WHITE PAPER

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ONCOLOGY | RARE DISEASE

Process and Regulatory Changes Making **Rare Cancer Drug Development More Efficient**

ABSTRACT

The study of rare cancers poses special challenges for drug developers, who often must draw on their experience in both oncology and rare disease. Careful consideration of clinical trial design and regulatory pathways can help increase the likelihood of success in rare oncology clinical trials.

Introduction

Researchers studying rare cancers must call on expertise in both oncology and rare disease. Current strategies and processes for general oncology drug development do not always apply to rare oncology, a field that today accounts for over 20 percent of new cancer diagnoses.

In 2014, more than 40 percent of U.S. Food and Drug Administration (FDA) orphan drug designations were for rare cancers.[1] With increasing international cooperation among big pharmaceutical companies, biotechnology companies, and academia, rare oncology research is becoming more efficient, and changes in the regulatory landscape are enabling sponsors to more quickly bring new therapeutic options to patients with rare cancers.

In this white paper, we examine how new processes and regulatory pathways are helping to accelerate development of novel therapies.

About rare oncology

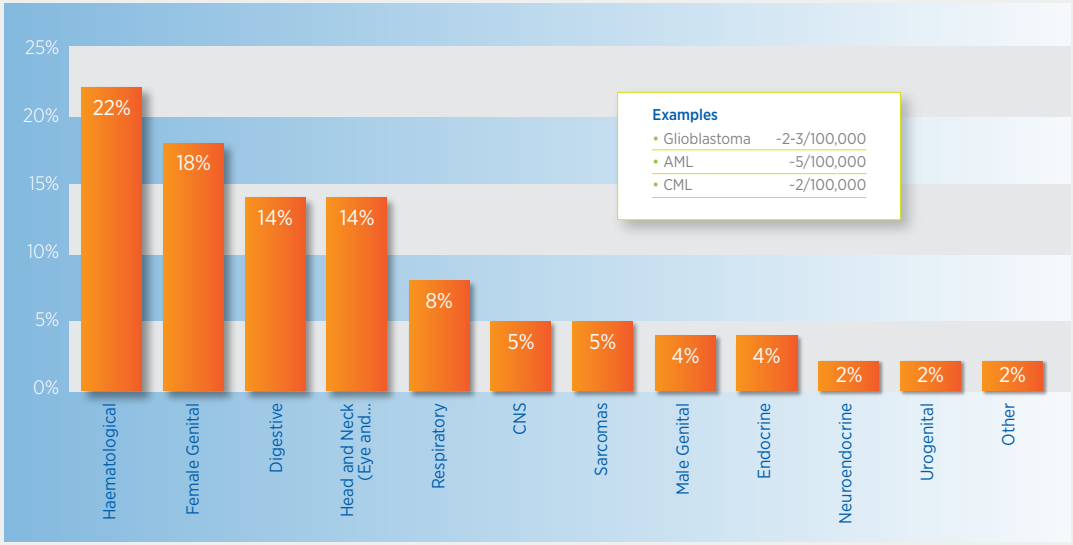
Rare oncology is defined as a disease with an incidence of less than six cases per 100,000 people.[2] Despite the relatively low incidence of each individual type, rare cancers as a whole account for 27 percent of all new cancer diagnoses in the U.S., and 22 percent of all new cancer diagnoses in the EU.[3] Over half a million rare cancers are diagnosed in the EU each year, and the incidence of all cases of rare oncology combined is 108 cases per 100,000 people. Currently, there are approximately 4.3 million people living with a rare cancer in the EU.[4]

With increasing international cooperation among big pharmaceutical companies, biotechnology companies, and academia, rare oncology research is becoming more efficient.

Rare cancers are also responsible for 20-30 percent of cancer deaths. Outcomes in rare cancers remain unsatisfactory with five-year overall survival rates of 47 percent, as compared to 65 percent for more commonly occurring cancers, making rare cancers a significant burden and a public health priority.[5]

Approximately 186 cancer types are considered rare.[6] Hematological malignancies account for approximately 22 percent of rare cancers, while female genital cancers account for approximately 18 percent (see Figure 1).

Figure 1. Rare cancer subtypes



Trial design considerations

Challenges associated with rare oncology studies include:

+ Small numbers of patients
+ Geographic dispersion
+ Ethical issues with placebo control and exposure to ineffective doses
+ No standard of care for comparison
+ Lack of defined biomarkers
+ Uncertain diagnosis

Utilizing traditional randomized trial design

Traditional randomized trial designs can be used for rare oncology studies, but may require collaboration or modification of study design. Collaborative study groups – including the International Rare Cancers Initiative, Pediatric Brain Tumor Consortium, and Alliance for Clinical Trials in Oncology (formerly CALGB) – allow for recruitment of required number of subjects for statistically powered studies. Endpoints other than the gold standard of overall survival – such as progression-free survival, overall tumor response, and time to progression – should be considered in order to shorten trial times. Studies with these endpoints may need to be followed by overall survival assessments where possible. In some circumstances, changes in biomarkers, once validated and accepted by competent authorities, may be used as trial endpoints.

The European Medicines Agency (EMA) Guideline on Clinical Trials in Small Populations provides useful guidance on methodological and statistical considerations relevant to rare oncology studies.[7] According to this guideline, there are no special methods for designing, carrying out, or analyzing clinical trials

in small populations, and, where possible, standard trial designs, comparators, and statistical analysis should be used. However, there is often a need for alternative approaches in order to conduct clinical trials in these rare indications. Examples of these are:

+ Finding a balance between statistical efficiency and the need for clinically relevant, interpretable results
+ Identifying appropriate control and comparator groups, where possible
+ Justifying surrogate endpoints by establishing a clear relationship to clinical efficacy to allow for evaluation of risks and benefits
+ Utilizing patient registries for insight into the natural history of the disease, or as a source for historical controls

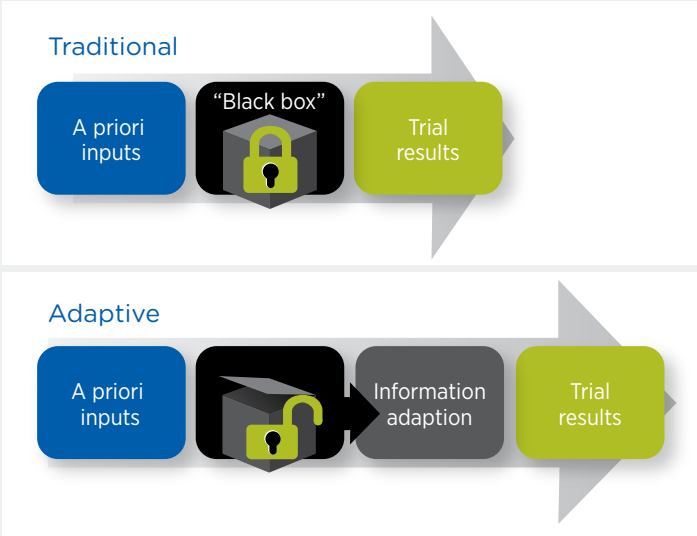
Sponsors are advised to obtain scientific advice regarding the use of alternative approaches as early as possible in the clinical trial development process.

Adaptive trial designs

To optimize rare cancer drug development, study designs should maximize the percentage of patients on effective treatment and minimize overall sample size to limit patient exposure to drugs or doses that have no effect. This can be achieved using adaptive design techniques and more rigorous oversight of patient eligibility to ensure that the right patients are enrolled to match the defined trial population. The latter will help ensure that every subject enrolled will be included in the population used to assess the primary endpoint.

Adaptive trial designs may help lower the risk of overall trial failure in rare oncology studies. Traditional design trials use only a priori inputs to obtain final trial results, and trial execution proceeds without change from first patient in (FPI) to last patient out (LPO), similar to a black box. Adaptive design trials include a prospectively planned opportunity for modification of one or more aspects of design and hypotheses based on analysis of accumulating (usually interim) data from subjects in the study without undermining study integrity and validity.[8]

Figure 2. Comparison of traditional and adaptive designs



The planned analysis of accumulating data in an adaptive design study informs potential prospectively planned modifications to trial execution, after a study is underway. Analysis of accumulating data is ideally done on data that is blinded with respect to the treatment arms. Plans for modification must be described prospectively in the protocol or statistical analysis plan (SAP) and for confirmatory trials (pivotal/registration trials) submitted to regulatory agencies for review. Of note, adaptive design does not include retrospective or ad hoc changes introduced after outcomes are known, and cannot be used in attempts to salvage failed trials.

The objective of adaptive design is to improve efficiency and increase the probability of showing effect. The advantages of adaptive-trial designs may include:

+ Improvement in study power
+ Reduction in sample size and total cost
+ Ability to treat more patients with more effective treatments
+ Ability to correctly identify efficacious drugs for subgroups of patients based on biomarker profiles
+ Shortened time for drug development

Adaptive designs can be utilized in both exploratory and confirmatory (pivotal) studies. For confirmatory trials using adaptive design, rigorous control of Type 1 error is essential.

Adaptations can include, but are not limited to:[8]

+ Eligibility criteria
+ Sample size adjustment
+ Drop/add/change treatment arms
+ Changes to the SAP or hypotheses
+ Endpoint changes, including changes in the primary endpoint (timepoint, unitary to composite, component of composite) or selection and/or order of secondary endpoints
+ Study duration can be increased in order to reach the required number of events

Prospectively defined interim analyses for efficacy, futility, and sample-size adjustments are considered adaptive designs. In order to prevent bias, trial staff (e.g., investigators, sponsor, and CRO staff who are operationally involved in study execution) must remain blinded, and these analyses of unblinded data require independent review committees who operate with directions to maintain blinding of critical trial staff. Independent data monitoring committees then report their recommendations, without revealing results that may introduce bias, to decision makers (e.g., the sponsor, senior staff, or a steering committee) for actions on trial execution.

Figure 3. Examples of adaptive design

Modification of Inclusion Criteria	Sample Size Increase
Examine baseline characteristics of enrolled subjects without regard to treatment arm • Does not introduce bias • Enhances enrollment • Deletes non-critical eligibility criteria • Expected population is not being enrolled –> Modify eligibility criteria	Information from the trial provides evidence that the study is underpowered • Blinded interim analysis of aggregate data • Event rate is well below the initial assumption – Sample size increase can maintain the power – Study duration can be increased to reach the additional endpoints • More risk if estimate is taken earlier in the study with fewer events • Decreasing sample size is not advisable • Sample size adjustment using blinded data in general should be considered for most studies

Figure 4. Pros and cons of adaptive designs

PRO	CON
Efficiency (patients, duration, money)	Complexity
May be shorter duration	Unknown duration, possibly longer
More likely to succeed	Results may be harder to interpret
Fail quickly	Harder to conduct
Patient protection	Potential operational bias
Flexibility	Not as flexible

Adaptive design in exploratory dose-escalation studies

Exploratory dose-escalation studies have less impact on regulatory approval as they do not rigorously control for Type 1 error and may be designed to allow for multiple changes throughout execution. In traditional study designs, the most common dose-escalation design is the rule-based "3+3 design." In this design, three patients are initially enrolled into a given dose cohort. If no dose-limiting toxicity (DLT) is observed in any of these subjects, additional subjects are enrolled into the next higher dose cohort. If one subject develops a DLT at a specific dose, an additional three subjects are enrolled into that same dose cohort. Development of DLTs in more than one of six subjects in a specific dose cohort suggests that the maximum tolerated dose (MTD) has been exceeded, and further dose escalation is not pursued.

Adaptive designs provide opportunities to probe the dose/toxicity relationship more efficiently than the standard 3+3 design. The continuous reassessment method (CRM) is an adaptive design in Phase I dose-finding studies that is increasingly used to estimate the MTD and define the recommended Phase II dose for proof of concept. In the CRM, dose determination and dose escalation is performed using data from each patient as that patient is treated. The dose-toxicity relationship is re-estimated after each patient outcome is observed, and the next patient is given the dose that is the current estimate of the MTD.[9]

Compared to the traditional 3+3 design, CRM:

+ Is less likely to underestimate MTD
+ Requires fewer patients
+ Results in a lower average number of DLTs

Seamless adaptive designs

In recent years, seamless adaptive clinical trials have gained popularity for reducing the projected time needed to complete the drug development process. A seamless trial, also called a combined-phase study, is an adaptive trial where the phases are separated by interim analyses, effectively combining two trials into a half trial that evaluates both toxicity and efficacy of drug combinations in a single trial. The first stage is a dose-ranging study based on toxicity, with the objective of finding the recommended dose(s) for initial proof of concept (Phase II). This recommended dose(s) is then used in the second stage to assess efficacy (initial POC).

Roles of study committees

Study committees play defined roles and interact with each other in the conduct of clinical trials, and may have expanded roles with an adaptive design trial. Sponsors and sponsor-defined independent oversight committees should keep in mind that study decisions should be made based on analysis on blinded data whenever possible. In addition, blinding of study personnel – study execution staff, investigators, monitors, sponsor staff involved in trial execution, study decision makers, and others – must be rigorously maintained to prevent basis.

Independent data monitoring committees (IDMCs) will often not maintain the blind. Their role is to assess safety signals/issues throughout the course of the trial. When the IDMC is charged with data safety and monitoring (DSM), their role in protecting subjects takes precedence. The IDMC may also be charged with interpreting interim analyses or determining adaptations. IDMCs typically work most effectively when an unblinded statistician with adaptive design knowledge is involved.

Steering committees should remain blinded. The steering committee may be an independent, third-party committee or a group of individuals from within the sponsors with the responsibility of making final decisions on changes to the trial execution. Their decisions should be based on recommendations from the independent data monitoring committees.

Institutional review boards are charged with subject protection. Advance planning is advised in order to minimize delays in IRB approval of adaptations.

Optimizing the trial population

More rigorous oversight of patient eligibility will help to ensure that the defined trial population is enrolled. Real-time monitoring of eligibility can:

+ Avoid ineligible patients, which can reduce power and increase cost
+ Improve the quality of the overall dataset
+ Avoid exposure of new molecules to patients who are unlikely to benefit

In addition to standard criteria, real-time monitoring of eligibility in oncology studies may include:

+ Ensuring appropriate imaging studies were performed properly and within the defined time window
+ Confirming tumor marker results
+ Assessing concomitant medications to exclude protocol-defined excluded drugs/therapies
+ Confirming that the correct histological diagnosis has been determined

Endpoints in rare oncology trials

Overall survival (OS) is the gold standard in oncology trials, but this is not always feasible as newer more effective therapies result in longer progression-free survival periods, and multiple lines of therapy are becoming available for many diseases. OS is universally accepted as a direct measurement of benefit, and is defined as the time from randomization until death from any cause. While OS is precise, easy to evaluate, and free from assessment bias, prolonged follow-up may be required to achieve mature data. Consequently, surrogate endpoints may be acceptable by health authorities for drug approvals.

Acceptable surrogate endpoints for OS are usually derived from evaluation of tumor assessments, including:

+ Progression-free survival (PFS)
+ Event-free survival (EFS)
+ Disease-free survival (DFS)

Payers and health resource policy makers are increasingly requiring demonstration of quality-adjusted survival benefits.

+ Relapse-free survival (RFS)
+ Objective response rate (ORR) to include complete responses, partial responses, or stable disease
+ Time to progression (TTP)
+ Time to treatment failure (TTF)

Often, endpoints require an evaluation of potential for bias or uncertainty when there may be operator variability such as interpretation of imaging studies. If critical for determination of primary endpoints, these assessments are best verified by independent central reviewers who are blinded to study treatments. To further limit bias, ideally target lesions are assessed at baseline, rather than retrospectively.

In some circumstances, symptomatic improvement may also be used as surrogate endpoints. However, to be used as primary endpoints to support cancer drug approval, agreement with health authorities should be reached a priori and symptoms of drug toxicity should be clearly distinguishable from those that are disease- or tumor-related. The rationale for use of symptomatic improvement includes the fact that there is typically a delay between tumor progression and the onset of cancer symptoms.

In addition, collecting information beyond survival is becoming more important. Payers and health resource policy makers are increasingly requiring demonstration of quality-adjusted survival benefits. Sponsors should keep in mind that health-related quality of life (HRQL) assessments are not suitable as primary efficacy endpoints in oncology, as differences in HRQL could represent a favorable safety profile between two treatments without associated survival benefit when confirmatory studies are conducted. Instead, such measures can be used to provide quality adjustment to survival endpoints, particularly in studies where survival time improvements are significant but small.

Biomarkers

Biomarkers are increasingly utilized as tools to help identify the patient population most likely to derive a benefit from the new therapeutic. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses (pharmacodynamics) to a therapeutic intervention. In rare circumstances after validation, biomarkers may be used to assess efficacy (e.g., in rare oncology BCR-ABL transcripts in chronic myelogenous leukemia; in infectious disease HIV viral load in HIV infection; blood pressure for hypertension; low density lipoprotein for atherosclerotic cardiovascular disease; or hemoglobin A1C for diabetes mellitus). Instead, most biomarkers are used to guide drug development, and not as a basis for regulatory approval. Biomarkers that are tumor markers may be accepted as part of a composite endpoint.

Biomarkers can be used for:

+ Identifying sub-groups based upon our knowledge of mechanism of action (MoA)
+ Enrichment of trial populations with patients most likely to benefit
+ Predictors of disease progression or response to therapy
+ When validated, as surrogate markers of efficacy

Health authorities may require that a companion diagnostic that assesses a relevant biomarker be developed in parallel and approved concurrently with a new drug. The diagnostic test is used to define patients for whom the drug is indicated.

Less than one in 1000 published biomarkers have clinical utility.

Figure 5. Examples of biomarkers in oncology

Biomarker	Drug	Drug Action	(Survival Benefit)
ALK	Crizotinib	Tyrosine kinase inhibitor of ALK	Lung cancer
BRAF (V600E)	Vemurafenib	Small molecule inhibitor of BRAF (V600E) kinase	Melanoma
CTLA-4	Ipilimumab	Monoclonal antibody directed against CTLA-4, enhancing T-cell activation	Melanoma
EGFR	Cetuximab	Recombinant, chimeric, monoclonal antibody directed against EGFR	Colorectal cancer, SCCHN
	Erlotinib	Reversible tyrosine kinase inhibitor of EGFR	Lung cancer, pancreatic cancer
KIT	Imatinib	Tyrosine kinase inhibitor of c-kit	GIST
MEK	Trametinib	MEK1/2 inhibitor	Melanoma
PD1	Pembrolizumab	Checkpoint inhibition	Multiple

Regulatory pathways to approval

Both the EMA and the FDA have put programs in place to expedite review and approval of investigative drugs designed to address an unmet need in the treatment of a serious condition – such as a rare cancer – with the goal of getting treatments to market faster for the people who need them. In some circumstances, this may also include a commitment to closer involvement with the sponsor to guide development.

EMA opportunities

Development support is available through **PRIority MEdicines (PRIME)**, which applies to medicinal products that offer a major therapeutic advantage over existing therapies or benefit patients without treatment options.[10] PRIME provides reinforced scientific and regulatory support, with the objective of improving early development plans. To be accepted for PRIME, a medicine must show potential to benefit patients with unmet medical needs based on early clinical data. PRIME status can reduce review time from 210 days to 150 days exclusive of clock-stops. Small- and medium-sized companies, as well as the academic sector, can apply for PRIME status earlier on the basis of compelling non-clinical data and tolerability data from clinical trials. To date, the majority of PRIME applications have been in oncology indications.

Expedited review pathways offered by the EMA include:

+ **Accelerated Assessment (AA)**, when a medicinal product is expected to be of major public health interest and can reduce review time from 210 days to 150 days exclusive of clock-stops.[11] Sponsors should request accelerated assessment at least two to three months before submitting the marketing authorization application, but the EMA strongly recommends that applicants request a pre-submission meeting six to seven months before submission.

- **Conditional Marketing Approval (CMA)**, applicable to medicinal products that address seriously debilitating or life-threatening diseases, emergency threats, or orphan indications, where the benefit of immediate availability to public health outweighs the risk that additional data are still required.[12] CMAs require post-marketing trials to confirm the expected benefit of the treatment. CMAs are valid for one year at a time and must be renewed annually until full approval is granted. Failure to comply with post-marketing requirements can result in withdrawal of the CMA.
- **Exceptional Circumstances (EC)**, when applicants are unable to provide comprehensive clinical data due to rarity of the disease, the present state of scientific knowledge, and/or ethical constraints.[13] Applicants must introduce specific procedures to monitor safety, and marketing approval is valid for five years, but requires Committee for Medicinal Products for Human Use (CHMP) review of risk/benefit on an annual basis. Of note, orphan drugs must still meet the additional criteria for orphan designation to be granted EC status.

FDA opportunities

Expedited programs offered by the FDA for serious conditions include:[14]

- **Fast Track Designation** to speed new drug development and review for drugs with the potential to address unmet medical needs by increasing FDA communication and enabling rolling review. It is the only expedited review program that includes review of non-clinical data to support the designation. Ideally, sponsors should request fast track designation no later than the pre-submission meeting. Of note, the designation may be rescinded if the drug no longer meets qualifying criteria.
- **Breakthrough Therapy Designation** to provide an opportunity for enhanced FDA guidance, including senior FDA staff when required, with the objective of achieving an efficient drug development program. It applies to drugs with preliminary clinical evidence demonstrating that the drug may result in substantial improvement on at least one clinically significant endpoint over available therapies. Ideally, sponsors should request breakthrough therapy designation no longer than the end of Phase II (EOP2) meeting. As with fast track designation, breakthrough therapy designation may be rescinded if the drug no longer meets qualifying criteria.

Figure 7. Pathways to approval in the EU[11,12,13]

	Development Support	Expedited Review Pathway	
	PRIority MEdicines (PRIME)	Accelerated assessment	Conditional marketing authorization
Qualifying criteria	Potential to benefit patients with unmet medical needs based on early clinical data	Addresses a major public health interest, new therapy or an improvement over an existing therapy	Orphan medicinal products and products for seriously debilitating diseases • Positive risk-benefit balance • Fulfilment of unmet medical need
Benefits	Reinforced scientific and regulatory support leading to better early development plans	Reduced MAA assessment time • Maximum 150 days (compared to 210 days)	Earlier authorization • Comprehensive data required post-authorization

Approval pathways include:

+ **Accelerated Approval** for early approval of a drug that offers a benefit over current treatments based on a surrogate endpoint, preliminary assessment of safety/efficacy, or other clinical measure that is reasonably likely to predict a clinical benefit. After accelerated approval is granted, the drug must undergo additional testing to confirm that benefit (post-marketing confirmatory trials).
+ **Priority Review**, which calls for review within six months instead of the standard ten months and is reserved for situations in which CDER has determined that the investigational drug could potentially provide a significant advance in medical care. Typically, priority review is requested with the original Biologics License Application (BLA), new drug application (NDA), or efficacy supplement.

In 2015, more than half of the novel drugs approved by the FDA – including four for rare cancers or rare genetic subsets of more common cancers – utilized one or more of these expedited review pathways.

Orphan designation

Orphan designation represents another opportunity for sponsors of rare oncology drugs, with slight differences in qualifying criteria and benefits between the U.S. and the EU. Orphan designation allows for financial benefits for the sponsor in the form of tax incentives, reduced or waived regulatory fees, and market exclusivity. An application for orphan designation may be submitted anytime in the product lifecycle.

Figure 8. Pathways to approval in the U.S[15]

	Development Support		Expedited Review Pathway
	Fast track designation	Breakthrough therapy designation	Accelerated approval
Qualifying criteria	Nonclinical/clinical data show potential unmet medical need	Preliminary clinical evidence suggests substantial improvement on a clinically significant endpoint(s) over available therapies	May provide a meaningful advantage over available therapies
Benefits	Actions to expedite development and review	Intensive guidance on efficient drug development	Initial approval based on an effect on a surrogate endpoint; confirmatory trial should ideally be enrolled prior to product approval
When	With IND or after; ideally, no later than the pre-BLA or pre-NDA meeting	With IND or after; ideally, no later than the end-of-phase 2 meeting	During development, supporting, for example, the use of the planned endpoint as a basis for approval and discussing the confirmatory trials, which should usually be already underway at the time of approval

Figure 9. Orphan designation in the U.S. and the EU

Feature	U.S.	Europe
Qualifying criteria	• Affects < 200,000 in U.S. • Costs development not commercially viable	• Prevalence in EU ≤ 5 in 100,000 • Costs development not commercially viable
Benefits	• Exclusivity • Tax credits • PDUFA fee exemption • Grants • Development advice	• Protocol assistance • Market exclusivity / SPC • Fee reductions
When to submit	Any time in product life-cycle	Any time in product life-cycle

Expanded access planning

Development plans should encompass expanded access to bridge the gap between clinical trials and market approval. The FDA defines expanded access as the use of an investigational drug prior to marketing authorization when the primary purpose is to diagnose, monitor, or treat a patient, rather than to obtain the kind of information about that drug that is generally derived from clinical trials.[16]

Providing expanded access should not draw patients who might otherwise participate in trials from clinical investigation. A sponsor or a physician may submit a protocol intended to provide widespread access to an investigational product for single or multiple patients. For single patients, the treating physician typically submits an individual investigational new drug (IND) request cross referencing (with permission) the manufacturer's IND application. For multiple patients, expanded access may be provided by the manufacturer or a qualified physician under protocol. Most often this is accomplished by the manufacturer as sponsor with the protocol conducted under an existing IND. In both scenarios, the FDA will permit the investigational product to be made available under a treatment IND if the following criteria are met:[17]

+ The investigational product is intended for use in the diagnosis, monitoring, or treatment of a serious or immediately life-threatening disease or condition
+ There is no comparable or satisfactory alternative therapy available to diagnose, monitor, or treat that stage of disease or condition in the relevant patient population
+ The investigational product is being studied in a controlled clinical trial for the same use, under an IND or all clinical trials necessary for approval of that use have been completed
+ The sponsor of the controlled clinical trials is actively pursuing, with due diligence, marketing approval, for the same use

- If the investigational product is being studied in a controlled clinical trial, under an IND, providing the investigational product under a treatment IND will not interfere with the enrollment in the ongoing clinical investigation(s)
- In the case of serious diseases, there is sufficient evidence of safety and effectiveness to support the use for the indication under the treatment IND
- In the case of immediately life-threatening diseases, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational product may be effective for its intended use and would not expose patients to an unreasonable and significant risk of illness or injury

In the EU, the EMA designates expanded access, referred to as Compassionate Use, as a responsibility of the Member States (MS), but the MS can ask for an opinion on the program from the CHMP if the program is being carried out in more than one MS.

Conclusion

Rare oncology clinical trials represent both an opportunity and a challenge for sponsors of rare cancer therapies. Having a better understanding of the drug development process – from optimizing trial design and selecting appropriate endpoints to providing rigorous oversight of patient eligibility and pursuing the appropriate regulatory pathways – can help sponsors expedite delivery of more safe, effective treatment options to patients with rare cancers.

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