Application of Phase 1 and Pre-clinical Data to Assist in Determining the Optimal Dosing Regimen (ODR) for Cancer Drugs Using the Principles of Project Optimus

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David Young, Sian Bigora, Peter Franks, Mary Nyberg, Yvonne Madden. Processa Pharmaceuticals, Hanover, Maryland

Abstract

Background: In 2022 and 2023 FDA introduced the Project Optimus initiative and the Draft Guidance "Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases." The FDA's desire is to move away from the maximum tolerated dose (MTD) approach in the development of all oncology drugs and to determine and justify the ODR, requiring one to evaluate the exposure-response relationship for both the safety and efficacy of oncology drugs. This approach has made the oncology drug developer re-examine their previous beliefs and reconsider the design of the clinical and pre-clinical studies. Processa has begun to implement the ODR evaluation in Phase 1 and pre-clinical studies and will be providing examples as well as how the findings may potentially affect the design of Phase 2/3 trials.

Methods/Results: For Next Generation Irinotecan (NGC-Iri), the toxicity and tumor growth inhibition after NGC-Iri administration (as well as tissue distribution of NGC-Iri) were compared to irinotecan in xenograft transplanted mice. Tumor growth inhibition remained constant at 100% for an NGC-Iri dose at the MTD and at 50% of the MTD. However, tumor growth inhibition after irinotecan administration decreased from 100% at the MTD to approximately 64% at 50% of the MTD. The differences seen in the tumor inhibition when NGC-Iri and irinotecan were administered illustrate that the exposure-efficacy profile of NGC-Iri follows a different pattern than the exposure-safety profile and is different from the irinotecan exposure-efficacy profile even though the active molecule is the same. The dose of NGC-Iri can be decreased to improve safety while not significantly sacrificing efficacy, different than what was seen with irinotecan. In a second example, we are evaluating the PK-safety relationship of a different Next Generation drug in our ongoing Phase 1 trial. We have recently found that the exposure-safety relationship is different for our NGC drug than for the approved drug with the same cancer-killing metabolite(s). Based on the difference in exposure-response in the Phase 1 study, we are designing the Phase 2 trial to determine the potential ODR.

Conclusion: Both preclinical and Phase 1 oncology trials can be designed to better understand the exposure-response relationships for safety and efficacy which will then help the drug developer in designing the Phase 2 and 3 trials for eventual FDA approval of the ODR.

Introduction to Project Optimus

- Historically, selection of the dosage regimen for oncology drugs was based on the maximum tolerated dose (MTD) safety-efficacy.
  - Safety & efficacy were assumed to be linked (i.e., increase toxicity increases cancer killing effect).
  - The Recommended Phase 2 Dose (RP2D) advancing to Phase 2 and 3 was typically the MTD.
  - Dose ranging efficacy/safety studies were not required for oncology drugs as required for other drugs.
- In 2021 FDA introduced Project Optimus which led to FDA's optimal dosing regimen (ODR) Draft Guidance "Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases" (Draft ODR Guidance) requiring:
  - Evaluation of the possible dose/exposure – response relationship for both safety and efficacy and
  - Clinical evidence and justification for a Recommended Dose Range (RDR) of at least 2-3 doses to be evaluated in Phase 2 as well as the ODR to use for Phase 3 and approval.
- FDA has noted that by NOT identifying the ODR, a poorly characterized dose and schedule may lead to:
  - Selection of a dosage regimen in Phase 3 that provides more toxicity without additional efficacy and/or
  - Toxicities requiring dose reductions, treatment interruptions, and/or treatment discontinuation.
- Project Optimus states that all cancer drugs may not follow the same dose/exposure – safety or efficacy pattern (Figure 1A versus Figure 1B) making the burden to define the relationship the sponsors responsibility.

Figure 1A. Assumed in the MTD Design: Dose-Response for Efficacy Parallels Toxicity

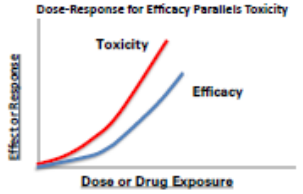
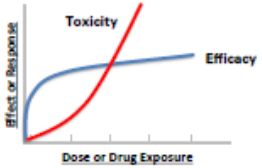


Figure 1B. Possible that Dose-Response for Efficacy Not Parallel to Toxicity



Project Optimus Starts with Preclinical Studies

- Preclinical pre-IND enabling studies in oncology typically include:
  - In vitro and in vivo pharmacology studies to assess tumor response,
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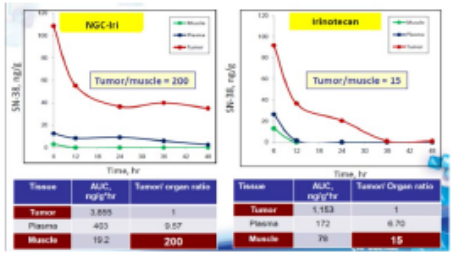
  - ADME (absorption, distribution, metabolism, excretion) and pharmacokinetic (PK) studies.
- Some limits of these studies when defining the dose/exposure – response (safety or efficacy) relationships are that the response is often evaluated at few doses and the doses chosen are typically closer to the MTD and not lower doses.
- Pre-clinical dose/exposure – response curves for safety and efficacy may provide insight into the clinical dose/exposure – response curves.

- Next Generation Irinotecan (NGC-Iri) is a pro-drug of SN-38 (the active metabolite of irinotecan). A molecular nano-motor (MNM) which interacts with tumor cell membranes preferentially over normal cells is linked to SN-38 allowing more of the SN-38 to enter the tumor core and less into other tissues compared to irinotecan.

Figure 2. Tissue distribution Differences of SN-38 after NGC-Iri (Tumor/Muscle Ratio = 200) vs Irinotecan (Tumor/Muscle Ratio = 15)



Tissue	AUC, ng/g*hr	Tumor/ organ ratio
Tumor	3,889	1
Plasma	403	0.97
Muscle	19.2	200

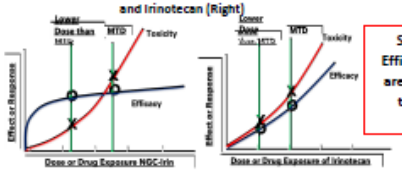
Tissue	AUC, ng/g*hr	Tumor/ Organ ratio
Tumor	1,153	1
Plasma	172	6.70
Muscle	76	15

Table 1: Tumor Growth Inhibition for NGC-Iri and Irinotecan at Different

Dose	NGC-Iri	Irinotecan
MTD	100%	85%
½ MTD	100%	64%
¼ MTD	100%	53%

NGI-Iri Efficacy Maintained at Doses with Less Toxicity (e.g., 25% x MTD) while Irinotecan Efficacy Decreases

Figure 4. Toxicity and Efficacy vs Dose for NGC-Iri (Left) and Irinotecan (Right)



Shapes of the Toxicity and Efficacy Dose-Response Curves are Different for NGC-Iri while the Shapes are Similar for Irinotecan

Phase 1 Design Considerations Given Project Optimus and the Determination of the ODR

- Previously, the objective of the First-in-human (FIH) oncology studies was to identify the MTD and RP2D (most often the MTD) in patients, either by conducting a:
  - Phase 1/2 study identifying the MTD during Phase 1 dose escalation in patients who have "no satisfactory alternative therapies", followed by expansion of selected Cohorts to further evaluate safety and efficacy or
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BASED ON PROJECT OPTIMUS INITIATIVE

- FIH Phase 1 should be modified to provide initial clinical information on both safety and efficacy from which at least 2-3 possible doses, including the MTD, can be selected as the Recommended Dose range (RDR) to run in a more comprehensive Phase 2 study to define the potential ODR.
- The 2 potential designs are 1) Phase 1/2 with dose confirmation expansion or 2) Phase 1 followed by separate Phase 2 study. Some considerations to consider when deciding on the design of the Phase 1 study are presented in Table 2.

Table 2: Some Considerations When Designing FIH Phase 1 to Determine the RDR for Phase 2 and 3

	Design Considerations
Patient Inclusion in Phase 1	Patients with no satisfactory alternative therapies
Cancer Type for Project Optimus Analysis	Phase 1 dose escalation may be mixture of cancers, but Phase 2 to define ODR needs to be more selective
Phase 1 Dose/Exposure - Response to Define RDR	Safety and efficacy to be evaluated (e.g., % of an AE by cohort, duration of clinical benefit by patient)
Number of Phase 1 Doses Selected for RDR	≥ 2, including the MTD
Arms to be Evaluated in Phase 2	Phase 1/2 cohort expansion ≥ 2 + historical control or Separate Phase 2 ≥ 2 + active or historical control

Processa Separated Phase 1 and 2 Studies Based on FDA's Following Recommendations

- Phase 2 & 3 should target a different cancer patient population than Phase 1 dose escalation.
- Dose/exposure-response analysis of Phase 1 to define the RDR for Phase 2.
- The RDR should include ≥ 2 regimens when conducting ODR Phase 2 evaluation.
- Phase 2 needs to include a randomized active control arm.

Conclusions

- Preclinical dose/exposure – toxicity/efficacy studies can provide some guidance on the pattern of the dose/response relationships as illustrated with NGC-Iri.
- Phase 1 studies can provide data to begin developing dose/exposure-toxicity/efficacy relationships if designed appropriately.
- Even with the small number of patients in Phase 1, the PK, toxicity, and efficacy data provides guidance to select the RDR for a Phase 2 safety/efficacy evaluation and Project Optimus analysis.
- Sponsors must consider that a Phase 1 study followed by a Phase 2 safety/efficacy study may be the design of choice given the requirements of FDA and Project Optimus.

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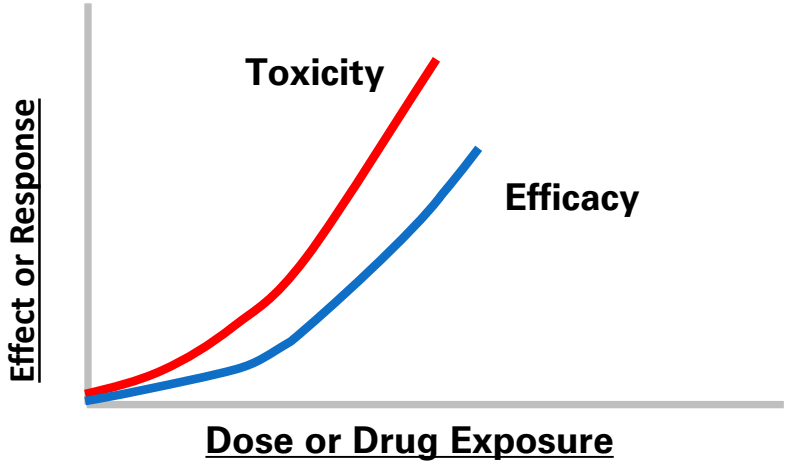

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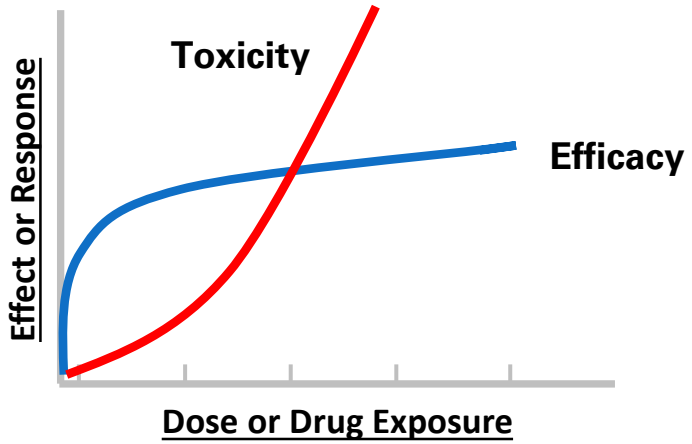

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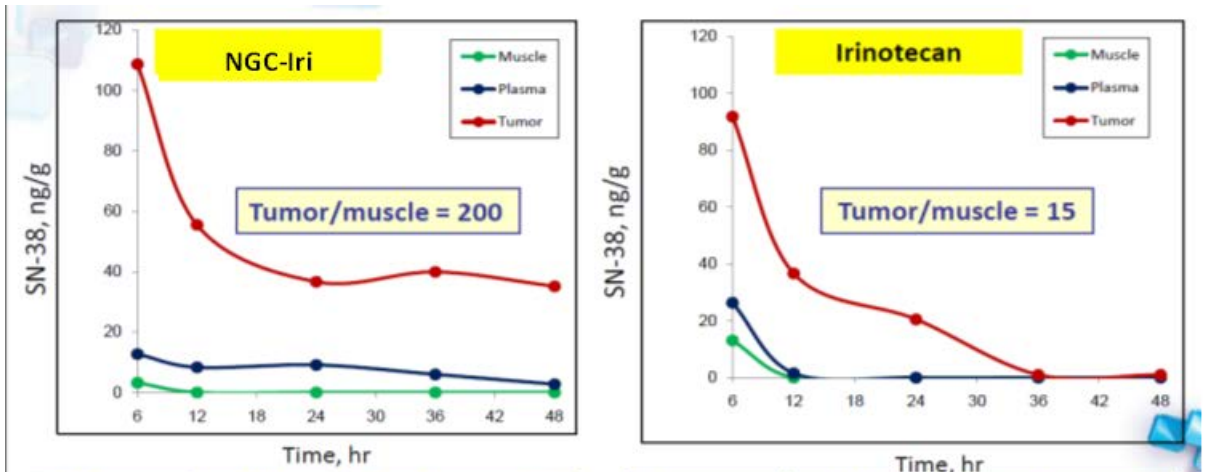

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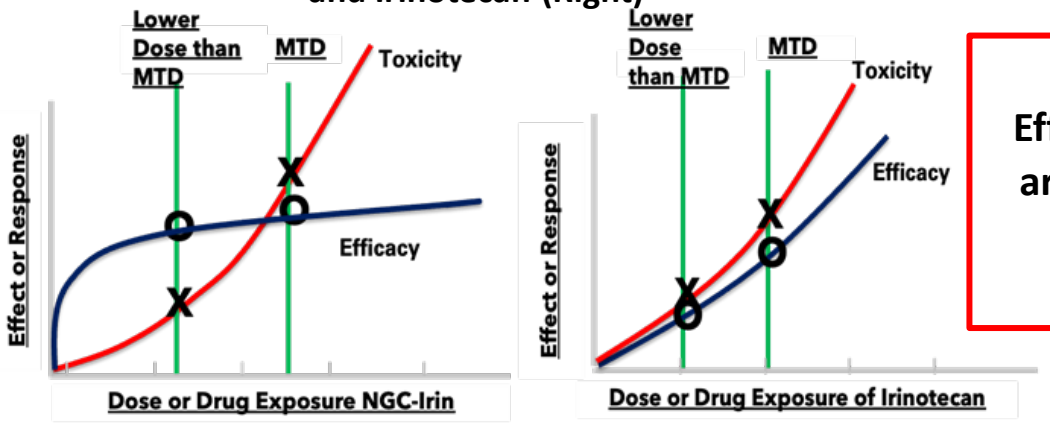

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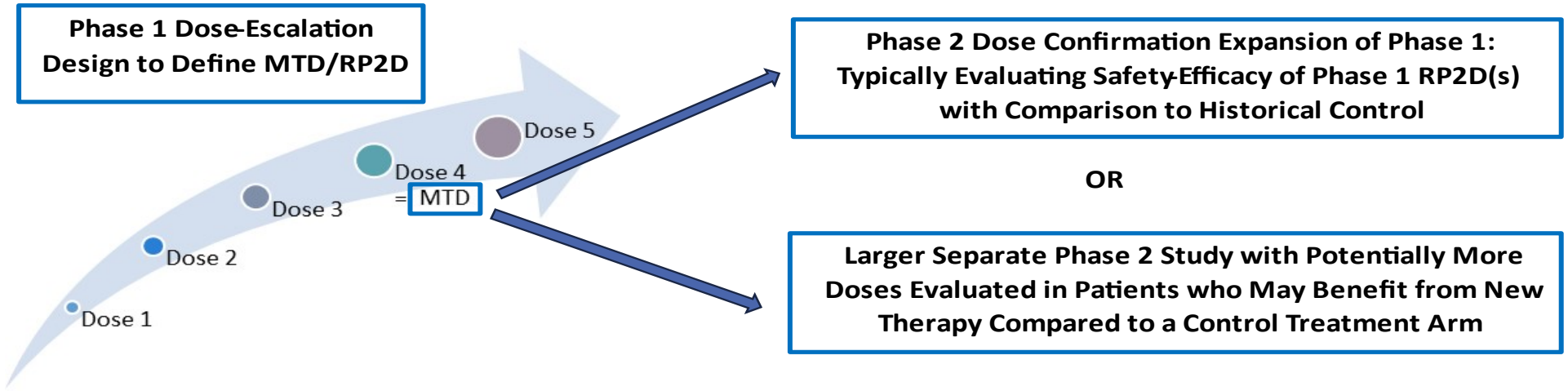

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