Patient Advocacy Strategies Evolve as Genomic Advances Change Understanding of Cancer

Sep 07, 2017 | Turna Ray

NEW YORK (GenomeWeb) – Over the past two weeks, a group of patients whose lung tumors are driven by rearrangements in the ALK gene have raised $120,000 that they hope to put toward advancing research for their specific cancer subtype.

"The current state of medical research is not enough to save our lives," said Laura Greco, a stage IV non-small cell lung cancer patient and a member of a support group called ALK Positive. "We have the most skin in the game and we definitely have a different perspective, and one that's generally lacking in research decisions."

Another group called the ROS1ders last month began working with researchers to build mouse models and cell lines that can facilitate clinical investigations into ROS1-positive cancers. ROS1 gene rearrangements not only show up in 1 percent of lung tumors but other tumor types as well.

The International Cancer Advocacy Network (ICAN) recently launched a group focused on advancing research for lung cancer patients with exon 20 insertions in the EGFR or HER2 gene, rare subgroups that lack treatment options. In August, Kevin Hanlon, CEO of technology firm ComSource and founder of the Exon20 Group, donated $100,000 to the John Heymach Laboratory at MD Anderson to support research into this subset of lung cancers.

Patients are organizing themselves into groups like Exon20 — focused on the specific molecular features driving their tumors — to better advocate for themselves, raise money, and influence the direction of cancer research.

"There's an element of not just offering yourself up [for research] and having someone then treat you as a piece of meat," said Ross Camidge, director of thoracic oncology at the University of Colorado, Denver, who has followed the formation of many of these groups. "Most of these people want a seat at the table."

These collectives are embracing the changing image of cancer — from a disease that takes hold in a part of the body, to many diseases distinguished by the perturbed genes driving them. But
they’re also forming in reaction to the disruption that so-called precision oncolgy has brought to the traditional drug development and research enterprise. While greater understanding of the genomic underpinnings of cancer has led to the development of personalized treatments in some cases, it has also uncovered a constellation of seldom-seen oncogenic tumor markers that are difficult for researchers to study and drug companies to advance therapies for.

This tension between precision medicine advances and unknowns is readily evident in lung cancer. Alterations in EGFR, ALK, ROS1, BRAF, ERBB2, MET, and RET are among the known drivers of NSCLC, and treatment guidelines recommend genetically testing patients for the markers to guide personalized treatments and clinical trial options. While genomically-targeted agents have enabled patients to live longer than those not receiving such drugs, researchers and patients alike remain disappointed that these drugs aren’t a cure, and in most cases, the cancers almost always recur.

"There has been a lot of progress already in terms of defining these targeted therapies, [but] the downside is the darn cancer continues to mutate, wiggle out, and become resistant," said Rita Johnson, who moderated an online informational group for NSCLC patients with EGFR mutations taking drugs like Tarceva (erlotinib), called the Tarceva Divas & Dudes, until last year, when she became treatment resistant.

For many patients there aren’t targeted treatment options at all because the molecular characteristics that make their cancer unique are so rare that it becomes difficult to find patients to study in clinical trials. Tarceva, for example, is approved for NSCLC cancer patients with common EGFR mutations (exon 19 deletions or exon 21 substitutions). But there are no approved treatments for patients with far rarer exon 20 EGFR mutations, many of whom are resistant to existing EGFR inhibitors like Tarceva.

Faced with the segmentation of cancer into smaller and smaller molecular subgroups, and the dearth of research and treatment options for rare tumor types, patients are finding one another in chatrooms and on social media, and organizing. "We have access to more people than my doctor has," said Greco, who was diagnosed with ALK-positive NSCLC two-and-a-half years ago. "It’s human nature to try to find others like you and try to glean from it. It’s a phenomenal source of patient empowerment."

'We’re interested in living'

Of the 222,500 new lung cancer cases this year, 85 percent will have NSCLC, and 4 percent to 7 percent of them will have tumors with ALK rearrangements. ALK Positive started as a Facebook group in 2015 with just a few members, and today has more than 650 members, most of whom have stage IV disease. The American Cancer Society estimates that 1 percent of stage IV NSCLC patients survive five years after diagnosis.

In some ways, patients with ALK-positive tumors have it better than other rare cancer subpopulations, since there are four US Food and Drug Administration approved drugs targeting ALK and more being researched. Using the information the ALK Positive group has collected on available research, treatments, side effects, and clinical trials, patients can advocate for what Greco described as a higher standard of care. They can ask their doctors, for example, why
they're not getting Alecensa (alectinib), which in a recent Phase III trial doubled median progression-free survival compared to the first generation ALK inhibitor Xalkori (crizotinib).

Although Xalkori is extremely effective for a time, patients often start progressing after a year of treatment and many experience metastases to the brain. Patients who know this risk, can advocate for brain scans if they're not receiving them frequently.

While searching for this type of information about their unique cancer, patients are also finding the ALK Positive group. "Every day there are more people joining," Greco said. "And unfortunately, every day, there are more people dying."

The recent passing of a member spurred a discussion about the lack of a concerted effort to raise money for more research into this lung cancer subtype. "There really wasn't a place that was directed toward our type of lung cancer," Greco said. "You can certainly donate to numerous organizations for lung cancer, but that doesn't mean it will move the needle forward on ALK-positive lung cancer."

Over a period of two weeks, the group has raised close to $120,000, which in collaboration with the advocacy organization LUNGevity it will award to research that has the potential to extend survival. The group is also exploring collaborations with drug developers and other healthcare companies interested in ALK-specific lung cancer research.

With these efforts, the members of the ALK-positive lung cancer group want to remind the medical research community that "we're interested in living," Greco, a 42-year-old lawyer and mother of two said. "I don't care about making it a nicer treatment, or a little bit more tolerable. I don't think most lung cancer patients care."

Within the lung cancer community there are stories of patients who live longer than the average seen in clinical trials. While statistically these examples can offer patients hope, "in reality it’s crappy," Greco said. If she beats the odds as a stage IV cancer patient and lives for five years, Greco won't even see her youngest child through elementary school.

"Our mission statement is survival," she said. "We're throwing our resources, financial, time, and effort, into activities that will directly have the possibility of extending our life."

A pan-cancer approach

The ROS1ders, meanwhile, are throwing their energy behind creating preclinical mouse models and cells lines that will inform drug development efforts and improve understanding of resistance mechanisms for all tumors driven by ROS1 rearrangements. Within the Global ROS1 Research Initiative, ROS1ders can donate their left-over tumor tissue after biopsies and surgeries, which a company called Champions Oncology will use to create patient-derived xenograft mouse models. These models will be available to researchers for the cost of shipping, but Champions can sell them to pharma partners for drug testing and development.

To date, Xalkori remains the only approved treatment option for ROS1-positive NSCLC, although some patients within the ROS1ders with other tumor types have received the drug off label and are benefitting. The approval for Xalkori in ROS1-rearranged NSCLC came five years after the
drug's approval in ALK-positive NSCLC, even though early research suggested that it might also work in ROS1-positive patients.

Typically, ROS1-positive NSCLC patients respond to Xalkori for a year-and-a-half and then recur. "Once we cross that 18-month threshold we start to get very nervous about what we would turn to after Xalkori," said Lisa Goldman, who got on the drug in the fall of 2014 and is one of the founders of the ROS1ders.

Goldman started the group along with two other ROS1-positive lung cancer patients, Janet Freeman-Daily and Tori Tomalia, who found each other online while researching their disease and blogging about their experiences. "I was scouring the web for anyone who wasn't in their 70s with lung cancer," recalled Tomalia, who was diagnosed with lung cancer at age 37. Those with ROS1-rearranged NSCLC are often female, non-smokers, physically fit, and younger than the typical lung cancer patient.

"I found people online and started messaging them and saying, 'Me, too! Me, too!'" she said. But when Goldman, Freeman-Daily, and Tomalia met at a lung cancer conference, they learned that researchers were having difficulty finding and studying patients like them. They started a Facebook page and eventually launched a website, and called themselves the ROS1ders. The group today includes 145 ROS1-positive cancer patients living around the world and approximately 200 members including patients' families.

Once the group started attracting members, the trio turned to the Bonnie J. Addario Lung Cancer Foundation (ALCF) to explore next steps. ALCF was unique in that through its partnership with the Addario Lung Cancer Medical Institute (ALCMI), the organization didn't just fund research but could organize and execute its own clinical investigations for minority populations, such as the Genomics of Young Lung Cancer Study.

By this time, the ROS1ders had noted these rare rearrangements occurred not just in NSCLC but also in 1 percent to 2 percent of melanoma, angiosarcoma, and pancreatic cancer cases. Just this week, the mother of a five-year old boy with a ROS1-positive inoperable brain tumor joined the group.

"We spoke to them and said this will be a more powerful group if we access patients across cancer types," said Guneet Walia, senior director of research and medical affairs at ALCF. "Despite us being a lung cancer foundation, we're doing this in a pan-cancer fashion. We're focusing on the molecular target."

Doing so could inform the development of more tissue-agnostic treatment indications, such as Keytruda (pembrolizumab), which the FDA approved earlier this year for the treatment of any advanced solid tumors characterized by high microsatellite instability or mismatch repair deficiency. The launch of the Global ROS1 Research Initiative has already attracted the attention of lung cancer patients with other rare oncogenic tumor drivers, who also want to pursue pan-cancer research.

And while ALCMI and ALCF are hoping to pursue similar projects for different genetic alterations, it will require collaboration with other patient advocacy groups that are mostly still focused on advancing research for specific tumor histologies and lack resources and infrastructure to take
on a tissue-agnostic effort. "This is extremely atypical. This almost never happens in clinical research. Three patients got together and approached a foundation," Walia acknowledged.

She added, however, that the ROS1 research initiative demonstrates that "if patients come together with organizations like ours, things can happen."

**Pushing for profiling**

Although cancer patients are increasingly forming groups based on their specific tumor markers, the success of this advocacy strategy is currently limited by the uneven adoption of genomic testing in oncology. Patients can't join groups like ROS1ders, ALK Positive, and Exon20 if they don't have their tumors analyzed for these markers. Many experts at major cancer centers and academic institutions say that in settings like NSCLC, where multiple oncogenic drivers are known and can have implications for treatments or enrollment in trials, patients should be assessed for alterations across a panel of genes, ideally via next-generation sequencing.

But such testing is not the standard of care and haphazardly covered by insurers. An evaluation of genomic testing patterns among more than 800 NSCLC treated by oncologists at more than dozen sites in New Jersey and Maryland found that only 57 patients received testing on an NGS panel for all seven oncogenes recommended by guidelines, while six patients were analyzed on a PCR panel.

Following the publication of this data earlier this year by Martin Gutierrez of Hackensack University Medical Center and colleagues, the Exon20 Group decided that its members (which include top cancer researchers, drug and testing companies, and patients) would also help raise global awareness about the need for genomic tumor profiling.

"Sequencing, sequencing, sequencing, profiling, profiling, profiling," is what's needed, according to ICAN CEO Marcia Horn, if drugmakers and researchers truly hope to improve cancer care for patients with rare oncogenic drivers. EGFR mutations occur in 10 percent of NSCLC patients in the US and 35 percent of Asians. Between 4 percent and 9 percent of EGFR mutations in NSCLC are exon 20 insertions, but as many as 20 different mutations have been seen in patients. And each exon 20 mutation needs to be detected first before it can be studied.

Even if next-generation sequencing isn't possible for all patients, oncogene-specific patient groups contain a wealth of knowledge about testing options. If not for the experience and insights of other cancer patients, Tomalia wouldn't have known to ask for ROS1 testing.

In 2013, her lung cancer tissue was only evaluated for EGFR and ALK alterations, and coming up negative, she started chemotherapy. When Tomalia learned from other lung cancer patients online that there were more genetic markers she could be tested for, she pushed for next-generation sequencing, but she didn't have enough tumor tissue available.

So, she asked to be assessed just for ROS1 rearrangements knowing she fit the clinical profile for the type of patient who tends to have such markers. "I sort of had this hopeful hunch that's what I had," Tomalia said.

Most of the patients who join the ROS1ders know their ROS1 status, but once their cancers
recur, they'll need to be tested again to be guided to other treatment options or clinical trials. Within the ROS1ders community, it's all too common to hear members share how they've stopped responding to Xalkori and their doctors don't know what to do next, according to Tomalia.

When members of the Tarceva Divas & Dudes wonder what to do next upon cancer progression, the discussion turns to testing for the common resistance mutation EGFR T790M. There's an approved drug, Tagrisso (osimertinib), for metastatic NSCLC patients with this mutation who have stopped responding to first generation EGFR inhibitors. Additionally, the companion diagnostic approved for this drug can analyze both tissue or blood samples for this mutation, which is important because often advanced lung cancer patients are unfit to undergo another biopsy.

Johnson, who became resistant to Tarceva last year, unfortunately doesn't have the T790M mutation, but noted that these discussions within the group provide valuable information to patients at a critical point in their illness and have "definitely prompted people to advocate for additional testing when they have progression."

"I don't mean to speak in hyperbole, but I'm pretty sure we've saved people's lives," Tomalia said, reflecting on the educational resources and support available through the ROS1ders. "Doctors might think this is just a bunch of patients and it's a support group for each other. But it's really a lot more than that."

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