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Interpreting Data from Dose-Finding Studies in Early Phase Oncology Trials to Determine the Optimal Dose

Introduction

A critical aspect of drug development is identifying the appropriate dose* that leads to maximal efficacy balanced with safety and tolerability. Oncology clinical trials historically focused on a maximum tolerated dose (MTD) because early systemic therapies such as cytotoxic chemotherapies often have steep dose–response curves that suggest a higher dose equates to higher efficacy.[1] Newer therapeutic classes like molecularly targeted therapies and immunotherapies may have wide separation of dose-response curves between safety and efficacy leading to efficacious doses that are lower than the MTD, and thus resulting in better tolerability while maintaining efficacy. In addition, some agents may have an efficacy curve that is bell-shaped, with higher doses delivering less efficacy than intermediate doses. In recent years, through Project Optimus and recent draft guidance, the U.S. Food and Drug Administration (FDA)'s Oncology Center of Excellence (OCE) has emphasized the need for premarket dose optimization in clinical trials to ensure patients receive drugs that are effective, safe, *and* tolerable.[2,3] The goal of Project Optimus is "to educate, innovate, and collaborate with companies, academia, professional societies, international regulatory authorities, and patients to move forward with a dose-finding and dose optimization paradigm across oncology that emphasizes selection of a dose or doses that maximizes not only the efficacy of a drug but the safety and tolerability as well."[2]

Oncology drug trial sponsors are generally moving towards early phase clinical trial designs that balance efficacy, safety, and tolerability to identify an optimized dose. However, a key uncertainty is how to establish the appropriate totality of evidence from these different endpoints and how to interpret the data to select optimal dose(s), which is a dose that can maximize the benefit/risk profile or provide the desired therapeutic effect while minimizing toxicity,[3] that align with the goals of Project Optimus. Specifically, a clear understanding of how to assess and generate evidence for tolerability and how it fits into the totality of evidence is needed. Several potential trial designs and statistical analyses that support improved approaches to collecting early phase trial data have been identified.[4,5] However, the desire for additional data collection adds complexity to study design and data interpretation. As such, it is also critical to be forward thinking and consider how emerging technologies can assist with data collection and analysis, including how to integrate new data with what is included in existing collection approaches.

* The term dose is used throughout this document to refer both to dose, the amount of the drug, and dosage, the amount of the drug and its schedule.

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This document reflects discussions that occurred among stakeholder groups on various topics. This document should not be construed to represent FDA's views or policies.

To support a comprehensive approach to data integration and interpretation for oncology drug dose optimization, Friends of Cancer Research (*Friends*) convened stakeholders to outline the types of data that are collected during dose-finding trials, consider how to prioritize data collection, and propose ways to interpret these data in the identification and selection of the optimal dose(s) for registrational trials. Given the current drug development environment where only 9% of Phase 1 experimental agents make it to registration,[6] there is risk in any decision-making. It is critical to make a concerted effort to identify the best possible dose that maximizes efficacy while reducing toxicity and asks the minimum possible number of patients needed to contribute to such an effort.

Data that Establish the Totality of Evidence

Data collected from dose-finding trials are encompassed within five main categories, each with a different purpose: pharmacokinetics (PK), pharmacodynamics (PD)/ target engagement (TE), efficacy, safety, and tolerability. For each of these categories, the purpose of including the data category, the type of data currently collected, challenges with the current data collection approaches, and opportunities for improving data collection are described below. When determining the data collection approach within these five categories, trialists should consider not only the methodological approach or assay used to collect these data, but also the appropriate assessment frequency of data collection.

Pharmacokinetics (PK)

Pharmacokinetics (PK) establishes how the body interacts with the drug and evaluates the absorption, distribution, metabolism, and elimination of the therapeutic. PK is often analyzed via serial plasma/serum concentrations collected within hours or days after the administration of a drug. Collecting information on food intake (e.g., through using a food diary) and concomitant medications can aid PK interpretation. Currently, drug distribution to specific tissues of interest (i.e., the tumor) is not commonly assessed, but novel techniques are emerging to assess distribution to target sites.

Given the importance of exposure-response analyses for dose decision-making, trialists should plan to include PK sampling in all patients during dose-finding trials. The extent of the PK sampling can vary from intensive (i.e., 8-10+ samples/patient) to sparse (i.e., 2-4 samples/patient) or a combination of both. Population PK modeling is a tool that should be leveraged to derive modeled parameters from both intensive and sparse PK data. When designing studies, it is critical to consider the time toxicity of cancer treatments for patients, which includes the time spent coordinating care and frequency of visiting the healthcare facility.[7] Incorporating flexibility into protocol language for the safety committee to make decisions about stopping or re-starting full PK sample collection based on emerging data can save time for the trialist rather than submitting and waiting for protocol amendments to be approved.

The main challenges in measuring PK in dose-finding studies are the operational and logistical considerations of sample collection due to the frequency/intensity, questions about which cycles to collect data, and the number of patients contributing PK samples. To help with the operation and recruitment burdens of PK sampling, at-home sampling and dried blood spot sampling[8] have emerged and could ultimately result in increased data collection and more accurate PK profiling because of the ability to collect PK samples more frequently at the timepoints that are important

for PK characterization. The use of these newer approaches requires additional validation steps to include as part of the totality of evidence.

Pharmacodynamics and Target Engagement (PD/TE)

Pharmacodynamics and target engagement (PD/TE) aim to assess how the drug interacts with the body and the tumor. Most PD/TE studies measure TE through tumor biopsies or peripheral sampling such as blood or cerebral spinal fluid. Depending on the location of the disease, performing multiple biopsies may be impractical or impossible. Protocols for early phase solid tumor trials that require multiple tumor biopsies might cause some patients to not enroll, ultimately precluding them from accessing potential life-prolonging therapy. To overcome this, imaging methods to assess receptor occupancy are increasing in use and can provide insights into tumor dynamics.

The clinical relevance of many PD biomarkers in the context of antitumor effects is often unknown in the first-in-human study and it is unclear how much receptor occupancy is necessary to elicit a drug response. There may be differences in timing to evaluate PD/TE according to the mechanism of action, which may be challenging for first-in-class drugs due to the lack of prior knowledge. Characterizing the dose to PD to activity relationship in relevant preclinical models in both the tumor and the periphery improves the ability to leverage PD biomarkers for decision-making.

When available, circulating PD biomarkers may be used, some of which are indicators of activity linking the impact of the drug on the tumor while others are purely mechanistic. The priority should be for early efficacy markers that help establish PK-response relationships. Some biomarkers that are indicators of activity are specific for certain cancer indications (e.g., protein derived tumor markers such as prostate specific antigen (PSA) in prostate cancer, M protein in multiple myeloma). Novel techniques like measuring the kinetics of circulating tumor DNA (ctDNA) may support an understanding of PD. For mechanistic biomarkers, there may be opportunities to monitor quantitative and qualitative changes in immune cell populations (e.g., T cells) in plasma specifically for therapies that target the immune system (i.e., immunotherapies). Peripheral biomarkers (e.g., T-cell activation and cytokines), when relevant like in the case of T-cell engagers, can help characterize the pharmacologically active dose range. However, analyses of circulating immune cells may not reflect tumor dynamics. Preclinical and clinical studies that aim to address whether peripheral blood reflects tumor PD (especially leveraging novel single cell technologies), will further improve the utility of peripheral blood-based assessment.

Overall, low specificity and high variability of circulating biomarkers and assays can make interpretability in clinical trials challenging. Characterizing PD biomarkers in clinically relevant samples to validate the assay (e.g., signal to noise, variability in longitudinal samples), should be leveraged to prioritize PD biomarkers and assays, prior to first-in-human studies. There are gaps regarding clinical relevance of thresholds and timing for measuring PD/TE, as circulating PD modulation may not correlate with anti-tumor effect. Standardization and alignment of many PD biomarkers (e.g., ctDNA) is ongoing and identifying the right biomarker to inform the dose selection is critical.

Efficacy

Efficacy provides information about whether the therapy treats the patient's disease. In solid tumors, assessment using Response Evaluation Criteria in Solid Tumors (RECIST) criteria is a common approach based on analyzing tumor measurements from radiographic imaging at different timepoints, while in hematologic malignancies, disease-specific imaging and/or blood test-based criteria have been defined.[9,10] Tumor burden as measured by imaging for solid tumors and/or blood test for hematologic malignancies can support the development of tumor growth kinetics models. There may be opportunities to compare the tumor growth kinetics before and after experimental therapy, and between doses or treatment options.[11] An emerging technology is the use of radiomics, which can provide further granularity into solid tumor dynamics. For hematological malignancies, minimal Residual Disease (MRD) is an emerging approach to measure the depth of response.[12]

One potential challenge to efficacy assessments is that the efficacy endpoints used for dose selection may not be the same as those used for marketing decisions. Overall survival (OS) is important for evaluating overall efficacy in clinical trials, however, using OS in dose-finding studies is not practical as the endpoint takes a long time to generate. Additionally, time-to-event endpoints are not reliable in single-arm cohorts due to confounding by baseline prognostic factors. Therefore, identifying relevant early efficacy endpoints is crucial for dose decisions. Prospective assessment of early efficacy endpoints (i.e., objective response rate (ORR), model-based tumor growth inhibition/ctDNA dynamic metrics, MRD) and an understanding of how they could relate to long-term clinical benefit might be valuable to support the selection of the appropriate earlier endpoints for dose decisions.[11]

Another challenge with measuring efficacy is that many emerging drug targets may be tissue agnostic and companies often consider multiple tumor types in their clinical development strategy; therefore, the earliest stages of trials may include multiple cancer types. When developing trial designs and analytic approaches, consider the level of homogeneity in the patient population, including whether it is by a biomarker or a histological type (or both). When considering dose-finding in multiple cancer types, one option is to focus dose-finding on one cancer type or a cluster of cancer types (e.g., cancer types driven by the same mutation, those with similar sensitivity to a certain class of agents) in a trial. Alternatively, patients can be stratified by tumor type and analyses can be performed on all patients and by tumor type if tumor type drives efficacy. A newer approach to analyzing the efficacy of multiple cancer types in early phase trials is using a pruning and pooling approach, where potentially inactive tumor indications are removed, and the efficacy data across the remaining doses is pooled for the analysis to enable the dose decision.[13]

Safety

A common approach to measuring safety is to use investigator reporting via the Common Terminology Criteria for Adverse Events (CTCAE), which includes a severity scale for each adverse event (AE). Typically, dose-finding trials focus on rates of serious Grade 3-4 events to determine safety. Together with laboratory results that also measure AEs, CTCAE graded AEs support an understanding of dose limiting toxicities (DLTs), or side effects that are serious enough to prevent an increase in dose. DLTs are generally defined as the presence of any Grade 3 or

higher nonhematological or Grade 4 or higher hematological toxicity at least possibly related to treatment within the DLT assessment window (i.e., the first few weeks of treatment).[14] In early phase clinical trials, there are sometimes difficulties with associating AEs to a drug rather than underlying disease because patients are often sicker, and there is no control arm. Paying close attention to Adverse Events of Special Interest (AESI) may help in focusing on AEs specific to the treatment and not the disease alone.

A key challenge to safety measurements is timing, which can be complicated by AEs that emerge later or are compounded as time goes on (i.e., those that are chronic, cumulative, or delayed). Early safety signals may not fully represent the safety events that happen outside of the DLT period, which is increasingly more common in newer classes of cancer therapeutics such as immuno-oncology drugs, targeted agents, and antibody-drug conjugates. Additionally, low-grade toxicities like Grade 1 and 2 AEs that occur frequently and/or compound over time impact patients more substantially when they receive therapy for months or years. Therefore, the assessment of AEs needs to consider these these later and compounding effects.

In the future, there may be opportunities to use biometrics measured by wearable devices, mobile applications, biosensors, and biomarkers for real-time monitoring signs of AEs to enable earlier intervention once biasing "noise" (i.e., excessive data collected) is sorted out. Real-time monitoring of certain health parameters (e.g., vital signs, physiological events) may support a clearer understanding of safety signals. If used successfully in clinical trials, these interventions would be expected to be used in clinical practice as well.

Tolerability

The tolerability of a medical product is the degree to which symptomatic and non-symptomatic AEs associated with the product's administration affect the ability or desire of the patient to adhere to the dose or intensity of therapy.[15] Because the goals of Project Optimus focus on tolerability and approaches to measuring tolerability are emerging, there is an increased emphasis on this topic included below. Currently, tolerability assessments in dose-finding studies are primarily measured by the number of dose reductions, interruptions, and discontinuations as well as physician-reported AEs as a proxy for the patient's ability or desire to adhere. Sometimes, dose modifications may be driven by physician or patient preferences, or logistical reasons unrelated to tolerability (e.g., due to the patient's schedule, including modifications for travel). Documentation of the reason for dose modifications or discontinuation, including a differentiation of dose changes due to tolerability versus other reasons, may support a more precise assessment of the relationship between dose intensity and tolerability.

It is increasingly recognized that any assessment of tolerability in a clinical trial without systematically collecting data about the patient's experience is incomplete.[15] In 2022, *Friends* developed a white paper highlighting key considerations for collecting patient-reported outcomes (PROs) in dose-finding studies.[16] PROs capture the patient perspective, are considered the gold standard when measuring patient experiences, and include key elements of tolerability such as symptomatic AEs, and bother with side effects of treatment.[17] Certain side effects measured by PROs can provide insights into larger problems as they precede long-term consequences of a drug, including nausea or anorexia that causes profound weight loss or neuropathy that becomes

irreversible. A challenge to using PROs in dose-finding studies is that this is a novel approach, and as a result there are not standard methods for how to use and interpret PROs to assist in making decisions about dose. Despite this, there are a variety of proposals for collecting PROs in early phase trials.[3,16,18]

A few outstanding considerations about incorporating PROs include:

- **Many AEs occur outside of office visits.** Ideally, PROs would assess the patients' experience on an event-driven basis (i.e., symptomatic AE onset or worsening) in addition to a calendar-driven basis at a regular cadence through an electronic PRO (ePRO) platform, which would allow for push notifications, time stamping, and assessing key domains when most relevant to the patients' experience (i.e., maximum experience of symptomatic AEs) independent of scheduled clinical encounters. Using ePRO collection requires effort to initially set up including implementation time, cost, considering patient factors (e.g., technology literacy, age, frailty), and practice factors (e.g., infrastructure and staffing of clinical team to review and respond to alerts). There is precedent and feasibility for using ePROs during later-stage trials and outside of trial settings, such as observational research for PRO evaluation and clinical assessment of PROs, which can be leveraged to inform approaches for ePRO collection in early phase trials.[19] Paper PRO collection could be employed when remote collection is not practical for patients who lack access to or are not comfortable with the use of technology. Awareness of the challenges, including confirming when the paper PRO collection was completed and by whom, should be addressed. When considering collection approaches, PRO instruments like the PRO-CTCAE are generally equivalent regardless of the mode in which they are administered, meaning that PRO-CTCAE surveys completed directly by the patient may be interchangeably administered by electronic system, paper, or automated telephone system, based on the preferences and circumstances of a given patient or study design.[20] The potential rigor lost by accepting multiple modes for self-administered PRO collection and the balance with what is gained in terms of more complete data and approaches that suit all types of patients should be considered.

- **The optimal timing of when PROs should be analyzed, including how this information may impact interpretation of tolerability.** One option is to analyze PROs at the end of the trial, which means that clinical trial staff would not have access to patient-level PROs as they arise. However, this approach can prevent PRO data from being used to inform clinician assessment. An emerging approach of interest is to share PRO data with site investigators during trial conduct to inform management of patients' symptoms. By sharing PRO data in real-time, clinicians can use patient responses to inform their own CTCAE reporting, which also ameliorates potential concerns about reconciliation of tolerability data. This approach has been shown to be feasible and improve alignment of CTCAE reporting with the patient experience.[21] As an example, **Figure 1** represents a form used in the NCI cooperative group randomized clinical trial, N1048. Patients reported the PRO-CTCAE electronically and this information auto-populated an AE form for clinical investigators to review and complete at the point of care during trial conduct.[22] A similar approach was used in early-phase trials at Memorial Sloan Kettering Cancer Center, in which patients report PROs in the waiting room prior to visits, and then the PROs populate a software interface through which investigators enter their own CTCAE scores (**Figure 2**). A benefit of this approach is that the patient's perspective on their treatment is used at the point of care to inform trial conduct. Patients

have noted concerns that their PRO data might be used as a rationale to remove them from trials, however, findings from prior cooperative group trials where PRO data was shared with investigators noted no increase in trial discontinuation even among patients with severe toxicities based on PRO data. Patient education is critical for each PRO approach at the outset of the trial, so patients understand how this information is and is not being used within the study.

Solicited Adverse Event

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Alliance for Clinical Trials in Oncology

Protocol Number: N1048
Patient ID: demo-mt
Institution (Inst. Number): [redacted]

Instructions: This form should be completed by the CRA per the Test Schedule (Section 4.0) using patient's medical records, starting from the first day since the prior reporting period if post-baseline. When completing this form, the patient's self-reported adverse event ratings (shown in the table below for the reporting period) should be used as a reference.

Reporting Period End Date (date on which the clinician evaluated patient's adverse events) (dd-MMM-yyyy) 29-MAY-2015

Adverse Event Text Name (CTCAE v 4.0)	MedDRA Adverse Event Code (v. 12.0)	Patient Self-Reporting Adverse Event Ratings			Check the circle next to event(s) not evaluated at this visit	Adverse Event Grade *(highest grade in this reporting period)* INCLUDE GRADE 0's						Has an adverse event expedited report been submitted?* *Enter a # below: 1=Yes 2=No*
		Severity	Frequency	Interference with Activities of Daily Life								
Dysphagia	10013920	*None*	-	-	O	0	1	2	3	4	5 (death)	
Diarrhea	10012727	-	*Rarely*	-	O	0	1	2	3	4	5 (death)	
Nausea	10028813	*Mild*	*Rarely*	-	O	0	1	2	3			
Vomiting	10047700	-	*Never*	-	O	0	1	2	3	4	5 (death)	
Dyspnea	10013963	*None*	-	-	O	0	1	2	3	4	5 (death)	
Peripheral sensory neuropathy	10034620	*None*	-	-	O	0	1	2	3	4	5 (death)	
Constipation	10010774	*Mild*			O	0	1	2	3	4	5 (death)	
Mucositis oral	10028130	*None*			O	0	1	2	3	4	5 (death)	

Figure 1. Example of a form used to populate PROs to provide information to clinicians during clinical trials by the Alliance for Clinical Trials in Oncology. *In the example, the patient portion of the form has been populated, and clinician reporting of CTCAE needs to be added to the form. This is an approach to generate patient-informed clinician-reported AEs in real time during a clinical trial.*

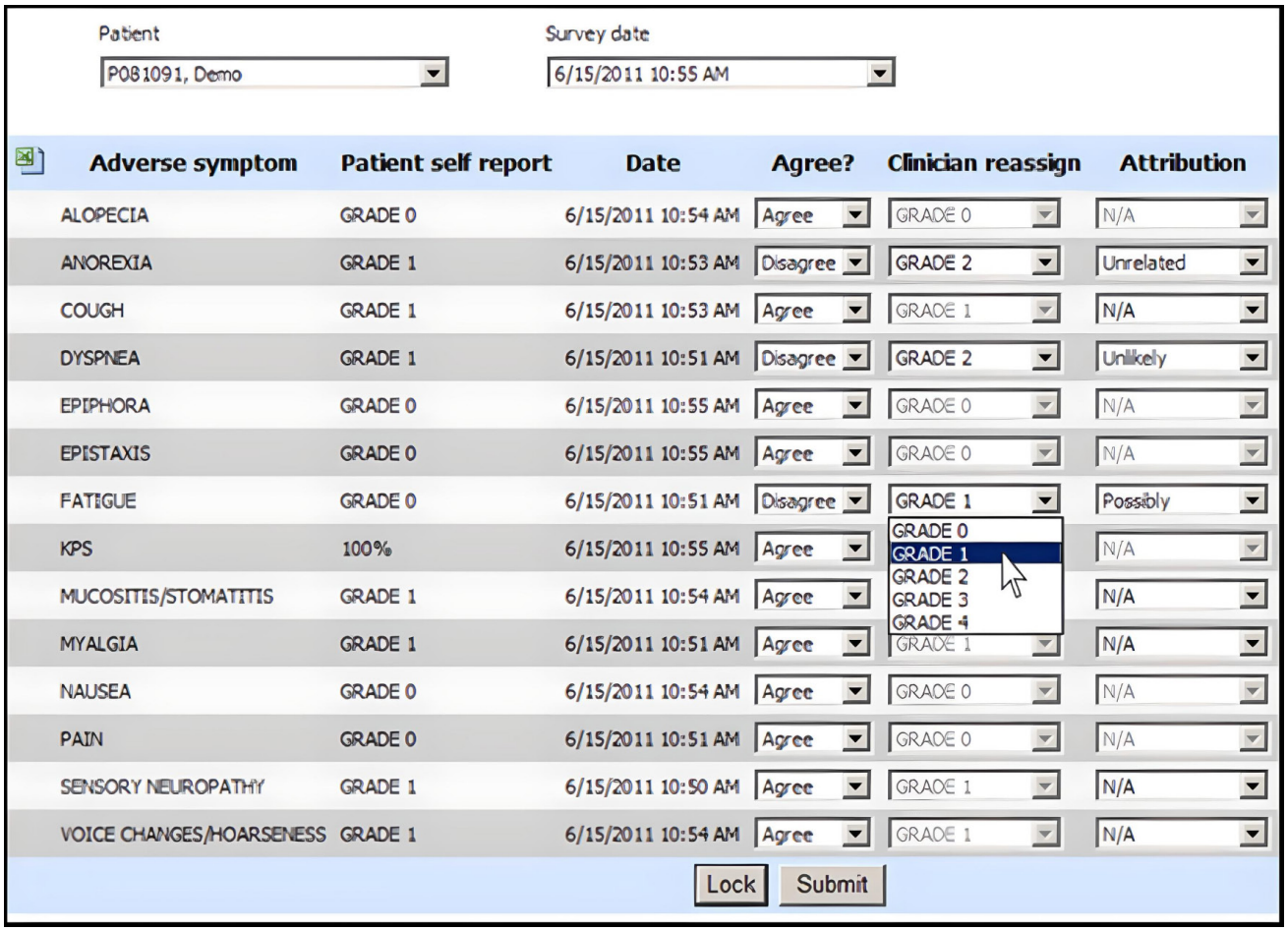

Figure 2. A second example of a form used to populate PROs to provide information to clinicians during clinical trials from Memorial Sloan Kettering Cancer Center.

- **Strategies for selecting which PROs to include for dose-finding trials are emerging.**[23–28] One approach is to start with an established group of core items from the PRO-CTCAE, then include additional PRO-CTCAE items for expected toxicities based on drug class or prior publications, a single-item global side effect impact item to capture the cumulative experience of toxicities, and a free text box for unsolicited AEs.[26] FDA guidance provides directions on which core domains are important to measure in cancer trials, although the guidance does not specify which measures are best suited for use in dose optimization trials.[3] Additional suggested approaches are included in the *Friends'* white paper from 2022, such as the use of a free-text item to capture newly emerging toxicities.[16] The use of a free-text item can inform selection of patient-reported symptoms for later drug development when the toxicity profile of a drug may be otherwise unknown.

Overall, how PRO data are considered in the totality of evidence and how they can contribute to decisions about dosing is not yet fully established and would benefit from additional standards or guidelines. PROs can complement investigator-derived safety information to determine the benefit-risk of different doses, particularly for treatment-related toxicities that are poorly captured

by investigator assessment (e.g., low-grade diarrhea, blurry vision that is transient but recurs daily, etc.). While standards and guidelines are being developed, including PROs in dose-finding studies to optimize dose is encouraged to capture a comprehensive assessment of tolerability.

Interpreting the Data that Establish Totality of Evidence to Determine the Optimal Dose

Dose decisions from dose-finding studies do not occur at a single timepoint, as the data that establish the totality of evidence are different at each decision point and should be interpreted as such. An idealized dose-finding clinical trial(s) includes two phases, the Dose Escalation phase and the Dose Expansion phase, which are often part of or completely encompass Phase 1 and Phase 2 clinical trials. Dose-finding trials have three decision points for dose selection (**Figure 3**): 1) during Dose Escalation, to determine whether more patients should be included in that dose level, whether the level should be increased or decreased, and whether to evaluate intermediate doses, 2) at the end of Dose Escalation, to identify the dose(s) and schedule(s) for Dose Expansion, and 3) at the end of Dose Expansion, to identify the dose(s) for subsequent clinical investigations or a registrational trial.

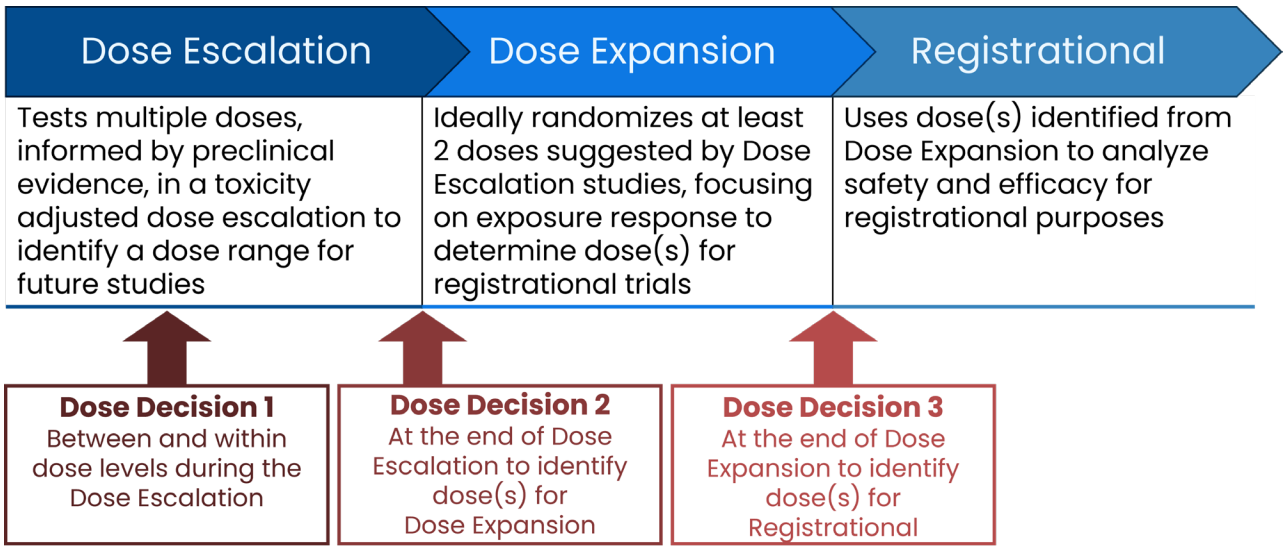

Figure 3. Dose-finding trials and the decisions about dose that occur throughout.

The analysis at each decision point should be a benefit-risk assessment using the totality of data available at that decision point, as not all categories of data will be available at all decision points and in the context of some of the data, there will not be enough of it at certain timepoints to make meaningful conclusions. Although data driven, the decisions are not necessarily statistically powered for each data element.

The approach to interpretation outlined below considers a monotherapy as a first indication in a population with metastatic disease.

Dose Decision 1 – During Dose Escalation

The Dose Escalation phase tests multiple doses and schedules, adjusting based on toxicity, to identify a dose range for future studies. The starting dose, and considerations for how many doses should be included at this point, are often driven by preclinical data. A dose range is an important output of Dose Escalation, which may include the MTD, as a necessary step to characterize the drug. The MTD is defined using DLTs and other severe toxicities that may happen outside of the DLT period. A common approach to defining MTD involves selecting a target DLT rate such as 25% and using a model-based or model-assisted approach for dose escalation.[29,30] Backfill cohorts of a select subset of doses are sometimes included in parallel during Dose Escalation to assess the safety, tolerability, and activity. Not all trial designs and Dose Escalation trial populations are well-suited for backfilling, therefore it is important to know if backfilling escalation cohorts will provide meaningful data and how these data would be interpreted and used to make decisions about dosing. Backfilling may use a significant amount of patient resources and limitations to control the number of patients enrolled into backfill should be established.

Dose-Escalation trials are often first-in-human and conducted in a heterogeneous patient population with respect to tumor type, prior treatments and patient co-morbidities which may confound detailed data interpretation at this stage but should yield useful trends to define a dose range for further evaluation. The patients enrolled typically have exhausted standard of care options. While understanding the lower limit of the dose range is critical, it is also important to not start too low. Preclinical data and/or clinical data from other treatments in the same class can support a starting dose. There is an increasing trend to not expose patients to inactive doses and rather use an accelerated titration, especially for those drugs which are not first in class.

When deciding about increasing doses within Dose Escalation, the focus is largely on safety (i.e., DLT criteria and severe AEs) and to some extent PK and PD data. However, PK and PD data availability and analysis typically lag safety and therefore are not often included in early Dose Escalation decision criteria. As PK and PD data emerge, even if they lag 1-2 cohorts behind, these data can be considered for decision-making during later parts of Dose Escalation and into Dose Expansion. Additional dose escalation may not always be warranted if exposure remains unchanged with dose due to saturation of absorption (i.e., solubility) or if a target threshold PK level is reached. Emerging safety signals and tolerability from earlier dose cohorts that occur after the DLT period should also be considered in the Dose Escalation decision, especially if they limit not only the dose, but how long a patient is likely to remain on treatment.

TE (i.e., receptor occupancy; RO) may play a role in the Dose Escalation decision provided these results are available within a reasonable turnaround time. Target-mediated drug disposition could provide indirect evidence of TE/RO for easily accessible targets. When relevant, PD/TE biomarkers may be used to define the range of active doses to backfill with safe and potentially active doses at the end of Dose Escalation.

While collecting and analyzing PRO data may not be the focus of Dose Escalation, these data can support an understanding of profiles of symptomatic AEs by dose[31,32] and support an understanding of tolerability in subsequent trials. Including PROs in Dose Escalation can help sites establish processes for PRO implementation to carry into later phase trials allowing the patient perspective to inform all phases of drug development. Failing to include PROs in this phase may miss the opportunity to consider the patient perspective in an appropriate and purposeful manner.

Dose Decision 2 – Selecting dose(s) for Dose Expansion

Dose Expansion ideally takes two or more doses and/or schedules from Dose Escalation and assesses them in a larger and potentially more homogeneous population with a focus on dose and exposure response analyses for safety and efficacy to determine the dose(s) for the registrational trials. Draft FDA guidance recommends randomized, parallel dose-response designs, where randomization helps to avoid selection bias.[3]

From a totality of evidence perspective, decisions about which dose(s) to bring to Dose Expansion should incorporate safety and PK, but also consider PD/TE, tolerability, and activity and should be supported by exposure-response analyses when feasible. Transitioning from Dose Escalation to Dose Expansion allows for an analysis of safety data collected during the entirety of Dose Escalation to identify emerging safety signals that may not have been evident during the DLT period. For PK, it is important to assess linearity to ensure that doses chosen for Dose Expansion do not have significantly overlapping exposures. Activity tracked by tumor dynamics or changes in ctDNA can give initial glimpses of efficacy. For tolerability, in addition to reviewing dose modifications and dose intensity, an assessment of patient-reported tolerability can be included with a focus on symptomatic adverse events, and side effect bother, assessed with validated PROs. For example, a single global side effect impact item can assess side effect bother (e.g., Functional Assessment of Cancer Therapy General item GP5 "I am bothered by side effects of treatment" or EORTC IL46 "troubled by your side effects" item). Co-administration of selected PRO-CTCAE items associated with symptomatic AEs, or other tools' symptom scales can help inform which side effects are contributing to tolerability-related concerns or confirm a signal seen in safety data.

From a decision-making perspective, there are limited examples of how including PROs influences decisions about dose to date. Currently, PROs are unlikely to change which doses are pursued in the Dose Escalation phase, however, they can aid in providing confidence in an AE profile to support the doses selected for further evaluation or signal the need for approaches that mitigate certain AEs. Additionally, PROs can help detect unanticipated toxicities or influence approaches to defining safety and tolerability in subsequent dose-finding studies. Future research should consider the best approaches for interpreting data about PROs.

When deciding about dose(s) to bring to Dose Expansion, the interplay between activity/efficacy and TE should be considered. Dose optimization without some level of observed efficacy, or at least of PD activity, may lead to choosing ineffective doses and may prevent optimization in the proper indication(s). Selection of a dose well above tumor RO saturation may not be warranted as it is unlikely to provide additional antitumor activity and may lead to increased toxicity. Caution should be made when RO is calculated but not measured unless the assumptions are validated

clinically. Because of these limitations (i.e., uncertainties about timing/ relationship to efficacy), PD/TE data should be used in conjunction with other data to identify doses for evaluation in Dose Expansion.

Regarding safety and tolerability, when evaluating exposure-response relationships, it may be helpful to consider exposure-response relationships for multiple safety and tolerability measures to support the dose(s) for further evaluation. Interpretation of exposure-response relationships should involve experts in quantitative pharmacology. When determining which doses to evaluate further, even if there are doses predicted to have efficacy and not associated with serious toxicity, but tolerability is poor, it would be helpful to include this dose and a lower dose or alternate regimen which could improve tolerability in the Dose Expansion study.

Dose Decision 3 – Selecting dose(s) for Registrational Trials

At the end of Dose Expansion, the totality of evidence is greater enabling more robust quantitative approaches to dose selection. The population in Dose Expansion is generally more focused on the final target indication, allowing for more accurate decision-making about dose regarding efficacy, safety, and tolerability. Additionally, findings from Dose Expansion will set the stage for the measurement of more targeted safety and tolerability endpoints. In some cases, when results of a randomized Dose Expansion are inconclusive, further randomized dose selection may be incorporated into a registrational trial.

When determining which dose(s) to evaluate in Registrational Trials, analyses will continue to incorporate PK and PD/TE and include longer term data for efficacy and tolerability. The use of population PK, exposure-response modeling, and longitudinal PK/PD model (e.g., PK-tumor dynamic or lab values if there is a lab AE) to characterize trends in exposure and activity, efficacy, safety, and tolerability is expected to support a dose for registration. It is important to consider the overall benefit-risk of the various doses, and clinical judgment will likely be required to evaluate potential tradeoffs between efficacy and safety.

Conclusions and Next Steps

Recent FDA draft guidance[3] and a recently posted FDA toolkit[33] provides considerations for dose optimization[3] and ongoing studies focused on dose-finding will provide supplementary information about additional settings. Increasingly in oncology, therapies are administered in combination. In September 2023, FDA co-hosted a workshop with ASCO focused on dose-finding in combination therapies.[24] Pediatric drug dosing is another area that will benefit from additional focus, and FDA hosted an Oncologic Drugs Advisory Committee meeting focused on dosing in drugs indicated for pediatric populations.[34] Further, it will be helpful to define the criteria necessary for extrapolating doses from one therapy, or therapeutic class, to another. Whether the same dose or a new dose would be necessary will depend on the available data and appropriate justification by the sponsor. In each of these situations, discussions outlined in this white paper should be considered as principles regarding what is included in the totality of evidence will remain. Future studies to support approaches to data extrapolation, which information to include in dose-finding trials, and how to interpret the data to select the dose will ensure patients receive the optimal dose that provides efficacy balanced with safety and tolerability.

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