Utilities of 2-Stage Designs for Addressing Dose Optimization in Pivotal Trials

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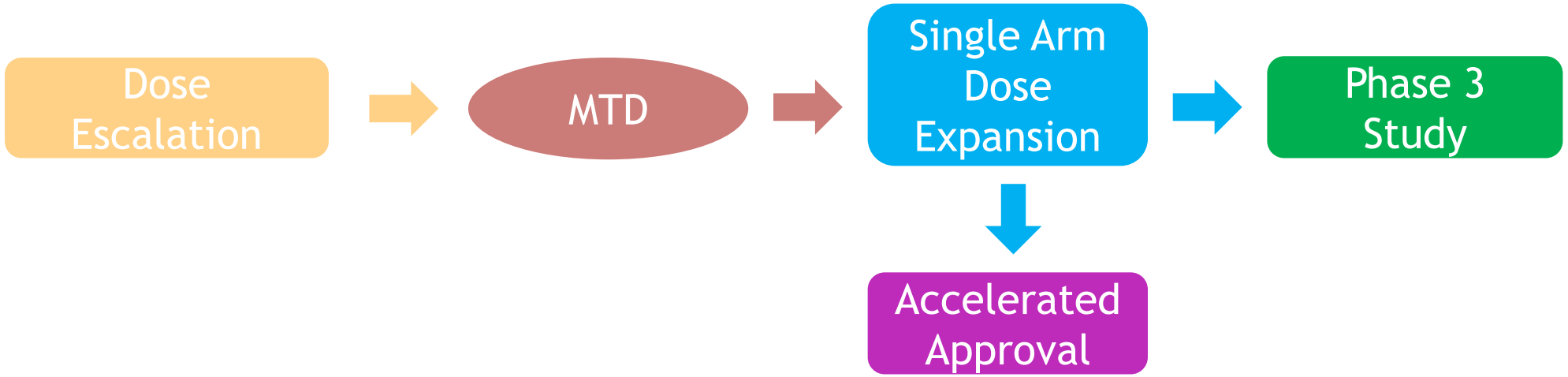
Outline of Presentation

- Introduction to Project Optimus and FDA Guidance on Dose Optimization
- Incorporating Dose Optimization in Drug Development
- Use of 2-Stage Adaptive Designs in Pivotal Trials
  - —Dose selection
  - —Combination of data in final analysis
  - —Multiplicity Adjustment
- Summary

Background

- Traditional oncology drug development has focused on identifying the maximum tolerated dose
  - A concept of higher dose associated with higher efficacy driven by cytotoxic drug development
  - Accelerated approval often pursued with a single arm dose expansion study
- Potential safety and excessive toxicity can lead to unfavorable benefit risk for patients



Drug Doses and Schedules May be Modified after Approval due to Safety and Toxicity

Examples of Drugs Whose Doses or Schedules Were Modified for Safety or Tolerability after Approval.*

Drug	Initial Dose and Trials	Modified or Added Dose and Trials	Reason for Modified or Added Dose
Small-molecule drugs			
Ceritinib (Zykadia)	750 mg PO daily fasted (ASCEND-1)	450 mg PO daily with food (ASCEND-8)	Reduce gastrointestinal toxic effects
Dasatinib (Sprycel)	70 mg PO twice daily (CA180013, CA180005, CA180006, and CA180015)	100 mg PO daily (CA180034)	Reduce hematologic toxic effects and fluid retention
Niraparib (Zejula)	300 mg PO daily (NOVA)	200 mg PO daily (PRIMA)	Reduce thrombocytopenia in patients with a lower platelet count or lower body weight
Ponatinib (Iclusig)	45 mg PO daily (PACE)	45 mg PO daily, then 15 mg PO daily once ≤1% *BCR-ABL* is achieved (OPTIC)	Reduce vascular occlusive events
Chemotherapy			
Cabazitaxel (Jevtana)	25 mg/m^2 IV every 3 wk (TROPIC)	20 mg/m^2 IV every 3 wk (PROSELICA)	Reduce hematologic toxic effects and infections
Antibody–drug conjugates			
Gemtuzumab ozogamicin (Mylotarg)	9 mg/m^2 IV on days 1 and 15 (Study 201, Study 202, and Study 203)	3 mg/m^2 IV on days 1, 4, and 7 (Mylofrance-1)	Reduce veno-occlusive disease and treatment-related mortality

* Adapted from the Food and Drug Administration.[2] IV denotes intravenous, and PO by mouth.

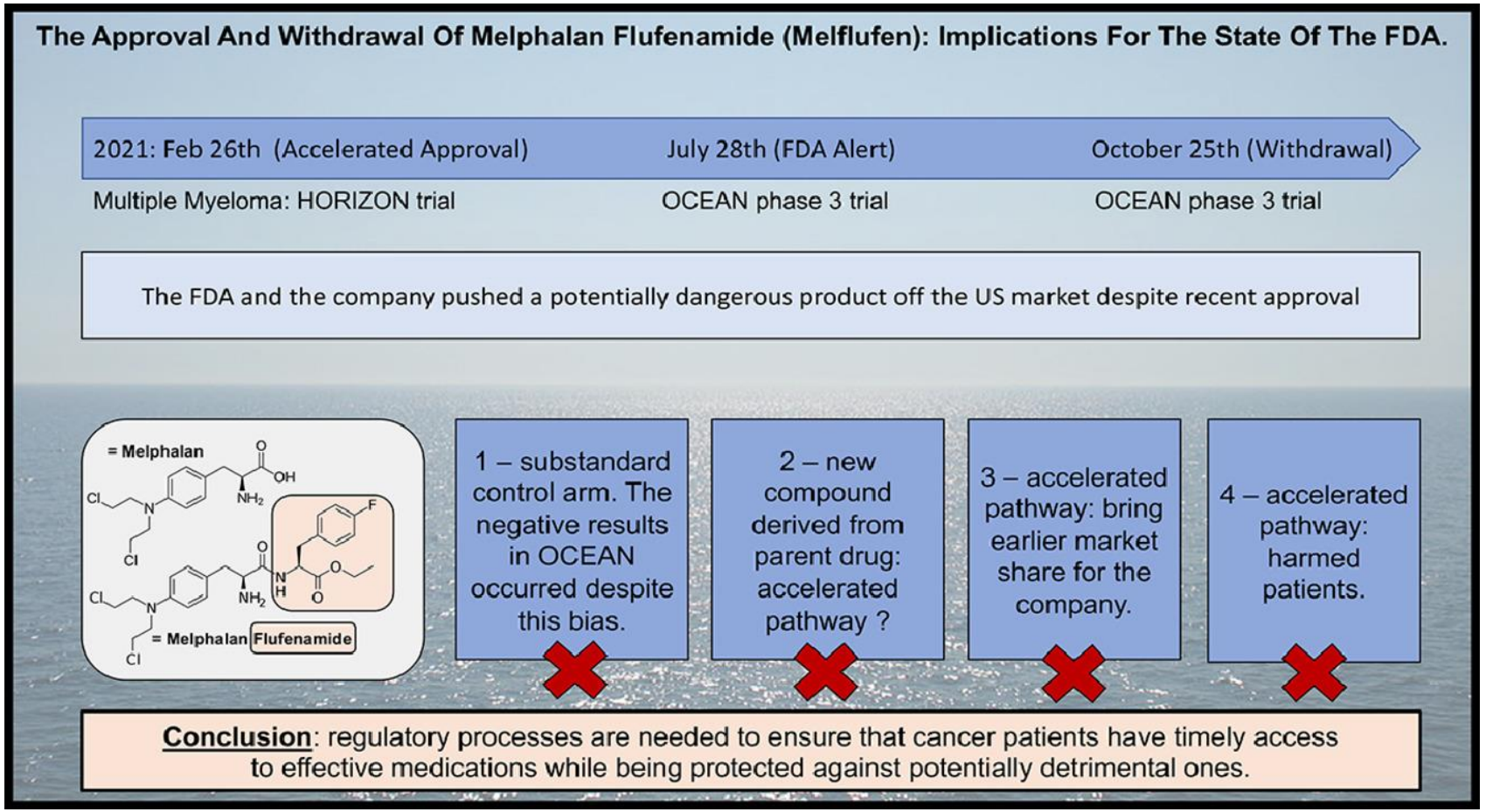
Shah et al, NEJM385:1445-1447, 2021

Perspective Translational Oncology 18 (2022) 101374

The approval and withdrawal of melphalan flufenamide (melflufen): Implications for the state of the FDA.

Timothée Olivier [a,b,*], Vinay Prasad [b]

- Accelerated approval based on a single arm trial (ORR = 23.7%, n=97)
- Phase 3 trial (n=495) showed excessive deaths (HR=1.10, median OS 5.2m shorter than pomalidomide) despite better progression free survival (PFS HR 0.79, p=0.032)



OCEAN Study Results

PFS

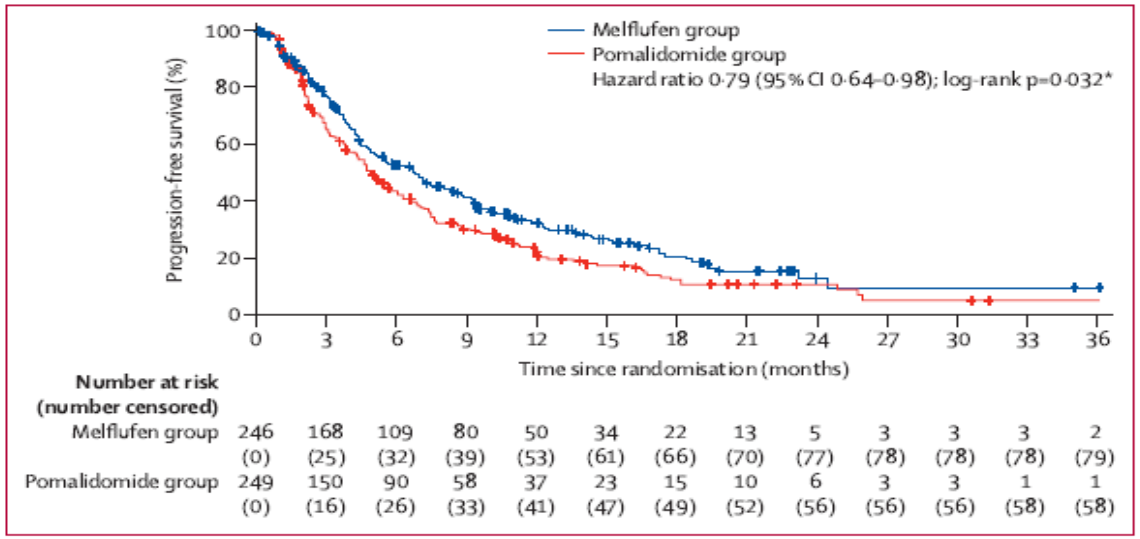


***Figure 2*: Progression-free survival, assessed by independent review committee**
Melflufen=melphalan flufenamide.

OS

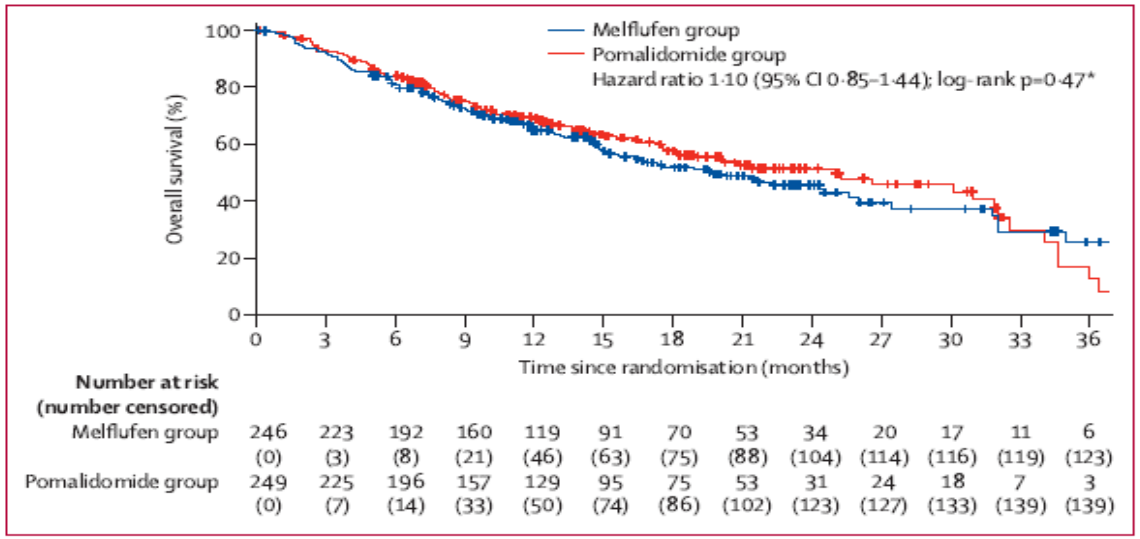


***Figure 3*: Overall survival assessed by independent review committee**
Melflufen=melphalan flufenamide.

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

NEJM Article Oct-2021

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

- Advances in cancer biology and molecular genetics has led to more targeted therapies
  - Higher dose beyond a certain level may not enhance anti-tumor activity
  - Long-term tolerability is important for chronic use of targeted therapies

- Sponsors should carefully evaluate exposure-response, efficacy, and safety data from early trials to inform dose selection, rather than automatically selecting the maximum tolerated dose. The answer to the dose-selection conundrum may sometimes be that *less is more*.

FDA Project Optimus and Draft Guidance on Dose Optimization

- FDA Oncology Center of Excellence (OCE) announced Project Optimus in May 2021 to investigate strategies for better dose optimization of oncology products
- FDA Draft Guidance on Dose Optimization (January 2023)
- Move away from automatically carrying the maximum tolerated dose to later development

Use a holistic approach in dose optimization

- Consider full spectrum of information – PK/PD, early efficacy and safety data
- Plan sufficient PK sampling to support population PK and dose- and exposure-response analyses for safety and efficacy
- Pursue multiple dosage levels in dose-finding trials
- Recommend randomized, parallel design to assess dose response
  - Sized for sufficient assessment of activity, safety and tolerability of each dosage
  - No need to power for statistical comparison among doses

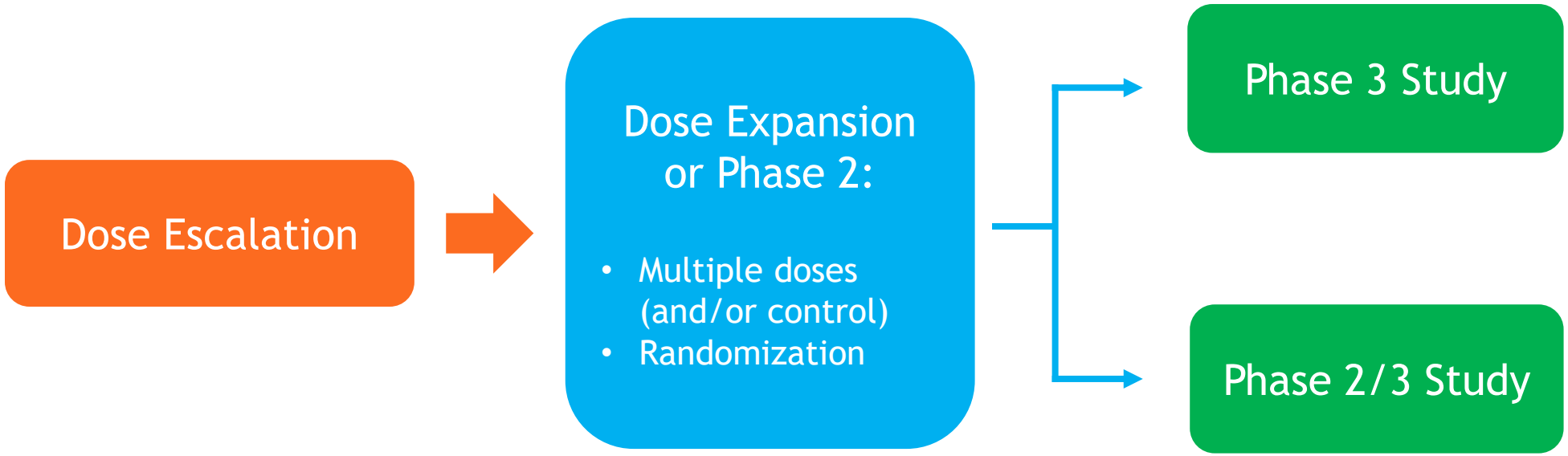
FDA Project Optimus and Draft Guidance on Dose Optimization

- Multiple dosages may be compared prior to a registration trial(s) or as part of a registration trial(s) by adding an additional dosage arm(s).
    - When a registration trial contains multiple dosages and a control arm and is designed to establish superior efficacy of one of the dosages compared to the control arm, the trial design should provide strong control of Type I error. The analysis plan should specify a multiple-testing procedure which accounts for testing multiple treatments versus a control as well as any interim assessments after which an inferior arm is dropped.

FDA Draft Guidance on Dose Optimization (2023)

– Potential use of adaptive design for dose selection
– Important to control the overall type I error in multiple dose comparisons

New Paradigm in Oncology Development - Dose Optimization



- Include at least 2 doses below MTD
- Evaluate PK/PD, exposure and dose responses
- Evaluate totality of data for overall benefit and risk
- Potential use of adaptive design with dose selection based on early biomarker

Role of 2-Stage Adaptive Design in Dose Optimization: Seamless Phase 2/3 Design

- Stage 1
  - To evaluate several and select one single dose formulation for further investigation in Phase 3
  - May include a control arm
  - Traditionally achieved in a Phase 2 study

- Stage 2
  - To demonstrate the superior treatment effect of the experimental therapy at the selected dose compared to a control
  - Traditionally the objective of a Phase 3 study

- Operational vs Inferential Seamless adaptive design

Benefit of Adaptive Design in Dose optimization

Comparing with traditional two separate clinical trials (phase 2 dose finding study + phase 3 confirmatory trial),

Operational seamless adaptive design will

- Save operational time by reducing the ‘white space’ between phase 2 and 3
- Speed up final phase 3 readout

Inferential seamless adaptive design will

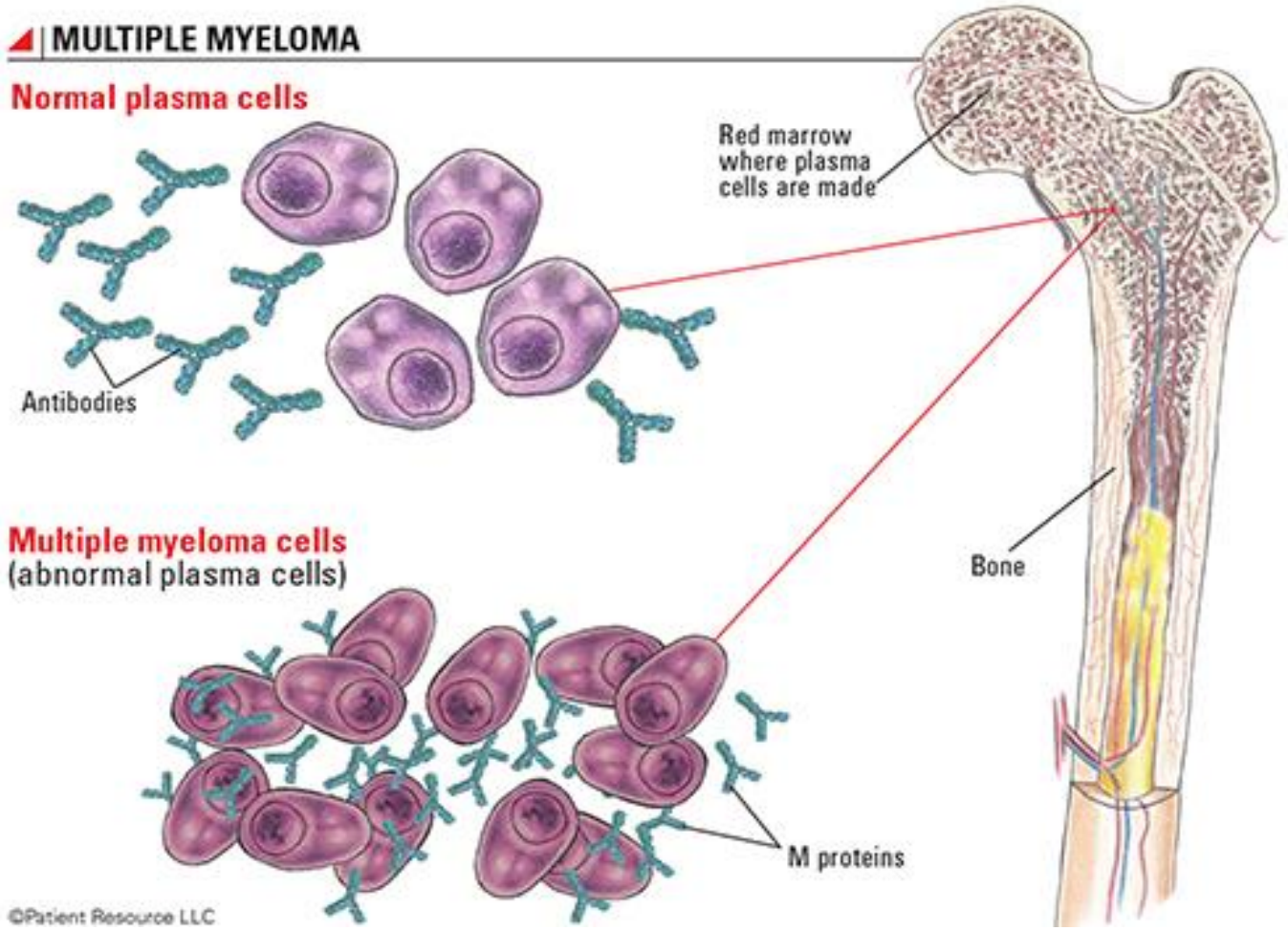
- Increase power and save sample size by including Phase 2 parts subjects (selected dose) in phase 3 analysis
- Need to manage data access and study blinding during adaptation

Example

Development of New Drugs for Multiple Myeloma

Multiple Myeloma

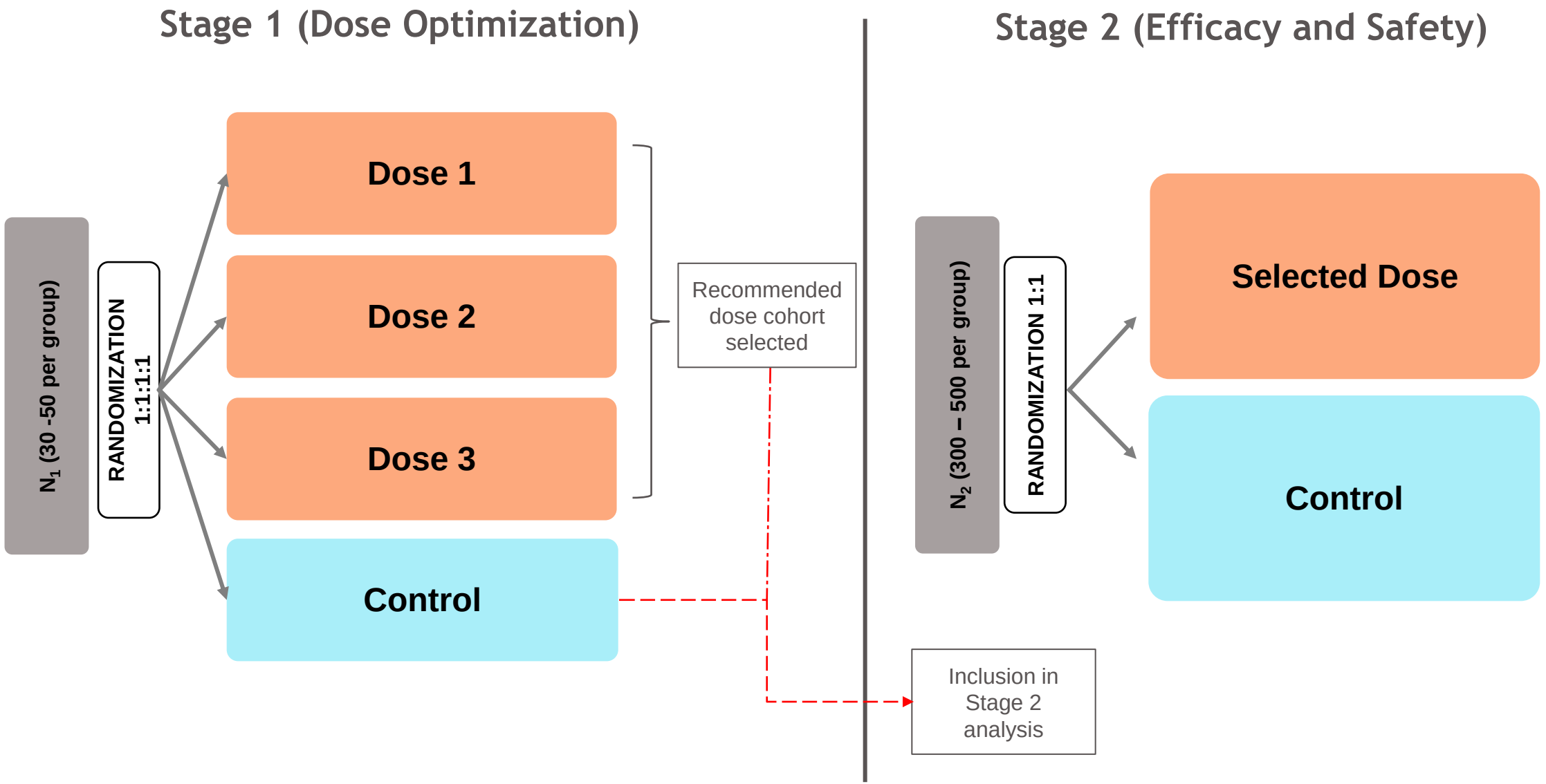
- Cancer of plasma cells, i.e., excessive numbers of abnormal plasma cells in bone marrow
- Among hematologic malignancies, multiple myeloma is the second most prevalent blood cancer after non-Hodgkin lymphoma, representing 10% of hematologic malignancies



New Class of Drugs Under Development

- CELMoDs are a new class of drugs that are functionally different from the immunomodulators like Revlimid and Pomalyst
  - Larger molecules and work by quickly degrading a specific set of proteins (Ikaros and Aiolos)
  - Potent modulators of the cereblon E3 ligase complex
  - Stimulate the immune system and kill myeloma cells directly
- B-cell maturation antigen (BCMA) targeted therapies (mAB, antibody-drug conjugate, CAR-T)
  - BCMA preferentially expressed on multiple myeloma cells
  - Important to the long-term survival of plasma cells in the bone marrow and can affect disease progression
- T-cell engager are antibodies targeting CD3 on T cells and antigens GPRC5D, BCMA or FcRH5 on myeloma cells

Example: Inferential Adaptive Seamless Phase 2/3 Design



Important Considerations for 2-Stage Adaptive Designs

- When and how to select dose in Stage 1?
  - Biomarker, ORR, or efficacy endpoints
  - PK/PD
  - Safety

- Who will make the dose selection?
  - DMC and sponsor
  - Data integrity and blinding of study team

- How to combine the data from both stages in final analysis?
  - Efficacy endpoint (PFS, OS)
  - Combination rule for p-value calculation
  - Adjustment for dose selection

Stage 1 Considerations For Dose Selection (Biomarker and safety)

- Dose selection will happen when X (e.g. 30-50) subjects in each arm are treated at least 3 cycles or discontinued from treatment.
- A composite measure 'Benefit-Risk score' consists both efficacy biomarker and safety parameters may be used to guide the dose selection. Dose level with highest Benefit-Risk score is preferred.
- Only one dose level to be selected to continue.
- An Independent Data Monitoring Committee (IDMC) will make recommendation on dose selection. Sponsor Executive Oversight Committee will review IDMC recommendation and make final decision.
- Study team will remain blinded and data integrity will be documented in a Data Integrity and Access Plan.

Potential dose selection strategy - Benefit-Risk Score

Endpoints		*High Dose*	*Medium Dose*	*Low Dose*
Efficacy	ORR or VGPR or Serum M-protein reduction	$\Delta_{11} = r_{11} - r_{13}$	$\Delta_{12} = r_{12} - r_{13}$	0
Safety	Decrease in absolute neutrophil count	$\Delta_{21} = r_{21} - r_{23}$	$\Delta_{22} = r_{22} - r_{23}$	0
	Decrease in platelet count	$\Delta_{31} = r_{31} - r_{33}$	$\Delta_{32} = r_{32} - r_{33}$	0
	Grade 3 or higher or any serious infections (SOC)	$\Delta_{41} = r_{41} - r_{43}$	$\Delta_{42} = r_{42} - r_{43}$	0
	Discontinue study treatment due to adverse events	$\Delta_{51} = r_{51} - r_{53}$	$\Delta_{52} = r_{52} - r_{53}$	0
Benefit-risk Score		$\Delta_{11} - \sum_{i=2}^{5} w_i \Delta_{i1}$	$\Delta_{12} - \sum_{i=2}^{5} w_i \Delta_{i2}$	0

r_{ij} are the response rate for dose level i and endpoint j; $w_2 = w_3 = w_4 = w_5 = \frac{1}{4}$.

- Choose Low Dose as the reference arm;
- The efficacy and safety scores for High and Medium dose level for each parameter are calculated as the difference from the reference arm; Safety score is averaged across the 4 parameters of interest
- Benefit-Risk Score = (Difference in Efficacy Rates – Average Difference in Safety Rate)

Dose Selection Strategy Operation Characteristics-Simulation (N=50)

Scenario 1: Big efficacy difference, same safety

Simulation Parameters (Rate)			
	High	Medium	Low
Efficacy	0.65	0.55	0.45
Safety1	0.75	0.75	0.75
Safety2	0.2	0.2	0.2
Safety3	0.17	0.17	0.17
Safety4	0.06	0.06	0.06

Selection Criteria	High Dose	Medium	Low Dose	Tie*
Benefit-Risk Score	80.7%	16%	1.7%	1.6%
Efficacy Only**	81%	12.5%	1%	5.5%

Scenario 2: Small efficacy difference, same safety

Simulation Parameters (Rate)			
	High	Medium	Low
Efficacy	0.6	0.55	0.45
Safety1	0.75	0.75	0.75
Safety2	0.2	0.2	0.2
Safety3	0.17	0.17	0.17
Safety4	0.06	0.06	0.06

Selection Criteria	High Dose	Medium	Low Dose	Tie*
Benefit-Risk Score	64%	30%	4%	2%
Efficacy Only**	63%	26.7%	2.5%	7.8%

Iteration 10,000; N=50;
*Only include ties that could not lead to a decision, i.e. more than one arm have the highest B-R scores;
**Only compare efficacy biomarker numerically and choose the arm with highest response rate;

Dose Selection Strategy Operation Characteristics-Simulation (N=50)

Scenario 3: Big efficacy difference, better safety in low dose

Simulation Parameters (Rate)			
	High	Medium	Low
Efficacy	0.65	0.55	0.45
Safety1	0.8	0.75	0.55
Safety2	0.22	0.21	0.2
Safety3	0.19	0.17	0.15
Safety4	0.07	0.06	0.05

Selection Criteria	High Dose	Medium	Low Dose	Tie*
Benefit-Risk Score	69.3%	20.2%	8.4%	2.1%
Efficacy Only**	81%	12.5%	1%	5.5%

Scenario 4: Small efficacy difference, better safety in low dose

Simulation Parameters (Rate)			
	High	Medium	Low
Efficacy	0.6	0.55	0.45
Safety1	0.8	0.75	0.55
Safety2	0.22	0.21	0.2
Safety3	0.19	0.17	0.15
Safety4	0.07	0.06	0.05

Selection Criteria	High Dose	Medium	Low Dose	Tie*
Benefit-Risk Score	49%	33%	15%	3%
Efficacy Only**	63%	26.7%	2.5%	7.8%

Iteration 10,000; N=50;
*Only include ties that could not lead to a decision, i.e. more than one arm have the highest B-R scores;
**Only compare efficacy biomarker numerically and choose the arm with highest response rate;

Dose Selection Strategy Operation Characteristics-Simulation (N=50)

Scenario 5: Same efficacy, same safety

Simulation Parameters (Rate)			
	High	Medium	Low
Efficacy	0.55	0.55	0.55
Safety1	0.75	0.75	0.75
Safety2	0.2	0.2	0.2
Safety3	0.17	0.17	0.17
Safety4	0.06	0.06	0.06

Selection Criteria	High Dose	Medium	Low Dose	Tie*
Benefit-Risk Score	32%	32%	33%	3%
Efficacy Only**	29%	29%	30%	12%

Scenario 6: Same efficacy, better safety in low dose

Simulation Parameters (Rate)			
	High	Medium	Low
Efficacy	0.55	0.55	0.55
Safety1	0.8	0.75	0.55
Safety2	0.22	0.21	0.2
Safety3	0.19	0.17	0.15
Safety4	0.07	0.06	0.05

Selection Criteria	High Dose	Medium	Low Dose	Tie*
Benefit-Risk Score	15%	22.3%	60.4%	2.3%
Efficacy Only**	29%	29%	30%	12%

Iteration 10,000; N=50;
*Only include ties that could not lead to a decision, i.e. more than one arm have the highest B-R scores;
**Only compare efficacy biomarker numerically and choose the arm with highest response rate;

Final Analysis Combining Data from Stages 1 and 2

- *Step 1*: Compute the p value $\boldsymbol{p_{1,s}}$ testing the difference between the selected treatment group and the control group regarding the efficacy endpoint for patients enrolled in Stage 1.
- *Step 2*: Conduct the multiplicity adjustment for dose selection and compute the first-stage adjusted p value, $\boldsymbol{p_1}$
- *Step 3*: Compute the p value $\boldsymbol{p_2}$ testing the difference between the selected treatment group and the control group regarding the efficacy endpoint for patients enrolled in Stage 2.
- *Step 4*: Combine the p values from both stages using inverse normal combination rule:

$$\boldsymbol{p = C(p_1, p_2) = 1 - \Phi\left(\sqrt{w_1}\Phi^{-1}(1-p_1) + \sqrt{1-w_1}\Phi^{-1}(1-p_2)\right)},$$

where w_1 is the weight for Stage 1. For example, $w_1 = N_1/(N_1 + N_2)$.

- *Step 5*: Compare the combined $\boldsymbol{p}$ value with the prespecified error level $\boldsymbol{\alpha}$.

Methods for Multiplicity Adjustment

- Dose selection is based on biomarker while final efficacy analysis is based on clinical endpoint
- Actual type I error depends on the correlation between biomarker and clinical endpoint
- Sidak and Dunnett adjustments have been proposed to account for the unknown correlation
- Further enhancement can be achieved by considering the ranking of selected dose based on the totality of benefit-risk profile

Correlation (ρ) between Biomarker and Efficacy	Empirical Type I Error Rate (%) for m = 3 Groups	
	Sidak	Dunnett
0	1.13	1.45
0.3	1.43	1.69
0.5	1.62	2.08
0.8	2.00	2.35
1.0	2.07	2.46

Efficiency Gain in Inferential Seamless Adaptive Design

- Increased power by ~4% compared with a stand-alone phase 3 trial in this example
- Equivalent to saving of ~12% of subjects
- Reduced study duration by ~9 months
- Efficiency gain consistent with reports by others (Li *et al* 2015; Jiang and Yang 2023)

Summary

- With more targeted therapies in development, dose optimization in oncology has shifted from MTD to holistic assessment
  - Characterize PK/PD and exposure response profiles early
  - Consider randomization to multiple doses

- Adaptive designs useful in addressing dose optimization in pivotal trials while enabling acceleration of drug development
  - Improve statistical and operational efficiency
  - Data access and trial blinding manageable

Key References

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