FRIENDS of CANCER RESEARCH

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Accelerating Investigation of New Therapies in Earlier Metastatic Treatment Settings

Friends of Cancer Research Annual Meeting 2022

Introduction

Over the past decade, an increasing number of breakthroughs in cancer research have translated into novel and highly effective therapies for patients. Investigational therapies are often first studied in patients with relapsed or refractory (r/r) disease and who have received multiple prior lines of therapy or have exhausted all available treatment options (i.e., later treatment setting or disease setting with lack of available treatments). Between January 2013 and July 2022, over 61% of oncology approvals for novel molecular entities were for patients with metastatic disease who had received prior therapies.[1] Studies of new investigational therapies are often conducted in the r/r patient population due to the unmet need for treatment options, ethical concerns about exposing newly diagnosed patients to therapies that may be ineffective, and potential earlier market access through the accelerated approval (AA) pathway.[2] Designing trials in the r/r setting yields important insights for investigational agents (e.g., dosing, tolerability, etc.) and provides access to investigational therapies for patients with r/r disease who may not have other acceptable options.

Recently, concerns have increased regarding the limitations of using single-arm trials to support AA, failure and delays in confirming benefit for drugs granted AA, and the inherent challenges of confirming clinical benefit in the r/r setting when trials are initiated after the AA has been granted.[2] Conducting trials in earlier metastatic settings (including but not limited to first-line therapy) as a strategy to support initial approval may address some of these limitations and has the potential to maximize the benefit of innovative treatments and expand access to more patients with metastatic disease more quickly.

The Oncology Center of Excellence (OCE) at the U.S. Food and Drug Administration (FDA), launched Project FrontRunner to initiate a discussion among stakeholders in oncology drug development for considerations on shifting the historical drug development paradigm which has focused on first developing and seeking approval of new therapies in the r/r metastatic setting.[3] As part of

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this initiative, OCE aims to propose, for use by pharmaceutical sponsors on a voluntary basis, a framework that helps identify clinical development programs that may benefit more patients earlier in the course of their disease and improve the data available at the time of approval to facilitate a benefit-risk assessment. Friends of Cancer Research (*Friends*) convened a multi-stakeholder group of experts including the OCE, drug developers (Sponsors), patient advocates, and academic clinicians to identify key opportunities and challenges for designing studies that support approval in earlier metastatic treatment settings and initiating such studies earlier in the overall drug development program.

Objectives

- Identify opportunities, challenges, and potential strategies to accelerate the study of investigational therapies in the earlier metastatic treatment setting.

- Develop a framework to facilitate determining when it is appropriate to initiate the study of investigational therapies in the earlier metastatic treatment setting, informed by important clinical, statistical, and regulatory considerations.

- Identify the critical components of a comprehensive development strategy to support accelerated clinical development and regulatory approvals.

At the outset, there was broad recognition that the Project FrontRunner paradigm may not be appropriate for every clinical setting or investigational drug. As such, this paper provides a proposed framework for considering whether the Project FrontRunner approach is appropriate in a given context and, outlines some important considerations for implementing this approach in the appropriate setting. Importantly, the framework and clinical development considerations may be subject to further revisions based on additional input and experience.

Rationale for Advancing Investigation of Novel Therapies Earlier in the Course of Metastatic Disease

Provide Greater Clinical Benefit to More Patients

Therapeutic investigations earlier in the course of metastatic disease have the potential to provide a greater benefit to patients with cancer since there are more patients with earlier metastatic disease and the absolute effect size of investigational therapies on endpoints such as progression-free survival (PFS) and overall survival (OS) tends to be greatest.[4–7] In the r/r setting, patients may have disease-related factors or complications or may have residual side effects from prior treatments that may confound the evaluation of an investigational therapy for safety and efficacy. In some cases, the effects of prior therapy or disease progression may preclude patient participation in clinical trials.[8] Investigation in early line metastatic disease increases the clinical trial opportunities for more patients with metastatic disease.

Accelerate Addressing Unmet Need in Earlier Metastatic Treatment Setting

While unmet need is not a regulatory requirement for AA, the intent of regulatory mechanisms and flexibilities that allow for earlier approval of drugs to treat serious conditions is to address

unmet medical needs.[10] It is important to note that investigational therapies in the earlier metastatic setting have the potential to address unmet need by providing therapeutic options, including potentially through the AA pathway, when no standard of care (SOC) treatment exists. This can help provide alternatives to or replace less effective or more toxic therapies in the earlier treatment setting, and/or enhance current SOC efficacy through a combination approach. Initiating investigations in early metastatic settings using the Project FrontRunner paradigm allows for comparison of the investigational therapy to established and approved therapies for enhanced benefit-risk assessments.

Lessons Learned from Past Drug Development Programs

A review of several past drug development programs informed learnings from conducting clinical trials in metastatic disease and strategies for future trial designs that may align with the goals of Project FrontRunner (see **Appendix 1** for case study reviews). Insights were gleaned from the Sponsors and publicly available FDA review summaries.[11] Summary key findings from these case studies include:

- Certain clinical scenarios and therapeutic regimens (e.g., when an investigational drug is not expected to be effective as monotherapy or requires a combination therapy that includes current SOC) may require initiation of registrational or pivotal studies in the frontline setting.
- Robust statistical approaches are necessary to address challenges associated with interim analyses. Conducting an interim analysis based on events with limited follow-up may result in an inaccurate estimation of clinical benefit. Statistical considerations for the required hazard ratios and alpha spending for interim analyses will be important.
- Endpoints used for interim analyses (e.g., overall response rate (ORR)) should be established to be reasonably likely to predict clinical benefit for the disease and the therapy being studied.
- The randomized controlled trial (RCT) planned to verify benefit observed in a single-arm trial should be nearly or fully enrolled at time of submission of the single-arm trial for AA.

Key Considerations for Initiating Clinical Development in Earlier Metastatic Settings

Studying investigational therapies earlier in the course of advanced/metastatic disease (e.g., first or second-line setting) may be appropriate for a subset of clinical and drug development scenarios. The proposed considerations for selecting a clinical development scenario appropriate for the Project FrontRunner setting are shown in **Table 1**.

Table 1: Considerations for Selecting a Project FrontRunner Clinical Development Paradigm

Factor	Characteristics	Considerations
Disease Characteristics	• Natural history of disease (e.g., long or short natural survival) • Size of eligible population (e.g., rare or more common)	• Natural history of the disease can impact the length of time it takes for data to mature to demonstrate treatment benefit. An earlier readout of a well-established intermediate endpoint could form the basis for AA ahead of clinical benefit outcomes. • The size of the eligible patient population is an important consideration because it can impact enrollment rate and ultimately the time it takes for trial results (interim and final) to be available.
Investigational Treatment Characteristics	• Novelty of mechanism of action (e.g., first-in-class or $3^{rd}/4^{th}$ in class) • Approval status (e.g., new molecular entity or expanding indication of approved drug) • Level of toxicity (e.g., high or low)	• Data (e.g., efficacy, dosing, toxicity profile) may be leveraged for drugs that have been previously approved in other indications or for investigational agents within an existing drug class, which can help de-risk the approach. • Investigational agents with high toxicity may not be amenable to study in early lines with existing, less toxic SOC options.
Other Available Therapies	• Efficacy, safety of approved available therapies in early metastatic setting (i.e., $1^{st}/2^{nd}$ line setting) • Efficacy of available therapies • Tolerability of available therapies	• Settings where established SOC is associated with modest-to-moderate outcomes or poor toxicity offers opportunities to demonstrate convincing and clinically meaningful improvement.
Clinical Endpoints	• Intermediate endpoints available and acceptable for regulatory use	• Disease settings that have well-established intermediate endpoints (e.g., correlation to long-term clinical endpoints) to support interim analyses may be most appropriate.

Some disease characteristics are more amenable to the FrontRunner paradigm than others, including those for which there is evidence to support the use of an intermediate endpoint, such as ORR, that is reasonably likely to predict clinical benefit and could support interim analyses evaluating treatment efficacy. These include diseases with long natural histories such as indolent non-Hodgkin lymphoma or multiple myeloma in the frontline setting. Alternatively, diseases where the natural history is short, but OS (rather than PFS) is the endpoint of interest for regulatory approval, such as second-line non-small cell lung cancer, would also be candidates for the FrontRunner approach. In this setting, the established SOC is associated with low-to-moderate outcomes (15-20% ORR) and an investigational therapy may demonstrate

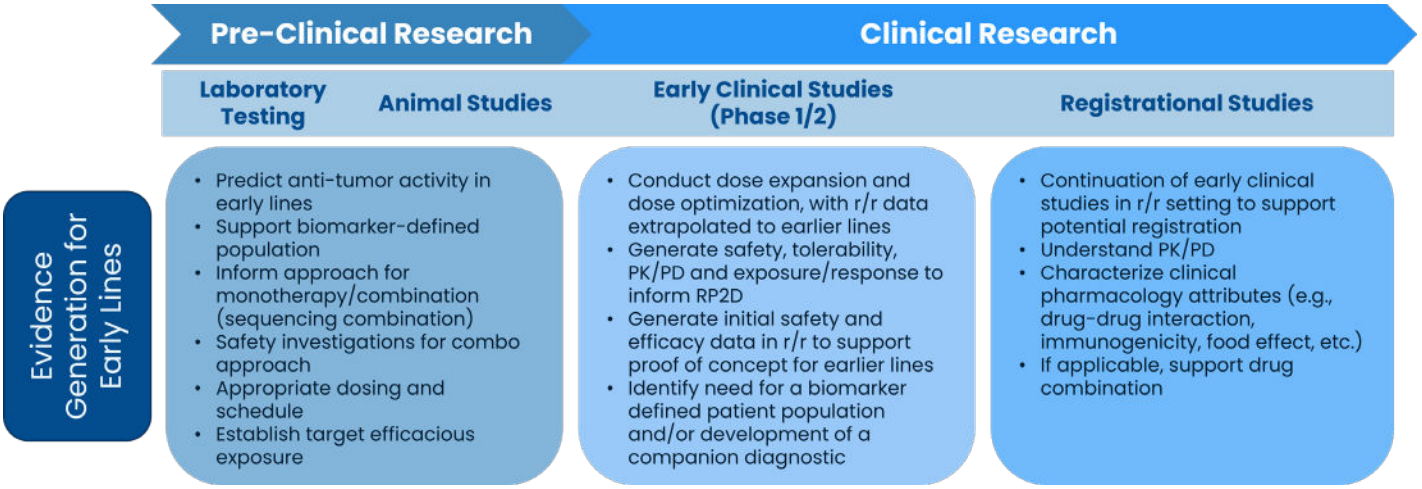
meaningful improvement. More common diseases in which trial enrollment can be completed expeditiously will likely also benefit from a FrontRunner approach, as accrual of a sufficient sample size will likely not be rate-limiting. These considerations are based on the use of ORR for interim analyses. However, in the future if other intermediate endpoints, such as those based on circulating tumor DNA (ctDNA) or minimal residual disease (MRD), are robustly characterized and accepted as reasonably likely to predict clinical benefit, additional clinical scenarios may become amenable.

Operationalizing a Project FrontRunner Approach During Clinical Development

Factors Influencing the Clinical Development

When establishing the development plan for an investigational drug, Sponsors should make plans beyond the initial indication, including establishing a holistic clinical and registration plan. This plan should determine the feasibility and applicability of investigating the agent in earlier settings, including establishing set decision points to determine when to initiate studies and what evidence is needed to support the move to earlier lines. These decisions should be based on early clinical and scientific evidence, further discussed below and highlighted in **Figure 1**, but may also be driven by factors such as the level of risk a sponsor and regulatory bodies are willing to accept, development timeline to regulatory approval, market opportunity (including an assessment of competition and potential changes in the treatment landscape), size of target population, relevance of the target in the earlier setting, and market access considerations of the portfolio. A Project FrontRunner approach would not preclude these decisions from being made, but rather it would clarify opportunities and encourage trial designs in earlier metastatic disease sooner in the development of an investigational agent.

Figure 1: Evidence to Support Investigation in Earlier Metastatic Treatment Settings. Evidence that may be leveraged to support initiating clinical development in earlier metastatic settings, obtained through pre-clinical research and/or clinical research in the r/r setting.



Treatment Landscape in the Earlier Metastatic Treatment Setting

Understanding the current treatment landscape in the early metastatic setting is key to informing clinical trial designs when moving treatments into earlier lines. The primary endpoint(s) used to support previous regulatory decisions in the specific cancer type as well as the magnitude of improvement observed in clinical trial readouts may help guide trial design considerations, including the level of evidence needed for AA decisions and the endpoints used to determine clinical benefit. These considerations may change if the proposed study is intended to replace current SOC as opposed to combining the investigational therapy with SOC. Additionally, the current SOC will impact selection of the control arm of a RCT. In some instances, it may be challenging to identify a single control arm if there are multiple treatments available in the earlier setting and a physician's choice may be most appropriate. Providers and patients may need additional education about the value of enrolling in a clinical trial in an earlier line if a well-established SOC and/or existing therapies for early line treatment already exists.

Pre-clinical and Early Clinical Studies

Figure 1 highlights data from pre-clinical research and early phase clinical studies that can be used to support investigation in earlier metastatic treatment settings. Robust pre-clinical disease models predict the potential anti-tumor activity in the intended tumor type(s) to support the selected patient population and provide insight into investigations in earlier lines. Pre-clinical data are also critical to inform the approach for studying an investigational therapy as a monotherapy or in combination with other therapies. If pursuing a combination therapy approach, early inclusion of the combination partner in nonclinical investigations is beneficial to begin to understand the drug-drug interaction profile as well as inform the dosing regimen. Enrolling patients with early metastatic disease in dose finding studies may be challenging and reaching time to event endpoints may take a long time. Therefore, extrapolating data from dosing studies in the r/r setting may be appropriate to aide dose selection for early metastatic settings. Alternatively, it may be beneficial to use earlier endpoints, such as ORR, for dose finding studies, if required, in the early metastatic disease setting.

Clinical Trial Design

Two strategies can be considered to facilitate regulatory review in earlier metastatic lines: a single RCT in the early treatment setting to support accelerated and full approval, and two concurrent studies that overlap, one of which is a single-arm trial in a r/r setting and the other a RCT in an earlier treatment setting (**Figure 2**). **Table 2** highlights advantages and disadvantages of these approaches. In addition to these designs, in rare patient populations with limited therapeutic options and feasibility challenges to enrolling a sufficient number of patients for a RCT, a single-arm trial may be acceptable. In this case, assuming data are available, there may be opportunities to use real-world data (RWD) on the natural disease history as supportive information, if proactively discussed and aligned with the Agency, to contextualize the effect seen in the single-arm trial or for use as an external control arm.

Table 2: Possible Strategies to Support Accelerated and Full Approval in Earlier Settings

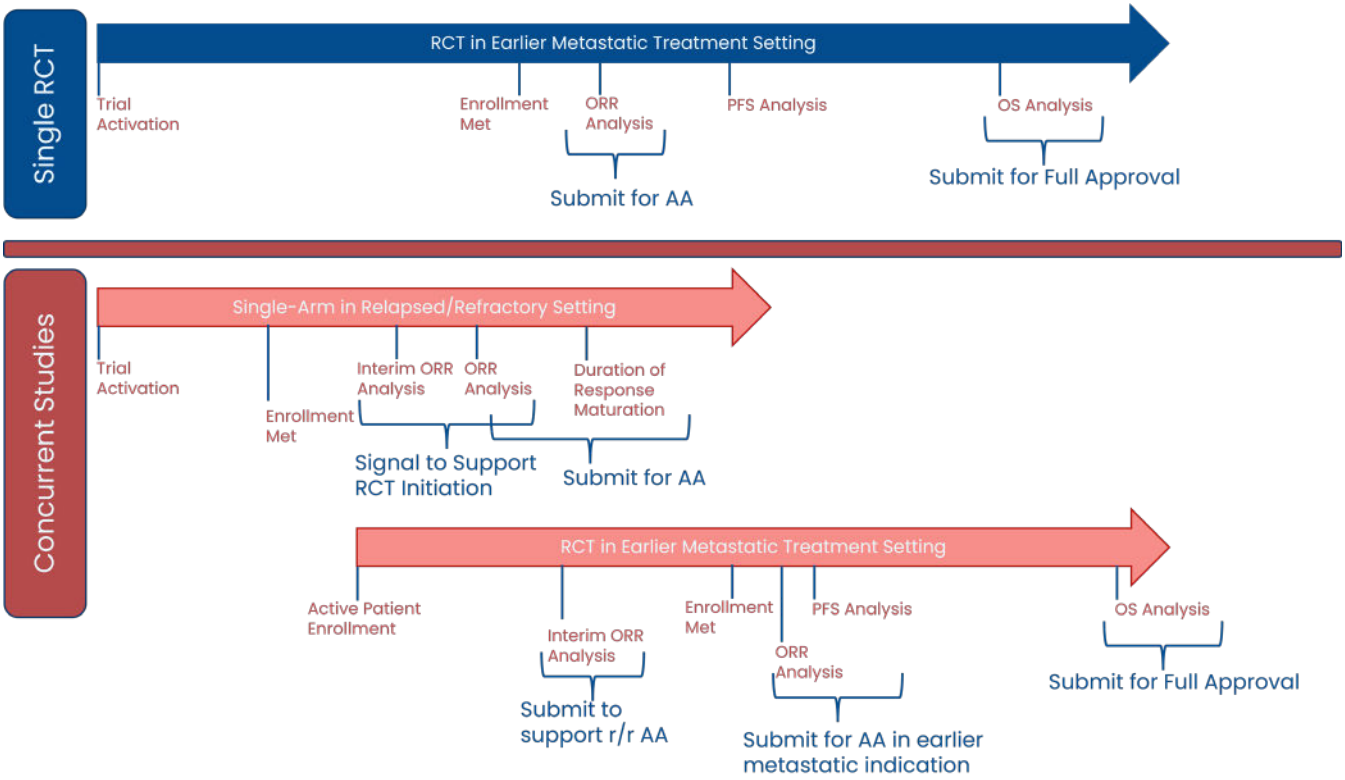
	Single Randomized Trial	Two Concurrent Studies

Approach	• The same study supports AA and subsequently verifies clinical benefit with guarantee of timely confirmatory readout
	  • AA granted on planned analysis of ORR (potentially in a subset of patients)
	  • Traditional approval granted on clinical benefit (e.g., PFS, OS)
		• Single-arm trial examining ORR in r/r setting, allowing for collection of data that supports an earlier initiation of a RCT in patients in earlier metastatic lines and AA in the r/r setting
		• RCT in patients in earlier treatment setting to support AA and subsequently confirm clinical benefit

Advantages	• More thorough safety assessment than single-arm trial • Definitive evidence of benefit-risk from single trial in same patient population • May reduce risk of prematurely halting drug with limited increment to ORR that may still improve OS, depending on characteristics of alpha spending approach	• Able to generate evidence to support investigation in earlier setting (if biology is similar) • Provides data to support indication in r/r setting • Potential to address unmet need in more expeditious manner in both the r/r setting and earlier setting • Interim analysis of safety and ORR in confirmatory trial could provide support for an AA in single-arm trial indication • ORR in this interim could support an earlier, additional, AA indication in the RCT population
Disadvantages	• Greater risk/higher investment with less clinical experience from r/r setting to inform study • Possible statistical concerns with more stringent alpha control with multiple endpoints	• Confirmation of clinical benefit (e.g., PFS, OS) in RCT is not the same patient population as single-arm trial for AA conversion • Timing of endpoint readouts in r/r may impact start of RCT (need full enrollment of RCT at submission of r/r single-arm trial for AA)

Adapted from Fashoyin-Aje, et al.[2]

Figure 2: Possible Clinical Development Approaches to Support Accelerating Investigation in Earlier Settings. Two possible strategies to facilitate regulatory review in earlier metastatic lines, including the submission to support AA and full approval through a single RCT in the early setting, or two concurrent studies of a single-arm trial in the r/r setting and a RCT in the early setting.



Single RCT

A single RCT could be initiated in an earlier metastatic setting with prospectively defined intermediate endpoints to support an AA (e.g., ORR) and traditional long-term clinical endpoints to confirm benefit. The ORR analysis could be conducted in a subset of the enrolled patient population for an initial signal of clinical benefit, triggering an increase in enrollment to confirm the benefit. Resulting data from the RCT are more robust than a single-arm trial due to evaluable clinical efficacy and safety data, however, RCTs may incur greater risk given the limited clinical experience from the r/r setting to inform RCT study design.

Two Concurrent Studies

A single-arm trial in the r/r setting can generate evidence to support investigation in the earlier treatment setting. These data may support an AA in the r/r setting as well as establish a proof of concept for clinical efficacy (based on the ORR and durability of response) and an understanding of the PK/PD including the potential drug-drug interaction profile, to inform the design of a RCT in an earlier setting. Additionally, continued clinical evaluation in the r/r setting supports development of therapies for this population in parallel while the randomized study in the earlier setting begins.

The RCT can serve four purposes:

1. An interim analysis of ORR to support AA in the r/r setting,
2. An analysis of ORR to support an AA in the early metastatic setting,
3. Confirmation of clinical benefit with PFS/OS to support full approval in the early metastatic setting and conversion of AA in the r/r setting to full approval, and
4. A clearer understanding of safety assessment.

In this approach, it is critical that the RCT is ongoing, with enrollment complete or near complete, prior to submission of data from the r/r single-arm trial to support a regulatory decision for AA.

Statistical Considerations for Endpoint Analyses in RCTs

When deciding planned endpoint analyses, multiple factors may influence the choice of endpoints: effect size, effect duration, depth of response, available therapy, disease setting, and risk-benefit relationship.[13] When analyzing multiple endpoints within a single trial, the optimal alpha spending and multiplicity control strategy must be considered. Allocation of alpha could be initially split between the AA endpoint and confirmatory endpoint and subsequently recycled upon successful demonstration of effects in corresponding endpoints, such that regardless of the ORR result, PFS/OS could potentially still reach significance. This may require a more stringent boundary for the AA endpoint, longer follow-up, and a higher event rate for the confirmatory endpoint, or both. FDA released final guidance to support the use of multiple endpoints in clinical trials which outlines key statistical considerations.[14] Various scenarios and assumptions that impact timing of data readouts and other endpoint considerations are described in **Appendix 2**.

Clinical Equipoise Considerations

There are ethical considerations for conducting randomized studies depending on the expected magnitude of effect based on early clinical signals and pre-clinical evidence. If a high magnitude of benefit is observed in either the r/r setting or as part of the intermediate endpoint analysis in the RCT, it may be challenging to enroll patients onto the control arm, demonstrating the importance of fully enrolling the RCT prior to submission of interim analyses for AA. The trial design and statistical analysis plan could incorporate unblinding during follow-up as data continue to accrue for long-term endpoints or consider challenges and opportunities of cross-over. However, this is similar to the current AA paradigm with ongoing studies to confirm benefit in earlier line settings.

Biomarker-Driven Development Considerations

There may be additional clinical development considerations for indications in biomarker-defined populations (for the purposes of this white paper, a biomarker is a predictive biomarker that is predictive of the efficacy of a specific therapy). Previously validated biomarkers can be utilized more quickly than novel biomarkers, which require more coordination for co-developing a drug and diagnostic. An in vitro diagnostic investigational device exemption (IDE) may be required if a novel biomarker is used in the early treatment setting where available approved therapies exist, as the study may be deemed a significant risk to patients if they are foregoing approved therapies. Establishing an IDE for multiple local tests may be burdensome and Sponsors should align with the Agency when using multiple tests for enrollment. While FDA has

approved therapeutic products when a companion diagnostic (CDx) device is not approved or cleared contemporaneously, this may be unlikely in the earlier treatment setting given the increased risk posed to patients if they receive a potentially ineffective treatment.

To support evidence generation for rare settings (e.g., a rare biomarker in a common disease setting or a rare disease with a common biomarker), RWD can support an understanding of biomarker prevalence, as well as identify high-risk populations who could be tested first, with supportive pre-clinical evidence (that may have the highest magnitude of effect). To determine whether the biomarker is predictive, biomarker-positive patients should be randomized into the investigational and SOC arms. If both biomarker-positive and -negative patients are included in the control, then one can only assess the prognostic role of the biomarker. This approach of first studying the investigational therapy in a pre-defined population with established medical need could also be employed to establish entry cohorts for special patient populations based on clinical characteristics that may be lacking in the clinical trial population but representative of the overall patient population with the disease.[9] Data from this entry cohort could then be appropriately extrapolated to the broader patient population.

Conclusions and Future Directions

This white paper provides parameters to help Sponsors identify candidates for a Project FrontRunner approach and outlines a framework for operationalizing this approach within the overall drug development plan. This approach is intended to be an adjunct to, but not replacement of, existing paradigms for accelerated approval of oncology products. Early interactions between Sponsors and the Agency are recommended to discuss and confirm the comprehensive development plan. Initiating discussions with international health authorities regarding clinical development plans is important as the acceptability of endpoints, such as ORR, may differ across health authorities and health technology assessment (HTA) bodies for approval and/or reimbursement, which may present challenges to broader adoption. While Project Orbis provides a framework for concurrent submission and review of oncology applications, expanding this framework to earlier phases of development could be beneficial.[15]

OCE's Project FrontRunner and the proposed framework for advancing the investigation of therapies in earlier treatment settings holds great promise to extend clinical benefit into broader patient populations. However, this paradigm will not be appropriate for all clinical and drug development scenarios. It will therefore be important to identify the scenarios amenable to this approach, as discussed herein, and hold disease-focused drug development workshops to further operationalize these concepts. Additionally, identifying and validating other novel early endpoints like ctDNA can help expand the application of this approach to other disease settings and therapies. Lastly, operationalizing the considerations and concepts of the framework to support the goals of the initiative at FDA would be beneficial, such as encouraged synergy with CDx development for biomarker-defined populations and designing dosing studies within the FrontRunner paradigm.

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Appendix 1
Lessons Learned from Recent Drug Development Programs

Case Study 1: Abemaciclib[16] – Potential challenges associated with performing interim PFS analyses.

Indication: Abemaciclib + fulvestrant for adult patients with HR+/HER2- advanced or metastatic breast cancer with disease progression following endocrine therapy.

Clinical Development Plan: Originally a single-arm Phase 2 trial designed to support an AA based on ORR in previously treated patients, with an initiated Phase 3 RCT. Submission on single-arm trial was discouraged. The Sponsor continued the Phase 3 trial with PFS as the primary endpoint. Regular approval was based on the final PFS analysis, as the originally planned PFS interim analysis did not meet the defined threshold.

Challenges Highlighted: FDA discouragement of a single-arm trial to support AA with a separate RCT to confirm benefit. Potential challenges associated with proposing submissions based on interim analysis for PFS. Statistical considerations, such as the required hazard ratios and alpha spending, may limit the ability to conduct interim analyses.

Key Learnings: In certain scenarios, such as abemaciclib + fulvestrant, with an approximately 50% overall response rate (ORR), assessing ORR and duration of response in a subset of the cohort of an ongoing RCT may be more informative as data to potentially support an AA, than a single-arm trial to support AA followed by a Phase 3 RCT. In certain disease settings, there may be benefit from endpoints other than ORR (e.g., pCR, ctDNA, MRD). However, additional evidence is needed to validate and evaluate the correlation of these endpoints, such as changes in ctDNA, with long-term outcomes to justify use as an alternative early endpoint to support regulatory approval.

Case Study 2: Relatlimab-rmbw[17] – Trial design to support an approval for a first-in-class drug in the early metastatic setting.

Indication: Relatlimab-rmbw + nivolumab for adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma.

Clinical Development Plan: An adaptive trial design for a first-in-class therapy in early metastatic disease. Patients were randomized to either relatlimab+nivolumab or nivolumab in a Phase 2 study and enrollment paused for a pre-planned PFS interim analysis. The interim analysis demonstrated benefit, thus triggering enrollment of additional patients into the Phase 3 RCT, which had a primary efficacy endpoint of PFS and secondary OS and ORR (with hierarchical testing) for full approval. In melanoma, there is a well-established correlation between PFS and OS, supporting PFS as an adequate endpoint for full approval. The adaptive trial design allowed for integration of Phase 2 with Phase 3 efficacy data.

Challenges Highlighted: The level of evidence to support an approval for a first-in-class drug in the early metastatic setting may be higher than in other settings where the mechanism of action is well known. Additional considerations for trial design include the magnitude of benefit of efficacy and use as a combination therapy.

Key Learnings: This scenario highlights when it may be necessary to investigate a new regimen in earlier settings. As relatlimab was studied as a combination therapy with nivolumab, targeting patients in the early treatment setting was necessary, as many r/r patients had received

nivolumab (the control arm) in prior lines, and rechallenge with nivolumab was considered inappropriate. Scenarios evaluating an add-on therapy may necessitate investigation in earlier settings, given the need to demonstrate contribution of components and that the add-on therapy provides additional benefit compared to monotherapy alone. Here, given the mechanism of action of the drug, a significant ORR was not expected and therefore assessing ORR in an attempt for AA was not likely to be successful. Additionally, it may not be advantageous to aim for an AA if a full approval can be supported in the early setting with an RCT. There is potential for an interim PFS analysis and an earlier readout to support AA, although the Agency has discouraged this as interim PFS analyses may overestimate the true PFS. An earlier PFS interim analysis may avoid exposing too many patients to a potentially inferior therapy compared to SOC.

Case Study 3: Retifanlimab-dlwr[18] – Utility of an ongoing RCT, as single-arm study data may not provide sufficient evidence to justify a regulatory decision when there is a low response rate.

Indication: Retifanlimab for adults with locally advanced or metastatic squamous carcinoma of the anal canal who have progressed on or who are intolerant of platinum.

Clinical Development Plan: A Phase 2 single-arm trial with ORR as the primary endpoint was submitted to the FDA for AA with an ongoing randomized Phase 3 trial in an earlier setting to provide confirmatory evidence.

Challenges Highlighted: A complete response letter (CRL) was issued identifying general concerns with using the data from the single-arm trial for regulatory decision-making due to the low response rate (e.g., 13.8% for retifanlimab). Further, given the high prevalence of potentially confounding factors in the intended population, determination of the safety and efficacy to inform the benefit: risk assessment was challenging in the absence of a control arm.

Key Learnings: There is significant concern with submissions based on preliminary evidence of benefit, particularly when the response rate is considered to be low. This scenario highlights the need for a RCT to be ongoing, with enrollment complete or near complete, prior to any analyses of the single-arm trial to support a regulatory submission for AA. If the drug receives AA, time to confirmation of clinical benefit is faster, and if the ORR analysis is not supportive of an AA, the RCT trial is already ongoing. Resulting data from the RCT will be more robust than a single-arm trial with clinical efficacy and safety data evaluable. However, there may be concerns raised by investigators about the ethics of initiating large Phase 3 trials when there is insufficient preliminary evidence to support the hypothesis of benefit for a new therapy. Pre-planned interim analyses for futility may be considered as one possible solution to this latter concern.

Appendix 2: Endpoint Considerations

Variability in Timing of Endpoint Readouts Based on Different Assumptions

The scenarios are not meant to be exhaustive but representative of what may occur in oncology to show, via these archetypes, how nuances arise amongst endpoints and how enrollment and event rates can come together and impact timings.

Table 1: Timing of RCT Endpoints Given Various Scenarios

Identity	Archetype	Enrollment (N)	mPFS Control (months)	ORR % (Control vs. Investigational)	ORR (N)	Enrollment Duration (months)	ORR Analysis (months)	PFS Interim (75% Info. Frac.) (months)	PFS Final (months)
A	Short PFS/ Slow Enrollment	450	10	55% vs. 70%	430	24	27	24	29
B				50% vs. 70%	240		19		
C	Longer PFS/ Slow Enrollment		20	65% vs. 80%	360		24	34	44
D				60% vs. 80%	210		18		
E	Short PFS/ Fast Enrollment		10	55% vs. 70%	430	12	16	17	22
F				50% vs. 70%	240		11		
G	Longer PFS/ Fast Enrollment		20	65% vs. 80%	360		14	26	36
H				60% vs. 80%	210		11		
I	Very Long PFS	660	45	75% vs. 85%	660	24	28	41	53
J									

ORR analysis triggered 4mos after enrollment of 'ORR N' achieved
PFS analyses powered at 80% for true PFS HR = 0.70 throughout (~250 final PFS events required)
ORR analyses powered at 90% for differences displayed in column 3, with 4 mos follow-up
Assume fixed testing sequence (ORR —> PFS) with overall α = 0.025 (1-sided)

Table 2: Timing of RCT Endpoints Given Various Scenarios, Powered for OS

Identity	Archetype	Enrollment (N)	mPFS (Cntrl)	mOS (Cntrl)	ORR %	ORR N	Enrollment Duration	ORR Analysis	PFS Interim (75% Info. Frac.)	PFS Final	OS Final
A	Short PFS / Slow Enrollment	685	10 mos	20 mos	55% vs. 70%	430	34	27	24	28	49
B					50% vs. 70%	240		19			
C	Longer PFS /Slow Enrollment		20 mos	35 mos	65% vs. 80%	360		24	31	36	72
D					60% vs. 80%	210		18			

OS powered 80% at HR = 0.75 (~390 OS events required) to be tested in a gated fashion after ORR and/or PFS
N = 685 was chosen to yield ≤ 72mos duration to OS for the 'Longer PFS' archetype

Further Endpoint Considerations for Clinical Trials

ORR

In settings where ORR is an established endpoint reasonably likely to predict clinical benefit, it may be appropriate to consider an initial, well-designed statistical comparison of ORR in treatment arms to support accelerated approval. This comparison should be powered to demonstrate a clear clinical benefit, and what constitutes a clinically meaningful benefit in ORR depends on the disease setting and should be agreed upon upfront, along with an agreed timeframe for establishing durability of response. Analyses of ORR may require fewer patients than required to support subsequent analysis of PFS or OS in the RCT. In general, it is preferred that enrollment be mostly complete prior to ORR analysis and be conducted at a timepoint that allows adequate characterization of durability of response, the latter being dependent on the disease setting. When evaluating whether ORR should be included as an interim analysis to support AA, the timing of the readout in relation to other endpoints should be considered in addition to the appropriateness of the endpoint to predict clinical benefit in the specific disease and therapy setting.

PFS

In some cases, based on disease setting and regulatory precedence considerations, a PFS analysis may best support an initial submission for accelerated or regular approval. Additionally, with some exceptions, the trial will need to be ultimately powered for OS. In these cases, enrollment timelines may influence the timing of PFS readout, with PFS readout often occurring shortly after enrollment completes. In scenarios where PFS interim analyses read out around the same time as ORR, and the investigational therapy (alone or in combination) is not expected to increase ORR, a PFS interim analysis to support AA may be considered. However, it is acknowledged that the appropriateness of an interim PFS analysis is situationally dependent and must take into consideration the relationship of PFS to OS to determine if the proposed analysis is fit for purpose. The appropriateness of conducting interim PFS analyses in any specific clinical trial should be discussed with the FDA, as interim PFS analyses may overestimate the true PFS. Additionally, in certain disease settings with a long natural history, the time to OS analysis may be considerably long, and PFS may be appropriate to confirm clinical benefit, depending on the disease, mechanism of action of the drug, and market access considerations. If PFS is used as the primary clinical endpoint for traditional approval, studies can be smaller, and ORR may be more feasible to support AA.

OS

Depending on the mechanism of action of the drug and disease setting, confirmation of clinical benefit through OS analysis may be required. Powering a trial for OS, compared to PFS, can increase the target enrollment size as well as enrollment duration. Given this, analyses for ORR and PFS may reach maturity prior to full enrollment. It is important that clinical trials meant to verify clinical benefit be substantially enrolled, as once results are public, it can be challenging to enroll a sufficient number of US patients in the confirmatory study with enrollment often completed based on non-US patients. If the study comprises a largely non-US population, it may be more challenging to equate to US populations given differing SOC. To mitigate against such challenges, the ORR analysis could be conducted for a pre-specified subset of enrolled patients that has been agreed to with regulators, and while durability of response data are maturing, enrollment continues such that at the time of submission of the application, enrollment is almost complete. Another consideration in the early metastatic setting is the confounding of a patient receiving subsequent therapies on the final OS analysis. This is a challenge in many frontline settings and is a consideration when confirming benefit for an AA.