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The European Society for Medical Oncology (ESMO) bestowed its ESMO Award upon **Alberto Sobrero, MD,** at the European Cancer Congress in Copenhagen, Denmark, on October 7. The award honors his outstanding contributions to the understanding and treatment of colorectal cancer—he has authored more than 200 articles on the disease—as well as his scholarship related to the design and interpretation of clinical trials. Sobrero heads the medical oncology unit at IRCCS San Martino IST in Genova, Italy, a role he has held since 2001.

Blood Assay Predicts Response to Pembrolizumab

Although some patients with advanced melanoma have dramatic responses to treatment with PD-1 inhibitors, most do not. Identifying which patients are most likely to respond to these immunotherapies has proven to be a significant challenge for researchers.

Eager to determine which patients might fare best with anti–PD-1 therapy, Alexander Huang, MD, and colleagues at the University of Pennsylvania in Philadelphia and Memorial Sloan Kettering Cancer Center in New York, NY, investigated whether tracking the effect of pembrolizumab (Keytruda; Merck) on immune cells in blood samples might provide an answer. Huang presented the team's findings at the Second CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference in New York, NY, held September 25–28.

Researchers analyzed blood samples from 29 patients with stage IV melanoma taken before and 3, 6, 9, and 12 weeks after beginning treatment with pembrolizumab. Exhausted phenotype CD8+ T cells express high levels of PD-1 on their surface, Huang explained, meaning that treatment with pembrolizumab could reenergize them.

The researchers assessed this effect and "found a modest but significant increase in the proliferative marker Ki67," Huang said. In fact, Ki67 levels were significantly higher in PD-1–expressing CD8+ T cells in posttreatment blood samples, compared with pretreatment samples, in 78% of the patients, indicating a strong, on-target immunologic response. "Yet only a fraction of the patients had significant tumor shrinkage—38% of the cohort," Huang noted, meaning that Ki67 alone did not predict clinical outcomes.

Instead, the researchers found that the magnitude of reinvigoration of exhausted T cells—the peak level of Ki67 after treatment—compared with tumor burden (the volume of all tumors added together) prior to treatment correlated with clinical response. In fact, all patients who had a ratio of reinvigorated T cells to pretreatment tumor burden greater than 1.94 were alive after 11 months, compared with 50% of patients with a ratio less than 1.94. In a second cohort of 18 patients, 75% of patients with a ratio greater than 1.94 were alive after 24 months, compared with 29% of patients with a ratio less than 1.94.

The findings suggest that the failure of pembrolizumab may be due not to the inability to reinvigorate exhausted T cells, but rather to an imbalance between CD8+ T-cell reinvigoration and tumor burden.

"These are still small trials and have to be validated in a larger [cohort]," said Huang. "But it raises the possibility of a blood draw during therapy, where clinicians can intervene early and, if necessary, add another immunotherapy" to augment the immune response.

Although a few studies have concluded that high expression of the PD-1 ligand, PD-L1, in tumor tissue predicts a response to pembrolizumab, its use as a biomarker is far from perfect: Some patients with high PD-L1 expression do not respond whereas some with low expression do. Huang said his team doesn't know whether their predictive ratio might be better at determining the likelihood of response than PD-L1—or whether assessing and combining both markers would prove more accurate than either method alone, a question that merits additional research.

"One of the limitations is whether we can get biopsies on a routine basis from these patients to compare with the blood, and if so, I think it's absolutely necessary to do that," Huang explained. *–Suzanne Rose* ■

Trio of Scientists Wins Lasker Award

The Albert and Mary Lasker Foundation honored three distinguished physician–scientists with a coveted award for their independent, groundbreaking research that led to the discovery of HIF1 and explained how the protein drives physiologic changes in response to hypoxia. Such changes can play a role in cancer progression and the development of other medical conditions.

Gregg L. Semenza, MD, PhD, of Johns Hopkins University School of Medicine in Baltimore, MD; Peter J. Ratcliffe, MD, of the University of Oxford and the Francis Crick Institute in the UK; and William G. Kaelin Jr., MD, of Dana-Farber Cancer Institute in Boston, MA, will share the 2016 Albert Lasker Basic Medical Research Award and the $250,000 honorarium it carries. The prize was bestowed during a September 23 ceremony in New York, NY.

In the early 1990s, Semenza was trying to explain how hypoxia triggers the production of erythropoietin, promoting the formation of red blood cells, which carry oxygen. Through a series of experiments, he hit upon a nuclear protein that he dubbed HIF1 (composed of HIF1α and HIF1β), which interacts with a particular DNA sequence when cells lack oxygen. However, HIF1, he found, does more than regulate erythropoietin: HIF1 induces VEGF, which plays a role in angiogenesis during tumor formation and development.

Although erythropoietin is produced mainly by kidney and liver cells, Ratcliffe found that HIF1 activates genes in an oxygen-dependent manner in a variety of cell types. He also demonstrated that HIF1 regulates the rate of glycolysis. These findings indicate that HIF1 is part of a universal cellular system that responds to hypoxia.

Kaelin was studying kidney tumors associated with a familial cancer syndrome called von Hippel-Lindau (VHL)