Session 1B: Alternative Designs for Dose-Finding Trials: Ending Reliance on Short-Term Safety

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New Haven, CT
Disclosure Information

Speaker Name

I have the following relevant financial relationships to disclose:

Employee of: Yale University

Paid Consultant (Scientific Advisory Board) for: NCI (BSC), AbbVie, Roche-Genentech, Takeda, SOTIO, Agenus, IQVIA, Pfizer, Glaxo-Smith Kline, QED Therapeutics, AstraZeneca, EMD Serono, Kyowa Kirin Pharmaceutical Development, Kineta, Inc, Zentalis Pharmaceuticals, Molecular Templates, ABL Bio, STCube Pharmaceuticals, I-Mab, Seagen, imCheck, Relay Therapeutics, Stemline, Compass BADX, Mekanistic, Mersana Therapeutics, BAKX Therapeutics, Scenic Biotech, Qualigen, Roivant Sciences, NeuroTrials, Actuate Therapeutics, Atreca Development, Amgen CodeBreak 202, Cullinan, DrenBio, Quanta Therapeutics, Schrodinger, Boehrigner Ingelheim: STING Agonist Global Advisory Board (2023)

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Stockholder in: None

Honoraria from: None
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U.S. Food and Drug Administration

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PumasAI

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Roche

Brian Koffman, MDCM (retired), MSEd
CLL Society
1\textsuperscript{st} Cycle MTD Identification no Longer Sufficient

- Phase I trials becoming more complex
  - Primary Objective(s): identification of RP2D & schedule – components going into making the right dose selection more complex
  - Historically 1\textsuperscript{st} cycle – defined MTD (RP2D)
  - “Next Generation Agents:” Determining MTD with C1 is becoming obsolete
    - Reason behind using 1\textsuperscript{st} cycle DLTs was time
    - Ideal Scenario: assessing totality of data to justify RP2D
Therapeutic Window

With wider therapeutic window – “more” not necessarily be better
Basic Dose Escalation Concepts

Responses
Toxicities
PD effects

Toxicities
DLTs 2/3 (MAD)
"MTD"

Therapeutic range
PD effects

FDA-AACR Public Workshop On
OPTIMIZING DOSAGES FOR ONCOLOGY DRUG PRODUCTS: QUANTITATIVE APPROACHES TO SELECT DOSAGES FOR CLINICAL TRIALS
With many novel agents, additional data beyond safety are becoming important:

- Preclinical Data
- Efficacy Data
- Pharmacokinetics
- Pharmacodynamics
- Patient Reported Outcomes
Are we even getting the dose right in phase I?

- Significantly increased G3-4 adverse events with small molecules vs monoclonal antibodies [40% vs. 27%; \(p=0.038\)] in phase III studies.
- 9% discontinuation rate

45% of patients on small molecules required dose modifications due to drug-related toxicity in phase III trials.

Important as combinations will be required for most small molecules to optimize efficacy.

Higher incidence of G3–4 toxicity in phase III trials in combos versus single-agent small molecules (64% vs. 37%; p=0.001).

25% SM-MTA Phase I trials recommended Phase II dose below the MTD based on PK/PD data and had fewer dose modifications in subsequent Phase III registration trials (32% vs 50%; RR 0.64; 95% CI 0.43-0.88).

Delayed immune-related adverse events in assessment for dose-limiting toxicity in early phase immunotherapy trials

Y. Kanjanapan a,b,c, D. Day a,b,c, M.O. Butler a,b,c, L. Wang d, A.M. Joshua a,b,c, D. Hogg a,b,c, N.B. Leighl a,b,c, A.R. Abdul Razak a,b,c, A.R. Hansen a,b,c, S. Boujouc e, M. Chappell e, K. Chow e, B. Sherwin a, L.-A. Stayner e, L. Soultani e, A. Zambrana a, L.L. Siu a,b,c, P.L. Bedard a,c, A. Spraggo a,b,c,e

a Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada
b Department of Medicine, University of Toronto, Toronto, Canada
c Drug Development Program, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada
d Biostatistics Department, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada

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Available online 7 December 2018
Risks of Clinically Significant Adverse Events Over Time on IO Therapy

352 trial enrollments:

- Odds Ratio of csAE within first 4 weeks vs after 4 weeks = 3.13 (95% CI 1.95-5.02)

- The median time to first onset csAE was significantly shorter amongst patients receiving combination compared with single-agent IO (32 vs 146 days, P < 0.0001)

- 5.7% of trial enrollments experienced delayed csAE (24 events) that qualify for DLT outside of DLT window

csAE = treatment-related adverse event requiring corticosteroids, hormone replacement, IO delay or discontinuation.
Conclusions

- Although many csAEs were delayed well beyond the DLT period (11-14w), it is important to collect and report delayed csAEs, as these may provide further refinement.

- As most IO agents do not report a linear relationship between dose and toxicity, the RP2D for most IO agents relies on PK/PD and not DLTs.
Phase I (Early Phase) Clinical Trials

- What we want:
  - minimize both under- and overdosing patients
  - maximize Patient Risk:Benefit

- Novel trial designs are overcoming some of the known deficiencies of Early Phase Clinical Trials
• Phase I trials typically not hypothesis-driven, e.g., the primary objective is to evaluate safety and establish MTD/RP2D

• Statistical analysis typically descriptive, e.g., tabulate toxicity by grade and type

• Challenging and critical part lies in gathering additional data to justify RP2D

• The data collected must be “fit for purpose”
Phase I Trial Designs

• Algorithm-based designs
  • Example: 3+3 design
  • Transparent, easy to implement, but poor performance

• Model-based designs
  • Examples: Continual Reassessment Method (CRM), Escalation With Overdose Control (EWOC), Bayesian Logistic Regression Method (BLRM)
  • Superior performance, but function as a “blackbox” and difficult to implement

• Model-Assisted Designs
  • Examples: Bayesian Optimal Interval (BOIN), and keyboard design
  • Transparent and easy to implement with superior performance

References: O’Quigley et al. 1990; Babb et al., 1998; Neuenschwander et al., 2008; Liu and Yuan, 2015; Yan, Mandrekar and Yuan, 2017
Model-based/Model-Assisted vs. Rule-Based Phase I Oncology Trials: Duration

172 articles published over 2 years

Model-based trials:
- needed 10 months less than rule-based trials (26 vs. 36 months; \( p = 0.25 \))
- Fewer patients treated at dose-levels below the RP2D (31 % versus 40 %; \( p = 0.73 \))
- Safety preserved (13 % DLTs versus 14 % DLTs)

ARROW Trial: Design

Phase 1, Dose Escalation

- Advanced MTC, NSCLC or other solid tumors
- 7 dose levels from 30-600 mg (PO QD or BID)

Phase 2, Dose Expansion

- Ret fusion NSCLC, prior platinum
  - N~80
- Ret fusion NSCLC, platinum naive
  - N~200
- MTC, prior cabozantinib and/or vandetanib
  - N~65
- MTC, no prior cabozantinib or vandetanib
  - N~40
- Other RET fusion solid tumors
  - N~40
- RET-altered solid tumors, prior selective RET TKI
- Other RET-mutated solid tumors
  - N~20

Abbreviations: BOIN = Bayesian optimal interval; MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; RET = rearranged during transfection; TKI = tyrosine kinase inhibitor; PO, orally; QD, once daily; BID, twice daily.
ARROW Trial: using BOIN

BOIN design
- Advance MTC, NSCLC or other solid tumor
- 30-600mg (PO QD or BID)
- RET alteration required at doses>120mg QD

# Phase II Dose Expansion Cohorts

**Table 2. Efficacy results in ARROW.**

<table>
<thead>
<tr>
<th>RET fusion–positive NSCLC</th>
<th>Previously treated w/platinum chemotherapy</th>
<th>Treatment naïve</th>
<th>( N = 87 )</th>
<th>( N = 27 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate(^a) (95% CI)</td>
<td>57 (46–68)</td>
<td>70 (50–86)</td>
<td>5.7</td>
<td>11</td>
</tr>
<tr>
<td>Complete response, %</td>
<td>52</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of response</td>
<td>( N = 50 )</td>
<td>( N = 19 )</td>
<td>9.0 (6.3–NE)</td>
<td>58</td>
</tr>
<tr>
<td>Median in months (95% CI)</td>
<td>NE (15.2–NE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% with ≥ 6 months(^b)</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prior cabozantinib or vandetanib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RET-mutant MTC</td>
<td>( N = 55 )</td>
<td>( N = 29 )</td>
<td>60 (46–73)</td>
<td>66 (46–82)</td>
</tr>
<tr>
<td>Overall response rate(^a) (95% CI)</td>
<td>1.8</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response, %</td>
<td>58</td>
<td>55</td>
<td></td>
<td></td>
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<tr>
<td>Partial response, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of response</td>
<td>( N = 33 )</td>
<td>( N = 19 )</td>
<td>NR (15.1–NE)</td>
<td>NR (NE–NE)</td>
</tr>
<tr>
<td>Median in months (95% CI)</td>
<td>NE (NE–NE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% with ≥ 6 months(^b)</td>
<td>79</td>
<td></td>
<td></td>
<td>84</td>
</tr>
<tr>
<td>Cabozantinib and vandetanib naïve</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RET fusion–positive thyroid cancer</td>
<td>( N = 9 )</td>
<td></td>
<td>89 (52–100)</td>
<td></td>
</tr>
<tr>
<td>Overall response rate(^a) (95% CI)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Complete response, %</td>
<td>89</td>
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<tr>
<td>Partial response, %</td>
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<td>Duration of response</td>
<td>( N = 8 )</td>
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<td>NR (NE–NE)</td>
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</tr>
<tr>
<td>Median in months (95% CI)</td>
<td>NE (NE–NE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% with ≥ 6 months(^b)</td>
<td></td>
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</tbody>
</table>
FDA approves pralsetinib for lung cancer with RET gene fusions

On September 4, 2020, the Food and Drug Administration granted accelerated approval to pralsetinib (GAVRETO, Blueprint Medicines Corporation) for adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.

Today, FDA also approved the Oncomine Dx Target (ODxT) Test (Life Technolo
gies Corporation) as a companion diagnostic for pralsetinib.

Efficacy was investigated in a multicenter, open-label, multi-cohort clinical trial (ARROW, NCT03037385) in patients whose tumors had RET alterations.

FDA approves pralsetinib for RET-altered thyroid cancers

On December 1, 2020, the Food and Drug Administration approved pralsetinib (GAVRETO, Blueprint Medicines Corporation) for adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy or RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

Efficacy was investigated in a multicenter, open label, multi-cohort clinical trial (ARROW, NCT03037385) in patients whose tumors had RET gene alterations. Identification of RET gene alterations was prospectively determined in local laboratories using either next generation sequencing, fluorescence in situ hybridization, or other tests.
What if 3+3 design was used?

If 3+3 design was used

Stop

Select 200mg as the MTD, 50% of the effective dose!

May lead to trial failure !!!

STOP

200mg
DLT:0/5

100mg
DLT:1/5

60mg
DLT:0/6

30mg
DLT:0/1

300mg
DLT:0/6

400mg
DLT:1/6

400mg
DLT:2/3

600mg
DLT:1/6

400mg QD

400mg
DLT:1/6

200mg
DLT:0/7

600mg
DLT:2/3

400mg
DLT:0/6

400mg
DLT:2/5

200mg
DLT:0/5

600mg
DLT:1/6

400mg
DLT:1/6

STOP

Select 200mg as the MTD, 50% of the effective dose!

May lead to trial failure !!!
Phase I (Early Phase) Clinical Trials – Opportunities & Challenges

- **Model Assisted/Based Designs**: more flexible, nimble and accurate in identifying the RP2D

- **Challenges**:
  - More patients may be needed
  - Most model designs still utilizing toxicity data from C1
  - Collecting and incorporating PD and efficacy data
  - **Investigator mindset**: rule-based → model-based designs
Flexible Smart Model

Dose Level 1

Pt 1  Pt 2  Pt 3

Dose Level 2

Pt 1  Pt 2  Pt 3

Pt 4  Pt 5  Pt 6

Cumulative Data
Flexible Smart Model

Collect Cumulative Data for RP2D Decision Making
Conclusions

- Primary Phase I Trial Objective(s): efficiently and accurately evaluate the safety profile of the drug at potentially therapeutic doses
- Model Based Designs: more flexible and accurate at identifying RP2D and can be as easy to implement as the 3+3 design
- Don't always aim to cut the sample size. A reasonable sample size will save on patient numbers, cost, and time by substantially improving the trial's success rate.
- Challenge: incorporation of later cycle safety data, efficacy, pre-clinical, PD and “class effects” in identification of the RP2D
Thank You!
How to Pivot Beyond Rule-Based and Model-Based Determinations to Support Dosage Selection

Ying Yuan, Ph.D.
The University of Texas MD Anderson Cancer Center
Ying Yuan
I have the following relevant financial relationships to disclose:
   Founder of Polaris Consulting LLC
Challenges of dose optimization

- Dose optimization presents a high-dimensional challenge, encompassing diverse data and considerations.
  - “Relevant nonclinical and clinical data, as well as the dose- and exposure-response relationships for safety and efficacy should be evaluated to select a dosage(s) for clinical trial(s).” (FDA Guidance)
- I will focus on two key areas for trial design and decision-making:
  - Risk-benefit tradeoff
  - Tolerability (e.g., late-onset toxicity and low-grade toxicity)
Target therapies demonstrate different dose-response relationships

Cytotoxic Chemotherapy

- MTD-based dose finding is often appropriate

Targeted Therapies

- **Safety alone is not sufficient to inform optimal RP2D** (recommended phase 2 dose)

**MTD**: maximum tolerated dose.  
**OBD**: optimal biological dose

MTD $\approx$ OBD

**Narrow Therapeutic Index**

**Wide Therapeutic Index**

Efficacy  
Toxicity

Response

Dose

0  20  40  60  80  100

FDA-AACR Public Workshop On

OPTIMIZING DOSAGES FOR ONCOLOGY DRUG PRODUCTS: QUANTITATIVE APPROACHES TO SELECT DOSAGES FOR CLINICAL TRIALS
To determine the optimal dose, it is imperative to consider both toxicity and efficacy.
Toxicity and efficacy endpoints should be carefully chosen to reflect the risk and benefit.

Utility provides an intuitive approach to evaluating risk-benefit tradeoff (aka., desirability)

- Example:

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Response</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>40</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>100</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>60</td>
</tr>
</tbody>
</table>
Desirability of a dose

- Example (cont.)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Response</th>
<th>Prob (occurrence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>0.1</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>0.4</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>0.2</td>
</tr>
</tbody>
</table>

\[
\text{Desirability} = 100 \times 0.4 + 40 \times 0.1 + 60 \times 0.2 + 0 \times 0.3 = 56
\]
Use the utility to identify the OBD

- Revise the example:

  \[
  \begin{align*}
  \text{MTD} \\
  \Pr(\text{toxicity}) &= (0.08, 0.12, 0.30, 0.45, 0.55) \\
  \Pr(\text{efficacy}) &= (0.30, 0.50, 0.51, 0.51, 0.52) \\
  \end{align*}
  \]
  
  Desirability = (54.8, 65.2, 58.6, 52.6, 49.2)

  \[
  \text{Dose } d = 2 \text{ is the OBD}
  \]
Advantages of utility approach

- **Easy to understand**: clinicians and patients understand clinical outcomes better than probabilities

- **Scalable**: straightforward to account for low-grade toxicity and more endpoints (Liu et al., 2018).

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>40</td>
</tr>
<tr>
<td>Low grade</td>
<td>20</td>
</tr>
<tr>
<td>DLT</td>
<td>0</td>
</tr>
</tbody>
</table>
Efficacy-integrated dose finding

1. Treat the first cohort at the starting dose
2. Collect efficacy and toxicity data
3. Update the estimate of desirability for each dose based on interim data
4. Treat the next cohort of patients at the recommended dose
5. Determine dose escalation/de-escalation based on the estimated desirability

- Model-based approach
- Model-assisted approach
Model-based approach

- Assume a statistical model describing dose-toxicity and dose-efficacy relationships
  - Often complicated

- Examples: EffTox (Thall and Cook, 2004), Late-onset EffTox (Lo-EffTox, Jin et al., 2014)

- Pros: accounts for risk-benefit tradeoff

- Cons: complicated to implement, real-time estimation, subject to the influence of model misspecification

Example: Gumbel model (e.g., EffTox design)

- Dose-toxicity model: \( \text{logit}(\pi_T|d_j) = \alpha_T + \beta_Td_j \), where \( d_j \) is the dose of level \( j \)
- Dose-efficacy model: \( \text{logit}(\pi_E|d_j) = \alpha_E + \beta_{E,1}d_j + \beta_{E,2}d_j^2 \)
- Joint model: \( \pi_{a,b} = (\pi_E)^a(1 - \pi_E)^{1-a}(\pi_T)^b(1 - \pi_T)^{1-b} + (-1)^{a+b}\pi_E(1 - \pi_E)\pi_T(1 - \pi_T)\left(\frac{e^\psi - 1}{e^\psi + 1}\right) \)

where \( \pi_T|d_j = \Pr(y_T = 1|d_j) \) and \( \pi_E|d_j = \Pr(y_E = 1|d_j) \)
Trial examples

- Dose optimization trials based on the Lo-EffTox design (Jin et al., 2014)

**Science Translational Medicine | Research Article**

**Cancer**

A phase 1-2 trial of sitravatinib and nivolumab in clear cell renal cell carcinoma following progression on antiangiogenic therapy

Pavlos Msaouel1,2,†, Sangeeta Goswami1,4,†, Peter F. Thall3, Xuemei Wang3, Ying Yuan3, Eric Jonasch5, Jianjun Gao1,2, Matthew T. Campbell1, Amishi Yogesh Shah1, Paul Gettys Corn1, Alda L. Tam3, Kamran Ahrar3, Priya Rao3, Kanishka Sirca3,†, Lorenzo Cohen6, Sreyashi Basu2, Fei Duan7, Sonali Jindal7, Yuwei Zhang7, Hong Chen7, Shalini S. Yadav7, Ronald Shazer7, Hirak Der-Torossian7, James P. Allison8, Padmanee Sharma1,4,9,†, Nizar M. Tannir1,9,†

**Lancet Oncol 2023; 24: 1387-98**

Stereotactic body radiotherapy with or without selective dismutase mimetic in pancreatic adenocarcinoma: an adaptive, randomised, double-blind, placebo-controlled, phase 1b/2 trial

Cullen M Taniguchi, Jessica M Frakes, Todd A Aguilera, Manisha Palta, Briton Cita, Manoop S Bhatani, Lauren E Colbert, Joseph Ali Jaoude, Vincent Bardin, Shubham Pant, Ching-Wei D Tseng, Dor Won Kim, Mokengo Malefo, James Costello, Genna Mathew, Niel Reuben, Eugene J Kepp, Pragin Das, Ethan B Ludmic, Matthew H G Katz, Robert A Wolff, Sam Beddar, Gabriel O Suvatsuki, Shalini Morning, Rebecca S Slack Tydwell, Ying Yuan, Peter F Thall, Robert A Brandley, Jon Holmblund, Joseph M Herman, Sarah E Hofe
Model-assisted approach

- An example: Decision tree of BOIN12 (Lin et al., 2020)

![Decision Tree Diagram]

- **Choose a dose from** \( \{ j - 1, j, j + 1 \} \) using the RDS table
- **Choose a dose from** \( \{ j - 1, j \} \) using the RDS table
- De-escalate the dose to \( j - 1 \)

* RDS: rank-based desirability score, see next page
## Desirability table

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<tr>
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Trial examples

- BOIN12 (NCT04835519, NCT05032599)
  - Phase I/II Study of Enhanced CD33 CAR T Cells in Subjects With Relapsed or Refractory Acute Myeloid Leukemia
  - Donor-Derived CD5 CAR T Cells in Subjects With Relapsed or Refractory T-Cell Acute Lymphoblastic Leukemia

*Journal of Clinical Oncology*
An American Society of Clinical Oncology Journal

HEMATOLOGIC MALIGNANCIES—LEUKEMIA, MYELODYSPLASTIC SYNDROMES, AND ALLOTRANPLANT

Phase I study of donor-derived CD5 CAR T cells in patients with relapsed or refractory T-cell acute lymphoblastic leukemia.

Jing Pan, Yue Tan, Lingling Shan, Biping Deng, Zhuojun Ling, Weiliang Song, ...
Targeted therapies are often administered for long periods, leading to late-onset toxicities and persistent low-grade toxicities.

**Key challenge**: these toxicity events require long observation windows over multiple cycles, thus very limited data are available during the trial.
Some solutions for late-onset toxicity

- Time-to-event (TITE) designs (e.g., TITE-BOIN12, Lo-EffTox)
  - Predict late-onset toxicity using a statistical method

- Two-stage approach
  - After the dose escalation, add a second stage of assigning more patients to two candidate RP2D. This buys some time and enables the collection of more long-term safety data

- Seamless phase 1-2-3 designs
  - Continue optimizing dose in phases 2 and 3
Two-stage dose finding

Stage 1: Dose escalation

TITE-BOIN12/BOIN design

Stage 2: Dose optimization

Identify admissible doses*

Randomize and select OBD based on utility

* doses are safe with promising antitumor activities

BOP2: Bayesian optimal phase 2 design (Zhou et al., 2017)

Interims

Adaptively drop futile or toxic doses based on BOP2 design
Two-stage dose finding

Stage 1: Dose escalation
- TITE-BOIN12/BOIN design

Stage 2: Dose optimization
- Identify admissible doses*
- Randomize and select OBD based on utility
- Interims
  - Dose Level 2
  - Dose Level 3

* Backfill to speed up

R: randomization

Adaptively drop futile or toxic doses based on BOP2 design

* doses are safe with promising antitumor activities
BOP2: Bayesian optimal phase 2 design (Zhou et al., 2017)
Backfilling Patients in Phase I Dose-Escalation Trials Using Bayesian Optimal Interval Design (BOIN)

Yixuan Zhao¹, Ying Yuan², Edward L. Korn³, and Boris Freidlin³

Abstract

In recent years, there has been increased interest in incorporation of backfilling into dose-escalation clinical trials, which involves concurrently assigning patients to doses that have been previously cleared for safety by the dose-escalation design. Backfilling generates additional information on safety, tolerability, and preliminary activity on a range of doses below the maximum tolerated dose (MTD), which is relevant for selection of the recommended phase II dose and dose optimization. However, in practice, backfilling may not be rigorously defined in trial protocols and implemented consistently. Furthermore, backfilling designs require careful planning to minimize the probability of treating additional patients with potentially inactive agents (and/or subtherapeutic doses). In this paper, we propose a simple and principled approach to incorporate backfilling into the Bayesian optimal interval design (BOIN). The design integrates data from the dose-escalation and backfilling components of the design and ensures that the additional patients are treated at doses where some activity has been seen. Simulation studies demonstrated that the proposed backfilling BOIN design (BF-BOIN) generates additional data for future dose optimization, maintains the accuracy of the MTD identification, and improves patient safety without prolonging the trial duration.
Thank You!
SESSION 1B: ALTERNATIVE DESIGNS FOR DOSE-FINDING TRIALS: ENDING RELIANCE ON SHORT-TERM SAFETY

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