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Bayesian Interim Monitoring for Faster Decision-Making in Early Oncology Trials

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Disclosure

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- Chang-Heok Soh and Victoria Chang are employees of AbbVie Inc.

Agenda of Presentation

- Interim analysis (IA) in Phase 1-2 oncology studies
- Decision-making at IA based on predictive probability of success
  - Is there sufficient confidence at IA in the outcome at final analysis to make decision early (though may still continue trial)?
  - Focus today: Phase 1 expansion cohorts or Phase 2 single-arm trials with binary efficacy endpoint (eg ORR, CBR)
  - Method extends to other endpoints and randomized trials
- Operating characteristics via simulations

Interim Analysis of Efficacy in Clinical Trials

- Efficacy IA is any analysis intended to evaluate efficacy prior to formal completion of a trial
- Some motivations for IA:
  - Ethical imperative to avoid treating patients with ineffective or inferior therapies
  - Efficient allocation of resources
  - Faster decision-making for drug development

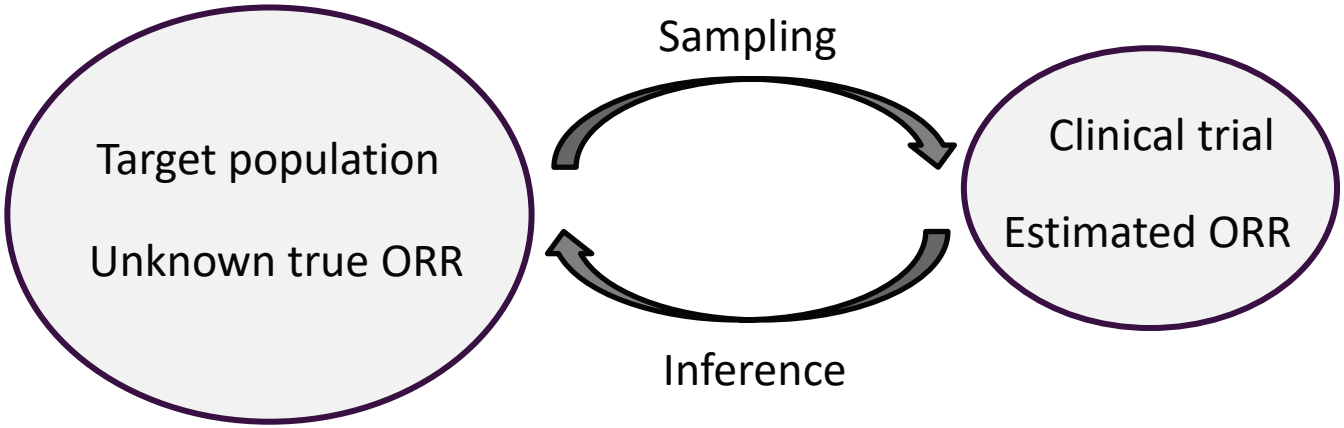
Interim Analysis of Efficacy in Phase 1-2 Oncology Studies

- May want to continue study in case of initial weak efficacy signals (unless unethical to continue)
  - Fuller understanding of drug's effect may require info on patient population, PK/PD, biomarkers, safety, etc, especially in signal-seeking Ph 1
  - Initial weak efficacy signals may lead to potentially enriched populations or other protocol changes

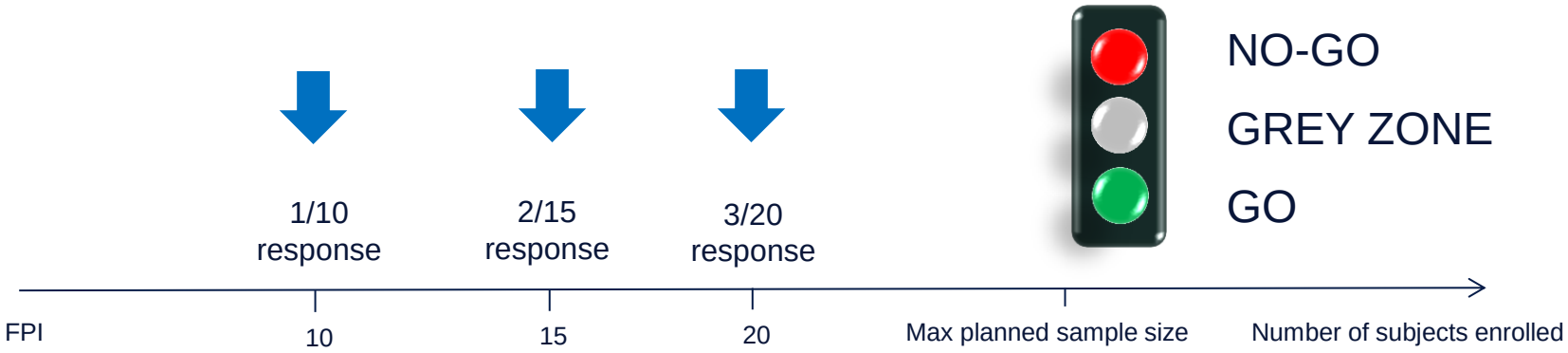
Interim Analysis of Efficacy in Phase 1-2 Oncology Studies

- Typically want to continue the trial even if early data drives early GO decision:
  - Collect more info on safety data, dosing schedules, biomarkers and efficacy
  - Identify appropriate populations
  - Data to inform possibility for treatment combination
- But early evidence of efficacy could accelerate development, e.g.
  - Start additional expansion arms, extend current study into Phase 1/2, or initiate planning of additional trial at-risk
  - Trigger decision to increase manufacturing spending

Decision-Making at Interim Analyses



Earlier and/or real-time monitoring



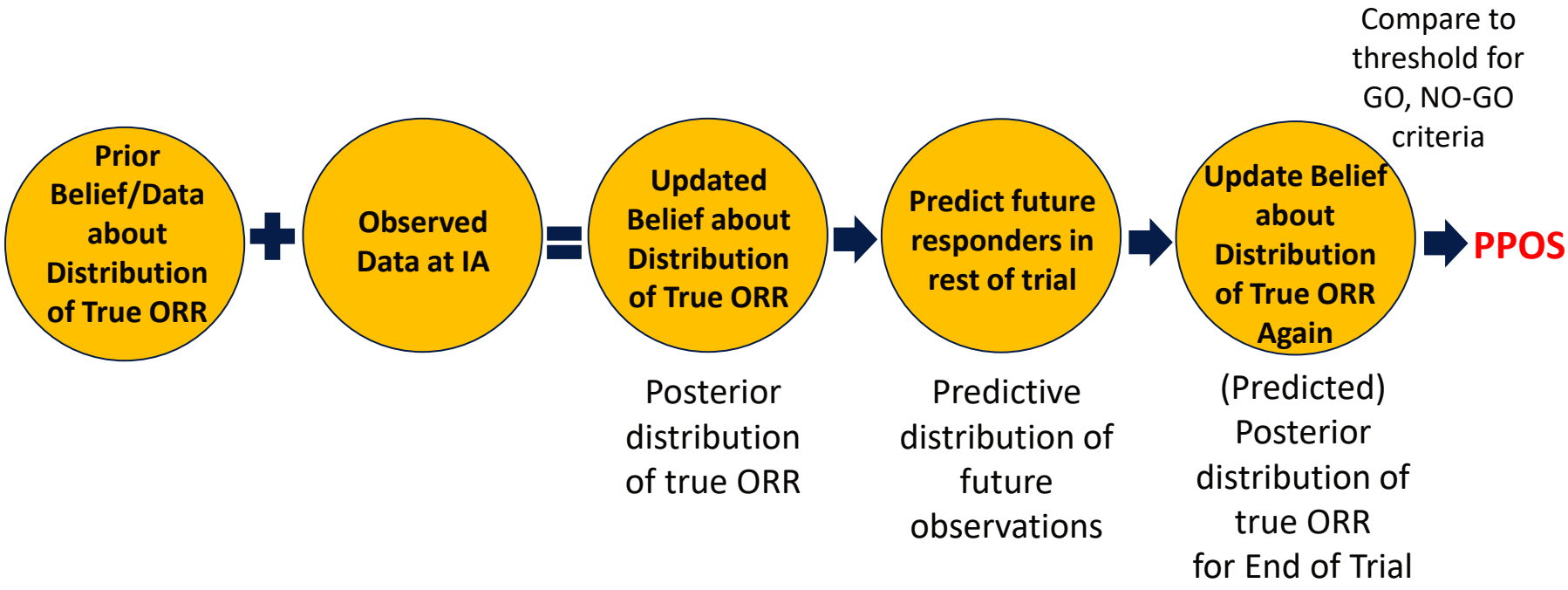
Interim Analyses: Is the trial very likely to show evidence supporting entering NO-GO, grey or GO zone at the end of the trial?

Bayesian Interim Analyses (IA) for Faster Decision-Making

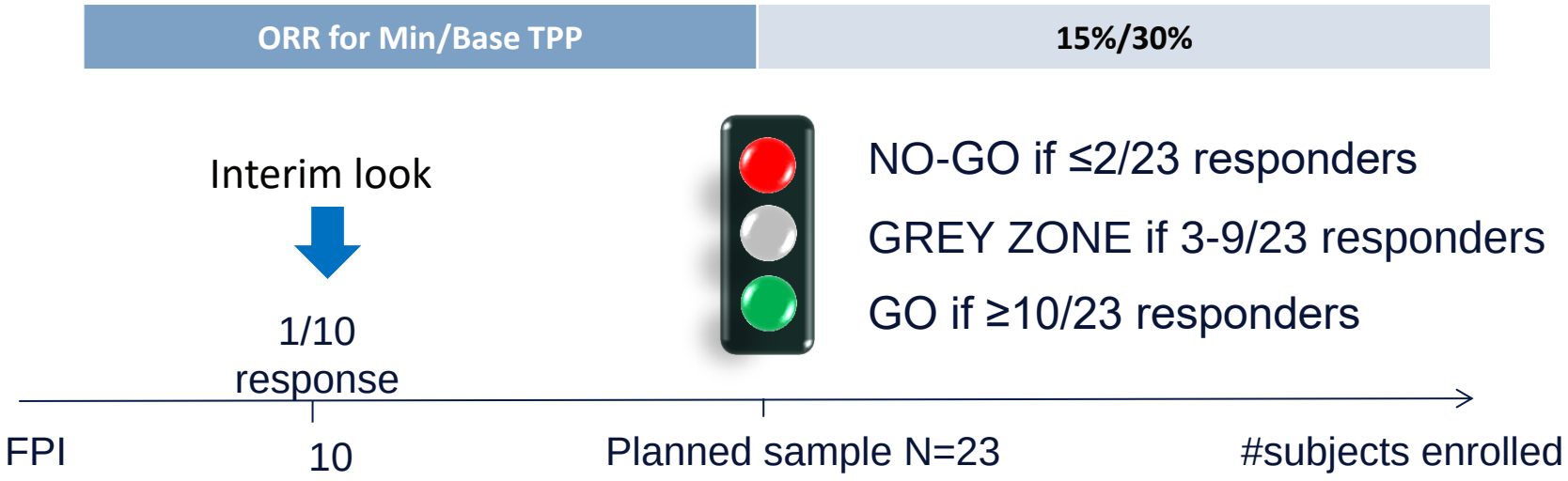
- Decision-making at IA based on predictive probability of success
  - Is there sufficient confidence at IA in the outcome at final analysis to make decision early (though may still continue trial)?
- Bayesian approach:
  - Allows flexibility in IA timing and uses data to-date for decision-making
  - Allows continuous monitoring of efficacy signals
  - Enables faster decision-making for drug development

Decision-Making at IA Using **Predictive Probability of Success** (**PPOS**)

- Definition: The probability of achieving a successful result at a future analysis, given current interim data
- Based on Bayesian framework and can incorporate prior belief or historical information



Hypothetical Example:



- 13 more patients for rest of Ph 1, need 2 more responders to enter grey zone, 9 more responders for GO-zone

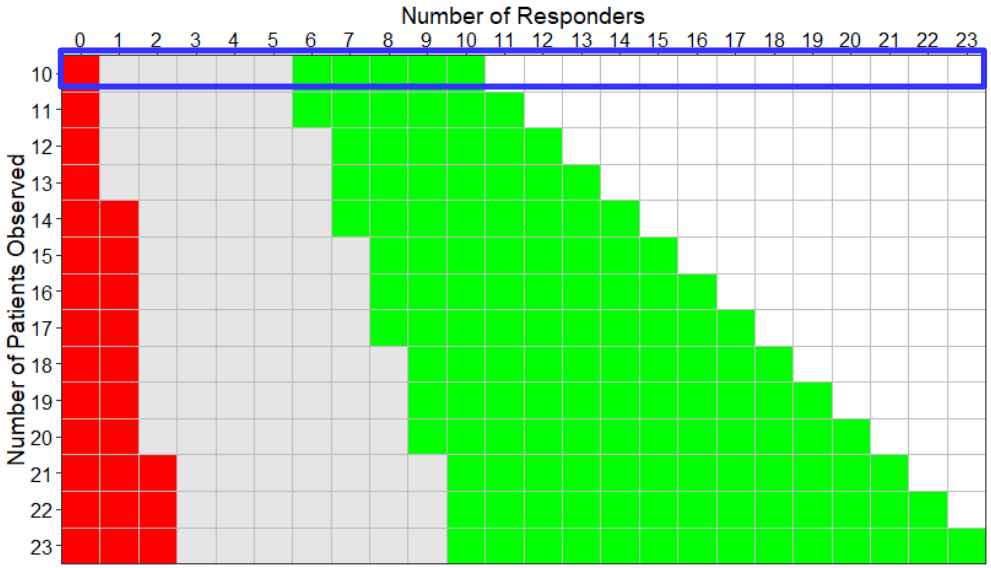
- **Based on current data and predicted future data**
  - Predictive prob that final decision is GO=Pr(≥9 responses in 13 more pts) =**0.1%**
  - Predictive prob that final decision is NO-GO=Pr (0-1 response in 13 more pts) **=63%**
  - Predictive prob that final decision is GREY =**37%**

- Should we make early GO or early NO-GO decision?

Hypothetical Example:

- If team specifies confidence thresholds for early No-GO and early GO, e.g.
  - Early NO-GO if predictive prob/confidence that final outcome is NO-GO ≥ 80%
    (the higher the bar, the harder to trigger early NO-GO)
  - Early GO if predictive prob/confidence that final outcome is GO ≥ 80%
    (the higher the bar, the harder to trigger early GO)

Observed ORR	Predictive prob for NO-GO (%)	Predictive prob for GO (%)
0/10	98	0.001
1/10	63	0.1
2/10	15	2
3/10	0	13
4/10	0	40
5/10	0	73
6/10	0	93
≥7/10	0	>99



Operating Characteristics
Hypothetical Phase 1

Design assumptions for simulations:

- Planned sample size of 23
- Min / Base TPP = 15% / 30%
- IA at n=10, 15 or continue to 23
- At end of Ph 1
  - NO-GO if Pr (true ORR < min TPP given final data) > 80%
  - GO if Pr (true ORR ≥ base TPP given final data) ≥ 80%
- At any IA,
  - Early NO-GO if predictive prob/confidence in final outcome being NO-GO given IA data > 80%
  - Early GO if predictive prob/confidence in final outcome being GO given IA data > 80%

Operating Characteristics
Hypothetical Phase 1

	At max sample size (n=23)			With IA at n=10, 15				% Concordance between IA and final analysis
True ORR	% Final decision is NO-GO	% Final decision is GREY	% Final decision is GO	Avg N	% Early Decision	% Early decision is early NO-GO	% Early decision is early GO	
10%	59.2	40.8	<0.01	16.6	57.9	57.8	<0.01	80.6
15%	30.9	69.0	0.1	19.2	35.5	35.3	0.2	81.4
20%	13.3	85.9	0.8	20.8	20.6	19.7	0.9	85.7
30%	1.5	86.3	12.2	21.7	11.9	4.8	7.1	86.4

Considerations for Implementation

- Real-time monitoring requires good real-time data cleaning and efficient operational coordination with sites to get the data in-house
- Operating characteristics should be assessed under different assumptions as part of design evaluation

THANK YOU