Disclaimer

The speaker is an employee of Astrazeneca, a pharmaceutical company. The opinions of the speaker do not necessarily reflect the company’s official position and should be taken as their personal opinion only.
Background

- Adaptive design is now common in pharmaceutical drug development, particularly in phase 1 and phase 2 trials. Pharma is now looking for the next innovation.

- The platform trial is popular in collaborative groups with pharma companies contributing treatments

- The design of single-sponsor platform trials is being explored
Agenda

• Some definitions

• Early phase platform trial concept

• Practicalities

• Implications for drug development
Basket Design

- Used where there is a single biomarker signature seen in different diseases
- Single treatment examined for all diseases with the same signature
- Use of control group considered for each disease
Basket Example
Vemurafenib in BRAF V600+ Nonmyeloma

BRAF V600 Positive

- NSCLC
- Anaplastic Thyroid Cancer
- Breast Cancer
- Ovarian Cancer
- Multiple Myeloma
- Cholangiocarcinoma
- ECD/LCH
- Colorectal Cancer

Vemurafenib Monotherapy

Vemurafenib + Cetuximab

Hyman et al 2015
Umbrella Design

- Used in a single disease
- Patient assigned to biomarker groups using a Biomarker Allocation Algorithm
- Different treatment examined in each biomarker group
- Biomarker groups enrol at different rates

- Biomarker tests may be new
- A ‘Miscellaneous’ biomarker group is common
- Use of control group considered for each biomarker group
- Trial stops when each biomarker group is complete
Umbrella Example

Lung-MAP Protocol

Lam and Papadimitrakopoulou (2018)
# Platform Design

<table>
<thead>
<tr>
<th>Type</th>
<th>Drug A</th>
<th>Drug B</th>
<th>Drug C</th>
<th>Drug K</th>
<th>Basket</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td></td>
<td></td>
<td>⬤ ⬤ ⬤</td>
<td></td>
<td>⬤</td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>⬤ ⬤ ⬤</td>
</tr>
<tr>
<td>Type N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Platform Design

<table>
<thead>
<tr>
<th></th>
<th>Drug A</th>
<th>Drug B</th>
<th>Drug C</th>
<th>Drug K</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td></td>
<td></td>
<td>⬤</td>
<td>⬤</td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td></td>
<td>⬤</td>
<td>⬤</td>
<td></td>
</tr>
<tr>
<td>Type N</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td>⬤</td>
<td></td>
</tr>
</tbody>
</table>

Umbrella
Platform Design

Platform
Platform Design

- Objective is to promote or relegate a new treatment to the next phase
- A biomarker algorithms is required
- Studies tend to be cooperative group and multi-sponsor
- Studies can learn about the disease as well as the treatments
- Data office and trial steering committee organisation is essential
- A ‘waitlist’ of replacement treatments is needed
- Biomarker groups complete at different times due to the biomarker prevalence
## Platform Design

<table>
<thead>
<tr>
<th>Biomarker Group</th>
<th>Year of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 1</td>
</tr>
<tr>
<td>BM1</td>
<td>Treatment A</td>
</tr>
<tr>
<td>BM2</td>
<td>Treatment B</td>
</tr>
<tr>
<td>BM3</td>
<td>Treatment C</td>
</tr>
<tr>
<td>Misc</td>
<td>Treatment D</td>
</tr>
</tbody>
</table>

### Treatment Design

- **Treatment A**: Year 1
- **Treatment B**: Year 2
- **Treatment C**: Year 3
- **Treatment D**: Year 4
- **Treatment E**: Year 5
- **Treatment F**: Year 6
# Fixed vs Platform Trial Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Traditional Trial</th>
<th>Platform Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scope</strong></td>
<td>Single agent in a homogeneous population</td>
<td>Multiple agents in a heterogeneous population</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Finite</td>
<td>Long-term</td>
</tr>
<tr>
<td><strong>Treatment groups</strong></td>
<td>Pre-specified and limited</td>
<td>Multiple and may change over time</td>
</tr>
<tr>
<td><strong>Stopping rules</strong></td>
<td>Entire trial may be stopped early</td>
<td>Arms may be removed from the trial, but the trial continues with new arms</td>
</tr>
<tr>
<td><strong>Allocation strategy</strong></td>
<td>Fixed randomisation</td>
<td>Response adaptive randomisation</td>
</tr>
<tr>
<td><strong>Sponsor support</strong></td>
<td>Single federal or industry sponsor</td>
<td>Multiple federal or industry sponsors, or a combination</td>
</tr>
</tbody>
</table>

Berry et al 2015
### Position in Development Program

<table>
<thead>
<tr>
<th>Phase</th>
<th>II A</th>
<th>II B</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High P(Phase 3 Success)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Confirmatory evidence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proof of concept</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Early Phase Platform Trial
Objectives

• Current assessing the phase 2A platform trial concept
• Objective to provide phase 2B ready candidates
  – Graduate drugs with activity using early phase endpoints
  – Relegate drugs quickly (fast fail)
  – Accelerate exceptional treatments
• Study acts as ‘early phase filter’
• Use current AZ decision-making framework (Frewer et al 2016)
• Over time the trial learns about disease, new endpoints, stratification biomarkers, prognostic vs predictive effects
Early Phase Oncology Platform Design

- Oncology Indication
- Response rate endpoint
- Clear interim and final decision criteria with historical response rates
- N in each treatment arm
- Interim at N/2
- Biomarkers fixed
- Can relegate, continue, graduate or accelerate at interim
- Relegate or Graduate at final
- Five modules
- Treatments can be combinations
- Waitlist for new treatments
Biomarker-Finding Platform Design

Stage 1
- Treatment A
- Treatment B
- Treatment C
- Treatment D
- Control

Stage 2
- BM 1
  - Treatment A
  - Control
- BM 2
  - Treatment B
  - Control
- BM ...
  - Treatment E
  - Control
- Misc
  - Treatment F
  - Control

Interim Analysis

Randomise
Protocol

- Single or aligned protocol
- Aligned and efficient review – centralised regulatory/ethics
- Flexible
- Modular
- Rolling – open ended
- Adaptable to emerging science
- Allows different datasets
- Allows regulatory interactions

Flexible protocol with central review

Hollingsworth (2015)
Biomarker Algorithm

- Defined in the protocol
- Prognostic v Predictive
- Categorise biomarkers
  - Clinical evidence
  - Pre-clinical evidence
  - Scientific hypothesis

Framework for incorporating biomarker stratification in a platform trial

1. Can the biomarker of interest be reliably measured using a validated assay?
2. What is test-performance in clinically available samples representative of the population of interest?
3. Is the biomarker prognostic necessitating a separate control in order to distinguish a prognostic from a predictive effect?
4. What is the biomarker prevalence in the population of interest?
5. What is the strength of evidence of a predictive effect, i.e. the specificity of the biomarker?
6. What is the strength of evidence to support the rationale and clinical efficacy of the targeted therapy in the biomarker-defined group?
7. What is the overlap between this biomarker-defined group and others of interest?
8. What are the implications for other overlapping accruing comparisons?

Hollingsworth (2015) Gilson et al 2018
Interim Analyses

- Frequency of interim analyses should be pre-determined and simulated
- Short term endpoints are preferred
- Efficient data process
- Data monitoring committee
- Automated as much as possible
- Timing
  - Regular times (e.g. once per month, quarter)
  - Data driven
Randomisation

- Control group selection
- Fixed randomisation
- Catch-up randomisation
- Adaptive randomisation
- Two-stage adaptive randomisation

Gu et al 2016
Decision Making

- Linked to the trial objective
- Defined in the protocol
- Decision-making for treatments
  - Graduation decisions
  - Relegation decisions
  - Accelerate decision
- Decision-making for biomarkers
  - Initial biomarker algorithm
  - Updating the algorithm
- Decisions at the beginning of the trial should be as good as decisions at the end of the trial (decision consistency)
Trial Simulation

• All platform trials should be thoroughly simulated and simulations should be used to decide among design options
• Simulations documented in a Simulation Plan and Report
• Simulation report is expected to be presented to ethics/regulatory bodies
• Simulation should comprise
  – Many scenarios, including null scenario to establish overall type I error
  – Decision operating characteristics
  – Estimation bias evaluation
  – Sensitivity to patient withdrawals, missing data, enrolment rates/patterns, IA timings, data access delays, data cleanliness, analysis delays
Statistical Challenges

- Short term endpoint
- Explicit model for outcomes
- Bayesian sharing
- Prognostic v predictive effects
- Adaptive randomisation
- Sharing of control groups
- Decision criteria
- Trial simulation
- Data office
Trial Governance: I-SPY2

Das and Lo (2017)
Trial Governance

Trial Steering Committee

Protocol/Amendments
Communications

Trial Office
Data Process
Data Management
Informatics
Randomisation
Analysis
Reporting
Presentations
Publications

Data Monitoring
Reviewing
Process
Decisions

Biomarkers
Initial set
Algorithm
Assays
Validation
New biomarkers

Endpoints
Measurement
Validation
New endpoints

Treatments
Initial set
Wait-list
Combinations
Keys to Success

- Trial Governance
- Clear Objectives
- Decision Criteria
- Biomarker Algorithm
- Modular Protocol
- Short term endpoint
- Data Flow
- Centralised Analysis
- Wait list Priority
Implications for Drug Development

- Drug development is disease-based
  - Project teams focus on disease not drugs
  - Budgets
  - Resourcing
  - Outsourcing
- Initially slow start and planning, but quick start up once initiated
- Learning trials
  - Biomarkers
  - Endpoints
- Early phase platform trial is ideal for combinations
- Could be slow if too many biomarker modules
- Quality, time and cost metrics need baselining and collecting
References

- Berry SM, Connor JT and Lewis RJ. The platform trial. An efficient strategy for evaluating multiple treatments. JAMA 2015 313, 1619-1620
- Saville BR and Berry SM. Efficiencies of platform clinical trials: A vision of the future. Clinical Trials 2016, 13, 358-366
Platform Studies in Drug Development

James Matcham, Head ECD Biometrics, IMED Biotech Unit
PSI Webinar

18 April 2018