Lowy remains a strong supporter of basic science who understands its integration with clinical and population-level research. Schiller added that he doesn’t expect changes in the current balance between basic and clinical research under Lowy, or in the relative support for intramural and extramural investigations.

“As deputy director, Lowy was already involved in those decisions during the last 5 years,” Schiller said.

For his part, Lowy acknowledged that given ongoing needs to better understand cancer and its treatment, basic science remains a priority at NCI. But he also emphasized a need to balance support across the continuum of research and clinical development, particularly for research that yields shorter-term benefits. He declined to speculate on potential changes to the R01 grant process, saying only that, as always, it would rely heavily on study section evaluations. But he did single out prevention and screening as priorities, as well as the vexing issues surrounding cancer disparities among populations.

“For some cancers, incidence and mortality rates differ by population, so we need to better understand the origin of those differences and then try to reduce them to the best extent that we can,” he said.

Lowy also spoke about opportunities arising from the Obama administration’s Presidential Initiative on Precision Medicine, announced last January with a $215 million budget. Of that amount, $70 million will go to NCI starting in 2016. Lowy said that as part of this initiative, NCI will investigate ways to focus cancer treatments on molecular abnormalities that could drive tumor growth in different organ systems.

“Say there’s evidence from a lung adenocarcinoma trial that someone with molecular abnormality A responds to drug B,” he said. “If you find that same abnormality in someone with liver cancer, then that person would be eligible to be treated with drug B. This is how we can advance precision treatment, using both experimental and FDA-approved drugs.”

Announced by NCI in March, two precision medicine clinical trials—the Molecular Analysis for Therapy Choice Program (MATCH) and Pediatric MATCH—both use this approach. Lowy added that research funded through the initiative will address related issues, including resistance to targeted treatments, developing preclinical models, and a bioinformatics structure that supports the whole endeavor. Projects relevant to each of these components are “shovel ready now,” Lowy said.

Lowy acknowledged the challenges ahead, especially that “we usually run out of money before we run out of good ideas to test.” But he emphasized that given its position at the forefront of cancer research, NCI can exploit enormous opportunities.

“I find [Lowy] to be an incredibly thoughtful person,” Wiltrout said. “He’s someone I’ve always relied on for advice and counsel on just about any issue. I think he’s got a very broad perspective—I don’t see him going down a narrow road.”

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Programmed Death Protein 1 Inhibitors Making Inroads in Multiple Cancers

By Vicki Brower

In a new study, patients with untreated metastatic melanoma who took nivolumab, a programmed death protein 1 (PD-1) inhibitor immunotherapy, had an overall survival rate of 72.9%, compared with 42.1% for those taking standard-of-care chemotherapy, dacarbazine.

In the 418-patient phase III median progression-free survival was 5.1 months and 2.2 months, respectively. Of these patients—none of whom had a BRAF mutation, which is present in about half of melanomas and is susceptible to targeted therapies—those taking nivolumab had an objective response rate of 40%, compared with 13.9% for patients taking dacarbazine. Side effects included fatigue, itching, and nausea, with grade 3 and 4 side effects occurring in 11.7% of those treated with nivolumab and 17.6% of those treated with chemotherapy (N. Engl. J. Med 2015;372:320–30; doi:10.1056/NEJMoa1412082).

“This is the first randomized trial to show a survival advantage for a PD-1 inhibitor in metastatic melanoma,” said Mario Sznol, M.D., professor of medicine at the Yale Cancer Center in New Haven, Conn., a melanoma expert not connected with this study. Nivolumab (Opdivo) and a second PD-1 inhibitor, pembrolizumab (Keytruda), which received approval in the second half of 2014 for metastatic melanoma, are the first approved PD-1 checkpoint inhibitors. Results from the new trial, however, indicate that PD-1 inhibitors, currently approved only for second-line melanoma treatment, could be used for frontline treatment now, Sznol said. Indeed, in late January, the National Comprehensive Cancer Network changed its melanoma guidelines to reflect results from this trial, called CheckMate-066. The new guidelines reflect this judgment that both PD-1 inhibitors can be used as frontline treatments (http://www.nccn.org/professionals/physician_gls/recently_updated.asp).

“Nivolumab’s activity and side-effect profile were superior to [those of] ipilimumab, the first checkpoint inhibitor approved for use as frontline therapy for wild-type melanoma in 2011,” Sznol said.

“These drugs [all three] are some of the most active drugs ever used in melanoma,” Sznol said. Ipilimumab inhibits another protein receptor, cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), which suppresses the immune system’s response to the cancer. These drugs are monoclonal antibodies. From trial results so far, many researchers believe that PD-1 inhibitors may have greater efficacy, with fewer side effects, than CTLA-4 inhibitors, though the reasons are not well understood.

“PD-1 is a dominant pathway by which cancer protects itself,” said Antonio
patients. Fifty-eight percent of patients had moderate side effects, with only 17% experiencing serious drug-related effects, including fatigue, itching, and nausea.

“PD-1 is a dominant pathway by which cancer protects itself. On the upside, inhibiting this pathway can have long-lasting effects with minimal side effects. But the downside is that only a subset of patients respond.”

Other researchers have tested nivolumab in Hodgkin lymphoma because preclinical studies have shown that Reed–Sternberg cells—the large, multinucleated cells that characterize this cancer—exploit the PD-1 pathway. In a new study of 23 patients with relapsed or refractory Hodgkin lymphoma treated with nivolumab20, or 87%, had an objective response, 60% of whom had a response within 8 weeks, said Alexander Lesokhin, M.D., assistant attending physician at Memorial Sloan–Kettering Cancer Center in New York and a study author (N. Engl. J. Med. 2015;372:311–9; doi:10.1056/NEJMoa1411087).

“The rapidity of response suggests two hypotheses, PD-1 addiction [of cancer cells] or the redirection of the influx of inflammatory cells to the killing of cancer cells,” he said.

Of these patients, 17% had a complete response, 70% had a partial response, and 13% had stable disease. At 24 weeks, 86% had progression-free survival.

“Results from this study suggest that in the future, anti–PD-1 therapy could become the foundation of Hodgkin lymphoma treatment over chemotherapy,” Szolov said.

Activity of these drugs in non–small-cell lung cancer (NSCLC) has been surprising because this cancer type was previously treated patients whose tumors were characterized as PD-L1 positive (Nature 2014;515:558–62; doi:10.1038/nature13904). At 12 weeks, patients had an overall response rate of 52%, with a rate of 11% for those with lower ligand expression. For patients with high PD-L1 expression, response lasted 0.1–30.3 weeks, and for those with lower expression it lasted 0.1–6.0 weeks. “Bladder cancers often have many mutations, which appear to alert the immune system to their presence and therefore render them susceptible to immunotherapies,” Powles said.

Scientists often discuss using biomarkers to stratify patients by likelihood of treatment response.

Testing Biomarkers

More studies are examining whether response is associated with PD-1 or PD-L1 status of patients to determine who is most likely to respond to these drugs. Bladder cancer is one malignancy in which PD-1 inhibitors are active and in which response seems to be associated with patients’ PD-L1 status.

“There have been no new treatments for bladder cancer in three decades,” said Thomas Powles, M.D., clinical professor of genitourinary oncology at Barts Cancer Institute at the Queen Mary University of London. Powles recently reported results of a phase I study in metastatic bladder cancer with Roche/Genentech’s anti–PD-L1 drug MPDL3280, which showed an overall response rate of 43% at 6 weeks, among 13 of 30 previously treated patients whose tumors were characterized as PD-L1 positive (https://www.webges.com/cslide/library/esmo/browse/itinerary/478/2014-09-28#9f9D).

With 23 HPV-positive and 37 HPV-negative patients in the study, response rates were similar in both groups, but progression-free survival and overall survival were longer in HPV-positive patients.

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Activity of these drugs in non–small-cell lung cancer (NSCLC) has been surprising because this cancer type was not considered immunogenic, said lead author Suresh S. Ramalingam, M.D., professor and director of medical oncology at the Winship Cancer Institute of Emory University in Atlanta, who presented results in (http://www.redjournal.org/article/S0360-3016(14)04191-1/abstract).

Response was durable and ongoing in 76% of patients.

In mid-January 2015, a phase III open-label, randomized study of nivolumab versus docetaxel in squamous NSCLC in previously treated, advanced patients was stopped early because an outside monitoring committee concluded that the study had met its endpoint, superior overall survival. Four phase III trials are evaluating nivolumab as monotherapy in patients with NSCLC: three in previously treated patients and one in the frontline setting.

Active in Many Cancers

Immunotherapies, starting with the approval of interleukin 2 in 1992, have traditionally tested well in melanoma and renal cell cancer because these cancers are immunogenic.

“But in numerous studies, anti–PD-1 drugs also are showing good activity in other cancers as well, including bladder, lung, head and neck, Hodgkin lymphoma—and the list is broadening,” said Suzanne Topalian, M.D., professor of surgery and oncology and director of the melanoma program at Baltimore’s Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. “The good news is that the benefit rate is much higher than the rate of toxicity, which is manageable,” she said. In PD-1 trials, mortality rates are less than 1%.

These drugs may work best in virus-associated cancers, such as Merkel cell and human papillomavirus (HPV)-associated head and neck cancers because they are more visible to the immune system,” Topalian said.

In a phase IV study of head and neck cancer with pembrolizumab in both HPV-positive and -negative tumors, discussed at the September 2014 European Society for Medical Oncology meeting, Laura Chow, M.D., associate professor of medical oncology at the University of Washington in Seattle reported on 104 head and neck cancer patients. The overall response rate was 20%, with responses lasting 8–41 weeks, and the median had not been reached (https://www.webges.com/cslide/library/esmo/browse/itinerary/478/2014-09-28#9f9D).

With 23 HPV-positive and 37 HPV-negative patients in the study, response rates were similar in both groups, but progression-free survival and overall survival were longer in HPV-positive
An analysis showing a striking statistical correlation between how often stem cells divide and cancer means that chance sometimes plays a powerful role in cancer’s development.

But that finding does not diminish the need for primary prevention, the study’s investigators said. Widely misinterpreted, the study (Science 2015;347:78–81; doi:10.1126/science.1260825) found that random mutations in genes during normal cell division account for two-thirds of variation in cancer risk—not for two-thirds of all cancers. Individual cancer risk, the researchers said, probably

**Understanding Random Cancers**

By Susan Jenks

“While this is a small trial, that is very impressive 2-year survival data,” primary investigator Sznol said. Whether sequential or concurrent drug administration is better is an open question that will be answered with randomized trials, including the phase III CheckMate-067 study under way.

In addition to combining PD-1 inhibitors with chemotherapies, scientists are exploring combinations of PD-1 inhibitors with cancer vaccines, radiation therapy, antiangiogenic drugs, and tyrosine kinase inhibitors, Topalian said. In November, three drug companies agreed to evaluate MEDI4736, an anti–PD-L1 drug, withibrutinib, an oral Bruton tyrosine kinase inhibitor that targets malignant B cells, in follicular lymphoma and diffuse large B-cell lymphoma.

Jennifer A. Wargo, M.D., assistant professor of surgical oncology at the University of Texas M. D. Anderson Cancer Center in Houston, is investigating the use of checkpoint inhibitors with BRAF inhibitors in melanoma. Her rationale is that BRAF inhibitors increase expression of melanoma antigens and lower expression of immunosuppressive cytokines. These drugs also have a rapid but short-term effect on the tumor microenvironment, increasing dense CD8 cytotoxic T-cell infiltration of tumors for about 14 days. She set out to determine whether PD-1 checkpoint inhibitors might extend this effect.

In human melanoma samples and mouse models of melanoma, Wargo explored the combination’s effects. In mice, it improved survival and delayed tumor growth more than either drug alone, and in both mice and humans it increased intratumoral CD8 cell density, as well as these cells’ production of the antitumor cytokines interferon γ and tumor necrosis factor α (Cancer Immunol. Res. 2014;2:643–54; doi:10.1158/2326-6066.CIR-13-0215).

“We found that the immune response to BRAF inhibition was early and transient but that T-cell infiltrate and an improved CD8:T-regulatory cell ratio could be sustained by adding an immune checkpoint blocker,” Wargo said. Researchers are hopeful that the discovery of additional drug synergies will further increase survival.

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