

## Letting Nature Loose

Two things stood out today when I scanned the news for interesting events in oncology. The first was that President Jimmy Carter announced that his melanoma, which had metastasized to the brain, was in remission after gamma knife treatment and therapy with an immune checkpoint inhibitor. He was taking a holiday from therapy, which would have been unheard of even 10 years ago. The second was an article in *Science*<sup>1</sup> that was an elegant attempt to explain why some cancers respond to immunotherapy and some don't. Unraveling the biologic basis for this is a necessary stepping stone to define strategies to make more cancers sensitive to immune-based treatments.

It also made me reflect on my experience at a recent Stand Up To Cancer (SU2C) Summit meeting. I'm part of a "Dream Team" focused on immunotherapy for pancreatic cancer—a tough nut to crack, for sure. But it seemed that in almost every team presentation, immunotherapy was in the forefront, including a new team focusing on RAS activation and immunotherapy in lung cancer. Katie Couric, one of the founders of SU2C, even blogged about the pervasive influence of immune-based strategies.

I am further amazed that, in some diseases, immunotherapy is working and transforming patient lives. For decades, immunotherapy was a kind of stepchild. The immunologists were convinced, but the rest of us waited for results. It took a better understanding of the tumor microenvironment and the relationship to the malignant compartment before the results started to show. And those results link back to a lot of important, groundbreaking research, much of it federally funded.

In our passion to improve treatment, we have focused on signaling pathways, using antibodies or small molecules to interrupt critical circuits, and we have probed the cancer genome searching for new and better targets. But in the process, we have uncovered amazing genetic heterogeneity, particularly in solid tumors. This heterogeneity raises more questions. How we can even begin to tackle this therapeutically? It occurs to me that we can't be smarter than nature itself; perhaps only innate immunity, enhanced through novel strategies, has the capacity to deal with this diversity.

Another lesson for me is the virtue of persistence in science. A dear friend—and internationally revered tumor immunologist—was amused when she saw that the journal *Science* named "immunotherapy" as the breakthrough development in cancer last year. Her comment was that she and her colleagues have appreciated the potential all along and that the only thing new in 2015 was that the rest of the world had now figured it out. She and her colleagues stuck to their guns, believed in their work, and never let it go. It's because of their collective work, each contributing building blocks, that we have successful immunotherapy today. And I think it will continue to improve.

I doubt that we will abandon useful older chemotherapy drugs or newer targeted agents, but it's definitely time to make room for nature and allow the immune system to join the fight.

### Reference

1. McGranahan N, Furness AJ, Rosenthal R, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. *Science* 2016;351:1463–1469.



### Margaret Tempero, MD

Dr. Tempero is a Professor of Medicine and Director of the UCSF Pancreas Center, and the editor-in-chief of *JNCCN*. Her research career has focused on pancreatic ductal adenocarcinoma, especially in the area of investigational therapeutics.

Dr. Tempero has served on the ASCO Board of Directors and as ASCO President. She co-directed the AACR/ASCO Methods in Clinical Cancer Research and taught this course and similar courses in Europe and Australia. She was founding Chair of the NCI Clinical Oncology Study Section (CONC) and served as a member and chair of the NCI Board of Scientific Counselors Subcommittee A. She is on the External Advisory Boards of the Pancreas SPOREs at Mayo Clinic and at UAB/Minnesota and the GI SPORE at the University of Arizona. She is, or has been, on the Scientific Advisory Boards of the Lustgarten Foundation, the Pancreatic Cancer Action Network, the V Foundation, The Alberta Canada Cancer Board, and the EORTC. She served as a member of the Oncology Drug Advisory Committee for the FDA.

She has served as Deputy Director and Interim Director for the UNMC Eppley Cancer Center. She is Chief Emeritus of the Division of Medical Oncology at UCSF and served as Deputy Director and Director of Research Programs at the UCSF Helen Diller Family Comprehensive Cancer Center.

The ideas and viewpoints expressed in this editorial are those of the author and do not necessarily represent any policy, position, or program of NCCN.

**What do you think?** Please e-mail correspondence (include contact information) to [JNCCN@nccn.org](mailto:JNCCN@nccn.org).