FDA-AACR Public Workshop On
OPTIMIZING DOSAGES FOR ONCOLOGY DRUG PRODUCTS: QUANTITATIVE APPROACHES TO SELECT DOSAGES FOR CLINICAL TRIALS
February 15 and 16, 2024 I Washington, DC

Introduction to Seamless Trial Design

Geoff Oxnard, MD
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Disclosure Information

Geoff Oxnard, MD

I have the following relevant financial relationships to disclose:

Employee of: Eli Lilly and Company

Stockholder in: Eli Lilly and Company, Roche

Disclaimer:

- The efficacy and safety of the investigational compound/uses discussed have not been established
- There is no guarantee the investigational compounds discussed will become commercially available for the uses under investigation
- These slides may contain information that has not been FDA approved

Seamless Trial Design

REVIEW

JNCI J Natl Cancer Inst (2019) 111(2): djy196

Seamless Designs: Current Practice and Considerations for Early-Phase Drug Development in Oncology

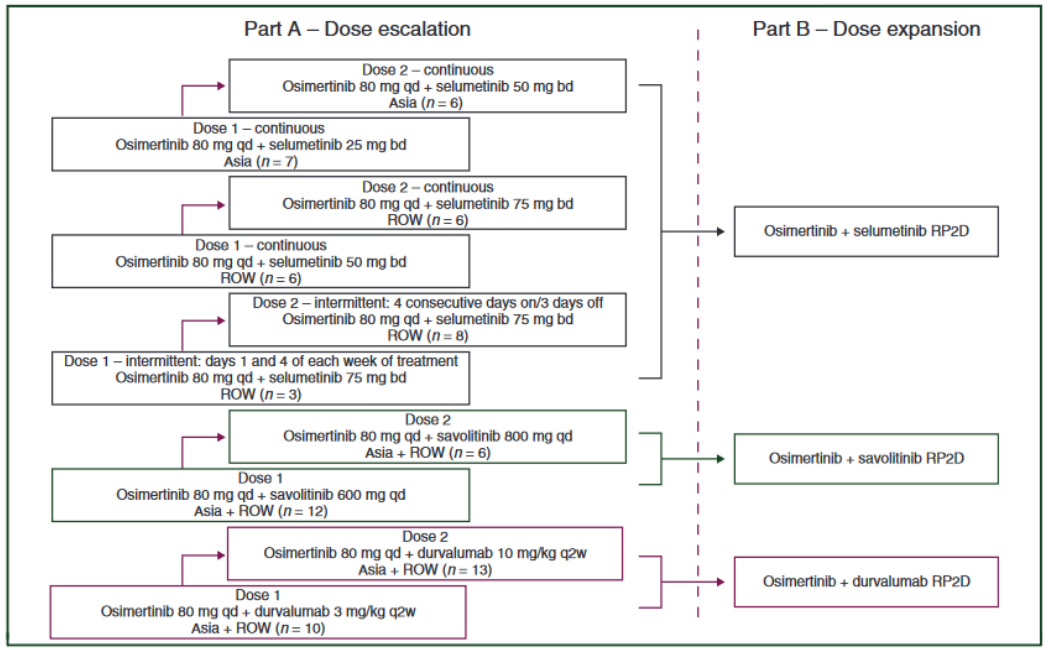
Brian P. Hobbs, Pedro C. Barata, Yada Kanjanapan, Channing J. Paller, Jane Perlmutter, Gregory R. Pond, Tatiana M. Prowell, Eric H. Rubin, Lesley K. Seymour, Nolan A. Wages, Timothy A. Yap, David Feltquate, Elizabeth Garrett-Mayer, William Grossman, David S. Hong, S. Percy Ivy, Lillian L. Siu, Steven A. Reeves, Gary L. Rosner

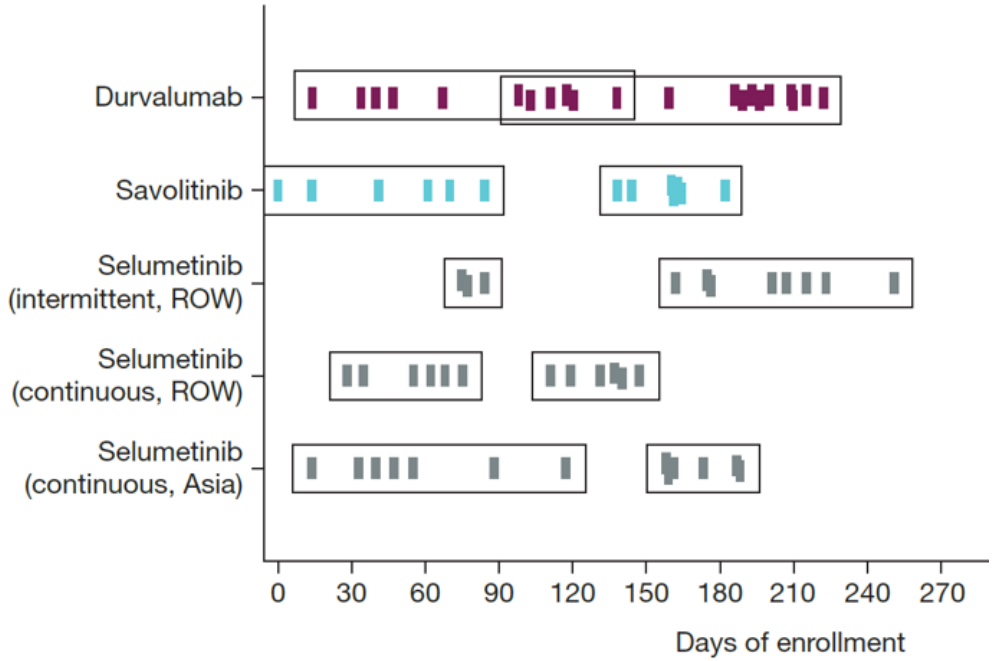
- "attempting to consolidate clinical phases of drug development into a single, repeatedly amended FiH protocol"
- Seamlessness can reduce enrollment pauses and increase patient access, but require intentional design considerations

Hobbs et al, JNCI, 2019

Platform phase I/II design

- TATTON trial: Osimertinib combinations in EGFR-mutant NSCLC
  - Seamless enrollment across multiple dose finding cohorts

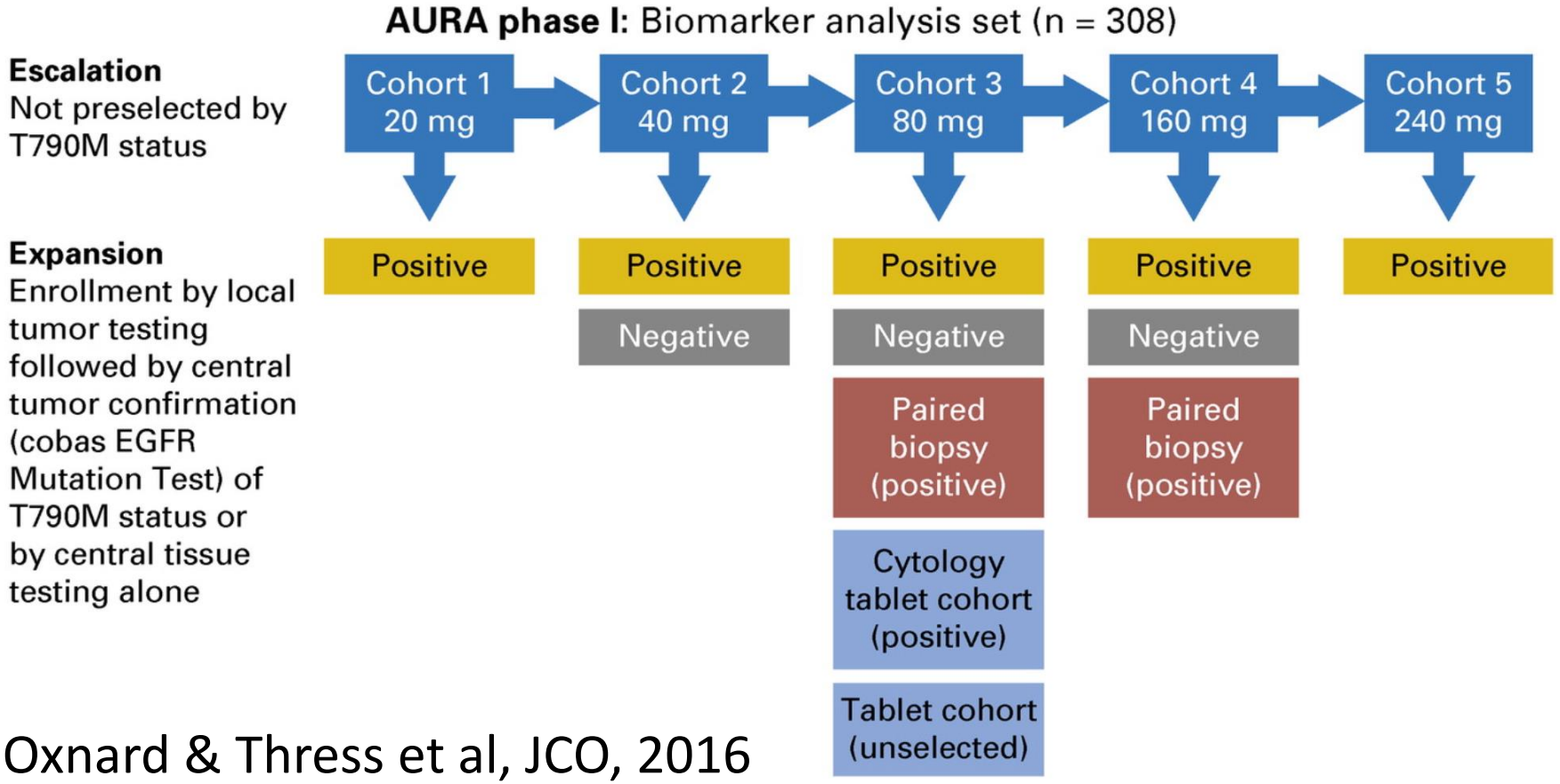




Oxnard et al, Ann Oncol, 2020

Registrational phase I/II studies

- AURA trial: FiH study of osimertinib in EGFR-mutant NSCLC



Oxnard & Thress et al, JCO, 2016

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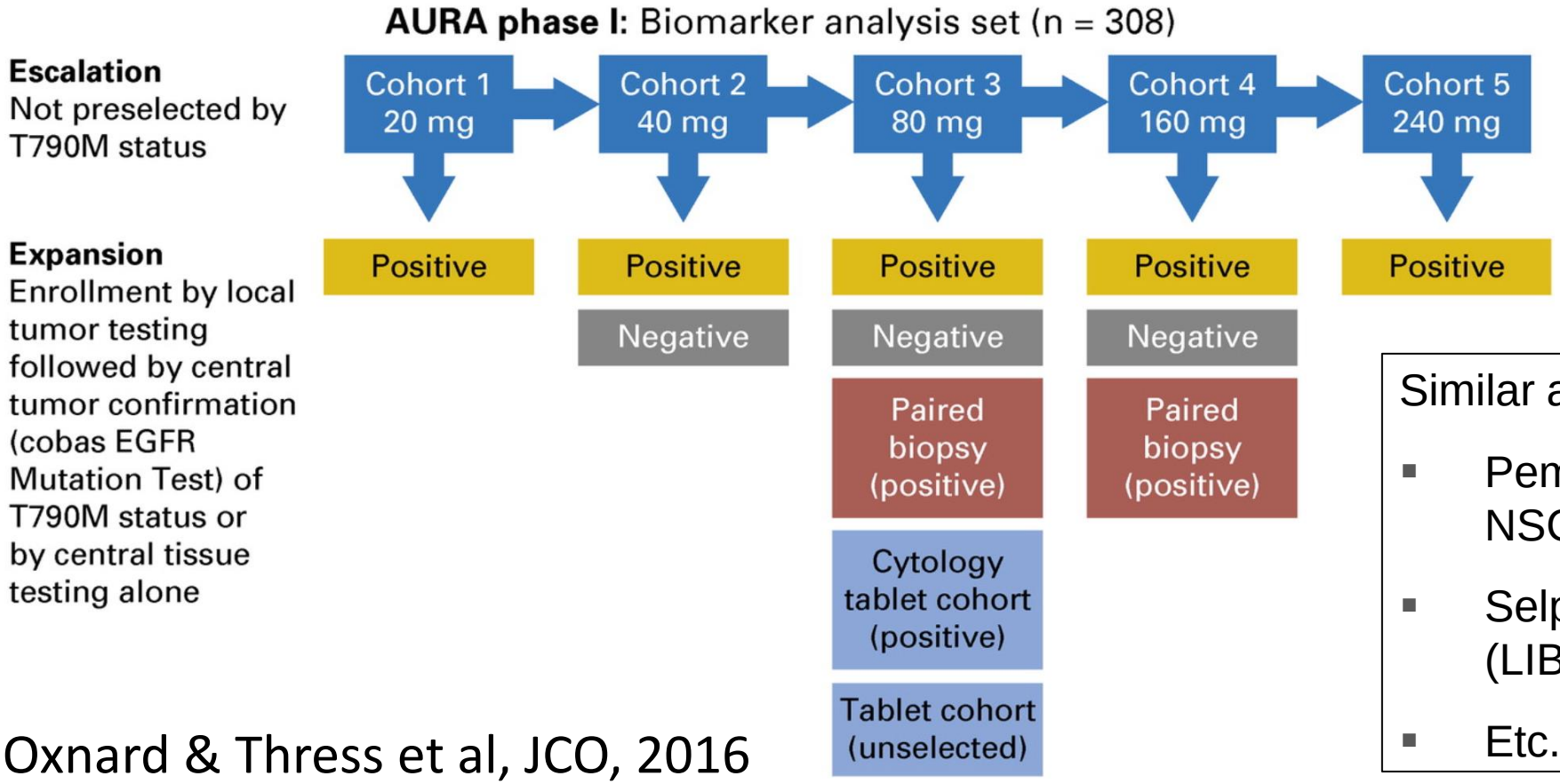


Oxnard & Thress et al, JCO, 2016

Similar approach for:

- Pembrolizumab in PDL1-high NSCLC (KN-001 part F)
- Selpercatinib in RET+ NSCLC (LIBRETTO-001)
- Etc.

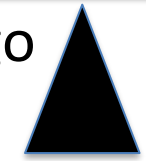
Re-considering trial phases

Phase I
(safety, dose)

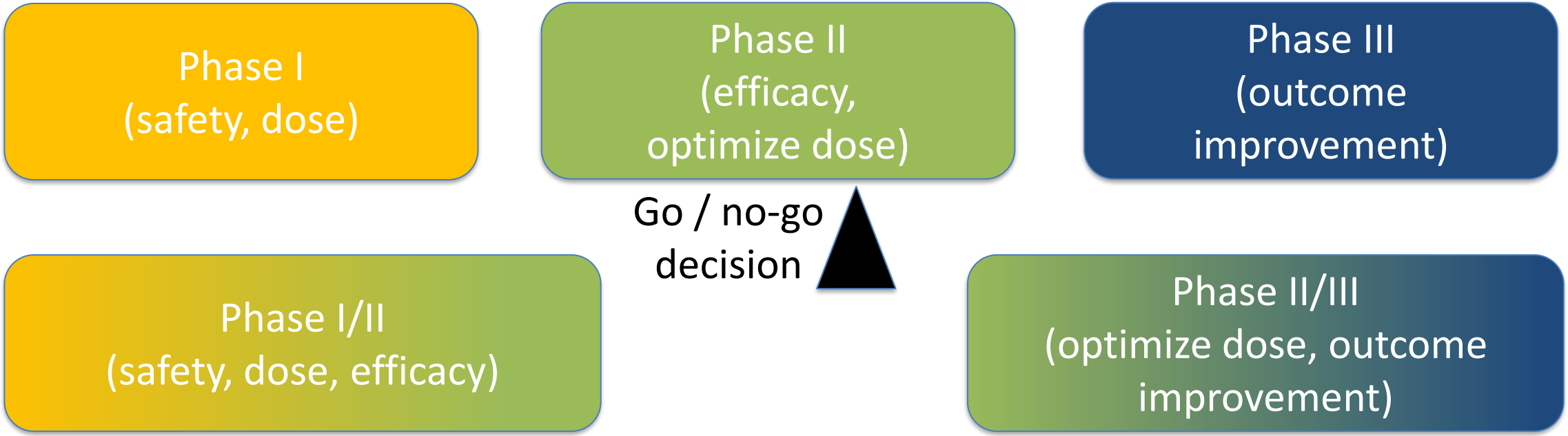
Phase II
(efficacy,
optimize dose)

Phase III
(outcome
improvement)

Go / no-go
decision



Re-considering trial phases



- Seamless protocols have the potential to allow efficient enrollment before and after go/no-go decision

Seamless II/III trials

- Systematic review of literature identified 28 lung cancer studies using a seamless phase II/III design, falling primarily in 3 categories:
  - Phase II/III trials with inefficacy/futility analyses (inferentially seamless)
  - Dose escalation phase II/III trials (operationally seamless)
  - Multi-arm multi stage phase II/III trials

Palermos et al, J Clin Med, 2022

Platform phase II/III design

A Study to Evaluate the Efficacy and Safety of Multiple Targeted Therapies as Treatments for Participants With Non-Small Cell Lung Cancer (NSCLC) (B-FAST)

ClinicalTrials.gov ID NCT03178552

Sponsor Hoffmann-La Roche

Information provided by Hoffmann-La Roche (Responsible Party)

Last Update Posted 2024-01-19

Blood First Assay Screening Trial (BFAST) in Treatment-Naive Advanced or Metastatic NSCLC: Initial Results of the Phase 2 *ALK*-Positive Cohort

Rafal Dziadziuszko, MD • Tony Mok, MD • Solange Peters, MD, PhD • ... David S. Shames, PhD • Michael S. Mathisen, PharmD • Shirish M. Gadgeel, MD • Show all authors

Open Access • Published: July 22, 2021 • DOI: https://doi.org/10.1016/j.jtho.2021.07.008 • Check for updates

Dziadziuszko et al, JTO, 2021

Article | Open access | Published: 22 August 2022

Atezolizumab versus chemotherapy in advanced or metastatic NSCLC with high blood-based tumor mutational burden: primary analysis of BFAST cohort C randomized phase 3 trial

Solange Peters, Rafal Dziadziuszko, Alessandro Morabito, Enriqueta Felip, Shirish M. Gadgeel, Parneet Cheema, Manuel Cobo, Zoran Andric, Carlos H. Barrios, Masafumi Yamaguchi, Eric Dansin, Pongwut Danchaivijitr, Melissa Johnson, Silvia Novello, Michael S. Mathisen, Sarah M. Shagan, Erica Schleifman, Jin Wang, Mark Yan, Simonetta Mocci, David Voong, David A. Fabrizio, David S. Shames, Todd Riehl, ... Tony Mok + Show authors

Nature Medicine **28**, 1831–1839 (2022) | Cite this article

Peters et al, Nat Med, 2022

Registrational phase II/III design

A Study of LY3537982 Plus Immunotherapy With or Without Chemotherapy in Participants With Non-Small Cell Lung Cancer (NSCLC) With a Change in a Gene Called KRAS G12C (SUNRAY-01)

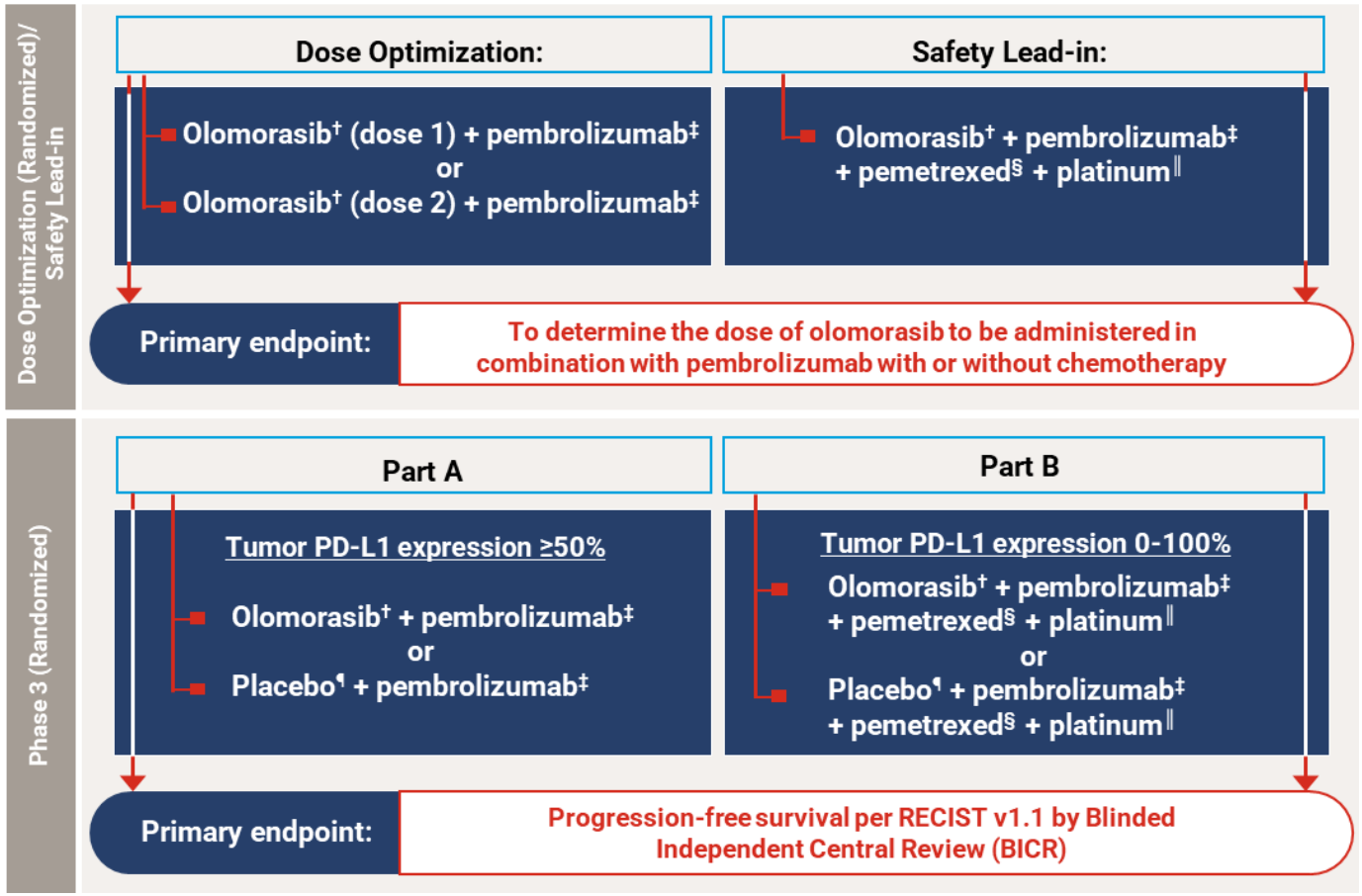
ClinicalTrials.gov ID NCT06119581

Sponsor Eli Lilly and Company

Information provided by Eli Lilly and Company (Responsible Party)

Last Update Posted 2024-01-24

- Initial dose optimization & safety lead-in
- Subsequent placebo-controlled phase 3



*This clinical trial is conducted globally. †Olomorasib is administered PO. ‡Pembrolizumab is administered IV. ¶Placebo is administered PO. §Pemetrexed is administered IV. ‖Platinum (cisplatin or carboplatin) is administered IV. https://clinicaltrials.gov/ct2/show/NCT06119581 (Accessed January 31, 2024).

Conclusions

- Operational seamlessness offers an opportunity to reduce enrollment gaps and development timelines
- Seamless studies can be complex and require intentional design
- For different programs, dose optimization may potentially fit as a seamless component either of a FIH trial or of a registrational phase III trial

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Adaptive Phase 2/3 Designs with Early Dose Selection: A Statistical Perspective

Cong Chen, PhD
Scientific AVP, Early Development Statistics, Merck & Co., Inc. Rahway, NJ, USA

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Disclosure Information

Cong Chen

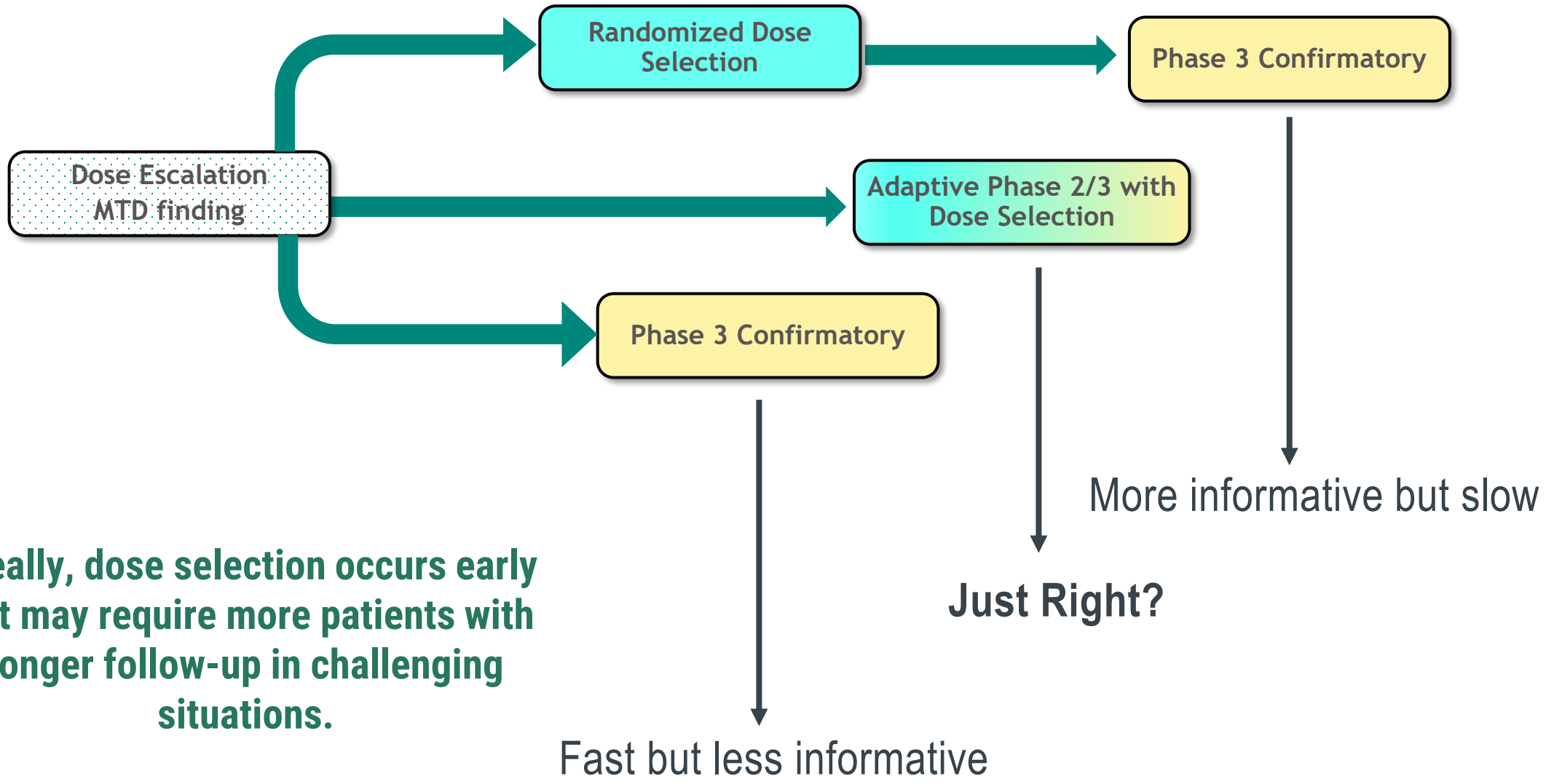
- I’m a stockholder of biopharmaceutical companies and may benefit from the presentation.
- The views presented here are those of the presenter and should not necessarily be viewed as those of my employer, Merck & Co., Inc., Rahway, NJ, USA.

Overview of seamless and adaptive Phase 2/3 trial designs

- Inferentially seamlessly adaptive Phase 2/3 designs, or adaptive Phase 2/3 designs for short, are highly appealing in theory but present significant challenges in practice.

		Inclusion of Phase 2 patients in Phase 3 primary analysis	
		Yes	No
Minimum pause after Phase 2	No	Inclusion can be questionable	Conventional sequential Phase 2/3
	Yes	Inferentially seamless adaptive Phase 2/3	Operationally seamless adaptive Phase 2/3

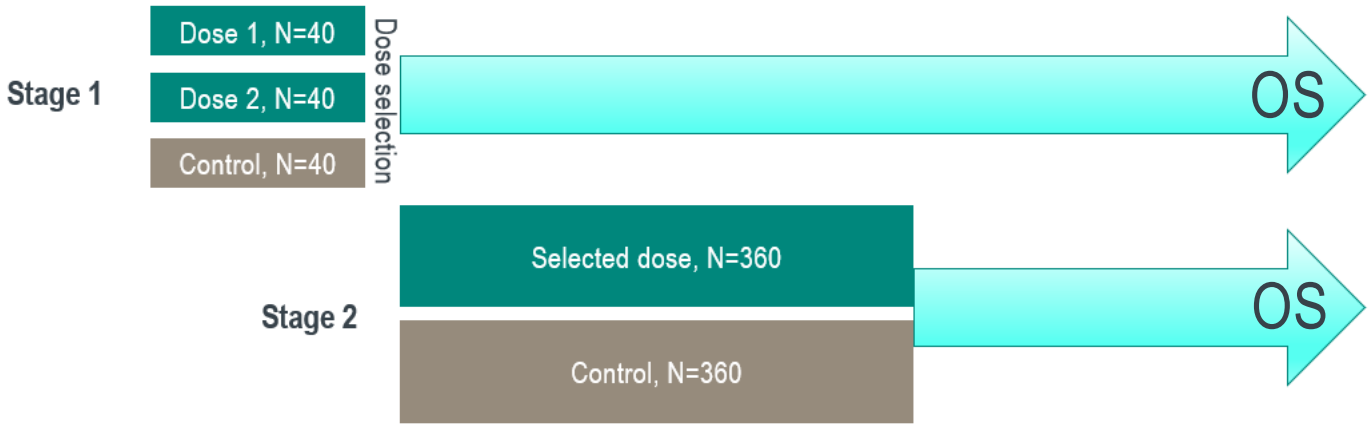
Typical options post preliminary dose finding



Ideally, dose selection occurs early but may require more patients with longer follow-up in challenging situations.

A hypothetical adaptive Phase 2/3 design

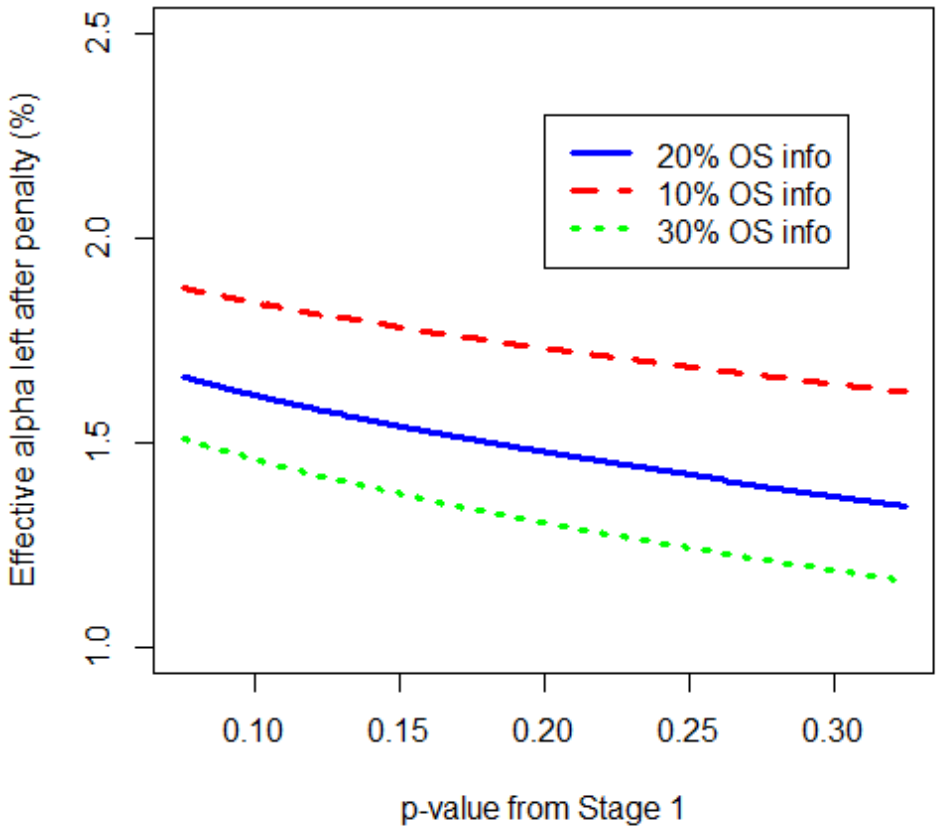
- Dose-selection is primarily based on the safety/PK data
  - The criteria are accepted FDA and the decision is made by an external DMC
- Overall survival (OS) after complete f/u from Stage 1 (Phase 2) and Stage 2 for the selected dose vs control are combined for the Phase 3 primary analysis
  - 10% of patients (selected dose and control) are from Stage 1
  - Stage 1 patients contributes disproportionally more OS information due to longer f/u



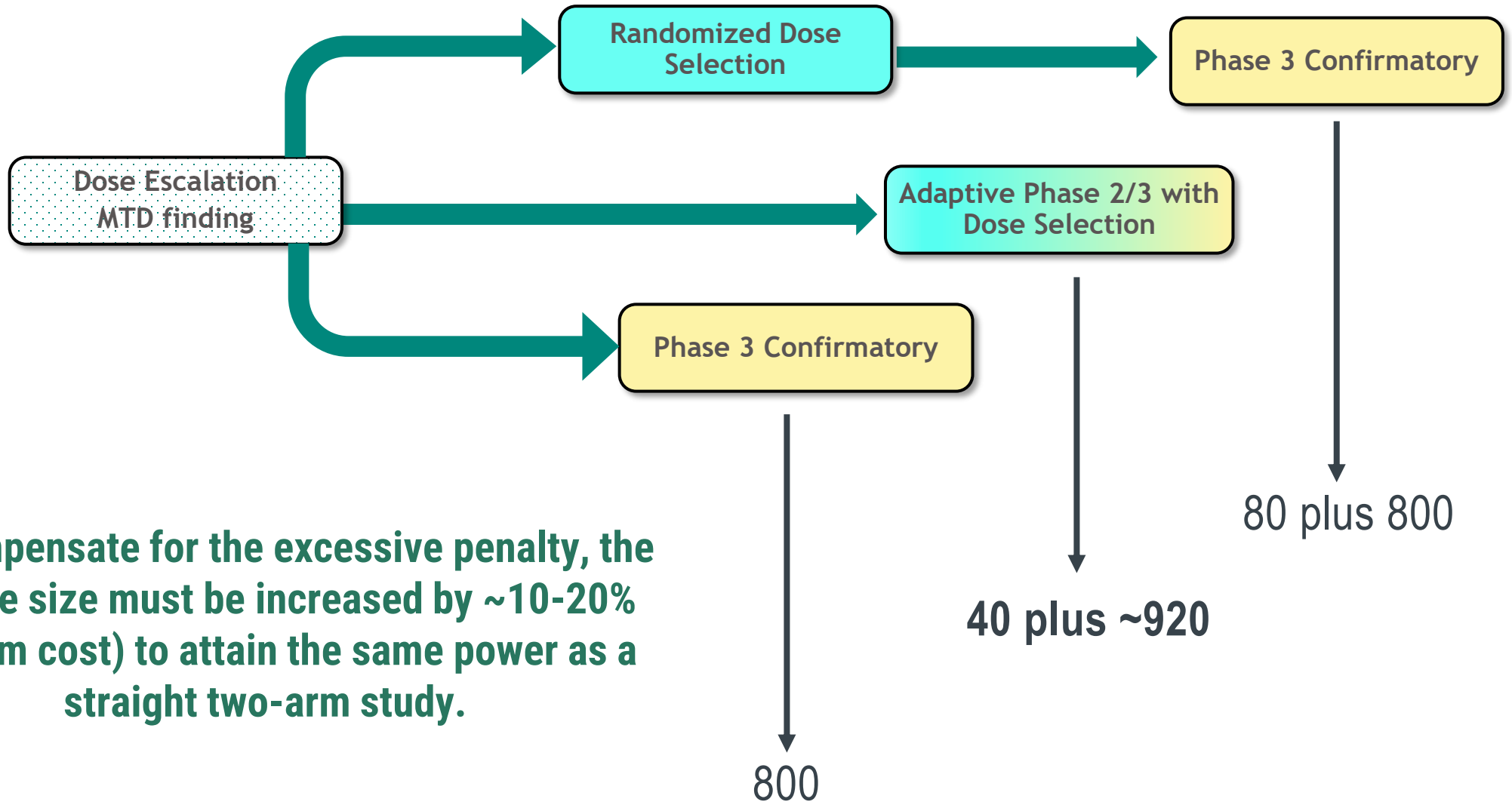
Phase 3 primary analysis

- An inverse normal combination test is often used for the primary analysis, which is a robust method for Type I error control but inefficient for analysis
  - A complicated combination of the two stage-wise p-values, where the one based on Stage 1 patients is multiplied by number of doses
  - It essentially assumes that a dose is cherry-picked based on better OS after complete f/u
- 40-50% of alpha is lost, even when selecting a dose based on better tolerability, despite a lower ORR
  - Penalty increases (effective alpha decreases) as OS information from Stage 1 patients increases

Large loss of alpha after taking the penalty



Sample size comparison based on the hypothetical design



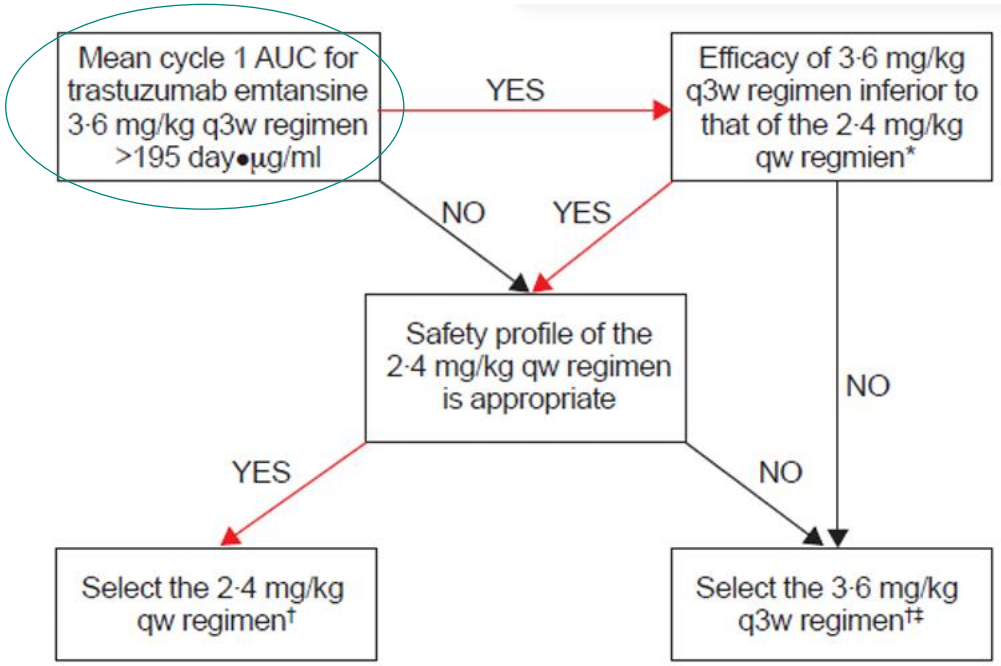
To compensate for the excessive penalty, the sample size must be increased by ~10-20% (~$20m cost) to attain the same power as a straight two-arm study.

A more nuanced approach to the statistical analysis

- Combination test is better suited for scenarios when dose-selection is primarily based on an efficacy endpoint, sample size is larger, and f/u is longer.
- When dose-selection is primarily based on safety/PK data in patients with short f/u, the selected dose should be simply tested at 2.5% level.
  - A small alpha will be spent for the administrative look as determined by the pre-specified alpha-spending function at the actual information fraction (e.g., 5%) observed at dose-selection.
  - Penalty should be paid when the decision is based on an efficacy endpoint that is highly correlated with the primary endpoint of the study.

Example of dose-selection rule

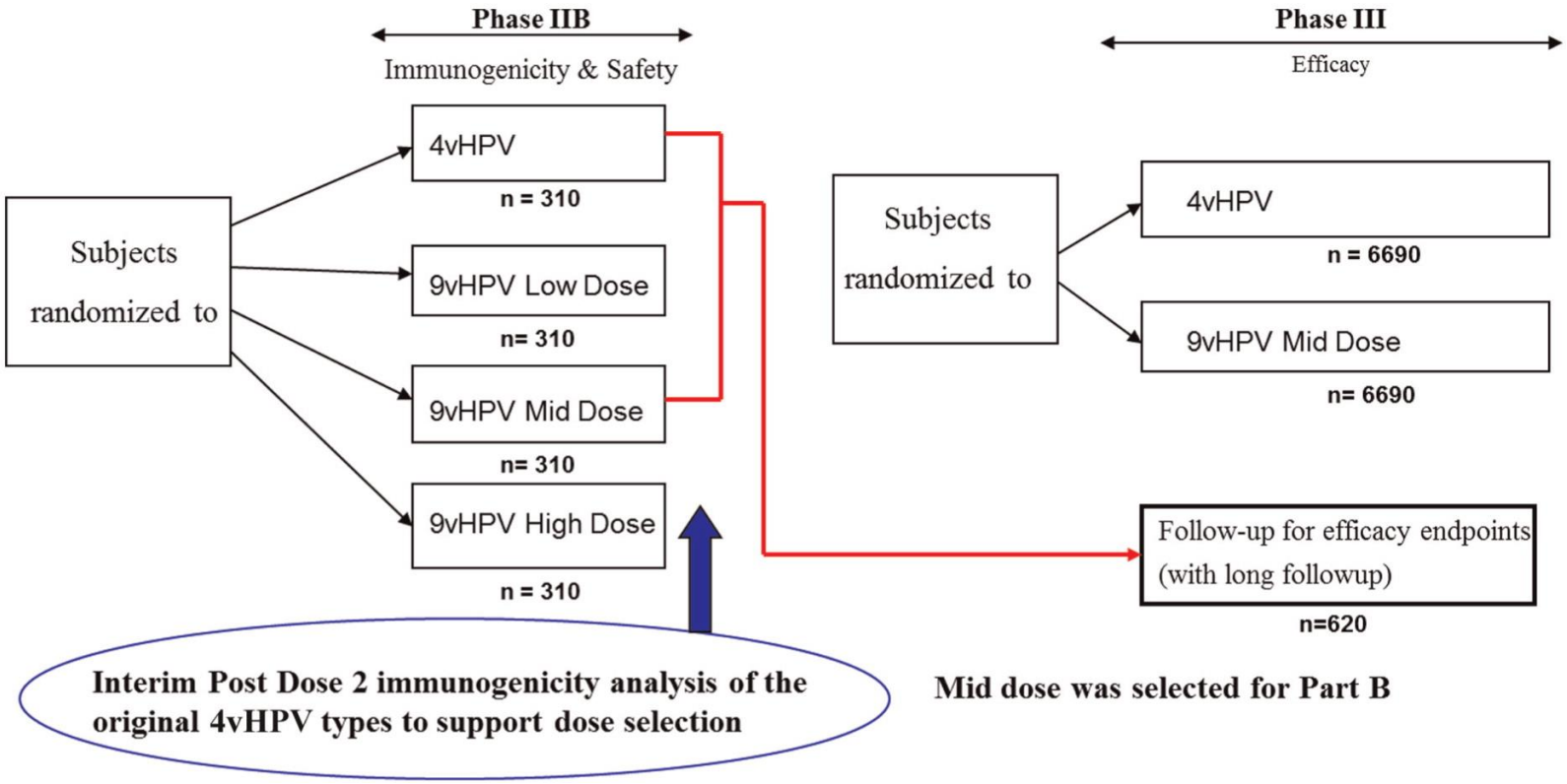
(GATSBY: trastuzumab emtansine vs taxane in patients with previously treated HER2-positive gastric cancer)



Lancet Oncol 2017; 18: 640–53

An example: a pivotal study of Gardasil 9

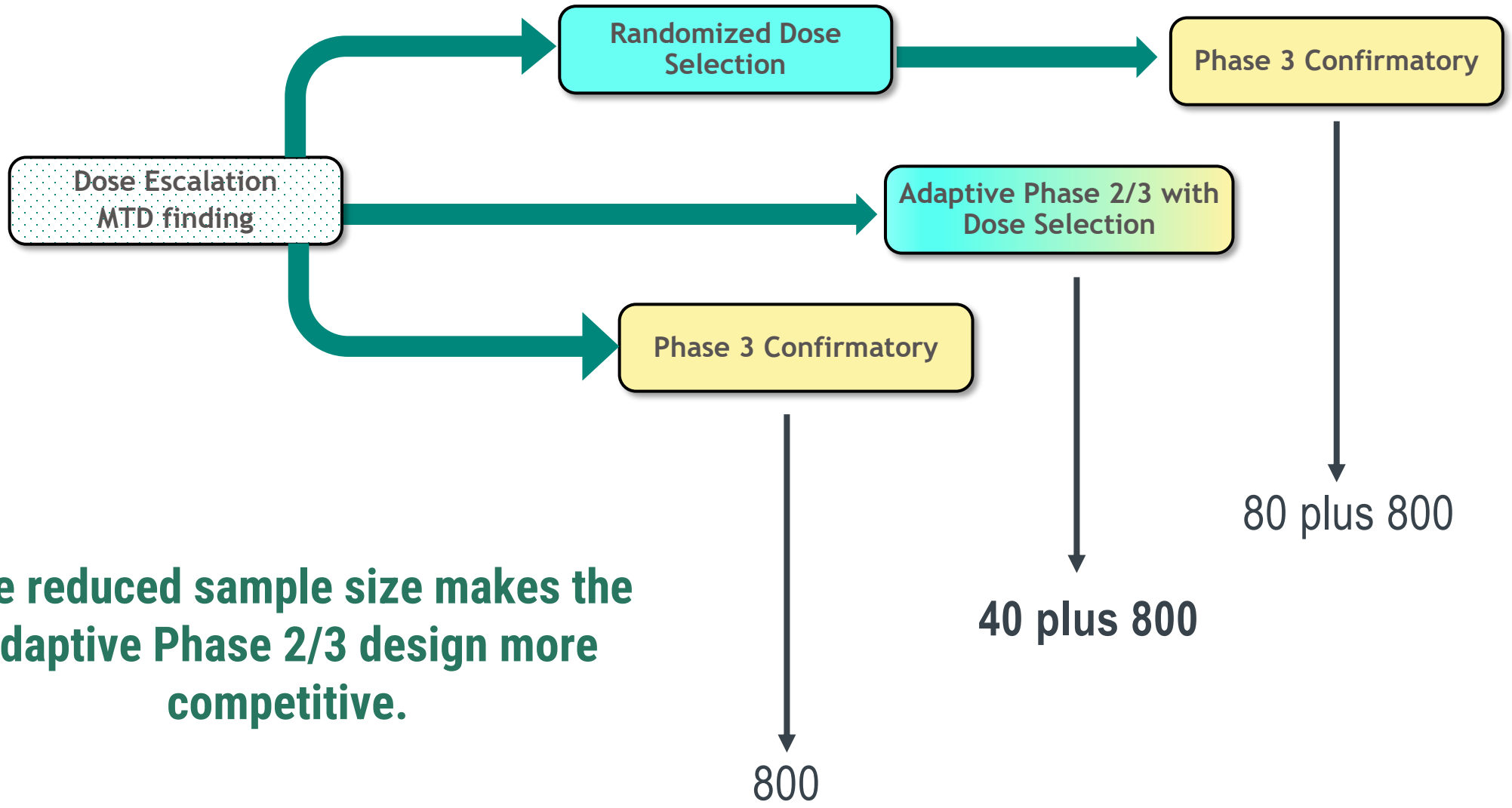
- Dose selection was based on immunogenicity and safety. No penalty was paid due to small correlation between biomarker and efficacy endpoint.



Enrollment pause for 9 months

Clin Trials 2015;12(1):84-90

Sample size comparison under the improved approach



The reduced sample size makes the adaptive Phase 2/3 design more competitive.

Discussion

- In general, seamless designs assisted with adaptive dose selection can make dose optimization more cost-effective and Project Optimus more appealing to sponsors.
  - The Pembrolizumab program not only randomized multiple doses in the FIH study but also took two doses to the end in the initial Phase 3 trials. However, it is unrealistic to expect a typical program to do the same, given the large sample size and substantial costs.
- As a viable approach to meet the Project Optimus requirement, adaptive Phase 2/3 designs may generate high-quality multi-dose randomized-controlled data for decision-making and hold great promise to expedite a development program.
  - Including additional doses in a confirmatory trial provides more data for the FDA to act upon than otherwise, and it undermines the purpose of the Project to have to pay a hefty penalty based on an unrealistically conservative assumption.

SESSION 3B: IMPLEMENTING SEAMLESS AND ADAPTIVE REGISTRATIONAL TRIAL DESIGNS

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