Pierre Fabre Optimus Journey: FDA-Approved Examples of Dose Optimization in FIH Oncology Trials

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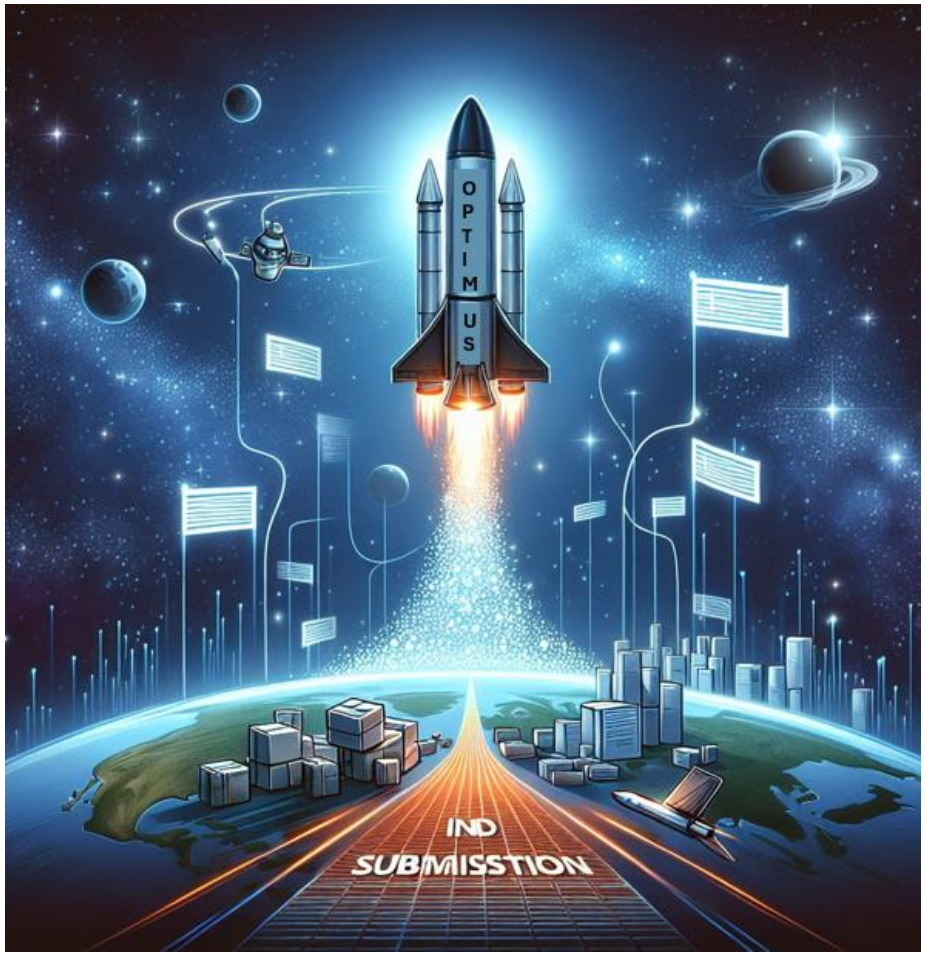
New ways to care

PSI 2025

FDA's Project Optimus – Key Principles

OPTIMUS redefines selection of optimal dose like a rocket seeking its perfect trajectory



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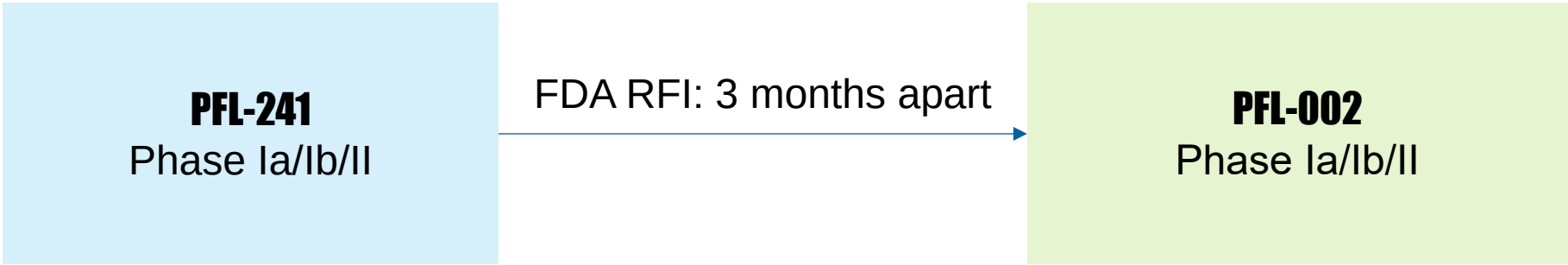
FDA's Project Optimus – Key Principles

- **Modernize oncology drug dosing:** moving beyond traditional maximum tolerated dose approaches
- Encourage **early and robust dose-finding studies:** balancing efficacy with tolerability
- Reduce unnecessary toxicity: improving **quality of life** for patients
- **Foster collaboration between the FDA and industry:** innovating trial design to support informed dosing decisions

PFL early phase studies

Under Optimus requirements

- Two targeted therapies in NSCLC
- First In Human studies, Phase I/II seamless design
  - Phase Ia: Dose Escalation with BOIN design
  - Phase Ib: Randomized Dose Optimization to determine RP2D
  - Phase II: Dose Expansion



BOIN: Bayesian Optimal Interval Design, NSCLC: Non-Small Cell Lung Cancer, PFL: Pierre Fabre Laboratory, RFI: Request for Information
RP2D: Recommended Phase 2 Dose

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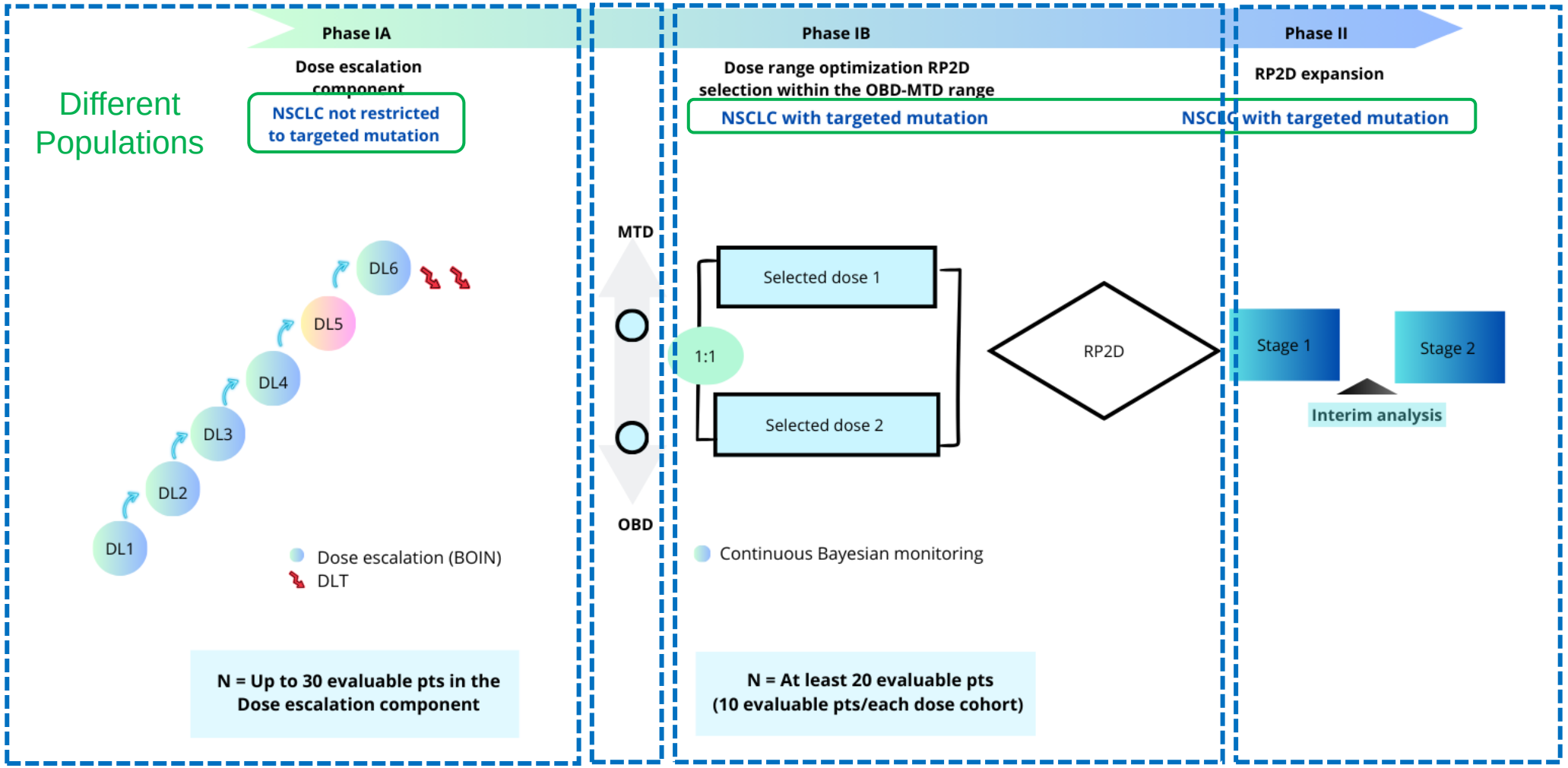
PFL-241/PFL-002 Initial study design



BOIN: Bayesian Optimal Interval Design, DL: Dose Level, DLT: Dose-Limiting Toxicity, MTD: Maximum Tolerated Dose
NSCLC: Non-Small Cell Lung Cancer, OBD: Optimal Biological Dose, RP2D: Recommended Phase 2 Dose

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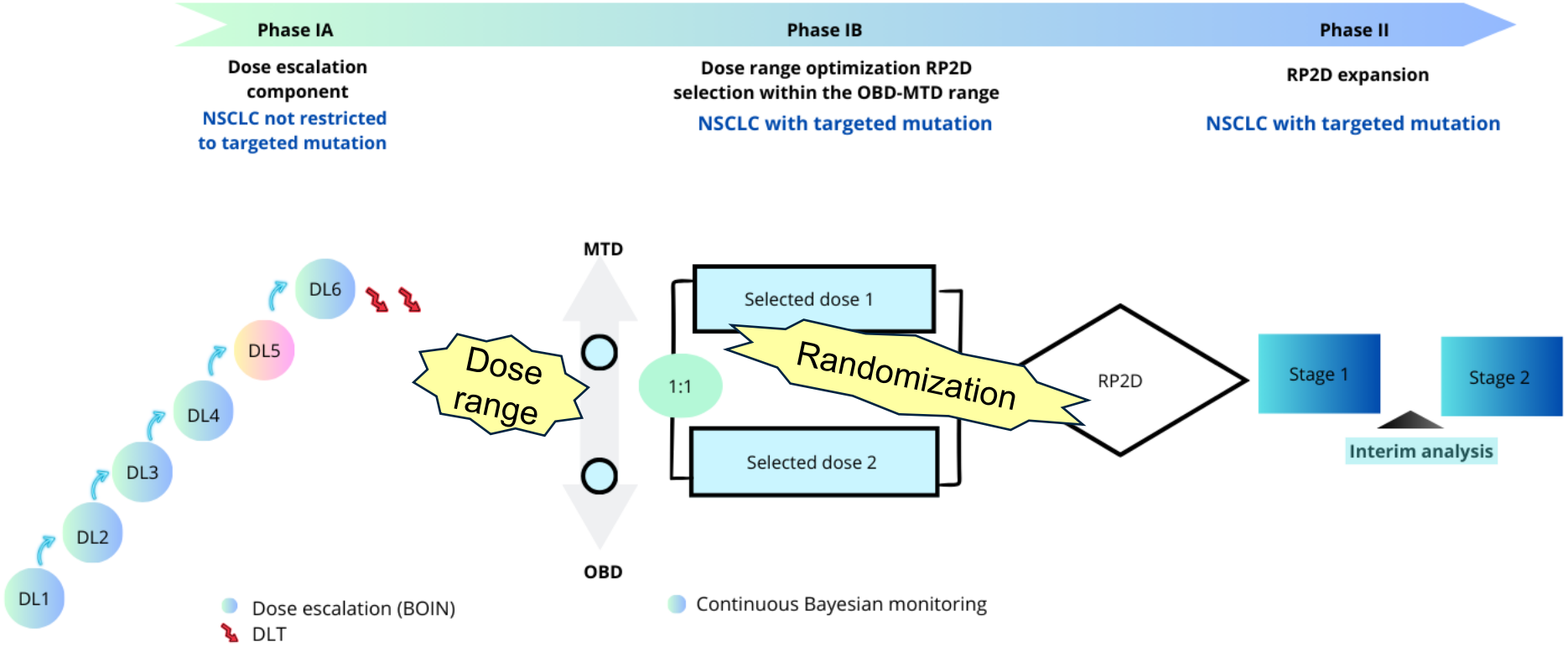
PFL-241/PFL-002 Initial study design

Optimus compliance



N = Up to 30 evaluable pts in the Dose escalation component

N = At least 20 evaluable pts (10 evaluable pts/each dose cohort)

PK/PD/Biomarkers analyzed at each Phase of the trial

PK/PD BioM

BOIN: Bayesian Optimal Interval Design, DL: Dose Level, DLT: Dose-Limiting Toxicity, MTD: Maximum Tolerated Dose, NSCLC: Non-Small Cell Lung Cancer, OBD: Optimal Biological Dose, RP2D: Recommended Phase 2 Dose

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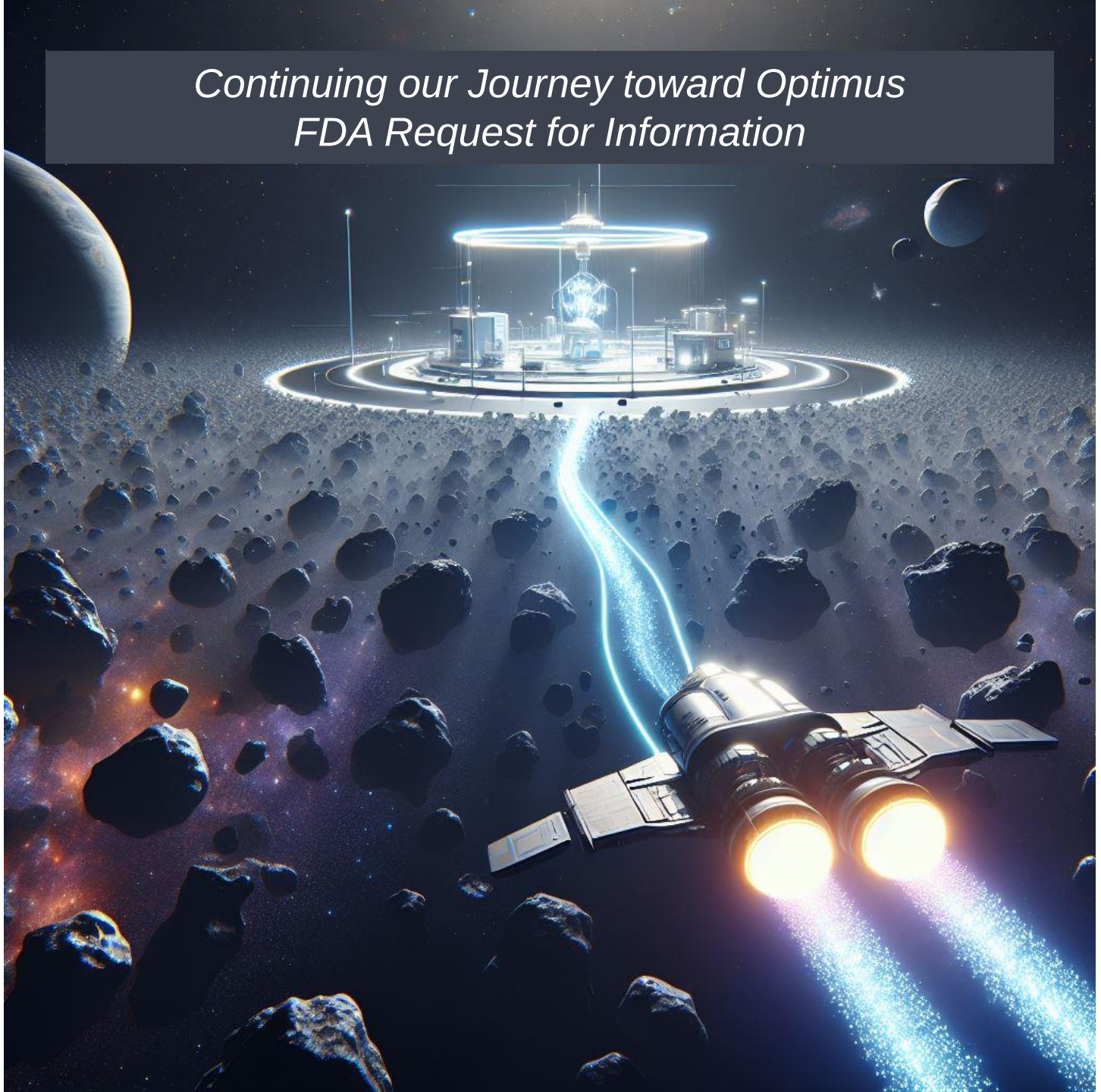

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PFL-241 FDA Hold Comment

Dose Escalation is unlikely to generate sufficient activity data prior Dose Optimization

3 options proposed by FDA

#1 **Backfilling** in Dose Escalation to include additional activity and longer-term tolerability assessment **in the selected patient population** prior to the dose randomization portion.

#2 **Modifying Dose Optimization** to assess additional activity and longer-term tolerability data **in your selected population** in a **cohort of up to 20 patients**, prior to the dose randomized portion.

#3 **Reordering Dose Optimization and Dose Expansion**, so that the dose randomization occurs after the Simon 2-stage assessment of activity.

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PFL-241

FDA Hold Comment

		Pros	Cons
#1	Backfilling	• Possible to combine with BOIN design • Can be conducted in parallel to Dose Escalation • Easy option to have first efficacy signal at “promising dose levels”	• Limited data supporting choice of backfilled doses
#2	Modifying DO	• Possibility to stop early for futility • Easy to implement to have first signal of efficacy	• Limited data supporting choice of the dose to be selected for the cohort • Risk to stop the trial if wrong dose selected • No data accumulation on lower doses to help in selection of doses for Dose Optimization
#3	Reordering DO and DE	• No pros identified	• Not very clear why moving Simon 2-stage before Dose Optimization

DO: Dose Optimization; DE: Dose Expansion

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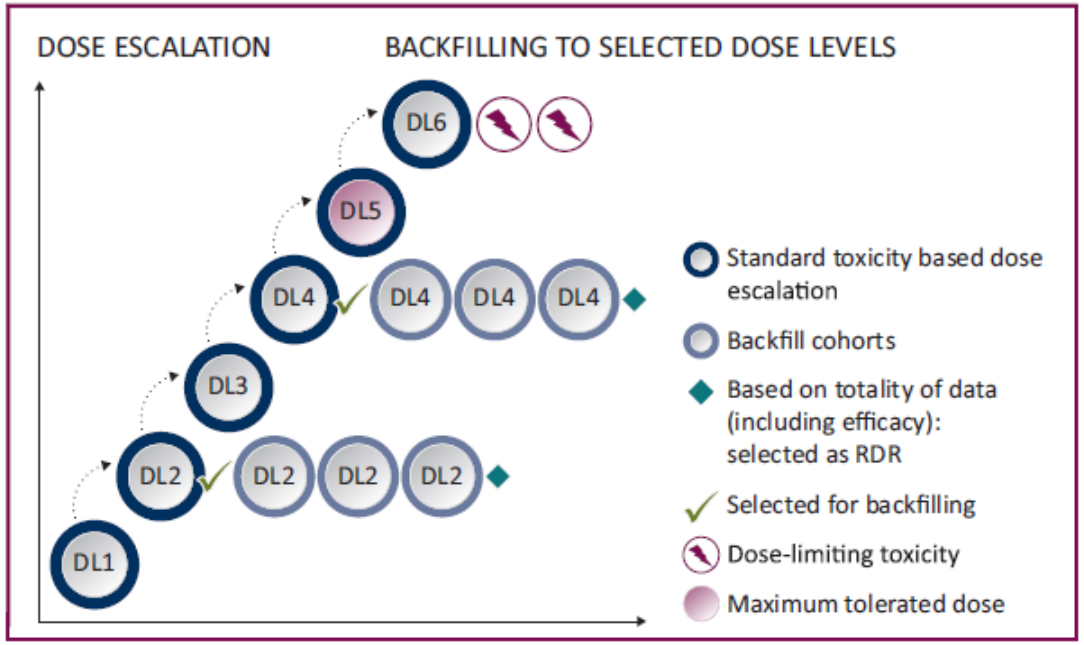
FDA Hold Comment

Option selected **#1**

Backfilling in the targeted population



Araujo et al., 2022

CLINICAL CANCER RESEARCH | PERSPECTIVE

Backfilling Patients in Phase I Dose-Escalation Trials Using Bayesian Optimal Interval Design (BOIN)

Yixuan Zhao[1], Ying Yuan[2], Edward L. Korn[3], and Boris Freidlin[3]

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PFL-241 FDA Hold Comment

Backfilling BOIN (BF-BOIN) design

- Conditions for opening dose *b* for backfilling:
  - Safety: Dose *b* should be lower than the current dose *c* of the dose escalation
  - Activity demonstrated: At least one response is observed at dose *b* or below

- Conditions for closing dose level *b* if:
  - DLT rate at dose level *b* is greater than BOIN de-escalation boundary (λd)
  - And, the pooled DLT rate based on pooled data over *b* and *b*+1 is greater than λd

PFL-241 FDA Hold Comment

Backfilling BOIN (BF-BOIN) design

- Additional DLTs emerging at backfilling can cause conflict with data collected in dose escalation

Decision according to the data observed at a backfilled dose *b*	Decision according to the data observed at the current dose *c*		
	Escalation	Stay	De-escalation or elimination
Escalation	no conflict	no conflict	no conflict
Stay	conflict	no conflict	no conflict
De-escalation or elimination	conflict	conflict	conflict

- Rules to resolve conflicts described in Zhao et al. 2024, using pooled DLT rates

PFL-241 FDA Non-Hold Comment

Expand the sample size in Dose Optimization to facilitate assessment of the dose

→ Modify Dose Optimization: Select at least 2 doses and up to 3 doses
→ Clarify Sample size: Target of 20 participants for each dose; Minimum 10 participants and maximum 30 participants for each dose

Limit enrollment in the dose expansion cohort to a max of 40 patients to limit the patients exposed to a potentially ineffective therapy

→ Modify Dose Expansion
- No statistical justification about the 40 participants
- Comment implemented, finally Dose Expansion has been removed during a later protocol amendment

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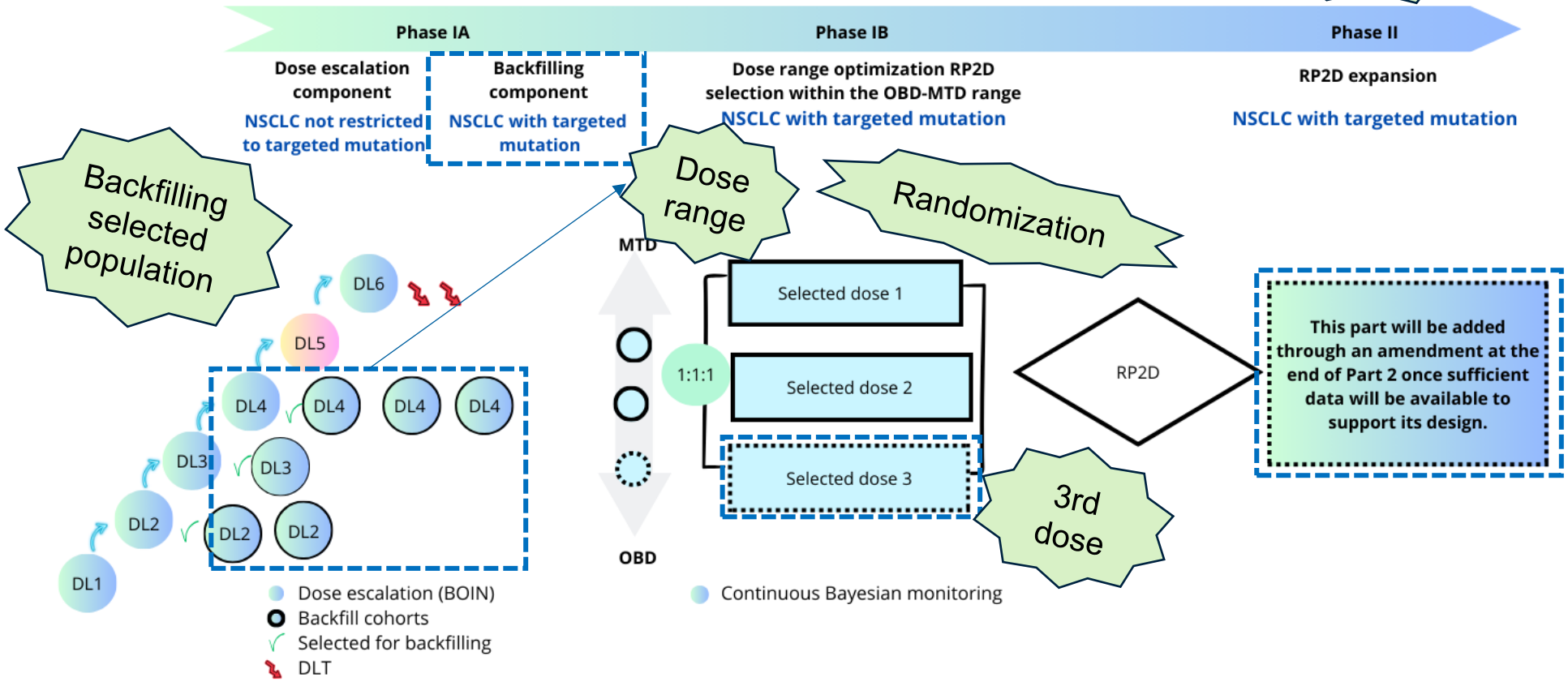
PFL-241 Final study design

Optimus compliance



N = Up to 30 evaluable pts in the Dose escalation component

N = Up to 15 evaluable pts in the backfilling component

N = Up to 90 evaluable* pts
(Min 10 - Max 30 evaluable pts/each dose cohort)

*possibility to explore a 3rd dose-level cohort

PK/PD BioM

PK/PD/Biomarkers analyzed at each Phase of the trial

BOIN: Bayesian Optimal Interval Design, DLT: Dose-Limiting Toxicity, MTD: Maximum Tolerated Dose, NSCLC: Non-Small Cell Lung Cancer, OBD: Optimal Biological Dose RP2D: Recommended Phase 2 Dose

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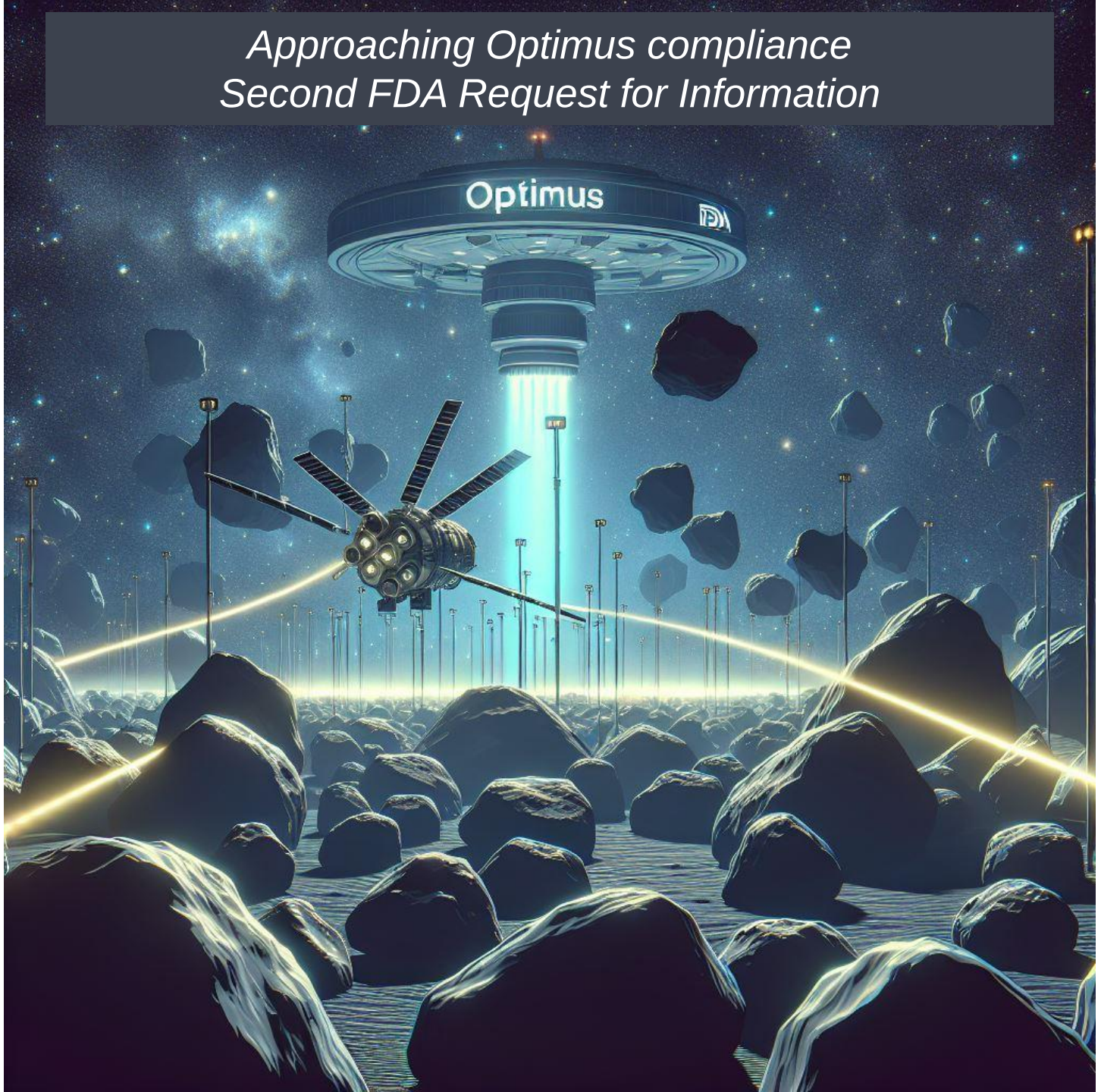
Approaching Optimus compliance
Second FDA Request for Information



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PFL-002

FDA Hold Comment

The current Dose Range Optimization design is likely insufficient to support the transition to a larger-scale study in Dose Expansion (Expansion at RP2D)

2 recommendations

#1 **Modifying Dose Optimization** to assess additional activity and longer-term tolerability data **in your selected population** in a **cohort of up to 20 patients**, prior to the dose randomized portion.

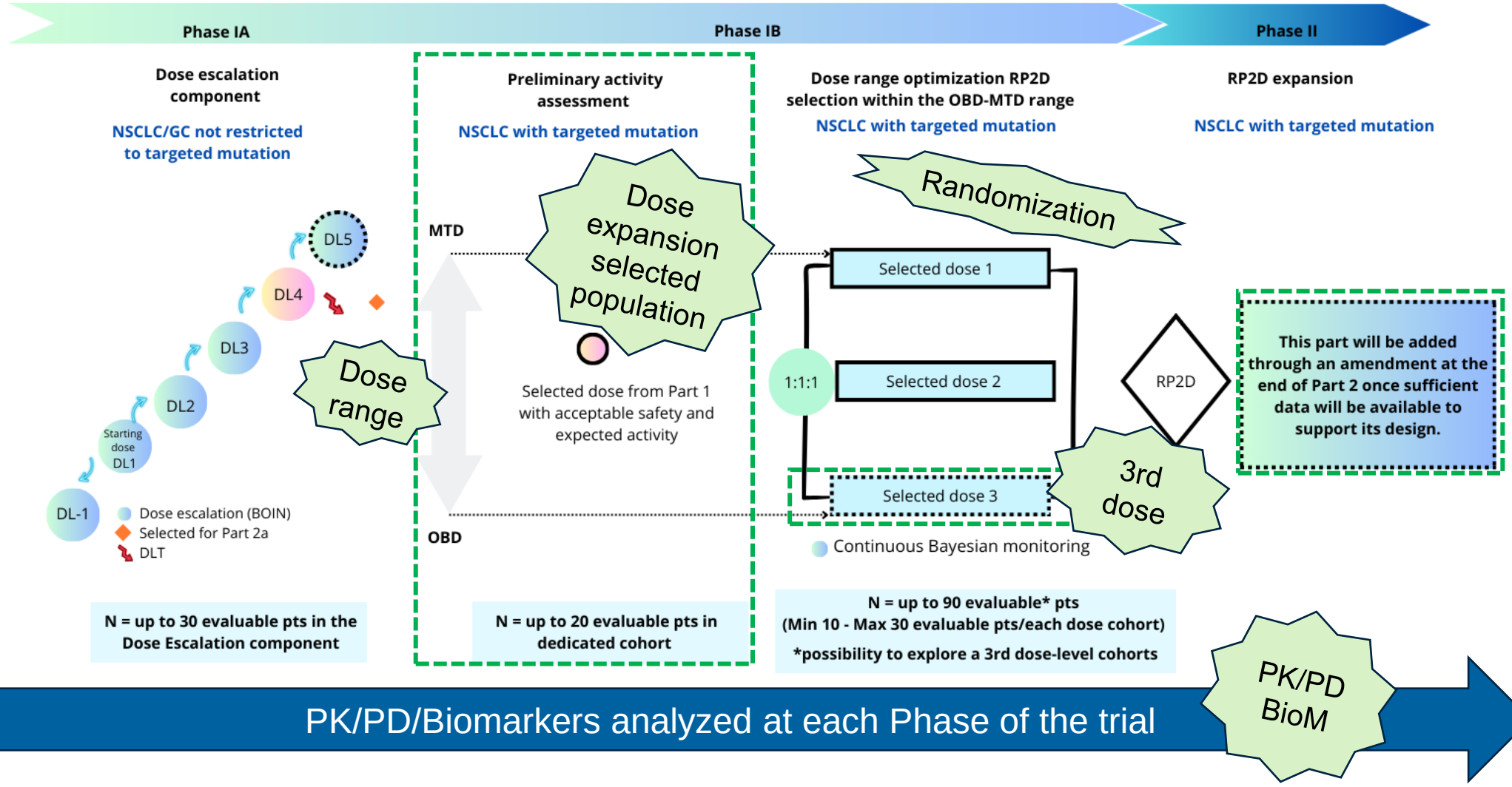
≈ **PFL-241 option #2**

#2 **Remove Dose Expansion**, it may be added as an amendment once the data from Dose Escalation and Dose Optimization are available, with adequate justification.

PFL-002

Final study design

Optimus compliance



BOIN: Bayesian Optimal Interval Design, DLT: Dose-Limiting Toxicity, GC: Gastric Cancer, MTD: Maximum Tolerated Dose, NSCLC: Non-Small Cell Lung Cancer, OBD: Optimal Biological Dose, RP2D: Recommended Phase 2 Dose

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Take-home messages

Accepted by FDA

- Identifying a **dose range** at the end of dose escalation
- **Randomizing** for dose optimization
- Supporting each step of the trial with **PK/PD/Biomarkers**
- Planning **PRO data** for dose optimization

Open questions

- What about Rare Diseases or Rare mutations?
- What about EMA?

Our recommendations

- Selecting participants from **the target population** earlier in the development process
- Generating more **activity data** prior to initiating randomized dose optimization (e.g. **backfilling** or **dedicated cohort**)
- Having possibility to test **3 doses** in dose optimization
- Designing Phase II once **data available** from Phase I
- Discussing design with FDA as early as possible (**Pre-IND meeting)**

Ending our Optimus journey

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Thank you for your attention.

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