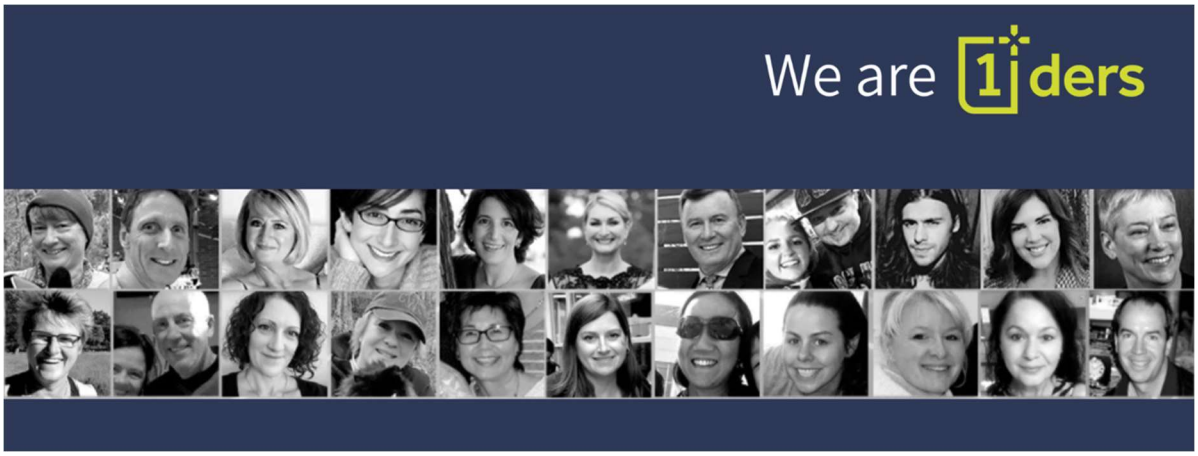

Real-World Data for ROS1+ Cancer and Other Rare Cancers

October 2022

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ROS1ders Research Roundtable Sponsors

Introduction

This publication addresses patient-driven collection of real-world data (RWD) for ROS1 positive (ROS1+) cancer. Its findings may be applicable to many types of rare cancers or rare molecular subgroups of frequent cancers. Throughout this document, the term "patient" is intended to include people living with this disease, whether patient, caregiver, or family member.

ROS1 positive cancer, or ROS1+ cancer, is any cancer that tests positive for a fusion in the *ROS1* gene. It is sometimes called *ROS1* fusion or *ROS1*-rearranged cancer. ROS1+ cancer occurs in 0.6%-2% of non-small cell lung cancers (NSCLC)[1,2] and has also been found in multiple other cancer types (see Figure 1).[3] ROS1+ cancer occurs when a gene called *ROS1* fuses with a nearby gene and swaps pieces of DNA; thus far over 20 different genes have been found to fuse with *ROS1* and drive ROS1+ cancer. The resulting protein expressed by the fusion gene exhibits abnormal functions and signaling. ROS1+ cancer tends to be aggressive and tends to spread to the bones and brain.

The rarity of ROS1+ cancer means the population is too small to ensure accrual of Phase 3 randomized studies of new treatments or care concerns.

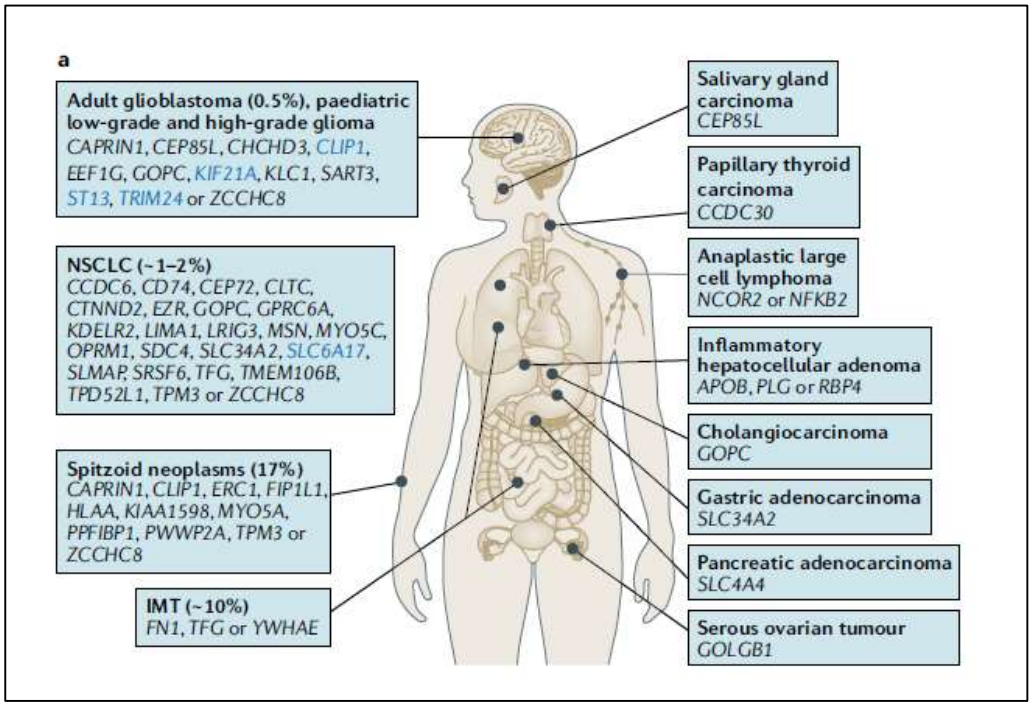

Figure 1. Types of cancer in which ROS1 fusions and associated fusion partners have been found. (Reprinted with permission from Springer Nature Customer Service Centre GmbH)

The ROS1ders, Inc.[4] is a non-profit public benefit corporation bringing together an international group of patients and family members living with ROS1+ cancer. As of August 2022, their private Facebook group has over 900 members in 30+ countries. The organization is internationally recognized in the oncology and patient advocacy communities as experts in their disease.[5,6,7,8,9]

Most physicians will never meet a patient who has ROS1+ cancer, and few oncology clinics see enough patients on their own to generate useful research and clinical care data. This presents the ROS1+ community with a significant challenge: how do we gather sufficient information to advance development and access to evidence-based treatment of this rare disease?

The ROS1ders believe collecting and compiling data on diagnosis, treatment, outcomes, and patient experience from a global group of patients over time is our best option for identifying optimal care (or gaps in care), as well as generating hypotheses for future preclinical and clinical research. This is the realm of Real-World Data (RWD).

One of The ROS1ders' first projects was a study to look at characteristics that might be common to many people who have ROS1+ cancer. As part of this observational study, participants provided information on past medical history, environmental exposures, and lifestyle. The intent was to periodically repeat and possibly update the survey to collect longitudinal data. Disappointingly, this effort did not lead to research that changed patient outcomes but did generate significant patient burnout (due to the length of the survey and detailed nature of the questions). The organization decided to find a better approach to generate results that would be useful to researchers.

On May 3, 2022, The ROS1ders convened a three-hour public webinar focusing on developing and leveraging real-world data (RWD) to advance progress in ROS1+ cancer. This event brought together members of The ROS1ders patient and caregiver community with international ROS1 clinicians and researchers. The video of the webinar[10] can be viewed on The ROS1ders' YouTube channel.

This white paper summarizes what we learned about collecting and using RWD for ROS1+ cancer research. It is divided into the following sections.

- What Is Real-World Data?
- RWD Priorities
- RWD Collection Approaches
- Challenges with RWD
- Call to Action

While this meeting focused on ROS1+ cancers in particular, the concepts and information discussed are relevant for all rare cancers and diseases.

What Is Real-World Data?

Real-world data (RWD), as defined by the US Food and Drug Administration (FDA), is "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources."[11] Examples of RWD (Figure 2) include surveys of patient experiences, patient registries, medical records, genomic test results, and data focused on areas of concern in patient groups, such as opportunities for dose reductions to mitigate side effects. RWD studies can help answer questions important to patients and identify best practices for the care and treatment of patients who have ROS1+ cancer no matter where they are treated. RWD can also help address clinical questions important to ROS1+ patients and assist patients in making treatment decisions when rigorous clinical trial data comparing treatment options is not available (a recurring problem for ROS1ders, since the population is too small to power most phase 3 clinical trials).

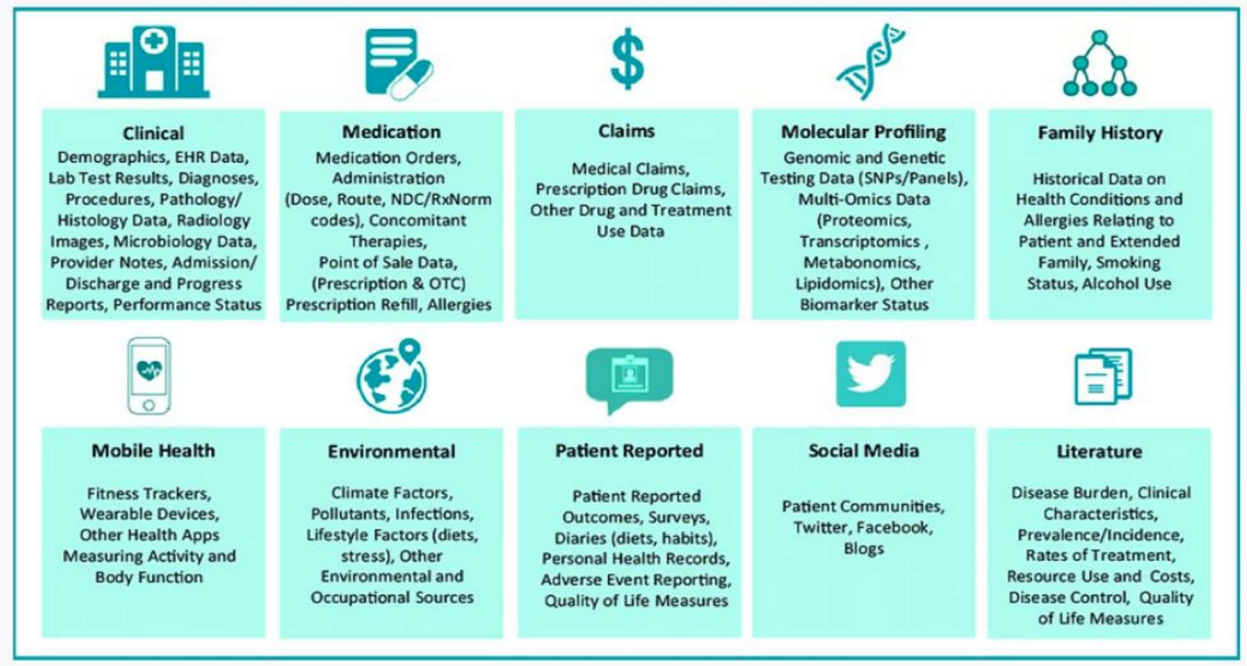

Figure 2. Possible Sources of Real-World Data (RWD)[12]

RWD can be used to generate Real-World Evidence (RWE), which is clinical evidence about the usage and potential benefits/risks of a medical product derived from analysis of RWD.[13] All RWE comes from RWD (Figure 3); however, not all RWD is of sufficient quality to be used in RWE, which must be held to higher data integrity standards to be used in support of regulatory decision making. The video "RARE-X Definition Series: Real-World Data and Real-World Evidence"[14] provides a helpful explanation of RWD and RWE in patient-friendly terms.

Terms commonly used in RWD projects are defined in the Glossary.

Real-World Data	Real-World Evidence
RWD -> are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources	RWE -> is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD
Sources of RWD	**Generation of RWE**
• Electronic health records (EHRs) • Claims and billing activities • Product and disease registries • Patient-generated data • Other sources that can inform on health status, such as mobile devices	RWE can be generated by different study designs or analyses, for example: • Randomized trials (open label or blinded) • Pragmatic trials • Observational studies

Figure 3. Relationship Between RWD and RWE.

Examples of important uses for RWD and RWE include tracking safety of a drug after regulatory approval, filling an evidence gap where a randomized control trial is impractical (for example, when the disease is rare), label expansion efforts to expand patient populations who can use an approved drug, and use of data by payers to support coverage of a new therapy.

RWD Priorities

A pre-webinar survey of The ROS1ders captured examples of questions that the ROS1+ cancer community would like RWD to answer (Figure 4). Patient priorities for ROS1+ cancer research projects include identifying optimal treatment sequencing, advancing side effects management, and helping patients have the best possible quality of life during prolonged treatment with targeted therapies (which can last for years).

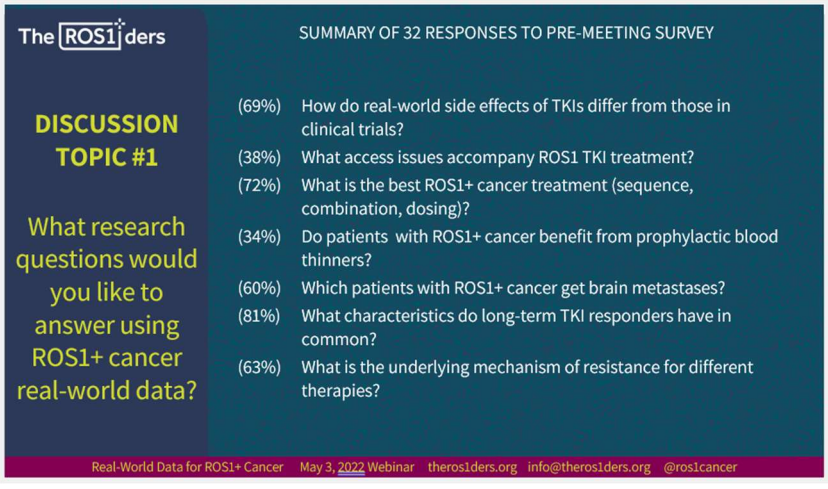

Figure 4. Priority research Questions for ROS1+ Cancer RWD.

During the webinar, expert panelists suggested additional priorities and opportunities in the ROS1+ cancer space, including:

- Develop a global RWD project for ROS1+ cancer.
- Expand the base of data that industry can use with payers and health technology assessments (HTAs) to encourage coverage of new therapies.
- Collect Patient-Reported Outcomes (PROs) data in ROS1+ clinical trials.
    - Quality of life data captured during clinical trials can support shared decision making when selecting treatment options.
    - The FDA is strongly emphasizing collection of PRO data during clinical trials. In 2021, the FDA Oncology Center of Excellence published their guidance to industry laying out the core patient-reported outcomes to include in clinical trials.[15]
- Explore possibility of using commercial datasets (such as Flatiron in the United States).
    - Determine constraints and pathways for access.
    - Identify desired data elements that are missing from a data set or measured differently in trials than in routine clinical care (e.g., date when a line of treatment ends).
    - Determine whether date range of data would capture current practice (e.g., cannot compare two different treatments using electronic health records when only one of the treatments has regulatory approval).

Additional potential research questions that emerged from the discussion include:

- What are the response rates to ROS1 TKIs in patients with poor performance status (2 or 3)? These results can be useful for payers and HTAs —some health systems (e.g., UK) consider performance status in their coverage determination process.
- Might quality of life data on symptoms and side effects generated by PROs in clinical care be used to support regulatory label changes for dose reduction? Many patients are on TKIs for years, and the side effects become less tolerable with time.
- Does ROS1 TKI response, duration, and tolerability correlate with patient characteristics such as race and ethnicity?
- What is the standard of care for ROS1+ cancer in various countries and communities (e.g., first- and subsequent-line treatments, types of scans, scan intervals, monitoring protocols, etc.)?
- Does family history, environmental exposure, diet, or use of supplements have any impact on outcomes?
- Does the sequence of the different therapies, in particular the intermittent use of chemotherapy, influence long-term outcome?
- What is the best management of brain metastases with regard to long-term outcome?
- What are striking differences (epidemiological, clinical, molecular) between patients who progress early compared to long-term responders?

- Can we collect more data on off-target resistance mechanisms by rebiopsies done outside clinical trials?

In addition to generating useful information about ROS1+ treatment and care, patients seek RWD research projects that include them as full partners. Specific patient goals for a RWD project include:

- Involving patients in all aspects from the outset
- Obtaining ethics approval for data collection
- Gathering comprehensive, useful data while avoiding participant "survey burnout"
- Enabling international participation
- Linking all data types across sources and silos
- Sharing data and results with all interested stakeholders
- Releasing data regularly and rapidly
- Allowing The ROS1ders to access identified data (with patient consent) to facilitate patient navigation
- Maintaining patient trust throughout the process

RWD Collection

An excellent example of successful RWD collection and use for patient- partnered research is the "Count Me In" project at the Broad Institute of Harvard and MIT,[16] which aims to generate a large, publicly available database of clinical, genomic, molecular, and patient reported data in cancer. The project is co-designed by patients and researchers to generate patient-reported data, genomics data, and data abstracted from patient's electronic health records to enable analysis of patterns, help accelerate discoveries, and advance development of new treatment strategies in all cancers, with a focus in several types of cancer, such as metastatic breast cancer and angiosarcoma.[17] The study also collects and analyzes tissue, saliva, and blood specimens. This has generated valuable information for investigators and offer patients the chance to leave a legacy of benefit for others. One example of the project's impact was in angiosarcoma (a very rare cancer that has no standard of care). An analysis of extraordinary responders identified a potentially effective immunotherapy treatment and enabled initiation of an angiosarcoma clinical trial.[18]

The pre-webinar survey was also used to determine the types of ROS1+ cancer RWD that webinar participants would be interested in collecting or contributing, (see Figure 5). This preliminary list was used during the webinar to stimulate discussion.

Some of the patient-reported data discussed included PRO measures that cover treatment side effects, overall quality of life, and use of palliative care.

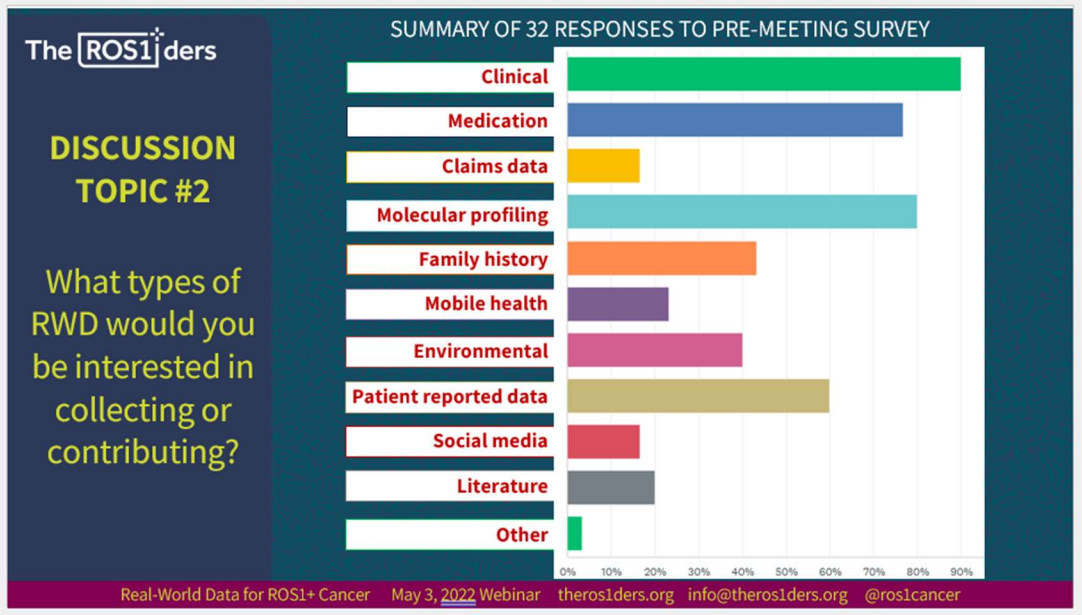

Figure 5. Types of ROS1+ Cancer RWD to Collect/Contribute.

Challenges with RWD

The presentations and discussions during the webinar identified several distinct challenges with collecting RWD and using it to generate RWE for ROS1+ cancer.

Ensure the data is fit for the purpose

Structured electronic health record (EHR) data can be used to generate RWE and support regulatory submissions. Data collected from some other sources (e.g., social media) is not considered sufficiently rigorous to support RWE, but may support different research goals, such as generating hypotheses for future study or evaluating feasibility of clinical trial eligibility criteria. Any project would need to achieve an acceptable completeness and quality of data to generate findings useful to researchers and clinicians.

Exercise caution when using RWD to generate external control groups for treatment comparisons

A randomized clinical trial (RCT) is a study in which the participants are divided by chance into separate groups that compare different treatments or other interventions. Using chance to divide people into groups means that the groups will be similar and that the effects of the treatments they receive can be compared more fairly. At the time of the trial, it is not known which treatment is best. RCT's are generally viewed as the "gold standard" for generating

evidence of safety and efficacy of medical interventions that are sufficiently rigorous for regulatory review. Regulators generally prefer to see RCT's because the control arm allows for the conclusion that a change in the experimental arm, when compared with a control, is a treatment effect. Randomization also reduces concern for systematic bias between arms within a study.

RWD and RWE are complementary to randomized clinical trials, especially when emerging from natural history studies that may contextualize single arm studies. Rare diseases like ROS1+ cancer often cannot supply enough participants to run an RCT. However, they may support a single-arm clinical trial (in which everyone receives the same experimental therapy). Single-arm studies are common in Phase 1 and 2 testing, and generally use different outcomes (endpoint measures) because there is no group for comparison within the trial. An Externally Controlled Trial compares a group of subjects receiving the test treatment with a group of patients external to the study (such as those in a real-world database). The external control can be historical (i.e., data from patients treated at an earlier time) or synthetic (i.e., can be derived from a group treated at the same time in a different setting).

RWD might enable creation of an external group whose treatment outcomes can be compared to clinical trial data. The challenge is finding patient records within the RWD dataset highlighting a group sufficiently similar to the trial group so that the comparison would be robust enough to be considered RWE. While there have been examples of the use of RWE to support regulatory approval of a new therapy, it is important to understand that RWD and RWE generally cannot replace the need for evidence generated from RCTs. To date there have been no primary efficacy analyses used to support approval of marketing application in oncology where there was a formal comparison to an external control arm.

Harmonize format and structure of data

Comparison of datasets requires similarity in data fields, formatting, and parameters of data collection. Count Me In found formatting and posting genomic data results on widely used public platforms such as cBioPortal involved considerable labor and cost because of data formatting differences. Also, data from EHRs or patient surveys might not collect the same milestones or endpoints as comparable clinical trial data.

Minimize demands on study participants

Excessive time and effort required for data collection can lead to "survey burnout" or cause participants to drop out of the study. While it can be tempting to run multiple studies in a patient registry, try to avoid asking participants to resubmit data that has already been collected in a previous survey. Simplify processes that enable participants to retrieve, submit, and share their data, such as having a study coordinator pursue collection of EHR data.

Address barriers to collecting, analyzing, and sharing patient-generated RWD

- *Extracting data from EHRs.* EHRs do not adhere to a common data standard, and often include free-text entries, which makes reviewing, extracting, and analyzing EHR data time-consuming and expensive.
- *Returning results to participants.* Patients want the ability to share data generated from their disease with researchers of their choosing—for example, sharing biomarker test results generated in one study with a researcher for a different study. Patients might not participate if they know their genomic and/or genetic results will not be returned to them. However, many Institutional Review Boards and research facility administrators resist returning test results to patients if the tests were not conducted in a CLIA-certified laboratory (non-CLIA data is not considered appropriate for clinical use).
- *Differences in international regulations, policies, and languages.* These pose barriers to international participation, data sharing, sample transport, and informed consent and privacy considerations. For instance, some countries forbid collecting data on patient race and ethnicity, which could complicate global studies that evaluate the effect of a drug by race and ethnicity or analyze disparities in access to care. Selection bias can be introduced into RWD if patients who belong to a specific demographic or community are not interest, willing, or able to assist in gathering and/or submitting their data. Some countries' regulations complicate sharing of human specimens or genomic data across international boundaries.[19,20]
- *Patient attrition.* This complicates completion of datasets and generates the potential need to re-contact patient participants to ask for updated information or additional tissue samples. This must be addressed up front in the consent process.
- *Value participants:* Provide feedback about participation, results, and how their data are being used to advance research. Well-respected patient advocate leaders can make good use of social media for recruiting and sharing of results with participants.

Call to Action

The topic of RWD is a complex and challenging one, especially for a rare cancer subtype like ROS1+ cancer. However, there is alignment among experts who participated in the webinar about the importance of pursuing this area of data development to support priority research and advance progress for patients.

The webinar participants agreed on a goal to develop a strategy and stepwise plans to build a global ROS1+ cancer RWD registry. This project will require coordination through working

groups to address the challenges we've identified. The ROS1ders will take the lead in initiating these steps and coordinating the working groups. The next steps are listed below.

The ROS1ders

- Identify advocate, researcher, and clinician champions in countries where ROS1+ cancer is treated.
- Gather working groups that include all stakeholders-- patients, researchers, regulators, pharma, and payers.
- Engage researchers who are willing to partner up front and generate "quick wins" from the project that could foster broader interest and engagement.

Working Groups

- Operations
    - Develop infrastructure requirements (e.g., patient registry) and create an inventory of suitable platforms.
    - Assess existing RWD datasets to see what kind of ROS1+ cancer populations and data they contain.
    - Address operational questions (e.g., where a registry would be housed, governance, funding, etc.)
- International Data Sharing
    - Determine any country- or institution-specific restrictions on data and specimen sharing.
    - Survey global ROS1+ scientific and clinical community to determine which kind of data could be contributed in each country.
- Research Design
    - Develop consensus among stakeholders about priority questions to pursue initially
    - Determine a limited number of discrete variables (e.g., age, sex, location, time of diagnosis, treatment, time on therapy, etc.) to collect in a basic registry.
    - Determine patient-reported data to include (e.g., symptom description and timing, quality of life measures).

If you are interested in learning more or partnering with us, please contact The ROS1ders at research@theros1ders.org .

Glossary

Unless otherwise indicated, all definitions come from US FDA publication "Framework for FDA's Real-World Evidence Program."[21]

Clinical Laboratory Improvement Amendments (CLIA)[22]**:** The Clinical Laboratory Improvement Amendments (CLIA) regulate laboratory testing and require clinical laboratories to be certified by the Center for Medicare and Medicaid Services (CMS) before they can accept human samples for diagnostic testing. Laboratories can obtain multiple types of CLIA certificates, based on the kinds of diagnostic tests they conduct.

Clinical Trial: a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. Clinical trials are interventional clinical studies.

Common Data Model: Data put into a common format with common representation (terminologies, vocabularies, and coding schemes). This is important for comparing data in different data sets.

EHR: Electronic Health Records maintained by medical facilities.

External Control Arm: An external control arm uses existing patient-level data, either clinical trial or real-world data, to create a cohort of patients to use as a comparator arm – or supplement an existing randomly allocated control arm – that mimics the characteristics of an RCT control arm.[23]

Health technology assessment (HTA)[24]**:** the systematic evaluation of properties, effects, and/or impacts of health care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods.

Medical Claims Data: the compilation of information from medical claims that health care providers submit to insurers to receive payment for treatments and other interventions. Medical claims data use standardized medical codes, such as the World Health Organization's International Classification of Diseases Coding (ICD-CM), to identify diagnoses and treatments.

Observational Study: a non-interventional clinical study design that is not considered a clinical trial.

Observational Study, Prospective: a study in which the population of interest is identified at the start of the study, and exposure/treatment and outcome data are collected from that point forward. The start of the study is defined as the time the research protocol for the specific study question was initiated.

Observational Study, Retrospective: a study that identifies the population and determines the exposure/treatment from historical data (i.e., data generated before the initiation of the study). The variables and outcomes of interest are determined at the time the study is designed.

Patient Registry: an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves one or more predetermined scientific, clinical, or policy purpose. Registries are generally defined either by diagnosis of a disease (disease registry) or usage of a drug, device, or other treatment (exposure registry).

Patient Reported Outcome (PRO): a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of the patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview, provided that the interviewer records only the patient's response.

Randomized Clinical Trial (RCT): A randomized controlled trial is a form of scientific experiment used to control factors not under direct experimental control. Generally, an RCT is a blinded study with a control arm and one or more experimental arms.

Real-World Data (RWD): data relating to patient health status and/ or the delivery of health care routinely collected from a variety of sources.

Real-World Evidence (RWE): clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

References

1. Steeghs EMP, Groen HJM, Schuuring E, PATH consortium, et al. Mutation-tailored treatment selection in non-small cell lung cancer patients in daily clinical practice. Lung Cancer. 2022 May;167:87-97. doi: 10.1016/j.lungcan.2022.04.001. Epub 2022 Apr 4. PMID: 35461050.
2. Marchetti A, Barberis M, Di Lorito A, et al. ROS1 Gene Fusion in Advanced Lung Cancer in Women: A Systematic Analysis, Review of the Literature, and Diagnostic Algorithm. JCO Precis Oncol. 2017 Nov;1:1-9. doi: 10.1200/PO.16.00010. PMID: 35172481.
3. Drilon A, Jenkins C, Iyer S, Schoenfeld A, Keddy C, Davare MA. ROS1-dependent cancers - biology, diagnostics and therapeutics. Nat Rev Clin Oncol. 2021 Jan;18(1):35-55. doi: 10.1038/s41571-020-0408-9. Epub 2020 Aug 5. PMID: 32760015; PMCID: PMC8830365.
4. The ROS1ders. http://theros1ders.org, *accessed September 1, 2022*.
5. National Cancer Institute Center for Cancer Genomics. ROS1+ Cancer Patients Partner to Increase Research. https://www.cancer.gov/about-nci/organization/ccg/blog/2017/ros1-patient-driven-research, *accessed September 1, 2022.*
6. University of Colorado Cancer Center School of Medicine. Global ROS1 Initiative combines patient experience with researcher expertise to target ROS1 cancer wherever it grows. https://coloradocancerblogs.org/global-ros1-initiative-combines-patient-experience-with-researcher-expertise-to-target-ros1-cancer-wherever-it-grows/, *accessed September 1, 2022.*
7. Anderson, A. ROS1 Cancer Model Project Demonstrates Power of Patient Advocacy. https://www.precisiononcologynews.com/cancer/ros1-cancer-model-project-demonstrates-power-patient-advocacy#.YDQoT-hKjyE, *accessed September 1, 2022.*
8. Camidge D. Motivated, Engaged, and Organized: The New Molecular Cohorts of Lung Cancer, https://www.iaslc.org/iaslc-news/ilcn/motivated-engaged-and-organized-new-molecular-cohorts-lung-cancer, *accessed September 1, 2022.*
9. D'Iaria I. Pazienti con la mutazione Ros-1, supereroi in cerca di una cura, https://www.repubblica.it/oncologia/news/2018/05/21/news/i_pazienti_con_la_mutazione_ros-1_super-eroi_della_ricerca-196973309/, *accessed September 1, 2022.*
10. 2022 ROS1ders Research Roundtable: Real World Data for ROS1+ Cancer, https://youtu.be/E5AdPFJNjEw, *accessed September 1, 2022.*
11. US Food and Drug Administration. Framework for FDA's Real-World Evidence Program, https://www.fda.gov/media/120060/download, *accessed September 1, 2022.*
12. Swift B, Jain L, White C, et al. (2018). Innovation at the Intersection of Clinical Trials and Real-World Data Science to Advance Patient Care. Clinical And Translational Science, 11: 450-460. https://doi.org/10.1111/cts.12559.
13. US Food and Drug Administration. Framework for FDA's Real-World Evidence Program, https://www.fda.gov/media/120060/download, *accessed September 1, 2022.*

14. RARE-X. RARE-X Definition Series: Real World Data and Real World Evidence, https://www.youtube.com/watch?v=pXK-aQsvVF8, *accessed September 1, 2022.*
15. US Food and Drug Administration. Core Patient-Reported Outcomes in Cancer Clinical Trials Guidance for Industry, https://www.fda.gov/media/149994/download, *accessed September 9, 2022.*
16. The Broad Institute of Harvard and MIT. Count Me In. https://www.broadinstitute.org/count-me-in, *accessed September 1, 2022*.
17. Painter CA, Jain E, Tomson BN, et al. The Angiosarcoma Project: enabling genomic and clinical discoveries in a rare cancer through patient-partnered research. Nat Med. 2020 Feb;26(2):181-187. doi: 10.1038/s41591-019-0749-z. Epub 2020 Feb 10. PMID: 32042194.
18. Wagner MJ, Othus M, Patel SP, et al. Multicenter phase II trial (SWOG S1609, cohort 51) of ipilimumab and nivolumab in metastatic or unresectable angiosarcoma: a substudy of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART). J Immunother Cancer. 2021 Aug;9(8):e002990. doi: 10.1136/jitc-2021-002990. PMID: 34380663; PMCID: PMC8330584.
19. Gordy D, Tashjian RS, Lee H, Movassaghi M, Yong WH. Domestic and International Shipping of Biospecimens. Methods Mol Biol. 2019;1897:433-443. doi: 10.1007/978-1-4939-8935-5_35. PMID: 30539463; PMCID: PMC6777724.
20. Wan Z, Hazel JW, Clayton EW et al. Sociotechnical safeguards for genomic data privacy. Nat Rev Genet 23, 429–445 (2022). https://doi.org/10.1038/s41576-022-00455-y.
21. US Food and Drug Administration. Framework for FDA's Real-World Evidence Program, https://www.fda.gov/media/120060/download, *accessed September 1, 2022* .
22. US Food and Drug Administration. Clinical Laboratory Improvement Amendments (CLIA). https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clinical-laboratory-improvement-amendments-clia#, *accessed September 11, 2022*.
23. Evidera PPD. External Control Arms. https://www.evidera.com/external-control-arms/, *accessed September 11, 2022*.
24. National Information Center on Health Services Research and Health Care Technology. HTA 101: Glossary, https://www.nlm.nih.gov/nichsr/hta101/ta101013.html#HTA, *accessed September 11, 2022*.