Group Sequential Trial with a Biomarker Subpopulation

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ASA Biopharm Workshop, Sep 13th. 2018
Outline

• Motivation: Phase III PD-L1/PD-1 Monotherapy Studies
• Introduction: Multiplicity Adjustment in Oncology Trials
• Method: Complete Correlation Structure (CCS) Incorporating both GSD and Sub-Population
• Evaluation of CCS
• Implementation
• Discussion & Conclusion
Motivation: Phase III, anti-PD-L1 Monotherapy Studies

• Tecentriq, IMvigor-211), May 2017
  o Open label, monotherapy Tecentriq vs. chemotherapies
  o They tested high PD-L1 population (IC2/3), followed by any level of PD-L1 (IC1/2/3), then overall population (ITT).
  o They failed at the primary endpoints (OS).

\[
2 - \text{sided } \alpha = 0.05
\]

- H1: OS on PD-L1 (IC 2/3)
- H2: OS on PD-L1 (IC 1/2/3)
- H3: OS on ITT
- H4: PFS on PD-L1 (IC 2/3)
- H5: PFS on PD-L1 (IC 1/2/3)
- H6: PFS on ITT

\[3\]

\[H1: \text{OS on PD-L1 (IC 2/3)}\]
\[H2: \text{OS on PD-L1 (IC 1/2/3)}\]
\[H3: \text{OS on ITT}\]
\[H4: \text{PFS on PD-L1 (IC 2/3)}\]
\[H5: \text{PFS on PD-L1 (IC 1/2/3)}\]
\[H6: \text{PFS on ITT}\]
Motivation: Phase III, anti-PD-1 Monotherapy Studies

- Opdivo, Phase III on NSCLC (CheckMate-026), Aug 2016
  - Open label, monotherapy Opdivo vs. chemotherapies
  - Failed at primary endpoint (PFS) in subpopulation PD-L1 >= 5%

$$2 \text{ -- sided } \alpha = 0.05$$

- H1: PFS on PD-L1 (>=5%)
- H2: PFS on all subjects
- H3: OS on PD-L1 (>=5%)
- H4: OS on all subjects
Multiplicty Adjustment in Oncology Trials

Strongly Control Family-wise Type I error

• Label as driver: Dual-Primary, Primary/Secondary
  o Subpopulation – biomarker/genomic characteristics (e.g. PD-L1/PD-1)
  o Multiple Endpoints: OS, PFS, ORR, DCR, DOR etc.
  o Dose-ranging (high-dose/low-dose) etc.

• Interim analysis – Group Sequential Design

*Figure from www.EUPATI.com
Temporal correlations in interim analyses and final analysis.

- **Pocock (1977)** presented constant Type I error in interim analyses and final analysis
  \[ \alpha_2^*(t) = \alpha \ln \{1 + (e - 1)t\} \]

- **O’Brien and Fleming (1979)** showed more conservative and unequal bounds in earlier stages
  \[ \alpha_1^* = 2 \{1 - \Phi(z_{\alpha/2}/t^{1/2})\} \]

- **Lan and DeMets (1983)** demonstrated a non-decreasing alpha-spending function and proposed (**Kim and DeMets, 1987**) the function with parameter \(q\),
  \[ \alpha_3^*(q, t) = \alpha t_k^q \]

- **Maurer and Bretz (2013)** published Graphical Approach in group sequential design when having multiple hypotheses
Interim analysis – Group Sequential Design

\[ \alpha_1^* \]: O’Brien and Fleming
\[ \alpha_2^* \]: Pocock
\[ \alpha_3^* \]: Kim and DeMets
Sub-population: Population correlations in subgroups and overall population.

- *Chen and Beckman (2009)*: use prior information (Phase II) to construct optimal alpha-spending function to subgroup and overall population in Phase III trials.

- *Spiessens and Debois (2010)*: use Group sequential design method in subgroup analysis.

- Limited published research on both temporal and population correlation.
Method Set Up: Complete Correlation Structure (CCS)

• Suppose a 2-arm trial comparing treatment effect in both a biomarker subgroup and overall population
• Information time: $t_{ki}, 0 < t_{ki} \leq 1$
• Proportion of population (prevalence) $p_{ki}, 0 < p_{ki} \leq 1$
• Stage: $k = 1, 2, ..., K$
• Population: $i = 1$ is subgroup, $i = 2$ is overall population
• $p_{k*i} = n_{ki}/n_{KI}$
• $n_{ki}$ is the number of observations at stage $k$ in population $i$
Method Set up: CCS (cont’d)

• Let $Z_{ki}$ be the standardized test statistics and, under $H_0$, asymptotically follows a multivariate normal distribution

$$Z_{ki} \sim N\left(0, \Sigma_{adj}\right) = N\left(\begin{pmatrix} 0 \\ \vdots \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & \sigma_{1,2} & \ldots & \sigma_{1,2k} \\ \sigma_{2,1} & 1 & \vdots & \vdots \\ \vdots & \vdots & 1 & \vdots \\ \sigma_{2k,1} & \ldots & \ldots & 1 \end{pmatrix}\right)$$

• $E(Z_{ki}) = \theta \sqrt{\frac{n_{ki}}{4}}$ when $H_a$ is true (e.g. 1:1 randomization ratio)

• $COV(Z_{ki}, Z_{k'i'}) = \frac{\min(p_{ki}p_{k'i'})\min(t_{ki}, t_{k'i'})}{\sqrt{p_{ki}t_{ki}p_{k'i'}t_{k'i'}}} = \sqrt{\frac{\min(p_{ki}p_{k'i'})\min(t_{ki}, t_{k'i'})}{\max(p_{ki}p_{k'i'})\max(t_{ki}, t_{k'i'})}}$
CCS: a simple example

- We have a 2-arm trial, only 1 interim analysis at 50% time is planned (k=2).
- The proportion of subgroup is 50%.
- So, $t_{1i}=0.5$, $t_{2i}=1$, $p_{k1}=0.5$, $p_{k2}=1$
- One-sided test, equally split FWER 0.025 to subgroup and overall population (0.0125 to each population)
- Correlation matrix $\Sigma_{adj}$ for interim analysis $Z_{11}, Z_{12}$ and final analysis $Z_{21}, Z_{22}$ will be

$$
\begin{bmatrix}
1 & \sqrt{0.5} & \sqrt{0.5} & 0.5 \\
\sqrt{0.5} & 1 & 0.5 & \sqrt{0.5} \\
\sqrt{0.5} & 0.5 & 1 & \sqrt{0.5} \\
0.5 & \sqrt{0.5} & \sqrt{0.5} & 1
\end{bmatrix}
$$
Evaluation of CCS

• Adjusted Type I error
  \[ P_{H_0}(Z_{11} > b'_1 \text{ or } Z_{12} > b'_1 \text{ or } Z_{21} > b'_2 \text{ or } Z_{22} > b'_2 | \Sigma_{adj}) - FWER = 0 \]

• Adjusted population power
  \[ P_{H_a}(Z_{11} > b'_1 \text{ or } Z_{21} > b'_2 | \Sigma_{adj}) \text{ and } P_{H_a}(Z_{12} > b'_1 \text{ or } Z_{22} > b'_2 | \Sigma_{adj}) \]

• Adjusted event(sample) size
  \[ SS_{sub} = GS(\alpha'_{sub}) \text{ and } SS_{ova} = GS(\alpha'_{ova}) \]
## Evaluation of CCS

<table>
<thead>
<tr>
<th>Improvements of CCS</th>
<th>Original Design</th>
<th>CCS-adjusted Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I error</td>
<td>0.0125</td>
<td>0.0147</td>
</tr>
<tr>
<td>Power</td>
<td>0.92</td>
<td>0.9</td>
</tr>
<tr>
<td>Event size</td>
<td>570/1140</td>
<td>551/1102</td>
</tr>
</tbody>
</table>
Evaluation of CCS

• Type I error
Evaluation of CCS

- Power
Evaluation of CCS

- Event Size
Discussion: Extended Application of CCS

• CCS in group sequential design can be applied to normal, binary, survival type of outcomes.
  - The advantage of standardized test statistics.

• CCS can be applied to most group sequential methods
  - Pocock, O’Brien and Fleming, Lan and DeMets, Kim and Demets, Maurer and Bretz.

• Graphical approach:
  - Only original Bonferroni-Holm amount of α (in red) in graphical approach can be transferred to the next hypothesis.

<table>
<thead>
<tr>
<th>Overall population</th>
<th>Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Z_{12}$</td>
<td>$Z_{11}$</td>
</tr>
<tr>
<td>$Z_{22}$</td>
<td>$Z_{21}$</td>
</tr>
<tr>
<td>$Z_{32}$</td>
<td>$Z_{31}$</td>
</tr>
</tbody>
</table>

- H3: OS in all subjects
  - $\alpha_0 = 0.0105$
  - $\alpha_{oVA} = 0.0128$

- H4: OS in PD-L1 + subjects
  - $\alpha_0 = 0.0105$
  - $\alpha_{sub} = 0.0128$
Extended Application of CCS

• CCS can be applied to multiple-arm trials.
  o EX. A 3-arm trial comparing treatment effect in High-dose vs. placebo and low-dose vs. placebo.
  o The covariance matrix will be extended to a 8*8 matrix
  o Off-diagonal sub-matrix is the correlations of test statistics from high-dose group and low-dose group

\[
\begin{bmatrix}
M_{1_{4\times4}} & M_{2_{4\times4}} \\
M_{3_{4\times4}} & M_{4_{4\times4}}
\end{bmatrix}
\]

\[
COV(Z_{Hki}, Z_{Lk'i'}) = \frac{\min(p_{Hki}, p_{Lk'i'}) \min(t_{Hki}, t_{Lk'i'})}{\sqrt{p_{Hki}t_{Hki}p_{Lk'i'}t_{Lk'i'}}} = \sqrt{\frac{\min(p_{Hki}, p_{Lk'i'}) \min(t_{Hki}, t_{Lk'i'})}{\max(p_{Hki}, p_{Lk'i'}) \max(t_{Hki}, t_{Lk'i'})}}
\]

o The correlation is contributed from placebo observations
Conclusion

• Complete Correlation Structure (CCS) accounts for *temporal* correlations and *population* correlations in test statistics.

• CCS will increase nominal Type I error and power, and require less sample size.

• Proportion of subgroup dominates the impact of CCS.

• CCS can be valuable in cost saving or hidden benefits in the pocket.

• Easy and comprehensive application to existing methods and current clinical trial designs.