Platform Trials and Precision Medicine in Early Oncology Drug Development – BI Experience

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• Dr. Mary Zhao
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• Dr. Natalja Strelkowa
• Dr. Kathrin Stucke-Straub
• Dr. Wenqiong Xue
BI experience with basket trials
BI experience with platform trials
Go/No-go decision with patient selection biomarkers in basket trials
Go/No-go decision with continuous biomarker
BI Experience with Basket Trials
Basket Trials – General Design Considerations

- **Multiplicity and Bias**
  - “Best” cohort(s) considered for further development

- **Homogeneity or Heterogeneity**
  - Expectation vs. reality
  - More factors can contribute to heterogeneity than possibly measurable: different prevalence of biomarker, prognostic difference, treatment landscape difference, etc.
  - If high heterogeneity is expected, how to implement in model?

- **Early stopping**
  - How to facilitate futility/interim analysis?

- **Logistics**
  - Biomarker test turn around time
  - Recruitment rate difference and timing of interim and final analysis
Basket Trial Example – Go/No-go Decision

- First (easy solution)
  - Consider a single cohort only for Go/No-go decision (although we may have four in real life)

- Example – observed outcomes in dose expansion (basket of multiple single arm cohorts, assume 25% suffice for Go)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>NSCLC #Patients</th>
<th>CRC #Patients</th>
<th>Melanoma #Patients</th>
<th>xxx #Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>#Patients</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>#Responders</td>
<td>3</td>
<td>7</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Obs. ORR</td>
<td>10.0%</td>
<td>23.3%</td>
<td>30.0%</td>
<td>26.6%</td>
</tr>
</tbody>
</table>
Shrinkage Estimators

- Example revisited (assume 25% as max. suffice for Go)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>NSCLC</th>
<th>CRC</th>
<th>Melanoma</th>
<th>xxx</th>
</tr>
</thead>
<tbody>
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<td>#Patients</td>
<td>30</td>
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<td>30</td>
</tr>
<tr>
<td>#Responders</td>
<td>3</td>
<td>7</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Obs. ORR</td>
<td>10.0%</td>
<td>23.3%</td>
<td>30.0%</td>
<td>26.6%</td>
</tr>
<tr>
<td>Shrinkage est.</td>
<td>18.3%</td>
<td>23.3%</td>
<td>26.2%</td>
<td>24.7%</td>
</tr>
</tbody>
</table>

Shrinkage estimator based on a prior for $\tau \sim HN(scale = 2.0)$
Basket Trial Example - Summary

• Go/No-go criterion
  – Should be based on shrinkage estimates (=adjusted)
  – Overall Go if at least one estimate achieves Go
  – Increase in correct decision rates due to information borrowing
  – Shrinkage estimate is far less biased then looking at max. observed ORR

• Clearly define in the presentations to management of Go/No-go boundaries
  – Single or multiple cohorts considered
  – Shrinkage or observed estimate considered
  – How is multiplicity addressed regarding
    • Time points
    • Number of cohorts/indications
BI Experience with Platform Trials
Scope of Platform Trial Development in BI

• **Concept**
  - Beyond the concept of umbrella trial which focus on one particular cancer type.
  - Exploration of multiple regimens in multiple tumour indications/settings,
    - by including patient cohorts with a variety of immunobiological baseline characteristics
    - to better understand how regimen efficacy depends on cancer immunobiology
  - Exploration of IO-retreatment after failure of prior IO therapy

• **Scope**
  - all current and future BI IO-combinations
Design with two IO combinations (expandable)

Indication 1: IO + A
Indication 1: IO + B
Indication 2: IO + A
Indication 2: IO + B

IO naive

IO pre-treated

Prior IO benefit

Primary IO failure

Patients will be able to cross over to any other arm they are eligible for.

Tumour types TBD
Treatment Assignment without Patient Selection

- For a certain tumor type with treatments entering the study at different time points

Tumor type

Equal allocation

PD1 + A

PD1 + B

PD1 + C

Etc.

Need an updated randomization list whenever a new treatment enters the study
Treatment Assignment with Patient Selection

- For a certain tumor type with enrichment is desired in a certain arm, e.g., PD1 + C

Randomization ratio needs to be adjusted in the BM+ stratum whenever a new treatment enters the study.
• Possible treatment switch after PD
  – multiple treatments are available
Go/No-go Decision with Biomarker
Trial Design investigating an IO combination

Part I
Monotherapy dose-finding (6-12 pts)
advanced solid tumour

Part II
Combination dose-finding (12-18 pts)
advanced solid tumour

Part III
Expansion (35 pts per cohort)

- Cohort A: Indication A
- Cohort B: Indication B
- Cohort C: Indication C

The dose-finding will be guided by Bayesian Logistics Regression Model (BLRM) and the final decision will be made by the Safety Monitoring Committee.
Decision framework for efficacy - Assumptions for ORR

- Assumed response rates in the clinical trial protocol:

<table>
<thead>
<tr>
<th></th>
<th>PD-1 mono</th>
<th>Presumed combi</th>
<th>Transformation</th>
<th>Difference for BHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10%</td>
<td>30%</td>
<td>As is</td>
<td>+ 20%</td>
</tr>
<tr>
<td>B</td>
<td>25%</td>
<td>45%</td>
<td>Obs RR - 15%</td>
<td>+ 20%</td>
</tr>
<tr>
<td>C</td>
<td>20%</td>
<td>40%</td>
<td>Obs RR - 10%</td>
<td>+ 20%</td>
</tr>
</tbody>
</table>

- All the observed RR will be transformed into the scale that historical control is ca. 10% RR
- Potential Go requirement is to add 20% on top of the historical control
- Hence the decision boundaries will be 30% for the cohorts A-C
### Decision framework for efficacy

**Cohorts A-C**

N=35 per indication expansion cohort, 3 indications

BHM estimated ORR of > 30% for Go and ≤20% for NoGo

Numbers are based on 100 simulations, therefore they are still approximations and can vary ca. +/-5%

#### Observed response rates (Obs RR)

- **< 20%**
- **≥ 20% - ≤30%**
- **> 30%**

#### Decision probabilities in the negative and positive scenario

- Red: wrong decision
- Green: correct decision

<table>
<thead>
<tr>
<th>Assumed RR for 3 cohorts ( %, %, %)</th>
<th>Obs RR &lt; 20%</th>
<th>Obs RR ≥ 20% - ≤30%</th>
<th>Obs RR &gt; 30%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative scenario:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10%, 10%, 10%)</td>
<td>71%</td>
<td>27%</td>
<td>2%</td>
</tr>
<tr>
<td>(20%, 20%, 20%)</td>
<td>33%</td>
<td>63%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Mixed response cohorts:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(30%, 25%, 5%)</td>
<td>17%</td>
<td>61%</td>
<td>22%</td>
</tr>
<tr>
<td>Nugget scenario</td>
<td>0%</td>
<td>11%</td>
<td>89%</td>
</tr>
<tr>
<td>(40%, 5%, 5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Positive scenario:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(27%, 27%, 27%)</td>
<td>0%</td>
<td>53%</td>
<td>47%</td>
</tr>
<tr>
<td>(30%, 30%, 30%)</td>
<td>3%</td>
<td>27%</td>
<td>70%</td>
</tr>
</tbody>
</table>
Decision framework for biomarkers - Patient populations & expected prevalences

- Cohorts A-C, Selection biomarker probably PD1-driven

<table>
<thead>
<tr>
<th></th>
<th>Prevalence (exp)</th>
<th>#patients per cohort (total)</th>
<th>RR (exp)</th>
<th>#responders per cohort (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall trial population</td>
<td>100%</td>
<td>35 (105)</td>
<td>30%</td>
<td>11 (33)</td>
</tr>
<tr>
<td>BMX+</td>
<td>30%</td>
<td>11 (33)</td>
<td>70%</td>
<td>8 (24)</td>
</tr>
<tr>
<td>BMX-</td>
<td>70%</td>
<td>24 (72)</td>
<td>13%</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>
Our hypothesis is that Biomarker X is associated with response across cohorts. If the biomarker is predictive/prognostic of clinical response, it is expected to work across cohorts. Borrowing of information across cohorts possible.

- **Bayesian Hierarchical Model with the Biomarker X as covariate**
  - Association is indicated if regression coefficient for Biomarker X $\neq 0$ with sufficient posterior probability.
  - If association is indicated -> Biomarker X may be used prospectively in Phase II.
• The decision is based on the model slope parameter of BHM

The cohort heterogeneity is expressed via the parameter $\tau$. Its distribution is assumed to be half-normal with zero mean and standard deviation 2. This setting corresponds to large heterogeneity between biomarker subgroups and indications. The prior for the slope parameter beta is set to 2 for the binary case.

• The slope parameter estimate is provided as posterior probability distribution

• The association between clinical response and biomarker is concluded if the posterior probability of the slope parameter in BHM is located above zero with the probability 97.5%
N=35 per indication, 11 assumed BM+, 3 indications - overall N=105

Decision rule:
The association between clinical response and biomarker is concluded if the posterior probability of the slope parameter in BHM is located above zero with the probability 97.5%

<table>
<thead>
<tr>
<th>Assumed RR for 3 cohorts (BM-,BM+) (BM-,BM+) (BM-,BM+)</th>
<th>Prob to conclude no association</th>
<th>Prob to conclude association</th>
</tr>
</thead>
<tbody>
<tr>
<td>No association scenario: (30%,30%) (30%,30%) (30%,30%)</td>
<td>97%</td>
<td>3%</td>
</tr>
<tr>
<td>Mixed association cohorts (10%,60%) (20%,35%) (5%,5%)</td>
<td>23%</td>
<td>77%</td>
</tr>
<tr>
<td>Nugget scenario (20%,85%) (5%,5%) (5%,5%),</td>
<td>6%</td>
<td>94%</td>
</tr>
<tr>
<td>Strong association in all cohorts: (13%,70%) (13%,70%) (13%,70%)</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Note: Nugget and Mixed association scenarios are more difficult to differentiate from random fluctuations compared to clean scenarios, but we still have an acceptable probability to conclude association in extreme cases.
Numbers are based on 100 simulations*
• Given the study design, sample size and the assumption that biomarker is associated with response across cohorts A-C, it is possible to detect the association with high probability
• On the other hand, if there is no association, the decision framework suggests to stop investigation of the biomarker with high probability
• Remarks:
  – We are investigating association between the biomarker and the clinical response
  – If association is detected, the biomarker could be only prognostic, then it is not a suitable patient selection biomarker
  – Randomized Phase II study needed to investigate if the biomarker is suited for patient selection
Go/No-go Decision with Continuous Biomarker
Continuous Patient Selection Biomarker

• There is a trade off between marker positive size and efficacy signal;

• Objectives:
  – Proof of Clinical Principle that treatment is efficacious in at least a subset of the patient population
  – Determine a biomarker cut-off for further evaluation

• Literature
Adaptive Enrollment

- Proof of clinical principle is most important for early oncology development, therefore biomarker positive only or enriched trial is of interest.

- Enrolment is challenged without a cut-off for the continuous biomarker.
  - A wrong cut-off may lead to recruitment failure for a marker+ only trial
  - All-comer enrolment may fail to prove clinical principle if the potential marker-positive population is small and under-represented.
Adaptive Enrollment Illustration

- Figure to the right: density function of biomarker distribution and histogram of sample from all-comer enrollment.
- Figure below: density and histogram of sample from adaptive enrollment.
Questions?