Population modeling framework with adaptive dosing for optimizing clinical utility of compounds in development for treatment of solid tumors

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Purpose

The aim was to develop a multi-model-informed drug development (MIDD) framework for informing and optimizing dosing regimens of oncology compounds for treatment of solid tumors in early to mid-phase development, through incorporation of population models of pharmacokinetics, tumor dynamics and longitudinal safety profile (e.g. myelosuppression) with consideration of expected dose modifications, ultimately expressed in simplified scores of clinical utility.

Methods

Population pharmacokinetic (popPK) models and longitudinal population exposure-response (ER) models for tumor dynamics[1,2] and myelosuppression[3] were developed as fit-for-purpose and refined as data arose throughout early-stage development of novel compounds.

Predictions of tumor response rate (TRR) and incidence of hematologic adverse events (AE) by severity were derived from longitudinal models across various starting dosing regimens of interest using adaptive dosing trial simulations (a Monte-Carlo simulation platform[4]).

This method allowed for simulating the impact of dose modifications. Future doses were dictated by simulated myeloid cell counts predicted from the longitudinal ER safety model with user-specified rules for lab sampling frequency and dosing modifications with levels (hold, retest, rechallenge, reduce or discontinue). Simulated dosing and subsequent PK profiles provided input into ER models to predict efficacy and safety outcomes.

Simulated TRR and incidence of Grade ≥3 hematologic AEs were calculated for each virtual trial using adaptive dosing and summarized across trials by dosing regimen (mean and 90% CI).

Logistic regression ER models for efficacy and safety were developed for other relevant endpoints, and same simulation method used to predict the probability of each event with confidence intervals.

The clinical utility score of each dosing regimen was calculated based on simulated safety and efficacy outcomes[5] to guide dosing decisions. Sensitivity analyses were conducted by varying the weight of safety and efficacy components (e.g. 50%/50% vs 25%/75%).

Figure 1. Illustration of MIDD Framework

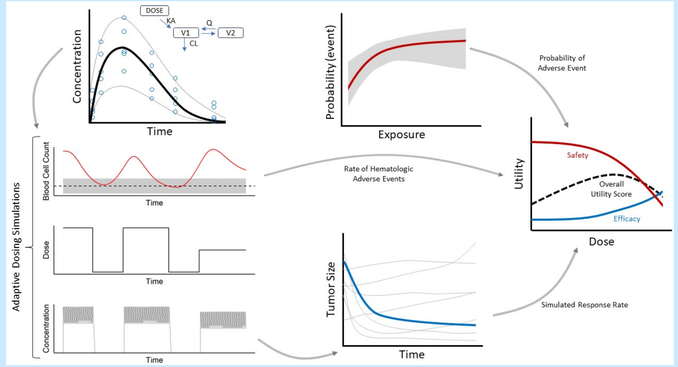


Figure 2. Semi-Mechanistic Myelosuppression Model[2]

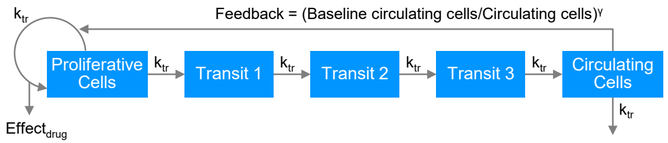
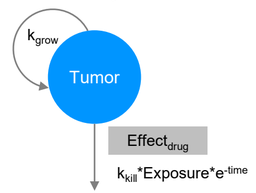


Figure 3. Representative Tumor Dynamic Model



Equation 1. Representative Clinical Utility Index (CUI) calculation

$$CUI = W1*efficacy + W2*safety$$

Where W1 and W2 are positive weights summing to 1, efficacy is the utility function (e.g., tumor response rate), and safety is the utility function (e.g., rate of Grade ≥3 hematologic AE, probability of other AEs)

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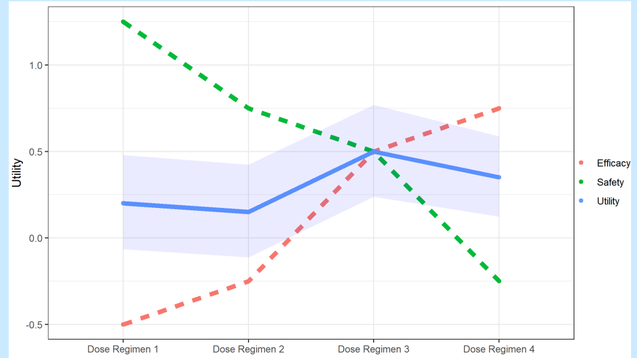
Results

Table 1. Simulated Efficacy & Safety Events

Dosing Regimen	Tumor Response Rate *(from tumor dynamic model)*	Rate of G ≥3 Hematologic AEs *(from myelosuppression model)*
1	30% (20-40%)	30% (20-40%)
2	35% (25-45%)	40% (30-50%)
3	50% (40-60%)	45% (35-55%)
4	55% (45-65%)	60% (70-80%)

Figure 4. Clinical Utility Score Results



Lessons Learned

Early development may be limited by lack of data for building reliable longitudinal ER models, as data is from small cohorts, and is quickly evolving.

Impact of clinical covariates may be unknown at this stage.

Adaptive dosing simulations sensitive to sampling frequency and user rules for dose holds, restarts (when, what dosing regimen) and discontinuations. Underlying ER model driving adaptive dosing should be sound.

Baseline safety lab parameter (e.g. cell count) will directly impact simulations of AE rates for such models.

Select endpoints for clinical utility will likely change over time as data evolves, new signals arise, and ER models are updated and expanded (e.g. incorporation of survival models).

Key Messages & Significance

This MIDD framework enables a holistic and integrated modeling approach, ideal for early to mid-phase development.

It can be expanded to combination therapies, including novel-novel combinations, and to evaluate utility of dosing regimens untested clinically.

This extends previous work[2,6] to solid tumor indications and incorporation of both longitudinal and logistic regression ER models with ability to expand to other ER modeled endpoints.

Incorporating model-informed adaptive dosing simulations better mimics real world clinical trials and general practice settings for robustly evaluating regimens.

This framework can be updated and adapted efficiently for use across programs once models are available.

References:

1. Stein WD, et al. *Clin Cancer Res*. 2011;17(4): 907-917. **2.** Bender BC, et al. *Br J Clin Pharmacol*. 2015 Jan;79(1):56-71. doi: 10.1111/bcp.12258. PMID: 24134068; PMCID: PMC4294077. **3.** Friberg LE, et al. *J Clin Oncol*. 2002;vol. 20: 4713-4721. **4.** Jermain B, et al. ACoP13 2022. **5.** Zhu R, et al. *CPT Pharmacometrics Syst Pharmacol*. 2019 Apr;8(4):240-248. doi: 10.1002/psp4.12394. Epub 2019 Mar 6. PMID: 30762302; PMCID: PMC6482275. **6.** Luu KT, Boni J. *Cancer Chemother Pharmacol*. 2016 Oct;78(4):697-708. doi: 10.1007/s00280-016-3118-3. Epub 2016 Aug 4. PMID: 27491482.