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Whitepaper

Considerations for Developing Oncology Rare Disease Medicines

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Summary

Abstract

Rare cancers in oncology are an area of significant unmet need but are challenging to address due to their infrequent occurrence and unique characteristics. Addressing these challenges requires a multifaceted and collaborative approach. Development of targeted therapies, efficient clinical trial design, access to medicines and optimised regulatory processes are essential for advancing treatment options for rare cancers and improving patient care. This whitepaper provides a comprehensive overview of considerations for industry stakeholders, including the opportunities and support available for small and medium-sized enterprises (SMEs).

Introduction

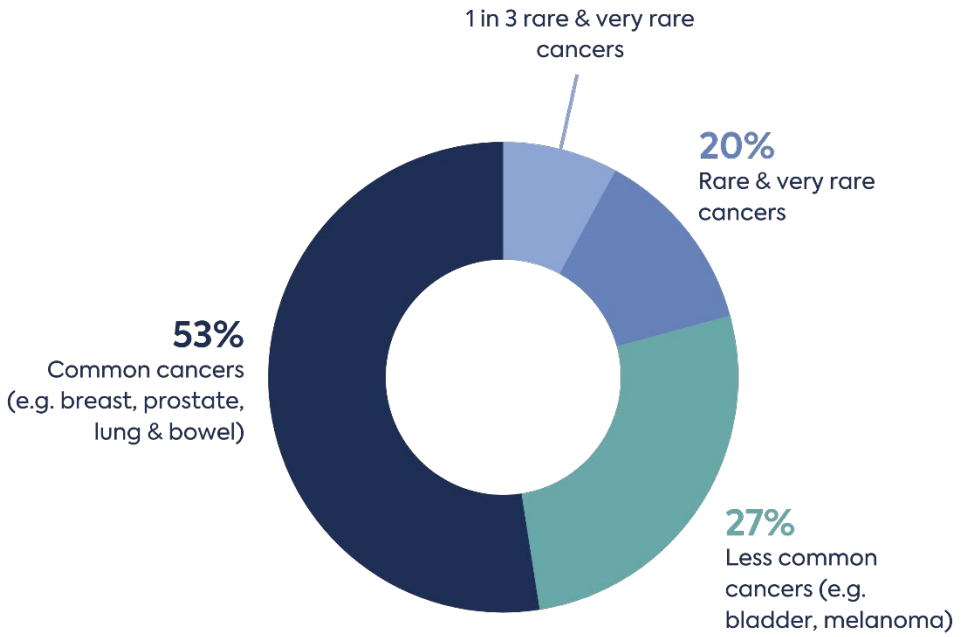
Rare diseases in oncology present a significant challenge due to their infrequent occurrence. They often exhibit unique biological characteristics, making accurate diagnosis and treatment particularly difficult.

This whitepaper aims to uncover the complexities of drug development for rare cancer medicines, highlighting the urgent need for specialised medications and the obstacles faced in clinical trials and research. By exploring recent drug approvals, innovative and realistic clinical trial designs, and streamlined regulatory pathways, this paper aims to provide a comprehensive roadmap to understand and address these challenges. Readers will gain insights into the critical importance of access to medicines in the rare cancer development space, the impact of pharmaceutical innovation, and the collaborative efforts needed to improve patient outcomes in this field.

For small and medium-sized enterprises (SMEs), this whitepaper will highlight the opportunities and support available for developing treatments for rare diseases in oncology and navigating the complex landscape of drug development to bring innovative therapies to market.

Rare Oncology Diseases: Diagnosis, Treatment, and Challenges

Rare cancers are malignancies that occur infrequently in the population, with an incidence defined by the Surveillance of Rare Cancers in Europe (RARECARE) project of fewer than 6 in 100,000 people annually (Gatta G, 2011). Five-year relative survival is on average worse for rare cancers than common cancers in the EU. Rare cancers also often exhibit unique biological and clinical characteristics, and occur only in specific subgroups of the population, setting them apart from more common types of cancer. Examples of such cancers include various types of sarcomas, certain brain tumours, and cancers of the salivary glands, among others. Their rarity presents unique challenges for diagnosis, treatment, and research due to limited clinical expertise, fewer options for clinical trials, and a scarcity of targeted therapies.



(Source: www.macmillan.org.uk)

One of the significant challenges in rare disease drug development is the difficulty in accumulating sufficient clinical experience and knowledge to provide proof of concept. Due to their low prevalence, healthcare providers may encounter these cancers infrequently, leading to potential delays in diagnosis and less familiarity with optimal treatment protocols. Additionally, the limited number of cases makes it difficult to conduct large-scale clinical trials within which the efficacy and safety of new treatments can be evaluated.

Importance of Access to Medicines

Patient access to medicines encompasses the ability for people to easily get the medications they need to treat their health conditions. It is not just about whether drugs are available; it's also about whether they're affordable and accessible. Access to medications for rare oncology diseases is crucial for several reasons:

- ***Unmet Medical Need:*** Patients with rare cancers often have limited treatment options, making access to effective therapies essential. Unlike more common cancers, where numerous treatment protocols and options may exist, rare cancers may lack approved therapies, leaving patients with few choices.
- ***Timely Treatment:*** These cancers can be particularly aggressive and challenging to treat, especially if diagnosis is delayed, necessitating prompt access to treatments to improve survival and quality of life. Delays in accessing effective treatments can have significant consequences for patients' prognoses.
- ***Healthcare Equity:*** Ensuring that all patients, regardless of the rarity of their condition, have access to the best possible care is a fundamental principle of healthcare equity. Patients should not be disadvantaged because of the scarcity of their condition.
- ***Pharmaceutical Innovation, Research, and Development:*** The development and availability of treatments for rare cancers can drive advancements in medical research and lead to new therapeutic breakthroughs. Research can also provide insights that may be applicable to more common types of cancer and other diseases. By ensuring access to medications and providing incentives for developing treatments, pharmaceutical companies and researchers are encouraged to invest in this area, despite the high costs and potential for limited financial return.

The ***Early Access to Medicines Scheme (EAMS)*** allows patients with life-threatening or seriously debilitating conditions to gain access to promising medicines before they receive marketing authorisation. EAMS provides scientific opinions on the benefit-risk balance of these medicines, ensuring that patients can benefit from them while further evidence is generated.

The following sections provide an overview of considerations for the development of medicines for treatment of rare cancers.

Exploring Clinical Trial Feasibility in Rare Oncology Diseases

Conducting clinical trial feasibility studies is one of the initial and essential steps in the clinical development process. These studies help evaluate patient availability in specific regions, which is crucial before starting a rare disease clinical trial. They also examine the availability of investigators and assess the country's potential for conducting the trial, and considering various other factors involved in the successful execution of a clinical trial.

By performing a thorough clinical trial feasibility assessment, it is possible to anticipate potential challenges in patient recruitment and prepare strategies to address these issues effectively.

Protocol Design

Clinical trial designs for orphan drugs, compared to non-orphan drugs, differ significantly and there is an even greater emphasis on patient centricity. When designing protocols, several key factors should be considered:

1. ***Trial Designs:*** Adaptive trial designs use accumulating data to modify trial aspects and are increasingly efficient, informative and more ethical for studying rare diseases with fewer participants. These designs maintain the validity and integrity of the trial while allowing for necessary adjustments based on ongoing results (Pallmann, 2018).

2. ***Meaningful Endpoints:*** Endpoints should be based not only on therapeutic efficacy but also on what is most meaningful to patients, such as impact to quality of life.

3. ***Minimising Patient Burden:*** Choose designs that limit patient burden and support patient retention without compromising data quality. Consider factors like travel, accommodation, special needs, and patient comfort. Designing protocols with minimal visit requirements, providing travel support, and using site-less or virtual site approaches, including video calls, can alleviate patient stress. For example, in-home Nurse Visits allow procedures like blood draws and infusions to be conducted at the patient's home to reduce travel burden.

4. ***Caregiver Involvement:*** In many rare disease trials, patients are children, and their caregivers are responsible for collecting data to support evaluation of primary and secondary endpoints. This necessitates additional resources to train caregivers on accurate and objective data collection.

5. ***Experienced Clinical Research Centres:*** Select centres with experience in treating the specific rare disease and conducting related clinical trials to ensure efficient trial conduct.

6. ***Dose-Response Challenges:*** Establishing a dose-response relationship in rare diseases is difficult, especially in paediatric populations, due to small patient populations that limit extensive dose-ranging phase 2 studies. The FDA's Project Optimus aims to reform dose optimisation and dose selection methodologies in oncology drug development, focusing on selecting doses that not only maximise a drug's efficacy but also ensure its safety and tolerability.

7. ***Physical Condition of Patients:*** Patients with uncommon diseases are often in poor physical condition, which may limit the number and type of procedures that can be performed.

8. ***Patient Population/Recruitment Focus:*** Identify the available patient population and use suitable recruitment strategies that match the specific needs. Spreading patients across multiple sites can increase financial burdens and the risk of trial failure due to logistical complexities and variations in site performance. To overcome these challenges, several methods could be considered, such as using technologies like the internet and social media, patient registries such as those supported by the National Institute for Health Research (NIHR) in the UK, and the European Reference Networks (ERNs) in the EU and conducting detailed clinical trial feasibility studies.

It is important to note that the EU operates under the Clinical Trials Regulation (CTR) (EU) No 536/2014, which came into force on 31 January 2022. This regulation replaced the older Clinical Trials Directive (2001/20/EC) and aims to streamline and harmonise the approval process across member states through the submission of a single application to run trials across multiple EU countries. From 31 January 2025, all clinical trials submitted in the EU must be compliant with CTR.

Agency Scientific Advice

Sponsors can ensure that their development plans align with regulatory requirements and expectations by seeking early input from regulatory bodies such as the EMA, MHRA and FDA. Engaging in scientific advice not only helps in refining the clinical trial design but also facilitates smoother regulatory procedures, via early identification of potential issues, reducing the likelihood of costly and time-consuming amendments later in the process.

Additionally, scientific advice can clarify the necessary documentation and evidence needed for regulatory submissions, enhancing the quality and completeness of subsequent marketing authorisation applications. This proactive approach can streamline the review process, expedite approval timelines, and increase the likelihood of successful market authorisation. Essentially, scientific advice bridges the gap between scientific innovation and regulatory compliance, ensuring that new therapies meet both clinical and regulatory standards efficiently.

The EMA offers scientific advice schemes to support the development of oncology medicines for rare diseases, ensuring that these treatments meet regulatory standards and address unmet medical needs. Examples of such schemes are:

- ***Scientific advice/Protocol Assistance*** provides comprehensive guidance on clinical and non-clinical development, including study design and regulatory requirements.
- ***PRIority MEdicines (PRIME)*** scheme, aimed at enhancing support for medicines that target unmet medical needs. PRIME offers early and proactive engagement with developers, fostering accelerated evaluation processes and timely access to promising therapies for patients.

In addition to traditional scientific advice meetings, the MHRA in the UK also provides targeted scientific advice schemes designed to accelerate the development and approval of innovative medicines. These include:

- ***The Innovative Licensing and Access Pathway (ILAP),*** an initiative that supports innovative treatments from the early stages of development through to patient access. ILAP offers a streamlined route to market by providing a roadmap for regulatory and development milestones, enhancing collaboration between stakeholders including a Target Development Profile (TDP) to align regulatory and reimbursement requirements early on.
- ***MHRA's Innovation Office*** offers a platform for developers to receive advice on regulatory requirements and development strategies for novel products, including those targeting rare oncological conditions. This service facilitates early dialogue and helps navigate the complexities of the regulatory landscape, ensuring that innovative therapies reach patients more efficiently.

The FDA also offer a variety of options to gain agency input on development programs, from **In**itial **T**argeted **E**ngagement for **R**egulatory **A**dvice on CDER and CBER Produ**ct**s (INTERACT) meetings for novel products and programs with unique challenges relating to Investigational New Drug applications, to end of phase meetings, to Type C meetings to discuss use of surrogate endpoints.
Fast Track and Breakthrough Therapy designation by FDA for drugs intended to treat serious conditions provide the opportunity for frequent interaction with the Agency in order to expedite product development.

Orphan Drug Designation

Orphan Drug Designation (ODD) is a special status granted by regulatory authorities to encourage the development of drugs for rare diseases. ODD is not specific to rare cancers.

To qualify for orphan designation in the EU or UK, a medicine must be intended for the treatment, prevention, or diagnosis of a life-threatening or chronically debilitating disease; the prevalence of the condition in the EU or UK must not exceed 5 in 10,000 people, or it must be unlikely that marketing the medicine would generate sufficient returns to justify the investment required for its development; and no satisfactory method of diagnosis, prevention, or treatment for the condition should already be authorised, or, if such a method exists, the new medicine must offer a significant benefit to those affected by the condition.

Similarly, the criteria for ODD in the US are that the medicine must be intended for the prevention, diagnosis, or treatment of a disease or condition affecting fewer than 200,000 persons, with a scientific rationale supporting the promise of efficacy and safety in that population. As an alternative to the prevalence criteria, designation can also be requested if the cost of developing the drug and making it available in the US for such diseases or conditions will exceed any potential profits from its sale within the first 7 years of marketing.

Once designated, orphan status offers several incentives to encourage development which include:

- ***Market Exclusivity:*** Orphan-designated drugs are granted a period of market exclusivity, lasting seven years in the U.S. and ten years in the EU and UK, during which no similar drug can be marketed for the same indication. This exclusivity period can be extended under certain conditions.
- ***Access to Centralised Procedures:*** In the EU, orphan designation grants access to centralised marketing authorisation procedures, making it easier and more efficient for SMEs to obtain approval for their drugs across all EU member states.

In addition, the EMA supports parallel orphan designation applications with regulatory authorities outside the EU particularly in the United States and Japan. However, these processes are independent, and sponsors should communicate with each authority individually when applying for orphan drug designation.

It is important to note that the EU Pharmaceutical legislation is undergoing a substantial revision, pending approval by the European Parliament and the Council of the European Union, with adoption expected by late 2024 or early 2025. This revision introduces proposals such as accelerated drug approval pathways, enhanced incentives for developing treatments for rare diseases, and strategies to mitigate medicine shortages across member states. These changes are positioned to significantly impact regulatory frameworks including orphan designation incentives, research priorities, and healthcare access the EU pharmaceutical sector.

SMEs

Small-medium enterprises (SMEs) can benefit from incentives offered by Regulatory agencies. These include fee reductions, deferrals or waivers for scientific advice services, and dedicated SME assistance programs or grant funding. These incentives aim to ease financial burdens, accelerate regulatory processes, and provide additional support to SMEs, promoting innovation and the development of new medicinal products by smaller companies.

For SMEs, obtaining orphan designation for a drug also brings several additional incentives designed to support the development of treatments for rare diseases. These include:

- ***Fee Reductions and Waivers:*** SMEs may receive substantial reductions or complete waivers for various regulatory fees, including application fees for marketing authorisation/exemption from user fees, pre-authorisation inspection fees, and annual fees for maintaining the authorisation.
- ***Scientific Advice and Protocol Assistance:*** SMEs can benefit from free or significantly reduced-cost scientific advice and protocol assistance from regulatory authorities.
- ***Grants and Funding Opportunities:*** SMEs may have access to grants and other funding opportunities from public and private sources to support research and development activities for orphan drugs.
- ***Tax Credits:*** In the US, SMEs can benefit from tax credits for qualified clinical testing expenses related to orphan drug development, significantly reducing the financial burden of conducting clinical trials.
- ***Regulatory Assistance:*** SMEs may receive assistance with clinical trial design and subsequent acceptability of applications for expedited regulatory review processes, including priority review and accelerated approval in the US, with the aim of bringing the orphan drug to market more quickly.

These incentives collectively lower the barriers to approval and reduce the financial risks associated with developing treatments, making it more feasible for SMEs to bring innovative therapies to market.

SME collaborations with academic institutions, research organisations, and larger pharmaceutical companies can also help provide necessary resources and expertise, as well as access to relevant patient populations for clinical trials.

Considerations for Paediatric Development

The paediatric oncology space, although challenging, presents significant opportunities to improve patient outcomes; many rare cancers occur in children. Furthermore, an agreed plan for investigation of a medicine in the paediatric population (paediatric investigation plan; PIP) is required prior to validation of a marketing authorisation application for an adult oncology indication in the EU and UK, unless paediatric development has been waived by EMA or MHRA. A paediatric study plan (PSP) is also required to be submitted for agreement with FDA.
The PIP and PSP ensure that paediatric studies address the unique needs of children.

Benefits associated with completion of paediatric studies in the EU and US include market exclusivity or extended patent protection for companies conducting paediatric studies.

Considerations for Marketing Authorisation Application

The demand for expedited access to innovative oncology treatments, particularly for rare cancers, has led to increased utilisation of expedited marketing authorisation pathways. These regulatory frameworks aim to facilitate quicker patient access to promising therapies that fulfil an area of unmet medical need, while ensuring rigorous assessment of safety and efficacy.

For example, EU and UK conditional marketing authorisation, and US accelerated approval can be granted based on surrogate or intermediate endpoints, provided that the benefit-risk balance is positive, and the applicant commits to completing the necessary studies post-approval to confirm benefit and long-term safety. Exceptional authorisations, such as the EMA's exceptional circumstances and the UK's exceptional case arrangements, allow for approval when comprehensive data on the efficacy and safety under normal conditions of use is not available, because the condition to be treated is rare or because collection of full information is not possible or is unethical.

Additionally, collaborative initiatives like Project Orbis, a global partnership led by the US FDA and involving regulatory agencies from the UK, Canada, Australia, and others, is designed to streamline the approval process for oncology drugs by allowing simultaneous submission and review.

The Access Consortium is another collaborative effort not limited to oncology products, and includes regulatory bodies from Australia, Canada, Switzerland, Singapore, and the UK, working together to enhance the efficiency of drug approval processes and ensure high standards of evaluation.

These pathways and collaborative efforts are particularly beneficial, as they aim to provide a more predictable and expedited route to market, reduce the administrative burden, and facilitate access to multinational markets and patients simultaneously.

The support mechanisms and early dialogues offered within these frameworks can help SMEs optimise their development plans, manage resources more effectively, increase their chances of successful market entry, and ensure that patients with rare cancers receive timely and effective treatment options.

Innovative Oncology Rare-Drug Approvals

Over the past decade, several rare oncology drugs have received approval by the EMA, FDA & MHRA, reflecting advancements in precision medicine and targeted therapies.

One such example is blinatumomab (Blincyto®), approved by the FDA in 2014 and EMA in 2015 for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL). Blinatumomab is a bispecific T-cell engager (BiTE) antibody that binds to both T-cells and cancer cells, effectively directing the body's immune response to target and destroy malignant cells. The FDA granted blinatumomab an accelerated approval and the EMA granted a conditional approval based on preliminary evidence showing substantial improvement over existing therapies, with ongoing studies to validate clinical benefit.

Another notable approval is larotrectinib (Vitrakvi®), a groundbreaking therapy approved by both the FDA (2018) and EMA (2019) for tumours with NTRK gene fusions, regardless of the cancer's location in the body. Larotrectinib is a first-in-class TRK inhibitor that targets and blocks the activity of tropomyosin receptor kinases (TRK), proteins that drive cancer cell proliferation in tumours with NTRK fusions. This "tumour-agnostic" therapy received FDA accelerated approval due to its high response rate across different types of cancer, and conditional marketing authorisation by the EMA, contingent upon additional clinical trial data to confirm efficacy and safety.

In the UK, larotrectinib received pre-licence positive opinion under the Early Access to Medicines Scheme (EAMS) from the MHRA. This pathway provides scientific opinions on the benefit-risk balance of medicines and allows patients with life-threatening conditions early access to promising treatments pending full marketing authorisation, mirroring global efforts to expedite access to innovative therapies for urgent medical needs.

Similarly, selpercatinib (Retevmo®) gained significant interest with its 2020 FDA and EMA approvals for RET fusion-positive cancers, including non-small cell lung cancer (NSCLC) and medullary thyroid cancer (MTC). This RET inhibitor specifically targets genetic mutations and fusions within the RET gene, offering a targeted therapeutic approach. Accelerated FDA approval and conditional EMA authorisation recognised promising clinical trial outcomes, addressing critical unmet needs in RET-altered cancers.

These medicines exemplify the trend towards targeted and personalised medicine in oncology, offering new hope for patients with rare and difficult-to-treat cancers.

Conclusion

Addressing the challenges posed by rare diseases in oncology requires a multifaceted and collaborative approach. The development of targeted therapies, efficient clinical trial designs, and streamlined regulatory processes are essential for advancing treatment options in this area of significant unmet medical need. This white paper provides a comprehensive overview for industry stakeholders, outlining the challenges of drug development for rare cancers and considerations for clinical trial feasibility, protocol design, and regulatory strategy.

For industry professionals and SMEs, an understanding of these dynamics is crucial to effectively navigate the complexities of rare disease research and development. DLRC's expertise in regulatory affairs and clinical trial management positions us as a valuable partner, offering strategic guidance and operational support to ensure that innovative therapies reach patients efficiently and meet rigorous regulatory standards. By leveraging DLRC's specialised knowledge, companies can enhance their chances of successful market authorisation and make significant strides in improving patient outcomes for those with rare cancers.

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DLRC is an award-winning consultancy team of more than 80 highly qualified, experienced regulatory professionals operating from our offices in the UK, Germany, and US. With a deep commitment to excellence, we are dedicated to helping clients navigate the complex regulatory landscape of the life science industry. We develop and execute innovative phase-appropriate regulatory strategies, providing comprehensive support from early development to post-licensing activities for medicinal products and medical devices. Our team comprises consultant experts in nonclinical, CMC, clinical and MedTech from pharmaceutical, medical device and regulatory agency backgrounds. We have proudly served companies of all sizes and backgrounds in various regulatory jurisdictions.

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