Optimal Seamless Phase 2/3 Oncology Trial Designs Based on Probability of Success (PoS)

Zhaoyang Teng[1], Liang Liang[2] , Guohui Liu[1], Yi Liu[3]

[1]Takeda Pharmaceuticals; [2]Harvard University; [3]Nektar Therapeutics

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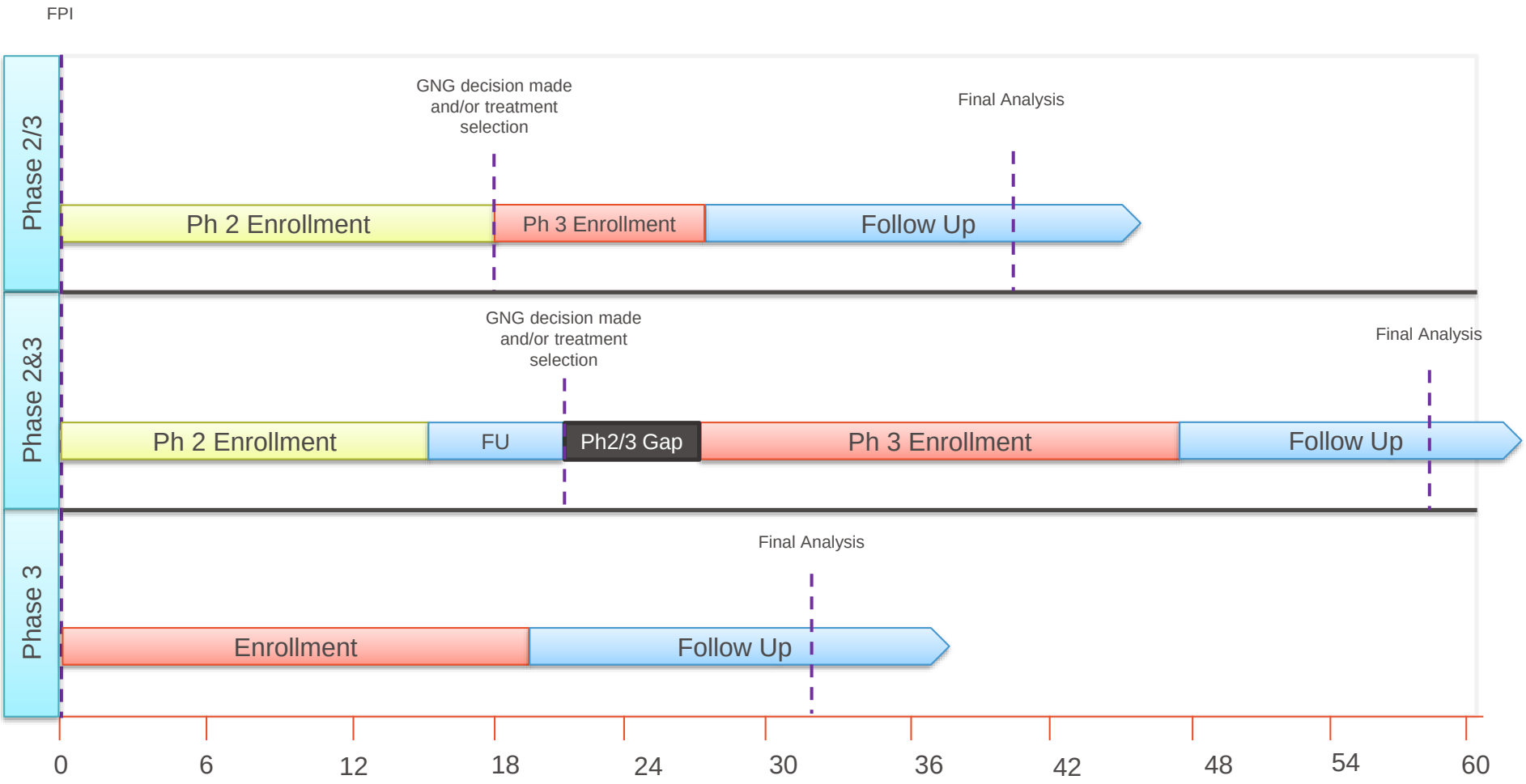
Introduction

- Seamless phase 2/3 clinical trials are conducted in two stages with Go/No-Go decision or/and treatment selection at the first stage and efficacy confirmation at the second stage.

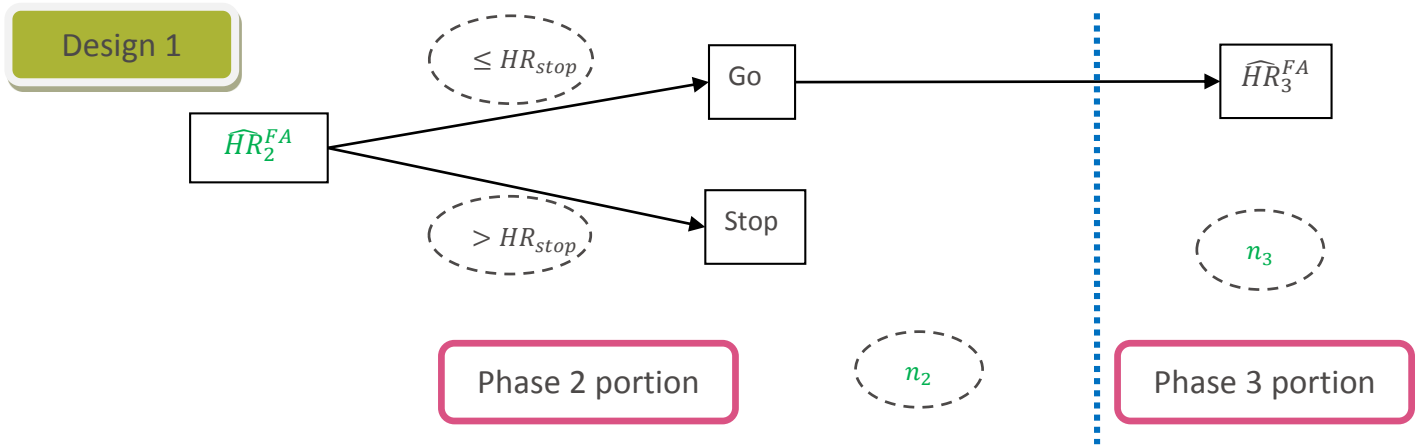
- Seamless phase 2/3 trials have a few advantages compared to the traditional approaches (phase 3 with 1 FA; phase 2 & 3).
  - Reduce the lead time between phase 2 and phase 3 studies. In practice, the lead time between phase 2 study and phase 3 study is about 6-12 months.
  - Mitigate risk of failed Phase 3 study with prespecified Go/No-Go criteria compared with traditional phase 3 design with only 1 final analysis.
  - Allow us to fully utilize data collected from both stages so that minimize study size because phase 2 patient data contribute to the phase 3 analysis by maintaining the same population and study design between phase 2 and phase 3.

Study Design Comparison:
Seamless Phase 2/3 vs. Phase 2 & 3 vs. Phase 3



Motivation

- For simplicity
  - Seamless phase 2/3 oncology trial with a single treatment vs. a control.
  - Go/No-GO decision after phase 2 portion is based on the same endpoint at the final analysis, e.g. Progression Free Survival (PFS)



- **Question: how to design a seamless phase 2/3 oncology trial : (n_2, HR_{stop}, n_3)**
  - How confident of making a right Go/No-Go decision?
  - What is the probability of success for the seamless phase 2/3 program?

Notations and Assumptions

- Proportional hazard: HR constant over time
- θ=-*log(HR)*: treatment effect.
- n_2, n_3: the number of events in phase 2 portion and phase 3 portion.
- $\hat{\theta}_2, \hat{\theta}_3$: estimates of θ obtained from the phase 2 portion and phase 3 portion.
  - 1:1 randomization between treatment and control
  - $\hat{\theta}_2 \sim N(\theta, 4/n_2)$, and $\hat{\theta}_3 \sim N(\theta, 4/n_3)$
- Number of events n_3 could be calculated based on log-rank test

$$n_3 = \frac{4(z_{1-\alpha/2} + z_{1-\beta})^2}{\theta^2}$$

  - α is the two-sided significance level, α=0.05
  - 1-β is the power

Methods

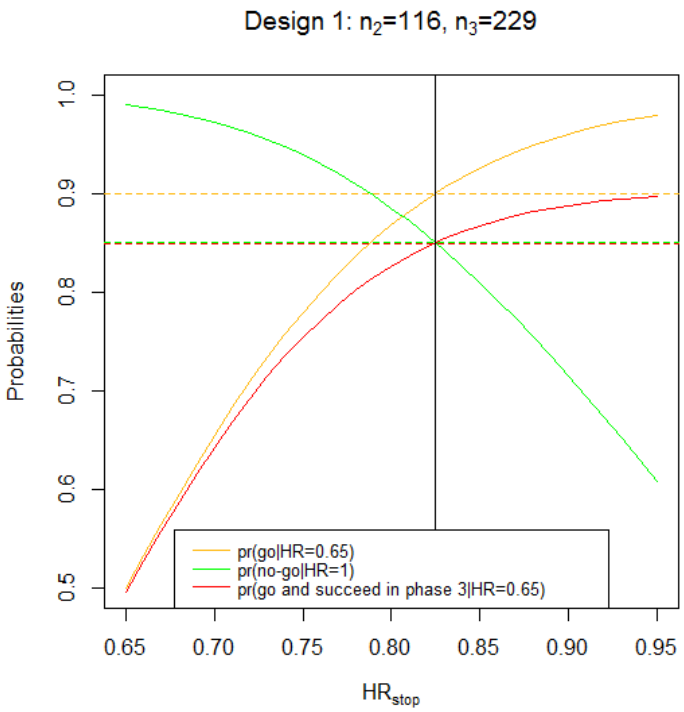
- **Goal:** design a seamless phase 2/3 oncology trial (n_2, HR_{stop}, n_3)
  - Certain confidence of making a right Go/No-Go decision
  - Ensure sufficient probability of success (Power) for the seamless phase 2/3 program

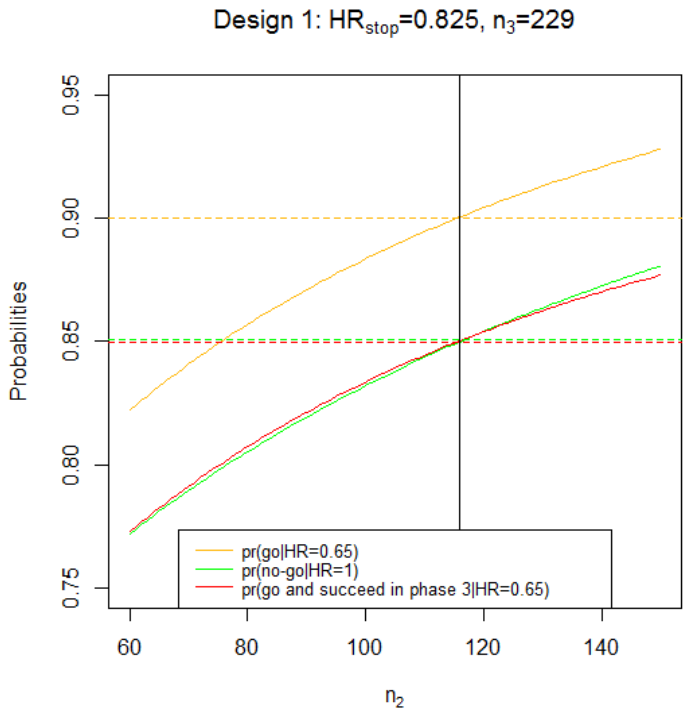
- Probabilities of Success (PoS) of Interest
  - given an **efficacious** treatment, e.g., HR_{eff} = 0.65
    - pr(go after phase 2 portion) $= pr(HR_2 \le HR_{stop} \mid HR_{eff})$
    - pr(go after phase 2 portion & successful phase 3) $= pr(HR_2 \le HR_{stop}, T_3 > z_{1-\alpha/2} \mid HR_{eff})$
  - given an **inefficacious** treatment, e.g., HR_{ineff} = 1
    - pr(no-go after phase 2 portion) $= pr(HR_2 > HR_{stop} \mid HR_{ineff})$

Seamless Phase 2/3 Study Design: Design 1

- Find the optimal combination of (n_2, HR_{stop}, n_3) which meet the following criteria
  - Treatment is **efficacious**, e.g., HR_{eff} = 0.65
    - pr(go after phase 2 portion) ≥ 90% (a)
    - pr(go after phase 2 portion &successful phase 3) ≥ 85% (b)
  - Treatment is **inefficacious,** e.g., HR_{ineff} = 1
    - pr(no-go after phase 2) ≥ 85% (c)
- Utility function:
  - Option 1: Earliest timing (n_2) for Go/No-Go decision making
  - Option 2: Average sample size (n_2, n_3)
- Two-step procedure to find $(n_2, HR_{stop}, n_3)^{\text{opt}}$ for option 1:
  - Step1: Find the combination $(n_2, HR_{stop})^{\text{opt}}$ with smallest n_2 based on (a) and (c) since both are not impacted by n_3
  - Step 2: Find the optimal/minimal $(n_3)^{\text{opt}}$ to meet (b) given the optimal combination $(n_2, HR_{stop})^{\text{opt}}$ identified from Step 1.

Design 1: Results





Design 1:

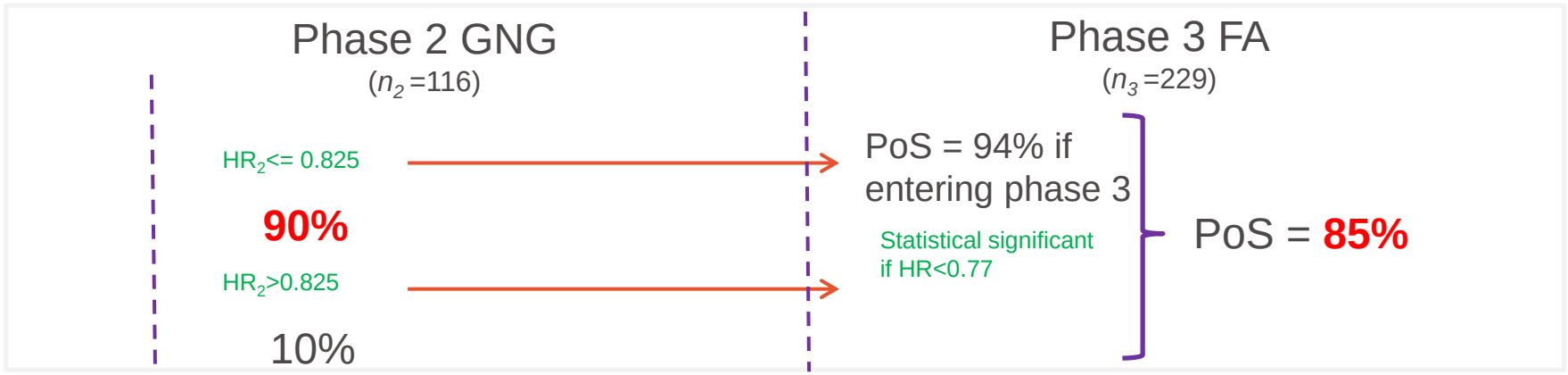
- n_2=116
- HR_{stop}=0.825
- n_3=229

PoS:

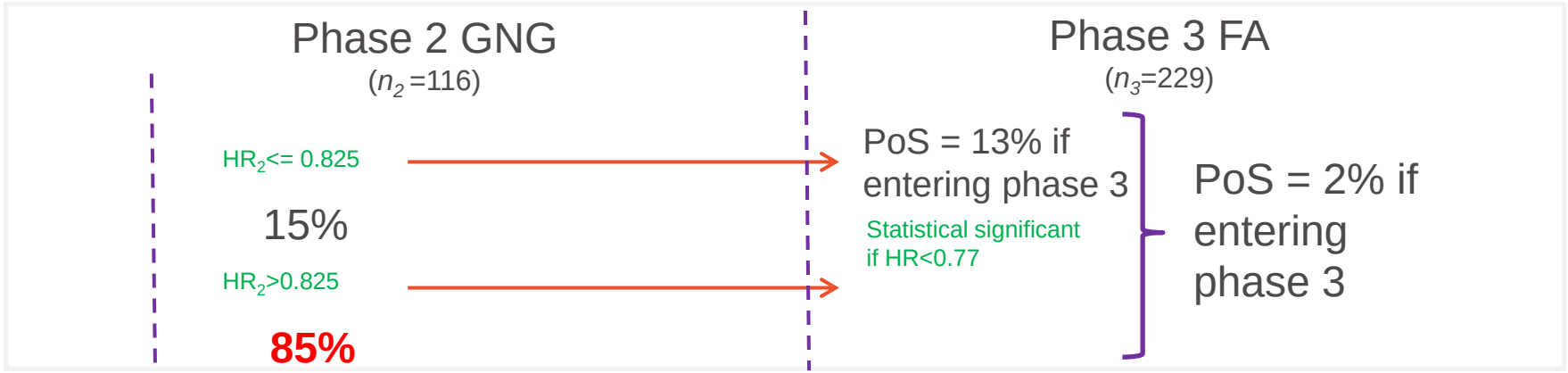
- pr(go|HR_{eff})=90%
- pr(go & success|HR_{eff})=85%
- pr(no-go|HR_{ineff})=85%

Design 1: Probability of Success (PoS)

Under HR_{eff}=0.65

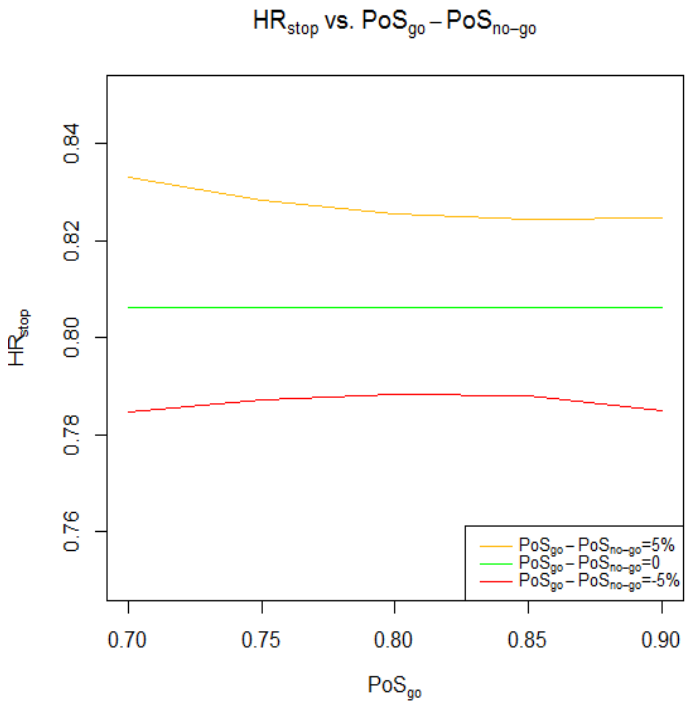


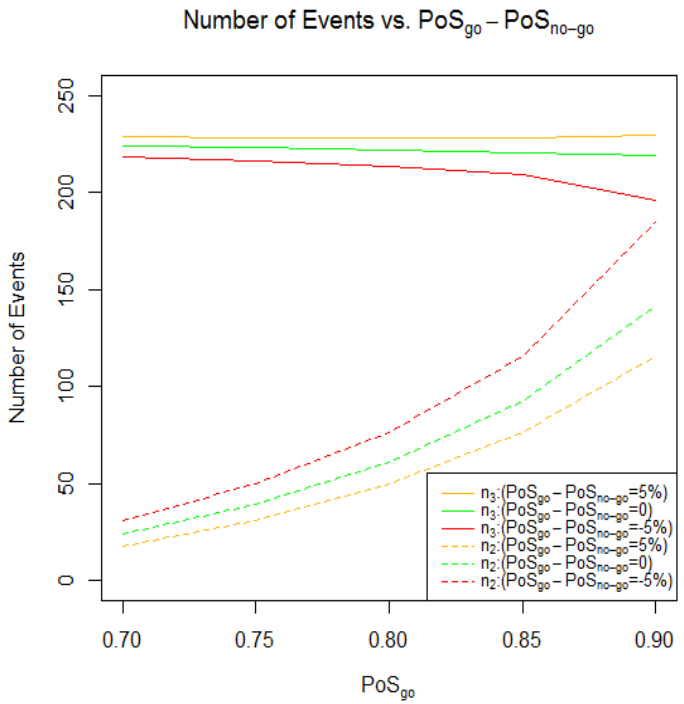
Under HR_{ineff}=1



Design 1: Operational Characteristics

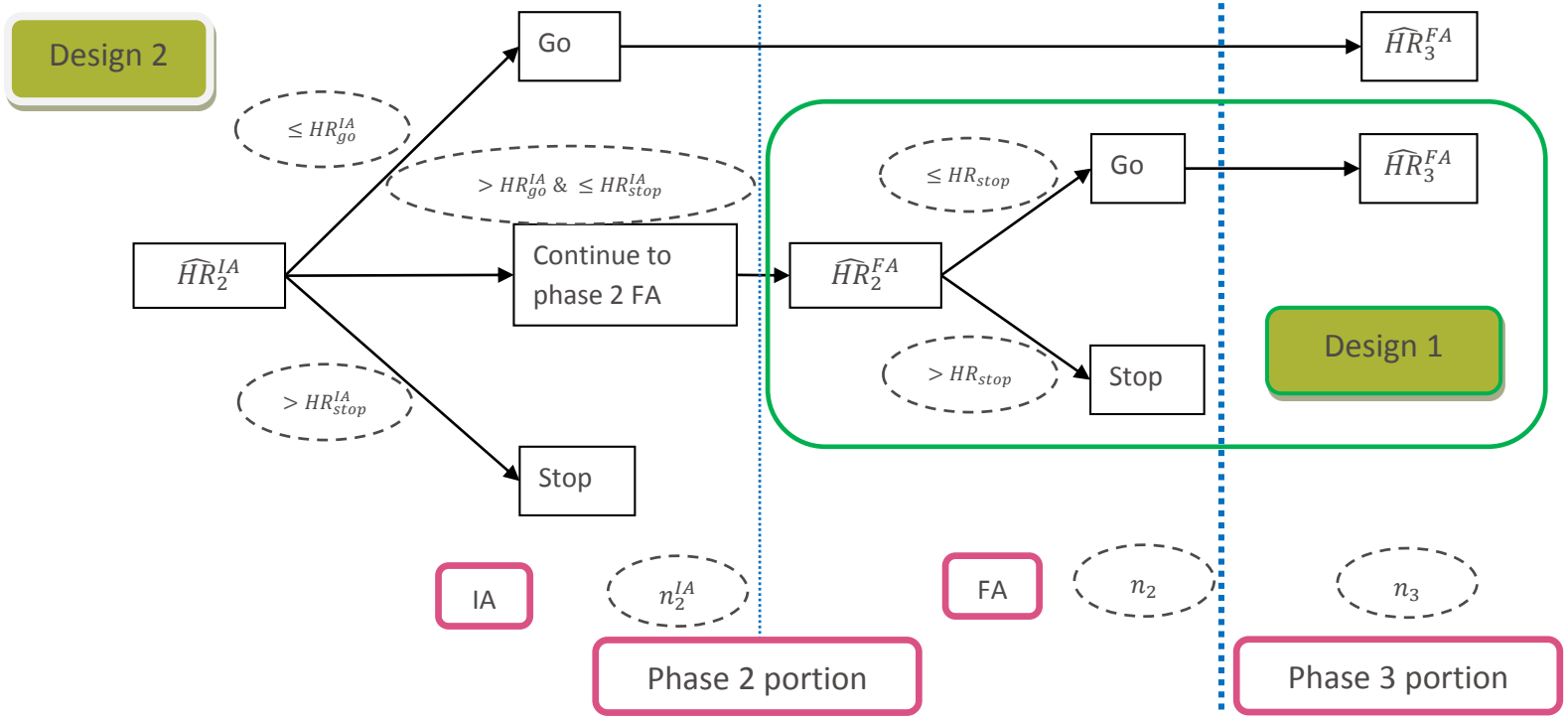
- HR_{stop} is mainly driven by the difference of PoS_{go} and PoS_{no-go}.
- n_2 is determined by the magnitude of PoS_{go} and PoS_{no-go}.
- n_3 is driven by (n_2, HR_{stop}) and the difference of PoS_{go} and PoS_{suc}.





Seamless Phase 2/3 Study Design: Design 2

- Usually, sponsor would like to make Go/No-Go decision as early as possible.
- Design 2: phase 2 portion with interim analysis to speed up the Go/No-Go decision making



Design 2: Probability of Success (PoS) with IA

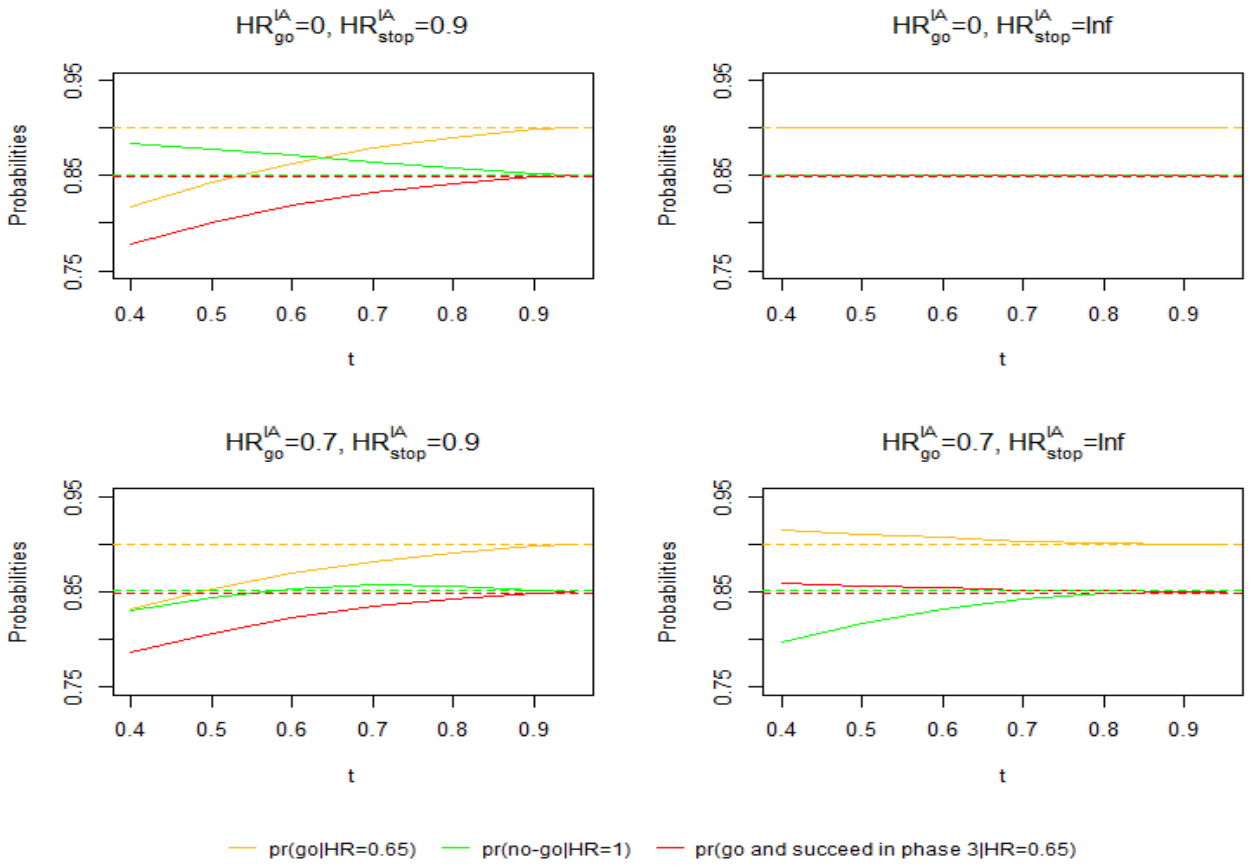
- Probabilities of success (PoS) with IA
  - given an efficacious treatment, e.g., HR_{eff} = 0.65
    - pr(go at either phase 2 IA or FA)
    - pr(go at either phase 2 IA or FA & successful phase 3)
    - pr(go at phase 2 IA)
  - given an inefficacious treatment, e.g., HR_{ineff} =1
    - pr(no-go at either phase 2 IA or FA)
    - pr(no-go at phase 2 IA)

- **Goal:** find the optimal combination $(n_2, HR_{stop}, n_3, n_2^{IA}, HR_{go}^{IA}, HR_{stop}^{IA})^{\text{opt}}$ which meet the following criteria
  - Treatment is **efficacious**, e.g., HR_{eff} = 0.65
    - pr(go at either phase 2 IA or FA) ≥ a
    - pr(go at either phase 2 IA or FA & successful phase 3) ≥ c
    - pr(go at phase 2 IA) ≥ d
  - Treatment is **inefficacious,** e.g., HR_{ineff} = 1
    - pr(no-go at either phase 2 IA or FA)≥ b
    - pr(no-go at phase 2 IA) ≥ e

Two Step Procedure for Design 2

- Find an optimal design is challenging: six parameters
  - go/no-go decision rule at phase 2 IA
  - go/no-go decision rule at phase 2 FA
  - phase 2 IA time
  - phase 2 number of events
  - Phase 3 number of events
- **Naive** two-step procedure
  - Step 1: find the optimal design under Design 1
    - n_2, HR_{stop}, n_3
  - Step 2: find the optimal IA time and go/no-go boundaries at IA given the optimal combination $(n_2, HRstop, n_3)^{\text{opt}}$ identified from Step 1.
    - $n_2^{IA}, HR_{go}^{IA}, HR_{stop}^{IA}$

Loss of PoS after adding IA at Phase 2



Design 1:

- pr(go)=90%
- pr(go & success)=85%
- pr(no-go)=85%

- There will be a certain extent of loss in PoS for at least one of three as long as go or/and no-go decision are allowed at phase 2 IA

Seamless Phase 2/3 Study Design: Design 2

- Three-step procedure for Design 2:
  - Step1: Find the optimal combination $(n_2, HR_{stop})^{\text{opt}}$ with smallest n_2 according to step 1 of Design 1 which meets the following criteria by assuming no interim analysis planned at phase 2 portion:

$$PoS'_{go} \geq a';\ PoS'_{no-go} \geq b'$$

    where $a' > a, b' > b$ are the inflated boundaries for each PoS. And $im_a = a' - a$ and $im_b = b' - b$ are defined as inflated margin.
  - Step2: Find combination $(n_2^{IA}, HR_{go}^{IA}, HR_{stop}^{IA})^{\text{opt}}$ with smallest n_2^{IA} which meets the following criterion with the optimal combination $(n_2, HR_{stop})^{\text{opt}}$ identified from Step 1.

$$PoS_{go} \geq a;\ PoS_{no-go} \geq b, PoS_{go}^{IA} \geq d, PoS_{no-go}^{IA} \geq e$$

  - Step 3: Find optimal/minimal $(n_3)^{\text{opt}}$ to meet the following criterion with the optimal combination $(n_2, HR_{stop}, n_2^{IA}, HR_{go}^{IA}, HR_{stop}^{IA})^{\text{opt}}$ identified from Step 1 and Step 2.

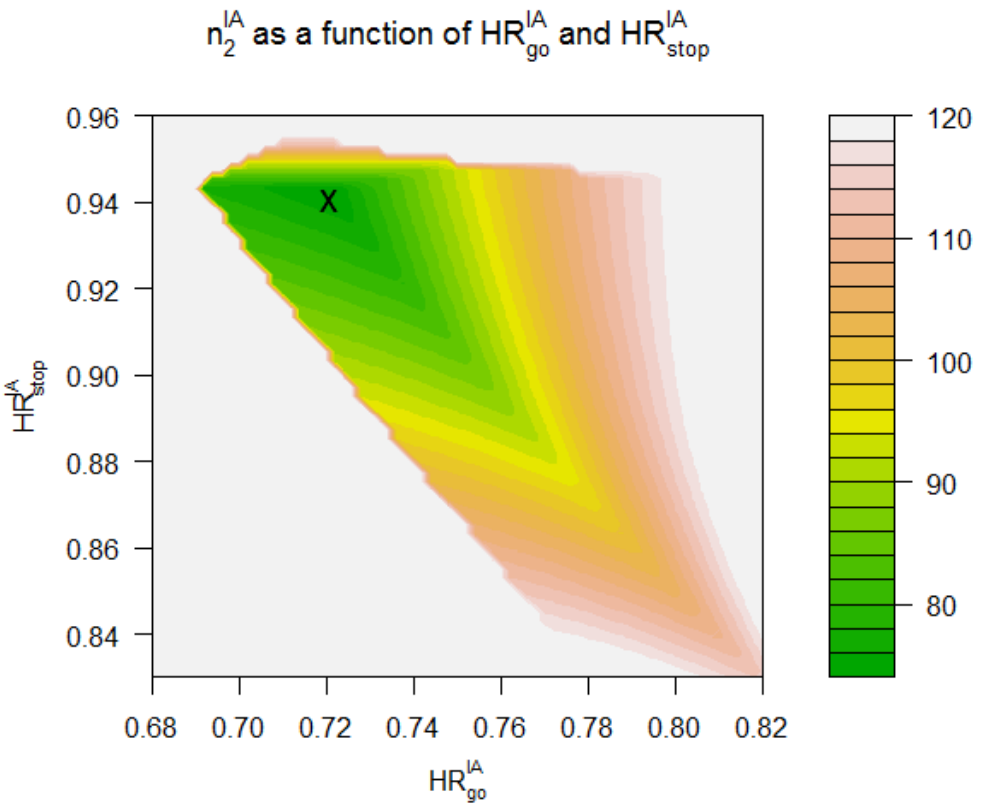
$$PoS_{suc} \geq c$$

Three-Step Procedure for Design 2

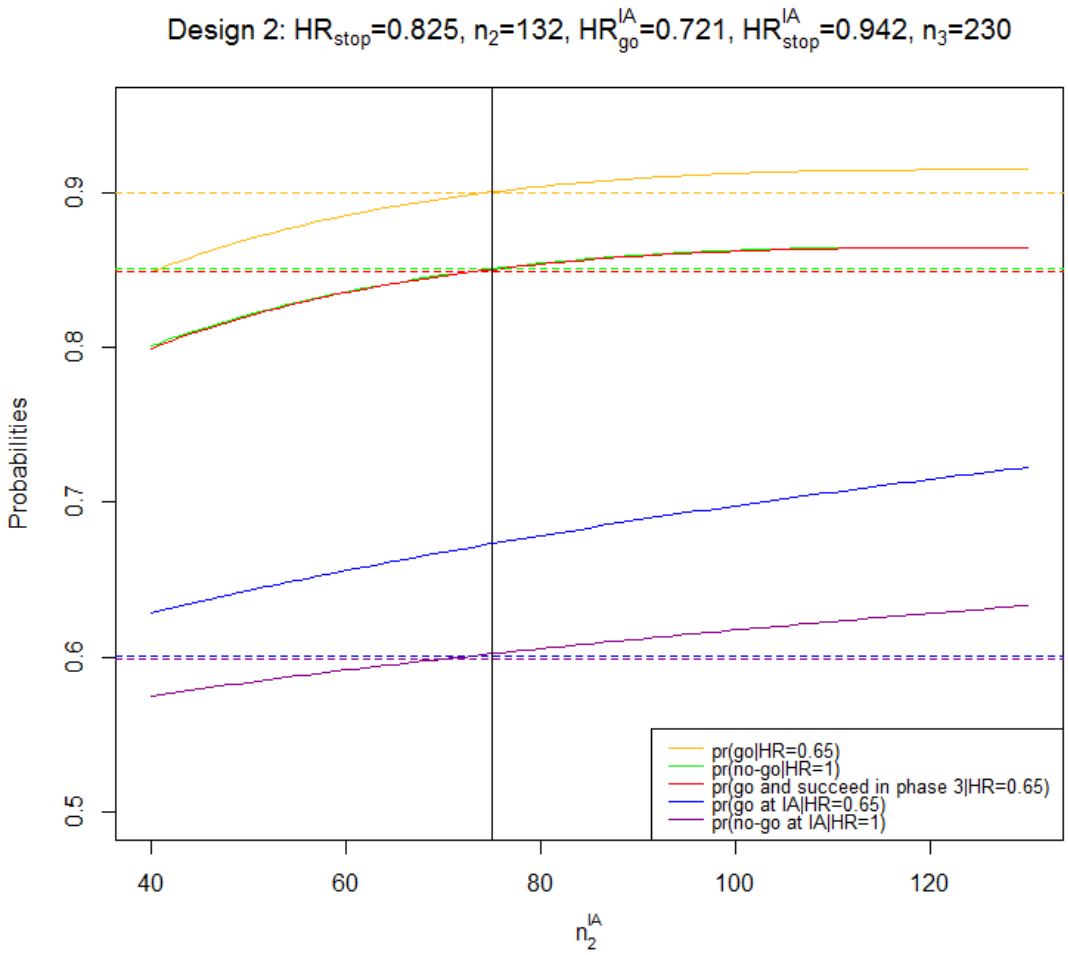
- PoS boundaries of Design 2 are selected as follows:
  $PoS_{go} \geq 90\%,\ PoS_{no-go} \geq 85\%,\ PoS_{suc} \geq 85\%, PoS_{go}^{IA} \geq 60\%, PoS_{no-go}^{IA} \geq 60\%$
- Three-Step Procedure with inflated margin of $im_a = im_b = 0.015$:
  - Step1: To achieve $PoS_{go} \geq 91.5\%, PoS_{no-go} \geq 86.5\%$ with smallest n_2, the optimal combination $(n_2, HR_{stop})^{\text{opt}} = (132,\ 0.825)$.
  - Step2: With the optimal combination $(n_2, HR_{stop})^{\text{opt}} = (132, 0.825)$ identified from step 1, the optimal combination $(n_2^{IA}, HR_{go}^{IA}, HR_{stop}^{IA})^{\text{opt}} = (75, 0.721, 0.942)$ which meets all following criteria and gives earliest phase 2 portion interim timing.
    $PoS_{go} \geq 90\%,\ PoS_{no-go} \geq 85\%, PoS_{go}^{IA} \geq 60\%, PoS_{no-go}^{IA} \geq 60\%$
  - Step 3: The optimal/minimal $(n_3)^{\text{opt}} = 230$ to meet the criterion of $PoS_{suc} \geq 85\%$ with the optimal combination $(n_2, HR_{stop}, n_2^{IA}, HR_{go}^{IA}, HR_{stop}^{IA})^{\text{opt}} = (132, 0.825, 75, 0.721, 0.942)$.
- Thus, the final optimal study design with an IA at phase 2 portion is $(n_2, n_3, HR_{stop}, n_2^{IA}, HR_{go}^{IA}, HR_{stop}^{IA})^{\text{opt}} = (132, 230, 0.825, 75, 0.721, 0.942)$.

Why $(n_2^{IA}, HR_{go}^{IA}, HR_{stop}^{IA})^{\text{opt}} = (75, 0.721, 0.942)$?

- Optimal phase 2 portion IA go/no-go boundaries, cross (x) in the figure represents the point of smallest n_2^{IA}

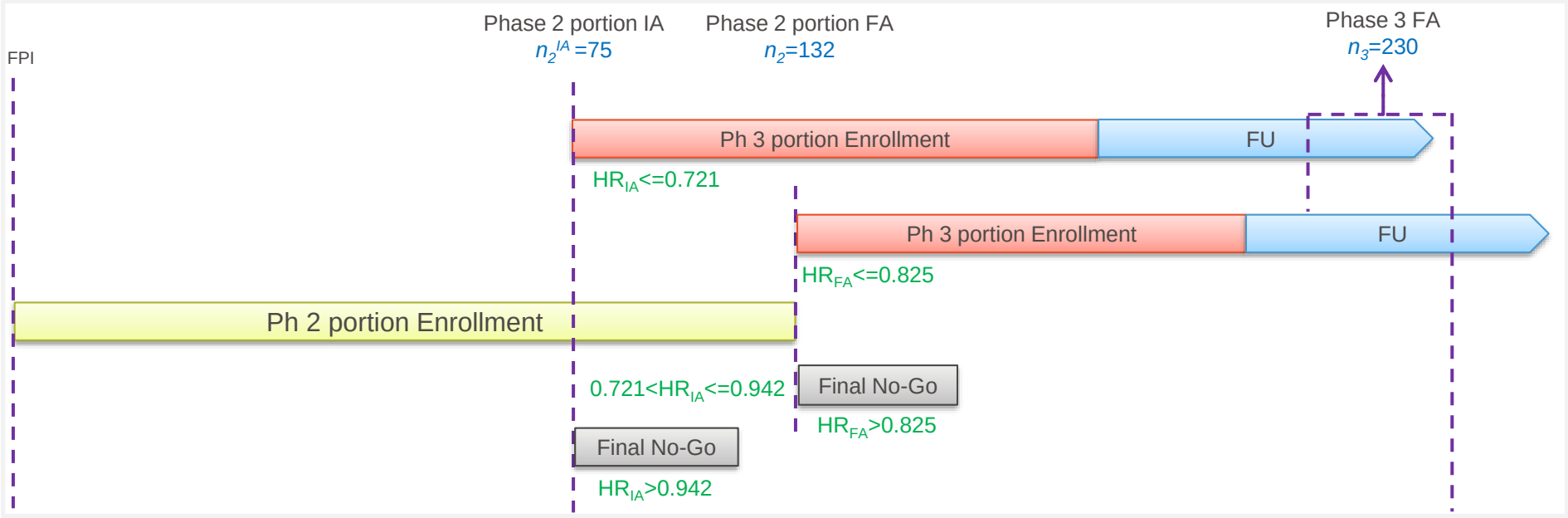


Design 2: PoS with Optimal Design

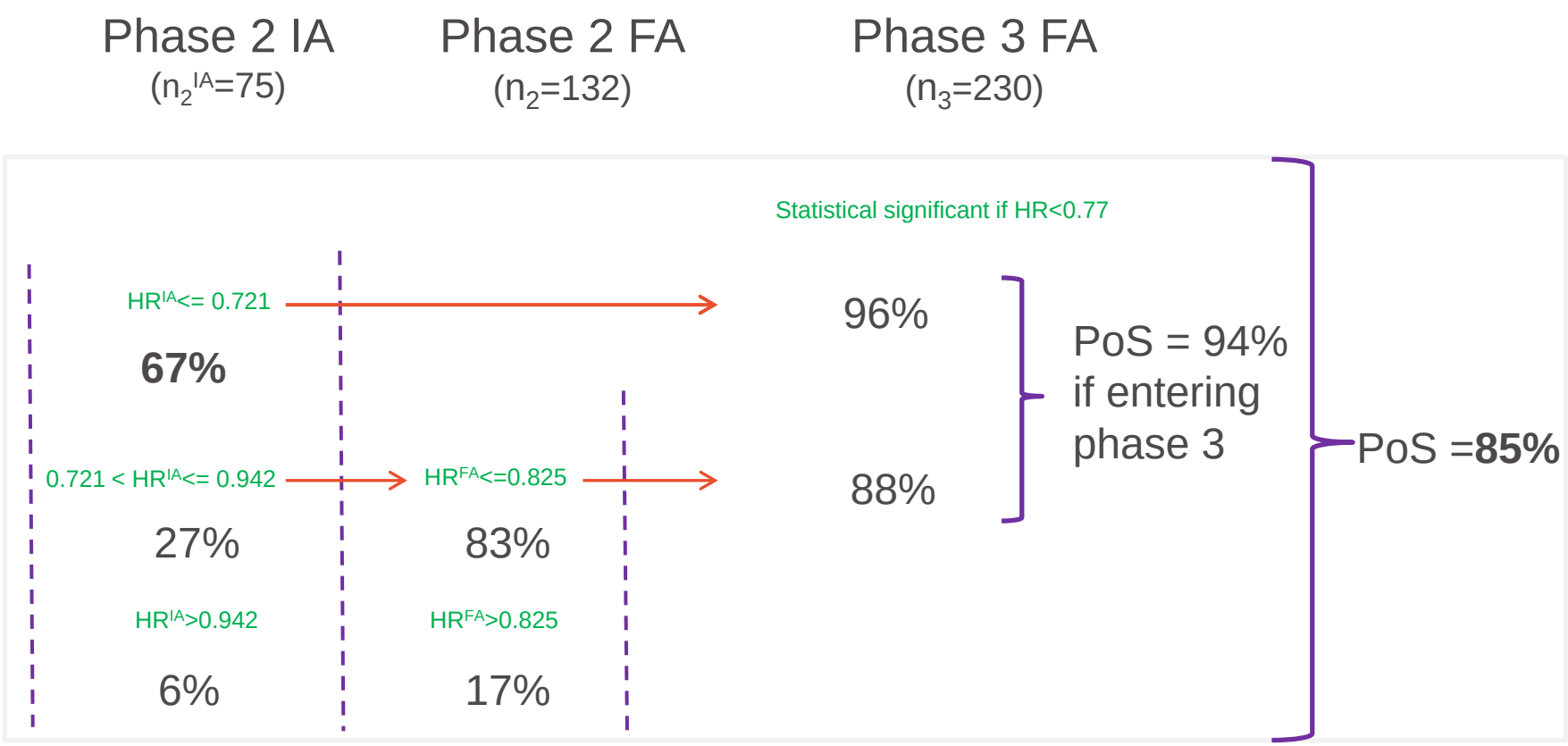


Seamless Phase 2/3 Study Design: Design 2

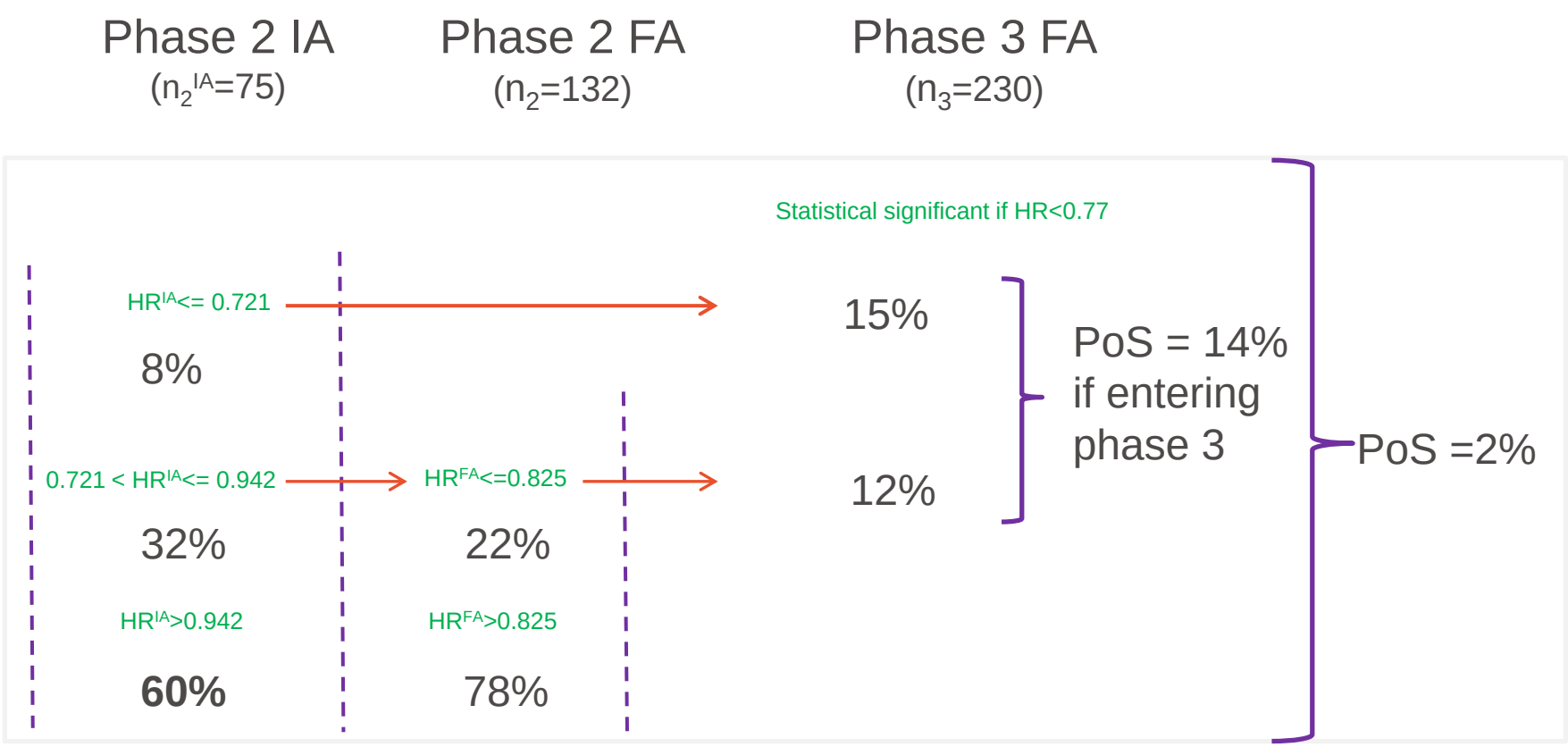
- Probability of Success(PoS):
  - pr(go at either phase 2 IA or FA | HR_{eff}) = 90%
  - pr(go at either phase 2 IA or FA & successful phase 3 | HR_{eff}) = 85%
  - pr(no-go at either phase 2 IA or FA | HR_{ineff}) = 85%
  - pr(go at phase 2 IA | HR_{eff}) = 67%
  - pr(no-go at phase 2 IA | HR_{ineff}) = 60%



Design 2: Probability of Success with true HR_{eff}=0.65



Design 2: Probability of Success with true $HR_{ineff}=1$



Design 2: How to Select Inflated Margin?

Scenario	PoS Boundaries			Optimal Study Design					
	Inflated margin	PoS'_{go}	PoS'_{no-go}	n_2	HR_{stop}	n_2^{IA}	HR_{go}^{IA}	HR_{stop}^{IA}	n_3
1 (Design 1)	0	0.85	0.90	**116**	0.825				229
2	0.005	0.855	0.905	**121**	0.825	**85**	0.718	0.946	230
3	0.01	0.86	0.91	**127**	0.825	**79**	0.720	0.944	230
4	0.015	0.865	0.915	**132**	0.825	**75**	0.721	0.942	230
5	0.02	0.87	0.92	**138**	0.826	**72**	0.722	0.941	230
6	0.025	0.875	0.925	**145**	0.826	**69**	0.723	0.940	230
7	0.03	0.88	0.93	**152**	0.826	**67**	0.724	0.939	230

- Trade-off between n_2 and n_2^{IA}: smaller n_2 leading to larger n_2^{IA}, and vice versa.
- Recommend the design with the ratio of n_2^{IA} to n_2 between 0.5 and 0.7 which usually can avoid the cases of too small n_2^{IA} and/or too large n_2.

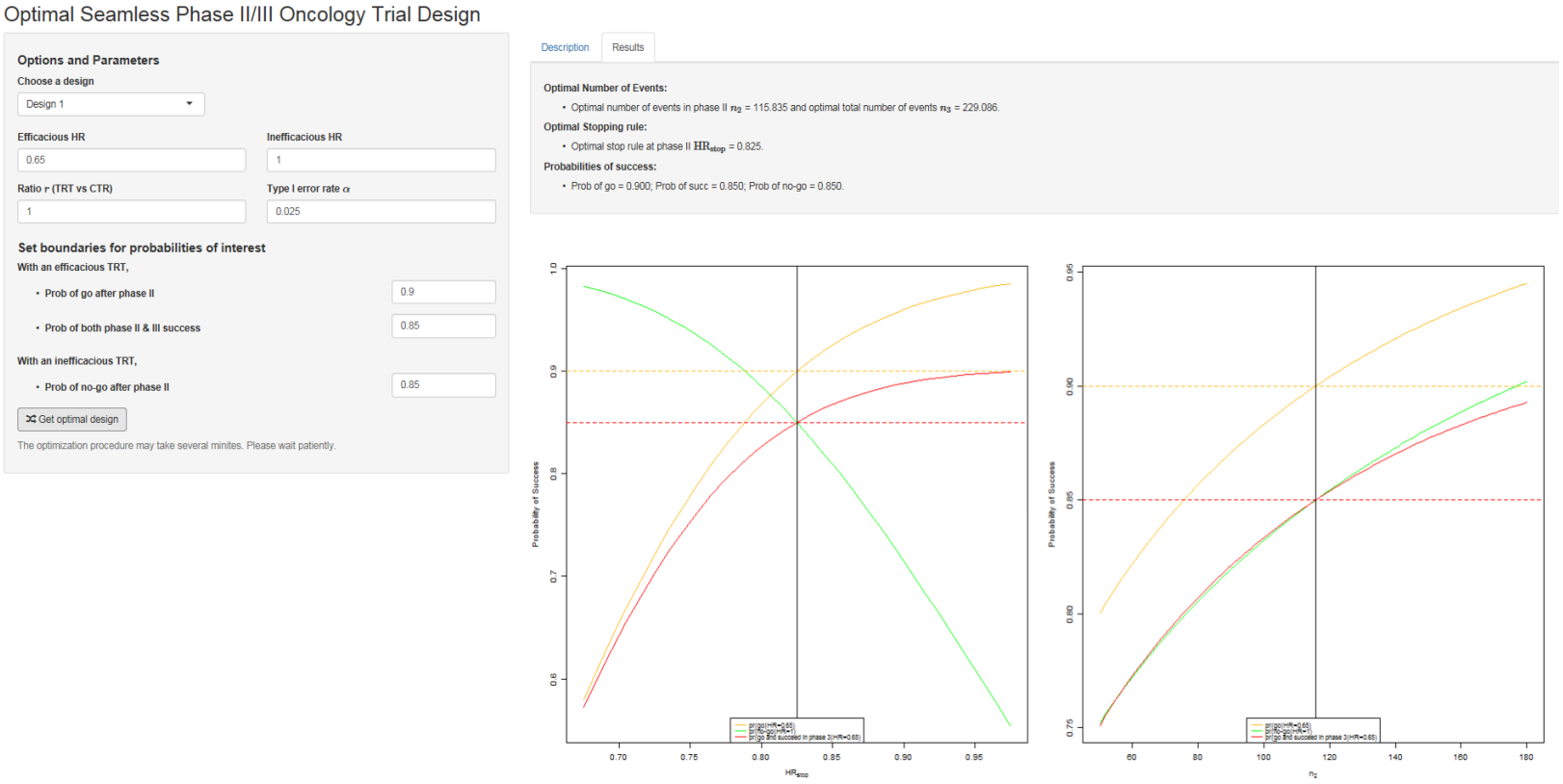
Comparison of Design 1 and Design 2

Scenario	PoS under Optimal Study Designs					Average Number of Events			
	PoS_{go}	PoS_{no-go}	PoS_{go}^{IA}	PoS_{no-go}^{IA}	PoS_{suc}	$\bar{n}_{2eff}$	$\bar{n}_{2ineff}$	$\bar{n}_{2/3eff}$	$\bar{n}_{2/3ineff}$
1 (Design 1)	0.90	0.85	**0**	**0**	0.85	116	116	218	133
2	0.90	0.85	**0.68**	**0.60**	0.85	95	97	217	116
3	0.90	0.85	**0.68**	**0.60**	0.85	92	95	217	113
4	0.90	0.85	**0.67**	**0.60**	0.85	91	93	216	112
5	0.90	0.85	**0.67**	**0.60**	0.85	90	93	216	112
6	0.90	0.85	**0.67**	**0.60**	0.85	89	92	216	112
7	0.90	0.85	**0.67**	**0.60**	0.85	89	93	216	112

- Smaller number of events is needed to make go/no-go decision in Design 2.
- Smaller number of events for phase 2/3 program under inefficacious treatment effect is needed in Design 2.
- Number of events for phase 2/3 program under efficacious treatment effect are comparable between Design 1 and Design 2.

R Shiny App

- Design a seamless phase 2/3 oncology trail using the user friendly Shiny App we developed.



Practical Considerations on Implementation of Seamless Phase 2/3 Oncology Trial

- What is the difference between seamless phase 2/3 oncology trial and group sequential oncology trial with futility analysis?
  - Enrolment is usually completed at the futility analysis for group sequential oncology trial, but not recommended for seamless phase 2/3 trial.
  - Have chance to claim efficacy at the “futility” analysis as well for group sequential oncology trial, but not the intention of phase 2 portion of seamless phase 2/3 oncology trial.

- Consideration on enrollment
  - Challenge: enrollment completed before accumulating target number of evens for go/no-go decision making.
  - Solutions:
    - 1. Control the enrollment rate of phase 2 portion (slow) and phase 3 portion
    - 2. Set a cap for number of patients for phase 2 portion
    - 3. Enrollment pause at either IA or FA of phase 2 portion
  - More patients are needed if OS benefit is important in addition to PFS
    - Slowing down enrollment rate at phase 2 portion can effectively prevent exposing large number of patients (for OS) to investigational treatment before the efficacy is proven.

Conclusion

- The proposed method provides an informative way to design seamless phase 2/3 oncology trials using PoS
  - Calculation of phase 2 and phase 3 sample size.
  - Determination of GNG boundaries.
- Interim analysis could be considered to add on phase 2 portion to speed up the GNG decision making process.
  - Smaller N to make go/no-go decision.
  - Smaller N for phase 2/3 program under inefficacious treatment effect; comparable under efficacious treatment effect between Design 1 and 2.
- With proposed study design (Design 1, Design 2), we are clear on
  - How confident of making a right Go/No-Go decision.
  - What is the probability of success for the seamless phase 2/3 program.
- Implement proposed study design using R Shiny App.

Key Reference

- **Teng Z**, Liang L, Liu G, Liu Y. *Optimal Seamless Phase 2/3 Oncology Trial Designs Based on Probability of Success (PoS).* Stat in Med. Aug 2018.

Thank you!