This issue of Innovations in Research highlights our lung cancer research and clinical trials at the UCI Chao Family Comprehensive Cancer Center.

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Leaders in advancing lung cancer treatment

The UCI Chao Family Comprehensive Cancer Center is a leader in first-in-human trials of targeted therapies for non-small-cell lung cancer for good reason. Actually, several reasons.

The cancer center's success with investigative drugs to block cancer-related genetic mutations is well known. It culminated in U.S. Food and Drug Administration approval in 2011 for crizotinib for ALK positive mutations, in 2016 for ROS1-positive mutations and in 2018 for breakthrough therapy designation for MET exon 14 mutations. The drug has effectively revolutionized the treatment of advanced non-small-cell lung cancer.

UCI Health oncologist Dr. Sai-Hong Ignatius Ou led the initial Phase 1 study of crizotinib in 2007 and some of his patients still remain on this protocal.

"Dr. Ou has created a successful trial portfolio for non-small-cell lung cancer patients," said Dr. Viola Zhu, a

UCI Health oncologist who works closely with Ou on the current targeted-therapy trials.

"Because of our history in this field, companies with innovative drugs are aware that we are able to run a successful study on targeted therapies," she said. "We have many, many unique trials for targeted therapies."

The new trials are not only targeting non-small-cell lung cancer, but also other solid tumors with various genetic mutations. Almost all of the investigational medications in these studies are oral, and because they target a specific mutation while potentially sparing normal tissue, side effects tend to be much lower.

"Once patients get used to oral drugs, they are very reluctant to go on IV chemo or immunotherapy drugs again because it's much easier," Zhu said. "And in our Phase 2 trials, the patients are stable. They can actually travel and still take their medications."

Learn about four of the lung cancer team's new clinical trials, which are now enrolling patients.

Meet our lung cancer specialists

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To learn more about UCI Health's low-dose CT lung cancer screening program and minimally invasive treatment options, visit ucihealth.org/lungcancer

Next generation drug targets ROS1 mutation

When the FDA granted approval for crizotinib to target the rare ROS1 genetic mutation in non-small-cell lung cancer in 2016, it capped years of clinical research.

Now UCI Health oncologists are testing a new drug, repotrectinib, to counter ROS1-driven tumors as well as those linked to the NTRK mutation. Repotrectinib is currently in a Phase 1 trial at UCI and is expected to move to a Phase 2 trial in the near future, said Zhu, who is involved in the trial.

The UCI Chao Family Comprehensive Cancer Center is one of just four U.S. sites to test the drug. Three additional sites are located in South Korea. Repotrectinib was developed by Turning Point Therapeutics, whose chief scientific officer designed crizotinib, which Zhu said has changed the entire field of lung cancer treatment.

Researchers had originally hoped that repotrectinib also would be a possible next-generation drug for ALK-positive cancer. So far, however, the drug does not appear to be active against that mutation. Zhu said the company is focusing instead on the other two mutations.

"Its efficacy for ROS1 and NTRK seems to be very robust," she said. "That's also true for patients who have failed prior treatments."

Both ROS1 and NTRK mutations are rare. The ROS1 mutation is linked to fewer than 2% of lung cancers. NTRK is rarer still.

Although Phase 1 patients are still being enrolled, there is currently a waiting list. "We are very close to finding the Phase 2 dose, and at that point there will be a global enrollment for Phase 2," Zhu said.

The drug has been well tolerated so far, with the most significant side effects being dizziness, some changes in taste and paresthesia, a tingling or burning sensation.

To be eligible, patients must have locally advanced or metastatic solid tumors with the ROS1 or NTRK mutation, and whose cancer has progressed under traditional treatment or who could not tolerate or declined those treatments.

The principal investigator is UCI Health oncologist Dr. Samuel Ejadi.

For more information, contact Dr. Samuel Ejadi at sejadi@uci.edu or Dr. Viola W. Zhu at zhuvw@uci.edu or 877-827-8839.

First in-human studies targeting KRAS gene mutation

The UCI Chao Family Comprehensive Cancer Center is one of three sites worldwide participating in the first-in-human study of the drug MRTX849 to attack the KRAS gene mutation, which is implicated in 20% to 30% of lung adenocarcinomas and 50% of colon cancers.

KRAS is one of the RAS family of genes responsible for 22% of all cancers, according to the National Cancer Institute.

"RAS functions as an 'on/off' switch for at least six downstream cellular signaling pathways that control growth and cell division," according to the National Cancer Institute. "Several of these pathways, including the PI3K and MAPK pathways, are known to play important roles in cancer development and progression."

This occurs when a mutation causes the gene to get stuck in the "on" position, leading to uncontrolled cell growth.

> "If the drug works, it's going to be almost like a miracle."

There are several different kinds of KRAS mutations. This Phase 1/2 study is specifically evaluating MRTX849 for the KRAS G12C mutation. The Phase 1 study seeks to enroll about 40 patients. Once the drug's safety is established and a standard dose is set, Zhu said the Phase 2 trial will enroll up to 160 patients.

Doctors with patients who may qualify for any of these trials are encouraged to contact the UCI Chao Family Comprehensive Cancer Center's clinical research line at 877-UC-STUDY (877-827-8839) or by emailing ucstudy@uci.edu

Zhu said the KRAS mutation is believed to constantly signal downstream pathways in ways that keep activating the cancer. "The idea is to block the mutation and shut off the downstream pathway."

One question, she said, will be whether shutting down the downstream pathways opens other bypass pathways.

The trial is open to patients with any advanced tumor type that has progressed despite conventional treatment, or for patients who have declined those treatments, as long as the tumor has the KRAS G12C mutation. MRTX849, developed by Mirati Therapeutics, has been generally well tolerated, Zhu said.

"If the drug works, it's going to be almost like a miracle," Zhu said. "We know this mutation, KRAS, but until now it has not shown to be targetable."

For more information, contact principal investigator Dr. Sai-Hong Ignatius Ou at siou@uci.edu or 877-827-8839.

KRAS subject of second first in-human study

The lung cancer team also has enrolled the world's first patient in a second trial targeting KRAS mutations.

Rather than directly inhibit the mutation, itself, a new experimental drug, RMC-4630, blocks a binding protein for a KRAS pathway called SHP2.

> "This study is very exciting because no one has managed to block KRAS."

"The signaling pathway of KRAS is very well known," Zhu said. "It often involves recruiting proteins to activate the path, and the SHP2 protein is essential to activating the KRAS pathway. Here at UCI, we have the very first patient who enrolled in this trial, which is being conducted at more than 10 sites."

The oral drug was developed by Revolution Medicines. The first dose was delivered at UCI in fall 2018.

This first-in-human clinical trial is enrolling from a broader group than the Phase 1/2 trial of MRTX849, which targets only the KRAS G12C mutation. Patients with any KRAS mutation, BRAF class 3 mutation and the NF1 mutation, which also seems to be involved in the KRAS pathway, may be enrolled in the RMC-4630 study.

Zhu said researchers are trying to determine an optimal dose. In addition, a new protocol has been developed to use RMC-4630 in combination with another drug to enhance its effectiveness. Investigators have been concerned that blocking the KRAS pathways may activate other pathways. The second drug would block such bypasses.

"This study is very exciting because no one has managed to block KRAS," Zhu said.

The RMC-4630 study has a waiting list, but physicians and their qualifying patients are encouraged to contact Dr. Sai-Hong Ignatius Ou at siou@uci.edu or 877-827-8839.

Drug trials attack rare RET gene mutation

Only 1% to 2% of non-small-cell lung cancers are caused by the rare gene mutation RET (short for "rearranged during transfection"). But RET is responsible for 10% to 20% of papillary thyroid cancer and as many as 60% of all sporadic medullary thyroid cancers.

A new Phase 2 trial of BLU 667, a highly selective RET inhibitor, is enrolling patients with either of these metastatic cancers, as well as other advanced solid tumors harboring this mutation.

"Traditionally, we have been using oral drugs that are not specific for the RET mutation," said Zhu, the trial's principal investigator. "But those drugs are not as potent and they also have many toxicities because they hit many different targets."

BLU 667, developed by Blueprint Medicines, is a very potent RET inhibitor that Zhu says also crosses the blood-brain barrier and thus may prove useful for patients with brain metastasis.

The UCI Chao Family Comprehensive Cancer Center was one of only four sites in the world selected to participate in the Phase 1 trial of BLU 667. Early results showed that tumor shrinkage and patient tolerance of the experimental medication was good, she said.

The rarity of the RET mutation means that finding populations large enough for large-scale Phase 3 studies would be nearly impossible. But the FDA has been approving targeted therapies against rare mutations discovered in solid tumors based just on Phase 2 studies — as long as the results are robust, Zhu said.

Although Zhu and her team already have received many patient referrals from community physicians and oncologists, she said the trial is still open for enrollment.

"Traditionally, we have been using oral drugs that are not specific for the RET mutation."

To be a candidate for the trial, patients must have advanced cancers with the RET mutation — non-small-cell lung cancer, thyroid cancer or other advanced solid tumors — and they must have exhausted or declined traditional therapies.

A second company, Loxo Oncology, has also developed another specific RET inhibitor that the UCI team is testing for efficacy and tolerability in a Phase 2 trial. The LOXO experimental treatment is for patients with either locally advanced or metastatic cancer that has either progressed under traditional treatment or for patients who could not tolerate or declined those treatments.

The BLU 667 trial also is open to patients whose cancers progress under the LOXO 292 treatment, Zhu said.

To learn more about the RET trials, contact Dr. Viola Zhu at zhuvw@uci.edu or 877-827-8839.

To learn more about our cancer clinical trials or determine whether we have one that may meet your patient's needs, call the UCI Chao Family Comprehensive Cancer Center at 877-827-8839 or email us at ucstudy@uci.edu

Here for you and your patients

The UCI Chao Family Comprehensive Cancer Center is Orange County's only National Cancer Institute-designated comprehensive cancer center. It is a vital resource for the people of Orange County and surrounding areas, generating and disseminating new knowledge about the causes, prevention and treatment of cancer, as well as training the next generation of cancer providers and caregivers, and alleviating the overall cancer burden on our population.

Based on the campus of UCI Medical Center in the heart of Orange County, the Chao Family Comprehensive Cancer Center integrates research, prevention and the most advanced diagnostics, treatment and rehabilitation programs to provide the best possible care for patients and their families. We also offer treatment, chemotherapy and infusion services, as well as access to clinical trials, at UCI Health Cancer Center — Newport.

Our cancer center researchers form disease-oriented teams that bring together patient-centered basic, translational and clinical investigators to facilitate the movement of discoveries through the pipeline into the clinical arena.

With a world-class, multidisciplinary team of surgeons, radiation oncologists, medical oncologists, pathologists, nurses, rehabilitation therapists, pharmacists, social workers and dietitians, the Chao Family Comprehensive Cancer Center is able to address cancers of all types and degrees of severity.

For more information about cancer clinical trials at the Chao Family Comprehensive Cancer Center, call 877-827-8839 or email ucstudy@uci.edu

REGISTER FOR THE UCI ANTI-CANCER CHALLENGE

Join us June 8, 2019 for the third annual UCI Anti-Cancer Challenge at UC Irvine's Aldrich Park. By riding, running, walking or volunteering, you move us one step closer to finding a cure for a disease that touches us all. All proceeds go directly to lifesaving cancer research at the Chao Family Comprehensive Cancer Center.

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