FRIENDS of CANCER RESEARCH

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Optimizing Dosing in Oncology Drug Development

Friends of Cancer Research Annual Meeting 2021

Introduction: Current dosing paradigm and ongoing challenges

Outside of oncology, most drugs are evaluated in randomized dose-ranging trials that support a broader understanding of the impact of different doses on efficacy and toxicity. In oncology, dose-finding studies are largely performed only in Phase 1 clinical trials and intended to identify the maximum tolerated dose (MTD), a dose initially developed for systemic chemotherapies. This paradigm relies on the notion that an increased dose leads to increased tumor suppression; therefore, the MTD is selected based on safety aspects focused primarily on tolerability.[1,2] With the advent of new molecular targeted agents (MTAs) and immunotherapies, oncology drug dose-finding approaches should be revised. In 2013, Friends of Cancer Research (*Friends*) released an issue brief on "Optimizing Dosing of Oncology Drugs" outlining strategies for optimizing dosing in oncology drug development while acknowledging key challenges and considerations (**Table 1**). Many of the challenges still persist in addition to nonoptimal approaches for dose selection.[3]

The continued focus on identifying and using the MTD may be driven by a desire for speed and misconceptions in the community. There is a notion that it is not worth performing randomized dose-finding clinical trials because they are too time consuming which may delay drug development and keep life-changing therapies from patients.

Objectives

Describe current challenges to the implementation of dose-finding studies in oncology

Discuss opportunities to improve dosing strategies given ongoing challenges

Set expectations for dose-finding studies in the oncology pre-market setting

Identify key considerations for selecting appropriate dose optimization strategies in oncology

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Additionally, there is a misconception that a higher dose leads to higher efficacy and patients often anticipate that cancer treatments come with side effects. However, newer treatments like MTAs and immunotherapies often have target saturation limits below the MTD suggesting drugs can be given at lower doses with similar efficacy and potentially fewer side effects.

Friends convened stakeholders from industry, academia, the U.S. Food and Drug Administration (FDA), and patient advocacy groups to discuss the opportunities for optimizing dosing in oncology. This white paper highlights key findings from the discussions and aims to provide recommendations that precipitate a paradigm shift in oncology drug development to support adequate dose optimization studies. First, we provide strategies for overcoming the challenges outlined above, then highlight expectations for dose-finding studies, and lastly suggest key considerations for improved study design. While improved dosing methods and education are needed in the post-market setting, the recommendations provide focus on the pre-market setting to improve clinical trial design.

Strategies to overcome perceived challenges associated with the execution of appropriate oncology dose-finding studies

Perceived Challenge 1: Dose-finding studies are too time consuming and will prevent patients from quickly getting the drugs they need.

Dose-finding studies are extremely important to understand the therapeutic window of a drug and to ensure patients with cancer are optimally treated. These studies can be completed efficiently, with appropriate planning. FDA expects that sponsors perform dose-finding studies to evaluate exposure-response, efficacy, and safety and inform dose selection for registrational trials.[4]

Performing dose-finding studies in the pre-market setting builds a comprehensive foundation regarding the scientific reason for selecting a dose that not only provides more optimal treatment for patients, but also supports more seamless updates to the drug post approval. Applications for utilizing these data post approval include their use in combinations, adjustments in frequency of administration (e.g., Q3W to Q6W), and changes in the route of administration (e.g., intravenous to subcutaneous). Additionally, adequate dose-finding trials pre-approval may prevent clinical holds, the need for additional studies later in development, or post-marketing requirements if an inadequate dose is selected.

Moving ahead with an ill-optimized dose for the registrational trial can negatively impact the ability to document the true benefit of the drug. Identifying a dose with improved tolerability will lead to more patients missing fewer treatments due to toxicities while enabling them to remain on a working treatment for longer. In addition to individuals staying on treatment longer, a more appropriate dose may also provide an opportunity for additional patients with poor performance status to gain access.

To reduce potential delays in approval, discussions with FDA about dose-finding studies ideally would occur as soon as possible in drug development, as early as in the pre-IND setting.

We have provided a list of questions to guide dosing discussions and strategies for different phases of development in **Table 2**. In addition to an early milestone meeting, sponsors could incorporate discussions about dosing in pre-IND meetings and consider additional meeting settings to discuss dose optimization. During the 2021 Beyond Breakthrough meeting hosted by *Friends*, a dosing snapshot was proposed for sponsors to help facilitate the exchange of key considerations and supporting evidence for dosing (**Appendix 1**).[5]

Perceived Challenge 2: Stakeholders believe that lower doses of drug are not as effective as higher doses.

Many involved in decision making for cancer treatment are accustomed to the MTD paradigm. They believe that higher drug doses will be more effective and fear that lower doses will lead to a subtherapeutic or less efficacious treatment regimen. Sponsors are encouraged to consider including an interim assessment and allowing intrapatient dose escalation (e.g., if the primary endpoint is based on early changes in tumor size metrics) into randomized trials of two or more doses to address the potential for underdosing. It is paramount that patient informed consent documentation clearly communicates the reasoning for various doses and explains that the lower dose was chosen based on data and modeling which inform its activity in a clinical trial. In addition, incorporation into clinical trials of tools to protect the patient interest, such as enabling treatment crossover or dose modifications based on interim analyses, is important.

A key solution in updating the approach for dose-finding studies is through stakeholder education. Concerns that lower doses lead to less efficacy can be mitigated through educating patients and providers about the value of using a lower dose, when appropriate, especially for MTAs. Sponsors should understand the utility of appropriate dose-finding trials in the long-term to support further analysis of their products and ensure that the greatest number of patients benefit from their product. An additional avenue of education about dose-finding trial design is enhanced guidance from FDA and how the agency plans to engage with sponsors in selecting the dose for oncology registrational trials.

Educating providers and patients about the outcomes from dose-finding studies could also support an understanding of how lower doses do not necessarily always lead to lower efficacy. Sponsors could be encouraged to publish the results from their dose-finding studies, including certain aspects of the process and rationale for selecting the dose used in the registrational trial. Clinical management guideline developers could consider incorporating information about different doses, including dose reductions, that provides data driven insights about the impact of different doses on safety and efficacy.

Expectations for dose-finding study designs and methodology

The goal of dose-finding studies is to adequately characterize the exposure/safety relationship as well as the exposure/activity relationship to select a dose that will be brought into the registrational trial and ultimately used post approval.[6,7] Establishment of a therapeutic window based on activity and an acceptable level of toxicity, derived from a characterization of pharmacokinetic (PK)/exposure and pharmacodynamic (PD) metrics is integral. Dose-finding

trials that effectively and efficiently evaluate at least two doses in a randomized manner are increasingly important for dose selection.

Selecting PK and PD Metrics. Sponsors can use pre-clinical data to define target saturation points and exposure to narrow the range of doses for further clinical evaluation. It is often very helpful to identify biomarkers that translate from animal models or protein modeling into the clinical trial design to characterize PK and PD metrics in addition to those used in patient selection, if appropriate.

When biomarkers are assessed in patients, it is important that the biomarker is well defined. The most appropriate biomarkers are blood-based or imaging biomarkers rather than biopsies to estimate dose-response, especially given the American Society of Clinical Oncology (ASCO) guidelines around such biopsy studies.[8,9] Tumor biopsies are also problematic because the sources of variability are rarely identified and may be influenced by the time of sampling. Blood-based biomarkers can be easily assayed at multiple timepoints but may be less informative than evidence of radiographic improvement.

Well-defined biomarkers can support an understanding of dose-response relationships along with the totality of safety and activity data. Biomarkers that measure activity include those that track the relationship between plasma exposure and change in tumor endpoints such as Response Evaluation Criteria in Solid Tumors (RECIST) measurements. Analysis of tumor dynamics (e.g., depth and duration of tumor change from baseline) as a function of dose using a modeling approach can support an understanding of activity.10 It is important to consider the nature of the disease when identifying biomarkers, as certain solid tumors (e.g., lobular breast cancer) may not be measurable by RECIST and hematologic cancers will have different measurements than solid tumors. Safety can be tracked through blood biomarkers like neutrophil counts when applicable.

The Dose-Finding Trial Design. Ideally, the pre-registrational dose-finding study would be randomized, compare at least two doses, and confirm the dose selected for the registrational trial, which is the dose that maximizes benefit-risk by measuring efficacy among a sizeable number of patients. The randomized dose-finding trials do not necessarily need to be powered to conduct a rigorous statistical comparison across doses; however, it is important that the trial is sufficiently sized to understand the general shape of the dose/exposure-activity/toxicity relationships, including the minimally active dose. To save time but provide robust data for multiple doses, sponsors could consider pre-registrational trial protocols that extend monitoring of patients after the registrational trial starts to allow for the long-term characterization of patients treated with different doses.

Important considerations when choosing the doses for comparison in the pre-registrational dose-finding study include selecting doses that are pharmacokinetically distinguishable and do not have overlapping PK exposures (i.e., doses that are 2-3 fold apart). The lowest dose is the minimal dose expected to provide activity based on PK/PD analyses, and the highest dose (chosen within safety allowance) is selected to ascertain whether dose increases result in increased activity with acceptable toxicity.

After the completion of the randomized dose-finding trial, data from this trial can be analyzed to characterize the exposure-response relationships for activity and safety and then integrate with the previous PK/PD analyses results to inform the final dose(s) for the registrational trial. If there is a clear differential benefit with acceptable safety compared to a lower dose, the higher dose can be selected for the registrational trial(s). If the efficacy and safety are similar between the lower and higher doses, the lower dose can be selected as the final dose for the registrational trials.

Key considerations for dose optimization strategies

The study design for determining the optimal dose will differ depending on the product, the target population, and the data that are available. There are key considerations when designing these studies (more details are included in **Appendix 2**):

- *Therapeutic properties.* Differences in the properties of drugs (e.g., small molecule vs. large molecule, agonist vs. antagonist) influence the way drugs interact with the body in terms of safety and efficacy. The selection of the initial doses for the dose-finding studies as well as methods for determining which dose to move into registrational trials are influenced by the therapeutic properties.

- *Patient populations.* There is heterogeneity in patient populations based on tumor type, disease stage, and comorbidities. Especially in the context of expanded clinical trial populations, an understanding of how various factors influence the efficacy of the drug may provide justification for adjusting the dose accordingly.

- *Supplemental vs. original approval.* The differences in disease characteristics and patient populations between tumor types and treatment settings (e.g., monotherapy vs. combination therapy) are important to consider in determining whether any additional dose exploration is necessary for a supplemental application. In instances where further dose exploration may be needed, the study design can incorporate prior understanding of exposure-response from the original approval.

Conclusions and future directions

In conclusion, randomized studies that formally evaluate at least two doses to support dosing decisions are increasingly important in oncology rather than using MTD as the default approach. These studies will improve care in oncology by decreasing toxicities while maintaining efficacy and ultimately allow for more patients to benefit from treatments for a longer period of time. The findings in this white paper provide considerations and expectations for dose-finding studies that offer opportunities for improved patient care.

In the short-term, continued education will support a realization of the value of these studies in the pre-market setting. Patients and providers should understand that treatment with higher doses of oncology therapies is not always better and may, in fact, lead to increased side effects without the added benefit of higher activity. Sponsors should recognize the long-term benefits

of these trials and appreciate that FDA has established the expectation to incorporate dose-finding studies in the drug development paradigm sooner.

To complement this, FDA has encouraged sponsors to discuss their dose-finding trial design early in clinical development, as supported by available clinical pharmacology data. FDA's focus has shifted over the past few years to encourage companies to have conversations about their drug development pipeline earlier in development. Additionally, an appreciation for cross-disciplinary discussions has led to an increase in interdisciplinary interactions to address dosing considerations early on. Sponsors should conduct pre-clinical research that supports a basic understanding of pharmacology based on suggestions from MAPPs and guidance documents. After performing pre-clinical work and establishing necessary data, sponsors should engage FDA to refine and build the dose-finding trial. The use of a dosing snapshot (Appendix 1) would likely support more targeted discussions.

How the data from dose-randomized trials are included in drug labels require further discussion among stakeholders (FDA, industry, patients, providers). There may be an opportunity to include data in labeling that may help patients and providers understand the range of efficacy and toxicity as it relates to dose. It may also be helpful to expand on what is included about different doses for different patient populations such as those with altered organ function or pharmacogenetics.

The overarching goal is that dose-finding studies will be a part of standard oncology drug development in the pre-market setting to allow delivery of efficacious and tolerable doses to patients at initial marketing approval of a new drug. Meetings held with sponsors on dose-finding and dose selection as early as possible in development provides an opportunity for the agency to convey their expectations sooner, potentially leading to more efficient studies. Communication of data from dose-ranging trials in drug labels or publications can support shared decision making between patients and providers about dosing choices. Also, rather than patients and providers expecting debilitating side effects, side effects would be regarded as possible but not inevitable. Ultimately, updating dosing regimens should allow patients to be on drugs providing benefit with fewer toxicities for longer and miss fewer treatments due to toxicities.

Table 1: Findings from *Friends'* 2013 White Paper "Optimizing Dosing of Oncology Drugs"

Proposal	Suggestion
Path for study	1. Phase 1 trials should include adequate PK sampling to enable a clear determination of the PK properties of the drug and preliminary characterization of dose-exposure relationships. When feasible and appropriate, PD endpoints should be incorporated to determine the drug exposure that results in inhibition of the drug target. 2. Phase 2 trials should go beyond assessment of drug activity and could include adaptive designs and/or randomized exploration of doses. Continued, sparse PK sampling should be included to gain a sense of relationships between exposure and clinical outcomes. If possible, measurements of PD endpoints should also be continued. 3. Phase 3 trials should incorporate population PK sampling to further evaluate the relationship between covariates influencing exposure and key clinical outcomes. 4. When subjective toxicities are identified in phase 1 trials, patient-reported outcomes (PROs) should be assessed using validated tools if available in phase 2 and phase 3 trials and could be used to guide dose optimization. 5. The PK and PRO dataset collected in phases 1-3 could be used to develop an approach to therapeutic drug monitoring in the post-market setting. This will enable the dose for an individual patient to be adjusted as needed based on observed drug exposure, treatment tolerance and clinical status.
Necessary data elements	1. Sponsors should collect PK and exposure data in oncology phase 2 and 3 clinical trials to estimate a therapeutic index for a defined patient population. Randomized dose comparison studies should be included in phase 2 studies and exposure-response analyses should be performed to better inform the selection of dose for phase 3 registrational trials. 2. PROs should also be collected to understand the patient experience more fully with a drug. PROs can be informative not only of the side-effects of a drug, but also of any beneficial effects a drug may have on symptoms of the cancer itself.
How to integrate data elements	In the proposed approach, the collection of exposure data and data regarding tolerability across a range of doses could enable the definition of a threshold exposure needed for anti-tumor effect as well as the determination of a peak exposure that correlates with excess toxicity. Collection of drug exposure and tolerability data, as well as ongoing evaluation of adverse events and dose modifications, from patients in real-world settings may be useful for post-market evidence generation.
Optimal timing of dose comparison studies	Ideally, randomized dose comparison studies and exposure-response analyses would be performed in the pre-market setting.

Table 2: Dosing Questions by Stage of Drug Development

	Key Questions
Pre-clinical	• What is the best model to identify the initial dose? • Is there established pharmacological and a dose-pharmacology relationship evidence? • Which biomarkers should be evaluated in the clinical trials to monitor safety? To monitor activity? • What enzymes metabolize the drug? How do polymorphic enzymes influence trial design? • For oral drugs, what is the Biopharmaceutical Classification System (BCS) classification of the drug?
Early phase trial	• How do the PK and PD characteristics justify the dosing interval? • Are there any intrinsic or extrinsic factors that would influence PK? • What is the degree of PK variability, considering both interindividual and intraindividual variability? • Are there any drug interactions that need to be evaluated? • For oral drugs, should the drug be administered with food? • For oral drugs, is there a better time of day to administer (AM vs. PM)?
Prior to conducting trial intended for drug approval*	• What is the relationship between dose/exposure and activity? • What is the relationship between dose/exposure and toxicity? • Are there concerns for chronic or delayed toxicities and have these been considered when evaluating dose/exposure-toxicity? • Is the dose schedule justified based on the Kinetics-PK-PD or modeling approaches? • Is the dosing regimen justified based on dose/exposure-response relationships and other relevant data?
Registrational Trials*	• Does the dosing regimen continue to demonstrate acceptable benefit-risk?
Post-market	• Are there unexpected toxicities which necessitate a re-evaluation of the dosing regimen? • Are there opportunities to optimize the dosing regimen for convenience (e.g., extended dosing interval, new route of administration, etc.)?

*For products with expedited development (for example: Breakthrough Therapy-designated products) these two phases could potentially be combined

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Appendix 1: Drug Development Snapshot Template—Clinical Pharmacology (Dose & Administration) Snapshot.

This table was first presented in Friends of Cancer Research white paper "Beyond Breakthrough: Optimizing the Breakthrough Therapy Designation."[5]

Please note: The table below describes the supportive evidence for the proposed dose and schedule. The target length of the completed snapshot would be 2-5 pages.

Key Area of Consideration	Supporting Evidence
Recommended dose, schedule, and route of administration	• *What is the current dose(s), schedule(s) and route of administration that are currently being evaluated in clinical trials? Has the RP2D been selected? If the RP2D has not been selected, what key questions are outstanding?* • *When do you anticipate that a R2PD will be selected?* • *Are other routes of administration being investigated?*
Mechanism of action (MOA) and format	• *Is the therapeutic a small or large molecule? Another platform? What is the MOA?*
Translational evidence	• *Is there established pharmacological evidence (e.g., target engagement, MOA, outcome-based biomarkers, tumor volume) in the relevant pre-clinical species?* • *Is the dose-PK relationship established in the non-clinical species (i.e., is the PK dose proportional)?* • *Are the pharmacological/efficacious target concentrations for patients defined?* • *Is the dose/exposure-response (i.e., biomarkers, tumor size, etc.) relationship identified from the in vitro cellular systems or the in vivo animal models?*
Clinical Evidence	

Clinical studies	• *List of ongoing and completed studies (i.e., single agent and/or combination studies, indication, etc.)*
	• *Brief description of study design including patient population/cancer type(s) under study, line of therapy, and doses and schedules evaluated, sample size. For example, the following elements can be considered:*
	  ◦ *Dose escalation, expansion cohorts with or without randomization*
	  ◦ *Single arm randomization (i.e., dose and/or control); adaptive design*

PK characteristics	• *Is the dose-PK relationship well established (i.e., is the PK dose proportional)?* • *Do the PK characteristics (accumulation, half-life) justify the dosing interval?* • *Are there any intrinsic or extrinsic factors (e.g., food, body weight, immunogenicity) that would majorly influence PK (i.e., if these warrant dose adjustments in a subset of patients)?* • *Was the PK variability considered when selecting a dose that would achieve target exposure for most patients?*

Safety summary	• *Is the dose-PK relationship well established (i.e., is the PK dose proportional)?* • *Summary of frequencies of key AEs (including chronic low grade AEs, which can affect tolerability) of interest by dose* • *Is there a dose/exposure-safety or PK-PD relationship, upon the adjustment of potential covariates, for safety? If yes, what is the nature of the relationship?* • *Summary of dose interruptions, reductions, and discontinuations by dose/exposures* • *Is there an increased frequency of dose interruptions or reductions or treatment discontinuations with increasing doses/exposures?* • *Are there any late occurrence toxicities beyond the DLT period? Are there early PD biomarkers reflective of the delayed safety endpoints?* • *Are there any overlapping toxicities with the concomitant medications in the patient population (e.g., treatment combinations for NME with SOC and/or treatments for comorbidities/cancer-related symptoms)?* • *Is there an increased frequency of dose interruptions, reductions, or treatment discontinuations with increasing doses/exposures?* • *If acute/transient toxicities were observed, were alternative dosing approaches considered (e.g., step-up dosing)?* • *Do existing data indicate this is a narrow therapeutic window drug with dose limiting toxicity that is monitorable (e.g., biomarkers, BP, HR, neuropathy)?* • *If yes, does this drug provide an opportunity to personalize the dose for an individual patient or a sub-population based on the emerging monitorable toxicity?*
Efficacy summary	• *If yes, does this drug provide an opportunity to personalize the dose for an individual patient or a sub-population based on the emerging monitorable toxicity?* • *Summary of response endpoints by dose (e.g., ORR, PFS)* • *Is there a dose/exposure – efficacy (primary efficacy endpoint) and PK-PD (e.g., mechanism of action/predictive biomarkers) relationship upon the adjustment of potential confounders? If yes, what is the nature of the relationship?* • *Is the dose schedule (e.g., frequency, dose holidays) justified based on the K/PK-PD and/or QSP modeling approaches?* • *Are the relevant exposure metrics for efficacy identified (e.g., AUC, C_{max}, C_{min}, concentration-time, RO)?*
Other considerations	• *Are there any manufacturing considerations (e.g., pill burden, maximal feasible dose, etc.) that need to be considered?* • *Are there any patient factors that need to be considered (e.g., patient convenience/compliance [QD, BID, TID), QW vs Q3W, SC vs IV)?* • *Complimentary M&S approaches (i.e., PK-TGI/QSP/ML, etc.) for dose optimization and/or inform dose adjustments*
Additional Clinical Evidence	
Planned clinical studies	• *Are there additional planned clinical studies that will contribute data to the current D&A plan/rationale or future D&A proposals?*
Other evidence	• *Does additional scientific evidence exist (e.g., from similar class, MOA, or indication) that may support the current D&A plan/rationale (e.g., publications, scientific presentations)?*

Abbreviations: AEs=adverse events; AUC=area under the curve; BP=blood pressure; C_{max}=maximum 'peak' concentration; C_{min}=minimum 'trough' concentration; D&A=dose & administration; DLT=dose-limiting toxicity; HR=heart rate; K=kinetic; MOA=mechanism of action; NME=new molecular entity; ORR=overall response rate; PD=pharmacodynamic; PFS=progression-free survival; PK=pharmacokinetic; QSP=quantitative systems pharmacology; RO=receptor occupancy; SOC=standard of care

Appendix 2: Expanded Key Considerations for Dose-Finding Studies

Therapeutic properties. Differences in the chemical structure of drugs influences the way it interacts with the body in terms of safety and efficacy. The selection of the initial doses for the dose-finding studies as well as methods for determining which dose to move into registrational trials are influenced by the therapeutic properties.

- *Large molecules.* Antibodies have the potential for demonstrating false positive exposure/response relationships with single-dose data due to the impact of confounding factors such as patient health status (i.e., cachexia) on survival. Ascertaining the Target-Mediated Drug Disposition (TMDD) during the dose escalation stage is important as it provides information about target expression and target turnover.
- *Antagonists.* For antagonist monoclonal antibodies, consider a dose that attains target engagement (TE) of >90% in systemic circulation and in tumors (where required). Assess data on target saturation in tumor, which can be informed by approaches like physiologically-based pharmacokinetic (PBPK) models.
- *Agonists.* Unlike antagonist monoclonal antibodies, a high level of receptor occupancy may not be necessary for agonists to elicit a maximum pharmacological effect. PK/PD analysis on biomarker data can help in determining the level of receptor occupancy needed for therapeutic effect.
- *Non-traditional therapies.* Specific consideration may be required for antibody drug conjugates (ADCs), bispecific antibodies, and cell therapies. ADCs have relatively narrow therapeutic indices and require optimization of both dose and dosing frequency to reduce toxicity. For bispecific antibodies, it may become challenging to optimize target engagement for two targets. Efficacy and on-target toxicity of bispecific antibodies may be driven by trimer formation (ternary complex) between bispecific antibody, T cell, and tumor cell. These ternary complexes usually have a bell-shaped exposure-response relationship, and it is important to determine optimal concentrations of bispecific antibodies that maximize formation of trimer formation for maximal pharmacological activity. For cell therapies, cellular kinetics models are used to describe the relationship between the number of cells infused and expansion of modified T-cells in vivo. The understanding of cell kinetics along with measurable PD response informs the selection of dose of cell therapy.
- *Combination regimens.* In combination trials, the dose of each drug in the combination is often based on the MTD of each drug, rather than considering their additive toxicities and efficacies.[11] Doses should be selected based on maximum pharmacology (and not MTD) with special

consideration when treatments have overlapping toxicities.

- *Drug-drug interactions.* Specific consideration may be required based on drug-drug interactions and effect of renal and hepatic impairment on PK. Sometimes drugs depend on pH for solubility so differences in body chemistry or use of proton pump inhibitors may impact efficacy.[12]

Patient populations. There is heterogeneity in patient populations based on tumor type, disease stage, and comorbidities. Especially in the context of expanded clinical trial populations, an understanding of how various factors influence the efficacy of the drug may provide justification for adjusting the dose accordingly.

- *Small molecules.* Drugs that are taken orally may have different bioavailability in a fed versus fasted states. If there is a food effect, then those prandial conditions that reduce bioavailability should be avoided (since that often increases GI toxicity).
- *Heavy pre-treatment.* Patients in Phase 1 dosing trials tend to be heavily pre-treated and have strict inclusion/exclusion criteria, which often differs from the average patient who will use the drug in registrational trials or in the real world and thus may impact metabolism or tolerability of the drug.
- *Altered organ function.* Some patients with cancer have altered end-organ function either due to their disease or previous treatments. Others may have differences in pharmacogenetics, specifically genetic polymorphisms in drug transporters or metabolizing enzymes which may ultimately impact drug clearance.
- *Changes in tolerability.* Some patients have changes in tolerability over time. Dosing efficacy may be impacted by age and bodyweight. Clearance may also change over time, particularly for monoclonal antibodies.
- *Tumor stage.* Clearance of monoclonal antibodies may be different between patients with metastatic disease and without metastatic disease. The latter patients will have lower clearance, and thus a lower dose may be effective than for patients with advanced disease.
- *Long-term treatment.* In the metastatic setting, patients can be treated regularly for years, so identifying the optimal dosing regimen is important since longer term safety is an issue. Special consideration should be taken for chronic treatment use to avoid buildup of toxicities.

Appendix 3: Questions and Answers Following the Event

During the *Friends* Annual Meeting, panelists discussed opportunities for Maximizing Benefit and Improving Tolerability for Patients Through Dose Optimization. Over 50 questions were submitted to the panel. Authors provided answers to selected questions, which were then added as this appendix. The initial questions below were asked of and answered by FDA representatives, while subsequent questions were answered by remaining members of the working group. As always, sponsors should engage FDA with questions specific to their drug development program.

Questions Answered by FDA

Does FDA anticipate releasing a draft guidance on the topic of dose optimization for oncology drugs?

The focus of Project Optimus is to emphasize the importance of dose optimization early and as a component of pre-market drug development. The FDA Oncology Center of Excellence is developing a draft guidance on dose optimization that would be broadly applicable across development programs. Within this framework, FDA is interested in working with stakeholders to ascertain how to apply the general recommendations to their specific development strategies.

When is it best for sponsors to engage with the FDA regarding dose-finding study design and what factors might influence timing of these discussions?

Sponsors should recognize the importance of dose optimization and consider initiating discussions about dose-finding and dose selection early in clinical development. FDA is very open to providing feedback during pre-IND meetings and would be open to continued updates as more data from the development program become available. Discussions about dose-finding paradigms do not necessarily need to be tied to milestone meetings. As was mentioned in the White Paper, tools may be explored to facilitate timely exchange of key considerations between sponsors and FDA to support evidence generation for dose optimization.

Are there opportunities to combine data from different doses if there are no differences in response rates?

Whether or not response rate data from different doses could be combined depends on the question(s) being asked and answered. There may be opportunities to use data from patients receiving multiple doses to support regulatory decision-making at different stages of development. However, such an approach would have to be discussed with FDA and must be backed by scientific rationale and be based on the totality of data, which includes overall response rate (ORR), duration of response (DOR), dose-toxicity relationships, and supportive pharmacologic data.

Would patients participating in dose optimization studies be permitted to cross over to an alternate dose?

Yes, there may be instances where it would be desirable for patients to receive an alternate dose from the dose assigned at trial initiation. For example, emerging safety data could suggest that one of the doses is associated with worse toxicity. In a case like this, patients could be permitted to cross over and receive the preferred dose. Alternately, a prespecified analysis may show that two doses have similar efficacy, but one dose has better tolerability. In this case, it would be reasonable to allow patients to cross over to the better tolerated dose. Sponsors are encouraged to discuss their plans to allow patients to cross over with FDA during the trial design phase.

Are there specific considerations for drugs being developed under an Expedited Pathway?

Timely availability of evidence to support dose selection is essential for all drugs, particularly those with expedited development timelines (e.g., a drug with Breakthrough Therapy Designation). It is important that sponsors have a plan for dose optimization early and communicate with FDA at relevant milestones. Randomized evaluation of multiple doses can support dose selection, including for drugs with a rapid development timeline.

Questions Answered by Remaining Panel Members

What endpoints could help determine the initial dose range for dose-finding studies? How will findings from those studies inform the dose(s) used in subsequent studies?

The endpoints should support the overall goal of determining a dose that is safe and effective and does not result in unnecessary toxicities. In the initial dose-finding trial, a variety of biomarker endpoints can be used to assess potential efficacy, including both imaging and blood-based biomarkers. Invasive tumor biopsies are unlikely to yield reliable data in this context. Endpoints that are selected should provide sufficient data to achieve the objectives of both initial dose-finding studies and later dose optimization studies. Initial dose-finding studies should focus on identifying a range of active doses for subsequent randomized dose optimization studies, prior to initiation of a registration trial.

An integrated pharmacokinetic (PK)/ pharmacodynamic (PD) analysis approach may help to interpret early clinical data. It may also be beneficial to review and leverage data from other compounds in the drug class. Models based on preclinical, competitor, or other data may also support a hypothesized target for plasma exposure or effect on a blood-based biomarker.

The early phase dose-finding studies should attempt to include a comprehensive analysis of the relationship of dose and exposure to both efficacy (using radiographic and blood-based biomarkers) and safety (using toxicity biomarkers, including both clinical events and other conventional toxicity biomarkers). The dose selected for the registration trial should be based on the dose optimization trial, and the lowest dose should be used if there is neither a dose-response nor exposure-response relationship.

Why is randomization for the dose-finding trial so important? How is this conducted without powering the study?

Sufficiently sized RCTs are important to understand the relationships between dose and toxicity as well as dose and efficacy. Randomization is critical because there are multiple potential sources of bias, especially regarding patient selection at higher doses. Nonrandomization can result in misleading conclusions because of these biases or intertrial variability.

Initial dose-finding trials do not necessarily need to be powered to determine statistical superiority but should allow assessment of the general shape of the dose-response curve. The goal of these studies is not to prove whether one dose is superior or inferior to another, but rather to ascertain whether higher doses, usually associated with greater toxicity, are likely to have a superior therapeutic index to lower doses. This assessment can be made with a relatively small sample size, particularly in the context of an extensive preclinical data package. Ultimately, when the assessment of two or more doses leads to comparable efficacy, the lowest effective dose should be used in the registration trial.

Are there specific considerations for drugs given in combination?

A dose established for one indication may or may not be the optimal dose for a different population, including for use in combination with other drugs. As such, additional dose optimization should be considered as part of development plans for drugs used in combination, whether both drugs are unapproved, or an unapproved drug is being combined with an approved drug or regimen. Part of the rationale for additional dose-finding studies when drugs are used in combination is that the drugs may have overlapping toxicities that when combined, can become intolerable.

It may be necessary to have or generate data regarding the contribution of each component in the selected combination. In some cases, it may be feasible to use a lower dose of an originally approved drug without extensive dose-finding studies. Sponsors should consider and discuss with FDA whether the standard of care arm should also utilize a dose lower than the labeled dose.