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## Director's Overview

# Believe in the possible, Adapt to the impossible

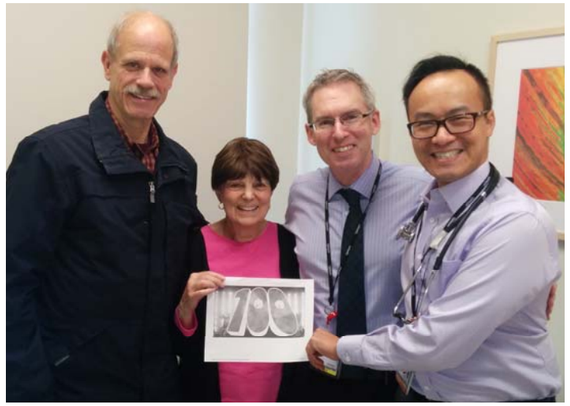
By:  D. Ross Camidge, MD, PhD

If you were diagnosed with a thoracic cancer today, your world might get suddenly turned upside down. But then your mind and the minds of all those who know and care about you will start thinking about what the future may hold. Dr Google can be a great place to start but its information can sometimes be either very out of date or just very 'out there' in other ways. So just what *is* possible after a life-changing diagnosis?

In this year's newsletter we continue to give 'possible' a face - 5 year stage IV survivors, 8 year stage IV survivors, and in 2018 we believe we will start to see a wave of 10 year stage IV survivors. These examples are not to underplay the seriousness of small cell and non-small cell lung cancer, mesothelioma and thymic cancer - the cancers which the CU program researches and treats. Instead it's just about showing that (to borrow a phrase from Jurassic Park) 'Life finds a way.'

Part of the way science and medicine continues to help life triumph is to not treat everyone the same. Sometimes, if you don't have one of the already identified actionable molecular subtypes of lung cancer personalized approaches seem impossible and then, suddenly, discoveries get made. In this newsletter we show a new example of discovering such 'diseases within diseases' and of repurposing old drugs to successfully treat these. Sometimes the successes are in patients and sometimes, offering hope more for the future, in laboratory models of patients.

Sometimes in a resource limited environment, ideas for improvements also hit walls of impossibility - and then you adapt, go at the wall again and suddenly a secret door opens up in it. By being small and adaptable the clinical and research programs at CU continue to grow and improve. Inside you will read about how  the Thoracic Program worked with the Skaggs School of Pharmacy to spearhead embedding clinical pharmacists in cancer clinics to help everyone deal with the complexities of new medicines. You will also read about our new research infrastructure called the Thoracic Oncology Research Initiative (TORI) and how the LCCF will help feed the clinical and basic science research opportunities being created by this. Finally, you will read about how radiation oncologists on the team engaged in 'myth-busting' the impossibility of using highly focused radiation on tens of different deposits in the brain showing not only that it was possible and effective but considerably safer than some of the alternative approaches being proposed.




Karen Scholet (with her husband and medical team) at the start of her 100th month on an experimental treatment controlling her stage IV lung cancer  for over 8 years to date

If you are reading this and you or someone you know has a thoracic cancer - please support the LCCF and help change the world for the better. Our LCCF website has now been updated (including an archive of all the past newsletters) and our total donations in 2018 are predicted to exceed $1M. Is the future going to be impossible or possible? **You get to decide.** www.ucdenver.edu/lccf

# New approach to genetic testing matches lung cancer patient with life-saving drug

By: Garth Sundem

There are many ways a gene can be altered and there are many genes that, when altered, can cause cancer. Testing individually for each possible alteration in every cancer-related gene is not feasible as it would require hundreds of individual tests and many, many thousands of dollars. A University of Colorado Cancer Center case study published in the journal *JCO Precision Oncology* highlights an alternative: Use testing that can look for gene alterations in many genes *simultaneously*. The technique results in the first published report describing successful targeting of MET fusion in a lung cancer patient.

In this study, researchers examined the tumor sample from a late-stage lung cancer patient using an assay that detects gene fusions in dozens of genes. The test identified a rare fusion involving the gene *MET*, leading researchers to treat the cancer with the targeted therapy crizotinib, which inhibits *MET* signaling (among other kinds of signaling). Now more than 8 months after the start of the targeted treatment, the patient who was diagnosed with stage IV lung cancer continues to show an almost complete response.

“The way we approach the workup and treatment of stage IV lung cancer patients includes broad molecular profiling, so that’s what we did,” says Terry Ng, MD, senior fellow in thoracic oncology at CU Cancer Center and first author of the publication.

*Testing for many gene alterations simultaneously let the CU Cancer Center team target a novel cancer-causing MET fusion with the drug crizotinib*

Among the tests used for this molecular profiling was a relatively new assay called Archer FusionPlex, developed by a Boulder-based biotechnology company ArcherDX, and validated for clinical testing by the Colorado Molecular Correlates Laboratory (CMOCO), an advanced molecular diagnostics laboratory within the Department of Pathology at the University of Colorado. Instead of testing for alterations in individual genes – for example, testing separately for changes to known oncogenes ALK, ROS1 or EGFR – the test explored an entire *class* of genetic changes, testing simultaneously for “gene fusions” in 53 cancer-related genes.

In these gene fusions, pieces of one gene accidently become attached to pieces from another. This creates “chimeric proteins” – new proteins made from parts of each – that can drive cancer growth. Two well-established examples of this in lung cancer are fusions involving genes *ALK* and *ROS1*. The gene *MET* has also been identified as a partner in cancer-causing fusions, and, in fact, other changes to the *MET* gene including mutation of *MET,* amplification of *MET*, and something called exon-14 skipping mutations have already been targeted by investigational drugs in lung cancer clinical trials. However, testing for *MET* fusions has been uncommon.

“The frequency of *MET* fusions is very low in lung cancer, well below one percent. You would never test for them individually. You need an assay that looks at many things simultaneously to catch these rare events,” says Kurtis Davies, PhD, lead assay development scientist CMOCO.

Adding to the challenge is that identifying a *MET* fusion gene requires not only testing for *MET*, but testing in a very specific way.

“A lot of tests say they cover *MET*, but that doesn’t mean they pick up this particular alteration. Depending on how you sequence *MET* and what regions you sequence, you may or may not find this alteration,” says Robert C. Doebele, MD, PhD, CU Cancer Center investigator and associate professor of Medical Oncology at the CU School of Medicine.

In 2016, the patient who is from out-of-state, planned to spend three months in Denver visiting her daughter. She had previously been diagnosed with lung cancer and knew that while in Colorado she would need care from a local treatment team.

When she came to University of Colorado Hospital, “We could see her tumors growing,” Ng says.

The team at CU requested a sample of the patient’s tumor that had been removed during an earlier surgery, and used that sample for molecular testing.

“At CU, in addition to the tests that most community centers would use, we do a broader panel. All those things were negative. But one other thing that we do is this RNA-based next-generation sequencing assay called FusionPlex. This NGS platform looks for gene fusions in 53 cancer-associated genes. The assay is unique in that is you don’t need to know a gene’s fusion partner to identify that there is a gene fusion,” Ng says.

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This is how the team identified the patient’s MET fusion. The next step was deciding how to treat it.

“A lot of people don’t know that the drug crizotinib was originally designed to be an inhibitor of the MET gene product,” Davies says, pointing out that the drug’s first FDA approval was not against MET but against ALK-positive lung cancer and was more recently approved to treat ROS1-positive lung cancer. “But the reality is that most drugs in this class hit many targets. Sometimes that’s detrimental – it hits things you don’t want to hit. This is an example of a case when it’s beneficial.”

In the current patient, this strategy of targeting MET with crizotinib showed dramatic results.

“Her first scan showed an almost complete response, a total absence of lung nodules,” Ng says. Side effects included increased fatigue, “but overall nothing that was life-threatening or would keep her from continuing the drug,” says Ng.

According to Doebele, the takeaway from this study is twofold. First, “This study shows the importance of broad molecular testing and also shows the importance of better transparency from commercial laboratories on what they cover,” he says. And second, “This case report and another describing the use of crizotinib with MET translocation in gliobastoma suggest this is a reasonable non-FDA approved way to treat these patients. However, the approach needs to be studied in clinical trials, and we hope this case shows that MET translocations should be included in trials of drugs evaluating efficacy of MET inhibitors.” As for the patient, Ng says, “She came in to visit us the other day, and she told me that she felt so lucky to have come to see us in Colorado. Otherwise, she never would’ve discovered this Achilles heel in her cancer.”

# Colorado C-stories: Images of life after a cancer diagnosis.

Receiving the news of any cancer diagnosis can be devastating. Patients may feel like their lives are coming to an end, that they will not be able accomplish many goals they had. Yet time and again the human spirit (with a little advanced medical care) prevails and people remember to be the people they were before they became patients – not just living with a cancer diagnosis, but thriving. At CU, we see patients from all over the country and the world. Here are a selection of the CU’s fi nest showing that life remains about living, even, or perhaps especially, after a cancer diagnosis. Send your pictures and a line or two to ross.camidge@ucdenver.edu and each newsletter going forward we’ll aim to show others what ‘hope’ really looks like. Look for more images scattered throughout this newsletter.


*Leslie Jordan (stage IV lung cancer survivor diagnosed in 2013, in green on the right) watches her champion whippet Ryder (born May 2016) taking home the winners ribbon at the Plum Creek Kennel Club dog show*

*Cindy Ware (stage IV lung cancer survivor) braving the mule ride to the bottom of the Grand Canyon*

# Increasing need for pharmacists in cancer care

By: Stephanie Carlson

Oncology pharmacists are in high demand. By 2020 cancer patient visits will increase by 48% with only a 14% increase in oncologists, according to the American Association of Medical Colleges Center for Workforce Studies. Oncology pharmacists can help offset this projected shortfall in patient visits. Pharmacists from The University of Colorado Skaggs School of Pharmacy are currently working as an integral part of the cancer team at The University of Colorado Cancer Center at UCHealth, “This isn’t just somebody who’s dispensing drugs in a pharmacy; this is somebody embedded in our clinic,” explains Director of the UCHealth Thoracic Oncology Program, Ross Camidge, MD. “In an ideal world, what we’d really like is one per clinic, on every day of the clinic. We need more pharmacists,” Camidge adds.

*Cindy O’Bryant, PharmD, BCOP (left) educating about treatments*

According to UCHealth, clinics with a pharmacist include the Bone Marrow Transplant Clinic, with two full-time clinic pharmacists, Jenni Tobin, PharmD, and Stephanie Chase, PharmD; the Gynecologic and Urologic Cancer Clinics, which split clinic pharmacist Sarah Weisdack, PharmD; and the Gastrointestinal Cancer and Phase 1 Clinical Trial Clinics split two part-time pharmacists, who are also professors at CU Pharmacy, Cindy O’Bryant, PharmD, BCOP and Ashley Glode, PharmD, BCOP.

Putting pharmacists in the cancer clinics started when O’Bryant, who manages the post-graduate year two oncology residency program, joined CU Pharmacy in 2000 and was tasked with developing an outpatient clinical oncology pharmacy program, “Through my time here, I’ve been able to integrate myself with our Phase 1/GI team, and through that, been able to really model what pharmacy can do to help enhance the care of patients,” says O’Bryant. As people began seeing the value of having a pharmacist within the clinic, demand started growing, “The physicians who don’t have pharmacists embedded in their clinics really do want them and are looking for ways to get them because they see the advantage of having those pharmacists and the level of care that we can provide” she adds.

The job of an oncology pharmacist is to educate both the patient and the physicians on medications, interactions and side effects. “A lot of times our physicians really rely on us to do the one-on-one patient education. So, they’ll make a treatment plan and then they want us to thoroughly explain it, talk about side effects, the schedule, what the patient can expect, what to call for, what’s okay to manage at home,” says Glode. “I talk a lot about just being there to support the patients. That’s really the most rewarding part of my day,” Glode adds.

In addition to educating patients and physicians, an oncology pharmacist also helps get access to treatments, “More and more, I prescribe a drug, and these hurdles have to be cleared in terms of what their insurance needs to do, whether it needs pre-authorizations, and having somebody who makes that their responsibility is just incredible,” says Camidge.

“We have literally new drugs approved almost every week; at least once a month, there’s a new drug approved, so it’s constantly moving. Being on the cutting edge of that and seeing those drugs come through the Phase 1 process and moving on through drug development and being FDA approved is really quite fascinating, and it helps me be able to identify how we can better help patients,” adds O’Bryant.

The pharmacists in the Cancer Center are part of a multidisciplinary team. It’s that team approach that gives patients the best possible care they could receive, “I think I have a really great opportunity to make a difference in a patient’s life,” says Glode.

**UPDATE: December 2017– UCHealth agrees to fund full time pharmacist position in the Thoracic Oncology Clinic!**

Smarter Than Cancer

# Who is TORI?

2017 saw the creation of the Thoracic Oncology Research Initiative (TORI) at CU. Designed to create an over-arching organization to help drive basic, translational and clinical research in thoracic cancers forward, TORI will replicate some of the strengths of CU’s long-running NCI-funded Specialized Program of Research Excellence (SPORE) in lung cancer. It will also expand the approach, adding new recruitments and funding streams, while shielding research from some of the vagaries of government funding. Kick-started by a philanthropic gift of $10M, after an international search, Robert C. Doebele, MD, PhD, was chosen to be the first Scientific Director of TORI, working in partnership with the clinical leadership of Ross Camidge, Director of Thoracic Oncology at CU.

*Robert Doebele*

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# LCCF Supported SPORE/TORI Pilot Project 2017

As in each year since its creation, the LCCF continues to fund research directly at the CU Cancer Center. In 2017, funds were again given to the scientific committee of the CU Specialized SPORE/TORI, which helps to organize cross-disciplinary research at the Cancer Center to support a pilot project. In 2017, Drs. Merrick and DeGregori’s project “Preliminary assessment as to whether tissue landscape changes are predictive of clonal expansions and Squamous cell carcinoma development”, was selected as this year’s beneficiary of the LCCF pilot grant, which they describe below.

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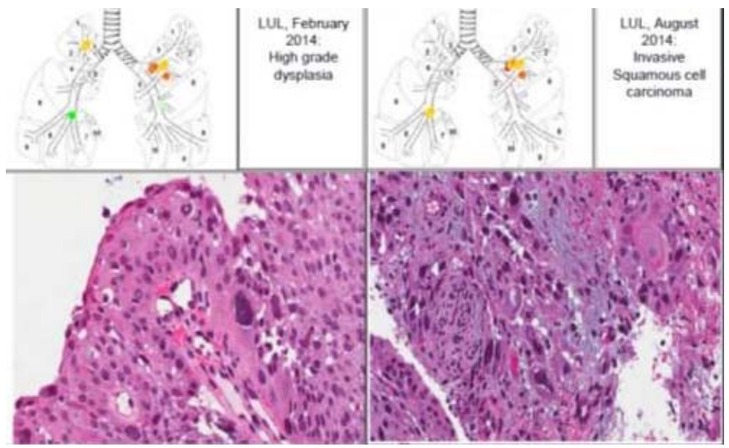
# Adaptive Oncogenesis

By: James DeGregori, PhD and Dan Merrick, MD

Lung cancers may have mutations, but the cells driven by these mutations also have to exist in an environment that permits them to thrive. To explore this we will look at the CU archive of biopsies taken from smokers who already have some abnormal changes in their lungs who underwent recurrent biopsies over time during bronchoscopic surveillance, some of whom later went on to develop lung cancer. We will look at whether the number of different mutations and the number of different families of cells (clones) with the same mutational changes evolve over time as the changes in the airways move closer and closer to a cancer. We will compare these changes in patients who never developed a cancer. We will also look at markers of cell growth and immune cell infiltrates to assess the ‘fitness’ of the pre-cancerous cell populations at different times. Our hypothesis is that smoking, old age, radon, COPD, etc - essentially all the known risk factors for lung cancer - partially work by changing the environment from one that is intolerant of mutations and rapid growth to one that is permissive.

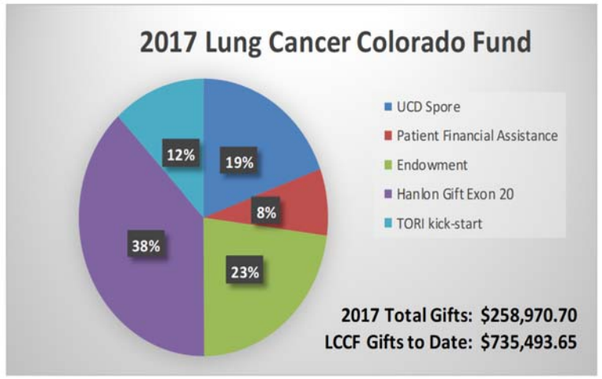



*Example (left) of the same patient showing high grade cellular changes in the left upper lung that became a squamous cancer 6 months later. What evolutionary cellular events were occurring over this time?*

*James DeGregori*

*Dan Merrick*


**If a legacy opportunity, such as completing this Fellowship endowment, is something you are interested in, or you are interested in other transformative gifts for thoracic oncology please contact your MD or Ross Camidge (ross.camidge@ucdenver.edu) or Bob Doebele (robert.doebele@ucdenver.edu), directly.**




## LCCF Expenditures:

By D. Ross Camidge, MD, PhD

By December 2017, when the LCCF committee met to review the distribution of the funds raised for the LCCF this year, the annual amount raised had exceeded $250,000.

- $100,000 of this was specifically earmarked by the Hanlon brothers to support work on EGFR exon 20 mutations (see article on page 10 in this newsletter).
- We gave $20,000 to support patient welfare through our social work department and $50,000 to fund pilot grant (s) to be awarded by the CU Lung Cancer SPORE/TORI scientific review process.
- For infrastructural improvements we committed to giving $30,000 to kick-start the administrative support underlying the Thoracic Oncology Research Initiative (see article on page 5 of this newsletter).

- ***Finally, we contributed ~$59,000 to reach our first medium term goal of ~50% of the planned total for a permanent endowment to help support the salary of trainees in any aspect of the program in the future.***

- ***We hope that a single donor/group will now complete this permanent Fellowship fund and have the Fellowship named by them if they so wish. Next year another crowd-sourced endowment kick-starter is planned, this time for an 'Innovation Fund.'***

## Best Quote

Left: Alan Lee (stage IV lung cancer survivor) and Amy got married in May 2017. Two days later Alan emailed his doctor: "I hope that this can be a reminder of our victories. We still have a long way to go, and many battles are in front of us. But last Saturday, we all beat lung cancer. "

Smarter Than Cancer

# Blood tumor markers may warn when lung cancer patients are progressing on targeted treatments

By: Garth Sundem

For many years, oncologists have known that cancers can secrete complex molecules into the blood and that levels of these molecules can be easily measured. These so-called 'tumor markers' are traditionally associated with a single dominant cancer type, for example Prostate Specific Antigen (PSA) linked to prostate cancer, Carcinoembryonic antigen (CEA) to colorectal cancer, CA125 to ovarian cancer, CA19.9 to pancreatic cancer and CA27.29 to breast cancer. However, the real challenge has been to determine a practical use for these markers. They don't appear to be useful as a means of screening otherwise healthy people for evidence of underlying cancers.

*Lung cancer hasn't read the textbooks and can commonly express blood markers traditionally associated with bowel, breast, ovarian and pancreatic cancer*

Now a University of Colorado Cancer Center study has begun to further define the potential of these markers by looking in a type of cancer not normally associated with them – non-small cell lung cancer (NSCLC). The study suggests that rather than screening for disease, these tumor markers could be useful in monitoring therapeutic outcomes in those with already established disease.

"If you ask some oncologists they might say that there's no point checking these markers in lung cancer as it doesn't express them," says D. Ross Camidge, MD, PhD, Joyce Zeff Chair in Lung Cancer Research at the University of Colorado Cancer Center and director of Thoracic Oncology at the CU School of Medicine. However, when Camidge and colleagues examined levels of four markers classically associated with other cancers, namely CEA, CA125, CA19.9 and CA27.29, they found that if all four were checked, at least one of them was elevated in 95 percent of advanced non-small cell lung cancers (NSCLCs). Some cases expressed only one marker; others expressed multiple markers together.

In recent years, dramatic anti-cancer responses have become possible for some patients with advanced NSCLC with targeted therapies used against specific mutations. By focusing on some of the most prominent examples of 'oncogene-addicted' NSCLC – notably, cases of advanced EGFR, ALK or ROS1 positive NSCLC treated with the appropriate EGFR, ALK or ROS1 targeted therapy – the Colorado group was able to study the potential for these blood tumor markers to reflect both initial therapeutic outcomes and the later development of treatment resistance.

In 126 patients with stage IV oncogene-addicted lung cancer, tumor markers were captured before and after the initiation of treatment. Among patients on targeted treatment expected to have a high response rate, 59 percent of patients had an initial increase in their marker levels during the first four weeks of therapy, with the elevated levels later falling below baseline values in 58 percent of cases.

"These data mean that you shouldn't worry about marker elevations in the first few weeks of targeted therapy in the absence of other evidence, such as worsening symptoms, as most of the time things settle down. Perhaps tumor markers shouldn't even be checked during this early time period at all," Camidge says.

While the tumor markers may not be very useful for predicting initial success or failure, once a patient is benefiting from a targeted treatment, increases in tumor markers from their lowest point may provide useful information about the development of resistance. When a patient's cancer was progressing in the body, a 10 percent or greater rise in the blood tumor markers occurred in 53 percent of patients. However, if the progression was limited to the brain, the tumor markers went up in only 22 percent of cases.

"Clearly, these markers are not a substitute for routine surveillance scans looking for progression, especially in the brain," says Camidge. "However, this is where the art of medicine may have to be appreciated. If the markers are going up but a CT scan says everything is still fine, maybe these data should nudge you to do a more detailed scan – like a PET/CT scan. Or if the best body scans are all stable, perhaps a rise in tumor markers should nudge you to do a brain scan looking harder for a hidden site of progression."

## Blood tumor markers (cont.)

Despite patients in this retrospective study having undergone multiple different types of scans and blood draws at many different frequencies, the data still show that rises in tumor markers on therapy could occur well in advance of radiographic changes of progression (up to 84 days). Although Camidge says a prospective, randomized trial is needed to fully validate the potential of these markers to act as an early warning system, the real question may turn out to be whether finding progression several months earlier matters.

“If adapting your treatment plan earlier versus later in progression doesn’t impact outcomes, an early warning system could just give everyone more time to stress about things,” he says. However, particularly for oncogene-addicted lung cancer, in which national guidelines now support using strategies such as targeted radiation to control small pockets of treatment-resistant disease, Camidge is optimistic that an early warning system for progression could be very useful.

“An ‘oligoprogressive’ state gives us therapeutic options that we wouldn’t have if the progression was more widespread,” he says. “Developing means to catch this earlier ‘stage’ of progression in more people should definitely be explored further.”

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Randy Cordova (stage IV lung cancer survivor) shows you can go fly fishing even when wearing oxygen http://lcam.org/richard-enjoying-life-due-to-research-advances/


Matt Payne (stage IV lung cancer survivor) and his daughter get all dressed for no reason at all. ‘Keeping things normal helps me deal with the diagnosis’


Danielle James (stage IV lung cancer survivor) achieves ’super mom’ recognition for her foster care work http://okgazette.com/2017/05/12/super-moms-gazette-celebrates-mothers-day-with-standout-tales-of-three-women-and-their-families/

Janet Freeman-Daily (stage IV lung cancer survivor) and her husband celebrate her 5 year ‘cancerversary’ with a cruise in the Mediterranean



## How many deposits of cancer should you individually treat with focused radiation in lung cancer patients with multiple brain metastases?

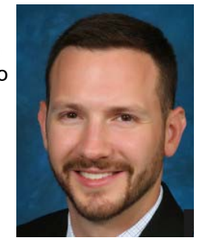
By: Garth Sundem

Although targeted therapies have produced dramatic advances in our ability to control the disease in key molecular subgroups of advanced lung cancer patients, growth of the disease in the brain remains a major problem. Radiation to the brain is often used to treat these deposits but the best technique to use for radiation delivery can be controversial. Whole-brain radiation therapy, as its name suggest, treats the entire brain and can be associated with cognitive side effects within a few years of treatment. Radiosurgery, which directs highly-focused radiation only to the sites of metastasis, sparing the normal brain is an alternative. However, if a patient has multiple brain metastases and you only treat the known sites of disease, is it effective in controlling the brain? If you treat multiple sites with radiosurgery, at some point does the dose to the normal parts of the brain become equivalent to that from whole brain radiotherapy?

A University of Colorado Cancer Center study published in the Journal of Thoracic Oncology offers evidence that may help to answer some of these questions.

The study focused on patients with advanced ALK or EGFR mutated non-small cell lung cancer on targeted therapy who received radiosurgery for four-or-more brain metastases. On average, these patients lived for years with this strategy, the vast majority without ever requiring whole brain radiation. The study also showed no difference in overall survival for patients who were treated with radiosurgery for 4-10 metastases and those treated for 10+ metastases, supporting the idea of increasing the feasible number of CNS lesions that can be treated with radiosurgery. The maximum number of CNS lesions treated in a patient within the study was 47 over multiple courses of radiosurgery.

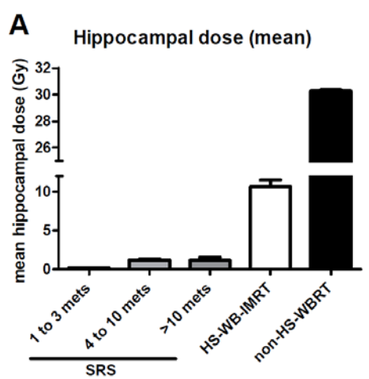
“It used to be that once lung cancer metastasized to the brain, the prognosis was poor. Whole brain radiation therapy can be utilized to help decrease the risk of death form neurologic causes, but at a steep cost. This study suggests that for lung cancer patients whose cancer has spread to the brain and are treated with radiosurgery and targeted drugs, it is rare to die of causes related to brain metastases,” says Tyler Robin, MD, PhD, senior resident in radiation oncology at the CU School of Medicine and the paper’s first author.



*Tyler Robin, MD,PhD*

However, as patients are now living longer, the tolerability of the treatment becomes all the more important. Therefore, one important question addressed in this study is whether radiosurgery to multiple lesions is likely to subject patients to the same cognitive risks as whole-brain radiation therapy.

“Even when we treated over ten brain metastases in one session, the dose to the whole brain was phenomenally lower than with whole-brain radiotherapy,” Robin says. The group measured radiation dose in this setting in two ways – to the whole brain and also the specific dose to the hippocampus, the brain structure responsible for processing new memories and considered the area responsible for the cognitive side effects of brain radiation.

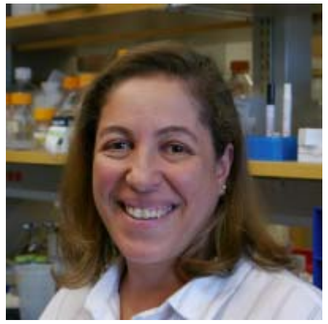



*Graph (above) showing radiation dose to the hippocampus of the brain (where memory is stored) after whole brain radiation therapy (WBRT), 'hippocampal-sparing' WBRT (HS-WB-IMRT) and after different numbers of lesions treated with stereotactic radiosurgery (SRS). Message: You can treat a lot of individual lesions in the brain with SRS without compromising safety.*

“The very low doses of radiation to the normal brain observed with radiosurgery compared to whole brain radiation has the potential to dramatically alter the long term side effects,” says Chad Rusthoven, MD, Radiation Oncologist at CU and the paper’s senior author. “As the field of oncology evolves, we have to evolve with it. Patients with cancer who are eligible for targeted therapies are living longer than ever before, making treatment strategies that support long term quality of life even more important.”

# Tarloxitinib puts tumor-seeking tail on anti-EGFR drug to precisely target lung cancer

By: Garth Sundem



*Adriana Estrada, PhD*

EGFR is a common genetic target in lung cancer, but not all EGFR mutations are created equal. Patients with a type of EGFR anomaly called an “EGFR exon 20 insertion” often fail to respond to existing drugs targeting EGFR. Previous work shows this is because it simply takes a much higher concentration of anti-EGFR drugs to combat the exon 20 form of the mutation – and at the concentration needed to be effective, these drugs are too toxic to use in human patients.

A University of Colorado Cancer Center study presented at the AACR-NCI-EORTC International Conference on Molecular Targets 2017 proposes a unique way to reach the concentration of anti-EGFR drug needed to fight exon 20 insertions without harming healthy tissues: By pairing an anti-EGFR drug with a “tail” that only activates the drug when it is very near tumor cells, tarloxitinib brings the drug to tumors while keeping concentrations safe in surrounding tissues.
Tarloxitinib is one in a class of new medicines called “prodrugs” that are introduced into the body in an inactive form and then depend on changes within the body to activate their effects. In this case, the prodrug is composed of two pieces: A drug that attaches to and blocks EGFR receptor activity, and another piece that only activates the drug in the absence of oxygen. Because tumors grow so fast, they often outpace the development of blood vessels that deliver oxygen and so survive in low-oxygen conditions called “hypoxia”. When tarloxitinib reaches a hypoxic tumor, the tail cleaves from the drug, activating the drug against EGFR receptors in the nearby tumor.

“The problem is that in order to treat patients with these mutations you would have to give existing drugs at levels that would be too toxic. With the prodrug, you can get those high doses but localized in the tumor,” says Adriana Estrada, PhD, research instructor at CU School of Medicine and the paper’s first author. Estrada worked in the lab of CU Cancer Center principal investigator Robert C. Doebele, MD, PhD.

One hurdle in testing tarloxitinib against lung cancer cells with EGFR exon 20 insertions was the fact that no patient-derived cell lines existed with this kind of mutation.

*Kevin Hanlon (in hat) and his brother Bob*

“We’ve known about the mutation from patient biopsies, but previous teams have studied exon 20 insertions by placing the mutation into cells or other artificial techniques. Our group was the first to isolate and maintain cell lines from patient samples that express exon 20 insertion,” says Estrada.

In fact, the group isolated three cell lines, each with a slightly different form of EGFR exon 20 insertion, allowing the researchers to test tarloxitinib against a range of related alterations. The group saw significant response in cells and when they tested the drug in mice, “the results are really promising,” says Estrada.

About 15 percent of lung cancers are caused by EGFR mutation. About 5-10 percent of these EGFR cancers are the subtype that depends on exon 20 insertions. The group now hopes to use their promising results with cells and mice to lay the groundwork for clinical trials of tarloxitinib specifically targeting lung cancers with EGFR exon 20 insertions.

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## Exon 20 Group Begins.

When Kevin Hanlon got diagnosed with a rare form of lung cancer (exon 20 EGFR mutant), he and his brother realized progress wouldn’t come from standing alone on an island. Together they started an international working group for those affected with the same disease (http://exon20group.org/) and began actively funding experts working in the area. In 2017, the Hanlons generously gave $100,000 through the LCCF directly to support Bob Doebele’s work, including that described above..

Smarter Than Cancer

# New Faces

Jose M. Pacheco, MD

Dr. Jose Maria Pacheco has recently joined as a Medical Oncology Attending in thoracic malignancies and phase I clinical trials. He completed his MD degree at University of Texas Medical Branch in Galveston and an Internal Medicine residency at Washington University Saint Louis. He continued his training in Hematology and Oncology at Baylor College of Medicine in Houston, Texas. In 2015 he received the Harris Health Hero award as a recognition for outstanding patient care.

His research interests center around solid tumor immunotherapy . His goal is to help increase the portfolio of investigator initiated studies at our institution. He is currently preparing a statewide cancer research fundraiser for Fall 2018.

Outside of work, Dr. Pacheco enjoys exercising and exploring the outdoors. He speaks Spanish and enjoys Hispanic culture.

Christopher D. Scott, MD

Dr. Chris Scott joins the thoracic surgery faculty after completing his cardiothoracic training at Duke University. He completed his undergraduate and medical education at the University of Virginia, followed by a surgery residency at the University of Cincinnati. He also completed a 2 year fellowship at the National Institutes of Health, National Cancer Institute, focusing on tumor immunology and basic science translational research.

His clinical interests include mediastinal, lung and esophageal surgery. Dr. Scott has an interest in minimally invasive thoracic surgery, VATS and robot assisted thoracic surgery. He has completed advanced training on the DaVinci Xi and DaVinci Si robotic systems. In addition, he has an interest in end stage lung disease, lung volume reduction surgery (LVRS) and lung transplantation.

In his free time, Dr. Scott enjoys being outdoors - hiking, trail running, camping, and when he's near the water, surfing and swimming.

Ronni Miller, PharmD

Ronni Miller will be joining Thoracic Oncology Clinic as our full time clinical pharmacist starting in January 2018. She completed her Doctorate in Pharmacy at Texas Tech Health Science Center; her PGY1 pharmacy practice residency at Parkland Health and Hospital System; and a PGY2 Oncology Specialty Residency at the University Of Colorado Skaggs School Of Pharmacy.

Ronni is currently the Medication Access and Renewal Center Prior Authorization (MARC-PAR) Clinical Oncology Pharmacist and practices in Thoracic Oncology twice a week.

Outside of work, she enjoys baking, sewing, and spending time with her family.

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(Left) What happens when patients self-organize and work with researchers to study their disease?

https://www.alkpositive.org/