Sustaining and Accelerating Research for ROS1+ Cancer

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THE ROS1DERS
BRIDGING ROS1+ PATIENTS TO RESEARCH

Prologue

The ROS1ders, Inc.[1] is a non-profit public benefit corporation bringing together an international group of patients and family members dealing with ROS1+ cancer. Group members use their professional skills and passion to help other ROS1+ patients and families and accelerate research. As of January 2021, The ROS1ders have over 500 active members distributed across 30 countries. The organization is internationally recognized in the oncology and patient advocacy communities as experts in their disease.[2,3,4,5,6]

The ROS1ders planned and held two virtual facilitated workshop meetings (titled ROS1der Research Roundtables) on October 14 and 22, 2020. These events brought together members of The ROS1ders patient community with leading ROS1 clinicians and researchers.

Objectives for the meetings were to identify barriers to ROS1 research, discuss ways to sustain and accelerate ROS1 research, and identify priority projects that The ROS1ders could implement to drive ROS1 research forward. While the group acknowledges that raising funds for research is an effective method for accelerating research, The ROS1ders wanted to explore options for partnering to develop and conduct projects that specifically addressed unmet needs in ROS1 diagnosis and treatment, as well as research questions important to patients.

Invited participants were selected from The ROS1ders and ROS1 experts and collaborators familiar with The ROS1ders across three continents. Discussions took place in two separate meetings to enable greater participation. Ten out of fifteen invited researchers and clinicians were available to attend. Each two-hour Zoom meeting was facilitated by an experienced patient research advocate from the cancer advocacy community and followed the same agenda.

- Meeting Objectives
- How the ROS1ders See Patient-Driven Research
- Researcher Pre-Meeting Survey Results
- Sustaining ROS1 Research – Discussion
- Accelerating ROS1 Research – Discussion

This white paper summarizes key themes from the meetings and subsequent discussions with the experts. Recommendations are synthesized as a “Call to Action” to help move ROS1 cancer research forward.

Overview of ROS1+ Cancer

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 1%-2% of non-small cell lung cancers (NSCLC) and has also been found in multiple other cancer types (see Figure 1).[7]

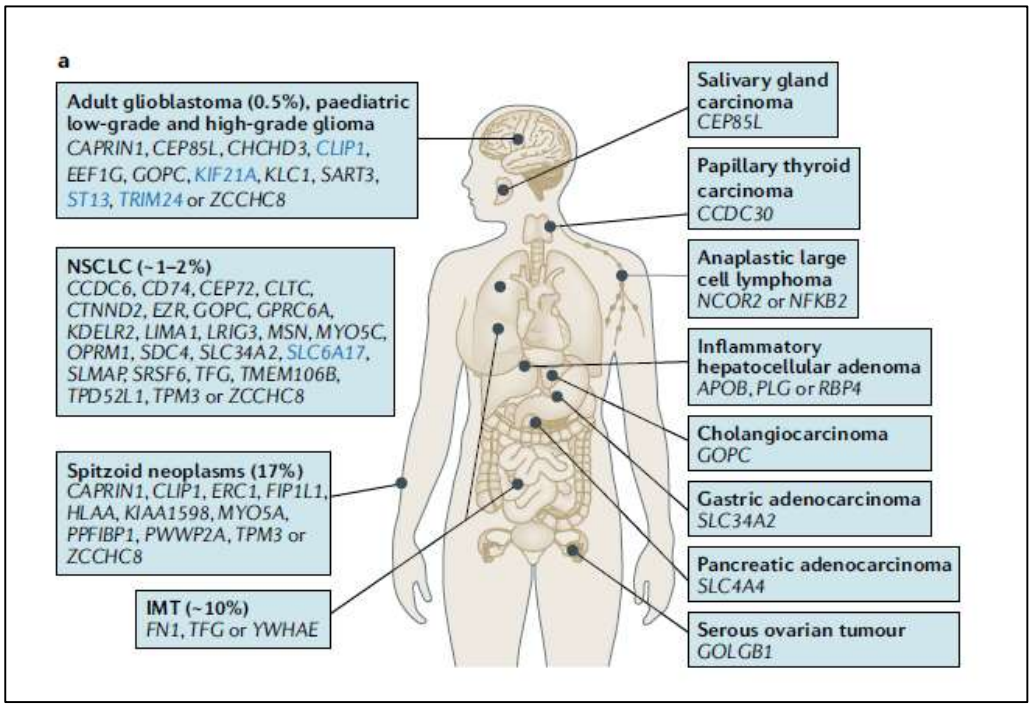

Figure 1. Types of cancer in which ROS1 fusions have been found. [8]
(Reprinted by permission from Springer Nature Customer Service Centre GmbH)

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 cancers tends to be aggressive and can spread to the bones and brain.

Overview of Patient-Driven Research

On behalf of The ROS1ders, Janet Freeman-Daily provided context to meeting participants by describing how The ROS1ders view patient-driven research.

Historically, many researchers think the primary contributions to research by patients and advocates is raising funds for research. While this is an important and essential task, it is not the only valuable contribution that patient research advocates can make. Patient research advocates can provide patient perspective to research—such as insights into ways protocols can be adjusted to enable greater accrual to trials—as well as become active partners in developing and implementing several types of research projects.

Partnered projects between researchers and groups like The ROS1ders can contribute to preclinical, translational, clinical, social, and observational research (Figure 2). In this context, **pre-clinical** cancer research (also known as basic or laboratory research) is conducted on the laboratory bench to understand basic biology of cancer, such as studies of cell or animal model behavior, or analyzing molecules. **Translational** research applies knowledge from pre-clinical research to develop treatments and tools to address patient needs. **Clinical** research tests drugs or treatments on humans in the clinic. **Social** research studies society and relationships of its members, such as psychological impact of cancer on caregivers. **Observational** research follows disease or behavior over time, such as a longitudinal study of patient physical activity after treatment is completed.

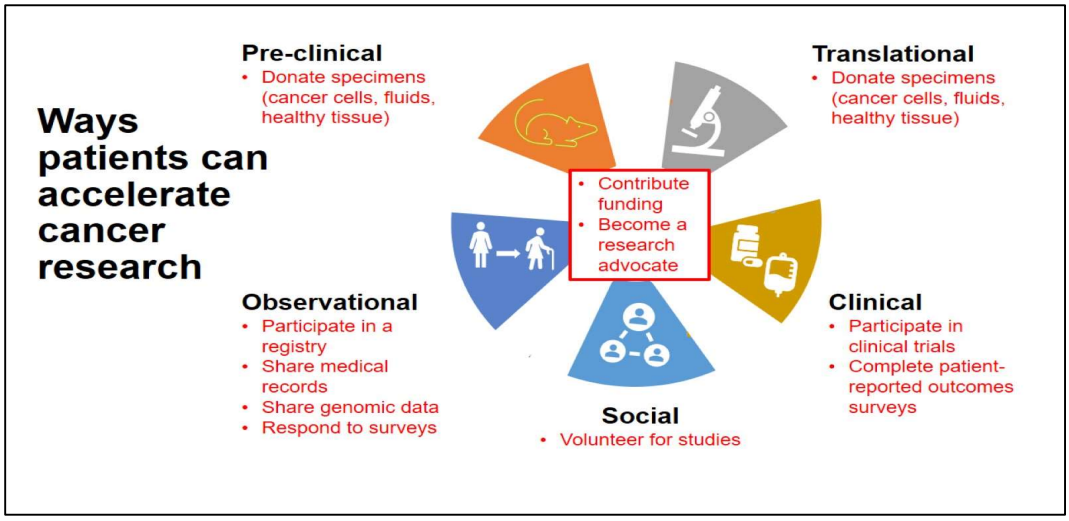

Figure 2. Ways patients can partner to accelerate cancer research.

Patient-driven research partnerships can encourage and empower patients and research advocates to engage in activities such as:

- Donate specimens to create cancer models or to supply biobanks
- Help patients navigate treatment and clinical trial options
- Participate in clinical trials
- Share real-world data in registries, surveys, and biorepositories (e.g., medical records, genomic data, lived experiences)
- Serve as active as patient representative in interdisciplinary cancer centers (e.g. in steering boards or in working groups)
- Participate in expert advisory and government committees focusing on patient rights, data protection, and implementation of genomic medicine.

Ms. Freeman-Daily presented seven key measures of successful patient-researcher partnerships, developed from lessons learned in various patient-researcher collaborations:[9]

1. Include patients and patient groups in all aspects of the program, from the very beginning
2. Address questions that are meaningful to the patients
3. Develop patient-centered measurements (such as patient reported outcomes)
4. Accommodate the patient's clinical realities (such as not requiring a two-week washout for patients on targeted therapies)
5. Leverage social media and patient groups
6. Share progress with study participants frequently
7. Make results rapidly and freely available

Ms. Freeman-Daily also described examples of successful research partnerships between patient groups and researchers. One example is the **ROS1 Cancer Model Project** [10,11,12], which began in 2017 and is continuing. The ROS1ders collaborated with nonprofits, academia, and industry to create preclinical cancer models (ROS1 cell lines and patient-derived xenograft mice, or PDX mice), with USA ROS1ders donating specimens of fresh tumor tissue or pleural fluid from medically necessary procedures. Unfortunately, despite five tissue donations, no PDX mouse model that expressed a ROS1+ fusion was created, and this arm of the project has been terminated. However, the project successfully created nine new ROS1+ lung cancer cell lines, and characterization of the models is underway. Several research papers regarding behaviors of these cell lines in the setting of acquired resistance to ROS1 TKIs (tyrosine kinase inhibitors, a type of oral targeted therapy) have been published.[13,14,15] These cell lines have been shared with other institutions for research into ROS1 biology, acquired resistance to TKIs, and improved biomarker testing.

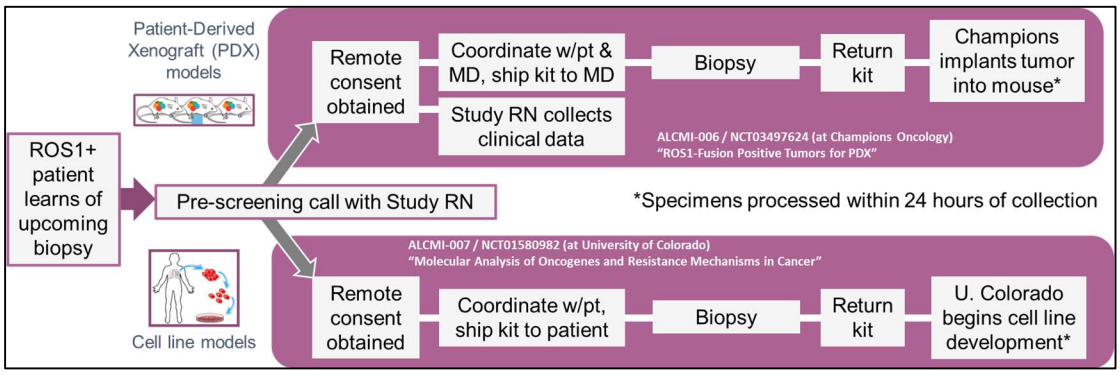

Figure 3. ROS1 Cancer Model Project schema.

A ROS1der who is a bioinformatics researcher in Belgium received a grant to make *in silico* structural predictions regarding 13 known and predicted ROS1 TKI resistance mutations; and replicate them by genetically engineering patient-derived ROS1ders cell lines from the Cancer Model Project.

ROS1der Merel Hennink in the Netherlands created a foundation[16] that is collaborating with researchers in Europe to cultivate cell lines from ROS1 and other oncogene-driven lung cancers and to study resistance mechanisms to the TKI lorlatinib (Figure 4).

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Who	What	Research	Research Team
University Medical Centre Groningen (UMCG)	EGFR, ALK, ROS1, etc	• Tissue repository • Detailed analysis • 3D modeling	• Lead researcher • Micro biologist • Pathologist • Postdoc • PhD
Hanze University of Applied Science	ROS1	• Cultivate cell lines • Resistance mechanisms (lorlatinib)	• PhD student • Postdoc • Students (Life Science and Technology)

Figure 44. Objectives of ROS1 project initiated by ROS1der Merel Hennink in Netherlands.

The ROS1ders and other patient groups occasionally conduct **informal surveys of their members** to gain perspective on the patient experience. These surveys are not approved by an ethics board (e.g., Institutional Review Board) and therefore are not acceptable for publication in most scientific journals. However, such data can help researchers form hypotheses for future studies. Figure 5 shows results of an informal poll conducted in the private Facebook group "ROS1 Positive (ROS1+) Cancer"[17] about the length of time patients remained on the ROS1 TKI Xalkori® (generic name crizotinib). An informal poll conducted among ROS1ders in 2016 prompted a retrospective analysis of patients at the University of Colorado institution, which led to the realization that brain metastases were much more common in ROS1+ cancer than previously thought.[18]

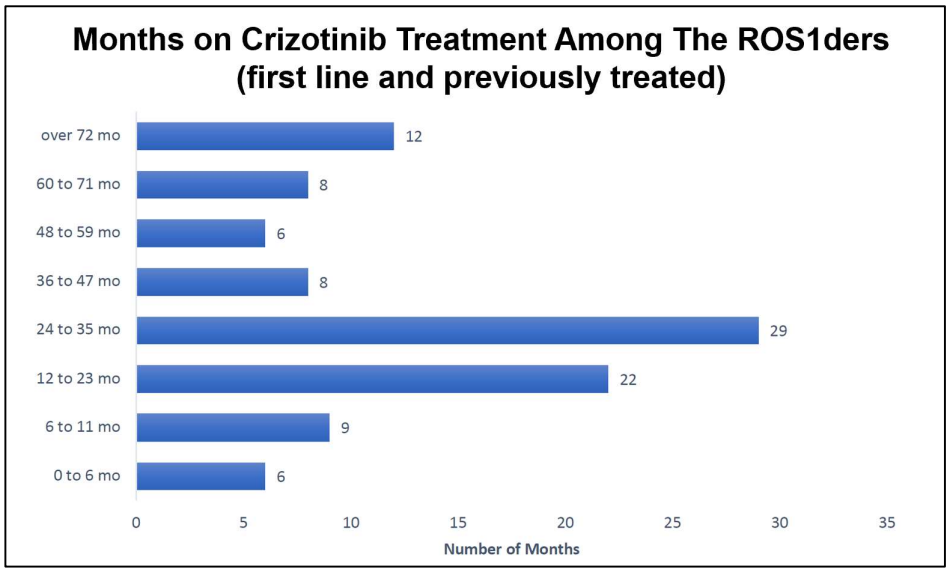

Figure 5. Informal 2020 poll within private Facebook group "ROS1 Positive (ROS1+) Cancer".

When **real-world data** is collected by biomarker patient groups, the results might be useful in generating real-world evidence for drug development and patient care. Clinical trial data is not the best proxy for actual patient experience living with a therapy. Trials tend to attract participants who possess necessary resources and support, and patients may not be totally honest about side effects if they fear they may be taken off the trial due to unmanageable side effects. The EGFR Resisters, a patient group dealing with EGFR-positive lung cancer, collaborated with LUNGevity to conduct Project PRIORITY[19], a survey which captured the real-world experience of their members on treatment. Figure 6 compares the side effects experienced by EGFR Resisters who took Tagrisso® (osimertinib) with the side effects reported in the FLAURA clinical trial[20] for Tagrisso®. As you can see by looking at the line labeled "fatigue," the side effects in the real-world cohort were significantly more severe and more widely experienced than in the clinical trial. Unfortunately, collecting data on average side effects across the entire cohort of patients in a trial doesn't provide information on how side effects (SEs) vary with demographics.

In addition to surveys of patient experiences, real-world data can also include medical records, genomic test results, and data focused on areas of concern in patient groups, such as increased frequency of blood clots, or dose reductions required due to side effects after drug approval. Such studies can help develop real-world evidence to answer questions important to patients, such as optimal treatment sequencing, side effects management, and living well during prolonged treatment with targeted therapies. Real-world data can 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).

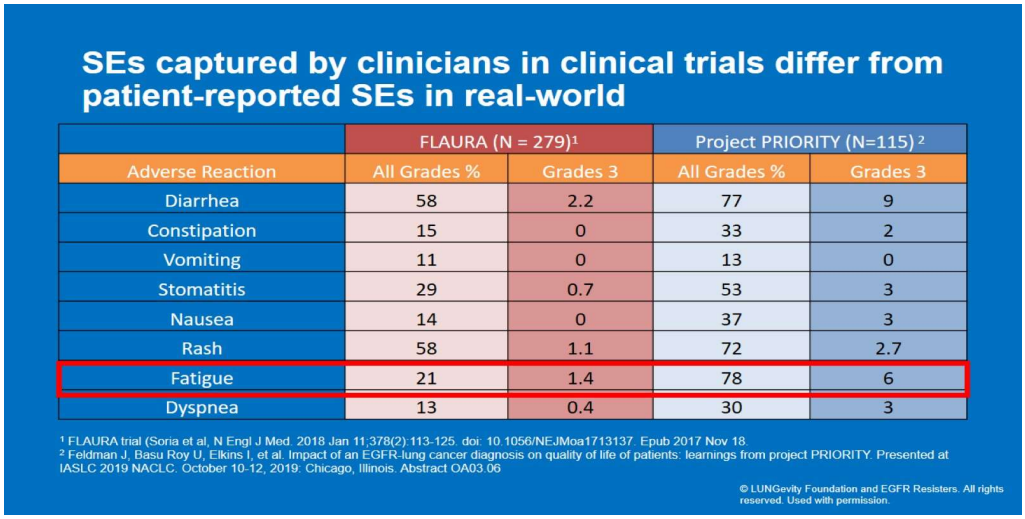

Figure 6. Analysis of real-world data collected by EGFR Resisters patient group.

Some of the urgent needs for ROS1 research from the patient perspective are:

- How long do patients stay on TKIs with good quality of life and control of tumor growth compared to chemo?
- What is the best sequence of ROS1 therapies? How does their tolerability compare?
- What factors predict long-term benefit for ROS1 TKIs? What are the characteristics of exceptional responders? What are the long-term and late side effects?
- Would ROS1 patients benefit from a prophylactic blood thinner?
- What is the role of immunotherapy for ROS1+ cancers?
- What options do we have for combination therapies to help reduce development of resistance?

Not all of these questions can be answered through patient-initiated research projects—some (like the prophylactic blood thinner question) will require a prospective clinical trial. However, all research into these questions would benefit from including patient perspectives and active participation from research advocates.

Pre-Meeting Survey

Prior to the meeting, The ROS1ders drafted a five-question survey in SurveyMonkey and sent it to the 15 invited ROS1 expert clinicians and researchers invited to the Roundtable. Responses were gathered over a one-week period.

The survey sought to gain insight into the professional interests and research perspectives of Roundtable attendees with three questions:

1. What is your professional interest in ROS1 cancer? (multiple choice)
2. What do you see as the most promising areas for ROS1 cancer research? (multiple choice)
3. How might The ROS1ders be most helpful in accelerating ROS1 cancer research?

Response options on the survey reflected The ROS1ders understanding prior to the meeting of promising areas of ROS1 research and ways The ROS1ders might be the most helpful. Seven participants responded to the survey. Results from the survey were shared in the meeting.

The majority of respondents (85.7%) were clinicians focused on thoracic cancers and/or those engaged in translational laboratory research. The same percentage were interested in mechanisms of acquired resistance. The range of professional interests appears in Figure 7.

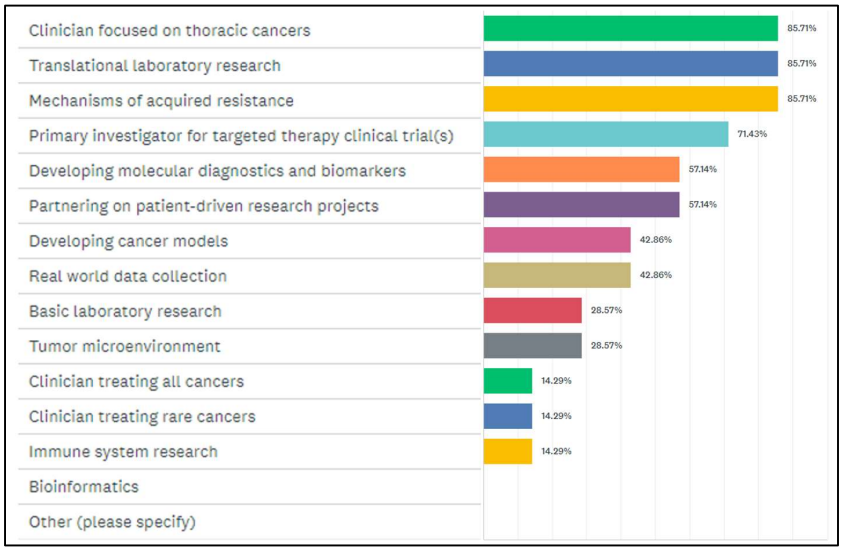

Figure 7. Survey responses on professional interest in ROS1 cancer.

The top three most promising areas of ROS1 cancer research identified by the survey (Figure 8) were:

- Developing new therapy combinations
- Identifying biology for off-target acquired resistance to ROS1 TKIs
- Exploring resistance mechanisms common to several oncogene-driven cancers

Translational: Developing new therapy combinations	85.71%
Basic/Preclinical: Identifying biology for off-target acquired resistance to ROS1 TKIs	71.43%
Basic/Preclinical: Exploring resistance mechanisms common to several oncogene-driven cancers	71.43%
Basic/Preclinical: Generating new ROS1 cancer models (cell lines, organoids, PDXs, GEM, etc.)	42.86%
Basic/Preclinical: Developing biomarkers to determine off-target resistance pathways	28.57%
Facilitating ROS1 data sharing among institutions and agencies	28.57%

Figure 8. Survey responses on most promising areas for ROS1 cancer research.

The top four ways in which The ROS1ders might be most helpful in accelerating research (Figure 9) were:

- Collecting real-world data on ROS1 cancer patients
- Providing ROS1+ patient specimens
- Co-developing Patient-Reported Outcome (PRO) measures
- Offering research grants

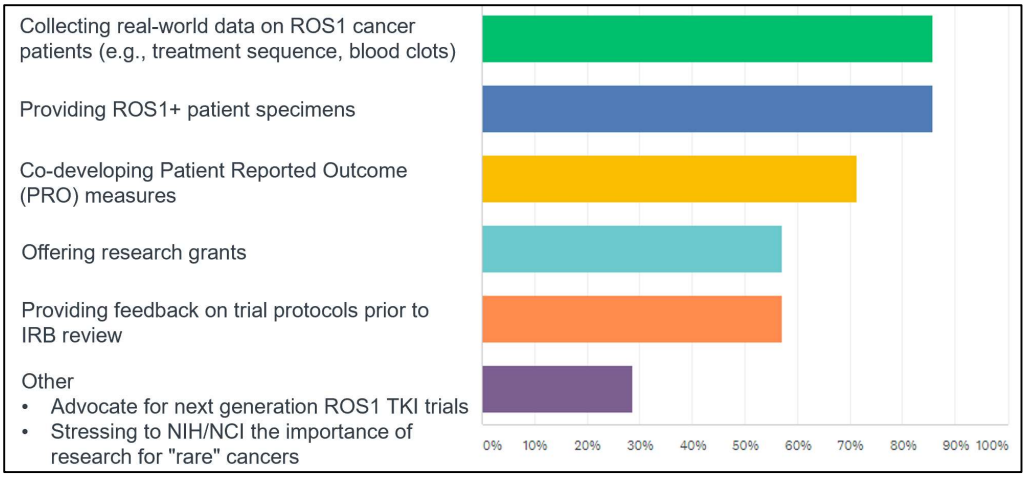

Figure 9. Survey responses for How The ROS1ders might be most helpful.

The information from the survey was used to develop discussion topics for the Roundtable. However, not all of the top interests identified in the survey were addressed during the Roundtable due to time limitations.

After review of patient-driven research and survey responses, participants then engaged in a moderated discussion about what they see as the most productive areas of ROS1 research, barriers to productive research, and how those barriers might be addressed. The key themes that emerged were broader and more detailed than responses on the pre-meeting survey.

Key Themes for ROS1 Research Barriers

ROS1 accounts for only a small percentage of patients in the cancers where it has been detected. This creates several barriers to research:

- Most research hospitals and clinics will encounter only a few ROS1 patients, if any.
- The small population does not generate many patient specimens for research or for creating cancer models.
- The small population does not easily support accrual for Phase 3 trials (to compare treatment options and identify best treatment sequencing).
- Some research centers cap the number of clinical trials they allow to be open at the same time, which means those cancers with smaller populations might not have priority.
- Survivors who have/had ROS1 cancer are widely scattered, so it's difficult to address research questions that require collection of longitudinal data.
- Some of the rare ROS1 cancer models, specimens, and research data may be inaccessible in silos.
- Few longitudinal specimens are available.
- Research funding may be less accessible because funders believe fewer patients are impacted.

In the clinical research space, ROS1 biology and treatment options create additional barriers:

- About half of ROS1 patients develop "off target" resistance mechanisms that are not understood or detectable through currently available technologies.
- Many ROS1 patients who seek to enroll in clinical trials do not meet eligibility requirements because they have been heavily pretreated.

- Limited clinical trial data indicates overall response rate in ROS1 lung cancer patients to single-agent immune checkpoint inhibitors like Opdivo (nivolumab) or Keytruda (pembrolizumab) is poor.
- Few immunocompetent cancer models are available to evaluate effectiveness of immunotherapy treatments.

Keys Themes for Accelerating ROS1 Research

- **Promote universal ROS1 testing for all solid tumors**. Current NCCN guidelines do not recommend ROS1 biomarker testing for patients who have cancers other than NSCLC. In the community setting, there is no acknowledged "best" test for ROS1, although NCCN guidelines do recommend broad panel biomarker testing for non-small cell lung cancer (NSCLC) patients.
    - Study ROS1 cancers across different cancer types to identify and understand the frequency of ROS1 fusion
    - Explore common factors across cancers, such as patient characteristics and co-existing biomarkers.
- **Expand access to ROS1 specimens, cancer models, and study results** for academic research to support successful grant submissions and preclinical research.
    - Increase transparency regarding availability of tissue samples collected during industry-sponsored ROS1 trials. Industry sits on a gold mine of rigorously collected, clinically annotated tissue samples of oncogene-driven cancers that could be used for critical research. The first biopsy in first-line trials generally goes to the pharmaceutical company. To study resistance, paired samples are needed with both the pre-treatment diagnostic biopsy and the biopsy at the time of resistance.
    - Collect serial plasma donations to support research into disease evolution, minimal residual disease (MRD), and plasma-based end points.
- **Leverage real-world data** to support answers to most pressing questions for the ROS1 community.
    - Evaluate how sequencing of treatment impacts outcomes. This is a challenge in the small ROS1 patient population, which is unlikely to successfully accrue a Phase 3 trial.
    - Expand understanding of proper management of brain metastases in this population.
    - Address side effects and quality of life for long-term treatment.
    - Compare tolerability of the different TKI agents.
    - Determine whether any ROS1 patients have benefitted from use of prophylactic blood thinners.
    - Evaluate value of existing real-world databases (such as Flatiron) and data-sharing platforms (such as GENIE and ORION) in this space.
- **Study novel mechanisms of resistance.**
    - Evaluate longitudinal plasma and tissue collection to move beyond on-target point mutations and identify secondary drivers of resistance.
    - Study small cell transformation as a resistance mechanism across multiple oncogenes and targeted therapies.
    - Study mechanisms of drug tolerant persister cells.
- **Explore the use of liquid biopsies and other biomarkers** to rapidly evaluate patient's likely response to treatment (especially for combination therapies), estimate risk of recurrence, and detect progression early.
    - Evaluate factors and potential biomarkers to predict long-term benefit from therapies.

    - Evaluate decreasing circulating DNA as an early marker of treatment response and prognosis to help define high and low risk groups early in treatment.
- **Expand basic research into the role of ROS1 in human biology.**
    - Understand its contribution to human development
    - Understand its behavior in children and adults
    - Understand its behavior in different organs
- **Develop Patient Reported Outcome (PRO) measures** to use in clinical trials of novel investigational agents. Sharing side effect profiles is key to evaluating unique TKI adverse events and overall toxicity data in small populations like ROS1.
- **Explore synthetic controls for trials.**
    - Collect historical ROS1 patient characteristics and outcomes in searchable databases for use in evaluating effectiveness of TKIs in specific populations. For instance, a ROS1 synthetic control arm was created from the Flatiron database to compare control of brain metastases in ROS1 patients who did not receive a brain-penetrating TKI versus ROS1 patients who received entrectinib (a TKI that does treat the brain). [21]
- **Expand approach to immunotherapy translational studies.**
    - Develop more immunocompetent ROS1 mouse models (the animals have intact immune systems and express induced ROS1 cancer in lung tissue) to study potential immune response and immunotherapy treatments.
    - Study the tumor micro-environment and how the immune system interacts with ROS1 and other oncogene driven lung cancer, with the goal of circumventing TKI saturation seen in current drug development
    - Explore how to convert “cold” tumors to “hot” tumors to improve response to immunotherapy.
    - Explore immunotherapy modalities beyond the checkpoint inhibitors, such as TKI-immunotherapy combinations and cell-based therapies.

Key Themes for Sustaining ROS1 Research

Roundtable participants also discussed how we might attract, develop, and retain researchers and resources for ROS1 research in academia, as well as the roles industry and international collaborations might play in ROS1 research. Key themes that emerged are listed below.

- **Share methods** for collecting fresh ROS1 patient specimens and creating more ROS1 cancer models**.**
- **Broaden studies of drug resistance to multiple oncogene-driven lung cancers** to identify common bypass mechanisms.
    - Study rarer oncogenes (e.g., ROS1, RET, NTRK, MET) collectively to increase the impact and eventual success of grant submissions by increasing the number of people potentially affected. This avoids the frequent feedback from grant makers that the "impact is not high enough” or the patient group is “too small."
- **Build the field of ROS1 investigators.**
    - Introduce younger trainees to the topic early in their careers, especially those with an interest in biomarker research.
    - Encourage young investigators to expand their research questions to a broader set of cell lines to explore common mechanisms of resistance.
    - Provide more mentorship and education for young investigators.

- **Include funding for correlative studies** in investigator-initiated trials.
- **Create bridges between academia and industry** to develop strategic partnerships that are a "win-win." This might include collaborative studies that utilize both academic samples and models as well as samples and models obtained by industry from specimens collected during clinical trials.
- **Design smart early trials** so that a preliminary read is available which, in turn, would drive researchers and pharma to carry on a large, randomized study.
- **Promote international collaborations** between ROS1 researchers in different countries.

Ways The ROS1ders Might Help Accelerate Research

The discussions highlighted several ways in which The ROS1ders might help accelerate research.

1. **Help generate more patient-derived ROS1 specimens and cancer models.**
    - Donate more fresh specimens (tissue and pleural effusion) to make cancer models.
    - Develop a model for tissue collection that can be expanded to other countries.
    - Develop a biorepository of blood samples from ROS1 patients for studies of liquid biopsies and/or unique antigens that might be useful in immunotherapy.
    - Support efforts to obtain biopsies at diagnosis and perform biomarker testing in a qualified laboratory.
    - Upon progression, discuss options for re-biopsy with their oncologist and donate to research all specimens not needed to guide medical care.

2. **Enable real-world data collection and surveys.**
    - Establish an international ROS1 registry, including basic questions that can be easily translated into several languages.
    - Aim to gather data from a representative population and look for differences between subgroups.
    - Collaborate with organizations in other countries and explore collaborative multinational registries, models, and access to data.
    - Work with advocacy organizations to implement a research accelerator model for correlative studies to tap into larger registrational studies.

3. **Provide research funding for ROS1 projects.**
    - Create grants to support early career (and other) investigators to build the field.

Although PROs were mentioned in the pre-meeting survey as one way The ROS1ders could help accelerate research, a method for The ROS1ders to contribute to PRO development was not clearly identified during the Roundtable.

Call to Action

As discussed above, three key areas in which The ROS1ders might help accelerate research into their disease are as follows:

1. Help generate more patient-derived ROS1 cancer specimens and models.
2. Enable real-world ROS1 data collection and surveys.
3. Provide research funding for ROS1 projects.

Although this report focuses on ROS1+ cancer, these three areas (as well as most of the barriers to research identified above) apply equally to other less common, genomically driven cancers such as RET, EGFR and HER2 Exon 20 insertions, MET, NTRK, and BRAF.

To address these areas, we propose developing a public-private partnership. This partnership would encompass all stakeholders in the genomically driven cancer space: patients, patient and advocacy groups, nonprofits, academia, and industry. Its objectives would be:

- Identify or define standards for fresh specimen collection and handling to provide the best chance of creating viable cancer models
- Facilitate creation, characterization and sharing of rare oncogene-driven cancer models (such as cell lines and patient-derived xenograft mice)
- Generate real-world data for rare oncogene-driven cancers
- Enable patients and patient groups to participate and fund research
- Provide mechanisms for collaborative research across oncogene types to increase impact

Products from this initiative could be adapted by other organizations, both in the USA and internationally, and would include research frameworks for:

- Patient consents, study protocols, logistical and contractual consideration for collecting patient specimens and data that maximizes resource sharing while minimizing privacy risks
- Characterizing cell lines of genomically driven cancers
- Tracking location and availability of less common genomically driven cancer models that are distributed in academic and industry facilities
- Open access sharing protocols of cancer models and their characterizations and related data via existing platforms and tools
- Processes for ensuring transparency and progress updates for all partners to encourage participation without increasing administrative burden
- A model for real-world data collection in partnership with biomarker patient groups that addresses research questions of interest to patients, academia, and industry
- A mechanism to facilitate international collaboration and funding for research on mechanisms of resistance, treatments, and patient care across oncogene types
- Enabling patients to fund research into their own disease

Initially, activities would focus on The ROS1ders as a test case, with the intent of proving the initiative concept for all less common oncogene-driven cancers.

- **Cancer models.** The cell lines generated by the ROS1 Cancer Model Project at the University of Colorado are currently being characterized, but the genomic characterization of each cell line has yet to be shared, except in some publications. First steps could bring together researchers from academic institutions that study less common oncogene-driven cancers to develop standard frameworks for model characterization and explore use of existing data sharing platforms and tools for sharing the information. Research advocates for other less common, genomically driven cancers—both in the US and other countries—could participate in development of the initiative to ensure it can be expanded to include their type of cancer.
- **Real-world data.** Explore existing models and platforms for real-world data collection among international patient groups. Investigate ways to facilitate collaboration between patients and

researchers to ensure the RWD generated can generate real-world evidence that is useful to patients, academia, and industry for improving treatments and patient care.

Patients would be motivated to participate in the initiative because it potentially:

- Enables research advocate participation
- Provides transparency and updates on projects and progress
- Accelerates research using shared resources and data
- Provides means to donate patient research specimens and data to a trusted broker
- Enables research into questions meaningful to patients
- Incorporates patient perspective into research protocols
- Provides mechanism for patients and patient groups to fund research
- Ensures resulting publications are open access
- Returns test results to patients where possible

Researchers would be motivated to participate in the initiative because it potentially:

- Encourages and enables patients to donation specimens and data
- Enables collaboration with patient research advocates
- Provides access to research resources for rare oncogene-driven cancers
    - Specimens and associated EHR
    - Characterized cancer models
    - Real-world data from patients who have rare oncogene-driven cancers
- Provides funding and open access to resources for rare oncogene research
    - Model creation and characterization
    - Real-world data analysis
    - Mechanisms of resistance by oncogene and across cancer types
    - Treatment sequencing and patient care
    - Opportunities for early career researchers
- Supports open access publishing for wider dissemination of research

Vision of how this initiative might support cancer model development when fully implemented:

1. A patient contacts a designated consenting organization (CO). This organization provides information to the physician regarding optimal specimen handling and sends a ship kit. The CO also performs all the consenting, specimen and medical records collection, and logistics of transporting of the specimen to the Modeling Facility (MF). If multiple MFs are available, the patient can designate the facility that will receive their donated specimen. The CO routes the de-identified specimen to the patient's selected MF and processes the medical records for future placement in the open access databank.
2. The MF proceeds with creating the cancer model. The status of the model is relayed to the CO, which informs the donor and the ROS1 patient network (without naming the donor). If a model is successfully created, the model and associated de-identified medical records are made available via the initiative's data sharing protocol. The Initiative tracks the physical location and availability of the model.
3. Researchers who wish may request to characterize the model as defined by the initiative's model characterization framework. If the initiative has raised funds from patients or other sources, they may offer a grant to fund model characterization.

4. Vetted interested researchers may access the model and deidentified data for research projects. Researchers agree that after a specified time (e.g., 12 months), completed research results will be placed on an open access platform per the initiative's data sharing policy, and all publications will be open access regardless of which journal accepts the manuscript.
5. The initiative provides a mechanism for patients and patient groups to fund model development, model characterization, and research projects conducted with the models.

A similar process would be developed for creation of analyzed, deidentified real-world ROS1 data that could be accessed by researchers to answer specific questions. ROS1 patients and researchers would collaborate to develop IRB-approved surveys capable of addressing questions of interest in a manner that will support scientific rigor sufficient for publication in scientific journals.

This concept requires further development to ensure all stakeholders in the partnership understand the terms and benefits of their participation, and all components are developed in such a way that they are widely applicable and compliant with all ethics and regulatory requirements. Clinicians, researchers, and patient groups involved in other rare lung cancer oncogenes (e.g., RET, MET, NTRK) will be included among the stakeholders to provide input to the collaboratively developed frameworks, selected informatics platforms, and organizations.

Managing Expectations

The initiative described in the Call to Action represents an aspirational collaborative to advance new research that benefits all rare oncogene communities, not just The ROS1ders. However, for this model to succeed, we must be careful to manage expectations of all the various stakeholder groups, particularly the patients and the researchers.

For patients, time is of the essence. Though we recognize the need to move swiftly in putting these structures in place, we must also balance the realities (and challenges) of operationalizing this model across all parties as well as the realities of the scientific process. Model creation takes time – the period from tissue acquisition to creation of a successful cancer model can often take a year or more, not including model characterization. Patients must embark on this venture in full recognition of the fact that their donations may or may not generate a model that is useful for their own treatment journey. The scientific process can only be accelerated so much.

Additionally, great care needs to be given to creating a governance structure that represents the needs and interests of all parties. Continuity is important, and in order to ensure the model moves forward as efficiently as possible, the initiative should have leadership in place that can operate above the challenges and limitations of those navigating an advanced stage diagnosis. Furthermore, in thinking about future fundraising needs and opportunities, the leadership of a broad oncogene-based initiative should not be directly affiliated with any one group.

In collaborations with patients such as what is proposed here, researchers often feel an even greater sense of responsibility. They must feel they can meet patients' expectations as much as possible without fear that the science will be compromised. Further, we acknowledge the inherent complexities of coordinating the various components of the proposed framework. A successful collaboration will take into consideration all the challenges related to intellectual property, storage of data and models and coordination across all stakeholders. Attention must also be given to address ethical, regulatory and

compliance issues, both nationally and internationally. In building out the structure for a future broad rare oncogene initiative, we can look to existing successful frameworks including NCI's PDXNet and Small Cell Lung Cancer Consortium.

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