ROS1derings

A newsletter by and for the ROS1 cancer community

Issue 3

ROS1der acquires grant to research ROS1 progression

By Joyce Hoelting with Geert Vandeweyer

Since June of 2018, Geert Vandeweyer has managed all the stresses that partners of ROS1 lung cancer take on – supporting his wife Valérie through a year of Crizotinib treatment before her progression and movement to Loratinib in August of 2019. Being a husband, a ROS1der volunteer and father of two is a heavy lift for anyone.

But Geert is about to add "ROS1 cancer researcher" to his caretaking roles. In early December, Geert was awarded a 2280380€ grant from the Flemish **Kom op tegen kanker** (Stand Up to Cancer) organization. With this funding, granted to the University of Antwerp where he works, Geert will use his expertise as a medical genetics and bio-informatics researcher to manage an ambitious project that aims to accelerate the study of resistance to TKIs among ROS1 patients.

About the study

The study will start from cell lines acquired from the University of Colorado. These are cell lines created from fluid and tumor samples donated by ROS1ders across the U.S. Geert's team will use these cell lines to test the hypothesis that modern genome

engineering techniques like CRISPR/Cas9 can be used to replicate resistance mutations that are seen in real patients into existing cancer models. If Geert's team can engineer representative cell models, those models would accelerate researchers' ability to study drug responses when ROS1ders progress, without the need for successful donations to the ROS1 cancer model project.

Second, they hypothesize that the response of drugs against specific resistance mutations, like the G2032R mutation, can be modeled using computer simulations. "Research on EGFR has already proven that one can model how effective binding of TKIs is to various types of progression mutations," says Geert. "By generating three dimensional models of the ROS1 protein, we hope to achieve the same accuracy for ROS1+ lung cancer. With such a model, we hope to be able to test more TKIs against more types of ROS1 progression mutations.

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The grant will fund two technicians at the University of Antwerp for two years, and will cover the cost of experiments. One technician will conduct the cell line work while the other does the computer simulations.

What the research will learn

If the team's hypothesis is correct, the two-year project can provide valuable knowledge. The project hopes to learn:

1. If there are differences in response to targeted therapy drugs (TKIs) between cell lines derived from patients and those generated by the CRISPR process.
2. Which ROS1 TKIs are effective to which resistance mutations. Currently, there is some knowledge about targets for G2032R, but other mutations are less clear.
3. Whether other drugs that are designed for ALK or even TRK might be effective against ROS1 progression mutations.

Ultimately, this knowledge could add models that researchers can use to study ROS1 progression, and offer clinicians more tools as they struggle to make good decisions about treating ROS1 progression.

"Up to now, my research has supervised CRISPR/Cas9 projects that focus on neuronal stem cell modification. I have been studying disorders like autism and intellectual disability," says Geert. "In order to turn my knowledge to cancer research, I have formed a collaboration with genetics group of the Center for Oncological Research headed by Prof. Guy Van Camp. Also, one of the pathologists at the University Hospital of Antwerp, Prof. Patrick Pauwels, has a long standing interested in ROS1 mutations and non-small lung cancer. He will be closely involved."

Geert has been active in the ROS1 leadership team since late 2018, and the leadership team is thrilled that Geert is taking his involvement to this next level.

"We are all doing the best we can as caregivers," says Geert. "Because I happen to be involved in genetic and oncology research, I wouldn't feel comfortable if I didn't try to push our University towards ROS1 research."

Joyce Hoelting is the proud wife of Jeff Wynne, a 4-year ROS1 survivor.

Fundraising Update

Thanks to the efforts of many ROS1ders, we have raised $424,398 of our $500,000 goal for the GO2 Foundation. This Foundation is deeply involved in research targeted specifically at what causes ROS1 cancer to progress.

Many thanks to those of you who have donated or raised money in the pat months. Special thanks to Aimee Parker, who provided great leadership to the November fundraising drive in recognition of lung cancer awareness month. With her leadership, we surpassed this goal, raising $70,9113. Thank you to all the fundraisers and donors!

Confused about 1st and 2nd line drugs? Here's a guide!

By Renee Parker

The mainstay drugs for ROS1+ nonsmall cell lung cancer (NSCLC) belong to a group of drugs called tyrosine kinase inhibitors (TKIs). Drug side effects vary, but are similar amongst the various drugs. They often occur within the first few months of starting a TKI.

Crizotinib, entrectinib, and ceritinib are first line therapies. First line therapies aren't able to control cancer after it has progressed while being treated by a TKI, with a few exceptions.

Crizotinib (Xalkori) is the standard of care for metastatic ROS1+ NSCLC in the USA. Crizotinib is effective even in patients previously treated with chemotherapy. While one case study suggests patients who develop certain lorlatinib resistance mutations might be resensitized to crizotinib, it is typically only a first line drug.

Entrectinib (Rozlytrek, RXDX-101) may become the new standard of care for ROS1+ NSCLC due to its ability to effectively treat the brain, which crizotinib doesn't do for most patients. Entrectinib is not an effective treatment for ROS1+ cancers that have progressed on crizotinib in the body. However, patients whose cancer is controlled by crizotinib in the body were allowed to enroll in the clinical trial if they developed brain metasisis. Entrectinib is also a frequent go-to TKI when patients cannot tolerate crizotinib.

Ceritinib has demonstrated potent clinical activity (including treating the brain) in ROS1+ NSCLC patients who had previously received platinum-based chemotherapy.

TKIs only inhibit cancer cells, so they cannot cure it. Most patients treated with TKIs find their cancer eventually starts to grow again. This is due to the cancer cells developing resistance mutations. Within a few years on first-line treatment, the drug often stops working. **Second line drugs** are drugs that are given when initial treatment (first-line therapy) doesn't work, or stops working. The two most commonly used second line TKI drugs for ROS1+ cancer are lorlatinib and repotrectinib.

1st and 2nd line drugs used for ROS1 mutations

DRUG	Date Approved for ROS1+ in US	% Effective for ROS1+ (+/-Brain Mets)	Availability in the U.S.	First/Second Line Drug	Disqualifying First-Line Drugs
Ceritinib	Not Approved		off label	First	
Crizotinib(Xalkori)	3/11/16	70%/80%	by prescription	First	
Entrectinib(Rozlytrek)	8/15/19	50%/70%	by prescription	Both	Crizotinib
Lorlatinib(Lorbrena)	Not Approved		off label	Second	
Reprotrectinib	Not Approved		clinical trial	Second	

Lorlatinib (Lorbrena, PF-06463922) can overcome certain resistance mutations that develop during treatment with crizotinib.. Lorlatinib is typically available off label for ROS1+ NSCLC, and some ROS1 NSCLC patients in the USA have been able to obtain insurance coverage with their

oncologist's assistance. It is available to ROS1+ NSCLC patients in other countries via expanded access and compassionate use. The 11/06/2019 NCCN Guidelines for NSCLC list lorlatinib as a treatment option for ROS1+ metastatic NSCLC after progression on crizotinib or ceritinib. Many oncologists will use it if you have progression on entrectinib, as well.

Repotrectinib (TPX-0005) was designed by Dr. Jean Cui, the Pfizer lead chemist who helped design crizotinib and lorlatinib. Repotrectinib is the most potent ROS1 inhibitor against the major resistant mechanism developed after crizotinib treatment. Like entrectinib and lorlatinib, this drug can treat brain mets.

A few notes about other drugs: Not all TKIs that effectively treat ALK patients are effective for ROS1. Preclinical tests show alectinib is not effective against ROS1 mutations. Brigatinib has not been clinically shown to be effective for ROS1 patients.

Renee Parker is an OB/GYN physician who now uses her expertise to help others and herself with ROS1+ and other lung cancers. She was diagnosed in April, 2017.

Parenting after a ROS1+ Cancer Diagnosis

By Lisa Goldman

My children were 7 and 10 when I was diagnosed. I used to think being a parent of young children was, emotionally, the hardest part of dealing with this disease. Since I've been lucky enough to survive six years, I've come to appreciate how much my children have grounded me, kept me in the present and motivated me to stay as healthy as possible.

I am now grateful to be a parent while traveling this path, but it isn't easy. Every family is different. And within a family, different children will have different responses and needs when faced with their parent's diagnosis. I would never presume to advise others. That said, I will share some of the things our family did to cope.

Teachers: Very soon after diagnosis, we spoke with the children's teachers to let them know what was going on. We wanted help keeping an eye out for atypical behavior, and perhaps extra support. Some teachers have proven more empathetic and skilled at this than others.

Individual Therapy: The kids went to their own individual therapists. Initially, we used a service offered through the school, and got really lucky the first few years. Our children were assigned to kind, competent therapists who were free and conveniently located at the school. Palliative care providers helped us find free therapy support through local hospitals. For young kids, therapists use alternative methods to foster connection and expression (e.g. art

projects, games). So our kids enjoyed the therapy time. Eventually, we shifted from free services to private therapists, whom the kids continue to visit fairly regularly

Family Therapy: In the early days, we saw a family therapist to give the kids an opportunity to approach us with questions. The therapist helped us find a balance between being honest and not overwhelming our children with details. We found it was imperative to be open and honest about my diagnosis, but also not bring them along on the rollercoaster that is every scan cycle. We still check in once in a while - sometimes with a therapist, sometimes without - to make sure the kids have a chance to ask about anything percolating under the surface One of our children is more interested in discussing cancer than the other, and that is fine.

Maintain normalcy: It has been very reassuring to the children to maintain normal activities and schedules. Lots of people volunteered to babysit or take them to activities, but our children are somewhat shy and uncomfortable with strangers. So unfortunately, we couldn't take advantage of generous offers.

Re-jiggering parental duties: Pre-diagnosis, I was the primary parent responsible for most child-centered tasks (carpooling, homework…). After, we reallocated tasks. My husband cut back hours at the office, and the kids took on more responsibility for cooking, cleaning, and laundry.

Here are a few things our family did not end up doing:

- Books: We were gifted books specifically written for kids with a parent with cancer. I confess, I didn't find any as useful as working with experienced therapists, so I don't have any to recommend.
- Letter writing: Some parents have written letters or birthday cards for children to open in the future, or recorded video messages. I think that can be beautiful, but I haven't been able to do it.
- Camp Kesem: Camp Kesem is a a free one-week camp for children of cancer patients. It is a fantastic resource, and many children adore it. My kids tried it, but ended up switching to other camps they preferred. Still, I highly encourage other parents to check it out.

Parenting with cancer can be tricky, but I think there are hidden rewards buried in the wreckage. I don't mean to polish a turd. I don't wish this on any parent or child. But I do believe my children will grow up to be more kind and empathetic than they might have been otherwise, and more kindness and empathy in the world is not a bad thing. Good luck.

Lisa Goldman is a co-founder of the ROS1ders. You can find her blog at https://lisa.ericgoldman.org/

About this newsletter...

ROS1derings is a quarterly newsletter of The ROS1ders patient advocacy group. The ROS1ders is a group of patients and caregivers dealing with ROS1+ cancer. We strive for better outcomes for all ROS1 cancers by supporting patients and caregivers, increasing awareness and education, accelerating research, and improving access to effective diagnosis and treatment.

We will use this space to share updates about our progress, to feature questions frequently asked by the ROS1 community, and to invite all ROS1 patients to join us in our mission. Learn about the ROS1ders.