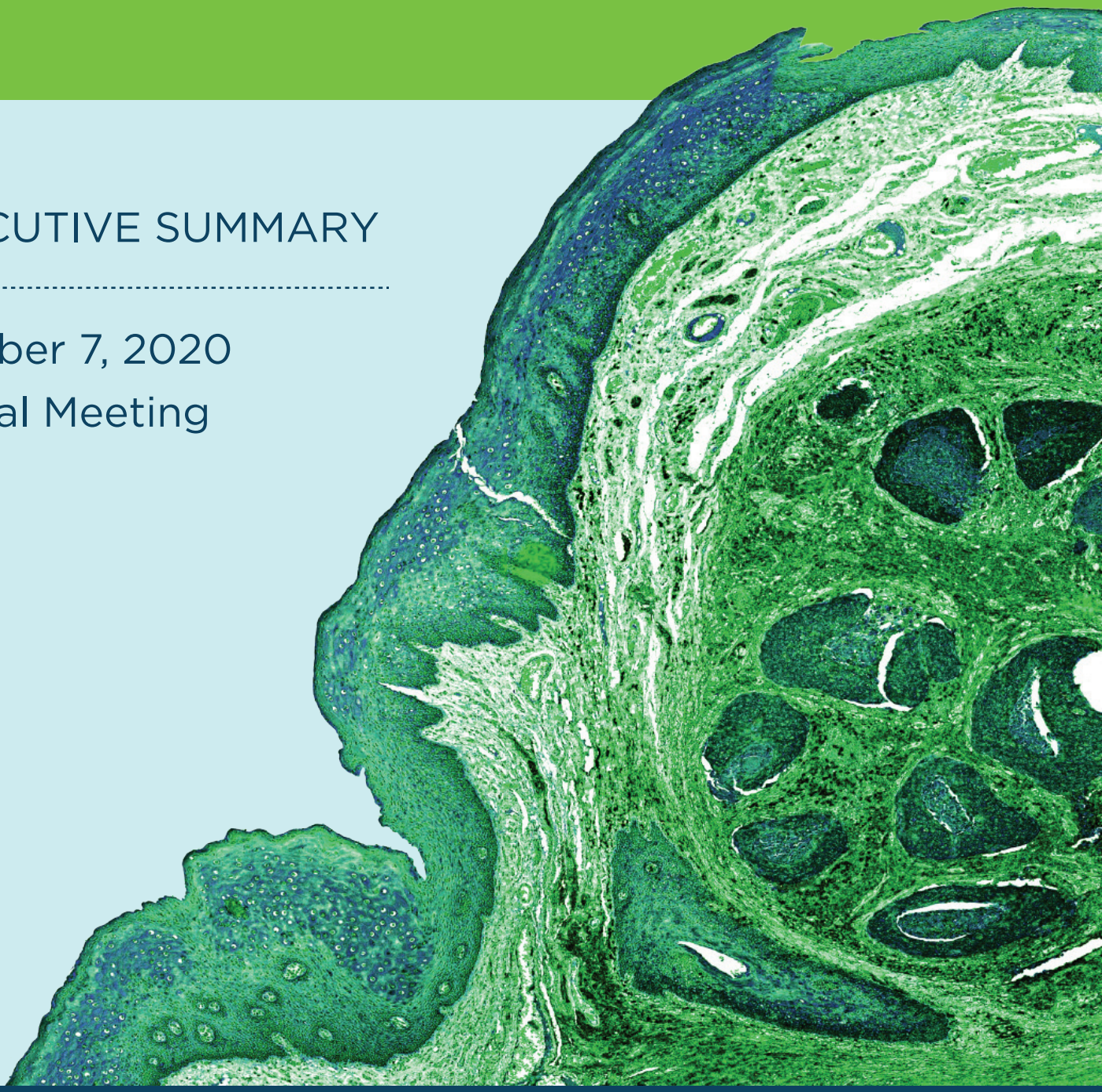
U.S. FOOD & DRUG ADMINISTRATION

Project Data Sphere®

FDA - PDS SYMPOSIUM IX

RARE CANCER REGISTRIES



EXECUTIVE SUMMARY

October 7, 2020

Virtual Meeting

Experts from the U.S. Food and Drug Administration (FDA), industry, and academia convened on October 7, 2020 for a virtual symposium on Rare Cancer Registries. The ambition for this symposium was captured in welcoming remarks by Julia Beaver, MD, Chief of Medical Oncology, Oncology Center of Excellence at the FDA. Our goal is,

> "To address critical questions in the field of rare cancer registries, with an ultimate goal to drive improvements in patient treatment, bringing safe and effective drugs to patients with rare malignancies in the most efficient and expeditious manner."

This was the ninth in a series of symposia co-sponsored by Project Data Sphere and the FDA since 2015 to address timely topics in biomedical research and drug development.

The speakers shared how registry data have been used to advance research and improve clinical care for rare cancers within their own disciplines, discussed best practices for registry construction and data application, addressed how to integrate diverse types of data to make rare cancer registry data even more valuable, and strategized how best to support data-sharing and generalizability. Throughout the presentations and discussions, collaboration, transparency, and long-term planning emerged as fundamental to the most effective use of this powerful research tool.

The importance of purpose and perseverance to achieving meaningful progress in rare disease was evidenced throughout the symposium, and was particularly resonant in the keynote presentation by David Fajgenbaum, MD, MBA, MSc, FCPP, Assistant Professor of Medicine, Translational Medicine & Human Genetics at the University of Pennsylvania, and the fireside chat with Loxo Oncology founder and Chief Executive Officer, Josh Bilenker, MD.

Dr. Fajgenbaum shared the inspiring story of his odyssey to a diagnosis of idiopathic multicentric Castleman disease (iMCD), his challenging treatment journey, and the decision to launch his own iMCD research program—which ultimately led him to discover a new therapeutic target in iMCD and a treatment that has provided him long-term remission. His parallel activities building a research community and advocacy organization have been highly effective in advancing care for this rare disease.

Dr. Bilenker spoke to Sean Khozin, MD, MPH, Vice President, Global Head of Data Strategy at Janssen Research & Development, about how he and his team at Loxo overcame tremendous obstacles to bring a tissue-agnostic, age-agnostic targeted treatment for rare solid tumors containing NTRK gene fusions to market, and how they had to change longstanding research & development and commercialization paradigms in the process.

Insights, opportunities, and priorities for rare cancer registries discussed in the symposium are described below.

Current and future opportunities to gain insight into rare cancers using registries

A registry is a "treasure trove," said Ting Yu, MD, MS, Medical Director at EMD Serono, and this enthusiasm was reflected by speakers throughout the symposium. Data from rare cancer registries could help chart the natural history of disease, reveal disease heterogeneity, identify possible prognostic factors or biomarkers, suggest therapeutic targets and treatments, give insight into treatment sequencing, and describe patients' experience of disease and treatment. As Michael Wong, MD, PhD, FRCPC, Professor, Department of Melanoma Medical Oncology, Division of Cancer Medicine at the University of Texas MD Anderson Cancer Center, pointed out,

> "these registries are not just hypothesis-testing, they can also be hypothesis-generating in a sense."

In the era of precision medicine, there is a trend for more and more rare cancer subtypes to be molecularly defined. Rare subtypes of common cancers present the same challenges as rare cancers. Speakers shared the expectation that registries will be a valuable source of data to help characterize rare subtypes of cancer and determine how best to treat them.

Registry data often drives standards of care in rare cancers. Gregory Reaman, MD, Associate Director, Pediatric Oncology, Oncology Center of Excellence at the FDA, shared an example in pleuropulmonary blastoma and David Miller, MD, medical oncologist at Massachusetts General Hospital, shared examples in Merkel cell carcinoma.

According to Dr. Miller,

> "For rare diseases, registry data is pivotal in how we practice."

Panelists described multiple current and potential uses of rare cancer registry data in clinical trial design. Martha Donoghue, MD, Pediatric Solid Tumors Scientific Liaison at the FDA described how the agency has used registry data to help inform the advice that FDA provides to sponsors, eg, to help define trial endpoints and to understand target effect sizes. She pointed to the value of registry data in providing a context in which to interpret available clinical trial data. Gregory Friberg, MD, Vice President Global Development, Therapeutic Area Head Heme/Onc & Bone at Amgen suggested that registry data could be used to inform more inclusive clinical trial design eg, by providing information about common concomitant medications. Conversely, he said the data could also help identify patient subpopulations for therapeutic development – those who are not being well-served with current therapies or those with the greatest opportunity for potential benefit, eg, based on biomarkers.

Although randomized controlled trials will continue to be the gold standard for clinical evidence, the speakers expected registry data and other sources of real world evidence to be increasingly important in rare cancers and rare cancer subtypes. As Zhen Su, MD, MBA, Senior Vice President, Head of US & Global Oncology Franchise at EMD Serono described it, oncology is at an "inflection point" in the use of registry data and other real world evidence to advance care for rare cancers and subtypes. The 2014 approval of blinatumomab and 2019 approval of palbociclib in rare cancer subtypes are some examples of the use of real world evidence to help support drug approvals.

The scope of data collection should be appropriate, meaningful, and not unduly onerous for contributors. Adequate demographic information should be collected so that comparability of the registry population to patient populations studied in other settings (eg, clinical trials) can be assessed.

Based on his experience, Dr. Miller recommended that a rare cancer registry should be prospectively designed to be adaptable to provide continuing value as knowledge about a disease matures. For example, the main objectives and applications of a rare cancer registry may evolve from characterizing disease presentation and natural history to defining best practices for clinical care to possibly even contributing support for a regulatory filing, eg, a label modification.

Be transparent and employ reasonable strategies to mitigate bias.

Possible sources of bias that limit generalizability are major concerns when analyzing any form of data, including registry data. Given the particular importance of registry data in clinical decision-making in rare cancers, transparency is critical. For example, how missing data are handled, what is known about potential sources of bias, and other quality measures should be detailed. The degree to which data elements are objectively vs subjectively determined should be clear.

In general, registry data collected from multiple institutions may be considered more generalizable than single-institution data. Similarly, data that reflect geographic and demographic diversity may have greater reliability.

The symposium speakers felt that ultimately it is incumbent on the end-user of registry data, whether it be a researcher or clinician, to critically evaluate registry data for possible sources of bias and to consider any findings in the context of clinical evidence from other data sources. If analyses from other data sources are confirmatory of the findings from registry data, this increases confidence in the reliability of the findings.

Be opportunistic and pragmatic in incorporating large-scale patient-level data.

Inclusion of the often complex information that is integral to work-up and monitoring, such as imaging, immunophenotyping, and genotyping, is an important ongoing operational challenge. Some of the challenges to integrating these data include the requirement for large amounts of storage, lack of standardization, and the need for quality control. A substantial amount of data may need to be manually extracted and/or converted from unstructured to structured data, and this curation is resource-intensive.

Registry design requires a strategic balancing of the imperative to collect as much data as possible and feasibility. A multiphase approach in which data are prioritized for integration into a rare cancer registry based on assessment of feasibility and clinical utility may be necessary. Standardization in initial data collection and improved data science tools will create efficiencies in the future.

Support broad access and interoperability.

The experts affirmed a strong commitment to the principle of broad access. They recognized that in practice, registries vary in the degree to which data are accessible for a number of reasons. Registries are

resource-intensive to develop and maintain, and the sponsoring entity may perceive limiting access as important to their ability to recoup value from investment. Corporate-sponsored registries created to comply with regulatory mandates may contain proprietary data. Tiered access with temporally phased data release is one possible solution; this is the approach used in the Merkel Cell Carcinoma Registry on the Project Data Sphere platform. As panel moderator, Dave Reese, MD, Executive Vice President of Research & Development at Amgen commented,

"It's a very interesting thought around a period of restricted access for those who have contributed data and sweat equity, then followed by open access — a way to sort of compromise and provide appropriate incentives."

Interoperability is an issue across systems used in medicine and registries are no exception. Achieving harmonization of data fields, terminology, and coding across registries is a complex challenge, but one that could yield tremendous scientific benefit and warrants pursuing.

What else can be done to expand rare cancer drug development?

New approaches are needed to improve the financial risk/reward of drug development for rare cancers.

Dr. Bilenker described the high fixed costs of drug development, even in rare cancer. The lack of drug pricing transparency at time of major investment, long timeline of development, and ever-present risk of failure make investment into drug development high risk. Dr. Bilenker recommended that a compassionate, nuanced discussion about drug pricing is needed because

"there is no other modality in the health care system like drugs that can bend the curve from a disease outcomes standpoint."

Decentralization could improve trial access and recruitment, but is not a solution in the near term.

Drs. Khozin and Bilenker discussed whether decentralizing clinical trials, by leveraging new remote monitoring and data collection technologies, could be a way to extend the reach of clinical trials in rare cancers and rare cancer subtypes. Practical challenges in the short term include the reality that patients who live far from a tertiary care center are less likely to receive the advanced molecular profiling typically needed for trial eligibility and sponsors' need to have more clarity on what will be acceptable to FDA.

Closing thoughts

Bill Louv, PhD, President of Project Data Sphere described Dr. Fajgenbaum as someone who used hope to inspire tangible actions and real progress. In fact, this captures the ethos of all the participants in this symposium. They share a great optimism about what can be achieved to improve the lives of patient with rare cancers, and a deep understanding of what actions

are needed today to make this a reality – because patients with cancer can't wait.

"Let's continue to work together as a community, keeping the patient in mind."

– Andy Crighton, MD, Chief Executive Officer; CEO Roundtable on Cancer and Project Data Sphere.

Project Data Sphere

Next Steps

Beginning in 2014, the US Food and Drug Administration (FDA) and Project Data Sphere (PDS) have jointly sponsored a series of Symposiums during which representatives from industry, academia, and government have come together around specific research topics seminal to the FDA's Oncology Center of Excellence. These symposia produce peer-reviewed journal articles and white papers, exemplifying the organization's role as

"convener, collaborator, catalyst"

in the fight against cancer.Each symposium also has yielded important lessons and questions to guide our research programs at PDS and hopefully at the organizations of symposia participants.

Background of PDS work on Rare Cancer Registries.

PDS began its work with rare cancer registries in 2018. Our program is physician-directed and focused on Merkel cell carcinoma (MCC). It is based at three cancer centers: Massachusetts General Hospital (MGH), MD Anderson (MDA), and George Washington University (GWU). The program is led by Dr. Mike Wong (MDA) and Dr. David Miller (MGH). By the end of 2021, we will have nearly 1,000 patients in the registry.

The purpose of the MCC registry is to: (1) document the presentation and natural history of MCC; (2) illuminate best practices; (3) document treatment toxicities; (4) document 'real world' response to therapy; and, (5) identify clues for novel therapeutic strategies for this disease. This initiative also aims to use patient-level data as real-world evidence for drug development by functioning as an external control.

Our regular engagement with strategic leaders ensures that the MCC registry will address unmet patient needs and support drug development and regulatory decision making. By the end of the second phase, the MCC registry will have incorporated longitudinal information of each patient's clinical course as well as genomic data. This body of work has immense potential to impact patient care and streamline the development of new therapies for this devastating disease.

Insights from Symposium IX

There are several broad areas from which we draw insight about how to progress our PDS sponsored registry programs.

1. Artificial Intelligence makes scalable registries possible.

Manual data abstraction by experts is the current norm but that requires a big investment of time, money and manual effort. There are two paths to scale registry development. One is a crowdsourced model but it has limited power. The other is automation and it offers

a clear path to developing scalable registries that are interoperable.

We look to adapt existing state of the art AI-empowered technologies/solutions to accelerate the pace of data (structured and unstructured) abstraction from Electronic Health Records to the registry database.

2. Patient engagement in registries is essential, but how?

Engagement with patients (one of the key points addressed by Dr. Fajgenbaum) to help them contribute to patient-reported outcomes (PROs) is an important dimension that we need to incorporate in PDS-sponsored registry programs. While the best path forward is a little unclear, adopting digital platforms such as ApricityCare can help capture patient-reported adverse events in a structured form, which will be a step forward in the right direction. We should exercise caution that PROs are likely to have noise and may require an expert to curate the data reported by the patient.

3. Are there new roles that registries could play?

Rare cancer registries - a resource for real-world adverse event reporting.

"A registry is a treasure trove for safety signal"

commented Dr. Ting Yu, Global Medical Director at EMD Serono, A business of Merck KGaA, Darmstadt, Germany. During Symposium VII, the experts identified that under-reporting of adverse events to FDA is one of the key gaps in real-world clinical practice. A meaningful next step would be to use registries to help address the gap (severe under-reporting) in real-world reporting of adverse events due to cancer therapy to FDA. The PDS-sponsored registry to catalog neuro-toxicity due to immunotherapy is a great starting point, although it still is limited to only a specific therapy. Indication-specific registries can become a source for adverse event reporting to FDA.

Other potential advantages of rare cancer registries.

1. Registries can help identify signals in drug activity. Well curated registries collect the required biomarker/genomics data and link them with clinical/phenotypic data. Such well-curated registries could be used to identify potential drug activity signals based on genomic profiles conducted by clinical oncologists (e.g. TAPUR).

2. There is immense potential to use sophisticated data science approaches to serendipitously discover the unknown relations between prognostic markers and clinical primary and secondary endpoints in the real-world data (registry data). In 2015, PDS conducted a crowdsource challenge based on well-curated prostate cancer clinical trial data. After acquiring curated registries from the institutions participating in the rare tumor registries program, we can conduct a crowdsource challenge to allow data scientists to apply state of the art machine learning techniques to discover new knowledge serendipitously.

Get Involved

PDS would like to hear from industry, academia and government representatives who are interested in pursuing these same topics. To learn more or get involved in this research, please contact PDS President Bill Louv or Program Director Ravi Komandur.