Multiplicity and other issues related to biomarker-based oncology trials
ASA NJ Chapter

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With thanks to Eric Rubin, Lu Wang
With highly active targeted therapies becoming more commonplace in recent years, strategies for development become increasingly important in terms of time-to-market, clinical trials size and the breadth of patient population that may benefit from a drug. We discuss strategies and corresponding statistical tools that have been applied. Early single-arm trials followed quickly by randomized trials is a bedrock approach for many indications, but not without pitfalls. The possibility of doing trials that are target-based rather than histology-based as well as other novel approaches are considered. Another challenge is developing one or more biomarkers at the same time that a drug is being developed.
Examples of completed and ongoing biomarker-based studies
- Generally based on checkpoint inhibitor MK-3475/pembrolizumab/Keytruda
- Progression of studies for a cancer type
- Companion vs. complementary diagnostic device
- Multiplicity control with the graphical method and group sequential design
PD-1: Programmed Cell Death Protein 1


- PD-1 is a protein and cell-surface receptor
- Binds to 2 ligands: PD-L1 and PD-L2
- “PD-1, functioning as an immune checkpoint, plays an important role in down regulating the immune system by preventing the activation of T-cells, which in turn reduces autoimmunity and promotes self-tolerance.”
- “A new class of drugs that block PD-1, the PD-1 inhibitors, activate the immune system to attack tumors...”
- “Many tumor cells express PD-L1, an immunosuppressive PD-1 ligand; inhibition of the interaction between PD-1 and PD-L1 can enhance T-cell responses in vitro and mediate preclinical antitumor activity.”

- Pembrolizumab and nivolumab are examples of antibodies that inhibit PD-1
- Each has been studied in patients with a diagnostic measuring PD-L1
Keynote 001: Objective Response by Biomarker Level

Pembrolizumab for non-small-cell lung cancer; $PS =$ proportion score
Early trial leading to randomized trial design

<table>
<thead>
<tr>
<th></th>
<th>PS 50+</th>
<th>PS 1–49</th>
<th>PS &lt; 1</th>
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</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
<td>13/38</td>
<td>4/43</td>
<td>4/40</td>
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<td><strong>Validation</strong></td>
<td>33/73</td>
<td>17/103</td>
<td>3/28</td>
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</table>

Garon et al. [2015]
Keynote 010: Design (NSCLC, biomarker-based)

Previously Treated PD-L1 Positive Advanced Non-Small-Cell Lung Cancer

Stratification by:
1. PD-L1 expression (weak vs. strong)
2. ECOG status (0 vs. 1)
3. Geographic region (East Asian vs. non-East Asian)

R = Randomization  PD = Progressive Disease  SFU = Survival Follow-up

Herbst et al. [2016]
Keynote 010 Statistical Methods: Multiplicity

Type I error divided and reallocated between statistical tests

Herbst et al. [2016]
Keynote 010: Overall Survival (OS) by Biomarker at IA2

OS achieved statistical significance according to multiplicity plan in both treatment groups, total positive and TPS $\geq 50\%$ populations

Herbst et al. [2016]; PFS = progression free survival
Keynote 010: OS and PFS Hazard Ratio by Biomarker

Herbst et al. [2016]
### CheckMate 57 Efficacy by Biomarker Status (Exploratory)

**Primary evaluations and approval in broad population**

<table>
<thead>
<tr>
<th>PD-L1 expression level</th>
<th>Nivolumab n</th>
<th>Docetaxel n</th>
<th>Unstratified HR (95% CI)</th>
<th>Interaction P-value</th>
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<td>123</td>
<td>123</td>
<td>0.59 (0.43, 0.82)</td>
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<td>&lt;1%</td>
<td>108</td>
<td>101</td>
<td>0.90 (0.66, 1.24)</td>
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<tr>
<td>≥5%</td>
<td>95</td>
<td>86</td>
<td>0.43 (0.30, 0.63)</td>
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<tr>
<td>&lt;5%</td>
<td>136</td>
<td>138</td>
<td>1.01 (0.77, 1.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥10%</td>
<td>86</td>
<td>79</td>
<td>0.40 (0.26, 0.59)</td>
<td>&lt;0.001</td>
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<tr>
<td>&lt;10%</td>
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<td>145</td>
<td>1.00 (0.76, 1.31)</td>
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<td>61</td>
<td>66</td>
<td>0.91 (0.61, 1.35)</td>
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<td><strong>PFS</strong></td>
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<td></td>
</tr>
<tr>
<td>≥1%</td>
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<td>0.70 (0.53, 0.94)</td>
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<td>0.54 (0.39, 0.76)</td>
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<tr>
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<td>138</td>
<td>1.31 (1.01, 1.71)</td>
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<tr>
<td>≥10%</td>
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<td>79</td>
<td>0.52 (0.37, 0.75)</td>
<td>&lt;0.001</td>
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<td>&lt;10%</td>
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<td>1.24 (0.96, 1.61)</td>
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<td>61</td>
<td>66</td>
<td>1.06 (0.73, 1.56)</td>
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</table>

Borghaei et al. [2015], supplementary materials
CheckMate 57 OS by Biomarker Status (Exploratory)

Borghaei et al. [2015], supplementary materials
PD-L1 Biomarker is Predictive

- Previously treated (non-squamous) NSCLC
- For high PD-L1 measures, PD-1 antibodies (nivolumab, pembrolizumab) are effective
- 'Exact' cutoffs for effectiveness unknown
- Companion diagnostic approach (pembrolizumab)
  - Trial and approval in targeted-population only
  - Possibility of patient benefit in broad population?
  - Likely higher probability of success from start
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- Complementary diagnostic approach (nivolumab)
  - No $\alpha$-controlled subgroup testing
  - Approval in broad population
  - Diagnostic approved (first 'complementary' diagnostic)
  - Risk that overall population could have not demonstrated statistical significance
PD-L1 Biomarker is Predictive

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Multiple histology, biomarker focused, single arm trials

- **Key endpoints:** response rate and duration of response
- **Phase IB studies**
  - **Keynote 12:** A Phase Ib Multi-Cohort Study of MK-3475 in Subjects With Advanced Solid Tumors
    - Cancer types: breast (triple negative), head and neck cancer, urothelial tract, gastric
  - **Keynote 28:** Phase IB Study of Pembrolizumab (MK-3475) in Subjects With Select Advanced Solid Tumors
Multiple histology, biomarker focused, single arm trials

- **Phase IB studies**
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  - **Keynote 28**: Phase IB Study of Pembrolizumab (MK-3475) in Subjects With Select Advanced Solid Tumors
  - **Keynote 158**: A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors
    - Cohorts A-J: 10 solid tumor types (overlap with Keynote 12, 28)
    - Cohort K: MSI-high (biomarker) selected population, any solid tumor type
    - N=1100
Multiple histology, biomarker focused, single arm trials

- Key endpoints: response rate and duration of response

- **Keynote 158: A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors**
  - Cohorts A-J: 10 solid tumor types (overlap with Keynote 12, 28)
  - Cohort K: MSI-high (biomarker) selected population, any solid tumor type
  - N=1100
Strong Type I error control for overall population and biomarker subgroups in randomized studies
Hypotheses, analyses and test statistics

- $h > 1$ hypotheses
- $k > 1$ analyses
- $T_1 < T_2 \cdots < T_k$ calendar times of analyses
- For hypothesis $i = 1, \ldots, h$
  - May not test at all times for each hypothesis
  - $1 \leq k(i) \leq k$ analysis times $T_{i,1} < T_{i,2} \cdots < T_{i,k(i)}$
    - Some or all of $T_1 < T_2 \cdots < T_k$
  - $d_{i,1} < d_{i,2} \cdots < d_{i,k(i)}$ events for each analysis
  - $I_{i,1} < I_{i,2} \cdots < I_{i,k(i)}$ statistical information for each analysis
    - For equal randomization with a time-to-event endpoint, this is approximated by $d_{i,j}/4$ [Schoenfeld, 1981]
  - $Z_{i,1}, Z_{i,2}, \ldots, Z_{i,k(i)}$ group sequential, normal test statistics with variance 1 to test hypothesis
Example 1: Calendar-based

- $h = 2$ hypotheses (2 endpoints)
  - PFS: progression free survival; time until progression or death
  - OS: overall survival; time until death
- $k = 3$ analyses at given calendar times
  - PFS analyzed at $T_1 = 18$ and $T_2 = 24$ months
  - OS analyzed at $T_1 = 18$, $T_2 = 24$ and $T_3 = 36$ months
  - Number of events ($d_{ij}$) is random
Example 2: Event-based

- $h = 2$, same hypotheses
  - PFS
  - OS
- $k = 3$ analyses at 3 times
  - PFS analyzed twice after $d_{1,1} < d_{1,2}$ endpoints
  - OS analyzed at same times plus final analysis with $d_{2,3}$ endpoints
  - Number of OS events at interims ($d_{2,1}, d_{2,2}$) are random
  - Analysis times $T_1, T_2, T_3$ are random
Example 3: Add biomarker hypothesis

- $h = 4$ hypotheses (2 endpoints $\times$ 2 populations)
  - PFS
    - $H_1$: BM+ population (biomarker positive subgroup)
    - $H_2$: Overall population
  - OS
    - $H_3$: BM+ population
    - $H_4$: Overall population
- $k = 3$ analyses
  - PFS analyzed twice after $d_{1,1} < d_{1,2}$ endpoints
  - PFS endpoints for overall population ($d_{2,1}, d_{2,2}$) are random
  - OS analyzed at same times plus final analysis with $d_{3,3}$ endpoints
  - Number of OS events are random for BM+ at interims ($d_{3,1}, d_{3,2}$)
  - Number of OS events are random for total population at all analyses ($d_{4,1}, d_{4,2}, d_{4,3}$)
  - Analysis times $T_1$, $T_2$, $T_3$ are random
Hypotheses, analyses and test statistics

Example 3 graph

Biomarker+ population

PFS Hypotheses

H1

OS Hypotheses

H3

Overall population

H2

H4
Methods summary

- Spending time concept importance when multiple hypotheses tested with varying rates of information accumulation
- Some key concepts for spending functions with group sequential combined with graphical multiplicity [Maurer and Bretz, 2013]
- Brief note on technical algorithm for testing
Slightly modified notation of Maurer and Bretz [2013]

All hypotheses controlled at 1-sided level $0 < \alpha < 1$

Spending function for hypothesis $i$

- $a_i(\gamma, y)$
- Non-decreasing for $y$ on $[0, 1]$, $\gamma$ on $[0, \alpha]$
- $a_i(\gamma, 0) = 0$
- $a_i(\gamma, y) = \gamma$ for $y = 1$
Spending times

For hypothesis $i = 1, \ldots, k$

- Test hypothesis at level $\gamma_i$
- $k(i) \leq k$ analysis times
- Spending times

$$0 = t_{i,0} < t_{i,1} \leq \cdots \leq t_{i,k(i)} = 1$$

- Type I error allocated to analysis $j = 1, \ldots, k(i)$

$$a(\gamma_i, t_{i,j}) - a(\gamma_i, t_{i,j-1})$$

- Bounds for Z-statistics then a standard group sequential calculation [Slud and Wei, 1982] based on statistical information (endpoint count; Tsiatis [1982])

- Any futility bound ignored in calculations per Liu and Anderson [2008]
Setting spending times

- $d_{i,\text{max}}$: maximum planned endpoints for hypothesis $i$
- Information time [Lan and DeMets, 1983]:
  \[ t_{i,j} = \min(1, \frac{I_{i,j}}{I_{i,\text{max}}} = \frac{d_{i,j}}{d_{i,\text{max}}}) \]

  Under-running variation is to set $t_{i,k(i)} = 1$ if planned information level not reached for hypothesis $i$ ($I_{i,k(i)} < I_{i,\text{max}}$)

- Calendar time [Lan and DeMets, 1989]:
  \[ t_{i,j} = \frac{T_{i,j}}{T_{i,k(i)}} \]

- Alternate information time:
  - e.g., set all OS hypotheses based on information time for biomarker positive subgroup OS hypothesis
  - Suggested in Proschan et al. [2006] (Section 5.1.1) based on the same logic as calendar time
In words: Cannot choose spending time or information time for an analysis based on value of current or former test statistic for any hypothesis.

Using notation: $t_{i,j}$ and $I_{i,j}$ are conditionally independent of $Z_{i',j'} - E\{Z_{i',j'}\}$ for $T_{i',j'} \leq T_{i,j}$, $i' = 1, 2, \ldots, k$. 
Testing algorithm

For a given analysis

1. Test each null hypothesis \( i \) to be tested at or before this analysis
   a) Analysis index \( j \), denote Type I error allocated to hypothesis \( \gamma_i \)
   b) Compute spending time \( t_{i,j} \)
   c) Compute boundaries \( b_{i,j'}, j' = 1, \ldots, j \) based on
      - \( \gamma_i \)
      - \( t_{i,j'}, j' = 1, \ldots, j \)
      - \( I_{i,j'}, j' = 1, \ldots, j \)
      - This is a standard group sequential design calculation
      - For \( j' < j \), \( b_{i,j'} \) will not change unless \( \gamma_i \) has changed due to reallocation

2. If \( Z_{i,j'} > b_{i,j'} \) for any \( j' = 1, \ldots, j \), reject null hypothesis \( i \)

3. If any hypothesis was rejected, reallocate \( \gamma_i \) per multiplicity graph
   [Bretz et al., 2009] and return to step 1
Return to historical example; Type I error allocation

Biomarker+ population

PFS Hypotheses

H1
\[ \alpha_1 = 0.0025 \]

OS Hypotheses

H3
\[ \alpha_2 = 0.01 \]

Overall population

H2
\[ \alpha_3 = 0.0025 \]

H4
\[ \alpha_4 = 0.01 \]

- Allocate most \( \alpha \) to OS
- Equal split between populations
Main reallocation within endpoints

**PFS Hypotheses**

- **H1**: \( \alpha_1 = 0.0025 \)
- **H2**: \( \alpha_3 = 0.0025 \)

**OS Hypotheses**

- **H3**: \( \alpha_2 = 0.01 \)
- **H4**: \( \alpha_4 = 0.01 \)

- Bonferonni-Holm between populations
- Motivated by PFS testing ending before OS testing
Final reallocation between endpoints

- **Biomarker+ population**
  - PFS Hypotheses
    - H1: \( \alpha_1 = 0.0025 \)
  - OS Hypotheses
    - H3: \( \alpha_2 = 0.01 \)

- **Overall population**
  - PFS Hypotheses
    - H2: \( \alpha_3 = 0.0025 \)
  - OS Hypotheses
    - H4: \( \alpha_4 = 0.01 \)

- **Bonferonni-Holm between populations**
- If both populations reject, reallocate to other endpoint [Bretz et al., 2009]
Summary and conclusions

- Biomarker-based development programs continue to be of interest
- Different approaches have been taken
- Personalized medicine results and multiple endpoints of interest can create a substantial multiplicity problem for oncology development
- Maurer and Bretz [2013] creates a framework for group sequential trials with multiple hypotheses
- Method extended here to apply to trials with time-to-event endpoints with varying rates of information (endpoint) accumulation


