Opportunities of Statistics for Precision Medicine in Drug Development

Ivan S.F. Chan, Ph.D.
AbbVie

IMS Workshop on Perspectives and Analysis Methods for Personalized Medicine
National University of Singapore
Singapore

July 10-14, 2017
Disclosure

The support of this presentation was provided by AbbVie. AbbVie participated in the review and approval of the content.

Ivan Chan is an employee of AbbVie, Inc.
Acknowledgement

- Xin Huang, AbbVie
- Yihua Gu, AbbVie
Outline

• Overview of Drug Development Process

• Opportunities of Statistics for Precision Medicine
  – Biomarker Strategy
  – Adaptive Patient Enrichment Strategy
  – Patient Subgroup Identification
  – Multiplicity Adjustment

• Statistical Leadership for Success
Discovery and Development of a Successful Drug/Vaccine

**Years**

1. **Basic Research**
   - 0 - 1 years
   - 3,000 - 10,000 substances

2. **Preclinical Test (Animals)**
   - 2 - 5 years
   - 2 - 5 phases
   - 5 - 10

3. **Clinical Test (Humans)**
   - 2 - 5 phases
   - 10 - 20 years

4. **Market Launch**
   - 1 year
   - 1 phase
   - 1

**Phases**

IV. Post-Marketing Surveillance
III. Clinical Test (Humans)
II. Preclinical Test (Animals)
I. Basic Research

*Modified from PhRMA analysis, updated for data per Tufts Center for the Study of Drug Development (CSDD) database.*
Key Scientific Principles of Clinical Development

ICH E8 (General Consideration for Clinical Trials):

“The essence of rational drug development is to ask important questions and answer them with appropriate studies.”

ICH E9 (Statistical Principles for Clinical Trials):

“To be able to minimize bias and maximize precision...and draw valid conclusions“

ICH = International Conference on Harmonization
Clinical Development Process

**Phase I**
- **Check Safety**
- 10 to 100 health volunteers
- 1st stage testing in human

**Phase II**
- **Check Efficacy Dose Selection**
- 100 to 500 patients
- How well does the drug work?

**Phase III**
- **Confirm Efficacy and Safety**
- 500 to 10000+ patients
- Compare to gold standard treatment

**FDA Review and Phase IV**
- Market launch after FDA approval
- - Safety surveillance
- - Study additional populations

**Real World Evidence**
- Real world studies
  - Medical claims
  - Cost effectiveness
  - Outcome research
Big Data and Predictive Analytics

- Biomarker Labs
- Clinical Trial
- Genomics Proteomics
- Chemistry
- Safety Surveillance
- Real World Data
- Health Claims
Statisticians Play an Important Role in Research and Development

- Design of experiments and clinical trials
- Statistical analysis and interpretation of data
- Statistical modeling and predictive analytics
- Biomarker and genomics
- Strategic planning
  - Product label versus clinical development plan
  - Decision making and probability of success
- Interaction with regulatory and external experts
  - FDA, NIH, World Health Organization (WHO)
  - Key opinion leaders (KOL)
Some Recent Statistical Innovations in Precision and Personalized Medicine

• Biomarker strategy for precision and personalized medicine

• Adaptive clinical trial design with patient enrichment

• Subgroup identification

• Multiplicity adjustment in enrichment designs and subgroup identification
Why Precision Medicine? – Patients can respond differently to the same treatment

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Percentage of Ineffective Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPERTENSION DRUGS</td>
<td>10-30%</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td></td>
</tr>
<tr>
<td>HEART FAILURE DRUGS</td>
<td>15-25%</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td></td>
</tr>
<tr>
<td>ANTI-DEPRESSANTS</td>
<td>20-50%</td>
</tr>
<tr>
<td>CHOLESTEROL DRUGS</td>
<td>30-70%</td>
</tr>
<tr>
<td>Statins</td>
<td></td>
</tr>
<tr>
<td>ASTHMA DRUGS</td>
<td>40-70%</td>
</tr>
<tr>
<td>Beta-2-agonists</td>
<td></td>
</tr>
</tbody>
</table>

Percentage of the patient population for which any particular drug is ineffective.

Biomarker Guided Design for Precision Medicine

- Modern technology advancement allow development of biomarker based on genomic data.

- Treatment response may be higher in biomarker+ subgroup

- Clinical trial design can be enriched using the predictive biomarker to increase the precision and power (Targeted therapy)
Biomarker Guided Design

Stratified randomization by Biomarker status

Test Biomarker

Marker +
Randomize
Treatment
Control

Marker -
Randomize
Treatment
Control
Example 1: Biomarker Guided Design for Venclexta

• Targets chronic lymphocytic leukemia (CLL)

• Venclexta (AbbVie) is a first-in-class, oral, once-daily medicine that selectively inhibits the BCL-2 protein that feeds CLL cancer cell growth

• Patients with 17p deletion lack a cancer suppressor gene in chromosome 17

• Biomarker guided study showed Venclexta achieved a high overall response rate in patients with 17p deletion
Example 2: To Enrich vs. Not to Enrich

Keytruda (Merck) and Opdivo (BMS) are same class immune-checkpoint (PD1) inhibitors targeted to treat lung cancer (1st line)

<table>
<thead>
<tr>
<th></th>
<th>Keytruda</th>
<th>Opdivo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III Design</td>
<td>Enrichment</td>
<td>No Enrichment</td>
</tr>
<tr>
<td>Biomarker</td>
<td>PD-L1 high positive (≥50%)</td>
<td>PD-L1 positive (≥5%)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Keytruda vs. Chemo</td>
<td>Opdivo vs. Chemo</td>
</tr>
<tr>
<td>Study outcome:</td>
<td>50% improvement</td>
<td>No improvement</td>
</tr>
<tr>
<td>Tumor progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>risk (PFS)</td>
<td>50% improvement</td>
<td></td>
</tr>
<tr>
<td>Regulatory Path</td>
<td>Study succeeded and indication approved</td>
<td>Study failed</td>
</tr>
</tbody>
</table>

Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

*DRAFT GUIDANCE*

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2012
Clinical Medical
Patient Enrichment Strategy in Clinical Trials

Enrichment Design

- Enrichment is the prospective use of any patient characteristic – demographic, pathophysiologic, historical, genetic, and others – to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population.

Benefits of Adaptive Enrichment Design

- Being flexible to allow pre-specified modifications to an ongoing trial and include broader target patient population,
- Prevents results to be diluted due to the heterogeneity of the patient characteristics (imbalanced performance) among the subpopulations,
- Being efficient if the benefits of drug/vaccine are only found in selective subpopulations.
Example 3: Sub-Population Enrichment Design

- Patient enrichment based on interim analysis result

Two stage design

Stage 1: $n_1$ subjects

Interim Analysis

Stage 2: $n_2$ subjects if full, $n^*_{2}$ if sub

Example 4: Population Enrichment in Vaccine Trial

Motivating Study:

• Phase III Vaccine Efficacy trial with **two target subpopulations (A/B)**: Event-driven Study

• Phase I study Immunogenicity results suggested that the immunogenicity is better in one population.

• The overall study could potentially be ‘diluted’ by a low efficacy in one individual study population.

Ref: Su et al. An adaptive design strategy with potential population enrichment for event driven study. DIA KOL Lecture Series on Adaptive Designs, October 2016
## Trial Design Strategies Considered

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined study, without adaptation</td>
<td>Simple ‘Low’ cost</td>
<td>High risk if VE is low in one population</td>
</tr>
<tr>
<td></td>
<td>[~5,000 patients]</td>
<td></td>
</tr>
<tr>
<td>Separate studies for each population, each target a Lower Bound of 25%</td>
<td>Simple Low risk</td>
<td>High cost [~10,000 patients]</td>
</tr>
<tr>
<td>Combined study, with adaptation (population enrichment)</td>
<td>Flexibility to continue with combined or the single (superior) population Low/moderate cost [~5,000-7,500 patients]</td>
<td>More complicated design</td>
</tr>
</tbody>
</table>
Vaccine Efficacy Trial Design Diagram

50% OF REQUIRED CASE - 1st FUTILITY ANALYSIS

- Subpop A: Pass
  - Subpop B: Pass
    - Continue study as planned with both Subpop A and Subpop B arms

- Subpop A: Pass
  - Subpop B: Fail
    - Study fails in Subpop B
      - Subpop B arm close-out
      - Continue study with Subpop A arm only
      - Enroll additional Subpop A patients

- Subpop A: Fail
  - Subpop B: Pass
    - Study fails in Subpop A
      - Subpop A arm close-out
      - Continue study with Subpop B arm only
      - Enroll additional Subpop B patients

- Subpop A: Fail
  - Subpop B: Fail
    - Study fails
      - Study close-out

75% OF REQUIRED CASE - 2nd INTERIM EFFICACY ANALYSIS

- Futility: Pass
  - Efficacy: Pass
    - Primary efficacy objective met
      - Study close-out

- Futility: Pass
  - Efficacy: Not Confirm
    - Continue study

- Futility: Fail
  - Study fails
    - Study close-out

100% OF REQUIRED CASES - FINAL EFFICACY ANALYSIS
Primary Efficacy Hypotheses

• Only one of the following alternative hypotheses will be tested at the end of the study:

(1) H1: Lower Bound of VE_{A+B} > 25% with \( \alpha_1 = 0.025 \)

(2) H2: Lower Bound of VE_A > 25% with \( \alpha_2 = 0.0115 \)

(3) H3: Lower Bound of VE_B > 25% with \( \alpha_3 = 0.0115 \)

• Statistical Considerations:
  – Type I error rate control/Power
  – Interim futility analysis planning (timing and futility boundary)
### Type I Error Rate/Power Under Global/Null Hypothesis

<table>
<thead>
<tr>
<th>Vaccine Efficacy in Subpopulation</th>
<th>Probability of Success in Subpopulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$VE_A$</td>
<td>$VE_B$</td>
</tr>
<tr>
<td>Overall (A/B/(A+B))</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Combined (A+B)</td>
</tr>
</tbody>
</table>

**Global Null: $H^0(A)$ is true; $H^0(B)$ is true**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>25%</td>
<td>0.024</td>
<td>0.005</td>
<td>0.005</td>
</tr>
</tbody>
</table>

**$H^0(A)$ is true; $H^0(B)$ is false**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>&gt;25%</td>
<td>0.737</td>
<td>0.001</td>
<td>0.472</td>
</tr>
</tbody>
</table>

**$H^0(A)$ is false; $H^0(B)$ is true**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;25%</td>
<td>25%</td>
<td>0.664</td>
<td>0.399</td>
<td>0.001</td>
</tr>
</tbody>
</table>
## Probabilities of Futility Stopping at Interim

### 50% information fraction for Subpopulation A

<table>
<thead>
<tr>
<th>If TRUE VE=</th>
<th>Prob(interim VE ≤ 0.2)</th>
<th>Prob(interim VE ≤ 0.25)</th>
<th>Prob(interim VE ≤ 0.3)</th>
<th>Prob(interim VE ≤ 0.35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.20</td>
<td>0.47</td>
<td>0.57</td>
<td>0.66</td>
<td>0.82</td>
</tr>
<tr>
<td>0.25</td>
<td>0.37</td>
<td>0.46</td>
<td>0.56</td>
<td>0.74</td>
</tr>
<tr>
<td>0.30</td>
<td>0.27</td>
<td>0.35</td>
<td>0.45</td>
<td>0.64</td>
</tr>
<tr>
<td>0.35</td>
<td>0.18</td>
<td>0.25</td>
<td>0.33</td>
<td>0.53</td>
</tr>
<tr>
<td>0.40</td>
<td>0.11</td>
<td>0.16</td>
<td>0.23</td>
<td>0.40</td>
</tr>
<tr>
<td>0.50</td>
<td>0.02</td>
<td>0.04</td>
<td>0.07</td>
<td>0.16</td>
</tr>
</tbody>
</table>

### 50% information fraction for Subpopulation B

<table>
<thead>
<tr>
<th>If TRUE VE=</th>
<th>Prob(interim VE ≤ 0.2)</th>
<th>Prob(interim VE ≤ 0.25)</th>
<th>Prob(interim VE ≤ 0.3)</th>
<th>Prob(interim VE ≤ 0.35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.20</td>
<td>0.49</td>
<td>0.61</td>
<td>0.72</td>
<td>0.72</td>
</tr>
<tr>
<td>0.25</td>
<td>0.41</td>
<td>0.52</td>
<td>0.64</td>
<td>0.64</td>
</tr>
<tr>
<td>0.30</td>
<td>0.32</td>
<td>0.43</td>
<td>0.55</td>
<td>0.55</td>
</tr>
<tr>
<td>0.35</td>
<td>0.24</td>
<td>0.34</td>
<td>0.45</td>
<td>0.45</td>
</tr>
<tr>
<td>0.40</td>
<td>0.16</td>
<td>0.25</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>0.50</td>
<td>0.06</td>
<td>0.1</td>
<td>0.16</td>
<td>0.16</td>
</tr>
<tr>
<td>0.55</td>
<td>0.03</td>
<td>0.05</td>
<td>0.09</td>
<td>0.09</td>
</tr>
</tbody>
</table>
Patient Subgroup Identification for Precision Medicine

• Statistical analytics and machine learning techniques can be used to
  – explore the heterogeneity of the patient profiles by biomarkers or gene
    signatures
  – identify subgroups of patients that will benefit more of the treatment

• Several methods/algorithms have been developed for subgroup
  identification:
  – Generalized, Unbiased, Interaction Detection and Estimation (GUIDE)
  – Subgroup Identification Based on Differential Effect Search (SIDES)
  – Bootstrapping & Aggregating of Thresholds from Trees (BATTing)
  – Sequential BATTing
  – Adaptive Index Modeling (AIM)-rule
Example 5: Therapeutic Response Guided Dosing Strategy for Long-term Humira Treatment of Hidradenitis Suppurativa (HS)

- Humira (originator adalimumab) 40 mg every-week (ADAew) dosing is approved for chronic treatment of patients with moderate to severe hidradenitis suppurativa (HS)

- Analysis aimed at identifying patients for whom long-term treatment with 40 mg ADAew had the most beneficial benefit-risk balance based on integrated data from the two PIONEER phase-3 trials (Kimball AB, et al. N Engl J Med. 2016;375:422-34)

- The efficacy endpoint for this analysis was Hidradenitis Suppurativa Clinical Response (HiSCR, defined as ≥50% reduction in total abscess and inflammatory nodule [AN] count with no increase in abscess or draining fistula count) at the end of Period B.
# Study Design for PIONEER Trials

<table>
<thead>
<tr>
<th>Screening</th>
<th>Period A</th>
<th>Period B</th>
<th>M12-555</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 mg ew§</td>
<td>40 mg ew</td>
<td>40 mg ew</td>
</tr>
</tbody>
</table>

**PIioneer I**
- N=307
- 40 mg ew§

**PIioneer II**
- N=326
- Placebo

Starting at Week 4 after 160 mg at Week 0, 80 mg at Week 2

Ref: Gulliver et al, Therapeutic Response Guided Dosing Strategy to Optimize Long-term Adalimumab Treatment in Patients with Hidradenitis Suppurativa: Integrated Results from the PIONEER Phase 3 Trials, the 75th Annual Meeting of the American Academy of Dermatology, Orlando, FL, March 3-7, 2017
Statistical Method for Subgroup Identification

• A threshold-based model, ensemble statistical algorithm, was applied to build predictive models
  – Sequential BATTing

• Candidate Variables:
  – Baseline BMI, Hurley Stage, Smoking Status, and Concomitant use of Baseline Antibiotics;
  – Initial response: Week 12 HiSCR status, percent reduction in AN count, reduction in abscess count, reduction in draining fistula count

• Cross-validation was used to assess both model building and predictive significance
Bootstrapping & Aggregating of Thresholds from Trees (BATTing)

Original Data

Tree 1
\[ < C_1 \leq C \leq C_1 \]

Tree 2
\[ < C_2 \leq C \leq C_2 \]

Tree B
\[ < C_B \leq C \leq C_B \]

Aggregate Thresholds
\( (C_1, C_2, \ldots, C_B) \)

Data 1

Data 2

Data B

Bootstrapping (sampling with replacement)

Threshold is robust
to small
perturbations in data,
outliers, etc.

BATTing Threshold (Median)

(Datawanarayan, 1999)
Sequential BATTing (Huang et al. Statistics in Medicine 2017)

Model Growing: within the potential Sig+ group
• Get the BATTing threshold for each unused marker
• The best marker is selected to split the current potential sig+ group
• This procedure continues in the new potential Sig+ group

Stopping Rule:
• The new added predictor goes through the likelihood ratio test for significance.
Predictive Significance – 5-fold Cross Validation

Aggregated cross-validated p values from M iterations ($p_1, p_2, \ldots, p_M$)

Note: other performance statistics, e.g., sensitivity, specificity, PPV, NPV, hazard ratio, odds ratio can be calculated similarly.
HiSCR Responses Improved in PRR Population

PRR Population:
- HiSCR Responders (achieved HiSCR at week 12), plus
- Partial Responders (did not achieve HiSCR but reached at least a 25% reduction in AN count [AN25] at week 12).
Success of the PRR Population Analysis

- Identified a subgroup of patients that will benefit from continued therapy
- Enhanced label language about continued therapy beyond 12 weeks
- Supported interactions with payors
Statistician as a Collaborator

• Work in a research team including
  – Basic research scientist
  – Clinician
  – Regulatory
  – Data manager
  – Statistical programmer
  – Health outcome researcher

• Interact with external key opinion leaders

• Represent company at external meetings
  – Statistical
  – Clinical
  – Regulatory/Government (FDA, EMEA, CDC, WHO)
Leadership Skills for Success

- **Strong technical skills**
  - Knowledge of statistical methods
  - Analytical thinking
  - Computing skills

- **Excellent consulting skills**
  - Understand the disease background
  - Communicate with non-statisticians
  - Team spirits / collaboration

- **Well connected to scientific community**
  - Research and publication
  - Participate in professional activities

- **Enterprise Leadership**
  - End-to-end business acumen
  - Strategic planning
Leadership for Success

- Passion
- Courage
- Vision
Summary

• Statisticians can have a diverse and rewarding career in pharmaceutical industry

• Statisticians’ innovative thinking plays an important role in the development of precision/personalized medicines

• Collaborative research skills and business leadership are key to success