Oncology Drug Development Using Molecular Pathology
Introduction

PRESENTERS

Lee Schacter, PhD, MD, FACP
Executive Medical Director, Oncology
Clinipace Worldwide

Martha Bonino
Director, Strategic Accounts
Clinipace Worldwide

Afshin Safavi, PhD
Founder and CSO
BioAgilytix
Cancer Treatment Drug Development History

PATHOLOGY
- c. 2000 BC: Clinical description of breast cancer
- c. 400 BC: Hippocrates determines cancer is caused by black bile
- 1798: Virchow (1821-1902) shows organisms are made of cells which derive from other cells and creates modern pathology as we know it
- 1860-1900: Paul Ehrlich coins terms "chemotherapy" and "magic bullet"

TREATMENT
- 1860-1900: Wm. Coley uses bacteria to treat cancer (1893)
- "Coley’s Toxin" first immunotherapy
- Halsted develops radical mastectomy (1890s)
- 1860-1900: Beatson performs oophorectomy for breast cancer
- c. 2000 BC: Homeopathic
Cancer Treatment Drug Development History: Early 1900s

**PATHOLOGY**
- 1911: Peyton Rous discovers viral cause of cancer in chickens
- 1919: Lymphoid depletion, marrow aplasia and neutropenia caused by mustard gas published
- 1920s-30s: Brachytherapy using radium
- 1937: George Clowes at Roswell Park develops animal models of cancer

**TREATMENT**
- Office of Cancer Investigations formed part of USPHS eventually becomes NCI

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Cancer Treatment Drug Development History:
1940 - 1960

PATHOLOGY

1941
Charles Higgins uses castration to treat prostate cancer

1943
Sulfa Mustard given to lymphoma patients at Yale

1948
Sydney Farber publishes data on aminopterin in childhood leukemia

1950s-60s
Multiple derivatives of mustard, folate analogs, nucleoside analogs
Advent of megavoltage teletherapy

TREATMENT

1958
Methotrexate used to cure choriocarcinoma
Cancer Treatment Drug Development History: 1960s - 1980

**PATHOLOGY**
- 1970: First oncogene, src, described
- 1971: Philadelphia chromosome described
- 1973: Kohler and Milstein create monoclonal antibodies
- 1975: Sanger DNA sequencing
- 1977: Phosphorylation of tyrosine in proteins discovered

**TREATMENT**
- “War” on cancer declared
Cancer Treatment Drug Development History: 1980 - 1995

**PATHOLOGY**

- **1984**: First receptor structure, EGF, described
- **1989**: First recombinant drug, Epogen, approved
- **1994**: "Age of the Chemist" ends. "Age of the Biologist" begins

**TREATMENT**

- **1984**: First MoAb approved by FDA
Cancer Treatment Drug Development History:
2000 – present day

**PATHOLOGY**
- **2001**: Human genome sequenced
- **2003**: Mutation responsible for activity of erlotinib in lung cancer identified

**TREATMENT**
- **2001**: First TKI, Imitinib, approved
- **2011**: First immune checkpoint agent, ipilimumab, approved
Changes in Tumor Classification

“The Right Drug for the Right Patient”

Percentage of patients whose tumors were driven by genetic mutations that could be targets for specific drugs, by type of cancer

Evolution of Molecular Treatment

New drug approvals by the FDA, with an observed increase in the approval of targeted therapies

Drug Development Using Molecular Profiling

Roles of molecular pathology in cancer drug development include:

- Identification of unique, modified, or over-expressed potential targets in malignant cells
- Classification of cancer by molecular pathology rather than histology
- Selection of patients for treatment based on molecular pathology
- Determining if agent is having the expected effect on the target
Molecular Profiling for Adaptive Clinical Trials

✓ Overview

✓ Example:

- I-SPY 2 Trial, developed by Biomarkers Consortium
- Phase II randomized controlled trial (RCT)
  - Women with higher risk, rapidly growing breast cancers received drugs individually targeted to biology of specific tumor based on biomarkers
  - Treated with targeted drugs prior to definitive surgery
  - Efficacy determined based on viability of excised tumor
- Therapy with specific agents stopped in tumor subtypes for which an effect was not observed in early patients, while use of therapy was increased in other subtypes where there was an observed effect

✓ Ineffective treatments and drugs eliminated more quickly
Technology Enabling Biomarker Identification

Following characteristics should be considered:

- Sensitivity
- Precision
- Dynamic range
- Adaptability to automation
- Ease and cost of implementation
- Suitability for measurement of a wide variety of analytes
- Matrix interference
- Robustness and ruggedness
- Total assay time
- Multiplexing
- Throughput

Platform choice should be evaluated on a case-by-case basis, depending on intended use of assay and phase of the trial.
Case Study 1: Biomarker Discovery

✓ Challenge:
  – 12 biomarkers of interest, but which one(s) are relevant?

✓ Solution:

- Selected Luminex as platform of choice
- Due to antibody cross-reactivity, developed 2 multiplex panels (7-plex and 5-plex)
- Validated a qualitative assay
- Analyzed all samples (Pre- versus post-dose)
- Used SAS-JMP statistical software to analyze data
- 1 biomarker discovered as a potential lead
- Quantitative assay developed on MSD-ECL, and fully validated for the next phase of study
Case Study 2: Use of MSD-ECL in Support of Multiplex Biomarker Study

Challenges:
- Matrix: Serum and/or plasma
- Analysis: Needed to quantify multiple biomarkers
- Sample volume: Small
- Specificity: Differentiate between multiple biomarkers
- Study size: Large number of samples

Solution:
- MSD-ECL technology
- Validated 7-plex oncology panel
- Used 100 ul of sample to quantify 7 biomarkers per sample
- Ran several thousands of samples/day
- Used biomarkers to support over 30 phase I, II and III for bladder, colon, breast, prostate and lung cancers
Case Study 3: Use of ProteinSimple Technology in Support of Biomarker Study

✓ Challenges:
  - Analysis: Phospho Protein (2 proteins each with 2 isoforms)
  - Sample volume: Small
  - Antibody Source: good antibody pair not available
  - Specificity: Needed separation before analysis
  - Study size: Large number of samples

✓ Solution:
  - ProteinSimple PeggySue system
  - Separation based on size and charge
  - Small sample volume
  - Required only one antibody for detection
  - Specificity obtained through size separation and one antibody
  - Fully automated Western blotting system
Biomarkers Definitions

- According to BQRT, valid biomarker if:
  - “it is measured in an analytical test system with well-established performance characteristics AND
  - there is an established scientific framework or body of evidence that elucidates the physiologic, pharmacologic, toxicologic, or clinical significance of the test results”

- Probable valid biomarker
  - Lacks wide acceptance or independent verification
  - Appears to predict clinical outcomes based on sufficient study data, treatment-related prognosis, dose strata
  - Data not required on INDs unless used to define inclusion/exclusion criteria

- Valid and probable valid biomarkers appropriate for decision-making

- Exploratory/observational biomarkers not sufficient for regulatory decisions
Regulatory Considerations

✓ Expedited Approvals - 4 FDA programs:

- Fast track
  - Information that can be used to support this designation include theoretical rationale, mechanistic rationale, or evidence of nonclinical activity

- Breakthrough therapy
  - As of May 2014, 48 of 186 requests for this designation have been granted

- Priority review designations
  - 6 month time for review, compared with 10-month standard review

- Accelerated approval pathway
  - More than 80 products approved in this pathway since it began in 1992
Regulatory Considerations

✔ Master Protocol Process
  - Facilitates effective collaboration between government, academia, nonprofit, and industry to test multiple drugs and biomarkers in a single, ongoing clinical trial
  - Encourages use of profiles to assign patients to targeted treatments
  - Aim of efficient clinical trials and delivery of safe and effective therapies
  - Example: Lung Cancer Master Protocol (Lung-MAP)
    • Multi-drug, multi-arm, biomarker-driven clinical trial
    • Will investigate investigational treatments for advanced squamous cell lung cancer at over 200 medical centers
    • Treatment typically limited to surgery
    • Genomic profiling will match patients to one of the 4 targeted treatments or an anti-PD-L1 immunotherapy, and enable simultaneous biomarker validation and drug development
Regulatory Considerations

✓ Test/Drug Co-Development

- Co-development status considered when products raise development issues affecting both drug therapy and diagnostic test, regardless of regulatory status as a combination product
- Combination product involves a therapeutic and a diagnostic medical product that are necessary together to achieve the indication
- 4 important considerations:
  • Review procedure issues
  • Analytical test validation
  • Clinical test validation
  • Clinical test utility
- Example: approval of Tafinlar/Mekinist for advanced or unresectable melanoma, granted by FDA (May 2013), along with the THxID BRAF test
Regulatory Considerations

✓ Labeling
  – Important for diagnosis and monitoring
  – Data may include:
    • Variability in drug exposure and clinical response
    • Risk for adverse events
    • Genotype-specific dosing
    • Mechanisms of drug action
    • Polymorphic drug target and disposition genes
  – Although labeling regarding biomarkers and genetic testing is currently included for 158 drugs, this represents <10% of drugs available
Future of Molecular Profiling

✓ Between 5,000 to 10,000 potential drug targets

✓ Where are we headed?
  
  – Focus on mutation identification and signaling pathway instead of histological characteristics
  
  – Modify thinking from, for example, treatment for a “malignant melanoma” to treatment for cancers with a BRAF V600E mutation
  
  – Disease classification systems must incorporate this new understanding
  
  – Shift from reactive to preventive medicine
  
  – Drug registration change from specific cancer location to molecular profile/mutation/driver
  
  – Sponsors should consider simultaneous development of drug and companion diagnostic to facilitate use of biomarkers in trials as well as clinical practice
Questions?