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
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
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”

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
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
Personalized Cancer Therapy

1. Molecular Profiling
   - Markers predict drug sensitivity/resistance

2. Prognostic Markers
   - Markers predictive of adverse events

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

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.


*Slide courtesy of Alex Snyder*
New Agents Challenge Historical Dichotomy of Biomarkers

**Targeted therapy**
- Biomarker assesses presence/absence of specific mutation or fusion required for response
- Absent | Present
- NO | Maybe

**Immunotherapy**
- Biomarker assesses tumor/immune biology related to response
- Where do you draw the line?

**Prevalence**
- Fixed for indication
- Examples: *EGFR, KRAS* mutations
- 100% | Not likely | Maybe | 0%

Biomarkers for PARP inhibitors and immunotherapy exemplify this challenge.
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
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

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

<table>
<thead>
<tr>
<th>TPS= tumor proportion score</th>
<th>No PD-L1 expression</th>
<th>PD-L1 expression</th>
<th>High PD-L1 expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPS &lt;1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPS ≥1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPS ≥50%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40x</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. **First-line KEYTRUDA + cisplatin or carboplatin and pemetrexed**
   - (nonsquamous; no EGFR or ALK genomic tumor aberrations)
   - No PD-L1 Expression (TPS <1%): ✓
   - PD-L1 Expression (TPS 1% to 49%): ✓
   - High PD-L1 Expression (TPS ≥50%): ✓

2. **First-line KEYTRUDA**
   - (nonsquamous or squamous; no EGFR or ALK genomic tumor aberrations)
   - High PD-L1 Expression (TPS ≥50%): ✓

3. **Second-line or greater KEYTRUDA**
   - (nonsquamous or squamous; prior treatment required for patients with EGFR or ALK genomic tumor aberrations)
   - No PD-L1 Expression (TPS <1%): ✓
   - High PD-L1 Expression (TPS ≥50%): ✓

https://www.keytruda.com/hcp/nsclc/pd-l1-expression-testing/#pathologists
KEYNOTE-024
First-Line Pembrolizumab vs

US Approval, October 2016

40% risk reduction of death

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

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 $\rightarrow$ greater immunogenicity

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

Razvan Cristescu et al. Science 2018;362:eaar3593

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)
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.

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

Built in flexibility based on trial outcome

Allows for
- intra and inter combo comparison
- patient re-entry in new combos

Max flexibility re combinations

Futility rules at each cohort to rapidly make decisions:
1. Stop
2. Continue, or
3. Go into registrational expansion

Endpoint flexible for each indication

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
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!