Design Strategies and Considerations for Oncology Dose Optimization

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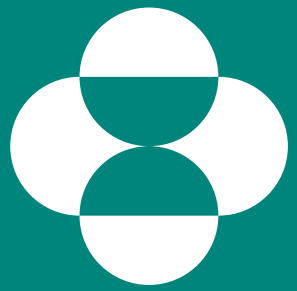

INVENTING FOR LIFE

ASA New Jersey Chapter Webinar

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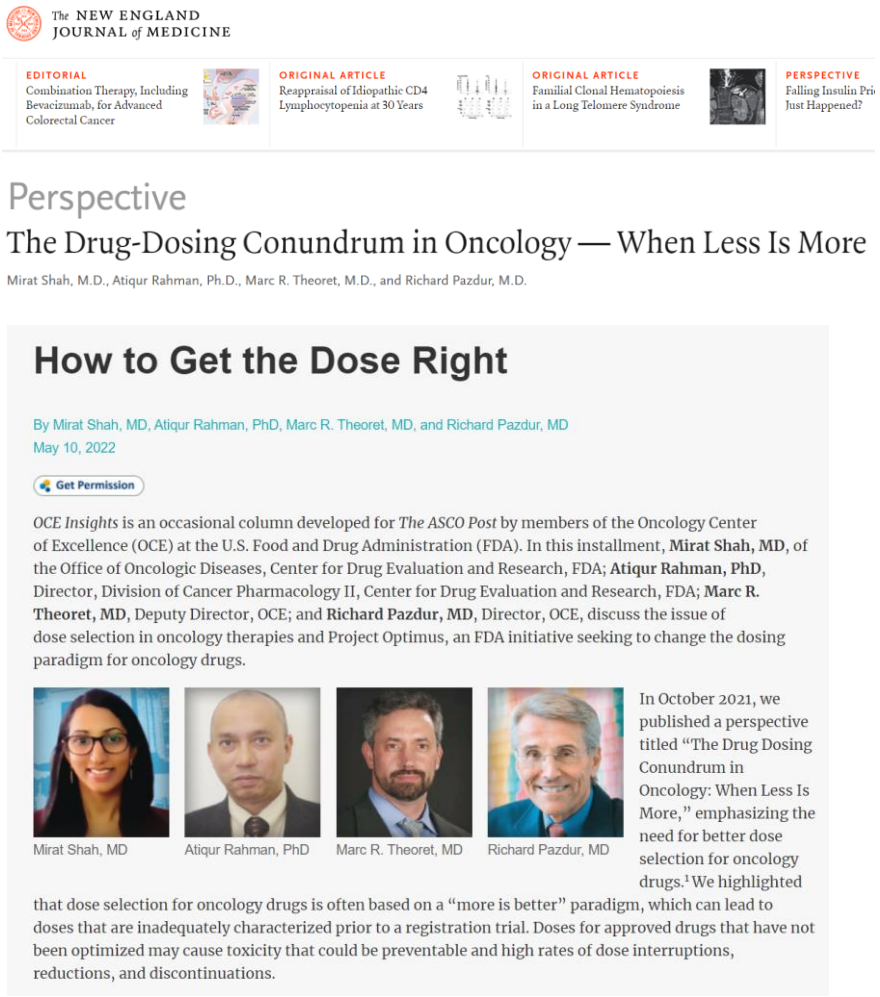
Project Optimus – Paradigm Shift



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EDITORIAL
Combination Therapy, Including Bevacizumab, for Advanced Colorectal Cancer

ORIGINAL ARTICLE
Reappraisal of Idiopathic CD4 Lymphocytopenia at 30 Years

ORIGINAL ARTICLE
Familial Clonal Hematopoiesis in a Long Telomere Syndrome

PERSPECTIVE
Falling Insulin Pri… Just Happened?

Perspective

The Drug-Dosing Conundrum in Oncology — When Less Is More

Mirat Shah, M.D., Atiqur Rahman, Ph.D., Marc R. Theoret, M.D., and Richard Pazdur, M.D.

How to Get the Dose Right

By Mirat Shah, MD, Atiqur Rahman, PhD, Marc R. Theoret, MD, and Richard Pazdur, MD
May 10, 2022

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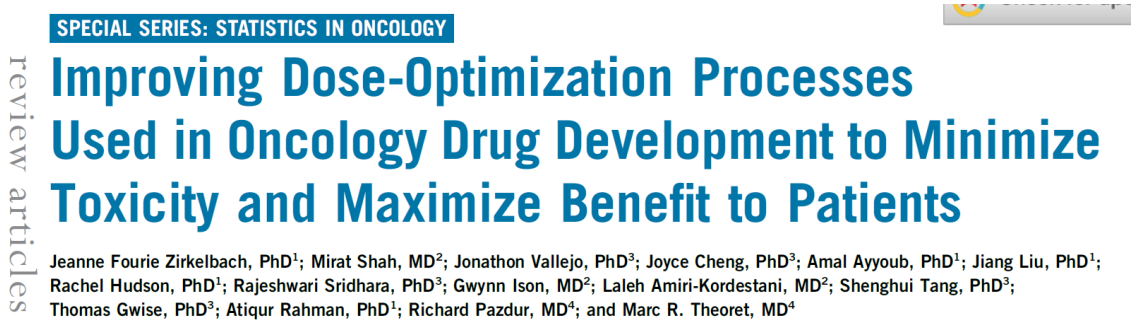
OCE Insights is an occasional column developed for *The ASCO Post* by members of the Oncology Center of Excellence (OCE) at the U.S. Food and Drug Administration (FDA). In this installment, **Mirat Shah, MD**, of the Office of Oncologic Diseases, Center for Drug Evaluation and Research, FDA; **Atiqur Rahman, PhD**, Director, Division of Cancer Pharmacology II, Center for Drug Evaluation and Research, FDA; **Marc R. Theoret, MD**, Deputy Director, OCE; and **Richard Pazdur, MD**, Director, OCE, discuss the issue of dose selection in oncology therapies and Project Optimus, an FDA initiative seeking to change the dosing paradigm for oncology drugs.

Mirat Shah, MD | Atiqur Rahman, PhD | Marc R. Theoret, MD | Richard Pazdur, MD

In October 2021, we published a perspective titled "The Drug Dosing Conundrum in Oncology: When Less Is More," emphasizing the need for better dose selection for oncology drugs.[1] We highlighted that dose selection for oncology drugs is often based on a "more is better" paradigm, which can lead to doses that are inadequately characterized prior to a registration trial. Doses for approved drugs that have not been optimized may cause toxicity that could be preventable and high rates of dose interruptions, reductions, and discontinuations.

- "More is better" paradigm characterized the development of cytotoxic agents due to the life-threatening nature of cancer that patients need maximum efficacy with maximum tolerated dose (MTD), quickly within just a few cycles of treatment.
- Advances in targeted therapies have extended survival among patients, with months or years of drug usage.
- Severe toxicities may occur after multiple treatment cycles, leading to undesirable dose reduction or drug discontinuation, thus affecting continued benefit from the drug.
- Dose optimization paradigm across oncology should emphasize selection of a dose or doses that maximizes not only the efficacy of a drug but the long-term safety and tolerability as well.

Design Strategies



review articles

SPECIAL SERIES: STATISTICS IN ONCOLOGY

Improving Dose-Optimization Processes Used in Oncology Drug Development to Minimize Toxicity and Maximize Benefit to Patients

Jeanne Fourie Zirkelbach, PhD[1]; Mirat Shah, MD[2]; Jonathon Vallejo, PhD[3]; Joyce Cheng, PhD[3]; Amal Ayyoub, PhD[1]; Jiang Liu, PhD[1]; Rachel Hudson, PhD[1]; Rajeshwari Sridhara, PhD[3]; Gwynn Ison, MD[2]; Laleh Amiri-Kordestani, MD[2]; Shenghui Tang, PhD[3]; Thomas Gwise, PhD[3]; Atiqur Rahman, PhD[1]; Richard Pazdur, MD[4]; and Marc R. Theoret, MD[4]

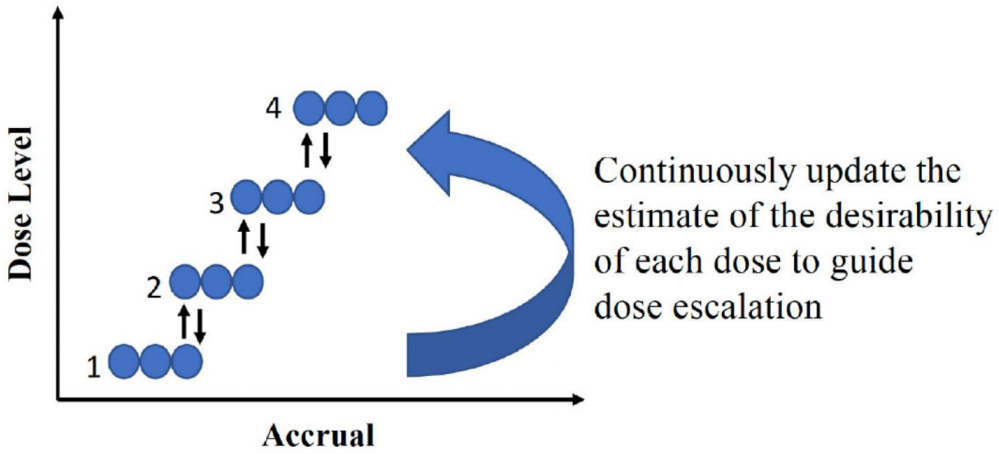
- Aim to identify several candidate dosages or a dosage range to further evaluate after dose escalation and initial dose expansion.
- Incorporate safety information beyond DLTs, such as dose modifications and low-grade but persistent toxicities which may affect ability to take a drug.
- Dose optimization can occur within a seamless development program with sufficient planning.

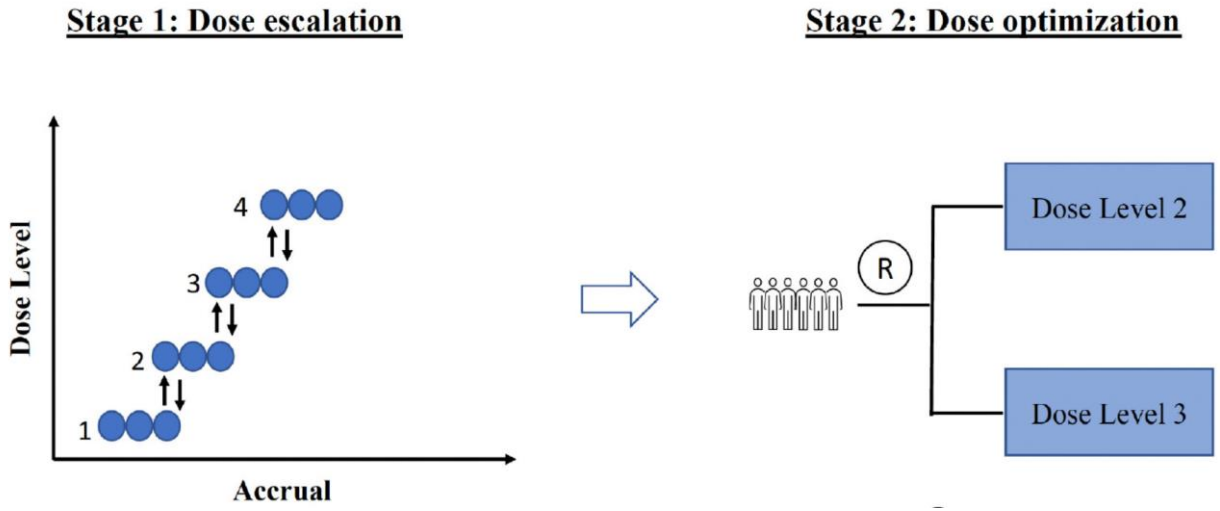
Efficacy and Toxicity Endpoints

- The concept of finding the optimal dose based on both efficacy and toxicity is not a new one.
  - Thall & Russell, 1998; O'Quigley et al., 2001; Braun, 2002
- More comprehensive toxicity endpoints that account for low-grade or cumulative toxicity may be preferred.
  - E.g., rate of dose modification, total toxicity burden, equivalent toxicity score.
- Benefit-risk tradeoff (BRT) should be explicitly defined to guide dose selection.
  - Eg1. EffTox design (Thall & Cook, 2004) uses $\pi_E - \omega\pi_T$ as the BRT, where ω is a penalty for an increase in the toxicity rate.
  - Eg2. BOIN12 design (Lin et al. 2020) uses utility-based BRT to identify the optimal biologic dose (OBD).

Phase 1/2 Designs

- Efficacy-integrated approach is more efficient to identify the optimal dose and requires smaller sample sizes.
  - Various designs have been proposed, e.g., EffTox, BOIN12, etc.
- Two-stage approach follows conventional develop-by-stage practices and is more well-aligned with Project Optimus to test on multiple candidate doses.





Yuan, Zhou and Liu. (2024) Statistical and practical considerations in planning and conduct of dose-optimization trials.

Two-stage Design Strategies

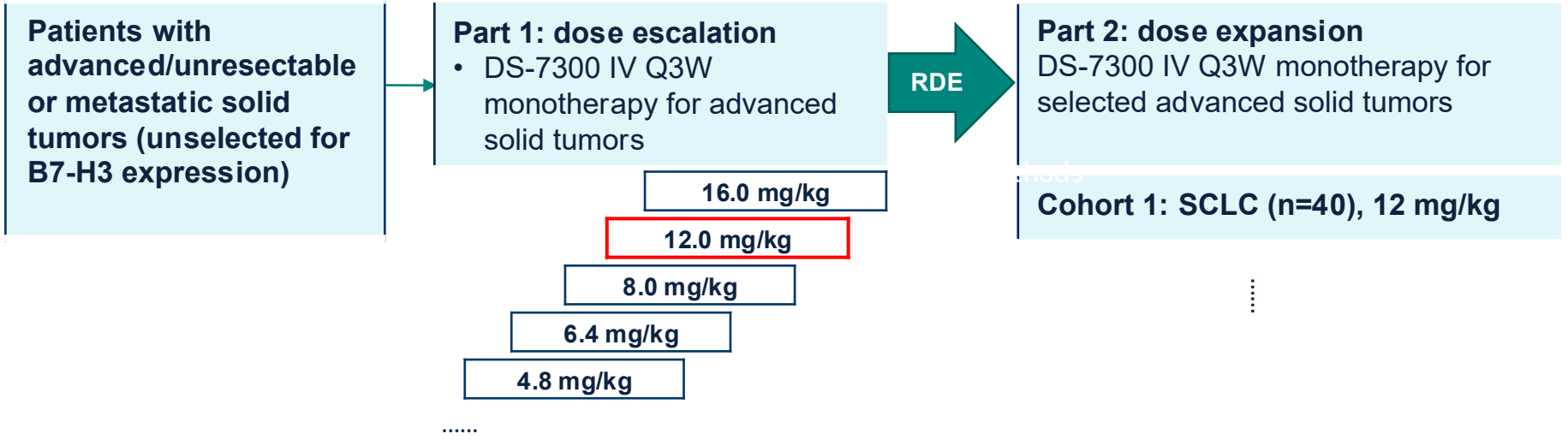
- Standard dose-finding designs are used in the dose escalation stage and usually MTD/RP2D and MTD/RP2D-1 are selected for randomization stage.
- FDA draft guidance on dose optimization: “The trial should be sized to allow for sufficient assessment of activity, safety, and tolerability for each dosage. The trial does not need to be powered to demonstrate statistical superiority of a dosage or statistical non-inferiority among the dosages.”
- Yang et al. (2023) proposed a MERIT design to optimize the sample size with clear power definition based on both efficacy and safety boundaries for decision-making in dose optimization.
- To collect more data to evaluate safety and preliminary efficacy, backfilling is encouraged in the dose escalation stage.
  - Multiple dose levels could be open for backfilling, either before or after MTD is determined.
  - Zhao et al. (2024) proposed rigorous rules for backfilling with BOIN design in dose escalation (BF-BOIN).

Practical Considerations of Backfilling

- Backfilling after dose escalation phase is clean and easy to implement, while is time-consuming.
- Backfilling during dose escalation phase requires operational guidance from the following perspectives:
  - What is the criterion to open/close a dose for backfilling?
  - How to allocate patients between dose escalation and backfilling components?
  - How to incorporate backfilling data into dose escalation? How to reconcile the potential conflict observed between the data from dose escalation and backfilling components?
- *Be clear AND flexible!*

Case Example: Ifinatamab deruxtecan (I-DXd, DS-7300),

DS-7300 is an investigational B7-H3-targeting antibody-drug conjugate (ADC).



DS7300-A-J101: A Multicenter, Open-Label, 2-Part, Multiple-Dose, First-in-Human, Phase 1/2 Study of DS-7300 in Patients With Advanced Solid Malignant Tumors

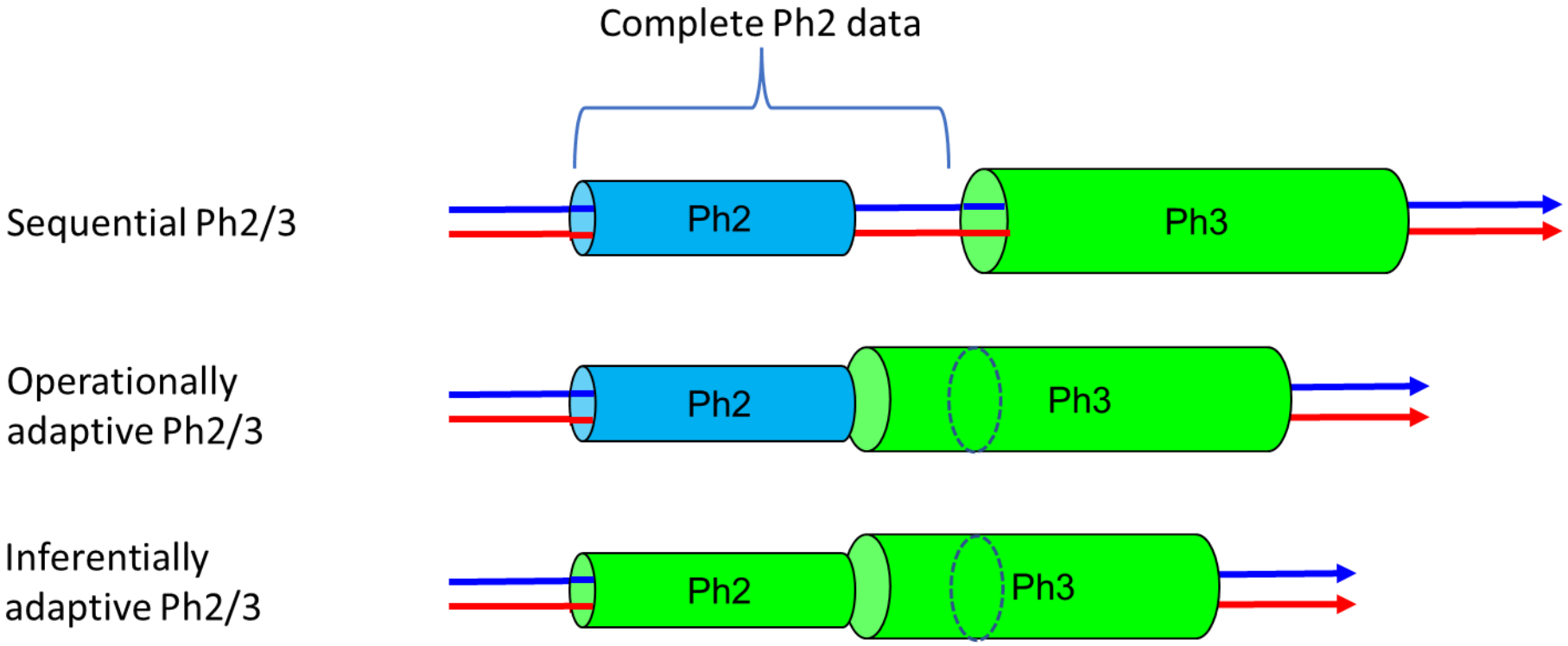
IDeate-Lung01: I-DXd Dose Randomization in ES-SCLC

End Point	Part 1 (dose optimization)		Part 2 (extension)	Parts 1 and 2
	8 mg/kg (n = 46)	12 mg/kg (n = 42)	12 mg/kg (n = 95)	Total 12 mg/kg (n = 137)
ORR, % (95% CI)	26.1 (14.3 to 41.1)	54.8 (38.7 to 70.2)	45.3 (35.0 to 55.8)	48.2 (39.6 to 56.9)
BOR, No. (%)				
CR	2 (4.3)	0	3 (3.2)	3 (2.2)
PR	10 (21.7)	23 (54.8)	40 (42.1)	63 (46.0)
SD	25 (54.3)	15 (35.7)	39 (41.1)	54 (39.4)
PD	5 (10.9)	2 (4.8)	8 (8.4)	10 (7.3)
Not evaluable	4 (8.7)	2 (4.8)	5 (5.3)	7 (5.1)
DCR, % (95% CI)	80.4 (66.1 to 90.6)	90.5 (77.4 to 97.3)	86.3 (77.7 to 92.5)	87.6 (80.9 to 92.6)
TTR, median (range), months	1.4 (1.3-2.6)	1.4 (1.0-8.1)	1.4 (1.2-3.9)	1.4 (1.0-8.1)
DOR, median (95% CI), months	7.9 (4.1 to NE)	4.2 (3.5 to 7.0)	5.6 (3.7 to 7.2)	5.3 (4.0 to 6.5)

I-DXd has been granted Breakthrough Therapy Designation for ES-SCLC with disease progression on or after platinum-based chemotherapy

Phase 2/3 Designs

- The gap between Phase 2 and Phase 3 in a sequential approach may be shortened to make it operationally seamless.
- Adaptive phase 2/3 design combines traditional Phase 2 and Phase 3 trials into one study for the primary analysis (i.e., inferentially seamless).



Chen (2023) To go or not to go in phase 2/3 oncology trials, a critical question with a unified answer.

Practical Considerations of Phase 2/3 Designs

- A sequential design has the greatest flexibility to optimize the dose and study population.
- An inferentially adaptive design has the smallest sample size overall and is the fastest to finish.
- The sponsor has full access to the Phase 2 data in an operationally adaptive trial while an external DMC is needed to make interim decision in an inferentially adaptive trial.
- Due to the complexity of inferentially adaptive design, sponsors and regulatory agencies should engage in discussions early and closely.
- A case example: Cediranib (a VEGFR TKI) with mFOLFOX6 versus Bevacizumab with mFOLFOX6 as first-line treatment for patients with advanced colorectal cancer, a double-blinded phase II/III study (HORIZON III)
  - Patients were randomly assigned 1:1:1 to receive Cediranib 20 or 30mg per day or Bevacizumab 5 mg/kg IV every two weeks, each combined with mFOLFOX6.
  - After 225 patients had 3-month follow-up in the phase II part, the independent DMC concluded that Cediranib 20mg met all predefined criteria for continuation.

An Emerging Trend of Phase 2/3 Adaptive Design with Dose Optimization

- BNT327 (PD-L1/VEGFA bispecific): the two doses are 1400 and 2000 mg flat
  - A phase 2/3, randomized, open-label trial of BNT327 in combination with chemo in 1L NSCLC (NCT06712316) – sequential dose randomization followed with Phase 3
  - A phase 3, double-blind, randomized trial of BNT327 plus chemo compared to Atezo plus chemo in 1L ES-SCLC (NCT06712355) – unclear about mid-trial dose selection
- BMS-986507 (EGFR/HER3 ADC): doses are undisclosed and unclear about mid-trial dose selection
  - A Phase 3 Study of BMS-986507 Versus Platinum-Pemetrexed for EGFR-mutated NSCLC After Failure of EGFR TKI Therapy (IZABRIGHT-Lung01) (NCT07100080)
  - A Phase 3 Study of BMS-986507 Versus Chemotherapy in 1L TNBC Participants Ineligible for Anti-PD-(L)1 Drugs (IZABRIGHT-Breast01) (NCT06926868)
  - A Phase 2/3 Trial of BMS-986507 vs Platinum-based Chemotherapy for Metastatic Urothelial Cancer With Disease Progression on or After Immunotherapy (NCT07106762)

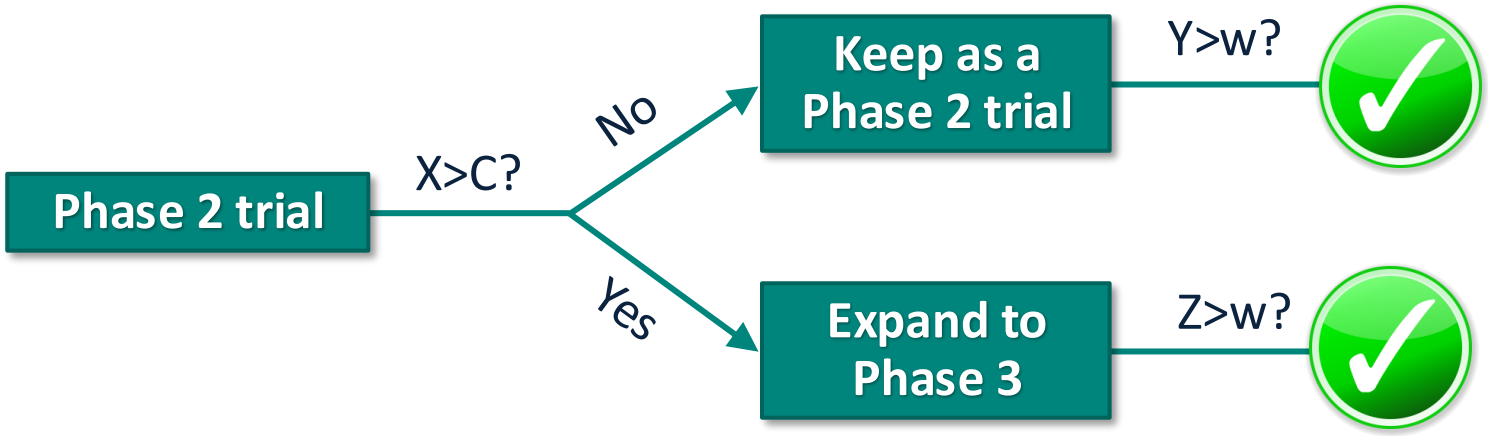
2-in-1 Design Framework

The 2-in-1 design is an adaptive design strategy that allows a study to choose the optimal path to success

- Under the conventional approach, a decision on whether to conduct a Phase 2 to establish a more solid PoC or Phase 3 is usually based on limited single-arm Phase 1 efficacy data.
- In comparison, the 2-in-1 approach starts the study as a Phase 2 trial and postpones the decision on whether to expand to Phase 3 until after an interim analysis in Phase 2.
  - When properly planned, Phase 2 data can be included in Phase 3 analysis with the Go decision to Phase 3.
  - A positive outcome from Phase 2 after a No-Go decision holds the same value as for a standalone Phase 2 and may be used to help expedite the drug approval
  - Either a win in Phase 2 after No-Go or a win in Phase 3 after Go is a win, and both can often be tested at full alpha level

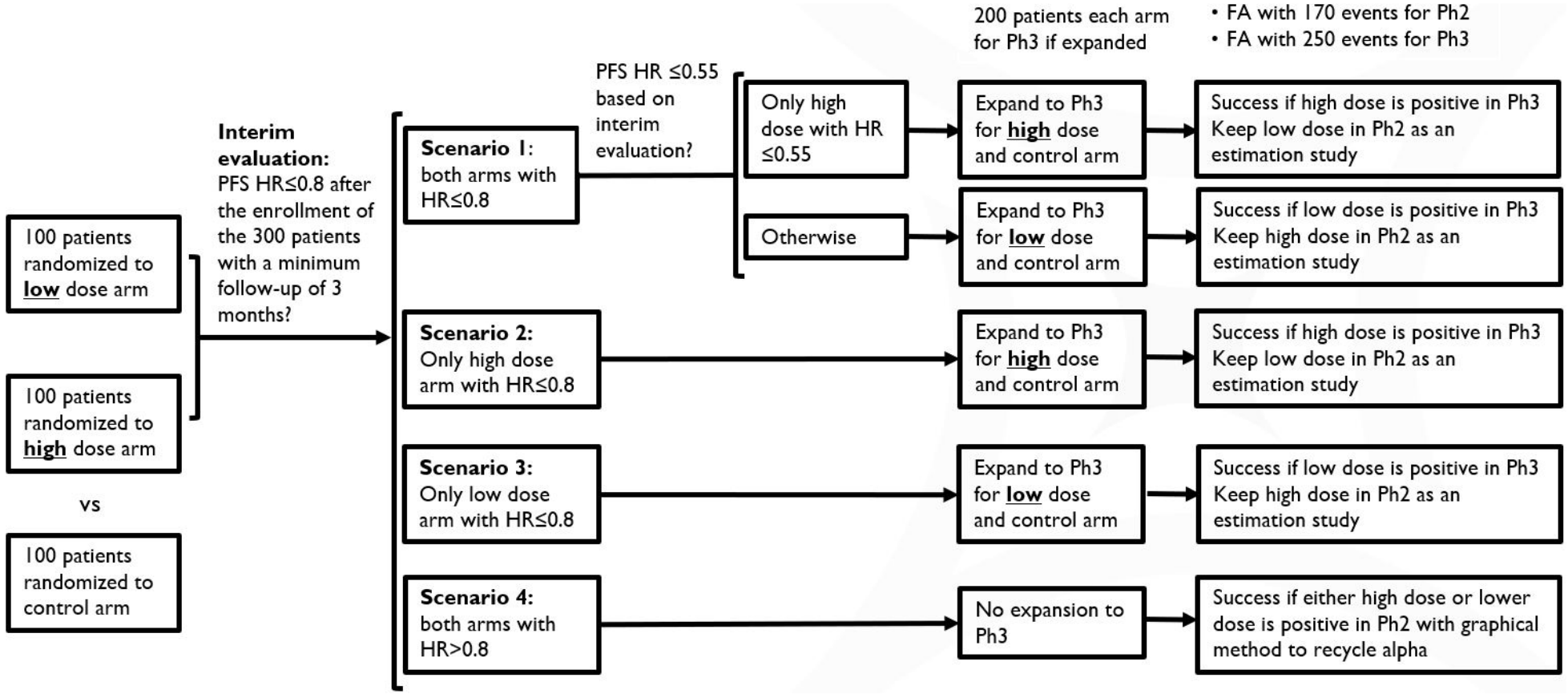
Chen C, Anderson K, Mehrotra DV, Rubin EH and Tse A. A 2-in-1 Adaptive Phase 2/3 Design for Expedited Oncology Drug Development. Contemporary Clinical Trials 2018; 64:238-242.

A Generic 2-in-1 Adaptive Phase 2/3 Design



- The 3 endpoints that the standardized test statistics are based upon can be different
- No penalty for multiplicity control as long as $\rho_{XY} \geq \rho_{XZ}$ (i.e., w=1.96 to control at 2.5%)
  - Automatically holds when Phase 2 endpoint is used for expansion decision-making
  - A direct consequence of Slepian's lemma, that the probability mass of a bivariate normal variable increases with the correlation.

2-in-1 Dose Selection Design



Zhang et al. (2022) A 2-in-1 Adaptive Design to Seamlessly Expand a Selected Dose from a Phase 2 Trial to a Phase 3 Trial for Oncology Drug Development.

BOP2-TE Design

- The Bayesian optimal phase 2 (BOP2) design is a unified framework for phase II clinical trials, which can be applied on various types of endpoints (e.g., binary, ordinal, TTE, co-primary, etc), including jointly monitoring efficacy and toxicity, i.e., BOP2-TE (Chen et al. 2024).
  - Go/no-go decisions are made based on adaptive Bayesian posterior probability cutoffs at interim analyses and final analysis.
  - Shiny app is available at https://trialdesign.org/
- BOP2-TE design incorporates one global null hypothesis and two partial null hypotheses.
  - H_{00}: the treatment is futile and toxic; H_{01}: the treatment is safe but futile; H_{10}: the treatment is efficacious but toxic.
- BOP2-TE design maximizes the power with type I error rates under three hypotheses are controlled at desirable levels simultaneously.

BOP2-TE in Dose Optimization

- FDA's dose optimization guidance suggested that "the use of an adaptive design to stop enrollment of patients to one or more dosage arms of a clinical trial following an interim assessment of efficacy and/or safety could be considered".
- For each dosage arm in dose optimization, interim monitoring could be performed with BOP2-TE and the dosage arms which cross the stopping boundaries will be stopped.
  - Early stopping by comparing efficacy and toxicity between dosage arms is not needed, as given a typical maximum sample size of 20-40 per dosage arm, there is little power at the interims to establish that one dose is better than another.
- At the end of the trial, the optimal dose could be selected based on a certain risk-benefit criteria from the doses that never cross the stopping boundaries.
- Simulation shows the BOP2-TE could achieve high percentage of selecting the true optimal dose in multiple dose optimization trials.

References

- Shah, M., et al. (2021). The drug-dosing conundrum in oncology—when less is more. *New England Journal of Medicine*, *385*(16), 1445-1447.
- Fourie Zirkelbach, J., et al. (2022). Improving dose-optimization processes used in oncology drug development to minimize toxicity and maximize benefit to patients. *Journal of Clinical Oncology*, *40*(30), 3489-3500..
- Thall, P. F., & Cook, J. D. (2004). Dose-finding based on efficacy–toxicity trade-offs. *Biometrics*, *60*(3), 684-693.
- Lin, R., Zhou, Y., Yan, F., Li, D., & Yuan, Y. (2020). BOIN12: Bayesian optimal interval phase I/II trial design for utility-based dose finding in immunotherapy and targeted therapies. *JCO precision oncology*, *4*, 1393-1402.
- Yuan, Y., Zhou, H., & Liu, S. (2024). Statistical and practical considerations in planning and conduct of dose-optimization trials. *Clinical Trials*, *21*(3), 273-286.
- Yang, P., Li, D., Lin, R., Huang, B., & Yuan, Y. (2024). Design and sample size determination for multiple-dose randomized phase II trials for dose optimization. *Statistics in Medicine*, *43*(15), 2972-2986.
- Chen, C. (2023). To go or not to go in phase 2/3 oncology trials, a critical question with a unified answer. *Contemporary Clinical Trials*, *128*, 107146.
- Chen C., et al. (2018) A 2-in-1 Adaptive Phase 2/3 Design for Expedited Oncology Drug Development. *Contemporary Clinical Trials*, *64*:238-242.
- Zhang, P., Li, X. N., Lu, K., & Wu, C. (2022). A 2-in-1 adaptive design to seamlessly expand a selected dose from a phase 2 trial to a phase 3 trial for oncology drug development. *Contemporary Clinical Trials*, *122*, 106931.
- Chen, K., Zhou, H., Lee, J. J., & Yuan, Y. (2024). BOP2-TE: Bayesian optimal phase 2 design for jointly monitoring efficacy and toxicity with application to dose optimization. *Journal of Biopharmaceutical Statistics*, 1-16.