Rapid Change, Real Promise: The Future of Rare Oncology Research

ABSTRACT

As our understanding of the genetic and molecular basis of cancer advances, rare oncology research is accelerating at an unprecedented pace. In fact, in 2014, more than 40 percent of U.S. Food and Drug Administration’s orphan drug designations were for rare cancers. Moreover, the trend toward increasing international cooperation among big pharma, biotech and academia is making rare oncology research more efficient than ever.

In this white paper, we provide insight on the major issues being raised in the rare oncology space today, including patient perspectives on rare cancer research, innovative trial designs, the regulatory landscape and pending legislation that may impact how studies are conducted.
About rare cancers

Rare cancers are generally classified among the larger group of rare diseases, defined in the U.S. as diseases that affect fewer than 200,000 people and in the European Union (EU) as diseases that affect less than one in 2,000. Given that prevalence is affected by mortality, the Surveillance of Rare Cancers in Europe (RARECARE) project has proposed a definition for rare cancers as those that have an incidence of less than 6 per 100,000 in the population. In the U.S., the de facto threshold for a rare cancer based on the literature is one with an incidence of less than 15 per 100,000 in the population. Using incidence rather than prevalence as a definition helps minimize the risk of under-representing the true impact and burden of rare cancers with high mortality rates.

Epidemiology

Approximately 186 cancer types are considered rare. 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. They are also responsible for 20-30 percent of cancer deaths. When looking at cancer incidence rates by age, the incidence of rare cancers significantly outpaces that of non-rare cancers in the pediatric population. And, survival rates for rare cancers are lower than those for non-rare cancers – 47 percent versus 65 percent – making rare cancers a significant burden and a public health priority.
Rare cancer types

Currently, rare cancers are primarily identified by tumor location, though the RARECARE project is discussing the possibility of grouping rare cancers into molecular “families.” With advancements in genomics and precision medicine, it is expected that a growing number of tumors will be categorized as rare cancers.

Rare cancers from a patient’s perspective

Patients and families affected by rare cancers face numerous challenges, beginning with a prolonged or delayed diagnosis process. Local pathologists may not recognize the tumor type and genetic testing may not be well characterized. Once the cancer has been diagnosed, patients and their families face additional obstacles:

- **Care coordination.** Finding a physician with experience in treating the rare cancer may require travel to a distant center of excellence, as well as coordination with the local care team. In addition, insurance companies may not be familiar with certain rare cancers and may be unwilling to pay for experimental treatments.

- **Lack of data.** Scarce or non-existent data on the natural history of the diseases makes it difficult to characterize disease progression and assess prognosis.

- **Limited treatment options.** There may be no approved treatments, let alone second-, third-, or fourth-line therapy options. Often, patients are treated with a “best guess” extrapolated from a cancer with a similar histology, or with the same mutation.

- **Sparse support.** Shared experience can help limit the stress associated with living with a rare cancer. However, due to the inherently small number of people living with a particular type of rare cancer, patients may not have access to support from others who are dealing with the same condition.
Even though information about their disease may be scarce, patients have access to a wealth of information about the clinical trial process and are demanding a voice. In 2014, Rare Cancers Europe published a consensus paper outlining patients’ perspectives on the status of rare oncology research in Europe, which is applicable to the rare cancer patient community at large. Patients and patient advocacy groups are calling for:

+ **Increased input** into the clinical research process
+ **Innovation in clinical research standards** for treatments for their cancers, such as:
  + Use of evidence gathered outside of randomized clinical trials
  + Use of adaptive designs
  + Use of biomarkers and surrogate endpoints
  + Streamlining of electronic records processes to facilitate greater data sharing
  + Consideration of options to permit patients and researchers to share data more freely with patient permission (i.e., “enduring consent”)
+ **Options to accept higher levels of risk** than other patient populations
+ **Support from industry and regulatory agencies** to recognize and address their needs

**Intersection between rare oncology and non-oncology rare disease research**

Often, rare oncology research has greater similarities to non-oncology rare disease research than it does to oncology studies of more common cancers. And, as oncology research has become more focused on the genetics of cancer, there has been increased emphasis on conducting research in smaller populations that exhibit certain genetic characteristics. As a result, considerations for how to conduct trials in these “rare” populations are becoming more and more important.

Many of the challenges associated with conducting rare oncology research overlap with those of rare disease research in general, including:

+ **Small, geographically-dispersed eligible patient population.** Utilizing or creating patient registries and providing logistical support can help to address this issue.
+ **Research- or indication-naïve sites and/or investigators.** This comes with the additional burden of training and increased oversight to ensure data integrity.
+ **Lack of natural history data to establish controls**
+ **Lack of defined biomarkers to measure disease activity**
+ **Lack of surrogate endpoints to define benefit or efficacy**
+ **Obstacles to patient retention.** Protocol design must take into account minimizing the clinical trial burden to the patient and the patient’s family.
However, there are also additional obstacles inherent in studying rare cancers:

- **Late or incorrect diagnosis** may delay or even preclude access to treatment or potentially beneficial clinical trials
- **Lack of local clinical expertise or access to a clinical trial site** may prevent a patient from participating in a study
- **Limited research experience** by the patient’s home/primary oncology team could inadvertently introduce protocol deviations or violations during the course of providing day-to-day care
- **Limited availability of tissue banks or registries** to support the development of research for a particular indication

**Applying rare disease best practices to rare oncology research**

When conducting rare oncology research, sponsors can leverage the following best practices learned from rare disease research:

- **Partnering with patient advocacy groups**. These partnerships are invaluable not only for pointing the way to where patients are currently being treated, but also for identifying potential investigators and spreading the word about the study through their social media outlets or postings on their websites. Patient advocacy groups can also provide insight into the unique challenges faced by their patient populations, and may be able to assist in the development of a patient-centric protocol that improves patient experience throughout clinical trial conduct.

- **Listening to the voice of the patient**. Another benefit of working with patient advocacy groups is gaining a better understanding of the patients’ contribution to the research process, while still respecting patient privacy. Aside from clinical endpoints, there may be quality-of-life issues for which the patients’ perspective is highly relevant. There may be a disconnect between what researchers believe is important to study participants and what patients actually hope to derive from treatment. As such, understanding patient values and preferences can be extremely illuminating.

- **Selecting the right sites**. Beyond having the experience and willingness to carry out research according to good clinical practice (GCP), sites must be open to dealing with the many logistical considerations that come with serving as a center for research that might attract patients who must travel significant distances to participate in the trial. Sites must be committed to going the extra mile to coordinate care and share updates with the patient’s primary physician. In addition to having a plan for recruiting and retaining patients, sites must also have defined pathways for managing these vulnerable patients every step of the way from identification to study close-out.

- **Focusing on site engagement**. Keeping a site motivated throughout the course of a clinical trial requires consistent effort, especially when patient enrollment is likely to be sporadic due to the rare nature of the cancer. Constant communication is the key to ensuring that sites are ready to go and well-trained on the protocol when a patient walks through the door. Proactively reaching out, inviting feedback and even creating mentor relationships for principal investigators or study coordinators with other more experienced sites can make a big difference.

**Rare oncology trial design considerations**

When working in rare oncology treatment development, just as in non-oncology rare disease research, every patient and every data point counts. By definition, clinical evidence is more difficult to build in rare cancers than in more frequent cancers. Fortunately, significant innovations in rare oncology research are helping sponsors preserve the potential of each data point, optimizing translation of clinical trial findings in a timely, but safe, way for patients.
### Adaptive trial designs

Increasingly, adaptive trial designs are being used to help ensure that every data point collected in a rare oncology trial is maximized. Adaptive design trials are studies that include a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (typically interim data) from subjects in the study. Analyses of the accumulated study data are performed at pre-planned time-points within the study, with or without formal statistical hypothesis testing.12

Recently, Miranta Antoniou and colleagues published a review in which they identified eight main types of adaptive design structures for biomarker-guided Phase II and Phase III studies:15

1. Adaptive signature design
2. Outcome-based adaptive randomization design
3. Adaptive threshold sample-enrichment design
4. Adaptive patient enrichment design
5. Adaptive parallel Simon two-stage design
6. Multi-arm multi-stage (MAMS) design
7. Stratified adaptive design
8. Tandem two-stage design

### Innovative approaches to trial design

A sampling of studies developed and discussed by the International Rare Cancers Initiative demonstrates some of the innovative approaches that have recently been used in the rare oncology space:14

- Accepting a greater type I error in salivary gland cancer
- Abandoning a trial early for lack of benefit in uterine leiomyosarcoma
- Testing only investigative treatments with early discontinuation for lack of activity in metastatic uveal melanoma
- Balancing scientific value and feasibility in high-grade undifferentiated uterine sarcoma
- Incorporating Bayesian elements to quantify resulting level of information in small bowel adenocarcinoma
- Utilizing multi-arm selection without assumption in Ewing sarcoma

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**Figure 3. Samples of adaptive design**13
Basket trials
Basket trial designs are becoming more and more common in oncology research, including rare cancer studies. Basket trials, such as the VE-BASKET trial of vemurafenib, test the effect of a single drug or drug combination on a specific mutation – independent of tumor histology – in a variety of cancer types ("baskets"), allowing researchers to analyze each cancer type individually, as well as to assess the impact of the drug or drug combination as a whole. Though only a small number of patients are enrolled in each arm, the trial can be expanded to enrich for a certain tumor type if a response signal is seen or a separate Phase II trial can be designed with the pilot data generated. Alternatively, arms may be deleted if a lack of preliminary response is seen. This approach makes it possible to combine what would have been multiple Phase II trials into a single study, greatly accelerating the development process, improving our understanding of different types of cancer and expediting the delivery of an effective treatment to the patients who need it.

Umbrella trials
Umbrella trial designs assess drug effectiveness on an individual tumor type by testing the impact of different drugs on different mutations in a single type of cancer. In this type of trial, patients are randomized based on the most prominent genetic mutation in their respective tumor and then treated with a number of medicines known to target that specific mutation. Given that identification is based on histology, this type of trial is less likely to be seen in rare oncology research, but it is not unheard of.

One example of an umbrella trial in rare oncology is the GBM AGILE study, which will enroll patients with glioblastoma multiforme (GBM), a rare cancer arising from astrocytes in the brain. GBM AGILE is being undertaken by a global coalition of more than 130 neurologists, neurosurgeons, statisticians, pathologists and other scientists who are participating in the design of a centralized master protocol. The adaptive design of GBM AGILE will utilize Bayesian statistics to incorporate information from patient experiences as the study progresses. In addition, the study design includes the evaluation and validation of biomarkers, as there are currently no validated biomarkers available for GBM research.
Impact of adaptive designs on clinical trials

A 2014 review in the Journal of Clinical Oncology analyzed adaptive Phase I oncology trials that used a statistical model to guide dose escalation to identify the maximum-tolerated dose (MTD), with the purpose of evaluating how adaptive designs work in practice. A total of 53 trials occurred between 2003 and 2013, all of which used the continuous reassessment method (CRM), whether it was CRM using escalation with overdose control or time-to-event CRM for late-onset toxicities.

These trials accrued, on average, 25-35 patients over a two-year period and tested five dose levels. The average dose-limiting toxicity (DLT) rate was 18 percent (much lower than the acceptable DLT rate of 26 percent). On average, 39 percent of patients were treated at the MTD and 74 percent were treated at either the MTD or an adjacent level (i.e., one level above or one level below). The authors concluded that this review confirmed the safety and generalizability of model-guided, adaptive dose-escalation designs and provided an approach for using, interpreting and understanding such designs to guide dose escalation in Phase I oncology trials.

When considering adaptive designs, it is important to consider the following questions:

+ Is the model-based, dose-escalation design safe, i.e., what is the DLT rate and the toxicity rate of the MTD?
+ Are patients being treated at sub-therapeutic levels, i.e., what percentage of patients is being treated at MTD or adjacent to MTD?
+ Does the trial design result in a longer trial duration?
+ Is the sample size too large?
+ Is the design flexible enough to deal with different schedules, patient populations or drug combinations?
+ Does the design recommend counterintuitive escalations? If so, reconsider and reassess.

Defining endpoints

Selection of endpoints differs significantly between solid tumors and hematological conditions. Most solid tumor cancer trials rely on the Response Evaluation Criteria in Solid Tumors (RECIST), whereas blood-based cancers rely on different measurements for capturing treatment-related changes and disease progression. This can add complexity to clinical trial design and conduct. While overall survival (OS) remains the gold standard for evaluating the effectiveness of cancer treatment, progression-free survival (PFS) is the most commonly-used surrogate endpoint for trials involving advanced cancers. Other progression-related surrogate endpoints include disease-free or event-free survival; response rate or objective response rate; and time to progression.

Keep in mind that it is important to take advantage of technological developments to measure survival and to provide greater specificity. For example, the 2011 biologics license application (BLA) submitted for brentuximab vedotin was the first to use the response criteria for lymphoma drugs set forth by the FDA in 2007, which included FDG-PET scans in the response assessments. The FDA considered PFS an acceptable endpoint to confirm clinical benefit because an OS endpoint would not likely occur within a reasonable timeframe. Brentuximab ultimately received approval for a subset of patients with Hodgkin lymphoma.

Selecting biomarkers

When defining endpoints, it is important to consider which biomarkers will be used to measure that endpoint. It is important to understand how biomarkers translate from the lab setting to the clinical research setting, and that translation may not always be straightforward. For example, the tumor-node-metastasis (TNM) staging system established in 1958 is useful when local therapies are the only ones available for cure. However, when looking at tumor grade, histological subtype or even age, the situation becomes more complicated, but also creates an opportunity for selection of therapy.
Certain molecular markers are better for dividing tumor types into subsets that act differently from each other. Many targeted agents, such as imatinib or cetuximab, are effective only if the respective molecular markers are sufficiently expressed. In breast cancer, estrogen receptor (ER) and HER2 status impact prognosis and treatment independently of TNM stage. ER positivity improves prognosis regardless of stage and makes the patient a candidate for treatment with a targeted hormonal agent such as tamoxifen.

Thus, sponsors should consider the following when selecting biomarkers:

- **Does the biomarker provide a quantitative response for determining predisposition to the cancer?**
- **What is the diagnosis – primary or metastatic?**
- **Does the biomarker provide information on the aggressiveness of the cancer?**
- **What does the pharmacokinetic/pharmacodynamic (PK/PD) profile look like?**
- **Does the biomarker measure treatment response?**
- **Does the biomarker offer value in predicting or monitoring recurrence?**

Surrogate biomarkers may offer greater efficiency if the surrogate endpoint can be obtained earlier, at less cost or with less variability than the clinical endpoint. In order for a surrogate biomarker to be useful, it must be:

- **Specific.** The biomarker should be involved in the process that causes the cancer.
- **Sensitive.** Changes in the biomarker should correlate with changes in the disease.
- **Measurable.** Levels of the biomarker should be high enough that they can be measured easily and reliably.
- **Accurate.** Levels or presence of the biomarker should readily distinguish among normal, cancerous and precancerous tissue.
- **Effective & Reproducible.** Effective treatment of the cancer should change the level of the biomarker. In addition, the level of the biomarker should not change spontaneously or in response to factors not related to the successful treatment of the cancer.

**Regulatory options for advancing agents for rare oncology indications**

Both the FDA and EMA 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, with the goal of getting treatments to market faster for the people who need them.

The FDA defines a serious condition as a disease or condition associated with morbidity that has substantial impact on day-to-day functioning.⁰²

**Expedited review pathways**

Expedited programs offered by the FDA for serious conditions include:⁰²

- **Fast Track** speeds 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** 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.

+ **Accelerated Approval** allows early approval of a drug that offers a benefit over current treatments based on a surrogate endpoint 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, 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 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.21

Expedited review programs offered by the EMA include:

+ **Accelerated Assessment (AA)** applies 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.22 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)** is 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.23 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)** apply 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.24 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.

+ **PRIority MEdicines (PRIME)**, effective as of March 2016, applies to medicinal products that offer a major therapeutic advantage over existing therapies or benefit patients without treatment options.25 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, are able to apply for PRIME status earlier on the basis of compelling non-clinical data and tolerability data from clinical trials.
Currently, there is significant momentum to further impact clinical research and accelerate the clinical trial and review process in the U.S. The 21st Century Cures Act in the House of Representatives and its companion bills in the Senate call for the FDA to establish guidance regarding the definition of a “precision drug”, a product targeted to treat patients with a specific genotype of a disease. This guidance would need to contain information to assist sponsors in the development of such a drug, including clinical studies.²⁶

Title II of this pending legislation in the House of Representatives seeks to build on the FDA’s 2012 launch of a Patient-Focused Drug Development Program and calls for the release of guidance on how companies can identify subsets of a disease for the purposes of advancing drug development. Such subsets may allow sponsors to market a drug to that subset and obtain orphan drug exclusivity. Title II also proposes meaningful incorporation of patient experience data into the regulatory decision-making process and broader use of innovative statistical methods in clinical protocols, including adaptive designs and Bayesian statistical methods.²⁶

Yet another section of the 21st Century Cures Act calls on the FDA to develop guidance based on the clinical experience of various products outside of clinical trials, including observational trials, product registries and therapeutic use. The legislation also outlines a “Streamlined Data Review Program”, which would enable an existing drug or biological to be reviewed for a new qualified indication based on the submission of qualified data summaries. Drugs would be eligible for a qualified indication if they are already approved for use in another indication and the new indication is a type of cancer.²⁶

Sections 2082-2083 of the 21st Century Cures Act calls for amendment of the FDA’s compassionate use policies to require any company whose drug is granted fast track, breakthrough or qualified infectious disease product (QIDP) designation to make an expanded access policy for compassionate use of the drug publicly available within 60 days of receiving that designation.²⁶

Conclusion

This is an exciting time to be in rare oncology research, as progressive regulatory policies, an increased awareness of – and sensitivity to – the patients’ perspective and innovative clinical trial designs promise to accelerate development and expedite review, enabling sponsors to more quickly bring new therapeutic options to patients with rare cancers.
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Juliet M. Moritz | Executive Director, Strategic Development, Oncology & General Medicine

Juliet Moritz has worked in clinical research for more than 25 years, and her extensive background covers the spectrum from single-site studies to large, multinational trials. She joined Premier Research in 2016 to specialize in rare diseases, supporting the strategic development of products that address unmet medical needs associated with rare and orphan afflictions.

Prior to joining Premier Research, Ms. Moritz was Associate Director of Global Project Management at PPD, overseeing infectious and respiratory disease research, and prior to that was Associate Director of Clinical Research at Knopp Biosciences. She has held senior positions at Wyeth (now Pfizer), Theravance and Medifacts International and began her career as a clinical research associate.

Ms. Moritz holds a Master of Public Health degree from the Drexel University School of Public Health and a bachelor’s degree in biology from the University of Pennsylvania.

Sachin Kulkarni | Executive Director, Strategic Development, Oncology & General Medicine

Sachin Kulkarni has over 14 years of experience in clinical research and project management. As an Executive Director, Strategic Development, Mr. Kulkarni is responsible for providing the strategic planning, coordination, and subject matter expertise for both projects and standalone consultative services. He oversees projects that span a broad therapeutic spectrum from oncology and rare disease to analgesia, GI disorders, etc.

Prior to Premier, Mr. Kulkarni worked at PPD Inc. as a Sr. Project Manager with a focus on oncology trials. Mr. Kulkarni has worked simultaneously on multiple Phase I studies/programs as a project manager. Being involved with hematology and oncology trials that range from single institution, single geographic region to multi-institution, global studies, he has a keen understanding of the study design and operational oversight of these trials.

Previously, Mr. Kulkarni worked at Fox Chase Cancer Center in Philadelphia, PA as a Project Manager. He holds a Master of Business Administration degree from the University of North Carolina at Chapel Hill and a Master’s degree in Pharmacy Administration from the University of the Sciences in Philadelphia.

About Premier Research

Premier Research is a leading clinical development service provider that helps highly innovative biotech and specialty pharma companies transform breakthrough ideas into reality. The company has a wealth of experience in the execution of global, regional and local clinical development programs with a special focus on addressing unmet needs in areas such as analgesia, CNS, oncology, pediatric and rare disease. Premier Research operates in 84 countries and employs 1,000 professionals, including a strong international network of clinical monitors and project managers, regulatory, data management, statistical, scientific, and medical experts. They are focused on smart study design for advanced medicines that allow life-changing treatments.