SESSION 2: SELECTING DOSAGES FOR ADDITIONAL EXPLORATION BASED ON NONCLINICAL AND EARLY CLINICAL DATA
Selecting Dosages for Additional Exploration
Based on Nonclinical and Early Clinical Data

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This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies
Reference to any marketed products is for illustrative purposes only and does not constitute endorsement by the FDA.
Traditional Dose Selection Strategy

Dose Escalation

- **Dose Level**
- **Time**

- Patient with No DLT*
- Patient with DLT*

- MTD*

Registration

- MTD
- Patients with Cancer
- Control

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

*DLT = Dose-limiting toxicity,
*MTD = Maximum tolerated dose
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Draft — Not for Implementation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

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 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

Optimized Dose

Control

Randomized Comparison to Standard-of-Care

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

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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_{\text{max}}: maximum concentration; C_{\text{trough}}: trough concentration; C(t): concentration over time; TST: testosterone; VEGF: vascular endothelial growth factor; mTORC1: mammalian target of rapamycin complex; ORR: Overall Response Rate; SLD: Sum of the Longest Diameters; SPD: Sum of the Products of the two largest Diameters; SUV_{\text{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.

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

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


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

Integrative Analysis Plan

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

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

\[ CUI = \sum_{i=1}^{n} \text{weight}_i \times \text{Utility Score}_i \]

CUI is the sum of the weighted (w) average utility functions (U) for all endpoints of interest (i).
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 \textit{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**

- **Monotherapy Dose Escalation**
  - N=27 Total
  - 0.01 mg/kg, n=2
  - 0.1 mg/kg, n=5
  - 0.3 mg/kg, n=5
  - 1.0 mg/kg, n=5
  - 3.0 mg/kg, n=5
  - 6.0 mg/kg, n=6

- **Monotherapy Dose Optimization**
  - 1 and 3 mg/kg, n=6 each

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

Caban et al. Cancer Res 2023;83(8_Suppl):Abstract nr CT265.
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**
1. Tumor Cell
2. Myeloid Cell
3. T cell
4. CD155/CD112
5. CD226
6. SEA-TGT
7. TIGIT
8. Block inhibitory TIGIT mediated checkpoint signal to memory CD8 T cells

**Treg Depletion**
1. NK Cell
2. Depletes T regulatory cells, which inhibit CD8s, by increased activation of NK cells

**NK Cell Proliferation**
1. T Regulatory Cell
2. SEA-TGT
3. Binds activating FcγRIIIa on myeloid cells & induces new antigen+ CD8 T cells

**Total CD8s**
1. Antigen Specific T Cells
2. Activated APC
3. FcγRIIIb
4. SEA-TGT
5. MHC
6. CD155/CD112
7. TCR
8. CD226

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.

\[ CUI = \sum_{i=1}^{n} w_i U_i \]

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

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

<table>
<thead>
<tr>
<th>Shading</th>
<th>Utility Score</th>
<th>Evidence of Biological Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dark gray</td>
<td>1</td>
<td>Strong</td>
</tr>
<tr>
<td>Light to medium gray</td>
<td>0.25 – 0.50</td>
<td>Limited</td>
</tr>
<tr>
<td>White</td>
<td>0</td>
<td>None</td>
</tr>
</tbody>
</table>

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

Patilea-Vrana et al. Cancer Res 2023;83(7_Suppl):Abstract nr 5668.
Dose Level with the Highest Utility Score Varies for Each CUI Endpoint

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.

Increase in mean utility scores with increase in dose

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.

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
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

Monotherapy dosage of **400 mg** QD dose established in patients with **CLL** (MTD not reached)

PK/PD model:

Efficacy

Higher doses did not result in improved OR rates

400 mg maximizes probability of achieving OR at >80% by 6 months of tx

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

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

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)

Combination dosage of 800 mg QD dose established in patients with MM
(MTD not reached)

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

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

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

FDA-AACR Public Workshop On
OPTIMIZING DOSAGES FOR ONCOLOGY DRUG PRODUCTS: QUANTITATIVE APPROACHES TO SELECT DOSAGES FOR CLINICAL TRIALS
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

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1. Leil et al, 2010, PMID: 20686477
2. Greef-van der Sandt et al, 2016, PMID: 26422298
5. Rogatko et al. 2004, PMID: 15269136
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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