New immunotherapy for lung cancer shows promise of success

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In a clinical trial, Mark Rubinstein, Ph.D., (left) and John Wrangle, M.D., used two drugs that have never been combined in humans before to slow the progression of lung cancer. Credit: Sarah Pack, Medical University of South Carolina

In a groundbreaking development, results from a recent clinical trial to treat lung cancer show that a novel immunotherapy combination is surprisingly effective at controlling the disease's progression. The study, published April 4 in the journal *The Lancet Oncology*, focused on non-small cell lung cancer, which is the most common form of lung cancer.

Immunologist John Wrangle, M.D., of the Hollings Cancer Center at the Medical University of South Carolina said it's a promising therapy that can be delivered in an outpatient setting. "People don't talk about 'curing' patients with metastatic lung cancer. We now get to flirt with the idea for certain patients using immunotherapy. And at the very least we have a significant proportion of patients enjoying prolonged survival even if we can't call them 'cured'," he said.

He, along with his colleague Mark Rubinstein, Ph.D. also of the Hollings Cancer Center, designed a clinical trial that started in 2016.

Patients with metastatic non-small cell lung cancer will always progress after chemotherapy, so most patients go on to be treated with immunotherapy, a type of therapy that uses the body's immune system to fight cancer. One class of immunotherapeutic drugs is known as "checkpoint" inhibitors, as they target checkpoints in immune system regulation to allow the body's natural defenses, such as white blood cells, to more effectively target the cancer.

Rubinstein said checkpoint therapies work by cutting the brake cables on the white bloods cells that are inherently able to kill tumor cells. "Tumor cells often produce suppressive factors which essentially turn the brakes on tumor-killing white blood cells. What's unique about the therapy that we're testing is that in addition to cutting the brake cables on white blood cells, we're providing fuel to them so that they can more effectively kill cancer cells."

Wrangle and Rubinstein's therapy is a combination of a checkpoint drug, nivolumab, with a new and powerful immune stimulation drug, ALT-803. "What's unique about our trial is that it's two completely different types of drugs that have never been combined in humans before, and the trial demonstrated that these drugs can be safely administered, and also, there's evidence that it may help patients where checkpoint therapy is not good enough alone," said Rubinstein.

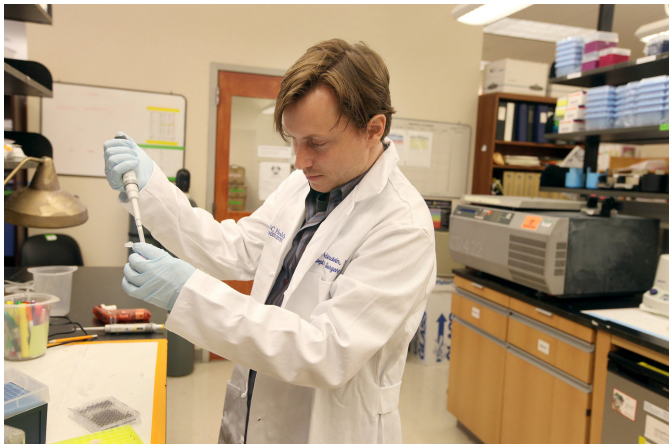
Patients who have stopped responding to checkpoint therapy may be helped significantly by adding ALT-803. Pre-clinical studies have shown that ALT-803 activates the immune system to mobilize lymphocytes against tumor cells and could potentially serve as an important component in combination treatments. Of the 21 patients treated, nine previously either had stable disease or

responded to single-agent immunotherapy before becoming resistant to this treatment. Of these nine patients, 100 percent either had stable disease or had a partial response to the treatment used in this study.

"We can reassert control, at least in terms of stable disease, in essentially everybody we've treated so far," Wrangle said.

This novel combination is a huge step forward in cancer treatment. "Whereas for decades the modalities of therapy were surgery, radiation, and chemotherapy, the last decade has brought targeted therapy, and more recently, immunotherapy. It fundamentally alters the balance of power between your body and your cancer," Wrangle said.

A lung cancer specialist, Wrangle said 75 percent of lung cancer patients unfortunately are diagnosed at an incurable stage. "If 10 years ago you were talking about defining a five-year survival rate for metastatic non-small cell lung cancer patients, someone would laugh in your face. It would be a joke. It's just a very different time now," he said of the progress being made in the treatment of lung cancer.



Rubinstein's work has been instrumental in the development of ALT-803. Credit: Sarah Pack

He credits Rubinstein's work, instrumental in the development of ALT-803, in helping to make this advance. Research into ALT-803 started years ago while Rubinstein was doing his postdoctoral training at the Scripps Research Institute. It was there that he co-discovered the powerful immune system stimulator used in this trial. The stimulator, known as IL-15 complexes, is actually a combination of an immune system growth factor and its soluble receptor. IL-15 is a growth factor for certain kinds of white blood cells including natural killer cells and T cells.

Wrangle explained that natural killer cells are the chief arm of the innate immune response. "They are an important part of anti-cancer response that haven't been really talked about for a long time."

Wrangle said his collaboration with Rubinstein is a powerful example of what team science can accomplish.

"His ownership of the intellectual foundation of this therapy is manifest," Wrangle said of Rubinstein's contribution. "He is brilliant and just works furiously to help understand how we can develop this therapy."

Successful trials for the treatment of cancer are incredibly rare, he said. "There are very few people in human history who get the privilege of developing a new therapy for any human disease, much less cancer. Mark and I are now in this weird micro-club of folks who have developed the promise of a new therapy for cancer. That's such an amazing privilege to be able to do that," he said.

In contrast to other immunotherapies that require admission to a hospital, this new therapeutic combination can be administered in an outpatient setting. "The plan was to do it all as an outpatient therapy because inpatient therapy is just infeasible. My patients feel like they have the flu, but they go about their day, and it's totally manageable. That's the kind of revolutionary part with regard to this class of agent," Wrangle said.

Wrangle and Rubinstein are surprised and elated at the success demonstrated in their latest study. Wrangle said the landscape of oncology is "eyeball-deep in failed trials," so he and Rubinstein are

hopeful this will provide more treatment options for patients. "The number of trials that work is miniscule, so was I surprised? I was ecstatic that it was working," he said.

Rubinstein agreed, adding that the success of the trial is a testament to the commitment, hard work and incredible insight that Wrangle has for making a difference for his patients. "He has an amazing vision for how to bridge the gap between basic and clinical research."

Wrangle said there's still plenty of work to do before the new combination of drugs can be used outside of a clinical trial. "We have a lot to figure out about how to use this therapy, and we need to treat a few hundred patients in order to get a better sense of how to refine the synergy of these two classes of drugs. That's just going to take time," he said.

Both of the researchers, who are in their early forties, said they were motivated by the need to give lung cancer patients better options. Wrangle plans to frame the study's publication. "I think this manuscript will be the thing that we have on the wall that we look back at 20 years from now, when we're still working together and discovering new therapies."

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