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Phase I and II clinical trials

The statistician view

The phase I landscape is changing

- The “traditional” 3+3 design was based on the *assumption* that higher doses of cytotoxics are always more effective
- Cohorts of 3 or 6 participants are small for decision making
- 90% confidence intervals:
  - 0/3: (0,0.63) 1/3: (0.02,0.86) 0/6: (0,0.39) 1/6: (0.008,0.58)
- Expansion cohorts contribute to awkward designs and analyses
- Ad hoc modifications to trial designs can be dangerous
- If a phase II study is going to be pivotal (Orphan, Fast Track, Accelerated Approval, Breakthrough Therapy), we want more out of phase I

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Model-based designs can help

- Alternatives to 3+3 come can be algorithmic or model-based
  - Algorithmic: Storer's up-and-down, Narayana k-in-a-row, mTPI (also 3+3)
  - Model-based: CRM and TITE-CRM, Bayesian model averaging
- All of these methods can be expanded to larger sample sizes, for better estimation quality and assessment of phase 2 endpoints
- Combination therapies and escalation on bivariate endpoints can be accommodated
- Phase I *designs* should be assessed and compared using statistical principles: precision of RP2D estimate, speed of trial completion, expected number of toxicities, handling of complexifactions*

*Sorry, I couldn't help myself

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Algorithmic phase 1 example

- Storer (1989)
- Phase 1 dose-escalation design to estimate RP2D based on DLT
- Treat k participants at dose level d
  - If 0/k DLTs, escalate to dose d+1 in next cohort
  - If 1/k DLTs, stay at dose d in next cohort
  - If >1/k DLTs, de-escalate to dose d-1 in next cohort
- Converges to the dose d^* with $E(P(DLT|d^*)=1/k$
- Combine with early rapid dose escalation
- Treat 30-50 patients

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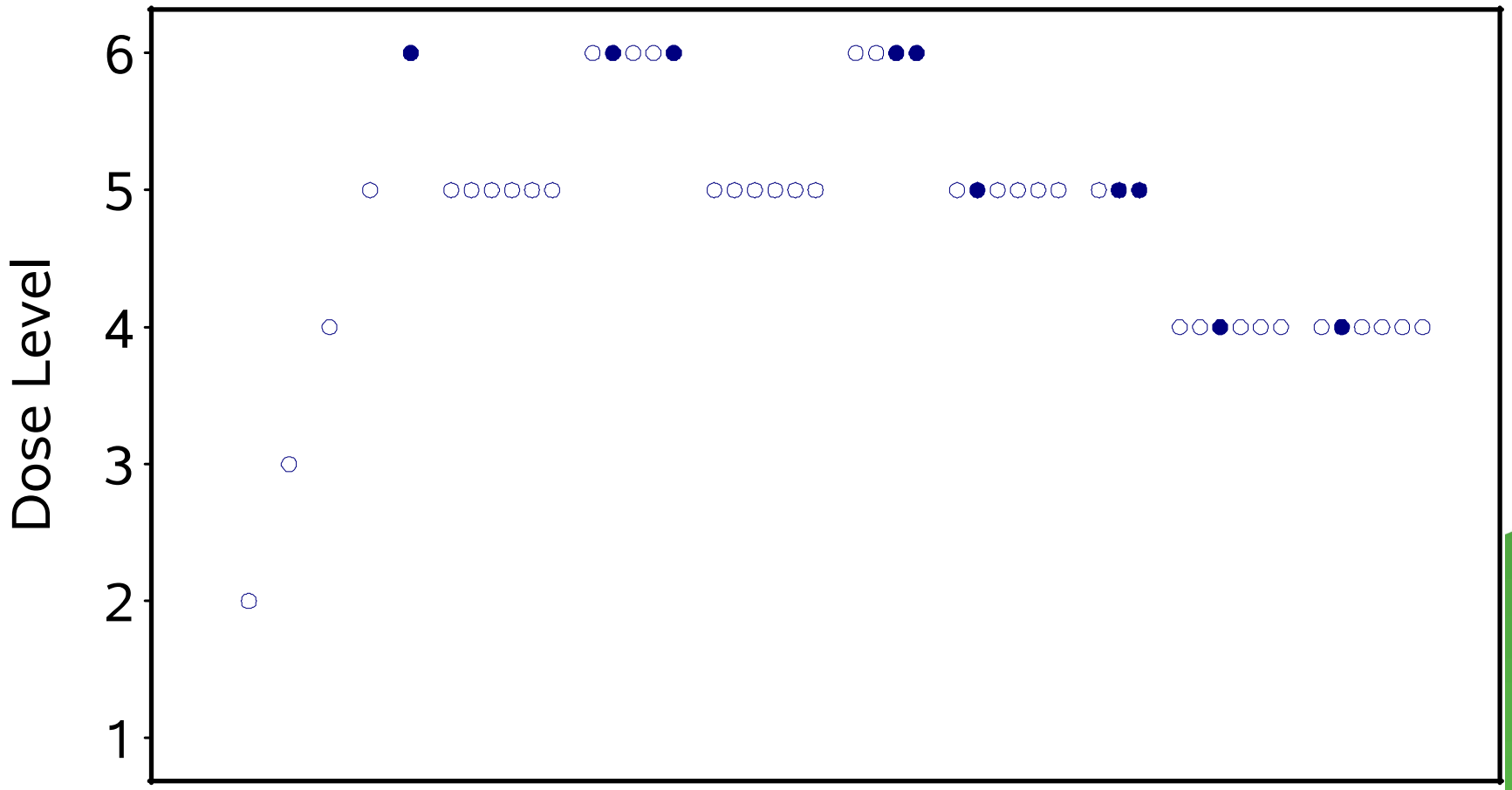
Algorithmic phase 1 example



Advantages of larger phase 1/2 design

- Use all participants' data to estimate RP2D
- Use regression to estimate dose-toxicity (phase 1) and dose-response (phase 2) functions
- Include sequential stopping rule for futility
- No "white space" between phase 1 and phase 2
- I generally categorize these as "simultaneous phase 1/2 designs," as both safety and efficacy endpoints are evaluated on the same participants

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Model-based phase 1 design example

- Time-to-Event Continual Reassessment Method, Cheung (1999)
- One-parameter dose-toxicity function $\mathrm{P}(\mathrm{DLT}|t_d) = \dfrac{e^{3+\alpha t_d}}{1+e^{3+\alpha t_d}}$
- Start at $\alpha = 1$, re-estimate α as patients accrue

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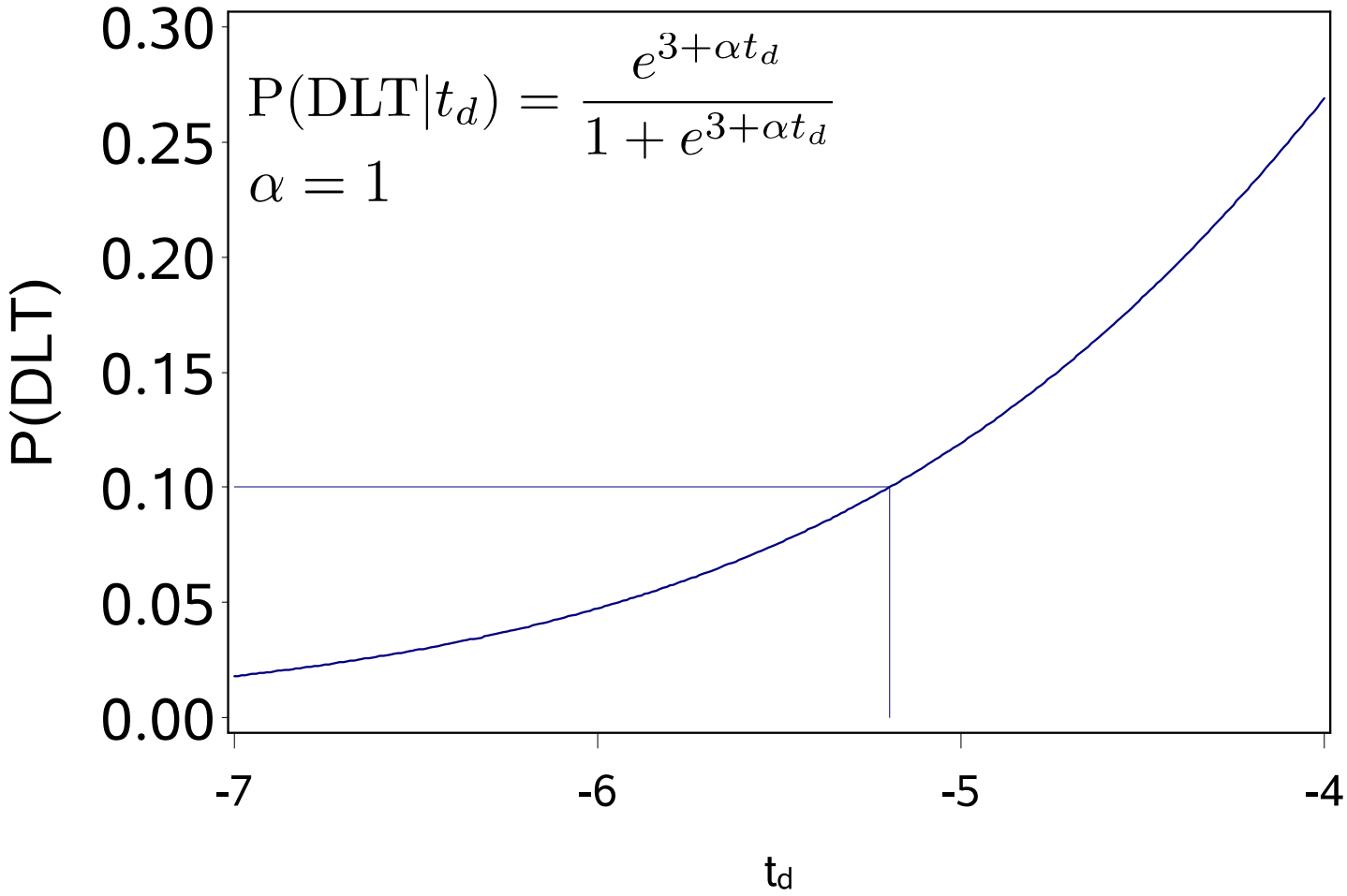
Model-based phase 1 design example



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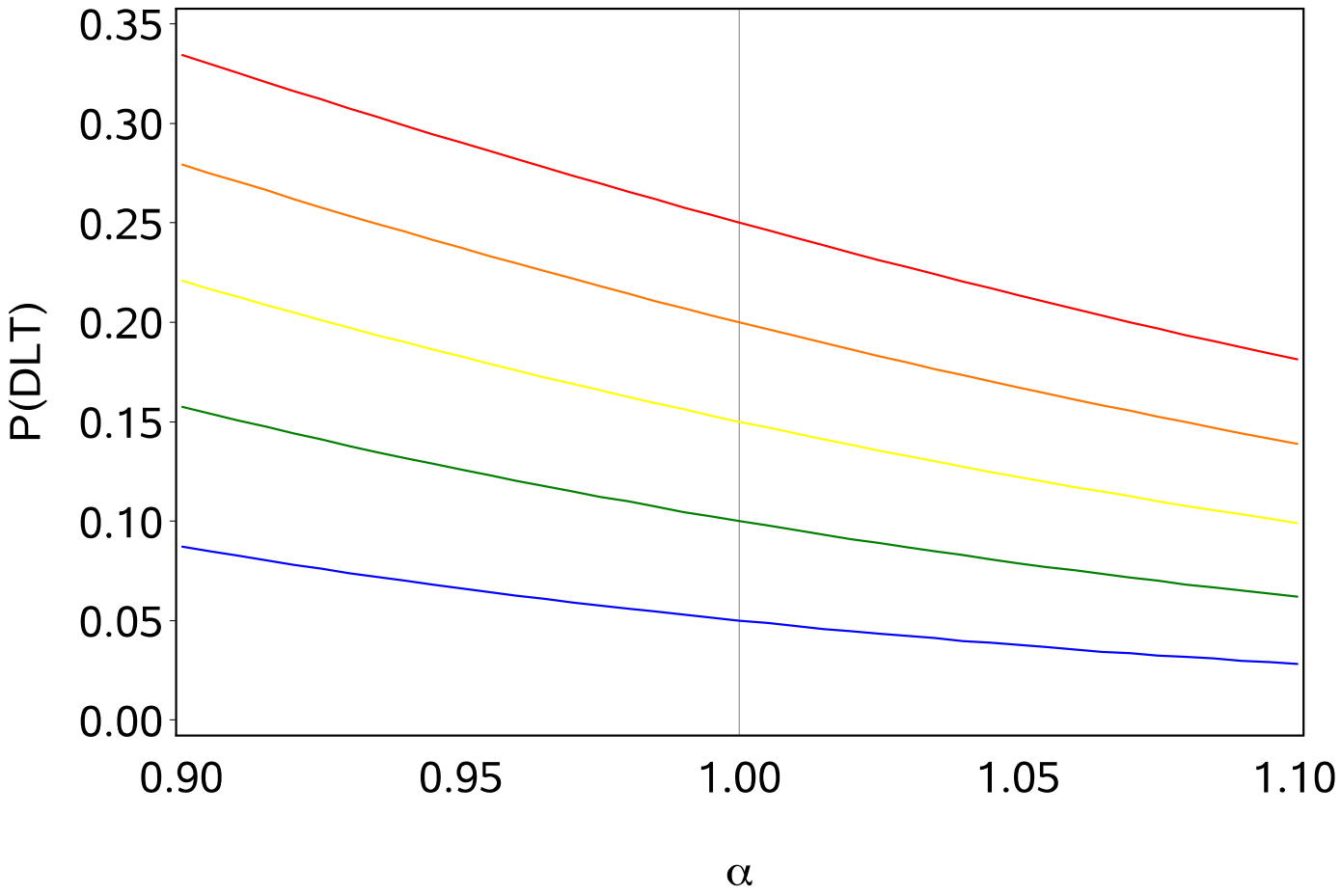
Model-based phase 1 design example



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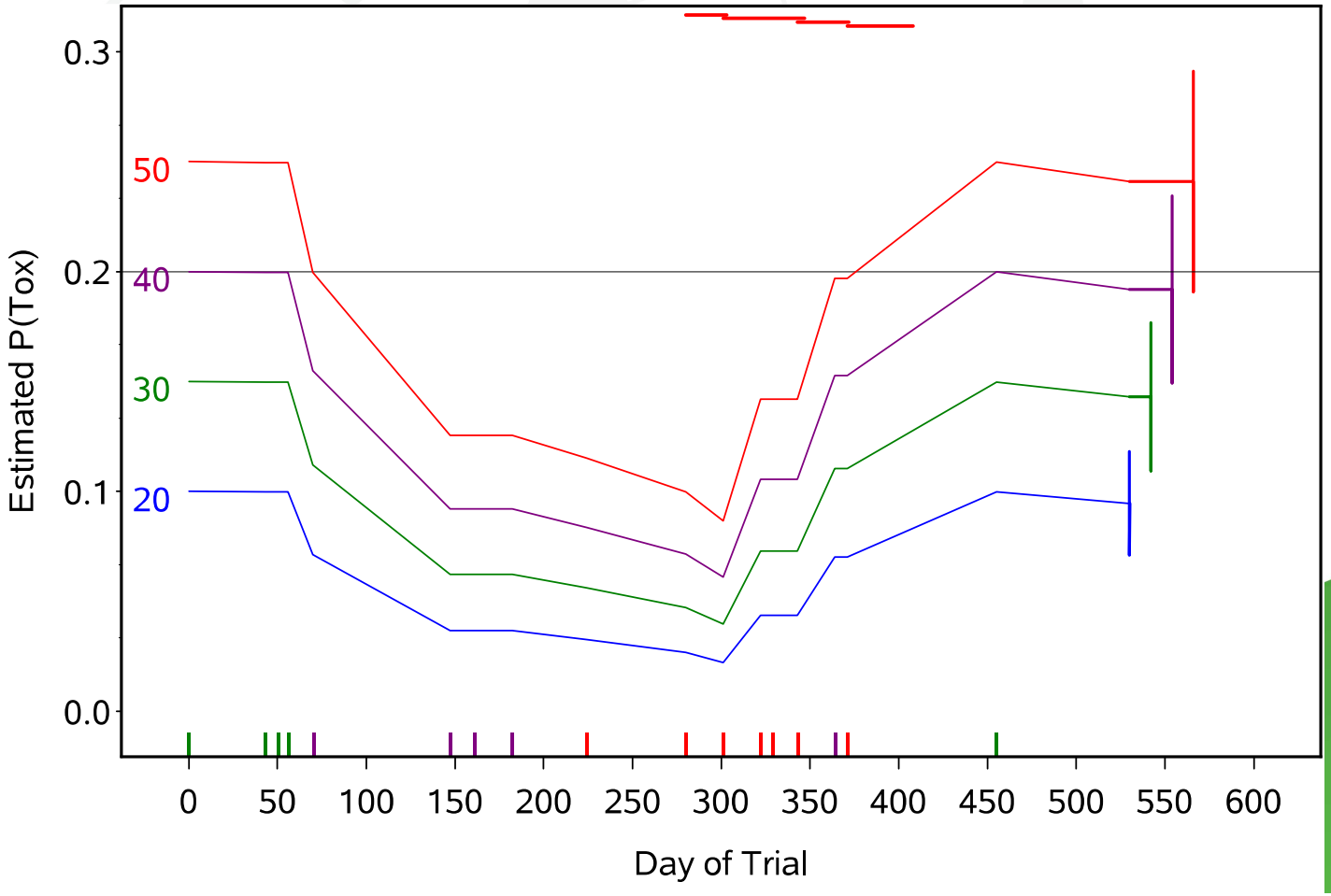
Model-based phase 1 design example

- Time-to-Event Continual Reassessment Method, Cheung (1999)
- One-parameter dose-toxicity function $\mathrm{P}(\mathrm{DLT}|t_d) = \dfrac{e^{3+\alpha t_d}}{1+e^{3+\alpha t_d}}$
- Re-estimate α as patients accrue
- Weight participants' contribution to estimation according to their cumulative time of evaluation
- No cohorts
- Accrual not closed between participants; observation period can be 5x mean inter-participant arrival time
- Accrue 30-100 participants (RTOG 0813)

Model-based phase 1 design example (UMCC9976)



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Model-based phase 1 trials can be extended

- Identify ordinal risk cohorts
  - Liver function
  - Normal tissue complication probability model
- Use TITE-CRM with ordered dose-toxicity parameters
  - Cohort 1: α
  - Cohort 2: $\alpha + \delta_1$
  - Cohort 3: $\alpha + \delta_1 + \delta_2$
- Use Markov Chain Monte Carlo to estimate parameters

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Escalation on multiple treatments

- Standard designs can be used for setting doses of combination therapies can be used if:
  - Risks of DLT per treatment can be ordered
  - The number of doses per treatment to be tested is small
  - Dose-toxicity and dose-toxicity are both expected to be monotonic
- If not…
  - "Windshield-wiper" designs
  - Optimization on both toxicity and efficacy
  - Larger samples are required (e.g., CheckMate 040 (n=640), CheckMate 142 (n=340)), but
  - These trials would be large enough to be considered pivotal

Sharing information between cohorts

- Phase 2 trial in HNSCC with *K* treatments and *J* risk cohorts
- Treatment is selected by checkpoint expression
- Endpoint: objective response
- Hierarchical beta-binomial model shares information between cohorts:
  - $y_{ijk} \sim \text{Bernoulli}(\pi_{jk})$
  - $\pi_{jk} \sim \text{Beta}(\alpha_{jk}, \beta_{jk})$
  - $\alpha_{jk} \leftarrow \gamma_{jk} \times \pi$
  - $\beta_{jk} \leftarrow \gamma_{jk} \times (1-\pi)$
  - $\gamma_{jk} \sim \text{Gamma}(0.1,0.1)\text{I}(0.1,)$
  - $\pi \sim \text{Beta}(y,n-y)$

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Bayesian models facilitate sequential decision making

- Thall, Simon & Estey (1995)
- Single-arm phase 2 design
- Continually model efficacy and toxicity
- Modify trial (e.g., stop, adapt) if $\mathrm{P}(\mathrm{P}(\mathrm{Efficacy}) < \pi_{\mathrm{E}}) > \pi_{\mathrm{C}}$ or

  $\mathrm{P}(\mathrm{P}(\mathrm{Toxicity}) > \pi_{\mathrm{T}}) > \pi_{\mathrm{D}}$
- π_{E} and π_{T} are *criterion* parameters, and π_{C} and π_{D} are *confidence* parameters
- Prior distribution allows correlation between efficacy and toxicity

Models allow adaptation of control models

- Feng (2017)
- Phase 2 trial of SBRT for intrahepatic cancer in pre-treated patients
- Standard SBRT in naïve patients is five treatments
- Test participants' liver function with indocyanine green assay (p_{15}) after 3 treatments at maximum dose of 12Gy/treatment
- Revise last two doses to reduce final doses to limit toxicity
- Dose-toxicity model is continually revised throughout trial

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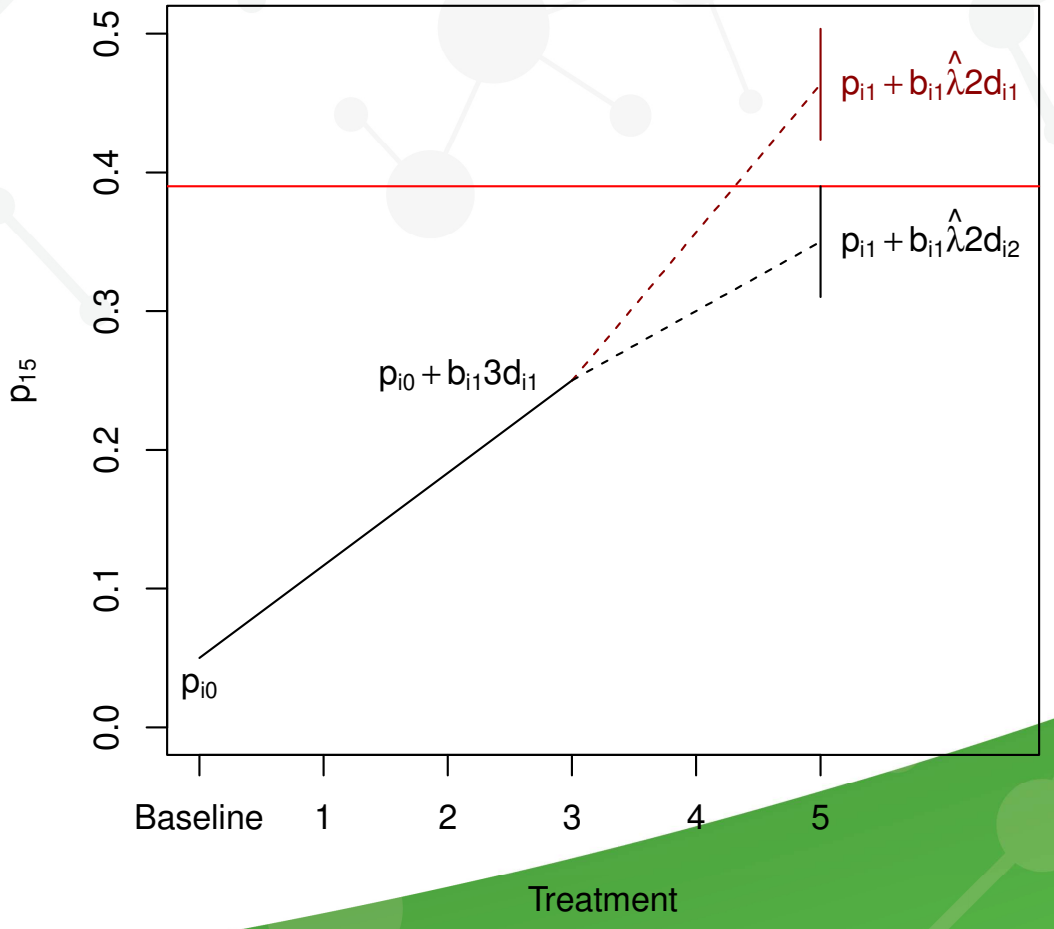
Models allow adaptation of control models



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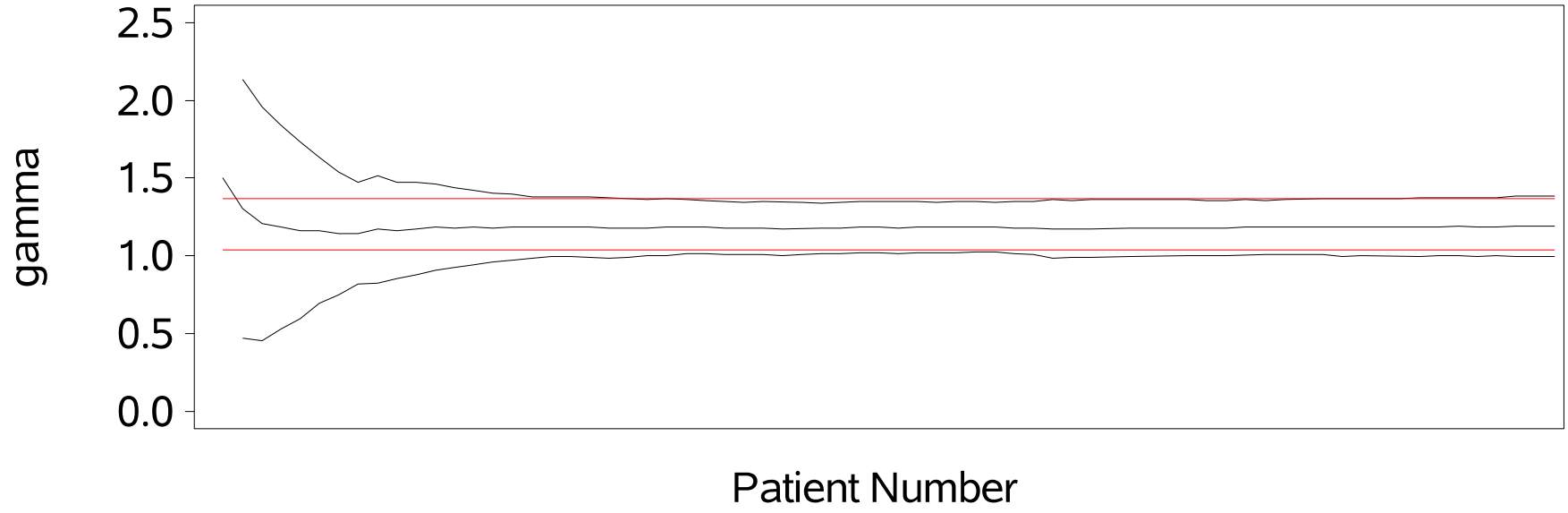
Models allow adaptation of control models

- γ is the adaptive estimand
- It is updated throughout the trial as dosing and p_{15} data accrue
- Simulated re-estimation of γ when true value is 1.2:



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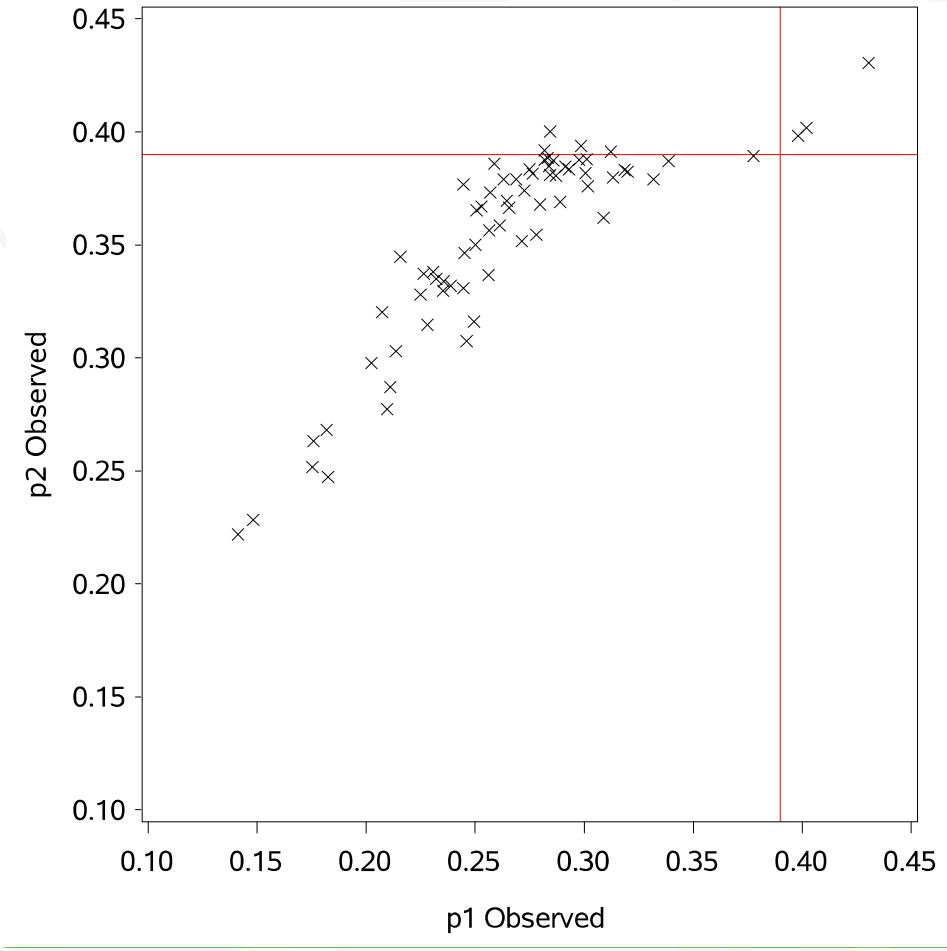
Models allow adaptation of control models



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Models allow adaptation of control models

- 90 higher risk patients treated
- Final 2 doses reduced in 45% of patients
- 99% 1-year local control
- 95% 2-year local control
- 0% classical RILD
- 2 Grade 3 toxicities

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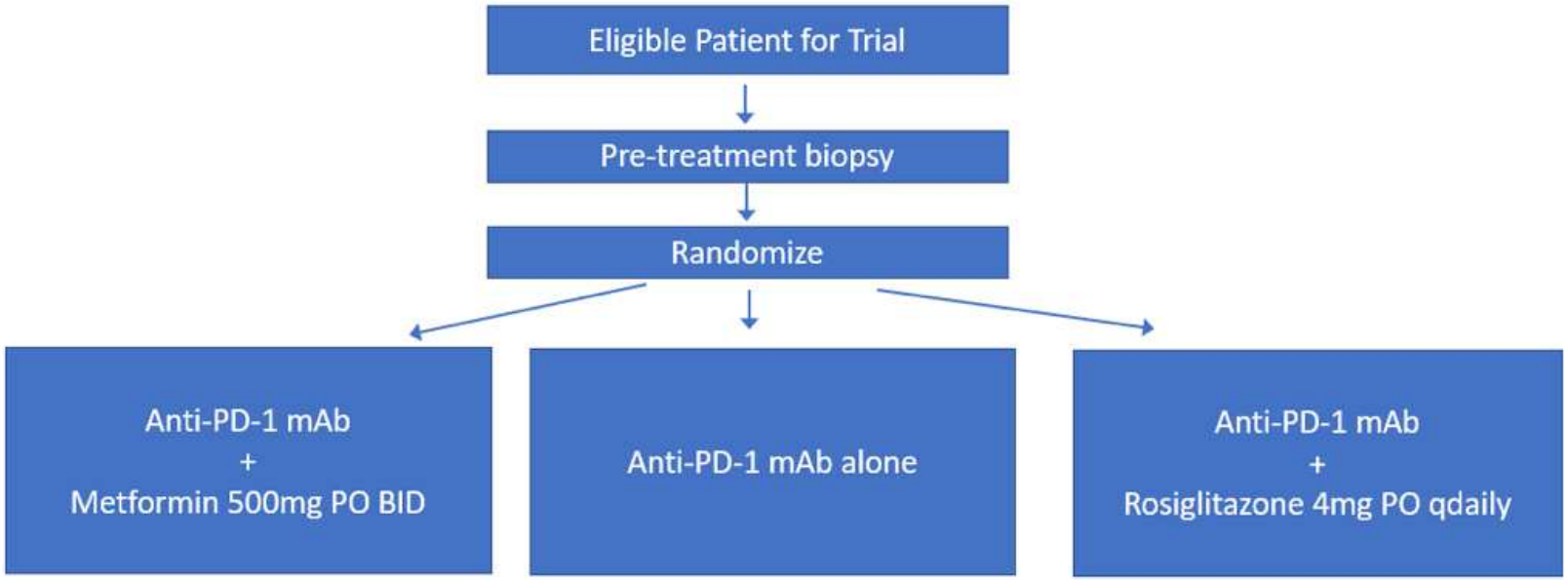
Basket trial example

- Phase 2 trial of metformin and rosiglitazone
  - Advanced melanoma
  - NSCLC
  - MSI-High solid tumors
  - GE junction/Gastric Adenocarcinoma
  - Renal cell carcinoma
  - HCC (Child Pugh Class A only)
  - Urothelial Cancer
  - HNSCC

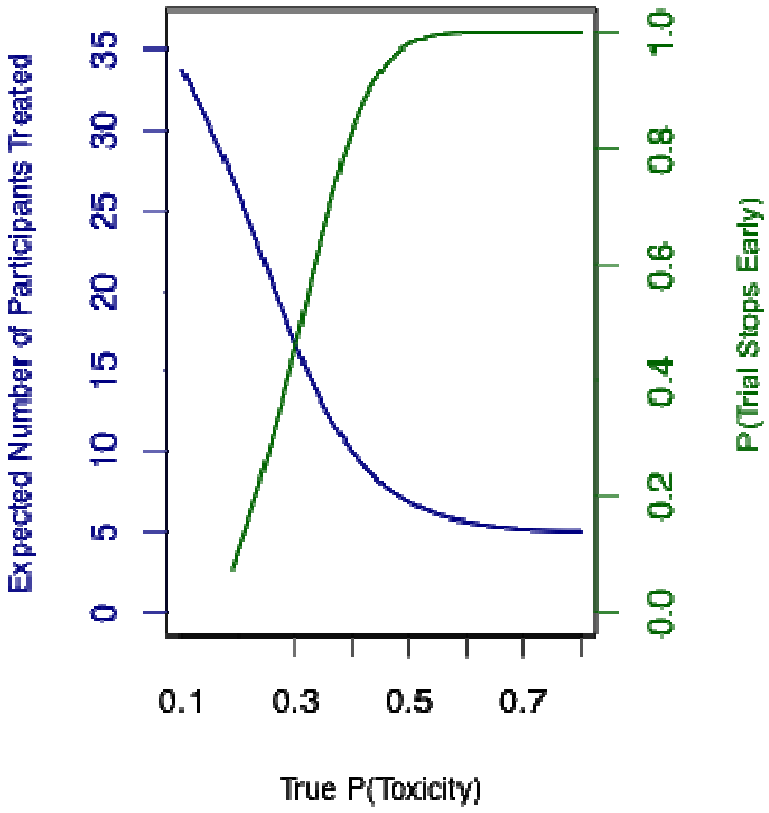


Basket trial example

- Rationale
  - Pembrolizumab or Nivolumab (in some diseases, both) are FDA-approved
  - Rosiglitazone and metformin will create a less hypoxic T-cell environment, restoring anti-tumor T cell effector function
  - Anti-PD1+metformin and anti-PD1+ rosiglitazone have been shown to be effective in pre-clinical models
  - Doses of metformin and rosiglitazone are below single agent dose
- Primary endpoint: best overall response
- Primary analysis: logistic regression on:
  - Treatment (control, metformin, rosiglitazone)
  - mAb (pembrolizumab or nivolumab)
  - Disease
  - Interactions

Basket trial example

- Sample size: 36/arm (n=108 total)
- Stratified randomization
- Stopping rule for excess toxicity evaluated every 5/participants/arm for criterion P(P(Unacceptable Toxicity)>0.3)>0.6 using beta-binomial rule
- Primary endpoint: best overall response
- Primary analysis: logistic regression on treatment, disease and their interaction.



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Model-based designs are flexible

- Bayesian models allow incorporation of information into decision making as trial progresses
- Decisions about early stopping and trial modification can be made without risks of multiple hypothesis testing
- Priors of Bayesian models allow use of data from prior studies
- Features of simple, approximate mathematical models can be combined to generate bespoke designs for complex environments
- Facilitate basket and umbrella trials

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