

PROGRESS AND POSSIBILITY: A MULTI-PRONGED APPROACH TO RESEARCH IN LUNG CANCER

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AUTHOR



Dr. Claudia-Nanette Gann
Executive Medical Director Global Medical Affairs, Oncology



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OVERVIEW

Innovation at Merck KGaA, Darmstadt, Germany and across the biopharmaceutical industry is fueling critical advances in lung cancer treatment

As a practicing medical oncologist for 12 years, I had the privilege of treating patients with lung cancer—and while I did everything in my power to help each patient, I felt limited in my impact. It was a pivotal moment when I realized that being involved in research and clinical development I could not only help those patients directly in my clinic, but extend that. First: to the many patients enrolled in clinical trials; and, potentially to people around the world, now, and for the future.

At Merck KGaA, Darmstadt, Germany, I am excited to be contributing to the development of cancer therapies that may help many patients with lung cancer. It is this possibility to drive progress in lung cancer treatment forward, that inspires me every day. We, alongside the cancer community, are committed to driving this innovation in lung cancer because the reality is, there are still too many patients being diagnosed with this disease every day, and a lack of optimal treatment options.

Yet, there is reason for hope. Over the last several years, the advances in the treatment of lung cancer have been remarkable. As more is learned about the biological variety in lung cancer types, more possibilities and opportunities for treatment continue to be discovered.¹

It's an extraordinary time to be working in lung cancer research.

Driving progress in non-small cell lung cancer

In non-small cell lung cancer (NSCLC) in particular, we have witnessed incredible progress. Until around 10-15 years ago, for decades there had been little to no change in available medicines for this disease, with only chemotherapy as an option. Now a variety of targeted therapies aimed at key oncogenic drivers and immuno-oncology (IO) therapies that harness the immune system to help fight the tumor have also brought remarkable benefits to patients with this form of lung cancer. In the US and Europe alone, we now have more than 15 approved treatments available.^{2,3}

And progress is continuing. Early research includes bi-specific antibodies and antibody-drug conjugates (ADCs) to harness antibodies in different ways; new therapies and drug combinations for patients whose tumors have grown resistant to available treatments. Research is also expanding the understanding of brain metastases, something that has a huge impact on a person's quality of life, and a frequent complication that affects approximately 25-40% of patients with NSCLC.⁴

Our Approach

At Merck KGaA, Darmstadt, Germany, we're taking a multi-pronged approach to clinical research and therapeutic development in lung cancer. This is driven by the understanding that lung cancer isn't one disease—it is incredibly heterogeneous. For example, in recent years we've learned that patients whose tumors have an oncogenic driver do not respond as well to IO treatment (or IO combined with chemotherapy) compared to those patients whose tumors do not have an oncogenic driver. In other words, what may be a highly effective treatment for one type of lung cancer may be wholly ineffective for another. And that is why biopsy and testing is so important to understand the molecular profile of a tumor—so that optimal treatment can be chosen and administered.

Our research is focused on therapeutic development in three key pathways, two of which I've already mentioned: oncogenic drivers and IO therapies. The third area is DNA damage response (DDR), a complex network that detects and repairs damage to DNA.

DDR pathways are particularly important in cancer. In many tumors, one DNA repair pathway is disabled, which allows the tumor cells to accrue potentially beneficial mutations—also allowing them to continue to grow uncontrollably or even evade treatment. But this advantage is also a liability because the cells deeply depend on the remaining DDR pathways for their survival. By developing therapies aimed at key parts of the DDR network, we can exploit this vulnerability to target lung cancer cells.

DDR in Small Cell Lung Cancer

One area where we have already seen some of the early potential of DDR is in small cell lung cancer (SCLC) where Merck KGaA, Darmstadt, Germany, is investigating a key protein in the DDR pathway known as ataxia telangiectasia RAD 3, or ATR.⁵ We believe by deploying a molecule to selectively bind and halt or impede the activity of the ATR protein—leading to ATR inhibition—may hold promise as a therapeutic approach, particularly in combination with other cancer treatments, such as immunotherapy, chemotherapy, and radiation.

The biology of SCLC is quite different from NSCLC so—despite all the advances made in NSCLC—targeted therapies aimed at oncogenic drivers as well as IO therapies have been largely ineffective in SCLC, leaving patients with this form of lung cancer with limited treatment options.⁶ Cancers, such as SCLC, that are highly aggressive, and replicate quickly, are thought to be especially efficient at repairing DNA damage caused by anti-cancer treatment. These cancer types may initially respond well to chemotherapy however, the therapeutic effect is often not durable. Additionally, SCLC carries a high burden of mutations that are closely linked to the DNA Damage Response pathways. Inhibiting the DNA Damage Response mechanism of cancer cells may hold the key to improving the treatment of these types of cancers.

There's much to be done, including to evolve the standards of lung cancer care so that the most effective therapies are given to patients earlier in the course of their disease, and accelerate the time it takes to get new treatments to patients, where and when it is possible. Innovation is in vain if it does not reach the patient, and it is the patient for whom we continue to work both with urgency and a strong commitment. But with the continued efforts and dedication of the oncology community, progress in lung cancer is continuing to improve the treatment of this disease and improve lives.

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