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Beyond Breakthrough: Optimizing the Breakthrough Therapy Designation

Introduction:

Advances in our understanding of disease processes, genetics, manufacturing technologies, and innovative clinical trial design have enabled the development of novel therapeutic agents for the treatment of patients with cancer. In oncology, the ability to target a novel agent against a driver oncogene or protective immune checkpoint has led to several therapeutic breakthroughs in diseases with limited or no systemic treatment options. These breakthroughs have established new classes of therapeutics leading to, in some instances, unprecedented improvements in clinical outcomes for patients with cancer.

Regulatory review processes are time and resource intensive for drug sponsors and the United States Food and Drug Administration (FDA). The FDA leverages several tools to safely and efficiently facilitate development and review of agents intended for treatment of patients with life-threatening conditions without compromising the rigorous standards established for their approval.

Breakthrough Therapy Designation (BTD) facilitates the efficient development of both drugs and biologics (hereafter referred to as "drugs") intended to treat serious or life-threatening illnesses for which there is preliminary clinical evidence demonstrating that the investigational therapy may offer substantial improvement on a clinically significant endpoint(s) over available therapies.[1] BTD pro-

Objectives

Characterize the rate-limiting steps and challenges encountered throughout the development of oncology products with Breakthrough Therapy Designation (BTD).

Propose recommendations that address commonly encountered challenges and identify best practices to ensure development programs maximize the benefits of BTD.

Delineate key topics and optimal timing for interactions with the FDA when requesting BTD (pre-BTD) and after receiving BTD (post-BTD).

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This paper reflects discussions that occurred among stakeholder groups, including FDA, on various topics. The topics covered in the paper, including recommendations, therefore, are intended to capture key discussion points. The paper should not be interpreted to reflect alignment on the different topics by the participants, and the recommendations provided should not be used in lieu of FDA published guidance or direct conversations with the Agency about a specific development program.

Disclaimer: This paper should not be construed to represent FDA's views or policies.

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vides sponsors with early opportunities for FDA interaction and enhanced guidance, including proactive organizational commitment and coordination involving senior FDA managers and experienced regulatory project management staff. Additionally, BTD often offers a pathway to eligibility for rolling or priority review and also provides support for consideration for review under the RTOR program.[2]

Since 2012, the number of BTD requests each year has increased. To date, the FDA has received over one thousand requests for BTD and granted more than four hundred requests.[3] Both FDA and commercial sponsors prioritize internal resources to help ensure that the most promising products receive BTD and undergo clinical development as efficiently as possible without compromising safety, efficacy, or quality. As a result of this work, BTD has facilitated timely development and approval of 205 products, 61% of which are oncology products. The program has been particularly successful in getting safe and effective novel treatments approved for patients with cancer, particularly new treatments that have not been previously approved for other indications. It is estimated that BTD has shortened the time from IND submission to approval for 60 original applications (not previously approved) for oncology products by a median of 2.3 years compared to oncology products without BTD.[4]

Historically, much of the focus on BTD has been on the qualifying criteria and processes leading to receipt of BTD; however, given the breadth of experience with BTD in oncology over the past eight years, stakeholders now have the opportunity to identify pressure points and best practices to help optimize its implementation in order to better support efficient, successful development of new safe and effective cancer treatments. To this end, Friends of Cancer Research (*Friends*) convened a multistakeholder working group to conduct a landscape analysis to identify opportunities for improved implementation of the BTD program in oncology. This effort focused on evaluation of the successful use of the BTD program and challenges associated with optimal use of BTD in oncology in order to help inform strategies for sustaining its impact on drug development.

Friends conducted a survey soliciting input from over 20 commercial sponsors that varied in company size and the range of experiences in terms of number of therapies that have received BTD and approved therapies with BTD to identify challenges and formulate recommendations for optimizing the use of BTD. All sponsors noted the positive impact of BTD in oncology drug development. Several key areas with the potential to further optimize use of BTD emerged.

1. **Clarify expectations for necessary evidence to receive BTD:** Sponsors may find it challenging to anticipate when and what to submit with preliminary and formal BTD requests. There is also a need for additional clarity about the types and quantity of evidence needed to support BTD, particularly with respect to early preliminary clinical evidence in oncology.

2. **Enhance communication between sponsors and FDA:** The opportunity for enhanced interactions with FDA provided by BTD support proactive identification and resolution of issues; however, at certain stages of development, such as pre-BTD or between milestone meetings, there may be additional opportunities to streamline clinical development through sponsor-FDA interaction.

3. **Support inter-disciplinary coordination and improve transparency:** In oncology, many drug development programs are increasingly complex and require close coordination between multiple disciplines, and often between Offices and Centers at the FDA (e.g., applications with BTD involving complimentary or companion diagnostics, employing a novel platform or endpoint, targeting rare diseases, and/or incorporating innovative trial designs). Additional guidance on how best to strengthen coordination between Centers, when relevant, at the time of BTD may be beneficial to ensure complexity does not lead to delays.

4. **Provide additional support to address rate-limiting steps in drug development:** BTD facilitates both clinical and CMC aspects of development; however, challenges can occur during drug development, particularly for novel or innovative technology platforms. CMC development issues can be the rate-limiting step in drug development and approval, and flexibility and timely interactions between FDA and sponsors can be crucial to identify and resolve these issues to mitigate delays. Dose selection and justification is also an important component of drug development and can be a challenge with an expedited drug development timeline.

After conducting the survey, *Friends* convened multiple focus groups with key stakeholders, including the FDA, to identify potential practical solutions in these key areas to support optimal use of BTD. A summary of the outcomes of these focus group discussions is provided below.

Opportunity 1. Optimize the timing of BTD and improve communication on expectations for data necessary to receive and maintain BTD.

Provide additional clarity regarding the criteria for BTD to optimize the timing for submission of a BTD request.

BTD has the most potential to positively impact development of drugs that have not previously received FDA approval for another indication because it confers opportunities for enhanced interactions between sponsors and a multidisciplinary FDA team including senior FDA staff. These interactions can help address critical aspects of drug development such as dose optimization and manufacturing, which can be rate-limiting. Similarly, the timing of BTD is critical; for example, when BTD is granted based on top-level results of a pivotal trial that will provide the primary evidence to support a marketing application, there may be limited potential for enhanced interactions to result in meaningful improvements to drug development, as opposed to when BTD is granted prior to initiation of a registrational trial.

It is important for sponsors to apply for BTD at a time when there is sufficient data to meet the qualifying criteria for BTD but early enough to fully leverage the enhanced interactions provided by BTD ideally no later than the time of completion of Phase 2 development. Among sponsors, there can be uncertainty regarding the level of clinical evidence required to meet the qualifying criteria for BTD. Routine use of preliminary BTD advice teleconferences to discuss eligibility of requests for BTD and gain a better understanding regarding the appropriate timeline and data package necessary to support a BTD request facilitates timely submission and review of BTD applications. Inclusion of additional annotation in the preliminary BTD teleconference template

to describe the type and scope of preliminary evidence that are generally needed to support a BTD request submission for an oncology product could help facilitate preparation of documents and meaningful preliminary BTD teleconference discussions, while also reducing the number of preliminary BTD teleconferences that clearly lack sufficient data. An oncology-specific guidance describing general guidelines for preparing for a preliminary BTD discussion, content of a BTD request submission, and efficacy considerations for meeting the criteria for BTD may be beneficial.

Clarify procedures and decision-making regarding withdrawing or rescinding BTD and better understand its downstream impact on development/approval to support integrity of the program.

If a program no longer qualifies for BTD, the sponsor can voluntarily withdraw their BTD, or FDA can rescind it. It is sometimes unclear what the timepoints are for re-evaluating the status of BTD or common reasons for withdrawal. Transparent communication regarding the considerations and procedures used by FDA to evaluate whether BTD should be rescinded or withdrawn could ensure a designation is robust and fair. There are context-dependent considerations, such as the timing of the receipt of BTD, stage of development of the program when BTD is withdrawn, and the status of other available therapies, which may impact the public messaging by a BTD sponsor around why withdrawal occurred. Prior to the voluntary withdrawal or rescinding of BTD, the sponsor and the FDA could engage in discussions surrounding the rationale for a planned withdrawal or rescinding of BTD and the implications of these actions on the drug development program. Sponsors may also benefit from an explanation of how withdrawal impacts a program's ability to participate in other Oncology Center for Excellence (OCE) pilots (e.g., Real Time Oncology Review, Project Orbis).

Opportunity 2. Improve mechanisms to enable meaningful discussions between FDA and sponsors that clearly align with key decision points.

Ensure productive and timely discussions between the FDA and sponsor.

It is beneficial to have post-BTD discussions as early as possible so the drug development program can take full advantage of BTD's enhanced opportunities for interaction and advice. Ideally, sponsors should prepare for and request the comprehensive post-BTD multidisciplinary meeting so that it occurs in a timely fashion (within the first six months of receiving BTD).[5] In this meeting, the sponsor may propose a high-level communication plan and estimated timeline for future interactions aimed at accelerating development of their BTD drug.

Meetings following the comprehensive post-BTD multidisciplinary meeting could be focused to align on the specific needs of a drug development program at each stage of development. The benefit of collaborative discussions with the FDA and sponsors may be more fully realized when questions are focused on a single discrete issue. This could also shorten the lead time for the meeting and reduce the burden on both the FDA and the sponsor to prepare for the meeting. If questions arise between formal meetings, meeting requests targeted to address specific topics could be considered. Proposed PDUFA VII goals include a proposed Type D meeting that would

be suitable to address a narrow set of issues[6] which will be further described in a revised draft of the draft guidance entitled "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products." Specifically, Type D meetings are intended to address a follow up issue after a formal meeting, a narrow issue the sponsor would like FDA input on that requires input from no more than 3 disciplines, or a general question that does not require detailed advice. During focus group discussions, participants suggested topics such as CMC/product quality-related hurdles, trial design-related issues, and timing of dose optimization studies for meetings like Type D meetings. Timelines for drug development may need to be coordinated when the program is expedited, and key questions that may be rate-limiting may not necessarily arise in alignment with the timing of traditional milestone meetings for aspects such as CMC and clinical considerations. The development of a mechanism to update FDA on key components of drug development could help both sponsors and the FDA identify when meetings might be valuable to head off potential rate-limiting obstacles to oncology drug development.

Provide additional clarity to ensure a better understanding of which types of meetings are optimal for specific aspects of drug development for products with BTD.

Formal meetings such as Type B meetings are generally held within 60 days of their request (70 days for end-of-phase meetings) and require extensive preparation on the part of sponsors and FDA staff. As such, these meetings may not always be amenable to post-BTD drug development timeframes, therefore additional meeting strategies are likely to be helpful for BTD product development. Table 1 outlines available and proposed meeting types to support development of drugs with BTD. Strategies to formally integrate and operationalize issue specific meetings for products with BTD could be informed through pilot projects such as the Complex Innovative Trial Design Pilot Meeting Program (CID) and Model-Informed Drug Development (MIDD) Pilot Program. Given the fast pace of development post-BTD, decisions are made decisively and quickly, and timely interactions are extremely important.

In addition to timely discussions, external stakeholders expressed that it may help to have enhanced interactions and feedback from the FDA. Proactive and thoughtful interactions support expedited development and review of products with BTD. Optimizing meeting structure and approach could enable discussions between FDA and sponsors to occur more frequently, help address issues earlier in development, and provide opportunities for proactive planning of manufacturing and testing strategies and clinical development relative to traditional drug development approaches. It may be important to promote timely dialogue between the sponsors and FDA review divisions to enable proactive management of potential issues, which could become major issues either for submission or review of the premarket application. Additionally, the development of guidance that outlines best practices or novel approaches for avoiding commonly encountered issues may be of value.

Rather than a lengthy briefing document, a proposed Type D meeting (See Table 1 below) may be supported by a more focused briefing document containing the information needed to address the drug development issue(s) at hand to inform the discussion and feedback provided for focused meetings. Additionally, templates that provide high-level summaries of specific aspects of drug development such as the status of CMC development and dose optimization might be beneficial; such high-level summaries could potentially facilitate early FDA identifica-

tion of potential drug development issues that could be addressed in future meetings with the sponsor post-BTD might be beneficial (see discussion on use of "Drug Development Snapshots" as a potential communication tool).

During the focus group meetings, there was discussion of informal meeting requests but ultimately the value of a more "informal request" may be limited when there are questions requiring input from multiple review disciplines or limited background is provided by the sponsor.

Table 1: Available FDA Meeting Types and Applicability for Products with BTD[7,8,9]

Meeting Type	General Purpose	Timeframe	Application for BTD Products
Type A Meetings	Meetings that are necessary for an otherwise stalled product development program to proceed or to address an important safety issue.	Within 30 days of request	Strengthening communication between the FDA and sponsor could help avoid issues that would require a Type A meeting for products with BTD.
Type B Meetings	Routine meetings occurring at pre-defined endpoints between FDA and a sponsor. Meetings typically occur right after or right before the submission of clinical data or a new drug filing.	Within 60 to 70 days of request	Formal meetings for products with BTD, including the initial comprehensive BTD meeting, are granted as Type B, unless they qualify as Type A meetings.
Type C Meetings	A meeting that is not a Type A or Type B meeting regarding the development and review of a product.	Within 75 days of request	Very rarely used for BTD products, as BTD default would be to Type B meetings unless reclassified by FDA and have a potentially shorter turnaround. With the addition of a Type D meeting (see below), Type C meetings could be reserved for development issues that would not warrant as quick of a turnaround.
Type F Meetings	Early advice meetings to discuss pediatric development plans.	Within 30 days of request	Meetings encouraged for BTD drugs to ensure that an agreed initial pediatric study plan (iPSP) is in place prior to marketing application. This may be particularly important with respect to mechanism of action based pediatric requirements (Section 504 of FDARA 2017) for original application of oncology drugs.
Proposed Type D Meetings*	Focused on a narrow set of issues (no more than 2 focused topics) which could include: • a follow-up question that raises a new issue after a formal meeting • a narrow issue with few associated questions • a general question about an innovative development approach	Within 50 days of request	This meeting type could promote proactive, collaborative discussion to help identify and mitigate/troubleshoot potential rate-limiting steps to development articulated by the sponsor in a more focused briefing document. Type D meetings could be reserved for issues that require more rapid feedback versus issues that may be best routed through a Type B meeting request.

*Meeting type described in the PDUFA VII Commitment Letter (https://www.fda.gov/media/151712/download)

The ability to connect informally with review staff, Division leaders, and Office Directors, while potentially valuable for timely decision making, may be counterproductive unless it includes all relevant members of the FDA review team and is incorporated as official FDA correspondence to the sponsor.

Opportunity 3. Develop communication tools and optimize processes to support interdisciplinary coordination within and between the FDA and sponsors.

Create a program for voluntary submission of "Drug Development Snapshots" for earlier identification of issues that could result in delays in development.

A strength of BTD is the product-specific dialogue provided through cross-functional structured interactions between the FDA and sponsors, which involves senior leadership at FDA. However, challenges may be encountered at different times and in different areas of drug development depending on the drug development program. Identification of challenges may not align with milestone meetings that are typically attended by cross-functional groups within the FDA and the sponsor drug development team, which can result in delays addressing these issues. Voluntary sponsor submission of high-level product development information in the form of periodic Drug Development Snapshots (see mock template for dosing snapshot in Appendix) could help prompt earlier identification of rate-limiting aspects of development (e.g., dosing, CMC/Product quality aspects, diagnostic co-development, plans for confirmatory trials if accelerated approval pathway is anticipated, etc.), serve as a vehicle to support information exchange, and help determine when meetings outside of the normal milestone cadence would be most beneficial. This increased transparency throughout development outside of normal milestone meetings can also promote FDA cross-discipline and inter-center communication on the development program, plans for upcoming milestones, and necessary interventions. While these snapshots could be particularly useful for enabling improved real-time communication, they could also be leveraged beyond BTD products. The FDA could consider a pilot project to explore the utility of Drug Development Snapshots, including their optimal timing with respect to drug development, frequency of submission, and content.

Refine best practices for communicating with RPMs to help facilitate efficient collaboration.

FDA Regulatory Project Managers (RPMs) play a vital role in triaging and prioritizing sponsors' requests, as well as in identifying the appropriate person(s) for FDA-sponsor and internal meetings, and in coordinating responses for such meetings when necessary. While sponsor interactions with RPMs are extremely helpful, there is opportunity to improve these interactions. Defining the best communication practices for sponsors and RPMs may help sponsors understand expectations specifically in the context of a program with BTD. One opportunity to optimize efficient communication is the ability for sponsors to "flag" requests for feedback that are time-sensitive, and clearly identify they are requesting a reviewer's feedback on a specific topic, to help RPMs appropriately prioritize requests. RPMs could also provide a time estimate for how long it will take to provide feedback for the request, at the point of acknowledgement of the request. Updating CDER's Manual of Policies and Procedures (MAPP) 6030.9 Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and

Review, which describes review management principles and practices, may provide additional clarity on best communication practices. A one-on-one meeting between the FDA and Sponsor RPMs could also help set communication expectations. Further, CDER's 2017 Best Practices for Communication Between IND Sponsors and FDA During Drug Development Good Review Practice[10] outlines appropriate communication strategies between sponsors and FDA, and additional awareness and following of the best practices may increase efficiencies.

Communicate the sponsor's role in preparing materials for cross-discipline meetings.

For cross-discipline meetings in BTD drug development to be productive, it may be helpful to outline the role of both sponsors and the FDA in identifying when general or more specific feedback is warranted and the key disciplines needed for each interaction. Sponsors could provide concise, focused information necessary for FDA to answer the questions at hand. RPMs could then distribute the materials to the review team, including to reviewers or consultants outside of the Division or Center.

Opportunity 4. Provide a roadmap for addressing key pressure points for products with BTD.

Encourage early collaboration, alignment, and prioritization between pharmaceutical and device sponsors and CDER and CDRH.

Challenges to efficient development of a companion diagnostic can arise particularly for drugs developed for rare patient populations or in the setting of a product with BTD. Early identification of the need for a companion diagnostic and plans for parallel development with the goal of contemporaneous approval of a BTD drug and companion diagnostic (if needed) could be a key component of the comprehensive interdisciplinary post-BTD meeting. As noted earlier, outlining specific meeting types (Type B meetings or otherwise) and timelines to focus on incorporating companion diagnostic co-development can increase collaboration between CDER, CDRH, the pharmaceutical sponsor, and the diagnostic sponsor and enable early preparation for possible bridging studies, as well as strategies for saving patient samples and adequate patient ascertainment. Additionally, notification to CDRH upon designation of a BTD could allow for efficient mobilization of appropriate resources. There is also a need for additional clarity around the level of evidence and data elements needed prior to approval for a companion diagnostic. It may be helpful if diagnostic tests developed to direct the use of therapies with BTD were also considered for breakthrough device designation to assist in alignment, prioritization, and collaboration between senior leadership within and across medical product Centers responsible for each breakthrough product.

Facilitate timely discussion and agreement on dose selection, exposure-response analyses, and study design.

Rapid development programs associated with BTD can give the impression that there is insufficient time for robust dose finding approaches; however, identifying the optimal dosage to support safe and effective use of oncology drugs, and accumulating sufficient information to support this dosage, is extremely important; the selection of the recommended dose without

adequate investigation is unacceptable. FDA's OCE has highlighted dose optimization, including for BTD drugs, as a priority by introducing Project Optimus, calling for dose selection justification and earlier discussion of dose selection during the IND phase. BTD may be granted prior to identification of the optimal dose; however, the approach planned to support the dosage(s) intended for further development could be discussed with the FDA prior to embarking on a clinical trial intended to provide evidence of safety and effectiveness to support a marketing application. These approaches could integrate PK, PD, efficacy, safety, and tolerability data to adequately support dose selection and may result in the selection of 2 or more doses for further exploration. Sponsors could seek out these discussions, which may occur before or after receipt of BTD, as early in the development process as possible. FDA could outline opportunities to discuss strategies for dose optimization and selection of the pivotal dose(s) in pre-BTD meetings. FDA could also clarify and provide feedback on the appropriate use of systems and model-based approaches to support dose selection, study design, and exposure-response analyses and provide feedback on proposals to leverage relevant markers of activity to inform the dosing decisions early in development. Further, learnings from FDA's work through its PDUFA VI commitment on model-informed drug development (MIDD) could be leveraged to facilitate appropriate dose selection. Clarity is needed on the appropriate use of MIDD to support dose selection, including the evidence needed to show that a model is credible and the role of the model in supporting or supplementing clinical data.

Identify processes to support early Office of Pharmaceutical Quality (OPQ) discussions and facilitate timely submission of CMC information to address rate limiting-steps in the commercialization process.

Sponsors are encouraged to provide available CMC/manufacturing information and commercialization plans, which may be in the form of a "Drug Development Snapshot," early to FDA to potentially maximize the ability to address rate-limiting steps in the development and marketing of a breakthrough product. Currently, discussions with CMC/OPQ generally occur later in development, as CMC development often lags behind clinical development for expedited programs. Sponsors may initiate these conversations earlier in the development program, in a more proactive manner, to aid in planning and development of manufacturing and product quality strategies. An opportunity to engage in a discussion specific to late phase/commercial manufacturing and testing approaches as well as to troubleshoot Quality-related development challenges may expedite the commercialization process. As described in the PDUFA VII Commitment Letter, FDA plans to issue a new MAPP on approaches to address CMC challenges for products with accelerated clinical development timelines and will describe early engagement with sponsors of such products. Further, early identification of the regulatory business project manager (RBPM) for the OPQ related inquiries would be helpful. Processes for rolling submission and review of information before all the necessary stability data are available could also be explored; this could lead to submission of all Module 3 content except for all or part of the 3.2.S.7 and 3.2.P.8 sections months ahead of the submission of the final components of the NDA or BLA, which could include these remaining sections. The sponsor should propose and reach agreement with FDA on plans for early rolling submission of segments of Module 3 at the EOP 2 or a Pre-NDA/BLA meeting. For example, early submission of detailed manufacturing site information (e.g., list of manufacturing facilities with addresses and FEI numbers, current CGMP

status, facilities' prior experience with similar manufacturing processes, manufacturing area and filling line or equipment used) can allow earlier coordination and planning if a pre-licensure or preapproval inspection is necessary. Discussions with OPQ to help clarify the level of CMC information needed for approval and types of plans that could be implemented in the post-approval setting can also be helpful.

Consider FDA's available strategies to assess facility risks and enable more efficient inspections.

Certain flexibilities were allowed during the COVID-19 pandemic, including operational processes (both for FDA and sponsors), and clarifications on regulatory approaches toward application components. The FDA has used alternative tools to inform facility assessments including examination of a firm's compliance history, inspection reports from trusted foreign regulatory partners, records requests, and the use of remote interactive evaluations.[11] Proposed PDUFA VII goals include that some of these flexibilities, or the principles behind them, will be explored to ensure that facility assessments for BTD products are timely and focused on critical areas for coverage, thus alleviating delays in approval and enabling sponsors and FDA to allocate resources efficiently.

Explore decoupling drug substance and drug product process performance qualification (PPQ).

When drug substance and drug product PPQ occur sequentially (for those programs requiring PPQ data in the initial application), the PPQ timeline may delay submission of the application and product approval. Inclusion of CMC into Real-Time Oncology Review (RTOR) and the development of the CMC Assessment Aid have brought flexibility and enhanced CMC review efficiency to oncology application reviews. Concurrent execution and completion of the drug substance and drug product PPQs could build on experiences in small molecule development and may result in expedited CMC readiness to meet clinical timelines. Feasibility of this approach has been demonstrated in the development of small molecules over the last few decades as well as for the BTD product pembrolizumab (a monoclonal antibody).[12] Exploring the conditions where it might be possible to successfully decouple drug substance PPQ and drug product PPQ, could help to expedite the timeline safely and efficiently. Concurrent validation approaches could be useful for a BTD product to market the PPQ batches. Circumstances and rationale for concurrent release could be fully described in a PPQ protocol, which for BLAs should be submitted in the application. More details can be found in the process validation guidance.[13]

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

Please note: The table below describes the supportive evidence for the proposed dose and schedule. The target length of the completed snapshot is 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 preclinical 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 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 warrants dose adjustments in a subset of patients) • Was the PK variability considered when selecting a dose that would achieve target exposure for the majority of patients?
Safety summary	• 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)? • Does 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	• 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 needs to be taken into account? • Is 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