Mechanism-of-Action–Based Master Trial Approach in Pediatric Oncology

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Abstract

In oncology, pediatric drug development can face unique challenges; however, the advent of molecularly targeted agents, as well as innovative clinical trial approaches, offers an opportunity to address these shortfalls. This paper outlines the feasibility and potential design of a mechanism-of-action (MOA)–based phase 1/2 Master Trial platform for concurrently studying multiple molecules across a range of relevant pediatric tumor types. In support of the MOA-based development approach, prioritization criteria to identify the most promising molecules to take forward from this Master Trial into pivotal studies are also discussed. For example, observed tumor responses, along with feasibility data based on disease epidemiology and historical data from participating academic sites, could improve the selection of optimal molecule/tumor-type pairs for further evaluation in pivotal trials in pediatric patients. The implementation of multisponsor master trial platforms in pediatric oncology will help create a new development paradigm that will enable the biopharmaceutical industry as a whole to fulfill its mission of addressing an unmet need for children with cancer. It will also identify an approach to pediatric drug development that preserves patients for the most promising therapies and uses resources in an efficient manner. The success of such targeted/MOA-based master trial programs requires a strong partnership between industry, academia, the patient community, and regulators for allowing the prioritization of molecules, as well as flexibility in the implementation of pediatric obligations under the Pediatric Research Equity Act (PREA) and incentive qualification under the Best Pharmaceuticals for Children Act (BPCA), while also fulfilling pediatric regulations in other countries (eg, the European Medicines Agency [EMA]).

The aim of this paper is to

1. Establish a design and facilitate the creation of an MOA-based phase 1/2 Master Trial platform to screen multiple agents across different pediatric tumor types.
2. Facilitate the standardization of targeted approaches in pediatric oncology to ensure consistent interpretation by health authorities and industry for widespread adoption and sustainability.

Introduction

Pediatric cancer represents an area of high unmet medical need. Despite legislative and regulatory initiatives in both the United States and European Union that mandate or provide incentives to sponsors to develop pediatric drugs, the number of approvals of new drugs and labeling updates that can guide treatment decisions for children with cancer remains insufficient.[1,2] The reason for this is multifactorial. The rarity of pediatric cancer creates substantial logistical challenges for sponsors in designing and executing clinical trials that can be completed within a reasonable time frame. The number of eligible pediatric patients is frequently further limited by enrollment restrictions in the phase 1 setting to patients with relapsed or refractory disease, thereby negatively impacting enrollment feasibility and limiting statistical power.

The conventional paradigm for oncology drug development for children is largely based on the adult clinical development program. In the field of oncology, however, there is little overlap in the specific indications or tumor types that represent an unmet need in adult versus pediatric patients. Additional challenges in pediatric oncology drug development include a lack of appropriate controls and pediatric-specific end points. Differences in regulatory timelines and procedures across different regions may also act as impediments to harmonizing global drug development and initiating pediatric studies in a timely manner. The requirement for a Pediatric Study Plan for products under development under the Food and Drug Administration Safety and Innovation Act, 2012 has greatly improved early planning for pediatric studies in the United States, and pediatric cluster meetings between regulatory health agencies have helped enhance global collaboration and exchange of scientific information regarding product-specific pediatric development. However, research in pediatric oncology is still insufficient to meet the needs of patients.

An increase in the understanding of cancer biology has led the drug portfolios of most pharmaceutical companies to become better suited to targeting specific molecular abnormalities/pathways in increasingly smaller molecular subsets of cancer populations. With the advent of precision medicine, the adult oncology/hematology field is also rapidly evolving. It is moving away from conventional study designs and toward novel clinical trial approaches, such as master trial platforms, to optimize cancer drug development and potentially enable faster regulatory approval. More recently, master protocols, along with the use of established pediatric clinical trial networks, have been proposed as a potential solution to challenges in pediatric drug development, including in pediatric cancer.[3-5]

Master trial platforms can enable the simultaneous assessment of multiple targeted agents, either alone or in combination with other therapies, in relatively small patient populations under a single, overarching master protocol. This can potentially maximize the therapeutic intent for individual patients. A master protocol can be conducted under a single Investigational New Drug (IND) application and contains the common protocol elements applicable for the development of each individual molecule that will enter the trial. Individual substudies associated with the common protocol contain molecule-specific information. The common study structure streamlines the regulatory review and study approval of subsequent molecules that are added to the IND application or when the substudies are amended.

Other advantages associated with master protocols include the standardization of study designs across molecule arms, a streamlined enrollment procedure that uses the same sites for patient enrollment, centralized biomarker assessment across diseases and molecules, improved screening success rates based on inclusion criteria, the ability to leverage a common standard-of-care (SOC) control arm across study arms for a specific disease, a central governance/review structure, the flexibility to add or remove molecules based on early evidence of safety and efficacy, and the faster and more reliable acquisition of early-stage data for informing pivotal/confirmatory studies. Master trials can also enhance operational efficiencies and reduce the cost of conducting studies because they utilize a common infrastructure.[3,5-8] Overall, master protocols can increase patient access to potentially new treatments and speed the pace of drug development and approval. They can also, however, be more complex to implement and more difficult for study sites to comprehend.[6]

To enable earlier access to innovative molecules for children with cancer and to optimize early-stage data collection for confirmatory trial decision-making, Genentech and Roche hereby propose an evidence-based, targeted Master Trial approach in pediatric oncology. This Master Trial platform will allow the concurrent and gated assessment of multiple molecules across a range of pediatric tumor types in order to identify the most promising molecules to advance into late-stage development. The assessment of these molecules will be based on prioritization criteria such as superior efficacy, safety, and unmet medical need.

- The proposed early phase 1/2 Master Trial takes the biology of each pediatric tumor type and the MOA of each drug into account. This MOA-based approach adjusts the focus of pediatric drug development toward the many pediatric diseases for which there are no adult counterparts rather than exclusively toward the tumor types investigated in adult development programs.[9]
- Furthermore, the MOA-based Master Trial approach is aimed toward exposing fewer children to ineffective or unsafe treatments and also toward rapidly identifying those pediatric tumor types for which a particular molecule may provide a clear therapeutic benefit.

As the MOA-based Master Trial will evaluate multiple molecules in multiple tumor types, treatment allocation rules will be described to provide guidance in the selection of treatment for patients who have a disease for which there are several molecules that would be plausible candidates based on their MOA. Additionally, predefined prioritization criteria will be provided for the gated assessment of molecules based on observed safety data and tumor responses in conjunction with feasibility data (based on disease epidemiology and historical data from participating academic sites) to improve the selection of optimal molecule/tumor-type pairs for further evaluation in registrational trials in pediatric patients. It is important to emphasize that the ultimate aim of this approach is to inform the label with data and increase access to medicines for pediatric use.

To facilitate the global implementation of master protocols, regulatory agencies and trial implementation groups in other regions, such as the EU Voluntary Harmonization Procedure (VHP) and Clinical Trial Facilitation Group, will need to accommodate the concept of studying multiple molecules on an ongoing basis under a single clinical trial application within their submission and approval

processes. For example, unlike a master Investigational New Drug application in the US, a new molecule arm may not be added as a substantial amendment to an already approved Clinical Trial Application via the current VHP or via the national submission procedure in the EU. Furthermore, when developing master protocols in pediatrics, development strategy must also factor in pediatric laws and regulations and ensure that each molecule in an ongoing study meets its pediatric obligations and/or qualifies for incentives under the pediatric study/investigation plans. If, however, the various stakeholders involved take appropriate collaborative steps, these operational and implementation issues may not be too difficult to resolve.

Because the MOA-based approach broadens the scope of investigation in pediatric cancers, it may not be possible or feasible for a sponsor to conduct pivotal studies in all tumor types for a molecule that are identified in the early-phase safety/efficacy trial. Regulatory flexibility must be exercised in making molecule prioritization decisions for confirmatory studies to ensure the success and feasibility of MOA-based approaches and to encourage precompetitive multisponsor collaborations. These decisions could be facilitated through the development of a molecule decision-making schema to select optimal molecules for further evaluation as well as through the development of a criterion for the fulfillment of regulatory obligations and/or incentive qualification when a sponsor's molecule is not selected to move forward into late-stage development.

Master Trial: Characteristics, Format, and Clinical Trial Design

The proposed Master Trial is a gated early-phase trial platform for studying multiple molecules across a range of relevant pediatric tumor types to allow the rapid prioritization of the most promising molecule for each tumor type based on an MOA-based drug development framework. Fundamental to the Master Trial platform is the ability to quickly identify molecules with sufficient efficacy and safety to pursue further development and conversely to stop development early for molecules that display evidence of pediatric safety concerns or limited early efficacy.

The Master Trial will evaluate the safety, pharmacokinetics (PK), and preliminary efficacy of each molecule eligible for development in pediatric and young adult patients who have no curative treatment options. Additional objectives of the Master Trial may include pediatric dose-finding and pediatric-specific biomarker research. The Master Trial will also consider combination treatment with established chemotherapy regimens or radiation where single-agent activity cannot be expected.

Genentech and Roche have already initiated two independent, early-phase pediatric studies for atezolizumab (TECENTRIQ®) and cobimetinib (COTELLIC®) that utilize an MOA-based approach. The proposed Master Trial that will concurrently assess several molecules across a range of pediatric tumor types is currently being discussed with regulatory health authorities. Both the stand-alone and Master Trial studies are intended to follow the same gated-development design, and the data obtained from these studies will be used to inform decisions on the design of subsequent confirmatory trials.

Characteristics of the Master Trial

The MOA-based Master Trial approach in pediatric oncology has many advantages:

- It maximizes early access to new therapies across a wide range of pediatric tumor types.

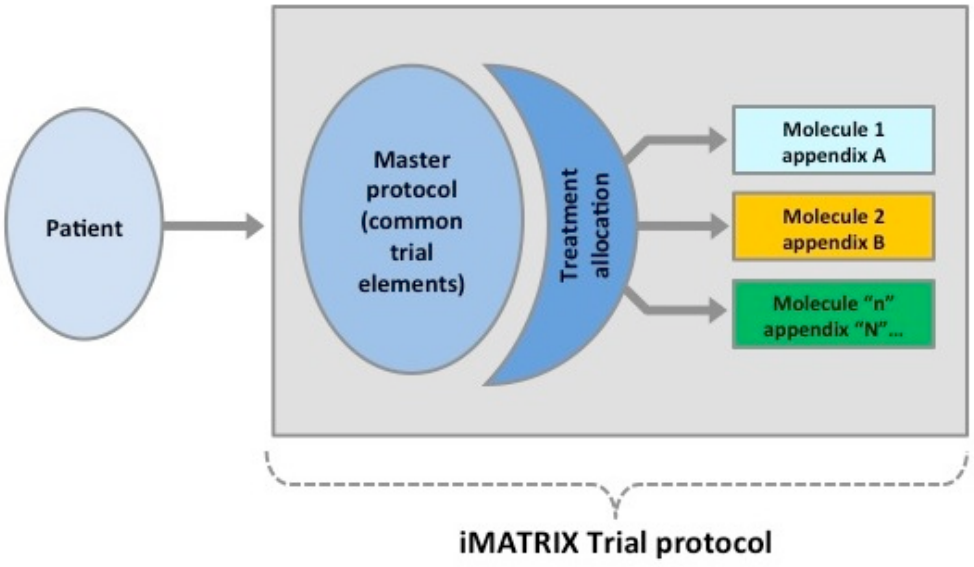
- It reduces the number of pediatric patients unnecessarily subjected to potentially subtherapeutic doses.
- It enriches the proportion of patients who have the potential to gain benefit on the basis of tumor biology or drug target prevalence.
- It produces a more robust data package with respect to PK, dosing, tolerability, and safety.
- It utilizes a gated design, allowing earlier identification of the best molecule/tumor-type combinations for continued development.
- It partners with established pediatric clinical trial networks globally and enables sponsors to align with a single set of sites and vendors.
- It provides operational efficiencies (similar databases, site equipment, training, etc) and establishes best practices for improving the quality and timeliness of data. Sites are enabled to offer multiple studies to patients with different tumor biologies, increasing the ability to enroll patients more quickly.
- It provides appropriate breadth of relevant tumor inclusion (eg, solid tumors) based on MOA/target of the drug, which should allow for regulatory obligations to be met for all molecules in adult development.

Format of the Pediatric Oncology Master Trial

The concurrent evaluation of multiple molecules in multiple tumor types within the Master Trial necessitates the development of the following (Figure 1):

- **Master protocol**: describes the main principles driving the development of molecules in the trial and contains the common protocol elements applicable for the development of each individual molecule that will enter the trial (eg, ethical considerations, a safety-reporting structure, and tumor-specific information)
- **Molecule arm appendices**: contain the molecule-specific elements of the protocol, such as dosing information, specific safety recommendations, and the schedule of assessments, and also include molecule-specific quality-control and manufacturing information and nonclinical data
- **Treatment allocation rules**: will be specified in the master protocol document to ensure that each patient is exposed to the most promising treatment under development in the trial for that patient's specific tumor type

Figure 1. Protocol Structure and Treatment Allocation



Together, the master protocol and a single molecule-arm appendix will constitute the full trial protocol for a specific molecule. These protocol documents will be used in conjunction with treatment allocation rules to determine the treatment assignment priorities for each tumor type across the active molecule arms in the Master Trial.

Treatment allocation decisions will be informed on the basis of data from completed gate assessments. Exceptions include emerging safety and scientific data with clear implications for the trial.

A steering committee (SC) that includes sponsor representatives and external experts will routinely monitor the scientific integrity of the trial. For example, they will

- Review the proposal for disease selection.
- Review the treatment assignment priorities for each tumor type.
- Review the clinical development recommendations for individual molecules.

The SC will receive and review the safety recommendations from an Internal Monitoring Committee.

Molecule Selection

The main considerations for molecule inclusion will be the safety profile established through nonclinical and clinical investigations and the strength of the mechanistic rationale to support pediatric indications based on nonclinical data. Other considerations will include the pharmacology, PK, expected dose, formulation requirements, and absorption, distribution, metabolism, and excretion (ADME) benefits or liabilities. In addition, the operational feasibility of including a molecule in the Master Trial will be assessed on the basis of the prevalence of eligible patients, the potential for and predicted extent of its therapeutic effect, and data from ongoing early pediatric trials with molecules of the same class.

Although these considerations (with the exception of safety) may not definitively exclude a molecule from consideration for pediatric studies, a careful assessment of these factors will allow the

prioritization of molecules that are the most promising for pediatric use in a given tumor type or mechanism.

Inclusion Criteria for Pediatric Tumor Types

The proposed Master Trial will initially investigate pediatric solid and brain tumors. Ongoing discussions with therapeutic area experts in pediatric hematology are exploring the feasibility of including hematopoietic malignancies in the trial. Within these general classes, the decision to include a particular tumor type in the trial for treatment with a specific molecule will be based on the MOA of the molecule and the involvement of the target (or its pathway) in the biology of that particular tumor type or its microenvironment, as well as the unmet medical need for the disease.

The strength of the match between the molecule's MOA and the biology of a pediatric tumor type will be assessed through

- A review of published literature regarding target actionability in preclinical models, including pediatric models, if available.
- The prevalence of the molecular target of the compound in the pediatric tumor type.
- Additional mechanistic proof of concept in nonclinical models of pediatric tumors, if available.
- Relevant adult clinical trial data.

The totality of this information will be used, together with other characteristics of a molecule, to determine the patient eligibility criteria.

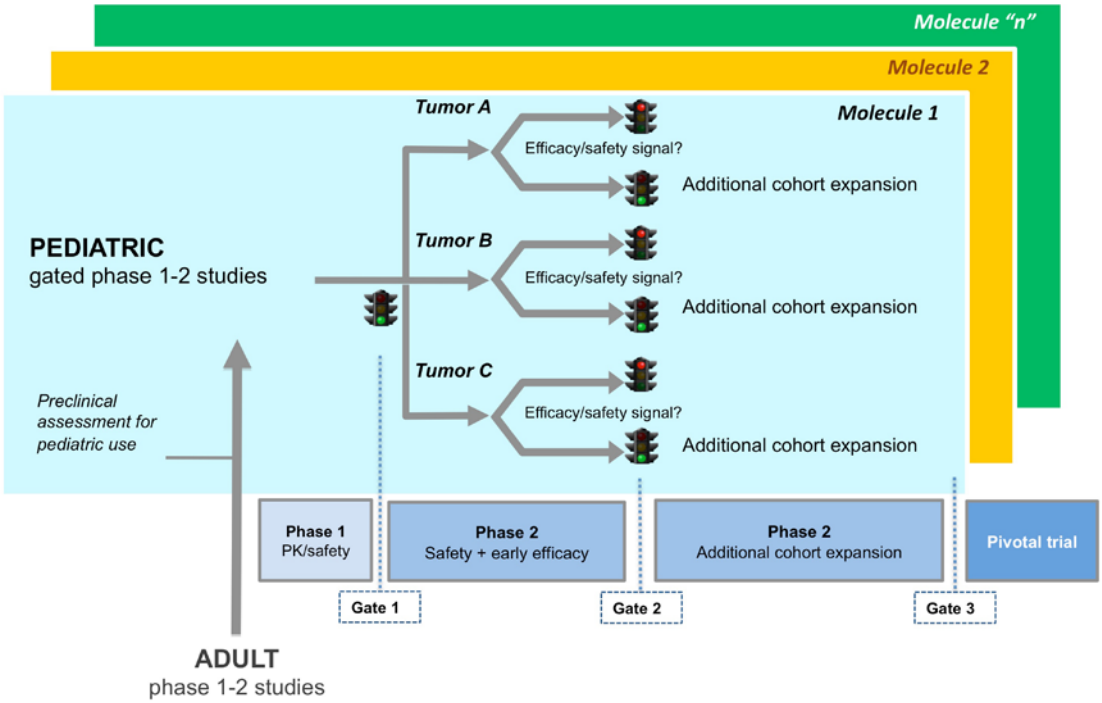
Inclusion Criteria for Patients

In an early-phase trial, inclusion and exclusion criteria will be specified to reflect the limited availability of pediatric clinical data at the time of trial initiation for any given molecule. This trial will enroll patients up to 30 years of age who have pediatric tumor types to ensure that adolescent and young adult patients with pediatric tumor types are able to access relevant clinical trials.

Clinical Trial Design

The gated assessment design of the proposed Master Trial (Figure 2) involves an initial safety-evaluation phase for each molecule at Gate 1, with predefined criteria for safety and PK assessments that are evaluated across tumor types. For monoclonal antibodies, the pediatric dose is selected to match adult exposure, and appropriate scaling methods are employed on the basis of PK, safety, and efficacy data from adults. For small-molecule targeted therapies, the starting dose in pediatrics would be approximately 80% - 100% of the adult dose depending on the adult safety profile.

Figure 2. MOA-Based Pediatric Drug Development: Preserve and Match Patients With Rare Tumors to the Most Promising Therapies



Abbreviations: MOA, mechanism of action; PK, pharmacokinetics.

To make the preliminary assessment of efficacy, 2 stages of response assessment are planned in the Master Trial, corresponding with Gates 2 and 3. Predefined disease-specific criteria and prioritization criteria will guide the advancement of molecules into late-stage development when the target treatment effect (TTE) is achieved in a specific disease.

This Master Trial will focus predominantly on the development of single agents; however, combination treatments with the SOC may also be included. In such instances, the same gates outlined below will be applied to the combination-treatment study arms.

Gate 1: PK and Initial Safety Assessment

The master protocol is designed with enough flexibility to allow optimization of the early-phase design (ie, Gate 1) for each molecule. An overall strategy for dose finding will be part of the master protocol. Molecule-specific details on the optimized PK/pharmacodynamic (PD)/dose-finding design will be placed in the molecule protocol appendices to allow flexibility to choose the most appropriate design for individual molecules.

Gate 1 PK analyses would include a comparison of the exposure in children with that observed in adults. Exploratory correlations of exposure with safety and efficacy may also be performed, as appropriate. The Gate 1 assessment would occur after approximately 20 patients have been treated with the molecule, irrespective of their tumor type. For those molecules requiring a dose-escalation phase, an appropriate dose-escalation design will be provided. The Gate 1 assessment will only occur after identification of the maximum tolerated dose (MTD) or maximum administered dose (MAD).

If a molecule meets the Gate 1 assessment criteria, enrollment will continue for preliminary assessment of efficacy. For molecules that do not meet the Gate 1 assessment criteria (ie, do not have an acceptable safety and tolerability profile in pediatric patients), development within the trial will be adapted (eg, via dose adjustment) or stopped. In such cases, further development will be reconsidered if new information arises that changes the risk-benefit assessment for the molecule.

For molecules determined to have acceptable PK, safety, and tolerability profiles in their Gate 1 assessment, enrollment will be continued into tumor type cohorts to determine preliminary efficacy in 2 stages (Gates 2 and 3).

Gate 2: Initial Response Assessment

Gate 2 will provide an evaluation of initial response assessment in the various tumor types, with early stopping rules for low efficacy. These evaluations will be done per tumor type; data will not be aggregated across tumor types. The sample size and responder requirement per tumor type and the type 1 error/power calculations will be specified.

For antitumor-activity evaluation, the historical objective response rate (ORR) and target improvement in each tumor type will be considered. The ORR will be adapted with evolving scientific knowledge and treatment options. Other relevant data, such as additional efficacy readouts, exploratory biomarker data, safety data, PK/PD data, and the enrollment rate, will also be considered at Gate 2.

The objective of the Gate 2 efficacy assessment is to identify tumor types that could potentially meet the target response criteria and to expand enrollment in such cohorts. Within each tumor-type cohort, the minimum number of responders required at Gate 2 to continue enrollment is defined on the basis of the target treatment effect for the Gate 3 assessment. If Gate 2 criteria are not satisfied for a particular tumor-type cohort, development of the molecule may stop for that cohort, a modification to the inclusion criteria may be considered to incorporate patient selection based on candidate biomarkers, or the molecule may be considered for development in combination. See the sections below for a proposed biomarker and combination strategy.

Gate 3: Additional Response Assessment

The Gate 3 response assessment will be conducted after the required number of patients, based on preliminary power calculations, has been enrolled in a specific tumor-type cohort. There are 2 key considerations in the Gate 3 assessment: TTE and enrollment feasibility. The TTE will be prespecified for each disease and will comprise both efficacy and safety criteria. With respect to efficacy, the TTE for a particular disease will reflect a clinically meaningful improvement, as defined by expert consensus and health authorities. This criterion may also be molecule specific. For example, a particular molecule may be expected to prolong the duration of response without a substantial improvement in response rate. In such a case, the TTE response criterion for the Gate 3 assessment would be defined as a target improvement in the duration of response. Ongoing communication and collaboration with academic collaborators and health authorities will be critical to the development of successful and meaningful TTE criteria to ensure that the prespecified TTE is optimally defined (and potentially redefined) as information accrues for each molecule through the drug development process.

Further development of a molecule, including the decision to pursue a confirmatory trial beyond Gate 3, the design and execution of that trial, or consideration for early registration in the case of exceptional efficacy, will occur outside the Master Trial framework. Decisions will be made in consultation with health authorities and academia and will be based on the totality of the data available, including efficacy, PK, safety, biomarker, preclinical, and adult data, the future combination potential of the molecule, the feasibility of a confirmatory trial, and characteristics of the specific tumor type.

No formal hypothesis testing is planned in the phase 1/2 Master Trial. The rules for stopping enrollment to a particular molecule or tumor-type cohort will be placed in the master protocol and be designed to protect patient interest by stopping unproductive development as early as possible in favor of developing other molecules that have greater promise of providing benefit. The decision to stop enrollment according to the presented rules will be overseen by the SC.

In addition to the Gates 1 and 2 decisions described above, development of a molecule may be stopped if any of the following are met:

- The benefit-risk profile changes such that the benefit of the pediatric study no longer outweighs the risk.
    - Unacceptable safety signals or new safety signals in adults
- At least 2 tumor-type cohorts have completed a response assessment.
    - Either initial response assessment at Gate 2 or additional response assessment at Gate 3
    - The sponsor can decide on a case-by-case basis to continue enrollment in cohorts that have not reached Gate 2.
- Enrollment has been open for more than 2 years and at least 20 patients have been treated.
    - The intent of this provision is to prevent situations in which the trial is not feasible and keeping the protocol arm open will not yield additional/conclusive data. This will also preserve trial participation and resources for molecule arms that have a higher feasibility of providing meaningful results to benefit patients.
- The sponsor decides to stop the entire development of a drug (ie, also in adults).
    - In such situations, if efficacy signals were observed in pediatric tumors, the sponsor should consider alternative solutions to continue development in pediatrics (eg, public-private partnerships) if possible.

Finally, beyond these stopping rules, when a cohort successfully meets Gate 3 criteria, development for the molecule will also be stopped in the context of the early-phase Master Trial, and patients may have the option to enroll in a subsequent confirmatory trial for that molecule.

Combination Principles

The proposed combination strategy is to continue single-agent development past the Gate 1 safety and PK assessment as long as clinical benefit is demonstrated. After Gate 1, molecules that do not demonstrate clinical benefit at any stage may be considered for development in combination. The decision for combination therapy would be based on strong scientific rationale, including any available

clinical data regarding safety and efficacy of the combination in adults. Data supporting the relevance of the combination to pediatric tumors, supplemented by single-agent safety and PK data for each molecule in the combination and the disease setting being explored with the combination (if different from the advanced relapsed/refractory setting), will also be considered. Combination partners will primarily be limited to standard chemotherapy regimens used for the treatment of relapsed/refractory tumors or investigational drugs that are already approved for use in another condition. The initiation of combinations of molecules without previous single-molecule pediatric evaluation will be considered.

This design will avoid terminating pediatric development for molecules that may demonstrate clinical benefit in combination therapy. Conversely, this approach does not prematurely terminate single-agent development in favor of combinations.

Biomarker Strategy

In the context of using biomarkers for indication selection and individual patient treatment allocation, the strategy will be specific to each treatment and based on the MOA of the molecule. The factors underlying the choice of an eligibility strategy for a molecule will be multifactorial, including the known MOA of the molecule, nonclinical or adult data supporting a strong mechanistic rationale regarding the role of the target as a candidate predictive biomarker, the presence of an assay that can be used for patient selection, and the known prevalence of the biomarker within a tumor type (eg, if a candidate biomarker is highly prevalent, a tissue may not be required to confirm the presence of the target). Many potentially predictive biomarkers, however, are not adequately characterized in adults or are inconsistent across adult tumor types such that the value for pediatrics is less clear and will require retrospective analyses.

Given the above criteria, 3 scenarios for patient selection are outlined:

- **Individual patient selection**: Some molecule arms of the trial may require patient selection based on the presence of a candidate predictive biomarker (ie, documentation of a particular molecular aberration in the patient's tumor is required for enrollment). A molecule-specific inclusion criterion within the respective molecule arm appendix will specify the appropriate assay to be used for patient selection and the biological tumor profiles that are eligible for enrollment. Tumor profiling may be performed within the Master Trial, or prior evidence of an approved test that documents an eligible aberration may be presented.
- **Disease-selection enrollment strategy**: Patients are enrolled to a particular molecule arm of the trial on the basis of their tumor type (ie, if they have tumor types with known or expected involvement of the target/pathway or the presence of microenvironment elements).
- **All-comer enrollment strategy**: Any patient may enroll provided he or she satisfies all other inclusion and exclusion criteria. This scenario would be considered when there is an insufficient understanding of the tumor biology and/or the biomarker data/assays to exclude patients or if the MOA of the drug is broadly applicable (tumor agnostic).

Across molecules, and irrespective of the eligibility strategy, a thorough retrospective analysis will be conducted for each tumor-type cohort at Gate 2 to determine if correlations can be made between a candidate biomarker and clinical responses. For cases in which the expression of a biomarker is

correlated with clinical activity, consideration will be given to adapt treatment allocation for subsequent expansion cohorts to include biomarker-positive patients. Exploratory biomarker analyses will be conducted across all samples collected in the Master Trial for further identification.

Evidence Requirements for Prioritization and Decision-making: Scientific and Regulatory Considerations

The gated-assessment design of the MOA-based Master Trial provides a decision point for the safety and PK at Gate 1, for predefined disease-specific therapeutic-effect criteria for early efficacy evaluation at Gate 2, and for an additional efficacy assessment at Gate 3. A successful Gate 3 assessment guides the advancement of molecules into late-stage pediatric development.

The selection of molecules and pediatric tumor types for confirmatory trials will be based on the totality of early-phase data observed in the trial (PK, safety, and efficacy) and other prioritization considerations, such as the unmet medical need, disease prevalence, line of treatment, potential combination partners, development status in pediatrics of other drugs in the same class, and operational feasibility. This will ensure the preservation of rare and pediatric patients to receive the most promising therapies.

The proposed MOA-based Master Trial approach fulfills the intent of the existing pediatric regulations in the United States and European Union by expanding the scope of pediatric investigations to include tumor types for which there are no adult counterparts or pediatric obligations, by increasing the number of evaluated patients across a range of pediatric ages, and by providing a clinically meaningful data package for pediatric labeling with respect to PK, dosing, tolerability, and safety. When appropriate, these data can be supplemented with Investigator Sponsored Trial (IST) data.

To ensure the feasibility of MOA-based or targeted approaches in pediatric oncology, greater regulatory flexibility should be exercised by health authorities in making molecule prioritization decisions for confirmatory trials, particularly as they apply to meeting regulatory obligations and qualifying for incentives. Although individual molecules may demonstrate efficacy trends in multiple tumor types, and although multiple molecules may demonstrate efficacy for the same tumor type, it may not be desirable or feasible to conduct multiple confirmatory trials (eg, an ongoing trial with a molecule of the same class or an ongoing trial in the same rare disease) in each rare tumor type identified in the Master Trial. Data collected in these early-phase studies, however, may still inform the label, and further study may be pursued through other avenues, such as investigator-initiated trials. These decisions will be made in consultation with the health authorities and other stakeholders to ensure a transparent decision-making process. For situations in which MOA-based pediatric studies are conducted through an agreed-upon Pediatric Study Plan, Written Request (US), and/or Pediatric Investigation Plan (EU), the regulatory requirement for multiple pivotal trials per molecule is likely to discourage sponsors from voluntarily pursuing pediatric drug development.

There may also be situations in which the tumor type prioritized for a molecule for a confirmatory study (based on the totality of the data and the feasibility) is not the specific indication that triggered a pediatric obligation on the basis of the planned marketing application in adults. In such cases, it is desirable that health authorities exert flexibility in applying the spirit of pediatric regulations and thus

allow the pediatric oncology community to preserve and match rare pediatric patients to the most promising therapies.

Furthermore, a molecule prioritization decision-making process needs to be defined, and an independent and transparent multistakeholder decision-making body must be established to facilitate these decisions. An FDA and EMA guidance that can outline a prioritization schema for the selection of molecules for advancement into late-stage clinical evaluation and for the fulfillment of regulatory obligations and qualification for obtaining incentives will help alleviate some of the concerns that industry may have when considering multisponsor master trial collaborations for pediatric patients.

Conclusion and Future Directions

MOA- or target-based drug development has largely benefited adult oncology patients. Children with cancer also need timely access to new and more effective therapeutic options in pace with the latest advances in science. Because the rarity of pediatric patients with cancer can impact the feasibility of running trials, it is essential that innovative clinical trial approaches, including master protocols, be considered to address the competition between companies to recruit patients for these studies.

The proposed Master Trial aims to investigate several molecules across a range of pediatric tumor types based on the MOA or target of the molecules. The MOA approach ensures a solid scientific rationale based on tumor biology and molecular mechanism established in the literature and, when possible, using relevant in vitro and in vivo nonclinical models. This enlarges the scope of pediatric investigations that are currently narrowly defined within the existing legislations that mandate investigations only for diseases in children that also exist in adults. The Master Trial includes treatment allocation rules and provides a gated assessment of molecules for safety and efficacy based on predefined prioritization criteria that may ultimately allow multiple sponsors to decide how to preserve and match rare pediatric patients with the best available therapies. The proposed Master Trial biomarker-enrichment strategy aims to maximize the potential benefit for each individual patient. In addition, the implementation of the Master Trial within established, expert pediatric oncology networks allows for the optimization of the duration of, and therefore resources required for, clinical trials, which in turn should incentivize sponsors to include additional drugs in this pediatric platform.

As the MOA-based Master Trial broadens the scope of early investigation in pediatric cancers, multistakeholder discussions are needed to identify a framework for prioritizing molecules into late-stage development in which definitive evidence may be generated to guide treatment decisions in the clinical setting. The standardization of MOA-based/targeted approaches in pediatric oncology, such as guidance regarding treatment allocation rules, biomarker and combination considerations, the use of tumor-type–specific end points, the use of historical controls versus a comparator arm, response criteria to guide gated development, and stopping rules for removing a molecule from a trial, would ensure consistent interpretation by health authorities and industry for widespread adoption and sustainability. This is particularly important for collaborative multisponsor master trials where legal barriers may be an added impediment to conducting such trials. The establishment of an independent, transparent multistakeholder decision-making body could facilitate these prioritization decisions in the context of multisponsor master trials.

In addition, it is important that the right balance be maintained between pediatric regulatory requirements and incentives to ensure the long-term feasibility of MOA-based/targeted approaches. Regulatory flexibility should be exercised to ensure that sponsors are able to meet regulatory obligations and qualify for incentives, even when a molecule is not selected to move forward to a pivotal study. Additional steps should be taken to incentivize MOA-based approaches in pediatric cancer. For example, incentive could be applied in the early drug-development process or applied in a staggered manner to encourage early participation in MOA-based approaches. Current incentive models only reward the sponsor once the pediatric program is completed. Because of the small number of pediatric cancer patients and the resources required for drug development, it may be difficult for small/start-up companies to volunteer for pediatric programs until a drug is already approved in adults.

In conclusion, greater cooperation and engagement between various stakeholders are essential to the success of master trial approaches in pediatric oncology, and global harmonization across national health authorities is needed to ensure consistency in planning and execution. Furthermore, the standardization of targeted approaches in pediatric oncology, particularly in the context of PREA and the BPCA, and pediatric regulations in other countries, such as the European Union, will ensure consistent interpretation by health authorities and industry for widespread adoption and sustainability.

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