SESSION 2: SELECTING DOSAGES FOR ADDITIONAL EXPLORATION BASED ON NONCLINICAL AND EARLY CLINICAL DATA

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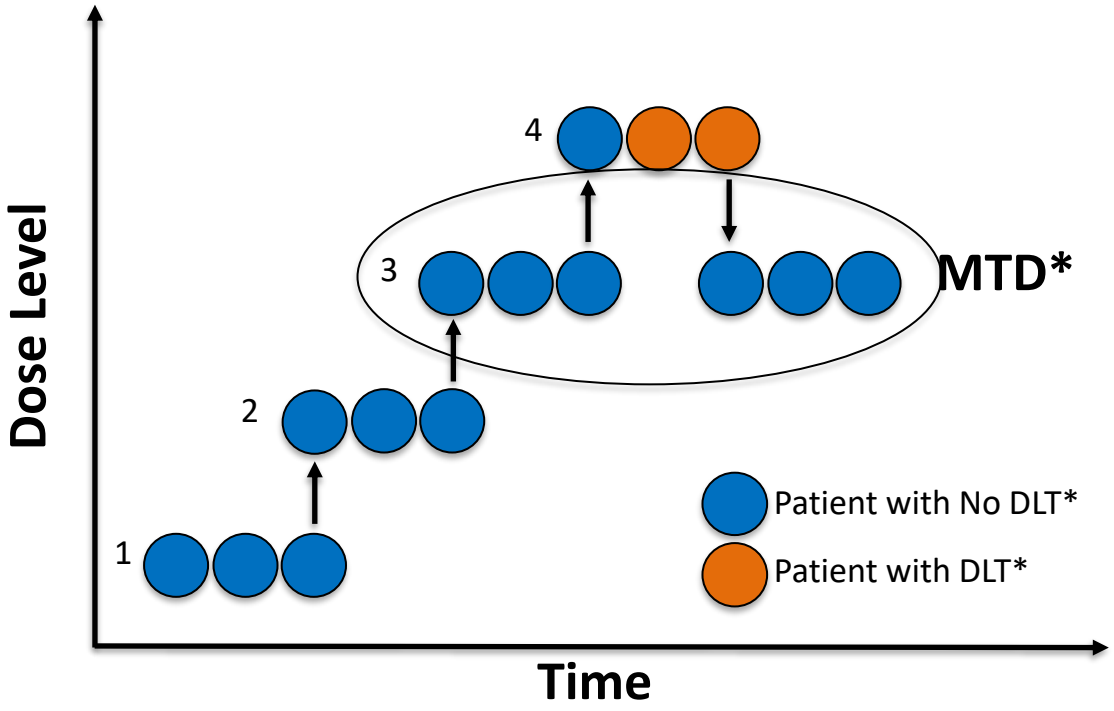
OFFICE OF CLINICAL PHARMACOLOGY

Selecting Dosages for Additional Exploration Based on Nonclinical and Early Clinical Data

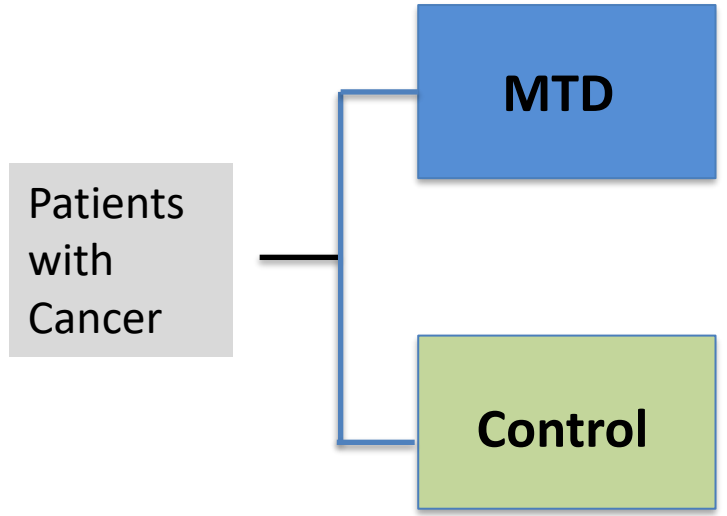
Olanrewaju Okusanya, Pharm.D, MS, BCPS
Deputy Director,
Division of Cancer Pharmacology 1

Traditional Dose Selection Strategy

Dose Escalation



Registration



*DLT= Dose-limiting toxicity,
*MTD= Maximum tolerated dose

Hallmarks:

- Few patients at each dose
- Short observation period for DLTs
- Emphasis on DLTs, but not other safety

Dose Optimization Guidance

Contains Nonbinding Recommendations
Draft — Not for Implementation

Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases
Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

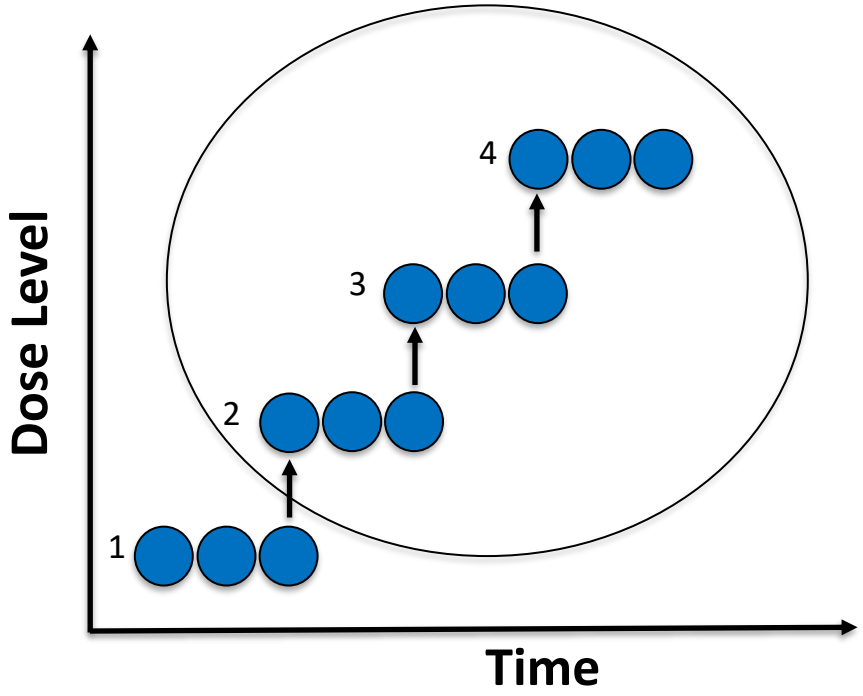
III. DOSE OPTIMIZATION RECOMMENDATIONS

Dosages selected for administration in a clinical trial(s) should be adequately supported by data appropriate to the stage of development for each indication and usage. Relevant nonclinical[7] and clinical data, as well as the dose- and exposure-response relationships for safety and efficacy should be evaluated to select a dosage(s) for clinical trial(s). An approach where a dosage is

Updated Dose Selection Strategy

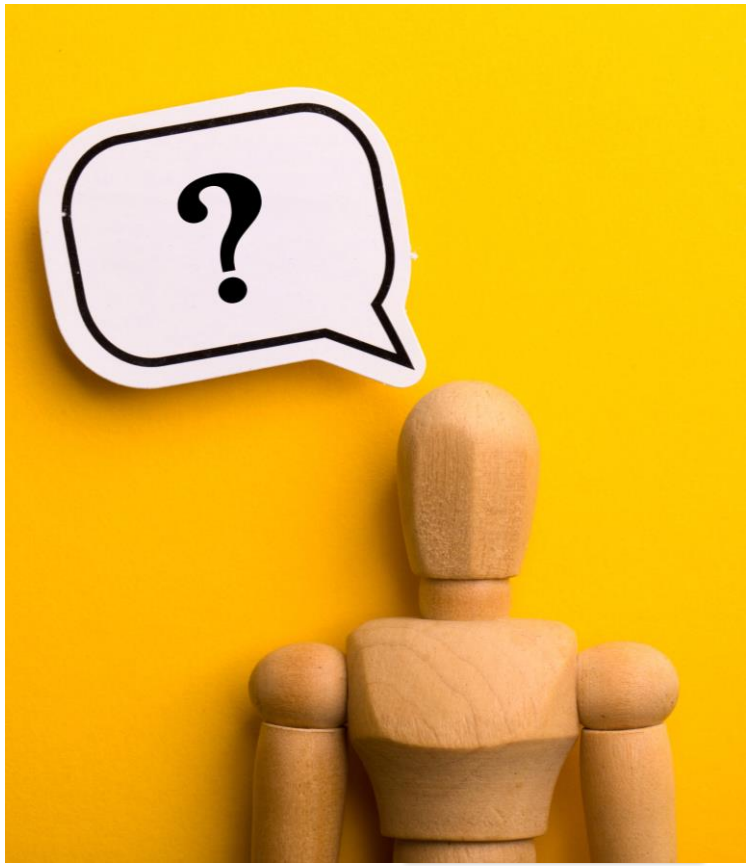
Step 1

Dose Escalation



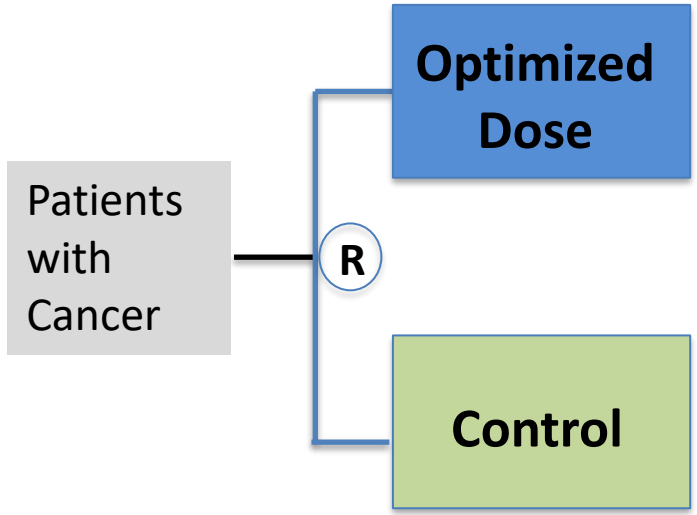
Select Dose Range

Step 2



Step 3

Comparison to Standard-of-Care



Randomized Comparison to Standard-of-Care

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Session 2A:
Evaluating and Modeling All Early Data to Select Recommended Phase II Doses

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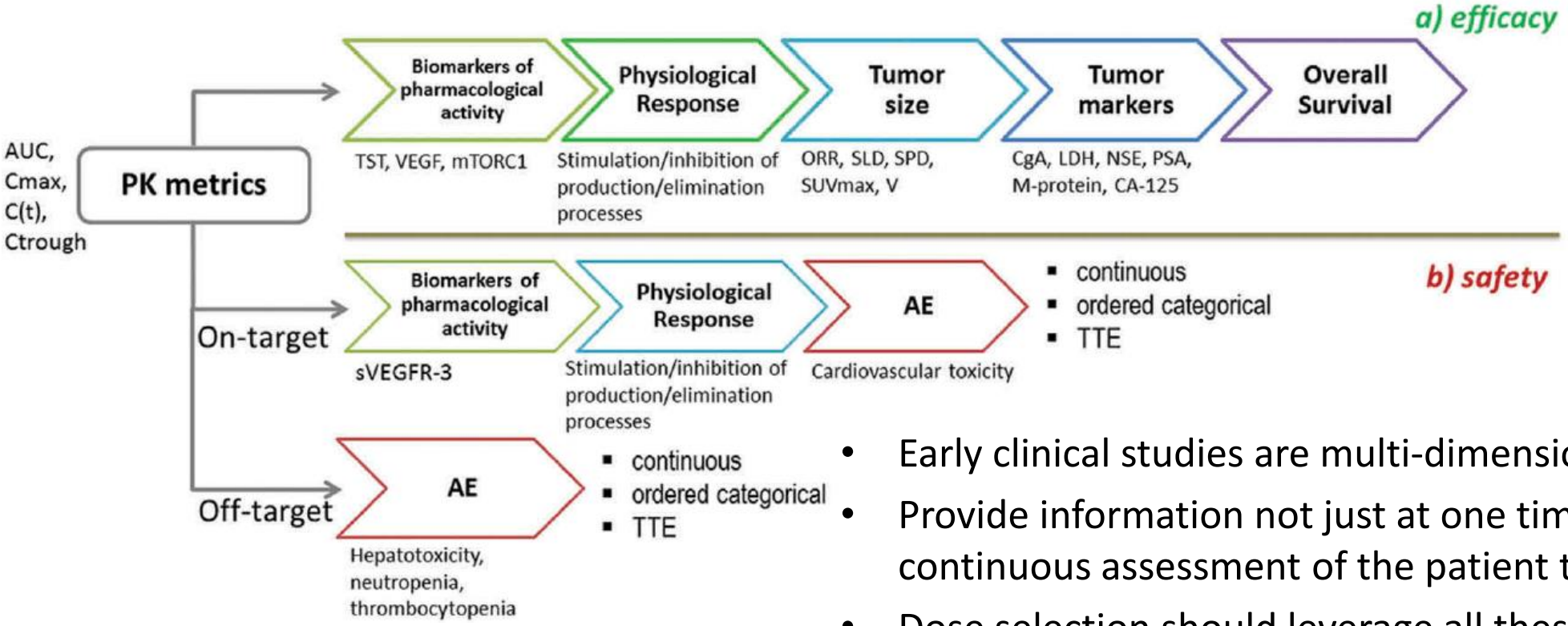
US. Food and Drug Administration

Data From Early Clinical Studies

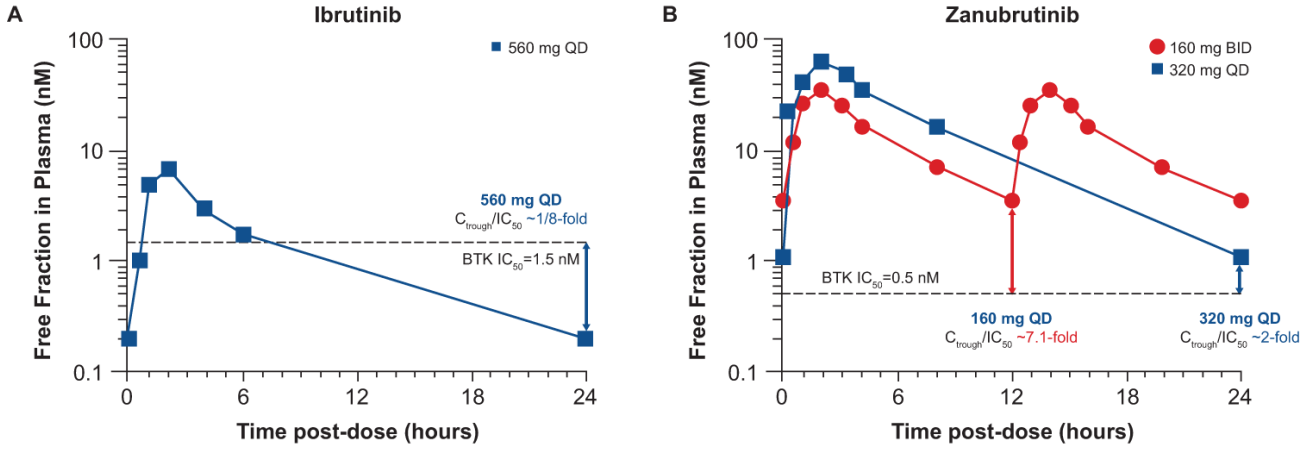


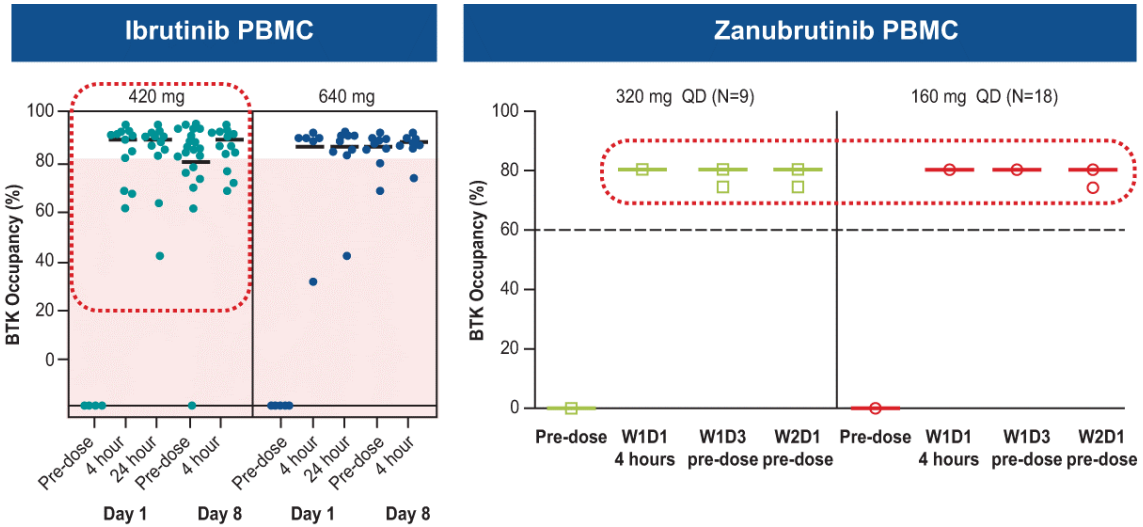
- Early clinical studies are multi-dimensional
- Provide information not just at one time point, but necessitate continuous assessment of the patient to obtain data
- Dose selection should leverage all these data
- Precision and sensitivity is limited by the number of patients

AUC: area under concentration vs time curve; C_{max}: maximum concentration; C_{trough}: trough concentration; C(t): concentration over time; TST: testosterone; VEGF: vascular endothelial growth factor; mTORC1: mammalian target or rapamycin complex; ORR: Overall Response Rate; SLD: Sum of the Longest Diameters; SPD: Sum of the Products of the two largest Diameters; SUV_{max}: maximum standardized uptake value; V: volume; CgA: Chromogranin A; LDH: lactate hydrogenase; NSE: neuron specific enolase; PSA: prostate specific antigen; CA-125: cancer antigen 125; sVEGFR-3: soluble vascular endothelial growth factor receptor 3.

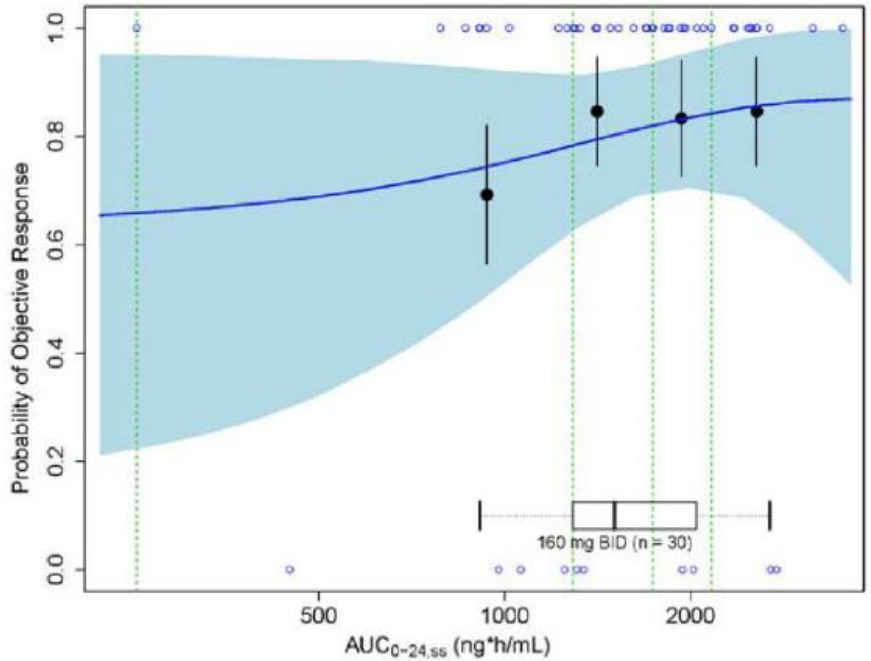
Silvia Maria Lavezzi, Elisa Borella, Letizia Carrara, Giuseppe De Nicolao, Paolo Magni & Italo Poggesi (2018) Mathematical modeling of efficacy and safety for anticancer drugs clinical development, Expert Opinion on Drug Discovery, 13:1, 5-21, https://doi.org/10.1080/17460441.2018.1388369

Integrative Clinical Pharmacology Analysis





- Leveraging early data is not uncommon in oncology
- Informed activity using non-clinical data
  - Zanubrutinib and BTK inhibition
- Empiric dose-response for efficacy and safety is typical but backwards looking



1.Ying C. Ou, Zhiyu Tang, William Novotny, Aileen Cohen, Kun Wang, Lucy Liu, Yuying Gao & Srikumar Sahasranaman (2021) Rationale for once-daily or twice-daily dosing of zanubrutinib in patients with mantle cell lymphoma, Leukemia & Lymphoma, 62:11, 2612-2624, DOI: 10.1080/10428194.2021.1929961
2.Zanubrutinib multidisciplinary review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/213217Orig1s000MultidisciplineR.pdf

Integrative Clinical Pharmacology Analysis

- Balance efficacy with multiple safety signals
- Some signals may occur late in therapy

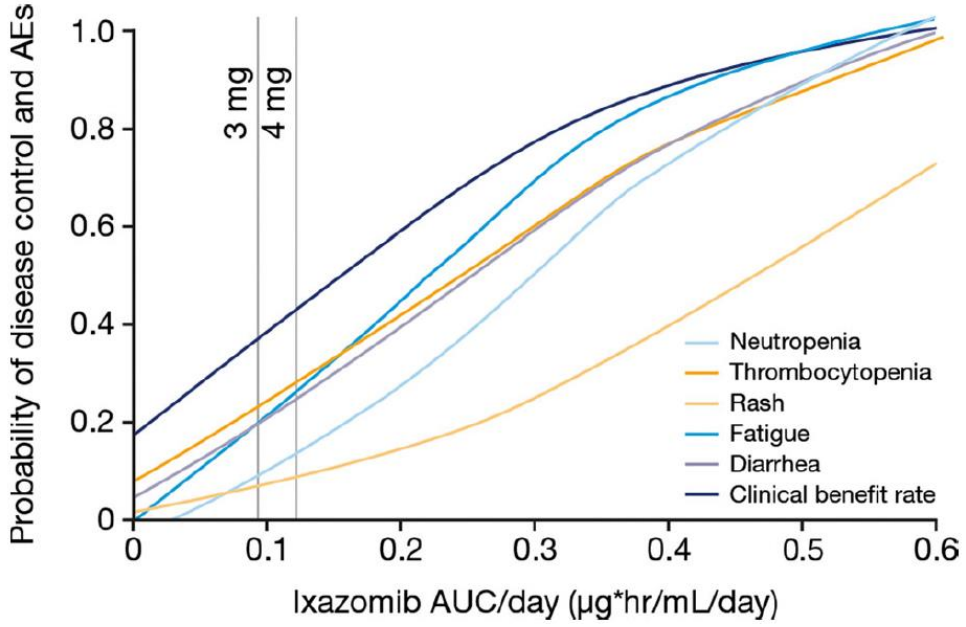


Fig. 2 Relationships between adverse events (grade ≥ 3 for hematologic and grade ≥ 2 for non-hematologic adverse events) or clinical benefit rate (≥stable disease) with single-agent weekly ixazomib, and ixazomib exposure associated with 3 mg and 4 mg fixed doses ($N = 44$). AEs, adverse events; AUC, area under the plasma concentration–time curve

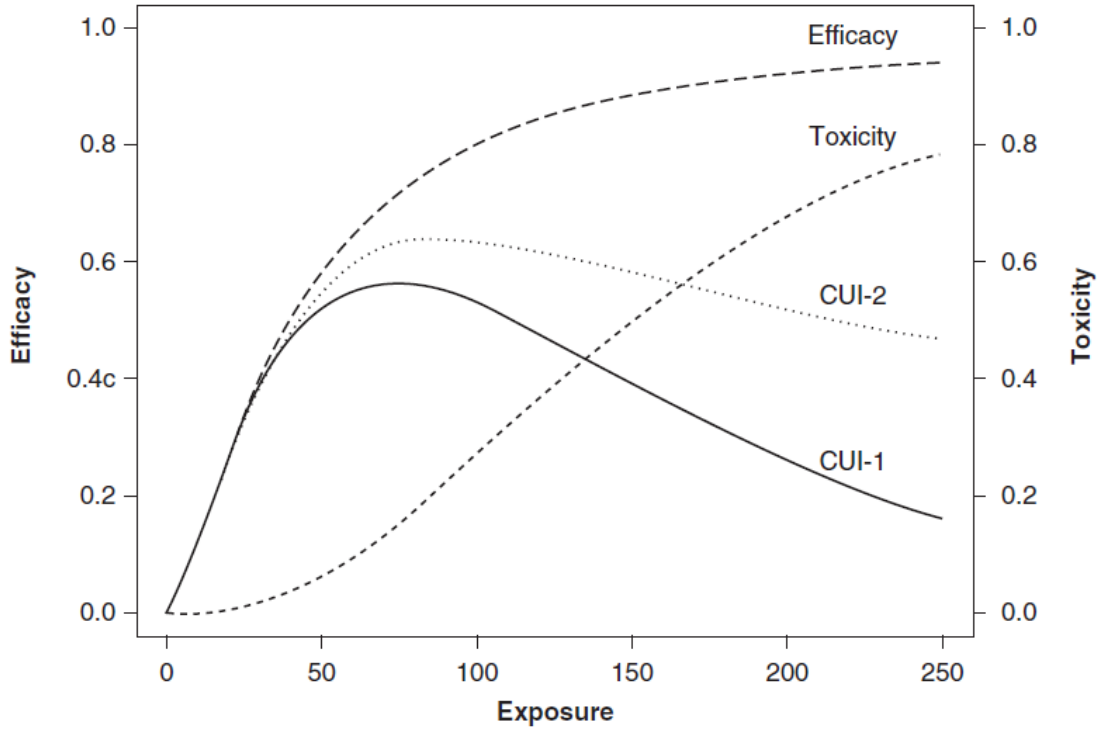
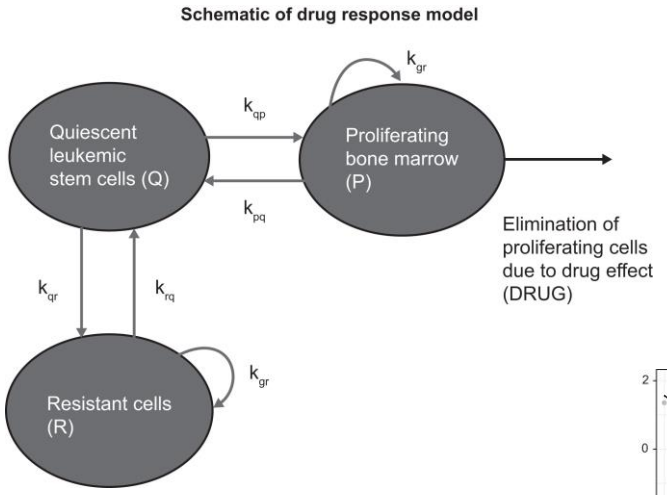


Figure 1. Dose–response relationship for efficacy (dashed line), toxicity (dotted line) and utility index. Utility Index is represented using two different weighting functions as described in text (1:1 ratio, solid line and 1:0.75 ratio, dash-dotted line).

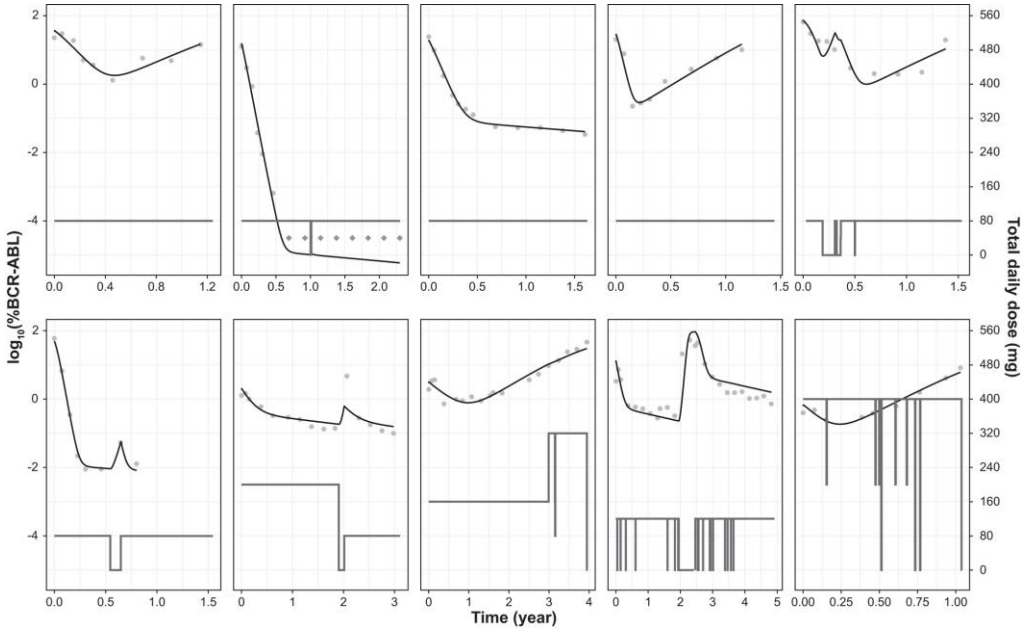
Gupta, N., Labotka, R., Liu, G. *et al.* Exposure–safety–efficacy analysis of single-agent ixazomib, an oral proteasome inhibitor, in relapsed/refractory multiple myeloma: dose selection for a phase 3 maintenance study. *Invest New Drugs* **34**, 338–346 (2016). https://doi.org/10.1007/s10637-016-0346-7

Daniele Ouellet (2010) Benefit–risk assessment: the use of clinical utility index, Expert Opinion on Drug Safety, 9:2, 289-300, DOI: 10.1517/14740330903499265

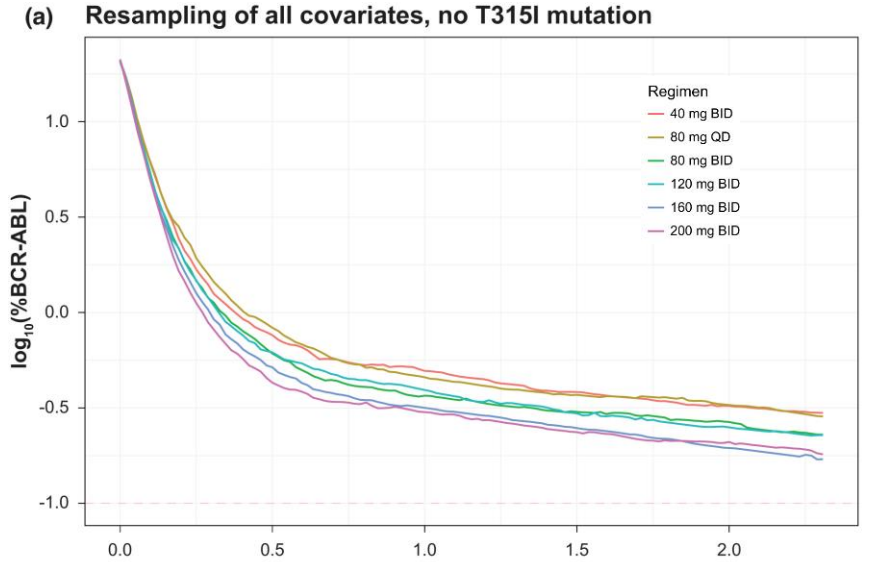
Early Clinical Studies - Time Course Data

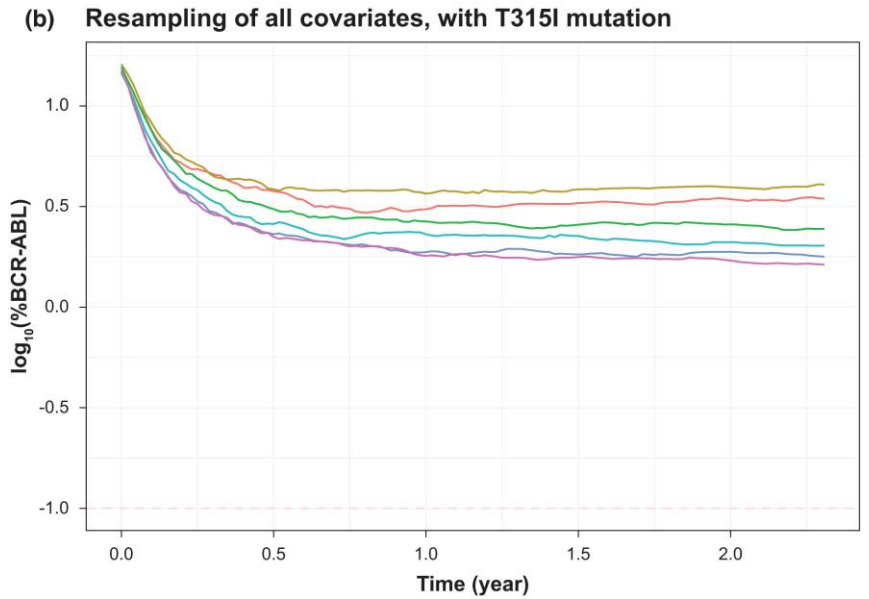


- Some signals may occur late in therapy well after response is observed
- Can support a de-escalation dosage regimen



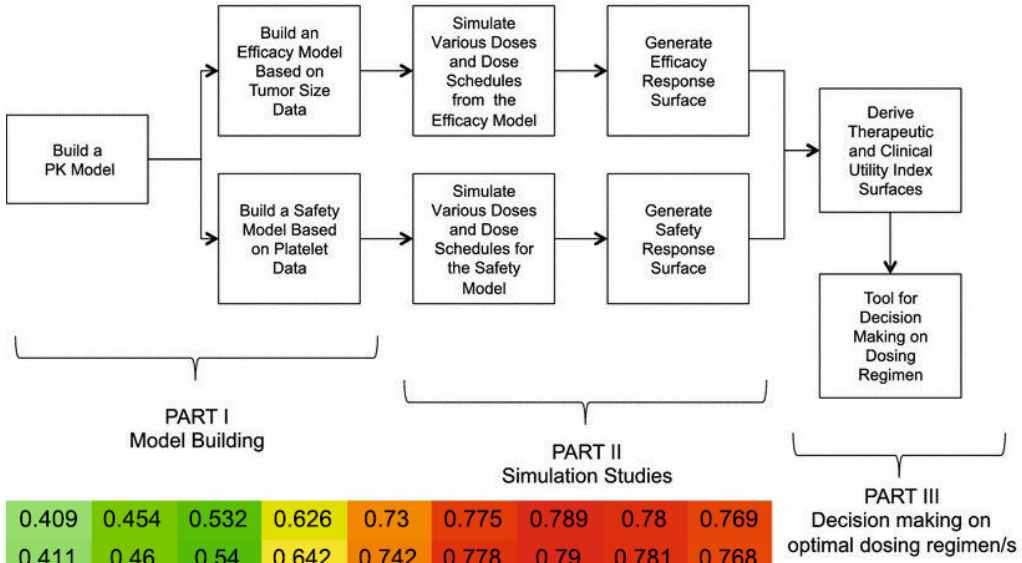
Time course data considers when activity relative to safety occurs

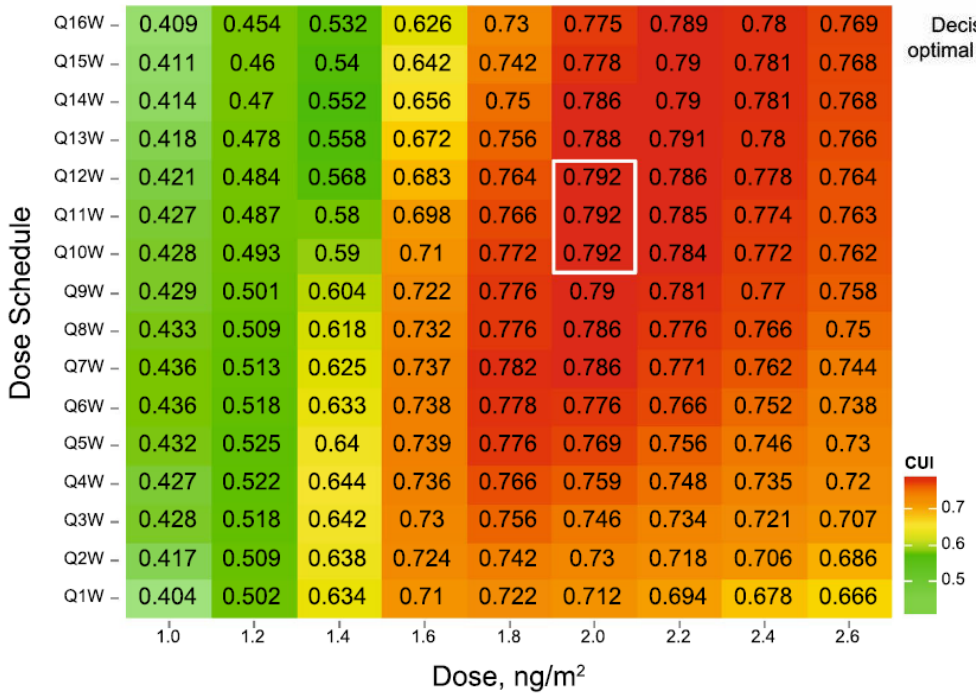


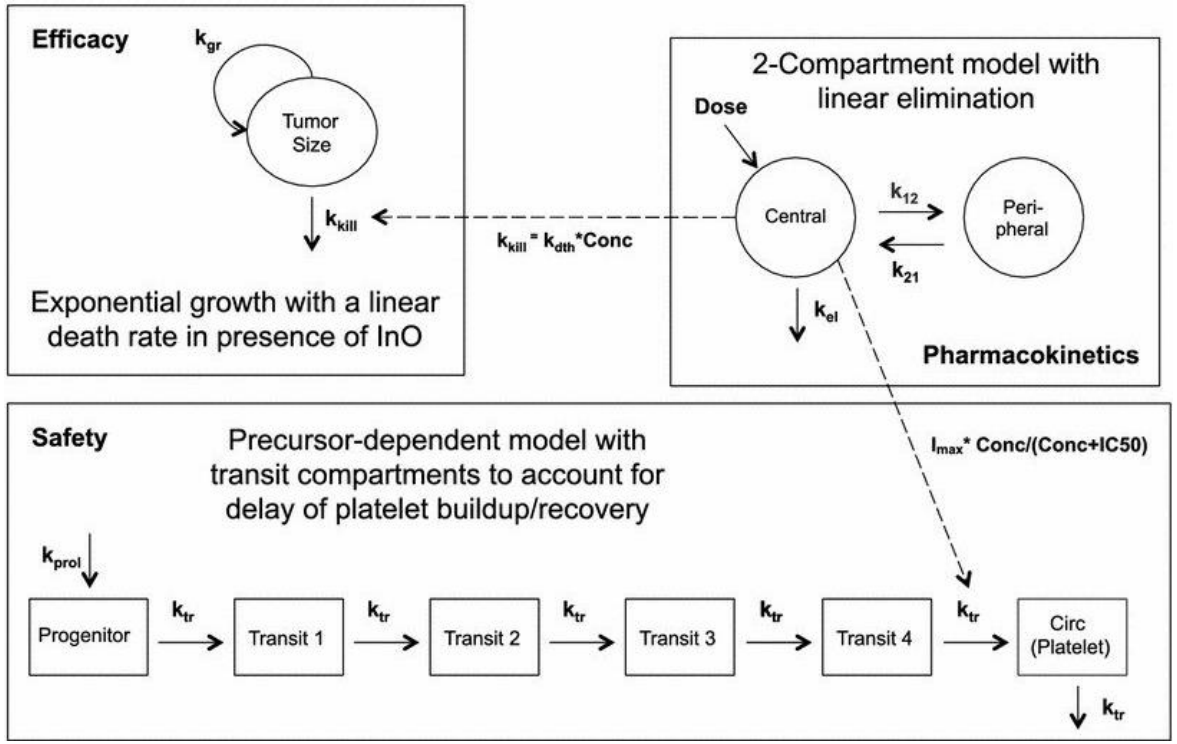


Combs, FP, Li, YF, Hoch, M, et al. Exposure-Efficacy Analysis of Asciminib in Philadelphia Chromosome-Positive Chronic Myeloid Leukemia in Chronic Phase. *Clin Pharm & Ther* **112**, 1040–1050 (2022). https://doi.org/10.1002/cpt.2699

Integrative Analysis Plan





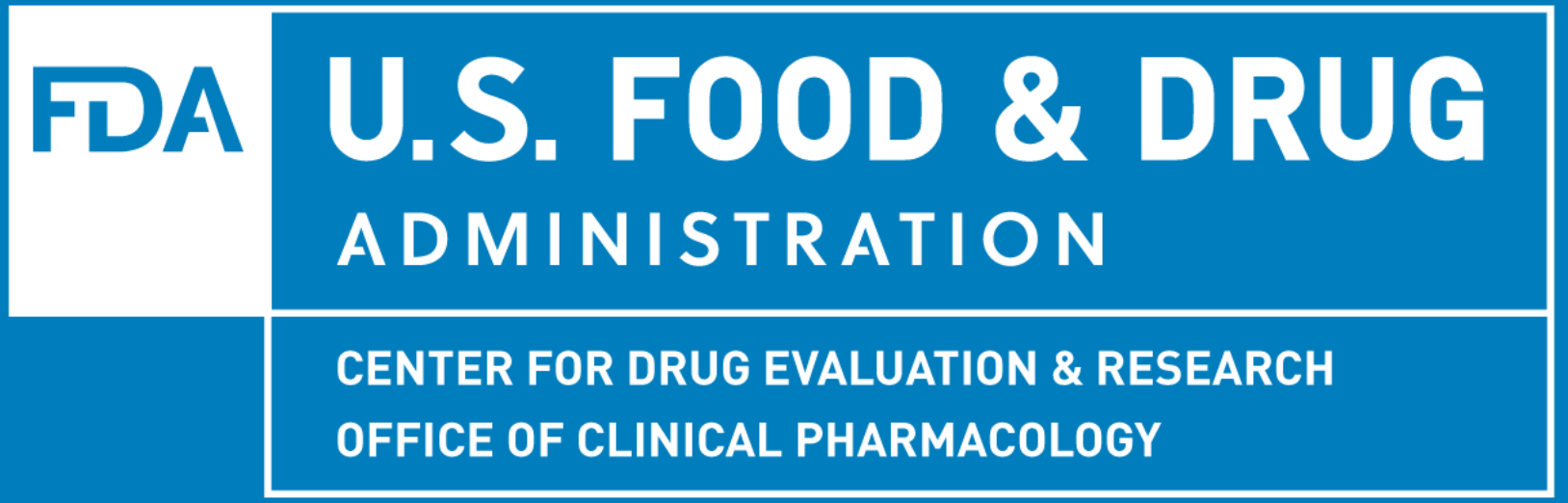


Luu, K.T., Boni, J. A method for optimizing dosage regimens in oncology by visualizing the safety and efficacy response surface: analysis of inotuzumab ozogamicin. *Cancer Chemother Pharmacol* **78**, 697–708 (2016). https://doi.org/10.1007/s00280-016-3118-3

Session Objectives

- Session 2A: Discuss strategies to leverage all available data from nonclinical studies and early human trials to inform selection of dosage(s) for further investigation
  - Gabby Patilea-Vrana, Ph.D, Pfizer

- Panel Discussion:
  - Jerry Yu, Ph.D, U.S Food and Drug Administration
  - Atiqur Rahman, Ph.D, U.S Food and Drug Administration
  - Lillian Siu, MD, Princess Margaret Cancer Center
  - Manju George, MvSc, PhD, COLONTOWN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FDA-AACR Public Workshop On
OPTIMIZING DOSAGES FOR ONCOLOGY DRUG PRODUCTS: QUANTITATIVE APPROACHES TO SELECT DOSAGES FOR CLINICAL TRIALS
February 15 and 16, 2024 I Washington, DC

Clinical Utility Index (CUI): a Tool to Support Dose Selection as an Alternative to Maximum Tolerated Dose (MTD)

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Oncology Clinical Pharmacology
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Disclosure Information

Gabby Patilea-Vrana, PhD

I have the following relevant financial relationships to disclose:

Employee of: Pfizer Inc and formerly Seagen Inc

Stockholder in: Pfizer Inc and formerly Seagen Inc

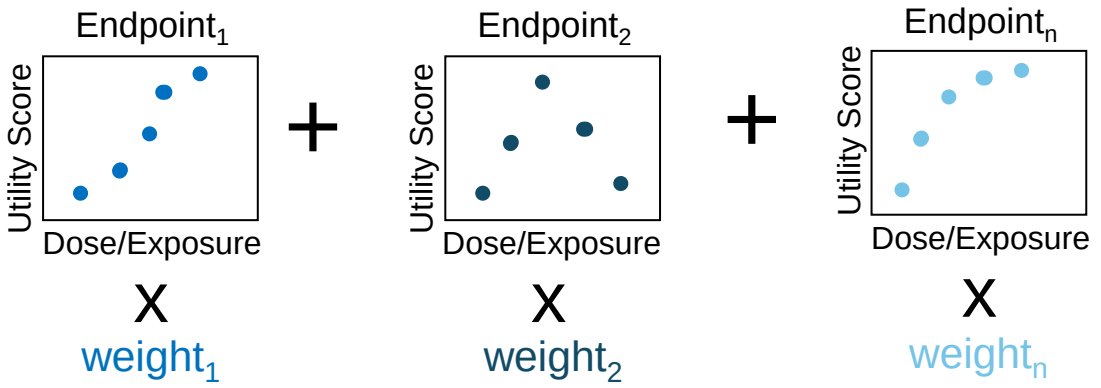
The information presented is solely intended to foster the exchange of scientific and medical information

What is a CUI?

- Clinical Utility Index (CUI) is a weighted approach for incorporating multiple endpoints into a single readout
  - Case example: CUI using PK/PD endpoints
  - Literature case example: CUI using safety and efficacy endpoints

CUI to Identify Optimum Dose

Clinically-meaningful *endpoints*, *cutoffs*, and *weights* are selected based on importance for biological activity, clinical efficacy and safety

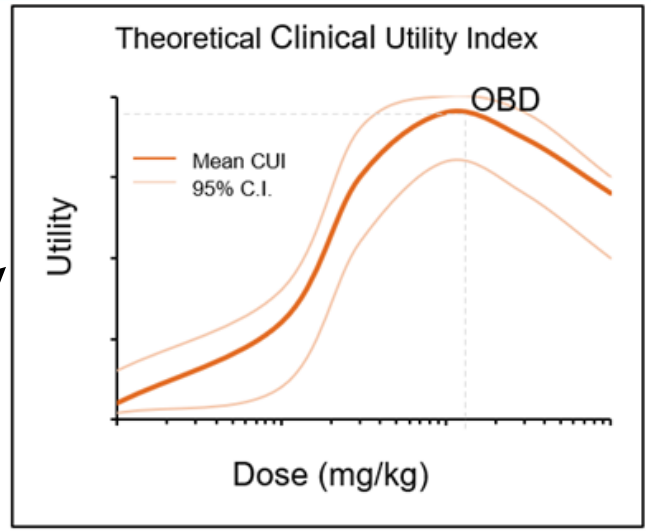


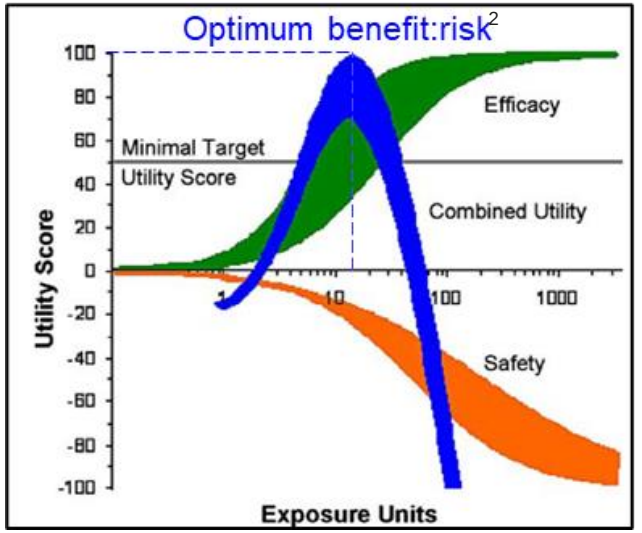
$$CUI = \sum_{i=1}^{n} weight_i \times Utility\ Score_i$$

CUI is the sum of the weighted (w) average utility functions (U) for all endpoints of interest (i)[1]

CUI for optimum biological dose (OBD)

CUI for optimum benefit-risk





[1]Ouellet D et al. Clin Pharmacol Ther. 2009. PMID: 19078947.
[2]Khan et al.. AAPS J. 2009. PMID: 19145490

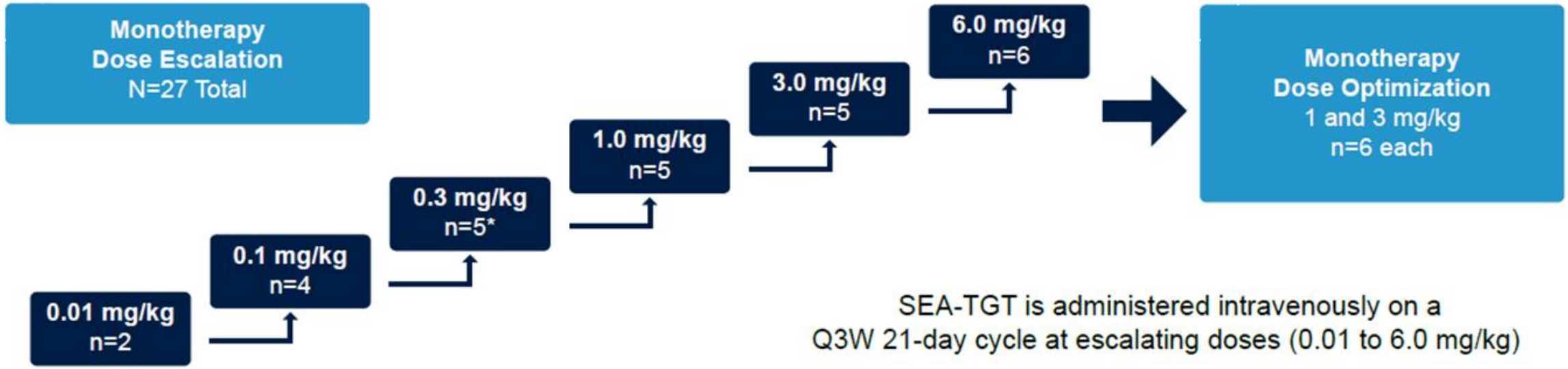
CUI Case Example

Informing the optimum biological dose of SEA-TGT, an investigational human, nonfucosylated monoclonal antibody directed against TIGIT, by comparing the relative biological activity across dose cohorts using an *a priori* developed CUI that incorporates PK and PD endpoints

SGNTGT-001: Ph1 Dose Escalation

Phase 1 Dose-Escalation Study of SEA-TGT Monotherapy In Patients with Advanced Malignancies (SGNTGT-001)

Study Design



SEA-TGT is administered intravenously on a Q3W 21-day cycle at escalating doses (0.01 to 6.0 mg/kg)

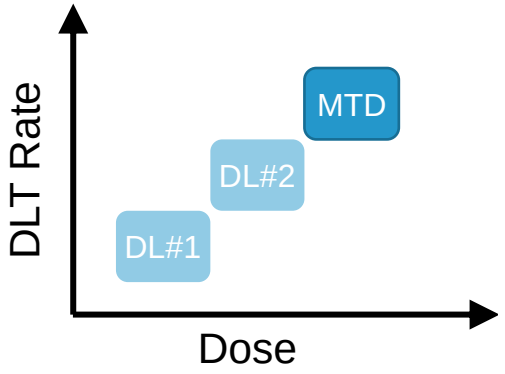
Data cut off: 05 October 2022

*One patient was enrolled at 0.3 mg/kg and was treated at this dose for Cycles 1-4 before switching to 3.0 mg/kg

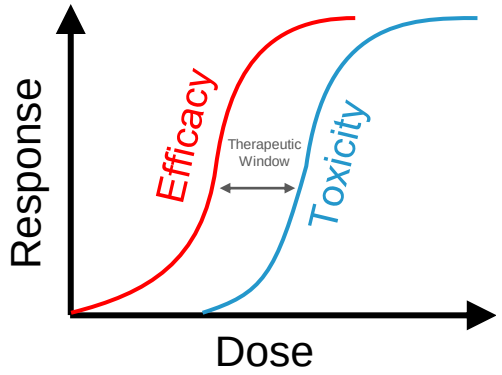
Cabanas et al. Cancer Res 2023;83(8_Suppl):Abstract nr CT265.

The Need for SEA-TGT Optimal Biological Dose (OBD) Selection

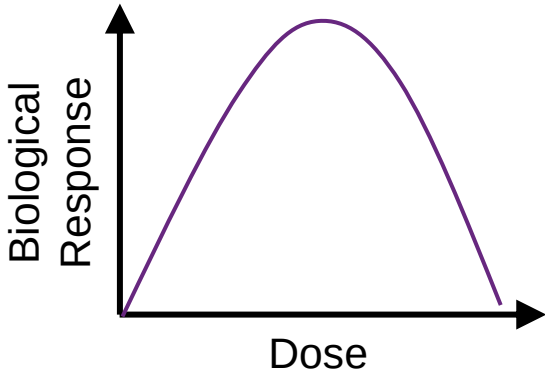
MTD approach ☒



Balance efficacy and safety ☒



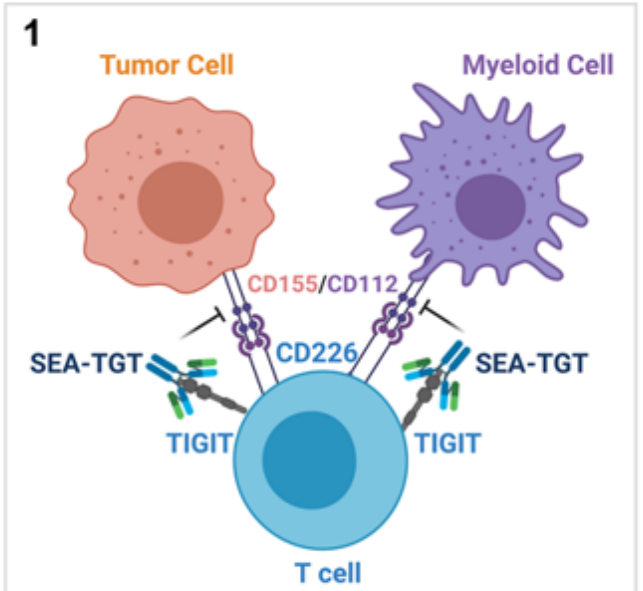
Optimum Biological Dose ☑



☑ A **Clinical Utility Index** (CUI) was developed prospectively to aid in Optimum Biological Dose (OBD) selection by integrating multiple PK/PD endpoints into a single output

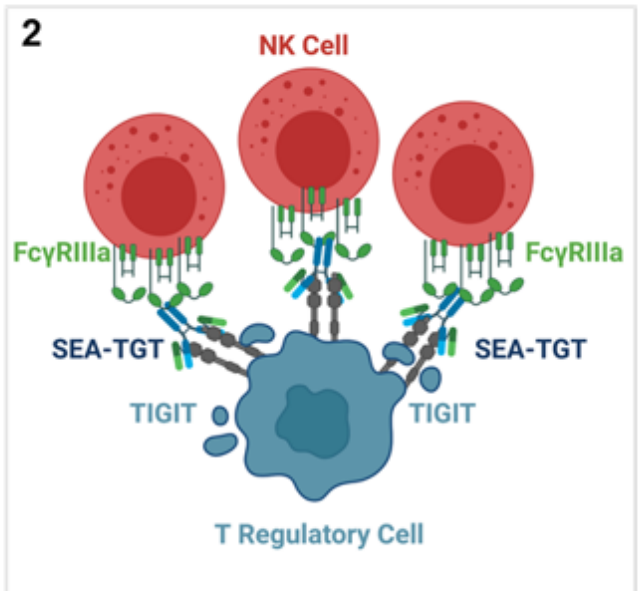
Multiple MOAs of SEA-TGT

Target Engagement, PK | **Total CD8s**



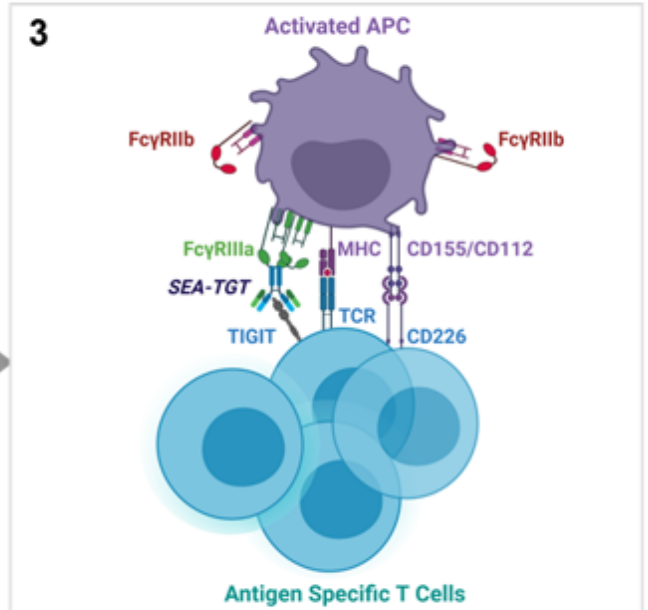
Blocks inhibitory TIGIT mediated checkpoint signal to memory CD8 T cells

Treg Depletion | **NK Cell Proliferation**



Depletes T regulatory cells, which inhibit CD8s, by increased activation of NK cells

Total CD8s | **CD8 T Cell Proliferation**

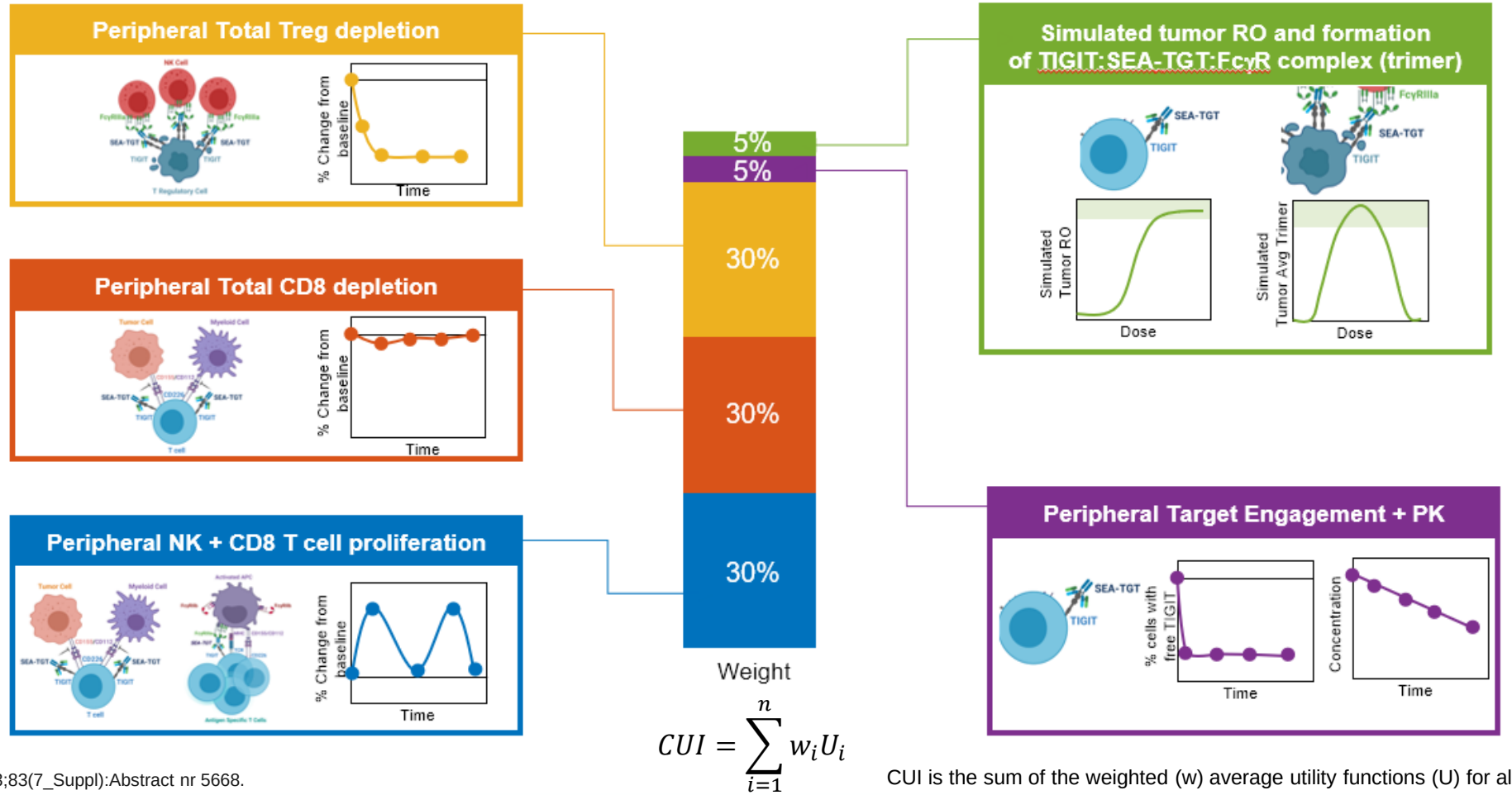


Binds activating FcγRIIIa on myeloid cells & induces new antigen+ CD8 T cells

Smith A et al. Front Immunol. 2023 Nov 1;14:1280986.PMID: 38022590
Patilea-Vrana et al. Cancer Res 2023;83(7_Suppl):Abstract nr 5668.

CUI to Compare Biological Activity Across Dose Cohorts

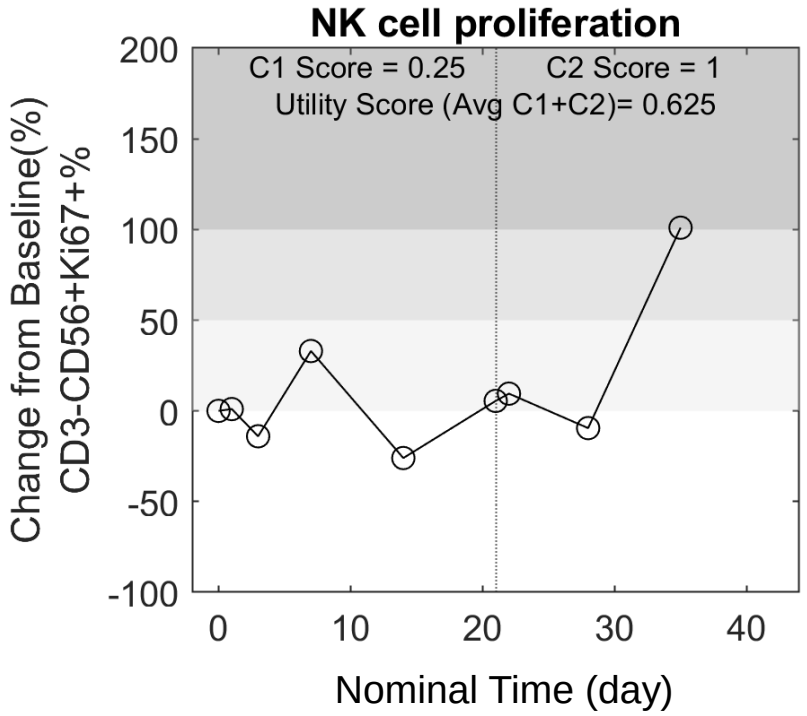
All selections were prespecified using SEA-TGT preclinical and literature-based data to limit bias. Endpoint weights were based on *a priori* consensus that balanced relevant biological activity with variability and/or uncertainty in output.



Patilea-Vrana et al. Cancer Res 2023;83(7_Suppl):Abstract nr 5668.

CUI is the sum of the weighted (w) average utility functions (U) for all endpoints of interest (i)

Illustration of Categorical Utility Scoring



The shaded areas are defined by the utility function categorical cutoffs and represent areas of biological activity defined as follows:

Shading	Utility Score	Evidence of Biological Activity
Dark gray	1	Strong
Light to medium gray	0.25 – 0.50	Limited
White	0	None

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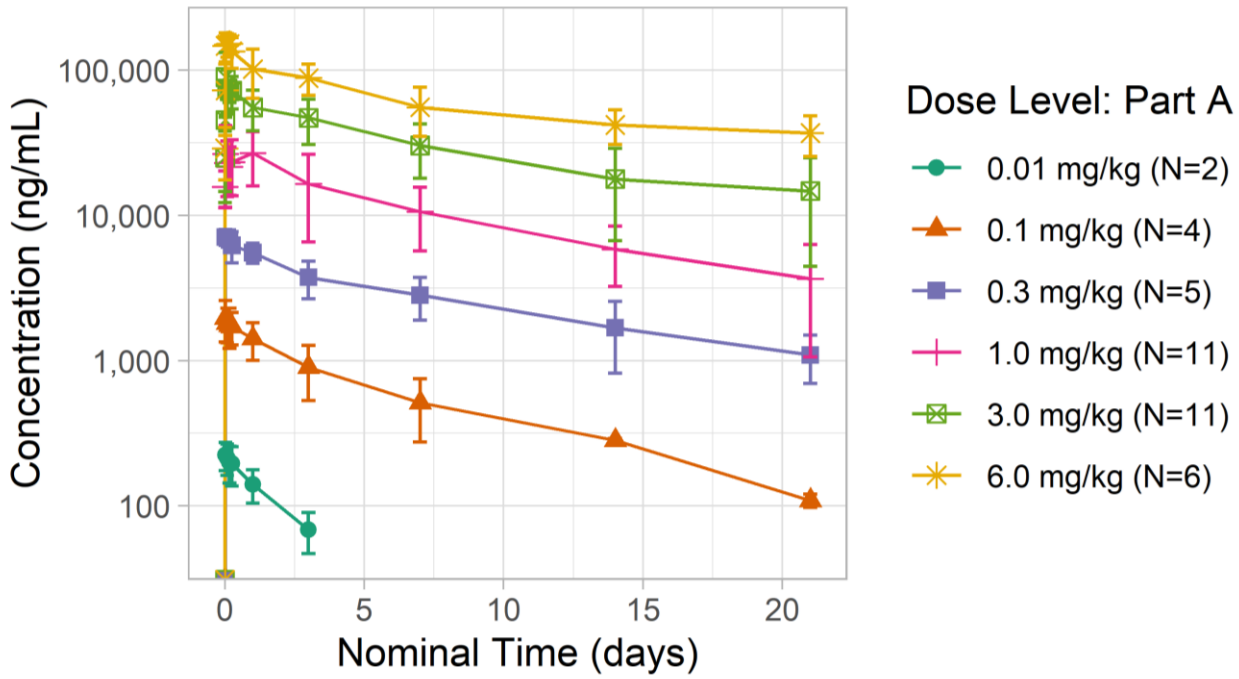
SEA-TGT Human PK Profiles

SEA-TGT pharmacokinetics were approximately dose-proportional from 0.3 to 6.0 mg/kg, with dose levels 0.1 and 0.01 mg/kg being within the nonlinear pharmacokinetic range



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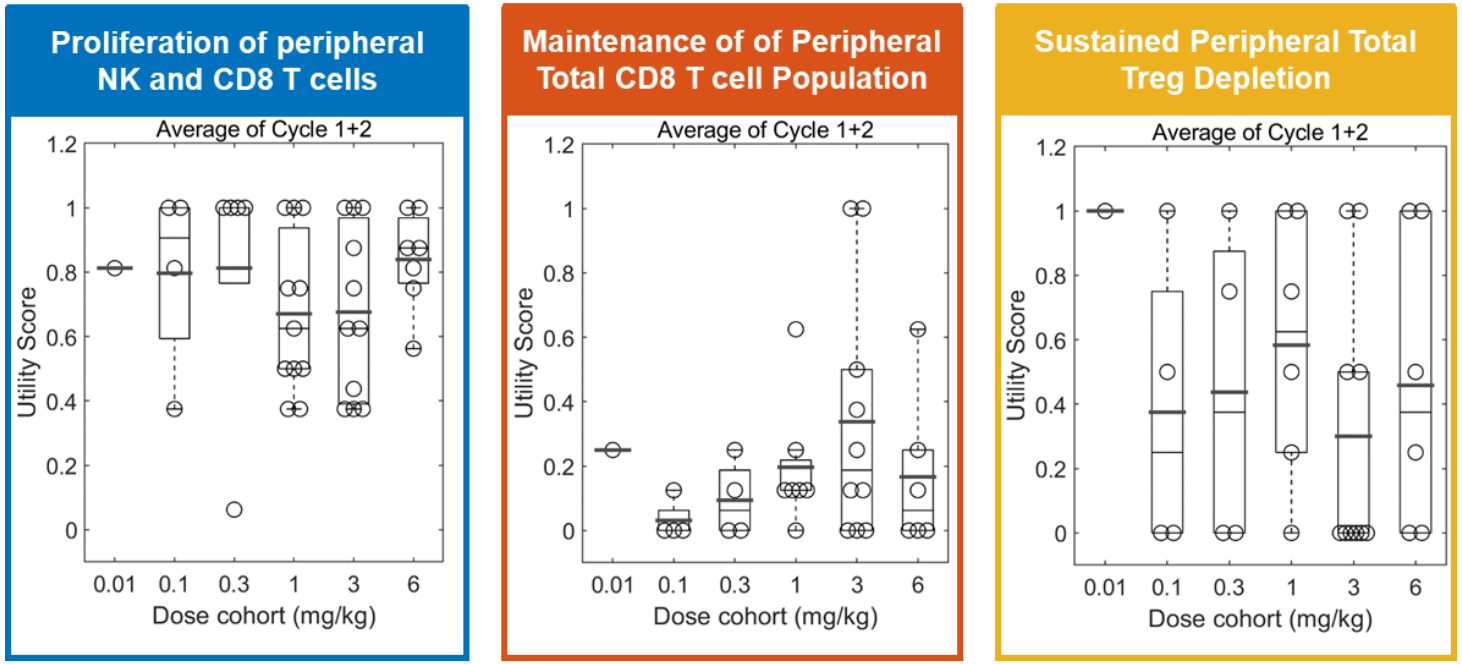
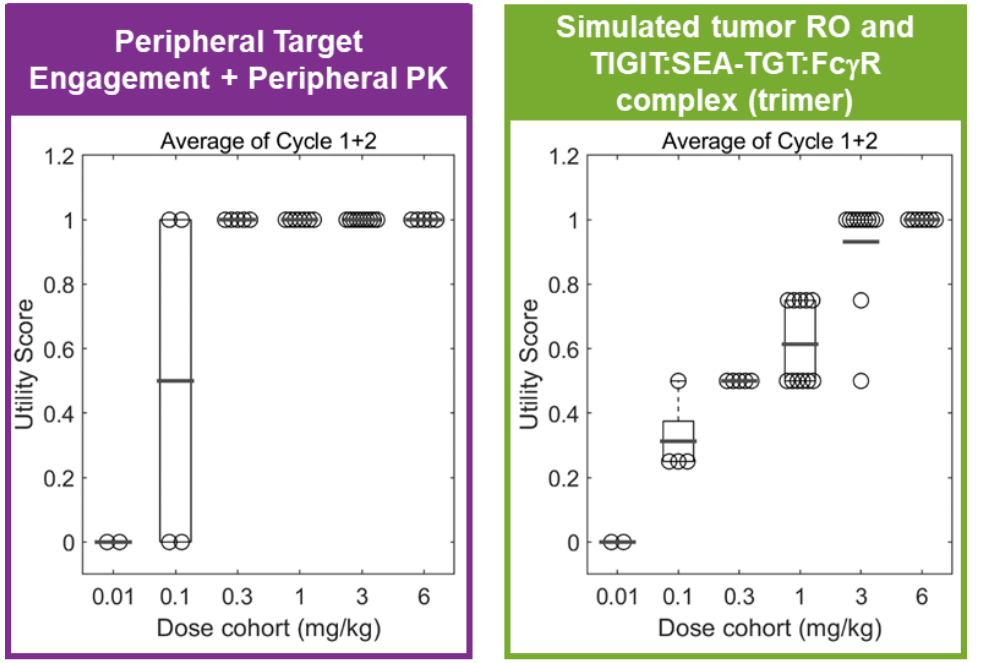
Dose Level with the Highest Utility Score Varies for Each CUI Endpoint

PD Endpoints



Dose level where mean utility score peaks varies for each PD endpoint.
Low patient numbers and high patient variability obscures strong conclusions regarding trends with dose.

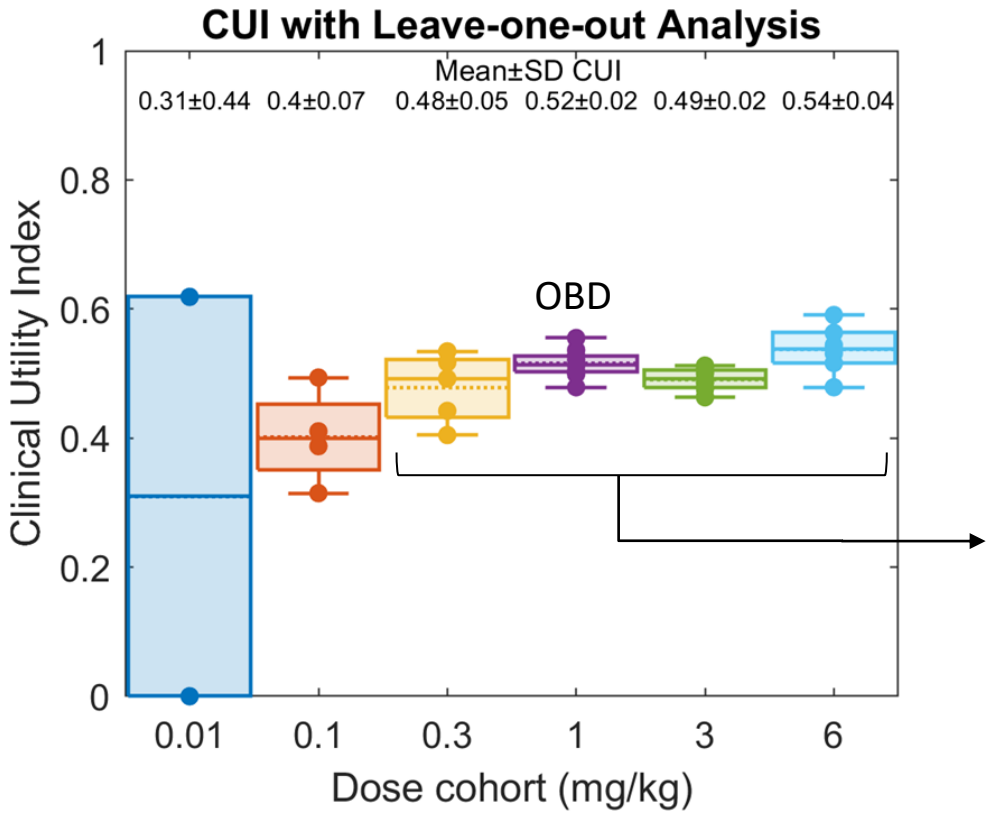
PK Endpoints



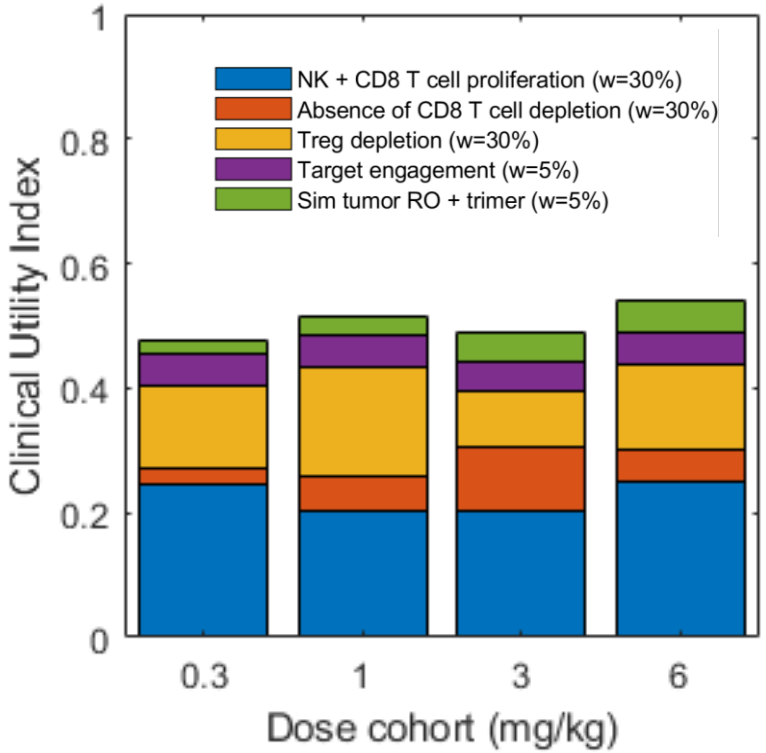
Increase in mean utility scores with increase in dose

Patilea-Vrana et al. Cancer Res 2023;83(7_Suppl):Abstract nr 5668.

Final Monotherapy SEA-TGT CUI



Mean CUI scores show an increase in biological activity from 0.01 to 0.3 mg/kg, with an apparent plateau between CUI scores across 0.3 to 6.0 mg/kg.



Due to differential weighting, the contribution of each endpoint to the mean CUI score at doses cohorts where biological activity plateaus (0.3 – 6 mg/kg) varies

Patilea-Vrana et al. Cancer Res 2023;83(7_Suppl):Abstract nr 5668.

Case Example Conclusions

- SEA-TGT demonstrated a manageable and tolerable safety profile; MTD was not reached
- A CUI model incorporating PK and PD endpoints was built to help inform dose selection in the absence of a clear dose-safety/response relationship in SEA-TGT monotherapy
- SEA-TGT pharmacokinetics were approximately dose-proportional at doses ranging from 0.3 to 6.0 mg/kg
- SEA-TGT at 1 and 3 mg/kg showed biological activity that was within desirable ranges and had similarly high overall CUI scores relative to all doses evaluated
- Based on overall clinical safety, PK, and CUI, 1 mg/kg represents the lowest biologically active dose with acceptable safety and tolerability → 1 mg/kg was selected for expansion cohorts

Literature Case Example

Identify the dosage of venetoclax, an anti-BCL-2 inhibitor, that optimizes safety and efficacy endpoints in two different indications with different exposure-response profiles

Optimum Venetoclax Dosage in Patients with CLL

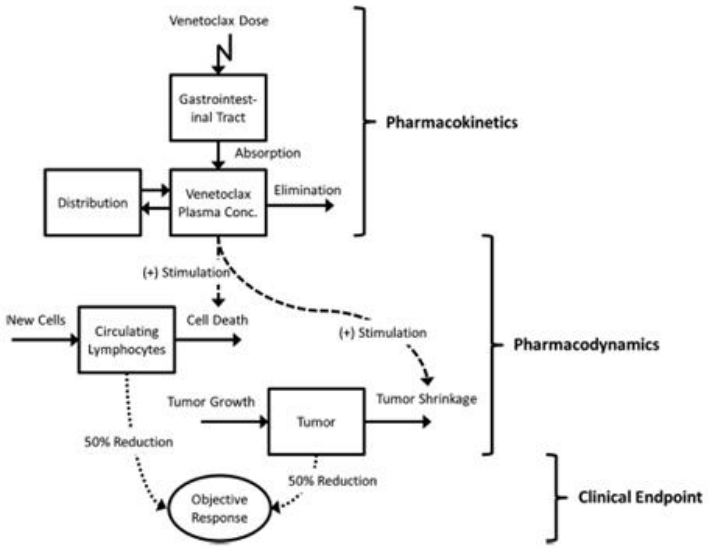
Impact of Venetoclax Exposure on Clinical Efficacy and Safety in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia

Kevin J. Freise[1] · Aksana K. Jones[1] · Doerthe Eckert[1] · Sven Mensing[1] · Shekman L. Wong[1] · Rod A. Humerickhouse[1] · Walid M. Awni[1] · Ahmed Hamed Salem[1]

Monotherapy dosage of **400 mg** QD dose established in patients with **CLL**

(MTD not reached)

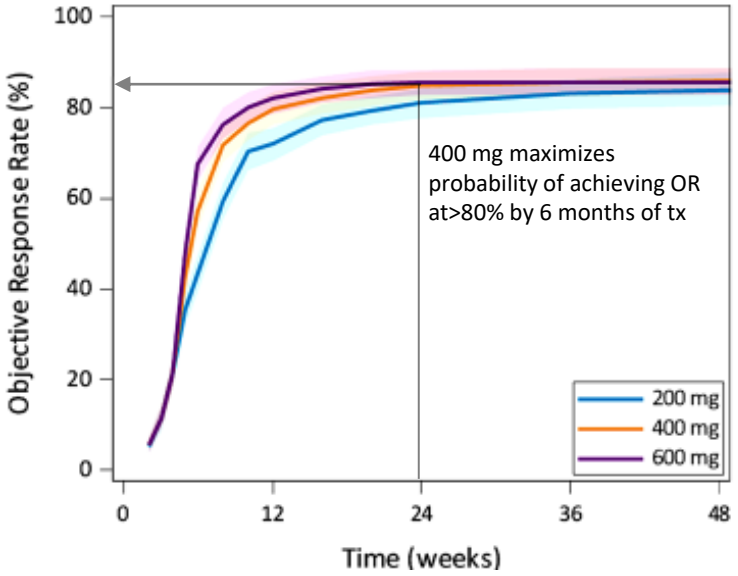
PK/PD model:



Freise KJ, et al. Clin Pharmacokinet. 2017. PMID: 27638334.

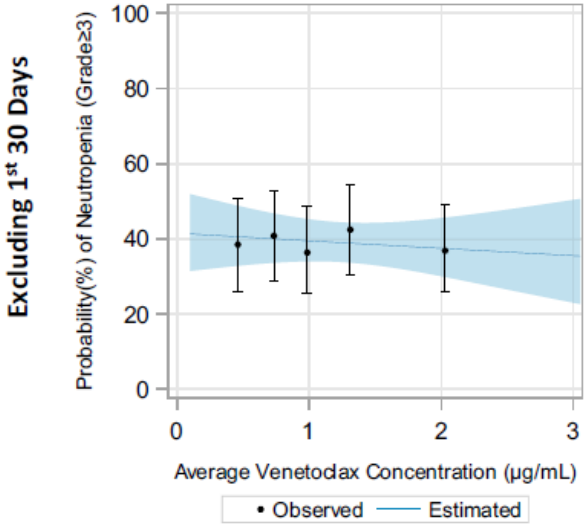
Efficacy

Higher doses did not result in improved OR rates



Safety

Higher exposure not associated with increase incidence of ≥G3 Neutropenia



Similar trends observed with ≥G3 Infection.
Initial ramp-up in dose in first 30 days

Optimum Venetoclax Dosage in Patients with MM

Moving Beyond Maximum Tolerated Dose for Targeted Oncology Drugs: Use of Clinical Utility Index to Optimize Venetoclax Dosage in Multiple Myeloma Patients

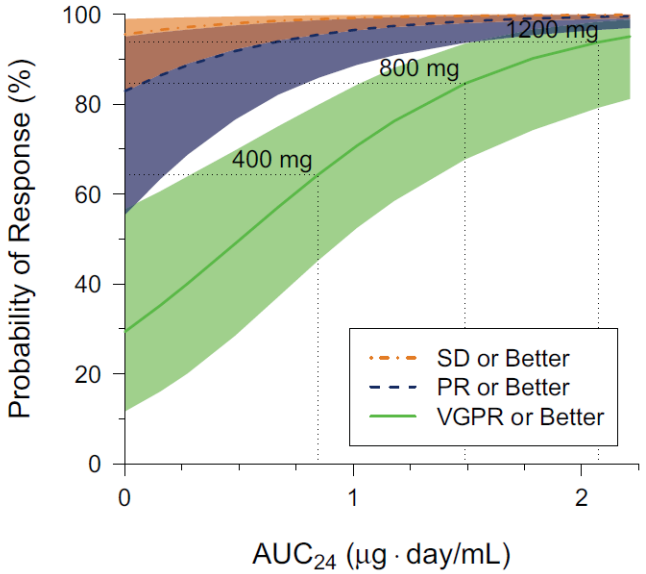
KJ Freise[1], AK Jones[1,2], ME Verdugo[1], RM Menon[1], PC Maciag[1] and AH Salem[1]

Combination dosage of **800 mg** QD dose established in patients with **MM**

(MTD not reached)

Efficacy

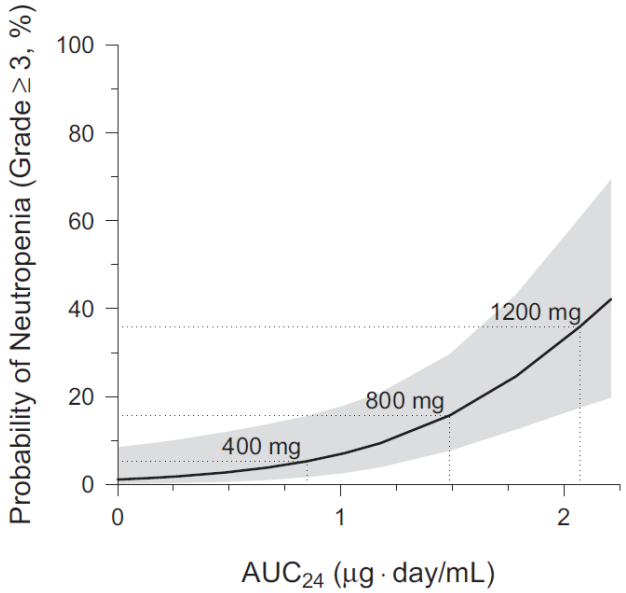
Increase in response* with venetoclax dose in combo with bortezomib and dexamethasone



*selected patient population that is non-refractory to bortezomib tx and received 1-3 prior tx

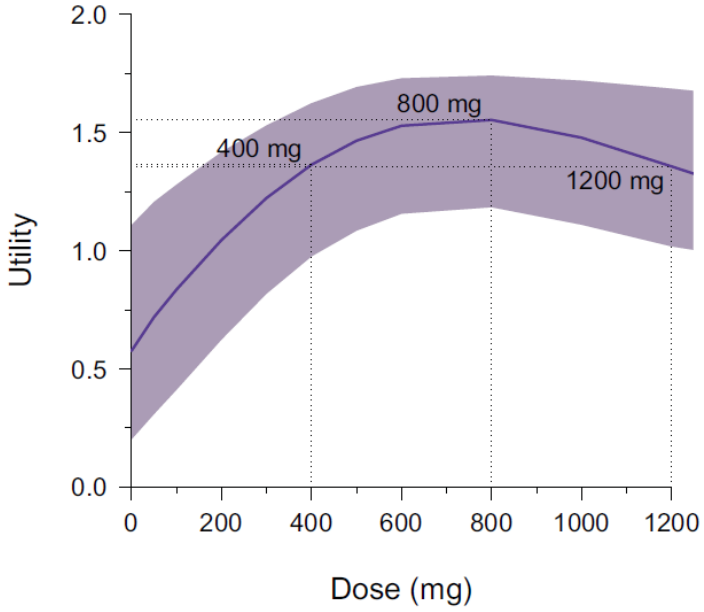
Safety

Increase in incidence of ≥G3 neutropenia with dose



Clinical Utility Index

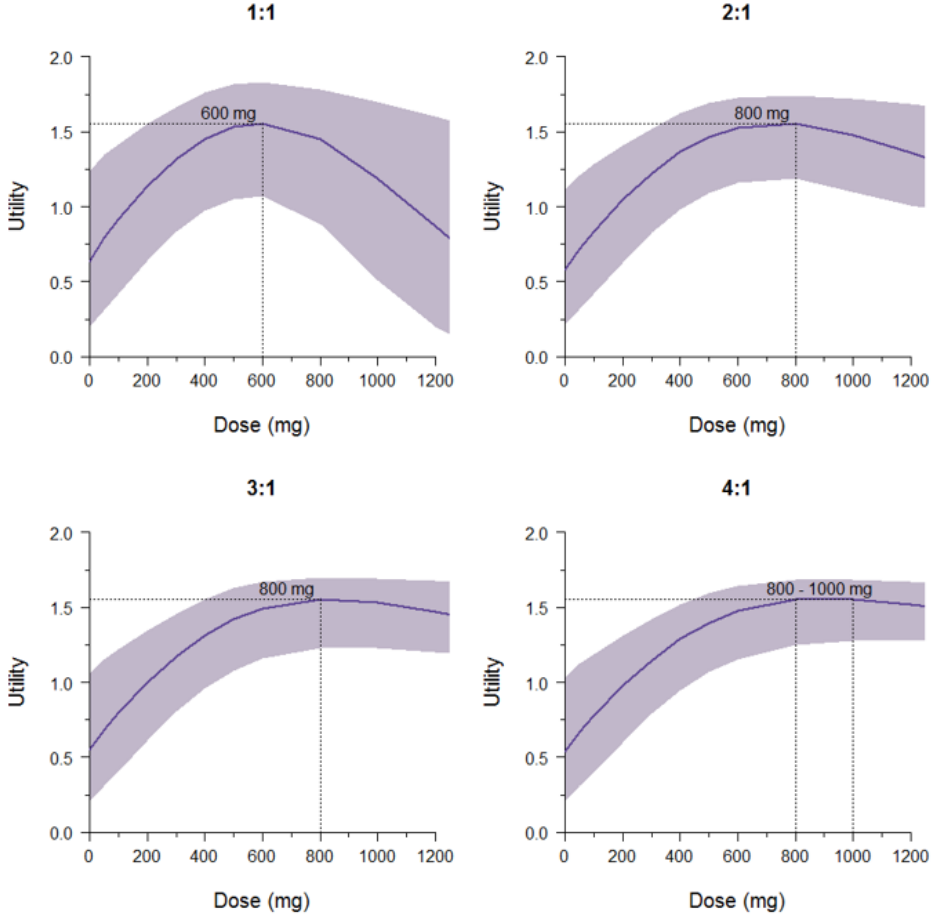
post-hoc selected 2:1 weighing of efficacy(VGPR) and safety (≥G3 neutropenia)



Freise KJ, et al. Clin Pharmacol Ther. 2017.PMID: 28419431.

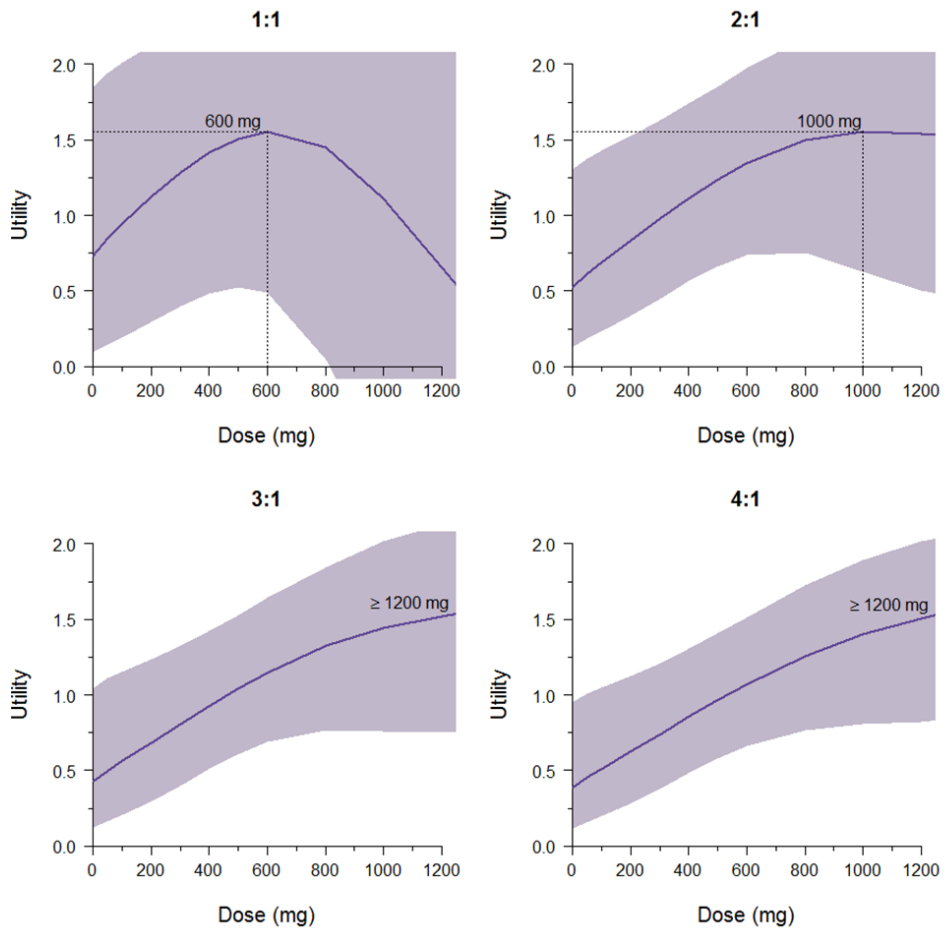
Venetoclax CUI Sensitivity Analysis

SA on weights (efficacy:safety)



1:1 not considered appropriate since neutropenia was manageable and did not lead to venetoclax discontinuations

SA using different endpoint (CR or better) & weights



CR or better leads to increased uncertainty in the CUI
VGPR or better correlates as well or better with mPFS than CR or better

Freise KJ, et al. Clin Pharmacol Ther. 2017.PMID: 28419431.

Literature Case Example Conclusions

- Optimum dosage of venetoclax differed across indications and in mono vs combo
  - 400 mg QD mono in patients with CLL vs 800 mg QD combo in patients with MM
- Post-hoc developed CUI using Ph1b data utilized to identify the optimum dosage in patients with MM by optimizing for endpoints that correlate with safety and efficacy
  - 800 mg QD selected dose for Ph3 study of venetoclax or placebo in combination with bortezomib and dexamethasone in relapsed/refractory multiple myeloma (BELLINI trial)

The Good, the Bad, and the CUI

Pros

- **Fit-for-purpose and flexible tool to quantify benefit-risk profiles**
- Totality of evidence approach: multiple endpoints mathematically integrated into a single, transparent, structured read-out/metric
  - Heightens cross-functional collaboration and alignment
- Simultaneous evaluation and trade-off of qualitatively different criteria
- Direct between-group comparison using identical criteria
- If developed *a priori*, minimizes bias by preselecting endpoints and criteria

Cons

- **Subjective selection of endpoints, cutoffs/utility functions, and weights**
  - May be difficult to achieve consensus
  - Check for robustness via sensitivity analysis
- Uncertainty in assumptions that define CUI criteria if data is limited
- CUI models may need to be developed separately for different indications or for mono vs combo dosing (fit for purpose)
- Static model, lacks time dependency
- Not statistically rigorous if low N's

Future Developments of CUI Models

- Inclusion of additional relevant endpoints for more comprehensive assessment of benefit-risk profiles:
  - Short vs long-term safety and efficacy, tolerability, time on treatment, biomarkers, patient characteristics, PROs
    - Non-oncology CUI examples include multiple endpoints per category[1,2], multiple combo doses[2], interaction between endpoints[3],personalization of weight selection[4]
  - More comprehensive metrics to define safety and tolerability endpoints
    - One vs multiple AEs (e.g. toxicity index[5,6])
    - Time dependency (e.g. toxicity over time analysis[7])
    - Individual higher grade AEs vs multiple lower grade AEs

[1] Leil et al, 2010, PMID; 20686477
[2] Greef-van der Sandt et al, 2016, PMID: 26422298
[3] Manner et al, 2014, PMID: 24825416
[4] Winzenborg, et al 2020, PMID: 33200566
[5] Rogatko et al. 2004, PMID: 15269136
[6] Gresham et al, 2020. PMID: 32091598
[7] Thanarajasingam et al, 2016. PMID: 27083333

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SESSION 2A: EVALUATING AND MODELING ALL EARLY DATA TO SELECT RECOMMENDED PHASE II DOSE

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