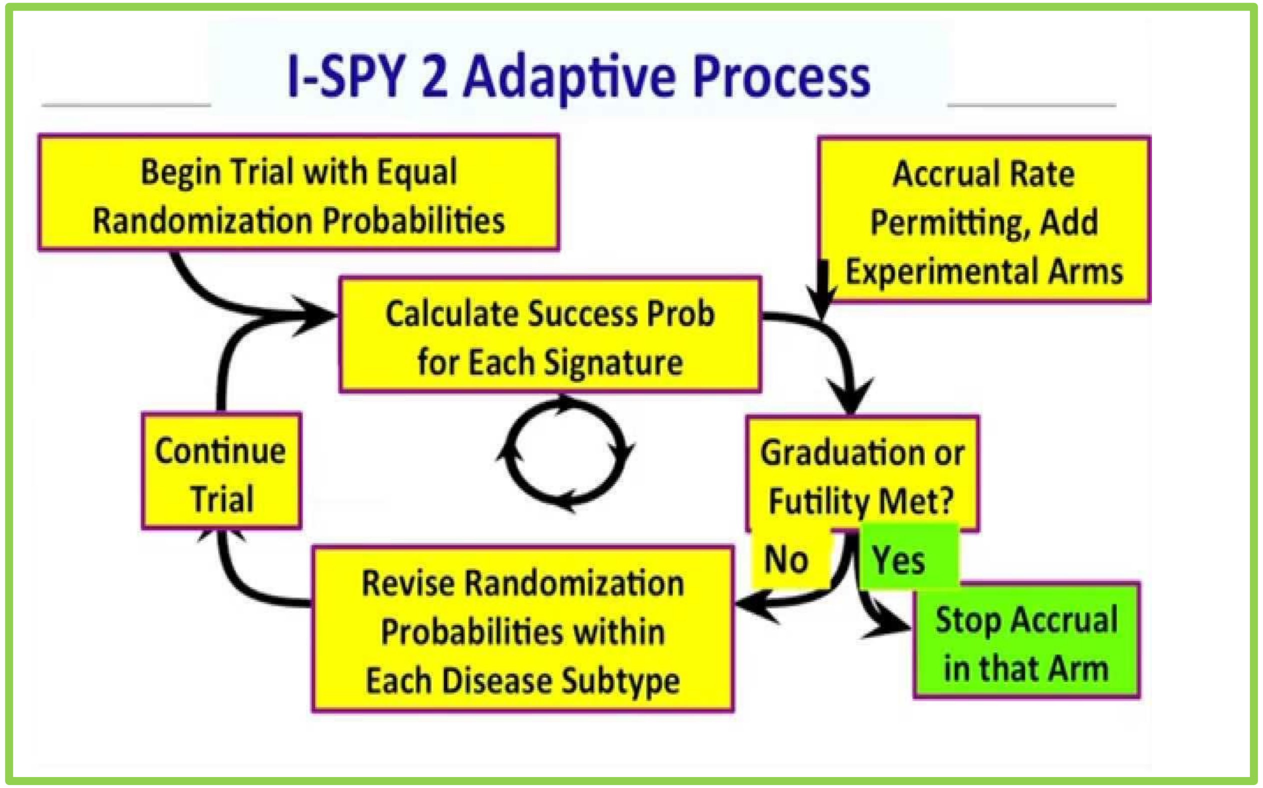
- Adaptiveness in phase I and II trials can help optimize the dose/schedule, regimen, patient population in order to develop the right pivotal trial

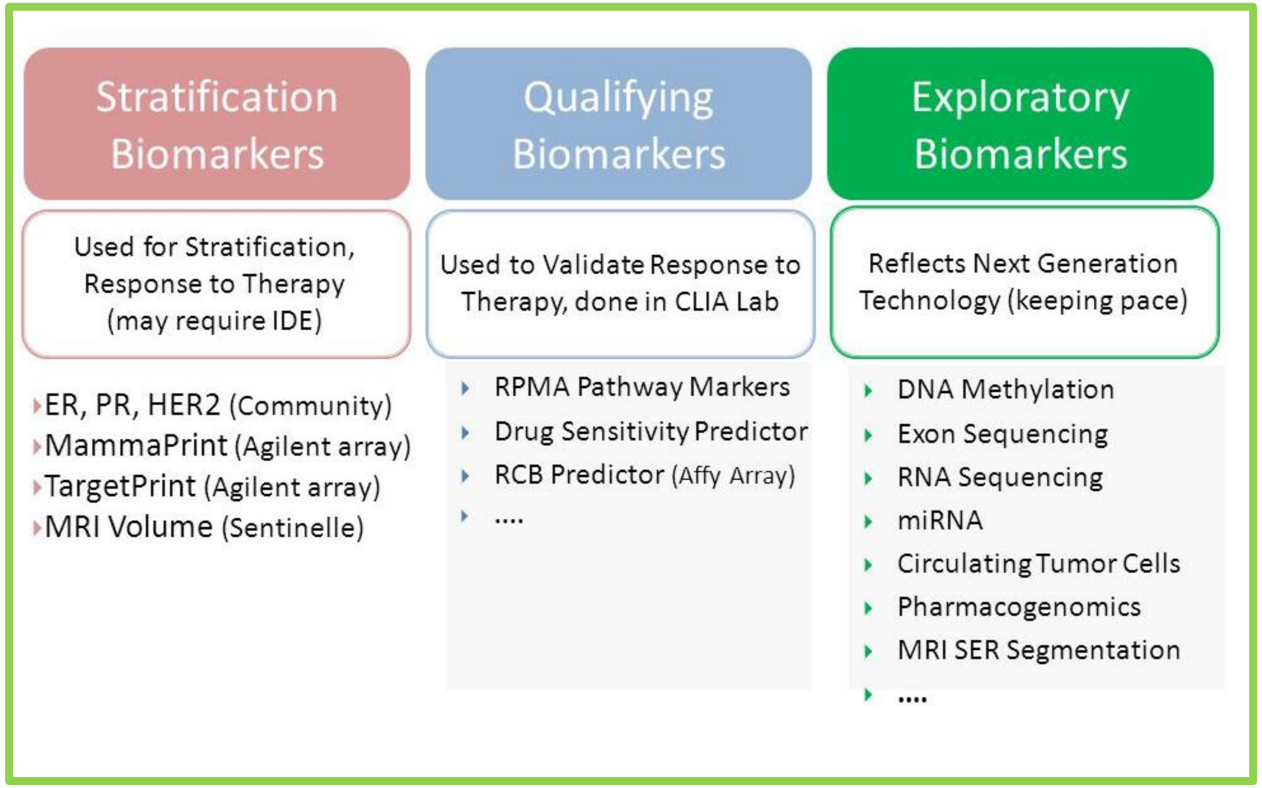
- Most drugs fail because
  - They are toxic
  - They are ineffective
  - They are not tested in the right dose/schedule/regimen for the right population of patients

- 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





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

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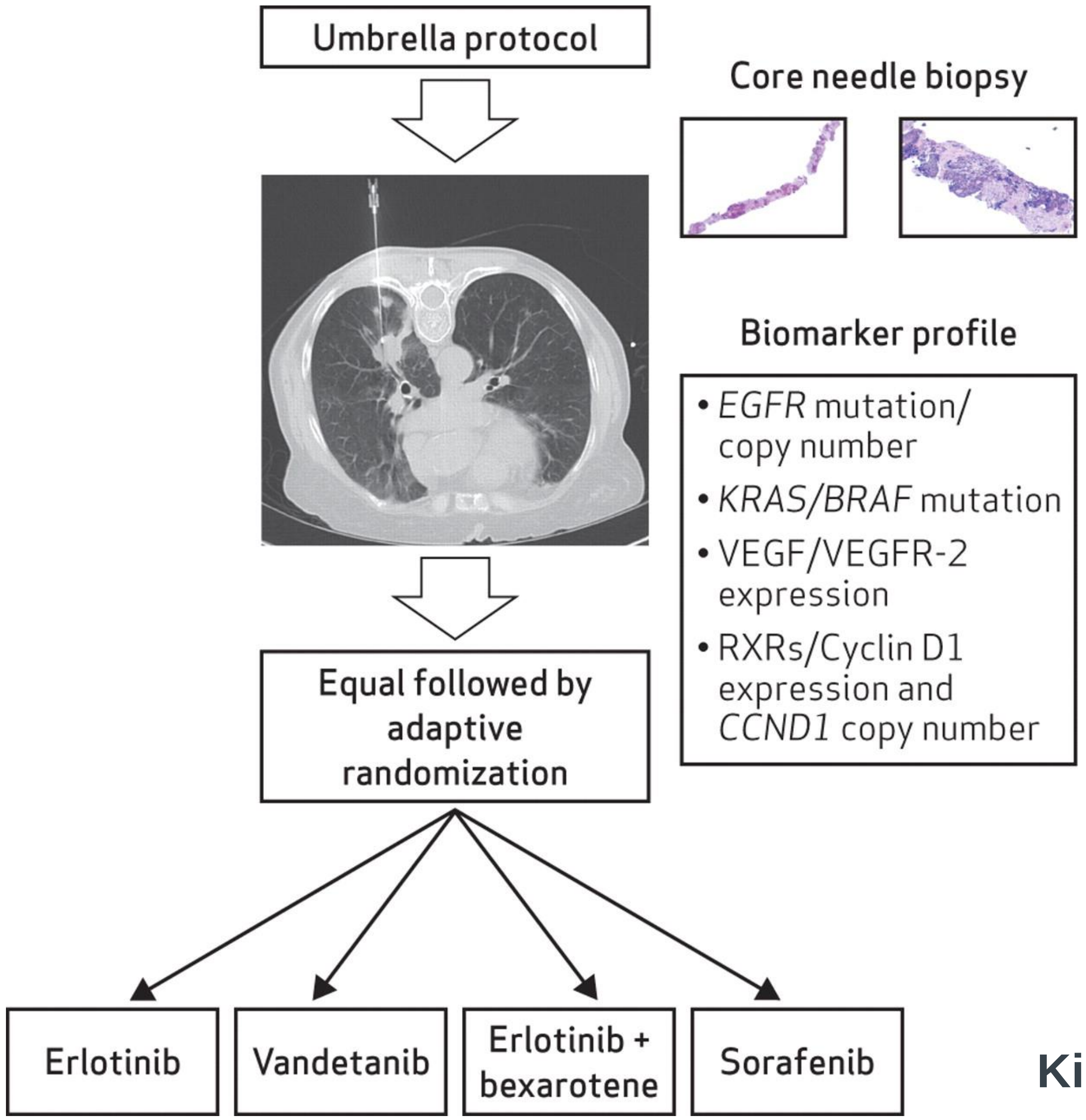
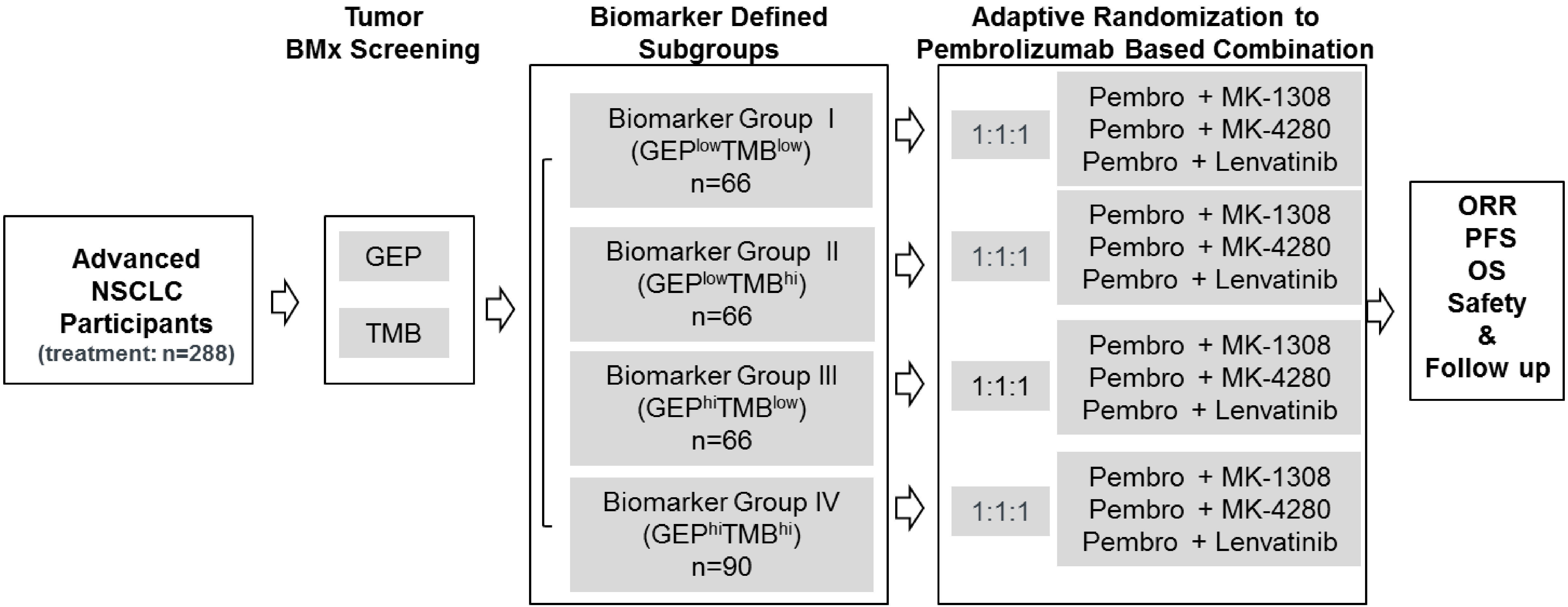
Adaptive Design and Multiple Biomarker: BATTLE Trial



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!

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